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NDA 20297

1 OF 11

ND A 220297



NDA 20-297

SEP 14 1995

SmithKline Beecham Pharmaceuticals
Attention: Ms. Catherine Clark
Four Falls Corporate Center
Route 23 & Woodmont Avenue
P.O. Box 1510
King of Prussia, PA 19406

Dear Ms. Clark:

Please refer to your March 31, 1993 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Coreg (carvedilol) 6.25, 12.5 and 25 mg tablets.

We acknowledge receipt of your amendments and correspondence dated April 22 and 30 (2), June 9, August 12, September 14, October 4, 25 and 29, November 2 and December 6, 1993; March 15, 22, 28, and 30, April 1 and 29, May 9, July 29, August 3, 4, 8, 9, 25 and 31, September 28, November 3, and December 5, 1994; and February 20, March 16, April 24, May 10 and 12, June 2, July 20, August 18 and September 8 and 12, 1995.

This new drug application provides for the use of carvedilol for the treatment of hypertension.

We have completed the review of this application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed package insert submitted on September 8, 1995 and the draft immediate container labeling submitted on September 12, 1995. Accordingly, the application is approved effective on the date of this letter.

The immediate container final printed labeling must be identical to that contained in the September 12, 1995 submission but please revise it to add the statement, "Protect from moisture." Marketing the product with FPL that is not identical to this draft labeling with the requested change may render the product misbranded and an unapproved new drug.

Please submit fifteen copies of the final printed labeling as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-297. Approval of this labeling by FDA is not required before it is used.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Cardio-Renal Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-240
5600 Fishers Lane
Rockville, Maryland 20857

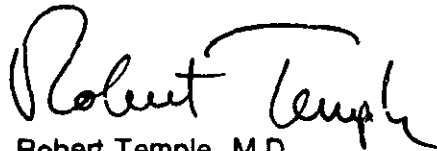
Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Ms. Zelda McDonald
Regulatory Health Project Manager
(301) 594-5300

Sincerely yours,

A handwritten signature in black ink that reads "Robert Temple". The signature is written in a cursive, flowing style.

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research



043 7

U.S.I.

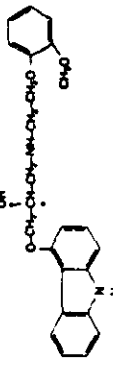
PRESCRIBING INFORMATION



COREG[®]
brand of
carvedilol
Tablets

043 7

DESCRIPTION
Carvedilol is a nonselective β -adrenoceptor blocking agent with α_1 blocking activity. It is (S)-1-(S)-1-(2-(2-(1,2,3,4-tetrahydroquinolin-3-yl)ethylamino)ethyl)propyl-2-propanol. It is a racemic mixture with the following structure:



carvedilol

Tablets for Oral Administration:
Coreg (carvedilol) is a white, oval, film-coated tablet containing 6.25 mg, 12.5 mg, or 25 mg of carvedilol. The 12.5 mg and 25 mg tablets are scored. Inactive ingredients consist of colloid silicon dioxide, croscarmellose sodium, hydroxypropylmethylcellulose, lactose monohydrate, magnesium stearate, polyethylene glycol, croscarmellose, D, L-tartrate, sucrose and titanium dioxide.

CLINICAL PHARMACOLOGY
Coreg is a racemic mixture in which nonselective β -adrenoceptor blocking activity is present in the (S)-enantiomer and α -adrenoceptor blocking activity is present in both (R)- and (S)-enantiomers at equal potency. Coreg has no intrinsic sympathomimetic activity.

Coreg is rapidly and extensively absorbed following oral administration, with absolute bioavailability of approximately 25% to 35% due to a significant degree of first-pass metabolism. Following oral administration, the apparent mean terminal elimination half-life of carvedilol generally ranges from 7 to 10 hours. Plasma concentrations achieved are proportional to the oral dose administered. When administered with food, the rate of absorption is slowed, as evidenced by a delay in the time to reach peak plasma levels, with no significant difference in extent of bioavailability. Taking Coreg with food should minimize the risk of orthostatic hypotension.

Carvedilol is extensively metabolized. Following oral administration of radiolabeled carvedilol to healthy volunteers, carvedilol accounted for only about 7% of the total radioactivity in plasma as measured by area under the curve (AUC). Less than 2% of the dose was excreted unchanged in the urine. Carvedilol is metabolized primarily by aromatic ring oxidation and glucuronidation.

7-fold) following single-dose therapy (see WARNINGS, Hepatic Injury).

Renal Insufficiency: Although carvedilol is metabolized primarily by the liver, plasma concentrations of carvedilol have been reported to be increased in patients with renal impairment. Based on mean AUC data, approximately 40% to 50% higher plasma concentrations of carvedilol were observed in hypertensive patients with moderate to severe renal impairment compared to a control group of hypertensive patients with normal renal function. However, the ranges of AUC values were similar for both groups. Changes in mean peak plasma levels were less pronounced, approximately 12% to 26% higher in patients with impaired renal function.

Consistent with its high degree of plasma protein-binding, carvedilol does not appear to be cleared significantly by hemodialysis.

Pharmacokinetics and Clinical Trials
 β -adrenoceptor blocking activity has been demonstrated in animal and human studies showing that carvedilol (1) reduces cardiac output, (2) reduces exercise- and/or isoproterenol-induced tachycardia and (3) reduces reflex orthostatic tachycardia. Significant β -adrenoceptor blocking effect is usually seen within 1 hour of drug administration. The mechanism by which β -blockade produces an antihypertensive effect has not been established.

β -adrenoceptor blocking activity has been demonstrated in human and animal studies. Carvedilol (1) attenuates the pressor effects of phenylephrine, (2) causes vasodilation, (3) reduces peripheral vascular resistance. These effects contribute to the reduction of blood pressure and usually are seen within 30 minutes of drug administration.

Due to the α_1 -receptor blocking activity of carvedilol, blood pressure is lowered more in the standing than in the supine position, and symptoms of postural hypotension (18%), including late instances of syncope, can occur following oral administration, when postural hypotension has occurred. It has been transient and is uncommon when Coreg (carvedilol) is administered with food at the recommended starting dose and titration increments are closely followed (see DOSAGE AND ADMINISTRATION).

In hypertensive patients with normal renal function, therapeutic doses of Coreg decrease renal vascular resistance with no change in glomerular filtration rate or renal plasma flow. Changes in excretion of sodium, potassium, uric acid and phosphorus in hypertensive patients with normal renal function were similar after Coreg and placebo.

Coreg has little effect on plasma catecholamines, plasma aldosterone or electrolyte levels, but does significantly reduce plasma renin activity when given for at least 4 weeks. It also increases levels of atrial natriuretic peptide.

CLINICAL TRIALS

Hypertension
Coreg was studied in two placebo-controlled trials that utilized twice-daily dosing. At total daily doses of 12.5 to 50 mg in these and other studies, the starting dose did not exceed 12.5 mg. At 60 mg per day, Coreg reduced sitting trough (12-hour) blood pressure by about 95.5 mm Hg, at 25 mg/day the effect was about 75.5 mm Hg. Comparisons of trough to peak blood pressure showed a trough to peak ratio (in blood pressure) of response of about 65%. Heart rate fell by about 7.5 beats per minute at 50 mg/day. In general, as is true for other β -blockers, responses were smaller in black than non-black patients. There were no age- or gender-related differences in responses.

The peak antihypertensive effect occurred 1 to 2 hours after a dose. The dose-related blood pressure response was accompanied by a dose-related increase in adverse effects (see ADVERSE REACTIONS).

INDICATIONS AND USAGE

Coreg (carvedilol) is indicated for the management of essential hypertension. It can be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics. (See PRECAUTIONS, Drug Interactions.)

CONTRAINDICATIONS

Coreg is contraindicated in patients with NYHA Class IV decompensated cardiac failure, bronchial asthma (two cases of death from status asthmaticus have been re-

ported in patients receiving single doses of Coreg) or related bronchospastic conditions, second or third-degree AV block, cardiogenic shock or severe bradycardia.

Use of Coreg in patients with clinically manifest hepatic impairment is not recommended.

Coreg is contraindicated in patients with hypersensitivity to the drug.

WARNINGS

Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. α_1 -blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although carvedilol has now been studied in over 1,300 patients with heart failure, the dosing and monitoring requirements are different from those for hypertension. In hypertensive patients who have congestive heart failure controlled with digoxin, diuretics and/or an angiotensin-converting enzyme inhibitor, Coreg (carvedilol) should be used with caution. Both digoxin and Coreg slow AV conduction.

Hepatic Injury: Mild hepatocellular injury, confirmed by retrograde has occurred rarely with Coreg therapy. In controlled studies of hypertensive patients, the incidence of liver function abnormalities reported as adverse experiences was 1.1% (13 of 1,142 patients) in those receiving Coreg and 0.9% (4 of 462 patients) in those receiving placebo. One patient receiving carvedilol in a placebo-controlled trial withdrew for abnormal hepatic function. Hepatic injury has been reversible and has occurred after short- and/or long-term therapy with mental clinical symptomatology. No deaths due to liver function abnormalities have been reported.

At the first symptom/sign of liver dysfunction (e.g., pruritus, dark urine, persistent anorexia, jaundice, right upper quadrant tenderness or unexplained "flu-like" symptoms), laboratory testing should be performed. If the patient has laboratory evidence of liver injury or jaundice, carvedilol should be stopped and not restarted.

Peripheral Vascular Disease: β -blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. Caution should be exercised in such individuals.

Anesthesia and Major Surgery: If Coreg treatment is to be continued perioperatively, particular care should be taken when anesthetic agents which depress myocardial function, such as ether, cyclopropane and trichloroethylene, are used. See OVERDOSAGE for information on treatment of bradycardia and hypotension.

Diabetes and Hypoglycemia: β -blockers may mask some of the manifestations of hypoglycemia, particularly subcutaneous hypoglycemia and delay recovery of serum glucose levels. Patients subject to spontaneous hypoglycemia or diabetic patients receiving insulin or oral hypoglycemic agents should be cautioned about these possibilities and carvedilol should be used with caution.

Thyroid disease: β -adrenergic blockade may mask clinical signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of β -blockade may be followed by an exacerbation of the symptoms of hyperthyroidism or may precipitate a thyroid storm.

PRECAUTIONS

General

Since Coreg has β -blocking activity, it should not be discontinued abruptly, particularly in patients with ischemic heart disease. Instead, it should be discontinued over 1 to 2 weeks.

In clinical trials, Coreg caused bradycardia in about 2% of patients. If pulse rate drops below 55 beats/min., the dosage should be reduced.

Postural hypotension occurred in 1.8% and syncope in 0.1% of patients, especially following the initial dose of Coreg. At the time of dose increase during repeated dosing, postural hypotension or syncope was a cause for discontinuation of therapy in 1% of patients.

To decrease the likelihood of syncope or excessive hypotension, treatment should always be initiated with a 6.25 mg dose of Coreg tablets. Dosage should then be increased slowly, according to recommendations in the DOSAGE AND ADMINISTRATION section, and the drug should always be taken with food. During initiation of therapy, the patient should be cautioned to avoid situa-

tions such as driving or could result should syncope occur.

Risk of Anaphylactic Reaction: Taking β -blockers, particularly anaphylactic reaction to more reactive to catecholamines or therapeutic response to the usual doses. A synergistic reaction.

Nonselective β -blockers and sympathomimetic agents: Patients with bronchospasm do not receive β -blockers. However, other antihypertensive, other antihypertensive, Coreg carvedilol is used at doses, so that inhibition of β -agonists is minimized.

Information for Patients: Patients taking Coreg should not interrupt therapy without a physician's advice; they may experience a rebound, resulting in a standing, resulting in a rebound. Patients should sit or lie down if lightheadedness or faintness occurs. Patients should consult a physician if they should take Coreg. They should take Coreg with a meal.

Drug Interactions: Also see CLINICAL PHARMACOLOGY.

Calcium channel blockers: Agents with β -blocking properties, calcium channel blockers (e.g., diltiazem, verapamil) should be discontinued when either is being administered, as the combination may decrease the dosage.

Digoxin: Digoxin concentrations increase about 15% when digoxin and carvedilol are administered together. Therefore, digoxin should be discontinued when either is being administered, as the combination may decrease the dosage.

Insulin or oral hypoglycemics: Insulin and oral hypoglycemics may enhance the effects of insulin and oral hypoglycemics. The combination of insulin and oral hypoglycemics and carvedilol should be discontinued when either is being administered, as the combination may decrease the dosage.

Concomitant with β -blockers: Concomitant with β -blockers, pressure- and heart-rate-lowering agents should be discontinued when either is being administered, as the combination may decrease the dosage.

Cardiovascular: Cardiac glycosides, digoxin, should be discontinued when either is being administered, as the combination may decrease the dosage.

Cardiovascular: Cardiac glycosides, digoxin, should be discontinued when either is being administered, as the combination may decrease the dosage.

At doses 2200 mg/kg/day (2.32 times the MRHD as mg/m²) carvedilol was toxic to adult rats (sedation, reduced weight gain) and was associated with a reduced number of successful matings, prolonged mating time, significantly fewer corpora lutea and implants, per dam and complete resorption of 18% of the litters. The no-observed effect dose level for overt toxicity and impairment of fertility was 80 mg/kg/day (10 times the MRHD as mg/m²).

Prepregnancy Teratogenic Effects. Pregnancy Category C. Studies performed in pregnant rats and rabbits given carvedilol revealed increased post-implantation loss in rats at doses of 300 mg/kg/day (50 times the MRHD as mg/m²) and in rabbits at doses of 75 mg/kg/day (25 times the MRHD as mg/m²). In the rats, there was also a decrease in fetal body weight at the maternally toxic dose of 300 mg/kg/day (50 times the MRHD as mg/m²), which was accompanied by an elevation in the frequency of fetuses with delayed skeletal development (missing or stunted 13th rib). In rats the no-observed-effect level for developmental toxicity was 60 mg/kg/day (10 times the MRHD as mg/m²); in rabbits it was 15 mg/kg/day (5 times the MRHD as mg/m²). There are no adequate and well-controlled studies in pregnant women. Corag should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Studies in rats have shown that carvedilol and/or its metabolites (as well as other β -blockers) cross the placental barrier and are excreted in breast milk. There was increased mortality at one week post-partum in neonates from rats treated with 60 mg/kg/day (10 times the MRHD as mg/m²) and above during the last trimester through day 22 of lactation. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from β -blockers, especially bradycardia, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. The effects of other α - and β -blocking agents have included prenatal and neonatal distress.

Pediatric Use
Safety and efficacy in patients younger than 16 years of age have not been established.

Geriatric Use
Of the 2,085 patients in U.S. clinical trials of efficacy or safety who were treated with Corag (carvedilol), 21% (436) were 65 years of age or older. Of 3,727 patients receiving Corag in hypertension clinical trials conducted worldwide, 24% were 65 years of age or older. There were no notable differences in efficacy or the incidence of adverse events between older and younger patients. With the exception of dizziness (incidence 3.8% in the elderly vs. 6% in younger patients), there were no events for which the incidence in the elderly exceeded that in the younger population by greater than 2.0%.

Similar results were observed in a postmarketing surveillance study of 3,328 Corag patients, of whom approximately 70% were 65 years of age or older.

ADVERSE REACTIONS

Corag has been evaluated for safety in hypertension in more than 2,193 patients in U.S. clinical trials and in more than 2,978 patients in international clinical trials. Approximately 36% of the total treated population received Corag for at least 6 months. In general, Corag was well tolerated at doses up to 80 mg daily. Most adverse events reported during Corag therapy were of mild to moderate severity. In U.S. controlled clinical trials directly comparing Corag monotherapy in doses up to 80 mg (n=1,142) to placebo (n=622), 4.9% of Corag 1-year patients discontinued for adverse events vs. 6.2% of placebo patients. Although there was no overall difference in discontinuation rates, discontinuations were more common in the carvedilol group for postural hypertension (1% vs. 0.2%). The overall incidence of adverse events in U.S. placebo-controlled trials was found to increase with increasing doses of Corag. For individual adverse events, this could only be distinguished for dizziness, which increased in frequency from 2% to 5% as total daily dose increased from 6.25 mg to 80 mg.

Table 1 shows adverse events in U.S. placebo-controlled clinical trials that occurred with an incidence of greater than 1% regardless of causality and that were more frequent in drug-treated patients than placebo-treated patients.

Table 1
Adverse Events in U.S. Placebo-Controlled Trials
Incidence $\geq 1\%$, Regardless of Causality;
Without a Reasonable Doubt Due to Adverse Events

Adverse Event	Corag (n=1142)	Placebo (n=622)	Corag (n=1142)	Placebo (n=622)
	% increase	% increase	% without doubt	% without doubt
Central Nervous System	82	54	84	13
Dizziness	18	8	—	—
Somnolence	18	15	—	—
Headache	18	15	—	—
Blurred vision	14	12	—	—
Abnormal eye	22	13	01	—
Diplopia	22	13	01	—
Vertigo	21	07	04	—
Postural hypertension	18	15	18	04
Postural hypotension	17	15	08	—
Postural dizziness	14	04	02	—
Headache	18	15	—	—
Dizziness	18	15	—	—
Somnolence	18	15	—	—
Blurred vision	14	12	—	—
Abnormal eye	22	13	01	—
Diplopia	22	13	01	—
Vertigo	21	07	04	—
Postural hypertension	18	15	18	04
Postural hypotension	17	15	08	—
Postural dizziness	14	04	02	—
Headache	18	15	—	—
Dizziness	18	15	—	—
Somnolence	18	15	—	—
Blurred vision	14	12	—	—
Abnormal eye	22	13	01	—
Diplopia	22	13	01	—
Vertigo	21	07	04	—

In addition to the events in Table 1, chest pain, dyspnea, headache, nausea, pain, sinusitis and upper respiratory tract infection were also reported, but rates were at least as great in placebo-treated patients. The following adverse events were reported as possibly or probably related in worldwide open or controlled trials with Corag (carvedilol):

Incidence $>0.1\%$ to $\leq 1\%$
Cardiovascular: AV block (see CONTRAINDICATIONS), extrasystoles, hypertension, hypotension, palpitations, peripheral ischemia, syncope.
Central and Peripheral Nervous System: Ataxia, hypotonia, paresthesia, vertigo.
Gastrointestinal: Bloating, constipation, flatulence, increased hepatic enzyme (0.2% of patients were discontinued from therapy because of increases in hepatic enzymes; see WARNINGS, Hepatic Injury), vomiting.
General: Asthenia, hot flashes, leg cramp, malaise.
Musculoskeletal System: Myalgia.

Psychiatric: Depression, nervousness.
Respiratory System: Asthma (see CONTRAINDICATIONS), cough.
Reproductive: Male: decreased libido, impotence.
Skin and Appendages: Pruritus, rash, rash erythematous, rash maculopapular, rash paronychia.
Special Senses: Abnormal vision, tinnitus.
Urinary System: Albuminuria, hematuria, micturition frequency.
Autonomic Nervous System: Dry mouth, sweating increased.

Metabolic and Nutritional: Hypochloremia, hypoglycemia, hyperuricemia.
Hematologic: Anemia, leukopenia.

The following eye events were reported in 50.1% of patients and are potentially important: angina, arrhythmias, atrial fibrillation, bundle branch block, cardiac failure, myocardial ischemia, cardiovascular disorder, migraine, neuropathy, paresis, atropia, anisocoria, conjunctivitis, bronchospasm, decreased hearing, respiratory alkalosis, increased IOP, glycosuria, decreased HbA_{1c}, hypotalemia, hypotalemia, increased NPN, increased alkaline phosphatase, increased weight, eczematoid, and atypical lymphocytes.

Other adverse events occurred sporadically in single patients and cannot be distinguished from concurrent disease states or medications.

Corag therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, fasting serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen or creatinine.

OVERDOSEAGE
The acute oral LD₅₀ doses in male and female mice and male and female rats are over 8000 mg/kg.

Overdose may cause severe hypotension, bradycardia, cardiac insufficiency, cardiogenic shock, and cardiac arrest. Respiratory problems, bronchospasm, vomiting, lapses of consciousness and generalized seizures may also occur.

The patient should be placed in a supine position and, where necessary, kept under observation and treated under intensive-care conditions. Gastric lavage or pharmacologically induced emesis may be used shortly after ingestion. The following agents may be administered:

for excessive bradycardia: atropine, 2 mg IV
to support cardiovascular function: phosprop, 5 to 10 mg IV rapidly over 30 seconds, followed by a continuous infusion of 5 mg/hour, sympathomimetics (dobutamine, dopamine, adrenaline) at doses according to body weight and effect.

If peripheral vasodilation dominates, it may be necessary to administer adrenaline or noradrenaline with continuous monitoring of circulatory conditions. For therapy-resistant bradycardia, pacemaker therapy should be performed. For bronchospasm, β -sympathomimetics (e.g. aerosol or IV) or aminophylline IV should be given in the event of seizures, slow IV injection of diazepam or clonazepam is recommended.

NOTE: In the event of severe intoxication where there are symptoms of shock, treatment with antidotes must be continued for a sufficiently long period of time consistent with the 7- to 10-hour half-life of carvedilol. Three cases of overdose have been reported. A 59-year-old male who ingested 200 mg experienced severe chest pain but recovered completely. A 2-year-old child who ingested an unknown quantity suffered no adverse effects following induced vomiting and observation. A 39-year-old female ingested 400 mg with an unknown amount of benzodiazepine. She was hospitalized in a state of stupor and hypotension, but recovered completely following supportive measures.

DOSEAGE AND ADMINISTRATION
DOSAGE MUST BE INDIVIDUALIZED. The recommended starting dose of Corag (carvedilol) is 6.25 mg twice daily. If this dose is tolerated, using standing systolic pressure measured about 1 hour after dosing as a guide, the dose should be maintained for 7 to 14 days, and then increased to 12.5 mg twice daily if needed, based on trough blood pressure, again using standing systolic pressure one hour after dosing as a guide for tolerance. This dose should also be maintained for 7 to 14 days and can then be adjusted upward to 25 mg twice daily if tolerated and needed. The full antihypertensive effect of Corag is seen within 7 to 14 days. Total daily dose should not exceed 50 mg. Corag should be taken with food to slow the rate of absorption and reduce the incidence of orthostatic effects.

Addition of a diuretic to Corag, or Corag to a diuretic can be expected to produce additive effects and exaggerate the orthostatic component of Corag action.
Corag should not be given to patients with severe hepatic impairment (see CONTRAINDICATIONS).

HOW SUPPLIED
Tablets: White, oval, film-coated (Tabac) tablets: 6.25 mg scored, imprinted with 4140 and SB, in bottles of 30 and 100 and in Single Unit Packages of 100 (intended for institutional use only); 12.5 mg-imprinted with 4141 and SB, in bottles of 30 and 100 and in Single Unit Packages of 100 (intended for institutional use only); 25 mg-imprinted with 4142 and SB, in bottles of 30 and 100 and in Single Unit Packages of 100 (intended for institutional use only).

Store between 15° and 30°C (59° and 86°F). Protect from moisture. Dispense in a tight, light-resistant container.
6.25 mg 30's: NDC 0007-4140-13
6.25 mg 100's: NDC 0007-4140-20
6.25 mg SUP 100's: NDC 0007-4140-21
12.5 mg 30's: NDC 0007-4141-13
12.5 mg 100's: NDC 0007-4141-20
12.5 mg SUP 100's: NDC 0007-4141-21
25 mg 30's: NDC 0007-4142-13
25 mg 100's: NDC 0007-4142-20
25 mg SUP 100's: NDC 0007-4142-21

DEC 21 1993

NDA 20-297 KREDEX

(Carvedilol) SmithKline Beecham

The attached Medical Officer Review does not have continuous page numbering nor continuous dialog. The Medical Officer used the pages from the Sponsors submission as a review and added comments to the original pages.

Carvedilol (KREDEX®) is presented as a non-cardio-selective β -blocker and an α_1 adrenergic blocker. In high concentrations it also has some blocking effect on slow calcium channels.

It has been studied as an antihypertensive drug. In addition the sponsor presents it as a protective agent in myocardial infarction, stroke, renal failure and heart failure; as a drug with antioxidant activity and an antiproliferative effect that may result in attenuation of the atherosclerotic process; a drug that prevents platelet aggregation and leads to an improvement in the hemorheologic properties. There is, however, insufficient clinical data to support these additional claims.

Boehringer-Mannheim (BM) submitted the first US IND in 1985. The phase I studies were interrupted when a subject collapsed during an IV infusion and had to be resuscitated. Details of this episode were scarce (no EKG) but there was apparently a cardiac arrest that needed intervention. The sponsor conducted an extensive literature search and a review of BM international safety data. The conclusion was that the episode could be ascribed to an overdose of β -blocker. Clinical trials were resumed with lower maximum doses, explaining why some of the initial protocols failed to explore the full range used in later studies. SmithKline & French (now SmithKline Beecham (SKB)) entered the picture in 1987.

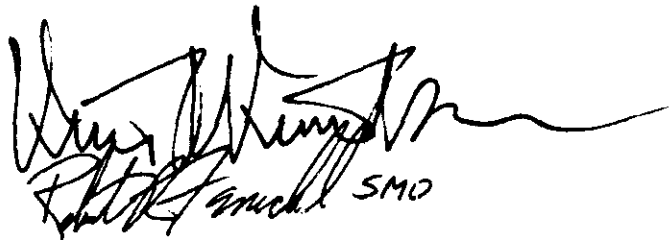
NDA 20-297 for use in hypertension was submitted in March 1993 . The CANUA

NDA 20-297 has been selected by the CardioRenal Division to test if parallel review is feasible. This portion of the team review addresses clinical efficacy, only.

1 Title and General Information

1.1 Medical Officer's Review

Reviewer: Knud Knudsen, M.D.



1.1.1 NDA # 20-297

1.1.2 M.O. Review # 1.

1.1.3 Submitted March 1993

1.1.4 Review Completed December 1993

1.2 Drug Name:

1.2.1 Generic Name: Carvedilol

1.2.2 Proposed Trade Name: KREDEX

1.2.3

The sponsor has submitted reports on 101 controlled clinical studies, conducted under the aegis of SKF or BM; and has filed reprints of a number of published papers relating to efficacy. Six of these studies: protocols B100, B101, B104, C1106, C1107 and C1109, all multicenter trials conducted in USA, carry the burden of showing that the drug works.

The remaining studies are submitted to support the claims and to evaluate safety in numbers. The complete list, compiled by the sponsor, is appended. Most of the studies, taken individually, are small. The well half-dozen sizable studies do not have placebo control but pit Carvedilol against other beta-blockers, calcium blockers ACE inhibitors and diuretics. The list speaks volumes (literally) about the intensive marketing effort all over Europe. The studies lack placebo control and do not provide independent evidence of efficacy.

Controlled Clinical Trials in Mild to Moderate Hypertension.

Carvedilol (KREDEX) NDA 20-297

Protocol #	Ctry	Study Design	Treatments	Doses (mg)	number randomized	n	sex M/F	Race B/NB	Duration	Results
B100	USA	DB, ran, parallel	Carvedilol bid Placebo	6.25 12.5 25	480	118 126 117 119	312/168	71/409	2 Mo	Moderate, dose related reduction of blood pressure. Mild reduction of heart rate. No subgroup effect.
B101	USA	DB, ran, parallel	Carvedilol QID Placebo	6.25 12.5 25 50	520	121 127 127 29 116	328/192	79/441	2 Mo	Moderate dose related reduction in BP at peak. No statistically significant difference at trough. Carvedilol does not appear useful as a once-a-day drug. No subgroup effect.
B104	USA	DB, ran, parallel titration. Black patients, only	Carvedilol BID Labetalol BID Placebo	6.25 12.5 25 100 200 400	85 79 82	(n at endpoint) 26 24 33 25 16 33 75	117/129	246/0	2 Mo	In the intent to treat analysis both Carvedilol and Labetalol lowered sitting diastolic blood pressure more than placebo did. No significant difference between the two active treatments. No convincing effect on several other BP measures.

Controlled Clinical Trials in Mild to Moderate Hypertension.
(cont.)

Carvedilol (KREDEX) NDA 20-297

Protocol #	Ctry	Study Design	Treatments	Doses (mg)	number randomized	n	sex M/F	Race B/NB	Duration	Results
C1107	USA	DB, ran, parallel, step II with HCTZ	Carvedilol UID (titrated) w/ HCTZ 25 mg/day Placebo w/HCTZ 25 mg/day	6.25 12.5 25	200 66	67 67 66 66	172/94	89/177	1 Mo	As step II in patients responding poorly to HCTZ 25 mg/day Carvedilol and Placebo were equally effective.
C1109	USA	DB, ran, parallel, titration.	Carvedilol UID (titrated) Atenolol UID Placebo	12.5 100 25 50 50 100	105 101 52	10 14 81 57 32 48	181/77	61/196	11 Wks	Both drugs beat placebo but atenolol was significantly better than carvedilol Aten vs Plac(-10.9, -5.9) <0.001* Carv vs Plac(-7.2, -2.2) <0.001* Carv vs Aten(1.6, 5.7) <0.001*
C1106	USA	DB, ran, parallel, titration.	Carvedilol UID (titrated) Carvedilol BID (titrated) Placebo	3.25 - 50 mg/day 6.25 - 50 mg/day	280	90 96 93	111/168	105/175	11- 22 wks	Carvedilol BiD and UID were better than placebo, and Carvedilol BiD was better than UID at endpoint. UID vs PLAC* (-5.83,-1.51) p=0.0009* BiD vs PLAC* (-8.79,-4.57) p=0.0001* UID vs BiD* (0.87, 5.15) p=0.0060*

Controlled Clinical Trials in Mild to Moderate Hypertension.
Foreign studies, all with positive control, no placebo arm

Carvedilol (KREDEX) NDA 20-297

Protocol #	Ctry	Study Design	Treatments	Doses (mg)	n	sex M/F	Duration	Results
CAR-UK-104	UK	DB/RAN/PAR	Carvedilol UID	12.5 - 50	232	89/143	3 Mo	All patients $\geq$ 65. Recommended start dose 12.5 mg
INT/CAR/07	Europe	DB/RAN/PAR	Carvedilol UID Atenolol	12.5 - 25 50	161 104	176/149	2 Mo	No difference between drugs
INT/CAR/08	France	DB/RAN/PAR	Carvedilol UID Acebutolol	12.5 - 25 200	105 112	101/116	2 Mo	No difference between drugs
INT/CAR/10	UK	DB/RAN/PAR	Carvedilol UID Nifedipine bid	25-50 (20-40)x2	103 102	118/87	2 Mo	No difference between drugs
INT/CAR/11	UK	DB/RAN/PAR	Carvedilol UID HCTZ	25-50 25-50	100 100	105/95	2 Mo	No difference between drugs
INT/CAR/12	Europe	DB/RAN/PAR	Carvedilol UID Captopril	12.5 - 50 25 - 50	147 151	140/158	2 Mo	No difference between drugs
MF3460	Europe	DB/RAN/PAR	Carvedilol UID Pindolol {+HCTZ prn}	25 - 50 7.5 - 15	337 165	278/224	3 Mo {1ye}	No difference between drugs
MF3461	Germany Belgium	DB/RAN/PAR	Carvedilol UID Pindolol	25-50-100 15	156 49	102/103	3 Mo	No difference between drugs
MF3948	UK	DB/RAN/PAR	Carvedilol UID Nifedipine bid Atenolol UID	25-50 (20-40)x2 50 - 100	103 102	118/87	3 Mo	Atenolol appeared more effective than either of the other.

ITEM 2 SUMMARY

C. FOREIGN MARKETING HISTORY

Carvedilol (Kredex[®]) was in-licensed from Boehringer Mannheim GmbH and is being co-developed by SmithKline Beecham and Boehringer Mannheim in the United States, Canada, Europe, Australia and New Zealand. Under a separate co-development agreement, carvedilol is being developed in Boehringer Mannheim. Additionally an NDA was filed in

As of August 31, 1992, carvedilol has been approved, and is on the market for the treatment of hypertension in four foreign countries: Germany (approved October 1990; launched January 1991), Belgium (approved November 1990; launched March 1991), South Africa (approved October 1991; launched February 1992), and Argentina (approved September 1991; launched May 1992). Table 2.C.1 provides the labeling information relating to dosage and administration in these countries. The complete text of the approved labeling for each country is provided in Section 8.F.3 (Appendix 1: Vol 1.89 page 0000014).

Carvedilol has not been withdrawn from marketing in any country. There have been no major changes in labeling in any of the foreign countries in which carvedilol has been approved for marketing.

Marketing applications have been filed in 41 foreign countries. Table 2.C.2 provides a summary of the regulatory status of these applications.

000076

Table 2.C.1 Countries in Which Carvedilol Has Been Approved for Marketing

COUNTRY	APPROVAL/LAUNCH	DOSAGE AND ADMINISTRATION
ARGENTINA Dilatrend®	Sep. 1991/May 1992 (Boehringer Mannheim)	Your doctor will decide on the amount of the daily dose and the length of time for which it must be taken. Unless otherwise prescribed, the dose is 1 Dilatrend tablet once daily. Treatment should begin with half a Dilatrend tablet (=12.5 mg) daily for the first two days. After that, treatment can continue with one tablet of Dilatrend once a day. Do not increase the dose unless directed to do so by your doctor. If the effect is insufficient, he may increase the dose to one tablet of Dilatrend twice a day, after 15 days at the earliest. A single dose of 25 mg or the total daily dose of 50 mg must not be exceeded. The tablet should be swallowed whole, without chewing, with sufficient liquid.
BELGIUM Kredex® Dimitone®	Nov. 1990/Mar. 1991 (SmithKline Beecham) Nov. 1990/Mar. 1991 (Boehringer Mannheim)	The recommended dose is 25 mg once daily. The initial dose is 12.5 mg (half a tablet) once a day, during the first two days of treatment. If necessary, the daily dose can be increased to 50 mg administered in one dose or in 2 doses of 25 mg. The daily dose must not exceed 100 mg. No development of tolerance to the therapeutic effect was observed during clinical trials. In the event of moderate hepatic or renal impairment a reduction in dose should be considered. The dose can then be increased gradually according to clinical results. Kredex should be withdrawn gradually in coronary patients.
GERMANY Dilatrend®	Oct. 1990/Jan. 1991 (Boehringer Mannheim)	Generally 1 Dilatrend tablet per day is sufficient. Treatment should be begun with one-half Dilatrend tablet (=12.5 mg) on the first two days. Then treatment may continue with 1 tablet per day: If the effect is insufficient the dose may be increased, not earlier than after 14 days, to 2 x 1 Dilatrend tablets per day, spread over the day. The single dose of 25 mg or daily amount of 50 mg must not be exceeded.
SOUTH AFRICA Kredex® Dilatrend®	Oct. 1991 (SmithKline Beecham) Oct. 1991/Feb. 1992 (Boehringer Mannheim)	The recommended dosage is 25 mg once daily. Combination with a diuretic may give the desired response. It is recommended that treatment is initiated with 12.5 mg (half of one 25 mg tablet) as a single dose for the first two days. At doses higher than 25 mg, the incidence of side-effects increases significantly with only a marginal increase in efficacy. It is not necessary to time the dose in relation to meals.

000077

Table 2.C.2 Foreign Countries in Which Marketing Applications Have Been Submitted

COUNTRY	SPONSOR	APPLICATION	APPROVAL	LAUNCH
ARGENTINA	Boehringer Mannheim	May 1989	Sep. 1991	May 1992
AUSTRIA	Boehringer Mannheim	Jun. 1989	Dec. 1991	
BELGIUM	SmithKline Beecham Boehringer Mannheim	Jul. 1988 Oct. 1988	Nov. 1990 Nov. 1990	Mar. 1991 Mar. 1991
CHILE	Boehringer Mannheim	Mar. 1989	May 1992	Oct. 1992
FRANCE	SmithKline Beecham Boehringer Mannheim	Nov. 1988 Nov. 1988	Aug. 1991 Aug. 1991	
GERMANY	Boehringer Mannheim	Dec. 1986	Oct. 1990	Jan. 1991

(E)=Expected

000078

Table 2.C.2 (cont.) Foreign Countries in Which Marketing Applications Have Been Submitted

COUNTRY	SPONSOR	APPLICATION	APPROVAL	LAUNCH
GUATEMALA	Boehringer Mannheim	Dec. 1991	Mar. 1992	
IRELAND	SmithKline Beecham	Dec. 1988/updated file Dec. 1990	Feb. 1992	
	Boehringer Mannheim	Dec. 1988/updated file Dec. 1990	Feb. 1992	
ITALY	SmithKline Beecham	Jul. 1989	Nov. 1990	Mar. 1993 (E)
	Boehringer Mannheim	Jul. 1989	Nov. 1990	Mar. 1993 (E)
LUXEMBOURG	Boehringer Mannheim	Dec. 1990	May 1991	
MEXICO	Farmacéuticos Lakeside	April 1989	Mar. 1992	Oct. 1992

(E) = Expected

000079

Table 2.C.2 (cont.) Foreign Countries in Which Marketing Applications Have Been Submitted

COUNTRY	SPONSOR	APPLICATION	APPROVAL	LAUNCH
SOUTH AFRICA	SmithKline Beecham	Aug. 1989	Oct. 1991	
	Boehringer Mannheim	Aug. 1989	Oct. 1991	Feb. 1992
SPAIN	SmithKline Beecham	Mar. 1988	Oct. 1992	2nd Q 1993
	Boehringer Mannheim	Mar. 1988	Oct 1992	2nd Q 1993

(E)=Expected

000030

8 Clinical Studies

8.1 Trial #B100

8.1.1 Objectives: Evaluate the safety and antihypertensive efficacy of carvedilol 6.25 mg, 12.5 mg, or 25 mg administered twice daily as compared to placebo, in patients with mild to moderate hypertension treated for eight weeks.

8.1.2 Design: Parallel, DB, placebo control.

n	Single Blind	n	Double Blind		Single Blind
742	Placebo up to 8 weeks	119	Placebo		Placebo for 2 weeks
		118	6.25 mg bid for 8 weeks		
		126	6.25 mg bid for 1 week	12.5 mg bid for 7 weeks	
		117	12.5 mg bid for 1 week	25 mg bid for 7 weeks	
742	8 weeks	480	1 week	7 weeks	419

8.1.3 Protocol

8.1.3.1 Population, procedures:

Males and females between the ages of 21 and 75 years with mild to moderate hypertension (SitDBP greater than or equal to 95 mm Hg and less than or equal to 115 mm Hg) were eligible for enrollment. Eligible female patients were post-menopausal for at least six months, surgically sterilized, or using an intrauterine device or oral contraceptives for at least three months prior to entry into the study.

Exclusion criteria were appropriate to rule out secondary hypertension or concurrent heart, liver or other systemic disorder. Concurrent medication was restricted.

8.1.3.2. Endpoints:

The primary parameter of efficacy in this study was change in mean *sitting Diastolic Blood Pressure (SitDBP)*.

Secondary Efficacy Parameters were Diastolic Pressure (*standing and supine*), *Systolic Pressure, Heart Rate, and Response Rates*. Patients were considered "responders" if their mean SitDBP was lowered during the study to 90 mm Hg or less and/or if it had decreased from baseline at least 10 mm Hg. (Although categorical endpoints are arbitrary in the evaluation of hypertension, 'response rate' may be a useful indicator for comparison of drugs. The 'and/or' term, however, makes it worthless. A drop from 95 to 89 is hardly a response worth the price in money or misery caused by the drug, nor is a drop from 110 to 100 sufficient unto the goal of treatment. A more meaningful - albeit still arbitrary - definition of response might be 'a lowering to 90 mmHg or below, and a drop of at least 10 mmHg'.)

8.1.3.3. Statistical Considerations:

Thirty-three (33) investigators enrolled 742 patients into the placebo baseline evaluation. *Two hundred sixty-two (262)* were withdrawn during this phase. Of these, 30 were withdrawn for an adverse event, the rest for failure to meet entry criteria. *Four hundred eighty (480)* entered the double blind treatment phase; of these 419 completed the study; a total of 306 were considered to have completed 'per protocol' but of the latter 74 had one or more censored data and additional data were excluded or missing due to the patients' failure to show up at the scheduled time. The main analyses, then, involved the '*intention to treat*' (480 patients) or the '*per protocol*' (306 patients) groups. The numbers raise the perennial issue: Do the weeding out of placebo responders bias the outcome?.

Subgroup analyses by sex, age, and race - according to current agency guidelines - were also performed. These subgroups tend to be too small to yield statistically meaningful data but gross discrepancies are not in evidence.

Summary of Baseline Characteristics

Intent-to-Treat Sample

	<u>Carvedilol</u> 6.25 mg (N = 118)	<u>Carvedilol</u> 12.5 mg (N = 126)	<u>Carvedilol</u> 25.0 mg (N = 117)	<u>Placebo</u> (N = 119)	<u>p-value</u> *
Number (%) of Patients					
Age (years):					
≤ 64	90 (76%)	93 (74%)	86 (74%)	101 (85%)	0.125
≥ 65	28 (24%)	33 (26%)	31 (24%)	18 (15%)	
Mean Age ± S.D.	56 ± 11	56 ± 11	57 ± 11	55 ± 10	0.3422
Gender:					
Male	85 (72%)	80 (63%)	77 (66%)	70 (59%)	0.193
Female	33 (28%)	46 (37%)	40 (34%)	49 (41%)	
Race:					
Non-black	99 (84%)	103 (82%)	104 (89%)	103 (87%)	0.426
Black	19 (16%)	23 (18%)	13 (11%)	16 (13%)	
Severity of Hypertension†:					
Normal	6 (5%)	3 (2%)	2 (2%)	5 (4%)	0.914**
Mild	86 (73%)	91 (72%)	83 (71%)	85 (71%)	
Moderate	26 (22%)	32 (25%)	31 (26%)	28 (24%)	
Severe	0	0	1 (1%)	1 (1%)	
Prior Anti-hypertensives:					
No	20 (17%)	24 (19%)	20 (17%)	21 (18%)	0.972
Yes	98 (83%)	102 (81%)	97 (83%)	98 (82%)	
Body Weight (kg):					
≤ 70	9 (8%)	22 (18%)	21 (18%)	22 (18%)	0.261
71-90	57 (48%)	57 (45%)	51 (44%)	49 (41%)	
≥ 91	52 (44%)	47 (37%)	45 (38%)	48 (41%)	
Mean ± S.D.	88 ± 13	87 ± 18	87 ± 17	87 ± 20	0.8704

Summary of Baseline Characteristics

Per-Protocol Sample

	Carvedilol <u>6.25 mg</u> (N=70)	Carvedilol <u>12.5 mg</u> (N=75)	Carvedilol <u>25.0 mg</u> (N=77)	Placebo (N=84)	p-value*
Number (%) of Patients					
Age (years):					
≤ 64	55 (79%)	53 (71%)	55 (71%)	72 (86%)	0.082
≥ 65	15 (21%)	22 (29%)	22 (29%)	12 (14%)	
Mean ± S.D.	56 ± 10	56 ± 12	58 ± 9	54 ± 10	0.1583
Gender:					
Male	51 (73%)	50 (67%)	49 (64%)	53 (63%)	0.576
Female	19 (27%)	25 (33%)	28 (36%)	31 (37%)	
Race:					
Non-black	55 (79%)	62 (83%)	68 (88%)	72 (86%)	0.410
Black	15 (21%)	13 (17%)	9 (12%)	12 (14%)	
Severity of Hypertension*:					
Normal	3 (4%)	0	1 (1%)	3 (4%)	0.660**
Mild	52 (74%)	52 (69%)	55 (71%)	62 (74%)	
Moderate	19 (23%)	15 (21%)	23 (31%)	20 (26%)	
Severe	0	0	1 (1%)	1 (1%)	
Prior Anti-hypertensives:					
No	9 (13%)	17 (23%)	14 (18%)	19 (23%)	0.381
Yes	61 (87%)	58 (77%)	63 (82%)	65 (77%)	
Body Weight (kg):					
≤ 70	2 (3%)	14 (19%)	13 (17%)	13 (15%)	0.055
71-90	37 (53%)	37 (49%)	37 (48%)	33 (39%)	
≥ 91	31 (44%)	24 (32%)	27 (35%)	38 (45%)	
Mean ± S.D.	89 ± 13	85 ± 17	88 ± 18	89 ± 21	0.3244

* p-value of Chi Square test

Mean SitDBP prior to receipt of first dose of randomized medication; Normal = < 95 mm Hg, Mild = 95-105 mm Hg, Moderate = 106-115 mm Hg, Severe = ≥ 116 mm Hg
 ** Test based on Mild and Moderate categories only.

**Number and Percentage of Patients with Data Included
and Excluded from the Efficacy Analysis**

	Carvedilol		Carvedilol		Carvedilol		Placebo	
	<u>6.25 mg</u>		<u>12.5 mg</u>		<u>25.0 mg</u>		<u>Placebo</u>	
	N		N		N		N	
Included <i>Intent-to Treat</i> analysis	118	100%	126	100%	117	100%	119	100%
Included <i>Per-Protocol</i> analysis	70	59.3%	75	59.5%	77	65.8%	84	70.6%
Completely excluded by protocol violation	48	40.7%	51	40.5%	40	34.2%	35	29.4%
Partially excluded by protocol violation*	17	14.4%	14	11.1%	22	18.8%	21	17.6%
Partially excluded by slotting procedure†	7	5.9%	8	6.3%	6	5.1%	11	9.2%

*

Patients had one or more visits excluded because of a protocol violation that did not cause complete exclusion of data.

† Patients had one or more visits excluded by the slotting procedure.

8.1.4 Results

8.1.4.1. Patient Disposition, procedures

Of the 480 patients who entered the double-blind treatment phase and received at least one dose of active study medication totals of 118, 126, 117, and 119 patients were randomized to carvedilol 6.25 mg, carvedilol 12.5 mg, carvedilol 25 mg, and placebo regimens, respectively.

While there may have been fewer elderly and more women in the placebo group than in the active treatment groups, there is no evidence that the differences have biased the outcome of the trial. Nor was the distribution skewed between the 'per protocol' and the 'intention to treat' populations. Baseline blood pressures and prior exposure to antihypertensive drugs were similar in all groups.

8.1.4.2. Efficacy Endpoint Outcomes

Mean Systolic Blood Pressure (mm Hg) at Baseline

Parameter	Treatment Group (bid)		Intent-to-Treat		Per-Protocol	
			n	Mean ± S.E.	n	Mean ± S.E.
SitSBP	Carvedilol	6.25 mg	118	151 ± 1.5	70	151 ± 1.8
		12.5 mg	126	154 ± 1.6	75	155 ± 2.2
		25.0 mg	117	155 ± 1.5	77	156 ± 1.8
	Placebo	119	153 ± 1.5	84	152 ± 1.8	
SupSBP	Carvedilol	6.25 mg	118	149 ± 1.5	70	150 ± 1.8
		12.5 mg	126	153 ± 1.6	75	155 ± 2.4
		25.0 mg	117	153 ± 1.6	77	155 ± 1.9
	Placebo	119	152 ± 1.8	84	151 ± 2.0	
StaSBP	Carvedilol	6.25 mg	118	147 ± 1.5	70	147 ± 1.9
		12.5 mg	126	150 ± 1.6	75	151 ± 2.3
		25.0 mg	117	150 ± 1.6	77	152 ± 1.8
	Placebo	119	148 ± 1.5	84	147 ± 1.9	
StaSBP (3 min)	Carvedilol	6.25 mg	118	148 ± 1.6	70	149 ± 2.1
		12.5 mg	126	153 ± 1.8	75	154 ± 2.6
		25.0 mg	117	153 ± 1.6	77	154 ± 1.7
	Placebo	119	150 ± 1.5	84	149 ± 1.8	

Mean Diastolic Blood Pressure (mm Hg) at Baseline

<u>Parameter</u>	<u>Treatment Group (bid)</u>		<u>Intent-to-Treat</u>		<u>Per-Protocol</u>	
			<u>n</u>	<u>Mean ± S.E.</u>	<u>n</u>	<u>Mean ± S.E.</u>
SitDBP	Carvedilol	6.25 mg	118	101 ± 0.5	70	101 ± 0.6
		12.5 mg	126	101 ± 0.5	75	102 ± 0.7
		25.0 mg	117	102 ± 0.5	77	102 ± 0.6
	Placebo	119	101 ± 0.5	84	101 ± 0.6	
SupDBP	Carvedilol	6.25 mg	118	97 ± 0.6	70	98 ± 0.8
		12.5 mg	126	99 ± 0.7	75	99 ± 0.9
		25.0 mg	117	99 ± 0.7	77	99 ± 0.8
	Placebo	119	98 ± 0.7	84	97 ± 0.8	
StaDBP	Carvedilol	6.25 mg	118	99 ± 0.7	70	100 ± 0.9
		12.5 mg	126	100 ± 0.7	75	100 ± 0.9
		25.0 mg	117	101 ± 0.8	77	102 ± 1.0
	Placebo	119	100 ± 0.7	84	99 ± 0.8	
StaDBP (3 min)	Carvedilol	6.25 mg	118	101 ± 0.7	70	101 ± 0.9
		12.5 mg	126	101 ± 0.7	75	102 ± 1.0
		25.0 mg	117	103 ± 0.7	77	104 ± 0.9
	Placebo	119	101 ± 0.7	84	101 ± 0.8	

Mean Change from Baseline in Sitting Diastolic Blood Pressure (mm Hg)

<i>Intent-To-Treat Analysis</i>								
<u>Visit</u>	Treatment Group	(bid)	n	MeanSE		Comparison with		p-value*
						Placebo	CI	
<u>Endpoint</u>	Carvedilol	6.25 mg	117	-5.4	0.7	-2.1	(-4.2, 0.1)	0.0265
		12.5 mg	125	-7.3	0.8	-4.0	(-6.1,-1.9)	0.0001*
		25.0 mg	114	-8.5	0.8	-5.2	(-7.4,-3.1)	0.0001*
	Placebo		117	-3.3	0.8			
<i>Per-Protocol Analysis</i>								
<u>Week 4</u>	Carvedilol	6.25 mg	60	-6.9	1.0	-1.9	(-4.5, 0.7)	0.2190
		12.5 mg	64	-8.0	1.0	-3.0	(-5.6,-0.4)	0.0137*
		25.0 mg	62	-9.6	1.0	-4.6	(-7.2,-2.0)	0.0002*
	Placebo		69	-5.0	0.9			
<u>Week 8</u>	Carvedilol	6.25 mg	56	-5.7	1.0	-0.7	(-3.7, 2.2)	0.5586
		12.5 mg	62	-8.6	1.0	-3.6	(-6.5,-0.8)	0.0108*
		25.0 mg	62	-9.6	1.0	-4.6	(-7.5,-1.7)	0.0005*
	Placebo		62	-5.0	1.1			
<u>Endpoint</u>	Carvedilol	6.25 mg	67	-5.4	0.9	-1.5	(-4.3, 1.2)	0.3218
		12.5 mg	74	-8.0	1.0	-4.1	(-6.7,-1.4)	0.0022*
		25.0 mg	74	-9.3	1.0	-5.4	(-8.1,-2.8)	0.0001*
	Placebo		81	-3.9	1.0			

• Sample sizes differ due to missing vital signs values.
 * Simultaneous confidence intervals based on Dunnett's One-sided Test for Multiple Comparisons with Placebo Control, ensuring 0.05 probability of significance. Values which were statistically significant when compared to placebo are indicated by * next to the p-value for that sample.
 † For two-sided comparisons with placebo of Least Squares Means.

Trough to Peak Ratios of Sitting and Standing Systolic and Diastolic Blood Pressures for Patients Completing Eight Weeks of Treatment

		<u>N</u>	<u>Mean Change ± S.E.</u>		<u>Trough/Peak Ratio</u>
			<u>Trough</u>	<u>Peak</u>	
<i>INTENT-TO-TREAT SAMPLE</i>					
<i>Change in Sitting Diastolic Blood Pressure</i>					
Carvedilol	6.25 mg bid	100	-5.5 ± 0.8	-7.0 ± 1.0	47%
	12.5 mg bid	106	-6.8 ± 0.8	-7.6 ± 0.9	65%
	25.0 mg bid	97	-8.5 ± 0.8	-11.8 ± 0.9	55%
Placebo		91	-3.2 ± 0.9	-2.1 ± 0.9	
<i>Change in Standing Diastolic Blood Pressure</i>					
Carvedilol	6.25 mg bid	100	-5.6 ± 0.9	-6.5 ± 1.0	94%
	12.5 mg bid	106	-2.7 ± 1.1	-7.9 ± 1.0	10%
	25.0 mg bid	97	-7.1 ± 1.0	-11.8 ± 1.0	55%
Placebo		91	-2.2 ± 1.0	-2.9 ± 1.0	
<i>Change in Sitting Systolic Blood Pressure</i>					
Carvedilol	6.25 mg bid	100	-7.4 ± 1.3	-9.4 ± 1.5	85%
	12.5 mg bid	106	-7.8 ± 1.6	-12.9 ± 1.5	63%
	25.0 mg bid	97	-9.5 ± 1.6	-14.8 ± 1.6	67%
Placebo		91	-0.4 ± 1.5	-1.2 ± 1.5	
<i>Change in Standing Systolic Blood Pressure</i>					
Carvedilol	6.25 mg bid	100	-8.2 ± 1.8	-9.1 ± 1.6	127%
	12.5 mg bid	106	-8.0 ± 1.7	-14.0 ± 1.6	63%
	25.0 mg bid	97	-8.8 ± 1.8	-16.4 ± 1.6	58%
Placebo		91	-1.6 ± 1.9	-3.9 ± 1.5	

The 'response' and 'normalization' as defined in this protocol (table below) suggests a dose related improvement of blood pressure values over and above the placebo response.

**Number and Percentage of Patients Responding to Treatment
at Endpoint According to Medication Regimen**

		<u>Normalized*</u>			<u>Responders**</u>		
		<u>Number</u>	<u>(%)</u>	<u>p-value[‡]</u>	<u>Number</u>	<u>(%)</u>	<u>p-value[‡]</u>
<i>Intent-to-Treat</i>							
Carvedilol	6.25 mg bid	32/117	27	0.081	41/117	35	0.077
	12.5 mg bid	44/125	35	0.003**	59/125	47	<0.001**
	25.0 mg bid	48/114	42	<0.001**	62/114	54	<0.001**
Placebo		22/117	19		30/117	26	
p value [†]	Linear				<0.001		
	Non-Linear				0.419		
<i>Per-Protocol</i>							
Carvedilol	6.25 mg bid	19/67	28	0.252	26/67	39	0.092
	12.5 mg bid	27/74	36	0.038**	37/74	50	0.003**
	25.0 mg bid	32/74	43	0.004**	38/74	51	0.002**
	Placebo	18/81	22		22/81	27	
p value [†]	Linear				0.002		
	Non-Linear				0.290		

* SitDBP $\leq$ 90 mm Hg.

** SitDBP normalized and/or a decrease from baseline in mean $\geq$ 10 mm Hg.

‡ For Fisher's Exact two-sided test for multiple comparisons with placebo.

§ ChiSquare p-values for significance of Linear Response and Deviation from Linear Response.

** Values are statistically significant.

Mean Change from Baseline at Endpoint in Secondary Blood Pressure (mm Hg) Parameters - Per-Protocol Analysis

	<u>Treatment Group</u> (bid)	<u>n</u>	<u>Mean ± S.E.</u>	<u>Comparison with Placebo</u>	<u>CI</u>	<u>p-value^a</u>
<u>SitSBP</u> **	Carvedilol 6.25 mg	67	-5.0 ± 1.5	-2.5	(-7.1, 2.1)	0.3490
	12.5 mg	74	-8.6 ± 1.8	-6.1	(-10.6, -1.6)	0.0050*
	25.0 mg	74	-10.4 ± 1.9	-7.8	(-12.3, -3.3)	0.0008*
	Placebo	81	-2.5 ± 1.5			
<u>SupSBP</u> **	Carvedilol 6.25 mg	67	-3.9 ± 1.6	-4.1	(-9.2, 1.0)	0.1156
	12.5 mg	74	-8.3 ± 1.9	-8.6	(-13.5, -3.6)	0.0010*
	25.0 mg	74	-8.3 ± 2.2	-8.5	(-13.5, -3.6)	0.0008*
	Placebo	81	0.3 ± 1.8			
<u>SupDBP</u> **	Carvedilol 6.25 mg	67	-3.5 ± 1.0	-1.3	(-4.3, 1.6)	0.3422
	12.5 mg	74	-5.9 ± 1.2	-3.7	(-6.6, -0.8)	0.0067*
	25.0 mg	74	-8.7 ± 1.2	-6.3	(-9.2, -3.5)	0.0001*
	Placebo	81	-2.2 ± 1.1			
<u>StaSBP</u> **	Carvedilol 6.25 mg	67	-5.0 ± 1.7	-3.5	(-9.2, 2.1)	0.2896
	12.5 mg	74	-8.1 ± 2.1	-6.6	(-12.1, -0.5)	0.0275*
	25.0 mg	74	-7.4 ± 2.0	-6.0	(-11.5, -1.1)	0.0337*
	Placebo	81	-1.5 ± 2.0			
<u>StaDBP</u> **	Carvedilol 6.25 mg	67	-4.4 ± 1.0	-0.4	(-3.4, 2.5)	0.9229
	12.5 mg	74	-3.7 ± 1.0	0.2	(-2.7, 3.1)	0.9487
	25.0 mg	74	-7.5 ± 1.2	-3.6	(-6.5, -0.7)	0.0117*
	Placebo	81	-3.9 ± 1.2			
<u>StaSBP</u> ** (3 min)	Carvedilol 6.25 mg	67	-2.8 ± 1.9	-2.1	(-8.0, 3.8)	0.5480
	12.5 mg	74	-7.4 ± 2.4	-6.7	(-12.4, -1.0)	0.0164*
	25.0 mg	74	-7.0 ± 2.3	-6.2	(-11.9, -0.5)	0.0194*
	Placebo	81	-0.7 ± 1.8			
<u>StaDBP</u> ** (3 min)	Carvedilol 6.25 mg	67	-3.5 ± 1.0	-0.4	(-3.4, 2.7)	0.8587
	12.5 mg	74	-5.8 ± 1.1	-2.7	(-5.7, 0.3)	0.0303
	25.0 mg	74	-8.5 ± 1.2	-5.3	(-8.3, -2.3)	0.0002*
	Placebo	81	-3.1 ± 1.0			

* Sample sizes differ due to missing vital sign values.

† Simultaneous confidence intervals based on Dunnett's One-sided Test for Multiple Comparisons with Placebo Control, ensuring 0.05 probability of significance. Values which were statistically significant when compared to placebo are indicated by * next to the p-value for that sample.

^a For two-sided comparisons with placebo of Least Squares Means.

Subgroup analysis showed no difference of concern. The comparison by race was confounded by small numbers and the high placebo response in the black subgroup.

**Change from Baseline in SitDBP (mm Hg) at Endpoint
for the Subgroup Analysis According to Medication Regimen
Intent-to-Treat**

Subgroup - Sex

<u>Treatment Group (bid)</u>		Male Patients			Female Patients		
		<u>n</u>	<u>Mean ± S.E.</u>	<u>p-value^f</u>	<u>n</u>	<u>Mean ± S.E.</u>	<u>p-value^f</u>
Carvedilol	6.25 mg	84	-5.9 ± 0.8	0.0168*	33	-4.7 ± 1.3	0.2360
	12.5 mg	79	-6.5 ± 0.9	0.0117*	46	-8.6 ± 1.3	0.0001*
	25.0 mg	75	-8.5 ± 1.0	0.0001*	39	-8.6 ± 1.3	0.0002*
Placebo		69	-3.1 ± 1.0		48	-3.6 ± 1.2	

Subgroup - Age

<u>Treatment Group (bid)</u>		Age < 64 years			Age > 64 years		
		<u>n</u>	<u>Mean ± S.E.</u>	<u>p-value^f</u>	<u>n</u>	<u>Mean ± S.E.</u>	<u>p-value^f</u>
Carvedilol	6.25 mg	89	-5.5 ± 0.8	0.0338	28	-5.1 ± 1.3	0.0735
	12.5 mg	92	-7.8 ± 0.9	<0.0001*	33	-5.8 ± 1.5	0.0494
	25.0 mg	84	-8.3 ± 0.9	<0.0001*	30	-9.1 ± 1.4	0.0016*
Placebo		100	-3.4 ± 0.8		17	-2.6 ± 2.3	

Subgroup - Race

<u>Treatment Group (bid)</u>		Black Patients			Non-Black Patients		
		<u>n</u>	<u>Mean ± S.E.</u>	<u>p-value^f</u>	<u>n</u>	<u>Mean ± S.E.</u>	<u>p-value^f</u>
Carvedilol	6.25 mg	19	-2.6 ± 1.9	0.0451	98	-5.9 ± 0.7	0.0010*
	12.5 mg	23	-8.7 ± 2.3	0.3482	102	-6.9 ± 0.8	<0.0001*
	25.0 mg	13	-8.3 ± 2.6	0.4248	101	-8.6 ± 0.8	<0.0001*
Placebo		15	-7.8 ± 2.1		102	-2.7 ± 0.8	

Subgroup - Severity of Hypertension

<u>Treatment Group (bid)</u>		Mild Hypertension ^g			Moderate Hypertension ^g		
		<u>n</u>	<u>Mean ± S.E.</u>	<u>p-value^f</u>	<u>n</u>	<u>Mean ± S.E.</u>	<u>p-value^f</u>
Carvedilol	6.25 mg	85	-4.2 ± 0.8	0.1340	26	-9.7 ± 0.7	0.0038*
	12.5 mg	90	-6.5 ± 0.9	0.0041*	32	-9.9 ± 0.8	<0.0039*
	25.0 mg	82	-7.7 ± 0.8	<0.0001*	29	-10.5 ± 2.1	<0.0001*
Placebo		84	-3.4 ± 0.9		27	-4.6 ± 0.9	

^a Sample sizes may differ due to missing vital sign values.

^b For one-sided comparisons with placebo of Least Squares Means.

^c Simultaneous confidence intervals based on Dunnett's One-tailed T-Test for Multiple Comparisons with Placebo, Control, ensuring 0.05 probability of significance. Values which were statistically significant when compared to placebo are indicated by * next to the p-value for that sample.

^d Mild = Baseline mean sitting DBP 95-105 mm Hg, moderate = baseline mean sitting DBP 106-115 mm Hg [not shown: ^e borderline = ≤ 95 mm Hg or severe = ≥ 115 mm Hg]

8.1.4.3. Safety comparisons

These matters are handled by another member of the team.

8.1.5 Reviewer's Comments/Conclusions of study results.

The above tables are copied from the submission and reflect accurately the information in the detailed listing of results. They show a moderate but statistically significant effect on blood pressure. Maximum effect was probably not achieved in this dose range but maximum dose was limited by concerns about side effects.

The following table shows the effect of this combined alpha and beta blockade on the heart rate.

The study population was shrinking throughout the study. This casts a pall on our efforts to generalize from the trial to a general population. The phenomenon is not specific for this drug or this trial but is a recurring cause of concern. In particular, if one wants to pay attention to the 'responder rate' as defined in this protocol, the response rates would be quite different when one included all the placebo responders that were weeded out.

Mean Change from Baseline at Endpoint in Heart Rate (bpm)

Intent-To-Treat Analysis

	<u>Treatment Group</u> (bid)	n	<u>Mean</u> ± <u>S.E.</u>	<u>Comparison</u> <u>with Placebo</u>	<u>CI</u> *	<u>p-value</u> ‡	
<u>SitHR</u>	Carvedilol	6.25 mg	117	-3.4±0.7	-2.6	(-4.7,-0.4)	0.0287
		12.5 mg	125	-6.6±0.7	-5.7	(-7.9,-3.6)	0.0001
		25.0 mg	114	-8.2±0.9	-7.4	(-9.6,-5.2)	0.0001
	Placebo	117	-0.8±0.7				
<u>SupHR</u>	Carvedilol	6.25 mg	117	-2.9±0.8	-2.0	(-4.3, 0.3)	0.1068
		12.5 mg	125	-5.6±0.7	-4.7	(-6.9,-2.4)	0.0001
		25.0 mg	114	-7.1±0.9	-6.2	(-8.5,-3.9)	0.0001
	Placebo	116	-0.9±0.8				
<u>StaHR</u>	Carvedilol	6.25 mg	117	-3.4±0.9	-3.6	(-6.1,-1.2)	0.0047
		12.5 mg	125	-6.8±0.8	-6.9	(-9.3,-4.5)	0.0001
		25.0 mg	114	-8.8±0.7	-8.9	(-11.4,-6.5)	0.0001
	Placebo	116	-0.2±0.9				
<u>StaHR</u> (3 min)	Carvedilol	6.25 mg	117	-3.6±0.7	-3.7	(-6.1,-1.2)	0.0035
		12.5 mg	125	-6.9±0.8	-7.0	(-9.4,-4.6)	0.0001
		25.0 mg	114	-8.8±0.9	-8.9	(-11.3,-6.4)	0.0001
	Placebo	116	0.1±0.9				

* Sample sizes differ due to missing vital sign values.

† Simultaneous confidence intervals based on Dunnett's One-sided Test for Multiple Comparisons with Placebo Control, ensuring 0.05 probability of significance.

‡ For two-sided comparisons with placebo of Least Squares Means. All comparisons are statistically significant with the exception of supine HR in the carvedilol 6.25 mg group.

8.2 Trial # B101

8.2.1 Objective/Rationale

The purpose of this study was to evaluate the safety and antihypertensive efficacy of carvedilol 6.25, 12.5, 25, or 50 mg administered *once daily* compared to placebo, in patients with mild to moderate hypertension treated for eight weeks.

8.2.2 Design Double blind, Parallel, Placebo Control.

n	Single Blind	n	Double blind Group	Double Blind			Single Blind
				Dose	Dose	Dose	
792	Placebo	116	Placebo	0.0			Placebo
		121	6.25 mg QD	6.25			
		127	12.5 mg QD	6.25	12.5		
		127	25 mg QD	12.5	25		
		29	50 mg QD	12.5	25	50	
up to 8 wks		520		wk 1	wk 2	wk 3-8	2 wks

8.2.3 Protocol

8.2.3.1 Population, Procedures

Males and females between the ages of 21 and 75 years with mild to moderate essential hypertension (Sistolic Blood Pressure greater than or equal to 95 mm Hg and less than or equal to 115 mm Hg) were eligible for enrollment.

Exclusion and inclusion criteria were adequate.

8.2.3.2 Endpoints

The primary index of efficacy for comparing the treatment groups was the *mean change from baseline in SitDBP*.

Secondary Indices

- Percentage of patients with SitDBP of 90 mm Hg or less
 - Mean change in standing diastolic blood pressure
 - Mean change in supine diastolic blood pressure
 - Mean change in standing systolic blood pressure
 - Mean change in supine systolic blood pressure
 - Mean change in sitting systolic blood pressure
 - Mean change in standing heart rate
 - Mean change in supine heart rate
 - Mean change in sitting heart rate

8.2.3.3 Statistical Considerations

The target sample size required for this study was a minimum of 224 patients for which procedurally correct case report forms were completed with sufficient information to evaluate efficacy. It was estimated that 30 centers be recruited with each center providing approximately 12 to 48 patients in the Treatment Phase.

In order to determine that the appropriate range of doses was being studied, the Colton and McPherson two-stage plan was implemented, such that after the case report forms for approximately half of the patients who had completed the study were received by the sponsor, an analysis would be done. The purpose of this analysis was administrative, and as such it was not intended as a basis for any decision to terminate the study. Therefore, no adjustment was planned for the significance level of the conclusions of the final analysis.

A more extended analysis than specified in the protocol was done for subgroups. These included comparison of the primary index for subgroups based on the following categories: sex; age(≤ 64 , > 64 years); severity of hypertension at baseline (mild: 95-105 mm Hg;

moderate: 106-115 mm Hg); and race (black, non-black, including8
caucasian and others races).

Trough to peak ratio of effects at steady state:

Patients who completed the protocol-specified period of double-blind treatment were used for determination of the trough to peak ratio of effects at steady state. Pulse and blood pressure for these patients were recorded in the doctor's office just before and then at 0.5, 1.0, 1.5 and 2.0 hrs in the doctor's office after dosing.

The submission works through three different methods for estimating trough/peak ratio. Needless to say, the conclusion may depend on which method is chosen, and it illustrates the difficulties of translating a sound idea into policy (*i.e.* for QD dosing a trough effect must be demonstrated; this effect must *not* be bought at the price of overdosing during the peak) . The statistician ends the discussion with this Parthian shot:

This estimate of the trough/peak ratio is derived as the mean of the ratio of the Trough(adj)/Peak(adj), effect computed for each patient. With this definition it is possible that this ratio for a particular patient might actually not be determinate because of division by zero (infinite ratio) or increase in steady state trough (negative ratio). Hence, the ratio is not clinically meaningful. Accordingly, this estimate was restricted to the subgroup (S_r) of patients treated with regimen *r* and for whom the $0 < \text{Adj\_Ratio}_r < 1$ (*i.e.*, there was efficacy at steady state and the "placebo adjusted" steady state trough was not greater than the "placebo adjusted" predose peak).

A total of 792 patients from 59 centers in the United States and six centers in Canada were screened for entry into the study. *Two hundred and seventy one (271)* patients were withdrawn during the screening phase and the remaining 521 patients were randomized into the double-blind treatment phase and received at least one dose of active study medication. One patient (patient 602) received randomized treatment, but was not entered into the database. Therefore, this patient was not included in the *intent-to-treat* sample of 520 patients.

The United States contributed the most patients (463 patients; 89%), while Canada contributed 57 patients (11%).

All 520 patients who received at least one dose of randomized treatment were included in the safety analysis and the *intent-to-treat* analysis of efficacy and make up the group hereafter referred to as the *intent-to-treat* sample.

Totals of 121, 127, 127, 29, and 116 patients were randomized to carvedilol 6.25 mg,

carvedilol 12.5 mg, carvedilol 25 mg, carvedilol 50 mg, and placebo, respectively.

The most prevalent protocol violation among the patients excluded was a failure to satisfy the blood pressure criteria for entering the treatment phase. Ninety-three (93) patients were excluded for this violation. (In other words: they had responded to placebo during the screening phase. This number is in addition to the 240, or so, who were excluded *prior* to randomization. This poses the same question that was raised in the discussion of protocol B100: To what extent does this practice bias the outcome of trials? (reviewer's comment)).

8.2.4 Results

8.2.4.1 Patient disposition. Procedures.

Number of Patients Excluded from the Per-Protocol Analysis of Efficacy According to Protocol Violation and Treatment Group

<u>Protocol Violation</u>	<u>Carvedilol 6.25 mg</u>	<u>Carvedilol 12.5 mg</u>	<u>Carvedilol 25 mg</u>	<u>Carvedilol 50 mg</u>	<u>Placebo</u>
<u>Baseline blood pressure criteria not satisfied</u>	15	21	23	15	21
<u>Predose vital signs not taken 22-26 hours after previous dose</u>	19	20	15	1	16
<u>Visit outside specified windows</u>	18	9	13	0	11
<u>Use of prohibited medications</u>	3	3	2	0	2
<u>Patient not withdrawn following protocol- defined insufficient therapeutic effect</u>	3	0	0	0	0
<u>Significant arrhythmias requiring therapy</u>	0	1	0	0	0
<u>WBC count < 3500 mm³</u>	0	1	0	0	0
<u>Total Number of Patients Completely Excluded</u>	56	54	53	14	53

Summary of Baseline Characteristics
Intent-to-Treat Sample

	<u>Carvedilol</u> <u>6.25 mg</u> (N = 121)	<u>Carvedilol</u> <u>12.5 mg</u> (N = 127)	<u>Carvedilol</u> <u>25 mg</u> (N = 127)	<u>Carvedilol</u> <u>50 mg</u> (N = 29)	<u>Placebo</u> (N = 116)	<u>P-value</u>
Number (%) of Patients						
Age (years):						
≤ 64	100 (83%)	101 (80%)	99 (78%)	25 (86%)	92 (79%)	0.784
> 64	21 (17%)	26 (20%)	28 (22%)	4 (14%)	24 (21%)	
Mean Age ± S.E.	54.0 ± 11.4	54.3 ± 10.5	56.6 ± 10.6	52.8 ± 11.6	55.2 ± 10.4	
Gender:						
Male	76 (63%)	78 (61%)	82 (65%)	19 (65%)	73 (63%)	0.876
Female	45 (37%)	49 (39%)	45 (35%)	10 (35%)	43 (37%)	
Race:						
Non-black	102 (84%)	110 (87%)	107 (84%)	24 (83%)	98 (84%)	0.941
Black	19 (16%)	17 (13%)	20 (16%)	5 (17%)	18 (16%)	
Severity of Hypertension:						
Normal	2 (2%)	0	1 (1%)	0	2 (2%)	0.880
Mild	86 (71%)	89 (70%)	93 (73%)	21 (72%)	81 (70%)	
Moderate	33 (27%)	38 (30%)	32 (25%)	8 (28%)	33 (28%)	
Severe	0	0	1 (1%)	0	0	
Mean Body Weight (kg) ± S.E.:						
	86.8 ± 18.8	89.6 ± 19.2	87.5 ± 18.9	86.1 ± 13.7	86.5 ± 21.6	0.502

Mean SitDBP prior to receipt of first dose of randomized medication; Normal = < 95 mm Hg, Mild = 95-105 mm Hg, Moderate = 106-115 mm Hg, Severe = ≥ 116 mm Hg

Summary of Baseline Characteristics
Per-Protocol

	<u>Carvedilol</u> <u>6.25 mg</u> (N=65)	<u>Carvedilol</u> <u>12.5 mg</u> (N=71)*	<u>Carvedilol</u> <u>25.0 mg</u> (N=74)*	<u>Carvedilol</u> <u>50.0 mg</u> (N=12)*	<u>Placebo</u> (N=59)	<u>p-value</u>
Number (%) of Patients						
Age (years):						
≤ 64	53 (82%)	53 (75%)	60 (81%)	10 (83%)	47 (80%)	0.784
> 64	12 (18%)	18 (25%)	14 (19%)	2 (17%)	12 (20%)	
Gender:						
Male	39 (60%)	44 (62%)	45 (61%)	7 (58%)	37 (63%)	0.859
Female	26 (40%)	27 (38%)	29 (39%)	5 (42%)	22 (37%)	
Race:						
Non-black	57 (88%)	62 (87%)	60 (81%)	9 (75%)	49 (83%)	0.784
Black	8 (12%)	9 (13%)	14 (19%)	3 (25%)	10 (17%)	
Severity of Hypertension [†] :						
Normal	1 (2%)	0	1 (1%)	0	0	0.436
Mild	47 (72%)	46 (65%)	51 (69%)	9 (75%)	40 (6%)	
Moderate	17 (26%)	25 (35%)	22 (30%)	3 (25%)	19 (3%)	
Severe	0	0	0	0	0	
Mean Body Weight (kg) ± S.E.:						
	85.9 ± 19.1	88.9 ± 19.6	87.9 ± 16.7	85.7 ± 17.1	84.7 ± 17.2	0.767

Mean SitDBP prior to receipt of first dose of randomized medication; Normal < 95 mm Hg, Mild = 95-105 mm Hg, Moderate = 106-115 mm Hg, Severe ≥ 116 mm Hg

* Nine patients who did not commit a protocol violation were not included in the *per-protocol* analysis (carvedilol 6.25 mg: 2 patients; carvedilol 50 mg: 3 patients; placebo: 4 patients).

**Number of Patients Withdrawn From Study
by Reason for Withdrawal**

<u>Reason for Withdrawal</u>	<u>Number and Percentage of Patients</u>				
	<u>Carvedilol 6.25 mg (n=121)</u>	<u>Carvedilol 12.5 mg (n=127)</u>	<u>Carvedilol 25 mg (n=127)</u>	<u>Carvedilol 50 mg (n=29)</u>	<u>Placebo (n=116)</u>
Adverse Experience	4 3.3%	5 3.9%	11 8.7%	4 13.8%	7 6.0%
Insufficient Therapeutic Response	17 14.0%	16 12.6%	16 12.6%	0	19 16.4%
Other	5 4.1%	4 3.1%	7 5.5%	18 62.1%	3 2.6%
Total	26 21.5%	25 19.7%	34 26.8%	22 75.9%	29 25.0%

8.2.4.2 Efficacy Endpoint Outcomes.

Mean Diastolic Blood Pressure (mm Hg) at Baseline

Parameter	Treatment Group		Intent-to-Treat		Per-Protocol			
			n	Mean ± S.E.	n	Mean ± S.E.		
SitDBP	Carvedilol	6.25	121	102.0 ± 0.5	65	101.9 ± 0.56		
		12.5	127	102.4 ± 0.5	71	102.6 ± 0.7		
		25	127	102.1 ± 0.5	74	101.6 ± 0.6		
		50	29	102.0 ± 1.0	12	102.8 ± 1.7		
	Placebo		116	102.0 ± 0.5	59	102.6 ± 0.7		
		SupDBP	Carvedilol	6.25	121	98.8 ± 0.6	65	98.8 ± 0.8
				12.5	127	98.0 ± 0.8	71	98.5 ± 1.0
				25	127	98.7 ± 0.7	74	98.7 ± 1.0
50	29			98.4 ± 1.1	12	97.3 ± 2.0		
Placebo		116	97.8 ± 0.7	59	97.3 ± 1.0			
	StaDBP	Carvedilol	6.25	121	100.6 ± 0.7	65	100.6 ± 0.8	
			12.5	127	100.5 ± 0.7	71	101.0 ± 1.1	
			25	126	100.8 ± 0.7	73	100.2 ± 0.9	
50			29	99.8 ± 1.3	12	100.3 ± 2.3		
Placebo		116	100.0 ± 0.7	59	100.0 ± 1.0			
	StaDBP (3 min)	Carvedilol	6.25	121	102.9 ± 0.7	65	101.7 ± 0.8	
			12.5	127	102.1 ± 0.7	71	102.7 ± 0.9	
			25	125	102.2 ± 0.6	72	100.9 ± 0.9	
50			29	101.3 ± 1.0	12	101.4 ± 2.1		
Placebo		116	101.9 ± 0.6	59	102.4 ± 0.8			

Analysis of variance showed no statistically significant difference ($p > 0.05$) between the regimens in the mean diastolic pressure at any of the positions recorded at baseline

**Mean Change from Baseline
in Sitting Diastolic Blood Pressure (mm Hg)**

<u>Visit</u>	<u>Treatment Group</u>	<u>n</u> ^a	<u>Mean</u>	<u>SE</u>	<u>Comparison with Placebo</u>	<u>CI</u> ^b	<u>p-value</u> ^c	
<i>Intent-To-Treat Analysis</i>								
<u>Endpoint</u>	Carvedilol	6.25	121	-4.4	0.7	-0.7	(-2.7, 1.3)	0.390
		12.5	126	-6.3	0.7	-2.5	(-4.5,-0.5)	0.004*
		25	126	-5.8	0.7	-2.1	(-4.1,-0.1)	0.016*
		50	28	-8.0	1.3	-4.2	(-7.5,-1.0)	0.083
	Placebo	115	-3.7	0.7				
<i>Per-Protocol Analysis</i>								
<u>Week 4</u>	Carvedilol	6.25	54	-5.0	0.8	0.6	(-1.8, 3.1)	0.843
		12.5	64	-8.0	0.8	-2.4	(-4.7,-0.04)	0.016*
		25	62	-7.2	1.0	-1.5	(-3.9, 0.8)	0.087
		50	4	-11.5	2.2	*		
	Placebo	51	-5.6	0.8				
<u>Week 8</u>	Carvedilol	6.25	47	-5.3	1.0	-0.02	(-2.8, 2.8)	0.934
		12.5	56	-9.0	1.1	-3.8	(-6.5,-1.1)	0.031*
		25	51	-7.3	1.0	-2.0	(-4.8, 0.7)	0.171
		50	2	-14.0	2.0	*		
	Placebo	44	-5.3	0.9				
<u>Endpoint</u>	Carvedilol	6.25	65	-4.3	0.9	0.2	(-2.4, 2.9)	0.862
		12.5	70	-8.2	1.0	-3.6	(-6.2,-1.1)	0.004*
		25	73	-5.7	0.9	-1.2	(-3.7, 1.4)	0.101
		50	12	-9.8	2.2	-5.3	(-9.9,-0.7)	0.115
	Placebo	59	-4.5	0.8				

* 50 mg excluded from analysis of per-protocol sample at Week 4 and Week 8 because of small number of cases.

^b Simultaneous confidence intervals based on Dunnett's One-tailed T-Test for Multiple Comparisons with Placebo Control, ensuring 0.05 probability of significance. Values which were statistically significant when compared to placebo are indicated by * next to the p-value for that sample.

^c For two-sided comparisons of Least Squares Means compared with placebo.

^d Sample sizes differ due to missing vital sign values.

**Mean Change from Baseline at Endpoint in Secondary Blood
Pressure (mm Hg) Parameters
Intent-to-Treat Analysis**

	<u>Treatment Group</u>		<u>n</u>	<u>Mean ± S.E.</u>	<u>Comparison with Placebo</u>	<u>CI*</u>	<u>p-value†</u>
<u>SitSBP</u>	Carvedilol	6.25	121	-4.8 ± 1.3	-1.9	(-5.7, 1.9)	0.239
		12.5	126	-7.1 ± 1.2	-4.2	(-8.0, -0.4)	0.012*
		25	126	-4.7 ± 1.2	-1.8	(-5.6, 2.0)	0.234
		50	28	-7.9 ± 2.5	-5.0	(-11.2, 1.2)	0.159
	Placebo		115	-2.9 ± 1.2			
<u>SupSBP</u>	Carvedilol	6.25	121	-3.6 ± 1.5	-2.4	(-6.6, 1.9)	0.254
		12.5	126	-4.9 ± 1.3	-3.7	(-7.9, 0.5)	0.053
		25	126	-5.7 ± 1.4	-4.5	(-8.7, -0.3)	0.021*
		50	28	-7.3 ± 2.5	-6.1	(-12.9, 0.8)	0.320
	Placebo		115	-1.2 ± 1.5			
<u>SupDBP</u>	Carvedilol	6.25	121	-3.3 ± 0.8	-1.0	(-3.4, 1.4)	0.259
		12.5	126	-4.9 ± 0.9	-2.6	(-5.0, -0.2)	0.011*
		25	125	-5.2 ± 0.8	-2.9	(-5.3, -0.5)	0.005*
		50	28	-5.9 ± 1.4	-3.6	(-7.5, 0.4)	0.188
	Placebo		115	-2.3 ± 0.8			
<u>StaSBP</u>	Carvedilol	6.25	121	-3.6 ± 1.6	-0.8	(-5.3, 3.6)	0.621
		12.5	126	-4.8 ± 1.4	-2.0	(-6.4, 2.4)	0.247
		25	125	-5.7 ± 1.4	-2.9	(-7.3, 1.5)	0.139
		50	28	-6.8 ± 2.5	-4.1	(-11.3, 3.1)	0.402
	Placebo		115	-2.7 ± 1.5			
<u>StaDBP</u>	Carvedilol	6.25	121	-3.0 ± 0.9	-0.7	(-3.2, 1.8)	0.459
		12.5	126	-5.1 ± 0.9	-2.7	(-5.2, -0.3)	0.006*
		25	126	-6.0 ± 0.8	-3.7	(-6.2, -1.2)	0.001*
		50	28	-7.5 ± 1.8	-5.2	(-9.2, -1.1)	0.019*
	Placebo		115	-2.3 ± 0.8			

* Sample sizes differ due to missing BP and HR values.

† Simultaneous confidence intervals based on Dunnett's One-tailed T-Test for Multiple Comparisons with Placebo Control, ensuring 0.05 probability of significance. Values which were statistically significant when compared to placebo are indicated by * next to the p-value for that sample.

* For two-sided comparisons of Least Squares Means with placebo.

Mean Change from Baseline at Endpoint in Heart Rate (bpm)

Intent-To-Treat Analysis

	Treatment Group	n	Mean ± S.E.	Comparison		p-Value ^a	
				with Placebo	CI ^b		
<u>SitHR</u>	Carvedilol	6.25	121	-2.7 ± 0.7	-0.4	(-2.9, 2.0)	0.774
		12.5	126	-3.5 ± 0.8	-1.2	(-3.6, 1.2)	0.256
		25	126	-5.6 ± 0.8	-3.4	(-5.8, -1.0)	0.002 [*]
		50	28	-4.6 ± 1.6	-2.3	(-6.3, 1.6)	0.309
	Placebo	115	-2.3 ± 0.9				
<u>SupHR</u>	Carvedilol	6.25	120	-2.1 ± 0.7	-0.7	(-2.9, 1.5)	0.606
		12.5	126	-2.6 ± 0.7	-1.2	(-3.4, 1.0)	0.229
		25	126	-4.5 ± 0.7	-3.1	(-5.3, -0.9)	0.002 [*]
		50	28	-4.6 ± 1.6	-3.2	(-6.8, 0.4)	0.079
	Placebo	115	-1.4 ± 0.8				
<u>StaHR</u>	Carvedilol	6.25	120	-3.0 ± 0.9	-1.4	(-4.1, 1.2)	0.300
		12.5	126	-2.8 ± 0.8	-1.2	(-3.8, 1.4)	0.340
		25	125	-5.3 ± 0.7	-3.7	(-6.3, -1.1)	0.002 [*]
		50	28	-4.9 ± 1.9	-3.3	(-7.6, 1.0)	0.119
	Placebo	115	-1.6 ± 0.9				

Per-Protocol Analysis

	Treatment Group	n	Mean ± S.E.	Comparison		p-value ^a	
				with Placebo	CI ^b		
<u>SitHR</u>	Carvedilol	6.25	65	-4.0 ± 1.0	-0.1	(-3.6, 3.4)	0.948
		12.5	70	-4.7 ± 1.0	-0.8	(-4.2, 2.6)	0.375
		25	73	-6.8 ± 1.0	-2.9	(-6.3, 0.5)	0.053 [*]
		50	12	-4.7 ± 2.8	-0.8	(-6.9, 5.3)	0.978
	Placebo	59	-3.9 ± 1.3				
<u>SupHR</u>	Carvedilol	6.25	65	-2.3 ± 1.0	-0.6	(-3.7, 2.5)	0.473
		12.5	70	-3.4 ± 0.9	-1.7	(-4.8, 1.3)	0.032
		25	72	-5.1 ± 0.9	-3.5	(-6.5, -0.4)	0.003 [*]
		50	12	-5.0 ± 2.8	-3.4	(-8.8, 2.1)	0.269
	Placebo	59	-1.6 ± 1.1				
<u>StaHR</u>	Carvedilol	6.25	64	-4.0 ± 1.2	-1.8	(-4.6, 3.0)	0.375
		12.5	70	-3.1 ± 1.1	-0.8	(-5.7, 2.1)	0.448
		25	72	-5.7 ± 1.0	-3.4	(-7.2, 0.4)	0.071
		50	12	-7.8 ± 4.0	-5.5	(-12.3, 1.4)	0.263
	Placebo	59	-2.3 ± 1.4				

* Sample sizes

† differ due to missing vital sign values.

^a Simultaneous confidence intervals based on Dunnett's One-tailed T-Test for Multiple Comparisons with Placebo Control, ensuring 0.05 probability of significance. Values which were statistically significant when compared to placebo are indicated by * next to the p-value for that sample.

^b For two-sided comparisons of Least Squares Means with placebo.

The moderate changes in heart rate suggests either a weak β -blocking effect on the heart or a masking due to the simultaneous α -blockade.

**Proportion and Percentage of Patients
Classified as Responders to
Randomized Treatment at Study Endpoint**

		<u>Intent-To-Treat</u>			<u>Per-Protocol</u>		
		<u>Number</u>	<u>(%)</u>	<u>p-value[†]</u>	<u>Number</u>	<u>(%)</u>	<u>p-value[†]</u>
<i>Sitting Diastolic Blood Pressure</i>							
Carvedilol	6.25	39/121	32	0.395	20/65	31	0.846
	12.5	47/126	37	0.099	30/70	43	0.141
	25	55/126	44	0.007**	34/73	47	0.048**
	50	11/28	39	0.248	7/12	58	0.09C
Placebo		31/115	27		17/59	29	
p value*	Linear	0.021			0.006		
	Non-Linear	0.409			0.782		
<i>Supine Diastolic Blood Pressure</i>							
Carvedilol	6.25	52/121	43	0.426	28/65	43	0.584
	12.5	60/126	48	0.119	35/70	50	0.159
	25	63/126	50	0.052	38/73	52	0.114
	50	12/28	43	0.667	6/12	50	0.521
Placebo		43/115	37		22/59	37	
p value*	Linear	0.197			0.135		
	Non-Linear	0.412			0.709		
<i>Standing Diastolic Blood Pressure</i>							
Carvedilol	6.25	48/121	40	0.173	26/65	40	0.348
	12.5	54/126	43	0.061	34/70	49	0.048
	25	65/125	52	0.001	36/72	50	0.032
	50	15/28	54	0.027	6/12	50	0.315
Placebo		35/115	30		18/59	31	
p value*	Linear	0.001			0.044		
	Non-Linear	0.467			0.473		

* Diastolic blood pressure normalized (≤ 90 mmHg) and/or decreased from baseline in mean SitDBP ≥ 10 mm Hg.
† ChiSquare p-values for significance of Linear Response and Deviation from Linear Response.
‡ Fisher exact test
** Statistically significant when compared to placebo.

A remarkable aspect of the numbers is that even after the intense effort to exclude placebo responders prior to randomization as well as after the fact, there is still a significant response rate in the placebo group. The observed differences between treatments are not statistically significant.

Trough to Peak Ratios of Sitting and Standing Diastolic Blood Pressures for Patients Completing Eight Weeks of Treatment

		Mean Change		Ratio of Means*	Mean Ratio'
		Trough	Peak	% (N)	% (N>)
<i>Change in Sitting Diastolic Blood Pressure</i>					
Carvedilol	6.25	4.7	10.4	45 (33)	56 (24)
	12.5	8.4	17.1	49 (36)	52 (33)
	25	7.4	18.2	41 (26)	44 (19)
Placebo		6.3	10.7	59 (31)	57 (23)
<i>Change in Standing Diastolic Blood Pressure</i>					
Carvedilol	6.25	4.3	10.7	40 (33)	59 (12)
	12.5	7.8	15.4	51 (36)	64 (25)
	25	7.0	18.3	38 (26)	49 (16)
Placebo		4.5	8.9	51 (31)	72 (15)

. 50 mg group excluded from analysis because of small number of cases.
 * Ratio of means: the ratio of the mean change in trough diastolic pressure to mean change in peak diastolic blood pressure, expressed as a percentage.
 ' Mean ratio: mean of the individual patient peak/trough ratios for those patients whose response led to a determinate (0-1) ratio.

The method used for calculating the above ratios is given as

$$\frac{\text{Mean Trough}_{\text{Active}} - \text{Mean Trough}_{\text{Placebo regimen}}}{\text{Mean Peak}_{\text{Active}} - \text{Mean Peak}_{\text{Placebo regimen}}}$$

In order to make sense of the placebo numbers the term '*placebo regimen*' must mean the value after single blind baseline observation. The ratios presumably show that the mean change in blood pressure at trough is more than half the change seen at peak, (and thus should qualify for QD dosing). What is interesting in the table is that even placebo has a peak and trough, and that at trough the placebo response is not significantly different from the Carvedilol response. The difference between drug and placebo in *peak* effect seems meaningful

and shows a dose response. The drug is clearly not a once-a-day preparation. To quote the sponsor's statistician:

This analysis suggests that the 12.5 mg and 25 mg doses of carvedilol are more effective than the 6.25 mg dose and placebo, but that the effect does not last through the day.

**Change from Baseline in SitDBP (mm Hg) at Endpoint
for the Subgroup Analysis According to Medication Regimen
Intent-to-Treat**

Subgroup - Sex

		Male Patients			Female Patients		
<u>Treatment Group (mg)</u>	<u>n</u>	<u>Mean+S.E.</u>	<u>p-value[†]</u>	<u>n</u>	<u>Mean+S.E.</u>	<u>p-value[†]</u>	
Carvedilol	6.25 mg	76	-2.9±0.9	0.3398	45	-6.9±1.2	0.2015
	12.5 mg	77	-5.6±1.0	0.0144*	47	-7.4±1.0	0.0371
	25.0 mg	81	-5.5±0.8	0.0111*	45	-6.3±1.1	0.1717
	50.0 mg	19	-8.2±1.6	0.0342	9	-7.6±2.8	0.2717
Placebo		73	-2.6±0.8		42	-5.6±1.1	

Subgroup - Age

		Age ≤ 64 years			Age > 64 years		
<u>Treatment Group (mg)</u>	<u>n</u>	<u>Mean+S.E.</u>	<u>p-value[†]</u>	<u>n</u>	<u>Mean+S.E.</u>	<u>p-value[†]</u>	
Carvedilol	6.25 mg	100	-4.4±0.8	0.1450	21	-4.5±1.7	0.4394
	12.5 mg	100	-6.3±0.8	0.0026*	26	-6.3±1.7	0.2135
	25.0 mg	98	-6.4±0.7	0.0013*	28	-3.8±1.6	0.2780
	50.0 mg	24	-7.1±1.4	0.0907	4	-13.0±3.5	0.0625
Placebo		91	-3.4±0.7		24	-4.8±1.3	

Subgroup - Race

		Black Patients			Non-Black Patients		
<u>Treatment Group (mg)</u>	<u>n</u>	<u>Mean+S.E.</u>	<u>p-value[†]</u>	<u>n</u>	<u>Mean+S.E.</u>	<u>p-value[†]</u>	
Carvedilol	6.25 mg	19	-4.9±1.9	0.1619	102	-4.3±0.7	0.3024
	12.5 mg	17	9.1±2.3	0.0038*	109	-5.8±0.7	0.0264
	25.0 mg	20	-3.6±1.8	0.2430	106	-6.2±0.7	0.0097*
	50.0 mg	5	-7.4±2.8	0.1372	23	-8.1±1.5	0.0721
Placebo		18	-1.7±1.7		97	-4.1±0.7	

* Sample sizes may differ due to missing vital sign values.

†

For one-sided comparisons with placebo of Least Squares Means.

* Simultaneous confidence intervals based on Dunnett's One-tailed T-Test for Multiple Comparisons with Placebo Control, ensuring 0.05 probability of significance. Values which were statistically significant when compared to placebo are indicated by * next to the p-value for that sample.

**Change from Baseline in SitDBP (mm Hg) at Endpoint (cont'd)
for the Subgroup Analysis According to Medication Regimen
Intent-to-Treat**

Subgroup - Severity of Hypertension

<u>Treatment Group (uid)</u>	<u>Mild Hypertension*</u>			<u>Moderate Hypertension*</u>			
	<u>n</u>	<u>Mean ± S.E.</u>	<u>p-value†</u>	<u>n</u>	<u>Mean ± S.E.</u>	<u>p-value†</u>	
Carvedilol	6.25 mg	86	-4.6 ± 0.8	0.2331	33	-4.0 ± 1.4	0.3371
	12.5 mg	89	-5.6 ± 0.7	0.0225	37	-8.0 ± 1.6	0.0155*
	25.0 mg	92	-5.2 ± 0.8	0.0578	32	-7.8 ± 1.2	0.0151*
	50.0 mg	20	-6.6 ± 1.4	0.2307	8	-11.4 ± 2.9	0.0173*
Placebo		80	-3.7 ± 0.7		33	-3.8 ± 1.4	

* Sample sizes may differ due to missing vital sign values.

† For one-sided comparisons with placebo of Least Squares Means.
 * Mild = Baseline mean sitting DBP 95-105 mm Hg, moderate = baseline mean sitting DBP 106-115 mm Hg [not shown: borderline = $\leq$ 95 mm Hg or severe = $\geq$ 115 mm Hg].
 † Simultaneous confidence intervals based on Dunnett's One-tailed T-Test for Multiple Comparisons with Placebo Control, ensuring 0.05 probability of significance. Values which were statistically significant when compared to placebo are indicated by * next to the p-value for that sample.

Subgroup Comparison by Age (quoted from submission):

Comparison by age at entry ($\leq$ 64 years versus $>$ 64 years) demonstrated a statistically significant decrease in mean change from baseline at endpoint in SitDBP compared to placebo in non-elderly patients in the carvedilol 12.5 mg uid regimen (D = -6.3 mm Hg, p = 0.0026), and carvedilol 25 mg uid regimen (D = -6.4 mm Hg, p = 0.0013). *In elderly patients, none of the carvedilol regimens demonstrated a statistically significant decrease in SitDBP from baseline compared with placebo. (emphasis added).*

Subgroup Comparison by Race:

Comparison by race (black versus non-black) in mean change in SitDBP at endpoint in non-black patients achieved statistical significance (D = -6.2 mm Hg, p = 0.0097) in the carvedilol 25 mg regimen. The carvedilol 12.5 mg regimen demonstrated a statistically significant decrease (D = -9.1 mm Hg, p = 0.0038) from baseline in SitDBP in black patients.

Subgroup Comparison by Severity of Hypertension at Baseline:

Comparison by severity of hypertension at baseline was carried out for mild and moderate hypertensives. For the *intent-to-treat* sample of mild hypertensives, none of the

carvedilol regimens demonstrated a statistically significant decrease in SitDBP at endpoint when compared with placebo. All carvedilol treatment groups, with the exception of the carvedilol 6.25 mg group, in the intent-to-treat sample, showed a statistically significant ($p < 0.0173$) decrease from baseline in SitDBP for moderate hypertensives.

8.2.5 Reviewer's Comments:

In the dose range tested, Carvedilol does not appear useful as once-a-day drug.

At the peak there is a moderate blood pressure lowering effect. It is clearly dose related, and it is possible that a maximum effect has not been achieved with a maximum dose of 25 mg/day.

Judged by a clinical evaluation of patient response, as defined by the protocol, the drug could not be differentiated from placebo.

Subgroup analyses by sex, age or race did not indicate any significant difference in response.

The large weeding out of participants during placebo observation is again in evidence. Even the moderate claims that can be made on the basis of this trial are tainted by the large drop-out which makes it difficult to generalize the results of the trial to a general population of hypertensive patients.

PROTOCOL B104:**8.3.1 Objectives:**

This study was designed to evaluate the safety and antihypertensive efficacy of carvedilol 6.25 to 25 mg twice daily and labetalol 100 to 400 mg twice daily, as compared to placebo, in *black* patients with mild to moderate hypertension treated for eight weeks.

8.3 Study Design:

Black patients 21 to 75 years of age, with a diagnosis of mild to moderate hypertension entered a two to eight week single-blind placebo run-in phase to confirm diagnosis and establish baseline blood pressure. Patients were then randomized to receive either carvedilol 6.25 mg twice daily, labetalol 100 mg twice daily or placebo twice daily.

Screening	n	Baseline	n	Double blind titration/treatment	Post treatment
Withdrawal from previous medication	315	Single blind placebo bid	246	Labetalol 100 - 400 mg bid	
				Carvedilol 6.25 - 25 mg bid	
				Placebo bid	
2 weeks		2 - 8 weeks		8 weeks	7 - 10 days

Population 3. Procedures.

The number of patients screened is not given. A total of 315 patients entered the single blind baseline phase. Sixty-eight patients were withdrawn during this phase and the remaining 247 patients were randomized into the treatment phase. One of these 247 patients (Pt. 14) was lost to follow-up after dosing day 1 and the inadvertent failure to account for the one dose of randomized during taken in the study medication record resulted in this patient being categorized as not being randomized. Accordingly, this patient was not included in the intent-to-treat sample of 246 patients, to which all tabulations and discussions that follow apply.

Among patients completely excluded from the per-protocol analysis, the most prevalent protocol violation was a failure to satisfy the blood pressure criteria for entering the treatment phase. Twenty-one patients were excluded for this violation.

One-hundred-seventeen (117) males and 129 females received randomized medication. The average age of patients in the study was 54 years (range 25 to 76 years) and the average body weight was 86 kg (range 47 to 159 kg). The sex, age and weight distribution of the patients assigned to the carvedilol (85 patients), labetalol (89 patients) and placebo (82 patients) treatment groups revealed no important differences in demographic characteristics.

Six patients (two in each of the three treatment groups) withdrew from the study, after at least one day of treatment without an evaluation of vital signs at the end of the dosing interval. The intent-to-treat endpoint analysis of predose (trough) vital signs, therefore, included 240 patients (83 in the carvedilol group, 77 in the labetalol group and 80 in the placebo group). From among these patients, 190 were included in the per-protocol endpoint analysis of *trough* vital signs (65 in the carvedilol group, 63 in the labetalol group and 62 in the placebo group), having had at least one set of trough vital signs measured in the treatment phase that was not excluded because of protocol violation.

Intent-to-Treat Sample

	Number (%) of Patients			
	<u>Carvedilol</u> (n = 85)	<u>Labetalol</u> (n = 79)	<u>Placebo</u> (n = 82)	<u>All</u> (n = 246)
Age (years):				
< 40	7 (8%)	6 (8%)	11 (13%)	24 (10%)
40-64	58 (68%)	54 (68%)	50 (61%)	162 (66%)
> 60	20 (24%)	19 (24%)	21 (26%)	60 (24%)
[mean age]	54	54	54	54
Gender:				
Female	50 (59%)	42 (53%)	37 (45%)	129 (52%)
Male	35 (41%)	37 (47%)	45 (55%)	117 (47%)
Severity of Hypertension:				
Mild	60 (71%)	58 (73%)	60 (73%)	178 (72%)
Moderate	24 (28%)	21 (27%)	20 (24%)	65 (26%)
Severe	1 (1%)	0 (0%)	2 (2%)	3 (1%)
Duration of Hypertension:				
≤ 24 months	10 (12%)	12 (15%)	13 (16%)	35 (14%)
> 24 months	75 (88%)	66 (84%)	68 (83%)	209 (85%)
unknown	0 (0%)	1 (1%)	1 (1%)	2 (1%)
Prior Antihypertensive Treatment:				
Yes	68 (80%)	63 (80%)	70 (85%)	201 (82%)
No	17 (20%)	16 (20%)	12 (15%)	45 (18%)
Body Weight (kg):				
≤ 70	14 (17%)	21 (27%)	18 (22%)	40 (16%)
71-90	38 (45%)	28 (35%)	36 (44%)	102 (41%)
> 91	33 (39%)	30 (38%)	28 (34%)	91 (37%)
[mean weight]	87	87	85	86

*Mean SitDBP prior to receipt of first dose of randomized medication; Mild = 95-105 mm Hg, Moderate = 106-115 mm Hg, Severe = > 115 mm Hg

Per-Protocol Sample

	Number (%) of Patients			
	<u>Carvedilol</u> (n = 71)	<u>Labetalol</u> (n = 71)	<u>Placebo</u> (n = 68)	<u>All</u> (n = 210)
Age (years):				
< 40	6 (8%)	5 (7%)	9 (13%)	20 (10%)
40-64	48 (68%)	48 (68%)	42 (62%)	138 (66%)
> 64	17 (25%)	18 (25%)	17 (25%)	52 (25%)
[mean age]	54	55	54	54
Gender:				
Female	41 (58%)	37 (52%)	29 (43%)	107 (51%)
Male	30 (42%)	34 (48%)	39 (57%)	103 (49%)
Severity of Hypertension:				
Mild	54 (76%)	51 (72%)	51 (75%)	156 (74%)
Moderate	17 (24%)	20 (28%)	17 (25%)	54 (26%)
Severe	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Duration of Hypertension:				
≤ 24 months	9 (17%)	10 (14%)	11 (16%)	30 (14%)
> 24 months	62 (87%)	60 (85%)	56 (82%)	178 (85%)
unknown	0 (0%)	1 (2%)	1 (2%)	2 (1%)
Prior Antihypertensive Treatment:				
Yes	54 (76%)	56 (79%)	58 (85%)	168 (80%)
No	17 (24%)	15 (21%)	10 (15%)	42 (20%)
Body Weight (kg)				
≤ 70	12 (17%)	19 (27%)	16 (24%)	47 (22%)
71-90	31 (44%)	27 (38%)	29 (43%)	87 (41%)
> 90	28 (39%)	25 (35%)	23 (34%)	76 (36%)
[mean Weight]	87	87	84	86

Withdrawals from the Study:

Of the 246 patients who received randomized study medication, 21% (18 of 85) in the carvedilol group, 18% (14 of 79) in the labetalol and 29% (24 of 82) in the placebo group were withdrawn prior to the completion of the study.

Number (%) of Patients Discontinued From the Study *after* Randomization

<u>Reason for Discontinuation</u>	<u>Carvedilol</u> (n=85)	<u>Labetalol</u> (n=79)	<u>Placebo</u> (n=82)
Adverse Experience (6%)	7 (8%)	6 (7%)	5
Insufficient Therapeutic Effect (16%)	7 (8%)	3 (4%)	13
Other (7%)	4 (5%)	5 (7%)	6
<u>Total Patients Discontinued</u> (29%)	18 (21%)	14 (18%)	24

**Distribution of Patients According to Dosage at
Endpoint of the Treatment Phase**

Number (%) of Patients

	<u>Intent-to-Treat Analysis</u> (n=83)	<u>Per-Protocol Analysis</u> (n=65)
Carvedilol		
6.25 mg bid	26 (31%)	25 (38%)
12.5 mg bid	24 (29%)	19 (29%)
25 mg bid	33 (40%)	21 (32%)
Atenolol	(n=77)	(n=63)
100 mg bid	25 (32%)	27 (43%)
200 mg bid	16 (21%)	15 (24%)
400 mg bid	33 (43%)	21 (24%)
Off Drug*	3 (4%)	
Placebo	(n=80)	(n=62)
1 capsule bid	30 (37%)	28 (45%)
2 capsules bid	13 (16%)	9 (15%)
4 capsules bid	32 (40%)	25 (40%)
Off Drug*	5 (6%)	

*Off study medication more than 24 hours prior to visit.

8.3.3.2 Endpoints:

Two categories defining *response* at a given treatment phase visit were used. For both the intent-to-treat and per-protocol samples, no statistically significant difference was detected among the three treatments in either the *normalized* or the *responder* rates at endpoint, which ranged in the three groups from 35% to 44% (normalized) and from 40% to 57% (responders) in the intent-to-treat sample, and from 32% to 40% (normalized) and from 37 to 48% (responders) in the per-protocol sample.

The primary index of efficacy in this study was change from baseline in mean sitting diastolic blood pressure (SitDBP).

The three treatment groups were also compared with regard to the following secondary parameters of efficacy:

- percentage of patients who achieved a mean SitDBP pressure of ≤ 90 mm Hg (normalized)
- percentage of patients who achieved a mean SitDBP of ≤ 90 mm Hg and/or with a decrease in mean SitDBP of ≥ 10 mm Hg (responders)
- change (from baseline) in supine diastolic blood pressure (SupDBP)
- change (from baseline) in mean standing diastolic blood pressure (SupDBP)
- change (from baseline) in mean sitting diastolic blood pressure (StaDBP)
- change (from baseline) in mean sitting systolic blood pressure (SitSBP)
- change (from baseline) in supine systolic blood pressure (SupSBP)
- change (from baseline) in mean systolic blood pressure (StaSBP)
- change (from baseline) in mean sitting heart rate (SitHR)
- change (from baseline) in supine heart rate (SupHR)
- change (from baseline) in mean standing heart rate (StaHR)

8.3.4 Results:

**Mean Baseline Blood Pressure (mm Hg)
and Heart Rate Data (bpm)**

Intent-To-Treat Analysis

<u>Parameter</u>	<u>Regimen</u>	<u>n</u>	<u>mean</u>	<u>SE</u>	<u>Comparison</u>	<u>(CI)</u>	<u>P-value</u>
SitSBP	Carvedilol	85	154	1.7	C vs P	(-3.25, 5.84)	0.5749
	Labetalol	79	152	1.8	L vs P	(-5.15, 4.13)	0.8289
	Placebo	82	153	1.7	C vs L	(-2.78, 6.39)	0.4393
SitDBP	Carvedilol	85	102	0.6	C vs P	(-2.16, 1.17)	0.5584
	Labetalol	79	102	0.6	L vs P	(-2.49, 0.91)	0.3612
	Placebo	82	102	0.7	C vs L	(-1.39, 1.97)	0.7309
SitHR	Carvedilol	85	75	0.9	C vs P	(-1.02, 3.71)	0.2644
	Labetalol	79	75	0.9	L vs P	(-1.43, 3.39)	0.4233
	Placebo	82	74	0.9	C vs L	(-2.03, 2.75)	0.7667
SupSBP	Carvedilol	85	154	1.7	C vs P	(-1.87, 7.49)	0.2377
	Labetalol	79	153	2.0	L vs P	(-2.31, 7.25)	0.3095
	Placebo	82	151	1.7	C vs L	(-4.39, 5.07)	0.8864
SupDBP	Carvedilol	85	100	0.8	C vs P	(-1.90, 2.46)	0.8028
	Labetalol	79	100	0.8	L vs P	(-1.50, 2.95)	0.5226
	Placebo	82	99	0.8	C vs L	(-2.65, 1.76)	0.6898
StaSBP	Carvedilol	85	153	1.6	C vs P	(-3.17, 5.86)	0.5574
	Labetalol	79	152	1.8	L vs P	(-3.61, 5.60)	0.6699
	Placebo	82	151	1.7	C vs L	(-4.21, 4.90)	0.8805
StaDBP	Carvedilol	85	102	0.7	C vs P	(-1.98, 2.29)	0.8856
	Labetalol	79	102	0.8	L vs P	(-1.96, 2.39)	0.8438
	Placebo	82	102	0.9	C vs L	(-2.22, 2.09)	0.9539

**Mean Change from Baseline at Endpoint in
Secondary Blood Pressure (mm Hg) Parameters**

Intent-To-Treat Analysis

<u>Parameter</u>	<u>Regimen</u>	<u>n</u>	<u>mean</u>	<u>SE</u>	<u>Comparison*</u>	<u>CI*</u>	<u>P-value*</u>
<u>SitSBP</u>	Carvedilol	83	-6.1	1.7	C vs P	(-10.12,-1.33)	0.0109 *
	Labetalol	77	-6.5	1.8	L vs P	(-10.45,-1.49)	0.0092 *
	Placebo	80	-0.7	1.4	C vs L	(-4.19, 4.67)	0.9146
<u>SupSBP</u>	Carvedilol	83	-3.9	1.7	C vs P	(-9.12,-0.39)	0.0330
	Labetalol	77	-5.3	1.7	L vs P	(-10.28,-1.38)	0.0104 *
	Placebo	80	0.3	1.4	C vs L	(-3.33, 5.48)	0.6302
<u>SupDBP</u>	Carvedilol	83	-5.0	1.0	C vs P	(-4.94, 0.35)	0.0885
	Labetalol	77	-7.3	0.8	L vs P	(-4.46,-2.08)	0.0006 *
	Placebo	80	-3.0	1.0	C vs L	(-0.19, 5.14)	0.0685
<u>StaSBP</u>	Carvedilol	83	-5.8	1.7	C vs P	(-10.16,-1.28)	0.0118 *
	Labetalol	77	-8.4	1.8	L vs P	(-12.49,-3.44)	0.0006 *
	Placebo	80	-0.5	1.5	C vs L	(-2.23, 6.72)	0.3238
<u>StaDBP</u>	Carvedilol	83	-6.3	1.0	C vs P	(-6.01,-0.73)	0.0127 *
	Labetalol	77	-8.8	1.0	L vs P	(-8.33,-2.95)	0.0001 *
	Placebo	80	-3.2	1.0	C vs L	(-0.39, 4.93)	0.0938

*Least squares 95% comparison-wise confidence interval and P-value of contrast from SAS General Linear Model.

*Comparison between groups significant at alpha = 0.05 using a modified Bonferroni adjustment for the 3 comparisons

**Mean Change from Baseline in
Sitting Diastolic Blood Pressure (mm Hg)**

Per-Protocol Analysis

<u>Visit</u>	<u>Regimen</u>	<u>n</u>	<u>mean</u>	<u>SE</u>	<u>Comparison</u> ⁺	<u>CI</u> ⁺	<u>P-value</u> ⁺
Week 2	Carvedilol	61	-6.2	0.9	C vs P	(-4.62, 0.45)	0.1035
	Labetalol	60	-6.1	0.9	L vs P	(-4.58, 0.56)	0.1236
	Placebo	54	-4.5	1.0	C vs L	(-2.53, 2.37)	0.9483
Week 4	Carvedilol	55	-6.1	0.8	C vs P	(-2.89, 1.72)	0.6188
	Labetalol	47	-8.0	1.0	L vs P	(-4.83, 0.05)	0.0547
	Placebo	48	-5.5	0.8	C vs L	(-0.49, 4.11)	0.1213
Week 6	Carvedilol	45	-8.2	0.9	C vs P	(-6.93, -0.48)	0.0249 *
	Labetalol	43	-10.0	1.2	L vs P	(-9.03, -2.38)	0.0009 *
	Placebo	43	-5.1	1.3	C vs L	(-1.23, 5.24)	0.2224
Week 8	Carvedilol	40	-7.6	1.2	C vs P	(-5.32, 1.91)	0.3504
	Labetalol	34	-9.8	1.3	L vs P	(-7.43, 0.08)	0.0549
	Placebo	30	-7.0	1.1	C vs L	(-1.42, 5.36)	0.2505
Endpoint	Carvedilol	65	-6.3	0.9	C vs P	(-4.70, 0.45)	0.1050
	Labetalol	63	-8.0	0.9	L vs P	(-6.73, -1.48)	0.0023 *
	Placebo	62	-4.2	0.9	C vs L	(-0.58, 4.53)	0.1283

⁺Least squares 95% comparison-wise confidence interval and P-value of contrast from SAS General Linear Model.

*Comparison between groups significant at alpha = 0.05 using a modified Bonferroni adjustment for the 3 comparisons

**Mean Change from Baseline at Endpoint in
Secondary Blood Pressure (mm Hg) Parameters**

Per-Protocol Analysis

<u>Visit</u>	<u>Regimen</u>	<u>n</u>	<u>mean</u>	<u>SE</u>	<u>Comparison</u> [†]	<u>CI</u> [†]	<u>P-value</u> [†]
SitSBP	Carvedilol	65	-5.5	1.8	C vs P	(-8.01, 1.57)	0.1866
	Labetalol	63	-5.6	1.9	L vs P	(-8.26, 1.49)	0.1723
	Placebo	62	-2.3	1.5	C vs L	(-4.59, 4.92)	0.9451
SupSPB	Carvedilol	65	-3.5	1.9	C vs P	(-7.88, 1.71)	0.2054
	Labetalol	63	-3.0	1.8	L vs P	(-7.54, 2.21)	0.2819
	Placebo	62	-0.5	1.4	C vs L	(-5.17, 4.33)	0.8617
SupDBP	Carvedilol	65	-4.3	1.3	C vs P	(-4.61, 1.36)	0.2839
	Labetalol	63	-6.2	0.9	L vs P	(-6.66, -0.59)	0.0194
	Placebo	62	-2.8	1.1	C vs L	(-0.96, 4.96)	0.1832
SBP	Carvedilol	65	-4.4	1.9	C vs P	(-8.00, 2.06)	0.2450
	Labetalol	63	-6.1	1.9	L vs P	(-9.86, 0.38)	0.0693
	Placebo	62	-1.1	1.7	C vs L	(-3.22, 6.76)	0.4855
StaDBP	Carvedilol	65	-5.8	1.2	C vs P	(-5.51, 0.68)	0.1249
	Labetalol	63	-7.2	1.2	L vs P	(-7.13, -0.84)	0.0133 *
	Placebo	62	-3.5	1.1	C vs L	(-1.49, 4.64)	0.3128

[†]Least squares 95% comparison-wise confidence interval and P-value of contrast from SAS General Linear Model.

*Comparison between groups significant at alpha = 0.05 using a modified Bonferroni adjustment for the 3 comparisons

Response Rates

Two categories defining response at a given treatment phase visit were used in the analysis of antihypertensive efficacy in this study. Patients considered "normalized" were those whose mean SitDBP was lowered during the treatment phase to 90 mm Hg or less. Patients considered "responders" were those who achieved a normalized mean SitDBP and/or demonstrated a decrease from baseline in mean SitDBP of at least 10 mm Hg.

**Number and Percent of Patients Normalized* and Responding*
to Randomized Treatment at Study Endpoint**

Intent-To-Treat Analysis

	<u>Total n</u>	<u>No. (%) Normalized</u>	<u>No. (%) Responding</u>
Carvedilol	83	34 (41%)	40 (48%)
Labetalol	77	34 (44%)	44 (57%)
Placebo	80	28 (35%)	32 (40%)
<u>P-value</u> [†] :			
C vs P		0.519	0.345
L vs P		0.257	0.038
C vs L		0.750	0.272

Per-Protocol Analysis

	<u>Total n</u>	<u>No. (%) Normalized</u>	<u>No. (%) Responding</u>
Carvedilol	65	26 (40%)	30 (46%)
Labetalol	63	23 (37%)	30 (48%)
Placebo	62	20 (32%)	23 (37%)
<u>P-value</u> [†] :			
C vs P		0.460	0.369
L vs P		0.707	0.279
C vs L		0.719	1.000

Subgroup efficacy results

**Mean Change from Baseline at Endpoint in
Sitting Diastolic Blood Pressure (mm Hg)**

Intent-To-Treat Subgroup Analyses^a

<u>Subgroup</u>	<u>Regimen</u>	<u>n</u>	<u>mean</u>	<u>SE</u>	<u>Comparison^b</u>	<u>CI^c</u>	<u>P-value^d</u>
Age ≤64 years	Carvedilol	63	-5.2	1.1	C vs P	-4.62, 1.05)	0.2142
	Labetalol	59	-7.6	0.9	L vs P	(-7.46,-1.67)	0.0022 *
	Placebo	59	-4.0	1.1	C vs L	(-0.07, 5.62)	0.0560
Age > 64 years	Carvedilol	20	-9.9	1.5	C vs P	(-10.70,-1.49)	0.0106 *
	Labetalol	18	-11.6	1.2	L vs P	(-10.85,-1.30)	0.0138 *
	Placebo	21	-4.3	1.7	C vs L	(-5.14, 5.09)	0.9926
Moderate Hyperten- sion	Carvedilol	24	-3.5	2.0	C vs P	(-6.96, 4.46)	0.6607
	Labetalol	21	-10.4	1.7	L vs P	(-14.99,-3.49)	0.0023 *
	Placebo	18	-1.2	1.8	C vs L	(2.75,13.22)	0.0036 *
Weight 71-90 kg	Carvedilol	37	-10.1	1.0	C vs P	(-9.24,-2.56)	0.0007 *
	Labetalol	26	-10.0	1.3	L vs P	(-10.38,-2.93)	0.0006 *
	Placebo	36	-4.9	1.3	C vs L	(-2.85, 4.36)	0.6771
Weight ≥91 kg	Carvedilol	33	-4.2	1.6	C vs P	(-6.21, 2.81)	0.4554
	Labetalol	30	-8.0	1.2	L vs P	(-11.53,-2.13)	0.0050 *
	Placebo	27	-2.6	1.6	C vs L	(0.63, 9.64)	0.0262

^aResults are only shown for the subgroups for which between-group comparisons revealed statistically significant differences

^bLeast squares 95% comparison-wise confidence interval and P-value of contrast from SAS General Linear Model. ^cComparison between groups significant at alpha = 0.05 using a modified Bonferroni adjustment for the 3 comparisons

Mean Change from Pre-dose in Blood Pressure (mm Hg) and Heart Rate (bpm) at Peak Post-Dose Effect

Intent-To-Treat Analysis

	<u>n</u>	<u>Mean</u>			<u>Supine</u>			<u>Immediate</u>			<u>3 Minute</u>		
		<u>Sitting</u>			<u>Supine</u>			<u>Standing</u>			<u>Standing</u>		
		<u>SBP</u>	<u>DPP</u>	<u>HR</u>	<u>SBP</u>	<u>DPP</u>	<u>HR</u>	<u>SBP</u>	<u>DPP</u>	<u>HR</u>	<u>SBP</u>	<u>DPP</u>	<u>HR</u>
Carvedilol													
6.25 mg	85	-13.8	-9.4	-5.8	-12.0	-8.5	-5.4	-16.0	-10.4	-7.2	-13.8	-9.5	-6.2
12.5 mg	59	-12.5	-8.9	-5.6	-10.8	-8.3	-4.6	-12.6	-9.4	-6.4	-14.0	-9.5	-6.4
25.0 mg	34	-17.0	-9.9	-4.4	-13.7	-8.7	-4.6	-19.3	-11.5	-6.3	-17.1	-10.9	-5.1
Labetalol													
100 mg	77	-15.3	-11.9	-7.1	-15.4	-11.3	-5.8	-18.6	-13.1	-6.5	-18.8	-13.8	-6.0
200 mg	51	-15.3	-9.5	-6.0	-13.1	-8.3	-5.3	-16.3	-10.9	-4.9	-18.0	-10.6	-4.5
400 mg	33	-14.5	-9.2	-5.7	-14.4	-6.7	-3.0	-17.2	-11.6	-4.5	-20.4	-11.1	-5.2
Placebo													
1 cap	81	-11.0	-8.6	-7.1	-8.2	-7.0	-5.9	-10.8	-7.4	-5.8	-8.8	-7.8	-4.4
2 caps	51	-7.4	-5.2	-6.3	-8.3	-5.8	-5.3	-6.3	-4.1	-5.5	-6.6	-5.7	-5.8
4 caps	36	-7.9	-4.7	-6.0	-7.3	-4.8	-5.0	-7.9	-6.2	-5.7	-6.7	-5.8	-6.4

Peak defined as the time at which the lowest SBP, DBP or HR was observed in the post-dose period for a given patient

Postural hypotension was specifically defined in the protocol as a reduction in blood pressure > 30 mm Hg systolic and > 15 mm Hg diastolic, concurrent with associated signs and symptoms (e.g., diaphoresis, dizziness, etc), with a change from the supine to standing position. One patient randomized to *labetalol* therapy had a postural hypotensive event so defined:

- Patient 149 (55 years old, female) experienced a fall in BP from 201/105 mm Hg, supine to 120/83, standing, on day 29 of *labetalol* treatment (approximately 45 minutes after receiving the first dose of 400 mg b.i.d.). Among the blood pressures recorded until the patient recovered after about 1.5 hours, the lowest was 96/56 mm Hg measured in the standing position about 1 hour after the initial event.

Two additional patients, each randomized to *labetalol* had a hypotensive event and additional post-dose vital signs recorded, but the conditions surrounding the event did not meet the protocol definition for postural hypotension:

- Patient 152 (55 years old, female) experienced a fall in BP from 186/105 mm Hg, supine to 156/83, standing (and therefore a fall of 30 mm Hg systolic, but not > 30 mm Hg systolic), on day 29 of *labetalol* treatment (approximately 30 minutes after receiving the first dose of 400 mg b.i.d.). Among the blood pressures recorded until the patient recovered after about 1.5 hours, the lowest was 115/84 mm Hg, measured in the standing position about 1 hour after the initial event.

- Patient 169 (51 years old, female) had a standing blood pressure of 84/54 mm Hg recorded about 30 minutes after dosing on day 50 of *labetalol* treatment (day 2 of treatment with 200 mg b.i.d., after having previously received 14, 14 and 20 days treatment with 100, 200 and 400 mg b.i.d., consecutively). While a supine blood pressure prior to this reading was not recorded, a reading of 120/94 mm Hg in the sitting position was taken prior to dosing that day.

Finally, Patient 43 experienced a hypotensive adverse experience on day 21 of treatment with 6.25 mg *carvedilol* b.i.d. The event resulted in a fall and injury to the face. Additional details from the serious adverse experience report indicate that the patient actually experienced a temporary loss of consciousness, and the event is therefore considered a "syncope". The patient was withdrawn from the study at that time because of the event.

Vital signs of possible clinical concern were defined as a systolic blood pressure < 100 mm Hg, a diastolic blood pressure of < 80 mm Hg and a heart rate < 50 bpm. Each of the three treatment groups demonstrated isolated cases of patients with vital signs of possible clinical concern within a given period of treatment, very few of which were for systolic blood pressure or heart rate.

DISCUSSION AND CONCLUSIONS (according to the Sponsor)

While beta-blocking agents as a class are generally established as being less effective in black as compared with non-black patients in the treatment of hypertension³, labetalol has been shown, although not in all studies⁴, to be more effective than propranolol^{5,6}. Carvedilol, like labetalol, has the combined pharmacologic activities of alpha- and beta-blockade, although at a different ratio; at dosage levels of equivalent beta-blocking potency, carvedilol is estimated to have approximately half as much alpha-blocking potency as labetalol (data on file). This study was designed to evaluate the antihypertensive efficacy and safety of carvedilol, as compared with placebo, in black patients, utilizing labetalol as a positive control.

The intent-to-treat and per-protocol analyses showed no difference at endpoint between carvedilol and labetalol with regard to the primary parameter of efficacy (mean change from baseline in SitDBP) nor for any of the secondary blood pressure parameters of efficacy. At the intent-to-treat endpoint of the treatment phase, labetalol achieved a statistically significant greater reduction from baseline in mean SitDBP (-8.6 mm Hg), as compared with placebo (-4.1 mm Hg). Carvedilol achieved a significantly greater reduction in mean SitDBP, as compared with placebo, at Week 6 of the per-protocol analysis (-8.2 mm Hg vs -5.1 mm Hg), but not at study endpoint. Both carvedilol and labetalol also achieved at intent-to-treat endpoint a statistically significant reduction from baseline in mean SitSBP, StaSBP and StaDBP, as compared with placebo.

With regard to response rates, there was no significant differences between the carvedilol, labetalol and placebo treatment groups in the percentage of patients normalized (mean SitDBP $\leq$ 90 mm Hg) or in the percentage of patients classified as responders (mean SitDBP $\leq$ 90 mm Hg or decreased from baseline $\geq$ 10 mm Hg).

The failure of this study to demonstrate more significant efficacy results with either active treatment, as compared with placebo, may be related in part to the study methodology. Previous studies demonstrating the efficacy of labetalol in blacks were with dosages up to 800 mg twice daily.⁸ This study may have been improved if an additional titration step to 50 mg carvedilol or 800 mg labetalol twice daily was permitted.

In summary, this clinical trial in black hypertensives demonstrated no statistically significant difference between carvedilol and labetalol, with regard to any of the parameters of efficacy in the overall sample. It did not demonstrate a statistically significant greater reduction in mean SitDBP at endpoint (the primary parameter of efficacy) with carvedilol at the dosage levels studied, as compared with placebo, although significant reductions in secondary assessments of diastolic blood pressure in the supine and standing positions were noted. Additional investigation allowing for the possible titration to 50 mg carvedilol twice daily is required to evaluate the full potential of carvedilol in treating hypertension in blacks.

Reviewer's Comment:

The study as a whole did not suggest that Carvedilol is useful in treatment of hypertension in Blacks, although the p-values reached significance in some subgroups. Labetalol did perform better. The sponsor makes the claim that there was no difference between the two active treatments. It is doubtful that the trial had enough power to warrant this conclusion.

8.4 PROTOCOL C1106:

A MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED TITRATION TRIAL OF CARVEDILOL ADMINISTERED ONCE (QD) OR TWICE (BID) DAILY TO PATIENTS WITH MILD TO MODERATE HYPERTENSION

8.4.1 Objective:

- study and compare the efficacy and safety of *titrated* doses of carvedilol administered once daily (every 24 hours) as compared to carvedilol administered twice daily (every 12 hours) and to placebo
- evaluate whether the antihypertensive effect demonstrated after *one* week of carvedilol is different from that observed after *two* weeks of the same dose of carvedilol
- assess the steady-state *peak* and *trough* effects of carvedilol.

8.4.2 Design:

Single Blind	Double Blind Group	Up titration: dose	Fixed dose	C1111 (open)
Placebo	Carvedilol once daily, Placebo once daily	Carvedilol 6.25 - 50 mg/day	same	optional continuation of maintenance medication
	Carvedilol twice daily	same as above	same	
	Placebo twice daily	0 mg Carvedilol	0 mg Carvedilol	
5 - 6 weeks	randomization	2 - 12 weeks	4 weeks	long term

Multicenter, double-blind, randomized, placebo-controlled, parallel group study. Patient eligibility was established at an initial screening visit. Eligible patients who were already taking antihypertensive medication had those medications withdrawn in a manner deemed appropriate by the investigator. A Placebo Baseline Phase was begun on the day following their last dose of antihypertensive medication

Patients qualified to enter the double-blind Treatment Phase when all of the following criteria were met:

- 1) the mean sitting diastolic blood pressure (SitDBP) and the mean standing diastolic blood pressure (StaDBP) were 95 - 115 mm Hg at the last three Placebo Baseline Phase visits;
- 2) the highest to the lowest mean SitDBP and StaDBP at the last three Placebo Baseline Phase visits did not vary by more than 10 mm Hg;
- 3) the mean SitDBP did not vary by more than 5 mm Hg at the last two Placebo Baseline Phase visits; and,
- 4) the mean StaDBP did not vary by more than 5 mm Hg at the last two Placebo Baseline Phase visits.

Exclusion criteria were adequate. Restrictions on concomitant medication were appropriate.

8.4.3 Protocol:

8.4.3.1 Population, Procedures

A total of 280 patients (169 males and 111 females; 167 Caucasian, 105 Black, and 8 Hispanic) received coded medication.

The average age of the patients in the study was 52.7 years (range: 22 to 84 years) and the average body weight was 89.1 kg (range: 39.1 to 178.8 kg).

The sex, age, weight, and race distributions revealed no important differences in demographic characteristics among the three treatment groups.

There were 57 additional patients who entered the placebo baseline phase and were excluded at randomization. Among them, 30 were excluded for 'failure to meet entry criteria' (n.o.s. but possibly the bulk of them were 'placebo responders').

**Summary of Baseline Characteristics for the *Intent-To-Treat*
Sample According to Regimen**

	Placebo		Carvedilol UID		Carvedilol BID		Total		p-Value*
	N	%	N	%	N	%	N	%	
TOTAL PATIENTS	93	100%	90	100%	96	100%	279	100%	
<u>AGE</u>									
< 40	9	10%	12	13%	14	15%	35	13%	0.862
40-64	71	76%	64	71%	68	71%	203	73%	
> 64	13	14%	14	16%	14	15%	41	15%	
<u>SEX</u>									
FEMALE	36	39%	32	36%	43	45%	111	40%	0.423
MALE	57	61%	58	64%	53	55%	168	60%	
<u>SEVERITY OF HYPERTENSION</u>									
MILD	72	77%	75	83%	81	84%	228	82%	0.415
MODERATE	21	23%	15	17%	15	16%	51	18%	
<u>RACE</u>									
BLACK	35	38%	33	37%	36	38%	104	37%	0.989
NON-BLACK†	58	62%	57	63%	60	63%	175	63%	
<u>PRIOR ANTI-HYPERTENSIVES</u>									
NO	32	34%	39	43%	33	34%	104	37%	0.353
YES	61	66%	51	57%	63	66%	175	63%	
<u>BODY WEIGHT AT BASELINE</u>									
< 70 Kgs	14	15%	15	17%	20	21%	49	18%	0.872
71-90 Kgs	36	39%	34	38%	36	38%	106	38%	
≥ 91 Kgs	43	46%	41	46%	40	42%	124	44%	
<u>DURATION OF HYPERTENSION‡</u>									
< 24 MONTHS	15	16%	11	12%	13	14%	39	14%	0.724
≥ 24 MONTHS	77	83%	79	88%	82	85%	238	85%	
MISSING	1	1%	0	0%	1	1%	2	1%	

	---PLACEBO---			---CARV UID---			---CARV BID---			p-value*
	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	
AGE (yrs)	93	53	11	90	53	11	96	52	11	0.6380
WEIGHT (kgs)	93	90	20	90	89	19	96	89	22	0.8402
DURATION OF HYPERTENSION (mos)	92	117	94	90	112	101	95	128	111	0.5091

* Randomized, received double-blind study medication, and had at least one on-therapy trough vital signs observation, regardless of protocol violations.

† p-Value of Chi-square test

‡ See Appendix 3.2.1 for breakdown of non-black category

§ Test excludes missing category for duration of hypertension

¶ F-test from SAS General Linear Model.

Primary efficacy index

The primary index of efficacy for comparing the treatment groups was the mean change from baseline SitDBP at endpoint.

Secondary efficacy indices

The treatment groups were compared with regard to the following secondary efficacy indices:

- Percentage of patients with a SitDBP of < 90 mm Hg (normalized SitDBP)
- Percentage of patients with a StaDBP of < 90 mm Hg (normalized StaDBP).
- Mean change in StaDBP and SuDBP.
- Mean change in StaSBP, SitSBP and SuSBP.
- Mean change in StaHR, SitHR and SuHR.

Subgroup analyses

Subgroups of patients in the *per-protocol* and *intent-to-treat* samples were compared, both within a given treatment and between the two treatments, with regard to the mean change from baseline in SitDBP, percentage of patients achieving the primary index of response, and the percentage of patients achieving a normalized (≤ 90 mm Hg) mean SitDBP at endpoint. The subgroups were based on the following categories: sex, age (≤ 64 , > 64 years old), severity of hypertension, and race (Black; Non-black, including Caucasian, Hispanic, and Other). The numbers of patients completing the study were also compared between Black and non-Black subgroups.

Reasons for Concluding Study by Medication Regimen
Comparison of Black Versus Non-black Patients
Randomized Sample

Reason for Concluding Study	<u>Placebo</u>		<u>Carvedilol</u> <u>UID</u>		<u>Carvedilol</u> <u>BID</u>	
	<u>Non- Black</u>	<u>Black</u>	<u>Non- Black</u>	<u>Black</u>	<u>Non- Black</u>	<u>Black</u>
<u>N(%)</u>	<u>N(%)</u>	<u>N(%)</u>	<u>N(%)</u>	<u>N(%)</u>	<u>N(%)</u>	<u>N(%)</u>
Insufficient Therapeutic Effect*	37(64)	27(77)	13(23)	12(35)	7(12)	7(19)
Adverse experience	1(1)	0(0)	2(4)	1(3)	3(5)	1(3)
Other†	2(3)	3(9)	4(7)	1(3)	3(5)	1(3)
Completed study	<u>18(31)</u>	<u>5(14)</u>	<u>38(67)</u>	<u>20(59)</u>	<u>47(78)</u>	<u>27(75)</u>
Total Patients	58(62)	35(38)	57(63)	34(37)	60(63)	36(37)

* Two patients (128 and 134) randomized to carvedilol once daily requested to be withdrawn for 'patient perceived' insufficient therapeutic effect.

† "Other" includes the following reasons: non-compliant, unable to keep appointments, or patient decided to stop.

The striking features of this table are the higher fraction of "insufficient therapeutic effect" in the black population, and the high dropout rate among blacks on *placebo* (only 5 of 35 completed the study). Two tentative conclusions might be that 1): The black participants had more intractable hypertension and 2): (the often repeated contention) Black patients with hypertension respond poorly to β -blockers (although in this case the latter observation is confounded by the high placebo response among non-blacks).

Distribution of Patients According to Regimen and Dose Level at Each Endpoint

	Placebo		Carvedilol UID*		Carvedilol BID	
	No.	%	No.	%	No.	%
Total Randomized	93	100.0	91	100.0	96	100.0
<u>Intent-to-Treat</u>						
Titration Endpoint						
Level 2 (.../6.25/3.125)	11	(11.8)	10	(11.1)	10	(10.4)
Level 3 (.../12.5/6.25)	9	(9.7)	15	(16.5)	6	(6.3)
Level 4 (.../25/12.5)	4	(4.3)	22	(24.2)	27	(28.1)
Level 5 (.../50/25)	67	(72.0)	41	(45.0)	52	(54.2)
Off drug [†]	2	(2.2)	2	(2.2)	1	(1.0)
Regimen total	93	(100.0)	90	(100.0)	96	(100.0)
[Percent of Randomized]		[100.0]		[98.9]		[100.0]
Maintenance Endpoint						
Level 2 (.../6.25/3.125)	10	(43.5)	5	(8.6)	8	(10.4)
Level 3 (.../12.5/6.25)	1	(4.3)	13	(22.4)	5	(6.3)
Level 4 (.../25/12.5)	2	(8.7)	18	(31.0)	25	(32.5)
Level 5 (.../50/25)	10	(43.5)	21	(36.2)	37	(48.1)
Off drug [†]	0	(0.0)	1	(1.7)	2	(2.6)
Regimen total	23	(100.0)	58	(100.0)	77	(100.0)
[Percent of Randomized]		[24.7]		[63.7]		[80.2]
Study Endpoint						
Level 2 (.../6.25/3.125)	11	(11.8)	10	(11.1)	9	(9.4)
Level 3 (.../12.5/6.25)	9	(9.7)	14	(15.6)	6	(6.3)
Level 4 (.../25/12.5)	4	(4.3)	22	(24.4)	26	(27.1)
Level 5 (.../50/25)	67	(72.0)	42	(46.7)	52	(54.2)
Off drug [†]	2	(2.2)	2	(2.2)	3	(3.1)
Regimen total	93	(100.0)	90	(100.0)	96	(100.0)
[Percent of Randomized]		[100.0]		[98.9]		[100.0]

* Study medication was administered by Levels in order to maintain double-blind conditions. The carvedilol doses (mg) for each level are displayed in parentheses: (placebo [...]; carvedilol once daily [mg]; carvedilol twice daily [mg]).

† Patient #164 was withdrawn after receiving the first dose of study medication and is excluded from efficacy analysis.

As in the previous table, the numbers here are confounded by the black/non-black dichotomy. On the face of it a drug effect is shown by the higher number of placebo patients who were titrated to the highest level. Nearly half of them, however, must have been blacks who then dropped out. Another way to look for a drug effect is to note that in the placebo group 3 out of 4 quit before the end of the study; in the UID group 1 out of 3 quit; while in the BID group 4 out of 5 stayed the course. The decision to quit depended on the patient's perception of benefit, as well as on the physician's evaluation. In this sense the drug was judged better than placebo, and BID better than UID.

**Summary of Tabulations and Analysis of Baseline SitDBP
and Change from Baseline at Titration, Maintenance and Study Endpoints
*Intent-to-Treat***

	<u>REGIMEN</u>	<u>N</u>	<u>MEAN*</u>	<u>SE</u>	<u>COMPARISON</u>	<u>ESTIMATE CONFIDENCE INTERVAL</u>	<u>p - VALUE</u>
Baseline	PLACEBO	93	102	0.5			
	CARV UID	90	101	0.4	UID vs PLAC*	(-2.09, 0.50)	0.2288
	CARV BID	96	101	0.4	BID vs PLAC*	(-2.26, 0.27)	0.1225
				UID vs BID *	(-1.08, 1.48)	0.7559	
End Titration	PLACEBO	93	-3.6	0.8			
	CARV UID	90	-9.1	0.9	UID vs PLAC*	(-6.94,-2.73)	0.0001*
	CARV BID	96	-11.8	0.7	BID vs PLAC*	(-8.98,-4.87)	0.0001*
				UID vs BID *	(0.00, 4.17)	0.0496*	
End Maintenance	PLACEBO	23	-10.2	1.7			
	CARV UID	58	-11.6	0.7	UID vs PLAC ^γ	(-4.10, 1.29)	0.3051
	CARV BID	77	-12.8	0.7	BID vs PLAC ^γ	(-5.23,-0.03)	0.0478
				UID vs BID ^γ	(-0.68, 3.13)	0.2056	
Study Endpoint	PLACEBO	93	-3.3	0.8			
	CARV UID	90	-7.9	0.8	UID vs PLAC*	(-5.83,-1.51)	0.0009*
	CARV BID	96	-10.9	0.8	BID vs PLAC*	(-8.79,-4.57)	0.0001*
				UID vs BID *	(0.87, 5.15)	0.0060*	

* MEAN is the unadjusted mean; units are mm Hg.

* Significant at $\alpha=0.05$ using modified Bonferroni procedure for the three comparisons.

* Least Squares 95% Comparisonwise Confidence Interval & p-value of contrast from SAS General Linear Model.

γ

Fisher's LSD 95% Comparisonwise Confidence Interval & p-value of t-test.

The high dropout rate in the placebo group continues to confound the issue. The average blood pressure results among the *completers* are not different in the 3 groups. Given all the practical problems of a titration study, and acknowledging the philosophical issues surrounding 'per protocol' vs 'intent-to-treat' analyses, it is difficult to evaluate a trial where the two analytical methods give such disparate results. There seems to be a drug effect on blood pressure even in this study but the outcome is not confidence-building.

**Mean* Change from Baseline in
Sitting Diastolic Blood Pressure
at Titration, Maintenance, and Study Endpoints
According to Dose*
Intent-to-Treat**

	<u>Placebo</u>			<u>Carvedilol UID</u>			<u>Carvedilol BID</u>		
	<u>n</u>	<u>Mean</u>	<u>SE</u>	<u>n</u>	<u>Mean</u>	<u>SE</u>	<u>n</u>	<u>Mean</u>	<u>SE</u>
	Baseline SitDBP:	93	102.1	0.5	90	101.3	0.4	96	101.1
Change from Baseline at Titration Endpoint									
Level 2 (.../6.25/3.125)	11	-11.3	2.6	10	-5.4	3.1	10	-9.5	1.5
Level 3 (.../12.5/6.25)	9	-2.4	4.0	15	-15.3	1.9	6	-14.3	1.3
Level 4 (.../25/12.5)	4	-8.5	2.5	22	-12.3	1.6	27	-15.1	1.3
Level 5 (.../50/25)	67	-2.3	0.7	41	-6.3	1.1	52	-10.1	1.0
Off Drug	2	-2.5	1.5	2	-3.0	3.0	1	-12.0	0
Change from Baseline at Maintenance Endpoint									
Level 2 (.../6.25/3.125)	10	-14.1	1.6	5	-7.8	2.9	8	-8.3	1.7
Level 3 (.../12.5/6.25)	1	-12.0	0	13	-12.8	1.3	5	-13.4	1.1
Level 4 (.../25/12.5)	2	-2.5	4.5	18	-13.3	1.3	25	-15.7	0.9
Level 5 (.../50/25)	10	-7.7	3.1	21	-10.3	1.1	37	-12.4	1.2
Off Drug	0	...	...	1	-12.0	0	2	-1.5	0.5
Change from Baseline at Study Endpoint									
Level 2 (.../6.25/3.125)	11	-11.7	2.8	10	-3.6	2.9	9	-7.2	1.8
Level 3 (.../12.5/6.25)	9	-2.3	4.0	14	-11.7	1.7	6	-14.2	1.2
Level 4 (.../25/12.5)	4	-4.0	2.7	22	-11.2	1.8	26	-14.7	1.4
Level 5 (.../50/25)	67	-2.0	0.7	42	-6.1	1.1	52	-9.6	1.2
Off Drug	2	-2.5	1.5	2	-6.0	6.0	3	-5.0	3.5

* Mean is the unadjusted mean; units are mm Hg.

* Study medication was administered by Levels in order to maintain double-blind conditions. The carvedilol doses (mg) for each level are displayed in parentheses.

This table adds nothing. The numerical distribution of patients between dose levels was presented in a previous table. The BP changes from baseline show, as expected, that those with the poorest response get titrated to the highest level and we get what looks like an inverted dose/response curve. It is not clear why the placebo group at 'level 2' beats the other two groups so handily. (I am sceptical, though, of the level of blinding in trials involving β -blockers. The side effects are too obvious to go unnoticed.)

Number and Percentage of Patients Responding to Treatment at Titration, Maintenance and Study Endpoints

Intent-To-Treat

		Total N	Normalized*		Responder*	
			N (%)	p-value*	N (%)	p-value*
TITRATION ENDPOINT						
PLACEBO	sitting	93	18 (19%)		22 (24%)	
	standing	93	15 (16%)		21 (23%)	
CARV UID	sitting	90	52 (58%)	<0.001 [#]	55 (61%)	<0.001 [#]
	standing	90	32 (36%)	<0.001 [#]	53 (59%)	<0.001 [#]
CARV BID	sitting	96	65 (68%)	<0.001 [#]	73 (76%)	<0.001 [#]
	standing	96 42 (44%)		<0.001 [#]	68 (71%)	<0.001 [#]
CARV UID vs CARV BID		sitting		0.116		0.018 [#]
		standing		0.192		0.067
MAINTENANCE ENDPOINT						
PLACEBO	sitting	23	14 (61%)		14 (61%)	
	standing	23	10 (43%)		13 (57%)	
CARV UID	sitting	58	41 (71%)		43 (74%)	
	standing	58	26 (45%)		39 (67%)	
CARV BID	sitting	77	50 (65%)		59 (77%)	
	standing	77	34 (44%)		55 (71%)	
STUDY ENDPOINT						
PLACEBO	sitting	93	17 (18%)		18 (19%)	
	standing	93	11 (12%)		19 (20%)	
CARV UID	sitting	90	43 (48%)	<0.001 [#]	46 (51%)	<0.001 [#]
	standing	90	28 (31%)	0.001 [#]	43 (48%)	<0.001 [#]
CARV BID	sitting	96	53 (55%)	<0.001 [#]	63 (66%)	<0.001 [#]
	standing	96	35 (36%)	<0.001 [#]	58 (60%)	<0.001 [#]
CARV UID vs BID		sitting		0.260		0.024 [#] CARV
		standing		0.348		0.051

- * Normalized is defined as a reduction of mean SitDBP to < 90 mm Hg; a responder is defined as a patient with a reduction of mean SitDBP to < 90 mm Hg patient with and/or a reduction of ≥ 10 mm Hg.
- # p-value of Paired Comparisons using CMH Chi-square.
- * Significant at experimentwise alpha = 0.05 using modified Bonferroni procedure.

The different views are consistent. The story, if there is one, is told by the drop-outs.

Peak and trough: (see table on next page)

The following is verbatim from the submission:

Both placebo-adjusted and unadjusted trough to peak ratios were calculated. The placebo adjustment is used to decrease the effect of carvedilol treatment by the amount that could be attributed to placebo treatment. But because of this study design, only patients with at least a minimal response to treatment have had post-dosing data collected. For patients randomized to placebo, this effect is greater at trough than at peak, and cannot be considered a representative peak effect. These placebo results cause the adjusted carvedilol trough to be reduced by a greater amount than the adjusted carvedilol peak for both regimens. Therefore, unadjusted trough to peak ratios are also presented.

Analysis of steady-state sitting diastolic trough and peak measurements for the *intent-to-treat* sample at Study Endpoint showed that 47.1% of the peak effect for carvedilol once daily and 65.5% of the peak effect for carvedilol twice daily is retained at trough, based upon placebo-adjusted trough to peak ratios. In comparison, unadjusted trough to peak ratios at Study Endpoint indicate that 71.6% of the peak effect for carvedilol once daily and 85.4% of the peak effect for carvedilol twice daily is retained at trough.

For patients who demonstrated an adequate response to treatment and therefore have peak data collected at Maintenance Endpoint, analysis of steady-state sitting diastolic trough and peak measurements for the *intent-to-treat* sample at Study Endpoint showed that 31.7% of the peak effect for carvedilol once daily and 39.8% of the peak effect for carvedilol twice daily is retained at trough, based upon placebo-adjusted trough to peak ratios. In comparison, unadjusted trough to peak ratios at Study Endpoint indicate that 76.9% of the peak effect for carvedilol once daily and 90.1% of the peak effect for carvedilol twice daily is retained at trough.

Anything I can add will only tend to magnify the mystery.

Summary of Mean Change from Baseline SitDBP at Peak and Trough at Study Endpoint and According to Phase of Last Visit
Intent-to-Treat

	REGIMEN	N	MEAN (SE) DIFFERENCE [ENDPOINT-BASELINE]				TROUGH/PEAK* RATIO	
			TROUGH:		PEAK:		Placebo	
			Mean	(SE)	Mean	(SE)	Adjusted	Unadjusted
TITRATION ENDPOINT	PLACEBO	54	-1.0	(0.9)	-1.8	(1.1)		
	CARV UID	23	-0.5	(1.3)	-6.9	(1.8)	-9.8%	7.2%
	CARV BID	13	-1.8	(2.2)	-6.8	(2.1)	16.0%	26.5%
MAINTENANCE ENDPOINT	PLACEBO	23	-9.8	(1.8)	-8.9	(1.7)		
	CARV UID	57	-11.3	(0.7)	-14.1	(0.9)	31.7%	76.9%
	CARV BID	74	-12.7	(0.8)	-14.1	(1.0)	39.8%	90.1%
STUDY ENDPOINT	PLACEBO	78	-3.5	(0.9)	-1.4	(1.1)		
	CARV UID	80	-8.3	(0.8)	-11.6	(0.9)	47.1%	71.6%
	CARV BID	87	-11.1	(0.8)	-13.0	(0.9)	65.5%	85.4%

* Mean is the unadjusted mean; units are mm HG.

$$\text{UNADJUSTED TROUGH/PEAK RATIO} = \frac{(\text{MEAN DIF ACTIVE TROUGH})}{(\text{MEAN DIF ACTIVE PEAK})} \times 100\%$$

where DIF = Study Endpoint - Baseline

$$\text{PLACEBO-ADJUSTED TROUGH/PEAK RATIO} = \frac{(\text{MEAN DIF ACTIVE TROUGH}) - (\text{MEAN DIF PLACEBO TROUGH})}{(\text{MEAN DIF ACTIVE PEAK}) - (\text{MEAN DIF PLACEBO PEAK})} \times 100\%$$

where DIF = Study Endpoint - Baseline

Subgroup analyses

A stated object was to compare results after week one and week two on any given dose level. One of the resulting tables is reproduced below. The discussion is not helpful. The concluding paragraphs are reproduced. Although the differences seen hardly are meaningful, it seems as if the initial response gets blunted.

Summary of Tabulations and Analysis of Baseline SitDBP and Change from Baseline at Study Endpoint for Subgroup Analyses Intent-to-Treat

	<u>REGIMEN</u>	<u>N</u>	<u>MEAN*</u>	<u>SE</u>	<u>COMPARISON</u>	<u>ESTIMATE CONFIDENCE INTERVAL *</u>	<u>p-VALUE*</u>
MALE							
Baseline	PLACEBO	57	102.0	0.6			
	CARV UID	58	100.7	0.5	UID vs PLAC	(2.9, 0.3)	0.0493
	CARV BID	53	100.6	0.6	BID vs PLAC	(-3.1, 0.2)	0.0823
					UID vs BID	(-1.5, 1.7)	0.8977
Study Endpoint	PLACEBO	57	-2.0	0.9			
	CARV UID	58	-6.5	1.0	UID vs PLAC	(-7.0, -2.1)	0.0004*
	CARV BID	53	-10.3	1.2	BID vs PLAC	(-10.9, -5.8)	0.0001*
Baseline	PLACEBO	36	102.3	0.7			
	CARV UID	32	102.4	0.8	UID vs PLAC	(-1.8, 2.0)	0.8939
	CARV BID	43	101.8	0.6	BID vs PLAC	(-2.2, 1.3)	0.6230
					UID vs BID	(-1.3, 2.4)	0.5391
Study Endpoint	PLACEBO	36	-5.4	1.5			
	CARV UID	32	-10.5	1.5	UID vs PLAC	(-8.0, -2.1)	0.0010*
	CARV BID	43	-11.5	1.1	BID vs PLAC	(-8.8, -3.4)	0.0001*
					UID vs BID	(1.8, 3.8)	0.4801
BLACK							
Baseline	PLACEBO	35	102.3	0.8			
	CARV UID	33	102.0	0.7	UID vs PLAC	(-2.2, 1.6)	0.7439
	CARV BID	36	101.3	0.7	BID vs PLAC	(-2.9, 0.8)	0.2754
					UID vs BID	(-1.2, 2.6)	0.4544
Study Endpoint	PLACEBO	35	-2.3	1.2			
	CARV UID	33	-6.5	1.7	UID vs PLAC	(-7.4, -1.0)	0.0113*
	CARV BID	36	-11.3	1.3	BID vs PLAC	(-12.2, -5.9)	<0.0001*
					UID vs BID	(1.6, 8.0)	0.0036*
NON-BLACK							
Baseline	PLACEBO	58	102.0	0.6			
	CARV UID	57	100.9	0.6	UID vs PLAC	(-2.6, 0.4)	0.1373
	CARV BID	60	101.1	0.5	BID vs PLAC	(-2.4, 0.5)	0.2020
					UID vs BID	(-1.6, 1.3)	0.8178
Study Endpoint	PLACEBO	58	-3.9	1.0			
	CARV UID	57	-8.8	0.8	UID vs PLAC	(-7.2, -2.5)	0.0001*
	CARV BID	60	-10.6	1.0	BID vs PLAC	(-9.0, -4.4)	<0.0001*
					UID vs BID	(-0.5, 4.4)	0.01196

* MEAN is the unadjusted mean, units are mm Hg.
 * Fisher's Least Significant Difference 95% Comparisonwise Confidence Interval & p-value of t-test.
 * Significant at $\alpha=0.05$ using modified Bonferroni procedure for the 3 comparisons.

Reference documentation: Appendixes 8.1.2, 8.1.3, 8.1.4, 8.1.5, 8.2.3, 8.2.5, 8.2.7, 8.2.9, and 8.11.3..

(cont.)

**Summary of Tabulations and Analysis of Baseline SitDBP
and Change from Baseline at Study Endpoint
for Subgroup Analyses
Intent-to-Treat**

	<u>REGIMEN</u>	<u>N</u>	<u>MEAN*</u>	<u>SE</u>	<u>COMPARISON</u>	<u>ESTIMATE CONFIDENCE INTERVAL *</u>	<u>p-VALUE*</u>
MILD ANTIHYPERTENSIVES							
Baseline	PLACEBO	72	100.3	0.4			
	CARV UID	75	99.9	0.3	UID vs PLAC	(-1.3, 0.4)	0.3464
	CARV BID	81	99.8	0.3	BID vs PLAC	(-1.3, 0.4)	0.2812
				UID vs BID	(-0.9, 0.8)	0.9043	
Study Endpoint	PLACEBO	72	-3.2	0.8			
	CARV UID	75	-7.8	0.9	UID vs PLAC	(-6.6, -2.5)	<0.0001*
	CARV BID	81	-9.9	0.9	BID vs PLAC	(-8.6, -4.6)	<0.0001*
				UID vs BID	(0.1, 4.1)	0.0400	
MODERATE ANTIHYPERTENSIVES							
Baseline	PLACEBO	21	108.5	0.4			
	CARV UID	15	108.5	0.6	UID vs PLAC	(-1.3, 1.3)	0.9884
	CARV BID	15	108.3	0.5	BID vs PLAC	(-1.5, 1.2)	0.8274
				UID vs BID	(-1.6, 1.3)	0.8283	
Study Endpoint	PLACEBO	21	-3.5	2.2			
	CARV UID	15	-8.8	2.1	UID vs PLAC	(-9.9, -0.6)	0.0277*
	CARV BID	15	-16.3	1.7	BID vs PLAC	(-17.7, -8.2)	<0.0001*
				UID vs BID	(2.5, 12.6)	0.0048*	
≤ 64 YEARS OLD							
Baseline	PLACEBO	80	102.7	0.5			
	CARV UID	76	101.2	0.5	UID vs PLAC	(-2.7, -0.2)	0.0208
	CARV BID	82	100.9	0.4	BID vs PLAC	(-3.0, -0.5)	0.0058*
				UID vs BID	(-1.5, 1.0)	0.6825	
Study Endpoint	PLACEBO	80	-3.8	0.8			
	CARV UID	76	-7.7	0.9	UID vs PLAC	(-6.0, -1.8)	0.0004*
	CARV BID	82	-10.8	0.8	BID vs PLAC	(-9.1, -4.9)	<0.0001*
				UID vs BID	(1.0, 5.2)	0.0038*	
> 64 YEARS OLD							
Baseline	PLACEBO	13	98.7	0.6			
	CARV UID	14	101.8	1.1	UID vs PLAC	(0.3, 5.9)	0.3020
	CARV BID	14	102.3	1.4	BID vs PLAC	(0.8, 6.4)	0.0138*
				UID vs BID	(-3.2, 2.2)	0.7018	
Study Endpoint	PLACEBO	13	-0.4	2.2			
	CARV UID	14	-9.4	2.2	UID vs PLAC	(-14.8, -3.30)	0.0041*
	CARV BID	14	-11.4	2.6	BID vs PLAC	(-16.8, -5.30)	0.0008*
				UID vs BID	(-3.64, 7.64)	0.4647	

* MEAN is unadjusted mean; units are mm Hg.
 * Fisher's Least Significant Difference 95% Comparisonwise Confidence Interval & p-value of t-test.
 * Significant at $\alpha=0.05$ using modified Bonferroni procedure for the 3 comparisons.

The subgroup analysis does not appear to show any striking difference in response based on sex, age, race, or level of untreated blood pressure, although, as noted before, in the placebo group a larger fraction of black patients was terminated for insufficient response.

The final concerns re efficacy were an investigator-by-treatment interaction (one investigator, -Gray,- was the largest contributor and showed the highest drug effect); and the protocol issue of week 1 vs week 2 results on a constant regimen. The sponsor's discussion of both issues is reproduced below.

**Frequency Distribution of Patients by Investigator
According to Randomization to Regimen**

INVESTIGATOR	Placebo		Carvedilol QID*		Carvedilol BID*		Total	
	N	%	N	%	N	%	N	%
Cushman*	8	8.6	6	6.6	8	8.3	22	7.9
Fischer	7	7.5	7	7.7	7	7.3	21	7.5
Fisk-Sander	3	3.2	3	3.3	4	4.2	10	3.6
Gray	14	15.1	14	15.4	14	14.6	42	15.0
Herron	9	9.7	10	11.0	10	10.4	29	10.4
Jenkins	7	7.5	6	6.6	6	6.3	19	6.8
Lonigro	11	11.8	12	13.2	12	12.5	35	12.5
Lucas	8	8.6	7	7.7	8	8.3	23	8.2
Miller	4	4.3	4	4.4	3	3.1	11	3.9
Schoenberger	7	7.5	5	5.5	6	6.3	18	6.4
Synhavsky	6	6.5	7	7.7	8	8.3	21	7.5
Wallin	6	6.5	7	7.7	6	6.3	19	6.8
Zinny	3	3.2	3	3.3	4	4.2	10	3.6
TOTAL	93	100	91*	100	96	100	280	100

* QID = once daily; BID = twice daily.

Evidence of possible investigator-by-regimen interaction ($p \leq 0.1$) was found in the analysis of the mean change from baseline for SBP, DBP, and HR for both *intent-to-treat* and *per-protocol* samples. One investigator's contribution toward the interaction was based on magnitude. At the other investigators, the interaction was directional. With statistical testing based on a model without inclusion of the interactive term, the interaction did not interfere with interpretation of the final results or the conclusions of the study.

The percentages of patients classified as normalized (DBP < 90 mm Hg) and as responders (DBP < 90 mm Hg or decreased by ≥ 10 mm Hg) were significantly greater ($p < 0.001$) for the carvedilol regimens than for placebo in both sitting and standing positions. At both Titration and Study Endpoints the differences between carvedilol regimens in sitting and standing normalized rates and in standing responder rates were not statistically significant. However, at these same endpoints, the difference between carvedilol regimens in sitting responder rates was statistically significant. For all three regimens, there were fewer patients normalized/responding at Study Endpoint than at Titration Endpoint.

Comparison of 1 week vs 2 weeks at the same dose

For patients who received two weeks of treatment with a given dose, the mean (SE) change in DBP from baseline at Week 1 and from the end of the Week 1 to the end of the Week 2 is presented below.

**Mean Change in SitDBP from 1 Week to 2 Weeks
at the Same Dose According to Double-Blind Dose Level
and Normalized Response
*Intent-to-Treat***

<u>Dose Level (mg)</u>	<u>n</u>	<u>Normalized</u>				<u>Not Normalized</u>				
		<u>Change</u> <u>from</u> <u>Baseline</u> <u>at Week 1</u>	<u>SE</u>	<u>Change</u> <u>from</u> <u>Week 1</u> <u>to Week 2</u>	<u>SE</u>	<u>Change</u> <u>from</u> <u>Baseline</u> <u>at Week 1</u>	<u>SE</u>	<u>Change</u> <u>from</u> <u>Week 1</u> <u>to Week 2</u>	<u>SE</u>	
Placebo										
Level 2	11	-13.2	1.5	+4.2	1.8	62	-2.7	0.5	-0.7	0.6
Level 3	7	-14.6	2.1	+5.0	3.3	54	-2.4	0.6	-0.4	0.7
Level 4	9	-10.1	0.7	+7.2	1.6	45	-2.6	0.5	+0.5	0.6
Level 5	4	-11.8	2.1	+4.5	3.8	60	-3.3	0.6	+0.6	0.6
Carvedilol Once Daily Regimen										
Level 2 (6.25)	11	-11.9	1.1	+6.4	2.4	67	-2.2	0.5	-0.6	0.6
Level 3 (12.5)	20	-14.5	0.8	+1.7	1.0	42	-3.4	0.6	-1.0	0.7
Level 4 (25)	20	-14.7	0.9	+2.5	1.0	34	-3.2	0.8	-2.4	1.2
Level 5 (50)	10	-14.3	1.7	+1.7	1.4	29	-3.8	1.1	-1.5	1.0
Carvedilol Twice Daily Regimen										
Level 2 (3.125)	14	-13.1	1.1	+7.9	1.8	71	-3.4	0.5	-0.2	0.6
Level 3 (6.25)	15	-15.3	1.0	+3.7	1.1	63	-4.7	0.7	-0.4	0.6
Level 4 (12.5)	28	-16.5	1.1	+2.7	0.8	40	-5.6	0.9	-1.8	0.9
Level 5 (25)	19	-14.3	0.9	+0.7	1.4	32	-7.6	1.0	-0.8	0.8

Reference documentation: Appendix 8.8.6.

Among patients who normalized after one week of treatment with a given dose, those randomized to placebo had increases from Week 1 to Week 2 that ranged from +4.5 ±

3.8 mm Hg to $+7.2 \pm 1.6$ mm Hg. Similarly, for patients who normalized after one week of treatment with the lowest dose levels of carvedilol, 6.25 mg once daily or 3.125 mg twice daily, mean changes from Week 1 to Week 2 were $+6.4 \pm 2.4$ mm Hg and $+7.9 \pm 1.8$ mm Hg, respectively. Smaller increases from Week 1 to Week 2 were observed for the other dose levels: for the once daily carvedilol regimen, these increases ranged from $+1.7 \pm 1.0$ mm Hg to $+2.5 \pm 1.0$ mm Hg, and for the twice daily regimen, these increases ranged from $+0.7 \pm 1.4$ mm Hg to $+3.7 \pm 1.1$ mm Hg.

For patients who did not normalize after one week of treatment with any given dose, an additional week of treatment at that dose did not produce a further meaningful reduction, regardless of dose or treatment regimen. Among these patients, there was only one dose, carvedilol 25 mg once daily for which an additional week of treatment produced a reduction greater than 2 mm Hg: -2.4 ± 1.2 mm Hg in addition to a change from baseline equal to -3.2 ± 0.8 mm Hg at the end of one week of treatment with this dose.

8.5 PROTOCOL C1107:

A MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED,
RANDOMIZED ASSESSMENT OF CARVEDILOL IN PATIENTS WHOSE
BLOOD PRESSURE IS UNCONTROLLED ON HYDROCHLOROTHIAZIDE
(HCTZ)

Investigators: This study was conducted by a total of 12 investigators in the United States of America.

8.5.1 Objective:

To assess the safety and efficacy of carvedilol 6.25 to 25 mg **once daily** when added to the treatment regimen of patients whose sitting and standing diastolic blood pressure (DBP) was uncontrolled (≥ 90 mm Hg) by treatment with hydrochlorothiazide (HCTZ) 25 mg once daily.

8.5.2 Study Design: This was a multicenter, double-blind, randomized, placebo-controlled, parallel group study. Patients qualified to enter the Treatment Phase when at both the third and fourth weekly baseline visits all of the following conditions were satisfied: the mean Sitting Diastolic Blood Pressure (SitDBP) and the mean Standing Diastolic Blood Pressure (StaDBP) were 90 - 115 mm Hg, and the mean SitDBP and mean StaDBP did not vary by more than 5 mm Hg between Visits 3 and 4.

n	Baseline (open)	n	Treatment Phase (blinded)	
	HCTZ 25 mg once daily	66	HCTZ + Placebo once daily	
		67	HCTZ 25 mg + Carvedilol 6.25 mg once daily	
		67	HCTZ 25 mg + Carvedilol 12.5 mg once daily	
		66	HCTZ 25 mg + Carvedilol 12.5 mg	HCTZ 25 mg + Carvedilol 25 mg once daily (elective)
410	4 weeks	266	1 week	3 weeks

The primary efficacy parameter was change (from baseline) in mean SitDBP.

Upon entry into the Treatment Phase, patients were stratified according to severity of hypertension (mild: SitDBP $\geq$ 90 mm Hg, < 100 mm Hg; moderate: SitDBP > 100 mm Hg, < 115 mm Hg) and randomized in a double-blind fashion.

Response to treatment was evaluated after one week of double blind treatment, and coded medication for all groups was increased if mean SitDBP was $\geq$ 90 mm Hg, (unless the mean StaSBP was $\leq$ 120 mm Hg or the mean StaDBP was $\leq$ 80 mm Hg). Although coded medication was increased for all four treatment groups according to these guidelines, the actual dose of medication increased only for Group 4, for which the initial dose of carvedilol 12.5 mg once daily was doubled to 25 mg once daily. Dose decreases (return to the first level of study medication) were not permitted.

Withdrawals from Study: Of 410 patients who were entered into the Baseline Phase, 35.1% (144/410) were withdrawn during this phase. Of these 144 patients, failure to meet selection criteria was the most common reason for discontinuation, reported for 31.2% (45/144).

Of 266 patients who received randomized medication, 91.3% (243/266) of the patients completed the four-week Treatment Phase.

Efficacy Results: *Intent-to-treat sample:* Statistically significant ($p \leq 0.05$) differences in mean SitDBP change from baseline were observed at Week 1, Week 4 and at endpoint for Group 4 (carvedilol 12.5/25 mg) compared to Group 1 (placebo). No statistically significant differences between the carvedilol 12.5 mg regimen and placebo or between the carvedilol 6.25 mg regimen and placebo were detected in mean SitDBP change from baseline at endpoint.

Comparisons of all carvedilol randomized groups to the placebo group showed no statistically significant differences in either normalized or response rates at endpoint. There were no indications of statistically significant center-by-regimen interactions ($p > 0.1$) in the analysis of mean SitDBP change from baseline at endpoint.

Per protocol sample: No statistically significant differences between any of the carvedilol regimens and placebo were detected for mean SitDBP change from baseline at any of the four weekly visits or at endpoint. There was no evidence of a significant linear or quadratic relationship between dosing level and mean SitDBP change from baseline at endpoint.

CONCLUSIONS: (according to Sponsor) The *intent-to-treat* analysis showed statistically significant differences from baseline at Week 1, at Week 4, and at endpoint between the carvedilol 12.5/25 mg group and the placebo group with regard to the primary parameter of efficacy (change from baseline in SitDBP). The results suggest

that, if a patient has not responded to one week of treatment with carvedilol 12.5 mg, continuation of the same dose for another three weeks results in no additional antihypertensive effect. However, for those patients who did not respond to one week of carvedilol 12.5 mg, doubling the dose of carvedilol to 25 mg produced a reduction in blood pressure comparable to that observed for patients who did respond earlier to treatment with carvedilol 12.5 mg.

The results from this study demonstrated that combined antihypertensive treatment with carvedilol added to pre-existing HCTZ therapy is both efficacious and well tolerated.

Subgroup analyses

Analysis of variance (ANOVA) of baseline and mean SitDBP change from baseline at endpoint according to randomized regimen was performed for five subgroups, defined by sex, age, severity of hypertension at baseline, race, and weight.

8.5.3 Protocol

8.5.3.1 STUDY POPULATION

Number and Percentage of Patients with Data Included and Excluded from Efficacy Analysis

	<u>Number and Percentage (%) of Patients</u>				<u>Total</u>
	<u>Placebo</u>	<u>Carvedilol</u>			
		<u>6.25 mg</u>	<u>12.5 mg</u>	<u>12.5/25 mg</u>	
N (%)	N (%)	N (%)	N (%)		
Included Intent-to-Treat analysis	66 (100.0)	67 (100.0)	67 (100.0)	66 (100.0)	266 (100.0)
Included Per-Protocol analysis	58 (87.9)	62 (92.5)	62 (92.5)	57 (86.4)	239 (89.8)
Completely excluded by protocol violation	8 (12.1)	5 (7.5)	5 (7.5)	9 (13.6)	27 (10.2)
Partially excluded by protocol violation *	8	6	12	6	32
Partially excluded by slotting procedure †	6	3	1	4	14

* Patients had one or more visits excluded because of a protocol violation that did not cause complete exclusion of data.

† Patients had one or more visits excluded by the slotting procedure.

**Summary of Baseline Characteristics According to Regimen
Intent-to-Treat***

	PLACEBO		CARVEDILOL (mg)						TOTAL		P-VALUE†
	N	%	6.25		12.5		12.5/25		N	%	
			N	%	N	%	N	%			
TOTAL PATIENTS	66	100	67	100	67	100	66	100	266	100	
<u>AGE (Yr)</u>											
< 64	51	77	58	87	52	78	58	88	219	82	0.221
> 64	15	23	9	13	15	22	8	12	47	18	
<u>SEX</u>											
FEMALE	24	36	24	36	24	36	22	33	94	35	0.984
MALE	42	64	43	64	43	64	44	67	172	65	
<u>RACE</u>											
BLACK	21	32	22	33	25	37	21	32	89	33	0.897
NON-BLACK	45	68	45	67	42	63	45	68	177	67	
<u>SEV. OF HYPERTENSION AT BASELINE</u>											
MILD	46	70	47	70	51	76	46	70	190	71	0.803
MODERATE	20	30	20	30	16	24	20	30	76	29	
<u>PRIOR ANTI-HYPERTENSIVES</u>											
NO	18	27	20	30	13	19	18	27	69	26	0.532
YES	48	73	47	70	54	81	48	73	197	74	
<u>BODY WEIGHT AT BASELINE</u>											
< 70 Kgs	7	11	4	6	10	15	10	15	31	12	0.116
71-90 Kgs	28	42	36	54	31	46	20	30	115	43	
≥ 91 Kgs	31	47	27	40	26	39	36	54	120	45	

	PLACEBO		CARVEDILOL (mg)						P-VALUE#				
	N	MEAN	STDERR	6.25		12.5		12.5/25					
				N	MEAN	STDERR	N	MEAN		STDERR	N	MEAN	STDERR
AGE (Yr)	66	56	1.4	67	54	1.2	67	54	1.4	66	55	1.2	0.7634
WEIGHT (Kg)	66	90	2.4	67	89	2.1	67	88	2.3	66	90	1.9	0.8931

- * Randomized and received active medication, regardless of protocol violations.
† P-value of Fisher's Exact Test
P-value of F-test from General Linear Model (section 2.9.2).

**Summary of Baseline Characteristics According to Regimen
Per-protocol***

	PLACEBO		CARVEDILOL (mg)						TOTAL	P-VALUE†	
	N	%	6.25		12.5		12.5/25				
TOTAL PATIENTS	58	100	62	100	62	100	57	100	239	100	
<u>AGE (Yr)</u>											
≤ 64	45	78	55	89	48	77	51	89	199	83	0.129
> 64	13	22	7	11	14	23	6	11	40	17	
<u>SEX</u>											
FEMALE	22	38	22	35	23	37	19	33	86	36	0.958
MALE	36	62	40	65	39	63	38	67	153	64	
<u>RACE</u>											
BLACK	17	29	19	31	22	35	14	25	72	30	0.638
NON-BLACK	41	71	43	69	40	65	43	75	167	70	
<u>SEV. OF HYPERTENSION AT BASELINE</u>											
MILD	38	66	43	69	47	76	39	68	167	70	0.646
MODERATE	20	34	19	31	15	24	18	32	72	30	
<u>PRJOR ANTI-HYPERTENSIVES</u>											
NO	15	26	20	32	13	21	15	26	63	26	0.572
YES	43	74	42	68	49	79	42	74	176	74	
<u>BODY WEIGHT AT BASELINE</u>											
≤ 70 Kgs	7	12	3	5	10	16	9	16	29	12	0.056
71-90 Kgs	27	46	33	53	29	47	16	28	105	44	
≥ 91 Kgs	24	41	26	42	23	37	32	56	105	44	

	PLACEBO		CARVEDILOL (mg)						TOTAL	P-VALUE‡			
	N	MEAN	STDERR	6.25		12.5		12.5/25					
AGE (Yr)	58	56	1.5	62	54	1.2	62	54	1.5	57	55	1.3	0.6105
WEIGHT (Kg)	58	88	2.5	62	90	2.2	62	88	2.4	57	90	2.1	0.9708

* Randomized and received active medication, with no protocol violations.

† P-value of Fisher's Exact Test

‡ P-value of F-test from General Linear Model(section 2.9.2).

Reference Documentation: Appendix 3.2.1, 3.3.1, 3.4.1, and 8.10.2.

Reason for Discontinuation

A total of 266 patients were randomized into the treatment phase. Overall, 91.5% (183/200) of patients randomized to carvedilol completed the study compared to 90.9% (60/66) of patients randomized to placebo. No deaths were reported on-therapy or within 30 days post-therapy for any of the patients randomized in this study, nor for any of the additional 144 patients treated only in the Baseline Phase. After entering the treatment phase, six patients (9.1%, 6/66) in the placebo group, four patients (6.0%, 4/67) in the carvedilol 6.25 mg group, seven patients (10.4%, 7/67) in the carvedilol 12.5 mg group, and six patients (9.1%, 6/66) in the carvedilol 12.5/25 mg group were withdrawn during the course of the four week period.

Among all patients randomized to treatment, 11 patients were discontinued due to an adverse experience: three received placebo, one received carvedilol 6.25 mg, five received carvedilol 12.5 mg, and two received carvedilol 25 mg (section 4.3.1 and Table 22). Of 200 patients randomized to carvedilol, 4.0% (8/200) were withdrawn from treatment because of an adverse experience. Of 66 patients randomized to placebo, there were 4.5% (3/66) withdrawn from treatment because of an adverse experience. In comparison, during the HCTZ monotherapy phase, 2.0% (8/410) were withdrawn for adverse experiences.

Four patients, one in each of the treatment regimens were discontinued due to insufficient therapeutic effect. Eight patients (two patients each in the placebo and the carvedilol 6.25 mg groups, three in carvedilol 12.5 mg group, and one in carvedilol 12.5/25 mg group) were discontinued for other reasons; none of these patients had the onset of adverse experiences associated with their withdrawal. Of the 266 randomized patients, 133/266 were entered into the long-term, open-label carvedilol protocol (C1111). Of the patients randomized to carvedilol, 50.0% (100/200) continued carvedilol treatment by entering into an open-label extension study; the same percentage of patients randomized to placebo, 50.0% (33/66), entered into the same open-label extension study.

8.5.4 RESULTS

**Distribution of Patients According to Randomized Regimen
at Endpoint of the Treatment Phase**

	<u>Intent-to-Treat</u> <u>Analysis</u> N = 264*		<u>Per-Protocol</u> <u>Analysis</u> N = 233	
	<u>Number</u>	<u>(%) of</u> <u>Patients</u>	<u>Number</u>	<u>(%) of</u> <u>Patients</u>
Placebo	66	(25.0)	58	(24.9)
Carv [†] 6.25 mg	67	(25.4)	62	(26.6)
Carv 12.5 mg	65 [‡]	(24.6)	57	(24.5)
Carv 12.5/25 mg [‡]	66	(25.0)	56	(24.0)

32 patients in the *intent-to-treat sample* and 28 patients in the *per-protocol sample* had their dose increased from 12.5 mg to 25 mg in Group 4 (carvedilol 12.5/25 mg).

[†] Carv = carvedilol

[‡] Two patients (85 and 261) had no records after dose-day 1 and therefore have no endpoint data.

Reference documentation: Appendix 8.1.1

**Summary of HCTZ Baseline Phase Vital Signs
According to Randomized Regimen during Treatment Phase
*Intent-to-Treat Sample***

	<u>REGIMEN</u> (mg)	<u>N</u>	<u>MEAN</u> SBP/DBP	<u>SE</u> HRSBP/DBPHR
SITTING:				
Screening visit:				
	Placebo	66	153/98	74 2.0/0.90.9
	Carv 6.25	67	151/97	77 2.2/0.71.2
	Carv 12.5	67	148/96	76 1.8/0.71.2
	Carv 12.5/25	66	148/98	74 1.9/0.61.0
Baseline Vital Signs (mean at last two visits of HCTZ Baseline Phase)				
	Placebo	66	150/98	74 1.8/0.71.0
	Carv 6.25	67	148/98	78 2.0/0.71.2
	Carv 12.5	67	148/97	75 1.6/0.61.0
	Carv 12.5/25	66	146/98	76 1.6/0.71.0
3-MINUTE STANDING:				
Screening visit:				
	Placebo	66	153/99	77 2.1/0.91.9
	Carv 6.25	67	150/99	80 2.3/0.82.1
	Carv 12.5	67	148/98	79 2.0/0.81.8
	Carv 12.5/25	66	148/100	77 1.9/0.81.7
Baseline Vital Signs (mean at last two visits of HCTZ Baseline Phase)				
	Placebo	66	150/101	79 1.9/0.81.0
	Carv 6.25	67	146/100	82 2.1/0.81.2
	Carv 12.5	67	147/99	80 1.8/0.71.1
	Carv 12.5/25	66	146/100	80 1.7/0.81.2

**Summary of Tabulations and Analysis of Baseline Sitting DBP (mm Hg)
and Change from Baseline at Each Visit and Endpoint by Randomized Regimen**

	<u>REGIMEN</u> (mg)	<u>N</u>	<i>Intent-to-Treat</i>		<u>95% CONFIDENCE INTERVAL*</u> (vs. placebo)
			<u>MEAN</u>	<u>SE</u>	
<u>SITTING:</u>					
<u>DIASTOLIC</u>					
Baseline	Placebo	66	98	0.7	
	Carv 6.25	67	98	0.7	(-2.68, 1.60)
	Carv 12.5	67	97	0.6	(-3.13, 1.15)
	Carv 12.5/25	66	98	0.7	(-1.96, 2.33)
Week 1 ^b (change)	Placebo	66	-3.7	0.8	
	Carv 6.25	65	-4.9	0.8	(-3.35, 1.30)
	Carv 12.5	63	-4.3	1.0	(-3.28, 1.91)
	Carv 12.5/25	65	-6.3	0.9	(-5.20, -0.50) ^c
Week 2 (change)	Placebo	60	-4.3	0.8	
	Carv 6.25	63	-5.4	1.0	(-3.59, 1.43)
	Carv 12.5	61	-4.9	0.8	(-3.13, 1.93)
	Carv 12.5/25	61	-6.3	0.9	(-4.49, 0.57)
Week 3 (change)	Placebo	60	-5.8	0.8	
	Carv 6.25	63	-4.8	0.8	(-1.47, 3.35)
	Carv 12.5	59	-4.7	0.7	(-1.38, 3.52)
	Carv 12.5/25	57	-6.6	1.0	(-3.36, 1.59)
Week 4 (change)	Placebo	61	-3.7	0.8	
	Carv 6.25	63	-5.1	1.0	(-3.99, 1.05)
	Carv 12.5	60	-5.3	0.9	(-4.14, 0.95)
	Carv 12.5/25	60	-6.7	0.8	(-5.56, -0.46) ^c
Endpoint (change)	Placebo	66	-3.3	0.8	
	Carv 6.25	67	-4.7	1.0	(-3.96, 1.22)
	Carv 12.5	65	-4.9	1.0	(-4.20, 1.03)
	Carv 12.5/25	66	-6.3	0.9	(-5.66, -0.46) ^c

* Dunnett's 95% Experimentwise Confidence Interval (Two-Tailed for Baseline Visits and One-Tailed for On-Therapy Visits).

^b Change from baseline at Week 1 represents Group 4 prior to any dose change, i.e., at 12.5 mg actual dose.

^c Significant at alpha = 0.05.

Dose-response: The relationship between dose levels and change in sitting DBP at endpoint was examined by analysis of variance according to actual doses rather than randomized regimen. For this analysis, the subset of Group 4 patients who were not titrated were excluded; thus, only the 52 patients for whom study medication was increased to carvedilol 25 mg were included in the analysis of the 25 mg group.

**Summary of Tabulations and Analysis by Dose Received
for Mean Sitting Diastolic Blood Pressure (mm Hg) Change from Baseline
at Endpoint
*Intent-to-treat***

<u>PLACEBO</u>	<u>CARVEDILOL (mg)</u>				<u>P-VALUE*</u>	
	<u>6.25</u>	<u>12.5</u>	<u>25</u>	<u>LINEAR</u>	<u>QUADRATIC</u>	
N	66	67	65	32*		
Mean	-3.3	-4.7	-4.9	-6.6	0.008*	0.504
Standard Deviation	6.5	7.9	7.9	6.3		

* Of 66 patients randomized to Group 4 (12.5/25 mg), the actual dose was increased to 25 mg for 32 patients who had endpoint data. Patient 135 was discontinued after one dose of 25 mg and had no endpoint data. The other 33 patients who remained on 12.5 mg were excluded from this analysis, but data for these patients are presented in Table 11.

In addition to this analysis, mean change from baseline in SitDBP at endpoint was examined for all randomized patients according to actual dose and for the subsets of patients according to study medication level.

**Mean SitDBP (mm Hg) at Baseline and
Change from Baseline at Endpoint
According to Dose Received at Endpoint
*Intent-to-Treat Sample***

	<u>Baseline</u>			<u>Change from Baseline at Endpoint</u>		
	n	Mean	SE	n	Mean	SE
<i>All patients</i>						
Placebo	66	98.1	0.7	66	-3.3	0.8
Carv 6.25 mg	67	97.6	0.7	67	-4.7	1.0
Carv 12.5 mg	101	97.0	0.5	99	-5.3	0.8
Carv 12.5/25 mg	32	99.8	1.1	32	-6.6	1.1
<i>Patients at Level 1</i>						
Placebo	26	94.2	0.5	26	-3.7	1.3
Carv 6.25 mg	28	94.5	0.8	28	-6.7	1.6
Carv 12.5 mg	29	96.0	0.6	27	-7.0	1.8
Carv 12.5 mg*	34	96.9	0.9	34	-6.1	1.3
<i>Patients at Level 2*</i>						
Placebo	40	100.7	1.0	40	-3.0	1.0
Carv 6.25 mg	39	99.8	0.8	39	-3.2	1.2
Carv 12.5 mg	38	98.0	0.9	38	-3.4	1.0
Carv 25 mg	32	99.8	1.1	32	-6.6	1.1

* Group 4 patients for whom dose was not increased.

These patients had not responded to one week of treatment with the initial dose (Level 1) and therefore had study medication increased to Level 2. However, only one treatment group had an actual increase in dose; the dose for Group 4 was increased from carvedilol 12.5 mg to 25 mg.

Dose-response: The relationship between dose levels and change in sitting DBP at endpoint was examined by analysis of variance according to actual doses rather than randomized regimen. For this analysis, the subset of Group 4 patients who were not titrated were excluded; thus, only the 28 patients for whom study medication was increased to carvedilol 25 mg were included. There was no indication of a statistically significant ($p > 0.05$) linear or quadratic relationship between dosing level and mean SitDBP change from baseline at endpoint. Table 13 summarizes the mean changes from baseline and corresponding linear and quadratic p-values.

Summary of Tabulations and Analysis by Dose Received for Mean Sitting Diastolic Blood Pressure (mm Hg) Change from Baseline at Endpoint
Per-protocol

<u>PLACEBO</u>	<u>CARVEDILOL (mg)</u>				<u>P-VALUE*</u>	
	<u>6.25</u>	<u>12.5</u>	<u>25</u>	<u>LINEAR</u>	<u>QUADRATIC</u>	
N	58	62	57	28*		
Mean	-3.8	-4.9	-5.8	-5.5	0.076	0.804
Standard Deviation	6.2	8.3	7.3	5.6		

* Of 56 patients evaluated in Group 4 (12.5/25 mg), the actual dose was increased to 25 mg for 28 patients. The other 28 patients who were not titrated to 25 mg were excluded from this analysis, but data for these patients are presented in Table 14.

Change from baseline mean SitDBP at endpoint did not increase with the increase in actual dose. The change from baseline mean SitDBP at endpoint observed for the lowest and highest doses of carvedilol (6.25 and 25 mg, respectively) were within one SE of that observed for placebo. Therefore, these data are consistent with the analysis of variance findings, which did not show an indication of linear or quadratic dose-response relationships.

**Summary of Tabulations and Analysis of Baseline Sitting DBP (mm Hg) and Change
from Baseline at Each Visit and Endpoint by Randomized Regimen
Intent-to-Treat**

	<u>REGIMEN</u> (mg)	<u>N</u>	<u>MEAN</u>	<u>SE</u>	<u>95% CONFIDENCE</u> <u>INTERVAL*</u>
					(vs. placebo)
SITTING:					
<u>DIASTOLIC</u>					
Baseline	Placebo	66	98	0.7	
	Carv 6.25	67	98	0.7	(-2.68, 1.60)
	Carv 12.5	67	97	0.6	(-3.13, 1.15)
	Carv 12.5/25	66	98	0.7	(-1.96, 2.33)
Week 1 (change)	Placebo	66	-3.7	0.8	
	Carv 6.25	65	-4.9	0.8	(-3.85, 1.30)
	Carv 12.5	63	-4.3	1.0	(-3.28, 1.91)
	Carv 12.5/25	65	-6.3	0.9	(-5.20, -0.50) [#]
Week 2 (change)	Placebo	60	-4.3	0.8	
	Carv 6.25	63	-5.4	1.0	(-3.59, 1.43)
	Carv 12.5	61	-4.9	0.8	(-3.13, 1.93)
	Carv 12.5/25	61	-6.3	0.9	(-4.49, 0.57)
Week 3 (change)	Placebo	60	-5.8	0.8	
	Carv 6.25	63	-4.8	0.8	(-1.47, 3.35)
	Carv 12.5	59	-4.7	0.7	(-1.38, 3.52)
	Carv 12.5/25	57	-6.6	1.0	(-3.36, 1.59)
Week 4 (change)	Placebo	61	-3.7	0.8	
	Carv 6.25	63	-5.1	1.0	(-3.99, 1.05)
	Carv 12.5	60	-5.3	0.9	(-4.14, 0.95)
	Carv 12.5/25	60	-6.7	0.8	(-5.56, -0.46) [#]
Endpoint (change)	Placebo	66	-3.3	0.8	
	Carv 6.25	67	-4.7	1.0	(-3.96, 1.22)
	Carv 12.5	65	-4.9	1.0	(-4.20, 1.03)
	Carv 12.5/25	66	-6.3	0.9	(-5.66, -0.46) [#]

* Change from baseline at Week 1 represents Group 4 prior to any dose change, i.e., at 12.5 mg actual dose.

Significant at alpha = 0.05.

Mean Change from Baseline at Endpoint in SitDBP and Secondary
Blood Pressure Parameters (mm Hg)
Intent-to-Treat Sample

<u>PARAMETER/ Regimen (mg)</u>	<u>n</u>	<u>Mean</u>	<u>SE</u>	Change from Baseline at		<u>SE</u>	95% CONFIDENCE <u>INTERVAL</u>
				<u>Baseline</u>	<u>Endpoint</u>		
COMPARISON vs PLACEBO							
Sitting Diastolic Blood Pressure							
Placebo	66	98.1	0.7	66	-3.3	0.8	
Carv 6.25	67	97.6	0.7	67	-4.7	1.0	(-3.96, 1.22)
Carv 12.5	67	97.1	0.6	65	-4.9	1.0	(-4.20, 1.03)
Carv 12.5/25	66	98.3	0.7	66	-6.3	0.9	(-5.66, -0.46)*
Sitting Systolic Blood Pressure							
Placebo	66	150.0	1.8	66	-2.0	1.4	
Carv 6.25	67	147.7	2.0	67	-3.5	1.5	(-5.71, 2.88)
Carv 12.5	67	148.3	1.6	65	-4.4	1.6	(-6.68, 1.97)
Carv 12.5/25	66	146.5	1.6	66	-4.5	1.4	(-6.72, 1.90)
Standing Diastolic Blood Pressure							
Placebo	66	100.6	0.8	66	-3.2	1.0	
Carv 6.25	67	99.5	0.8	66	-4.1	0.9	(-3.6, 1.7)
Carv 12.5	67	99.4	0.7	65	-4.7	0.9	(-4.2, 1.1)
Carv 12.5/25	66	100.1	0.8	66	-5.6	0.9	(-5.1, 0.2)
Standing Systolic Blood Pressure							
Placebo	66	149.8	1.9	66	-2.6	1.5	
Carv 6.25	67	146.4	2.1	66	-2.4	1.4	(-4.10, 4.50)
Carv 12.5	67	146.8	1.8	65	-3.4	1.5	(-5.03, 3.60)
Carv 12.5/25	66	146.0	1.7	66	-4.0	1.5	(-5.69, 2.90)

**Summary of Tabulations and Analysis of Baseline Heart Rate and Change from
Baseline at Each Visit at Endpoint**

Intent-to-Treat

	<u>REGIMEN</u> (mg)	<u>N</u>	<u>MEAN</u>	<u>SE</u>	<u>95% CONFIDENCE</u> <u>INTERVAL*</u>
SITTING:					
<u>HEART RATE</u>					
					(vs. placebo)
Baseline	Placebo	66	74	1.0	
	Carv 6.25	67	78	1.2	(0.65, 7.53) [#]
	Carv 12.5	67	76	1.0	(-0.94, 5.95)
	Carv 12.5/25	66	76	1.0	(-1.43, 5.49)
Week 1 (change)	Placebo	66	-0.2	0.9	
	Carv 6.25	65	-2.8	1.1	(-5.11, -0.09) [#]
	Carv 12.5	63	-4.3	1.1	(-6.21, -1.18) [#]
	Carv 12.5/25	65	-3.8	0.9	(-6.71, -1.65) [#]
Week 2 (change)	Placebo	60	-0.3	0.9	
	Carv 6.25	63	-3.9	1.2	(-6.21, -0.96) [#]
	Carv 12.5	61	-4.2	1.1	(-6.56, -1.26) [#]
	Carv 12.5/25	61	-4.5	0.9	(-6.77, -1.48) [#]
Week 3 (change)	Placebo	60	1.1	1.0	
	Carv 6.25	63	-1.9	1.1	(-5.85, -0.09) [#]
	Carv 12.5	59	-3.2	1.1	(-7.24, -1.40) [#]
	Carv 12.5/25	57	-5.1	1.2	(-9.21, -3.31) [#]
Week 4 (change)	Placebo	61	0.2	1.1	
	Carv 6.25	63	-4.6	1.1	(-7.07, -1.29) [#]
	Carv 12.5	60	-4.0	1.1	(-7.65, -1.95) [#]
	Carv 12.5/25	60	-6.7	1.1	(-9.70, -3.98) [#]
Endpoint (change)	Placebo	66	0.3	0.9	
	Carv 6.25	67	-4.7	1.1	(-7.75, -2.23) [#]

* Dunnett's 95% Experimentwise Confidence Interval (Two-Tailed for Baseline Visits and One-Tailed for On-Therapy)
Change from baseline at Week 1 represents Group 4 prior to any dose change, i.e., at 12.5 mg actual dose.

Significant at alpha = 0.05.

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**Mean Change from Baseline at Endpoint in Sitting and
Standing Heart Rate Parameters (bpm)
*Inter. to-Treat Sample***

<u>PARAMETER/ Regimen (mg)</u>	<u>n</u>	<u>Baseline</u>		<u>n</u>	<u>Change from Baseline at Endpoint</u>		<u>95% CONFIDENCE INTERVAL* (vs. placebo)</u>
		<u>Mean</u>	<u>SE</u>		<u>Mean</u>	<u>SE</u>	
SitHR							
Placebo	66	74.0	1.0	66	0.3	0.9	
Carv 6.25	67	78.1	1.2	67	-4.7	1.1	(-7.75, -2.23)*
Carv 12.5	67	76.5	1.0	65	-3.3	1.0	(-6.34, -0.79)*
Carv 12.5/25	66	76.0	1.0	66	-6.3	1.1	(-9.31, -3.78)*
StaHR							
Placebo	66	78.8	1.0	66	-0.8	0.7	
Carv 6.25	67	81.8	1.2	66	-3.8	1.1	(-5.92, 0.01)
Carv 12.5	67	80.1	1.1	65	-3.4	1.1	(-5.60, 0.35)
Carv 12.5/25	66	80.4	1.2	66	-7.0	1.1	(-9.19, -3.26)*

Dunnnett's 95% Experimentwise Confidence Interval (Two-Tailed for Baseline Visits and One-Tailed for On-Therapy visits).

* Significant at alpha = 0.05.

Reference Documentation: Appendixes 8.1.1, 8.2.1, 8.11.1, and 8.12.1

Response rates to treatment

Two categories defining "response" were used in the analysis of antihypertensive efficacy in this study. Patients considered 'normalized' were those whose mean SitDBP was lowered during the treatment phase to less than 90 mm Hg. Patients considered 'responders' were those who achieved a normalized mean SitDBP and/or demonstrated a decrease from baseline in mean SitDBP of at least 10 mm Hg.

**Number and Percentage of Patients Normalized* and
Responding* by Randomized Treatment at Study Endpoint**

Intent-To-Treat Analysis

	<u>Total No.</u>	<u>No. (%) Normalized</u>	<u>No. (%) Responding</u>
Placebo	66	18 (27.3%)	21 (31.8%)
Carv 6.25 mg	67	30 (44.8%)	30 (44.8%)
Carv 12.5 mg	65	26 (40.0%)	30 (46.2%)
Carv 12.5/25 mg	66	27 (40.9%)	31 (47.0%)
<u>P-value</u> [†] :			
Carv 6.25 vs P		0.047	0.154
Carv 12.5 vs P		0.141	0.108
Carv 12.5/25 vs P		0.141	0.108

Per-Protocol Analysis

	<u>Total No.</u>	<u>No. (%) Normalized</u>	<u>No. (%) Responding</u>
Placebo	58	14 (24.1%)	20 (34.5%)
Carv 6.25 mg	62	29 (46.8%)	29 (46.8%)
Carv 12.5 mg	57	23 (40.4%)	27 (47.4%)
Carv 12.5/25 mg	56	23 (41.1%)	25 (44.6%)
<u>P-value</u> [†] :			
Carv 6.25 vs P		0.013 [‡]	0.196
Carv 12.5 vs P		0.074	0.187
Carv 12.5/25 vs P		0.072	0.338

- * Achieving a Mean SitDBP < 90 mm Hg
† Achieving a Mean SitDBP < 90 mm Hg and/or a decrease from baseline in mean SitDBP ≥ 10 mm Hg

Subgroup comparisons

Analysis of variance of baseline and mean SitDBP change from baseline at endpoint was performed for four subgroups (sex, age-group, severity of hypertension at baseline, and weight group).

Within the non-black sub-group, which included 157 Caucasian and 20 Hispanic patients, statistically significant ($p \leq 0.05$) differences in the mean SitDBP change from baseline at endpoint were observed for carvedilol 25 mg when compared to placebo (*intent-to-treat sample*). However, within the black subgroup, no statistically significant differences were observed (*intent-to-treat sample*). Neither non-black nor black subgroups were found to have statistically significant differences in mean change from baseline SitDBP at endpoint when the *per-protocol sample* was analyzed.

Summary of Tabulations and Analysis of Baseline SitDBP (mm Hg) and Change from Baseline at Endpoint for the Non-black and Black Subgroups According to Randomized Regimen

Intent-to-Treat

95% CONFIDENCE

<u>REGIMEN</u>	<u>N</u>	<u>MEAN</u>	<u>SE</u>	<u>INTERVAL*</u>
(mg)				
<u>Subgroup: Non-black</u>				<u>(vs. placebo)</u>

Sitting Diastolic Blood Pressure at Baseline (mm Hg)

Placebo	45	98.1	0.8	
Carv 6.25	45	97.0	0.8	(-1.9, 3.3)
Carv 12.5	42	97.2	0.7	(-3.5, 1.7)
Carv 12.5/25	45	98.8	0.9	(-3.7, 1.5)

Change from Baseline at Endpoint (mm Hg)

Placebo	45	-3.1	1.0	
Carv 6.25	45	-5.1	1.0	(-4.8, 0.9)
Carv 12.5	40	-5.3	1.2	(-5.1, 0.8)
Carv 12.5/25	45	-6.4	0.9	(-6.2, -0.5)*

Subgroup: Black

Sitting Diastolic Blood Pressure at Baseline (mm Hg)

Placebo	21	98.2	1.5	
Carv 6.25	22	98.7	1.1	(-3.1, 4.2)
Carv 12.5	25	97.0	0.9	(-4.7, 2.4)
Carv 12.5/25	21	97.2	1.1	(-4.7, 2.7)

Change from Baseline at Endpoint (mm Hg)

Placebo	21	-3.6	1.5	
Carv 6.25	22	-3.8	2.1	(-5.6, 5.3)
Carv 12.5	25	-4.1	1.3	(-5.8, 4.8)
Carv 12.5/25	21	-6.1	1.8	(-8.0, 3.0)

**Summary of Tabulations and Analysis of Baseline Sitting Diastolic Blood Pressure
and Change from Baseline at Endpoint for the Non-elderly and Elderly Subgroups**

Per-protocol

<u>REGIMEN</u> (mg)	<u>N</u>	<u>MEAN</u>	<u>SE</u>	<u>95% CONFIDENCE</u> <u>INTERVAL*</u> (vs. placebo)

Subgroup: Non-elderly (≤ 64 yrs)

Sitting Diastolic Blood Pressure at Baseline (mm Hg)

Placebo	45	99.0	0.9	
Carv 6.25	55	97.9	0.7	(-3.7, 1.4)
Carv 12.5	48	97.4	0.7	(-4.2, 1.1)
Carv 12.5/25	51	98.5	0.8	(-3.1, 2.2)

Change from Baseline at Endpoint (mm Hg)

Placebo	45	-4.1	0.9	
Carv 6.25	55	-4.3	1.1	(-3.1, 2.8)
Carv 12.5	44	-5.5	1.2	(-4.5, 1.7)
Carv 12.5/25	50	-5.9	0.9	(-4.8, 1.3)

Subgroup: Elderly (> 64 yrs)

Sitting Diastolic Blood Pressure at Baseline (mm Hg)

Placebo	13	97.5	1.4	
Carv 6.25	7	94.4	0.9	(-5.1, 4.7)
Carv 12.5	14	96.2	1.1	(-5.2, 2.5)
Carv 12.5/25	6	97.3	1.4	(-7.8, 1.6)

Change from Baseline at Endpoint (mm Hg)

Placebo	13	-2.5	1.9	
Carv 6.25	7	-10.1	2.1	(-13.4, -1.8)*
Carv 12.5	13	-6.5	1.5	(-8.9, 0.9)
Carv 12.5/25	6	-8.7	1.7	(-12.3, -0.01)*

Within the subgroups defined according to sex, severity of hypertension at baseline, and weight, no statistically significant differences among treatment groups were found in SitDBP change from baseline at endpoint in either the *intent-to-treat* or *per-protocol* samples.

In addition, multiple subgroup analyses of response rates were performed. No significant differences in response rates were observed within or between treatment groups, for the various subgroups tested, including those within the categories of age, sex, and severity of hypertension.

Adverse experiences (postural hypotension) recorded during the assessment of post-dose vital signs

Marked postural hypotension was defined in the protocol as a reduction in blood pressure both of > 30 mm Hg systolic and > 15 mm Hg diastolic, concurrent with associated signs and symptoms (e.g. diaphoresis, dizziness, etc.), upon change from the supine to standing position. One patient randomized to carvedilol therapy had a postural hypotensive event so defined:

- Patient #135 (45 years old, male) experienced a fall in BP from 146/82 mm Hg supine to 85/57 mm Hg standing (and a fall of 61 mm Hg systolic, and 25 mm Hg diastolic), on day 7 of carvedilol treatment (approximately 30 minutes after receiving the first dose of carvedilol 25 mg). Among the blood pressures subsequently recorded until the patient recovered (after about 2 hours), the lowest was 85/57 mm Hg, measured in the standing position about 90 minutes after the initial event. The patient had associated symptoms of diaphoresis, lightheadedness (dizziness), unsteadiness on feet, and headache and was withdrawn from study. Complete vital signs listings for this patient on the day of the hypotensive event can be found in Appendix 16.0.

One additional patient (#112) experienced a "passing out episode," but the conditions surrounding the event did not meet the protocol definition for postural hypotension:

- Patient #112 (43 year old, female) experienced a "passing out episode" on day 13 of treatment with carvedilol 6.25 mg. The investigator considered this adverse experience unrelated to study medication, but related to reactive anxiety secondary to chest pain which she also experienced on Day 13. Both adverse experiences of chest pain and "passing out episode" were of mild severity.

and considered by the investigator to be unrelated to study medication. The patient completely recovered on the same day and continued in the study until completion. No vital sign information was obtained since the patient was not treated for the adverse experiences (chest pain, "passing out episode").

Comments:

Apart from isolated (and inconsistent) records, there is no evidence in these data that carvedilol once a day is different from placebo as a second step treatment - - following HCTZ - - in patients with mild or moderate hypertension.

8.6 PROTOCOL C1109:**CARVEDILOL (SK&F 105517) VERSUS ATENOLOL AND PLACEBO IN PATIENTS WITH MILD TO MODERATE ESSENTIAL HYPERTENSION**

8.6.1 Objective: Compare the efficacy and safety of carvedilol (12.5 mg, 25 mg and 50 mg), atenolol (50 mg and 100 mg), and placebo administered *once daily* for the treatment of patients with mild to moderate essential hypertension .

8.6.2 Study Design:

baseline observation	randomization n	up titration	n	fixed dose maintenance	n	down titration
Single blind placebo once daily	52	placebo once daily	48	placebo once daily	19	
	105	carvedilol 12.5 mg/day - 50 mg/day	10	carvedilol 12.5 mg/day	66	
			14	carvedilol 25 mg/day		
			81	carvedilol 50 mg/day		
	101	atenolol 50 mg/day - 100 mg/day	57	atenolol 50 mg/day	89	
			32	atenolol 100 mg/day		
5-6 wks	258	1-6 wks	242	4 wks	174	1 week

This was a multicenter (13 centers), double-blind, double-dummy, randomized, placebo-controlled, parallel group study where patients were titrated to a therapeutic effect. The study consisted of a Screening visit, a single-blind Placebo Baseline Period (1-6 weeks), and a double-blind Treatment Period which included an Up-Titration Period (1-6 weeks), a Fixed-Dose Maintenance Period (4 weeks), and a Down-titration Period (1 week).

The skewed numbers at the different treatment levels indicate that at the doses permitted in the study, atenolol 50 mg/day was perceived by the investigators to be more effective than carvedilol 25 mg/day.

Of 258 patients who received randomized medication, 65.9% (170/258) of the patients completed the study. Also, four additional patients completed all but the Down-Titration Period. It is difficult, if not impossible to decide from the report how many dropped out in each phase on each dose level. The total number entering baseline observation is not given. The number randomized to each drug is given but not the number completing the titration, nor the number completing maintenance. The sponsor has promised to submit precise numbers in a desk copy. (10/1/93).

Reason for Discontinuation

After entering into the treatment phase, 40 patients (38.1%) in the carvedilol group, 34 patients (65.4%) in the placebo group, and 14 patients (13.9%) in the atenolol group were *withdrawn* during the course of the treatment period (Up Titration, Fixed-Dose Maintenance, and Down Titration). Completion rates were 86.1% (87/101) for the atenolol treatment group, 61.9% (65/105) for the carvedilol treatment group, and 34.6% (18/52) for the placebo treatment group.

Safety Results: No deaths were reported on-therapy or within 30 days post-therapy for any of the 258 patients randomized in this study. One of the 52 patients (1.9%) randomized to placebo, two of the 101 patients (2%) randomized to atenolol, and five of the 105 patients (4.8%) randomized to carvedilol were withdrawn from the study because of one or more adverse experiences.

The distribution of patients according to the reason for concluding the study is presented below.

Reasons for Concluding Study by Medication Regimen
Intent-to-Treat Sample

<u>Reasons for Concluding Study</u>	<u>Placebo</u>		<u>Atenolol</u>		<u>Carvedilol</u>	
	n	(%)	n	(%)	n	(%)
Insufficient therapeutic effect*	31	(59.6)	9	(8.9)	31	(29.5)
p-value*						
Aten vs Plac		<0.0001				
Carv vs Plac		0.0001				
Aten vs Carv		<0.000				
Adverse experience	1	(1.9)	2	(2.0)	5	(4.8)
Other*	1	(1.9)	1	(1.0)	3	(2.9)
Completed study	18	(34.6)	87	(86.1)	65	(61.9)
Patient completed all but Down-Titration Period: AE	0	(0.0)	1	(1.0) ^y	0	(0.0)
Patient completed Down-Titration I Other	1	(1.9)	1	(1.0)	1	(1.0)

- * Insufficient therapeutic effect includes cases that meet the protocol-specific definition (section 2.6.3); that were perceived by the investigator as insufficient; or, that were perceived by the patient as insufficient.
- * Statistically significant based on Fisher's exact test, two-tailed, and the modified Bonferroni procedure.
- * "Other" includes the following reasons: non-compliant, unable to keep appointments, or patient decided to stop.
- ^y Patient #52 (atenolol 50 mg) was discontinued prior to Down-titration Period due to a nervous condition (self-hospitalization) which was considered by the investigator to be not related to study medication.

**Number and Percentage of Patients with Data Included or
Excluded from Efficacy Analysis**

	<u>Placebo</u> N (%)	<u>Atenolol</u> N (%)	<u>Carvedilol</u> N (%)	<u>Total</u> N (%)
Randomized patients	52 (100.0)	101 (100.0)	105 (100.0)	258 (100.0)
Included Intent-to-Treat analysis	52 (100.0)	100 (99.0)	105 (100.0)	257 (99.6)
Included Per-Protocol analysis	48 (92.3)	90 (88.1)	93 (88.6)	231 (89.5)
Patients with Data Excluded from the Per Protocol Analysis:				
Completely excluded by protocol violation	4 (7.7)	11 (10.9)	12 (11.4)	27 (10.5)
Partially excluded by protocol violation	12	22	28	62
Partially excluded by slotting procedure	3	0	4	7

STUDY POPULATION

A total of 258 patients from 13 centers in the United States entered the double-blind treatment phase and received at least one dose of randomized study medication. A total of 52, 101, and 105 patients were randomized to placebo, atenolol and carvedilol, respectively. Because one patient had no data 257 randomized patients were included in the *intent-to-treat sample*.

3.1 Demographic Characteristics

There were no statistically significant differences between the regimens, in any of the demographic parameters, in either the *intent-to-treat* or *per-protocol* samples. In both samples, the majority of patients were Caucasian, 25 to 80 years, and 80% of the patients had mild essential hypertension, defined as a mean SitDBP 90 - 105 mm Hg at baseline Visit 4.

**Summary of Baseline Characteristics
According to Regimen
*Intent-to-Treat***

	<u>Placebo</u>		<u>Atenolol</u>		<u>Carvedilol</u>		<u>Total</u>		<u>P-Value*</u>
	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>	
Total Patients	52	100	100	100	105	100	257	100	
<u>Age</u>									0.716
< 64	41	79	92	82	81	77	204	79	
≥ 64	11	21	18	18	24	23	53	21	
<u>Sex</u>									0.407
Female	16	31	34	34	27	26	77	30	
Male	36	69	66	66	78	74	180	70	
<u>Race</u>									1.000
Black	12	23	24	24	25	24	61	24	
Non-Black	40	77	76	76	80	76	196	76	
<u>Severity of Hypertension</u>									0.277
Mild	48	92	87	87	87	83	222	86	
Moderate	4	8	13	13	18	17	35	14	
<u>Prior Anti-Hypertensives</u>									0.188
No	13	25	34	34	24	23	71	28	
Yes	39	75	66	66	81	77	86	72	
<u>Body Weight At Baseline</u>									0.838
< 70 Kgs	7	13	15	15	14	13	36	14	
71-90 Kgs	25	48	48	48	44	42	117	46	
≥ 91 Kgs	20	38	37	37	47	45	104	40	

	<u>Placebo</u>			<u>Atenolol</u>			<u>Carvedilol</u>			<u>P-Value*</u>
	<u>N</u>	<u>Mean</u>	<u>Std</u>	<u>N</u>	<u>Mean</u>	<u>Std</u>	<u>N</u>	<u>Mean</u>	<u>Std</u>	
Age	52	54.1	11.0	100	53.7	11.4	105	53.6	12.0	0.954
Weight	52	85.7	13.1	100	86.4	17.1	105	91.5	20.7	0.050

* P-value of Fisher's Exact Test
 * P-value of F-test from General Linear Model (see statistical methods).

Reference documentation: Appendixes 8.10.1, 8.10.2

**Summary of Baseline Characteristics
According to Regimen
Per-Protocol**

	<u>Placebo</u>		<u>Atenolol</u>		<u>Carvedilol</u>		<u>Total</u>		<u>P-Value*</u>
	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>	
Total Patients	48	100	89	100	93	100	230	100	
<u>Age</u>									0.749
< 64	37	77	72	81	71	76	180	78	
> 64	11	23	17	19	22	24	50	22	
<u>Sex</u>									0.383
Female	16	33	31	35	24	26	71	31	
Male	32	67	58	65	69	74	159	69	
<u>Race</u>									0.884
Black	12	25	23	26	21	23	56	24	
Non-Black	36	75	66	74	72	77	174	76	
<u>Severity of Hypertension at Baseline</u>									0.262
Mild	45	94	77	87	78	84	200	87	
Moderate	3	6	12	13	15	16	30	13	
<u>Prior Anti-Hypertensives</u>									0.230
No	12	25	30	34	21	23	63	27	
Yes	36	75	59	66	72	77	167	73	
<u>Body Weight at Baseline</u>									0.848
< 70 Kgs	7	15	12	13	13	14	32	14	
71-90 Kgs	23	48	43	48	38	41	104	45	
≥ 91 Kgs	18	38	34	38	42	45	94	41	

	<u>Placebo</u>			<u>Atenolol</u>			<u>Carvedilol</u>			<u>P-Value*</u>
	<u>N</u>	<u>Mean</u>	<u>Std</u>	<u>N</u>	<u>Mean</u>	<u>Std</u>	<u>N</u>	<u>Mean</u>	<u>Std</u>	
Age	48	54	11.3	89	53	11.7	93	54	11.8	0.750
Weight	48	86	13.4	89	87	17.4	93	91	20.2	0.114

* P-value of Fisher's Exact Test
 * P-value of F-test from General Linear Model (see statistical methods).

**Distribution of Patients
According to Type of Pre-trial Antihypertensive Medication
Intent-to-treat Sample**

	Number (%) of Patients			
	<u>Placebo</u> (n = 52)	<u>Atenolol</u> (n = 100)	<u>Carvedilol</u> (n = 105)	<u>Total</u> (n = 257*)
No Treatment	13 (25.0)	34 (34.0)	24 (22.9)	71 (27.6)
Treated*	39 (75.0)	66 (66.0)	81 (77.1)	186 (72.4)
Type of Medication				
Diuretic	15 (28.8)	23 (23.0)	36 (34.3)	74 (28.8)
Beta Blocker	9 (17.3)	29 (29.0)	22 (21.0)	60 (23.3)
ACE Inhibitor	13 (25.0)	15 (15.0)	23 (21.9)	51 (19.8)
Peripheral Vasodilators	13 (25.0)	23 (23.0)	25 (23.8)	61 (23.7)
Other	10 (19.2)	30 (30.0)	23 (21.9)	63 (24.5)

* Patients treated with multiple agents of different pharmacologic actions are tabulated within each of the appropriate categories.

* Patient #82, who was withdrawn after receiving one dose of atenolol 50 mg, received Corgard 20 mg and Maxzide prior to enrolling in this study.

Evaluation of Efficacy

Primary efficacy results are presented for two analyses, the *intent-to-treat* analysis and the *per-protocol* analysis (Tables 8 to 15). All secondary efficacy results are presented for the *intent-to-treat* sample (Tables 16 to 20).

Baseline demographic characteristics did not differ between regimens for either the *intent-to-treat* sample or *per-protocol* sample. No statistically significant differences among the regimens in any sitting or standing baseline vital sign measurements were found.

Efficacy Results: Statistically significant ($p \leq 0.05$) differences in the mean change from baseline for both SitDBP and StaDBP at Titration and Study Endpoints were observed between carvedilol and placebo, between atenolol and placebo, and between carvedilol and atenolol. The mean $\pm$ SE change from baseline SitDBP at Study Endpoint was: -7.5 ± 0.8 mm Hg for carvedilol, -11.3 ± 0.6 mm Hg for atenolol, and -3.5 ± 0.9 mm Hg for placebo. The mean $\pm$ SE change from baseline StaDBP at Study Endpoint was: -6.4 ± 0.9 mm Hg for carvedilol, -9.9 ± 0.7 mm Hg for atenolol, and -2.3 ± 1.0 mm Hg for placebo.

At Study Endpoint, the percentages of patients normalized were 19% (10/52), 51% (51/100), and 33% (35/105) for placebo, atenolol, and carvedilol, respectively, and statistically significant ($p < 0.05$) differences in SitDBP normalized rates were found for atenolol vs placebo and for atenolol vs carvedilol. Responder rates were 23% (12/52), 63% (63/100), and 45% (47/105) for placebo, atenolol, and carvedilol, respectively, and statistically significant ($p < 0.05$) differences in the percentage of patients who were responders for SitDBP were found for all three comparisons.

Primary efficacy parameters: Mean SitDBP and Mean StaDBP

Results of the *intent-to-treat* and *per protocol* analyses of the change in SitDBP and StaDBP were consistent in that all three comparisons were statistically significant at Titration and Study Endpoints. The changes were similar in magnitude, and the rank order (atenolol > carvedilol > placebo) was the same among regimens.

**Summary of Tabulations and Analysis of Baseline *SizDBP* (mm Hg) and Change from
Baseline at Titration and Study Endpoints
Intent-to-Treat Sample**

	<u>Regimen</u>	<u>N</u>	<u>Mean</u>	<u>SE</u>	<u>Comparison</u>	<u>Estimate Confidence Interval⁺</u>	<u>P-Value⁺</u>
<u>Baseline <i>SizDBP</i></u>							
Diastolic	Placebo	52	100	0.6			
	Atenolol	107	100	0.4	Aten vs Plac	(-1.4, 1.1)	0.826
	Carvedilol	105	101	0.4	Carv vs Plac	(-0.8, 1.7)	0.486
					Carv vs Aten	(-0.4, 1.6)	0.265
<u>Change from Baseline at Titration Endpoint</u>							
Diastolic	Placebo	52	-4.6	1.0			
	Atenolol	100	-13.0	0.6	Aten vs Plac	(-10.6, -6.0)	<0.001 ⁺
	Carvedilol	105	-9.1	0.7	Carv vs Plac	(-6.6, -2.1)	<0.001 ⁺
					Carv vs Aten	(2.0, 5.8)	<0.001 ⁺
<u>Change from Baseline at Maintenance Endpoint</u>							
Diastolic	Placebo	19	-8.4	1.2			
	Atenolol	91	-12.0	0.6	Aten vs Plac	(-6.4, 0.5)	0.090
	Carvedilol	69	-9.5	0.9	Carv vs Plac	(-3.9, 3.2)	0.838
					Carv vs Aten	(0.5, 4.7)	0.018
<u>Change from Baseline at Study Endpoint</u>							
Diastolic	Placebo	52	-3.5	0.9			
	Atenolol	100	-11.3	0.6	Aten vs Plac	(-10.1, -5.3)	<0.001 ⁺
	Carvedilol	105	-7.5	0.8	Carv vs Plac	(-6.3, -1.5)	0.002 ⁺
					Carv vs Aten	(1.8, 5.8)	<0.001 ⁺

**Summary of Tabulations and Analysis of
Baseline StaDBP (mm Hg) and Change from Baseline
at Titration, and Study Endpoints
Intent-to-Treat Sample**

<u>Baseline StaDBP</u>	<u>Regimen</u>	<u>N</u>	<u>Mean</u>	<u>SE</u>	<u>Comparison</u>	<u>Estimate Confidence Interval*</u>	<u>P-Value*</u>
Diastolic	Placebo	52	102	0.7			
	Atenolol	100	102	0.5	Aten vs Plac	(-2.0, 1.1)	0.540
	Carvedilol	105	102	0.6	Carv vs Plac	(-1.7, 1.3)	0.757
					Carv vs Aten	(-1.0, 1.5)	0.710
<u>Change from Baseline at Titration Endpoint</u>							
Diastolic	Placebo	52	-3.2	1.1			
	Atenolol	100	-11.6	0.6	Aten vs Plac	(-10.9, -5.9)	<0.001*
	Carvedilol	105	-8.0	0.8	Carv vs Plac	(-7.2, -2.2)	<0.001*
					Carv vs Aten	(1.6, 5.7)	<0.001*
<u>Change from Baseline at Maintenance Endpoint</u>							
	Placebo	19	-8.1	1.3			
	Atenolol	91	-10.6	0.7	Aten vs Plac	(-5.6, 1.8)	0.307
	Carvedilol	69	-8.8	1.0	Carv vs Plac	(-3.9, 3.7)	0.962
					Carv vs Aten	(-0.5, 4.1)	0.119
<u>Change from Baseline at Study Endpoint</u>							
Diastolic	Placebo	52	-2.3	1.0			
	Atenolol	100	-9.9	0.7	Aten vs Plac	(-10.2, -5.0)	<0.001*
	Carvedilol	105	-6.4	0.9	Carv vs Plac	(-6.7, -1.5)	0.002*
					Carv vs Aten	(1.3, 5.6)	0.002*

* Least Squares 95% Comparison-wise Confidence Interval & p-value of contrast from SAS General Model.

* Significant at alpha = 0.05 using modified Bonferroni procedure for the three comparisons.

Comparing the two tables, orthostatic hypotension, at least at trough levels, does not appear to be a major problem.

**Mean (SE) Change from Baseline
in Sitting Diastolic Blood Pressure (mm Hg)
at Titration, Maintenance, and Study Endpoints
According to Dose Level
Intent-to-Treat Sample**

<u>Baseline Sitting DBP</u>	<u>n</u>	<u>Mean</u>	<u>SE</u>						
Placebo	52	100.2	0.6						
Atenolol (50/50/100 mg)	100	100.1	0.4						
Carvedilol (12.5/25/50 mg)	105	100.8	0.4						
				Level 2		Level 3		Level 4	
				<u>n</u>	<u>Mean</u>	<u>SE</u>	<u>n</u>	<u>Mean</u>	<u>SE</u>
<u>Change from Baseline at Titration Endpoint</u>									
Placebo	4	-12.3	2.7	3	-5.3	4.2	45	-3.8	1.1
Atenolol (50/50/100 mg)	35	-16.1	0.9	22	-15.2	0.7	43	-9.5	0.9
Carvedilol (12.5/25/50 mg)	10	-6.9	4.6	14	-11.6	1.4	81	-8.9	0.7
<u>Change from Baseline at Maintenance Endpoint</u>									
Placebo	3	-11.0	3.1	2	-4.0	5.0	14	-8.5	1.4
Atenolol (50/50/100 mg)	35	-13.4	0.9	22	-12.3	1.2	33	-9.7	1.1
Carvedilol (12.5/25/50 mg)	8	-7.4	2.3	11	-9.6	1.9	50	-9.8	1.1
<u>Change from Baseline at Study Endpoint</u>									
Placebo	4	-11.3	2.2	3	-1.7	3.7	45	-3.0	0.9
Atenolol (50/50/100 mg)	35	-13.4	0.9	22	-12.3	1.2	42	-8.6	1.0
Carvedilol (12.5/25/50 mg)	10	-2.9	3.8	14	-9.0	1.7	81	-7.8	0.8

Reference documentation: Appendix 8.1.8, 8.2.15, and 8.2.16

When means $\pm$ standard errors for StaDBP are compared, there are differences in effect among different dose levels. At Study Endpoint, the largest mean changes in StaDBP were observed for the atenolol and carvedilol regimens at the middle dose level (a result not surprising in a titration trial).

**Mean (SE) Change from Baseline
in Standing Diastolic Blood Pressure (mm Hg)
at Titration, Maintenance, and Study Endpoints
According to Dose Level
Intent-to-Treat Sample**

<u>Baseline Standing DBP</u>	<u>n</u>	<u>Mean</u>	<u>SE</u>						
Placebo	52	102.4	0.7						
Atenolol (50/50/100 mg)	100	101.8	0.5						
Carvedilol (12.5/25/50 mg)	103	102.2	0.6						
				Level 2		Level 3		Level 4	
				<u>n</u>	<u>Mean</u>	<u>SE</u>	<u>n</u>	<u>Mean</u>	<u>SE</u>
<u>Change from Baseline at Titration Endpoint</u>									
Placebo	4	-12.0	1.5	3	-4.0	4.2	45	-2.4	1.2
Atenolol (50/50/100 mg)	35	-13.6	1.7	22	-13.9	1.0	43	-8.9	0.9
Carvedilol (12.5/25/50 mg)	10	-3.1	4.2	14	-10.9	2.1	81	-8.1	0.8
<u>Change from Baseline at Maintenance Endpoint</u>									
Placebo	3	-11.0	2.1	2	-3.0	3.0	14	-8.1	1.6
Atenolol (50/50/100 mg)	35	-11.5	1.0	22	-12.5	1.4	33	-8.0	1.1
Carvedilol (12.5/25/50 mg)	8	-8.6	1.6	11	-10.2	1.8	50	-8.6	1.3
<u>Change from Baseline at Study Endpoint</u>									
Placebo	4	-11.3	1.5	3	-0.7	2.9	45	-1.6	1.1
Atenolol (50/50/100 mg)	35	-11.5	1.0	22	-12.5	1.4	42	-7.0	1.0
Carvedilol (12.5/25/50 mg)	10	-3.3	4.3	14	-8.6	2.0	81	-6.4	0.9

Reference documentation: Appendix 8.1.8, 8.2.15, and 8.2.16

Mean SitDBP and mean StaDBP at Baseline and the mean change from baseline at Titration, Maintenance, and Study Endpoints for trough (pre-dose) measurements for the *per-protocol* samples were consistent with the *intent-to-treat* results.

In comparison to SitDBP results, mean changes in mean StaDBP were slightly less for all three regimens at all three endpoints, as was observed for the *intent-to-treat* analysis.

Per-Protocol Sample

	<u>Regimen</u>	<u>N</u>	<u>Mean</u>	<u>SE</u>	<u>Comparison</u>	Estimate Confidence <u>Interval*</u>	<u>P-Value*</u>
<u>Baseline Standing DBP</u>							
Diastolic	Placebo	48	102	0.7			
	Atenolol	89	101	0.5	Aten vs Plac	(-1.8, 1.1)	0.626
	Carvedilol	93	101	0.5	Carv vs Plac	(-2.1, 0.9)	0.407
					Carv vs Aten	(-1.5, 1.0)	0.683
<u>Change from Baseline at Titration Endpoint</u>							
Diastolic	Placebo	48	-2.8	1.1			
	Atenolol	89	-11.1	0.8	Aten vs Plac	(-10.8, -5.7)	<0.001*
	Carvedilol	93	-7.6	0.7	Carv vs Plac	(-7.2, -2.2)	<0.001*
					Carv vs Aten	(1.4, 5.6)	<0.001
<u>Change from Baseline at Maintenance Endpoint</u>							
Diastolic	Placebo	14	-6.4	1.9			
	Atenolol	69	-10.3	0.7	Aten vs Plac	(-7.5, 1.4)	0.174
	Carvedilol	47	-9.0	1.3	Carv vs Plac	(-5.9, 3.4)	0.606
					Carv vs Aten	(-0.9, 4.6)	0.187
<u>Change from Baseline at Study Endpoint</u>							
Diastolic	Placebo	48	-1.8	1.1			
	Atenolol	89	-9.3	0.8	Aten vs Plac	(-10.0, -4.7)	<0.001*
	Carvedilol	93	-6.3	0.8	Carv vs Plac	(-7.0, -1.7)	0.001*
					Carv vs Aten	(0.8, 5.2)	0.008*

* Least Squares 95% Comparison-wise Confidence Interval & p-value of contrast from SAS General Model.

† Significant at alpha = 0.05 using modified Bonferroni procedure for the three comparisons.

**Mean (SE) Change from Baseline
in Sitting Diastolic Blood Pressure (mm Hg)
at Titration, Maintenance, and Study Endpoints
According to Dose
Per-Protocol Sample**

<u>Baseline Sitting DBP</u>	<u>n</u>	<u>Mean</u>	<u>SE</u>						
Placebo	48	99.9	0.6						
Atenolol (50/50/100 mg)	89	100.1	0.4						
Carvedilol (12.5/25/50 mg)	91	100.4	0.4						
				Level 2	Level 3	Level 4			
				<u>n</u>	<u>Mean</u>	<u>SE</u>	<u>n</u>	<u>Mean</u>	<u>SE</u>
<u>Change from Baseline at Titration Endpoint</u>									
Placebo	6	-5.8	4.4	7	-4.7	2.1	35	-3.1	1.1
Atenolol (50/50/100 mg)	33	-15.2	1.3	24	-13.3	1.4	32	-9.7	1.1
Carvedilol (12.5/25/50 mg)	9	-10.3	3.3	23	-7.0	1.4	61	-9.5	0.7
<u>Change from Baseline at Maintenance Endpoint</u>									
Placebo	1	-15.0	0.0	2	-4.0	5.0	11	-7.1	1.1
Atenolol (50/50/100 mg)	28	-13.4	1.0	17	-12.9	1.1	23	-8.7	1.2
Carvedilol (12.5/25/50 mg)	4	-6.0	2.9	7	-10.4	2.6	36	-9.8	1.3
<u>Change from Baseline at Study Endpoint</u>									
Placebo	6	-5.2	4.0	7	-3.1	2.1	35	-2.2	1.0
Atenolol (50/50/100 mg)	33	-12.9	1.2	24	-11.2	1.2	31	-8.4	1.2
Carvedilol (12.5/25/50 mg)	9	-8.2	3.6	23	-5.9	1.3	61	-8.3	0.9

Reference documentation: Appendix 8.1.8, 8.2.15, and 8.2.16

"Responders":

Intent-to-treat analysis: Statistically significant ($p \leq 0.05$) differences in SitDBP *normalized* and *responder* rates were found at Titration Endpoint (all three comparisons for both rates).

At Study Endpoint, statistically significant ($p \leq 0.05$) differences in SitDBP *normalized* and *responder* rates were found for carvedilol vs atenolol and atenolol vs placebo for *normalized* rates and for all three comparisons for *responder* rates.

**Number and Percent of Patients Normalized* and
Responders* to Randomized Treatment at Study Endpoint:
Sitting Diastolic Blood Pressure**

Intent-To-Treat Sample

	<u>Total No.</u>	<u>No. (%) Normalized</u>	<u>No. (%) Responders</u>
Titration Endpoint			
Placebo	52	13 (25%)	16 (31%)
Atenolol	100	76 (76%)	81 (81%)
Carvedilol	105	48 (46%)	60 (57%)
<u>P-value[†]:</u>	Carv vs Aten	< 0.001 [‡]	< 0.001 [‡]
	Aten vs Plac	< 0.001 [‡]	< 0.001 [‡]
	Carv vs Plac	0.015 [‡]	0.002 [‡]
	<u>Total No.</u>	<u>No. (%) Normalized</u>	<u>No. (%) Responders</u>
Maintenance Endpoint			
Placebo	19	8 (42%)	10 (53%)
Atenolol	91	50 (55%)	61 (67%)
Carvedilol	69	28 (41%)	37 (54%)
	<u>Total No.</u>	<u>No. (%) Normalized</u>	<u>No. (%) Responders</u>
Study Endpoint			
Placebo	52	10 (19%)	12 (23%)
Atenolol	100	51 (51%)	63 (63%)
Carvedilol	105	35 (33%)	47 (45%)
<u>P-value[†]:</u>	Carv vs Aten	0.011 [‡]	< 0.012 [‡]
	Aten vs Plac	< 0.001 [‡]	< 0.001 [‡]
	Carv vs Plac	0.091	0.008 [‡]

- * Normalized: sitting diastolic pressure of less than 90 mm Hg.
- * Responders: sitting diastolic pressure normalized and/or decreased from baseline by 10 mm Hg or more.
- * P-value of Fisher's Exact Test (Two-Tailed) to test differences between active groups versus placebo and carvedilol group versus atenolol.
- † Significant: at alpha = 0.05 using modified Bonferroni procedure for the comparisons.

**Number and Percent of Patients Normalized*
and Responders[†] to Randomized Treatment at Study Endpoint:
Standing Diastolic Blood Pressure**

Intent-to-Treat Sample

	<u>Total No.</u>	<u>No. (%) Normalized</u>	<u>No. (%) Responders</u>
Titration Endpoint			
Placebo	52	11 (21%)	14 (27%)
Atenolol	100	51 (51%)	65 (65%)
Carvedilol	105	31 (30%)	49 (47%)
<u>P-value[‡]:</u>	Carv vs Aten	< 0.003 [‡]	< 0.011 [‡]
	Aten vs Plac	< 0.001 [‡]	< 0.001 [‡]
	Carv vs Plac	0.339	0.024 [‡]
	<u>Total No.</u>	<u>No. (%) Normalized</u>	<u>No. (%) Responders</u>
Maintenance Endpoint			
Placebo	19	6 (32%)	10 (53%)
Atenolol	91	39 (43%)	51 (56%)
Carvedilol	69	30 (43%)	38 (55%)
	<u>Total No.</u>	<u>No. (%) Normalized</u>	<u>No. (%) Responders</u>
Study Endpoint			
Placebo	52	7 (13%)	12 (23%)
Atenolol	100	41 (41%)	55 (55%)
Carvedilol	105	33 (31%)	43 (41%)
<u>P-value[‡]:</u>	Carv vs Aten	0.190	0.051
	Aten vs Plac	< 0.001 [‡]	< 0.001 [‡]
	Carv vs Plac	0.019 [‡]	0.033

- * Normalized: sitting diastolic pressure of less than 90 mm Hg.
- † Responders: sitting diastolic pressure normalized and/or decreased from baseline by 10 mm Hg or more.
- ‡ P-value of Fisher's Exact Test (Two-Tailed) to test differences between active group versus placebo and carvedilol group versus atenolol.
- § Significant at alpha = 0.05 using modified Bonferroni procedure for the comparisons.

4.2.3 Maintenance of effect

Change from Titration Endpoint to Maintenance Endpoint was calculated for the subset of patients who had Maintenance Endpoint data: 19 patients receiving placebo, 91 patients receiving atenolol, and 69 patients receiving carvedilol.

**Change in Mean* SitDBP and StaDBP from End-Titration
to End-Maintenance for Patients with Maintenance Endpoint Data According
to Medication Regimen***Intent-To-Treat* Sample

	Placebo			Atenolol			Carvedilol		
	<u>n</u>	<u>Mean</u>	<u>SE</u>	<u>n</u>	<u>Mean</u>	<u>SE</u>	<u>n</u>	<u>Mean</u>	<u>SE</u>
<u>Sitting DBP (mm Hg)</u>									
Baseline	19	100.2	1.1	91	99.7	0.3	69	100.4	0.5
Change from baseline to end-titration	19	-11.3	1.4	91	-13.9	0.6	69	-11.9	0.7
Change from end-titration to end- maintenance	19	+2.8	1.6	91	+1.9	0.7	69	+2.4	0.9
<u>Three Minute Standing DBP (mm Hg)</u>									
Baseline	19	101.1	1.1	91	101.4	0.5	69	101.7	0.7
Change from baseline to end-titration	19	-10.5	1.2	91	-12.5	0.6	69	-11.3	0.8
Change from end-titration to end- maintenance	19	+2.5	1.9	91	+1.9	0.6	69	+2.4	1.0

* Mean is the unadjusted mean.

4.2.4 Subgroup comparisons

Analysis of variance of baseline and mean SitDBP change from baseline at endpoint was performed for four subgroups (sex, age, severity of hypertension at baseline, and race) for both the *intent-to-treat* and *per-protocol* samples.

Analysis of the *intent-to-treat* and *per-protocol* samples found no statistically significant ($p > 0.05$) differences between the regimens at baseline for any category of sex and race subsets.

For the black subgroup, the *change from baseline* at Study Endpoint was less than the corresponding change for the non-black subgroup by more than two standard errors of the mean for both atenolol and carvedilol treatment groups; (Tables 27 and 28). For the placebo treatment group, however, changes from baseline in both SitDBP and StaDBP were similar (within $\pm$ one SE of the mean), although the changes were smaller than those observed for the active treatments.

The black subgroup did not show any statistically significant differences in mean change from baseline for SitDBP and StaDBP, except for the comparison of atenolol to placebo for SitDBP ($p = 0.020$) at Study Endpoint (*intent-to-treat analysis*).

Mean Change from Baseline at Study Endpoint
Intent-to-Treat Sample
FEMALE SUBGROUP

SitDBP (mm Hg)

<u>Regimen</u>	<u>n</u>	<u>Mean</u>	<u>SE</u>
Placebo	16	-3.7	1.8
Atenolol	34	-11.5	0.9
Carvedilol	27	-7.6	1.4

<u>Comparison</u>	<u>CI*</u>	<u>P-Value*</u>
C vs P	(-8.5, 0.5)	0.077
A vs P	(-11.9, -3.2)	0.001*
C vs A	(0.1, 7.0)	0.045

StaDBP (mm Hg)

<u>Regimen</u>	<u>n</u>	<u>Mean</u>	<u>SE</u>
Placebo	16	-1.0	2.0
Atenolol	34	-10.7	1.0
Carvedilol	27	-4.5	1.4

<u>Comparison</u>	<u>CI*</u>	<u>P-Value*</u>
C vs P	(-6.8, 2.5)	0.358
A vs P	(-12.3, -3.2)	0.001*
C vs A	(2.1, 9.2)	0.002*

4.2.5 Analysis of peak and trough sitting DBP

Assessments were taken 30, 60, 90 and 120 minutes post-dosing at Baseline visit 4 as well as the Study Endpoint. Only patients with a set of both trough and peak measurements recorded on the same day and having a set at both the baseline and end-of-study observations were selected for these tabulations.

Analysis of steady-state sitting diastolic peak and trough measurements at Study Endpoint (*intent-to-treat* sample) showed 53.3% of the peak effect for carvedilol and 86.5% of the peak effect for atenolol is retained at trough, based on unadjusted trough/peak ratios. Adjusting these ratios for the placebo response among patients with maintenance data (ie, those patients for whom a placebo effect was observed) resulted in estimates of 32.2% of the peak effect for carvedilol and 67.9% of the peak effect for atenolol is retained at trough.

than those produced by carvedilol, administration of carvedilol once daily was superior to placebo in reducing SitDBP and StaDBP in patients with mild to moderate essential hypertension. At Study Endpoint, the mean change ($\pm$ SE) produced by carvedilol was -7.5 ± 0.8 mm Hg in Sit DBP and -6.4 ± 0.9 mm Hg in StaDBP. Among patients receiving carvedilol during the maintenance period, more than 50% of the peak effect was retained at trough. Also, the safety profile was similar for both atenolol and carvedilol. Most adverse experiences were mild and transient, with the majority (52%) of adverse experiences classified as mild. The results of this study demonstrate that carvedilol once daily is both safe and efficacious.

Reviewer's comments:

In the dose range tested Carvedilol is not a particularly effective drug and can not be recommended for once-a-day dosing. In a direct comparison, Atenolol is clearly more effective. This could be a consequence of dose rather than potency but the study does not address this issue.

The drug does not appear to be effective in black patients.

Age and sex of patients played no significant role in the outcome of this trial.

The drop-out rate is high and may have biased the outcome in favor of both active treatments.

Protocol CAR-UK-104

This multicenter study in UK had an unusual twist. Although the treatment phase lasted 12 weeks, it was unblinded to the investigators after week 4. Its purpose was to establish a dose range and evaluate safety in elderly patients (≥ 65 years old). There was no concurrent placebo arm. Efficacy was estimated by calculating the proportion of 'responders' in each group. Median values and ranges are also presented in the tables together with confidence intervals for the comparisons between treatment groups.

The titration at week 4 was based on efficacy, with the caveat that dose could not be increased if adverse effects were a problem.

Safety issues are discussed in some detail with summaries of individual case histories.

CAR-UK-104										
n	single blind	n	double blind	n	n	single blind	n	n	% response	Δ DBP(sitting) mm Hg (median)
262	Placebo	114	Carvedilol 12.5 mg UID	106	?	carvedilol 12.5 mg UID	56	93	73%	-10
					?	carvedilol 25 mg UID	37			
		118	Carvedilol 25 mg UID	104	?	Carvedilol 25 mg UID	62	90	70%	-12
					?	Carvedilol 50 mg UID	28			
262	3-6 weeks	232	4 weeks	210		8 weeks	183	183		

SUMMARY

This study was conducted as a double-blind, parallel group, multicentre study in hospital and in general practice. 262 elderly hypertensive patients (aged 65 to 89), including 6 protocol violators aged under 65 years, were recruited in order to obtain 183 who completed the protocol. All patients had to have a diastolic blood pressure of between 95 and 115mmHg and a systolic blood pressure of no more than 220mmHg confirmed during the baseline period. Each patient was randomised to receive either carvedilol 12.5mg or carvedilol 25mg at the end of the baseline period. After four weeks of treatment, the dose was titrated to "double dose" if the blood pressure remained uncontrolled (diastolic blood pressure being greater than 90mmHg and had decreased by less than 10mmHg). However, if patients were experiencing side effects which were likely to be exacerbated by increasing the dose then they remained on the lower dose. Following dose titration, if applicable, the patients continued in the study for a further eight weeks making the total study period twelve weeks.

Two statistical analyses were performed: an intention-to-treat analysis which considered all patients present at a particular visit, and a per-protocol analysis which considered only those patients present at a particular visit who were eligible under the terms of the protocol (i.e. non-protocol violators). Three time points were also used: final baseline visit, following four weeks of treatment (before any dose titration) and following twelve weeks of treatment (end of study). The primary efficacy parameter was to show a reduction in mean sitting diastolic blood pressure below 90mmHg and/or a fall of 10mmHg over the study period. The statistical analyses concentrated on the dose as randomised as this eliminates potential bias. However, similar numbers of patients were titrated correctly at week 4 in both treatment groups making it possible and logical to compare dose as randomised without adjustment for dose titration. A total of 114 and 118 patients were randomised to receive carvedilol 12.5mg and 25mg, respectively. At week 4, 106 patients were taking carvedilol 12.5mg and 104 patients were taking carvedilol 25mg. Of these patients 88 in the carvedilol 12.5mg group and 86 in the carvedilol 25mg group were eligible for the per-protocol analysis. By the end of the study 93 patients were remaining in the carvedilol 12.5mg starting dose group (56 patients on 12.5mg, 37 patients titrated up to 25mg at week 4) and 90 patients were remaining in the carvedilol 25mg starting dose group (62 patients on 25mg, 28 patients titrated up to 50mg at week 4). Of these patients 75 in the carvedilol 12.5mg starting dose group (46 patients on 12.5mg, 29 patients on 25mg) and 74 in the carvedilol 25mg starting dose group (52 patients on 25mg, 22 patients on 50mg) were eligible for the per-protocol analysis.

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The following table presents the results of the responders in each treatment group, according to the analysis performed, following four weeks and twelve weeks of treatment.

DOSE	INTENTION-TO-TREAT (all patients present for assessment)		PER-PROTOCOL (eligible patients)	
	Week 4	Week 12	Week 4	Week 12
Carvedilol 12.5mg	63/106 (59%)	63/93 (68%)	52/88 (59%)	50/75 (67%)
Carvedilol 25mg	72/104 (69%)	63/90 (70%)	60/86 (70%)	50/74 (68%)
% difference between groups	10% p=0.14	2% p=1.00	11% p=0.14	1% p=0.83

From this table it would appear that carvedilol 25mg is slightly more effective following four weeks of treatment compared to carvedilol 12.5mg, although this result is not statistically significant. However, following twelve weeks of treatment (post dose titration if applicable) the difference between these two groups narrows.

Safety is another important issue to consider when treating elderly hypertensive patients as they appear to be more prone to side effects than a younger population of patients. The safety section of this report was split into two sections: (a) those adverse events related to dizziness and/or postural hypotension and (b) others. Statistical analyses were only performed on the group of patients that fell into section (a) above. No statistically significant difference was observed between the two treatment groups as randomised although almost one and a half times as many adverse events related to dizziness and/or postural hypotension were reported by patients started on carvedilol 25mg compared to 12.5mg. This becomes a little clearer when we split the groups into treatment schedules (i.e. 12.5mg → 12.5mg, 12.5mg → 25mg, 25mg → 25mg, 25mg → 50mg) although these results should be treated with caution as patients involved in treatment schedules that require a dose titration (i.e. 12.5mg → 25mg and 25mg → 50mg) had to have received at least four weeks' treatment before inclusion. Adverse events occurring during the first four weeks of the study tended to appear in the groups where the dose was not subsequently doubled, whereas adverse events occurring at a later stage tended to appear in groups where the dose was doubled.

The following table presents the percentage of patients suffering adverse events related to dizziness and/or postural hypotension in each treatment schedule.

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TREATMENT SCHEDULE	TOTAL REPORTS	TOTAL PATIENTS	% OF PATIENTS
12.5mg → 12.5mg	9	7	10%
12.5mg → 25mg	7	6	14%
25mg → 25mg	21	13	15%
(Total 25mg)	(28)	(19)	(15%)
25mg → 50mg	6	6	19%

Therefore it would appear that the higher the dose of carvedilol, the higher the incidence of adverse events related to dizziness and/or postural hypotension. Increasing the dose from 12.5mg to 25mg does increase the incidence of these adverse events although the incidence is no greater in this group of patients compared to the group who remained on 25mg throughout the study.

Regarding other adverse events a greater number was again reported by the higher dose group (96 reports by 57 patients randomised to carvedilol 12.5mg compared to 104 reports by 63 patients randomised to carvedilol 25mg). Although the total numbers of adverse events reported is high, it is what one might expect from this population of patients. Similarly, many of the laboratory values taken throughout the study were out of the normal range, although not necessarily clinically significant, and reflects the elderly population studied.

In conclusion, carvedilol 12.5mg and carvedilol 25mg have very similar efficacy as starting doses in the elderly hypertensive population, provided titration to a higher dose occurs, if necessary. However, it does appear that the higher the dose of carvedilol the higher the incidence of adverse events related to dizziness and/or postural hypotension which is also true to some extent for all other adverse events. It would therefore seem prudent to initiate treatment in the elderly with 12.5mg once daily and there may be individual patients who can be maintained on this dosage.

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analyse parameters expressed as counts of patients (e.g. number of patients whose dose was increased, number fulfilling the primary efficacy criteria, etc.). All changes or differences described as statistically significant in this report are significant at least at the 5 percent level.

The Mantel-Haenszel Chi-square test was used to compare the starting dose groups with respect to the incidence of adverse events related to dizziness and/or postural hypotension, both overall and during each stage of the study. The Mantel-Haenszel Chi-square test adjusted for whether or not the dose was doubled at week 4 in the analysis of the stage following the dose titration step.

Fisher's Exact test was used to compare these adverse events between the starting dose groups at the increased dose monitoring visit since only a small number of events occurred at this stage. The two-sided p-value was obtained by doubling the one-sided value.

4. RESULTS

4.1 Number of Patients

A total of two hundred and sixty two patients were recruited to take part in the study. Two hundred and thirty two patients entered the active phase of the study. The first dose of study medication was administered in March 1989 and the last dose in February 1991. The thirty patients who did not receive active medication were withdrawn by the investigators for the following reasons: diastolic blood pressure below level for inclusion (13), abnormal renal function (3), standing systolic blood pressure too low (1), concomitant treatment with additional antihypertensive medication (2), patient request (4), adverse event (4), non-compliance with study medication (2) and investigator absence (1).

Of the 232 patients who received active medication 22 patients withdrew during the first 4 weeks, 16 due to adverse events (6 in the carvedilol 12.5mg group, 10 in the carvedilol 25mg group), 1 as he did not meet study eligibility criteria (carvedilol 25mg group), 1 due to non-compliance with study medication (carvedilol 25mg group), 2 requested to withdraw (carvedilol 25mg group) and 2 defaulted (both carvedilol 12.5mg group).

A further 27 patients withdrew before the week 12 visit, 21 due to adverse events (6 taking carvedilol 12.5mg, 11 taking carvedilol 25mg and 4 taking carvedilol 50mg), 2 requested to withdraw (one in each group), 1 had a diastolic pressure greater than 115 mmHg (carvedilol 12.5mg starting dose group), 2 defaulted (one in each group)

000014

and one due to additional antihypertensive treatment being given by his GP (carvedilol 25mg starting dose group).

Forty investigators located within the UK were involved in recruiting patients into the study (Table 1). It was not possible to assess treatment x centre interactions as the numbers of patients recruited by each centre were far too small. This report presents data on two hundred and thirty two patients who were randomised to receive either carvedilol 12.5mg or carvedilol 25mg during the initial period of the active phase of the study. If necessary, dose titration to "double-dose" occurred following four weeks of active treatment according to the criteria detailed in "Procedure, section 3.3.3, Treatment Phase Visits". The safety section of this report will also consider data on those patients who dropped out during the baseline period.

Of the 232 patients who received active medication 14 had all data excluded from the per protocol analysis due to the following reasons: diastolic pressure less than 95mmHg at baseline (7), age under 65 years (6) and emphysema (1). An additional 22 patients had their week 4 data excluded due to a late visit, where the patient would have run out of medication. Twenty patients also had week 12 data excluded for the same reason. Compliance less than 75% affected one patient at week 4 and one patient at week 12. These violations affected 36 patients at week 4 and 34 patients at week 12.

4.2 Demographic Data

No statistical tests were performed on the demographic data at the preliminary examination. Data is presented in terms of median, minimum and maximum values for all demographic parameters for the 232 patients who received active treatment. Table 3 presents the demographic data for all randomised patients (232 patients), table 4 presents the demographic data for all randomised patients that were present at week 12 (183 patients) and table 5 presents the demographic data for all eligible patients present at week 12 (149 patients).

At the preliminary examination, for all patients randomised, there were 48 males and 66 females in the carvedilol 12.5mg group, and 41 males and 77 females in the carvedilol 25mg group, median age and range being 71 (30-87) and 71 (62-86) years, respectively. A qualitative examination of the data presented in table 3 does not reveal any striking differences in any of the demographic parameters, apart from perhaps the male to female proportions (42%:58% carvedilol 12.5mg group, 35%:65% carvedilol 25mg group). 183 of these patients were present at the end of the study and had data available for comparisons on an intention-to-treat basis. Again, table 4 does not appear to reveal any differences in the demographic data of

ALL RANDOMISED PATIENTS PRESENT AT WEEK 12
 CLINICAL EFFICACY DATA
 FINAL PLACEBO BASELINE PERIOD VALUES

		Treatment Group			Comparison of Treatment Groups			
		Carvedilol 12.5mg	Carvedilol 25mg	Overall	Median Difference	95% C.I.		P-value
						Lower	Upper	
Mean Systolic BP (mmHg) Sitting	Median	177	182	179	-6	-11	-2	0.01
	Min							
	Max							
	N	93	90	183				
Mean Diastolic BP (mmHg) Sitting	Median	103	102	102	0	-1	2	0.71
	Min							
	Max							
	N	93	90	183				
Systolic BP (mmHg) Immediate Standing	Median	170	180	175	-6	-10	-2	0.01
	Min							
	Max							
	N	93	90	183				
Diastolic BP (mmHg) Immediate Standing	Median	102	102	102	0	-1	2	0.63
	Min							
	Max							
	N	93	90	183				
Postural Drop in Systolic BP (mmHg)	Median	-2	-2	-2	0	-2	1	0.56
	Min							
	Max							
	N	93	90	183				
Postural Drop in Diastolic BP (mmHg)	Median	0	0	0	0	-1	1	0.86
	Min							
	Max							
	N	93	90	183				
Pulse Rate (bpm) Sitting	Median	76	76	76	0	-3	2	0.70
	Min							
	Max							
	N	93	90	183				
Pulse Rate (bpm) Immediate Standing	Median	80	80	80	0	-2	4	0.96
	Min							
	Max							
	N	93	90	183				
Weight (kg)	Median	74	70	71	3	-1	6	0.12
	Min							
	Max							
	N	93	89	182				

TABLE 24

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ALL RANDOMISED PATIENTS PRESENT AT WEEK 12
 CLINICAL EFFICACY DATA
 WEEK 12 VALUES

		Treatment Group			Comparison of Treatment Groups			
		Carvedilol 12.5mg	Carvedilol 25mg	Overall	Median Difference	95% C.I. Lower Upper		P-value
Mean Systolic BP (mmHg) Sitting	Median	163	163	163	-1	-8	5	0.62
	Min							
	Max							
	N	93	90	183				
Mean Diastolic BP (mmHg) Sitting	Median	90	89	90	1	-2	3	0.53
	Min							
	Max							
	N	93	90	183				
Systolic BP (mmHg) Immediate Standing	Median	160	160	160	0	-10	5	0.54
	Min							
	Max							
	N	93	89	182				
Diastolic BP (mmHg) Immediate Standing	Median	90	90	90	0	-3	4	0.87
	Min							
	Max							
	N	93	89	182				
Postural Drop in Systolic BP (mmHg)	Median	-1	-1	-1	-1	-3	1	0.38
	Min							
	Max							
	N	93	89	182				
Postural Drop in Diastolic BP (mmHg)	Median	0	0	0	0	-1	1	0.61
	Min							
	Max							
	N	93	89	182				
Pulse Rate (bpm) Sitting	Median	71	72	71	0	-3	2	0.63
	Min							
	Max							
	N	93	90	183				
Pulse Rate (bpm) Immediate Standing	Median	72	72	72	0	-2	2	0.63
	Min							
	Max							
	N	92	88	180				
Weight (kg)	Median	74	70	71	2	-1	5	0.17
	Min							
	Max							
	N	92	89	181				

000099

ALL RANDOMISED PATIENTS PRESENT AT WEEK 12
 CLINICAL EFFICACY DATA
 CHANGES (WEEK 12 - BASELINE)

		Treatment Group			Comparison of Treatment Groups			
		Carvedilol 12.5mg	Carvedilol 25mg	Overall	Median Difference	95% C.I.		P-value
						Lower	Upper	
Mean Systolic BP (mmHg) Sitting	Median	-13	-20	-17	5	0	11	0.07
	Min							
	Max							
	N	93	90	183				
Mean Diastolic BP (mmHg) Sitting	Median	-10	-12	-11	1	-2	4	0.41
	Min							
	Max							
	N	93	90	183				
Systolic BP (mmHg) Immediate Standing	Median	-12	-20	-16	5	-1	10	0.15
	Min							
	Max							
	N	93	89	182				
Diastolic BP (mmHg) Immediate Standing	Median	-10	-10	-10	0	-3	4	0.86
	Min							
	Max							
	N	93	89	182				
Postural Drop in Systolic BP (mmHg)	Median	0	1	1	-1	-3	1	0.53
	Min							
	Max							
	N	93	89	182				
Postural Drop in Diastolic BP (mmHg)	Median	0	1	0	-1	-2	1	0.27
	Min							
	Max							
	N	93	89	182				
Pulse Rate (bpm) Sitting	Median	-5	-6	-6	0	-2	3	0.68
	Min							
	Max							
	N	93	90	183				
Pulse Rate (bpm) Immediate Standing	Median	-7	-7	-7	0	-2	2	0.87
	Min							
	Max							
	N	92	88	180				
Weight (kg)	Median	0	0	0	0	-1	3	0.17
	Min							
	Max							
	N	92	88	180				

Patient 244 had a sudden drop in WBC from 6.59 to $2.18 \times 10^9/L$ between week 2 and week 8 of treatment. This was repeated at week 12 and returned to normal. The patient had no symptoms and the investigator thought that this spurious result was a lab error or maybe due to an old sample (5 days).

Patient 249 was diagnosed as diabetic after the preliminary examination and treated with an oral hypoglycaemic agent. Relationship: not related.

Patient 304 was also diagnosed as mildly diabetic (glucose = 16.3mmol/L) following the preliminary examination and a diet was recommended.

Patient 305 had elevated renal function tests throughout the study. Relationship: not related.

Many patients also had clinically significant abnormal lipids (total cholesterol and triglycerides) which were only analysed at the preliminary examination visit.

There was a relatively high incidence of elevated chloride values and low bicarbonate values both pre- and post-treatment in both dose groups, although these were not statistically or clinically significant.

8. DISCUSSION

The concept of reducing high blood pressure in elderly patients in order to reduce cardiovascular morbidity and non-fatal cerebrovascular incidents is well documented. This study was designed to compare two dosage regimes of carvedilol in elderly hypertensive patients with special reference to any safety issues that may occur.

This report presents the results of 262 patients who were recruited to take part in the study. 30 patients were not randomised, 114 patients received carvedilol 12.5mg as a starting dose and 118 patients received carvedilol 25mg as a starting dose. The response rates at week 4 for carvedilol 12.5mg and 25mg starting doses were 59% and 69% respectively and at week 12 were 68% and 70% respectively. Results were similar from the per protocol analysis and the differences detected were not statistically significant.

Figures 15 and 16 illustrate the falls in median sitting and standing blood pressure in each group over time. Figures 17 and 18 show median postural blood pressure drop during the study. These figures highlight the lack of statistically significant differences between the two groups. However, the 95% confidence intervals suggest

that carvedilol 25mg may be more effective at four weeks compared to carvedilol 12.5mg although at twelve weeks the confidence intervals could favour either treatment.

There was a significant difference between the two groups in standing systolic blood pressure at week 4, carvedilol 25mg producing a median drop 16mmHg, carvedilol 12.5mg producing a median drop of 9mmHg. Sitting systolic blood pressure showed marginal significance ($p=0.07$). These results again suggest that carvedilol 25mg may be more effective at four weeks compared to carvedilol 12.5mg.

Figures 19 and 20 show median falls in pulse rate during the study which seem to be reduced to a similar extent in each treatment group. Finally Figure 21 illustrates the median body weight during the study with minimal changes in each group although patients randomised to carvedilol 12.5mg tended to be heavier than those randomised to carvedilol 25mg.

Approximately 40% of patients receiving carvedilol 12.5mg compared to 30% of patients receiving carvedilol 25mg, had their dose doubled at week 4. This result was not statistically significant but it does suggest that, clinically, more patients will require a titration of their dose if they are started on carvedilol 12.5mg compared to carvedilol 25mg. Similar numbers of patients were titrated correctly at week 4 which rules out the possibility of any bias within treatment groups.

Safety is a very important issue in this population of patients and adverse events are discussed in detail in the main body of this report. All patients included in the study have been considered in this report. In total, 55% of patients designated to receive carvedilol 12.5mg reported a total of 121 adverse events, and 60% of patients designated to receive carvedilol 25mg reported a total of 145 adverse events. The safety section has been split into two sections a) those adverse events relating to dizziness and/or postural hypotension which is what one might expect from an anti-hypertensive agent with alpha blocking activity, and b) any others. Statistical significance tests were performed only on those adverse events relating to dizziness and/or postural hypotension and no significant difference between the two treatment groups was observed.

However, the difference in the incidence of these adverse events between the two groups may have clinical relevance as it appears that almost one and a half times the number of events were reported by patients randomised to carvedilol 25mg (16%) compared to patients randomised to carvedilol 12.5mg (11%). In many cases, these adverse events were recorded after the first dose or any increase in dose and seem to be related to the first dose. This is true in both treatment groups.

Therefore this trend suggests that a starting dose of carvedilol 12.5mg should reduce the incidence of adverse events related to dizziness and/or postural hypotension to a minimum. Increasing the dose to 25mg increases the incidence of adverse events. However this incidence is no higher than that reported by patients who were initially given carvedilol 25mg. These results are illustrative of more potent alpha blocking activity at higher doses of carvedilol.

The most commonly reported "other" adverse event was fatigue which was suffered by a total of 28 patients. Three patients experienced a cerebrovascular incident, one just two days following the first dose of carvedilol 25mg (relationship: not known), one patient suffered a fatal stroke approximately 9 months after the trial period (not related), and the other patient suffered a mild stroke 16 days after he defaulted from the study (not related). Overall the occurrence of these adverse events appear to be what one might expect from this population of patients.

The majority of patients had abnormal laboratory results during the course of the study although not all of these were clinically significant. The main abnormality which was highlighted at the preliminary examination was a high glucose level usually treated by diet or oral hypoglycaemic agents.

The differences between treatment groups in median changes over 12 weeks with respect to creatinine and urea were statistically significant. These results do not suggest clinical significance. A marginally statistically significant difference in the median changes from baseline in white cell count was also observed although this is not clinically relevant.

In conclusion these results suggest that elderly hypertensive patients should start on 12.5mg once daily. This may be an effective dose in some patients and it is likely that individual patients could be maintained on this dosage. However, dose titration to 25mg, and perhaps 50mg, may be necessary to control the blood pressure in the long term, although it is important to note that exacerbation of some side effects may occur on an increased dose.

9. REFERENCES

1. Heber ME et al. (1987) Carvedilol for systemic hypertension. *Am. J. Cardiol.*, **59**, 400-405.
2. European Working Party on High Blood Pressure in the Elderly Trial, *Lancet* 1985; **1**: 1349.

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**KREDFX (CARVEDILOL - SKF 105517)
NEW DRUG APPLICATION**

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**ITEM 8
CLINICAL DATA SECTION**

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Protocol: INT-CAR-07	Report: MP/0021/SKF-105517	000002
Comparison of carvedilol with atenolol in the treatment of mild to moderate essential hypertension		

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Protocol INT-CAR-07

This was a multicenter, multinational trial conducted in Europe. The purpose was to compare carvedilol and atenolol. The study was blinded with random allocation. An up-titration after 4 weeks was outcome dependent. The primary endpoint was the proportion of responders. Blood pressure data as means in several tables.

There was no evidence of difference between treatments, nor in any of the subgroup analyses performed after the fact.

INT-CAR-07								
n	single blind	n	double blind	n	double blind	n	% response	Δ DBP mm Hg (mean)
	Placebo	161	Carvedilol 25 mg UID	110	carvedilol 25 mg UID	161	35%	- 15
				51	carvedilol 50 mg UID			
		164	Atenolol 50mg UID	114	Atenolol 50mg UID	163	43%	-14
				50	Atenolol 100 mg UID			
	3-6 weeks	325	4 weeks	325	4 weeks	324		

CLINICAL REPORT SUMMARY

PROTOCOL INT-CAR-07: COMPARISON OF CARVEDILOL TO ATENOLOL IN THE TREATMENT OF MILD TO MODERATE ESSENTIAL HYPERTENSION

Investigators: This study was conducted by a total of 38 investigators in seven countries: Belgium, Germany, Italy, The Netherlands, Portugal, Spain, and the United Kingdom.

Objective: This study was designed to compare the safety and antihypertensive efficacy of carvedilol 25 to 50 mg once daily with atenolol 50 to 100 mg once daily in patients with mild to moderate essential hypertension over a period of eight weeks.

Study Design: Patients, at least 18 years of age, with a diagnosis of mild to moderate essential hypertension, defined as a mean sitting diastolic blood pressure of 95-115 mm Hg (disappearance of Korotkoff sound-Phase V) entered a single-blind placebo run-in phase to confirm diagnosis and establish baseline blood pressure. At each visit, blood pressure and heart rate were measured three times, at approximately one-minute intervals, in the sitting position. At the final placebo run-in phase visit and at each visit of the treatment phase, single measurements of immediate standing blood pressure and heart rate were also assessed. Patients qualified to enter the Treatment Phase when the three measurements of sitting diastolic blood pressure at each of 3 consecutive weekly visits satisfied the following conditions: 1) the mean of all 9 measurements was 95-115 mm Hg, 2) the range of the individual measurements was not more than 30 mm Hg, and 3) there was an absence of a placebo response, defined as a continuous fall at each visit, with the decline over the last two visits being more than 4 mm Hg. Patients were then randomized in the treatment phase in a double-blind fashion to receive either 25 mg carvedilol once daily or 50 mg atenolol once daily. Carvedilol therapy was initiated with 12.5 mg once daily for two days. Visits were scheduled after 2, 4 and 8 weeks of treatment, at the time of day corresponding to 22-26 hours after the previous day's dosing. After four weeks of treatment, the dosage of study medication was doubled if adequate response to treatment (mean sitting diastolic blood pressure $\leq$ 90 mm Hg or decreased from the baseline value by at least 10 mm Hg) was not achieved. Baseline vital sign values were the means at the final placebo baseline period visit, just prior to the first dosing with active study medication.

The primary index of efficacy was the reduction of mean sitting diastolic blood pressure to 90 mm Hg or less and/or by at least 10 mm Hg from baseline. Secondary efficacy parameters were mean change in blood pressure and heart rate from baseline and achievement of a normalized blood pressure (mean sitting diastolic blood pressure $\leq$ 90 mm Hg). Safety was evaluated by monitoring for adverse events and by comparing clinical laboratory test results obtained at baseline with those obtained during the treatment period.

Demography: A total of 325 patients (176 males and 149 females; 316 Caucasian and 9 other) received coded medication. The average age of the patients in the study was 53.5 years (range:

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Additionally, if a patient required concomitant treatment with any antihypertensive medication, had a known hypersensitivity to carvedilol or atenolol, was known to be a non-responder to or intolerant of carvedilol or atenolol at the dosage levels used in this study, had used an investigational drug within 30 days of entry into this study or 5 half-lives of the investigational drug (the longer period applied) or, in the investigator's opinion, was unsuitable to participate in the study for any other reason, then he/she was to be excluded from the study.

2.2 Study Design

The study was conducted in two phases. There was a single-blind Placebo Baseline Period of three to six weeks. The double-blind Treatment Phase then followed, during which patients were randomized to receive either carvedilol or atenolol for a period of eight weeks. Visits were scheduled after two, four and eight weeks of treatment.

2.3 Materials and Dosage Schedule

A complete description of medication supplies used in this study can be found in Appendix 25. Patients were randomized in blocks of two, within each country (see Appendix 26). Each center within a country was initially allocated a sequentially numbered set of an even number of randomized supplies (e.g., supplies 001 to 020). Some supplies were subsequently redistributed among centers in a given country, in cases of under- or extra-enrollment.

Supplies were dispensed at each visit. During the placebo baseline period, all patients took two tablets once daily, consisting of one placebo matching carvedilol 12.5 mg and one placebo matching atenolol 50 mg.

During the treatment phase patients randomized to carvedilol took one 12.5 mg tablet for two days, then one 25 mg tablet until the Week 4 visit (12.5 mg and 25 mg carvedilol tablets, both active and placebo, were of identical appearance). If an upward titration of the dosage was warranted at the Week 4 visit, patients took two 25 mg carvedilol tablets once daily; if the dose was not increased at the Week 4 visit, patients continued with one 25 mg carvedilol tablet once daily. Each carvedilol regimen was provided with placebo matching 50 mg atenolol which was also doubled, if warranted, at the Week 4 visit. Patients randomized to atenolol took one atenolol 50 mg tablet until the Week 4 visit. If an upward titration of the dosage was warranted at the Week 4 visit, patients took two 50 mg tablets once daily; if the dose was not titrated at the Week 4 visit, patients continued with one tablet once daily. Patients randomized to the atenolol treatment group also received an equivalent number of placebo tablets matching carvedilol once daily. In each treatment group, therefore, patients took two tablets once daily prior to a possible upward titration, and four tablets once daily, if the titration was implemented.

Table 3
Summary of Baseline Characteristics

	Intent-to-Treat Sample		Per-Protocol Sample	
	Carvedilol (n=161)	Atenolol (n=164)	Carvedilol (n=150)	Atenolol (n=148)
Number (%) of Patient				
Age (years):				
18-40	15 (9%)	22 (13%)	15 (10%)	20 (14%)
41-64	122 (76%)	120 (73%)	113 (75%)	105 (72%)
≥ 65	24 (15%)	22 (13%)	22 (15%)	21 (14%)
Gender:				
Female	76 (47%)	73 (45%)	70 (47%)	67 (46%)
Male	85 (53%)	91 (55%)	80 (53%)	79 (54%)
Race:				
Caucasian	157 (98%)	159 (97%)	147 (98%)	142 (97%)
Other	4 (2%)	5 (3%)	3 (2%)	4 (3%)
MSDBP* (mm Hg):				
< 95	3 (2%)	1 (1%)	0 (0%)	0 (0%)
95 - 105	119 (74%)	115 (70%)	114 (76%)	104 (71%)
105 - 115	39 (24%)	48 (29%)	36 (24%)	42 (29%)
Prior Antihypertensive Treatment:				
Yes	94 (58%)	107 (65%)	88 (59%)	96 (66%)
No	67 (42%)	57 (35%)	62 (41%)	50 (34%)
Mean Value				
Age (years)	53.9	53.1	53.7	52.9
Weight (kg)	76.0	77.0	75.7	76.5
MSDBP* (mm Hg)	103	104	104	104
Duration of Hypertension (months)	55.3	51.0	56.0	50.8

* At the final baseline period visit

Reference Documentation: Tables 8.2 - 8.5.2.

The distribution of patients according to type of pre-trial antihypertensive medication(s) used by 201 of the 325 patients in the intent-to-treat sample are detailed in Table 4. With the exception of one patient in each treatment group, all patients who had been previously treated with antihypertensive medication(s) were reported as not having been adequately controlled by such treatment.

Table 6
Summary of Efficacy Analysis Results

	Intent-to-Treat Analysis			Per-Protocol Analysis		
	Carvedilol (n=161)	Atenolol (n=163)	p-value ^a	Carvedilol (n=150)	Atenolol (n=148)	p-value ^a
Mean Duration of Treatment (Days)	58	55		52	52	
Mean Sitting Systolic BP (mm Hg):						
Baseline	163	167	0.30	165	167	0.36
Endpoint	148	148		147	150	
Change from Baseline	-19 .	-17 .	0.23	-18 .	-17 .	0.61
Mean Sitting Diastolic BP (mm Hg):						
Baseline	104	104	0.80	104	104	0.98
Endpoint	89	89		89	90	
Change from Baseline	-15 .	-14 .	0.39	-14 .	-14 .	0.81
Mean Sitting Heart Rate (bpm):						
Baseline	76	76	0.68	76	76	0.63
Endpoint	70	68		70	68	
Change from Baseline	-6 .	-8 .	0.13	-6 .	-8 .	0.14
Endpoint Response Rates:						
MSDBP $\leq$ 90 mm Hg	66%	63%	0.49	60%	61%	0.91
MSDBP $\leq$ 90 or $\downarrow$ $\geq$ 10 mm Hg	80%	82%	0.57	75%	82%	0.21
Non-responders at Week 4 (thus requiring dose titration)	34%	33%	1.00	33%	33%	1.00
Response Rates After Titration:	(n=51)	(n=51)		(n=39)	(n=39)	
MSDBP $\leq$ 90 mm Hg	35%	43%	0.54	26%	42%	0.15
MSDBP $\leq$ 90 or $\downarrow$ $\geq$ 10 mm Hg	61%	77%	0.14	61%	71%	0.10

Reference Documentation: Tables S.7, S.16.1, 3.16.2, and S.19

^aBetween group comparisons.

. Statistically significant reduction from baseline ($p < 0.05$).

Primary Efficacy Parameter

Response was defined as achieving a normalized MSDBP ($\leq$ 90 mm Hg) and/or demonstrating a reduction from baseline in MSDBP by at least 10 mm Hg. Response rates in the carvedilol and atenolol treatment groups were 75% and 82%, respectively, in the per-protocol analysis of efficacy at endpoint. The difference in response between the two regimens (compared at a power of 0.80 to detect a difference of 15%) was not statistically significant. In the per-protocol analysis at endpoint 74% of the responders in the carvedilol group and 71% of the responders in the atenolol group received the once-daily dosage regimen of 25 mg carvedilol or 50 mg atenolol.

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normal being 24 U/L) after 58 days of treatment with carvedilol. This event was not considered to be related to study treatment, and the ALAT level returned to normal (14 U/L) 14 days after the study stop date. Finally, hyperglycemia of mild severity and considered by the investigator to be related to study treatment was reported for Patient 8006. This patient's fasting serum glucose level rose from a baseline of 5.9 mmol/L to 6.5 mmol/L after 15 days of treatment with carvedilol. After 58 days of treatment, the fasting serum glucose returned to baseline (5.57 mmol/L).

5.0 DISCUSSION AND CONCLUSIONS

The results of this study demonstrate that carvedilol (25 mg to 50 mg once daily) is as effective as atenolol (50 to 100 mg once daily) in the control of mild to moderate essential hypertension. Both drugs significantly lowered blood pressure at the endpoint of treatment as compared to baseline. There were no statistically or clinically significant differences between the treatment groups in blood pressure response, either at week 4 of treatment (before the titration step) or at endpoint.

For the primary efficacy parameter, data were included from 296 patients in the per-protocol and 324 in the intent to treat analyses. The primary efficacy index (or "response"), defined as a reduction in MSDBP to 90 mmHg or less, or a reduction from baseline of at least 10 mm Hg, was met in the per-protocol analysis by 75% and 82% of the carvedilol and atenolol treatment groups, respectively. More than two-thirds of these responders to treatment at endpoint (74% in the carvedilol group; 71% in the atenolol group) were treated with 25 mg carvedilol once daily or 50 mg atenolol once daily.

A MSDBP of 90 mm Hg or less was achieved at endpoint in 60% of the carvedilol patients in the per protocol analysis, as compared with 61% of patients in the atenolol group. Of these patients achieving a "normalized" MSDBP, 87% in the carvedilol group and 80% in the atenolol group received the once-daily dosage regimen of 25 mg carvedilol or 50 mg atenolol, respectively.

Among the patients included in the per-protocol analysis, one-third in each treatment group were considered non-responders at the Week 4 treatment visit and had their doses doubled. Of these, 51% of those who received carvedilol and 71% of those who received atenolol were classified as responders after four additional weeks of treatment at the higher dosage level. A sitting diastolic blood pressure of 90 mmHg or less was achieved by 26% of the patients titrated to 50 mg carvedilol, and 42% of the patients titrated to 100 mg atenolol.

Multiple subgroup analyses of response were made. No significant differences in response rates were observed within or between treatment groups for the various subgroups tested, including those within the categories of age, gender, baseline and severity of hypertension. It is noteworthy that elderly patients did not appear to have different dosage requirements in either treatment group.



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Protocol: INT-CAR-08

Report: MP/0020/SKF-105517

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Comparison of carvedilol with acebutolol in the treatment of mild to moderate essential hypertension

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Protocol INT-CAR-08

This trial involved 13 centers in France. The purpose was to compare carvedilol and acebutolol. The study was blinded with random allocation of subjects in each group. The up-titration after week two was, however, result driven. There was no concurrent placebo control. The primary endpoint was, as in most of the European studies, the proportion of patients 'normalized' in each group. Mean blood pressures in each group are also presented in the tables.

The trial is remarkable in that practically every patient accounted for completed the study. The dropout during the baseline is not ascribed to 'placebo response' but to 'failure to meet entry criteria'. Of the 207 patients who completed the study, 148 met all the provisions in the protocol and provided data for the 'per protocol analysis'.

There is no evidence of significant differences in treatment. Subgroup analyses by sex and age showed no differences.

INT-CAR-08								
n	single blind	n	double blind	n	double blind	n	% response	Δ DBP mm Hg (mean)
217	Placebo	100	Carvedilol 25 mg UID	65	carvedilol 25 mg UID	98	67%	- 13
				35	carvedilol 50 mg UID			
		109	Acebutolol 200 mg BID	86	Acebutolol 200 mg BID	109	75%	
				23	Acebutolol 400 mg BID			
217	2-5 weeks	209	2 weeks	209	6 weeks	207		

CLINICAL REPORT SUMMARY

PROTOCOL INT-CAR-08: COMPARISON OF CARVEDILOL TO ACEBUTOLOL IN THE TREATMENT OF MILD TO MODERATE BENIGN ESSENTIAL HYPERTENSION

Investigators: This study was conducted by a total of 13 centers in France.

Objective: This study was designed to compare the safety and antihypertensive efficacy of carvedilol 25 to 50 mg once daily with acebutolol 200 to 400 mg twice daily in patients with mild to moderate essential hypertension over a period of eight weeks.

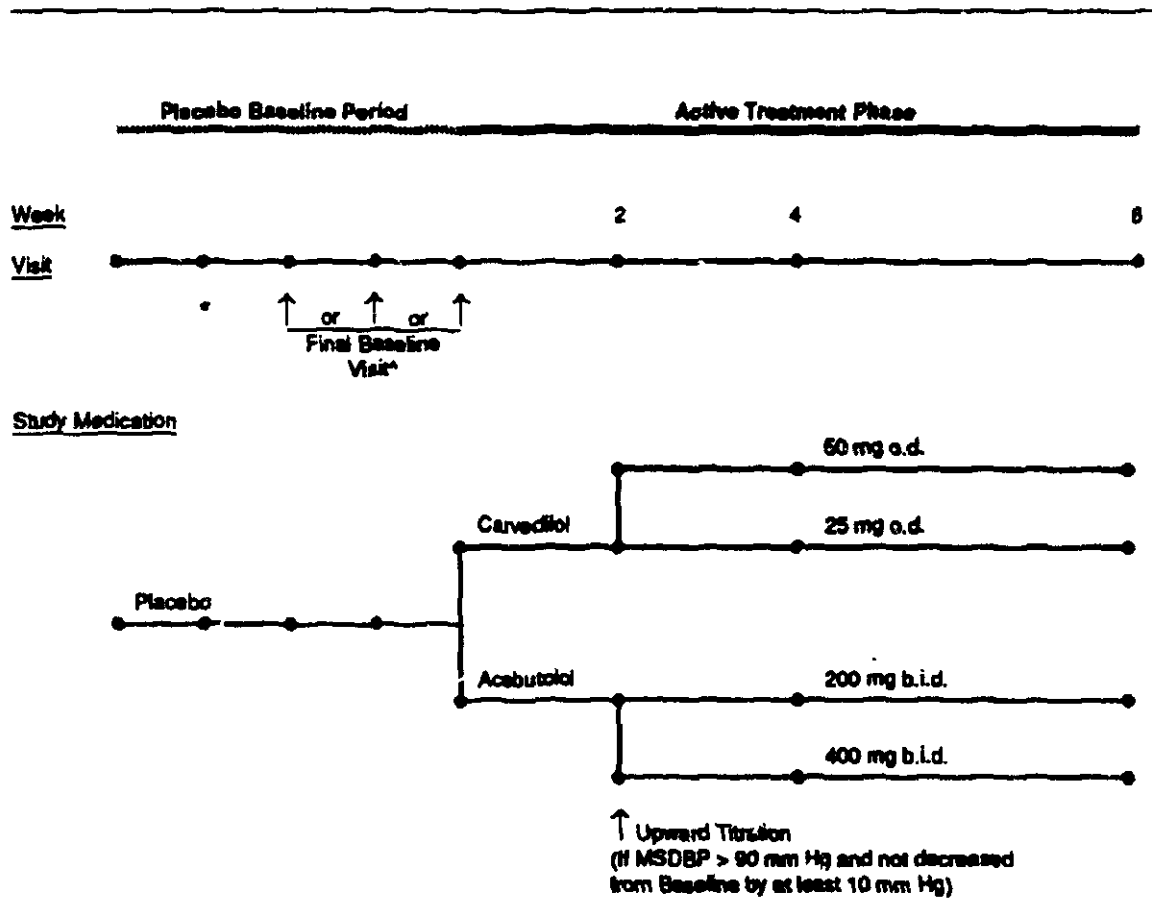
Study Design: Patients, 18 to 70 years of age, with a diagnosis of mild to moderate essential hypertension, defined as a mean supine diastolic blood pressure of 95-115 mm Hg (disappearance of Korotkoff sound-Phase V) entered a single-blind placebo run-in phase to confirm diagnosis and establish baseline blood pressure. At each visit, blood pressure and heart rate were measured three times in the supine position and twice in the standing position. Patients qualified to enter the Treatment Phase when the three measurements of supine diastolic blood pressure at each of two consecutive weekly visits satisfied the following conditions: 1) the mean of the three measurements was 95-115 mm Hg, 2) the range of all six measurements was not more than 30 mm Hg, and 3) there was an absence of a placebo response, defined as a continuous fall in mean supine diastolic pressure at each visit, with the decline over the last two visits being more than 5 mm Hg. Patients were then randomized in the treatment phase in a double-blind fashion to receive either 25 mg carvedilol once daily or 200 mg acebutolol twice daily. Carvedilol therapy was initiated with 12.5 mg for two days. Morning visits were scheduled after 2, 4 and 8 weeks of treatment, at the time of day corresponding to 20 to 24 hours after the previous day's dosing with once-daily study medication, and 10-14 hours after the previous day's dosing with twice-daily medication. After two weeks of treatment, the dosage of study medication was doubled if adequate response to treatment (supine diastolic blood pressure $\leq$ 90 mm Hg and/or decreased from the baseline value by at least 10 mm Hg) was not achieved. Baseline vital signs were the mean values at the final placebo baseline period visit, just prior to the first dosing with active study medication. The primary index of efficacy was the reduction of mean supine diastolic blood pressure to 90 mm Hg or less and/or by at least 10 mm Hg from baseline. Secondary efficacy parameters were mean blood pressure and heart rate values, mean change in these parameters from baseline and achievement of a normalized blood pressure (mean supine diastolic blood pressure $\leq$ 90 mm Hg). Safety was evaluated by monitoring for adverse events and by comparing clinical laboratory test results obtained at baseline with those obtained during the treatment period.

Demography: A total of 217 patients (101 males and 116 females; 211 Caucasian and 6 other) received coded medication. The average age of the patients in the study was 53 years (range: 22 to 76 years) and the average body weight was 72.3 kg (range: 43 to 130

2.2 Study Design

The study was conducted in two phases (See Figure 1). There was a single-blind Placebo Baseline Period of two to five weeks, for patients not previously treated for hypertension, or of four to seven weeks, for patients who received pre-trial antihypertensive medication. The double-blind Treatment Phase then followed, during which patients were randomized to receive either carvedilol or acebutolol for a period of eight weeks. Visits were scheduled after two, four and eight weeks of active treatment.

Figure 1: Study Design



* The first baseline visit was scheduled after 3 weeks in patients previously treated with antihypertensive medication, for a total baseline period of 4 to 7 weeks duration, or after 1 week in patients who were not previously treated, for a total baseline period of 2 to 5 weeks duration.

* One or two additional baseline visits could have been scheduled if the blood pressure criteria for entering the active treatment phase were not satisfied at the second or third baseline visit.

Of the patients whose dosage of study medication was increased, the percentage whose MSDBP was normalized at endpoint.

Mean change and mean percent change (from baseline) in vital signs at endpoint.

Subgroup Analyses

While not specifically addressed in the protocol, subgroups of patients in the per-protocol and intent-to-treat sample were compared, both within a given treatment and between the two treatments, with regard to the percentage of patients achieving the primary index of response and the percentage of patients achieving a normalized (≤ 90 mm Hg) MSDBP at endpoint. The subgroupings were based on the following categories: gender, age (≤ 64 , ≥ 65 years old), severity of hypertension (baseline MSDBP 95 to 105 mm Hg, baseline MSDBP 106 to 115 mm Hg), duration of hypertensive condition (≤ 24 months, > 24 months), and prior use of antihypertensive pharmacotherapy (yes, no).

2.8.2 Planned Safety Evaluation

For all patients receiving at least one dose of active treatment, the two treatment groups were compared with regard to the following parameters:

The percentage of patients experiencing one or more adverse event(s) during active treatment, regardless of the investigator-determined relationship to study medication.

The percentage of patients experiencing specific adverse events of clinical interest (events which occurred during active treatment in $\geq 1\%$ of the patients in either treatment group).

The percentage of patients discontinued from the study because of one or more adverse event(s) considered possibly or probably related to active study medication.

Mean change from baseline in select laboratory parameters: liver function tests (ALAT, ASAT, alkaline phosphatase, total bilirubin), renal function tests (creatinine, urea, BUN), uric acid, fasting serum glucose and fasting serum lipids.

Within each treatment group, descriptive statistics for laboratory parameters assessed at baseline, at treatment phase Week 2, at treatment phase Week 8 and at endpoint (if not Week 8) were calculated.

Table 3
Summary of Baseline Characteristics

Number (%) of Patient or Mean Values and Range	Intent-to-Treat Sample		Per-Protocol Sample	
	Carvedilol (n=105)	Acebutolol (n=112)	Carvedilol (n=71)	Acebutolol (n=77)
Age (years):				
18-40	12 (11%)	15 (13%)	6 (9%)	12 (16%)
41-64	80 (76%)	79 (71%)	56 (77%)	51 (66%)
≥ 65	13 (12%)	18 (16%)	10 (14%)	14 (18%)
mean	53	54	54	54
Gender:				
Female	56 (53%)	60 (54%)	44 (62%)	41 (53%)
Male	49 (47%)	52 (46%)	27 (38%)	36 (47%)
Race:				
Caucasian	103 (98%)	108 (96%)	70 (99%)	75 (97%)
Other	2 (2%)	4 (4%)	1 (1%)	2 (3%)
MSDBP* (mm Hg):				
< 95	0 (0%)	1 (1%)	0 (0%)	1 (1%)
95 - 105	78 (72%)	81 (72%)	53 (75%)	57 (74%)
106 - 115	29 (28%)	30 (27%)	18 (25%)	19 (25%)
mean [range]	102 [90-113]	102 [94-114]	102 [95-113]	102 [94-114]
MSSBP* (mm Hg):				
mean [range]	167 [129-195]	168 [127-202]	169 [141-195]	169 [127-202]
Mean Duration of Hyper- tension (months):				
	34	47	31	46
Prior Antihypertensive Treatment:				
Yes	49 (47%)	50 (45%)	28 (39%)	33 (43%)
No	56 (53%)	62 (55%)	43 (61%)	44 (57%)
Smoking habits:				
Non-Smoker	79 (75%)	91 (81%)	52 (73%)	65 (84%)
Light Smoker	12 (11%)	14 (13%)	7 (10%)	10 (13%)
Heavy Smoker	14 (13%)	7 (6%)	12 (17%)	2 (3%)
Mean Weight (kg)	71.5	73.2	69.2	73.9

* At the final baseline period visit

Reference Documentation: Tables S.2 - S.5.2.

Table 6
Summary of Efficacy Analysis Results

	Intent-to-Treat Analysis			Per-Protocol Analysis		
	Carvedilol (n=104)	Acebutolol (n=111)	p-value ^a	Carvedilol (n=71)	Acebutolol (n=77)	p-value ^a
Mean Duration of Treatment (Days)	57	59		42	47	
Mean Supine Systolic BP (mm Hg):						
Baseline	167	168	0.81	169	168	0.92
Endpoint	146	147		149	148	
Change from Baseline	-20 .	-22 .	0.75	-19 .	-20 .	0.91
Mean Supine Diastolic BP (mm Hg):						
Baseline	102	102	0.44	102	102	0.62
Endpoint	89	87		90	88	
Change from Baseline	-13 .	-15 .	0.18	-12 .	-14 .	0.18
Mean Supine Heart Rate (bpm):						
Baseline	79	78	0.21	79	78	0.59
Endpoint	67	67		68	67	
Change from Baseline	-12 .	-11 .	0.83	-12	-11 .	0.97
Mean Standing Systolic BP (mm Hg):						
Baseline	167	168	0.78	168	168	0.87
Endpoint	146	146		147	147	
Change from Baseline	-21 .	-22 .	0.77	-22 .	-21 .	0.60
Mean Standing Diastolic BP (mm Hg):						
Baseline	103	103	0.31	102	102	0.82
Endpoint	90	89		90	89	
Change from Baseline	-13 .	-15 .	0.13	-12 .	-14 .	0.26
Mean Standing Heart Rate (bpm):						
Baseline	83	82	0.16	82	82	0.81
Endpoint	70	70		70	70	
Change from Baseline	-13 .	-12 .	0.48	-12 .	-13 .	0.78
Endpoint Response Rates:						
MSDBP $\leq$ 90 mm Hg	67%	75%	0.23	54%	65%	0.18
MSDBP $\leq$ 90 and/or $\downarrow \geq$ 10 mm Hg	78%	83%	0.39	68%	73%	0.48
Non-responders at Week 2 (thus requiring dose titration-)	(n=97) 45%	(n=104) 34%	0.11	(n=67) 46%	(n=76) 34%	0.17
Response Rates After Titration [†] :						
MSDBP $\leq$ 90 mm Hg	(n=31) 32%	(n=21) 38%	0.77	(n=13) 23%	(n=12) 42%	0.41
MSDBP $\leq$ 90 and/or $\downarrow \geq$ 10 mm Hg	58%	57%	1.00	46%	50%	1.00

Reference Documentation: Tables S.7, S.16.1, S.16.2, and S.19

^aBetween group comparisons.

[†]Statistically significant reduction from baseline ($p < 0.01$)

-Regardless of whether titration was implemented.

[†]Of the 15 patients in the carvedilol group and 23 patients in the acebutolol group whose dosage was doubled, 31 and 21 patients, respectively, completed a Week 8 visit at this dosage level and were included in the intent-to-treat analysis of response after titration. Only 13 and 12 of these patients, respectively, were available for inclusion in the per-protocol analysis at the Week 8 visit.

possibly related to study medication. All parameters returned to normal nine days after the last dose of study medication, which was given for a total of 20 days.

5.0 DISCUSSION AND CONCLUSIONS

The results of this study demonstrate that carvedilol (25 mg to 50 mg once daily) is as effective as acebutolol (200 to 400 mg twice daily) in the control of mild to moderate essential hypertension. Both drugs significantly lowered blood pressure at the endpoint of treatment as compared to baseline. There were no statistically or clinically significant differences between the treatment groups in blood pressure response, either at week 2 of treatment (before the titration step) or at endpoint.

For the primary efficacy parameter, data were included from 148 patients in the per-protocol and 215 in the intent to treat analyses. The primary index of efficacy or "response", defined as a reduction at endpoint in MSDBP to 90 mm Hg or less and/or a reduction in MSDBP from baseline of at least 10 mm Hg, was met in the per-protocol analysis by 66% and 73%, and in the intent-to-treat analysis by 78% and 83% of the carvedilol and acebutolol treatment groups, respectively. More than two-thirds of the responders at endpoint in each treatment group were treated with 25 mg carvedilol once daily or 200 mg acebutolol twice daily, respectively.

A MSDBP of 90 mm Hg or less was achieved at endpoint in 54% of the carvedilol patients in the per protocol analysis, as compared with 65% of patients in the acebutolol group. In the intent-to-treat analysis, the incidence of this "normalization" of diastolic blood pressure was 67% and 75% in the carvedilol and acebutolol groups, respectively. More than 85% of the patients in each treatment group who achieved a MSDBP of 90 mm Hg or less received the initial dosage level of 25 mg carvedilol once daily or 200 mg acebutolol twice daily, respectively.

In the per-protocol analysis, 31 of 67 patients (46%) in the carvedilol group and 27 of 76 patients (34%) in the acebutolol group were considered non-responders at the Week 2 treatment visit. Among these patients whose dosage of study medication was increased and who were included in the per-protocol analysis at the Week 8 visit, six of 13 patients (46%) in the carvedilol group and six of 12 patients (50%) in the acebutolol group were responders after six additional weeks of treatment at the higher dosage level. A normalized MSDBP was achieved by three patients (23%) treated with 50 mg carvedilol once daily and by five patients (42%) treated with 400 mg acebutolol twice daily.

Multiple subgroup analyses of response were made. No significant differences in response rates were observed within or between treatment groups for the various subgroups tested, including those within the categories of age, gender, baseline and severity of hypertension.



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A comparison of carvedilol with hydrochlorothiazide in the treatment of moderate to benign essential benign hypertension	

Protocol INT-CAR-10

In this multicenter trial in UK the primary endpoint was the proportion of patients who achieved a sitting DBP $\leq$ 90 mm Hg. Median values at baselines and the different scheduled visits are also presented. The study was blinded and randomized and had a placebo baseline observation but no concurrent placebo arm in the active treatment phase. The purpose of this study was to compare carvedilol 25 mg once daily with nifedipine 20 mg bid. After 2 weeks of double blind treatment, patients with an inadequate response could have their dose doubled.

Of 272 patients who entered the trial 171 made it to the end, and of these 138 were eligible by protocol standards. There was no significant difference between the treatments.

INT-CAR-10								
n	single blind	n	double blind	n	double blind	n	% response	Δ DBP mm Hg (median)
272	Placebo	103	Carvedilol 25 mg UID	~80	carvedilol 25 mg UID	86	64%	-16
				~20	carvedilol 50 mg UID			
		102	Nifedipine 20 mg BID	~80	Nifedipine 20 mg BID	85	82%	-16
				~20	Nifedipine 40 mg BID			
272	3-6 weeks	205	2 weeks	189	6 weeks	171		

RESULTS

1. Number of Patients

Two hundred and seventy two patients were recruited to take part in the study. Sixty seven patients were withdrawn before the start of active therapy. The 58 patients who received placebo medication were withdrawn by the investigators for the following reasons: adverse events (7), default (9), non-compliance (2), underlying condition (3) (myaesthemia gravis, carcinoma lung, elevated LFTs), diastolic blood pressure below level for inclusion (25), mean diastolic above 115 mmHg (5), patient taking prohibited medication ('Frumil') (1), domestic or administrative reason (2), withdrawal of consent (1), unknown (CRFs not received) (3).

A total of 32 investigators recruited patients to the study. (Table 1). This report presents data on 205 patients for whom records are available who were randomised to receive either carvedilol or nifedipine in the active treatment phase of the study. The safety section of the report will also consider data on placebo baseline phase patients who dropped out before receiving active medication.

Statistical analyses utilise data from all patients for whom results were available at a given point on an "intention to treat" basis; however "per protocol" analyses exclude data (individual visits or all data for a given patient, as appropriate) for reasons of protocol violation (Table 2).

The Mann Whitney U test was used to compare treatment group medians of efficacy parameters and laboratory values. Chi Squared tests were used to analyse parameters expressed as counts of patients (e.g. numbers of smokers, numbers of patients whose dose was increased, numbers fulfilling the primary efficacy criterion, etc). All changes or differences described as statistically significant in this report are significant at least at the 5 percent level.

Int-Car-10

Recruited - 272 Patients

67 Withdrawn before active treatment

205 Randomized

103 Carvedilol

102 Nifedipine

Week 2

84

95

Total = 189
Intent-to-treat

19-Dose 2X (20%)
[3 T who responded]
[5 not T who should have been]

20-Dose 2X (20%)
[1 T who responded]
[5 not T who should have been]

Total = 168
per protocol

Week 8 Intent-to treat

86 68/86 = 79% response

85 77/85 = 91% response Total = 171

Per Protocol- 72 A. 59/72=82% response
B. 49/72=68% response

66 A. 60/66=91% response Total=138
B. 54/66=82% response

A. = ↓ BP to 90 or ↓ of 10
B. = ↓ BP to 90

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000010

SUMMARY

Results are presented for 205 patients with mild to moderate essential hypertension who were randomised to receive either a once daily dose of carvedilol 25 mg or nifedipine 20 mg bd in a double blind study, following washout of existing antihypertensive medication and a 3-6 week placebo baseline period to confirm diagnosis. Duration of active treatment was 8 weeks and after 2 weeks the dose of either medication could be doubled according to response. The population comprised 63 males and 40 females, median age 59 years, range 30-82 years in the carvedilol group and 55 males and 47 females, median age 59 years, range 26-79 years in the nifedipine group. Losses occurred due to patient withdrawal, and, for "per-protocol" analyses, due to protocol violations, which are discussed in this report. There were no significant differences between the two groups with respect to demographic factors at entry or baseline efficacy assessments with the exception of end of baseline postural change in systolic blood pressure. Baseline sitting blood pressures were 168/102 mmHg for carvedilol and 167.5/102 mmHg for nifedipine and immediate standing blood pressures were 164/102 mmHg and 170/102 mmHg respectively, among 198 patients eligible per protocol analyses. (Korotkoff phase V readings).

There were no statistically significant differences between groups in changes in vital signs during the 2 hours following the first dose of active medication, except for immediate standing heart rate where the median decrease was greater in the carvedilol group. Confidence intervals revealed that this difference (max 3 b/min) was unlikely to be clinically important, however. Effects in the sub-population who were 65 years of age or under showed statistically significant differences between treatments for immediate standing and sitting diastolic blood pressure, with greater falls in the nifedipine group. Again, confidence intervals revealed maximum likely differences of only 5 mmHg. The over 65 years subgroup showed effects during the first 2 hours similar to those observed in the population as a whole. However, a greater median systolic blood pressure postural change occurred in the nifedipine group. The difference between treatments was statistically significant.

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At treatment week 2 there were statistically significant differences between groups for sitting and standing heart rate, together with the respective changes from baseline (the latter were no more than 5 b/min different between groups as indicated by confidence intervals with greater changes occurring with carvedilol) and change from baseline in systolic postural drop (maximum 4 mmHg as indicated by confidence intervals with greater changes occurring for nifedipine). Similar statistically significant differences between treatments occurred at treatment week 8. Additionally, although not achieving statistical significance changes from baseline in standing systolic blood pressure at week 8 were greater in the nifedipine group (confidence intervals: 0,10%). Median decreases of blood pressure from baseline were, at week 2, -14/-13 mmHg sitting for each group, -12.5/-12 mmHg standing for carvedilol and -17/-12 mmHg standing for nifedipine. At week 8 median decreases were -20/-16 mmHg sitting and standing for carvedilol, -21/-16 mmHg sitting and -24/-16 mmHg standing for nifedipine. Median heart rate decreases were -3 b/min sitting and standing for carvedilol, -1 b/min sitting and standing for nifedipine at week 2, while at week 8 decreases were -4 b/min sitting, -5 b/min standing for carvedilol and -1 b/min sitting, -2 b/min standing for nifedipine. At treatment week 2 approximately 20% patients in each treatment group had their dose doubled because of insufficient therapeutic response.

Seventy nine percent of carvedilol patients and 91% of nifedipine patients in the intention to treat analysis had a reduction of sitting diastolic pressure to 90 mmHg or below or a reduction of 10 mmHg or more after 8 weeks' treatment, a result which was statistically significant. The per-protocol analysis did not achieve statistical significance (82% carvedilol, 91% nifedipine) although a possible difference favouring nifedipine was indicated by the confidence intervals (-20%, 2%). Sixty four percent of carvedilol patients and 82% of nifedipine patients in the intention to treat analysis and 68% and 82%, respectively, in the per protocol analysis had diastolic pressures of 90 mmHg or below at week 8.

Both provided evidence of a difference favouring nifedipine ($p=0.01$ and 0.06 , respectively).

There were differences in the safety profiles of the two drugs, with 55 events reported by 31 patients taking carvedilol, 11 of whom were withdrawn and 60 events reported by 35 patients taking nifedipine, 18 of whom were withdrawn. Dizziness, tiredness and headaches were reported with both drugs, the incidence of dizziness being slightly greater with carvedilol. However, flushing occurred in 9 patients on nifedipine and ankle or peripheral oedema in 8 patients on this drug, with no reports of these symptoms in carvedilol patients. Most commonly contributing to patient withdrawal were dizziness and tiredness in carvedilol patients and flushing and oedema in nifedipine patients. One carvedilol patient experienced syncope after 6 weeks in the study but recovered fully within 24 hours of hospital admission. Seven patients were withdrawn from the placebo baseline period because of adverse events. Laboratory studies revealed no consistent trends or differences between treatments with the exception of a tendency of nifedipine patients to show increases in platelet counts and serum alkaline phosphatase with higher week 8 values and a tendency for carvedilol patients to show increases in uric acid while nifedipine patients showed decreases in uric acid. There were several isolated abnormalities in most parameters for individual patients, the more noteworthy of which are detailed in this report.

DISCUSSION

The results of the present study indicate that both carvedilol (25mg to 50mg od) and nifedipine (20mg bd to 40 mg bd) are effective in lowering blood pressure in mild to moderate hypertensive patients over an eight week treatment period from receipt of the first dose of active medication. With the exception of systolic blood pressure in the nifedipine group neither drug produced a noteworthy postural fall in blood pressure. Both drugs also reduced heart rate, but, as would be expected with a β -blocking drug, these were more marked with carvedilol. Figures 1 and 2 illustrate the falls in median values of blood pressure in each group over time, while Figure 3 illustrates the changes in heart rate over time.

The patient numbers used in this study were sufficient to detect statistical significance for very small differences between treatments and, in most analyses, any true differences of clinical importance would also have attained statistical significance.

The purpose of aiming for a population of 200 patients was so that a 15 percent difference between groups for response according to the primary efficacy parameter could be detected at 5% significance and 80% power. A 15% difference between treatments was judged to be clinically important where the response rate for one of the groups was between 80-90%. The primary efficacy parameter is based upon proportions of patients with a given response and is in essence a summary of clinical efficacy parameters. Because of this there is a reduction in sensitivity when compared to analyses of values of efficacy parameters. The primary efficacy parameter utilises data from 138 patients in the per-protocol analysis and 171 in the intention to treat analyses. The primary efficacy parameter shows response rates of 82% and 79% for carvedilol, respectively for the two analyses and 91% for nifedipine for each analysis. This response rate is

marginally lower than has been shown for carvedilol previously (84% in INT CAR07 (UK), 86% in INTCAR11) and somewhat higher than would have been expected for nifedipine. However, it is notable that there was no statistically significant difference between treatments in change from baseline for diastolic blood pressure (Table 17); nor was there a significant difference between treatments for baseline or week 8 blood pressures (Tables 8 and 16).

As with previous studies in which high proportions of patients fulfilled primary efficacy criteria, an alternative criterion (reduction of sitting diastolic pressure to 90mmHg or below, i.e. normotensive levels) was also considered. As expected the proportions of patients fulfilling this criterion were reduced in both treatment groups. Sixty eight percent of carvedilol patients and 82% of nifedipine patients in the per protocol analysis and 64% of carvedilol patients and 82% of nifedipine patients in the intention-to-treat analysis were thereby judged to be responders. These represent differences in response of 14% and 18% respectively (confidence intervals: -28%, 0% per protocol; -31%, -5% intention-to-treat).

Approximately 20% patients in each dosage group required a dosage increase after 2 weeks treatment. For the carvedilol group these proportions did not change when patients were subgrouped by age at entry. In the nifedipine group a smaller proportion of patients over the age of 65 years (16%) required titration compared with 20% in the group overall; however patient numbers in this subgroup were small, such that one additional patient requiring titration would have eliminated this difference.

During the 2 hours following the first dose of active medication the only statistically significant difference between treatments was in change in standing heart rates, with carvedilol, as expected, having more marked, but probably

clinically irrelevant effects. When results were examined by age-subgroup some differences between treatments for blood pressure were observed. Greater falls in sitting and standing diastolic blood pressure occurred in the nifedipine group, although confidence intervals indicate that the magnitude of these differences do not constitute a clinically relevant effect.

In the older age subgroup a statistically significant difference in pre-to-post changes in systolic blood pressure postural drop was found between treatments, greater changes being observed in nifedipine patients, although again confidence intervals indicate that this difference was within 5 percent of pre-dose levels. Median sitting systolic blood pressure was lower on carvedilol than on nifedipine in this sub-group. Median reductions over the two hours were -7/-4 mmHg sitting -10/-4 mmHg standing for carvedilol and -8/-6 mmHg sitting, -10/-8 mmHg standing for nifedipine in the younger age group, compared with -8/-4 mmHg sitting, -4.5/-3.5 mmHg standing for carvedilol and -2.5/-2.0 mmHg sitting, -3.5/-2.0 mmHg standing for nifedipine in the more elderly population. Thus in this study the more elderly population appeared no more susceptible to marked blood pressure reduction following the first dose compared to their younger counterparts. The carvedilol patient who was withdrawn mid-study following syncope was 58 years of age, although 5 other patients aged 56, 67, 69, 76 and 82 years experienced a sensation of faintness or dizziness between 2 days and 4 weeks after the start of active medication which contributed to eventual withdrawal. Five patients on nifedipine complained of giddiness/dizziness or light-headedness which contributed to withdrawal. In two cases (patients aged 61 and 37 years) this was associated with the first dose of active medication and in the other 3 (aged 59, 67 and 69 years) onset of symptoms was between 1 day and 2 weeks after starting active medication.

There were some noteworthy differences in the adverse event profiles of the two drugs, which were typical of their respective drug class. There was a slightly higher incidence of adverse events in patients on nifedipine overall. Flushing and oedema occurred only in this group and contributed to patient withdrawal in a number of cases. However dizziness and tiredness were the events most frequently associated with patient withdrawal in the carvedilol group. Both treatments were associated with reports of headaches, tiredness and dizziness, although the latter was reported with a slightly higher frequency in the carvedilol group. There were a number of reports in each treatment group of symptoms which might be associated with reduced general physical performance (e.g. 2 reports of lethargy, 1 of somnolence, 1 of fatigue and 4 of tiredness in the carvedilol group, and 2 reports of drowsiness, 1 of fatigue and 4 of tiredness in the nifedipine group.) Overall there were higher incidences of adverse events and withdrawals during active treatment with either drug and during placebo baseline therapy than would have been expected from experience with previous studies.

There were many individual patients' laboratory parameters outside normal range but there did not appear to be any significant trends for either treatment other than a tendency of nifedipine patients to show increases in platelet counts and serum alkaline phosphatase with higher 8 week values. These findings are of dubious clinical relevance. However, there was also a tendency for carvedilol patients to show increases in uric acid while nifedipine patients tended to show decreases in this parameter. This contrasts with findings in a previous study (INTCAR11) in which decreases of uric acid in carvedilol patients were observed.

In this study population, both carvedilol and nifedipine were highly effective antihypertensive agents. The per protocol analysis did not show statistically significant differences between treatments in response rate or in changes in blood pressure from baseline, although the intention-to-treat analysis showed a significant difference in response rate favouring nifedipine after 8 weeks' treatment. The number of withdrawals for adverse events indicates that carvedilol at the doses employed may be better tolerated than nifedipine.

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Table 3

DEMOGRAPHIC DATA AT PRELIMINARY EXAMINATION

All randomised patients (N=205)

VARIABLE		CARVEDILOL	NIFEDIPINE	OVERALL	MEDIAN DIFFERENCE	95% C.I.		P-VALUE
						LOWER	UPPER	
DIASTOLIC IMMEDIATE	MEDIAN	104.0	105.0	104.0	-1.0	-2.0	0.0	0.13
	MAX							
	MIN							
	N	102.0	101.0	203.0				
SYSTOLIC IMMEDIATE	MEDIAN	170.0	170.0	170.0	-2.0	-6.0	2.0	0.40
	MAX							
	MIN							
	N	102.0	101.0	203.0				
DIASTOLIC SITTING	MEDIAN	102.0	103.0	102.0	0.0	-1.0	1.0	0.58
	MAX							
	MIN							
	N	103.0	102.0	205.0				
SYSTOLIC SITTING	MEDIAN	170.0	170.0	170.0	-1.0	-6.0	3.0	0.51
	MAX							
	MIN							
	N	103.0	102.0	205.0				
DIASTOLIC POSTURAL	MEDIAN	0.0	1.0	0.0	-1.0	-2.0	0.0	0.10
	MAX							
	MIN							
	N	102.0	101.0	203.0				
SYSTOLIC POSTURAL	MEDIAN	0.0	1.0	0.0	-1.0	-2.0	1.0	0.65
	MAX							
	MIN							
	N	102.0	101.0	203.0				
PULSE IMMEDIATE	MEDIAN	76.0	76.0	76.0	0.0	-2.0	2.0	0.88
	MAX							
	MIN							
	N	98.0	93.0	191.0				
PULSE SITTING	MEDIAN	76.0	76.0	76.0	1.0	-1.0	2.0	0.23
	MAX							
	MIN							
	N	103.0	102.0	205.0				

000051

Table 17

WEEK 8 ELIGIBLE PATIENTS (N=138)
ANALYSIS OF CHANGES WEEK 8 - WEEK 0

VARIABLE		CARVEDILOL	NIFEDIPINE	OVERALL	MEDIAN DIFFERENCE	95% C.I.		P-VALUE
						LOWER	UPPER	
DIASTOLIC IMMEDIATE	MEDIAN	-16.0	-16.0	-16.0	2.0	-2.0	5.0	0.27
	MAX							
	MIN							
	N	71.0	66.0	137.0				
SYSTOLIC IMMEDIATE	MEDIAN	-20.0	-24.0	-20.0	5.0	0.0	10.0	0.06
	MAX							
	MIN							
	N	71.0	65.0	137.0				
DIASTOLIC SITTING	MEDIAN	-16.0	-16.0	-16.0	1.0	-2.0	4.0	0.55
	MAX							
	MIN							
	N	72.0	66.0	138.0				
SYSTOLIC SITTING	MEDIAN	-20.0	-21.0	-20.0	1.0	-3.0	7.0	0.56
	MAX							
	MIN							
	N	72.0	66.0	138.0				
DIASTOLIC POSTURAL	MEDIAN	0.0	0.0	0.0	0.0	-1.0	2.0	0.57
	MAX							
	MIN							
	N	71.0	66.0	137.0				
SYSTOLIC POSTURAL	MEDIAN	0.0	-2.0	-1.0	3.0	1.0	5.0	0.00
	MAX							
	MIN							
	N	71.0	66.0	137.0				
PULSE IMMEDIATE	MEDIAN	-6.0	-2.0	-4.0	-4.0	-6.0	-2.0	0.00
	MAX							
	MIN							
	N	70.0	65.0	135.0				
PULSE SITTING	MEDIAN	-4.0	-1.0	-3.0	-4.0	-6.0	-2.0	0.00
	MAX							
	MIN							
	N	72.0	66.0	138.0				
WEIGHT	MEDIAN	0.0	0.0	0.0	0.0	0.0	1.0	0.04
	MAX							
	MIN							
	N	68.0	66.0	134.0				

000070

Protocol INT-CAR-11

This multicenter study in UK compared carvedilol 25 or 50 mg/day with HCTZ 25 or 50 mg/day. Titration to the higher dose after 4 weeks was result driven.

The study was randomized, double blinded in the active treatment phase, and while it had a single blinded placebo baseline observation, there was no concurrent placebo arm in the active treatment phase. Of 235 patients recruited, 200 continued to the double blind phase; 190 were included in the intent to treat analysis, 179 met all protocol criteria. The study could not find any difference between the two drugs. The data are presented as a median response with confidence limits. The actual analysis was based on a comparison of the proportion of 'responders' in each group.

INT-CAR-11								
n	single blind	n	double blind	n	double blind	n	% response	Δ DBP mm Hg (median)
235	Placebo	100	Carvedilol 25 mg UID	62	carvedilol 25 mg UID	93	85%	- 18
				32	carvedilol 50 mg UID			
		100	HCTZ 25 mg UID	67	HCTZ 25 mg UID	97	88%	-16
				33	HCTZ 50 mg UID			
235	3-6 weeks	200	4 weeks	191	4 weeks	190		

SUMMARY

Results are presented for 200 patients with mild to moderate essential hypertension who were randomised to receive either carvedilol 25 mg or hydrochlorothiazide 25 mg in a double blind study, following washout of existing antihypertensive medication and a 3-6 week placebo baseline period to confirm diagnosis. Duration of active treatment was 8 weeks and after 4 weeks the dose of either medication could be doubled according to response. The population comprised 49 males and 51 females, median age 59 years, range 34-88 years in the carvedilol group and 56 males and 44 females, median age 59 years, range 27-83 years in the hydrochlorothiazide group. Losses occurred due to patient withdrawal, and for "per-protocol" analyses, due to protocol violations which are discussed in this report. There were no significant differences between the two groups with respect to demographic factors at entry or baseline efficacy assessments. Baseline sitting blood pressures were 167/105 for carvedilol and 168.5/103 for hydrochlorothiazide (HCTZ) and immediate standing blood pressures were 166/102 in both groups. (Korotkoff phase V readings).

There were statistically significant falls in blood pressure and heart rate measurements in both treatment groups during the 2 hours following the first dose of active medication, which were greater in the carvedilol group and statistically significantly different from HCTZ at the 5% level or less. Effects in the sub-population who were over 65 years of age appeared to contribute substantially to the differences between carvedilol and HCTZ, but resulted in quite small median differences between treatments of changes over time in the population as a whole (0-5 mm Hg systolic, 0-2 mm Hg diastolic, 0-2 b/min heart rate, from 95% confidence intervals) and there was no evidence for significantly different changes in postural blood pressure drop.

There were no significant differences ($p > 0.05$) between treatments with respect to median blood pressures (sitting or immediate standing) at weeks 4 and 8 of treatment but there were greater

Patient Withdrawals

Thirty four of the 235 recruited to the study were withdrawn during the placebo baseline period. Eleven of the patients who received active medication were withdrawn prior to the end of the study. Five were withdrawn due to adverse events, four in the carvedilol group and one in the hydrochlorothiazide group.

Demography

No significant differences between the groups in respect of age, height, weight, sex, initial blood pressures, previous hypertensive treatment, or drinking habits. This was true for both statistical analyses.

Effect on Sitting Diastolic Blood Pressure

Good response was defined as a sitting diastolic blood pressure to below 90 mmHg or a decrease of at least 10 mmHg.

PERCENTAGE RESPONDERS

	<u>CARVEDILOL GROUP</u>	<u>HYDROCHLOROTHIAZIDE GROUP</u>
WEEK 4	*67.8	*69.6
WEEK 8	*86	*88

* No statistically significant difference between treatments.

Statistically significant falls in blood pressure (both diastolic and systolic) occurred in both groups, in both sitting and standing positions over the eight week period of treatment. Median changes for each group are shown below:

Antinuclear Antibodies

No trends occurred in the positivity rates of either group.

DISCUSSION

The results of this study show that carvedilol 25 mg and 50 mg once daily is as effective as hydrochlorothiazide 25 mg and 50 mg in the control of mild to moderate essential hypertension.

The response rate as determined by the primary efficacy parameter was 85% in the carvedilol group and 87.6% in the hydrochlorothiazide group at week 8, a non-significant difference at the 5% level.

This surprisingly high response rate led to a second statistical analysis utilizing a revised efficacy parameter. This new definition of efficacy was a diastolic blood pressure of less than 90 mmHg at week 8.

The response rates using this parameter were 69% for the carvedilol group and 74.1% for the hydrochlorothiazide group, again a non-significant difference at the 5% level.

Approximately one third of patients required an increase in dose after four weeks treatment, this was true of both treatment groups and was not affected by age of patient. 25% of each group was over 65 years and this did not appear to affect dosage requirements.

This study shows that over the 2 hours following the first dose of either preparation there were significant falls in blood pressure and heart rate measurements, sitting and standing. These changes were statistically significantly different between the groups, with greater changes for the carvedilol group than for the hydrochlorothiazide group as would be expected with a drug with vasodilatory properties. However, these reflect quite small differences between the treatment groups overall.

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000216

Table 3

All Randomised Patients
Demographic data at Preliminary Examination

# of patients	Treatment Group		Level of Significance
	Carvedilol	HCZ	
	100	100	
Sex			
Female	51(51%)	41(41%)	0.37
Male	49(49%)	56(56%)	
Recent Hypertensive Treatment			
No	55(55%)	46(46%)	0.20
Yes	45(45%)	54(54%)	
Drinking Habit			
No	46(46%)	42(42%)	0.57
Yes	54(54%)	58(58%)	
Smoking Habit			
High	10(10%)	17(17%)	0.09
Low	10(10%)	9(9%)	
None	72(72%)	74(74%)	

Comparison of Treatment Groups

	Treatment Group		Median Difference	95% C.I. for Difference		Level of Significance
	Carvedilol	HCZ		Lower	Upper	
Age at Entry (yrs)						
Median	59	59	0	-3	4	0.80
Min						
Max						
N	100	100				
Height (cms)						
Median	168	168	-1	-3	1	0.10
Min						
Max						
N	100	100				
Weight (kgs)						
Median	71	71	1	-2	4	0.62
Min						
Max						
N	100	100				

86030

000254

Table 4

Patients used for Intention to Treat Analyses
Demographic data at Preliminary Examination

# of patients	Treatment Group		Level of Significance
	Carvedilol	ICI2	
	100	100	
Sex			
Female	48(52%)	43(44%)	0.32
Male	45(48%)	54(56%)	
Recent Hypertensive Treatment			
No	58(54%)	43(44%)	0.19
Yes	43(46%)	54(56%)	
Drinking Habit			
No	41(44%)	41(42%)	0.80
Yes	52(56%)	56(58%)	
Smoking Habit			
High	10(11%)	17(18%)	0.08
Low	38(40%)	39(40%)	
None	65(70%)	71(73%)	

Comparison of Treatment Groups

	Treatment Group		Median Difference	95% C.I. For Difference		Level of Significance
	Carvedilol	ICI2		Lower	Upper	
Age at Entry (yrs)						
Median	59	59	0	-3	3	0.99
Max						
Min						
N	93	97				
Height (cms)						
Median	168	168	-1	-3	1	0.48
Max						
Min						
N	93	97				
Weight (kgs)						
Median	71	71	1	-2	5	0.47
Max						
Min						
N	93	97				

RG03D

000256

Table G

ALL PATIENTS RANDOMISED TO ACTIVE THERAPY (N=200)
 CLINICAL EFFICACY DATA
 FINAL PLACEBO BASELINE PERIOD VISIT

VARIABLE		CARVEDILOL	ICTZ	OVERALL	MEDIAN DIFFERENCE	95% LOWER	C.I. UPPER	P-VALUE
SYSTOLIC SITTING	MEDIAN	169.0	168.5	169.0	1.0	-3.0	5.0	0.47
	MAX							
	MIN							
	N	100.0	100.0	200.0				
DIASTOLIC SITTING	MEDIAN	105.0	103.0	104.0	1.0	0.0	2.0	0.22
	MAX							
	MIN							
	N	100.0	100.0	200.0				
SYSTOLIC IMMEDIATE	MEDIAN	166.0	166.0	166.0	2.0	-2.0	6.0	0.28
	MAX							
	MIN							
	N	100.0	100.0	200.0				
DIASTOLIC IMMEDIATE	MEDIAN	102.0	102.0	102.0	0.0	0.0	2.0	0.45
	MAX							
	MIN							
	N	100.0	100.0	200.0				
SYSTOLIC POSTURAL	MEDIAN	-2.0	-3.0	-3.0	1.0	0.0	2.0	0.13
	MAX							
	MIN							
	N	100.0	100.0	200.0				
DIASTOLIC POSTURAL	MEDIAN	-1.0	-1.0	-1.0	0.0	-1.0	0.0	0.57
	MAX							
	MIN							
	N	100.0	100.0	200.0				
PULSE SITTING	MEDIAN	77.0	77.0	77.0	0.0	-2.0	2.0	0.97
	MAX							
	MIN							
	N	100.0	100.0	200.0				
PULSE IMMEDIATE	MEDIAN	77.0	78.0	78.0	0.0	-2.0	2.0	0.87
	MAX							
	MIN							
	N	100.0	99.0	199.0				
WEIGHT	MEDIAN	71.0	71.0	71.0	0.0	-1.0	1.0	0.76
	MAX							
	MIN							
	N	100.0	98.0	198.0				

06/030

000260

Table 17

PATIENTS ELIGIBLE FOR ANALYSIS AT WEEK 8 OF THE TREATMENT PHASE (N=179)
 CLINICAL EFFICACY DATA
 WEEK 8 VALUES

VARIABLE		CARVEDILOL	HCTZ	OVERALL	MEDIAH DIFFERENCE	95% LOWER	C.I. UPPER	P-VALUE
SYSTOLIC SITTING	MEDIAN	149.0	148.0	149.0	1.0	-3.0	6.0	0.59
	MAX							
	MIN							
DIASTOLIC SITTING	MEDIAN	87.0	87.0	87.0	0.0	-2.0	2.0	0.80
	MAX							
	MIN							
SYSTOLIC IMMEDIATE	MEDIAN	148.0	144.0	146.0	2.0	-2.0	8.0	0.30
	MAX							
	MIN							
DIASTOLIC IMMEDIATE	MEDIAN	86.0	86.0	86.0	0.0	-2.0	2.0	0.86
	MAX							
	MIN							
SYSTOLIC POSTURAL	MEDIAN	-2.0	-2.0	-2.0	0.0	-1.0	2.0	0.68
	MAX							
	MIN							
DIASTOLIC POSTURAL	MEDIAN	-1.0	-1.0	-1.0	0.0	-1.0	0.0	0.42
	MAX							
	MIN							
PULSE SITTING	MEDIAN	71.0	74.0	72.0	-2.0	-4.0	-1.0	0.00
	MAX							
	MIN							
PULSE IMMEDIATE	MEDIAN	72.0	74.0	74.0	-2.0	-4.0	0.0	0.01
	MAX							
	MIN							
WEIGHT	MEDIAN	71.0	70.5	71.0	2.0	-2.0	5.0	0.33
	MAX							
	MIN							

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**KREDEX (CARVEDILOL - SKF 105517)
NEW DRUG APPLICATION**

Volume 1.344 of 1129

**ITEM 8
CLINICAL DATA SECTION**

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Protocol: INT-CAR-12	Report: MP/0019/SKF-105517	000002
Comparison of carvedilol with captopril in the treatment of mild to moderate essential hypertension		

000001.

Protocol INT-CAR-12

In this multicenter, multinational (Belgium, France, Holland, Italy, Portugal, Spain and West Germany) study the assignment to medication was random and blinded but the up titration was result driven and obvious to both investigator and patient.

The study leaves the impression of being a marketing tool, or a safety evaluation, rather than an efficacy investigation.

The primary endpoint was 'response' rate but values for mean differences from baseline are also given. The two treatment appeared identical in efficacy.

INT-CAR-12						
n	single blind	n	double blind	n	double blind	Δ DBP mm Hg
298 ?	Placebo	147	Carvedilol 25 mg UID	141	carvedilol 25 mg UID	- 16
					carvedilol 50 mg UID	
		151	Captopril 25 mg BID	142	Captopril 25 mg BID	-13
					Captopril 50 mg BID	
	3 weeks	298	2 weeks	283	6 weeks	

CLINICAL REPORT SUMMARY

PROTOCOL INT-CAR-12: COMPARISON OF CARVEDILOL TO CAPTOPRIL IN THE TREATMENT OF MILD TO MODERATE BENIGN HYPERTENSION

Investigators: This study was conducted by a total of 30 investigators in seven countries: Belgium, France, Germany, Italy, The Netherlands, Portugal, and Spain.

Objective: This study was designed to compare the safety and antihypertensive efficacy of carvedilol 25 to 50 mg once daily with captopril 25 to 50 mg twice daily in patients with mild to moderate essential hypertension over a period of eight weeks.

Study Design: Patients, at least 18 years of age, with a diagnosis of mild to moderate essential hypertension, defined as a mean sitting diastolic blood pressure of 95-115 mm Hg (disappearance of Korotkoff sound-Phase V) entered a single-blind placebo run-in phase to confirm diagnosis and establish baseline blood pressure. At each visit, blood pressure and heart rate were measured three times, at approximately one minute intervals, in the sitting position. Patients qualified to enter the Treatment Phase when the three measurements of sitting diastolic blood pressure at each of 3 consecutive weekly visits satisfied the following conditions: 1) the mean of all 9 measurements was 95-115 mm Hg, 2) the range of the individual measurements was not more than 30 mm Hg, and 3) there was an absence of a placebo response, defined as a continuous fall at each visit, with the decline over the last two visits being more than 4 mm Hg. Patients were then randomized in the treatment phase in a double-blind fashion to receive either 25 mg carvedilol once daily or 25 mg captopril twice daily. Carvedilol therapy was initiated with 12.5 mg once daily for two days. Visits were scheduled after 2, 4 and 8 weeks of treatment, at the time of day corresponding to 22-28 hours after the previous day's dosing with once-daily study medication 10-14 hours after the last dosing with twice-daily study medication. After two weeks of treatment, the dosage of study medication was doubled if adequate response to treatment (mean sitting diastolic blood pressure $\leq$ 90 mm Hg or decreased from the baseline value by at least 10 mm Hg) was not achieved. Baseline vital sign values were the means at the final placebo baseline period visit, just prior to the first dosing with active study medication.

The primary index of efficacy was the reduction of mean sitting diastolic blood pressure to 90 mm Hg or less and/or by at least 10 mm Hg from baseline. Secondary efficacy parameters were mean change in blood pressure and heart rate from baseline and achievement of a normalized blood pressure (mean sitting diastolic blood pressure $\leq$ 90 mm Hg). Safety was evaluated by monitoring for adverse events and by comparing clinical laboratory test results obtained at baseline with those obtained during the treatment period.

Demography: A total of 298 patients (140 males and 158 females; 295 Caucasian and 3 other) received coded medication. The average age of the patients in the study was 52.6 years (range:

weight, and race distributions of the patients assigned to the carvedilol (147 patients) and captopril (151 patients) treatment groups revealed no important differences in demographic characteristics.

Prior and Concomitant Medications: All antihypertensive medications were discontinued at least two weeks prior to the start of the placebo run-in phase and were not permitted for the remainder of the study. The use of any other investigational drug was not permitted during the study.

Withdrawals from Study: Of 298 patients who received coded medication, 98% (141 of 147) of the patients who received carvedilol and 94% (142 of 151) of the patients who received captopril completed the eight-week study. Two patients (1%) who received carvedilol and four patients (3%) who received captopril were withdrawn because of clinical events. Of the remaining discontinuations from the carvedilol group, one patient was discontinued for insufficient therapeutic effect, two requested withdrawal and one failed to return. In the captopril group, the discontinuations which were not due to adverse events were three cases of patients who failed to return, and two cases of failing to meet eligibility criteria.

Efficacy Results: Response was defined as achieving at endpoint a normalized mean sitting diastolic blood pressure (≤ 90 mm Hg) and/or demonstrating a reduction from baseline in mean sitting diastolic blood pressure by at least 10 mm Hg. Response rates in the carvedilol and captopril treatment groups were 72% and 65%, respectively, in the per-protocol analysis of efficacy at endpoint. The intent-to-treat analysis of efficacy demonstrated similar response at endpoint, with rates of 79% in the carvedilol group and 70% in the captopril group. The difference in achieving response between the two regimens was not statistically significant. Subgroup analyses, however, indicated a greater proportion of responders with carvedilol, as compared to captopril, in elderly patients (age ≥ 65 years) and in patients with mild hypertension (baseline diastolic pressure of 95-125 mm Hg).

A normalized mean sitting diastolic blood pressure was achieved at endpoint in 58% of the carvedilol patients in the per-protocol analysis, as compared with 50% of the patients in the captopril group. In the intent-to-treat analysis, the incidence of achieving a normalized sitting diastolic blood pressure was 66% in the carvedilol group and 60% in the captopril group. The difference in achieving a normalized pressure between the two regimens was not statistically significant.

Two-thirds or more of the responders to treatment at endpoint, as well as of the patients who achieved a normalized pressure at endpoint, received either 25 mg carvedilol once daily or 25 mg captopril twice daily.

In the per-protocol analysis, 52 of 120 patients (43%) in the carvedilol group and 59 of 129 patients (46%) in the captopril group were considered non-responders at the Week 2 treatment visit. Among these patients whose dosage of study medication was increased, and who were

included in the per-protocol analysis at the Week 8 visit, 23 of 39 patients (59%) in the carvedilol group and 22 of 40 patients (55%) in the captopril group were responders after six additional weeks of treatment at the higher dosage level. A normalized sitting diastolic blood pressure was achieved by 18 of the 39 patients (46%) treated with 50 mg carvedilol once daily and by 17 of the 40 patients (43%) treated with 50 mg captopril twice daily. Differences between regimens with regard to responder rate or incidence of achieving a normalized pressure after upward titration were not statistically significant.

In the per-protocol analysis, mean sitting blood pressure was significantly reduced ($p < 0.05$) in the carvedilol group from 164/104 mm Hg at baseline to 150/90 mm Hg at endpoint; mean change from baseline was -15/-14 mm Hg. In the captopril group, mean sitting blood pressure was significantly reduced ($p < 0.05$) from 165/103 mm Hg to 149/92 mm Hg; mean change from baseline was -15/-11 mm Hg. Mean change at endpoint in sitting heart rate was -7 beats/minute in the carvedilol group, representing a significant ($p < 0.05$) reduction from baseline, and -1 beat/minute in the captopril group. Intent-to-treat results for all parameters were similar to those in the per-protocol analysis. The analysis of mean change in blood pressure indicated no statistically significant difference between treatments in the per-protocol sample. There was, however, a statistically significant ($p < 0.01$) greater mean decrease in heart rate with carvedilol as compared with captopril.

SAFETY: No deaths occurred during or within 30 days after completion of the study. Eight patients in the study were reported as having an adverse event which met the definition of serious (two in the carvedilol group, five in the captopril group, and one never receiving active study medication). One of the serious events in the carvedilol group and two in the captopril group were considered at least possibly related to treatment. Twenty-four percent (36 of 147) of patients who received carvedilol reported clinical events compared to 26% (39 of 151) of patients who received captopril. The most commonly reported adverse events (i.e., those occurring in greater than 2% of the patients in either treatment group) which were considered by the investigator to be related to study medication were headache, dizziness/vertigo and gastrointestinal events in the carvedilol group and headache and dizziness/vertigo in the captopril group. There was no statistically significant difference between treatments with regard to the overall incidence of adverse events. Laboratory studies were unremarkable in each treatment group. This study supports the safe use of oral carvedilol in patients with mild to moderate hypertension.

CONCLUSIONS: In patients with mild to moderate hypertension, both carvedilol and captopril significantly lowered mean sitting diastolic blood pressure after eight weeks of treatment in this study. At endpoint, there was no statistically significant difference between the two treatment groups with regard to the degree of reduction in blood pressure or the percentage of patients achieving a reduction in mean sitting diastolic blood pressure to 90 mm Hg or less and/or by at least 10 mm Hg. Subgroup analyses, however, suggested some trends toward an increased response with carvedilol. Both carvedilol and captopril were well-tolerated in this study.

Table 3
Summary of Baseline Characteristics

	Intent-to-Treat Sample		Per-Protocol Sample	
	Carvedilol (n=147)	Captopril (n=151)	Carvedilol (n=120)	Captopril (n=129)
Number (%) of Patients				
Age (years):				
18-40	20 (14%)	27 (18%)	17 (14%)	23 (18%)
41-64	109 (74%)	102 (67%)	87 (73%)	91 (70%)
≥ 65	18 (12%)	22 (15%)	16 (13%)	15 (12%)
Gender:				
Female	78 (53%)	80 (53%)	65 (54%)	70 (54%)
Male	69 (47%)	71 (47%)	55 (46%)	59 (46%)
Race:				
Caucasian	144 (98%)	151 (100%)	118 (98%)	129 (100%)
Other	3 (2%)	0 (0%)	2 (2%)	0 (0%)
MSDBP^a (mm Hg):				
< 95	0 (0%)	2 (1%)	0 (0%)	0 (0%)
95 - 105	95 (65%)	107 (71%)	81 (68%)	94 (73%)
106 - 115	47 (32%)	42 (28%)	39 (32%)	35 (27%)
>115	4 (3%)	0 (0%)	0 (0%)	0 (0%)
Prior Antihypertensive Treatment:				
Yes	91 (62%)	86 (57%)	78 (65%)	73 (57%)
No	56 (38%)	65 (43%)	42 (35%)	56 (43%)
Mean Value				
Age (years)	53	52	53	51
Weight (kg)	78	77	77	77
MSDBP ^a (mm Hg)	103	103	103	103
Duration of Hypertension (months)	71	62	78	66

^aAt the final baseline period visit

[^]At the preliminary examination visit

Reference Documentation: Tables S.2 - S.5.2

The distribution of patients according to type of pre-trial antihypertensive medication(s) used by 177 of the 298 patients in the intent-to-treat sample are detailed in Table 4. With the exception of

Table 5
Summary of Efficacy Analysis Results

	Intent-to-Treat Analysis			Per-Protocol Analysis		
	Carvedilol (n=146)	Captopril (n=150)	p-value*	Carvedilol (n=120)	Captopril (n=129)	p-value*
Mean Duration of Treatment (Days)	57	56		50	48	
Mean Sitting Systolic BP (mm Hg):						
Baseline	166	166	0.81	164	165	0.87
Endpoint	149	149		150	146	
Change from Baseline	-17 .	-17 .	0.89	-15 .	-15 .	0.40
Mean Sitting Diastolic BP (mm Hg):						
Baseline	105	103	0.05	104	103	0.87
Endpoint	89	90		90	92	
Change from Baseline	-16 .	-13 .	0.09	-14 .	-11 .	0.31
Mean Sitting Heart Rate (bpm):						
Baseline	77	78	0.24	77	78	0.40
Endpoint	70	78		70	77	
Change from Baseline	-7 .	-1	<.001	-7 .	-1	<0.01
Endpoint Response Rates:						
MSDBP < 90 mm Hg	63%	65%	0.34	68%	50%	0.37
MSDBP < 90 or ↓ ≥ 10 mm Hg	79%	70%	0.11	72%	65%	0.28
Non-responders at Week 2 (thus requiring dose titration)	40%	44%	0.55	43%	46%	0.89
Response Rates After Titration:	(n=58)	(n=56)		(n=38)	(n=40)	
MSDBP < 90 mm Hg	55%	49%	0.36	48%	43%	0.82
MSDBP < 90 or ↓ ≥ 10 mm Hg	71%	57%	0.17	59%	55%	0.82

Reference Documentation: Tables S.7, S.16.1, S.16.2, and S.19

*Between group comparisons.

*Statistically significant reduction from baseline ($p < 0.05$).

Primary Efficacy Parameter

Response was defined as achieving a normalized MSDBP (< 90 mm Hg) and/or demonstrating a reduction from baseline in MSDBP by at least 10 mm Hg. Response rates in the carvedilol and captopril treatment groups were 72% and 65%, respectively, in the per-protocol analysis of efficacy at endpoint. The difference in response between the two regimens (compared at a power of 0.80 to detect a difference of 15%) was not statistically significant. In the per-protocol analysis at endpoint 63% of the responders in each of the carvedilol and captopril treatment

5.0 DISCUSSION AND CONCLUSIONS

The results of this study demonstrate that carvedilol 25 mg to 50 mg once daily is as effective as captopril 25 to 50 twice daily in the control of mild to moderate essential hypertension. Both drugs significantly lowered blood pressure at the endpoint of treatment as compared to baseline. There were no statistically or clinically significant differences between the treatment groups in blood pressure response, either at week 2 of treatment (before the titration step) or at endpoint.

For the primary efficacy parameter, data were included from 249 patients in the per-protocol and 298 in the intent-to-treat analyses. The primary efficacy index (or "response"), defined as a reduction in MSDBP to 90 mm Hg or less, and/or a reduction from baseline of at least 10 mm Hg, was met in the per-protocol analysis by 72% and 65%, and in the intent-to-treat analysis by 79% and 70% of the carvedilol and captopril treatment groups, respectively. Two-thirds of the responders at endpoint in each treatment group were treated with 25 mg carvedilol once daily or 25 mg captopril twice daily.

A MSDBP of 90 mm Hg or less was achieved at endpoint in 56% of the carvedilol patients in the per-protocol analysis, as compared with 50% of patients in the captopril group. Of these patients achieving at endpoint a "normalized" MSDBP, 70% in each of the carvedilol and captopril groups achieved this level of blood pressure control while receiving the initial dosage level of 25 mg carvedilol once daily or 25 mg captopril twice daily, respectively.

Among the patients included in the per-protocol analysis, 43% in the carvedilol group and 46% in the captopril group were considered non-responders to treatment at the Week 2 visit and had their doses doubled. Of these, 59% of those who received carvedilol and 55% of those who received captopril were classified as responders after six additional weeks of treatment at the higher dosage level. A sitting diastolic blood pressure of 90 mm Hg or less was achieved by 46% of the patients titrated to 50 mg carvedilol once daily, and 43% of the patients titrated to 50 mg captopril twice daily.

Multiple subgroups analyses of response were made which suggested some indication of regimen by response association within specific subgroups. While many of these associations are weak, some trends are noteworthy. In the intent-to-treat sample, a greater proportion of elderly patients were responders to treatment ($p=0.08$) with carvedilol (89%) as compared with captopril (64%). Similarly, the incidence of response in mild hypertensives (MSDBP of 95 to 105) was greater with carvedilol (89%) as compared with captopril (69%, $p=0.08$).

The effect of carvedilol and captopril on heart rate was also assessed. Both the per-protocol and intent-to-treat analyses showed a statistically significant ($p < 0.01$) greater mean decrease in heart rate of 6 beats/minute with carvedilol as compared to captopril. The decrease in heart rate observed in patients treated with carvedilol is reflective of carvedilol beta-blocking activity.

No deaths occurred during or within 30 days after completion of the study. Eight patients in the study were reported as having an adverse event which met the definition of serious (two in the carvedilol group, five in the captopril group, and one never receiving medication). One of the events in the carvedilol group and two in the captopril group were considered at least possibly related to treatment. Twenty-five percent of patients in each group were reported as having clinical events, regardless of attribution to study drug. One and three patients in the carvedilol and captopril groups, respectively, were withdrawn from the study because of adverse events considered by the investigator to be related to treatment. The adverse event profiles were similar in the two treatment groups. With regard to severity of events and their relationship to treatment, there were no notable differences in the patterns between the two groups. Related adverse events reported most commonly (i.e., in at least 2% of the patients receiving either treatment) were headache, dizziness/vertigo and gastrointestinal events in the carvedilol group and headache and dizziness/vertigo in the captopril group.

Adverse events typical of those which also were observed during active therapy were reported during the placebo run in phase in approximately 10% of patients, so that the incidences occurring on carvedilol and captopril treatment should be viewed in the context of this relatively high background incidence. Many individual patients had laboratory parameters outside normal ranges, but there did not appear to be any significant trends in either group. The differences in the adverse event profiles of the two drugs used in this study are likely related to their individual pharmacological actions. The results suggest that the most commonly reported clinical events for carvedilol are associated with vasodilation, one of its two primary pharmacologic effects.

In conclusion, carvedilol once daily demonstrated in this study similar reductions in blood pressure as captopril twice daily, with some trends toward improved efficacy with carvedilol in certain populations. These results strongly support the antihypertensive efficacy of carvedilol administered in a once daily regimen. Furthermore, of the patients who responded to treatment, the majority achieved this response while receiving the initial dosage of 25 mg carvedilol once daily or 25 mg captopril twice daily. In addition, although the safety profiles of carvedilol and captopril were generally comparable, the observed trend toward improvement in patient tolerability with carvedilol, as evidenced by the lower discontinuation rates, indicate that carvedilol should be an important addition to the list of preferred antihypertensive treatments.

SMITHKLINE BEECHAM PHARMACEUTICALS

SK&F 105517
Protocol MF3460

A MULTICENTER DOUBLE-BLIND, CONTROLLED, RANDOMIZED STUDY
COMPARING THE ANTIHYPERTENSIVE EFFICACY AND LONG-TERM SAFETY
OF CARVEDILOL WITH THAT OF PINDOLOL IN AMBULATORY PATIENTS
WITH MILD TO MODERATE ESSENTIAL UNCOMPLICATED HYPERTENSION

By

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SK&F Report No.:Mc/0090/105517
November 1991

000002

Protocol MF3460

This trial involved 44 centers in Germany, Austria, Belgium and Holland. The data from 6 centers were discarded for efficacy purposes due to sloppy practices at the centers. The protocol is rather involved but has considerable value from a safety point of view in that the trial lasted a whole year. There was a single blind placebo baseline period but no placebo arm during the blinded portions of the trial. After 4 weeks the dose could be doubled; after 8 weeks the investigator might during the year add or withhold HCTZ to the regimen as they saw fit. The different permutations are presented in the analysis.

The changes from baseline in sitting diastolic Blood Pressure are larger than those seen in most other studies. The results after 8 weeks were all but identical to those after 1 year, although a large fraction received added HCTZ. It should be noted that both the up-titration after 4 weeks and the HCTZ addition were not random but result driven. One would expect, then, that those with the poorest response were pushed to maximum therapy.

Protocol MF3460										
n	Single blind (phase A)	n	Double blind (phase B)	n	Double blind (phase C)	Double blind (phase C)	n (completed)	n (endpoint)	ΔDBP mmHg	
?	502	?	264	Carvedilol 25 mg BID	135	Carvedilol 25 mg BID	Carvedilol 25 mg BID	92	104	-16
							Carvedilol + HCTZ	29	31	-8
					110	Carvedilol 50 mg BID	Carvedilol 50 mg BID	28	39	-16
							Carvedilol + HCTZ	63	71	-10
			132	Pindolol 7.5 mg BID	69	Pindolol 7.5 mg BID	Pindolol 7.5 mg BID	45	56	-16
							Pindolol + HCTZ	11	13	-8
					59	Pindolol 15 mg BID	Pindolol 15 mg BID	15	18	-12
							Pindolol + HCTZ	31	41	-11
	2- 4 weeks	396	4 weeks	373	4 weeks	44 weeks	314	373		

SK&F 105517
Protocol MF3460

**Table 10: Effect of Titration on Peak MSDBP Among
Patients Continuing to Phase C
According to Medication Regimen and Dose:
Per Protocol and Basic Intent-to-Treat Analyses
(Appendix 8.2.20.1)**

	<u>PER PROTOCOL</u>		<u>BASIC INTENT-TO-TREAT</u>			
	<u>CARVEDILOL</u>	<u>PINDOLOL</u>	<u>CARVEDILOL</u>	<u>PINDOLOL</u>	<u>CARVEDILOL</u>	<u>PINDOLOL</u>
ACCORDING TO TREATMENT GROUP						
Baseline MSDBP — Visit 5 Predose (mm Hg)						
n	139	75	245	128		
Mean (SE)	101 (0.3)	102 (0.6)	102 (0.3)	102 (0.4)		
Peak Observations Visit 5: Change from Baseline (mm Hg)						
n	137	75	242	128		
Mean change (SE)	-10 (0.6)	-12 (0.8)	-10 (0.5)	-10 (0.6)		
ACCORDING TO DOSE						
Baseline Observations: Visit 5 Predose (mm Hg)						
-- Not titrated at Visit 7						
n	70	39	135	69		
Mean (SE)	100 (0.3)	100 (0.6)	100 (0.4)	101 (0.5)		
-- Titrated at Visit 7						
n	69	36	110	59		
Mean (SE)	103 (0.5)	104 (0.9)	104 (0.4)	103 (0.7)		
Visit 5 Peak Observations: Change from Baseline (mm Hg)						
-- Not titrated at Visit 7						
n	69	39	133	69		
Mean change (SE)	-12 (0.8)	-13 (1.3)	-12 (0.6)	-11 (1.0)		
-- Titrated at Visit 7						
n	68	36	109	59		
Mean change (SE)	-8 (0.8)	-10 (0.9)	-9 (0.7)	-10 (0.7)		
Visit 7 Predose Observations: Change from Baseline (mm Hg)						
-- Not titrated at Visit 7						
n	66	37	135	69		
Mean change (SE)	-16 (0.6)	-17 (0.9)	-15 (0.5)	-15 (0.7)		
-- Titrated at Visit 7						
n	68	36	110	59		
Mean change (SE)	-5 (0.6)	-6 (1.1)	-5 (0.6)	-4 (1.0)		
Visit 7 Peak Observations: Change from Baseline (mm Hg)						
-- Not titrated at Visit 7						
n	56	29	122	61		
Mean change (SE)	-19 (0.7)	-20 (1.2)	-19 (0.6)	-19 (0.9)		
-- Titrated at Visit 7						
n	68	36	110	59		
Mean change (SE)	-13 (1.0)	-13 (1.1)	-13 (0.8)	-11 (1.0)		

* Patients who were not titrated received either carvedilol 25 mg twice daily or pindolol 7.5 mg twice daily, and patients who were titrated received either carvedilol 50 mg twice daily or pindolol 15 mg twice daily.

SK&F 105517
Protocol MF3460

Table 12: Change from Baseline MSDBP According to Maintenance Regimen for Patients Continuing into Phase C at Phase B Endpoint, Visit 8, One-Year and Phase C Endpoint: Per Protocol and Basic Intent-to-Treat Analyses (Table S-4; Appendixes 8.2.33, 9.2.34, 8.2.34.1)

	<u>PER PROTOCOL</u>						<u>BASIC INTENT-TO-TREAT</u>					
	<u>CARVEDILOL</u>			<u>PINDOLOL</u>			<u>CARVEDILOL</u>			<u>PINDOLOL</u>		
	<u>n</u>	<u>Mean</u>	<u>(SE)</u>	<u>n</u>	<u>Mean</u>	<u>(SE)</u>	<u>n</u>	<u>Mean</u>	<u>(SE)</u>	<u>n</u>	<u>Mean</u>	<u>(SE)</u>
Baseline MSDBP (mm Hg)												
Not titrated,												
monotherapy	59	99	(0.3)	35	100	(0.6)	104	100	(0.3)	56	100	(0.5)
+ HCTZ [‡]	11	100	(1.2)	4	103	(1.4)	31	102	(1.1)	13	102	(1.1)
Titiated,												
monotherapy	19	103	(1.2)	8	103	(2.4)	39	103	(0.8)	18	102	(1.3)
- HCTZ	50	103	(0.5)	28	105	(1.0)	71	104	(0.5)	41	104	(0.9)
<u>Reduction in MSDBP: Change from Baseline (mm Hg)</u>												
Phase B endpoint*												
Not titrated,												
monotherapy	59	-16	(0.7)	35	-16	(0.9)	104	-16	(0.5)	56	-15	(0.7)
- HCTZ	11	-16	(1.6)	4	-20	(1.4)	31	-14	(1.3)	13	-15	(2.7)
Titiated,												
monotherapy	19	-7	(1.1)	8	-12	(3.3)	39	-7	(0.9)	18	-6	(2.4)
+ HCTZ	50	-4	(0.7)	28	-5	(0.9)	71	-4	(0.7)	41	-3	(0.9)
Visit 8 Pradose (mm Hg)[§]												
Not titrated,												
monotherapy	55	-17	(0.7)	32	-17	(1.1)	99	-17	(0.5)	54	-17	(0.9)
+ HCTZ	10	-11	(2.3)	1	-8	(…)	31	-11	(1.2)	13	-7	(1.5)
Titiated,												
monotherapy	14	-16	(1.6)	6	-20	(4.3)	38	-16	(1.2)	18	-12	(2.6)
+ HCTZ	40	-8	(1.1)	25	-9	(1.3)	71	-8	(0.9)	41	-7	(1.0)
One-Year (Visit 16)												
Not titrated,												
monotherapy	30	-20	(1.2)	17	-19	(1.9)	92	-16	(0.8)	45	-16	(1.1)
+ HCTZ	3	-18	(1.8)	1	-16	(…)	29	-8	(2.0)	11	-8	(1.6)
Titiated,												
monotherapy	3	-18	(2.7)	1	-8	(…)	28	-16	(1.3)	15	-12	(1.7)
- HCTZ	30	-12	(1.2)	14	-12	(1.4)	63	-10	(1.2)	31	-11	(1.2)
Phase C endpoint												
Not titrated,												
monotherapy	59	-17	(0.9)	35	-17	(1.1)	104	-16	(0.7)	56	-16	(1.0)
+ HCTZ	11	-13	(2.4)	4	-16	(0.9)	31	-8	(1.9)	13	-8	(2.1)
Titiated,												
monotherapy	19	-17	(1.6)	8	-20	(3.8)	39	-15	(1.3)	18	-11	(2.3)
+ HCTZ	50	-11	(1.0)	28	-11	(1.5)	71	-9	(1.4)	41	-9	(1.2)

* Maintenance regimens were the following: Not titrated, monotherapy: carvedilol 25 mg or pindolol 7.5 mg twice daily; or, Not titrated + HCTZ: carvedilol 25 mg twice daily with HCTZ 25 mg once daily or pindolol 7.5 mg twice daily with HCTZ 25 mg once daily; Titrated, monotherapy: carvedilol 50 mg or pindolol 15 mg twice daily; Titrated + HCTZ: carvedilol 50 mg twice daily with HCTZ 25 mg once daily or pindolol 15 mg twice daily with HCTZ 25 mg once daily.

† Patients were titrated at the end of Phase B (Visit 7).

‡ HCTZ could be added at Visit 8 or any later visit.

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(31081), for whom the first finding was observed on Day 26, had experienced an adverse experience of precordial pressure on Day 14. The precordial pressure was considered by the investigator to be mild and possibly related to study medication; it cleared after 7 days with no treatment and no change in study medication. The patient continued on carvedilol therapy and completed the study after a total of 371 days with no other reports of precordial pressure or other related adverse experiences.

5.0 DISCUSSION AND CONCLUSIONS

Totals of 337 and 165 patients with mild to moderate hypertension were randomized to carvedilol and pindolol, respectively, at 44 centers in West Germany, Austria, Belgium, and Holland. Of these, data from 70 patients randomized to carvedilol and 33 patients randomized to pindolol at six centers were completely excluded from the *per protocol* analysis of efficacy and were analyzed separately in a *limited intent-to-treat* analysis (carvedilol, 65 patients; pindolol, 31 patients) because of questions regarding the conduct of study at the six centers. Efficacy results were comparable between the *basic intent-to-treat* and *per protocol* analyses.

The results of this study are consistent with those reported in an earlier open study in which carvedilol 25 mg twice daily was administered for one year.³⁵ In that study, 55.8% (86/154) of the patients completed the one-year treatment period. In the present study, 63.2% (213/337) of patients randomized to carvedilol and 61.8% (102/165) of patients randomized to pindolol completed the one-year treatment period (*full sample*).

In the same one-year open study of carvedilol 25 mg twice daily, the median sitting BP was decreased from 170/105 mm Hg to 145/90 mm Hg. At baseline in the present study, mean sitting BP was 160/102 mm Hg for 264 patients randomized to carvedilol and 159/102 mm Hg for 132 patients randomized to pindolol. After four weeks (Phase B endpoint), mean sitting BP (trough values) was reduced to 147/91 mm Hg for 263 patients who had received carvedilol 25 mg twice daily and to 146/92 mm Hg for 132 patients who had received pindolol 7.5 mg twice daily (*basic intent-to-treat* analysis).

In the present study, blood pressure response at the end of the four-week treatment phase (Phase B) was comparable between carvedilol and pindolol according to both the *per protocol* and *basic intent-to-treat* analyses of efficacy; mean changes from baseline for carvedilol 25 mg twice daily and pindolol

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adverse experiences that occurred while the patient was taking active study medication.

Dizziness was the most common on-therapy adverse experience reported for both treatment groups: 6.8% (23/337) of carvedilol patients and 10.3% (17/165) of pindolol patients. Bronchitis was reported for 6.8% (23/337) of carvedilol patients and for 5.5% (9/165) of pindolol patients. Hyperuricemia was reported for a similar percentage of both treatment groups, 5.3% (18/337) of carvedilol patients and 5.5% (9/165) of pindolol patients.

Differences between treatment groups were observed for the following adverse experiences reported for more than 5% of patients in one or both groups (*Fisher's exact test*):

- *back pain* 5.9% (20/337) of carvedilol patients (vs. 1.2%, 2/165, of pindolol patients; $p=0.018$)
- *increased sweating* 6.1% (10/165) of pindolol patients (vs. 0.9, 3/337, of carvedilol patients; $p=0.0018$).

Laboratory data were examined by comparing the number and percentage of patients with values of sponsor-defined concern at baseline to those on- and 1-day post-therapy. Results showed no consistent increase in the numbers or percentages of patients with values of concern relative to time on drug and there was no consistent difference between monotherapy versus combination therapy or between patients titrated versus patients not titrated.

In the earlier one-year open study of carvedilol,³⁵ lipid data were evaluated for 36 patients, and no effect was observed for serum triglycerides, total cholesterol, LDL cholesterol, or HDL cholesterol. In this study, the data suggest that both carvedilol and pindolol cause similar increases in serum triglycerides, with median percent change from baseline of 10.1% at endpoint. After one year, the median percent increases were also similar between groups: 11.7% for carvedilol and 13.9% for pindolol ($p=0.8051$, *Wilcoxon rank sum*, between groups).

Such changes are not believed to represent a clinically significant effect on coronary heart disease (CHD) risk, since similar changes were reported after one year of treatment with cholestyramine and mean percent increases of approximately 20% were observed after seven years of treatment with cholestyramine in the Lipid Research Clinics Primary Prevention Trial.^{36,37} In that same trial, mean percent increases in serum triglycerides of



**KREDEX (CARVEDILOL - SKF 105517)
NEW DRUG APPLICATION**

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CLINICAL DATA SECTION**

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Protocol: MF 3461

Report: MC 009 BS

000002

A multicenter, double-blind, randomized, controlled study comparing the efficacy and safety of carvedilol and pindolol in ambulatory patients with mild to moderate essential uncomplicated hypertension (O21)

000001

Protocol MF 3461

This multicenter study in Germany and Belgium compared once a day doses of Carvedilol up to 100 mg/day with pindolol 15 mg/day in patients with mild/moderate essential hypertension. The study was blinded and randomized but did not involve placebo control.

n	baseline (single blind)	n	Double blind	n	results, supine DBP Δ mmHg from baseline
	Placebo		25 mg carvedilol UID	39	-15.1 ± 1.24
			50 mg carvedilol UID	40	-16.7 ± 1.23
			100 mg carvedilol UID	38	-17.8 ± 1.25
			15 mg Pindolol UID	35	-16.3 ± 1.30
235	up to 4 weeks	205	13 weeks	152	

Of 235 patients who entered the study, 170 completed. Because of sloppy practices at 4 centers, only 152 patients were included in the analysis. On the face of it, the results seem better than those obtained in the US studies. The lack of placebo control precludes any further conclusions. It appears, however, that in the doses employed here carvedilol and pindolol were equivalent in their effect on blood pressure.

A selection of unedited pages from the report is appended.

OBJECTIVE

To compare the blood pressure lowering effect and the safety and tolerability of three different dosages of carvedilol with that of one dosage of pindolol, both administered once daily, and to characterize the dose-response relationship of carvedilol with respect to blood pressure reduction in patients with mild to moderate essential uncomplicated hypertension.

STUDY DRUG

Carvedilol was provided as 25 mg (batch number, 819156Ec); 50 mg (batch number, 819163Fc); and 100 mg (batch numbers, 819152Aa and 819703Aa) capsules. Placebo (batch numbers, 816349Ab and 819166Cb) and pindolol 15 mg (batch number 819187Bb) were provided as capsules identical in appearance to those containing carvedilol. Study medications were supplied by BOEHRINGER MANNHEIM GmbH, D-6800 Mannheim 31, Federal Republic of Germany.

MATERIALS AND METHODS

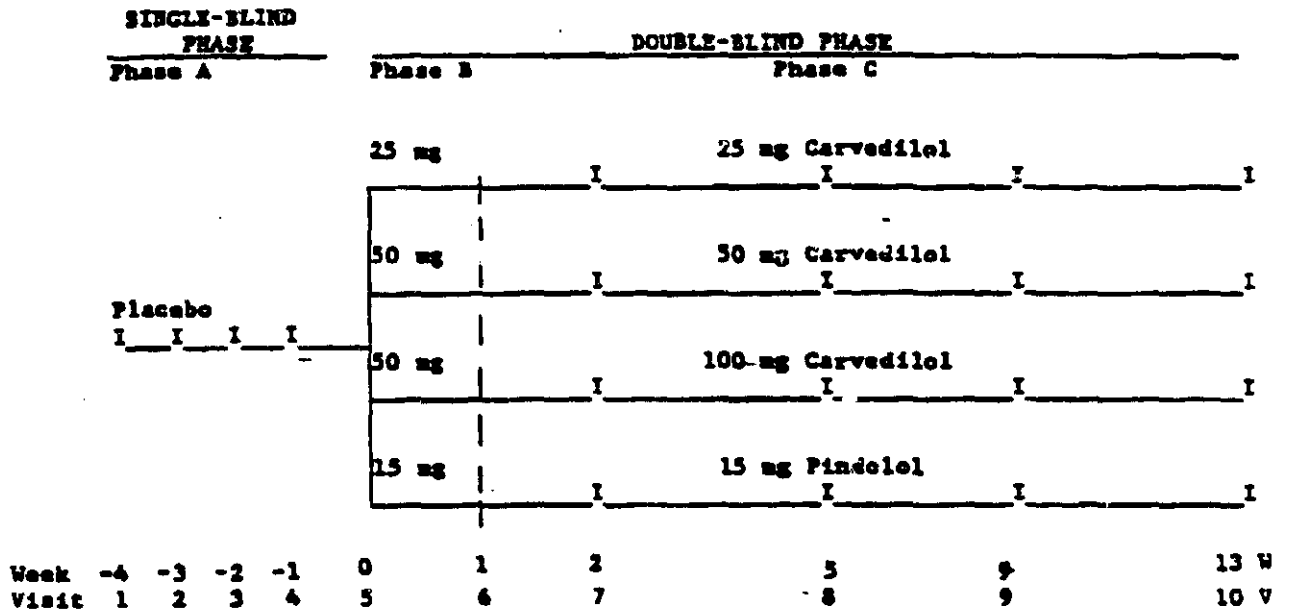
OVERALL DESIGN AND PLAN

This was a randomized double-blind, multicenter study in which patients with mild to moderate uncomplicated essential hypertension (defined as an untreated supine diastolic blood pressure (SDBP) ranging from 95 to 115 mmHg, inclusive) were randomly assigned to receive either 25 mg, 50 mg or 100 mg of carvedilol or 15 mg of pindolol once daily for 13 weeks. In order to avoid an acute marked reduction in blood pressure, patients assigned to the 100 mg carvedilol group received 50 mg carvedilol once daily for the first week of double-blind treatment and 100 mg carvedilol from the second week. Each patient received a single daily oral dose of placebo medication during a single-blind placebo baseline period which

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extended from a minimum of two weeks (for patients who had never previously received antihypertensive medication) to a maximum of four weeks (for previously-treated patients). Patients were eligible for admission into the double-blind phase of the study when their supine diastolic blood pressure on two consecutive visits ranged between 95 and 115 mmHg inclusive and varied not more than 10 mmHg.

The study design is graphically presented below:



Phase A: Placebo Weeks -4 to 0 (or -4 to -2, see Visit 5)
Phase B: Double-Blind Adaptation Phase (first week of active treatment)
Phase C: Double-Blind Continuation Phase, Weeks 2 to 13
Visit 5: (or Visits 3 or 4) Admission to the double-blind phase if the SDBP was within the range of ≥ 95 - < 115 mmHg and did not vary by > 10 mmHg on two consecutive visits.

STUDY DESIGN: CHOICE OF CARVEDILOL

The doses of carvedilol were selected on the basis of experience with the drug prior to initiation of this study. Multiple dose levels of carvedilol were used in order to investigate a dose-response relationship in patients with mild to moderate essential hypertension. The reference drug (pindolol) served as the positive control in order to compare the effect of carvedilol with changes in blood pressure associated with another nonselective beta-adrenergic receptor blocking agent known to reduce blood pressure.

STUDY POPULATION

A total of 205 patients, 102 male and 103 female, who ranged in age from 23 to 70 years, qualified for participation in the study. All patients had uncomplicated essential hypertension with untreated supine diastolic blood pressure values during placebo screening that ranged between 95 and 115 mmHg inclusive on two consecutive occasions and varied by no more than 10 mmHg. Patients were excluded from the study if their medical history revealed a tendency to hypotension, hypotensive collapse or shock or if they had any of the following: mitral valve stenosis, decompensated congestive heart failure, bradycardia (<55 bpm), sinoatrial block, AV block grades II and III, complete bundle branch block, bifascicular block, sick-sinus syndrome, unstable angina pectoris, any degree of cor pulmonale, metabolic acidosis or obstructive lung disease. In addition, patients were excluded from the study if they had renal insufficiency (creatinine >1.5 mg/dl); hepatic insufficiency (GPT >40 U/l); insulin-dependent diabetes mellitus; body weight greater than 20% above normal as defined by the Broca Index (height in cm. - 100). Female patients were excluded if pregnant, lactating or without satisfactory contraception. Concomitant use of oral contraceptives, cimetidine, thyrostatics, antiarrhythmics, psychotherapeutics, antihypertensive agents,

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NDA 20297

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CRITERIA FOR PATIENT WITHDRAWAL

Patients were withdrawn from the study for the following reasons: any violation of the exclusion criteria; noncompliance in visiting schedule (deviation of more than three days between Visits 3 and 6 or more than four days during Visits 7 through 10); noncompliance in study drug intake (deviation of more than 25% of drug intake); SDBP >115 mmHg at Visit 3 (end of the placebo period); SDBP >115 mmHg at any time during the study; serious adverse experience; serious concurrent illness or laboratory test abnormality; or when withdrawal was considered by the investigator to be in the patient's best interest.

STATISTICAL ANALYSIS PLAN

The analysis of this study was complicated by the fact that there were doubts concerning the conduct of four investigators in relation to study administration. In some cases it was impossible to obtain patient source information to verify participation in the study. It was considered necessary, therefore, to perform two statistical analyses: the primary analysis excluded data from these four unreliable investigators; the secondary analysis included data from all investigators. The four investigators who were excluded from the primary analysis and the reasons for their exclusion are as follows:

1. Boxdorfer - Poor administration; poor compliance

Comment

Study results were poorly documented. According to the study monitor, Dr. Boxdorfer appeared to fill out the casebooks in a retrospective manner. Data on the case record forms could not be verified against original documents.

000031

2. Huttemann - Protocol violation; poor compliance

Comment

Dr. Huttemann elected not to allow his patients to participate in the pre-randomization placebo screening phase of the study. According to GHBA monitors, Dr. Huttemann stated that when he informed his patients that they were to be given placebo, they refused to take an "inactive drug". Therefore, none of his patients received placebo medication. This is a significant violation of the protocol. The placebo screening phase is necessary to demonstrate that patients are indeed hypertensive. All other investigators adhered to the protocol in this regard.

3. Maetz - Protocol violation; poor compliance

Comment

Approximately eight weeks after starting, Dr. Maetz abruptly stopped the study and returned all supplies to the sponsor.

4. Vorberg - Poor administration; poor compliance

Comment

Dr. Vorberg did not enter study-related data in the patient records, but instead kept separate tables for enrolled patients. Therefore, no source data could be obtained to verify the existence of his patients.

EFFICACY RESULTS

INTRODUCTION

This was a randomized double-blind study in which 205 patients with mild to moderate uncomplicated essential hypertension (defined as an untreated mean supine diastolic blood pressure ranging from 95 to 115 mmHg inclusive) were randomly assigned to receive either 25 mg, 50 mg or 100 mg of carvedilol or 15 mg of pindolol once daily for 13 weeks. Each patient received daily oral doses of placebo medication during a single-blind placebo baseline period which extended from a minimum of two to a maximum of four weeks. Patients were eligible for admission into the double-blind phase of the study when their supine diastolic blood pressure (SDBP) on two consecutive visits ranged between 95 and 115 mmHg and varied not more than 10 mmHg. The primary efficacy variable was SDBP which was measured at every study visit prior to drug administration. On study visits 5, 6 and 8, SDBP was also measured two hours after drug administration. A reduction of SDBP to < 90 mmHg or a decrease in SDBP $\geq$ 10 mmHg from the baseline value was considered a satisfactory response to drug treatment. Although SDBP was the primary efficacy variable, changes in other blood pressure variables were also assessed.

DATA SET ANALYZED

During the monitoring of this study, serious doubts were raised concerning the integrity of study administration at the sites of four investigators: Boxdorfer, Huttemann, Maetz and Vorberg. In some cases it was impossible to obtain patient source information to verify participation in the study. As a result, two statistical analyses were performed on the data collected from this multicenter center: the primary analysis included data for 152 patients from ten investigators and excluded data from the four listed investigators; the secondary analysis included data from all fourteen investigators

and was done to ensure that the primary analysis was not biased by the exclusion of data from the four investigators (Maetz, Huttemann, Vorberg and Boxdorfer) which was considered unreliable.

The primary statistical analysis includes ten investigators, who enrolled one hundred and fifty-two patients who were randomized to double-blind treatment. The following table presents the numbers of patients entered by the respective investigators and the treatments received.

TABLE B
NUMBERS OF PATIENTS IN THE PRIMARY STATISTICAL ANALYSIS
RANDOMIZED TO DOUBLE-BLIND TREATMENT BY INVESTIGATORS

Investigator	Carvedilol			Pindolol	Total
	25 mg	50 mg	100 mg	15 mg	
Bruhl	2	2	3	1	8
Eckert	7	4	5	6	22
Hunnerscheidt	3	3	1	1	8
Kredel	1	2	2	2	7
Muller	12	13	13	11	49
Pirlet	2	3	1	2	8
Schutz	5	5	5	5	20
Sosna	3	4	4	3	14
van Kuyk	2	2	2	2	8
von Behren	2	2	2		8
Total	39	40	38	35	152

Data from these 152 randomized patients were included in the primary statistical analysis, including data from patients who discontinued participation during the double-blind phase or had the following protocol deviations: did not meet all inclusion and exclusion criteria, did not satisfy requirements for entry into the double-blind phase, had SDBP values below 95 mmHg at baseline, were noncompliant

TABLE E
MEAN SUPINE DIASTOLIC BLOOD PRESSURE (mmHg) VALUES FOR
PATIENTS INCLUDED IN THE PRIMARY ANALYSIS

Double-blind Week, Hour		Carvedilol			Pindolol
		25 mg	50 mg	100 mg	15 mg
Baseline	N	39	40	38	35
	Mean	102.9	102.0	102.9	101.0
	S.E.	0.80	0.87	0.76	0.77
0, 2	N	39	39	37	34
	Mean	94.9	91.6	90.8	90.1
	S.E.	1.10	1.74	1.49	1.47
1, 0	N	39	39	36	35
	Mean	94.0	91.2	89.9	90.0
	S.E.	1.09	1.25	1.33	1.12
1, 2	N	39	39	36	35
	Mean	88.4	86.9	84.6	84.7
	S.E.	1.14	1.25	1.40	1.37
2, 0	N	38	39	36	34
	Mean	89.3	88.3	85.3	86.9
	S.E.	1.12	1.36	1.32	1.12
5, 0	N	37	39	35	32
	Mean	90.0	88.7	87.6	86.6
	S.E.	1.28	1.39	1.44	1.52
5, 2	N	37	39	33	32
	Mean	84.3	81.7	80.8	83.2
	S.E.	1.03	1.55	1.47	1.42
9, 0	N	37	37	32	32
	Mean	87.1	84.8	84.9	86.1
	S.E.	1.09	1.18	1.21	1.15
13, 0	N	37	37	32	31
	Mean	86.7	84.9	82.8	84.3
	S.E.	1.20	1.18	1.40	1.25
Endpoint	N	39	40	38	35
	Mean	86.6	84.1	83.4	84.9
	S.E.	1.22	1.38	1.59	1.18

0 Hour = 24 hours after drug administration

000051

Carvedilol/Pindolol
GHEA-471

TABLE F
ADJUSTED MEAN CHANGES FROM BASELINE FOR SUPINE DIASTOLIC
BLOOD PRESSURE (mmHg) FOR PATIENTS IN PRIMARY ANALYSIS

Double-blind		Carvedilol			Pindolol	P-value
Week	Hour	25 mg	50 mg	100 mg	15 mg	
Baseline	N	39	40	38	35	0.279
	Mean	102.9	102.0	102.9	101.0	
	S.E.	0.77	0.80	0.75	0.80	
0, 2	N	39	39	37	34	0.040**
	Mean*	-6.3	-9.7	-10.8	-10.4	
	S.E.	1.25	1.25	1.28	1.33	
1, 0	N	39	39	36	35	0.055
	Mean*	-8.1	-9.9	-12.2	-11.0	
	S.E.	1.08	1.10	1.12	1.14	
1, 2	N	39	39	36	35	0.088
	Mean*	-13.1	-14.0	-17.0	-16.1	
	S.E.	1.21	1.22	1.25	1.27	
2, 0	N	38	39	36	34	0.068
	Mean*	-12.8	-12.8	-16.5	-14.3	
	S.E.	1.16	1.16	1.18	1.23	
5, 0	N	37	39	35	32	0.461
	Mean*	-12.1	-12.3	-13.8	-14.7	
	S.E.	1.35	1.31	1.35	1.43	
5, 2	N	37	39	33	32	0.173
	Mean*	-17.4	-19.4	-20.8	-17.3	
	S.E.	1.28	1.25	1.32	1.36	
9, 0	N	37	37	32	32	0.645
	Mean*	-14.5	-15.7	-16.1	-14.9	
	S.E.	0.97	0.96	1.02	1.03	
13, 0	N	37	37	32	31	0.118
	Mean*	-14.6	-15.3	-18.0	-16.2	
	S.E.	1.03	1.03	1.08	1.12	
Endpoint	N	39	40	38	35	0.462
	Mean*	-15.1	-16.7	-17.8	-16.3	
	S.E.	1.24	1.23	1.25	1.30	

*Mean change from baseline adjusted by analysis of covariance

** p ≤ 0.050

000054

DISCUSSION

021-102

In the management of essential hypertension, beta-blockers and vasodilators are often used in combination. Carvedilol is a new compound which combines nonselective beta-adrenergic blocking and vasodilating activities without demonstrating intrinsic sympathomimetic activity.

In the present study carvedilol was evaluated as an antihypertensive agent, administered once daily for a 13-week period. Three dosages, 25 mg, 50 mg and 100 mg of carvedilol were used to determine a dose-response pattern and to evaluate the safety and tolerability of the drug in different dosages. The three carvedilol dosages were compared with one dosage, 15 mg, of a known nonselective beta-adrenergic blocking agent with intrinsic sympathomimetic activity, pindolol.

Reductions in mean supine diastolic blood pressure (MSDBP) occurred at all measurement points for the four treatment groups but maximum reductions occurred at Week 5, Hour 2. Mean supine systolic blood pressure was also reduced at all time points for all groups; at Week 5, Hour 2, the reduction in MSSBP in the 100 mg carvedilol group was significantly greater than the reductions measured in the other three dose groups. There were also reductions at all time points in mean diastolic pressure when measured immediately after standing, with significantly greater reductions occurring in the 50 mg and 100 mg carvedilol groups at Week 5, Hour 2, than for those occurring in the 25 mg carvedilol and the pindolol groups. Maximum reductions in mean standing diastolic blood pressure for the pindolol group occurred at Week 13 and at Endpoint. Reductions in mean systolic blood pressure when measured immediately upon standing occurred at all time points but maximum reductions occurred at Week 5, Hour 2. At Week 13, reductions in mean standing systolic blood pressure were considerable for all dose groups, but the largest reduction occurred in the 100 mg carvedilol group.

000107

Several patients experienced postural changes in blood pressures that were potentially clinically important but only two of these patients discontinued treatment as a result of symptoms which may have been related to hypotension. Mollendorff et al¹ have theorized that postural effects may be encountered as a consequence of enhanced vasodilator effect of the drug (carvedilol).

The acute reduction in blood pressure seen in this study and the apparent sustained reduction after 13 weeks of treatment, suggest that carvedilol has a good antihypertensive effect both acutely and chronically. In a study by Eggertson comparing carvedilol with propranolol, a widely-used nonselective beta-blocker with no other autonomic nervous system activity, it was shown that propranolol did not reduce blood pressure acutely except for standing systolic pressure.³

At all time points during the 13-week trial, the adjusted mean change from baseline in supine diastolic blood pressure became larger as the carvedilol dosage increased, with significant dose-responses at Weeks 0, 1, 2 and 13. Mean heart rate values for all treatment groups in this study were relatively stable at all measurement points, with no significant differences occurring during acute or chronic treatment. Because of the vasodilating properties of carvedilol, there is no rise in total peripheral resistance or no decrease in blood flow, as with propranolol³, and less of a decrease in heart rate with carvedilol than with propranolol.

Twenty-two patients of the 205 evaluated for safety had one or more clinical laboratory test results that were not previously outside of predefined limits but became so after double-blind treatment. Upon

medic. review, none of these values were considered to be clinically important or likely to represent a drug effect, with the exception of two patients with elevated SGPT values at Endpoint.

All dosages of carvedilol in the study appeared to be well tolerated, with the most commonly occurring adverse experiences being dizziness and fatigue.

CONCLUSIONS

As a result of this study, in which three dosages of carvedilol were administered to patients with mild to moderate essential hypertension for a duration of 13 weeks, it may be concluded that carvedilol was well tolerated, had a good blood pressure lowering effect both acutely and chronically without causing a compensatory change in heart rate, and this effect increased with increasing doses of carvedilol. These results show carvedilol to be equally as effective and safe as pindolol.



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Protocol: MF 3948

Report: MC-0129/SKF-105517

000002

**A comparative study of carvedilol, nifedipine retard and atenolol in the
management of essential hypertension - randomized, double-blind study
(Carvedilol doses: 25 and 50 mg x 13 weeks)**

000001

Protocol MF3948

This multicenter trial (41 centers in UK and Ireland) tested carvedilol against nifedipine and atenolol. The study was randomized and blinded but had no placebo control. The initial dose of carvedilol, -- 25 mg once a day -- appears to be suboptimal. Four weeks into the double blind phase the dose could be doubled for all patients with inadequate response. It is not clear how many fell into each subgroup. There is a general statement (vol 419, p135) that "... dose modifications after four weeks treatment or or 6 weeks treatment did not appear to produce a general improvement in the anti-hypertensive effect of treatment for those whose dose was increased." Consequently, the statistical analysis is presented without this grouping. The analysis (ibid p 160) gives averages of actual recordings. The changes from first entry in that table are given in the table below. (It may be that the first entry is not baseline, but one week into the study. If so, I have not found a table of baseline values.)

It seems that in the dose ranges tested, Atenolol was superior in effect when compared with the other two treatments. Without a real placebo arm an argument is specious but the effect of carvedilol and nifedipine is hardly more than one might expect from placebo. The main value of the study lies in the lucid discussion of side effects.

A few unedited pages from the report are appended.

Trial MF3948							
n	Single blind	n	Double blind	n	Double Blind	n	Results Δ mmHg Sit DBP
312	Placebo	102	Carvedilol 25 mg UID		Carvedilol 25 mg UID	83	-6.3
					Carvedilol 50 mg UID		
		97	Nifedipine SR 20 mg BID		Nifedipine SR 20 mg BID	84	-5.9
					Nifedipine SR 40 mg BID		
		99	Atenolol 50 mg UID		Atenolol 50 mg UID	91	-9.4
					Atenolol 100 mg UID		
312		298				258	
one week		4 weeks		8 weeks			

A comparative study of Carvedilol, Nifedipine retard and Atenolol in the management of essential hypertension (MF 1948)

Table 11: Sitting Diastolic Blood Pressure: Results from separate analyses of covariance on acute testing, at each clinic visit after randomisation and for the last reading obtained, using the visit 2 level as a covariate

	Adjusted Mean Values* (Standard Errors)					
	Acute	Visit 3	Visit 4	Visit 5	Visit 6	Last Values
Carvedilol	97.8 (0.8)	94.5 (0.9)	93.0 (0.9)	92.8 (1.0)	90.4 (0.9)	91.5 (0.9)
Nifedipine	96.4 (0.8)	93.2 (0.9)	92.3 (0.9)	89.8 (1.0)	90.3 (0.9)	90.5 (0.9)
Atenolol	98.0 (0.8)	91.3 (0.9)	91.2 (0.9)	88.5 (1.0)	88.7 (0.9)	88.6 (0.9)
<u>Analysis of Covariance</u>						
Treatment mean square	79.52	261.83	74.65	426.62	78.08	215.05
Covariate mean square	7958.45	2690.20	1853.05	1289.05	383.68	837.74
Error mean square	67.33	73.88	71.99	87.83	70.14	78.90
<u>Significance Levels</u>						
Between all 3 treatments	0.31	0.030	0.36	0.008	0.33	0.067
Carvedilol v Nifedipine	0.21	0.29	0.58	3.042	0.91	0.44
Carvedilol v Atenolol	0.87	0.009	0.15	0.002	0.18	0.022
Nifedipine v Atenolol	0.16	0.12	0.39	0.32	0.22	0.14

* All adjusted to a mean baseline level of 103.5 mmHg.

2.0 STUDY OBJECTIVES**2.1 Primary Objective**

To compare the blood pressure control in patients treated with carvedilol 25mg once daily, atenolol 50mg once daily and nifedipine retard 20mg twice daily at 24 hrs, 24 hrs and 12 hrs post-dosing respectively.

2.2 Secondary Objectives

2.2.1 To compare the patient's tolerance of the above drug regimens.

2.2.2 To examine the effect of doubling the dose on blood pressure control and patient tolerability, where patients show insufficient response to the initial dose.

000036

Demography: A total of 311 patients were entered into the placebo run-in phase. Thirteen patients were withdrawn prior to randomisation at visit 2 or soon thereafter. Acute testing data was available from 102 patients who received carvedilol, 96 who received nifedipine and 100 who received atenolol. There were no important differences between the treatment groups with respect to age, sex, height or weight.

Prior and Concomitant Medications: All anti-hypertensive medication was discontinued at visit 1, one week prior to receiving any randomised medication. No other hypotensive medication was permitted for the remainder of the study period. The use of any other investigational drug was contra-indicated during the study.

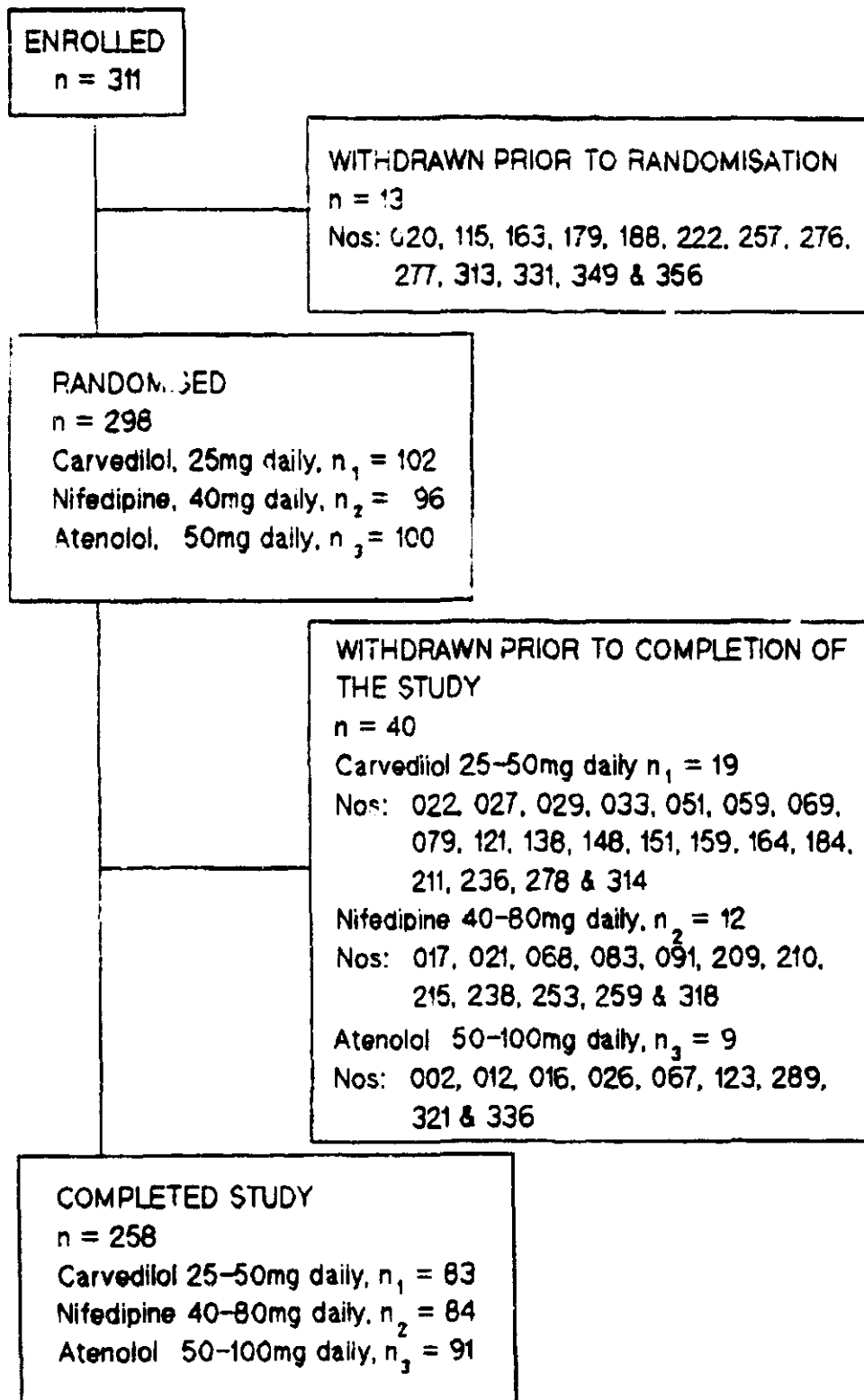
Withdrawals During the Study: Of 298 patients randomised according to the safety analysis 253 patients completed the study to visit 6 (82 patients on carvedilol, 81 patients on nifedipine retard and 90 patients on atenolol). Thirty-five patients withdrew from the study due to adverse events; six patients in the placebo run-in phase, fifteen patients randomised to carvedilol, thirteen randomised to nifedipine and one randomised to atenolol. Twelve patients withdrew from the study due to other reasons (n=5 from the placebo phase, n=3 randomised to carvedilol, n=3 randomised to nifedipine and n=1 from the atenolol group).

All concomitant medication given thereafter was recorded. Drugs with a potentially hypotensive action, for example, benzodiazepines were not permitted. Patients requiring such therapy were withdrawn. Strict attention was paid to known drug interactions with any of the study medication. No special restrictions of diet applied.

3.2 Design (see schematic protocol)

This was a multicentre, between group, randomised, double-blind comparison between carvedilol (25mg and 50mg once daily), nifedipine retard (20mg and 40mg twice daily) and atenolol (50mg and 100mg once daily) lasting 3 months. Suitable patients were treated with placebo for one week. Thereafter they were randomised to carvedilol (25mg once daily) or nifedipine retard (20mg twice daily) or atenolol (50mg once daily). Patients whose blood pressure remained uncontrolled after four weeks treatment had their dose of medication doubled. Patients whose blood pressure remains uncontrolled after a further two weeks treatment with twice the initial dose were withdrawn whilst patients adequately controlled remained in the study for a further six weeks.

PATIENT COMPLETION FLOW CHART FOR EFFICACY ONLY



The possible effects of patient withdrawals on these results cannot be determined satisfactorily, and a further analysis was undertaken, using the observations from the last visit of each patient. This analysis showed a significant treatment difference overall, with the mean levels on atenolol being significantly lower than on carvedilol. Nifedipine did not show statistically significant differences from either of the other treatments. Examination of the mean levels (Tables 8,9) shows, however, an unexpected pattern, with the last reading on atenolol being lower than that seen at any individual visit. This indicates that the patients on atenolol who did not complete the study were showing a more marked hypotensive effect than those completing the study. Thus the analysis of the last value does not entirely resolve the ambiguity in the systolic blood pressure results.

To investigate further the possible time dependent effects of treatment, the results at visit 3 to 6 were analysed for those with complete data. This was undertaken using a repeated measures analysis of variance with the visit 2 level used as a covariate (Table 10). The absence of significant treatment by time interactions (sitting $p=0.075$; standing $p=0.40$) gives no evidence that the magnitude of the treatment effect has changed over time. The treatment effects just fail to achieve statistical significance at the 5% level, for both sitting and standing systolic blood pressures ($p=0.057$; $p=0.086$). Thus the evidence for treatment differences in systolic blood pressure remains equivocal.

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In summary the three treatments showed significant differences with respect to the haemodynamic variables. Whereas nifedipine produced no appreciable changes in heart rate, atenolol reduced the heart rate by around 7 beats per minute, with carvedilol having an intermediate effect. There was a marked fall in blood pressure and rate pressure product for all treatments. Carvedilol and nifedipine did not differ significantly from one another in respect of rate pressure product, but the increased reduction on atenolol was significantly larger. The observed fall in blood pressure was less for carvedilol than for the other treatments, but evidence for the significance of this difference is conflicting and positive conclusions cannot be drawn. If this difference in efficacy is genuine, it is nevertheless small in comparison to the overall anti-hypertensive effect of both treatments, with observed reductions ranging from around 17/11 mmHg on carvedilol to around 22/14 mmHg on atenolol.

The ECG data on the RR interval reflected the clinical observations on heart rate, with longer intervals on atenolol. The corrected QT interval showed a reduction on atenolol with no evidence of change on the other treatments. Although the treatment differences are only significant at one of the two visits, the magnitude of the effect on atenolol is consistent. There was no evidence of a treatment effect on the left ventricular voltages or the PR interval.

Refer to Appendix 12.8.2. for the patient data listings.

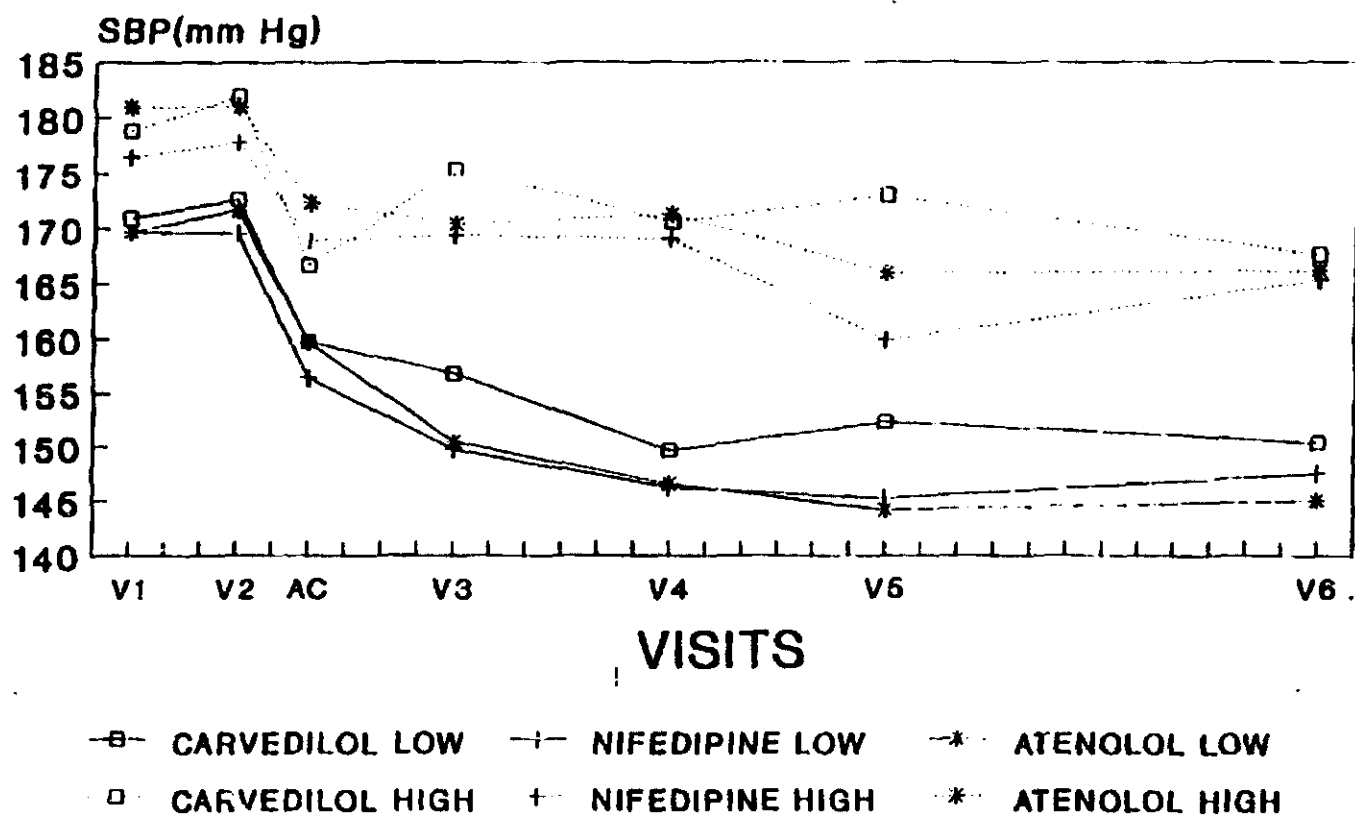
000090

The increase in dose for some patients after visit 4 raises questions as to the efficacy of continuing low dose treatments, and to the value of doubling the doses in those with an inadequate response to lower dosing. The problem in answering these questions arises from the self-selection (via response) of the low dose and high dose groups. In addition, although the proportions of patients moving to high dose medication does not differ greatly between the three treatment groups. It does not necessarily follow that the same patients would be non-responders to every treatment. Thus, the use of inferential statistics (significance tests and confidence intervals) cannot be justified and analysis will be limited to a descriptive summary of the data. Figures 9-12 give the mean values for systolic and diastolic blood pressures, subdivided by whether or not the dose of medication was increased at visit 4. These figures confirm that those patients receiving the higher dose were indeed uncontrolled at visit 4, and that any subsequent improvement in systolic blood pressure was slight. Although those on nifedipine appeared to have gained greatest benefit at visit 5, by visit 6 all treatment means were similar.

A comparative study of Carvedilol, Nifedipine retard and Atenolol in the management of essential hypertension. (MP 3948)

FIGURE 9

Sitting Systolic Blood Pressure IN RELATION TO THE DOSE



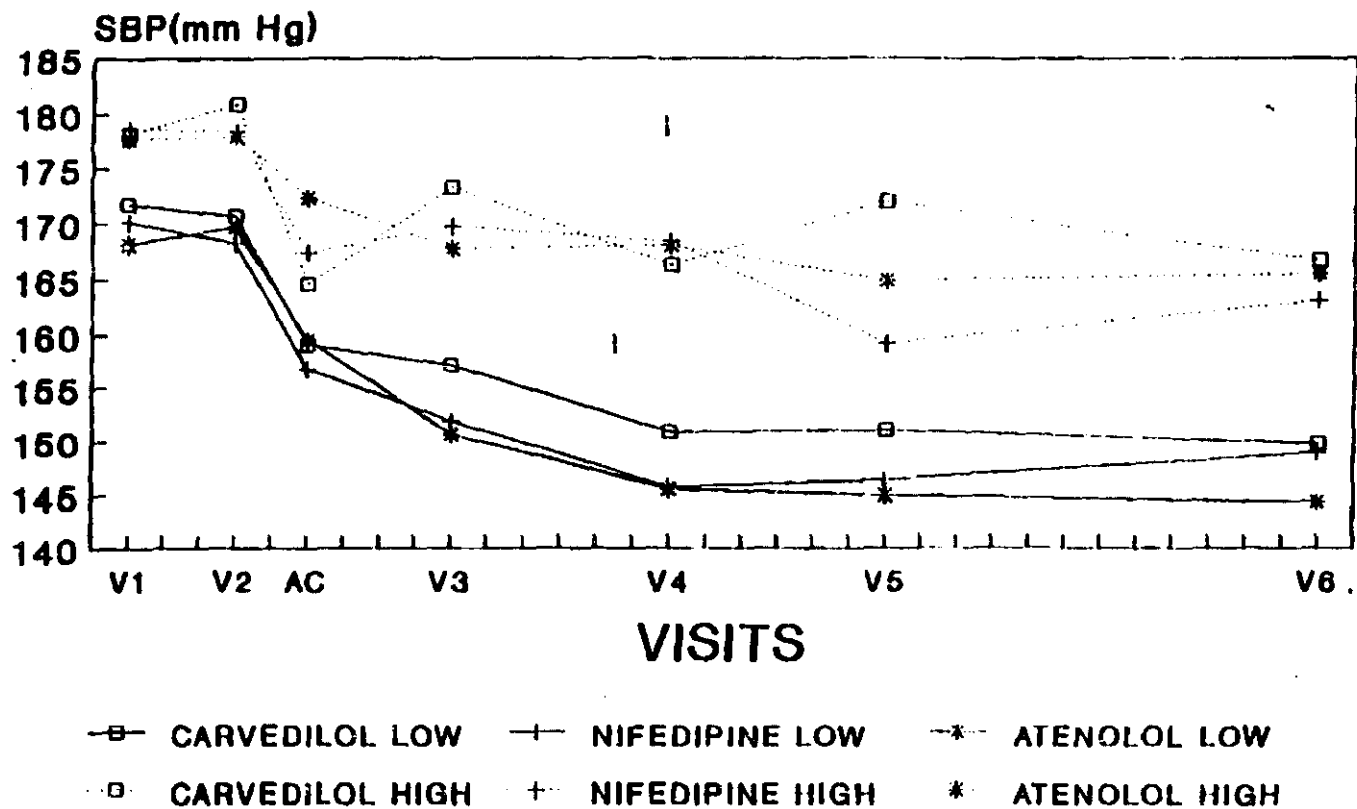
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A comparative study of Carvedilol, Nifedipine retard and Atenolol in the management of essential hypertension, (MF 3948)

FIGURE 10

Standing Systolic Blood Pressure IN RELATION TO THE DOSE



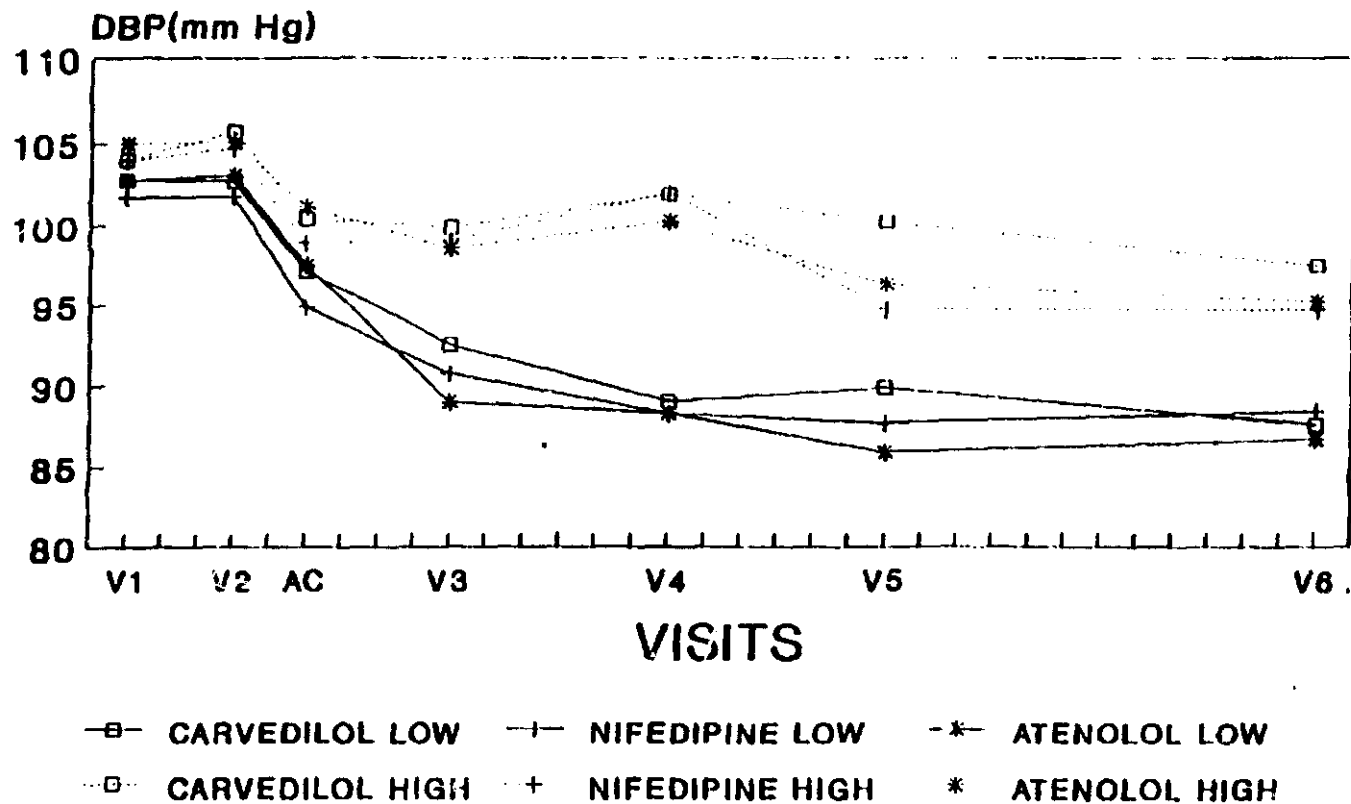
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A comparative study of Carvedilol, Nifedipine retard and Atenolol in the management of essential hypertension. (MP 3948)

FIGURE 11

Sitting Diastolic Blood Pressure IN RELATION TO THE DOSE



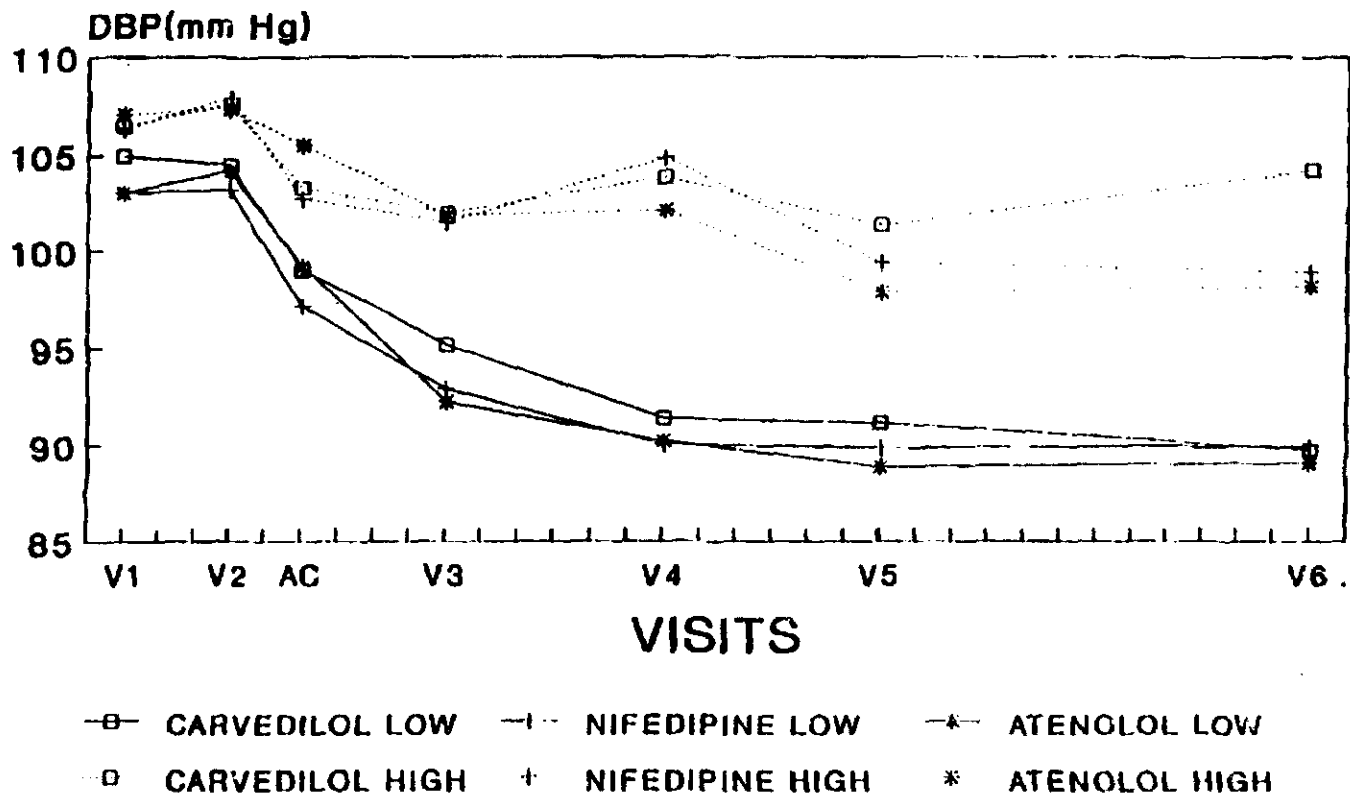
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A comparative study of Carvedilol, Nifedipine retard and Atenolol in the management of essential hypertension. (MF 3948)

FIGURE 12

Standing Diastolic Blood Pressure IN RELATION TO THE DOSE



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11
11
11
11
11
11

The incorporation into the trial of possible dose modifications after four weeks treatment or 6 weeks treatment did not appear to produce a general improvement in the anti-hypertensive effect of treatment for those whose dose was increased. Such a design cannot allow any comment on the most effective dose of any treatment, because of the selection involved in determining the dose level. Overall patients at the higher doses of carvedilol and atenolol had a smaller induced risk of recording an adverse event than at the lower doses. Asthenia still remained the major problem. Whether the patients were 65 years and older or below 65 years of age did not make any difference to the adverse event profile.

There was also no increase in the incidence of any adverse event which lead to the withdrawal of patients, attributable to any of the study medications.

In conclusion, the results from this study showed that all agents were equally efficacious in reducing high blood pressure. Clinically important laboratory measurements were extremely rare. Serious adverse events were reported by only 3.2% of patients. Perhaps further evaluation of the efficacy and safety, with particular emphasis on 'cold extremities' between carvedilol and atenolol is warranted.

The results presented from this study demonstrate the dual pharmacology of carvedilol; that of non-selective β -blockade and vasodilating activity (predominantly alpha-blockade) when compared with a cardio-selective β -blocker and a class II calcium antagonist, in that carvedilol exhibited aspects characteristic of both comparator drugs with equal efficacy and safety.

8.0 CONCLUSIONS

The results of this multicentre study show that when compared with atenolol and slow release nifedipine, carvedilol (25-50mg) produced a similar acute reduction in both systolic and diastolic blood pressure measured in the sitting and standing positions. Differences between the drugs following chronic treatment became more obvious. For example, whereas nifedipine produced no appreciable change in heart rate, atenolol reduced the heart rate by around 7 beats per minute, with carvedilol having an intermediate effect (around 3 beats per minute). Carvedilol and nifedipine did not differ significantly from one another in respect to rate pressure product. The observed fall in blood pressure was less for carvedilol than for the other treatments. The evidence for the significance of this difference is conflicting. The ECG data on the RR interval supported the clinical observations on the heart rate. Only patients on atenolol showed a reduction in the corrected QT interval, whereas there was no evidence of change on the other treatments.

There were no significant differences between treatments in the proportion of abnormal laboratory values for haematology and biochemical variables. There was no evidence of a treatment effect on any laboratory variables.

Adverse events in this study were either volunteered by the patients or elicited from a symptom questionnaire. The majority (approx. 80-90%) of the adverse events were contributed from the questionnaire. Only 37.3% of carvedilol patients, 34% of nifedipine patients and 30.3% of patients treated with atenolol volunteered an adverse event.

Table 2.G.2
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
B100 (SB)	U.S. Multicenter (33 Investigators.)	820169 40Cc	C	i.146 000002	Antihypertensive efficacy in patients with mild to moderate hypertension	DB, PL, R, PA	carvedilol	6.25	2 M	361	23-75	312/168	
		820173 40Lg					BID	12.5					
		820176 40Lh	C				placebo	25		119			
B101 (SB)	U.S. Multicenter (47 Investigators.)	820169 40Cc	C	1.174 000002	Antihypertensive efficacy and safety in patients with mild to moderate hypertension	DB, PL, PA, R	carvedilol	6.25	2 M	404	23-79	328/192	
		820173 40Lg					UID	12.5					
		820176 40Lh	C				placebo	50		116			

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Degree of Blinding

O = Open
SB = Single Blind
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OBS = Observer Blind

Invest. = Full List of Investigators
is provided in
Vol. 1.83 Page: 000077

DF = Dose Form

iv = Intravenous
C = Capsule
sr = Sustained Release
T = Tablet
PO = Oral, Nos

Treatment Assignment

R = Random
NR = Nonrandom

Degree of Control

UC = Uncontrolled
PL = Placebo
POS = Positive

Other

* = Ongoing Study as of 31 August 1992
NS = Information Not Specified or Not
Available

Pub. Ref. = Location of Publication
See Vol. 1.86 Page: 000274

Treatment Sequence

CO = Crossover
PA = Parallel
AD = Ascending Dose

Duration

H = Hour(s)
D = Day(s)
W = Week(s)
M = Month(s)
Y = Year(s)

Treatment Frequency

SD = Single Dose
UID = Once Daily
BID = Twice Daily
TID = Three Times Daily

Pop. = Population

CAD = Coronary Artery Disease
CHF = Congestive Heart Failure
HTN = Hypertension

000435

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DE	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.		
B102 (SB)	U.S. Multicenter (44 Investigators)	820468 40L.g/	C	1.271 000002	Safety in patients with mild to moderate hypertension	POS, O, R	carvedilol	12.5	1 Y	361	24-76	374/166			
		BID					25								
		labetalol					100.0								
		BID					200.0								
820173 40L.g															
820176 40L.h/							400.0								
820469 40L.h							with HCTZ added as indicated (except labetalol 100.0 mg)	25.0							
B103 (SB)	U.S. Multicenter (34 Investigators)	820468 40L.g/	C	1.300 000002	Safety in patients with mild to moderate hypertension	POS, O, R	carvedilol	12.5	1 Y	333	26-77	309/187			
		UID					25.0								
		labetalol					100.0								
		BID					200.0								
820173 40L.g							50.0								
820729 40L.h/							400.0								
820469 40L.h/							with HCTZ added as indicated	25.0							
820176 40L.h							50.0								

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Treatment Sequence
XC = Crossover
PA = Parallel
AD = Ascending Dose

Duration
H = Hour(s)
D = Day(s)
W = Week(s)
M = Month(s)
Y = Year(s)

Treatment Frequency
SD = Single Dose
UID = Once Daily
BID = Twice Daily
TID = Three Times Daily

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HTN = Hypertension

000436

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
B104 (SB)	U.S. Multicenter (23 Investigators)		C	1.231 000002	Antihypertensive efficacy in Black patients	DB, PL, R, PA	carvedilol	6.25	2 M	85	25-76	117/129	
							BID	12.5					
								25.0					
							labetalol	100.0					
	200.0	79											
	400.0												
		placebo		82									
C1106 (SB)	U.S. Multicenter (14 Investigators)	820354 40Aa 820169 40Cc 820469 40Lg 820469 40Lh	C	1.206 000002	Antihypertensive efficacy and safety in patients with mild to moderate hypertension	DB, PL, R, PA	carvedilol BID	3.125	4 M	187	2-84	169/111	
							UID, BID	6.25					
								12.5					
								25.0					
								50.0					
		placebo		93									

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Treatment Sequence
XO = Crossover
PA = Parallel
AD = Ascending Dose

Duration
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W = Week(s)
M = Month(s)
Y = Year(s)

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Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
C1107 (SB)	U.S. Multicenter (15 Investigators)	820169 40C.c	C	1.219 000002	Antihypertensive efficacy and safety in patients whose blood pressure is uncontrolled on HCTZ	DB, PL, R, PA	carvedilol / HCTZ	6.25 / 25.0	1 M	200	25-80	172/94	
		820468 40L.g					12.5 / 25.0						
		820469 40L.h					placebo / HCTZ	placebo / 25.0		66			
C1109 (SB)	U.S. Multicenter (13 Investigators)	820468 40L.g	T	1.255 000002	Antihypertensive efficacy and safety in patients with mild to moderate hypertension	DB, POS, PA, R, PL	carvedilol	12.5	11 W	105	25-80	181/77	
		820469 40L.h	T				UID	25.0					
							atenolol	50.0					101
							placebo	100.0		52			

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Treatment Sequence
XO = Crossover
PA = Parallel
AD = Ascending Dose

Duration
H = Hour(s)
D = Day(s)
W = Week(s)
M = Month(s)
Y = Year(s)

Treatment Frequency
SD = Single Dose
UD = Once Daily
BID = Twice Daily
TID = Three Times Daily

Pop. = Population
CAD = Coronary Artery Disease
CHF = Congestive Heart Failure
HIN = Hypertension

030458

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DE	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
CAR/SA/01 (SB)	S. Africa (Sareli, P.) (Borow, K.) (Lang, R.)	1/25 B/7	T iv	1.54 000002	Efficacy on left ventricular contractility and myocardial oxygen consumption in hypertensive patients with systolic dysfunction	SD,O	carvedilol nitro-prusside	25.0 0.250- 0.750 µg/ kg/ min	one dose	10	27-64	7/3	
CAR/JK/104 (SB)	U.K. Multicenter (39 Investigators)	1/25 B/7 2/12.5 B/3	T	1.350 000002	Antihypertensive efficacy and safety in elderly patients with mild to moderate hypertension	DB, PA, R	carvedilol III)	12.5 to 25.0 25.0 to 50.0	3 M	232	30-87	89/143	
CAR/UK/105 (SB)	U.K. (Webster, J.) (Lyons, D.) (Fowler, G.) (Petrie, J.C.)	2/12.5 B/3 1/25 B/8	T	1.114 000002	Hypotensive efficacy in patients who received bendrofluzide continuously and whose blood pressure remains uncontrolled	DB, PL, POS, R, XO	carvedilol SD atenolol SD placebo	12.5 25.0 50.0	1 D per period	12	36-65	4/8	

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Treatment Assignment
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UC = Uncontrolled
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Pub. Ref. = Location of Publication
See Vol. 1.86 Page: 000274

Treatment Sequence
XO = Crossover
PA = Parallel
AD = Ascending Dose

Duration
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D = Day(s)
W = Week(s)
M = Month(s)
Y = Year(s)

Treatment Frequency
SD = Single Dose
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BD = Twice Daily
TID = Three Times Daily

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CHF = Congestive Heart Failure
HTN = Hypertension

655010

Table 2.G.2 (cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
CARV0003 (BM)	U.S. (Zinny, M.)	819176 40Ge	C	1.76	Dose finding study for antihypertensive efficacy in patients with mild to moderate hypertension	DB, Pl., PA, R	carvedilol	12.5	1 M	33	26-68	34/10	17
		819177 40Fc		000G03			110	25.0					
		819178 40Ge	C				placebo	50.0					
CARV0004 (BM)	(Petrin, T.)	819176 40Ge	C	1.114	Antihypertensive efficacy in patients with mild to moderate hypertension	DB, R, PA, Pl.	carvedilol	12.5	1 M	6	40-70	4/5	
		819177 40Fc		00016R			110	25.0					
		819178 40Ge					placebo (11)	50.0					
CARV0005 (BM)	U.S. (Garrett, B.) (Levy, B.)	819176 40Ge 819177 40Fc 819178 40Ge	C	1.329 000002	Antihypertensive efficacy of carvedilol administered once a day compared with carvedilol administered twice a day in patients with hypertension	DB, PA, R	carvedilol 110 110	25.0 50.0	7 W	6	36-66	4/2	

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Vol. 1.83 Page: 000177

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Pl = Oral, Non

Treatment Assignment
R = Random
NR = Nonrandom

Degree of Control
UC = Uncontrolled
Pl. = Placebo
PlS = Positive

Notes
* = Ongoing Study as of 31 August 1992
NS = Information Not Specified or Not
Available

Pub. Ref = Location of Publication
See Vol. 1.86 Page: 000274

Treatment Sequence
XC = Crossover
PA = Parallel
AD = Ascending Dose

Duration
H = Hour(s)
D = Day(s)
W = Week(s)
M = Month(s)
Y = Year(s)

Treatment Frequency
SD = Single Dose
110 = Once Daily
BID = Twice Daily
TID = Three Times Daily

Pop = Population
CAD = Coronary Artery Disease
CHF = Congestive Heart Failure
HTN = Hypertension

000570

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
CARV0006 (BM)	Bahamas (Lunn, J.) (Mosier, M.)	CTM027	C	1.330	Antihypertensive efficacy and safety in black patients with mild to moderate hypertension	R, DB, PA, POS	carvedilol	3.125	2 M	19	36-69	8/31	
		CTM026 819176 40Gc 819177 40Fc					BID	6.25 12.5 25.0 20.0 40.0 60.0 80.0					
CARV0021 (BM)	U.S. (Grasela, T.) (Schultz, R.)	CTM027	C	1.79	Antihypertensive and hypotensive efficacy in patients with mild to moderate hypertension	DB, PL, PA, R	carvedilol	3.125	2 W	28 ¹	23-67	27/10	
		CTM026 819176 40Gc					BID	6.25 12.5					
							placebo						
							BID						

¹A total of 37 patients were analyzed for efficacy; 41 patients were randomized.

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 DS = Daiichi Sankyo

Degree of Blinding

O = Open
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 DB = Double Blind
 OHS = Observer Blind

Invest = Full List of Investigators is provided in Vol 1.81 Page 000077

DF = Dose Form

iv = Intravenous
 C = Capsule
 sr = Sustained Release
 T = Tablet
 PO = Oral, Nos

Treatment Assignment

R = Random
 NR = Nonrandom

Degree of Control

UC = Uncontrolled
 PL = Placebo
 POS = Positive

Other

* = Ongoing Study as of 31 August 1992
 NS = Information Not Specified or Not Available

Pub Ref = Location of Publication
 See Vol. 1.86 Page 000274

Treatment Sequence

XO = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration

H = Hour(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency

SD = Single Dose
 QD = Once Daily
 BID = Twice Daily
 TID = Three Times Daily

Exp. = Population

CAID = Coronary Artery Disease
 CHF = Congestive Heart Failure
 HTN = Hypertension

000479

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
INT/CAR/02 (SB)	Netherlands, Belgium (Dupont, A.) (Gerlag, P.) (Braun, J)	1 B/1 lot 1 820378 20G	T	1.110 000002	Efficacy and safety of carvedilol added to HCTZ therapy	SB	carvedilol/ HCTZ UID	12.5/ 25.0 25.0/ 25.0	10 D	25	41-69	13/12	6

Sponsor
 SB = SmithKline Beecham
 BM = Boehringer Mannheim
 DS = Daiichi Seiyaku

Degree of Blinding
 O = Open
 SB = Single Blind
 DB = Double Blind
 OBS = Observer Blind

Invest. = Full List of Investigators
 is provided in
 Vol. 1.11 Page: 000077

DF = Dose Form
 iv = Intravenous
 C = Capsule
 sr = Sustained Release
 T = Tablet
 PO = Oral, Nos

Treatment Assignment
 R = Random
 NR = Nonrandom

Degree of Control
 UC = Uncontrolled
 Pl. = Placebo
 POS = Positive

Other
 * = Ongoing Study as of 31 August 1992
 NS = Information Not Specified or Not
 Available

Pub. Ref = Location of Publication
 See Vol. 1.16 Page: 000274

Treatment Sequence
 XO = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration
 H = Hour(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency
 SD = Single Dose
 UID = Once Daily
 BID = Twice Daily
 TID = Three Times Daily

Pop. = Population
 CAD = Coronary Artery Disease
 CHF = Congestive Heart Failure
 HTN = Hypertension

000572

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
INTCAR/05 (SB)	France (Honore, P.) (Olive, T.)	2/12.5 B/2 1/25 B/6	T	1.111 000002	Antihypertensive effect and safety of the addition of carvedilol to existing captopril therapy and vice versa	PO5, DB, R	Treatment 1:			14	36 - 77	14/14	
							Monotherapy carvedilol (HD)	12.5	2D				
								25.0	12D				
							Combination carvedilol (HD)	25.0	10D				
							captopril BID	12.5	2D				
								25.0	8D				
							Treatment 2:			14			
							Monotherapy captopril BID	25.0	14D				
Combination captopril BID	25.0	10D											
	12.5	2D											
	25.0	8D											

Summary

SB = SmithKline Beecham
 BM = Boehringer Mannheim
 DS = Daiichi Sankyo

Degree of Blinding

O = Open
 SB = Single Blind
 DB = Double Blind
 OBS = Observer Blind

Invest = Full List of Investigators
 is provided in
 Vol. 1.83 Page: 000077

DF = Dose Form

iv = Intravenous
 C = Capsule
 sr = Sustained Release
 T = Tablet
 PO = Oral, Non

Treatment Assignment

R = Random
 NR = Nonrandom

Degree of Control

UC = Uncontrolled
 Pl. = Placebo
 POS = Positive

Notes

* = Ongoing Study as of 31 August 1992
 NS = Information Not Specified or Not
 Available

Pub. Ref. = Location of Publication
 See Vol. 1.86 Page: 000274

Treatment Sequence

XO = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration

H = Hour(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency

SD = Single Dose
 QD = Once Daily
 BID = Twice Daily
 TID = Three Times Daily

Pop = Population

CAD = Coronary Artery Disease
 CHF = Congestive Heart Failure
 HTN = Hypertension

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Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
INT/CAR/06 (SB)	The Netherlands (Juttman, J.)	2/12.5 B/2 1/25 B/6, B/7	T	I.112 000002	Antihypertensive effect and safety of the addition of carvedilol to existing nifedipine therapy and vice versa	DB, R, PA	Treatment I: Monotherapy carvedilol UID Combination Phase carvedilol UID/ + nifedipine BID	12.5 25.0 25.0/ 20.0	2D 12D 10D	7	27 - 83	8/6	14

Sponsor

SB = SmithKline Beecham
 BM = Boehringer Mannheim
 DS = Daiichi Seiyaku

Degree of Blinding

O = Open
 SB = Single Blind
 DB = Double Blind
 OBS = Observer Blind

Invest = Full List of Investigators
 is provided in
 Vol. 1 B3 Page: 000077

DF = Dose Form

iv = Intravenous
 C = Capsule
 sr = Sustained Release
 T = Tablet
 PO = Oral, Not

Treatment Assignment

R = Random
 NR = Nonrandom

Degree of Control

UC = Uncontrolled
 Pl. = Placebo
 POS = Positive

Other

* = Ongoing Study as of 31 August 1992
 NS = Information Not Specified or Not
 Available

Pub. Ref = Location of Publication
 See Vol. 1 B6 Page: 000274

Treatment Sequence

XO = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration

H = Hour(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency

SD = Single Dose
 UID = Once Daily
 BID = Twice Daily
 TID = Three Times Daily

Pop. = Population

CAD = Coronary Artery Disease
 CHF = Congestive Heart Failure
 HTN = Hypertension

000077

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DE	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
INT/CAR/06 (Cont'd)							Treatment 2: Monotherapy nifedipine BID	20.0	14D	7			
							Combination nifedipine BID carvedilol UID	20.0/ 12.5 25.0	10D 2D 8D				
INT/CAR/07 (SB)	Europe Multicenter (38 Investigators)	2/12.5 B/1, B/2 1 B/2, 1/25 BM/ 1/25 B/8	T	1.336 000002	Anti-hypertensive efficacy and safety of carvedilol and atenolol in patients with mild to moderate hypertension	DB, POS, R	carvedilol UID	12.5 first 2 days, then 25.0	2 M	161	20 - 84	176 / 149	27
							atenolol	50.0		164			

Sponsor
SB = SmithKline Beecham
BM = Boehringer Mannheim
DS = Daiichi Sankyo

Degree of Blinding
O = Open
SB = Single Blind
DB = Double Blind
OBS = Observer Blinded

Invest. = Full List of Investigators is provided in Vol. 1.83 Page: 000077

DE = Dose Form
iv = Intravenous
C = Capsule
sr = Sustained Release
T = Tablet
PC = Oral, Nas

Treatment Assignment
R = Random
NR = Nonrandom

Degree of Control
UC = Uncontrolled
Pl. = Placebo
POS = Positive

Other
* = Ongoing Study as of 31 August 1992
NS = Information Not Specified or Not Available

Pub. Ref. = Location of Publication
See Vol. 1.86 Page: 000274

Treatment Sequence
XO = Crossover
PA = Parallel
AD = Ascending Dose

Duration
H = Hour(s)
D = Day(s)
W = Week(s)
M = Month(s)
Y = Year(s)

Treatment Frequency
SD = Single Dose
QD = Once Daily
BID = Twice Daily
TID = Three Times Daily

Pop. = Population
CAD = Coronary Artery Disease
CHF = Congestive Heart Failure
HTN = Hypertension

01075

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Spanner)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
INT/CAR/08 (SB)	France (13 Investigators)	2/12.5 B/2 1/25 B/3	T	1.331 000002	Antihypertensive efficacy and safety in patients with mild to moderate benign essential hypertension	DB, R, POS, PA	carvedilol TID	12.5 for the first 2 days, then 25.0	2 M	105	22 - 76	101 / 116	
							acebutolol BID	200.0		112			
INT/CAR/10 (SB)	U.K. Medical & Clinical Research Associates	1 B/2	T	1.343 000002	Antihypertensive efficacy and safety in patients with mild to moderate benign essential hypertension	DB, POS, R, PA	carvedilol TID	25.0 50.0	2 M	103	26 - 82	118 / 87	26
							nifedipine BID	20.0 40.0		102			

Sponsor

SB = SmithKline Beecham
 BM = Boehringer Mannheim
 DS = Daiichi Sankyo

Degree of Blinding

O = Open
 SB = Single Blind
 DB = Double Blind
 OBS = Observer Blind

Invest. = Full List of Investigators
 is provided in
 Vol. 1 B3 Page. 000077

DF = Dose Form

iv = Intravenous
 C = Capsule
 sr = Sustained Release
 T = Tablet
 PO = (oral, Non)

Treatment Assignment

R = Random
 NR = Nonrandom

Degree of Control

UC = Uncontrolled
 PL = Placebo
 POS = Positive

Other

* = Ongoing Study as of 31 August 1992
 NS = Information Not Specified or Not
 Available

Pub. Ref. = Location of Publication
 See Vol. 1 B6 Page. 000274

Treatment Sequence

XO = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration

H = Hour(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency

SD = Single Dose
 TID = (Once Daily)
 BID = Twice Daily
 TID = Three Times Daily

Exp. = Population

CAD = Coronary Artery Disease
 CHF = Congestive Heart Failure
 HTN = Hypertension

925030

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DE	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	n	Age Range (yrs)	Sex M/F	Pub. Ref.
INT/CAR/11 (SB)	U.K. Multicenter (21 Investigators)	1 B/2	T	1.343 000203	Antihypertensive efficacy and safety in patients with mild to moderate benign essential hypertension	DB, POS, PA, R	carvedilol HCTZ	25.0 50.0 25.0 50.0	2 M	100 100	27-88	105/95	16
INT/CAR/12 (SB)	Europe Multicenter (30 Investigators)	1 B/2; 1/25 B/6 2/12.5 B/2	T	1.344 000002	Antihypertensive efficacy and safety in patients with mild to moderate benign essential hypertension	DB, POS, R, PA	carvedilol UID captopril BID	12.5-2D, 25.0 50.0 25.0 50.0	2 M	147 151	23 - 84	140 / 158	
INT/CAR/14F	France (Luccioni, R.)	2/12.5 B/3 1/25 B/8 lot 1	T	1.335 000002	Antihypertensive efficacy and tolerance in patients with mild to moderate benign hypertension	DB, XO, POS, R	carvedilol UID labetalol BID	12.5 for 2 Days, then 25.0 200.0	4W per period	16	48 - 69	9/7	

Sponsor
SB = SmithKline Beecham
BM = Boehringer Mannheim
DS = Daiichi Sankyo

Degree of Blinding
D = Open
SB = Single Blind
DB = Double Blind
OBS = Observer Blind

Invest. = Full List of Investigators is provided in Vol. 1.83 Page: 000077

DE = Dose Form
iv = Intravenous
C = Capsule
sr = Sustained Release
T = Tablet
PO = Oral, Not

Treatment Assignment
N = Random
NR = Nonrandom

Degree of Control
UC = Uncontrolled
Pl. = Placebo
POS = Positive

Other
* = Ongoing Study as of 31 August 1992
NS = Information Not Specified or Not Available

Pub. Ref. = Location of Publication
See Vol. 1.86 Page: 000274

Treatment Sequence
XO = Crossover
PA = Parallel
AD = Ascending Dose

Duration
H = Hour(s)
D = Day(s)
W = Week(s)
M = Month(s)
Y = Year(s)

Treatment Frequency
SD = Single Dose
UID = Once Daily
BID = Twice Daily
TID = Three Times Daily

Exp. = Evaluation
CAD = Coronary Artery Disease
CHF = Congestive Heart Failure
HTN = Hypertension

000077

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
INT/CAR/14/ HOL (SB)	The Netherlands (Schalekamp, M.)	2/12.5 B/3 1/25 B/1 / 1/25 B/8	T	1.350 000152	Monitor 24 hour blood pressure during carvedilol treatment	DB, R, PL, XO	carvedilol daily placebo	25.0	21D per period	13	38-70	8/5	
INT/CAR/15/ UK	U.K. (James, I.)	1/25 B/6/ 1/25 B/8	T T	1.112 000208	Cerebral flow in patients with mild to moderate hypertension	DB, POS, XO, R	carvedilol III propranolol BID	25.0 80.0	4W per period	13	29-63	8/5	
INT/CAR/17F (SB)	France (Cournot, A.)	1/25 B/8 lot1 2/12.5 B/3	T T	1.84 000296	Peripheral hemodynamic effects in patients with mild to moderate hypertension	DB, R, PL, XO	carvedilol SD placebo SD	25.0 50.0	1D per period	12	37-60	9/3	
MF2774 (BM)	Germany (Franz, I.W.)	814965 Aa	C C	1.117 000158	Antihypertensive efficacy at rest and during exercise in patients with hypertension	R, SB, XO, POS	carvedilol BID III metoprolol BID	25.0-2W 50.0-2W 100.0	4 W per period	20	33-57	20/0	11

Sponsor
SB = SmithKline Beecham
BM = Boehringer Mannheim
DS = Daiichi Selyaku

Degree of Blinding
O = Open
SB = Single Blind
DB = Double Blind
OBS = Observer Blind

Invest = Full list of investigators is provided in Vol. 1 B Page: 000077

DF = Dose Form
iv = Intravenous
C = Capsule
sr = Sustained Release
T = Tablet
PO = Oral, Nas

Treatment Assignment
R = Random
NR = Nonrandom

Degree of Control
UC = Uncontrolled
PL = Placebo
POS = Positive

Other
* = Ongoing Study as of 31 August 1992
NS = Information Not Specified or Not Available

Pub. Ref. = Location of Publication
See Vol. 1 B Page: 000274

Treatment Sequence
XO = Crossover
PA = Parallel
AD = Ascending Dose

Duration
H = Hour(s)
D = Day(s)
W = Week(s)
M = Month(s)
Y = Year(s)

Treatment Frequency
SD = Single Dose
III = Once Daily
BID = Twice Daily
TID = Three Times Daily

Pop = Population
CAD = Coronary Artery Disease
CHF = Congestive Heart Failure
HTN = Hypertension

000478

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DE	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
MF2813 (BM)	Germany (Boehr, G.)	814965 Aa	C	1.118 000002	Antihypertensive efficacy at rest and during exercise in patients with essential hypertension	DB, PA, R, POS	carvedilol	25.0	2 M	8	30-54	NS	
		814966 Ab					propranolol BID	50.0 80.0 160.0					
MF2872 (BM)	Austria (Klein, W.)	815066	C	1.119 000026	Antihypertensive efficacy at rest and during exercise in patients with hypertension	DB, R, POS, PA	carvedilol BID	25.0-4W	8W	12	24-69	18/6	
			C				atenolol QID	25.0-4W 100.0					
MF2938 (BM)	Sweden (Hansson, L.)	814965 Aa	C	1.120 000002	Antihypertensive efficacy in patients with hypertension	DB, PA, R, POS	carvedilol	25.0	4 W	20	26-60	23/7	11
		814966 Ab					propranolol BID	50.0 80.0					

Sponsor
 SB = SmithKline Beecham
 BM = Boehringer Mannheim
 DS = Daiichi Soryaku

Degree of Blinding
 O = Open
 SB = Single Blind
 DB = Double Blind
 OBS = Observer Blind

Invest. = Full List of Investigators
 is provided in
 Vol. 1.83 Page: 000077

DE = Dose Form
 iv = Intravenous
 C = Capsule
 sr = Sustained Release
 T = Tablet
 PO = (Oral, Nas)

Treatment Assignment
 R = Random
 NR = Nonrandom

Degree of Control
 UC = Uncontrolled
 PL = Placebo
 POS = Positive

Other
 * = Ongoing Study as of 31 August 1992
 NS = Information Not Specified or Not
 Available

Pub. Ref. = Location of Publication
 See Vol. 1.86 Page: 000274

Treatment Sequence
 XO = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration
 H = Hour(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency
 SD = Single Dose
 QD = Once Daily
 BID = Twice Daily
 TID = Three Times Daily

Pop. = Population
 CAD = Coronary Artery Disease
 CHF = Congestive Heart Failure
 HTN = Hypertension

625050

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DE	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
MF2954 (BM)	Australia (Morgan, T.)	818902 4017b	C T	1.120 000241	Antihypertensive efficacy and peripheral hemodynamic changes in patients with hypertension	DB, PA, R, POS	carvedilol (III) metoprolol (II)	50.0 100.0	4W	18 15	38-70	31/2	21
MF2978 (MF)	Germany (Schoeppe, B.)	815066 814966 Ab	C	1.122 000002	Antihypertensive efficacy and the alterations to plasma lipoprotein in patients with hypertension	DB, R, PA	carvedilol (II) carvedilol (III)	25.0 50.0	12W	17 ^a	25-59	8/9	21

^a17 patients were analyzed for efficacy; 25 patients were randomized.

05/05/0

Sponsor
 SB = Sankyo
 BM = Boehringer Mannheim
 DS = Daiichi Sankyo

Degree of Blinding
 O = Open
 SB = Single Blind
 DB = Double Blind
 OBS = Observer Blind

Invest. = Full List of Investigators is provided in Vol. 1.81 Page: 000077

DE = Dose Form
 iv = Intravenous
 C = Capsule
 sr = Sustained Release
 T = Tablet
 PO = Oral, solution

Treatment Assignment
 R = Random
 NR = Nonrandom

Degree of Control
 UC = Uncontrolled
 PL = Placebo
 POS = Positive

Other
 * = Ongoing Study as of 31 August 1992
 NS = Information Not Specified or Not Available

Pub. Ref. = Location of Publication
 See Vol. 1.86 Page: 000274

Treatment Sequence
 X = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration
 H = Hour(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency
 SD = Single Dose
 OD = Once Daily
 BID = Twice Daily
 TID = Three Times Daily

Pop. = Population
 CAD = Coronary Artery Disease
 CHF = Congestive Heart Failure
 HHN = Hypertension

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DE	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
MF3000 (BM)	Germany (Meyer-Sabellek)	815293	C	1.351 000002	Antihypertensive efficacy in patients with hypertension	DB, AD, PA, R, POS	carvedilol UID BID UID metoprolol UID BID UID	25.0-2W 25.0-3W 50.0-3W 100.0-2W 100.0-3W 200.0-3W	2 M	6 ³	27 - 59	9/4	18, 22
MF3056 (BM)	Germany (Vetter, H.)	819268 40Ec	C	1.352 000002	Antihypertensive efficacy and safety in propranolol-pretreated patients	DB, R, PA, POS	carvedilol BID propranolol / dihydratazinc BID	25.0 80.0 25.0	3 M	14 12	18 - 63	18/4 ⁴	

³A total of 13 patients were analyzed for efficacy. 18 patients were randomized.
⁴Includes one patient (sex unknown) who withdrew before randomization.

Sponsor
 SB = SmithKline Beecham
 BM = Boehringer Mannheim
 DS = Daiichi Sankyo

Degree of Blinding
 O = Open
 SB = Single Blind
 DB = Double Blind
 OBS = Observer Blind

Invest. = Full List of Investigators is provided in Vol. 1.8 Page: 00077

DE = Dose Form
 iv = Intravenous
 C = Capsule
 sr = Sustained Release
 T = Tablet
 PO = Oral, Not

TREATMENT ASSIGNMENT
 R = Random
 NR = Nonrandom

Degree of Control
 UC = Uncontrolled
 P. = Placebo
 POS = Positive

Other
 * = Ongoing Study as of August 1992
 NS = Information Not Specified or Not Available

Pub. Ref. = Location of Publication
 See Vol. 1.86 Page: 00274

Treatment Sequence
 X() = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration
 H = Hour(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency
 SC = Single Dose
 QD = Once Daily
 BID = Twice Daily
 TID = Three Times Daily

Pop. = Population
 CAD = Coronary Artery Disease
 CHF = Congestive Heart Failure
 HTN = Hypertension

000002

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Repor. Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
MF3072 (BM)	Argentina (Hauger-Klevene, J.)	816820 40Bc	C	1.124 000089	Efficacy, safety, and influence on serum lipid concentrations and respiratory parameters in patients with mild to moderate hypertension	DB, R, AD,PA, POS	carvedilol	12.5	99D	24 ⁵	39-66	12/32	
		816616 Bc	C				BID	25.0 50.0					
MF3303 (BM)	Germany (Muller, G.)	816034 Bb	C	1.126 000002	Determine antihypertensive threshold dose	DB, Pl., XO, R	carvedilol	25.0	1D per period	35 ⁶	32-62	19/16	
			C				SD placebo						

⁵A total of 44 patients were analyzed for efficacy; 60 patients were randomized.

⁶35 patients were analyzed for efficacy; 40 patients were randomized.

Sponsor

SK = SmithKline Beecham
 BM = Boehringer Mannheim
 DS = Daiichi Selyaku

Degree of Blinding

O = Open
 SB = Single Blind
 DB = Double Blind
 OBS = Observer Blind

Invest = Full List of Investigators
 is provided in
 Vol. 1.83 Page: 000077

DF = Dose Form

iv = Intravenous
 C = Capsule
 sr = Sustained Release
 T = Tablet
 PO = Oral, Nas

Treatment Assignment

R = Random
 NR = Nonrandom

Degree of Control

UC = Uncontrolled
 Pl. = Placebo
 POS = Positive

Other

* = Ongoing Study as of 31 August 1992
 NS = Information Not Specified or Not
 Available

Pub Ref = Location of Publication
 See Vol. 1.86 Page: 000274

Treatment Sequence

XO = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration

H = Hour(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency

SD = Single Dose
 QD = Once Daily
 BID = Twice Daily
 TID = Three Times Daily

Pop. = Population

CAD = Coronary Artery Disease
 CHF = Congestive Heart Failure
 HTN = Hypertension

000032

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
MF3304 (BM)	Germany Multicenter (21 Investigators)	818000 Cb	C	1.127 000002	Antihypertensive efficacy, tolerability, and threshold	DB, R, PL, PA	carvedilol BID placebo	25.0	1SD	417	20-75	37/43	
			C							39			
MF3352 (BM)	Austria (Slany, J.)	818330 40Dd	C	1.353 000001	Antihypertensive efficacy at rest and during exercise in patients with mild to moderate hypertension	DB, PL, R	carvedilol BID placebo	12.5	6 W	12	37-63	13/5	
								25.0		6			
MF3412 (BM)	Belgium Multicenter (9 Investigators)	818173 Cd	C	1.130 000002	Effects on blood pressure, renal hemodynamics, and cardiac function in patients with mild to moderate hypertension	DB, PL, R, PA	carvedilol UID placebo	50.0	31 D	10	37-66	16/4	7-9
			C							10			

⁷A total of 80 patients were analyzed for efficacy; 98 patients were randomized.

Sponsor
SB = SmithKline Beecham
BM = Boehringer Mannheim
DS = Daiichi Seiyaku

Degree of Blinding
O = Open
SB = Single Blind
DB = Double Blind
OBS = Observer Blind

Invest. = Full List of Investigators
is provided in
Vol. 1.81 Page: 000077

DF = Dose Form
iv = Intravenous
C = Capsule
sr = Sustained Release
T = Tablet
PO = Oral, Nos

Treatment Assignment
R = Random
NR = Nonrandom

Degree of Control
UC = Uncontrolled
PL = Placebo
POS = Positive

Other
* = Ongoing Study as of 31 August 1992
NS = Information Not Specified or Not
Available

Pub. Ref. = Location of Publication
See Vol. 1.86 Page: 000274

Treatment Sequence
XO = Crossover
PA = Parallel
AD = Ascending Dose

Duration
H = Hour(s)
D = Day(s)
W = Week(s)
M = Month(s)
Y = Year(s)

Treatment Frequency
SD = Single Dose
UID = Once Daily
BID = Twice Daily
TID = Three Times Daily

Pop. = Population
CAD = Coronary Artery Disease
CHF = Congestive Heart Failure
HTN = Hypertension

000533

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DE	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
MF3458 (BM)	Germany (Steger, W.)	819148 40DF	C	1.134 000246	Determine antihypertensive threshold dose and safety in elderly patients with mild to moderate hypertension	DB, PA, R, POS	carvedilol UID,	25.0	3 M	36	60 - 89	30/45	
							pindolol UID, BID	7.5		39			
MF3460 (BM)	Europe Multicenter (4 Investigators)	819291 40DF	C	1.355 000002	Long-term efficacy and safety in patients with mild to moderate hypertension	DB, PA, R, POS	carvedilol	25.0	1Y	337	20 - 74	278/224	
							BID	50.0		165			
							pindolol	7.5					
							BID with HCTZ added as indicated	15.0					

Sponsor

SB = SmithKline Beecham
 BM = Boehringer Mannheim
 DS = Daiichi Seiyaku

Degree of Blinding

O = Open
 SB = Single Blind
 DB = Double Blind
 OBS = (Observer Blind)

Invent. = Full List of Investigators is provided in Vol. 1.83 Page: 000077

DF = Dose Form

iv = Intravenous
 C = Capsule
 sr = Sustained Release
 T = Tablet
 PO = Oral, Nos

Treatment Assignment

R = Random
 NR = Nonrandom

Degree of Control

UC = Uncontrolled
 Pl. = Placebo
 POS = Positive

Other

* = Ongoing Study as of 31 August 1992
 NS = Information Not Specified or Not Available

Pub. Ref. = Location of Publication

See Vol. 1.86 Page: 000274

Treatment Sequence

XO = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration

H = Hour(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency

SD = Single Dose
 UID = Once Daily
 BID = Twice Daily
 TID = Three Times Daily

Pop. = Population

CAD = Coronary Artery Disease
 CHF = Congestive Heart Failure
 HTN = Hypertension

030533

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
MF3461 (BM)	Germany, Belgium Multicenter (13 Investigators)	819156 40Ec 819163 40Fc 819152 40Aa/ 819703 40Aa	C	1.410 000002	Antihypertensive efficacy and safety in patients with mild to moderate uncomplicated essential hypertension	DB, PA, R, POS	carvedilol (III) pindolol (III)	25.0 50.0 100.0 15.0	13 W	156 49	23-70	102/103	
MF3464 (BM)	Germany Multicenter (14 Investigators)	819156 40Ec/ 819562 40Fc 819163 40Fc	C C	1.131 000002	Antihypertensive efficacy in insulin dependent diabetics with mild to moderate hypertension	DB, R, POS, PA	carvedilol BID metoprolol BID	25.0 50.0 50.0 100.0	8W	40 39	18-82	40/39	
MF3465 (BM)	Germany Multicenter (19 Investigators)	819156 40Ec/ 819562 40Fc 819163 40Fc	C C	1.133 000002	Efficacy and safety in patients with non-insulin dependent diabetes and mild to moderate hypertension	DB, R, POS, PA	carvedilol BID metoprolol BID	25.0 50.0 50.0 100.0	8W	45 44	23-92	44/45	10

Sponsor
 SB = SmithKline Beecham
 BM = Boehringer Mannheim
 DS = Daiichi Soryaku

Degree of Blinding
 O = Open
 SB = Single Blind
 DB = Double Blind
 ORS = Observer Blind

Invest = Full list of investigators is provided in
 Vol. 1.83 Page: 000077

DF = Dose Form
 iv = Intravenous
 C = Capsule
 sr = Sustained Release
 T = Tablet
 PO = Oral, Non

Treatment Assignment
 R = Random
 NR = Nonrandom

Degree of Control
 UC = Uncontrolled
 Pl. = Placebo
 POS = Positive

Other
 * = Ongoing Study as of 31 August 1992
 NS = Information Not Specified or Not Available

Pub. Ref. = Location of Publication
 See Vol. 1.86 Page: 000274

Treatment Sequence
 XO = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration
 H = Hour(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency
 SD = Single Dose
 (III) = Once Daily
 BID = Twice Daily
 TID = Three Times Daily

Pop. = Population
 CAD = Coronary Artery Disease
 CHF = Congestive Heart Failure
 HTN = Hypertension

000035

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
MF3679 (BM)	France Multicenter (15 Investigators)	819776 4011c	C	1.412 000002	Efficacy and safety in patients with mild to moderate hypertension	DB, PA, R, POS	carvedilol	25.0	2 M	30	26 - 64	48/13	
							UID	50.0					
							labetalol BID	200.0 400.0					
MF3718 (BM)	Germany Multicenter (6 Investigators)	819854 40Gf 819818 4011f	C	1.136 000002	Antihypertensive efficacy and safety in patients with hypertension	DB, R, PA	carvedilol	25.0 ^a	1D	13 ^a	27 - 81	14/12	
							+ torsemide SD	1.25					
							carvedilol +torsemide SD	12.5/ 2.5					

^aA total of 26 patients were analyzed for efficacy; 34 patients were randomized.

Sponsor
 SB = SmithKline Beecham
 BM = Boehringer Mannheim
 DS = Daiichi Soryaku

Design of Blinding
 O = Open
 SB = Single Blind
 DB = Double Blind
 OBS = Observer Blind

Invest. = Full List of Investigators
 is provided in
 Vol. 1 R.3 Page: 000077

DF = Dose Form
 iv = Intravenous
 C = Capsule
 sr = Sustained Release
 T = Tablet
 PO = Oral, Nus

Treatment Assignment
 R = Random
 NR = Nonrandom

Degree of Control
 UC = Uncontrolled
 Pl. = Placebo
 POS = Positive

(Other
 * = Ongoing Study as of 31 August 1992
 NS = Information Not Specified or Not
 Available

Pub. Ref. = Location of Publication
 See Vol. 1 R.6 Page: 000274

Treatment Sequence
 XO = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration
 H = Hour(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency
 SD = Single Dose
 UID = Once Daily
 BID = Twice Daily
 TID = Three Times Daily

Pop. = Population
 CAD = Coronary Artery Disease
 CHF = Congestive Heart Failure
 HTN = Hypertension

000536

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
MF3780 (BM)	Germany Multicenter (7 Investigators)	819818 40Hc	C	1.136 000205	Antihypertensive efficacy and safety in patients with hypertension	DB, R, PL, PA	carvedilol +torasemide SD placebo	12.5/ 1.25	1D	20 ^a 17	31/71	21/16	
MF3816 (BM)	Germany Multicenter (12 Investigators)	819843 40Hc/ 819843 40Hc	C	1.413 000002	Antihypertensive efficacy and safety in elderly patients with mild to moderate hypertension	DB, PA, R, POS	carvedilol UID, BID nitrendipine UID, BID	25.0 20.0	3 M	39 38	58 - 83	28/49	15

^aA total of 37 patients were analyzed for efficacy; 45 patients were randomized.

000437

Sponsor
 SB = SmithKline Beecham
 BM = Boehringer Mannheim
 DS = Daiichi Sankyo

Degree of Blinding
 O = Open
 SB = Single Blind
 DB = Double Blind
 OBS = Observer Blind

Invest = Full List of Investigators
 is provided in
 Vol. 1 #1 Page: 000077

DF = Dose Form
 iv = Intravenous
 C = Capsule
 sr = Sustained Release
 T = Tablet
 PO = Oral, Non

Treatment Assignment
 R = Random
 NR = Nonrandom

Degree of Control
 UC = Uncontrolled
 PL = Placebo
 POS = Positive

Other
^a = Ongoing Study as of 31 August 1992
 NS = Information Not Specified or Not
 Available

Pub Ref = Location of Publication
 See Vol. 1 #6 Page: 000274

Treatment Sequence
 XC = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration
 H = Hour(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency
 SD = Single Dose
 UID = Once Daily
 BID = Twice Daily
 TID = Three Times Daily

Pop. = Population
 CAD = Coronary Artery Disease
 CHF = Congestive Heart Failure
 ICH = Hypertension

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
MF3830 (BM)	Germany (Dichm, C.)	819843 40Hc/	C	1.137 000002	Acute and subchronic effects on regional perfusion in hypertensive patients without peripheral occlusive disease	DB, PA, R, POS	carvedilol	25.0	6 W	16	42 - 69	25/8	
		819843 40Hc	C				UID	50.0					
MF3887 (BM)	Germany Multicenter (11 Investigators)	819843 40Hc/ 819843 40Hc	C	1.415 000003	Antihypertensive efficacy and safety in patients with hypertension	DB, PA, R, POS	carvedilol	25.0	10W	63	23-73	77/49	25
							UID	25.0					
							carvedilol/ ICTZ	25.0					
							UID	50.0					
							atenolol	50.0					
atenolol/ ICTZ	25.0												
										63			

Sponsor
 SB = SmithKline Beecham
 BM = Boehringer Mannheim
 DS = Daiichi Seiyaku

Degree of Blinding
 O = Open
 SB = Single Blind
 DB = Double Blind
 OBS = Observer Blind

Invest = Full List of Investigators is provided in Vol. 1 B3 Page: 000077

DF = Dose Form
 iv = Intravenous
 C = Capsule
 sr = Sustained Release
 T = Tablet
 IV = (Inal, Nos)

Treatment Assignment
 R = Random
 NR = Nonrandom

Degree of Control
 UC = Uncontrolled
 PL = Placebo
 POS = Positive

Other
 * = Ongoing Study as of 31 August 1992
 NS = Information Not Specified or Not Available

Pub. Ref. Location of Publication
 See Vol. 1 B6 Page: 000274

Treatment Sequence
 X() = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration
 H = Hour(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency
 SD = Single Dose
 OD = Once Daily
 BID = Twice Daily
 TID = Three Times Daily

Pop. = Population
 CAD = Coronary Artery Disease
 CHF = Congestive Heart Failure
 HTN = Hypertension

000538

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
MF3890 (BM)	Germany Multicenter (11 Investigators)	819843 4011c/ 819843 4011c	C	1.417 000002	Antihypertensive efficacy and safety in hypertensive patients pretreated with HCTZ	DB, PA, R, POS	carvedilol/ HCTZ UID atenolol / HCTZ UID	25.0 / 25.0 50.0 / 25.0	6 W	61 61	19 - 80	69/53	
MF3893 (BM)	Germany (Ludwig)	819843 4011c/ 819843 4011c 820175 400c	C C	1.138 000002	Comparison of carvedilol and atenolol on blood flow and microcirculation	DB, R, PA, POS	carvedilol UID atenolol UID	25.0 50.0 50.0	4W	14 14	22-57	21/7	
MF3916 (BM)	Germany (Hombach, V.)	819776 4011c	C	1.140 000141	Effects on peripheral circulation in hypertensive patients with peripheral arterial disease stage II	DB, PA, R, POS	carvedilol UID nitrendipine UID	25.0 20.0	4 W	1	64	1/0	

Sponsor
 SB = SmithKline Beecham
 BM = Boehringer Mannheim
 DS = Daiichi Seiyaku

Degree of Blinding
 () = Open
 SB = Single Blind
 DB = Double Blind
 OBS = Observer Blind

Invest. = Full List of Investigators is provided in Vol. 1 B3 Page: 000077

DF = Dose Form
 iv = Intravenous
 C = Capsule
 sr = Sustained Release
 T = Tablet
 PO = Oral, Nus

Treatment Assignment
 R = Random
 NR = Nonrandom

Degree of Control
 UC = Uncontrolled
 PL = Placebo
 POS = Positive

Other
 * = Ongoing Study as of 31 August 1992
 NS = Information Not Specified or Not Available

Pub. Ref. = Location of Publication
 Sec Vol.: 1.B6 Page: 000274

Treatment Sequence
 XO = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration
 H = Hour(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency
 SD = Single Dose
 UID = Once Daily
 BID = Twice Daily
 TID = Three Times Daily

Pop. = Population
 CAD = Coronary Artery Disease
 CHF = Congestive Heart Failure
 HTN = Hypertension

000539

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
MF3948 (BM)	U.K. Multicenter (44 Investigators)	820156 40Kc	C	1.419 000002	Antihypertensive efficacy and safety in patients with mild to moderate hypertension	DB, PA, R, POS	carvedilol nifedipine BID atenolol UID	25.0 50.0 20.0 40.0 50.0 100.0	3 M	106 ¹⁰ 101 104	57.3 57.1 56.0 (means)	145/16M 1 (NS)	12
MF9019 (BM)	Australia (Louis, W.J.)	820169 40Cc 820777 40Kc/ 820173 40Lg 820156 40Kc/ 820176 40Lh	C C C C	1.84 000406	Antihypertensive efficacy in elderly patients with mild to moderate hypertension	DB, Pl., R, XO, POS	carvedilol SD pindolol SD placebo	12.5 25.0 15.0	11) per period	16	58-78	9/7	

¹⁰A total of 311 patients were enrolled; 298 patients received medication.

Sponsor
 SB = SmithKline Beecham
 BM = Boehringer Mannheim
 DS = Daiichi Seiyaku

Degree of Blinding
 O = Open
 SB = Single Blind
 DB = Double Blind
 OBS = Observer Blind

Invest. = Full List of Investigators is provided in Vol. 1.83 Page: 000077

DF = Dose Form
 iv = Intravenous
 C = Capsule
 sr = Sustained Release
 T = Tablet
 IN = Oral, Non

Treatment Assignment
 R = Random
 NR = Nonrandom

Degree of Control
 UC = Uncontrolled
 Pl. = Placebo
 POS = Positive

Other
 * = Ongoing Study as of 31 August 1992
 NS = Information Not Specified or Not Available

Pub. Ref = Location of Publication
 See Vol.: 1.86 Page: 000274

Treatment Sequence
 XO = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration
 H = Hour(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency
 SD = Single Dose
 UID = Once Daily
 BID = Twice Daily
 TID = Three Times Daily

Pop. = Population
 CAD = Coronary Artery Disease
 CHF = Congestive Heart Failure
 HTN = Hypertension

000077

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
MF9609 (BM)	Mexico (Escarcega, J.)	820956 40Kc		1.423 000002	Antihypertensive efficacy in patients with mild to moderate uncomplicated essential hypertension	DB, R, POS, PA	carvedilol	25.0	6 W	49	36 - 79	30/69	
			UID				50.0						
		820175 40Oc					nifedipine	20.0		50			
G-8 (DS)	Japan (Goto, Y.)			1.424 000002	Antihypertensive efficacy in patients with mild to moderate hypertension	DB, PA	carvedilol	5-20	3 M	114	NS	NS	
			UID										
							labetalol	150 450		115			
							TID						

Studies Ongoing or Completed Without Report

B1102 (SB)	U.S. (Stote, R.)	820468 40I.g	C	1.84 000281	Effects on renal hemodynamics in patients with mild to moderate hypertension	XO, O, POS, R	carvedilol	12.5	4 W per period	16	31-65	
							UID	25.0				
			T					50.0				
		820729 40I.h					atenolol	50.0				
							UID	100.0				

Sponsor
 SB = Sankyo/Kline Beecham
 BM = Boehringer Mannheim
 DS = Daiichi Seiyaku

Degree of Blinding
 O = Open
 SB = Single Blind
 DB = Double Blind
 OBS = Observer Blind

Invest. = Full List of Investigators
 is provided in
 Vol. 1.83 Page: 000077

DF = Dose Form
 iv = Intravenous
 C = Capsule
 sr = Sustained Release
 T = Tablet
 (O) = Oral, Nas

Treatment Assignment
 R = Random
 NR = Nonrandom

Degree of Control
 UC = Uncontrolled
 Pl. = Placebo
 POS = Positive

(M)az
 * = Ongoing Study as of 31 August 1992
 NS = Information Not Specified or Not
 Available

Pub. Ref. Location of Publication
 See Vol. 1.86 Page: 000274

Treatment Sequence
 XO = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration
 H = Hours(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency
 SD = Single Dose
 UID = Once Daily
 BID = Twice Daily
 TID = Three Times Daily

Pop. = Population
 CAD = Coronary Artery Disease
 CHF = Congestive Heart Failure
 HTN = Hypertension

000077

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
C1112 (SB)	U.S. (Bialy, G.)	820729 401.h	C	1.86 000104	Antihypertensive efficacy and safety in patients with mild to moderate hypertension	DB, R, PA	carvedilol UID	25.0 50.0	1 M	33	NS	NS	
CARV0020 (BM)	U.S. (Cohen, A.)		C	1.48 000323	Antihypertensive efficacy in patients with mild to moderate hypertension	DB, PL, PA, R	carvedilol BID placebo	6.25 12.5 25.0	2 W	30 10	33-70	29/11	
CAR/DEN/01 (SB)	Denmark Multicenter (9 Investigators)	1/25 B/8 2/12.5 B/3	T	1.86 000157	Antihypertensive efficacy in hypertensive patients inadequately treated with a diuretic or a beta-blocker	Partly DB, Partly SB, POS, PA, R	carvedilol daily atenolol bendroflumeth- iazide daily	25.0 50.0 50.0 / 2.5 100.0 / 2.5	24W	165 (Total)	NS	NS	

Sponsor

SB = SmithKline Beecham
 BM = Boehringer Mannheim
 DS = Daiichi Seiyaku

Degree of Blinding

O = Open
 SB = Single Blind
 DB = Double Blind
 OBS = Observer Blind

Invest. = Full List of Investigators
 is provided in
 Vol. 1.83 Page: 000077

DF = Dose Form

iv = Intravenous
 C = Capsule
 sr = Sustained Release
 T = Tablet
 PO = Oral, Not

Treatment Assignment

R = Random
 NR = Nonrandom

Degree of Control

UC = Uncontrolled
 PL = Placebo
 POS = Positive

Other

* = Ongoing Study as of 31 August 1992
 NS = Information Not Specified or Not
 Available

Pub. Ref. Location of Publication

See Vol.: 1.86 Page: 000274

Treatment Sequence

XO = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration

H = Hour(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency

SD = Single Dose
 UID = Once Daily
 BID = Twice Daily
 TID = Three Times Daily

Pop = Population

CAD = Coronary Artery Disease
 CHF = Congestive Heart Failure
 HTN = Hypertension

000032

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DE	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
CAR/FR/01 (SB)	France (Zech, P.)	2/12.5 B/3 1/25 B/8 lot 1	T	1.86 000259	Effects on renal hemodynamics and mental stress in hypertensive patients without renal dysfunction	DB, POS, PA, R	carvedilol daily atenolol daily	25.0 100.0	8W	NS	NS	NS	
CAR/FR/02 (SB)	France Multicenter (7 investigators)	1/25 B/8 lot 1 2/12.5 B/3	T	1.86 000137	Effects on cardiac performance in patients with mild to moderate hypertension	R, DB, POS, XO	carvedilol (TID) metoprolol (SID)	25.0 200.0	4 W per period	NS	NS	NS	

Sponsor
SB = SmithKline Beecham
BM = Boehringer Mannheim
DS = Daiichi Seiyaku

Degree of Blinding
O = Open
SB = Single Blind
DB = Double Blind
OBS = Observer Blind

Invest. = Full List of Investigators
is provided in
Vol. 1.83 Page: 000077

DE = Dose Form
iv = Intravenous
C = Capsule
sr = Sustained Release
T = Tablet
PO = Oral, Nas

Treatment Assignment
R = Random
NR = Nonrandom

Degree of Control
UC = Uncontrolled
PL = Placebo
POS = Positive

(Other)
* = Ongoing Study as of 31 August 1992
NS = Information Not Specified or Not Available

Pub. Ref. = Location of Publication
See Vol. 1.86 Page: 000274

Treatment Sequence
KO = Crossover
PA = Parallel
AD = Ascending Dose

Duration
H = Hour(s)
D = Day(s)
W = Week(s)
M = Month(s)
Y = Year(s)

Treatment Frequency
SD = Single Dose
QD = Once Daily
BID = Twice Daily
TID = Three Times Daily

Pop. = Population
CAD = Coronary Artery Disease
CHF = Congestive Heart Failure
HTN = Hypertension

060333

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
CAR/FR/03 (SB)	France (Planchon, B.)	2/12.5 B/3 1/25 B/8 lot I	T	1.86 000155	Safety in patients complaining of cold extremities while previously treated with atenolol or acebutolol	R, DB, XO	carvedilol UID acebutolol UID atenolol UID	25.0 400.0 100.0	1 M per period	8	42-67	5/3	
CAR/FR/04 (SB)	France (Reinberg, A.)	1/25 B/8 km I 2/12.5 B/3	T	1.86 000184	Efficacy and safety of two dosage regimens in middle-age patients with benign essential, mild to moderate hypertension	R, DB, XO	carvedilol UID am or pm	25.0	3 W per period	1	35	1/0	
CAR/FR/05 *(SB)	France (Mallion, J.)	2/12.5 B/4 lot I 1/25 B/12 km I	T	1.86 000260	Effects on peripheral hemodynamics during exercise in patients with mild to moderate hypertension	DB, PA, POS, R	carvedilol UID propranolol BID	25.0 40.0	6 W	NS	NS	NS	

Sponsor
SB = SmithKline Beecham
BM = Boehringer Mannheim
IS = Daiichi Seiyaku

Degree of Blinding
O = Open
SB = Single Blind
DB = Double Blind
OBS = Observer Blind

Invest. = Full List of Investigators is provided in Vol. 1.83 Page: 000077

DF = Dose Form
iv = Intravenous
C = Capsule
sr = Sustained Release
T = Tablet
PO = Oral, Nos

Treatment Assignment
R = Random
NR = Nonrandom

Degree of Control
UC = Uncontrolled
PL = Placebo
POS = Positive

Other
* = Ongoing Study as of 31 August 1992
NS = Information Not Specified or Not Available

Pub. Ref. Location of Publication
See Vol. 1.86 Page: 000274

Treatment Sequence
XO = Crossover
PA = Parallel
AD = Ascending Dose

Duration
H = Hour(s)
D = Day(s)
W = Week(s)
M = Month(s)
Y = Year(s)

Treatment Frequency
SD = Single Dose
UID = Once Daily
BID = Twice Daily
TID = Three Times Daily

Pop. = Population
CAD = Coronary Artery Disease
CHF = Congestive Heart Failure
HTN = Hypertension

000077

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DE	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
CAR/HOL/07 (SB)	The Netherlands (Mooij, J.) (Van Bortel, L.)	2/12.5 B/3 1/25 B/7	T	1.86 000156	Effects on exercise performance in patients with mild to moderate hypertension	DB, POS, R, XO	carvedilol UID propranolol UID	25.0 80.0	2 W per period	30	NS	NS	
CAR/UK/103 *(SB)	U.K. (Dunn, F.)	1/25 B/12 lot 1	T T	1.84 000416	Effects on hemodynamic parameters in patients with mild to moderate hypertension	DB, POS, R, PA	carvedilol UID atenolol UID	25.0 50.0 50.0 100.0	12W	NS	NS	NS	

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DE = Dose Form
 iv = Intravenous
 C = Capsule
 sr = Sustained Release
 T = Tablet
 PO = Oral, Mos

Treatment Assignment
 R = Random
 NR = Nonrandom

Degree of Control
 UC = Uncontrolled
 Pl. = Placebo
 POS = Positive

Other
 * = Ongoing Study as of 31 August 1992
 NS = Information Not Specified or Not Available

Pub. Ref. = Location of Publication
 See Vol. 1.86 Page: 000274

Treatment Sequence
 XO = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration
 H = Hour(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency
 SD = Single Dose
 UID = Once Daily
 BID = Twice Daily
 TID = Three Times Daily

Pop. = Population
 CAD = Coronary Artery Disease
 CHF = Congestive Heart Failure
 HTN = Hypertension

000435

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
CAR/UK/107 *(SB)	U.K. Multicenter (18 Investigators)	2/25 B/3 1/50 B8	T	1.86 000264	Antihypertensive efficacy and safety in patients with moderate to severe hypertension	DB, PA, R	carvedilol UII, BID carvedilol BID enalapril UII enalapril UII, BID carvedilol/ben- drofluzide BID/UII enalapril/ben- drofluzide BID/UII	25.0 50.0 5.0 10.0 20.0 50.0 5.0 20.0 5.0	12W	NS	NS	NS	
CAR/UK/108 *(SB)	U.K. (Petrie, J.) (Reckless, J.)	1/25 B8	T T T	1.84 000417	Effects on lipid profiles in patients with essential hypertension	OBS, POS, R, PA	carvedilol UII atenolol UII NS up-titrations	12.5 50 0	16 W	NS	N	NS	

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Invest. = Full List of Investigators
is provided in
Vol. 1.83 Page: 000077

DF = Dose Form
iv = Intravenous
C = Capsule
sr = Sustained Release
T = Tablet
PO = Oral, Non

Treatment Assignment
R = Random
NR = Nonrandom

Degree of Control
UC = Uncontrolled
PI = Placebo
POS = Positive

Other
* = Ongoing Study as of 31 August 1992
NS = Information Not Specified or Not
Available

Pub. Ref = Location of Publication
See Vol. 1.86 Page: 000274

Treatment Sequence
XO = Crossover
PA = Parallel
AD = Ascending Dose

Duration
H = Hour(s)
D = Day(s)
W = Week(s)
M = Month(s)
Y = Year(s)

Treatment Frequency
SD = Single Dose
UII = Once Daily
BID = Twice Daily
THI = Three Times Daily

Pop. = Population
CAD = Coronary Artery Disease
CHF = Congestive Heart Failure
HTN = Hypertension

000264

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
INT/CAR/01 (SB)	S. Africa, Netherlands (Leary, W.)	1B1 lot 2 1/25 B/6	T	1.86 000185	Compare first dose effect on orthostatic blood pressure changes with and without 2 days predosing with 12.5mg in hypertensive patients	DB, XO, R	carvedilol UID SD carvedilol UID	12.5-2D 25.0-1D 25.0	3D per period	120	26-77	74/46	
INT/CAR/09A (SB)	Germany Multicenter (12 Investigators)	1/25 B/6, B/7 2/12.5 B/3	T	1.86 000138	Antihypertensive efficacy and safety in patients with benign essential hypertension not adequately controlled on diuretic therapy	DB, POS, R, PA	carvedilol UID tenoretic UID	25.0 50.0 50.0 100.0	8W	200 (Total)	NS	NS	

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Invest = Full List of Investigators is provided in Vol. 1.83 Page: 000077

DF = Dose Form
iv = Intravenous
C = Capsule
sr = Sustained Release
T = Tablet
PO = Oral, Not

Treatment Assignment
R = Random
NR = Nonrandom

Degree of Control
UC = Uncontrolled
PL = Placebo
POS = Positive

Other
* = Ongoing Study as of 31 August 1992
NS = Information Not Specified or Not Available

Pub Ref = Location of Publication See Vol. 1.86 Page: 000274

Treatment Sequence
XO = Crossover
PA = Parallel
AD = Ascending Dose

Duration
H = Hour(s)
D = Day(s)
W = Week(s)
M = Month(s)
Y = Year(s)

Treatment Frequency
SD = Single Dose
UID = Once Daily
BID = Twice Daily
TID = Three Times Daily

Pop. = Population
CAD = Coronary Artery Disease
CHF = Congestive Heart Failure
HTN = Hypertension

000037

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
INT/CAR/09B (SB)	Germany Multicenters (11 Investigators)	1/25 B/6, B/7 2/12.5 B/3	T	1.86 000139	Antihypertensive efficacy in patients with benign essential hypertension inadequately controlled on β -blocker therapy	DB, POS, R, PA	carvedilol UID tenoretic UID	25.0 50.0 50.0 100.0	BW	200 (Total)	NS	NS	
INT/CAR/13 (SB)	Multicenters Norway (1 Investigator) Sweden (15 Investigators)	1/25 B/8 lot 1 2/12.5 B/3	T	1.86 000154	Effect of carvedilol as compared to an ACE-inhibitor (enalapril) on hypertension and quality of life related well-being	DB, R, PA, POS	carvedilol UID Carvedilol/ HCTZ UID enalapril/UID enalapril/ HCTZ UID	12.5 50.0 50.0/12.5 10.0 20.0 40.0 40.0/ 12.5	B M	251 (Total)	NS	NS	

Sponsor

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Invest = Full List of Investigators is provided in Vol. 1.83 Page. 000077

DF = Dose Form

iv = Intravenous
 C = Capsule
 sr = Sustained Release
 T = Tablet
 PO = Oral, Nas

Treatment Assignment

R = Random
 NR = Nonrandom

Degree of Control

UC = Uncontrolled
 PL = Placebo
 POS = Positive

Other

* = Ongoing Study as of 31 August 1992
 NS = Information Not Specified or Not Available

Pub. Ref. = Location of Publication
 See Vol. 1.86 Page. 000274

Treatment Sequence

XC = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration

H = Hour(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency

SD = Single Dose
 QD = Once Daily
 BID = Twice Daily
 TID = Three Times Daily

Exp. = Population

CAI = Coronary Artery Disease
 CHF = Congestive Heart Failure
 HTN = Hypertension

000538

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DE	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
INT/CAR/14/UK *(SB)	U.K. (Elliott, H.) (Venkat-Raman, G.) (Conway, I.)	3/6.25 B/1 2/12.5 B/3 1/25 B/7	T	1.84 000415	Effects on 24-hour blood pressure in patients with mild to moderate hypertension	DB, PL, R, XO	carvedilol UID placebo	6.25 12.5 25.0	4 W per period	NS	NS	NS	
INT/CAR/16/UK *(SB)	U.K. (Venkat-Raman, G.)	1/25 B/6	T	1.86 000258	Renal hemodynamics in patients with mild to moderate hypertension	DB, XO, PL, R	carvedilol daily placebo	25.0	4 W per period	NS	NS	NS	
INT/CAR/21/UK (SB)	U.K. (Breckenridge, A.)	1/25 B/6 1/25 B/8	T	1.86 000158	Antihypertensive efficacy and safety in patients with chronic stable intermittent claudication and mild to moderate hypertension	DB, POS, XO, R	carvedilol daily captopril daily	25.0/ 50.0 25.0/ 50.0	8 W per period	14	NS	NS	2.3

Sponsor
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Invest. = Full List of Investigators
is provided in
Vol. 1.83 Page: 000077

DE = Dose Form
iv = Intravenous
C = Capsule
sr = Sustained Release
T = Tablet
PO = Oral, Non

Treatment Assignment
R = Random
NR = Nonrandom

Degree of Control
UC = Uncontrolled
PL = Placebo
POS = Positive

Other
* = Ongoing Study as of 31 August 1992
NS = Information Not Specified or Not Available

Pub. Ref. = Location of Publication
See Vol. 1.86 Page: 000274

Treatment Sequence
XO = Crossover
PA = Parallel
AD = Ascending Dose

Duration
H = Hour(s)
D = Day(s)
W = Week(s)
M = Month(s)
Y = Year(s)

Treatment Frequency
SD = Single Dose
UD = Once Daily
BD = Twice Daily
TID = Three Times Daily

Pop. = Population
CAD = Coronary Artery Disease
CHF = Congestive Heart Failure
HTN = Hypertension

000039

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
INT/CAR/22/ UK *(SB)	U.K. (Mannes, G.)	1/25 B8	T	1.86 000262	Effects on exercise performance and metabolic demand in patients with mild to moderate hypertension	DB, XO, POS, R	carvedilol daily atenolol daily	25.0 100.0	2W per period	NS	NS	NS	
IT/88/CAR/G1 (SE)	Italy (Muesan, G.) (Paciaroni, P.)	2/12.5 B/3 1/25 B/8 lot 1	T	1.86 000188	A pilot study on the efficacy and safety of carvedilol in elderly patients with mild to moderate hypertension	DB, R	carvedilol daily	12.5 25.0	8W	10 11	65-78	11/10	
IT/88/CAR/02 (SB)	Italy (Mancia, G.)	1/25 B/8 lot 1	T	1.84 000292	α -blocking efficacy of acute and subchronic carvedilol in patients with mild to moderate essential hypertension	DB, R, XO	carvedilol SD prazosin SD (open carvedilol 25.0 daily for 3W between treatments)	25.0 2.0	1 D per period	8	22-55	7/1	

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Degree of Blinding
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OBS = Observer Blind

Invest. = Full list of investigators
is provided in
Vol. 1.83 Page: 000077

DF = Dose Form
iv = Intravenous
C = Capsule
sr = Sustained Release
T = Tablet
PO = Oral, Nas

Treatment Assignment
R = Random
NR = Nonrandom

Degree of Control
UC = Uncontrolled
Pl. = Placebo
POS = Positive

Other
* = Ongoing Study as of 31 August 1992
NS = Information Not Specified or Not Available

Pub. Ref. = Location of Publication
See Vol. 1.86 Page: 000274

Treatment Sequence
X() = Crossover
PA = Parallel
AD = Ascending Dose

Duration
H = Hour(s)
D = Day(s)
W = Week(s)
M = Month(s)
Y = Year(s)

Treatment Frequency
SD = Single Dose
OD = Once Daily
BID = Twice Daily
TID = Three Times Daily

Pop. = Population
CAD = Coronary Artery Disease
CHF = Congestive Heart Failure
HTN = Hypertension

000200

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DE	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
IT/88/CAR/04 (SB)	Italy (Adezani, L.)	NA	T	1.84 000294	Antihypertensive efficacy and safety in patients with mild to moderate benign essential hypertension and type II diabetes	O, POS, R, PA	carvedilol UID nifedipine TID	25.0 10.0	4W	20 (Total)	48-84	8/12	1, 4
MF3815 (BM)	U.K. (Prichard, B.N.C.)	820139 40Kc 820156 40Kc/ 819843 40Hc/ 819843 40Hc 820175 40Oc	C	1.86 000230	Antihypertensive efficacy and safety in hypertensive patients treated with a diuretic	DB, R, XO, POS,	carvedilol daily/diuretic atenolol daily/diuretic	12.5 - 50/NS 50 - 200/NS	10 W per period	11	NS	NS	
MF3892 (BM)	Germany (Lenga, P.)	819843 40Hc/ 819843 40Hc 820175 40Oc	C	1.84 000387	Effects on central hemodynamics and exercise blood pressure in patients with mild to moderate hypertension	DB, R, PA, POS	carvedilol daily atenolol daily nitrendipine daily	25.0 50.0 20.0	4W	19 (Total)	NS	NS	

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DS = Daiichi Seiyaku

Degree of Blinding
O = Open
SB = Single Blind
DB = Double Blind
OBS = Observer Blind

Invest. = Full List of Investigators
is provided in
Vol. 1 83 Page: 000077

DE = Dose Form
iv = Intravenous
C = Capsule
sr = Sustained Release
T = Tablet
PO = Oral, Nas

Treatment Assignment
R = Random
NR = Nonrandom

Design of Control
UC = Uncontrolled
Pl. = Placebo
POS = Positive

Notes
* = Ongoing Study as of 31 August 1992
NS = Information Not Specified or Not Available

Pub. Ref. = Location of Publication
See Vol. 1 86 Page: 000274

Treatment Sequence
XO = Crossover
PA = Parallel
AD = Ascending Dose

Duration
H = Hour(s)
D = Day(s)
W = Week(s)
M = Month(s)
Y = Year(s)

Treatment Frequency
SD = Single Dose
UID = Once Daily
BID = Twice Daily
TID = Three Times Daily

Pop. = Population
CAD = Coronary Artery Disease
CHF = Congestive Heart Failure
HTN = Hypertension

000502

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
MF3901 (BM)	Germany Multicenter (15 Investigators)				Efficacy and tolerance of a carvedilol/torsemide combination compared to each of the monosubstances	DB, R, PA	carvedilol/ torsemide daily carvedilol daily torsemide daily	12.5/ 1.25 12.5 2.5	15M	176 (total)	NS	NS	
MF4036 (BM)	U.K. (Machias)	820777 40Kc 820775 40Kc	C	1.86 000248	A comparative study for the management of moderate and severe hypertension with carvedilol or captopril as an adjunct to a thiazide diuretic	DB, R, XO, POS	carvedilol UID captopril BID	12.5 25.0 12.5 25.0	6 W per period	20	NS	NS	

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 DS = Daiichi Seiyaku

Degree of Blinding
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 DB = Double Blind
 OBS = Observer Blind

Invest. = Full List of Investigators
 is provided in
 Vol. 1.83 Page: 000077

DF = Dose Form
 iv = Intravenous
 C = Capsule
 sr = Sustained Release
 T = Tablet
 PO = Oral, Nos

Treatment Assignment
 R = Random
 NR = Nonrandom

Degree of Control
 UC = Uncontrolled
 Pl. = Placebo
 POS = Positive

Other
 * = Ongoing Study as of 31 August 1992
 NS = Information Not Specified or Not
 Available

Pub. Ref. = Location of Publication
 See Vol. 1.86 Page: 000274

Treatment Sequence
 XO = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration
 H = Hour(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency
 SD = Single Dose
 UID = Once Daily
 BID = Twice Daily
 TH = Three Times Daily

Pop. = Population
 CAD = Coronary Artery Disease
 CHF = Congestive Heart Failure
 HN = Hypertension

000502

Table 2.G.3
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF UNCONTROLLED HYPERTENSION CLINICAL TRIALS

Project (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
A0004 (SB)	U.S. (Storz, R.)	820173 40Lg 820176 40Lh	C	1.108 000063	Effects on renal hemodynamics in patients with mild to moderate hypertension	O, AD, UC	carvedilol BID	6.25 12.5 25.0	4W	4	37 - 65	3/1	
INT/CAR/11/ UK (SB)	U.K. (Richardson, P.)	2/12.5 B/2 1/25 B/6	T	1.113 000002	Effects on patients with impaired left ventricular function	O, UC	carvedilol UID	12.5 25.0 50.0	16W	14	35 - 71	8/6	39
MF2644 (BM)	Germany (Ritz, E.)	814228 30A	T	1.116 000002	Antihypertensive efficacy in hospitalized patients with arterial hypertension	SB, UC	carvedilol SD	25.0 50.0 100.0	Cancelled	2	22 - 45	0/2	
MF2717 (BM)	Germany (Gotzen, R.) (Meyer-Sabellek, W.)	814965 40Aa 814966 40AL	C	1.116 000051	Antihypertensive efficacy in patients with arterial hypertension	O, R, PA, UC	carvedilol SD	25.0 50.0	1 D	18	35 - 62	10/8	

Sponsor

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Degree of Blinding

O = Open
SB = Single Blind
DB = Double Blind
OBS = Observer Blind

Invest. = Full List of Investigators
is provided in
Vol. 1.83 Page: 000077

DF = Dose Form

iv = Intravenous
C = Capsule
sr = Sustained Release
T = Tablet
PO = (Oral), Nas

Treatment Assignment

R = Random
NR = Non-random

Degree of Control

UC = Uncontrolled
PL = Placebo
POS = Positive

Other

* = Ongoing Study as of 31 August 1992
NS = Information Not Specified or Not
Available

Pub. Ref. = Location of Publications
See Vol. 1.87, Page: 000111

Treatment Sequence

XO = Crossover
PA = Parallel
AD = Ascending Dose

Duration

H = Hour(s)
D = Day(s)
W = Week(s)
M = Month(s)
Y = Year(s)

Treatment Frequency

SD = Single Dose
UID = Once Daily
BID = Twice Daily
TID = Three Times Daily

Pop. = Population

CAD = Coronary Artery Disease
CHF = Congestive Heart Failure
HTN = Hypertension

000502

Table 2.G.3 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF UNCONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
MF2744 (BM)	Italy (Zanchetti, A.)	814893 41	C	1.117 000002	Antihypertensive and hemodynamic efficacy in patients with mild to moderate hypertension at rest and during exercise	O, UC	carvedilol BID	25.0	1 W	12	33 - 62	2/10	18
MF2824 (BM)	Germany (Schoeppe, B.)	814370 Ba	T	1.118 000090	Antihypertensive efficacy in patients with essential hypertension	O, UC	carvedilol BID	50.0	1 W	7	21 - 48	3/4	
MF2830 (BM)	Germany (Bonner, G.)	814370 Ba	T	1.118 000132	Antihypertensive efficacy in patients with essential hypertension	O, UC	carvedilol BID	25.0	1 W	7	39 - 70	3/4	
MF2831 (BM)	Germany (Rosenthal, J.)	814370 Ba	T	1.118 000207	Antihypertensive efficacy in patients with essential hypertension	O, UC	carvedilol TID	25.0	1 W	7	41 - 60	5/2	

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Invest. = Full List of Investigators is provided in Vol. 1.83 Page 000077

DF = Dose Form
 iv = Intravenous
 C = Capsule
 sr = Sustained Release
 T = Tablet
 PO = Oral, Nos

Treatment Assignment
 R = Random
 NR = Non-random

Degree of Control
 UC = Uncontrolled
 PL = Placebo
 POS = Positive

Other
 * = Ongoing Study as of 31 August 1992
 NS = Information Not Specified or Not Available

Pub. Ref. = Location of Publications
 See Vol. 1.87, Page 000111

Treatment Sequence
 XO = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration
 H = Hour(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency
 SD = Single Dose
 QD = Once Daily
 BID = Twice Daily
 TID = Three Times Daily

Pop. = Population
 CAD = Coronary Artery Disease
 CHF = Congestive Heart Failure
 HTN = Hypertension

000508

Table 2.G.3 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF UNCONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
MF2846 (BM)	Sweden (Eggersten, R.) (Hansson, L.)	814965 40Aa	T	1.119 000002	Hemodynamic effects in patients with essential hypertension	O, UC	carvedilol SD	25.0	2 H	10	33 - 55	10/0	9, 10
MF2968 (BM)	Germany (Schoeppe, B.) (Meyer-Sabellek, W.)	814966 40Ab	C	1.121 000002	Antihypertensive efficacy and safety at rest and during exercise in patients with arterial hypertension	O, UC	carvedilol UD	50.0	1 Y	32	24 - 57	18/14	
MF3341 (BM)	Germany (Meyer-Sabellek, W.)	818188 Cb 818173 Cd	C	1.441 000002	Antihypertensive efficacy and safety in patients with arterial hypertension	O, UC	carvedilol BID	25.0 50.0	1 Y	28	29-67	19/9	
MF3343 (BM)	U.K. (Heber, M.) (Raftery, E.)	818000 Cb/ 818188 Cb 818055 Cd/ 819009 40Ed	C	1.128 000002	Antihypertensive efficacy in patients with mild to moderate hypertension (24-hour blood pressures)	O, UC	carvedilol BID	25.0 50.0	4 W	12	45 - 64	7/5	14, 15

Sponsor

SB = SmithKline Beecham
 BM = Boehringer-Mannheim
 DS = Daiichi Seiyaku

Degree of Blinding

O = Open
 SB = Single Blind
 DB = Double Blind
 OBS = Observer Blind

Invest. = Full List of Investigators is provided in Vol. 1.83 Page: 000077

DF = Dose Form

iv = Intravenous
 C = Capsule
 sr = Sustained Release
 T = Tablet
 PO = Oral, Nos

Treatment Assignment

R = Random
 NR = Non-random

Degree of Control

UC = Uncontrolled
 PL = Placebo
 POS = Positive

Other

* = Ongoing Study as of 31 August 1992
 NS = Information Not Specified or Not Available

Pub. Ref. = Location of Publications

See Vol. 1.87, Page: 000111

Treatment Sequence

XO = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration

H = Hour(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency

SD = Single Dose
 UD = Once Daily
 BID = Twice Daily
 TID = Three Times Daily

Pop. = Population

CAD = Coronary Artery Disease
 CHF = Congestive Heart Failure
 HTN = Hypertension

60500

Table 2.G.3 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF UNCONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
MF3529 (P-23) (EM)	Belgium (Dupont, A.)	818173 Cd	C	1.443 000002	Antihypertensive efficacy, safety, and tolerability in patients with mild to moderate hypertension	O, UC	carvedilol UID, BID carvedilol BID/MKTZ	50.0 50.0 25.0 50.0 50.0	2 Y	20	35 - 65	17/3	
MF3562 (BM)	Germany (Schoeppe, B.)	819148 40Df 819009 40Ed	C	1.444 000002	Antihypertensive efficacy and safety in patients switched from BID to UID regimen	O, UC	carvedilol UID, BID	50.0	1 Y	7	25 - 55	5/2	
MF3591 (MF3742 /3743 ext)	Germany Multicenter (22 investigators)	819008 40Db 819009 40Ed	C	1.445 000002	Maintenance of antihypertensive efficacy, and safety of UID regimen	O, UC	carvedilol UID	25.0 50.0 100.0	1 Y	123 ¹	21-73	67/56	

¹123 patients were evaluated for efficacy; 149 patients were enrolled.

Sponsor

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Invest. = Full List of Investigators is provided in Vol. 1.83 Page: 000077

DF = Dose Form

iv = Intravenous
 C = Capsule
 sr = Sustained Release
 T = Tablet
 PO = Oral, Nos

Treatment Assignment

R = Random
 NR = Non-random

Degree of Control

UC = Uncontrolled
 PL = Placebo
 POS = Positive

Other

* = Ongoing Study as of 31 August 1992
 NS = Information Not Specified or Not Available

Pub. Ref. = Location of Publications

See Vol.: 1.87, Page: 000111

Treatment Sequence

XO = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration

H = Hour(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency

SD = Single Dose
 UID = Once Daily
 BID = Twice Daily
 TID = Three Times Daily

Pop. = Population

CAD = Coronary Artery Disease
 CHF = Congestive Heart Failure
 HTN = Hypertension

000520

Table 2.G.3 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF UNCONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DE	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
MF3623 (BM)	Germany (Meyer-Sabelfek)	818996 40Db 819009 40Ed	C	1.447 000002	Antihypertensive efficacy and safety in patients on a UID regimen after 12 months of treatment	O, UC	carvedilol UID	25.0 50.0 100.0	1 Y	16	29 - 59	13/3	
MF3698 (BM)	Germany (Krepp, H.)	819148 40Df	C T	1.135 000002	Antihypertensive efficacy and safety in patients with essential hypertension	O, UC	carvedilol / torsemide SD	25.0/ 2.5	1 D	5	31 - 73	3/2	
MF3702 (BM)	Australia (Morgan, T.) (Anderson, A.)	820020 40Jd 819789 49Ib 819787 40Jd	C	1.61 000002	Comparison of the steady state pharmacokinetics and efficacy between young and elderly patients with hypertension	O, UC, SB	carvedilol UID	12.5 25.0 50.0	3 M	29 ²	39 - 79	25/4	24, 25

² Younger patients (8 men, 39-47 years) and 21 elderly patients (17 men, 4 women; 63-79 years) were enrolled.

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Invest = Full List of Investigators
 is provided in
 Vol. 1.83 Page: 000077

DE = Dose Form
 iv = Intravenous
 C = Capsule
 sr = Sustained Release
 T = Tablet
 PO = Oral, Nus

Treatment Assignment
 R = Random
 NR = Non-random

Degree of Control
 UC = Uncontrolled
 PL = Placebo
 POS = Positive

Other
 * = Ongoing Study as of 31 August 1992
 NS = Information Not Specified or Not
 Available

Pub. Ref. = Location of Publications
 See Vol. 1.87, Page: 000111

Treatment Sequence
 X() = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration
 H = Hour(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency
 SD = Single Dose
 UID = Once Daily
 BID = Twice Daily
 TID = Three Times Daily

Pop. = Population
 CAD = Coronary Artery Disease
 CHF = Congestive Heart Failure
 HHN = Hypertension

010517

Table 2.G.3 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF UNCONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
MF3711 (BM)	Germany (Steeger, W)	819008 40Ib 819789 40Ib	C	1.448 000002	Antihypertensive efficacy and safety in elderly patients with hypertension	O, UC	carvedilol IID	25.0 50.0	1 Y	12	63 - 85	2/10	34
MF3742 (BM)	Germany Multicenter (27 Investigators)	818000 Cb/ 818188 Cb 818173 Cd	C	1.449 000002	Antihypertensive efficacy and safety in patients with arterial hypertension	O, UC	carvedilol IID IID	25.0 25.0 50.0	1 Y	145	21 - 76	75/70	
MF3743 (BM)	Germany Multicenter (17 Investigators)	818000 Cb/ 818188 Cb/ 818902 Ib/ 818996 40Db/ 819008 40Ib 818173 Cd	O	1.451 000002	Antihypertensive efficacy and safety in patients with arterial hypertension	O, UC	carvedilol IID IID	25.0 50.0 25.0	1 Y	82	24 - 72	51/31	
P16 (BM)	Italy (Rizzon, P.)	816616 Bc 816392 40Cc	C	1.142 000098	Efficacy and tolerance in patients with essential hypertension	O, UC	carvedilol IID IID	25.0 50.0 50.0	4D 3D	10	51 - 66	3/7	

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OBS = Observer Blind

Invest = Full List of Investigators
is provided in
Vol. 1 B3 Page: 000077

DF = Dose Form
iv = Intravenous
C = Capsule
sr = Sustained Release
T = Tablet
PO = Oral, Nos

Treatment Assignment
R = Random
NR = Non random

Degree of Control
UC = Uncontrolled
Pl. = Placebo
POS = Positive

Other
* = Ongoing Study as of 31 August 1992
NS = Information Not Specified or Not
Available

Pub. Ref = Location of Publications
See Vol. 1 B7, Page: 000111

Treatment Sequence
XO = Crossover
PA = Parallel
AD = Ascending Dose

Unitation
H = Hour(s)
D = Day(s)
W = Week(s)
M = Month(s)
Y = Year(s)

Treatment Frequency
SD = Single Dose
IID = Once Daily
IID = Twice Daily
III = Three Times Daily

Pop. = Population
CAD = Coronary Artery Disease
CHF = Congestive Heart Failure
HTN = Hypertension

010522

Table 2.G.3 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF UNCONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
G-4 (DS)	Japan Multicenter (35 Investigators)		T	1.143 000125	Antihypertensive efficacy on diurnal blood pressure changes in hospitalized patients with mild to moderate essential hypertension	O, UC	carvedilol (III)	5.0 10.0 20.0	3 - 15 D	20 ³	58.7 (mean)	12/B	28
G-5 (Ds)	Japan Multicenter		NS	1.452 000418	Antihypertensive efficacy and safety in patients with mild to moderate essential hypertension	O, UC	carvedilol	5.0 10.0 20.0	>2 W	63	NS	NS	
G-6 (DS)	Japan Multicenter		NS	1.143 000166	Dose-effect relationship in patients with mild to moderate essential hypertension	O, UC	carvedilol (III)	5.0 10.0 20.0	>2 W	145	NS	NS	27

³20 patients were analyzed; 25 patients were enrolled.

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Invest. = Full List of Investigators
 is provided in
 Vol. 1.81 Page: 000077

DF = Dose Form
 iv = Intravenous
 C = Capsule
 sr = Sustained Release
 T = Tablet
 (N) = Oral, Nos

Treatment Assignment
 R = Random
 NR = Non-random

Degree of Control
 UC = Uncontrolled
 Pl. = Placebo
 POS = Positive

Other
 * = (Ongoing Study as of 31 August 1992
 NS = Information Not Specified or Not
 Available

Pub. Ref. = Location of Publications
 See Vol. 1.87, Page: 000111

Treatment Sequence
 CO = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration
 H = Hour(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency
 SD = Single Dose
 QD = Once Daily
 BID = Twice Daily
 TID = Three Times Daily

Pop. = Population
 CAD = Coronary Artery Disease
 CHF = Congestive Heart Failure
 HTN = Hypertension

Table 2.G.3 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF UNCONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
G-7 (DS)	Japan Multicenter		NS	1.143 000189	Efficacy and tolerance of carvedilol with a thiazide diuretic in the treatment of patients with mild to moderate essential hypertension	O, UC	carvedilol DDD/thiazide diuretic	5 (V) NS 10 (V) NS 20 (V) NS	12 W	82	NS	NS	40, 11
G-9 (DS)	Japan Multicenter		NS	1.143 000214	Antihypertensive efficacy in patients with severe hypertension	O, UC	carvedilol	5 (V) 10 (V) 20 (V)	NS	26	NS	NS	28, 41
G-11	Japan (Takabatake, T.)		PO	1.143 000275	Antihypertensive efficacy and safety of carvedilol added to nifedipine in hypertensives who have not sufficiently responded to nifedipine	O, UC	carvedilol DDD/ nifedipine	5 (V) 60 (V) 60 (V) 20 (V) 60 (V)	12 W	35	27-71	11/24	35

Sponsor
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Invest. = Full List of Investigators is provided in Vol. 1.83 Page: 000077

Dose Form
 iv = Intravenous
 C = Capsule
 sr = Sustained Release
 T = Tablet
 PO = Oral, Not

Treatment Assignment
 R = Random
 NR = Non-random

Degree of Control
 UC = Uncontrolled
 Pl. = Placebo
 POS = Positive

Other
 * = Ongoing Study as of 31 August 1992
 NS = Information Not Specified or Not Available

Pub. Ref. = Location of Publications
 See Vol. 1.87, Page: 000111

Treatment Sequence
 XC = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration
 H = Hour(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency
 SD = Single Dose
 BD = Once Daily
 BID = Twice Daily
 TID = Three Times Daily

Pub. Ref. =
 CAD = Coronary Artery Disease
 CHF = Congestive Heart Failure
 HM = Hypertension

0105517

Table 2.G.3 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF UNCONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
G-12 (DS)	Japan (Ogihara, T.)		PO	1.143 000303	Effects on plasma hormones and renal function in patients with mild to moderate essential hypertension	O, UC	carvedilol UID	20.0	1 W	18	52 (mean)	8/10	16
G-13 (DS)	Japan Multicenter (6 Investigators)		PO	1.144 000002	Effects on serum lipids in patients with mild to moderate hypertension and non-intensive patients	O	carvedilol UID	5.0 20.0	3 M	36	31 - 79	18/18	25
G-14 (DS)	Japan Multicenter (8 Investigators)		PO	1.144 000002	Effects on serum lipids of patients with mild to moderate essential hypertension	O, UC, SB placebo run-in	carvedilol UID	10.0 20.0 40.0	3 M	21	34 - 70	14/7	13
G-16 (DS)	Japan		NS	1.145 000002	Antihypertensive efficacy and safety in patients with mild to moderate essential hypertension	O, UC	carvedilol UID	10.0 20.0 30.0	2 M	NS	NS	NS	

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DS = Daiichi Seiyaku

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Invest. = Full List of Investigators
is provided in
Vol. 1.83 Page: 000077

DF = Dose Form
iv = Intravenous
C = Capsule
sr = Sustained Release
T = Tablet
PO = Or., Nos

Treatment Assignment
R = Random
NR = Non-random

Degree of Control
UC = Uncontrolled
Pl. = Placebo
POS = Positive

Other
* = Ongoing Study as of 31 August 1992
NS = Information Not Specified or Not
Available

Pub. Ref. = Location of Publications
See Vol. 1.87, Page: 000111

Treatment Sequence
XO = Crossover
PA = Parallel
AD = Ascending Dose

Duration
H = Hour(s)
D = Day(s)
W = Week(s)
M = Month(s)
Y = Year(s)

Treatment Frequency
SD = Single Dose
UID = Once Daily
BID = Twice Daily
TID = Three Times Daily

Pop. = Population
CAD = Coronary Artery Disease
CHF = Congestive Heart Failure
HTN = Hypertension

000515

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
MF4061 (BM)	Multicenter (24 Investigators)	820956 40Kc 820175 40Oc	C	1.86 000249	Safety and effects on blood pressure and lipids in hypertensive patients with hyperlipidemia	DB, PA, R, POS	carvedilol UID captopril UID	25.0 50.0 25.0 50.0	26W	115 ¹¹ 111	30-77	135/91	
MF4210 *(BM)	Germany (Fritschka, E.)	820777 40Kc 780234 40Kc	C	1.86	Effects on renal hemodynamics in hypertensive patients with impaired renal function	DB, R, PA, POS	carvedilol UID to BID Metoprolol UID to BID	25.0 50.0 50.0- 100.0	16W	NS	NS	NS	
MF4215 (BM)					Efficacy of carvedilol plus HCTz in non- responders treated with carvedilol alone	O, R	carvedilol daily carvedilol daily carvedilol/ HCTZ daily	25 50 25/NS	12W	~500 as stated	NS	NS	

¹¹A total of 226 patients were analyzed for efficacy; 233 were randomized.

000503

Sponsor
SB = SmithKline Beecham
BM = Boehringer Mannheim
DS = Daiichi Selyaku

Degree of Blinding
O = Open
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DB = Double Blind
OBS = Observer Blind

Invest. = Full List of Investigators
is provided in
Vol. 1.83, pg. 000077

DF = Dose Form
iv = Intravenous
C = Capsule
sr = Sustained Release
T = Tablet
PO = Oral, Nos

Treatment Assignment
R = Random
NR = Nonrandom

Degree of Control
UC = Uncontrolled
Pl. = Placebo
POS = Positive

Other
* = Ongoing Study as of 31 August 1992
NS = Information Not Specified or Not
Available

Pub. Ref. = Location of Publication
See Vol. 1.86, Page. 000274

Treatment Sequence
CO = Crossover
PA = Parallel
AD = Ascending Dose

Duration
H = Hour(s)
D = Day(s)
W = Week(s)
M = Month(s)
Y = Year(s)

Treatment Frequency
SD = Single Dose
UID = Once Daily
BID = Twice Daily
TID = Three Times Daily

Pop. = Population
CAD = Coronary Artery Disease
CHF = Congestive Heart Failure
HTN = Hypertension

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
MF4291 *(BM)	Germany (Dietze, G.J.)	780177 40Kc 820777 40Kc	C	1.84 000418	Effect on insulin sensitivity in hypertensive patients with abnormal glucose tolerance	DB, PA, R, POS	carvedilol UID metoprolol UID	25.0 50.0 100.0 200.0	12W	NS	NS	NS	
MF9002 (BM)	Belgium (Duprez, D.) (Clement, D.)	820956 40Kc	C	1.86 000251	Effects on peripheral blood flow during reactive hyperemia	DB, XO, R, POS	carvedilol UID atenolol UID	25.0 50.0 50.0 100.0	6 W per period	15	NS	NS	
MF9003 *(BM)	Belgium (Deguste, J.P.)	820956 40Kc	C	1.86 000267	Efficacy on renal hemodynamics in hypertensive renal transplant patients with mild to moderate moderate renal impairment	DB, XO, R, POS	carvedilol UID metoprolol	25.0 50.0 100.0 200.0	8W per period	NS	NS	NS	

Sponsor
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BM = Boehringer Mannheim
OS = Onishi Seiyaku

Degree of Blinding
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Invest. = Full List of Investigations
is provided in
Vol. 1.81 Page: 000077

DF = Dose Form
iv = Intravenous
C = Capsule
sr = Sustained Release
T = Tablet
PO = Oral, Nos

Treatment Assignment
R = Random
NR = Nonrandom

Degree of Control
UC = Uncontrolled
PL = Placebo
POS = Positive

Other
* = Ongoing Study as of 31 August 1992
NS = Information Not Specified or Not
Available

Pub. Ref. Location of Publication
See Vol. 1.86 Page: 000274

Treatment Sequence
XO = Crossover
PA = Parallel
AO = Ascending Dose

Duration
H = Hour(s)
D = Day(s)
W = Week(s)
M = Month(s)
Y = Year(s)

Treatment Frequency
SD = Single Dose
OD = Once Daily
BID = Twice Daily
TID = Three Times Daily

Pop. = Population
CAD = Coronary Artery Disease
CHF = Congestive Heart Failure
HTN = Hypertension

010534

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DE	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
MF9013 *(BM)	Spain (Martinez-Amenos, A.) (Luque Otero)	780177 40Kc/ 820956 40Kc 820777 40Kc	C	1.86 000268	Effects on peripheral vasodilatation in hypertensive patients	DB, PA, POS, R	carvedilol UID atenolol UID	25.0 50.0	6W	NS	NS	NS	
MF9014 *(BM)	Spain (Mas, Jose Redon) (Javier, R.)	780177 40Kc 820777 40Kc	C	1.86 000269	Effect on metabolism of lipids and carbohydrates in hypertensive patients	DB, PA, POS, R	carvedilol daily atenolol daily	25.0 50.0 50.0 100.0	6 M	NS	NS	NS	
MF9015 *(BM)	Spain (Fernandez, J.M.)		PO	1.86 000270	Effects on circadian blood pressure in hypertensive patients	DB, PA, POS, R	carvedilol UID atenolol UID	25.0 50.0	4W	NS	NS	NS	
MF9016 *(BM)	Sweden Multicenter (13 Investigators)	820956 40Kc 820175 40Oc 820777 40Kc	C	1.86 000271	Effects on lipid metabolism in hypertensive patients	DB, PA, POS, R	carvedilol UID atenolol UID	25.0 50.0 50.0 100.0	6M	NS	NS	NS	

Sponsor
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Invest. = Full List of Investigators
is provided in
Vol. 1.83 Page: 000077

DE = Dose Form
iv = Intravenous
C = Capsule
sr = Sustained Release
T = Tablet
PO = Oral, Not

Treatment Assignment
R = Random
NR = Nonrandom

Degree of Control
UC = Uncontrolled
Pl. = Placebo
POS = Positive

Other
* = Ongoing Study as of 31 August 1992
NS = Information Not Specified or Not
Available

Pub. Ref. Location of Publication
See Vol: 1.86 Page: 000274

Treatment Sequence
XO = Crossover
PA = Parallel
AD = Ascending Dose

Duration
H = Hour(s)
D = Day(s)
W = Week(s)
M = Month(s)
Y = Year(s)

Treatment Frequency
SD = Single Dose
UID = Once Daily
BID = Twice Daily
TID = Three Times Daily

Pop. = Population
CAD = Coronary Artery Disease
CHF = Congestive Heart Failure
HTN = Hypertension

000077

Table 2.G.2 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF CONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
MF9607 (BM)	Portugal (Diniz, M.A.)	820956 40Kc 820175 40Kc	C	1.86 000253	Efficacy and safety in patients with mild to moderate hypertension	DB, PA, R, POS	carvedilol UID nifedipine BID	25.0 50.0 20.0 40.0	6 W	NS	NS	NS	
MF9608 (BM)	Portugal (Pimenta, D.A.) (Freitag, D.M.)	820956 40Kc 820175 40Kc	C	1.86 000254	Efficacy and safety patients with mild to moderate hypertension	DB, PA, POS, R	carvedilol UID enalapril UID	25.0 50.0 10.0 20.0	6 W	NS	NS	NS	

Sponsor

SB = SmithKline Beecham
 BM = Boehringer Mannheim
 DS = Daiichi Seiyaku

Degree of Blinding

O = Open
 SB = Single Blind
 DB = Double Blind
 OBS = Observer Blind

Invest. = Full list of investigators
 is provided in
 Vol. 1.83 Page: 000077

DF = Dose Form

iv = Intravenous
 C = Capsule
 sr = Sustained Release
 T = Tablet
 PO = Oral, Nos

Treatment Assignment

R = Random
 NR = Nonrandom

Degree of Control

UC = Uncontrolled
 PL = Placebo
 POS = Positive

Other

* = Ongoing Study as of 31 August 1992
 NS = Information Not Specified or Not
 Available

Pub. Ref. = Location of Publication

See Vol. 1.86 Page: 000274

Treatment Sequence

XO = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration

H = Hour(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency

SD = Single Dose
 UID = Once Daily
 BID = Twice Daily
 TID = Three Times Daily

Pop. = Population

CAD = Coronary Artery Disease
 CHD = Congestive Heart Failure
 HTN = Hypertension

000036

Table 2.G.3 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF UNCONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
G-17 (DS)	Japan		NS	1.453 000028	Antihypertensive efficacy and safety in hypertensives on carvedilol monotherapy or + diuretic	O, UC	carvedilol daily or + diuretic daily	13.5 13.5/ NS (final mean daily dose)	1 Y	94 (total)	NS	NS	
G-18 (DS)	Japan (Multicenter)		PC*	1.453 000058	Antihypertensive efficacy and safety in patients with renal hypertension	O, UC	carvedilol TID	5.0 10.0 20.0	1 M	9	33 - 64	4/5	17

Sponsor

SB = SmithKline Beecham
 BM = Boehringer-Mannheim
 DS = Daiichi Seiyaku

Degree of Blinding

O = Open
 SB = Single Blind
 DB = Double Blind
 OBS = Observer Blind

Invest = Full List of Investigators
 is provided in
 Vol. 1.83 Page: 000077

DF = Dose Form

iv = Intravenous
 C = Capsule
 sr = Sustained Release
 T = Tablet
 PC = Oral, Nos

Treatment Assignment

R = Random
 NR = Non-random

Degree of Control

UC = Uncontrolled
 Pl. = Placebo
 POS = Positive

Other

* = Ongoing Study as of 31 August 1992
 NS = Information Not Specified or Not
 Available

Pub. Ref. = Location of Publications

See Vol. 1.87, Page: 000111

Treatment Sequence

XO = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration

H = Hour(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency

SD = Single Dose
 QD = Once Daily
 BID = Twice Daily
 TID = Three Times Daily

Pub. = Population

CAID = Coronary Artery Disease
 CHF = Congestive Heart Failure
 HTN = Hypertension

010516

Table 2.G.3 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF UNCONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
G-19 (DS)	Japan Multicenter		T	1.53 000066A	Antihypertensive efficacy of monotherapy or + diuretic in patients with renal hypertension	O, UC, NR, SB placebo run-in	carvedilol UID or + diuretic UID	5.0 10.0 20.0 5.0 NS 10.0 NS 20.0 NS	1 to 2 M	42 ^a (total)	56.4 (mean)	27/15	
G-20 (DS)	Japan			1.81 000097	Acute and long-term antihypertensive efficacy, safety and pharmacokinetics in hypertensive patients undergoing hemodialysis	O, UC	carvedilol SD, UID	10.0	1 M	6	48 - 65	5/1	23

^a42 patients were included in the statistical analysis; 52 patients were enrolled.

Sponsor
 SB = SmithKline Beecham
 BM = Boehringer-Mannheim
 DS = Daiichi Seiyaku

Degree of Blinding
 O = Open
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 OBS = Observer Blind

Invest = Full List of Investigators is provided in Vol. 1.83 Page: 000077

DF = Dose Form
 iv = Intravenous
 C = Capsule
 sr = Sustained Release
 T = Tablet
 PO = Oral, Nus

Treatment Assignment
 R = Random
 NR = Non-random

Degree of Control
 UC = Uncontrolled
 PL = Placebo
 POS = Positive

Other
 * = Ongoing Study as of 31 August 1992
 NS = Information Not Specified or Not Available

Pub. Ref. = Location of Publications
 See Vol. 1.87, Page: 000111

Treatment Sequence
 XC = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration
 H = Hour(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency
 SD = Single Dose
 UID = Once Daily
 BID = Twice Daily
 TID = Three Times Daily

Pop. = Population
 CAD = Coronary Artery Disease
 CHF = Congestive Heart Failure
 HTN = Hypertension

010527

Table 2.G.3 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF UNCONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
G-21 (DS)	Japan Multicenter		T	1.454 000001A	Antihypertensive efficacy and safety in patients with renal hypertension	O,UC	carvedilol UHD, + diuretics if needed	5.0 10.0 20.0	1 Y	19	49.7 (mean)	13/6	36

G-21

Sponsor
 SB = SmithKline Beecham
 BM = Boehringer-Mannheim
 DS = Daiichi Seiyaku

Degree of Blinding
 O = Open
 SB = Single Blind
 DB = Double Blind
 OBS = Observer Blind

Invest = Full List of Investigators is provided in Vol. 1.83 Page: 000077

DF = Dose Form
 iv = Intravenous
 C = Capsule
 sr = Sustained Release
 t = Tablet
 PO = Oral, Nos

Treatment Assignment
 R = Random
 NR = Non-random

Degree of Control
 UC = Uncontrolled
 PL = Placebo
 PC+ = Positive

Other
 * = Ongoing Study as of 31 August 1992
 NS = Information Not Specified or Not Available

Pub. Ref = Location of Publications
 See Vol. 1.87, Page: 000111

Treatment Sequence
 XO = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration
 H = Hour(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency
 SD = Single Dose
 QD = Once Daily
 BID = Twice Daily
 TID = Three Times Daily

Exp. = Population
 CAD = Coronary Artery Disease
 CHF = Congestive Heart Failure
 HTN = Hypertension

Table 2.G.3 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF UNCONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
B102A (SB)	U.S. Multicenter (30 Investigators)	820173 49L.g/ 820468 40L.g 820176 40L.h/ 820469 40L.h	C	1.87 000041	Safety in patients with mild to moderate hypertension (extension of B102)	O, UC	carvedilol BID with HCTZ added if indicated	12.5 25.0 25.0	1 Y	149	NS	NS	
B103A (SB)	U.S. Multicenter (22 Investigators)	820468 40L.g 820469 40L.h	C	1.87 000047	Safety in patients with mild to moderate hypertension (extension of B103)	O, UC	carvedilol TID with HCTZ added if indicated	12.5 25.0 50.0 25.0 50.0	1 Y	176	NS	NS	

Studies Ongoing or Without Completed Report

Sponsor
 SB = SmithKline Beecham
 BM = Boehringer-Mannheim
 DS = Daiichi Seiyaku

Degree of Blinding
 O = Open
 SB = Single Blind
 DB = Double Blind
 OBS = Observer Blind

Invest. = Full List of Investigators is provided in Vol. 1.83 Page: 000077

DF = Dose Form
 iv = Intravenous
 C = Capsule
 sr = Sustained Release
 T = Tablet
 PO = Oral, Nos

Treatment Assignment
 R = Random
 NR = Non-random

Degree of Control
 UC = Uncontrolled
 Pl. = Placebo
 POS = Positive

Other
 * = Ongoing Study as of 31 August 1992
 NS = Information Not Specified or Not Available

Pub. Ref. = Location of Publications
 See Vol.: 1.87, Page: 000111

Treatment Sequence
 XO = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration
 H = Hour(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency
 SD = Single Dose
 QD = Once Daily
 BID = Twice Daily
 TID = Three Times Daily

Pop. = Population
 CAD = Coronary Artery Disease
 CHF = Congestive Heart Failure
 HTN = Hypertension

010519

Table 2.G 3 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF UNCONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
B1103 *(SB)	U.S. (Cehr, T)	820468 40Lg 820729 40Lh	C	1.48 000190	Effect of renal insufficiency on the pharmacokinetics of carvedilol in patients with mild to moderate hypertension	SB, UC	carvedilol UII)	12.5 25.0	2 D 7 D	12	NS	NS	
B1104 (SB)	U.S. (John, W.)	820173 40Lg/ 820468 40Lg 820469 40Lh/ 820729 40Lh	C	1.48 000186	Effects of chronic carvedilol on the steady-state pharmacokinetics of digoxin in patients with mild to moderate hypertension	O, UC	carvedilol/ digoxin UII)	12.5/ 25.0 25.0	2 W 12 D	12	NS	NS	

Sponsor

SB = SmithKline Beecham
 BM = Boehringer-Mannheim
 DS = Daiichi Seiyaku

Degree of Blinding

O = Open
 SB = Single Blind
 DB = Double Blind
 OBS = Observer Blind

Invest = Full List of Investigators is provided in
 Vol. 1.81 Page: 000077

DF = Dose Form

iv = Intravenous
 C = Capsule
 sr = Sustained Release
 T = Tablet
 PO = Oral, Nus

Treatment Assignment

R = Random
 NR = Non-random

Degree of Control

UC = Uncontrolled
 PL = Placebo
 POS = Positive

Other

* = Ongoing Study as of 31 August 1992
 NS = Information Not Specified or Not Available

Pub. Ref. = Location of Publications

See Vol. 1.87, Page: 000111

Treatment Sequence

XO = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration

H = Hour(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency

SD = Single Dose
 UID = Once Daily
 BID = Twice Daily
 TID = Three Times Daily

Pop. = Population

CAD = Coronary Artery Disease
 CHF = Congestive Heart Failure
 HTN = Hypertension

010510

Table 2.G.3 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF UNCONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
C1111 ⁵ (SB)	U.S. Multicenter (45 Investigators)	820173 40Lg/ 820468 40Lg 820469 40Lh/ 820729 40Lh	C	1.425 000002	Antihypertensive efficacy and safety in patients with mild to moderate hypertension	O, UC	carvedilol UID with HCTZ added if indicated	12.5 25.0 50.0 25.0 50.0	1 Y	406	54 (mean)	262/ 144	
CARAGER02 (SB)	Germany (Hofling, B.)	2/12.5 B/3 1/25 B/8 lot1	T	1.87 000060	Antihypertensive efficacy and safety in hypertensive patients with peripheral vascular disease	O, UC	carvedilol UID	12.5- 20 25.0 50.0	1 M	11	49-88	9/2	

⁵Interim report

Sponsor
 SB = SmithKline Beecham
 BM = Boehringer-Mannheim
 DS = Daiichi Seiyaku

Degree of Blinding
 O = Open
 SB = Single Blind
 DB = Double Blind
 OBS = Observer Blind

Invest = Full List of Investigators
 is provided in
 Vol. 1.83 Page: 000077

DF = Dose Form
 iv = Intravenous
 C = Capsule
 sr = Sustained Release
 T = Tablet
 PO = Oral, Nos

Treatment Assignment
 R = Random
 NR = Non-random

Degree of Control
 UC = Uncontrolled
 Pl. = Placebo
 POS = Positive

Other
 * = Ongoing Study as of 31 August 1992
 NS = Information Not Specified or Not
 Available

Pub. Ref = Location of Publications
 See Vol. 1.87, Page: 000111

Treatment Sequence
 XO = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration
 H = Hour(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency
 SD = Single Dose
 UID = Once Daily
 BID = Twice Daily
 TID = Three Times Daily

Pop. = Population
 CAD = Coronary Artery Disease
 CHF = Congestive Heart Failure
 HTN = Hypertension

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Table 2.G.3 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF UNCONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
CAR/GER/08 (SB)	Germany (Law, B.) (Miller, D.) (Herbst, H.) (Roth, W.) (Sack, D.)	1/25 B/8 lot I 2/12.5 B/3	T	1.87 000061	Antihypertensive efficacy in hypertensive patients with left ventricular hypertrophy	O, UC	carvedilol UID with fICTZ 25 mg added if indicated after 6-9 months	25.0 50.0	1 Y	NS	NS	NS	
CAR/HOL/MCT/01 *(SB)	The Netherlands (Visser, F.)	2/12.5 B/3 1/25 B/8	T	1.84 000413	Hemodynamic effects in hypertensive patients with stable left ventricular failure	O, UC, SB placebo run-in	carvedilol UID 50.0	12.5 25.0 50.0	58 W	NS	NS	NS	
CAR/HOL/MCT/02 *(SB)	The Netherlands (Visser, F.)	2/12.5 B/3, B/4 lot I 1/25 B/8, B/4/ 1/25 B/1	T	1.84 000414	Hemodynamic effects in patients with combined hypertension and chronic stable angina pectoris	O, UC, SB placebo run-in	carvedilol UID 50.0	12.5 25.0 50.0	58 W	NS	NS	NS	38

Sponsor
SB = SmithKline Beecham
BM = Boehringer-Mannheim
DS = Daiichi Seiyaku

Degree of Blinding
O = Open
SB = Single Blind
DB = Double Blind
OBS = Observer Blind

Invest = Full list of investigators is provided in Vol. 1.83 Page: 000077

DF = Dose Form
iv = Intravenous
C = Capsule
sr = Sustained Release
T = Tablet
PO = Oral, Nos

Treatment Assignment
R = Random
NR = Non-random

Degree of Control
UC = Uncontrolled
Pl. = Placebo
POS = Positive

Other
* = Ongoing Study as of 31 August 1992
NS = Information Not Specified or Not Available

Pub. Ref. = Location of Publications
See Vol. 1.87, Page: 000111

Treatment Sequence
XO = Crossover
PA = Parallel
AD = Ascending Dose

Duration
H = Hour(s)
D = Day(s)
W = Week(s)
M = Month(s)
Y = Year(s)

Treatment Frequency
SI = Single Dose
UID = Once Daily
BID = Twice Daily
TID = Three Times Daily

Fig. = Population
CAD = Coronary Artery Disease
CHF = Congestive Heart Failure
HIN = Hypertension

000077

Table 2.G.3 (Cont'd)
SK&F 10551*
TABLE OF INVESTIGATIONS
SUMMARY OF UNCONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
CAR/UK/101 (SB)	U.K. (Timmis, A.)	1/25 B/6	T	1.87 000065	Effects on left ventricular hypertrophy in patients with mild to moderate essential hypertension	O, UC, SB placebo run-in	carvedilol UID	25.0 50.0	12 M	NS	NS	NS	
INT/CAR/31 (SB)	Spain (Saez de la Calzada, C.)	1.5 B/8 2/12.5 B/3	T	1.87 000064	Effects on left ventricular hypertrophy in patients with mild to moderate essential hypertension	O, NR, UC	carvedilol UID	25.0 50.0	1 Y	2	50-55	0/2	

Sponsor

SB = SmithKline Beecham
 BM = Boehringer-Mannheim
 DS = Daiichi Seiyaku

Degree of Blinding

O = Open
 SB = Single Blind
 DB = Double Blind
 OBS = Observer Blind

Invest = Full List of Investigators
 is provided in
 Vol. 1.83 Page: 000077

DF = Dose Form

iv = Intravenous
 C = Capsule
 sr = Sustained Release
 T = Tablet
 PO = Oral, Not

Treatment Assignment

R = Random
 NR = Non-random

Degree of Control

UC = Uncontrolled
 PL = Placebo
 POS = Positive

Other

* = Ongoing Study as of 31 August 1992
 NS = Information Not Specified or Not Available

Pub. Ref. = Location of Publications

See Vol.: 1.87, Page: 000111

Treatment Sequence

XC = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration

H = Hour(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency

SD = Single Dose
 UID = Once Daily
 BID = Twice Daily
 TID = Three Times Daily

Pop. = Population

CAD = Coronary Artery Disease
 CHF = Congestive Heart Failure
 HTN = Hypertension

010522

Table 2.G.3 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF UNCONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
INTACAR/99 *(SB)*	Europe Multicenter Belgium (5 Investigators) France (20 Investigators) Germany (14 Investigators) Italy (7 Investigators) Netherlands (7 Investigators) UK (34 Investigators)	1/25 B/3, B/8/ 1 & 2; 1/25 B/6, B/7 1/25 B/12 lot 1	T	1.455 000002	Long-term antihypertensive efficacy and safety in patients with mild to moderate essential hypertension	O, UC	carvedilol UID, BID + other anti- hypertensives if indicated	12.5 25.0 50.0	1+ Y.	432	21-88	209 / 223	1-5

⁶Interim report

Sponsor
 SB = SmithKline Beecham
 BM = Boehringer-Mannheim
 DS = Daiichi Sanyo

Degree of Blinding
 O = Open
 SB = Single Blind
 DB = Double Blind
 OBS = Observer Blind

Invest = Full List of Investigators
 is provided in
 Vol. 181 Page 000077

DF = Dose Form
 iv = Intravenous
 C = Capsule
 sr = Sustained Release
 T = Tablet
 PO = Oral, Nos

Treatment Assignment
 R = Random
 NR = Non-random

Degree of Control
 UC = Uncontrolled
 Pl. = Placebo
 POS = Positive

Other
 * = (Ongoing Study as of 31 August 1992)
 NS = Information Not Specified or Not
 Available

Pub. Ref. = Location of Publications
 See Vol. 187, Page 000111

Treatment Sequence
 XO = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration
 H = Hour(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency
 SD = Single Dose
 UID = Once Daily
 BID = Twice Daily
 TID = Three Times Daily

Pop. = Population
 CAD = Coronary Artery Disease
 CHF = Congestive Heart Failure
 HN = Hypertension

0105517

Table 2.G.3 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF UNCONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
SW/CAR/01 (SB)	Sweden (Andersson, P.E.) (Nordstrom, B.) (Stalhammar, J.) (Tommesen, E.)	1/25 B/B 2/12.5 B/B	T	1.84 000316	Effect on insulin sensitivity in patients with hypertension	SB, UC	carvedilol UII)	12.5- 20 25.0 50.0	6 M	56	NS	NS	
MF4041 (BM)	Norway (Lund-Johansen, P.)	820378 20G	T	1.84 000396	Acute and chronic hemodynamic effects at rest and during exercise in patients with mild to moderate essential hypertension	O, UC	carvedilol SD daily	25.0 25.0- 100.0	1 D 6 - 9 M	20	33 - 59	20/M	19, 22, 31, 32
MF4042 (BM)	Belgium NS	820775 40Kc	C	1.87 000095	Efficacy and tolerability in patients with essential hypertension	O, UC	carvedilol UII)	25.0	3 Y (terminated)	3	NS	NS	
MF4076 (BM)	Germany (Eichstadt, H.)	820409 20G 820408 20G	T	1.87 000097	Efficacy in patients with hypertension and LV hypertrophy	O, UC	carvedilol UII) BII)	25.0 to 50.0	6 M	27	53.9 (mean)	21/M	11, 12

Sponsor
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Degree of Blinding
 O = Open
 SB = Single Blind
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Invest. = Full list of investigators is provided in Vol. 1.83 Page: 000077

DF = Dose Form
 iv = Intravenous
 C = Capsule
 sr = Sustained Release
 T = Tablet
 PO = Oral, Nos

Treatment Assignment
 R = Random
 NR = Non-random

Degree of Control
 UC = Uncontrolled
 PL = Placebo
 POS = Positive

Other
 * = Ongoing Study as of 31 August 1992
 NS = Information Not Specified or Not Available

Pub. Ref. = Location of Publications
 See Vol. 1.87, Page: 000111

Treatment Sequence
 XO = Crossover
 PA = Parallel
 AD = Ascending Dose

Duration
 H = Hour(s)
 D = Day(s)
 W = Week(s)
 M = Month(s)
 Y = Year(s)

Treatment Frequency
 SD = Single Dose
 UD = Once Daily
 BID = Twice Daily
 TID = Three Times Daily

Pop. = Population
 CAD = Coronary Artery Disease
 CHF = Congestive Heart Failure
 HHN = Hypertension

000077

Table 2.G.3 (Cont'd)
SK&F 105517
TABLE OF INVESTIGATIONS
SUMMARY OF UNCONTROLLED HYPERTENSION CLINICAL TRIALS

Protocol (Sponsor)	Country (Invest.)	Formulation	DF	Report Location Vol. Page	Objective	Study Design	Treatment	Dose (mg)	Dur.	N	Age Range (yrs)	Sex M/F	Pub. Ref.
MF4278 *(BM)	Germany (Doctjen, A.)	746873 02	T	1.87 000110	Efficacy and safety in patients with mild to moderate hypertension undergoing hemodialysis	O, UC	carvedilol daily	25 0 50 0	12W	NS	NS	NS	

Sponsor

SB = SmithKline Beecham
BM = Boehringer-Mannheim
DS = Daiichi Selye

Degree of Blinding

O = Open
SB = Single Blind
DB = Double Blind
OBS = Observer Blind

Invest. = Full List of Investigators
is provided in
Vol. 1.83 Page: 000077

DF = Dose Form

iv = Intravenous
C = Capsule
sr = Sustained Release
T = Tablet
PO = Oral, Non

Treatment Assignment

R = Random
NR = Non-random

Degree of Control

UC = Uncontrolled
Pl. = Placebo
POS = Positive

Other

* = Ongoing Study as of 31 August 1992
NS = Information Not Specified or Not Available

Pub. Ref. = Location of Publications

See Vol. 1.87, Page: 000111

Treatment Sequence

XO = Crossover
PA = Parallel
AD = Ascending Dose

Duration

H = Hour(s)
D = Day(s)
W = Week(s)
M = Month(s)
Y = Year(s)

Treatment Frequency

SD = Single Dose
QD = Once Daily
BID = Twice Daily
TID = Three Times Daily

Pop. = Population

CAI = Coronary Artery Disease
CHF = Congestive Heart Failure
HTN = Hypertension

G105517

131 11/22/94

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AUG 3 1994
AUG 3

NDA #20-297
DRUG NAME: CARVEDILOL
SPONSOR: SmithKline Beecham
TYPE OF DOCUMENT: NDA VOLUMES 1.48 - 1.145
DATE RECEIVED: 07 SEP 93
DATE REVIEW COMPLETED: 25 MAY 94 REVISED 28 JUNE 1994
MEDICAL OFFICER: JAMES F. GRAUMLICH, MD

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CLINICAL PHARMACOLOGY SECTION: INTRODUCTION

There were 84 clinical studies reviewed for the following Clinical Pharmacology section of the NDA review. The first part of the summary report presents studies with pharmacodynamic objectives in humans. Next are summaries of studies with pharmacokinetic objectives. Many studies with combined pharmacodynamic and pharmacokinetic endpoints will be listed in more than one part of the summary review. Following the summaries of studies, there are three appendices. The first appendix presents reviews of individual studies in tabular format. The reason for presentation of the reviews in tabular format was to expedite the review process. The last appendix contains individual study reviews in narrative format.

The following table shows the numbers of studies in the review based on route of dose and frequency of dose.

	multiple dose	single dose	sum
oral dose	22	49	71
IV dose	0	6	6
oral and IV dose	0	7	7
sum	22	62	84

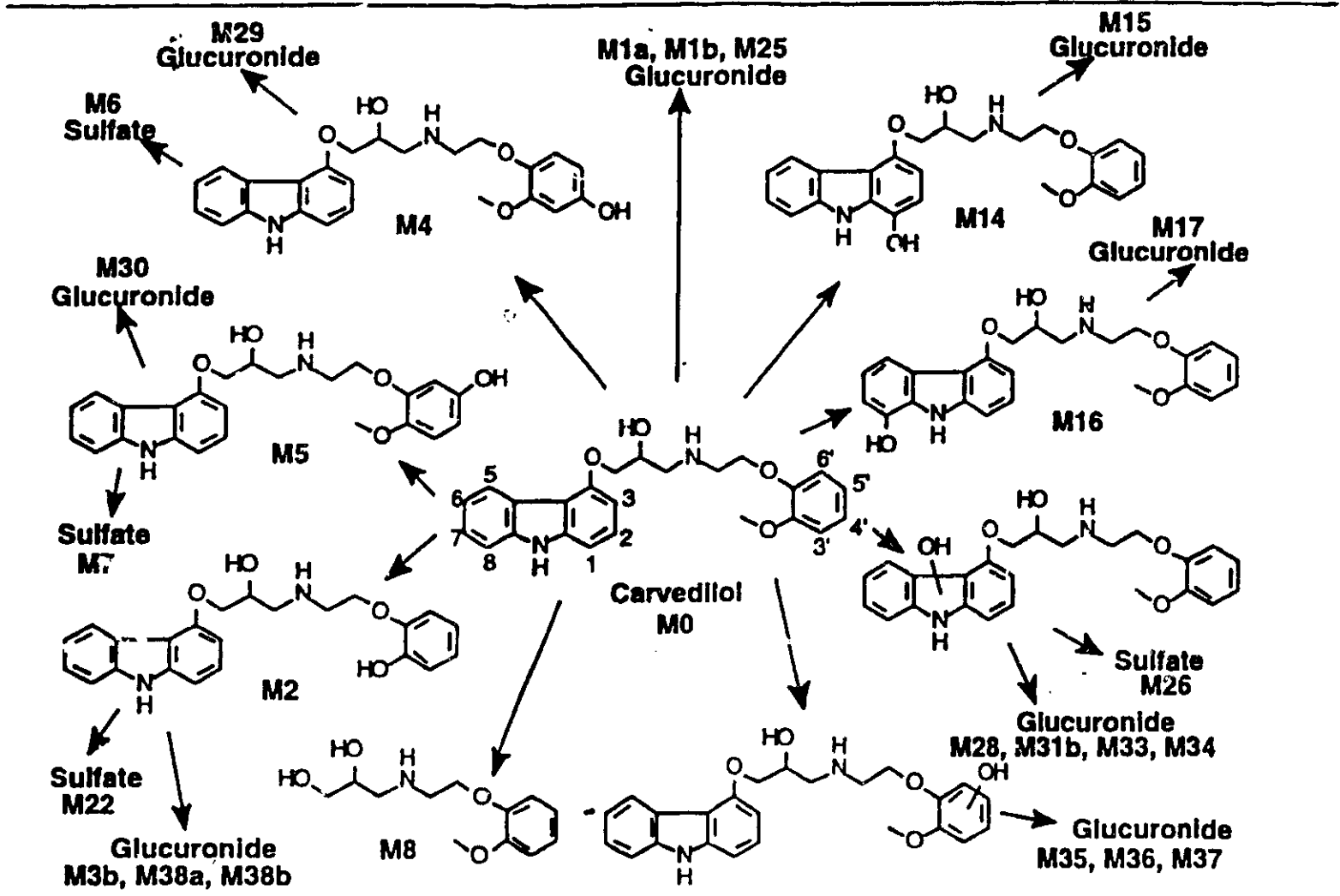
Carvedilol is a drug with non-selective beta adrenoreceptor blocking activity and alpha blocking activity. There are 23 studies attempting to demonstrate beta blockade and/or alpha blockade. Some of these studies fail to show an effect. The drug has been developed as an antihypertensive agent.

Metabolism of carvedilol primarily involves hepatic phase I and phase II reactions. The metabolites found most abundantly were R- and S-carvedilol-O-glucuronide (metabolite M1), des-methyl-carvedilol (metabolite M2), 4'-hydroxyphenyl-carvedilol (metabolite M4), 5'-hydroxyphenyl-

carvedilol (metabolite M5). None of the metabolites were tested for activity in humans.

The chemical structure of carvedilol and the metabolic pathways of elimination are depicted in the figure below.

Figure 1. Metabolic Profile of Carvedilol in Man
(Data from Protocol MF-7029 Addendum)



LIST OF ABBREVIATIONS

?	unknown, questionable
AC	active control
ADR	adverse drug response
ASCHD	atherosclerotic coronary heart disease
CI	cardiac index
CL	clearance
C _{max}	maximum concentration
CXR	chest x-radiograph
CYP	cytochrome P450
DB	double blind
DBP	diastolic blood pressure
DI	drug-drug interaction
DIG	digoxin or digitoxin
DM	diabetes mellitus
E _{max}	maximum effect
ESS	essential
Fe	fractional excretion
GFR	glomerular filtration rate
HR	heart rate
HTN	hypertension
LV	left ventricular
M0	parent carvedilol
M2	desmethylcarvedilol
M4	4'-hydroxyphenyl-carvedilol
M5	5'-hydroxyphenyl-carvedilol
MAP	mean arterial pressure
MR _T	mean residence time
NB	no blind
NC	no control
NR	not randomized
OGTT	oral glucose tolerance test
PAH	para amino hippurate
PC	placebo control
PCWP	pulmonary capillary wedge pressure
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
q	every
R	randomized
RPP	rate pressure product
RV	right ventricular
SB	single blind
SBP	systolic blood pressure
SEQ	sequence
T _{E_{max}}	time to maximum effect
T _{max}	time to maximum concentration
TORA	torasemide
Ur	urine
VES	ventricular extrasystole
WT	weight
Xover	crossover

PART I: CLINICAL PHARMACODYNAMICS**Studies looking at beta blockade and/or alpha blockade**

CAR-SA-01 (NB, AC, NR)

CAR-UK-106 (SB dose escalation, DB R SEQ placebo, crossover)

CARV0001 (SB, PC, AC, parallel)

CARV0011 (DB, PC, R SEQ, crossover)

G28 (NB, NC, NR)

G29 (NB, NC, NR)

INT-CAR-22SCA (NB, NC, NR, parallel, dose escalation)

INT-CAR-30A (DB, PC, crossover, ascending dose sequence, R SEQ placebo only, crossover)

INT-CAR-30B (DB, PC, AC, partially R SEQ, crossover)

MF2740 (DB, AC, NR, parallel)

MF2971 (DB, PC, R SEQ, crossover with extension SB, NC, NR, dose escalation)

MF3070 (DB, PC, R SEQ, crossover)

MF3132-I (DB, PC, AC, R SEQ, crossover)

MF3132-II (DB, PC, R SEQ, crossover)

MF3223-I (DB, PC, AC, R SEQ, crossover)

MF3223-II (DB, PC, R SEQ, crossover)

MF3270 (SB, PC, NR, crossover)

MF3413 (DB, PC, AC, NR, crossover)

MF3548 (DB, PC, AC, R SEQ, crossover)

MF3898 (DB, PC, AC, R SEQ, crossover)

MF7016.0539 (NB, NC, NR, dose escalation)

MF7016.0540 and 0541 (DB, AC, NR, crossover)

MF7027 (SB, PC, NR, crossover)

Beta effect in patients with coronary artery disease

The lowest oral dose of carvedilol demonstrating beta blockade was 25 mg. Only one study in patients with coronary artery disease taking oral doses of carvedilol 25 mg showed blockade of beta adrenergic responses.

CARV0011 (12 patients with coronary artery disease)

Carvedilol 25 mg po, single dose, blocked exercise-induced increases in heart rate and systolic blood pressure. These effects were demonstrated in 12 patients with coronary artery disease but no hypertension nor low ejection fraction.

MF3270 (15 patients with chronic stable angina)

After 2 weeks of treatment, carvedilol 25 mg po bid and carvedilol 50 mg po bid decreased resting heart rate when compared to placebo. In addition, the two regimens blocked exercise-induced increases in heart rate. Among the two active regimens, only carvedilol 50 mg po bid blocked exercise-induced increases in systolic blood pressure. There was a non-significant trend suggesting carvedilol decreased heart rate when measured hourly with a holter monitor. However, there was no difference between the two carvedilol regimens with respect to heart rate on the holter monitor.

MF2740 (16 patients)

Single oral doses of carvedilol 50 mg po failed to block exercise-induced increases in heart rate or systolic blood pressure.

G28 (10 elderly Japanese patients with a history of myocardial infarction)
Single oral doses of carvedilol 20 mg failed to block exercise-induced increases in heart rate or systolic blood pressure.

G29 (11 Japanese patients)
After one week of treatment with carvedilol 10 mg po per day, carvedilol failed to block exercise-induced increases in heart rate or blood pressure.

Beta effect in healthy volunteers

Beta blockade was demonstrated in healthy volunteers in at least one study using oral doses of carvedilol as low as 6.25 mg. Several studies showed blockade of beta adrenergic responses using oral doses of carvedilol greater than 12.5 mg.

CARV0001 (8 healthy men)
Intravenous carvedilol 15 mg blocked isoproterenol-induced tachycardia for up to 8 hours after the carvedilol infusion. In addition, carvedilol blocked isoproterenol-induced decreases in supine diastolic blood pressure and increases in supine systolic blood pressure. Beta blockade occurred with carvedilol concentrations between 8-70 ng/mL.

CAR-UK-106 (7 healthy men)
Single doses of carvedilol 50 mg po, but not carvedilol 25 mg or 12.5 mg, caused decreases in resting heart rate 10-20 beats per minute. The beta effect on heart rate was demonstrated only from 3-7 hours after the dose (CAR-UK-106).

INT-CAR-30B (10 healthy men)
When compared to placebo, single oral doses of carvedilol 12.5 mg, carvedilol 25 mg, labetalol 400 mg (but not carvedilol 6.25 mg) significantly blocked increases in systolic blood pressure caused by isoproterenol in 9 of 10 subjects. The blockade of tachycardia induced by isoproterenol was not as convincing after carvedilol because 3 of 10 subjects did not achieve the target heart rate change. Single doses of carvedilol 6.25 mg, 12.5 mg, and 25 mg blocked exercise-induced increases in heart rate. The exercise test was performed at approximately T_{max}.

MF3223-I (6 healthy men) and MF3223-II (6 healthy men)
Single oral doses of carvedilol 12.5 mg, 25 mg, 50 mg, 100 mg, and 200 mg significantly blocked exercise-induced increases in heart rate and systolic blood pressure when the 12 subjects were analyzed together.

MF3132-I (6 healthy men) and MF3132-II (6 healthy men)
Single oral doses of carvedilol 100 mg blocked exercise-induced increases in heart rate and systolic blood pressure. The time of maximum effect was 1-2 hours after the dose. Carvedilol 100 mg po did NOT significantly affect supine or standing pulse in MF3132I. However, when the 12 subjects from MF3132-I and MF3132-II are analyzed together, there is a statistically significant change in supine (resting) mean heart rate (3-4 beats per minute decrease) and standing (resting) mean heart rate (6-8 beats per minute decrease) caused by carvedilol 100 mg po.

MF2971 (6 healthy men)
Single oral doses of carvedilol 50 mg blocked exercise-induced increases in heart rate and systolic blood pressure. There was no evidence of blockade after 8 hours.

MF3548 (8 healthy men)

Single oral doses of carvedilol 50 mg and 100 mg blocked exercise-induced increases in heart rate and systolic blood pressure. In addition, both doses blocked isoproterenol-induced increases in heart rate. Carvedilol 50 mg, but NOT carvedilol 100 mg, blocked increases in systolic blood pressure caused by isoproterenol. Carvedilol 100 mg did not show convincing evidence of increased beta blockade when compared to carvedilol 50 mg.

MF3898 (4 healthy men)

One week of therapy with carvedilol 25 mg po q day or carvedilol 50 mg po q day blocked exercise-induced increases in heart rate and systolic blood pressure.

INT-CAR-30A (5 healthy men)

There was NOT a significant difference in the percent reduction of exercise-induced tachycardia by single oral doses of carvedilol 6.25 mg, 12.5 mg, 25 mg, or 50 mg.

MF3070 (8 healthy men and women)

Single oral doses of carvedilol 25 mg blocked exercise-induced increased in heart rate and systolic blood pressure.

Other supportive, but not convincing, studies of blockade of exercise-induced tachycardia and/or systolic blood pressure include: INT-CAR-22SCA, MF3413, MF7016.0540 and 0541

Alpha effect in patients

CAR-SA-01 (10 patients with hypertension and mild left ventricular dysfunction)

After a single oral dose of carvedilol 25 mg, there was no consistent effect on systemic vascular resistance.

Alpha effect in healthy volunteers

The lowest oral dose of carvedilol that demonstrated blockade of alpha adrenergic responses was 50 mg.

CARV0001 (8 healthy men)

Intravenous carvedilol 15 mg blocked phenylephrine-induced increases in systolic and diastolic blood pressure. Carvedilol concentrations greater than 25-28 ng/mL were associated with blockade of phenylephrine pressor responses.

MF3548 (8 healthy men)

Single oral doses of carvedilol 50 mg and 100 mg blocked phenylephrine-induced increases in systolic blood pressure but did not block increases in diastolic blood pressure.

MF3898 (4 healthy men)

Carvedilol 50 mg po q day for one week blocked phenylephrine and norepinephrine effects on blood pressure. The amount of blockade was similar on day 1 and day 7 of treatment. Carvedilol 25 mg po q day for one week did not demonstrate alpha effect in this study.

INT-CAR-30B (10 healthy men)

Single oral doses of carvedilol 6.25 mg, 12.5 mg, and 25 mg were NOT convincingly different from placebo with respect to mean per cent response in systolic blood pressure to various doses of phenylephrine.

CAR-UK-106 (7 healthy men)

Alpha effect was NOT demonstrated during non-invasive tests (aortic doppler and forearm venous plethysmography). When compared to placebo, carvedilol 12.5 mg and 25 mg, single oral doses, showed no effect. Single doses of carvedilol 50 mg po caused INCREASED systemic vascular resistance.

MF3898 (4 healthy men)

Multiple dose therapy with carvedilol 25 mg or 50 mg po q day for one week failed to demonstrate a difference in calf blood flow.

MF7016.0539 (15 healthy men)

The data do not convincingly demonstrate an effect on systolic baseline amplitude using digital plethysmography after single oral doses of carvedilol ranging from 15 mg to 76.5 mg.

MF7027 (8 healthy men)

Single doses of carvedilol 50 mg po did not convincingly block response to norepinephrine when measuring the change in diameter of the dorsal hand vein.

Studies in asthmatics

Patients with asthma were excluded from almost all of the clinical pharmacodynamic and clinical pharmacokinetic studies. One asthma patient in study G15 had an exacerbation while receiving carvedilol.

Studies of pulmonary function in healthy volunteers

MF3070 (DB, PC, R SEQ, crossover)

MF3364 (DB, PC, R SEQ, crossover)

MF7024 (NB, NC, R SEQ, crossover)

In healthy men and women, carvedilol 25 mg po does not appear to affect pulmonary function tests.

MF3070 (8 healthy men and women)

Single oral doses of carvedilol 25 mg did not change resting FEV₁, FVC, or FEV₁/FVC.

MF3364 (10 healthy men and women)

After histamine provocation, FEV₁ decreased more than 20% in 2 of 10 volunteers. These volunteers received single oral doses of carvedilol 25 mg.

MF7024 (12 healthy men)

Multiple oral doses of carvedilol 25 mg per day for 5 days alone or in combination with torasemide 5 mg po per day for 5 days did not change FVC, FEV₁, FEV₁/FVC, FEF₂₅₋₇₅.

Studies of effect on left ventricular function in patients

CAR-SA-01 (NB, AC, NR)

CARV0011 (DB, PC, R SEQ, crossover)

G29 (NB, NC, NR)

MF2740 (DB, AC, NR, parallel)

MF3817 (DB, PC, R SEQ, crossover)

MF3924 (NB, NC, NR)

In patients with coronary artery disease, oral doses of carvedilol up to 50 mg did not cause decreases in left ventricular function based on invasive and non-invasive tests.

CAR-SA-01 (10 patients with hypertension and mild left ventricular dysfunction)

After a single oral dose of carvedilol 25 mg, carvedilol caused non-significant decreases in mean aortic pressure, pulmonary capillary wedge pressure, cardiac output, cardiac index, and myocardial oxygen consumption. There was a non-significant increase in right atrial pressure.

CARV0011 (12 patients with coronary artery disease)

Carvedilol 25 mg po, single dose, did not affect ejection fraction on MUGA scan at rest or with exercise in 12 patients with coronary artery disease but no hypertension. Patients with low baseline ejection fraction were excluded from CARV0011.

G29 (11 Japanese patients with coronary artery disease)

In this uncontrolled study, carvedilol 10 mg po per day for one week did not change cardiac output, stroke volume, total peripheral resistance, rate pressure product, left ventricular ejection fraction, left ventricular end diastolic volume, central venous pressure.

MF274C (16 patients with coronary artery disease)

Single oral doses of carvedilol 50 mg failed to cause changes in pulmonary artery pressure, pulmonary capillary wedge pressure, cardiac index, stroke volume, systemic arterial resistance pulmonary artery resistance.

MF3817 (17 patients with coronary artery disease)

A single intravenous dose of carvedilol 5 mg did not show changes in echocardiographic parameters of left ventricular function. The interpretation of this negative study is subject to question (see comments in table, page A6).

MF3924 (10 patients with coronary artery disease)

Similar to MF3706, a single dose of intravenous carvedilol 5 mg decreased aortic (Ao) systolic pressure, Ao diastolic pressure, mean Ao pressure. In addition, carvedilol decreased left ventricular (LV) systolic pressure, LV positive dP/dt max (an index of contractility). Carvedilol did not change LV wall motion, LV ejection fraction, LV end diastolic pressure, LV stroke volume index, or cardiac output. Changes in pulmonary artery diastolic pressure and total systemic resistance were not convincing.

Studies of effect on hemodynamic parameters

CAR-UK-106 (DB, dose escalation, R SEQ placebo)

G2 (NB, NC, NR)

G28 (NB, NC, NR)

MF2684 (DB, AC, R SEQ, crossover)

MF3706 (DB, AC, R SEQ, parallel)

MF3898 (DB, PC, AC, R, crossover)

invasive tests in patients with coronary artery disease do not provide consistent or convincing results.

MF3706 (17 patients with coronary artery disease)

A single dose of intravenous carvedilol 5 mg decreased heart rate, aortic systolic pressure, aortic diastolic pressure, coronary artery flow and rate-pressure-product. Intravenous carvedilol increased coronary artery resistance.

G28 (10 elderly Japanese patients with a history of myocardial infarction)

Single oral doses of carvedilol 20 mg did not change central venous pressure nor systemic vascular resistance.

Non-invasive tests in healthy volunteers caused decreases in cardiac index after single oral doses of carvedilol 50 mg. Lower doses did not cause similar changes.

CAR-UK-106 (7 healthy men)

When compared to placebo in CAR-UK-106, single doses of carvedilol 50 mg po, but not carvedilol 25 mg or 12.5 mg, decreased aortic doppler stroke distance, a parameter proportional to stroke volume, by 2-6 cm. In addition, single doses of carvedilol 50 mg po, but not carvedilol 12.5 mg or 25 mg, decreased aortic doppler peak velocity 10-40 cm/sec.

G2 (5 healthy Japanese men)

On a multiple dose regimen of carvedilol 20 mg po q day for 14 days, subjects had decreased cardiac index or ejection fraction (non-invasive measure not described) on days 1, 3, 5 which subsequently returned to baseline despite continued therapy.

MF2684 (10 healthy volunteers)

Single doses of carvedilol 50 mg po caused more decrease in echocardiographic cardiac index, preload, peripheral resistance than single doses of propranolol 40 mg po.

MF3898 (4 healthy men)

Non-invasive measures of cardiac impedance stroke volume and cardiac output were not changed by one week of therapy with carvedilol 25 mg or 50 mg po q day.

Studies of effect on exercise tolerance

CARV0011 (DB, PC, R SEQ, crossover)

G29 (NB, NC, NR)

MF3270 (SB, PC, NR, crossover)

Studies of the effect of carvedilol on exercise tolerance reveal conflicting results.

CARV0011 (12 patients with coronary artery disease)

Exercise time was significantly shorter by 0.9 minutes after a single oral dose of carvedilol 25 mg. Patients with low baseline ejection fraction were excluded from CARV0011.

MF3270 (15 patients with chronic stable angina)

After 2 weeks of treatment, carvedilol 25 mg po bid and 50 mg po bid prolonged exercise time and time to 1 mm ST segment depression. The maximum number of millimeters of ST segment depression at each stage of exercise was not significantly influenced by carvedilol. Neither regimen decreased radionuclide ventriculographic (MUGA) ejection fraction with rest or exertion.

G29 (11 Japanese patients with coronary artery disease and angina)

In this uncontrolled study, carvedilol 10 mg po per day for one week caused increases in pulmonary vascular resistance with exercise.

Studies of effect on renal parameters

A0003 (DB, PC, R SEQ, crossover)

E32 (NB, NC, NR)

P15 (NB, NC, NR, dose escalation)

Studies did not reveal deterioration of renal function after single and multiple oral doses of carvedilol as high as 50 mg per day.

A0003 (6 healthy men)

Single oral doses of carvedilol from 12.5 mg to 50 mg did not change the fractional excretion of sodium, potassium, chloride, uric acid, calcium, phosphorus. In addition, there was no change in the renal clearance of creatinine, osmol, or free water.

E32 (10 Japanese patients with mild-moderate essential hypertension)

In this uncontrolled study, patients received carvedilol 5 mg, 10 mg, or 20 mg po q day. The mean duration of therapy was 17.3 weeks. There were no changes in glomerular filtration rate, effective renal plasma flow, filtration fraction, renal vascular resistance, BUN, plasma creatinine, plasma uric acid. There were several problems with the study (see table, page A2).

P15 (6 healthy men)

Multiple oral doses of carvedilol from 10 mg per day up to 50 mg per day for a maximum of 4 days revealed no abnormalities of the following urine tests: Na, K, creatinine, volume, pH.

Studies of effect on cardiac electrophysiology

MF3898 (DB, PC, AC, R, crossover)

MF7097 (NB, NC, NR), see PK interaction with cimetidine, page 20

Electrocardiographic intervals were not affected by multiple oral doses of carvedilol up to 50 mg per day.

MF3898 (4 healthy men)

Electrocardiographic intervals, i.e., PR and QT, were not affected by one week of therapy with carvedilol 25 mg or 50 mg po q day.

Studies of effect on response to hypoglycemia or hyperglycemia

G15 (NB, NC, NR)

INT-CAR-30B (DB, PC, AC, partially R SEQ, crossover)

G15 (17 Japanese patients with essential hypertension +/- diabetes mellitus)

Problems with this study (see table) prevent conclusions regarding the effect of carvedilol on the results of the oral glucose tolerance test.

In INT-CAR-30B, 4 of 10 healthy men developed hypoglycemia associated with carvedilol 6.25 mg, carvedilol 25 mg, and labetalol 400 mg. There is a possible role for an interaction with isoproterenol in this study.

Studies of selective blockade of beta receptors

There were no studies with this objective.

Studies of blood flow

CAR-UK-106 (7 healthy men)

MF2740 (DB, AC, NR, parallel)

MF3710 (DB, PC, R SEQ, crossover)

MF7017 (DB, AC, R SEQ, crossover with SB, NR, placebo)

E31 (NB, NC, NR)

NDA 28297

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MF7018 (NB, PC, NR, parallel)

Venous plethysmography in patients revealed conflicting results.

E31 (11 elderly Japanese patients with essential hypertension)

After multiple doses (carvedilol 10-20 mg po q day for 8 weeks), patients in an uncontrolled study had increases in forearm and calf blood flow and venous outflow.

MF2740 (16 patients with coronary artery disease)

Single oral doses of carvedilol 50 mg failed to show changes in leg blood flow.

Venous plethysmography in healthy men did not reveal convincing effects of carvedilol.

CAR-UK-106 (7 healthy men)

Compared to placebo, carvedilol 50 mg po single dose (not 12.5 mg or 25 mg) caused significant decrease in corrected flow time during the 5-24 hours of observation after the dose. There was no consistent effect on forearm blood flow caused by single oral doses of carvedilol 12.5 mg, 25 mg, or 50 mg.

MF7017 (12 healthy men)

Active control (metipranolol suspension) was not active in this study. Single oral doses of carvedilol 50 mg and 75 mg suspensions did NOT show convincing changes in arm arterial flow, peripheral resistance, venous capacity, venous efflux, venous tone, venous pressure-volume curve.

MF7018 (46 healthy men)

Single intravenous doses of carvedilol from 0.313 mg up to 26.27 mg did NOT cause convincing increases in systolic baseline amplitude of the pulse curve during finger plethysmography.

Artery studies using pulsed doppler sonography in patients did not reveal convincing effects of carvedilol.

E31 (11 elderly Japanese patients with essential hypertension)

In an uncontrolled study, bilateral common carotid artery doppler flow increased only during the measurement at the 8th week of carvedilol 10-20 mg po q day.

Artery studies using pulsed doppler sonography in healthy volunteers did not reveal convincing effects of carvedilol.

MF3710 (9 healthy men)

Single oral doses of carvedilol 50 mg (not 25 mg) decreased brachial artery wall tension. Single oral doses of carvedilol 25 mg and 50 mg failed to change brachial artery diameter, blood flow velocity, arterial flow rate, peripheral resistance, arterial compliance, or pulse wave velocity.

Effect on *in vitro* platelet function

B1101 (DB, PC, NR, crossover)

CAR-UK-110 (see below)

Platelet aggregation was increased in healthy volunteers taking carvedilol 12.5 - 25 mg po per day.

B1101 (12 healthy men)

Multiple oral doses of carvedilol 12.5 - 25 mg po q day for 3 days produced decreases in the threshold for ADP-induced and epinephrine-induced platelet aggregation. Carvedilol concentrations were not measured in this study.

CAR-UK-110

Carvedilol acts like propranolol and inhibits platelet aggregation in platelets from healthy donors. The lowest IC50 (in vitro) for inhibition by carvedilol in CAR-UK-110 was 54 μ M. The upper end of the range for Cmax (in vivo) after carvedilol 25 mg po is 0.5 μ M (208 ng/mL).

Pharmacodynamic interaction with loop diuretic

MF3698 (NB, NC, NR)

After a single oral dose of carvedilol 25 mg with torasemide 2.5 mg, 4 of 5 hypertensive patients experienced decreases in systolic blood pressure of 20 - 70 mm Hg and decreases of diastolic blood pressure of 20 - 30 mm Hg. Three of 5 patients complained of orthostatic symptoms.

PART II: CLINICAL PHARMACOKINETICS**Studies of bioequivalence**

O20 (NB, no placebo, R SEQ, crossover)

A0001 (NB, no placebo, R SEQ, crossover)

A0008 (NB, no placebo, R SEQ, crossover)

A9902 (NB, no placebo, R SEQ, crossover)

A9908 (NB, no placebo, R SEQ, crossover)

A9910 (NB, no placebo, R SEQ, crossover)

A9912 (NB, no placebo, R SEQ, crossover)

F39 (NB, no placebo, NR, crossover)

F40 (NB, no placebo, NR, crossover)

MF7008 (NB, no placebo, R SEQ, crossover)

MF7019 (NB, no placebo, R SEQ, crossover with formulation containing Myrj-52)

MF7022 (NB, no placebo, R SEQ, crossover with various capsule formulations)

MF7023 (NB, no placebo, R SEQ, crossover with suspension and slow release tablet)

MF7025 (NB, no placebo, R SEQ, crossover with 3 enteric-coated tablet formulations)

Comments regarding bioequivalence may be found in the Biopharmaceutics review and in the appendices A, B, and C of the Clinical Pharmacology review.

Studies of PK parameters in normal healthy volunteers

A9901 (NB, NC, NR, crossover), see studies of enantiomers, page 19

A9902 (NB, no placebo, R SEQ, crossover), bioequivalence study, page C14

A9907 (NB, NC, R SEQ, crossover), see effect of food, page 16

A9908 (NB, no placebo, R SEQ, crossover), bioequivalence study, page C28

CARV0001 (SB, PC, AC, parallel), see beta effect in healthy volunteers, page 6

CARV0002 (NB, NC, NR study of intravenous formulation)

CARV0012 (NB, NC, R SEQ, crossover of intravenous, oral solution, and capsule formulations)

MF2971 (DB, PC, R SEQ, crossover), see dose proportionality, page 16

MF3413 (DB, PC, AC, NR, crossover), see young and elderly subjects, page 18

MF3950 (NB, NC, NR, parallel), see multiple doses and younger and elderly, page 18

MF7008 (NB, no placebo, R SEQ, crossover), bioequivalence study, C157

MF7016.0539 (NB, NC, NR, dose escalation), see alpha effect in healthy volunteers, page 7
MF7016.0540 and 0541 (DB, AC, NR, crossover), see alpha effect in healthy volunteers, page 7
MF7018 (NB, PC, NR, parallel), see appendix, page A7, B35
MF7020 (NB, NC, R SEQ, crossover with intravenous and capsule formulations)
MF7029 (NB, NC, NR, metabolism study), see studies of metabolites, page 14
MF7034 (NB, NC, R SEQ, crossover), see PK of enantiomers, page 19
MF7038 (NB, NC, NR, crossover), see appendix, page C177
MF7097 (NB, NC, NR), see PK interaction with cimetidine, page 20

A9901 (12 healthy men)

After single oral doses of carvedilol 25 mg, the C_{max} (mean 55 ng/mL) varies over a 10-fold concentration range (12 - 112 ng/mL). AUC (mean 215 ng*hr/mL) varies over a 10-fold range (42 - 434 ng*hr/mL). T_{max} (mean 1.2 hours) varies between 0.5 and 4 hours. Elimination half-life (mean 9.71 hours) varies between 6.7 hours and 15 hours.

MF7018 (46 healthy men)

Single intravenous doses of carvedilol 0.313 mg up to 26.37 mg produced increasing AUC until the dose of 16.88 mg. There was no further increase in AUC for doses on 21.09 mg or 26.37 mg. The fractional excretion (t = 8 hours after the dose) of unchanged carvedilol in the urine was less than 1% for all intravenous doses.

Additional comments regarding PK may be found in the Biopharmaceutics review and in the appendices of the Clinical Pharmacology review.

Studies of metabolites in humans

MF7029 (NB, NC, NR, metabolism study)

MF7029 (3 healthy men over 50 years old)

After single oral doses of radio-labelled carvedilol 50 mg, most of the radioactivity (56% - 64% of ingested radioactivity) was excreted in the feces. Due to a dosing error, the proportion of metabolites excreted in the feces is uncertain. Less than 19% of fecal radioactivity represented parent carvedilol. Between 15% - 17% of ingested radioactivity was excreted in the urine. Most of the urinary radioactivity came from various glucuronide conjugates of carvedilol and its metabolites. Less than 2% of urinary radioactivity represented parent carvedilol. The median elimination half-life for total radioactivity was 39 hours (range 20 - 50 hours).

Studies measuring metabolite, M2, desmethylcarvedilol

A0001 (NB, NC, R SEQ, crossover), bioequivalence study, page C4

A0008 (NB, NC, R SEQ, crossover), bioequivalence study, page C6

A9901 (NB, NC, NR, crossover), see studies of enantiomers, page 19

CAR8902 (NB, NC, NR, crossover), see interaction with cimetidine, rifampin, page 20

F34 (NB, NC, NR), see appendix, page A3, B10

MF3413 (DB, PC, AC, NR, crossover), see young and elderly subjects, page 18

MF3459 (NB, NC, NR), see PK in renal failure, page 17

MF3476 (NB, NC, NR, crossover), see PK in liver insufficiency, page 17

MF3702 (SB, NC, NR, dose escalation), see young and elderly subjects, page 18

MF3950 (NB, NC, NR, parallel), see young and elderly subjects, page 18

MF7029 (NB, NC, NR, metabolism study)

MF7097 (NB, NC, NR), see PK interaction with cimetidine, page 20

MF7108 (NB, NC, NR, crossover), see digitoxin interaction, page 21

A0001 (12 healthy men)

This is a study of bioequivalence using single oral doses of carvedilol 25 mg capsules. C_{max} desmethylcarvedilol is approximately 10% of C_{max} carvedilol. AUC desmethylcarvedilol is approximately 5% of AUC carvedilol. Six of 12 healthy men had symptomatic orthostatic hypotension in this study.

MF7029 (3 healthy men over 50 years old)

After volunteers ingested an uncertain amount of radiolabelled carvedilol, the sponsor reported that desmethylcarvedilol accounted for 1% - 6% of plasma radioactivity, 0.3% - 0.6% of urine radioactivity, and 8% - 10% of fecal radioactivity. There were no studies in humans measuring the pharmacodynamic effects of administration of desmethylcarvedilol.

Studies measuring metabolite, M4, 4'-hydroxyphenyl-carvedilol

F34 (NB, NC, NR), see appendix, page A3, B10

MF3459 (NB, NC, NR), see PK in renal failure, page 17

MF7097 (NB, NC, NR), see PK interaction with cimetidine, page 20

There were no studies in humans measuring the pharmacodynamic effects of administration of 4'-hydroxyphenyl-carvedilol.

Studies measuring metabolite, M5, 5'-hydroxyphenyl-carvedilol

F34 (NB, NC, NR), see appendix, page A3, B10

MF3459 (NB, NC, NR), see PK in renal failure, page 17

MF7029 (NB, NC, NR, metabolism study)

MF7097 (NB, NC, NR), see PK interaction with cimetidine, page 20

MF7029 (3 healthy men over 50 years old)

After volunteers ingested an uncertain amount of radiolabelled carvedilol, the sponsor reported that 5'-hydroxyphenyl-carvedilol accounted for 15% of fecal radioactivity. There were no studies in humans measuring the pharmacodynamic effects of administration of 5'-hydroxyphenyl-carvedilol.

Studies with PK data after multiple doses

F31 (NB, NC, NR, crossover)

MF3950 (NB, NC, NR, parallel)

MF7097 (NB, NC, NR), see PK interaction with cimetidine, page 20

F31 (25 healthy Japanese men)

There was no evidence for accumulation while subjects took carvedilol 20 mg po per day for 14 days.

MF3950 (10 healthy men aged 20 - 26 years and 11 healthy elderly men and women aged 66 - 77 years) Based on C_{max} and AUC values, carvedilol did not appear to accumulate after 13 days of treatment (carvedilol 25 mg po per day) in 10 healthy young men. Since 4 elderly subjects with elevated C_{max} and AUC withdrew, this study should not be used to claim the presence or absence of accumulation in the elderly.

Studies comparing single dose PK with multiple dose PK

F31 (NB, NC, NR, crossover), see dose proportionality, page 16

MF3702 (SB, NC, NR, dose escalation in non-responders), see PK in young and elderly, page 18

Studies of dose proportionality

A9903 (NB, NC, R SEQ, crossover)

F31 (NB, NC, NR, crossover)

MF2971 (DB, PC, R SEQ, crossover with extension SB, NC, NR, dose escalation)

MF3413 (DB, PC, AC, NR, crossover), see young and elderly subjects, page 18

MF3702 (SB, NC, NR, dose escalation in non-responders)

Two of three studies suggest proportional increases in C_{max} and AUC after single oral doses of carvedilol between 6.25 mg and 200 mg.

A9903 (12 healthy men)

After single oral doses of carvedilol 6.25 mg, 12.5 mg, 25 mg, and 37.5 mg, mean AUC and C_{max} for R(+)-carvedilol and S(-)-carvedilol showed increases that were approximately dose-proportional.

MF2971 (6 healthy men)

After single oral doses of carvedilol 50 mg, 100 mg, and 200 mg, there were proportional increases in C_{max} and AUC.

F31 (5 healthy Japanese men)

After single oral doses of carvedilol 5, 10, 20, 40, 60 mg, there was a lack of dose proportional increases in C_{max} and AUC. There was a plateau of C_{max} and AUC at doses above 20 mg.

MF3702 (8 young and 21 elderly hypertensive patients)

Multiple dose therapy with carvedilol 12.5 mg, 25 mg, or 50 mg per day for 4 - 8 weeks did not reveal convincing PK results for the 12.5 mg and 25 mg doses because of missing data or small sample size. See studies of PK in young and elderly subjects (page 18).

Studies of the effect of food on absorption

A9907 (NB, NC, R SEQ, crossover)

F31 (NB, NC, NR, crossover)

MF3413 (DB, PC, AC, NR, crossover), see young and elderly subjects, page 18

MF7021 (NB, NC, R SEQ, crossover)

Reference is made to the Biopharmaceutics review.

A9907 (12 healthy men and women)

The fat content of the meal was 40%. After single oral doses of carvedilol 25 mg, carvedilol absorption was significantly delayed by the presence of food. Median T_{max} was approximately one hour later in fed subjects. Carvedilol C_{max}, AUC, and elimination half-life were not significantly different between the fed and fasted conditions. There was a tendency for food to attenuate the effect of carvedilol on decreasing systolic blood pressure. In contrast, food tended to magnify the effect of carvedilol on decreasing diastolic blood pressure. The magnitude of the blood pressure differences resulting from food is difficult to interpret since there was no placebo.

F31 (25 healthy Japanese men)

The fat content of the meal used in this study was probably too low.

MF3413

The fat content of the meal used in this study was probably too low.

MF7021 (20 healthy men)

Assuming the fat content of the meal is appropriate, then single oral doses of carvedilol 25 mg do not affect C_{max}, AUC, or elimination half life. Food effects were limited to increases in absorption lag time and T_{max}.

Studies of PK in chronic renal failure and insufficiency**G20 (NB, NC, NR)****MF3459 (NB, NC, NR)**

There are no convincing studies assessing the PK of carvedilol after chronic therapy. See comments below (MF3459) regarding PK after single doses.

G20 (6 hypertensive Japanese patients on hemodialysis)

Only 3 patients had measurements of carvedilol concentrations to assess accumulation after carvedilol 10 mg po per day for 4 weeks. Unexplained missing data hinder interpretation of the presence or absence of accumulation in patients on dialysis. One of 6 patients required dose reduction of carvedilol to 5 mg per day because she developed unspecified decreases in blood pressure.

MF3459 (24 hypertensive patients stratified into 3 groups based on creatinine clearance)

After single oral doses of carvedilol 50 mg, there was significantly less renal clearance of carvedilol and metabolites (M2, M4, M5) in patients with severe renal failure versus moderate renal failure. However, the amount of carvedilol, M2, M4, and M5 excreted in the urine is a small percentage of the total dose for all groups of creatinine clearance. In this study, the decrease in renal clearance of carvedilol and metabolites in patients with renal failure is not clinically meaningful. The concentration-versus-time curves show an interesting delayed peak that is compatible with entero-hepatic circulation of carvedilol, M2, M4, and M5. Two patients with the lowest AUCs were taking concomitant vitamin D3. There may be a pharmacokinetic drug interaction between carvedilol and vitamin D3. There is a non-significant trend toward more decrease in systolic and diastolic blood pressure in patients with the lowest creatinine clearance. In contrast, there is an opposite non-significant trend showing less decrease in heart rate in patients with the lowest creatinine clearance.

Studies of dialysis clearance**G20 (NB, NC, NR)****G20 (6 hypertensive Japanese patients on hemodialysis)**

Only 2 patients had measurements of carvedilol concentrations to determine dialyzer clearance. Unexplained missing data hinder interpretation of dialyzer clearance.

Studies of PK in chronic liver failure and insufficiency**MF3476 (NB, NC, NR, crossover)****MF3837 (NB, NC, R SEQ, crossover)**

There is increased bioavailability and decreased total clearance in patients with liver insufficiency. Severe side effects were reported in this patient population.

MF3476 (10 healthy volunteers and 21 patients with mild - severe liver insufficiency)

In vitro protein binding studies using plasma samples from 8 subjects with severe chronic liver insufficiency was 98.2% ± 0.4%. Some of the subjects had huge concentrations of carvedilol that were attributed to dosing error. The results of this study are not reliable.

MF3837 (6 patients with cirrhosis)

Single oral doses of carvedilol 25 mg were compared with single intravenous infusions of carvedilol 12.5 mg. When cirrhotic patients are compared to healthy historical controls, patients with cirrhosis have higher carvedilol bioavailability (mean F 99.7% versus. mean F 22.4%), higher volume of distribution (mean Vd 311.1 L versus. mean Vd 137.6 L), and lower plasma clearance (mean CL 449 mL/min versus. 624 mL/min). One patient had much higher plasma carvedilol concentrations (2 - 3 times higher than the mean of all six subjects) after a single intravenous dose of carvedilol 12.5 mg. This same patient developed hypotension, nausea, and oliguria.

Studies of PK in young and elderly subjects

MF3413 (DB, PC, AC, NR, crossover)

MF3950 (NB, NC, NR, parallel)

MF3702 (SB, NC, NR, dose escalation in non-responders)

Elderly healthy volunteers and hypertensive patients appear to have increased C_{max} and AUC when compared to younger control subjects. The magnitude of the effect on decreasing blood pressure appears to be greater in healthy older subjects. One study in patients (MF3702) does not provide enough information to confirm or refute the magnitude of the effect on blood pressure in elderly hypertensive patients.

MF3413 (10 healthy men between 20 and 40 years old, 10 healthy men and women between 57 and 66 years old)

Single oral doses of carvedilol 25 mg and 50 mg showed median bioavailability in older subjects is 1.6 times the bioavailability in younger subjects. Median total clearance in the older subjects is 0.6 times the clearance in younger adults. Median volume of distribution in the older subjects is 1.5 times the volume in the younger subjects. Median AUC for the older subjects is 1.7 times the AUC of the younger subjects. There were no convincing differences between C_{max}, T_{max}, and half-life between the two age groups. The proportion of subjects unable to stand for blood pressure determination after carvedilol was similar in the younger and older groups. There was no dose-dependent difference in the proportion of subjects unable to stand for blood pressure. The maximum fall in supine or standing blood pressure in the older subjects was 2 times greater than in the younger subjects. The time to maximal fall in blood pressure was 2 - 4 hours after the dose. Older subjects showed a non-significant trend toward later times to E_{max}. There was no significant difference between age groups with regard to decreases in heart rate.

MF3950 (10 healthy men aged 20 - 26 years and 11 healthy elderly men and women aged 66 - 77 years)

After multiple oral doses of carvedilol 25 mg per day for 2 weeks, four of 11 elderly subjects could not tolerate carvedilol because of symptomatic orthostatic hypotension. The C_{max} and AUC for elderly subjects withdrawn for adverse events were 2 - 3 times greater than the corresponding values for elderly subjects completing the trial.

MF3702 (8 young and 21 elderly hypertensive patients)

Multiple dose therapy with carvedilol 12.5 mg, 25 mg, or 50 mg per day for 4 - 8 weeks did not reveal convincing PK results for the 12.5 mg and 25 mg doses because of missing data or small sample size. After the 50 mg dose, mean C_{max} carvedilol was significantly greater in elderly patients versus young patients, 220 ng/mL versus 117 ng/mL. Time to C_{max} was between 0.5 and 2 hours. AUC was 49% higher for elderly patients. There was no dose-response correlation for diastolic blood pressure or systolic blood pressure.

Studies of PK of enantiomers

A9901 (NB, NC, NR, crossover)

A9903 (NB, NC, R SEQ, crossover)

CAR-SA-01 (NB, AC, NR)

F30 (NB, NC, NR)

MF7034 (NB, NC, R SEQ, crossover)

MF7097 (NB, NC, NR), see PK interaction with cimetidine, page 20

There are no studies in which only enantiomers of carvedilol were administered to humans. All studies administered racemic carvedilol. There is no information about the interconversion between enantiomers. There are no clinical trials testing the difference in hemodynamic effects between the enantiomers of carvedilol. Reference is made to the Biopharmaceutics review for further comments about the PK of enantiomers.

A9901 (12 healthy men)

Mean C_{max} and AUC values for R(+)-carvedilol are two to four times greater than values for S(-)-carvedilol. Since half-life for R(+)-carvedilol and S(-)-carvedilol are almost the same, there may be stereoselective absorption favoring R(+)-carvedilol or stereoselective first-pass hepatic metabolism. Plasma concentrations of desmethylcarvedilol are 5% - 10% of plasma concentrations of carvedilol. C_{max} for desmethylcarvedilol is the same as R(+)-desmethyl-carvedilol. C_{max} of S(-)-desmethylcarvedilol was quantifiable, i.e., greater than 1.25 ng/mL, in only 3 of 12 men.

A9903 (12 healthy men)

After single oral doses of racemic carvedilol 6.25 mg, 12.5 mg, 25 mg, and 37.5 mg, geometric mean AUC and C_{max} were approximately 3 times greater for R(+)-carvedilol than for S(-)-carvedilol.

CAR-SA-01 (10 patients with hypertension and mild left ventricular dysfunction)

After a single oral dose of racemic carvedilol 25 mg, mean C_{max} values for R(+)-carvedilol and S(-)-carvedilol in these patients were 2 - 3 times lower than C_{max} values achieved in healthy volunteers. Mean T_{max} values for R(+)-carvedilol and S(-)-carvedilol were 1.8 times longer than T_{max} values recorded in healthy volunteers. Plasma concentrations of R(+)-carvedilol and S(-)-carvedilol did not correlate with hemodynamic parameters measured during right heart catheter study.

F30 (5 healthy men)

After single oral doses of racemic carvedilol 20 mg, mean AUC and C_{max} were approximately 2 - 3 times greater for R(+)-carvedilol than for S(-)-carvedilol. The elimination half-life for each enantiomer was approximately equal.

MF7034 (10 healthy men)

After single oral doses of racemic carvedilol 50 mg, the ratio of R(+)-carvedilol to S(-)-carvedilol was 2.6 for C_{max} and 2.7 for AUC. This is the only study showing a difference in half-life after oral carvedilol with a ratio R(+)/S(-) of 0.4. After intravenous infusion of racemic carvedilol 12.5 mg, the ratio of R(+)-carvedilol to S(-)-carvedilol was 1.2 for C_{max} and 1.3 for AUC. These results are consistent with stereoselective first-pass metabolism.

Studies of PK in people with slow and normal metabolism (CYP450IID6, etc)

A9911 Ongoing study (no report)

Studies of PK: drug interaction with cimetidine, rifampin

CAR8902 (NB, NR, crossover)

MF7097 (NB, NR)

There are PK interactions between carvedilol and cimetidine and between carvedilol and rifampin. The pharmacodynamic consequences of these interactions in patients are unknown.

MF7097 (10 healthy men)

After multiple oral doses of carvedilol 25 mg per day for 4 - 7 days, carvedilol PK values were compared before and after therapy with oral cimetidine 1000 mg per day for 48 hours. Cimetidine caused a 30% increase in racemic carvedilol AUC and 27% increase in the amount of racemic carvedilol excreted in urine. Cimetidine caused a 25% increase in R(+) carvedilol AUC and 39% increase in the amount of R(+) carvedilol AUC excreted in the urine. Cimetidine caused a 15% increase in S(-) carvedilol AUC and 20% decrease in C_{max} for S(-) carvedilol. The differences in amount excreted in the urine (Ae%) and CL_{renal} between R(+) carvedilol and S(-) carvedilol might result from stereoselective renal elimination of carvedilol. Only oral racemic carvedilol was administered in this study. Therefore, no information is available from this study to answer questions about the interconversion of enantiomers of carvedilol. The enantiomers of the metabolites were not assayed in this study. The AUCs for M2, M4, and M5 are all less than 4% of the AUC of racemic carvedilol. The renal clearance of the M2, M4, and M5 is approximately 5 times greater than the renal clearance of racemic carvedilol.

The mechanism for cimetidine's effect on carvedilol kinetics is unknown. Cimetidine may cause an increase in carvedilol oral bioavailability perhaps through a change in gastric pH. The more likely explanation is cimetidine inhibits first-pass hepatic clearance by CYP450. Cimetidine does not appear to decrease the tubular secretion of carvedilol, carvedilol enantiomers, or carvedilol metabolites.

There was no placebo group with which to compare pharmacodynamic responses. In this small group of healthy men, the pharmacokinetic interaction between cimetidine and carvedilol did not cause clinically significant changes in blood pressure, pulse, or electrocardiographic intervals.

CAR8902 (8 healthy men)

Single oral doses of carvedilol 25 mg were used in this study. After therapy with rifampin 600 mg po per day for 11 days, mean carvedilol C_{max} was 33% of the mean carvedilol C_{max} prior to induction. Mean carvedilol AUC_∞ after rifampin was 31% of mean carvedilol AUC_∞ prior to induction. Standing systolic blood pressure fell more than 20 mm Hg in 7 of 8 men receiving carvedilol alone and in 4 of 8 men receiving carvedilol plus rifampin. After therapy with cimetidine 400 mg po every 12 hours for 72 hours, mean carvedilol AUC_∞ was 118% of the mean carvedilol AUC_∞ prior to cimetidine. Standing systolic blood pressure fell more than 20 mm Hg in 3 of 8 men receiving carvedilol plus cimetidine. The PK parameters of demethylcarvedilol were not changed by rifampin or cimetidine.

Studies of PK interaction with warfarin

There were only *in vitro* tests of the interaction between carvedilol and warfarin. Reference is made to the Biopharmaceutics review for comments.

Studies of PK, drug interaction with diuretic

MF3877 (DB, AC, R SEQ, crossover)

MF7024 (NB, NC, R SEQ, crossover)

Concomitant administration of carvedilol and hydrochlorothiazide did not result in adverse PK or pharmacodynamic interaction. In contrast, concomitant administration of carvedilol and torasemide caused intolerable orthostatic side effects in 3 of 5 hypertensive patients.

MF3877 (12 men and women with diastolic BP > 110 mm Hg and systolic BP > 160 mm Hg)
After a single oral dose of carvedilol 25 mg with a single oral dose of hydrochlorothiazide 25 mg, there were no significant differences in PK values for either drug caused by combination therapy. Combination therapy did not cause significant changes in blood pressure or pulse when compared to either drug alone.

MF7024 (12 healthy men)

Multiple oral doses of carvedilol 25 mg per day for 5 days alone or in combination with torasemide 5 mg po per day for 5 days did not change PK parameters for carvedilol, torasemide, or torasemide M5 metabolite. There was no accumulation of carvedilol, torasemide, or torasemide M5 metabolite after 5 days of combination therapy. The absence of adverse events in this young population (mean age 24.6 years) in MF7024 contrasts with the intolerable orthostatic side effects in 3 of 5 hypertensive patients (age range 31 - 73 years) in MF3698 who received single oral doses of carvedilol 25 mg and torasemide 2.5 mg.

Studies of PK, drug interaction with digoxin or digitoxin

A9904 (DB, PC, R SEQ, crossover)

A9905 (DB, PC, R SEQ, crossover)

MF7108 (NB, NC, NR, crossover)

There is a pharmacokinetic interaction between carvedilol and digoxin resulting in increased C_{max} and AUC for digoxin. The pharmacodynamic consequences of this interaction in patients is unknown. There were no PK nor pharmacodynamic interactions between carvedilol and digitoxin in healthy volunteers.

A9904 (8 healthy men) and A9905 (8 healthy men)

After single oral dose of carvedilol 25 mg with single oral dose of digoxin 0.5 mg, there were significant increases in digoxin C_{max} and AUC. The differences in digoxin PK are probably caused by an increase in digoxin bioavailability as a result of concomitant carvedilol. When digoxin was administered intravenously, there was no difference in digoxin PK caused by concomitant carvedilol (see study A9905). Carvedilol was not assayed in either study. There were no significant differences in supine blood pressure or pulse as a result of the concomitant administration of carvedilol and digoxin.

A9905 (8 healthy men)

This study used a single oral dose of carvedilol 25 mg with a single intravenous dose of digoxin 0.5 mg. Other comments are included with study A9904.

MF7108 (12 healthy men and women)

After single oral doses of digitoxin 0.56 mg, carvedilol and desmethylcarvedilol PK parameters are not affected after multiple oral doses of carvedilol 25 mg per day for 7 days. There were no significant changes in systolic blood pressure, diastolic blood pressure, or heart rate caused by concomitant digitoxin and carvedilol.

Studies of PK in hypertensive patients

CARV0003 reviewed by Dr. Knudsen

CARV0021 reviewed by Dr. Knudsen

MF3877 (DB, AC, R SEQ, crossover), see drug interaction with diuretic, page 20

MF3702 (SB, NC, NR, dose escalation) see young and elderly subjects, page 18

CAR-SA-01 (NB, AC, NR), see PK in enantiomers, page 18

Studies of PK in patients with congestive heart failure

CAR-SA-01 (NB, AC, NR), see PK in enantiomers, page 18

Studies of PK in circadian variation

CARV0021 reviewed by Dr. Knudsen

Studies raising safety concerns

MF2971 (DB, PC, R SEQ, crossover with extension SB, NC, NR, dose escalation)

MF3132-I (DB, PC, AC, R SEQ, crossover)

MF3132-II (DB, PC, R SEQ, crossover)

MF3950 (NB, NC, NR, parallel)

Dose limiting side effects (orthostatic hypotension) occurred in the majority of healthy young volunteers taking oral doses of carvedilol 100 mg.

MF3132-I and MF3132-II (12 healthy men)

Single oral doses of carvedilol 100 mg caused statistically significant changes in standing mean systolic blood pressure (20-22 mm Hg decreases) and standing mean diastolic blood pressure (13-18 mm Hg decreases). Four of 6 healthy men in MF3132-II had symptomatic orthostatic faintness that prevented them from exercising.

MF2971 (6 healthy men)

Orthostatic hypotension was the dose-limiting side effect that prevented 4 of 6 healthy men from tolerating single oral doses of carvedilol greater than 200 mg. One subject (#5) tolerated single doses of carvedilol as high as 800 mg. When compared to other subjects, subject #5 had the lowest AUCs for the 50 mg, 100 mg, and 200 mg doses. Subject #5 was also the only subject to prolong his QTc from 0.41 to 0.46 seconds. The QTc prolongation was associated with ingestion of carvedilol 800 mg.

MF3950 (10 healthy men aged 20 - 26 years and 11 healthy elderly men and women aged 66 - 77 years)

After multiple oral doses of carvedilol 25 mg per day for 2 weeks, four of 11 elderly subjects could not tolerate carvedilol because of symptomatic orthostatic hypotension.

The following table shows noteworthy side effects of carvedilol. Please see appendices A, B, and C for details.

Adverse event	Study
urticaria in one subject	A0003
paresis in one subject	G10
asthma exacerbation in one hypertensive patient	G15
hypotension, oliguria in one cirrhotic patient	MF3837
syncope with seizure in one healthy subject	MF7019
elevated AST, ALT	MF7019
syncope, seizure, sinus arrest, hypotension	CARV0002
elevated serum phosphorus in 10 healthy men	MF3950
symptomatic hypotension in elderly man with carcinoma and anemia	MF3476



James F. Graumlich, MD

Appendix A
Appendix B
Appendix C

Distribution: Orig NDA
HFD-110 file
HFD-110 CSO
HFD-110 C. Ganley

Appendix A (NDA 20-297) Abbreviations: R= randomized, NR= not randomized, SEQ= sequence, Xover= crossover

PROTOCOL	VOL	Objective	Design	Subject	Treatment	single vs multi dose	n completed (enrolled)	Results
A0003	1.108	PD, renal inulin	DB, PC, R SEQ	healthy men	po carv 12.5 mg (n=4), 25 mg (n=6)	single	6(6), age 22 - 33 yrs. 1 dropout 2nd	results not believable. For inulin clearance, only n=3 placebo, n=2 carv 12.5 mg, n=3 carv 25 mg 2nd to fructose contamination in inulin. no change inulin clear but results doubtful 2nd small n. PAH clearance increased 2nd to placebo (n=5)
A0003, cont	1.108	urine chemistry	3-Xover		50 mg (n=2)		to urticaria	PAH clear no change 2nd carv 25 mg (n=6). unreliable PAH results 2nd small n for carv 12.5 mg (n=4), carv 50 mg (n=2). Creatinine clear, FeNa, FeK, FeCl, FeUricAc, FeCalcium, FePhos, clear osm, clear free water no change.
A0006	1.108	DI, HCTZ	SB, R SEQ no placebo 2-Xover	healthy men age 22 - 32 yrs	carv 6.25 mg (n=3) or 12.5 mg (n=3) one po/day x 4 day+HCTZ 25 mg on day 4	multi x 4 days	5(n=24 in protocol). no dropouts. unknown reason for stopping at	hard to draw conclusions. only 3 subjects per treatment group. largest fall in standing SBP (approx 15 mm Hg) occurred after HCTZ x 4 days + carv (6.25 or 12.5 mg) on day 4 at 45-60 minutes after the dose.
A0006, cont	1.108				HCTZ 25 mg po/day x 4 day; carv 6.25 mg (n=3) or 12.5 mg (n=3) on day 4 only		n=6. Per protocol, only 2 subjects should get carv 6.25 mg	
B1101	1.109	PD, platelet	DB, PC, NR	healthy men	po carv 12.5 mg, 25 mg	multi x 3 doses only	12(12), 2 of 1st 3 subjects had bradycardia	25 mg dose deleted for last 9 subjects. carv(dose?) increased plasma norepi level (over placebo) at 1 hr post dose supine and stand 78-152 pg/mL. ADP induced platelet aggregation threshold borderline decreased by carv(dose?) pre exercise only
B1101, cont	1.109		2-Xover				or orthostat low BP on carv 25 mg	epinephrine induced plate aggreg threshold decreased by carv (dose unknown) 1 hr post dose (supine) (n=11) and pre exercise. no change in euglobulin clot lysis time. plasma epinephrine level no change. no carv concentration measured
CAR.UK.109	1.84	PD, EEG, psychometric	DB, 4-Xover, R, PC, AC	healthy, sex?	carv 12.5 mg/d po, atenolol 5 mg/d po, enalapril 5-10 mg/d po	multi x 8 days	12(15), age 19-40 yr. 3 withdrew for "personal reasons"	no protocol, no full report, no tables, no figures; ? clin meaning of changes in EEG, auditory vertex potential, memory, mood. ? equipotent doses of active controls

Appendix A (NDA 20-297) Abbreviations: R= randomized, NR= not randomized, SEQ= sequence, Xover= crossover

PROTOCOL	VOL	Objective	Design	Subject	Treatment	single vs multi dose	n completed (enrolled)	Results
CAR8902, see appendix B1, B2	1.73	PK, metabolism, CYP induction	NB, NC, NR, 3-way-Xover	healthy men, avg 29 yrs	carv 25 mg po capsule, cimetidine 400 mg po q 12 hr days	single, carv on day 1, 5, 30	8(8)	Standing BP not recorded at Tmax for 4 subjects (reasons not reported). Standing SBP fell >20 mm Hg in 7/8 men on carv alone, 3/8 on carv+cimet, 4/8 on carv+rifamp. Time to lowest stand SBP 1.1-1.5 hrs post dose, unchanged by treatment. One symptomatic
CAR8902, cont	1.73	inhibition			2-5, rifampicin 600 mg po/day on day 19-30			orthostat hypotension in each treatment group. mean carv Cmax after rifamp was 33% of Cmax carv alone. mean carv AUC _∞ after rifamp was 31% of AUC _∞ carv alone. mean carv AUC _∞ after cimet was 118% of AUC _∞ carv alone. desmethylcarv not changed in any group
CARV0012, see appendix B3-B6	1.78	PK, bioavailability	NB, NC, R SEQ, Xover	healthy men, no coffee, non-	carv 50 mg po capsule, carv 50 mg po soln, carv IV	single	12(12), mean age 25.7 yr, mean weight	BP, pulse, orthostat BP, ECG intervals not tabulated. symptomatic orthostat SBP fall >20 mm Hg in 3/12 men. PK parameters in tables 3-6, pp 27-30. mean IV half-life less than half po half-life. F = 29-33% (geometric mean). less than 1% of dose excreted in
CARV0012, cont	1.78			smoker	0.084 mg/kg		81.5 kg	urine as unchanged carv. no oliguria.
E31	1.143	PD vein flow, RBCs	NB, NC, NR	elder Japanese (62-69 yr)	carv 10 or carv 20 po/d x 8 weeks	multi	11(11)	no protocol, ADR unknown, response measurement time after dose unknown; response 10-20 mg together; All responses compared to pretreatment baseline; SBP, DBP, HR decreased at 4, 8 weeks (clin significance?); cardiac output no change (method of measure?)
E31, cont	1.143	viscosity, platelets		ESS HTN	criteria for dose escalation not reported		power to detect difference unknown	bilat common carotid doppler flow increased, 8 wk only; venous occlusion plethysmography: bilat forearm and calf blood flow and venous outflow increased (clin significance?); plasma viscosity and RBC aggregation decreased; Ptt aggregation no change
E32	1.143	PD GFR renal plasma	NB, NC, NR	Japanese, mild - mod ESS HTN	carv 5, 10, 20 mg po/d; criteria for dose escal-	multi > 12 wk, mean 17.3 wk	10(10)	no protocol; ADR unknown; response measurement time after dose or after enroll unknown; response 5-20 mg together; all responses compared to pretreatment baseline; SBP, DBP decreased; method renal function measure unknown: GFR, eff ren plas flow, filt
E32, cont	1.143	flow		41-71 yr	ation not reported			fraction, ren vas resist, BUN, plas creatinin., plas uric acid showed no change; power to detect difference unknown

Appendix A (NDA 20-297) Abbreviations: R= randomized, NR= not randomized, SEQ= sequence, Xover= crossover

PROTOCOL	VOL	Objective	Design	Subject	Treatment	single vs multi dose	n completed (enrolled)	Results
F31, see appendix B7-B9	1.81	PK	NB, NC, NR, Xover	Japanese healthy men	carv (single) 5,10,20,40,60 mg po	multi 20 mg or 40 mg po/d x 2d; 10 or 20 mg po bid x 2d	25(26); 1 dropout reason unknown	no protocol; ? 2-compartment model with absorp lag; single-dose studies (n=5/study) non-dose-proportional Cmax, AUC not consistent with model; fecal elimination 20% of 20 mg dose, 1 dose tested (?carv + conjugates); food study non-defined "light meal"
F31 cont	1.81					20 mg po/d x 14d		no dose accumulation on 20 mg/d x 14 d; 48-hr urine excretion mean (% of dose) 0.09, 0.24% after single dose 5-60 mg; see table 1, fig 2,3 pg 22,26,27
F34, see appendix B10	1.81	metab	NB, NC, NR	Japanese healthy men	carv 20 mg po	single	5(5)	no protocol; parent carvedilol, metabolite M2, M4, and M5 detected in stool. No quantification. M8, M9, M12 not detected in stool. chemical structure fig 1, pg 53
F39	1.81	bioequiv	NB, NC, NR, Xover	Japanese healthy men	carv 5,10,20 mg po	single	?(22)	abstract only, no protocol, no tables, no data, no figures. cannot corroborate claims in abstract
F40	1.81	bioequiv	NB, NC, NR, Xover	Japanese healthy men	carv 5,10,20 mg po	single	?(22)	abstract only, no protocol, no tables, no data, no figures. cannot corroborate claims in abstract
G2, see appendix B11-B12	1.143	PD, beta, LV eject fraction, cardiac index	NR, NB, NC	healthy Japanese men	carv 20(n=5) or 40(n=5) mg po q day pc x 2 d, carv 10 (n=4) or 20 (n=5) mg po	multi	15(16)	protocol Japanese. cover sheet English. projected n=24. no explanation for lower n enrolled no change in resting pulse with any treat. Both 20 and 40 mg po q day blocked exercise induced tachycardia day 1 (magnitude, onset, duration?) ?training effect
G2, cont	1.143	circadian			bid pc x 2d, carv 20 mg po q day x 14 d (n=5)			Fig 8 pg 70, 2 hours after dose (20 mg/day), cardiac index or EF decreased on days 1, 3, 5. Resting SBP decreased 12.4% on 40 mg. Resting DBP decreased 18%. SBP, DBP T,Emax=3 hr. Fig 7 pg 69 Circadian BP, pulse. Missing results=standing BP, PR, QRS, CXR
G3	1.143	PD	NR, DB, placebo washout	hypertension	carv 10 mg po a day x 5-7 d, nonresponders	multi	12(12), 6 took 10 mg/d and 5	protocol Japanese. cover sheet English. projected n=12. carv concentration results for only 4 patients. Responders and nonresponders not defined a priori. Pretreat vs end of treat (mean±SD) SBP 170.4±2.3 vs 149±2.3, DBP 99.6±1.7 vs 83.4±1.5, HR 69.8±3 vs
G3, cont	1.143		no concurrent control		increased to carv 20 mg po q day x 5-7 d		took 20 mg/d	HR 69.8±3 vs 64.2±2.3. No circadian variation in response. Onset of effect = 1 hr. Duration of effect = 24 hrs. All results for 10 and 20 mg lumped together. No orthostat (seat to stand) change in SBP or DBP. Time after dose of orthostat measure unknown.

Appendix A (NDA 20-297) Abbreviations: R= randomized, NR= not randomized, SEQ= sequence, Xover= crossover

PROTOCOL	VOL	Objective	Design	Subject	Treatment	single vs multi dose	n completed (enrolled)	Results
G10, important AE, see appendix B13	1.143	PD, echocardiography	NB, NC, NR, 6 centers	Japanese, mild - mod ESS HTN, 61-82 yr	carv 10 mg po/d (n=6), carv 10 mg then 20 mg po/d (n=5)	multi x 8 weeks	9(11), 2 withdrawn: 1=rash, 1=paresis	no protocol; response measurement time after dose unknown; response 10-20 mg lumped together; results in table 5, pg 251; no significant hemodynamic changes measured with echo
G15, important asthma data	1.144	PD, oral gluc tol test	NB, NC, NR	Japanese ESS HTN	carv 10-30 mg po/day, mean 19 +/- 2.5	multi x 8-12 wks	17(20), 1 exclu for taking	no protocol. 75 g OGTT pre therapy then at end of 8-12 wks. criteria for dose escalation not defined. 1 asthma patient had asthma exacerbation while on carv improved with dechallenge. HTN+DM insulin grp n=4, HTN+DM diet+/-sulfonyl urea n=8 (missing data)
G15, cont, see appendix B14-B15	1.144			+/- DM	mg/day po		nifedipine, 2 exclu 2nd to no OGTT	HTN no DM group n=5 (missing data). no difference in OGTT not believable. 2nd to small n and dropouts and missing data. See fig 3, pp 78-79. reason for excluding nifedipine subject not given.
G20, see appendix B16-B17	1.81	PD	NB, NC, NR	Japanese HTN, hemo-	carv 10 mg po/d	multi x 4 weeks	6(6), 1 female	no protocol; all results compared with pretreatment baseline; 1 female (wt ?) required dose reduction to 5 mg for decreased BP (amount ?). Only 2 patients had CL _{urea} (dialyzer) measured. Sponsor says no CL _{urea} (dialyzer). Data insufficient on CL _{urea} (dialyzer)
G20, cont	1.81			dialysis				AUC not reported. C _{max} not changed by dialysis in 5-6 patients (missing data not explained). claim no accumulation after multi dose not justified, only 3 patients measured. mean BP on fig 3,4,5 pg 120-121 (see appendix B16-B17)
G28, see appendix B18-B21	1.145	PD, LV function	NB, NC, NR	Japanese + MI	carv 20 mg po	single	10(10), mean age 67.6 yrs	no protocol. Swan-Ganz cath. radionuclide angiography. response (rest, max exercise, post exercise) measured pre and 1 hr post drug. carv failed to block exercise-induced increases in heart rate or SBP. (SBP baseline decreased).
G28, cont	1.145							no change in eject fract ? believable 2rd to 2 missing subjects data. no change central venous press or syst vasc resist. ? alpha-beta blockade claim. see fig table pp 17-20. No post exercise results reported. No change in HR reported at rest
G29, see appendix B22-B24	1.145	PD, LV function	NB, NC, NR	Japanese ASCHD on cor	carv 10 mg po/d	multi x 1 week	11(11), mean age 52 yrs	no protocol. Swan-Ganz cath. radionuclide angiography. response (rest and max exercise) measured prestudy then after carv x 1 wk (2-3 hrs after dose). max exercise is angina (n=8), ST depress (n=1), fatigue (n=2). results see fig 2,3,7, pp 52,53,57
G29, cont	1.145			angio				carv failed to block exercise induced increases in SBP, heart rate. No change card output, stroke vol, tot periph resist, rate press product, LV eject %, LV end diast vol, central venous press. carv increased pulm vasc resist with exercise (? significance)

Appendix A (NDA 20-297) Abbreviations: R= randomized, NR= not randomized, SEQ= sequence, Xover= crossover

PROTOCOL	VOL	Objective	Design	Subject	Treatment	single vs multi dose	n completed (enrolled)	Results
MF2684	1.84	PD, echocardiography	DB, R SEQ, AC, Xover	healthy, sex?	carv 50 mg po, propranolol 40 mg po	single	10(10)	no protocol, no full report, response (echo) measured ? time after dose; carv caused more decrease in cardiac index, preload, periph resist than propranolol; equipotent doses ?
MF2740, see appendix B25-B31	1.116	PD, beta no block, invasive hemo-	DB, no placebo, AC, parallel	ASCHD on angio, post	carv 50 mg po, propranolol 40 mg po	single	16(16), age 37-61 yr	? dose choice. ? equipotent doses. rest-exercise Swan-Ganz cath pre-90 min post dose. leg plethysmography. baseline different in rest syst BP. mixed exercise stoppoint=angina or exhaust in carv grp; endpt=angina, exhaust, VES, dyspnea in propran grp
MF2740, cont	1.116	dynamics, vein flow		PTCA, men only				See appendix B25-B31. carv showed no beta blockade of exercise-induced increases in heart rate or syst BP. carv (? propran) showed no change pulm art press, PCWP, CI, stroke vol, syst art resist, pulm art resist, leg blood flow.
MF3070	1.124	PD, FEV1, peak flow, FVC	DB, PC, R, 2-Xover	healthy men and women	carv 25 mg po, placebo	single	8(8)	Measures pre, 2 hr post dose at rest, exercise. carv blocked exercise induced increase in heart rate (-10 bpm at 200 watts) and SBP (-20 mm Hg at 150-200 watts)(delta rest, delta pbo). No change in resting FEV1, FVC, FEV1/FVC. peak flow not reported
MF3364	1.129	PD, lung	DB, PC, R SEQ, 2-Xover	healthy men and women	carv 25 mg po, placebo	single	10(11), 8 in protocol, 1 dropout reason ?	Measures pre, 2 hr post dose, pre and post histamine provocation. 2/10 decreased FEV1 more than 20% after carv + histamine. body plethysmography TLC, RV not analyzed in report. possible decreased mean peak expir flow 3 min post carv
MF3697	1.84	PD, PK	SB, NR, plac control ?	young 12, elder 9, ? healthy	carv 12.5 mg bid po x 7d, carv 25 mg bid po x 7d	multi	1 withdrew in placebo phase, ? young or elder	no protocol, no full report, no tables, no results, no figures
MF3698, important AE	1.135	PD, drug interaction loop diuretic	NB, NC, NR	hypertension diast BP 100-115	carv 25 mg capsule po with torasemide 2.5	single	5(5), n=15 intended per protocol	Seated BP only hourly 1-4 hrs, then 6,8,12,24 hours post dose. 1/5 patients with diast BP $\geq$ 70 failed inclusion criteria. Syst BP fell 20-70 mmHg and diast BP fell 20-30 mmHg in 4/5 patients. Mean SBP, DBP, pulse showed decreasing trend over 24 hrs.
MF3698, continued	1.135			mmHg, 31-73 yrs old	mg tablet po			2/5 patients complained of orthostat symptoms. Lab results not reported. No standing BP reported. Trial enrolment cancelled due to adverse events in first 5 patients.

Appendix A (NDA 20-297) Abbreviations: R= randomized, NR= not randomized, SEQ= sequence, Xover= crossover

PROTOCOL	VOL	Objective	Design	Subject	Treatment	single vs multi dose	n completed (enrolled)	Results
MF3706	1.106	PD, invasive hemodynamic	DB, AC, R SEQ, parallel group	men, ASCHD on cor angio	carv 5 mg IV, propranolol 6 mg IV	single	17(19), 2 propran subject excluded	No placebo arm. Equipotent doses carv and propran not known in this population. Question appropriate dose for comparison carv vs propranolol. Compared to predose, carv decreased heart rate, aort syst and diast BP
MF3706, cont	1.106						2nd to total cor occlusion	compared to predose, carv decreased cor flow, rate press product and cor resist x RPP. carv increased cor resistance. inconsistent statistical alpha error used (0.01-0.10, 1 and 2-side alpha)
MF3710	1.135	PD, forearm vasodilation	DB, PC, R SEQ, Xover	healthy men	carv 25, 50 mg po, placebo po	single	9(10), 1 dropout for "personal reasons"	brachial artery pulsed doppler pre, 3,6,9 hrs post dose. SBP, MAP decreased by carv. carv 25 mg(not 50 mg) non-significant increased art diameter (vasodilate). No change blood flow velocity, art flow rate, periph resist, pulse wave velocity (missing data).
MF3710,cont	1.135							no change arterial compliance. Wall tension decreased for carv 50 mg (not 25 mg)
MF3817	1.106	PD, echocardiography	DB, PC, R SEQ, Xover	patients, ASCHD on cor angio	carv 5 mg IV, placebo	single	17(21), withdrawals: 1 arrhythmia, 1 calcified aortic valve, 2 problem echo equip	No change in LV parameters on echo. No positive control. No power analysis. Heart rate, DBP, SBP not affected by carv. Question appropriate choice of dose. ? appropriate withdrawals
MF3837, important AE, see appendix B32-B34	1.61	PK, liver impairment	NB, NC, R SEQ, Xover	cirrhosis cholinesterase <1800,	carv 25 mg capsule po, carv 12.5 mg IV over 1 hr	single	6(6), mean age 52.5 yrs, mean weight 76.9	After IV dose, 2 men sampled at wrong times but were included in calculation of PK parameters. Patient #6 with high carv concentration after IV excluded from all PK analyses. #6 (possible slow metabolizer) developed hypotension, nausea, oliguria requiring
MF3837, cont	1.61			Quick <70%			kg, 20 historical healthy controls	med treatment (no details). #6 carv conc 0.25-1 hr post po dose= 2-3 x above mean (n=6). F=>82.6% (much higher than healthy men). Carv dose excreted in urine after IV or po <1%. Compared to healthy, liver disease increase V, decrease CL. see appendix B32
MF3897	1.139	PD, skin temperature	DB, AC, R SEQ, 2-Xover	healthy men, women, non smoke	carv 25 mg po, propranolol 80 mg po, equipotent ?	single	14(14), 20 in protocol	hand thermography pre, 2 hr post dose showed no change for either drug. no conclusions can be drawn from this study. active control was not active. there was no placebo comparison.

Appendix A (NDA 20-297) Abbreviations: R= randomized, NR= not randomized, SEQ= sequence, Xover= crossover

PROTOCOL	VOL	Objective	Design	Subject	Treatment	single vs multi dose	n completed (enrolled)	Results
MF3898, important study	1.140	PD, beta, alpha block, blood	R, DB, PC, AC, Xover	healthy men	carve 25 mg/d, carve 50 mg/d, labetalol 400 mg/d,	multi for 1 week	4(4)	Measures 1.3 and 3 h 50 min after dose. Supine and tilt SBP fell 10-20 mm Hg. All active drugs blocked exercise-induced tachycardia and rise in SBP. Carv 50 blocked phenylephrine, noradrenaline. (angiotensin effect equivocal) Day 1 and 7 changes similar
MF3898, cont		flow, hemodynamics			placebo/d			Per protocol, 12 subjects were to be enrolled. No explanation for failure to enroll 8. No difference in supine DBP, tilt DBP, supine pulse, tilt pulse, calf blood flow, PR and QT intervals, card impedance stroke vol, card output
MF3924	1.107	PD angio hemodynamic	NB, NC, NR	patients, ASCHD on cor	carv 5 mg IV	single	10(10), all men, age 44 - 68 yrs	? dose choice. did not correlate carv concentration with effect. rt heart press no change except possible decreased pulm art diast press. no change cardiac output. poss decrease total systemic resist. LV segmental wall motion no change.
MF3924, cont	1.107	LV, RV function		angio				no change LV eject fraction, LV end diast press, LV stroke vol index. carv decreased LV systolic press, aort syst press, aort diast press, mean aort press, LV pos DP/dt max (contractility). PCWP not measured.
MF7017	1.141	PD alpha vaso-dilation	DB, AC, R SEQ, X-over, NR	healthy men, avg age	carv 50, 75 mg suspension po metipranolol	single	12(12). no dropouts reported	no protocol. Hourly venous plethysmography (arm) to 6 hrs post dose. Changes 2nd to meal confound after 3rd hour. Arterial flow non-significant increase from baseline with carv 50, 75 but not metipran. Periph resistance non-significant decrease from
MF7017, cont	1.141	vein flow	SB placebo	24.3 yrs	7 mg susp po		ECG results not reported	baseline with carv 50, 75 but not metipran. No convincing change with any active treatment on venous capacity, venous efflux, venous tone, venous pressure-volume curve. No placebo results reported. Alpha blockade questionable.
MF7018, see appendix B35	1.64	PD, dose finding, PK	NB, NR, PC, parallel	healthy men	carv mg IV: 0.313, 0.625, 1.25, 2.5, 5.0, 6.1, 7.5, 9.2	single	46(46), n=24 carv (2 men per dose level)	no protocol. doses changed from coversheet (reason ?). PK included only 5 samples in 2 hrs post infusion. orthostat BP measured only 2 (7 3) and 7 hrs post infusion. at doses above 17 mg, AUC falls. question saturation of hepatic reabsorption.
MF7018, cont	1.64				carv mg IV: 11.25, 16.88, 21.09, 26.37		n=22 placebo subjects	fractional excretion (0-8 hrs after dose) of carv in urine < 1% for all IV doses. orthostat SBP fell > 20 mm Hg (with no increase in pulse > 20 bpm) for 1 of 2 subjects on carv 0.625, 9.2, 21.09, and 26.37 mg at 3 hrs post infusion.
MF7018, cont	1.64							n-octanol/phosphate buffer partition coefficient = 817 (at pH 7.0) and 1993 (at pH 7.4). when dose increases, there is no convincing increase in systolic baseline amplitude of the pulse curve during finger plethysmography

Appendix A (NDA 20-297) Abbreviations: R= randomized, NR= not randomized, SEQ= sequence, Xover= crossover

PROTOCOL	VOL	Objective	Design	Subject	Treatment	single vs multi dose	n completed (enrolled)	Results
MF7019, important AE	1.65	PK, bioavailability	NB, NC, R SEQ, Xover	healthy men	carv 50 mg po capsule with Myrj-52, carv 50 mg po capsule no Myrj-52, carv 50 mg po tablet with	single	20(20), 1 withdrawal syncope + seizure while seated 20 min post dose with full recovery	no protocol. elevated AST, ALT (up to 10x up limit normal) with no elevated GGT in 1 subject withdrawn from one period in Xover. MYRJ-52 increases Cmax (doubles), increases AUC (x 1.4). 6 - 10 fold inter-individual variability or, both parameters
MF7019, cont	1.65				Myrj-52		after 5 hrs post dose	MYRJ-52 shortens half-life (trend yes, significant no), No change in Tmax. No BP, pulse reported. These formulations not planned for market.
MF7020	1.66	PK, bioavailability	NB, NC, R SEQ, Xover	healthy men	carv 12.5 mg IV infuse over 1 hr, carv 50 mg po suspension, carv	single	20(20)	no protocol. F: susp 22%(10-73), 50 cap 24%(12-46), 25 cap 22%(10-49), total CL(iv) 589 mL/min(375-848). Vd(iv) 132 L(92-255)= 1.68 L/kg(1.1-2.9 L/kg). Cmax IV=173 ng/mL(109-234), susp 128 ng/mL(55-237), 50 cap=66 ng/mL(34-130), 25 cap=21.4 ng/mL(4.7-99)
MF7020, cont	1.66				50 mg po capsule, carv 25 mg po capsule			elim t1/2: IV=2.38 hr(1.95-4.17), 50 mg susp=4.3 hr(1.9-8.7), 50 mg cap=6.35 hr(4.1-14.6), 25 mg cap=7.06 hr(2-20.9). no significant increase in serum K. urine chloride (24 hr) twice urine Na (24 hr). reason unknown. serum chloride had no change.
MF7021, see appendix B36	1.67	PK, bioavailability, food effect	NB, NC, R SEQ, Xover	healthy men, avg age 27.8 yr	carv 25 mg po	single	20(20), no dropouts reported	no protocol. breakfast= 40% bread, 29% ham, 17% cheese, 14% jam. breakfast before dose increased absorp lag time and Tmax but did not affect elim half life, Cmax, AUC, MRT. data from 2 subjects deleted. reason unknown. see appendix B36
MF7022, important AE	1.67	PK, bioavailability, capsule effect	NB, NC, R SEQ, Xover	healthy men, avg age 31.6 yr	carv 50 mg po caps (size 0), carv 25 mg po caps (size 0)	single	18(20), 1 dropout due to influenza	no protocol. no BP pulse reported. 1 dropout (2nd period) circulatory collapse. syncope, vomit, urine void 1.75 hr post dose. only 9/19 had samples after 14 hrs post dose. 3-4 men excluded from analysis for ? reasons included men with lowest AUC.
MF7022, note cont, see appendix B37	1.67				carv 50 mg po caps (size 3)		had highest Cmax	lowest Cmax, or highest Cmax. PK unremarkable in syncope subject. PK parameters in table (see appendix B37)

Appendix A (NDA 20-297) Abbreviations: R= randomized, NR= not randomized, SEQ= sequence, Xover= crossover

PROTOCOL	VOL	Objective	Design	Subject	Treatment	single vs multi dose	n completed (enrolled)	Results
MF7023, see appendix B38	1.68	PK, bio-availability, resistant tab	NB, NC, R SEQ, Xover	healthy men, avg age 32.1 yr	carv 34 mg po suspension, carv 16.67 mg 2 tabs po	single	10(10)	no protocol. creatinine clearance no change. coated tablet resistant to gastric acid had delayed Tmax, lower Cmax, and lower AUC compared to suspension. PK parameters in table (see appendix B38). results do not represent commercial formulation.
MF7024, see appendix B39-B40	1.68	PK, interaction torasemide	NB, NC, R SEQ, Xover	healthy men, avg age 24.6 yr	carv 25 mg po capsule, torasemide 5 mg po tab, combo	multi, 1 dose/day x 5 days	12(13), 1 excluded had no measurable drug	body weight stable for all subjects throughout study. predose carv concentration on days 3-5 were borderline detectable(1-2 ng/mL) in 8/12 men and < 1 ng/mL in 4/12 men, ie showing no accumulation. No subject had detectable torasemide > 40 ng/mL or toras-
MF7024, cont	1.68	see tables pp 157, 162			carv 25 + torasemide 5 po		level, which drug, not reported	emide M5 metabolite > 20 ng/mL. predose on days 3-5 on combo carv + torasemide, ie, no accumulation. PK parameters for toras, toras M5, and carv unchanged by combo therapy. no change in mean heart rate, FVC, FEV1, FEV1/FVC, FEF25-75, SPEP by any treatment
MF7025	1.70	PK, bioavailability, enteric coated	NB, NC, R SEQ, Xover	healthy men, age 21-46 yrs	carv 25 mg, 2 tabs po, 3 enteric coated forms with different pH-resistances	single	9(9)	no withdrawals for adverse events. the formulations were not bioequivalent with large changes in Cmax and AUC. none of these forms is commercial form. no BP pulse recorded.
MF7027	1.84	PD, alpha B, hand vein	SB, 4-Xover, NR, PC	healthy men	carv 50 mg po	single	8(8) age 23-30 yr	no protocol, no full report, no tables, no figures; measured response= dorsal hand vein diameter pre and post carv. carv blocked response to norepinephrine and PGF2alpha at 1, 3.5 hrs post dose; placebo response not reported. ? alpha blockade
MF7108, see appendix B41-B43	1.72	PK, carv-digitoxin interaction	NB, NC, NR, Xover	healthy men and women, avg age 27.4 yrs	digitoxin 0.07 mg/tab, 8 tabs po/day, carv 25 mg tab, 1 po/day	multi carv x 7 days (days 31-37)	12(12), no dropouts	pp 209-231, including most of protocol, missing. PK measured on day 1 (dig alone), day 35 (carv alone at steady state), day 36 (carv + dig). one woman collapsed at work 2 hrs after 7th carv dose. Dig PK not affected by carv. Carv and desmethylcarv PK not
MF7108, cont	1.72					digitoxin single dose days 1, 36		affected by dig. see fig 1-3, table 2 in appendix B41-B43. Digitoxin did not change carv or desmethylcarv excreted in urine. no significant change in SBP, DBP, heart rate. ECG data not reported.
P15	1.142	safety, urine chemistry	NR, NB, NC	healthy men	carv 10 mg po x 1 day, 25 mg x 2 days, 25 mg q 12 h x 4 days	multi	6(6)	no protocol submitted. No ECG intervals reported. normal urine Na, Ur K, Ur creatinine, Ur volume, Ur pH. Supine and standing pulse and BP were not compared. Pulse and BP changes between doses not compared

A1 B1

PHARMACOKINETIC DATA - COMPARISON BY SUBJECT

PROTOCOL ID.	: RD134/16996	SAMPLE TYPE	: PLASMA
FIRST SAMPLE TIME	: 01 00:00	COMPONENT	: CARVEDILOL
LAST SAMPLE TIME	: 01 12:00	TARGET DOSE	: 25 mg.
FORMULATION	: CARVEDILOL	DOSE TIME	: 01 00:00

ADMINISTRATION 01

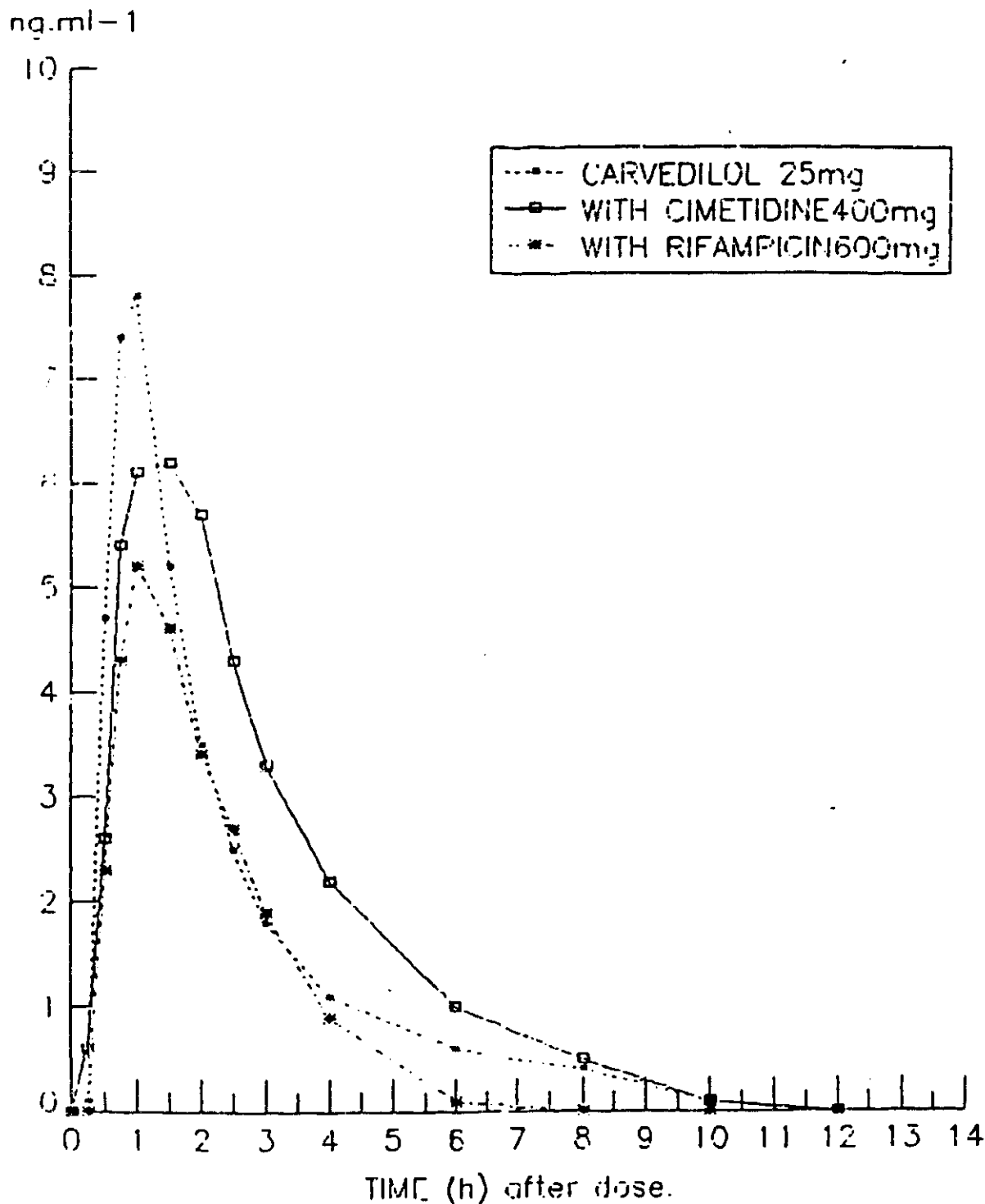
VSN INITIALS	C _{max} (ng.ml ⁻¹)	T _{max} (hr)	AUC(T) (ng.ml ⁻¹ .h)	AUC(I) (ng.ml ⁻¹ .h)	K _{elim} (hr ⁻¹)	T _{1/2} (hr)	Cl (l/hr)
01							
02							
03							
04							
05							
06							
07							
08							
MEAN	86.5	MEDIAN 0.75	202.830	214.392	0.2915	2.43	0.135
S.D.	35.4	RANGE 0.75- 2.00	86.908	95.748	0.0484	0.36	0.055

CAR 8902
VOL 1.73

000073

FIGURE 5

MEAN PLASMA DESMETHYL CARVEDILOL LEVELS
AFTER THREE SEPARATE CARVEDILOL DOSES.



CAR 8902
VOL 1.73

000092

BMP STUDY: CARV 0012
 INVESTIGATOR: KISICKI

TABLE 3
 INDIVIDUAL PHARMACOKINETIC PARAMETERS

INTRAVENOUS SOLUTION 0.084 MG/KG

SUBJECT	AUC 0-T MG HR/ML	AUC 0-INF MG HR/ML	C MAX MG/ML	KEL /HOUR	T HALF HOURS	MRT HOURS	CL SYSTEMIC L/HR	Vss L/HR
01								
02								
03								
04								
05								
06								
07								
08								
09								
10								
11								
12								
MEAN	214.5	227.7	203.3	0.258	3.22	3.64	32.8	114.0
S.D.	73.3	78.6	54.1	0.105	1.73	1.60	9.2	30.4
MIN								
MAX								

SOURCE: BOEHR:[BIS.CARV.CARV0012]LIST.SAS RUN 8/4/87 BY ERH, TE; TE BY GTS 2/27/89

CARV 0012
 VOL 1.78
 000027

25
 83

BMP STUDY: CARV 0012
INVESTIGATOR: KISICKI

TABLE 4
INDIVIDUAL PHARMACOKINETIC PARAMETERS

CAPSULE 50 MG

SUBJECT	AUC 0-T NG HR/ML	AUC 0-INF NG HR/ML	C MAX NG/ML	T MAX	KEL /HOUR	T HALF HOURS	MRT HOURS	CL SYSTEMIC L/HR
01								
02								
03								
04								
05								
06								
07								
08								
09								
10								
11								
12								
MEAN	555.9	626.9	128.0	1.35	0.101	7.53	8.61	110.5
S.D.	341.4	410.1	87.1	0.89	0.031	2.62	2.65	59.5
MIN								
MAX								

SOURCE: BOEHR:[BIS.CARV.CARV0012]LIST.SAS RUN 8/4/87 BY ERH, TE

CARV 0012

VOL 1.78

000028

B4

26

BMP STUDY: CARV 0012
INVESTIGATOR: KISICKI

TABLE 5
INDIVIDUAL PHARMACOKINETIC PARAMETERS

ORAL SOLUTION

SUBJECT	AUC 0-T NG HR/ML	AUC 0-INF NG HR/ML	C MAX HG/ML	T MAX	KEL /HOUR	T HALF HOURS	MRT HOURS	CL SYSTEMIC L/HR
01								
02								
03								
04								
05								
06								
07								
08								
09								
10								
11								
12								
MEAN	445.3	518.9	120.7	0.85	0.099	9.06	9.55	119.5
S.D.	207.3	270.3	57.9	0.70	0.060	4.37	3.66	52.4
MIN								
MAX								

SOURCE: BOEHR:[BIS.CARV.CARV0012]LIST.SAS RUN 8/4/87 BY ERH, TE

000029
CARV 0012
VOL 1.28

165
27

BMP STUDY: CARV 0012
INVESTIGATOR: KISICKI

TABLE 6
INDIVIDUAL DOSE ABSORPTION FRACTIONS

SUBJECT NUMBER	AUC CAPSULE	AUC SOLUTION	AUC* IV	F CAP/SOL	F CAP/IV	F SOL/IV
01						
02						
03						
04						
05						
06						
07						
08						
09						
10						
11						
12						
GEOMETRIC MEAN				1.14	0.33	0.29

* ADJUSTED FOR DOSE

SOURCE: BOEHR: [BIS.CARV.CARV0012]ANOVA.SAS RAN 8/4/87 BY ERH, TE

CARV 0012
VOL 178
000030

Be

Table 1 Pharmacokinetic parameters of carvedilol in healthy male subjects

Parameter	Dose (mg/man)			
	10	20	40	60
Lag time (hr)	0.00±0.00	0.14±0.09	0.17±0.11	0.25±0.12
Tmax (hr)	0.9±0.3	0.9±0.1	1.3±0.4	1.6±0.2
Cmax (ng/ml)	22.6±4.7	53.1±14.7	78.7±20.4	78.0±20.0
t _{1/2β} (hr)	4.28±1.43	8.03±1.92	6.28±1.84	13.67±2.78
AUC(0-∞) (ng·hr/ml)	59.9±12.7	232.5±88.1	285.2±89.9	389.5±94.8
Vd (l)	247±33	347±88	425±128	618±212
Ka (hr ⁻¹)	7.268±3.293	3.052±0.815	3.765±1.443	1.688±0.544
Ke (hr ⁻¹)	0.815±0.128	0.368±0.044	0.527±0.171	0.414±0.124
K12 (hr ⁻¹)	0.819±0.229	0.204±0.031	0.511±0.305	0.211±0.042
K21 (hr ⁻¹)	0.452±0.128	0.225±0.088	0.307±0.219	0.134±0.059

Results are expressed as mean values±S.E. for five subjects.

000022

VOL 1.81

F 31

67

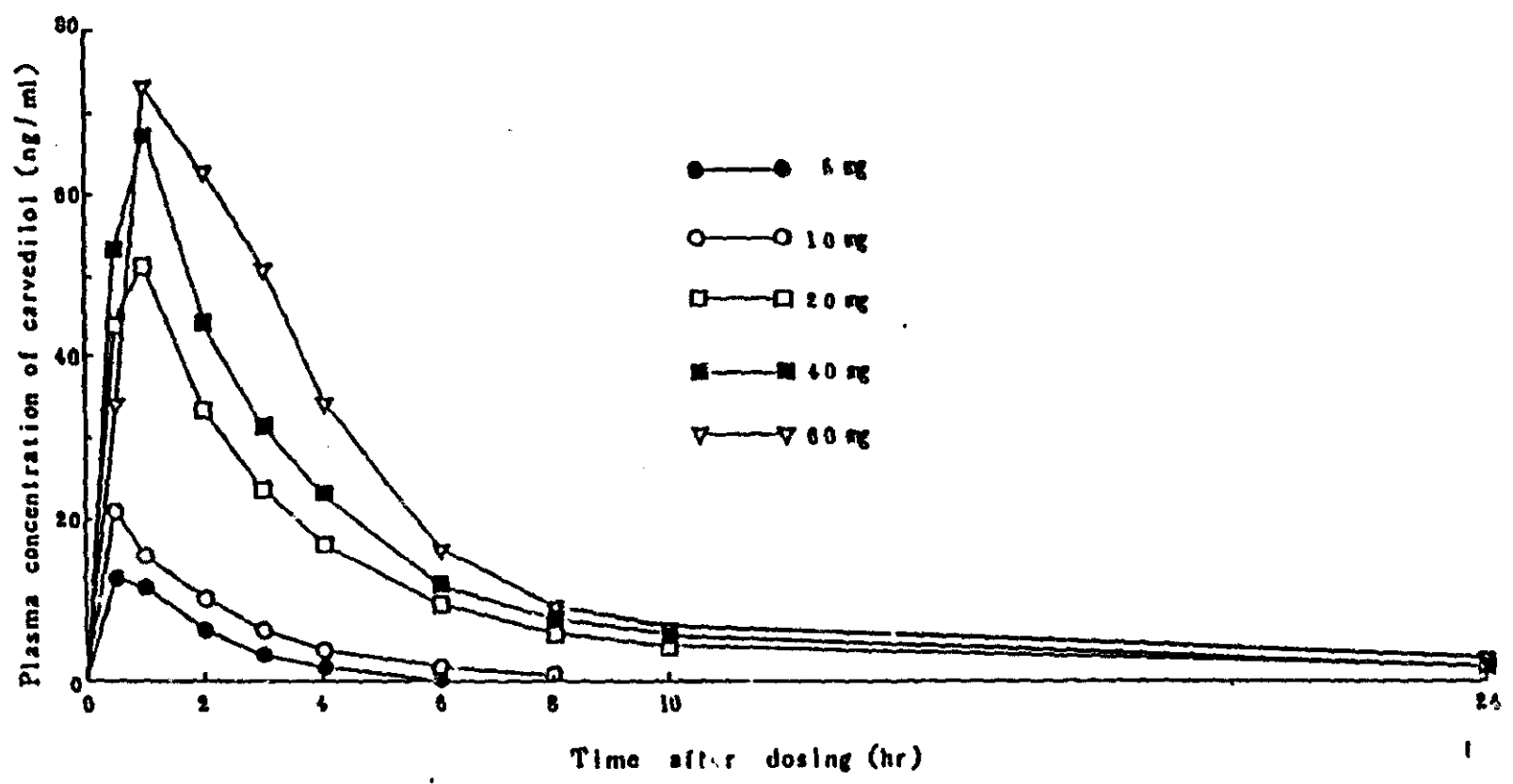


Fig. 2 Mean plasma concentrations of unchanged carvedilol following a single oral administration of carvedilol at various doses to healthy male subjects (n=5).

F31
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000026

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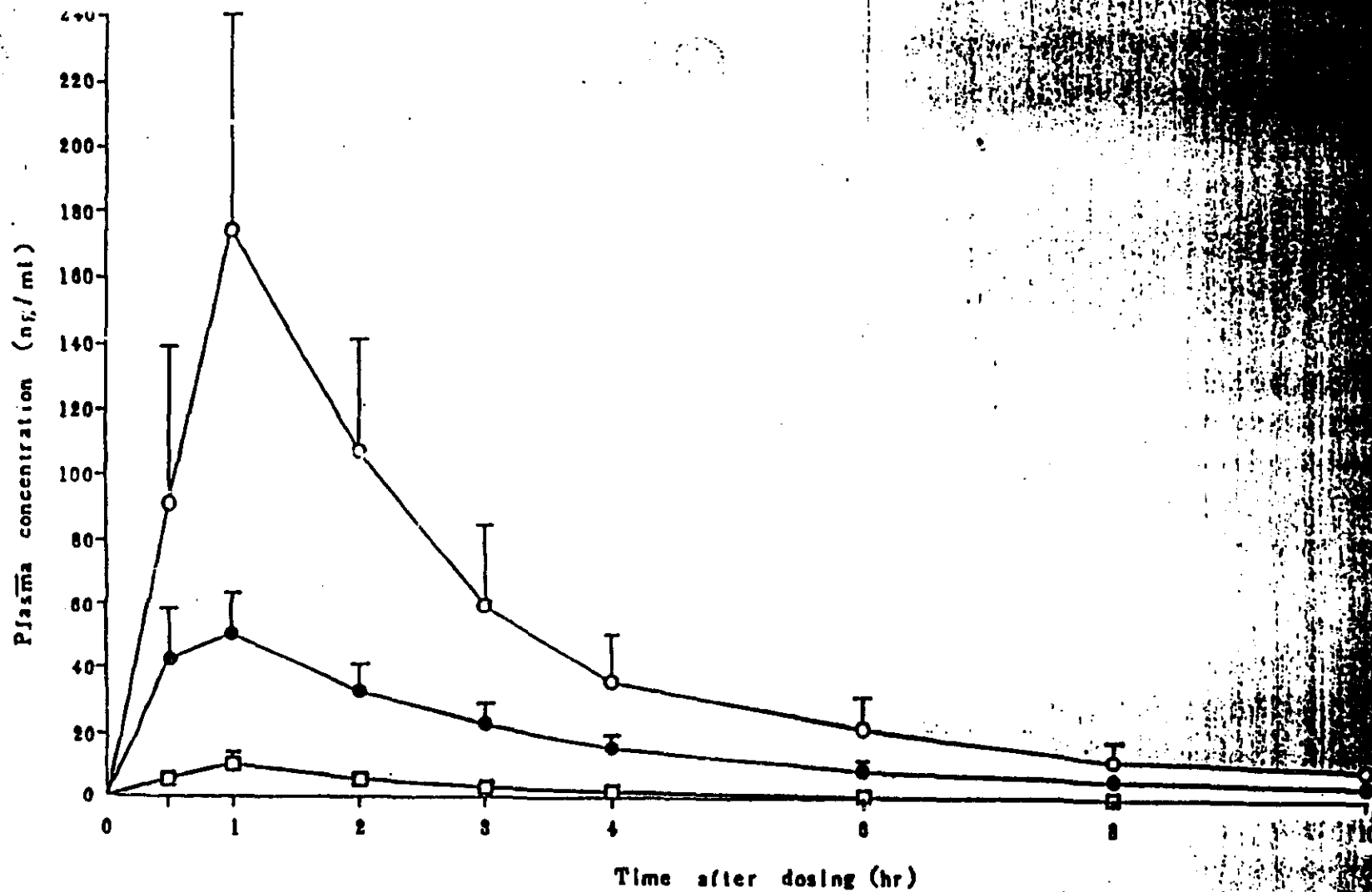


Fig. 3 Mean plasma levels of carvedilol glucuronide (O), desmethyl carvedilol (□) and carvedilol (●) in healthy subjects following a single oral dose of 20mg carvedilol (n=5). Plots are mean values $\pm$ S.E. from five subjects.

F-31
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000027

100-27664-311
 100-27664-311

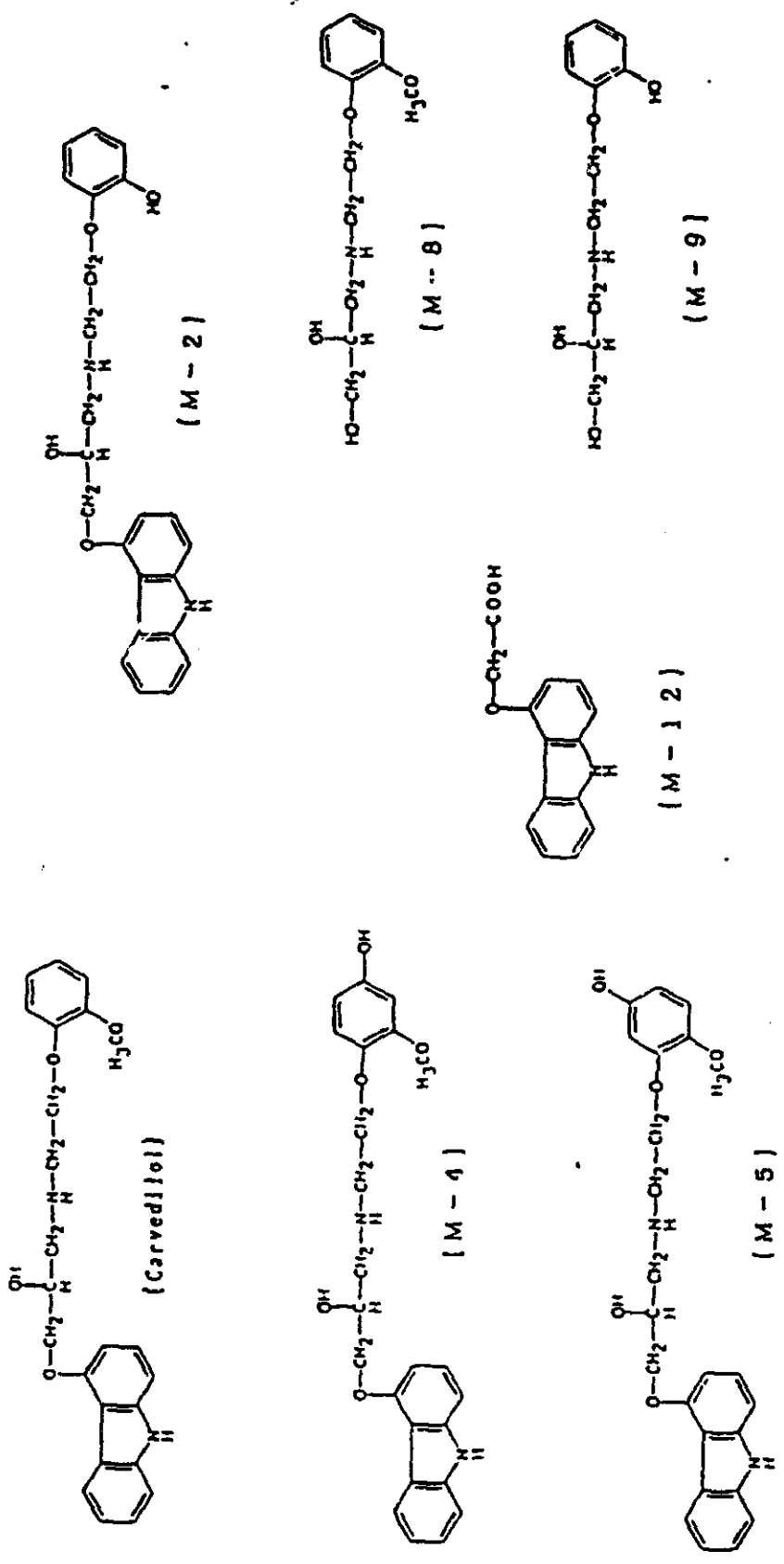


Figure 1. Chemical structures of DU-2460(carvedilol) and its metabolites.

B10

F 34
vol 1. 81
000053

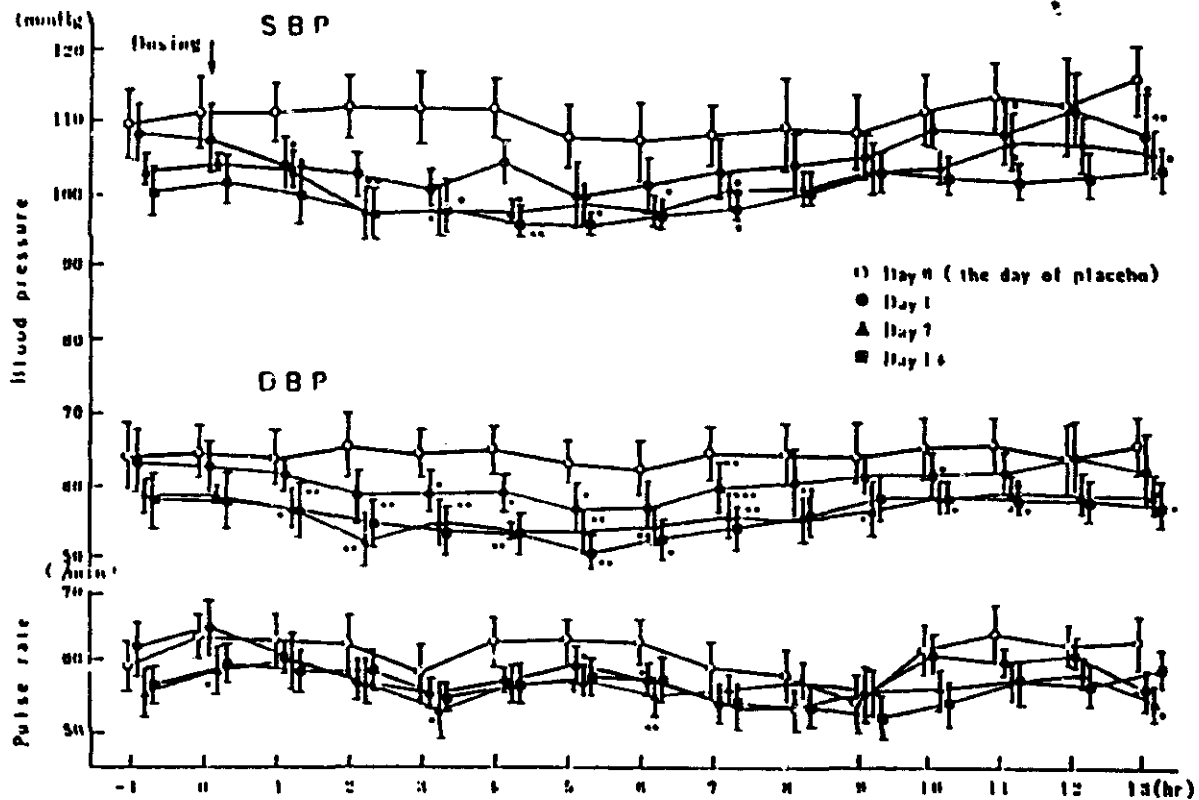


Fig. 7 Circadian variation of blood pressure and pulse rate at rest in sitting position in 14 days multiple dosing, 20mg once daily regimen

SBP : Systolic blood pressure, DBP : Diastolic blood pressure

* : $P < 0.05$, ** : $P < 0.01$, *** $P < 0.001$

(Compared with Day 0 (the day of placebo dosing))

G2
VOL 1.143
6900069

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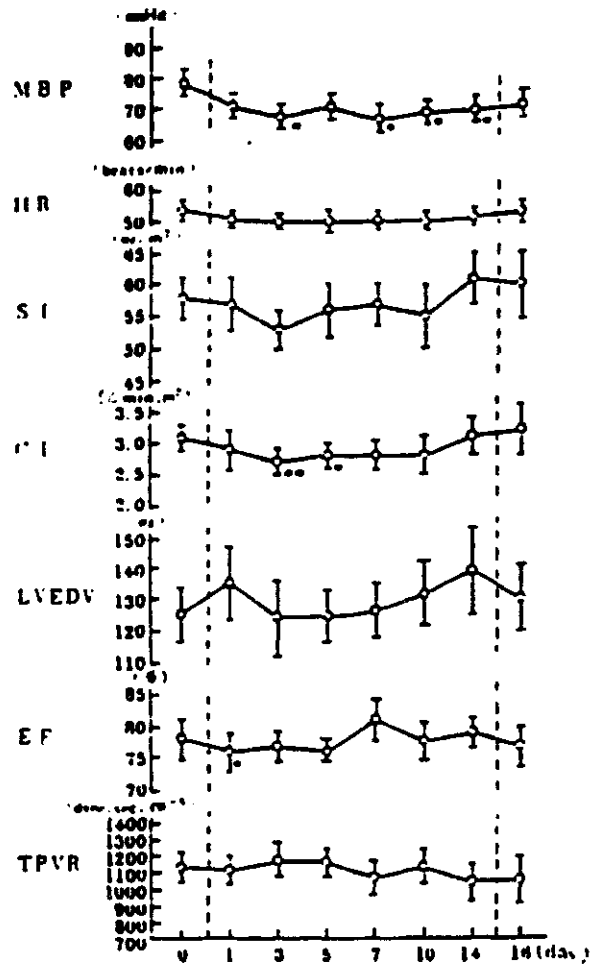


Fig. 8 Changes in hemodynamic parameters at rest in supine position in 14 days multiple dosing of carvedilol, 20mg once daily regimen (measurement 2 hrs after daily dosing)

MBP: Mean blood pressure, HR: Heart rate, SI: Stroke index, CI: Cardiac index
 LVEDV: Left ventricular end diastolic volume, EF: Ejection fraction,
 TPVR: Total peripheral vascular resistance
 (Mean ± S.E.)

*: P < 0.05, **: P < 0.01, ***: P < 0.001 (compared to before dosing)

G2
 VOL 1.143
 000070

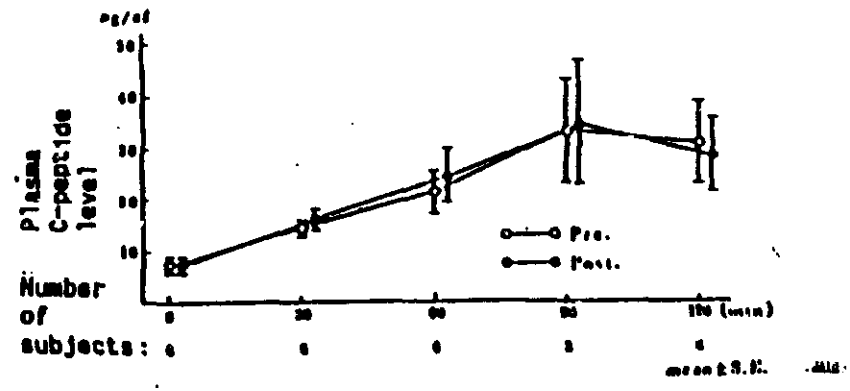
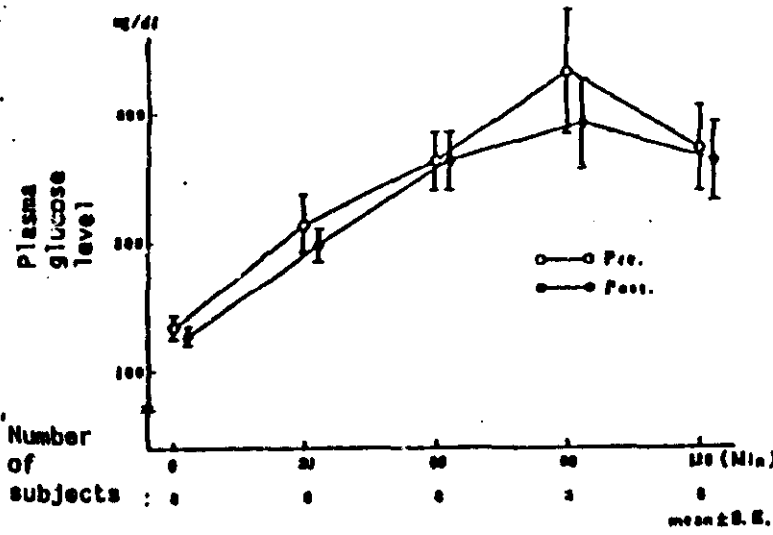
Table 5. Changes in hemodynamic parameters

Item	Number of subjects	Observation period	End of treatment period	Test
SBP (mmHg)	9	166.9 ± 2.8	154.2 ± 6.6	n.s.
MBP (mmHg)	9	117.3 ± 2.9	106.7 ± 2.8	p < 0.01
DBP (mmHg)	9	92.7 ± 4.3	83.1 ± 3.4	p < 0.001
Heart rate (beats/min)	9	65.8 ± 2.4	60.8 ± 2.3	p < 0.05
PRP (×10 ²)	9	109.9 ± 4.3	93.6 ± 4.4	p < 0.05
LVDd (mm)	9	45.6 ± 1.8	45.1 ± 2.1	n.s.
LVDs (mm)	9	24.8 ± 1.7	26.4 ± 1.9	n.s.
ET (msec)	9	318.6 ± 13.7	332.3 ± 13.7	n.s.
LVEDV (ml)	9	98.2 ± 11.2	96.8 ± 13.2	n.s.
LVESV (ml)	9	16.9 ± 3.4	20.7 ± 3.9	n.s.
SV (ml)	9	81.2 ± 8.4	76.1 ± 11.1	n.s.
SI (ml/m ²)	9	54.1 ± 4.5	51.0 ± 7.2	n.s.
CO (l/min)	9	5.4 ± 0.6	4.6 ± 0.7	n.s.
CI (l/mm · m ²)	9	3.6 ± 0.3	3.1 ± 0.4	n.s.
EF (%)	9	83.7 ± 1.7	78.2 ± 4.1	n.s.
mVcr (msec ⁻¹)	9	1.5 ± 0.1	1.3 ± 0.1	n.s.
TPVR (dyne · sec · cm ⁻³)	9	1942.2 ± 216.4	2317.2 ± 347.9	n.s.

Mean ± S.E.

In the dietary/SU-therapy group

SULFONYL UREA



In the insulin-therapy group

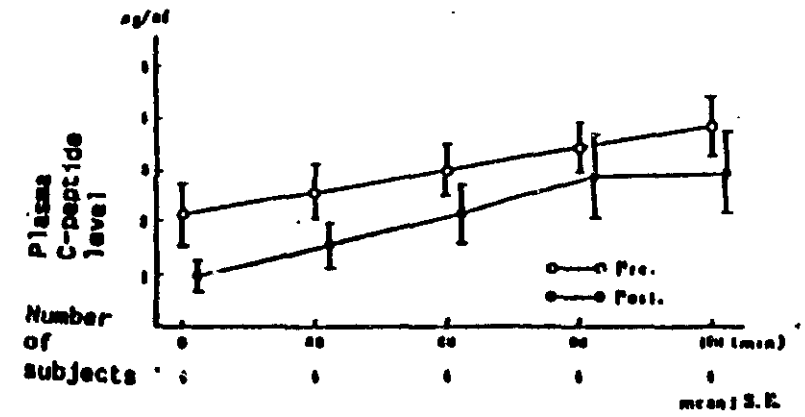
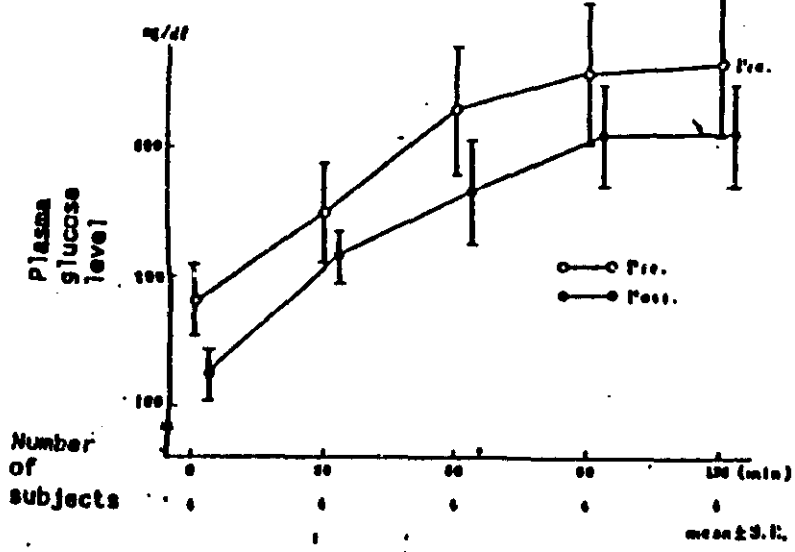


Figure 3. Effect of carvedilol on glucose tolerance

000078
VOL 1144
G15

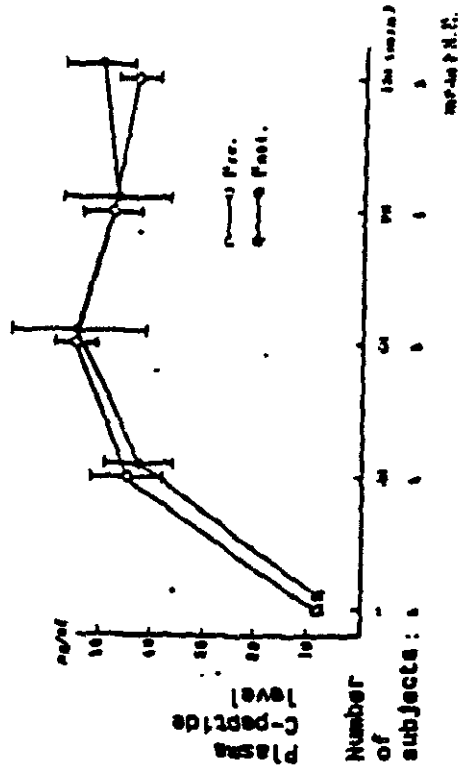
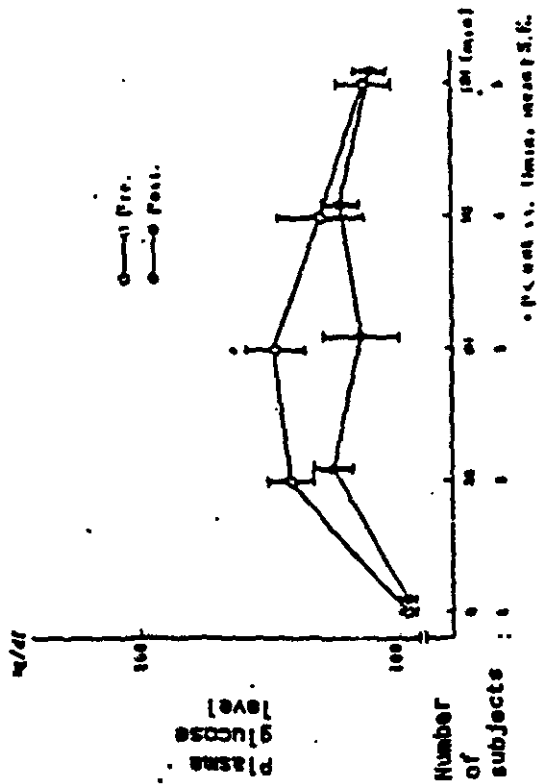
[Figure 3 continued next page]

B14

B15

[Figure 3, continued]

In the nondiabetic group:



[Translation by Josephine Howe (215) 348-7864, May 30, 1991]

G15
VOL 1.144
000079

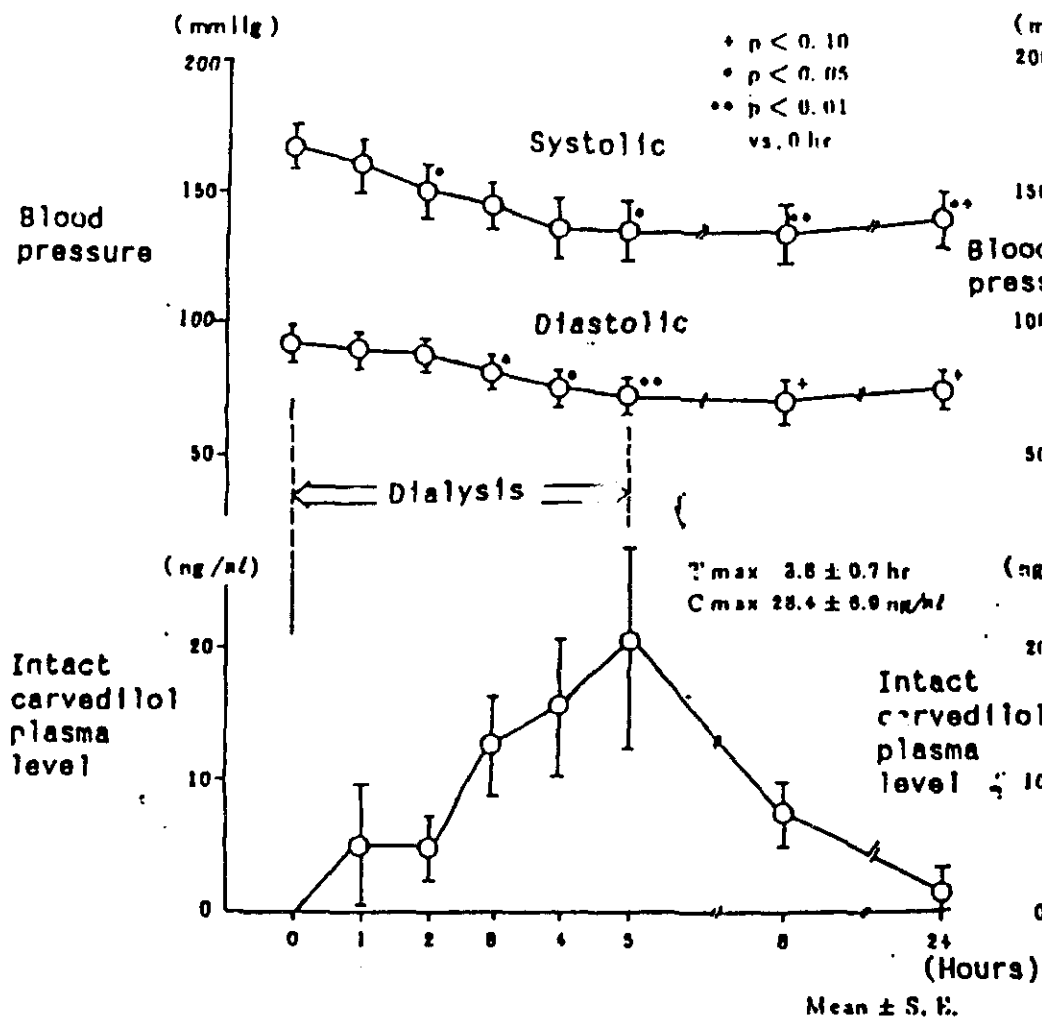


Figure 3 Changes in the blood pressure and intact carvedilol plasma level when a single dose of carvedilol was administered on a day the subjects underwent dialysis (n = 5-6)

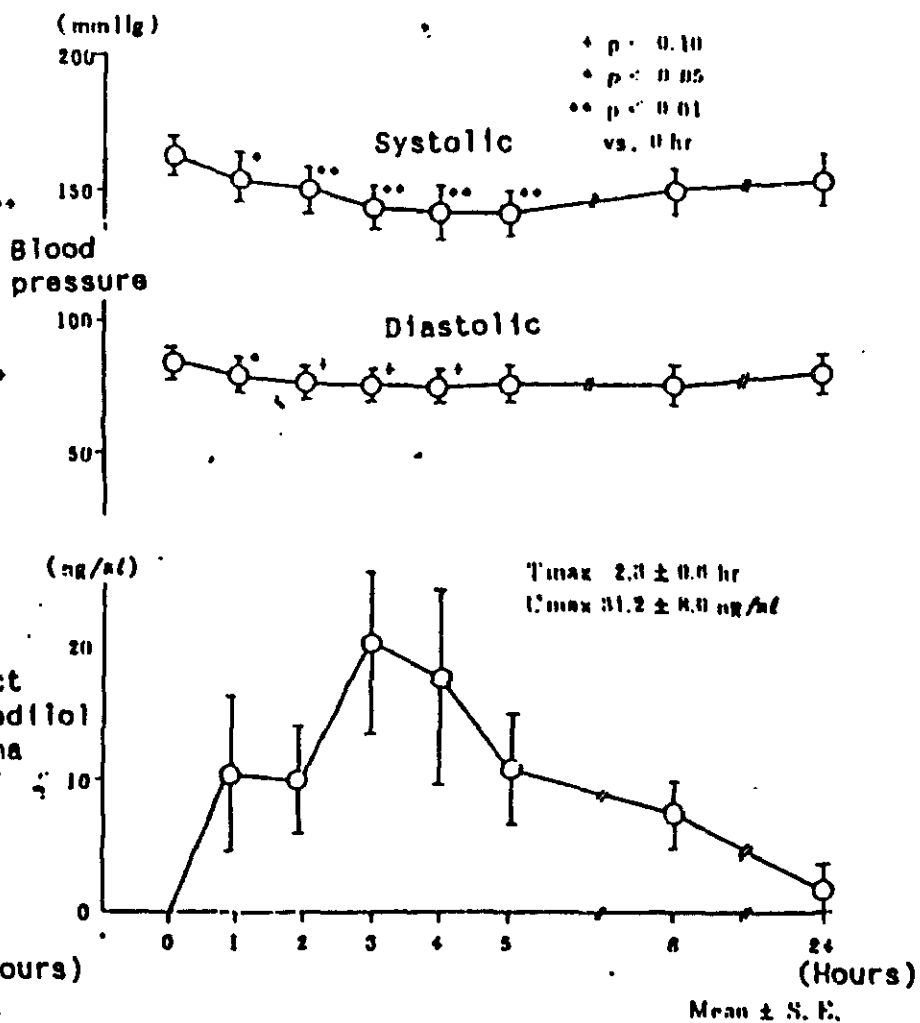


Figure 4 Changes in the blood pressure and intact carvedilol plasma level when a single dose of carvedilol was administered on a day the subjects did not undergo dialysis (n = 5-6)

000120
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G 20

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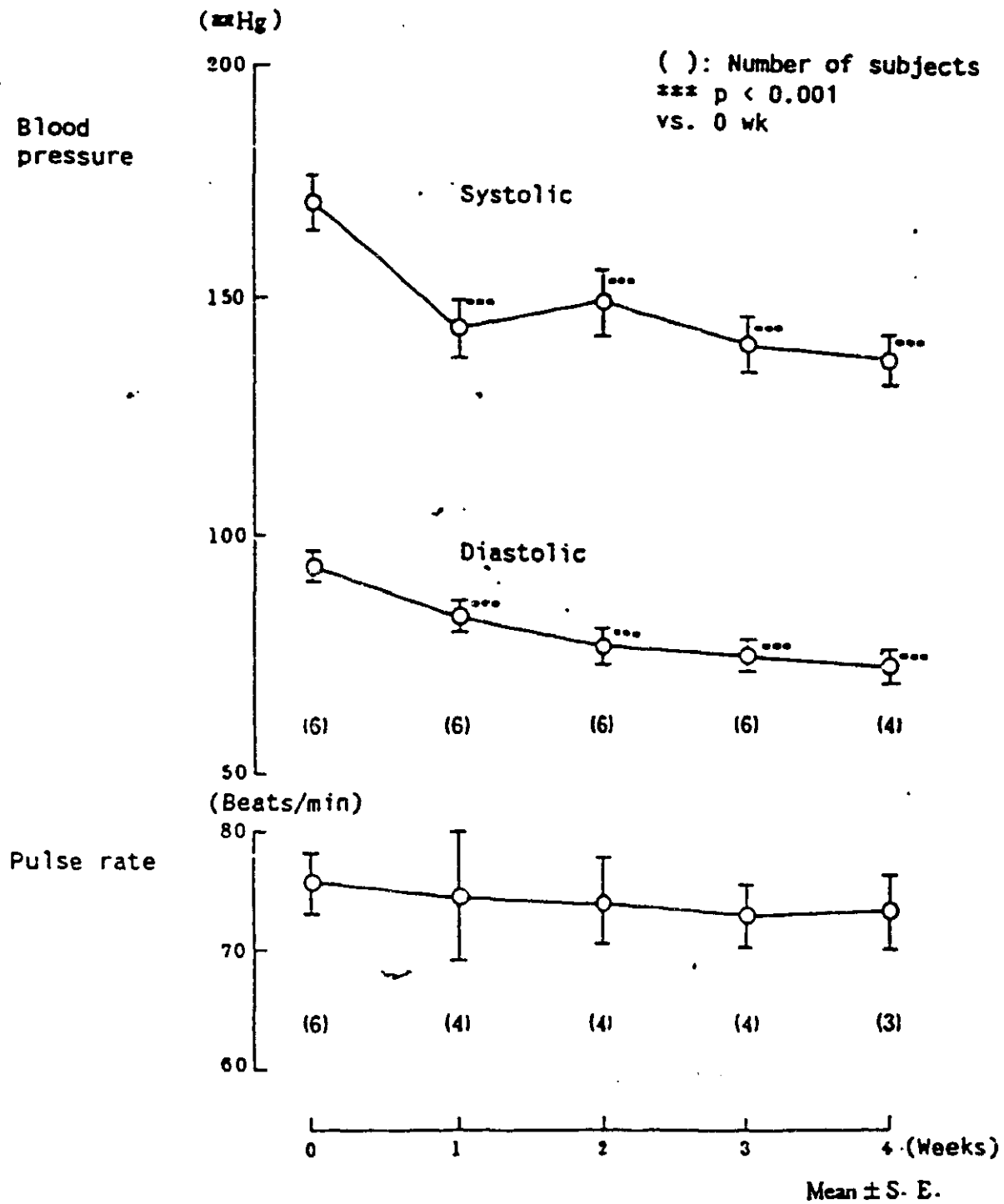


Figure 5. Changes in the blood pressure and pulse rate during long-term continuous administration of carvedilol

G 20
 VOL 1.81

000121

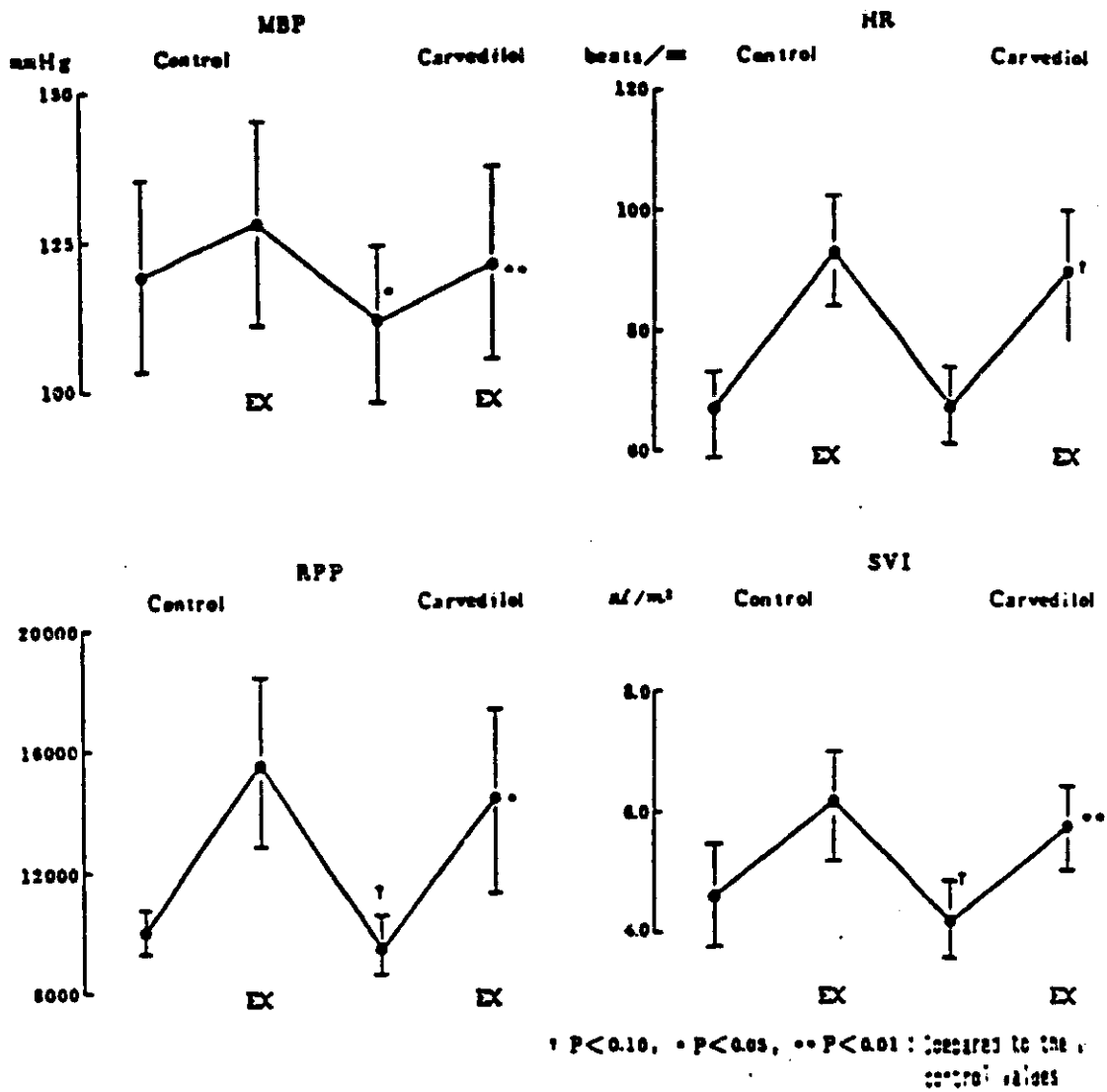


Figure 1-1. Effect of carvedilol on various hemodynamic values

ERROR BARS UNKNOWN STD DEV
VS SEM

G 28

VOL 1.145

000017

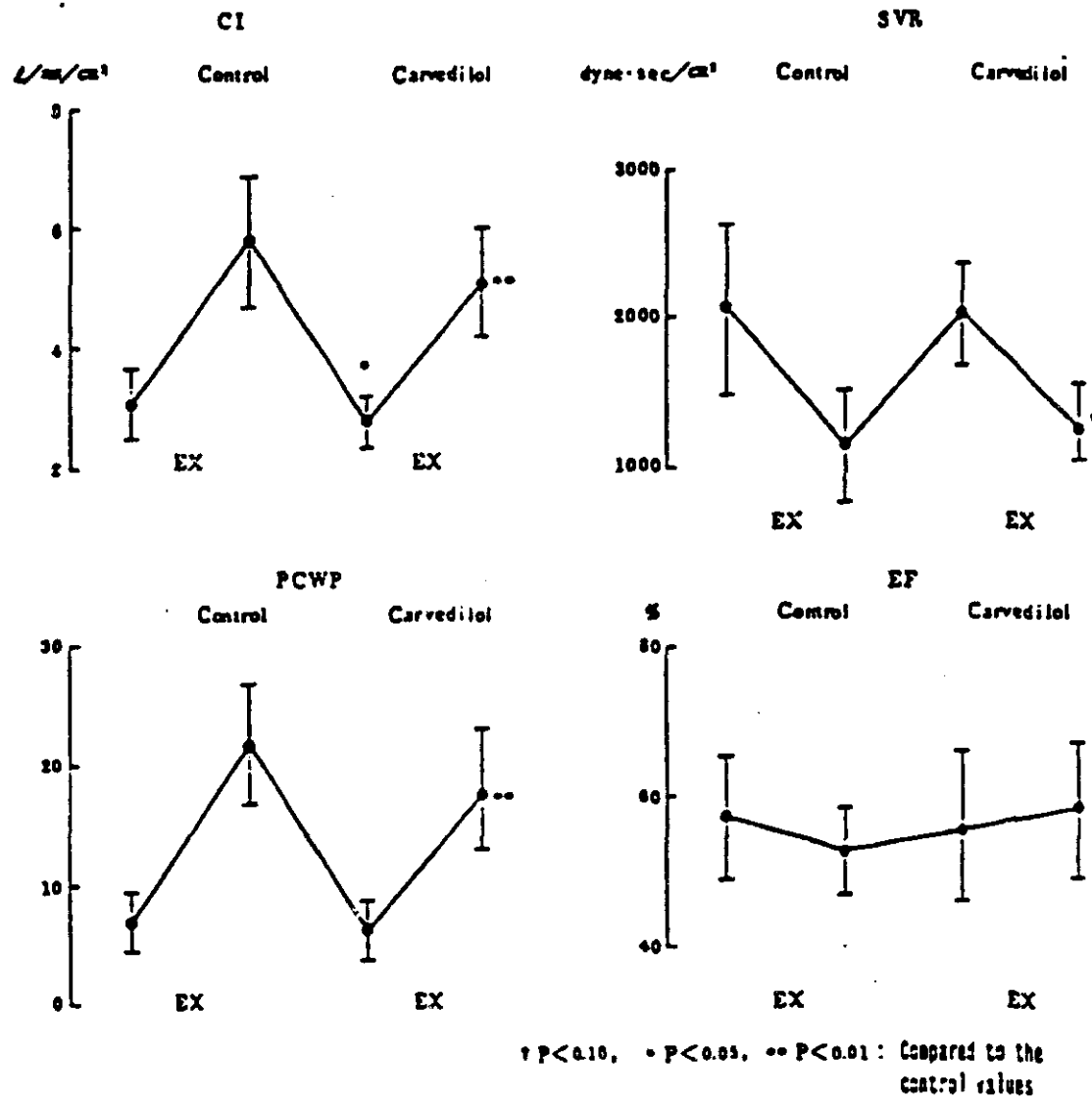


Figure 1-2. Effect of carvedilol on various hemodynamic values

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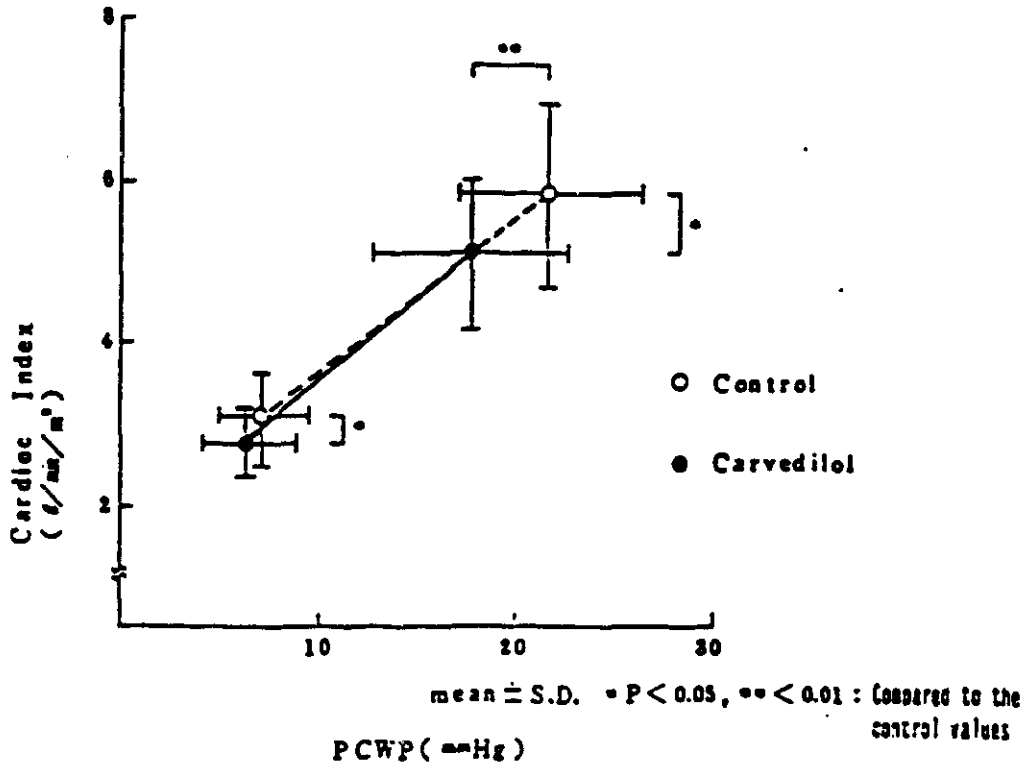


Figure 2. Effect of carvedilol on cardiac pump function during exercise loading

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Table 1. Various hemodynamic values

Item	No. of subjects	Before administration		One hour after administration		Test (Comparing values before and after administration of carvedilol)	
		While resting	During exercise loading	While resting	During exercise loading	While resting	During exercise loading
SBP (mmHg)	10	154±26.5	170±27.5 [*]	144±22.4	161±25.0 ^{**}	P<0.01	P<0.05
DBP (mmHg)	10	102±13.8	107±13.4	95.6±11.0	102±12.8 [*]	P<0.1	P<0.05
MBP (mmHg)	10	119±16.1	128±17.5 ⁺	112±13.5	121±16.1 ^{**}	P<0.05	P<0.01
HR (拍/分)	10	66.9±7.3	93.1±9.3 ^{***}	67.1±6.4	89.7±12.0 ^{***}	N. S.	P<0.1
RPP (×10 ³)	10	102±15.4	158±25.1 ^{***}	96.0±10.8	144±29.9 ^{***}	P<0.1	P<0.05
CI (L/m ² ·m)	10	3.1±0.6	5.8±1.1 ^{***}	2.8±0.4	5.1±0.9 ^{***}	P<0.05	P<0.05
SVI (ml/m ²)	10	4.6±0.9	6.2±1.0 ^{***}	4.2±0.7	5.7±0.7 ^{***}	P<0.1	P<0.01
SVR (dyne·sec·cm ⁻⁵)	10	2035±576	1154±346 ^{***}	2012±378	1246±289 ^{***}	N. S.	P<0.1
EF (%)	8	57.1±8.2	53.1±6.3 ⁺	55.8±10.1	58.0±9.0	N. S.	N. S.
SWI (g·m/m ²)	10	6.8±0.6	9.8±0.8 [*]	6.0±0.4	8.1±0.7 ^{**}	P<0.001	P<0.01
PCWP (mmHg)	10	7.2±2.4	21.8±5.0	6.5±2.4	17.6±5.0	N. S.	P<0.01
CVP (mmHg)	9	5.3±2.8	8.3±3.5 ^{***}	4.6±1.5	8.3±4.5 ^{**}	N. S.	N. S.

+ P<0.10 *P<0.05 **P<0.01 ***P<0.001: In comparison to the resting values

UNKNOWN STA DEV VS SEM

B22

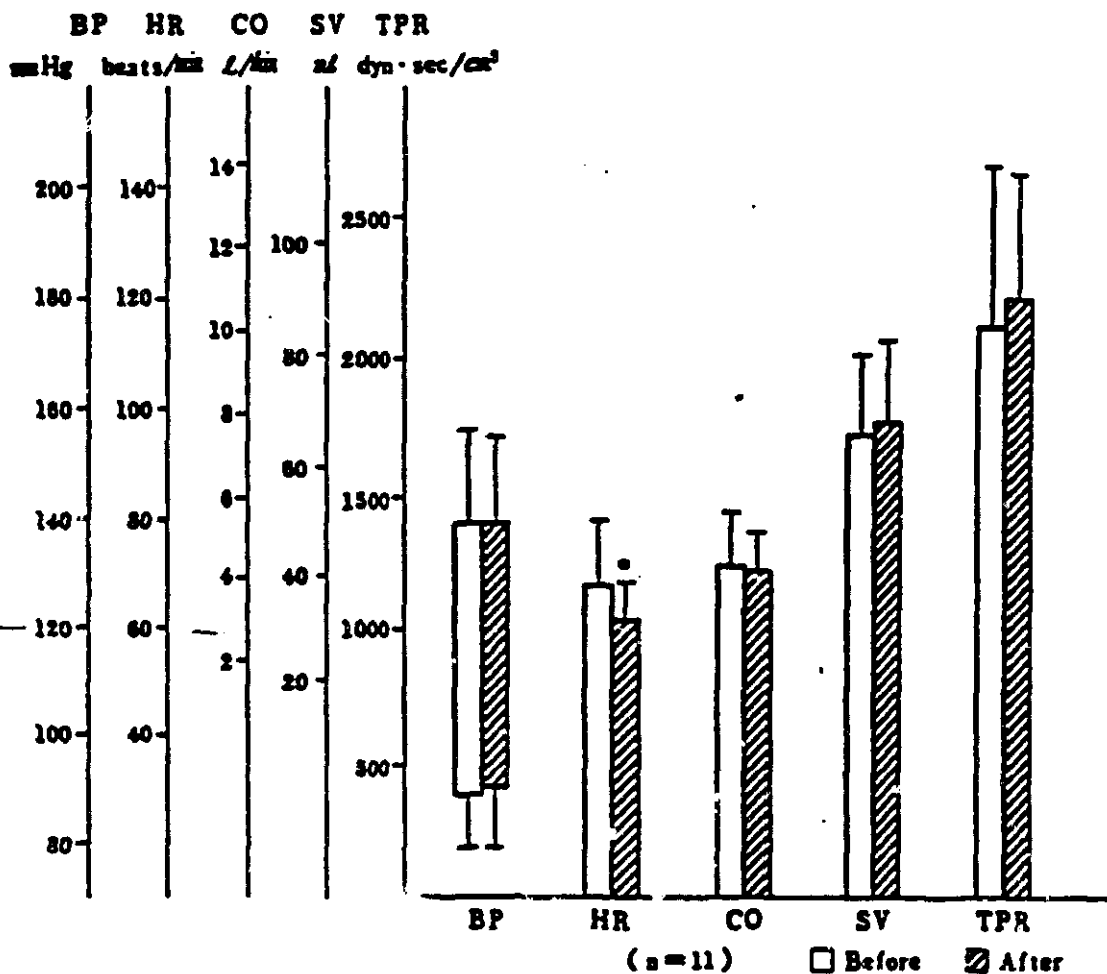


Figure 2. Resting hemodynamics before and after carvedilol treatment

BP: Blood pressure HR: Heart rate
 CO: Cardiac output SV: Stroke volume
 TPR: Total peripheral resistance

(Each bar graph shows the mean ± S.E., and the BP bar graph shows the SBP and the DBP.)

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 VOL 1.145
 000052

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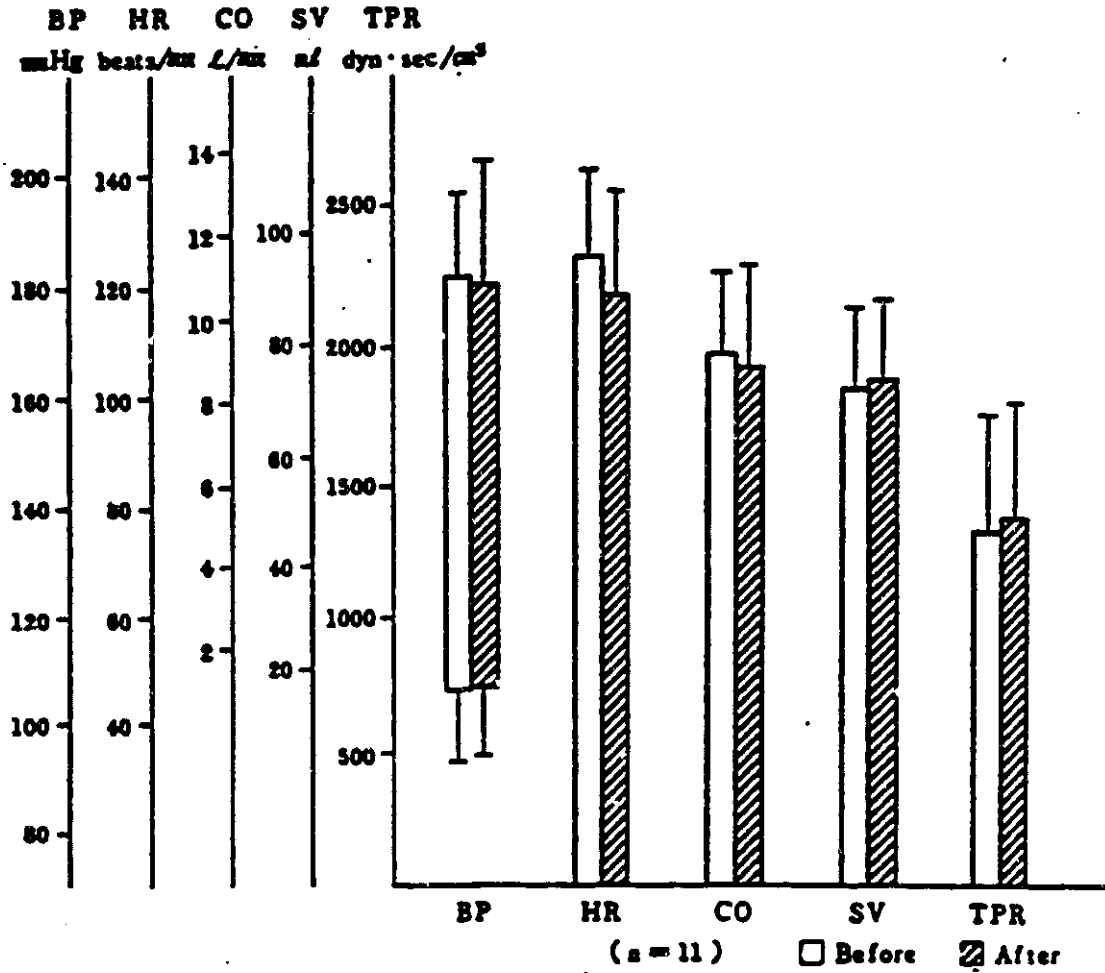


Figure 3. Hemodynamics during exercise loading before and after carvedilol treatment

BP: Blood pressure HR: Heart rate
 CO: Cardiac output SV: Stroke volume
 TPR: Total peripheral resistance

(Each bar graph shows the mean $\pm$ S.E., and the BP bar graph shows the SBP and the DBP.)

G 29
 VOL 1.145
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624

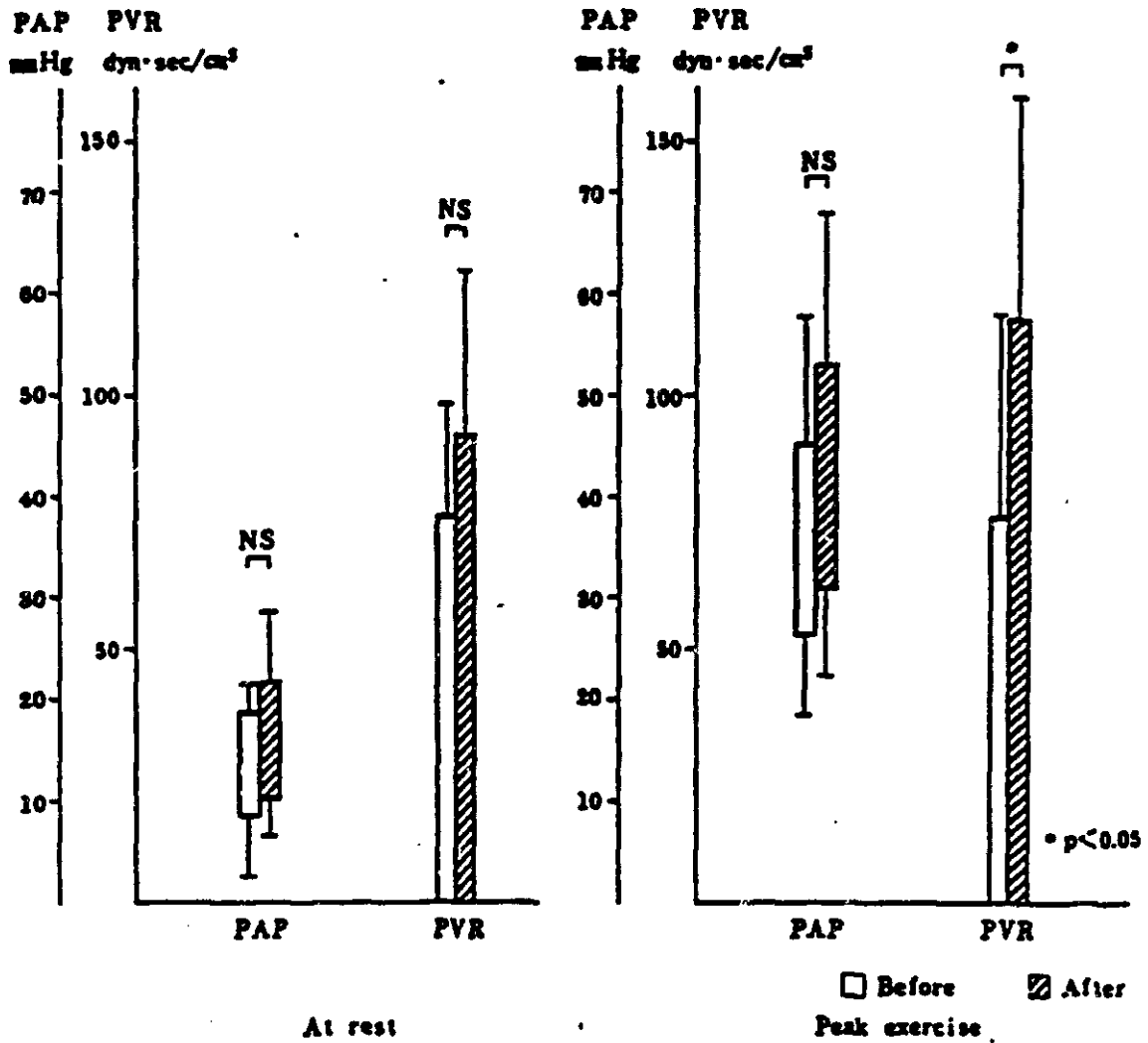


Figure 7. Changes in the pulmonary arterial pressure and pulmonary vascular resistance at rest and during exercise loading before and after carvedilol treatment

(n = 11, mean ± S.E.)

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B25

ABB. 1
HERZFREQUENZ
HERZSCHLAG

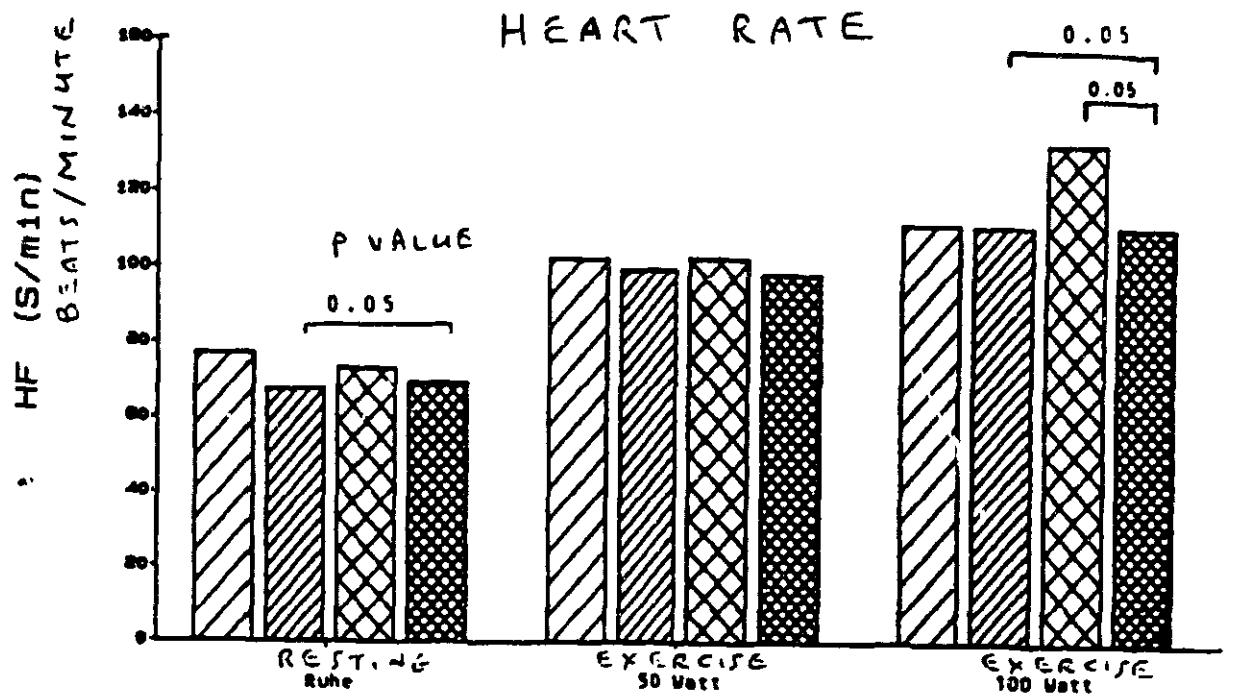
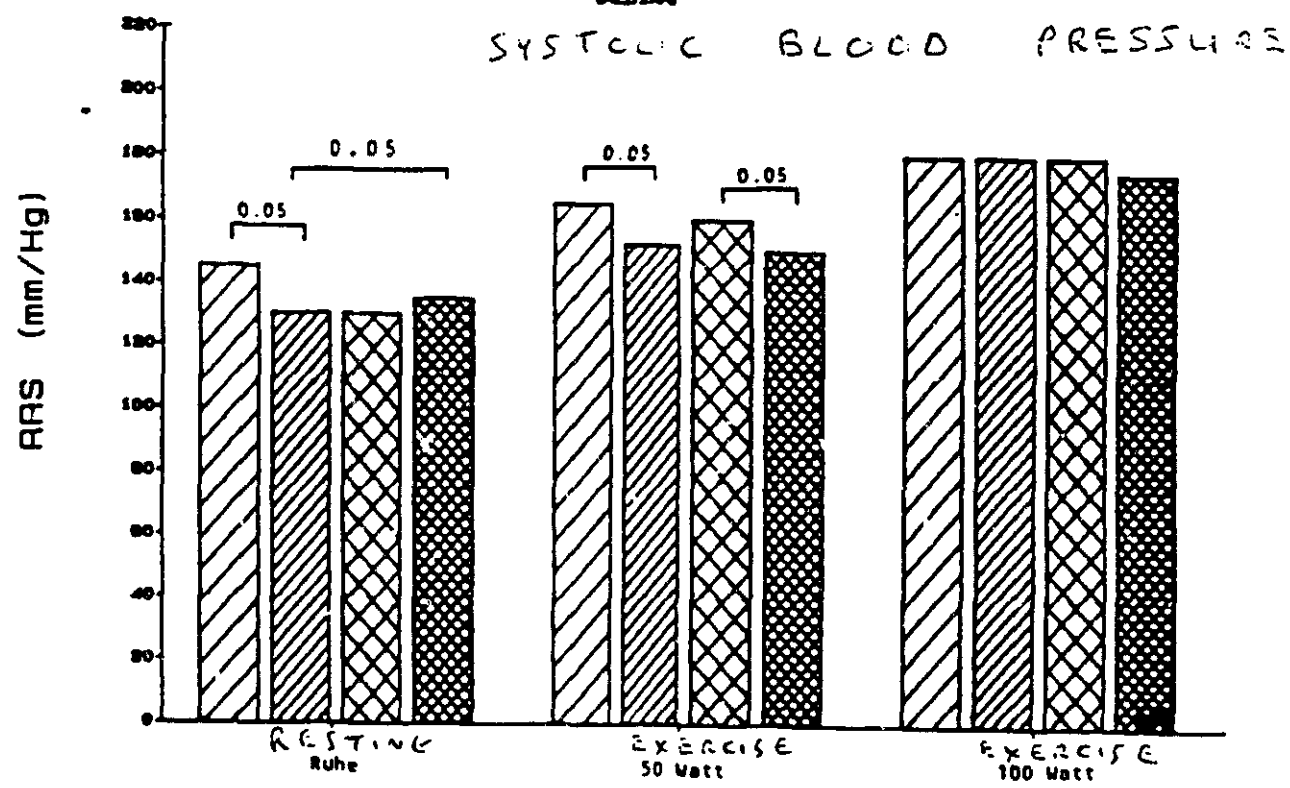


ABB. 2
SYSTOLISCHER BLUTDRUCK
BLUTDRUCK



vor Carvedilol. nach Carvedilol. vor Propranolol. nach Propranolol.

 BEFORE AFTER BEFORE AFTER
 ————— = statistisch signifikant

MF 2740
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ABB. 3
DIASTOLISCHER BLUTDRUCK

DIASTOLIC BLOOD PRESSURE

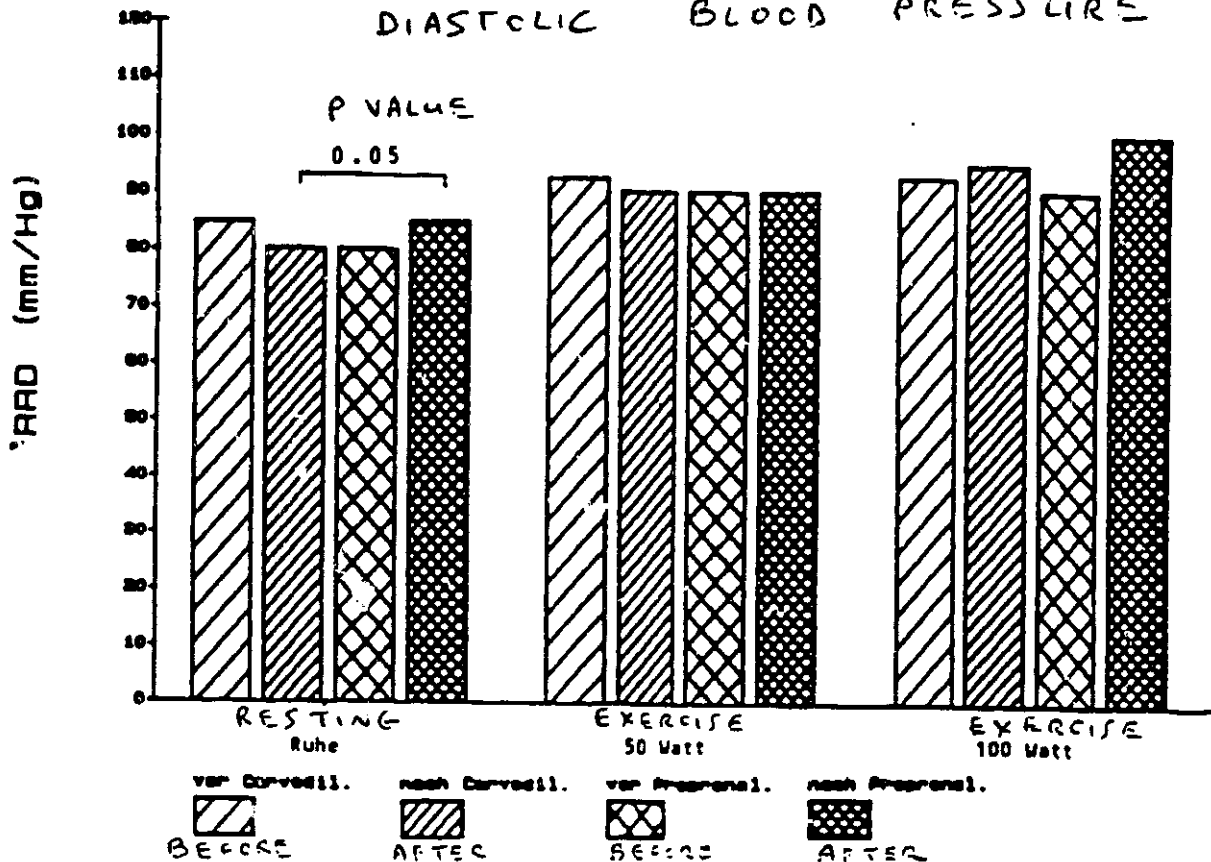
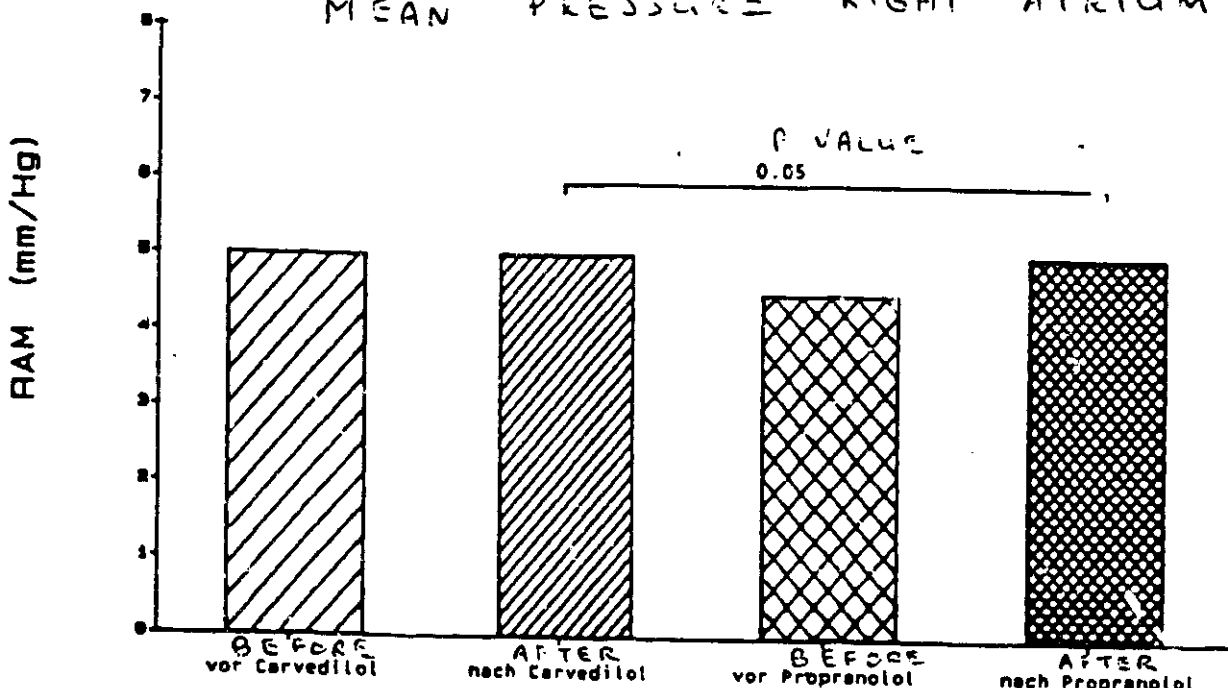


ABB. 4
MITTELDRUCK RECHTER VORHOF

MEAN PRESSURE RIGHT ATRIUM



— * statistisch signifikant

MF 2740

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627

ABB. 5
SYSTOLISCHER PULMONALARTERIENDRUCK
(MEDIAN)

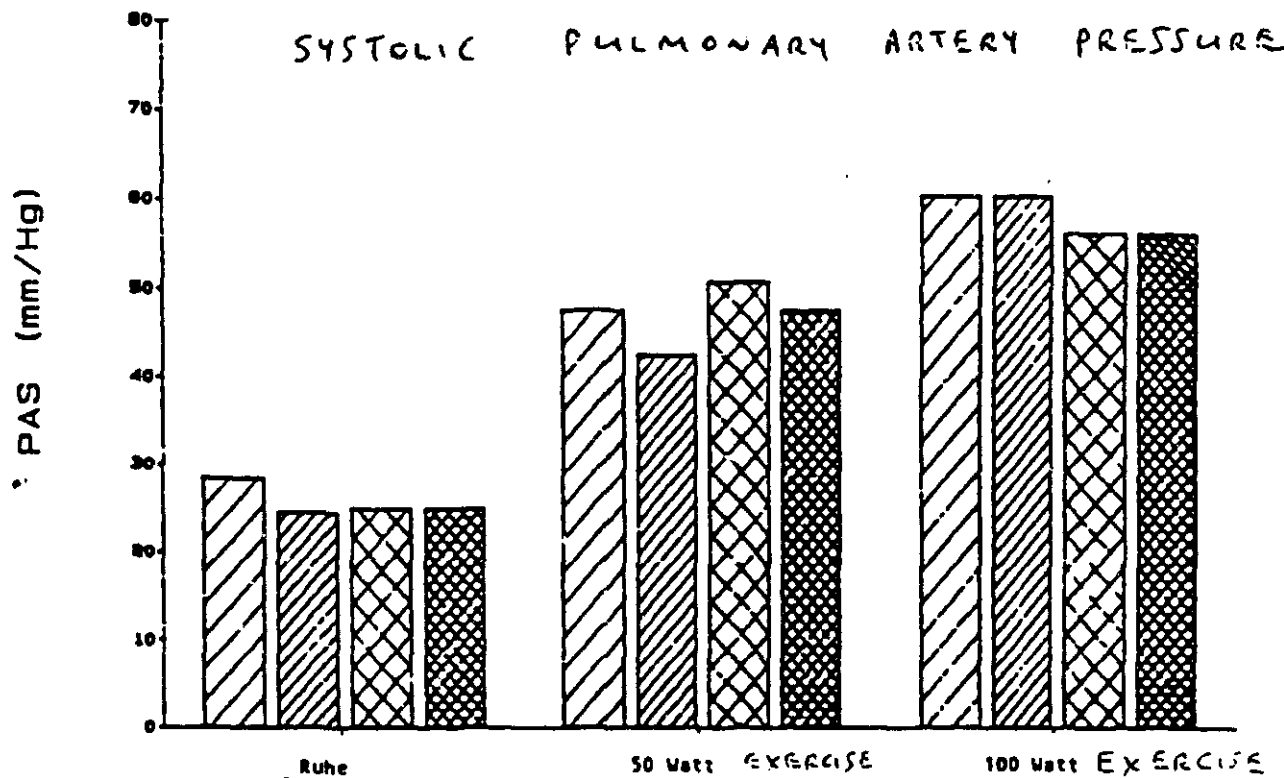
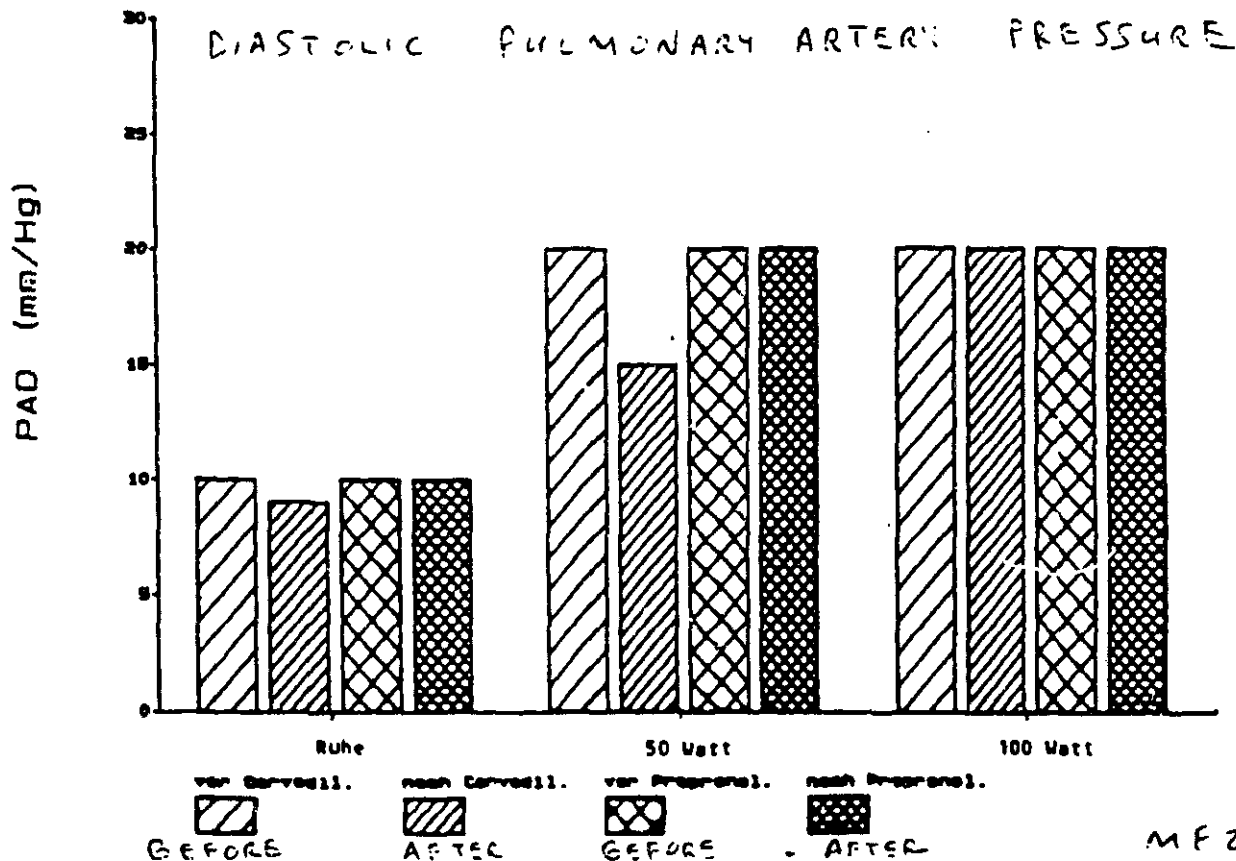


ABB. 6
DIASTOLISCHER PULMONALARTERIENDRUCK
(MEDIAN)



vor Carvedilol. nach Carvedilol. vor Propranolol. nach Propranolol.

 GEFORE AFTER GEFORE AFTER

— * statistisch signifikant

MF 27 40

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ABB. 7
PULMONALKAPILLARER MITTELDRUCK
MEDIAN

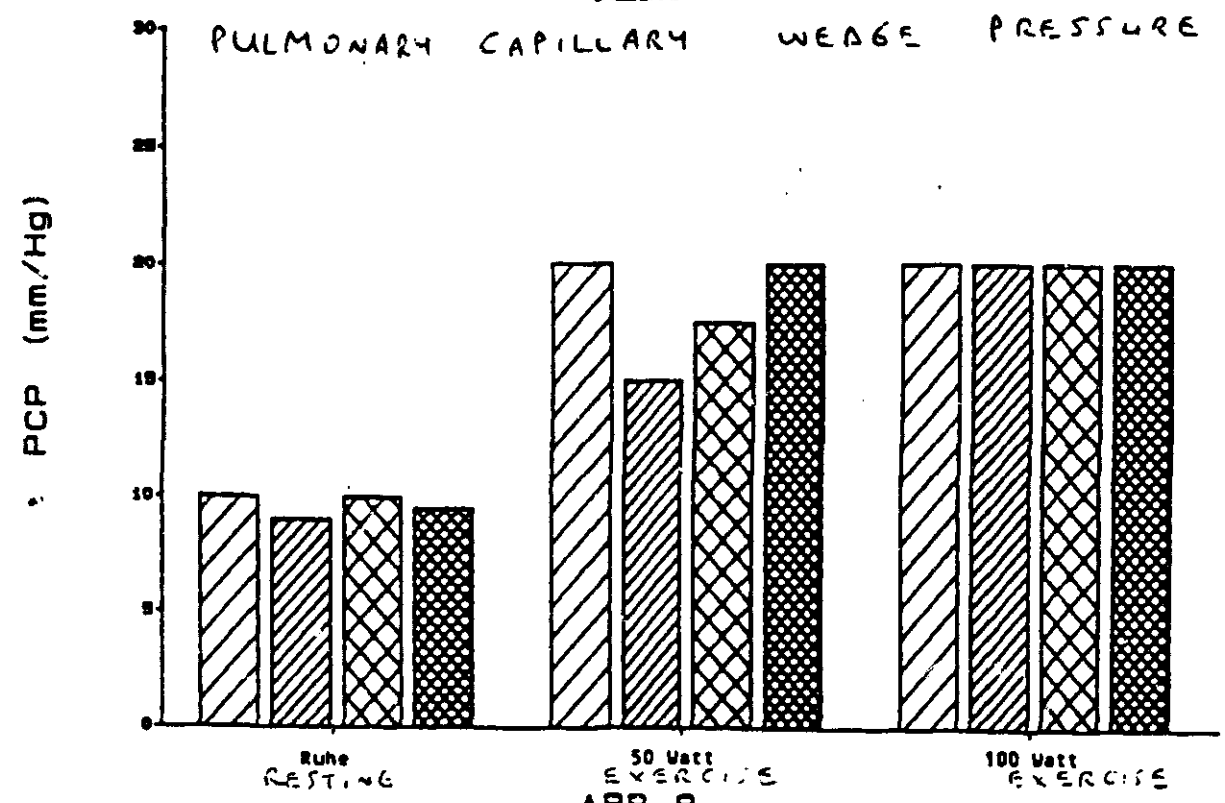
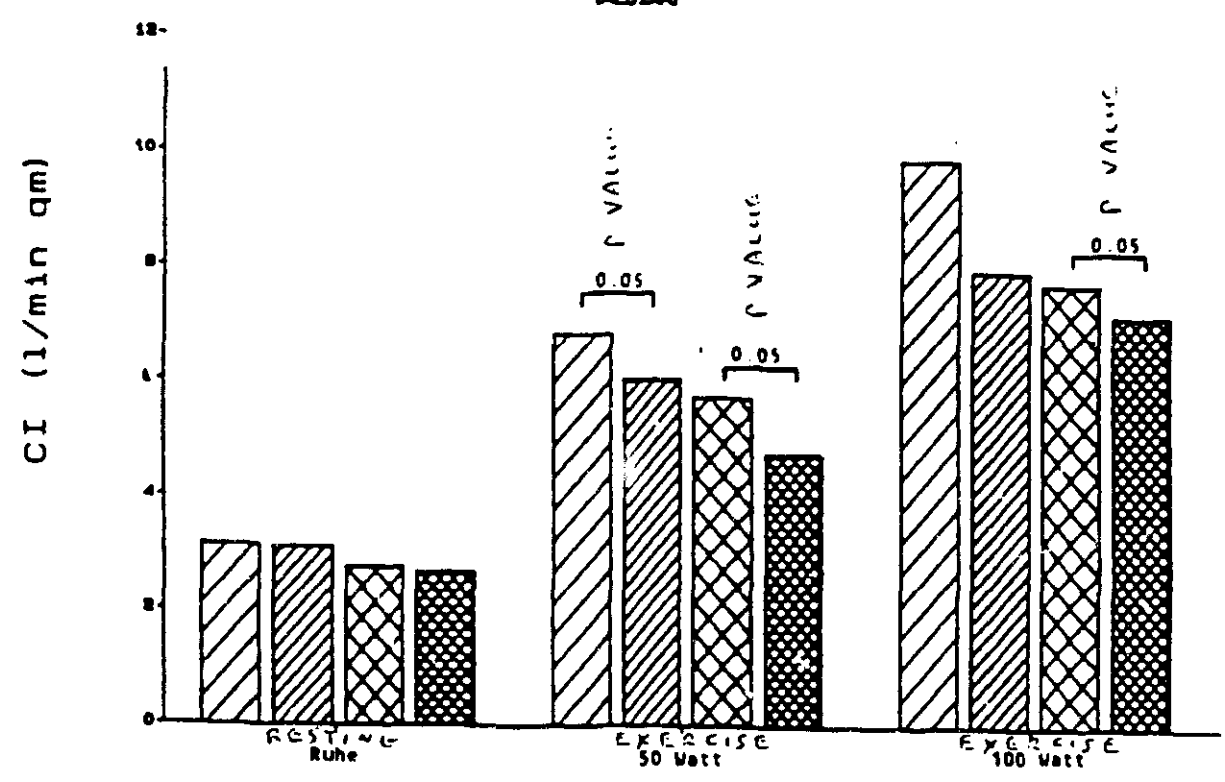


ABB. 8
CARDIAC - INDEX
MEDIAN



vor Carvedilol. nach Carvedilol. vor Propranolol. nach Propranolol.
 BEFORE AFTER BEFORE AFTER

— p < 0.05 = statistisch signifikant

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VOL 1116

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ABB. 9
SCHLAGVOLUMEN
MEDIAN

STROKE VOLUME

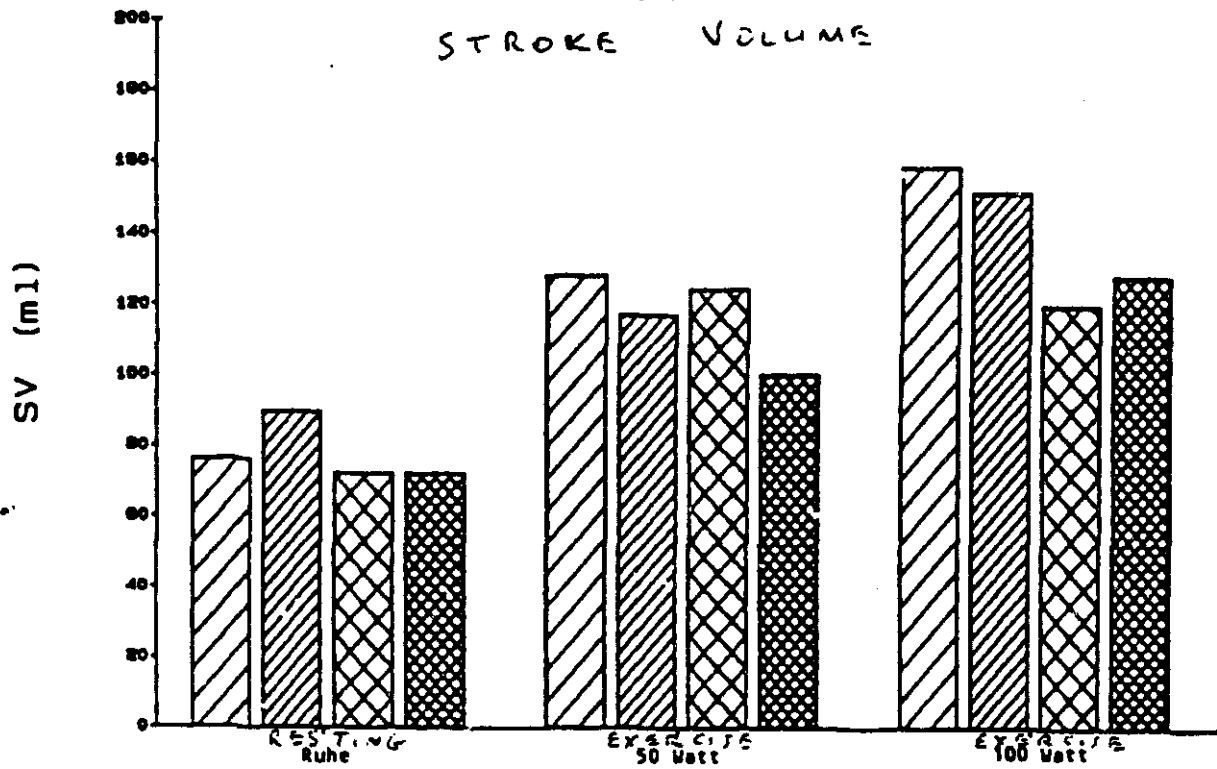
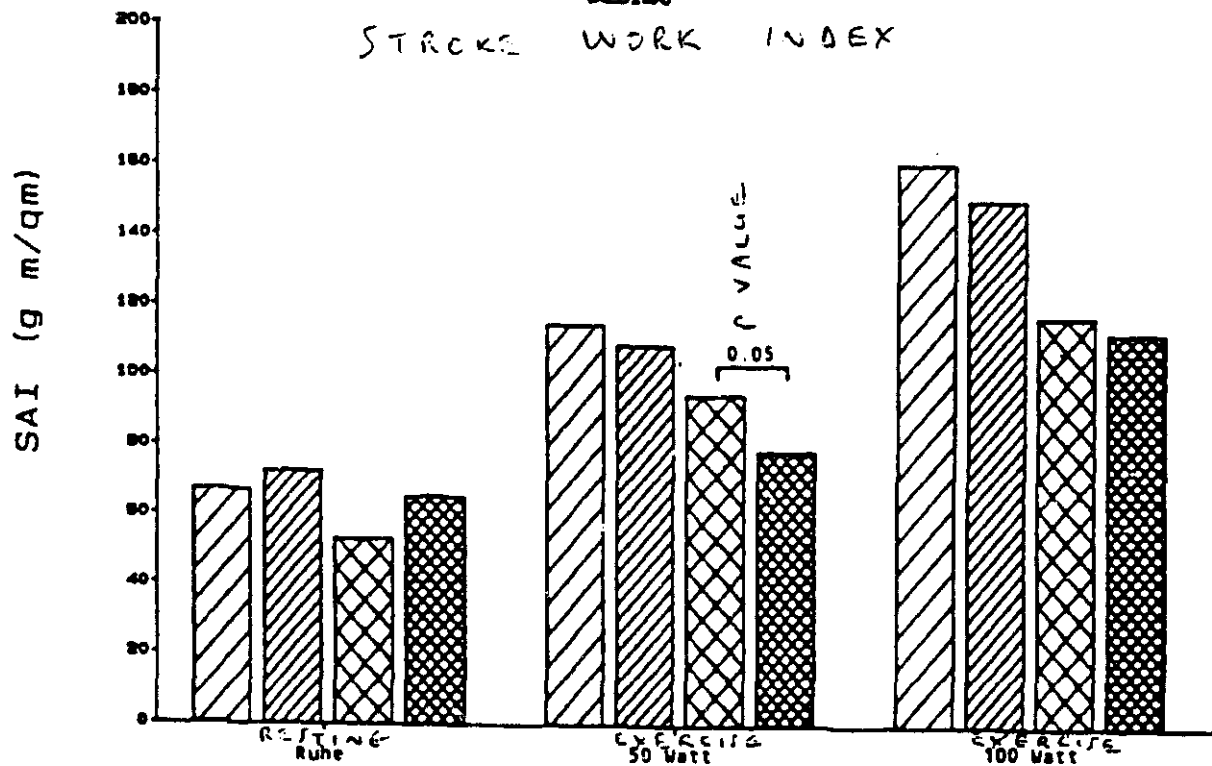


ABB. 10
SCHLAGARBEITSINDEX
MEDIAN

STROKE WORK INDEX



vor Carvedilol. nach Carvedilol. vor Propranolol. nach Propranolol.

 BEFORS AFTERS BEFORS AFTERS

—] = statistisch signifikant

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ABB. 11 SYSTEMISCHER ARTERIELLER WIDERSTAND SYSTEMIC MEDIAN ARTERIAL RESISTANCE

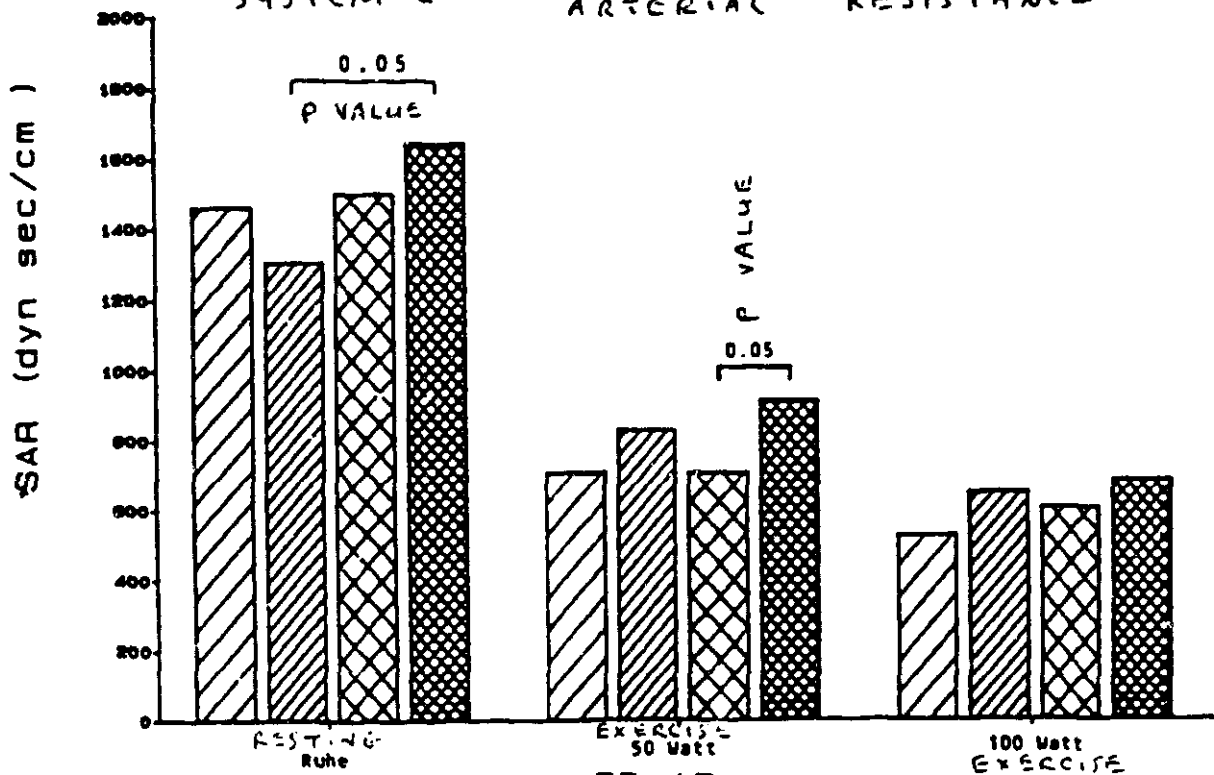
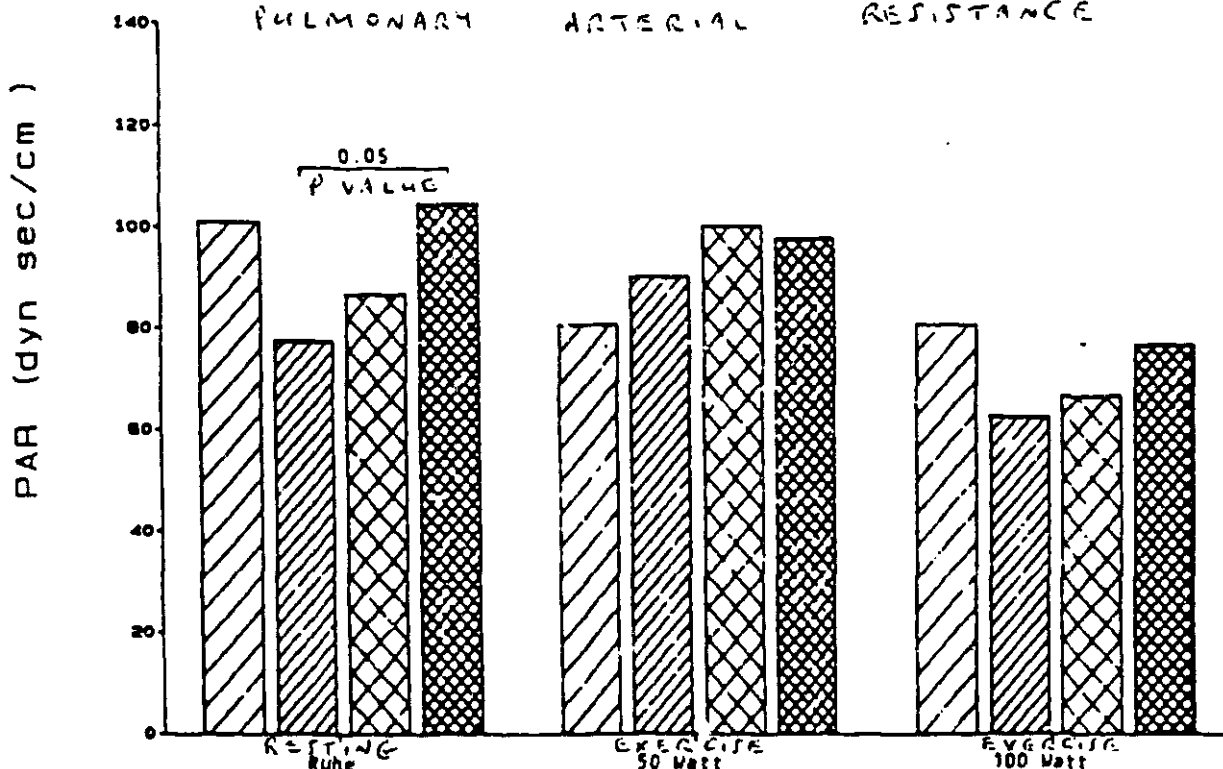


ABB. 12 PULMONALER ARTERIOLEN WIDERSTAND PULMONARY MEDIAN ARTERIAL RESISTANCE



vor Carvedilol. nach Carvedilol. vor Propranolol. nach Propranolol.

 BEFORE AFTER BEFORE AFTER

— = statistisch signifikant

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MF 2740

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B31

ABB. 13
DRUCKFREQUENZPRODUKT
MEDIAN
PRESSURE - RATE - PRODUCT

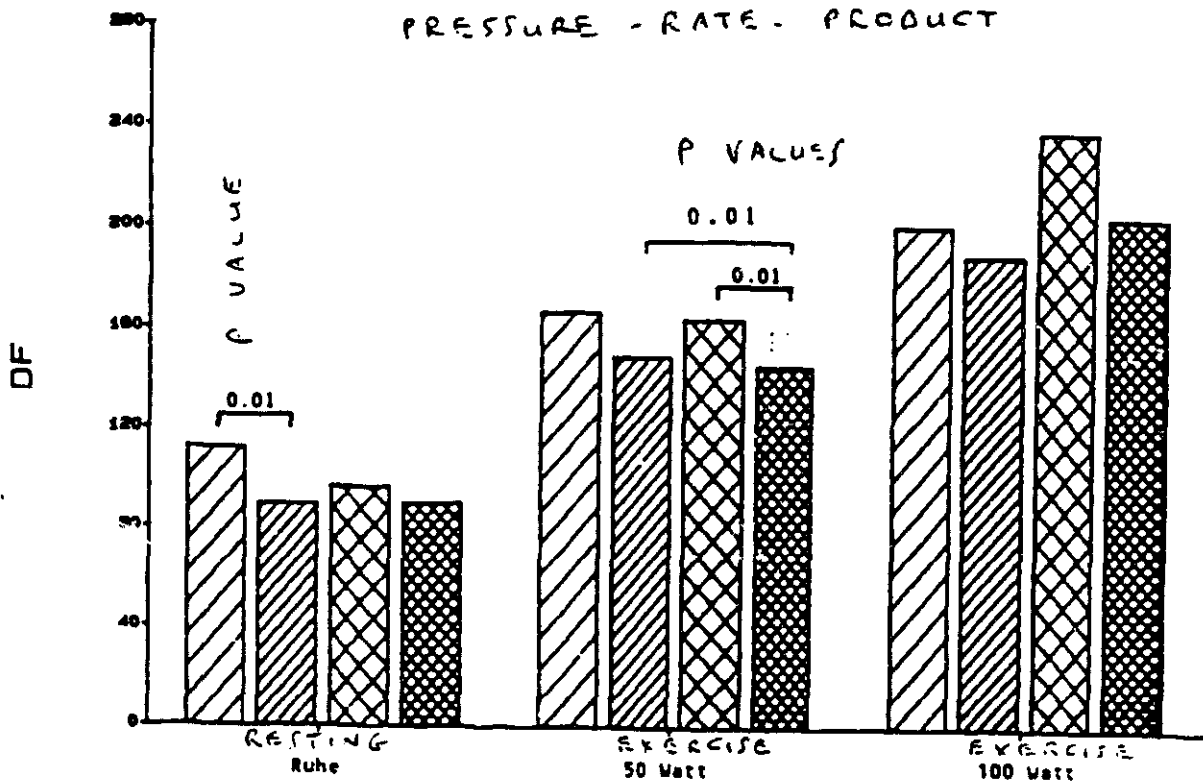
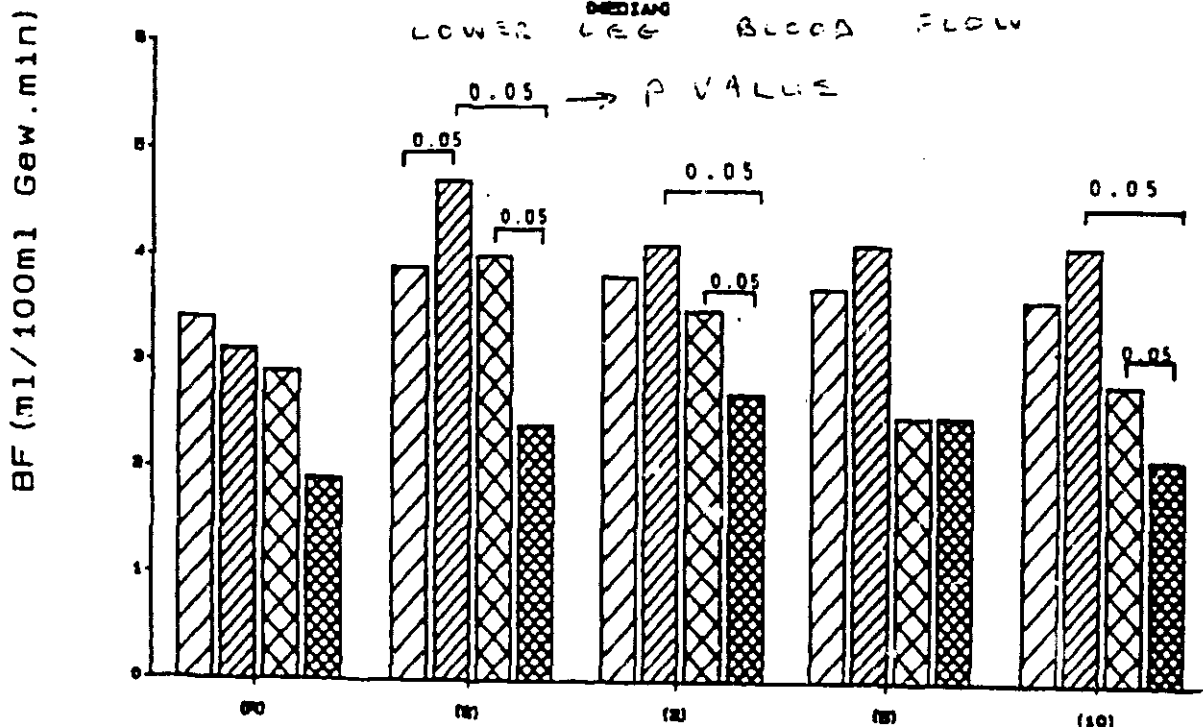


ABB. 14
UNTERSCHENKELBLUTFLUSS
MEDIAN
LOWER LEG BLOOD FLOW



(R) = in Ruhe RESTING
 (S) = sofort nach Belastung IMMEDIATELY AFTER EXERCISE
 (2), (5), (10) = 2, 5, 10 min nach Belastung 2, 5, 10 MINUTES AFTER EXERCISE

vor Carvedil. nach Carvedil. vor Propranol. nach Propranol.

BEFORE AFTER BEFORE AFTER

— | — = statistisch signifikant

MF2740

VOL 1.116

000233

920413

BOEHLINGER MANNHEIM GMBH
 KLINISCHE PHARMKOLOGIE - KLINIK
 PROGRAM: KNO
 DATE OF COMPUTATION: 29-JAN-68

Tab: 1

B32

GROUP A : PROJECT : MF 3837 : BM 14.190 - PHARMACOKINETICS IN PATIENTS WITH LIVER INSUFFICIENCY (DR. GABOR, BERGLISCH GLADBACH) MF 3837
 DOSE : 12.5 MG BM 14.190 OVER 1 H I.V. INFUSION ; LOT : 819 673 59 D
 SIGASSAY : BM 14.190 IN PLASMA ; METHOD : HPLC

N:2-1:

GROUP B : PROJECT : BM 14.190 (AMPOULES) ; SERIAL NO. OF STUDY: 0 6 4 6
 LOT : 816 000 A
 DOSE : 12.5 MG ; ADM.: IV. INFUSION OVER 1 HOUR
 SIGASSAY : BM 14.190 IN SERUM, DETERMINATION: HPLC-FLUOROM.

GROUP C : PROJECT : MF 3837 : BM 14.190 - PHARMACOKINETICS IN PATIENTS WITH LIVER INSUFFICIENCY (DR. GABOR, BERGLISCH GLADBACH) MF 3837
 DOSE : 25 MG BM 14.190 PERORAL ; LOT : 819 834 00 OF
 SIGASSAY : BM 14.190 IN PLASMA ; METHOD : HPLC

GROUP D : PROJECT : BM 14.190 : SERIAL NO. OF STUDY: 0 6 4 7
 LOT : 816 034 80
 DOSE : 25 MG = 1 CAPSULE NO.3, WITHOUT PHTJ ; ADM.: PERORAL
 SIGASSAY : BM 14.190 IN SERUM, DETERMINATION: HPLC-FLUOROM.

PARAMETER (RAW - DATA)	UNIT		"A"	"B"	"C"	"D"
AUC	per l mg	N	5.	20.	5.	19.
		MEAN	46.072	32.474	45.060	6.407
		C.V. (%)	48.00	82.48	67.60	53.03
		MEDIAN	42.816	27.388	35.374	5.934
		MINIM. MAXIM.				
Cmax	per l mg	N	5.	20.	5.	20.
		MEAN	11.242	13.093	3.952	1.270
		C.V. (%)	72.25	42.50	21.62	67.25
		MEDIAN	8.084	14.108	4.000	0.946
		MINIM. MAXIM.				
tmax	[h]	N	5.	20.	5.	20.
		MEAN	1.000	1.250	0.700	1.300
		C.V. (%)	30.62	90.15	39.12	41.18
		MEDIAN	1.000	1.000	0.500	1.500
		MINIM. MAXIM.				
t 1/2	[h]	N	5.	20.	5.	19.
		MEAN	9.319	2.501	12.383	7.882
		C.V. (%)	61.30	20.22	98.17	48.89
		MEDIAN	7.109	2.460	9.015	7.110
		MINIM. MAXIM.				
Cl or Cl / f	[ml/min]	N	5.	20.	5.	19.
		MEAN	449.00	623.99	496.06	3417.05
		C.V. (%)	54.42	27.80	53.01	95.31
		MEDIAN	389.08	608.54	471.21	1808.88
		MINIM. MAXIM.				
Vd	[l]	N	5.	20.		
		MEAN	311.3	137.6		
		C.V. (%)	41.16	35.58		
		MEDIAN	322.1	125.0		
		MINIM. MAXIM.				
Vd0	[l]	N	5.	20.		
		MEAN	226.78	80.99		
		C.V. (%)	53.98	30.40		
		MEDIAN	294.00	77.35		
		MINIM. MAXIM.				
A0	[%]	N	5.		6.	
		MEAN	0.90		0.51	
		C.V. (%)	42.43		46.51	
		MEDIAN	1.02		0.41	
		MINIM. MAXIM.				
ClR	[ml/min]	N	5.		6.	
		MEAN	3.75		2.49	
		C.V. (%)	26.62		39.07	
		MEDIAN	3.54		2.62	
		MINIM. MAXIM.				
f	[%]	N			5.	19.
		MEAN			99.65	22.42
		C.V. (%)			41.50	53.17
		MEDIAN			82.58	18.64
		MINIM. MAXIM.				

p < 0.001

MF 3837

VOL 1.61

000280

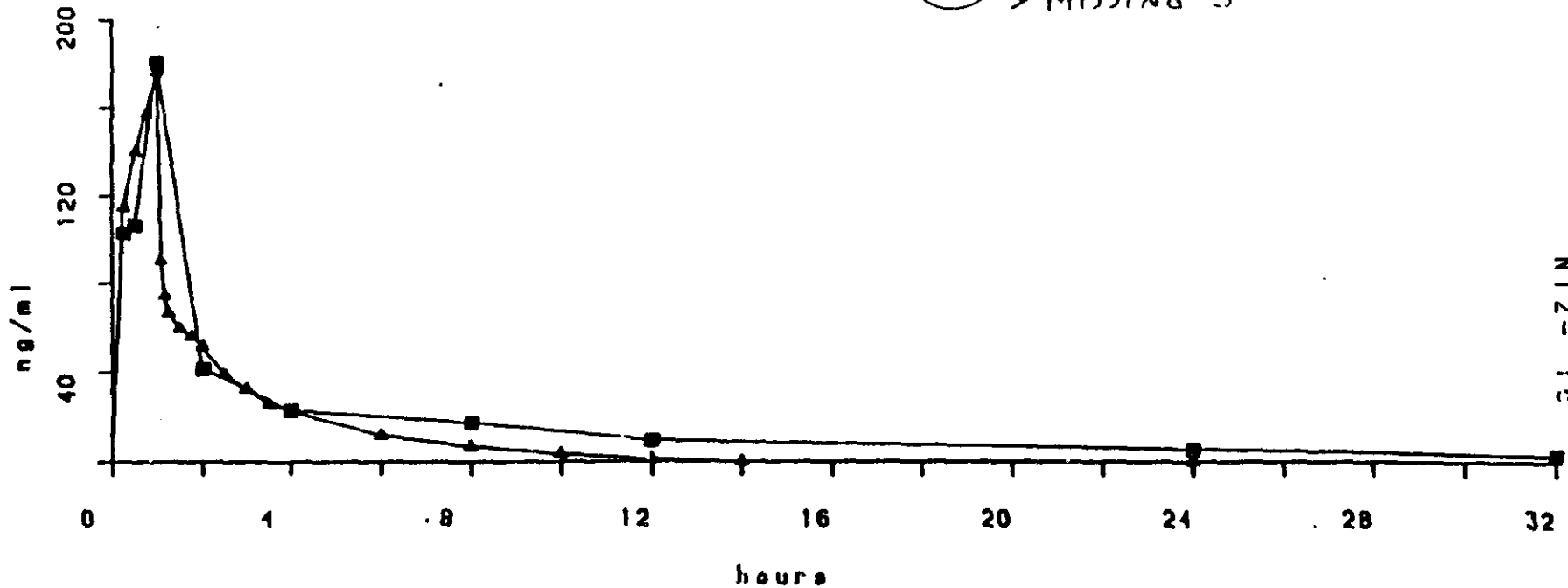
Fig 1

PROJECT : BM 14.190
DOSE : 12.5 MG ; ADM. : IV. INFUSION OVER 1 HOUR
BIOASSAY : BM 14.190 IN SERUM. DETERMINATION : HPLC-FLUOROM.
MEDIAN - VALUES
DATE : 09-FEB-88

▲ - SERIAL NO. OF STUDY : 0 6 4 6 N = 20
LOT : 816 000 A

■ - MF 3837 - PHARMACOKINETICS IN PATIENTS WITH LIVER INSUFF.
LOT : 819 873 59 D N = 3 → MISSING 3

MF 3837



N12-16

MF. 3837
VOL 1.61
000281

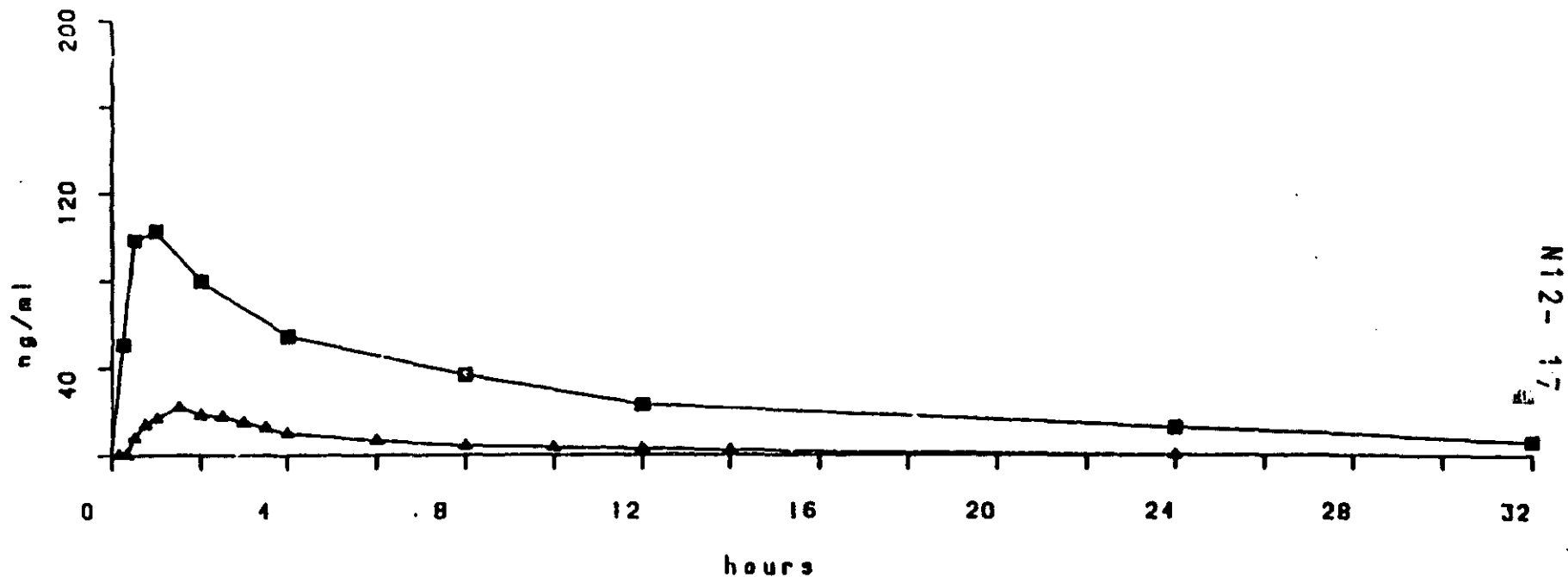
333

Fig 2

PROJECT : BM 14.190
DOSE : 25 MG PERORAL
BIOASSAY : BM 14.190 IN SERUM. DETERMINATION : HPLC-FLUOROM.
MEDIAN - VALUES
DATE : 09-FEB-88

▲ - SERIAL NO. OF STUDY : 0 6 4 7 N = 20
LOT : 816 034 8B

■ - MF 3837 - PHARMACOKINETICS IN PATIENTS WITH LIVER INSUFF. MF 3837
LOT : 819 854 40 GF N = 6



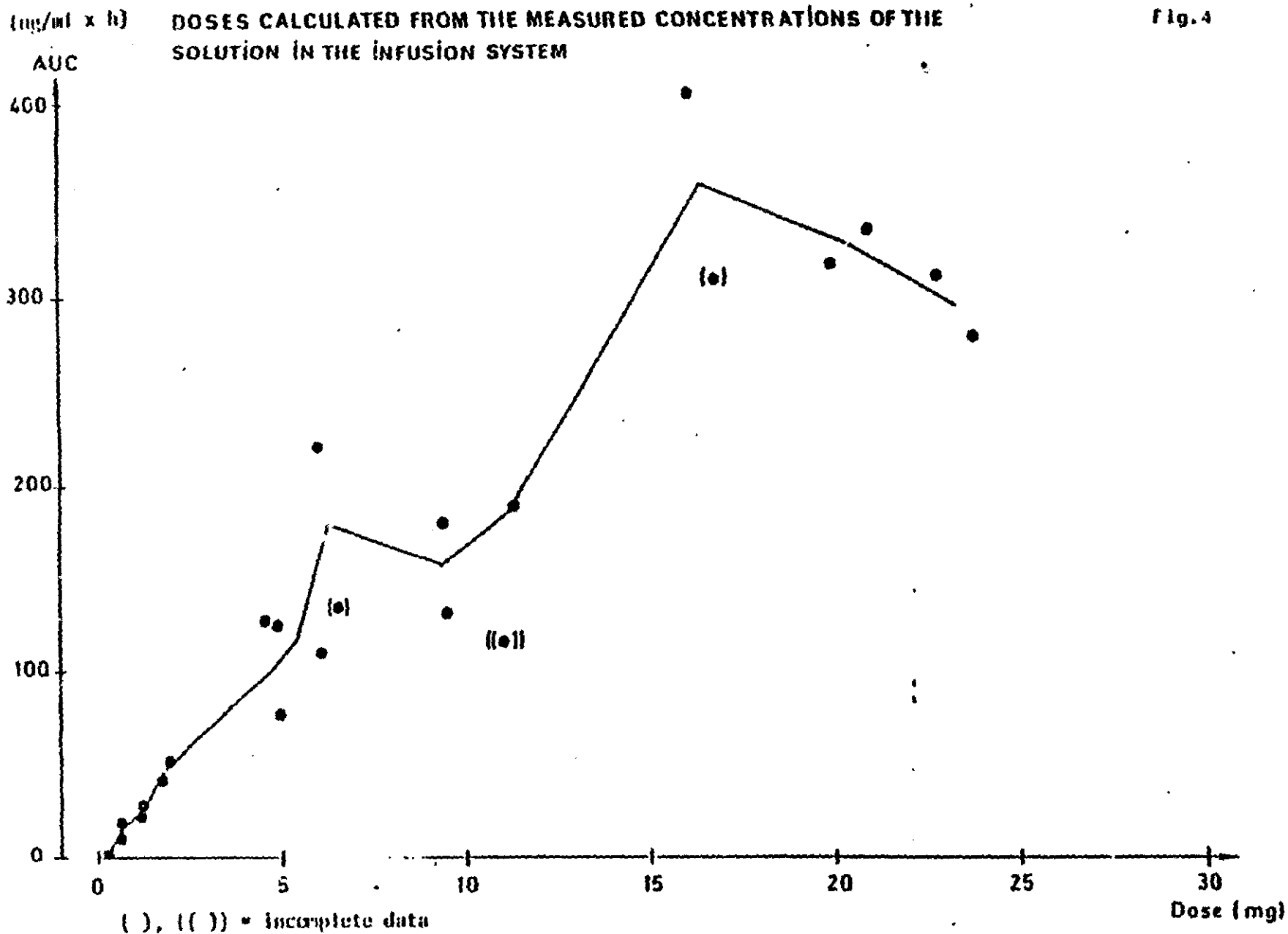
N12-17

834

MF 3837
Vol 1.61
000282

Concentration-time-areas (3hrs) after increasing i.v. doses of BM 14.190
 DOSES CALCULATED FROM THE MEASURED CONCENTRATIONS OF THE
 SOLUTION IN THE INFUSION SYSTEM

Fig. 4



M 3-19

1835

Mf-7018
 vol 1.64
 000343

Results

The results are summarized in the tables and figures in the Appendix and in the following survey table.

Pharmacokinetic parameter	Breakfast	
	0.5 h before substance administration (human study no. 0636/A)	2 h after administration (human study no. 0636/B)
lag time (h)	0,752 0,822 (0,233-1,532)	0,451 0,426 (0,183-0,969)
initial increase (mcg/l/h)	104,92 41,57 (7,82-1157,82)	227,88 103,33 (10,16-1536,99)
$t_{1/2}$ (h)	3,731 3,478 (2,038-7,107)	4,052 4,480 (1,602-7,520)
C_{max} (mcg/l)	49,21 47,39 (18,22-97,35)	55,40 46,00 (15,23-143,85)
t_{max} (h)	2,732 2,514 (0,556-4,759)	1,466 1,249 (0,584-2,915)
AUC (mcg x h/l)	246,24 196,87 (80,38-637,28)	234,68 173,14 (82,12-675,67)
MRT (h)	5,384 5,225 (3,380-8,138)	5,009 4,933 (2,584-9,371)

(AUC: area under the curve, MRT: mean residence time)

Survey table of pharmacokinetic characteristic data from the substance concentrations in serum after oral administration of 25 mg Carvedilol (BM 14.190) with (human study no. 0636/A) and without breakfast (human study no. 0636/B). Stated are the mean values, below these the medians and in brackets the minima and maxima. The parameters were calculated from the compensation curves which were obtained by means of adapted regression functions for compensation of the measured data (2).

MF 7021

VOL 1.67

000013

Kinetic data, BM 14.190 oral
 $\bar{x}$, x, (minimum, maximum)

	(50 mg Caps. 0) n = 15	Result Wilcoxon-Test ↔	(25 mg Caps. 0) n = 16	Result Wilcoxon-Test ↔	(50 mg Caps. 3) n = 19	Result Wilcoxon-Test ↔	(50 mg Caps. 0) n = 15
init. increase conc. ($\mu\text{g}/\text{l}/\text{h}$)	201.8 55.15	n.s.*	123.9 90.3	n.s.	351.3 198.25	p = 0.008	
lag time (h)	0.42 0.38		0.46 0.44		0.34 0.31		
C_{max} ($\mu\text{g}/\text{l}$)	59.4 60.5	n.s.	42.1 47.8	n.s.	94.8 89.0	p = 0.001	see first column
t_{max} (h)	1.78 1.64	n.s.	1.51 1.55	n.s.	1.20 0.95	p = 0.035	
AUC_{0-24} ($\mu\text{g}\cdot\text{h}/\text{l}$)	316.57 317.08		195.48 183.52		368.91 379.61		
$\text{AUC}_{0-\infty}$ ($\mu\text{g}\cdot\text{h}/\text{l}$)	376.42 372.05	n.s.	217.26 194.45	n.s.	389.10 387.10	n.s.	
$t_{1/2}$ (h)	8.40 6.24	n.s.	6.06 5.61	n.s.	4.73 4.24	p = 0.048	N 5 - 11
mean residence time (h)	10.53 7.42	n.s.	7.29 6.19	n.s.	5.37 4.72	p = 0.007	

* Statistical differences calculated with the Wilcoxon test for paired differences; the n-numbers were in some cases smaller than stated in the table heading; n.s. = not significant

MF 7022

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637

Table 1:

Pharmacokinetic data of BM 14.190 after administration of a gastric juice-resistant tablet in comparison with a suspension

Parameter		Tablet (2x16.67 mg) Human Exp. No. 0642	Suspension (34 mg) Human Exp. No. 0643
AUC 0 - 24 ($\mu\text{g} \times \text{h/l}$)	$\bar{x}$	171	382
	$\tilde{x}$	158	310
C_{max} ($\mu\text{g/l}$)	$\bar{x}$	13.7	107.5
	$\tilde{x}$	13.5	98.9
t_{max} (h)	$\bar{x}$	9.0	0.64
	$\tilde{x}$	9.0	0.62
$t_{1/2}$ (h)	$\bar{x}$	not determinable	7.3
	$\tilde{x}$		7.2

$\bar{x}$: mean
 $\tilde{x}$: median

MF 7023
 vol 1.68

000015

TREATMENT TYPE

Parameter	Toraseמיד	Toraseמיד Combination
Coefficient of correlation (fitted to mathematical model [r])	0.985	0.973
AUD* ₀₋₂₄ [ng*h/ml]	2032 ± 571	1998 ± 656
c _{max} [ng/ml]	592.73 ± 174.99	539.54 ± 181.81
t _{max} [h]	1.24 ± 0.46	1.49 ± 0.57
Absorption half-life [h]	0.28 ± 0.16	0.31 ± 0.13
Elimination half-life [h]	5.25 ± 3.72	4.71 ± 2.41
Mean time [h]	5.86 ± 2.94	5.52 ± 2.49

*AUD = Area Under Data

(calculated using the linear trapezoidal rule)

Table 3: Means and standard deviations of the pharmacokinetic parameters (after fitting to the mathematical model) for toraseמיד in overview after administration of toraseמיד as a single entity and after administration of toraseמיד in combination.

MF 7024

VOL 1.68

000157

B 40

N11-49

TREATMENT TYPE

Parameter	Carvedilol	Carvedilol Combination
Coefficient of correlation (fitted to mathematical model [r])	0.993	0.993
AUD* ₀₋₂₄ [ng*h/ml]	168 ± 58	192 ± 39
c _{max} [ng/ml]	43.60 ± 16.85	45.56 ± 12.24
t _{max} [h]	1.30 ± 0.56	1.73 ± 0.43
Absorption half-life [h]	0.23 ± 0.15	0.27 ± 0.08
Elimination half-life [h]	6.17 ± 1.85	6.38 ± 3.23
Mean time [h]	5.91 ± 1.45	5.86 ± 2.15

*AUD = Area Under Data
(calculated using the linear trapezoidal rule)

Table 5: Means and standard deviations of the pharmacokinetic parameters (after fitting to the mathematical model) for carvedilol in overview after administration of carvedilol as a single entity and after administration of carvedilol in combination.

MF.7024
VOL. 68
000162

B41

5. Results

5.1 Digitoxin in Plasma

The individual values of the plasma digitoxin concentration and the individual plasma concentration-time curves (for the sake of clarity shown only up to 24 hours) are presented in the appendix (Appendix III, Tables 1 and 2; Appendix VI, Figures 1 to 12). An examination of the individual curves reveals no marked difference between the two study phases. The mean value curves of the two study phases (Figure 1) are almost identical.

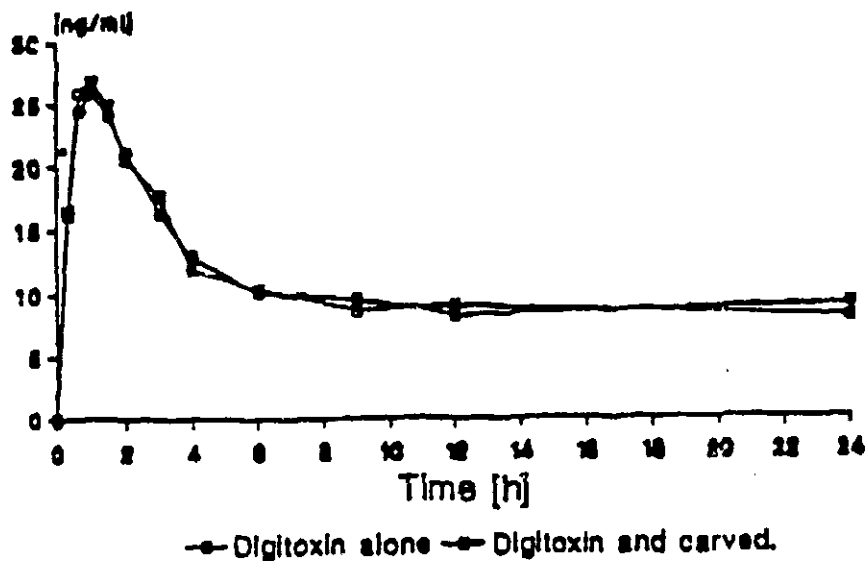


Figure 1: Mean plasma concentration-time curves of digitoxin after oral dosing of 0.56 mg digitoxin alone and in combination with 25 mg carvedilol under steady state conditions (n = 12)

As the Wilk-Shapiro test showed that the hypothesis of normal distribution could not be rejected at the 5 % level, parametric statistical methods were used. The intra-individual paired comparisons using Student's t-test did not show any significant differences for any of the parameters.

MF 7108

VOL 172

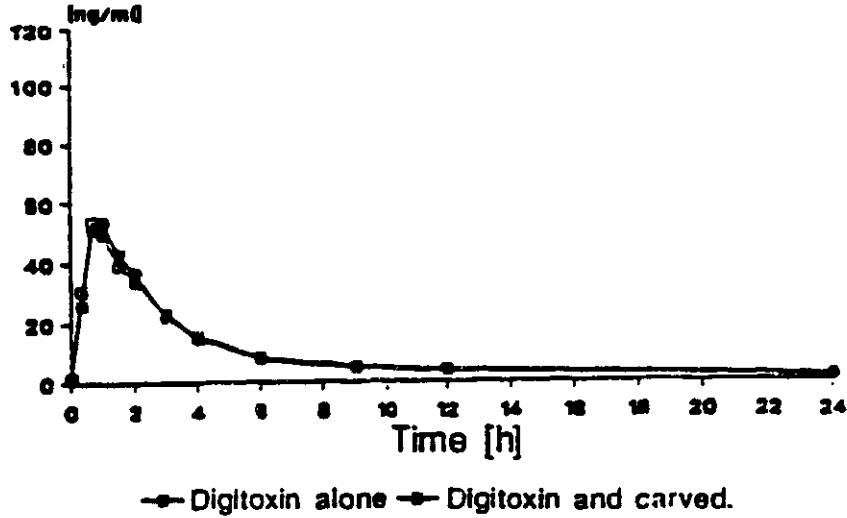


Figure 2: Mean plasma concentration-time curves of carvedilol under steady state conditions after oral administration of 25 mg carvedilol (n = 12).

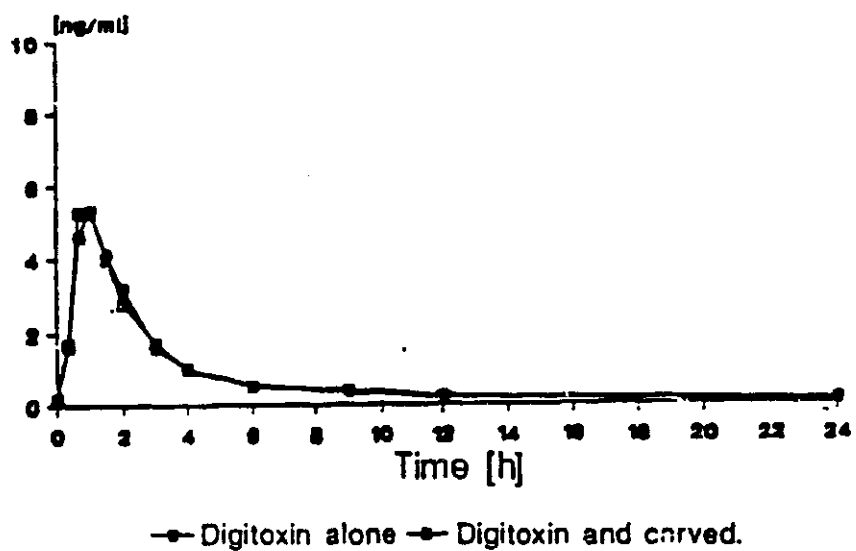


Figure 3: Mean plasma concentration time curves of demethylcarvedilol after oral administration of 25 mg carvedilol under steady state conditions (n = 12).

MF 7108



somewhat greater but also non-significant difference was found for the mean AUC_{0-24h} of demethylcarvedilol (study phase (II) 14.62 ± 5.22 ng/ml*h; study phase (III) 16.01 ± 6.24 ng/ml*h) (Appendix IV, Tables 5, 6 and 7; Appendix VII, Figures 13 and 16).

The AUC ratio as the relation of AUC (carvedilol) to AUC (demethylcarvedilol) was not significantly changed between study phase (II) with 12.89 ± 3.42 and study phase (III) with 12.20 ± 3.00 (Appendix IV, Table 7).

Table 2: Means of pharmacokinetic parameters of carvedilol and demethylcarvedilol

	Carvedilol alone (II)	Carvedilol + digitoxin (III)
Carvedilol		
C _{max} (ng/ml)	60.37 ± 19.87	60.47 ± 21.39
t _{max} (h)	0.90 ± 0.45	0.82 ± 0.33
AUC (ng*h/ml)	200.84 ± 127.10	199.22 ± 105.62
Demethylcarvedilol		
C _{max} (ng/ml)	5.83 ± 1.60	5.55 ± 1.30
t _{max} (h)	0.91 ± 0.38	0.93 ± 0.24
AUC (ng*h/ml)	14.62 ± 5.22	16.01 ± 6.24
AUC ratio (Carvedilol/demethylcarvedilol)	12.89 ± 3.42	12.20 ± 3.00

MF 7108

Protocol	Vol	Objective	Design	Subjects	Treatment	single vs multi dose	n completed (enrolled)	page
A0001	1.50	PK, bioequiv	NB, NC, R SEQ, Xover	healthy men	carv 25 mg capsule po	single	12(12)	C4
A0008	1.50	PK, bioequiv	NB, NC, R SEQ, Xover	healthy men	carv 25 mg capsule and tab po	single	12(13)	C6
A9901	1.51	PK, stereochem	NB, NC, NR, Xover	healthy men	carv 25 mg po	single	12(12)	C11
A9902	1.51	PK, bioequiv	NB, NC, R SEQ, Xover	healthy men	carv 25 mg capsule po, carv 25 mg tab po	single	12(13)	C14
A9903	1.51	PK, stereochem	NB, NC, R SEQ, Xover	healthy men	carv 6.25 mg po, carv 12.5 mg po, carv 25 mg po	single	12(12)	C16
A9904	1.52	PK, digoxin	DB, PC, R SEQ, Xover	healthy men	carv 25 mg po with digoxin 0.5 mg po, placebo with digoxin 0.5 mg po	single	8(8)	C19
A9905	1.52	PK, digoxin	DB, PC, R SEQ, Xover	healthy men	carv 25 mg po with digoxin 0.5 mg IV, placebo with digoxin 0.5 mg IV	single	8(8)	C21
A9907	1.52	PK, food effect	NB, NC, R SEQ, Xover	healthy men, women	carv 25 mg po	single	12(12)	C25
A9908	1.52	PK, bioequiv	NB, NC, R SEQ, Xover	healthy men, women	carv 25 mg po capsule	single	12(12)	C28
A9910	1.53	PK, bioequiv	NB, NC, R SEQ, Xover	healthy men	carv 25 mg po capsule and tab	single	16(17)	C30
A9912	1.53	PK, bioequiv	NB, NC, R SEQ, Xover	healthy men	carv 25 mg po capsule and tab	single	20(20)	C33
CAR.SA-01	1.54	PD, invasive hemodynamic, PK, stereochem	NB, AC, NR	patients, HTN, LV fail	carv 25 mg po, nitroprusside IV	single	10(10)	C36
CAR.UK-105	1.114	PD, non invasive hemodynamic	DB, PC, R SEQ (placebo only), dose escalation	healthy men	carv 12.5 mg, 25 mg, 50 mg, placebo po	single	7(8)	C40
CAR.UK-110	1.114	PD, platelet	in vitro	healthy donor	NA	NA	NA	C51
CARV.0001	1.114	PD, alpha beta	SB, PC, AC, parallel	healthy men	carv 15 mg IV, labetalol 80 mg IV, placebo IV	single	24(25)	C55
CARV.0002	1.75	PK	NB, NC, NR	healthy men	carv 0.042 mg/kg IV, carv 0.084 mg/kg IV	single	6(11)	C61

Protocol	Vol	Objective	Design	Subjects	Treatment	single vs multi dose	n completed (enrolled)	page
CARV.0011	1.115	PD, beta, LV function	DB, PC, R SEQ, Xover	patients ASCHD	carv 25 mg po	single	12(20)	C64
F30	1.44	PK, stereochem	NB, NC, NR	healthy men	carv 20 mg po	single	5(5)	C66
INT-CAR-22SCA	1.53	PD, beta	NB, NC, NR, parallel, dose escalation	healthy men	carv 12.5 mg/day for 1 week, carv 25 mg/day for 2 weeks po	multiple for 3 weeks	10(10)	C69
INT.CAR.30 A		PD, beta	DB, R SEQ placebo only, ascending dose SEQ, Xover	healthy men	carv 6.25 mg, 12.5 mg, 25 mg, 50 mg po	single	5	C74
INT.CAR-30B	1.113	PD, alpha	DB, PC, partially R SEQ, Xover	healthy men	placebo; labetalol 400 mg po; carv 6.25 mg, 12.5 mg, 25 mg po	single	10(10)	C82
MF2971	1.56	PD, beta	DB, PC, R seq, Xover, with SB, NC, NR extension	healthy men	po carv 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 600 mg, 800 mg	single	6(6)	C88
MF3132 I	1.125	PD, beta	DB, PC, AC, R SEQ, Xover	healthy men	carv 100 mg, labetalol 200 mg, propranolol 160 mg, pindolol 10 mg, placebo po	single	6(7)	C93
MF3132 II	1.125	PD, beta	DB, PC, R SEQ, Xover	healthy men	carv 100 mg, placebo po	single	6(6)	C103
MF3223 I and II	1.125	PD, beta	DB, PC, AC, R SEQ, Xover	healthy men	carv 12.5 mg, 25 mg, 50 mg, 100 mg, 200 mg; labetalol 50 mg, 100 mg, 200 mg, 400 mg; propranolol 40 mg, 80 mg, 160 mg, 320 mg; pindolol 2.5 mg, 5 mg, 10 mg, 20 mg; placebo po	single	6(6)	C105
MF3270	1.125	PD, beta, exercise tolerance	SB, PC, NR, Xover	patients stable angina pectoris	carv 25 mg bid, 50 mg bid, placebo bid po	multiple doses for 2 weeks	15(20)	C109
MF3413	1.57	PK, PD, young, old	DB, PC, AC, NR, Xover	healthy men and women	carv 12.5 mg, 25 mg, 50 mg po, labetalol 200 mg po, carv 5 mg iV, placebo	single	8(20)	C122

Protocol	Vol	Objective	Design	Subjects	Treatment	single vs multi dose	n completed (enrolled)	page
MF3459	1.58	PK, renal fail	NB, NC, NR	patients with HTN and renal insufficiency	carv 50 mg po	single	24(25)	C133
MF3476	1.60	PK, liver fail	NB, NC, NR, Xover	patients with liver insufficiency	carv 25 mg po, carv 12.5 mg IV	single	28(31)	C140
MF3548	1.134	PD, alpha, beta	DB, PC, AC, R SEQ, Xover	healthy men	carv 50 mg, 100 mg; propranolol 160 mg; prop.anolol 80 + hydralazine 50 mg; labetalol 400 mg; placebo po	single	8(8)	C142
MF3702	1.61	PK, young, old	SB, NC, NR, dose escalation in non responders	patients HTN	carv 12.5 mg/day, 25 mg/day, 50 mg/day po	multiple for 12 weeks	29(32)	C144
MF3877	1.62	PK, interaction HCTZ, diuretic	DB, AC, R SEQ, Xover	patients HTN	carv 25 mg, HCTZ 25 mg, placebo po	single	12(12)	C145
MF3950	1.63	PK, young, old	NB, NC, NR, parallel	healthy men and women	carv 25 mg/day po	multiple for 2 weeks	17(21)	C153
MF7008	1.64	PK, bioequiv	NB, NC, R SEQ, Xover	healthy men	carv 25 mg tab po, carv 25 mg capsule po	single	20(20)	C157
MF7016-0539	1.64	PD, alpha	NB, NC, NR, dose escalation	healthy men	carv 2.5, 5, 10, 15, 22.5, 30, 34, 51, 76.5 mg suspension po	single	15(23)	C160
MF7016-0541	1.64	PD, beta	DB, AC, NR, Xover	healthy men	carv 50 mg; metipranolol 5 mg and 10 mg suspension po	single	6(7)	C163
MF7029	1.71	PK, metabolism	NB, NC, NR	healthy men	carv 50 mg po	single	6(6)	C169
MF7034	1.71	PK, stereochem	NB, NC, R SEQ, Xover	healthy men	carv 50 mg po, carv 12.5 mg IV	single	10(10)	C175
MF7038	1.71	PK	NB, NC, NR, Xover	one healthy man	carv 25 mg po, carv 10 mg IV	single	1(1)	C177
MF7097	1.71	PK, cimetidine	NB, NC, NR	healthy men	carv 25 mg/day, cimetidine 1000 mg/day po	multiple for 9 days	10(10)	C179
protocol-020	1.49	PK, bioequiv	NB, NC, R SEQ, Xover	healthy subjects	carv 25 mg capsule, 25 mg Tiltab® po	single	32(34)	C187

NDA 20-297 CARVEDILOL, Protocol A0001, Vol 1.50
 BIOEQUIVALENCE
 Reviewer: James F. Graumlich

Design: open label, randomized, period balanced, 4 way crossover with all four formulations in 12 - 24 healthy male subjects. Study periods were separated by one week.

Response variable: AUC, Cmax, Tmax, half-life, BP, and heart rate

Blood sampling times: baseline then 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 14, 20, and 24 hours after dose administration. Supine BP and heart rate were measured after the dose administration every 10 minutes x 4 hours then every 15 minutes x 4 hours.

Materials	Treatment	Studies
carvedilol 25 mg capsule, lot number Ch 819 854 40 Gf	A	Clinical supplies in 1987
carvedilol 25 mg capsule, lot number Ch 819 291 40 Df	B	Used in efficacy studies
carvedilol 25 mg capsule, lot number Ch 819 861 40 Df	C	Used in safety studies
carvedilol 25 mg capsule, lot number Ch 819 177 40 Fe	D	Used in dose ranging studies

Assay: plasma carvedilol concentration and plasma O-desmethyl-carvedilol concentration. HPLC reference is Varin. J Pharm Sci 1986; 75:1195-1197. Lower limit of quantification = 0.3 ng/mL.

Results: Standing BP and heart rate were not measured 1, 2, 4, 6 and 8 hours after dose administration because of symptomatic orthostatic "faintness," hypotension, and bradycardia in 6 of 12 subjects, i.e., subjects 4, 8, 6, 5, 7, 12.

formulation A, n = 12 [carvedilol]		min	max		
Parameter	mean±SD				
AUC(0-24)	136.05±53.63			ng*hr/mL	
Cmax	45.19±22.86			ng/mL	
Tmax	1.02±0.27			hr	
half-life	4.96±1.43			hr	n = 11
formulation B, n = 12 unless noted otherwise [carvedilol]		min	max		
Parameter	mean±SD				
AUC(0-24)	95.06±32.85			ng*hr/mL	
Cmax	26.8±15.03			ng/mL	
Tmax	1.27±0.87			hr	
half-life	6.8±4.92			hr	n = 7
formulation C, n = 12 unless noted otherwise [carvedilol]		min	max		
Parameter	mean±SD				
AUC(0-24)	136.77±60.78			ng*hr/mL	
Cmax	43.17±22.86			ng/mL	
Tmax	1.02±0.34			hr	
half-life	5.33±2.0			hr	n = 12
formulation D, n = 12 unless noted otherwise [carvedilol]		min	max		
Parameter	mean±SD				
AUC(0-24)	119.51±37.12			ng*hr/mL	
Cmax	37.21±17.12			ng/mL	
Tmax	1.15±0.58			hr	
half-life	9.53±11.99			hr	n = 12

formulation A, n = 12 unless noted otherwise			[0-desmethylcarvedilol]		
Parameter	mean±SD	min	max		
AUC(0-t)	7.82±3.18			ng*hr/mL	
Cmax	4.14±1.79			ng/mL	
Tmax	1.19±0.34			hr	
half-life	1.63±1.15			hr	n = 10

formulation B, n = 12 unless noted otherwise			[0-desmethylcarvedilol]		
Parameter	mean±SD	min	max		
AUC(0-t)	5.77±3.11			ng*hr/mL	
Cmax	2.78±1.15			ng/mL	
Tmax	1.40±0.62			hr	
half-life	0.98±0.28			hr	n = 10

formulation C, n = 12 unless noted otherwise			[0-desmethylcarvedilol]		
Parameter	mean±SD	min	max		
AUC(0-t)	7.64±2.2			ng*hr/mL	
Cmax	3.66±0.65			ng/mL	
Tmax	1.23±0.34			hr	
half-life	1.36±0.46			hr	n = 9

formulation D, n = 12 unless noted otherwise			[0-desmethylcarvedilol]		
Parameter	mean±SD	min	max		
AUC(0-t)	6.25±2.96			ng*hr/mL	
Cmax	3.25±1.20			ng/mL	
Tmax	1.38±0.53			hr	
half-life	2.31±2.34			hr	n = 9

Adverse events: See above regarding orthostatic hypotension.

Other lab abnormalities associated with drug treatment were elevated LDH, elevated CK and CK-MB, decreased hemoglobin, decreased platelets, decreased total protein

Conclusions:

None of the formulations were bioequivalent. *what about A+E*

There was a range of Cmax [carvedilol] within the four formulations from 26.8 to 45.19 ng/mL.

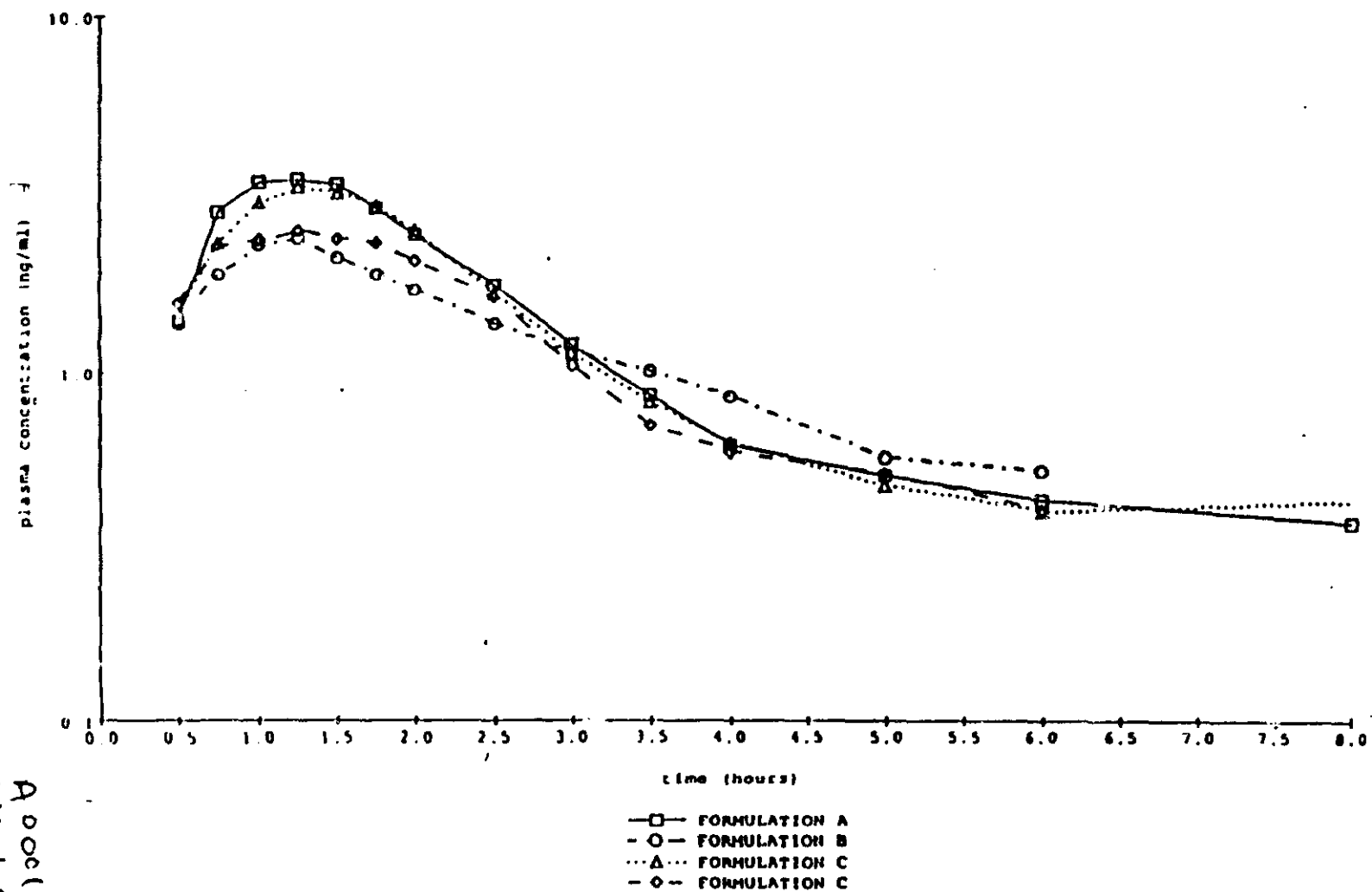
Tmax [carvedilol] was consistent at around 1 hour.

Cmax [0-desmethylcarvedilol] is about 10% of Cmax [carvedilol].

Orthostatic hypotension occurred in 6 of 12 healthy volunteers. There was no placebo comparison.

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FIGURE 26
MEAN PLASMA O-DESMETHYLCARVEDILOL CONCENTRATION VERSUS TIME
IN NORMAL SUBJECTS (n=12) FOLLOWING ADMINISTRATION
OF 25 mg CAPSULES

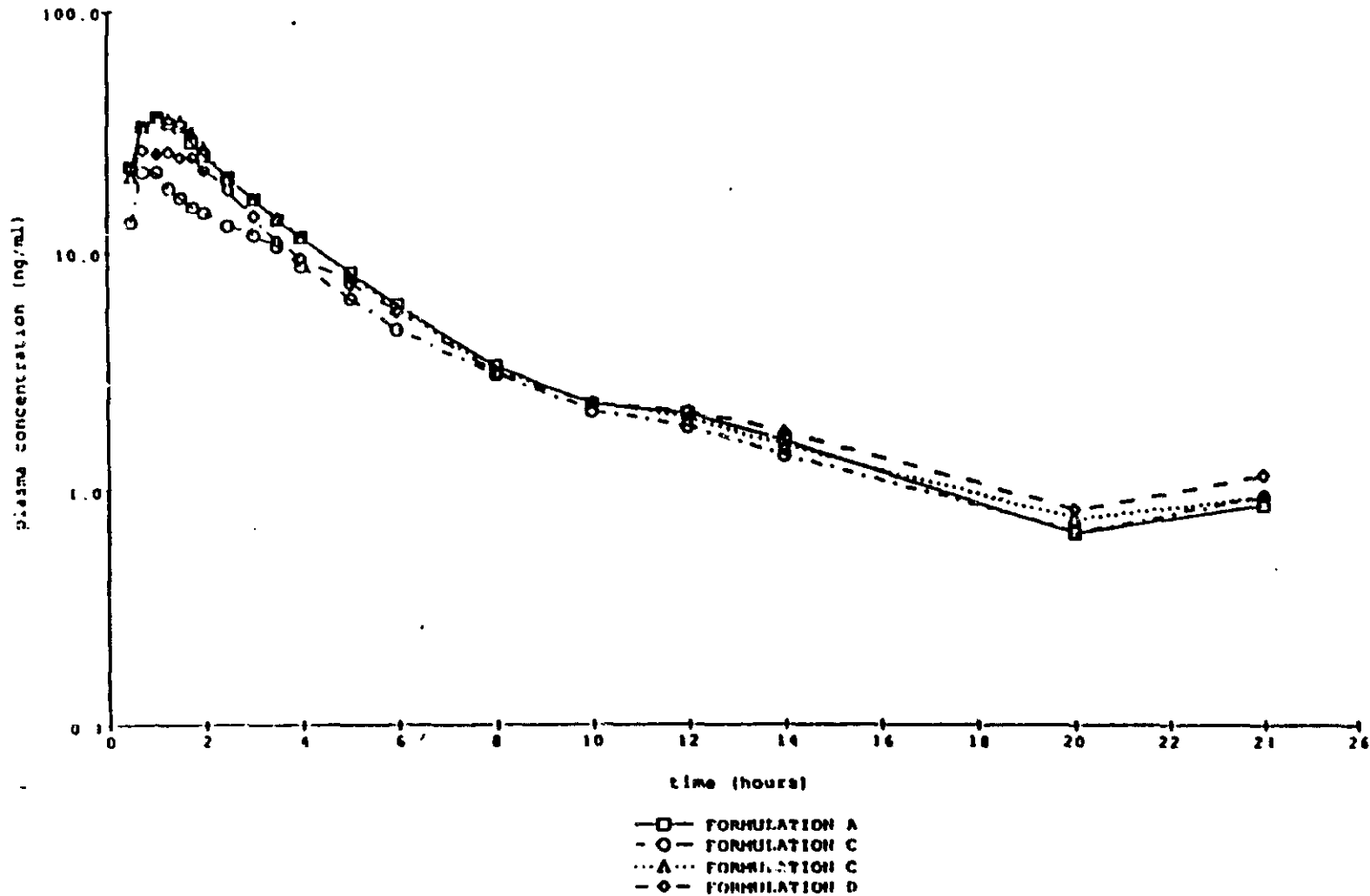


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VOL 1.50
A 0001

551

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FIGURE 13
MEAN PLASMA CARVEDILOL CONCENTRATION VERSUS TIME
IN SUBJECTS (n=12) FOLLOWING ADMINISTRATION
OF 25 mg CAPSULES



A0001
VOL 1.50
000091

**NDA 20-297 CARVEDILOL, Protocol A0008, Vol 1.50
BIOEQUIVALENCE
Reviewer: James F. Graumlich**

Objectives: Describe and compare the pharmacokinetics of single doses of carvedilol 25 mg given in 4 different formulations to determine bioequivalence.

Study design: Open label, randomized, period balanced, 4 way crossover with all four formulations in 12 healthy male subjects. Study periods were separated by one week.

Response variables: AUC, Cmax, Tmax, half-life, BP, and heart rate

Blood sampling times: baseline then 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3, 4, 6, 8, 10, 12, 14, and 24 hours after dose administration. Supine BP and heart rate were measured after the dose administration every 10 minutes x 4 hours then every 15 minutes x 4 hours. Standing BP and heart rate were measured 2 and 8 hours after dose administration.

Materials:

- A=carvedilol 25 mg capsule, lot number Ch 819 854 40 Gf = A in A0001
- B=carvedilol 25 mg capsule, lot number Ch 819 291 40 Df = B in A0001
- C=carvedilol 25 mg capsule, lot number Ch 820 176 40 Lh = reference
- D=carvedilol 25 mg tablet, lot number Ch 819 896 20 B

C was used by SK Beecham for US clinical trials for hypertension.

Assay: plasma carvedilol concentration and plasma O-desmethyl-carvedilol concentration. HPLC reference is Varin. J Pharm Sci 1986; 75:1195-1197. Lower limit of quantification = 0.3 ng/mL.

Results: 13 subjects were recruited. Subject 13 was withdrawn due to adverse event. 12 subjects completed the study. See tables for carvedilol for AUC, Cmax, and Tmax means (pages 204, 205 volume 1.50).

AUC O-desmethyl-carvedilol (ng*hr/mL)

formulation	A	B	C	D
mean±SD	9.35±4.86	7.62±4.35	9.2±3.88	8.64±4.66
min				
max				

Cmax O-desmethyl-carvedilol (ng/mL)

formulation	A	B	C	D
mean±SD	3.44±1.57	2.7±1.02	4.15±1.89	3.26±1.65
min				
max				

Tmax O-desmethyl-carvedilol (hours)

formulation	A	B	C	D
mean±SD	1.59±0.72	1.17±0.29	1.35±0.62	1.33±0.66
min				
max				

The means for supine DBP, SBP, and pulse are shown vs time in Figure 25 from volume 1.50. There were minimal drug effects during the first 8 hours after the dose.

Adverse events:

Subject 13 had a wide complex tachycardia before dosing on the second study day. He received treatment A on the first study day. Since the arrhythmia occurred one week after a single dose of carvedilol, I do not associate the adverse event with the drug.

Subjects 1, 2, 3, 4, 5, 7, 9, 10 and 13 developed one or more symptoms with standing.

Conclusions:

None of the formulations were bioequivalent to formulation C for AUC and C_{max}.

Formulation B had less bioavailability than formulation C.

O-desmethyl-carvedilol concentrations were less than 5% carvedilol concentrations.

Subjects developed orthostatic symptoms.

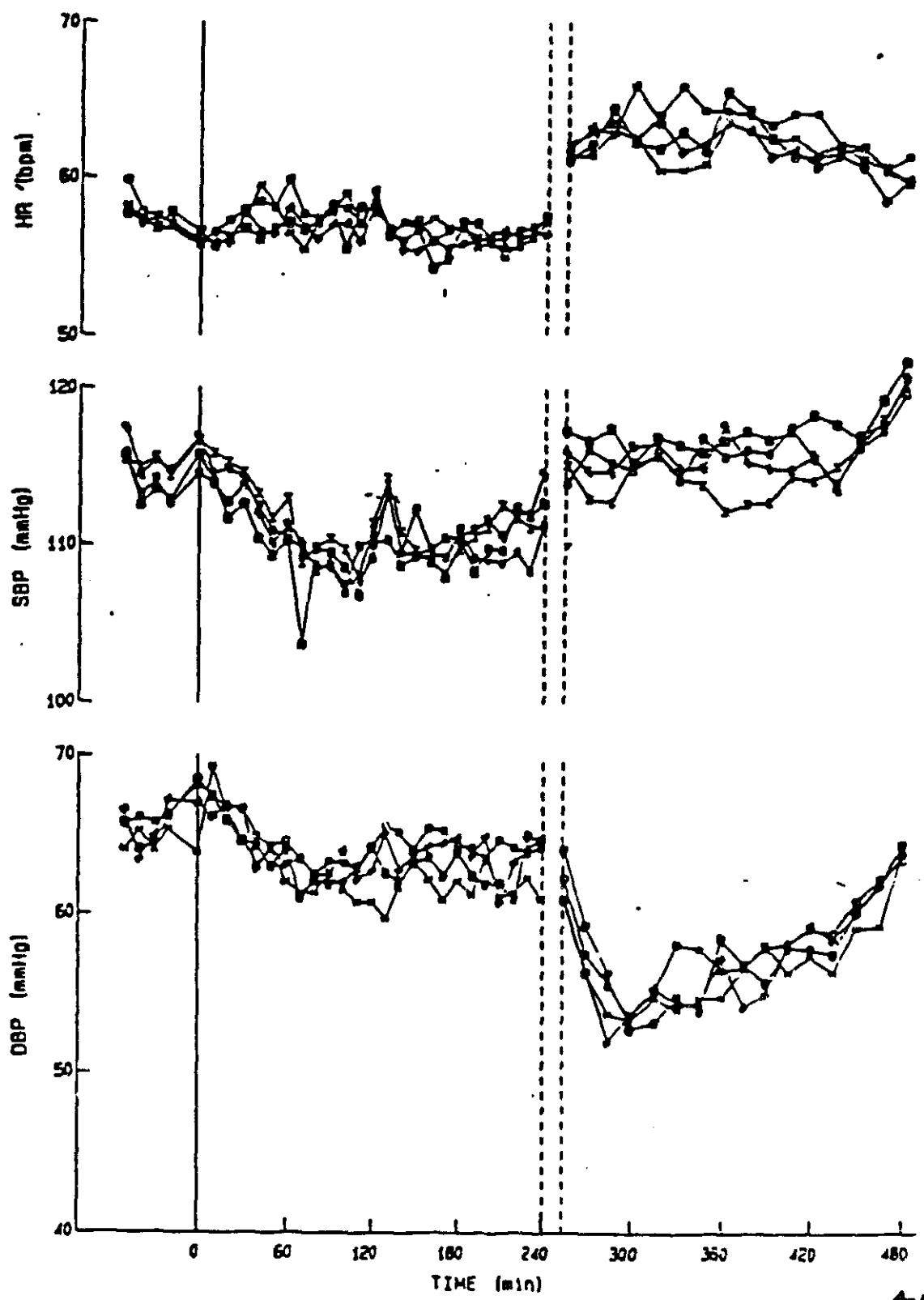
There was no definite effect of the drug on supine SBP, DBP, or pulse in these healthy men. There was no placebo comparison.

The conclusions of the sponsor appear valid.

Figure 25

CARVEDILOL/A08 : MEAN SUPINE VALUES

●: A / ■: B / ○: C / □: D (25 mg)



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Time course of Treatment Means (n=12) of HR, SBP and DBP
Dotted lines equals lunch time.

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The means, medians, and ranges of CMAX data for each formulation were:

<u>Formulation</u>	<u>CMAX</u> <u>(ng/ml)</u>		
	<u>Mean</u>	<u>Median</u>	<u>Range</u>
C	62.99	70.90	
A	61.36	55.58	
B	47.96	40.37	
D	49.52	44.10	

The ratio of the mean CMAX for Formulations A, B, and D expressed as a percentage of the mean CMAX of Formulation C (reference) and the corresponding 90% confidence intervals for the true ratio of means (arithmetic scale analysis) were as follows:

	<u>Ratio %</u>	<u>90% Confidence Interval</u>
A/C	97.4	73.3 - 121.6
B/C	76.1	52.0 - 100.3
D/C	78.6	54.5 - 102.8

The means, medians, and ranges of TMAX data for each formulation were:

<u>Formulation</u>	<u>TMAX</u> <u>(hr)</u>		
	<u>Mean</u>	<u>Median</u>	<u>Range</u>
C	1.13	1.00	
A	1.52	1.13	
B	1.06	1.00	
D	1.38	1.00	

2. Pharmacokinetics of O-desmethylocarvedilol

Graphical and tabular representation of the plasma O-desmethylocarvedilol concentrations at all sampling times for each subject are provided in Figures 13 to 24 and Appendix III.

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VOL 1.50
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1. Comparative Pharmacokinetics

1. Pharmacokinetics of Carvedilol

The plasma concentrations of carvedilol at all sampling times for each subject are reported in Appendix I. The plasma concentration-time profiles for each subject are shown in Figures 1-12. The individual and mean values for area under the concentration-time curves (AUC), peak plasma concentration (C_{MAX}), and time until peak plasma concentration (T_{MAX}) are reported in Tables 4-5.

The means, medians, and ranges of AUC data for each formulation were:

<u>Formulation</u>	<u>AUC</u> <u>(ng*hr/ml)</u>		
	<u>Mean</u>	<u>Median</u>	<u>Range</u>
C	221.89	201.24	
A	234.72	181.31	
B	198.61	165.90	
D	206.08	172.12	

The ratio of the geometric mean AUC for Formulations A, B, and D expressed as a percentage of the geometric mean AUC of Formulation C (reference) and the corresponding 90% confidence intervals for the true ratio of means (logarithmic scale analysis) were as follows:

	<u>Ratio %</u>	<u>90% Confidence Interval</u>
A/C	100.9	85.8 - 118.5
B/C	85.8	73.0 - 100.9
D/C	91.5	77.8 - 107.5

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A 0008
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NDA 20-297 CARVEDILOL STEREOSELECTIVE PK, Protocol A9901, Vol 1.51

Reviewer: James F. Graulich

Name of study: A pharmacokinetic study of carvedilol, 25 mg orally, (SK&F 105517) to study the intra-subject variability and stereoselectivity of the pharmacokinetics in healthy subjects.

Objectives: To estimate the intra-subject variability for AUC, C_{max}, and T_{max} after a single dose of one capsule formulation.

Study design: Open label, non-randomized, 3 period study with single doses in 12 healthy male subjects. There was no placebo group. Study periods were separated by one week.

Response variables: AUC, C_{max}, T_{max}, half-life, BP, pulse

Blood sampling times: baseline then 10, 20, 30, 45 minutes then 1.0, 1.25, 1.5, 2.0, 2.5, 3, 4, 6, 8, 10, 12, 14, and 24 hours after dose administration. Supine BP and heart rate were measured 15, 30, 45 minutes then 1.0, 1.25, 1.5, 2.0, 2.5, 3, 4, 6, 8, 10, 12, 14, and 16 hours after dose administration.

Materials: carvedilol 25 mg capsule, lot number BM 820-176-40 Lb

Assay: Assay involved solid phase extraction and HPLC with fluorescence detection of plasma carvedilol concentration and plasma O-desmethyl-carvedilol concentration. Limit of quantification = 0.3 ng/mL. Plasma R (+) carvedilol and S (-) carvedilol concentration and plasma R (+) O-desmethyl-carvedilol and S (-) O-desmethyl-carvedilol concentrations were measured with chiral assay. Limit of quantification = 1.25 ng/mL.

Results: Twelve healthy male subjects between 22 and 33 years of age and weighing between 70.0 and 86.1 kg completed the study.

Pharmacokinetic parameters for carvedilol

	Period 1 mean±SD min, max	Period 2 mean±SD min, max	Period 3 mean±SD min, max	All periods mean
AUC(0-t)	222.64±147.4	205.67±111.79	217.73±115.74	215.35
AUC(0-∞)	278.45±158.17	229.19±128.67	235.97±125.74	
C _{max}	59.61±31.48	46.54±21.98	59.46±32.49	55.20
T _{max}	0.93±0.28	1.6±0.94	1.1±0.7	1.21
Half-life	9.71±1.72	10.03±2.44	8.96±1.65	

AUC in ng*hr/mL, C_{max} in ng/mL, T_{max} in hours, half-life in hours
t = time of last measured concentration

Pharmacokinetic parameters for R (+) carvedilol and S (-) carvedilol Enantiomers were measured only on samples from period 3.

	R (+) carvedilol mean $\pm$ SD min, max	S (-) carvedilol mean $\pm$ SD min, max	R/S ratio geometric mean min, max
AUC(0-t)	156.74 $\pm$ 99.31	43.93 $\pm$ 27.43	3.57
AUC(0- ∞)	169.29 $\pm$ 106.34	51.21 $\pm$ 29.20	not tabulated
Cmax	44.27 $\pm$ 25.21	16.68 $\pm$ 9.99	2.62
Tmax	1.1 $\pm$ 0.72	1.02 $\pm$ 0.69	
Half-life λ_{2}	2.84 $\pm$ 0.98	2.7 $\pm$ 0.73	
Half-life λ_{3}	8.25 $\pm$ 2.79*	missing data	

AUC in ng*hr/mL, Cmax in ng/mL, Tmax in hours, half-life in hours

*Represents only 3 subjects

t = time of last measured concentration

Pharmacokinetic parameters for O-desmethyl-carvedilol

	Period 1 mean $\pm$ SD min, max	Period 2 mean $\pm$ SD min, max	Period 3 mean $\pm$ SD min, max	R (+) O-desmethyl-carvedilol mean $\pm$ SD min, max
AUC(0-t)	12.5 $\pm$ 9.63	15.33 $\pm$ 7.67	13.89 $\pm$ 7.52	7.18 $\pm$ 5.07
Cmax	3.68 $\pm$ 1.28	3.17 $\pm$ 1.12	4.62 $\pm$ 1.81	4.17 $\pm$ 1.61
Tmax	0.99 $\pm$ 0.23	1.44 $\pm$ 0.97	1.13 $\pm$ 0.25	1.29 $\pm$ 0.52

Half-life not tabulated

AUC in ng*hr/mL, Cmax in ng/mL, Tmax in hours

t is the last measurable time point.

O-desmethyl-carvedilol not quantifiable (< 0.3 ng/mL) in 6 of 12 subjects at 12 hours after dose administration.

O-desmethyl-carvedilol not quantifiable (< 0.3 ng/mL) in 10 of 12 subjects at 24 hours after dose administration.

Enantiomers were measured only on samples from period 3.

S (-) O-desmethyl-carvedilol was quantifiable ($\geq$ 1.25 ng/mL) in 3 of 12 subjects. Cmax ranged from 1.37 to 2.48 ng/mL. Tmax ranged from 0.75 to 1.5 hours after administration of the dose.

Supine systolic blood pressure SBP (mean $\pm$ SEM mm Hg), supine diastolic blood pressure DBP (mean $\pm$ SEM mm Hg), and pulse (mean $\pm$ SEM beats per minute) in 12 subjects. Time (T) to Emax is in hours.

Parameter	Period 1	Period 2	Period 3
SBP baseline	118 $\pm$ 2	116 $\pm$ 2	113 $\pm$ 2
SBP Emax	103 $\pm$ 2	103 $\pm$ 2	100 $\pm$ 2
SBP, T, Emax	0.75	1.5	1.5
SBP, 16 hours	111 $\pm$ 3	111 $\pm$ 2	109 $\pm$ 2
DBP baseline	73 $\pm$ 3	67 $\pm$ 2	71 $\pm$ 2
DBP Emax	64 $\pm$ 3	61 $\pm$ 3	59 $\pm$ 3
DBP, T-Emax	8	6	8
DBP, 16 hours	63 $\pm$ 2	72 $\pm$ 2	68 $\pm$ 2
Pulse baseline	63 $\pm$ 2	63 $\pm$ 2	64 $\pm$ 2
Pulse Emax	60 $\pm$ 2	57 $\pm$ 1	55 $\pm$ 2
Pulse, T-Emax	2	3	4
Pulse, 16 hours	66 $\pm$ 2	69 $\pm$ 2	63 $\pm$ 2

Adverse events:

headache
 orthostatic lightheadedness
 nausea
 elevated AST
 elevated ALT
 elevated total bilirubin
 elevated uric acid

Conclusions:

There is inter-subject and intra-subject variability in PK parameters.

Mean Cmax and AUC(0-t) values for R (+) carvedilol are two to four times greater than values for S (-) carvedilol.

Plasma concentrations of O-desmethyl-carvedilol are 5 - 10% of plasma concentrations of carvedilol.

There is no placebo group with which to compare pharmacodynamic effects.

NDA 20-297 CARVEDILOL BIOEQUIVALENCE

Protocol A9902, Vol 1.51

Reviewer: James F. Graumlich

Name of study: A pharmacokinetic study of carvedilol (SK&F 105517), 25 mg orally, tablet vs capsule, in healthy subjects.

Objectives: To determine if 25 mg carvedilol "Tiltab" tablets and 25 mg carvedilol capsules are bioequivalent.

Study design: Open label, randomized, 2 period crossover study with single doses in 13 healthy male subjects. There was no placebo group. Study periods were separated by one week.

Response variables: Primary outcome: AUC (trapezoidal method)
Secondary outcome: Cmax, Tmax, half-life, BP, pulse

Blood sampling times: baseline then 10, 20, 30, 45 minutes then 1.0, 1.25, 1.5, 2.0, 2.5, 3, 4, 6, 8, 10, 12, 14, and 24 hours after dose administration.

Supine BP and heart rate were measured at baseline and 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2.0, 2.5, 3, 4, 5, 6, 8, 10, 12, and 14 hours after dose administration.

Materials: carvedilol 25 mg capsule, lot number IPO #87148
carvedilol 25 mg tablet, lot number IPO #88144 Tiltab

Assay: Assay involved solid phase extraction and HPLC with fluorescence detection of plasma carvedilol concentration. Limit of quantification = not stated

Results:

Thirteen healthy male subjects between 22 and 35 years of age and weighing between 63.0 and 87.8 kg enrolled in the study. One subject withdrew because of a headache.

Pharmacokinetic parameters for carvedilol

	Capsule mean±SD min, max	Tablet mean±SD min, max	90% Confidence Interval for ratio of means
AUC(0-t)	242.38±82.12	269.95±103.17	100.5, 118.6
Cmax	62.16±19.67	72.8±23.94	99.5, 134.8
Tmax	1.55±1.02	1.05±0.62	50.0, 86.6

Half-life not calculated

Log transformed AUC used to calculate confidence interval.

AUC in ng*hr/mL, Cmax in ng/mL, Tmax in hours, half-life in hours

t = time of last measured concentration

Supine systolic blood pressure SBP (mean±SEM mm Hg), supine diastolic blood pressure DBP (mean±SEM mm Hg), and pulse (mean±SEM beats per minute) in 12 subjects. Time (T) to Emax is in hours.

Parameter	Tablet	Capsule
SBP baseline	112±2	110±2
SBP Emax	98±1	100±2
SBP, T,Emax	2	4
SBP, 14 hours	104±4	108±3
DBP baseline	71±2	67±2
DBP Emax	61±2	61±2
DBP, T-Emax	6	14
DBP, 14 hours	58±2	61±2
Pulse baseline	64±2	65±3
Pulse Emax	57±2	57±2
Pulse, T-Emax	3	4
Pulse, 14 hours	70±2	67±2

Adverse events:

headache
 orthostatic lightheadedness
 nasal stuffiness
 elevated alkaline phosphatase
 elevated AST
 elevated total bilirubin
 elevated glucose
 decreased CO₂
 decreased potassium
 decreased WBC

Conclusions:

The two formulations were bioequivalent based on log transformed AUC.

The two formulation were not bioequivalent based on C_{max} (not transformed).

There is no placebo group with which to compare pharmacodynamic effects.

CARVEDILOL NDA 20-297

PROTOCOL A9903

DOSE PROPORTIONALITY AND STEREOSELECTIVE PK

Protocol A9903, Vol 1.51

Reviewer: James F. Graumlich

Name of study: A dose proportionality study of carvedilol enantiomers following doses of racemic carvedilol (SK&F 105517 capsules) of 6.25, 12.5, 25.0 and 37.5 mg orally in healthy subjects.

Objectives: To assess the dose proportionality of plasma concentrations of carvedilol enantiomers following single oral doses of racemic carvedilol.

Study design: Open label, randomized, 4 period crossover study with single doses in 12 healthy male subjects. There was no placebo group. Study periods were separated by one week.

Response variables: Primary outcome: AUC (trapezoidal method)
Secondary outcome: Cmax, Tmax, half-life, BP, pulse

Blood sampling times: baseline then 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2.0, 2.5, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours after dose administration. Supine BP and heart rate were measured at baseline then 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2.0, 2.5, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours after dose administration.

Materials: carvedilol 6.25 mg capsule, lot number IPO #87144
carvedilol 12.5 mg capsule, lot number IPO #88081
carvedilol 25.0 mg capsule, lot number IPO #88083

One carvedilol 12.5 mg capsule plus one carvedilol 25.0 mg capsule were given for the 37.5 mg dose.

Assay: Assay involved solid phase extraction, derivitization with GITC, and HPLC with fluorescence detection of plasma R (+) carvedilol and plasma S (-) carvedilol concentration. Limit of quantification for each enantiomer was 0.3 ng/mL.

Results: Twelve healthy male subjects between 23 and 35 years of age and weighing between 66.6 and 91.1 kg completed the study.

PK parameter values for different doses for carvedilol, mean±SD. n=12

AUC(0-t) in ng*hr/mL, Cmax in ng/mL t = time of last quantified concentration.

	6.25 mg	12.5 mg	25.0 mg	25 + 12.5 mg
Parameter				
Cmax R (+)	8.90±5.12	21.39±10.63	40.09±26.35	66.20±35.47
minimum				
maximum				
Cmax S (-)	3.52±3.01	8.19±4.54	15.61±11.03	29.01±16.23
min				
max				
AUC(0-t) R (+)	32.1±20.7	78.4±44.7	155.9±120.0	237.7±145.7
min				
max				
AUC(0-t) S (-)	9.5±6.6	23.7±10.7	50.4±25.6	85.2±36.4
min				
max				

PK parameter values for different doses for carvedilol, mean±SD. n=12 with exceptions noted in table. The sponsor

CARVEDILOL NDA 20-297

PROTOCOL A9903

did not attempt to calculate half-life for subjects with less than three quantified plasma concentrations from 10 to 24 hours after dose administration. As a result of lost samples and samples with concentrations below the lower limit of quantification (<0.3 ng/mL), there were few subjects contributing data to half-life calculations as indicated below.

Parameter	6.25 mg	12.5 mg	25.0 mg	25 + 12.5 mg
Tmax R (+)	1.58±1.06	1.29±0.7	1.29±0.96	0.96±0.28
minimum				
maximum				
Tmax S (-)	1.17±0.96	1.06±0.66	1.13±0.96	0.79±0.23
min				
max				
Half-life R (+)	5.01±1.1 (n=3)	6.29±2.2 (n=7)	8.13±2.6 (n=9)	9.2±3.9 (n=11)
min				
max				
Half-life S (-)	10.5±6.97 (n=2)	10.51±4.57 (n=5)	10.21±3.85 (n=6)	7.39±2.56 (n=7)
min				
max				
AUC ratio (R/S)*	3.46	3.01	2.64	2.53
min				
max				
Cmax ratio (R/S)*	2.8	2.63	2.57	2.3
min				
max				

AUC(0-t) in ng·hr/mL, Cmax in ng/mL, Tmax in hours, half-life in hours
t = time of last quantified concentration. * = geometric mean

Pharmacodynamic response:

Supine systolic blood pressure SBP (mean±SEM mm Hg), supine diastolic blood pressure DBP (mean±SEM mm Hg), and pulse (mean±SEM beats per minute) in 12 subjects. Time (T) to Emax is in hours. Also shown are responses 12 and 24 hours after the dose administration.

Parameter	6.25 mg	12.5 mg	25.0 mg	25 + 12.5 mg
SBP baseline	116±3	115±2	113±4	114±2
SBP Emax	104±4	103±2	101±3	100±2
SBP T-Emax	4	3	3	2
SBP 12 hour	110±3	117±3	111±2	113±2
SBP 24 hour	114±2	115±2	112±3	115±2
DBP baseline	71±3	69±2	71±2	73±2
DBP Emax	60±2	60±2	60±2	61±2
DBP T-Emax	6	6	6	6
DBP 12 hour	66±2	63±2	63±2	65±2
DBP 24 hour	71±2	72±2	74±2	74±2
Parameter	6.25 mg	12.5 mg	25.0 mg	25 + 12.5 mg
Pulse baseline	66±3	67±5	69±3	68±3

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PROTOCOL A9903

Pulse Emax	64±3	62±4	62±2	62±2
Pulse T-Emax	2.5	0.75	2.5	2.5
Pulse 12 hour	71±3	71±5	70±2	70±2
Pulse 24 hour	66±2	67±5	63±3	66±2

Adverse events:

headache in 6 of 12 subjects

orthostatic lightheadedness in 3/12: 1/12 with BP86/60, 1/12 with BP 78/52

elevated AST (normal 11-29): 1/12 = peaked at 32 and improved during follow-up

1/12 = peaked at 48 and improved during follow-up

elevated ALT (normal 2-27):

1/12 = peaked at 32 and improved during follow-up

1/12 = peaked at 48 and improved during follow-up

Conclusions:

The report does not provide 90% confidence intervals for the dose corrected AUC and Cmax for R(+) carvedilol and for S(-) carvedilol.

Claims of dose proportionality appear to be justified between the doses of 12.5 and 25.0 mg for Cmax and AUC for R(+) carvedilol and for S(-) carvedilol concentrations.

With respect to dose proportionality between doses of 6.25 and 12.5 mg and between doses of 25.0 and 37.5 mg, I would request the guidance of the biopharmaceutics reviewer before I would support a claim for dose proportionality based on this study. Claims in the label regarding dose proportionality will require documentation of bioequivalence of 12.5 and 25.0 mg capsules used in this study and 12.5 and 25.0 mg tablets proposed for the marketplace. The sponsor does not intend to market a 6.25 mg tablet according to the proposed draft label.

The calculations of half-life for R(+) carvedilol and for S(-) carvedilol are not reliable from this study since many subjects were excluded from analysis. When I apply the sponsor's criteria for exclusion from analysis of half-life, I exclude fewer subjects than the sponsor excluded.

Geometric mean AUC(0-t) and Cmax were 2 - 3 times greater for R(+) carvedilol than for S(-) carvedilol.

There is no placebo group with which to compare pharmacodynamic effects. No dose-response relationship was evident for supine SBP, DBP, or pulse.

Other trials addressing stereoselective metabolism include A9901, CAR-SA-01, MF7034, MF7097, F-30. A9911 is ongoing.

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CARVEDILOL NDA 20-297

CARVEDILOL EFFECT ON DIGOXIN PK

Protocol A9904, Vol 1.52

Reviewer: James F. Graumlich

Name of study: A study to assess the effects of the co-administration of a single oral dose of 25 mg carvedilol (SK&F 105517) on the plasma and urinary pharmacokinetics of digoxin after administration of a single oral dose of 0.5 mg digoxin in normal man.

Objectives: To assess the effects of a single oral dose of 25 mg carvedilol on the plasma and urinary pharmacokinetics of a single oral dose of 0.5 mg digoxin.

Study design: Double blind, randomized, placebo controlled, period balanced, 2 period crossover study with single doses in 8 healthy male subjects. Study periods were separated by one week.

Intervention: 1 tablet carvedilol (25 mg) plus 2 tablets of digoxin (0.25 mg)
1 placebo tablet identical to carvedilol plus 2 tablets of digoxin (0.25 mg)
The protocol was modified to decrease digoxin tablets from 3 to 2 tablets.

Response variables:

Primary outcome: digoxin AUC (0-t) calculated with trapezoidal rule

Secondary outcome: digoxin Cmax, Tmax, Ke, AUC (0-∞), AUMC (0-t), AUMC (0-∞), MRT, fractional and total urinary digoxin excretion, BP, pulse

Blood sampling times were at baseline then 0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 6, 8, 12, 24, 36 and 48 hours after dose administration. Urine collection were at: baseline then 0-8, 8-24, 24-36, and 36-48 hours after dose administration.

Supine BP and pulse were measured at baseline then every 10 minutes for 4 hours then every 15 minutes for 4 hours. One-lead ECG was monitored for 8 hours. Twelve-lead ECGs were performed at baseline then 4 and 8 hours after dose administration.

Materials: digoxin 0.25 mg (Lenoxin®, Wellcome)
carvedilol 25.0 mg tablet, formulation 1/25, batch 6
placebo matched to carvedilol

Assay: Plasma digoxin assay was a radioimmunoassay. Limit of quantification for plasma digoxin was 0.07 ng/mL. Urine digoxin assay involved HPLC with ultraviolet detection. Limit of quantification for urine digoxin was 10 ng/mL. The report claims no interaction between the assay and carvedilol or carvedilol metabolites.

Results: Eight healthy male subjects between 23 and 27 years of age and weighing between 65 and 87 kg completed the study.

The table below is from A9904, vol 1.52, page 6: Digoxin PK parameters

Fig 1 from A9904, vol 1.52 page 45 shows the plasma digoxin concentration vs time for the two treatment groups.

Digoxin PK parameters

? Figure 1

Pharmacodynamic response: Treatment means were compared between digoxin + placebo vs digoxin + carvedilol.

- (1) Supine systolic blood pressure: Mean changes from baseline were significantly different and more than 3 mm Hg lower with carvedilol at 1-2, 2-3, and 3-4 hours after the dose (range -5.1 to -5.6 mm Hg difference between the mean change from baseline for placebo and the mean change from baseline for carvedilol).
- (2) Supine diastolic blood pressure: No significant differences.
- (3) Heart rate: No significant differences.

Adverse events: No symptoms were reported. No significant abnormalities of liver function tests (AST, ALT, gamma GT, total bilirubin).

Conclusions:

Concomitant administration of a single oral dose of carvedilol and a single oral dose of digoxin significantly increases the C_{max} and AUC of digoxin. The most likely explanation for the difference is an increase in the systemic bioavailability of digoxin.

No effects on supine diastolic blood pressure or supine heart rate were seen in this trial. Effect on supine systolic blood pressure was small and transient.

I agree with the conclusions of the sponsor with the following exceptions:

- (1) The sponsor speculates that the difference in C_{max} and AUC may result from "either an increase in digoxin's bioavailability and/or a decrease in its clearance." Review of the individual plasma-concentration-vs-time curves does not suggest a change in clearance (see Fig 1, A9904, vol 1.52, page 45). Differences in the elimination rate constant and U₄₈ (the renal excretion in 48 hours) do not appear to be clinically relevant.
- (2) The sponsor states the differences between the treatment groups are not related to assay interference. The sponsor does not provide assay validation data to support this assertion.

CARVEDILOL NDA 20-297

CARVEDILOL EFFECT ON DIGOXIN PK

Protocol A9904, Vol 1.52

Reviewer: James F. Graumlich

Name of study: A study to assess the effects of the co-administration of a single oral dose of 25 mg carvedilol (SK&F 105517) on the plasma and urinary pharmacokinetics of digoxin after administration of a single oral dose of 0.5 mg digoxin in normal man.

Objectives: To assess the effects of a single oral dose of 25 mg carvedilol on the plasma and urinary pharmacokinetics of a single oral dose of 0.5 mg digoxin.

Study design: Double blind, randomized, placebo controlled, period balanced, 2 period crossover study with single doses in 8 healthy male subjects. Study periods were separated by one week.

Intervention: 1 tablet carvedilol (25 mg) plus 2 tablets of digoxin (0.25 mg)
1 placebo tablet identical to carvedilol plus 2 tablets of digoxin (0.25 mg)
The protocol was modified to decrease digoxin tablets from 3 to 2 tablets.

Response variables:

Primary outcome: digoxin AUC (0-t) calculated with trapezoidal rule

Secondary outcome: digoxin C_{max}, T_{max}, K_e, AUC (0-∞), AUMC (0-t), AUMC (0-∞), MRT, fractional and total urinary digoxin excretion, BP, pulse

Blood sampling times were at baseline then 0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 6, 8, 12, 24, 36 and 48 hours after dose administration. Urine collection were at baseline then 0-8, 8-24, 24-36, and 36-48 hours after dose administration.

Supine BP and pulse were measured at baseline then every 10 minutes for 4 hours then every 15 minutes for 4 hours. One-lead ECG was monitored for 8 hours. Twelve-lead ECGs were performed at baseline then 4 and 8 hours after dose administration.

Materials: digoxin 0.25 mg (Lenoxin®, Wellcome)
carvedilol 25.0 mg tablet, formulation 1/25, batch 6
placebo matched to carvedilol

Assay: Plasma digoxin assay was a radioimmunoassay. Limit of quantification for plasma digoxin was 0.07 ng/mL. Urine digoxin assay involved HPLC with ultraviolet detection. Limit of quantification for urine digoxin was 10 ng/mL.

Results: Eight healthy male subjects between 23 and 27 years of age and weighing between 65 and 87 kg completed the study.

The table below is from A9904, vol 1.52, page 6: Digoxin PK parameters

Fig 1 from A9904, vol 1.52 page 45 shows the plasma digoxin concentration vs time for the two treatment groups.

CARVEDILOL NDA 20-297

Digoxin PK parameters

The treatment means (R: [digoxin + placebo], T: [digoxin + carvedilol]), their contrast and related 2-sided 95% confidence interval are detailed here below :

	R	T	T-R	T/R	95% CI
C _{max}	1.62	2.59	0.97		0.20 to 1.73
C(24)	0.23	0.28		1.19	1.10 to 1.27
AUC(0-T)	15.0	17.9		1.19	1.10 to 1.30
AUC(0-i)	25.6	30.7		1.19	0.97 to 1.46
K	.0166	.0170		1.00	0.76 to 1.31
U48	216	188	- 28		-113 to 57

Pharmacodynamic response: Treatment means were compared between digoxin + placebo vs digoxin + carvedilol.

- (1) Supine systolic blood pressure: Mean changes from baseline were significantly different and more than 3 mm Hg lower with carvedilol at 1-2, 2-3, and 3-4 hours after the dose (range -5.1 to -5.6 mm Hg difference between the mean change from baseline for placebo and the mean change from baseline for carvedilol).
- (2) Supine diastolic blood pressure: No significant differences.
- (3) Heart rate: No significant differences.

Adverse events: No symptoms were reported. No significant abnormalities of liver function tests (AST, ALT, gamma GT, total bilirubin).

Conclusions:

Concomitant administration of a single oral dose of carvedilol and a single oral dose of digoxin significantly increases the C_{max} and AUC of digoxin. The most likely explanation for the difference is an increase in the systemic bioavailability of digoxin.

No effects on supine diastolic blood pressure or supine heart rate were seen in this trial. Effect on supine systolic blood pressure was small and transient.

I agree with the conclusions of the sponsor with the following exceptions:

(1) The sponsor speculates that the difference in C_{max} and AUC may result from "either an increase in digoxin's bioavailability and/or a decrease in its clearance." Review of the individual plasma-concentration-vs-time curves does not suggest a change in clearance (see Fig 1, A9904, vol 1.52, page 45). Differences in the elimination rate constant and U48 (the renal excretion in 48 hours) do not appear to be clinically relevant.

(2) The sponsor states the differences between the treatment groups are not related to assay interference. The sponsor does not provide assay validation data to support this assertion.

105517/A9904-GER : MEDIAN VALUES

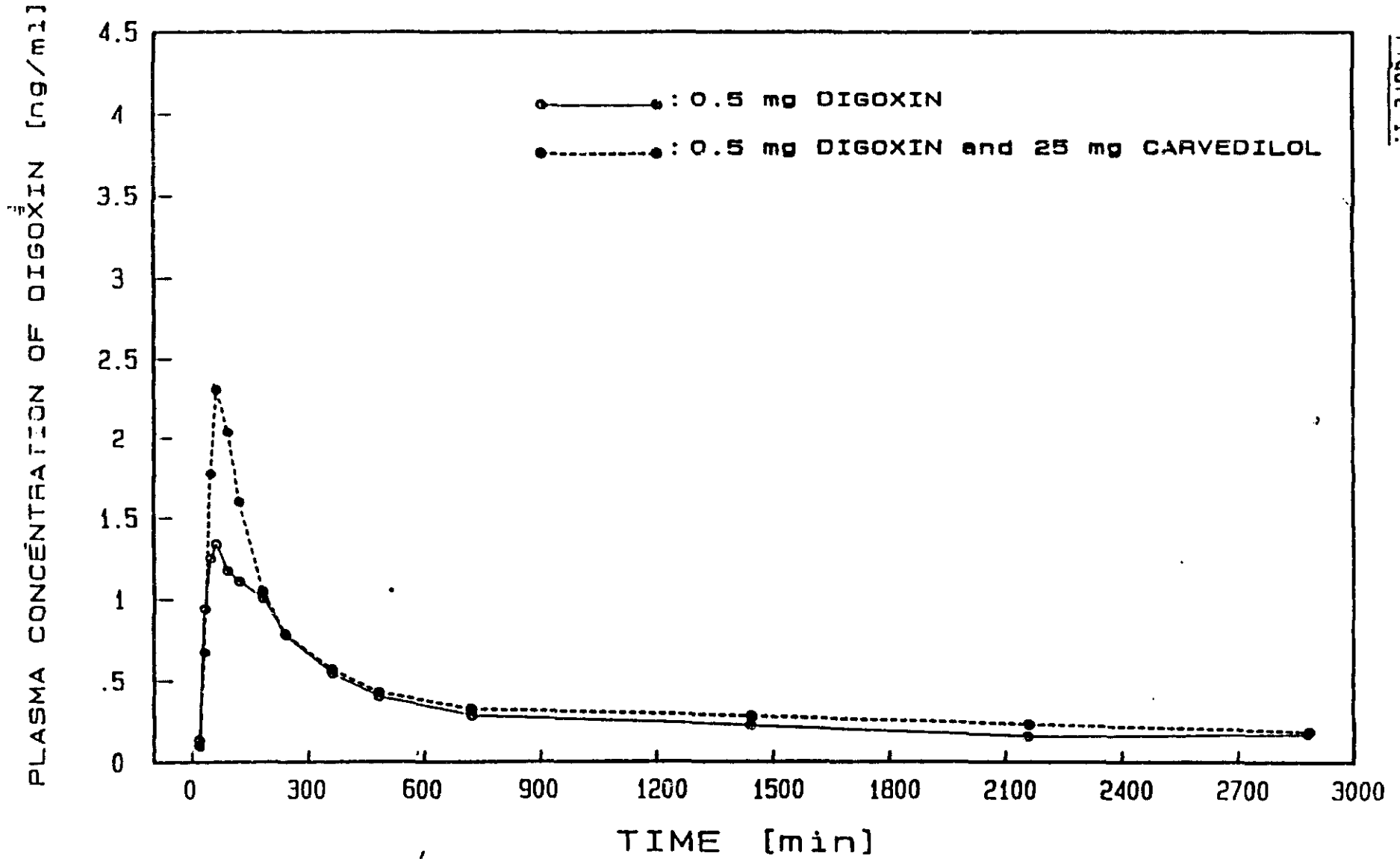


Figure 1:

A9904
Vol 1.5
000045

CARVEDILOL NDA 20-297

CARVEDILOL EFFECT ON DIGOXIN PK

Protocol A9905, Vol 1.52

Reviewer: James F. Graumlich

Name of study: A study to assess the acute effects of the co-administration of a single oral dose of 25 mg carvedilol (SK&F 105517) on the plasma and urinary pharmacokinetics of digoxin after administration of a single intravenous dose of 0.5 mg digoxin in normal man.

Objectives: To assess the effects of a single oral dose of 25 mg carvedilol on the plasma and urinary pharmacokinetics of a single IV dose of 0.5 mg digoxin.

Study design: Double blind, randomized, placebo controlled, period balanced, 2 period crossover study with single doses in 8 healthy male subjects. Study periods were separated by two weeks.

Intervention: 1 tablet carvedilol (25 mg) plus digoxin (0.5 mg IV)
1 placebo tablet identical to carvedilol plus digoxin (0.5 mg IV)

Response variables:

Primary outcome: digoxin AUC (0-t) calculated with trapezoidal rule

Secondary outcome: digoxin C_{max}, T_{max}, K_e, AUC (0-∞), AUMC (0-t), AUMC (0-∞), MRT, CL (total), V_{dss} (calculated), fractional and total urinary digoxin excretion, BP, pulse

Blood sampling times were at baseline then 2, 5, 10, 15, 20, 30, 45 minutes then 1.0, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48 and 72 hours after dose administration. Urine collection were at baseline then 0-8, 8-24, 24-36, and 36-48 hours after dose administration.

Supine BP and pulse were measured at baseline then every 10 minutes for 4 hours then every 15 minutes for 4 hours. One-lead ECG was monitored for 8 hours. Twelve-lead ECGs were performed at baseline then 4 and 8 hours after dose administration.

Materials: digoxin 0.25 mg (Lenoxin®, Wellcome)
carvedilol 25.0 mg tablet, formulation D, batch AAA
placebo matched to carvedilol

Assay: Plasma digoxin assay was a radioimmunoassay. Limit of quantification for plasma digoxin was 0.07 ng/mL. Urine digoxin assay involved HPLC with ultraviolet detection. Limit of quantification for urine digoxin was 10 ng/mL. The report claims no interaction between the assay and carvedilol or carvedilol metabolites.

Results: Eight healthy male subjects between 22 and 31 years of age and weighing between 63 and 92 kg completed the study.

The table below is from A9905, vol 1.52, page 78: Digoxin PK parameters
Figures 1 and 2 from A9905, vol 1.52 pages 125-126 show the plasma digoxin concentration vs time for the two treatment groups.

During the elimination phase, Subject 1 had one unexplained increase in plasma digoxin concentration 30 minutes after treatment with carvedilol. The single value was thought to be spurious and was not included in the analysis.

CARVEDILOL NDA 20-297**Digoxin PK parameters**

The treatment means (R: [digoxin + placebo], T: [digoxin + carvedilol]) and their contrast are detailed here below. Point (PE) and 95% confidence interval (CI) estimates are provided for the true difference of the treatment means (T-R) as based on untransformed data, or the true ratio of the treatment means (T/R) as backtransformed from log-transformed data.

	R	T	Treatment Contrast PE	CI
C _{max}	16.7	17.6	T/R: 1.06	0.93 to 1.20
C(24)	0.29	0.27	T-R: -0.026	-0.054 to 0.002
AUC(0-T)	27.9	26.7	T-R: -1.20	-2.71 to 0.31
AUC(0-24)	19.3	17.8	T-R: -0.50	-1.19 to 0.20
k	.0169	.0152	T/R: 0.89	0.73 to 1.10
U ₄₈	258	246	T/R: 0.95	0.83 to 1.08

Pharmacodynamic response: Treatment means were compared between digoxin + placebo vs digoxin + carvedilol.

- (1) Supine systolic blood pressure: Mean changes from baseline were significantly different and more than 3 mm Hg lower with carvedilol at 2-3, and 4-7 hours after the dose (range -4.1 to -7 mm Hg difference between the mean change from baseline for placebo and the mean change from baseline for carvedilol).
- (2) Supine diastolic blood pressure: No significant differences.
- (3) Heart rate: No significant differences.

Adverse events: No symptoms were reported. No significant abnormalities of liver function tests (AST, ALT, gamma GT, total bilirubin).

Conclusions:

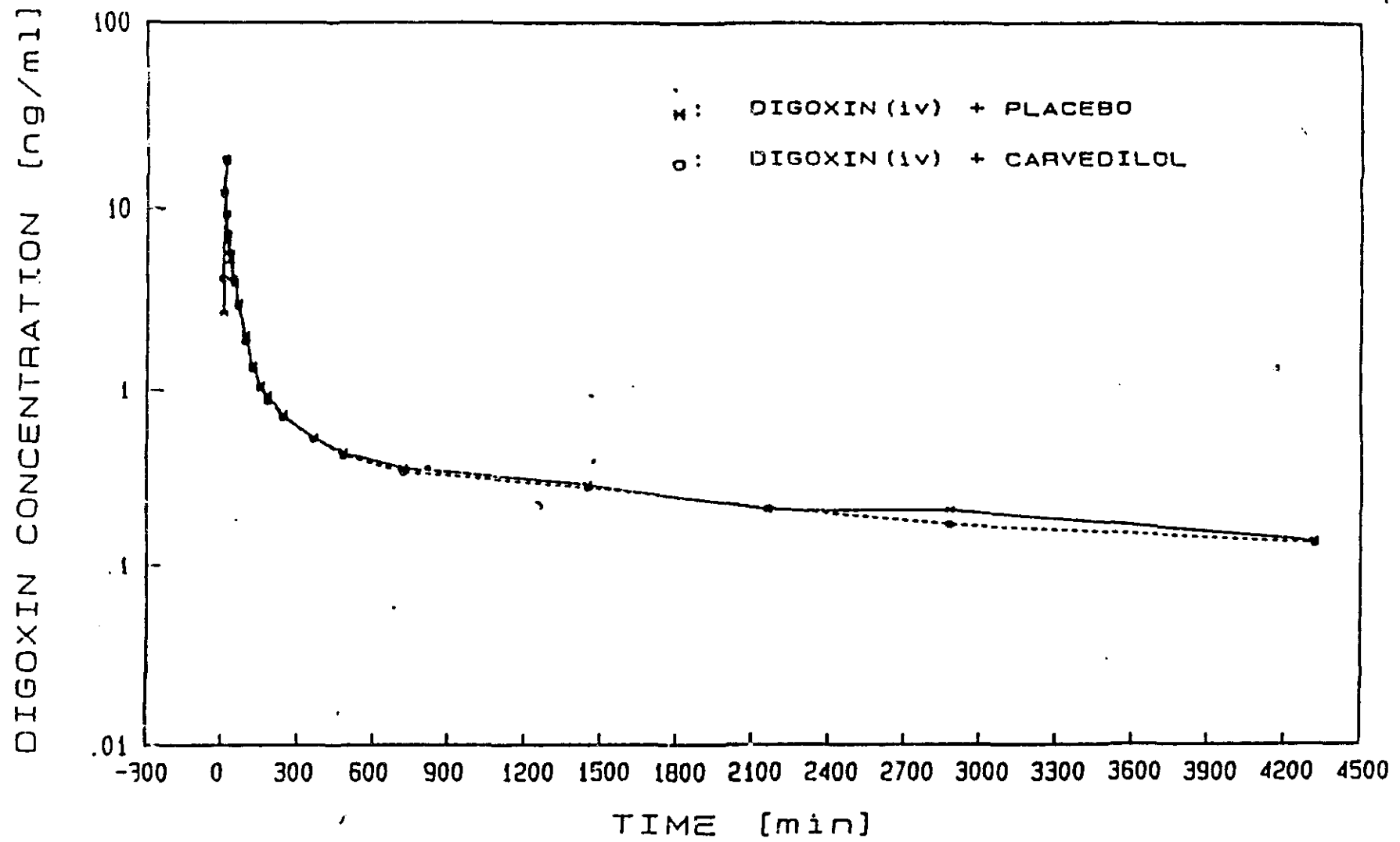
Concomitant administration of a single oral dose of carvedilol and a single IV dose of digoxin did not significantly change digoxin's C_{max}, AUC, k_e, or U₄₈ (renal excretion of digoxin in 48 hours).

Study A9904 showed a significant increase in digoxin's C_{max} and AUC after concomitant single oral doses of digoxin and carvedilol. The most likely explanation for the difference is an increase in the systemic bioavailability of digoxin.

No effects on supine diastolic blood pressure or supine heart rate were seen in this trial. Effect on supine systolic blood pressure was small and transient.

I agree with the conclusions of the sponsor.

105517/A9905-GER : MEDIAN VALUES



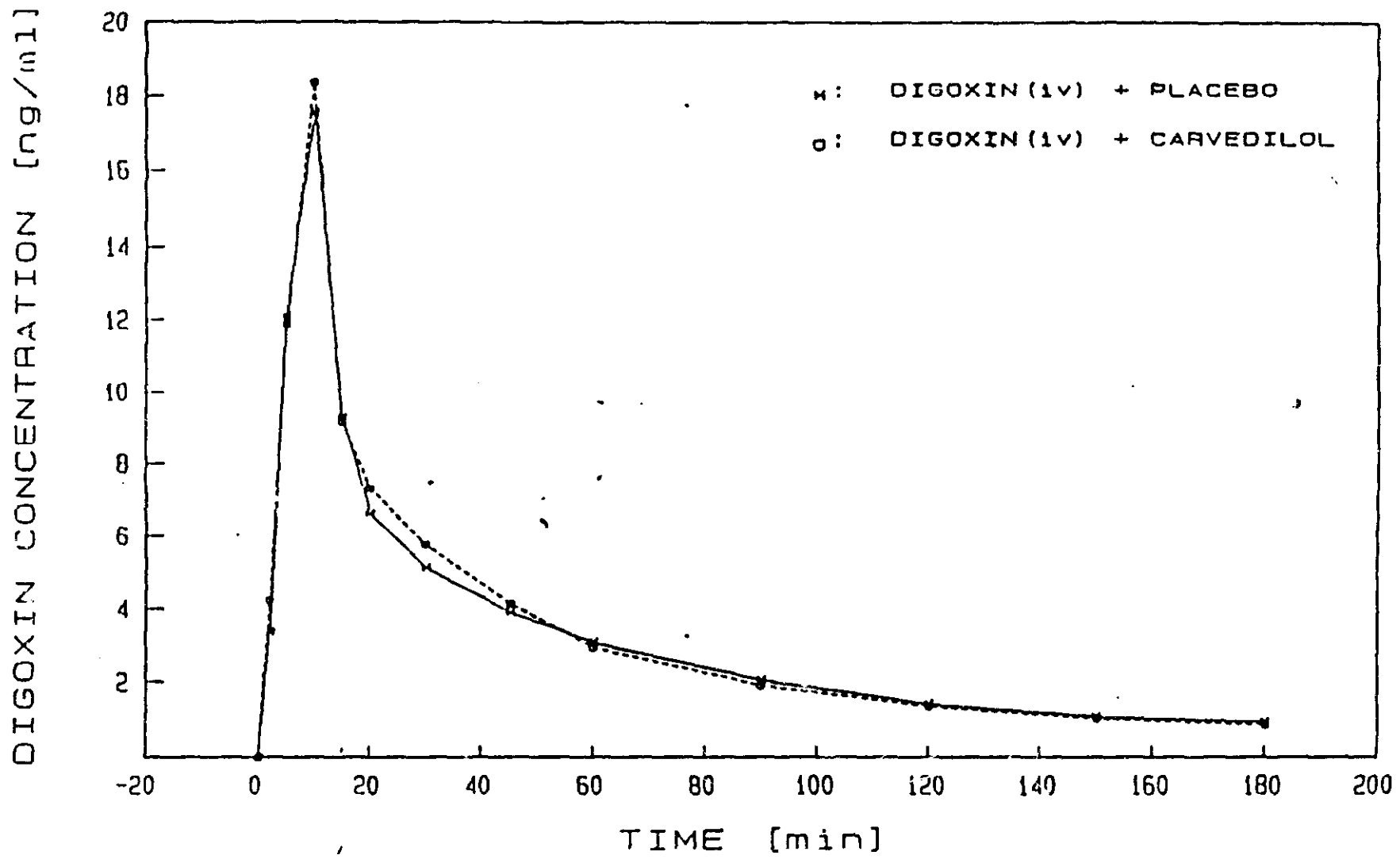
49

000125

C 23

105517/A9905-GER : MEDIAN VALUES

Figure 2:



000126

C 24

CARVEDILOL NDA 20-297

5

FOOD EFFECT ON CARVEDILOL PK

Protocol A9907, Vol 1.52

Reviewer: James F. Graulich

Name of study: A study to assess the acute effects of a standard meal dose on the pharmacokinetics of carvedilol after administration of a single oral dose of 25 mg carvedilol in normal man.

Objectives: To describe and compare the plasma pharmacokinetics of carvedilol after a single oral dose of 25 mg carvedilol either in fasting condition or at the end of a standard meal.

Study design: Open label randomized sequence, period balanced, 2 period crossover study with single doses in 12 healthy subjects. Study periods were separated by 7-14 days. There was no placebo control. Contraceptive medications were permitted.

Intervention: 1 tablet carvedilol (25 mg) with water (controlled for volume) after overnight fast since 10:00 PM
1 tablet carvedilol (25 mg) 5 min after the end of a standard meal that followed an overnight fast since 10:00 PM

Response variables:

Primary outcome: carvedilol AUC (0-t) calculated with trapezoidal rule

Secondary outcome: carvedilol C_{max}, T_{max}, K_e, AUC (0-∞), AUMC (0-t), AUMC (0-∞), MRT, half-life, BP, pulse

Blood sampling times were at baseline then 15, 30, 45 minutes then 1.0, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, and 24 hours after dose administration. There was no urine collection.

Supine BP and pulse were measured at baseline then every 10 minutes for 4 hours then every 15 minutes for 4 hours. One-lead ECG was monitored for 8 hours. No twelve-lead ECGs were performed.

Materials: standard meal (17% protein, 40% fat, 43% carbohydrate)
carvedilol 25.0 mg tablet, Tiltab® formulation IPO#88144, Lot #15444-195

Assay: Plasma carvedilol assay involved solid phase extraction, HPLC with fluorescence detection. The lower limit of quantification for plasma carvedilol was 0.3 ng/mL.

Results: Six male and 6 female healthy subjects between 23 and 32 years of age and weighing between 54 and 82 kg completed the study.

Carvedilol PK parameters are in the attached table.

Pharmacodynamic response: Treatment means were compared between carvedilol + fasting vs carvedilol + fed. There was no placebo group.

(1) Supine systolic blood pressure: Mean changes from baseline were significantly different from baseline during 0 - 2 hours after dose administration. Fed subjects had significantly less fall in SBP than fasted patients. Change from baseline was in the range of +3.5 to +5.2 mm Hg more in fed subjects than in fasted subjects. The difference in effect was at maximum 1 - 2 hours after dose administration.

(2) Supine diastolic blood pressure: Mean changes from baseline were significantly different from baseline during 0 - 1 and 2 - 4 hours after dose administration. Fed subjects had significantly less fall in DBP than fasted patients. Change from baseline was in the range of -3.6 to -4.7 mm Hg more in fed subjects than in fasted subjects. The difference in effect was at maximum 0 - 1 hours after dose administration.

CARVEDILOL NDA 20-297

6

(3) Heart rate: Mean changes from baseline were significantly different from baseline during the first 5 hours after dose administration. Fed subjects had a higher pulse than fasted patients. Change from baseline was in the range of 2.9 to 8 beats per minute greater in fed subjects than in fasted subjects. The difference in effect was at maximum 1 - 2 hours after dose administration.

Adverse events: headache 2/12 subjects
 nausea 2/12 subjects
 elevated ALT = 24 (normal 0-22) in 1/12 subjects
 elevated ALT = 27 (normal 0-17) in 1/12 subjects

Conclusions:

The presence of food delays the absorption of carvedilol. There is a significant increase in carvedilol T_{max} associated with ingestion of food.

Carvedilol C_{max} and systemic bioavailability were minimally different between fasting and fed conditions. The study lacked statistical power to claim bioequivalence in the presence or absence of food.

Half-life was not significantly different in the presence of food.

The extrapolated AUMC(t-∞) had a wide range from 13% to 56% of the AUMC(0-t). The sponsor did not consider MRT for statistical analysis because of this variability.

Food tended to attenuate the systolic blood pressure lowering effect of carvedilol. Food tended to increase the diastolic blood pressure lowering effect of carvedilol. The magnitude of the difference is difficult to assess since the effect of placebo is unknown in this sample of subjects.

The increase in pulse in the fed group was small and not clinically meaningful.

Table

Carvedilol treatment means, point estimates, and 90% confidence intervals are detailed below

	FASTING		FED		POINT ESTIMATE		90% CI	
mean		SD		SD				
Cmax (ng/mL)	53.56	± 27.82	48.35	± 28.31	E/F (note 1)=	0.9	62% to 129%	
	min							
	max							
Tmax (hours)	1.15	± 0.60	2.75	± 2.22	E-F (note 2)=	0.9	0.25 to 2.5	
	min							
	max							
AUC(0-t) (ng*hr/mL)	166.3	± 100.37	171.7	± 81.98	E/F (note 3)=	1.07	89% to 130%	
	min							
	max							
AUC(0-∞) (ng*hr/mL)	174.9	± 105.12	180.7	± 87.82	E/F (note 3)=	1.07	90% to 128%	
	min							
	max							
half-life (hours)	7.1	± 1.97	5.9	± 1.17	E-F (note 1)=	-67.3	-2.3 to 0.04	
	min							
	max							
MRT (hours)	6.3	± 1.57	7.0	± 2.75				
	min							
	max							

- note 1: parametric analysis of untransformed data
- note 2: non-parametric analysis of medians, not means
- note 3: parametric analysis of log-transformed data

CARVEDILOL NDA 20-297

PROTOCOL A9908 VOL 1.52

BIOEQUVALENCE

Reviewer: James F. Graumlich

Name of study: A study in healthy volunteers to assess the in vivo bioequivalence of two granulation processes for 25 mg carvedilol tablets

Objectives: To describe and compare the pharmacokinetics of plasma carvedilol after administration of an investigational 25 mg formulation relative to the administration of the same dose by the standard product.

Study design: Open label, randomized sequence, 4 period crossover study with two administrations of each formulation given as single doses in 12 healthy male and female subjects. There was no placebo group. Study periods were separated by one week.

Response variables: Primary outcome: AUC (trapezoidal method)
Secondary outcome: Cmax, Tmax, ke, half-life, BP, pulse

Blood sampling times: baseline then 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3, 3.5, 4, 6, 9, 12 and 24 hours after dose administration. Supine BP and heart rate were measured at baseline then every 10 minutes for 4 hours then every 15 minutes for the next 4 hours.

Materials: reference: carvedilol 25 mg capsule, 1/25 batch 8, BPBR 1450
test: carvedilol 25 mg capsule, 1/25 batch 4, BPBR 1449

Assay: Carvedilol assay involved HPLC with fluorescence detection. The lower limit of quantification for carvedilol was 0.3 ng/mL.

Results: Six male and 6 female healthy subjects between 21 and 31 years of age and weighing between 46 and 85 kg completed the study. Three of 6 women were taking oral contraceptives.

PK parameter values for 2 formulations of carvedilol (n=12) from pages 327-328, vol 1.52

Parameter	Reference	Test	Ratio	90% CI	90% CI
			T/R	lower	upper
AUC (ng*hr/mL)			100.7	89.4	112
mean	218.60	220.12			
min					
max					
Cmax (ng/mL)			101.4	86.4	116.4
mean	57.67	58.49			
min					
max					
Tmax (hr)					
mean	1.5	1.7			
min					
max					

Pharmacodynamic response:

The mean of responses in one hour were reported. The sponsor did not calculate the difference between the mean baseline response and the mean response at specific times after dose administration. There was no placebo response to compare in this study. Lunch was consumed 4 hours after dose administration.

Supine heart rate: The mean of responses for each of the first eight hours after dose administration did not show meaningful changes from baseline. During 8 hours of observation after dose administration, the lowest heart rate mean was 51 and the highest mean was 81 beats per minute. Heart rate increased after the subjects ate lunch.

Supine diastolic blood pressure: The difference between the mean at baseline and the mean of the maximum decrease from baseline was 10 mm Hg. The maximum decrease occurred 5-6 hours after dose administration. During 8 hours of observation after dose administration, the lowest mean was 38 mm Hg. The highest mean was 80 mm Hg. Since E_{max} occurred after the subjects ate lunch, the effect of the drug is questionable.

Supine systolic blood pressure: The difference between the mean at baseline and the mean of the maximum decrease from baseline was 7 mm Hg. The maximum decrease occurred 1-3 hours after dose administration. During 8 hours of observation after dose administration, the lowest mean was 84 mm Hg. The highest mean was 133 mm Hg. SBP had an upward trend after the subjects ate lunch.

Adverse events:

headache 1/12 subjects
vomit 1/12
malaise 1/12
orthostatic lightheadedness in 1/12 with BP 90/62

decreased WBC in 2 of 12 subjects: 4.31 in 1/12, 3.51 in 1/12 (normal 4.6-6.2)
decreased hemoglobin in 4 of 12 subjects: 13.5 in 1/12, 10.6 in 1/12, 11.7 in 1/12, 12.4 in 1/12 (normal 14-18)
elevated potassium in 3 of 12 subjects who had no concomitant elevation of LDH: 7.1 in 1/12, 7.3 in 1/12, 11.2 in 1/12 (normal 3.5-5.5)
No AST, ALT, gamma GT abnormalities

Conclusions:

The report does not provide calculations for half-life or k_e .

The two formulations were bioequivalent.

Side effects were noted above.

There is no placebo group with which to compare pharmacodynamic effects.

NDA 28297

5 OF 11

BIOEQUIVALENCE

Reviewer: James F. Graumlich

Name of study: A study in healthy volunteers to assess the in vivo bioequivalence of two 25 mg carvedilol formulations (SK&F 105517).

Objectives: To demonstrate the bioequivalence of a 25 mg carvedilol tablet formulation relative to a 25 mg carvedilol capsule formulation in healthy subjects.

Study design: Open label, randomized sequence, 4 period crossover study, single dose per period, two periods with same formulation, in 16 healthy male subjects. There was no placebo group. Study periods were separated by one week.

Response variables: Primary outcome: AUC (trapezoidal method)
Secondary outcome: Cmax, Tmax, ke, half-life, BP, pulse

Blood sampling times: baseline then 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3, 4, 6, 8, 10, 12 and 24 hours after dose administration. Supine BP and heart rate were measured at baseline then 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3, 4, 6, 8, 10, and 12 hours after dose administration.

Materials: reference: carvedilol 25 mg capsule, IPO#88083, LOT 82046940 Lh
test: carvedilol 25 mg tablet, IPO#90022 1/25 batch 4, process BPBR 1449

Assay: Carvedilol assay involved liquid/liquid extraction from plasma then HPLC with fluorescence detection. The lower limit of quantification for carvedilol was 0.3 ng/mL.

Results: Seventeen male healthy subjects between 23 and 39 years of age and weighing between 67 and 89.2 kg enrolled in the study. One subject withdrew after study day 2 because of a schedule conflict. The plasma concentrations of the subject who withdrew resembled the other subjects. Half-life calculations were not done by the sponsor.

PK parameter values for 2 formulations of carvedilol (n=16) from A9910, vol 1.53, page 16.

The mean AUC and Cmax values and median Tmax values along with the range of individual values are presented below:

	AUC (ng*hr/ml)	Cmax (ng/ml)	Tmax (hr)
<u>Capsule</u>			
First Administration	246.1	60.1	2.2
Repeat Administration	266.3	73.1	2.0
<u>Tablet</u>			
First Administration	213.9	48.8	2.6
Repeat Administration	213.8	41.9	2.3

Point estimates of ratios and differences and 90% confidence intervals from A9910, vol 1.53, page 17.

The point estimates and the 90% confidence intervals for the estimate of the true ratio (tablet/capsule) of AUC, C_{max} and the difference (tablet/capsule) of T_{max} medians were:

AUC (log-transformed)	
Mean Ratio:	82.0%
90% confidence Interval:	76.1% to 88.4%
C _{max} (log-transformed)	
Mean Ratio:	63.7%
90% confidence Interval:	53.4% to 76.1%
T _{max} (non-parametric)	
Median of Differences:	0.44
90% Confidence Interval:	0.25 to 0.88

Pharmacodynamic response:

The sponsor did NOT calculate the difference between the mean baseline response and the mean response at specific times after dose administration. There was no placebo response to compare in this study. Meals were consumed 4 and 9 hours after dose administration.

All values in the table are supine values. All blood pressure is in mm Hg. Pulse is in beats per minute. SBP = systolic blood pressure. DBP = diastolic blood pressure. E_{max} = maximum effect. T-E_{max} = time in hours after dose administration when maximum effect occurred. 24 hr = response 24 hours after dose administration.

	25 mg Capsule	25 mg Tablet
SBP, baseline	114±12	114±11
SBP, E _{max}	101±10	103±11
SBP, T-E _{max}	1.75	1.25
SBP, 24 hr	109±10	108±9
DBP, baseline	71±10	71±8
DBP, E _{max}	62±9	63±7
DBP, T-E _{max}	6	6
DBP, 24 hr	70±7	69±8
Pulse, baseline	64±9	66±7
Pulse, E _{max}	58±8	59±7
Pulse, T-E _{max}	4	2.5
Pulse, 24 hr	66±10	62±8

CARVEDILOL NDA 20-297

PROTOCOL A9910 VOL 1.53

Adverse events:

headache 3/17 subjects

nausea 1/17

dizzy 1/17

orthostatic lightheadedness in 2/17: no orthostatic vital signs recorded

lowest supine BP 82/52 with pulse 42 in one symptomatic subject

lowest supine BP 102/66 with pulse 64 in other symptomatic subject

diarrhea 2/17

dry skin 1/17

elevated AST (normal 11-29): peak 45 then returned to normal

Conclusions:

The report does not provide calculations for half-life or k_e .

The two formulations were **NO**, bioequivalent.

Side effects were noted above.

There is no placebo group with which to compare pharmacodynamic effects.

CARVEDILOL NDA 20-297

PROTOCOL A9912 VOL 1.53

BIOEQUIVALENCE

Reviewer: James F. Graumlich

Name of study: A study in healthy male volunteers to assess the in vivo bioequivalence of two 25 mg carvedilol formulations (SK&F 105517).

Objectives: To demonstrate the bioequivalence of a 25 mg carvedilol tablet Tiltab® formulation relative to a 25 mg carvedilol capsule formulation in healthy subjects.

Study design: Open label, randomized sequence, 4 period crossover study, single dose per period, two periods with same formulation, in 20 healthy male subjects. There was no placebo group. Study periods were separated by one week.

Response variables: Primary outcome: AUC (trapezoidal method)
Secondary outcome: Cmax, Tmax, ke, half-life, BP, pulse

Blood sampling times: baseline then 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3, 4, 6, 8, 10, 12 and 24 hours after dose administration. Supine BP and heart rate were measured at baseline then 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3, 4, 6, 8, 10, and 12 hours after dose administration.

Materials: reference: carvedilol 25 mg capsule, IPO#88083, LOT not specified
test: carvedilol 25 mg tablet Tiltab®, IPO#90122 Lot not specified

Assay: Carvedilol assay involved extraction (not specified) from plasma then reverse-phase HPLC with fluorescence detection. The lower limit of quantification for carvedilol was 0.3125 ng/mL.

Results: Twenty male healthy subjects between 22 and 44 years of age and weighing between 57.7 and 91.0 kg completed the study. Half-life calculations were not done by the sponsor.

PK parameter values for 2 formulations of carvedilol (n=20) are in Table 1 on next page. The difference between the medians for Tmax was 0.0 hours (90% confidence interval -0.3, 0.25).

Pharmacodynamic response:

The sponsor did NOT calculate the difference between the mean baseline response and the mean response at specific times after dose administration. There was no placebo response to compare in this study. Meals were consumed 4 and 9 hours after dose administration. See responses in Table 2 on next page.

Table 1

Parameter	Reference	Test	Ratio	90% CI	
	25 mg capsule	25 mg Tiltab®		T/R	lower
AUC (ng*hr/mL)			99.1	92.28	106.44
mean	254.30	257.10			
SD	123.8	147.7			
min					
max					
Cmax (ng/mL)			103.46	91.75	116.65
mean	62.51	67.30			
SD	28.7	37.3			
min					
max					
Tmax (hr)					
mean	1.4	1.4			
SD	0.8	1.0			
min					
max					

Table 2

All values in the table are supine values. All blood pressures in mm Hg. Pulse is in beats per minute. SBP = systolic blood pressure. DBP = diastolic blood pressure. Emax = maximum effect. T-Emax = time in hours after dose administration when maximum effect occurred. 12 hr = response 24 hours after dose administration.

	25 mg Capsule 1st, 2nd administration	25 mg Tiltab® 1st, 2nd administration
SBP, baseline	119±7, 116±9	117±11, 117±9
SBP, Emax	105±13, 102±7	103±9, 104±9
SBP, T-Emax	1.25, 2.5	2.5, 2
SBP, 12 hr	116±11, 112±11	112±8, 109±10
DBP, baseline	72±7, 69±7	69±8, 70±8
DBP, Emax	59±8, 60±12	60±9, 60±8
DBP, T-Emax	3, 3	4, 8
DBP, 12 hr	67±9, 64±7	65±8, 62±7
Pulse, baseline	67±12, 66±12	62±11, 66±10
Pulse, Emax	56±9, 56±8	57±9, 57±7
Pulse, T-Emax	3, 2.5	3, 2.5
Pulse, 12 hr	65±10, 64±9	64±11, 67±9

CARVEDILOL NDA 20-297

PROTOCOL A9912 VOL 1.53

Adverse events:

no orthostatic vital signs recorded

headache 10/20 subjects

subject J-161-90 became lightheaded, diaphoretic, and pale with BP 75/42. He was treated with saline infusion. His AUC was the fourth highest.

chest tightness (no ECG mentioned): 1/20

excess bleeding when IV removed: 1/20

constipation: 1/20

The following table comes from A9912, vol 1.53, page 142.

The number of clinically significant changes in blood pressure and heart rate are summarized as follows (n = 20 for each regimen):

<u>Parameter</u>	<u>First Capsule</u>	<u>Second Capsule</u>	<u>First 'Tiltab'</u>	<u>Second 'Tiltab'</u>
Systolic > -30 (mmHg)	5	1	4	0
Diastolic > -20 (mmHg)	10	6	3	3
HR < 35 or > 120 (bpm)	0	0	0	0

decreased HGB (normal 13.5-17.2): dropped to 12.3

decreased HGB (normal 13.5-17.2): dropped to 12.1

elevated AST (normal 11-29): peak at 41 then returned to baseline

elevated AST (normal 11-29): peak at 85 then returned to normal

elevated ALT (normal 2-27): peak at 46 then returned to normal

elevated ALT (normal 2-27): peak at 77 then returned to normal

elevated ALT (normal 2-27): peak at 60 then returned to baseline

Conclusions:The report does not provide calculations for half-life or k_e .

The two formulations were bioequivalent.

Side effects were noted above.

There is no placebo group with which to compare pharmacodynamic effects.

This study contrasts with A9902 which failed to demonstrate bioequivalence. The sponsor claims a switch from _____ contributed to the difference in the study outcomes. This hypothesis is unproven.

CARVEDILOL NDA 20-297

PROTOCOL CAR-SA-01 VOL 1.54

PD and STEREOSELECTIVE PK

Reviewer: James F. Graumlich

Name of study: Carvedilol: effects on left ventricular contractility and myocardial oxygen consumption in hypertensive patients with systolic dysfunction

Objectives: Measure the effect of carvedilol on left ventricular contractility, myocardial oxygen consumption

Study design: Open label, uncontrolled, single dose study in 10 patients (all black South Africans) with hypertension and mild left ventricular dysfunction determined by right heart catheterization. Prior to therapy with carvedilol, incremental doses of nitroprusside (starting at 0.125 $\mu\text{g}/\text{kg}/\text{min}$) were given until systolic blood pressure fell to 120 mm Hg, or mean aortic pressure fell to 80 mm Hg, or systolic or mean blood pressure fell by 40 mm Hg, or heart rate increased by ≥ 10 beats per minute. After recording hemodynamic results with nitroprusside, the nitroprusside was discontinued. After hemodynamic variables returned to baseline, patients received carvedilol. Other antihypertensive medications were prohibited.

Intervention: carvedilol 25 mg tablet po single dose (racemic carvedilol)

Response variables: Primary outcome: heart rate, cardiac index

Secondary outcome: R(+) and S(-) carvedilol concentrations in plasma, C_{max} , T_{max} , pulmonary capillary wedge pressure, mean aortic pressure, mean pulmonary artery pressure, systemic vascular resistance, circumferential stress, stroke volume, velocity of shortening, myocardial oxygen consumption, lab safety tests

Hemodynamic responses were measured with a right pulmonary artery catheter, coronary sinus catheter, and femoral artery catheter. Hemodynamic sampling times were at baseline then 0.5, 1, 1.5, 2, 2.5, and 3 hours after carvedilol administration. Plasma samples for carvedilol concentration were obtained at the same times as hemodynamic samples.

Materials: 25 mg carvedilol tablet (racemic carvedilol)

Assay: Plasma assay of R(+) and S(-) carvedilol involved liquid/liquid extraction, GTC derivatization, HPLC with fluorometric detection. The lower limit of quantification was 1 ng/mL for S(-) carvedilol and 2 ng/mL for R(+) carvedilol.

Results: 10 patients (7 men and 3 women) between 27 and 64 years of age completed the study. There were no dropouts. Weights of subjects were between 48.5 and 81 kg.

9 of 10 patients took furosemide during the study. There were protocol violations by investigators during the infusion of nitroprusside.

Pharmacodynamic response:

The nitroprusside hemodynamic data were used in a linear regression of wall stress versus rate-corrected velocity of fiber shortening. Carvedilol-induced deviations from this regression represented changes independent of heart rate or afterload. Means for all subjects were compared to baseline.

At baseline immediately before carvedilol, the patients had elevated mean aortic pressure, pulmonary capillary wedge pressure, mean pulmonary artery pressure, systemic vascular resistance.

At baseline immediately before carvedilol, the patients had normal heart rate, right atrial pressure, cardiac index.

The following variables changed more than 10% from baseline during 3 hours of observation after carvedilol therapy.

CARVEDILOL NDA 20-297

PROTOCOL CAR-SA-01 VOL 1.54

Mean aortic pressure (see table, page C39): The mean time to maximum change was 99 ± 53 minutes

Mean pulmonary capillary wedge pressure (see table, page C39): The mean time to maximum change was 63 minutes

Mean right atrial pressure (see table, page C39): The mean time to maximum change was 90 ± 62 minutes

Mean cardiac output and cardiac index (see table, page C39): The mean time to maximum change was 114 ± 64 minutes

Mean myocardial oxygen consumption (see table, page C39): The mean time to maximum change was 99 ± 38 minutes

The following variables changed less than or equal to 10% from baseline during 3 hours of observation after carvedilol therapy.

mean ejection time	mean heart rate
mean pulmonary artery pressure	mean systemic vascular resistance (SVR)
mean stroke volume	mean velocity of shortening
mean percent shortening	mean circumferential wall stress
mean meridional wall stress	

There was a large amount of variability of response to carvedilol.

Following carvedilol therapy, 5 patients had increased SVR and 5 patients had decreased SVR.

Plasma concentrations of R(+) carvedilol and S(-) carvedilol did not correlate with hemodynamic variables. Subjects 8 and 10 had no quantifiable R(+) carvedilol or S(-) carvedilol in their plasma.

PK parameters for carvedilol are presented below

Parameter	R(+) carvedilol n = 8	S(-) carvedilol n = 8
Cmax (ng/mL)		
mean	23.99	10.06
SD	21.18	9.92
minimum		
maximum		
Tmax (minutes)		
mean	140	140
SD	43	43
minimum		
maximum		

Adverse events: There were no deaths nor withdrawals. Due to the design of the study, delayed adverse events from nitroprusside are indistinguishable from events caused by carvedilol. Treatment emergent symptoms and signs were

1/10 ventricular trigeminy	2/10 nausea	1/10 vomiting
1/10 dizziness	1/10 diarrhea	4/10 decreased hemoglobin

CARVEDILOL NDA 20-297

PROTOCOL CAR-SA-01 VOL 1.54

Conclusions:

Nitroprusside served as active control in this study. All subjects had a decrease in aortic systolic and diastolic blood pressure (minimum change defined in study design) as a response to nitroprusside.

Carvedilol decreased mean aortic pressure, decreased pulmonary capillary wedge pressure, decreased cardiac output, decreased myocardial oxygen consumption, and increased right atrial pressure.

Carvedilol did not demonstrate a consistent effect on systemic vascular resistance.

Mean C_{max} values of R(+) carvedilol and S(-) carvedilol in these patients were 2 - 3 fold lower than C_{max} values achieved in healthy volunteers.

Mean T_{max} for R(+) carvedilol and S(-) carvedilol in these patients was 1.8 times longer than mean T_{max} in healthy volunteers.

Orthostatic hypotension was not assessed with this protocol.

Plasma concentrations of R(+) carvedilol and S(-) carvedilol did not correlate with hemodynamic variables.

There was no placebo group with which to compare pharmacodynamic responses.

The results of this study must be interpreted in the context of a single dose, open label study.

Table 2

**EFFECT OF CARVEDILOL ON HEMODYNAMIC VARIABLES IN HYPERTENSIVE
PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION (N=10)**
Baseline Values, Maximum Change, % Maximum Change
Mean (SD)
(Appendixes 10 and 12)

<u>VARIABLE</u>	<u>BASELINE</u>	<u>MAXIMUM CHANGE</u>	<u>MAXIMUM % CHANGE</u>
Ejection time (sec)	0.257 (0.027)	-0.012 (0.019)	-4 (7)
Heart Rate (bpm)	79 (14)	-4 (14)	-3 (19)
Mean Aortic Pressure (mmHg)	125 (9)	-14 (14)	-11 (11)
Pulmonary Capillary Wedge Pressure (mmHg)	12.3 (5.2)	-1.3 (4.8)	-12 (43)
Right Atrial Artery Pressure (mmHg)	7.3 (5.9)	1 (5)	40 (78)
Mean Pulmonary Artery Pressure (mmHg)	31 (12)	0 (11)	4 (35)
Systemic Vascular Resistance (dyne/sec/cm ⁻⁵)	2110 (402)	110 (521)	4 (24)
Cardiac Output (L/min)	4.53 (0.56)	-1 (1)	-12 (16)
Cardiac Index (l./min/m ²)	2.66 (0.42)	-0.29 (0.42)	-12 (16)
Stroke Volu	59.3 (12.4)	-3.2 (10.9)	-6 (19)
Myocardial Oxygen Consumption (ml/min)	9.92 (2.86)	-1.3 (2.15)	-13 (18)
Velocity of Shortening (circ/secX100)	52.2 (10.1)	-0.8 (8.7)	0 (19)
Percent Shortening (%)	15.2 (3.1)	-0.7 (2.6)	-3 (19)
Circumferential Wall Stress (gm/cm ²)	283 (51)	-26 (60)	-10 (22)
Meridional Wall Stress (gm/cm ²)	123 (29)	-10 (30)	-10 (25)

Reviewer: James F. Graumlich

CAR-UK-106 is a dose escalation design with double-blind, random-sequence placebo. Treatments were single doses of carvedilol 12.5 mg, 25 mg, 50 mg and placebo. Treatments were separated by one week. Efficacy measurements made for 24 hours after each treatment were pulse, BP, aortic doppler stroke distance (proportional to stroke volume), aortic doppler peak velocity, aortic doppler flow time, aortic doppler acceleration, forearm blood flow (venous occlusion plethysmography). Significant differences in these parameters were not defined a priori. The objective was to assess the relative contribution of vasodilation produced by carvedilol and its effect on myocardial contractility. Subjects were 8 healthy men. One subject experienced nausea and palpitations after 25 mg carvedilol and withdrew from the study. Other treatment-emergent symptoms were postural hypotension (BP changes not specified) after 25 mg carvedilol in 2 subjects. Other symptoms were headache and nausea. In one subject, T. bili (normal 0-20) rose from 17 (pre-study) to 38 on carvedilol 50 mg.

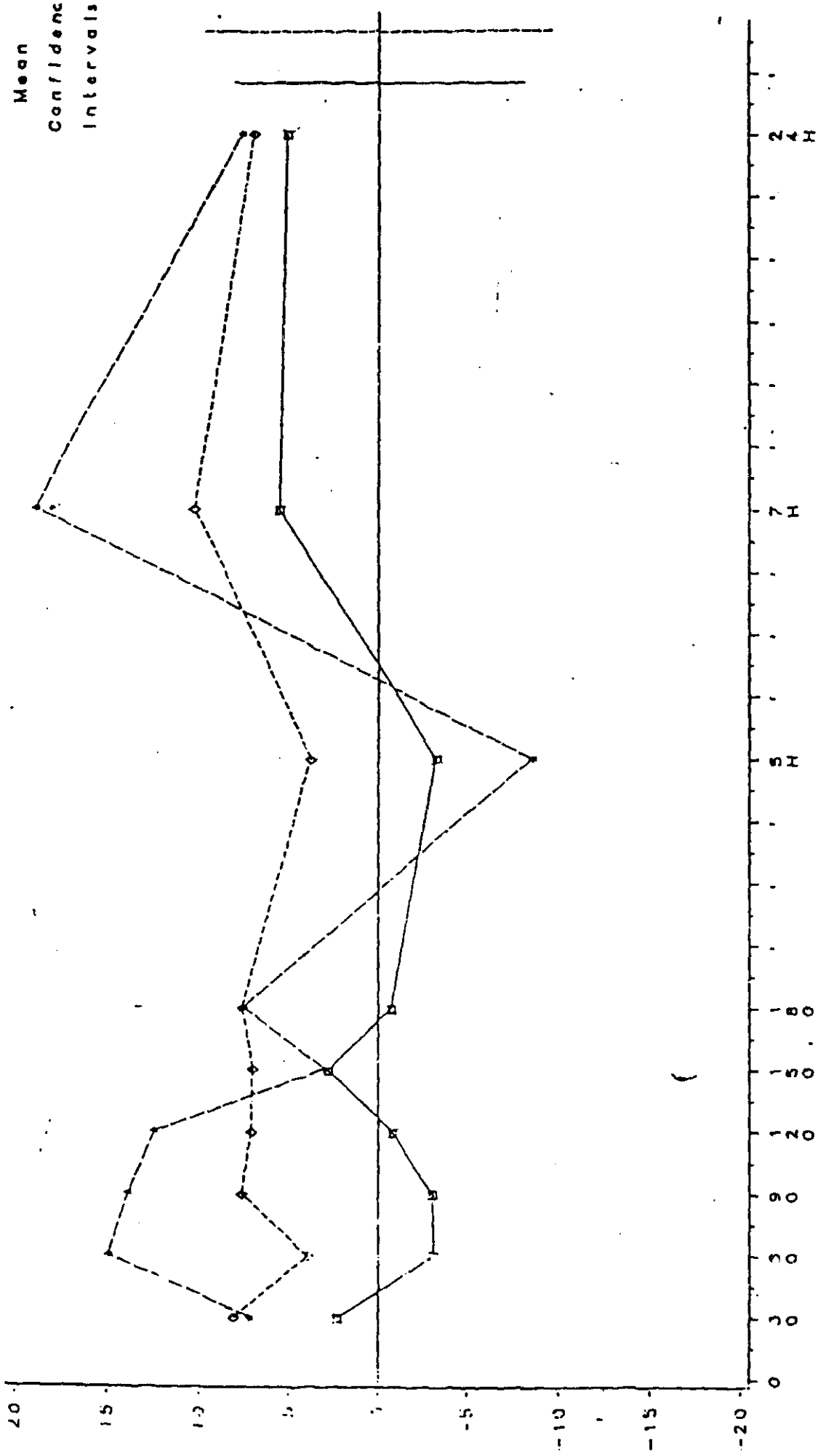
The report does not contain efficacy data for individual subjects.

Figure 4, page 98, volume 1.114, shows systolic blood pressure changes from baseline. The effect of carvedilol on SBP was inconsistent over 24 hours. Figure 5, page 99, volume 1.114, shows diastolic blood pressure effects were not clinically meaningful. Heart rate (Figure 6, page 100, volume 1.114) was significantly decreased between 5 and 7 hours after carvedilol 50 mg. Stroke distance (Figure 7, page 101, volume 1.114) was significantly decreased between 0.5 and 24 hours after carvedilol 50 mg. Other doses did not significantly change stroke distance. Minute distance (Figure 8, page 102, volume 1.114) was significantly decreased between 2 and 24 hours after carvedilol 50 mg. Peak velocity (Figure 9, page 103, volume 1.114) was significantly decreased between 0.5 and 24 hours after carvedilol 50 mg. Changes of mean acceleration (Figure 10, page 104, volume 1.114) were inconsistent among the doses of carvedilol. Corrected flow time (Figure 12, page 106, volume 1.114) was significantly decreased between 5 and 24 hours after carvedilol 50 mg. The index of systemic vascular resistance (Figure 13, page 107, volume 1.114) was significantly increased between 5 and 24 hours after carvedilol 50 mg.

Conclusions: In these healthy men, non-invasive tests showed carvedilol 50 mg decreased heart rate, decreased stroke volume (stroke distance), decreased peak velocity, and increased systemic vascular resistance. These changes are not consistent with carvedilol's putative role as an alpha blocker. It is difficult to predict if these changes are clinically meaningful.

SYSTOLIC BLOOD PRESSURE (MMHG)
 (Changes from Baseline)

FIGURE 4



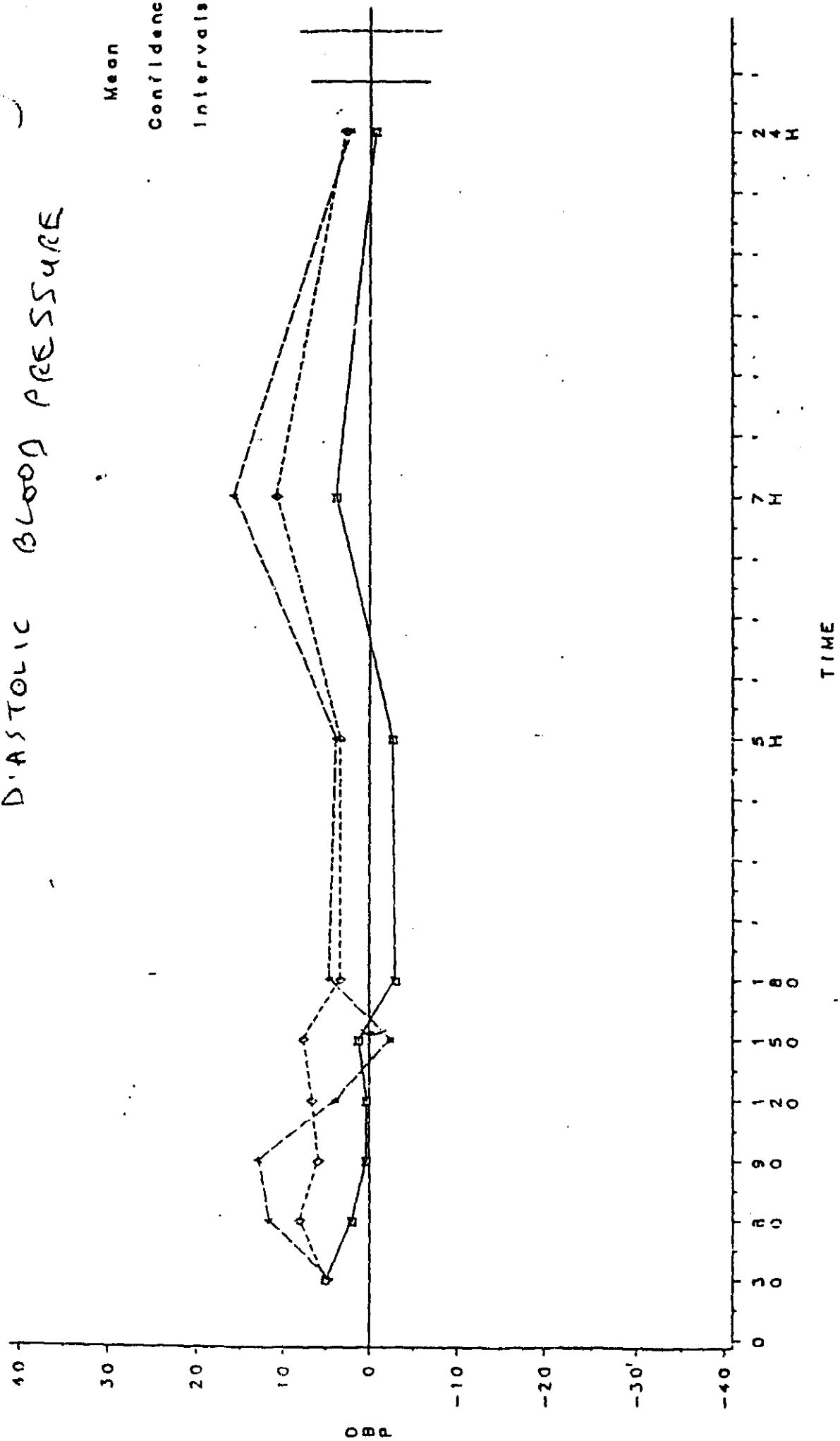
-□- 12.5MG CARVEDILOL - PLACEBO
 -◇- 25MG CARVEDILOL - PLACEBO
 -△- 50MG CARVEDILOL - PLACEBO

FIGURE 3

Change from Baseline

DIASTOLIC BLOOD PRESSURE

Mean
Confidence
Intervals

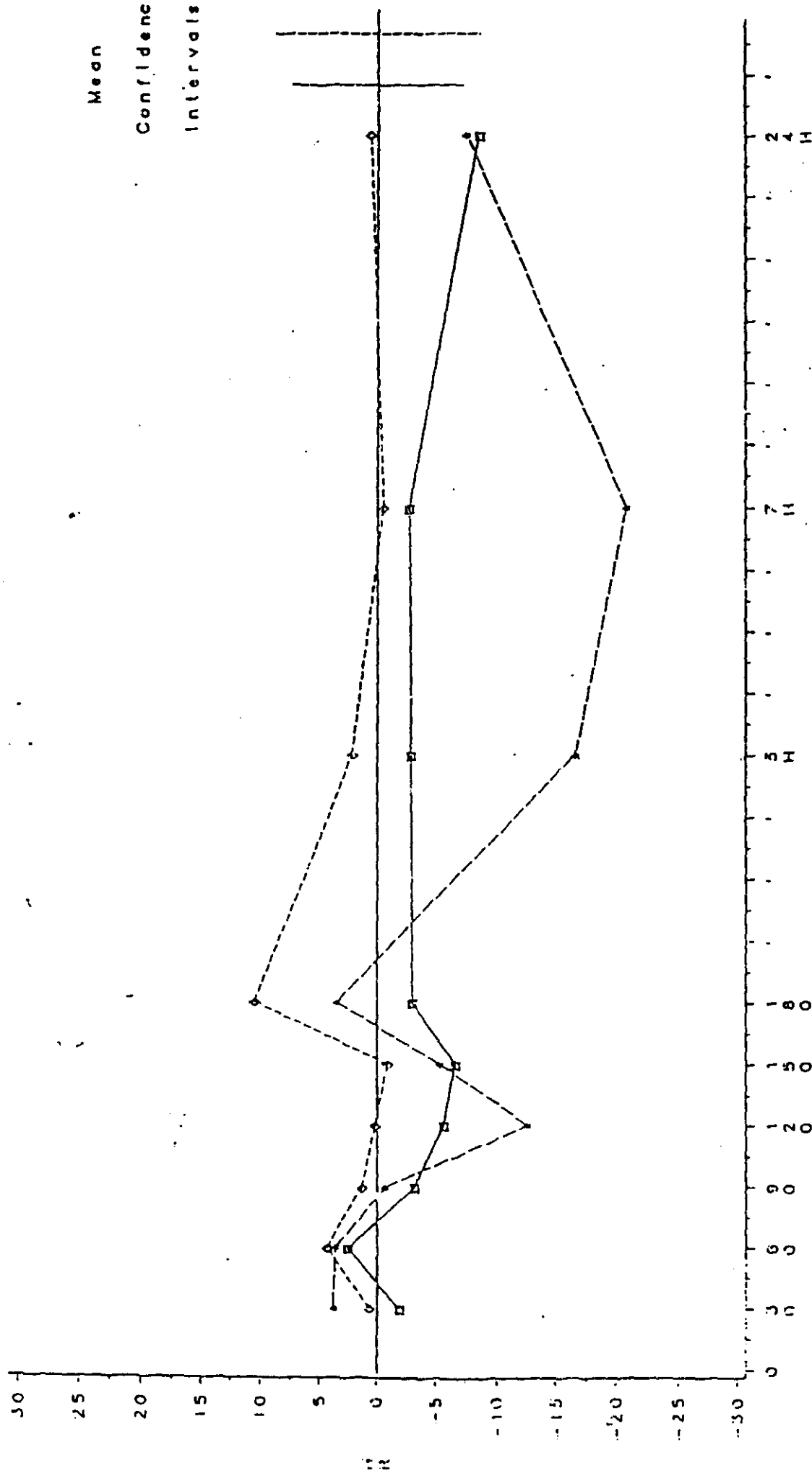


-□- 12.5MG CARVEDILOL - PLACEBO
 -○- 25MG CARVEDILOL - PLACEBO
 -△- 50MG CARVEDILOL - PLACEBO

000099

C42

HEART RATE (BEATS/MIN) (Change from Baseline)



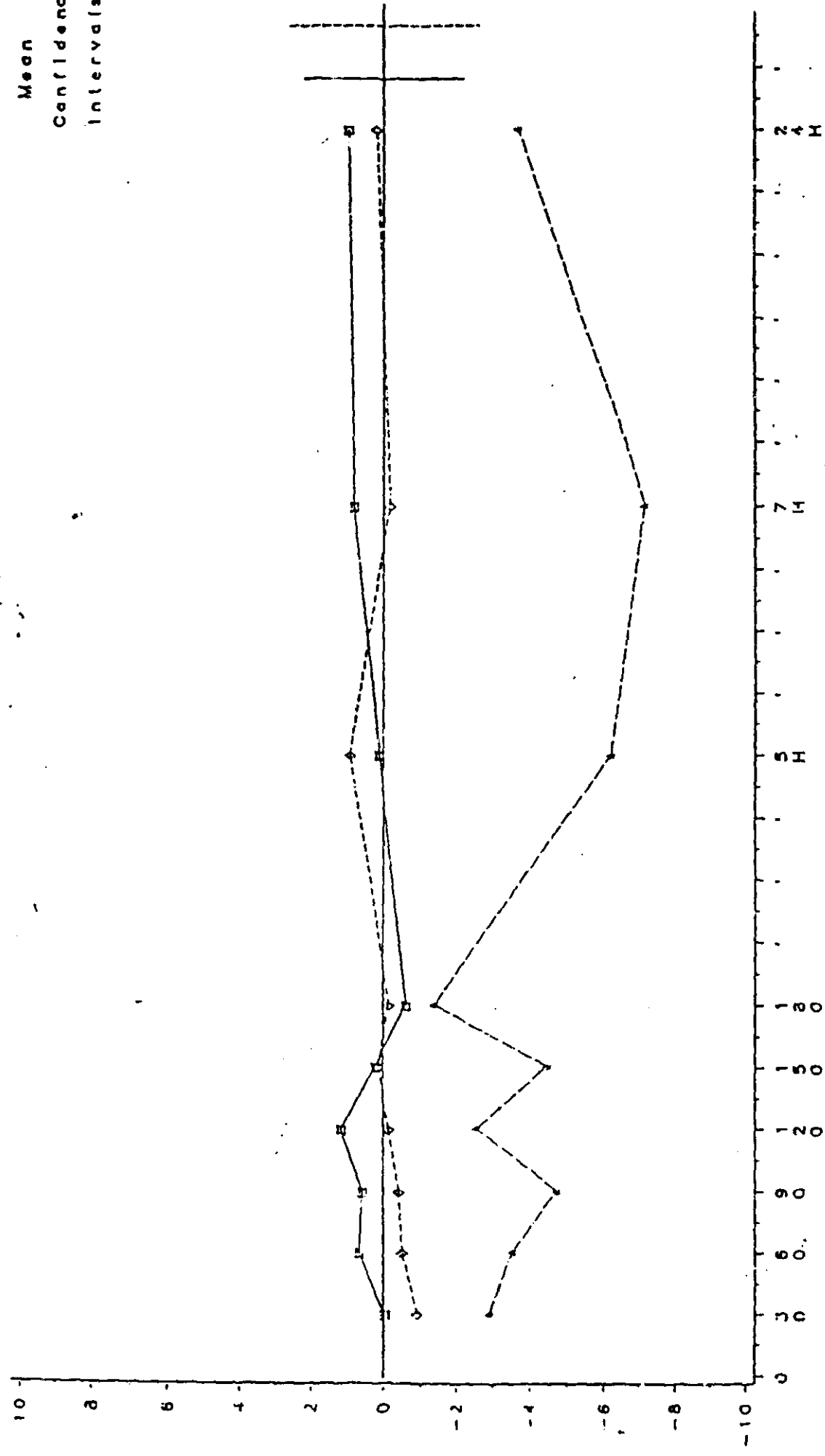
-□- 12.5MG CARVEDILOL - PLACEBO
 -○- 25MG CARVEDILOL - PLACEBO
 -▲- 50MG CARVEDILOL - PLACEBO

000100

STROK DISTANCE (CM)
 (Change from Baseline)

Mean
 Confidence
 Intervals

FIGURE 7



-□- 12.5MG CARVEDILOL - PLACEBO
 -○- 25MG CARVEDILOL - PLACEBO
 -▲- 50MG CARVEDILOL - PLACEBO

000101

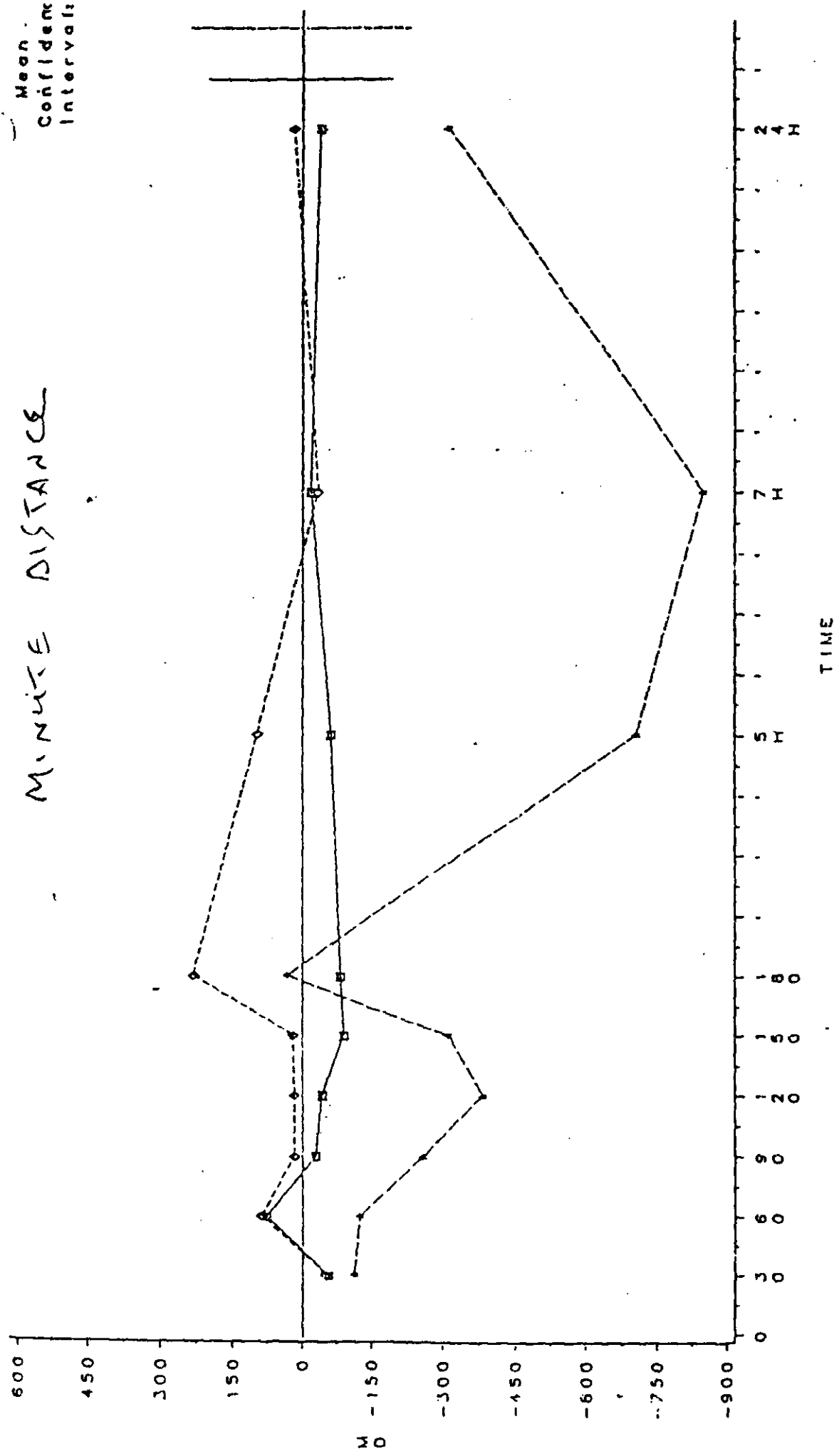
C44

FIGURE 8

MINUTE
(Chang)

MINUTE DISTANCE

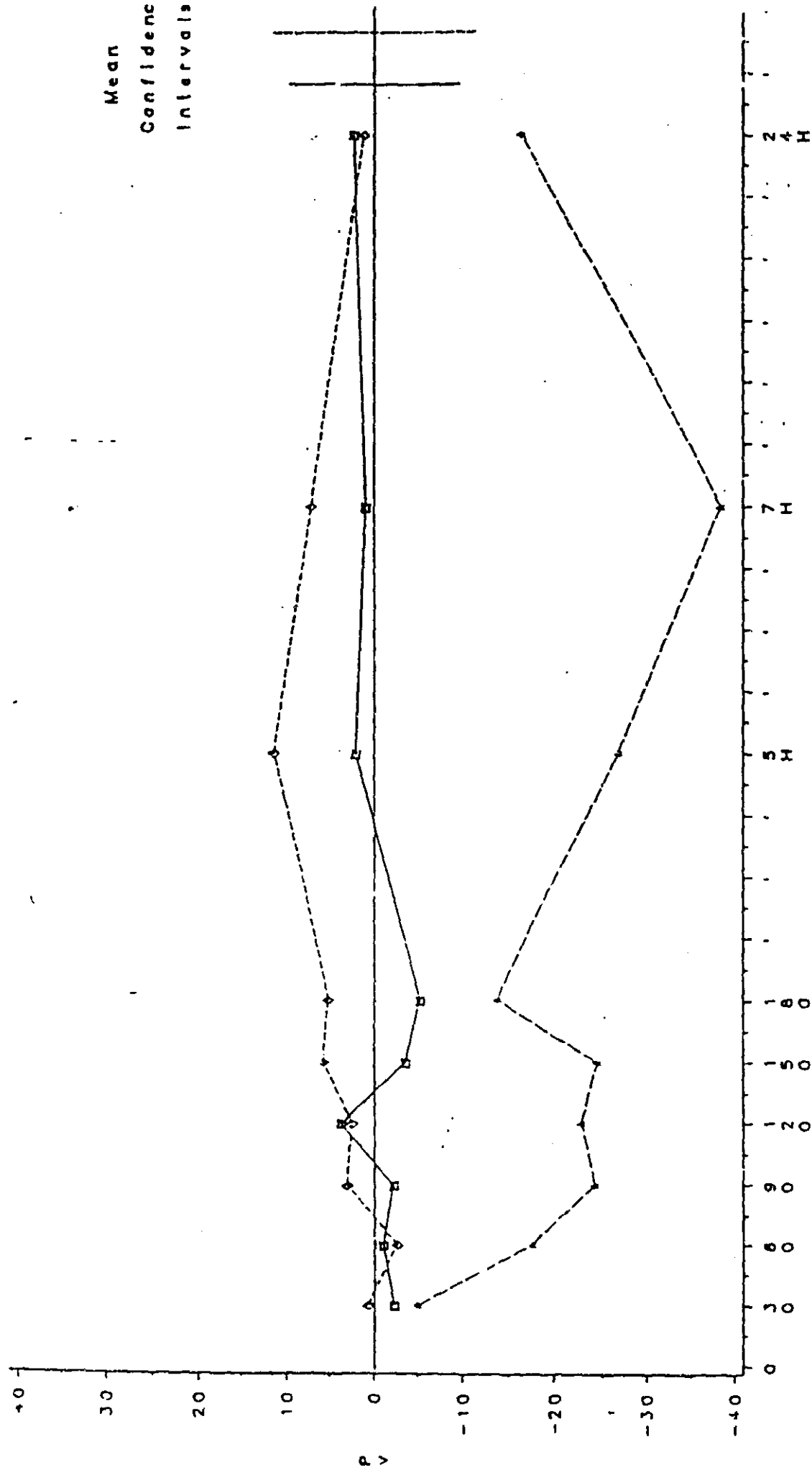
Mean
Confidence
Interval:



-□- 12.5MG CARVEDILOL - PLACEBO
 -○- 25MG CARVEDILOL - PLACEBO
 -*- 50MG CARVEDILOL - PLACEBO

FIGURE 9

PEAK VI: VELOCITY (CM/SEC)
(Change from Baseline)



Mean
Confidence
Intervals

—□— 12.5MG CARVEDILOL - PLACEBO
-◇- 25MG CARVEDILOL - PLACEBO
-▲- 50MG CARVEDILOL - PLACEBO

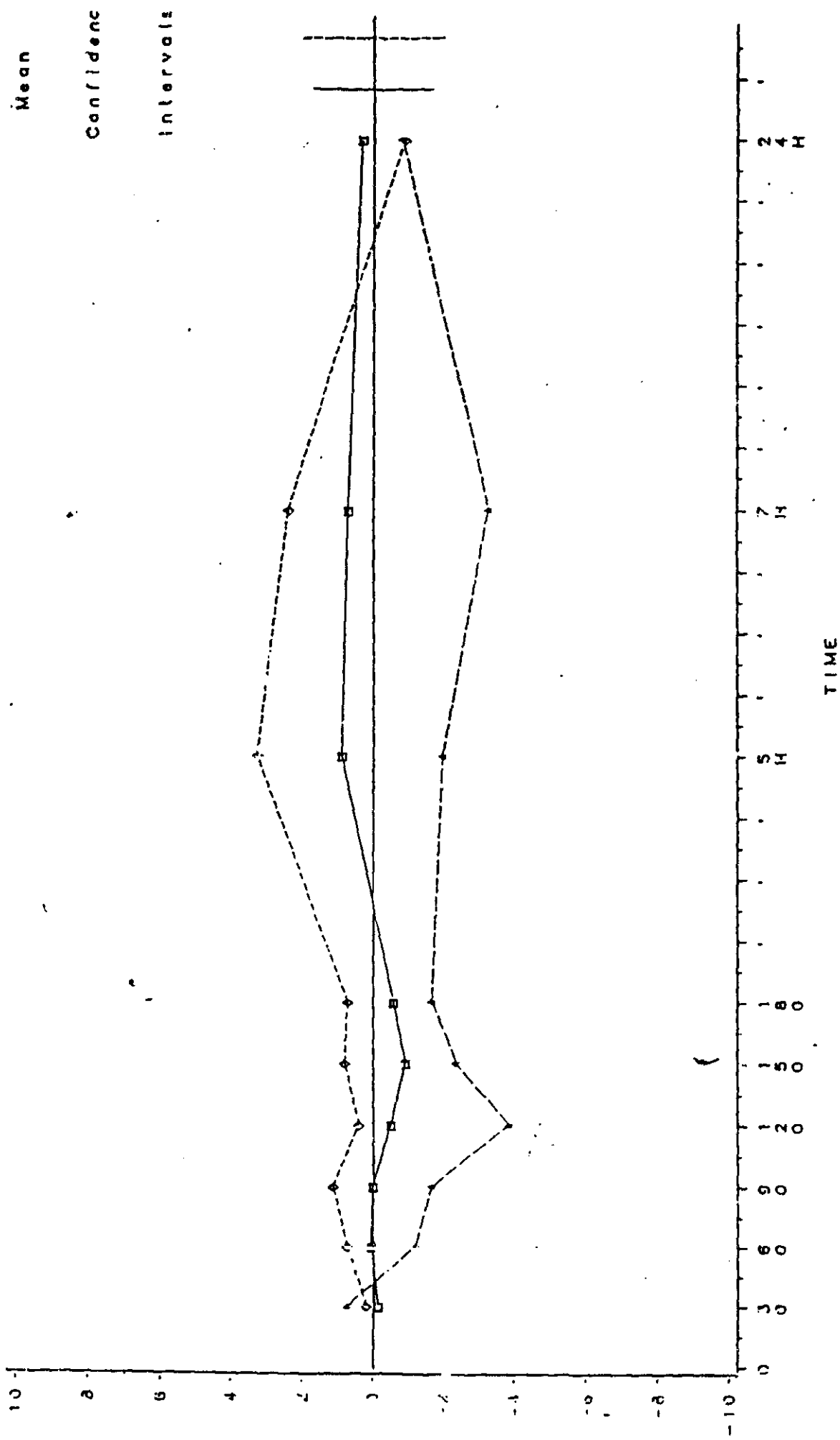
TIME

000103

C46

FIGURE 10

MEAN ACCF RATION (CM/S/ST)
(Change from Baseline)



12.5MG CARVEDILOL - PLACEBO
25MG CARVEDILOL - PLACEBO
50MG CARVEDILOL - PLACEBO

000104

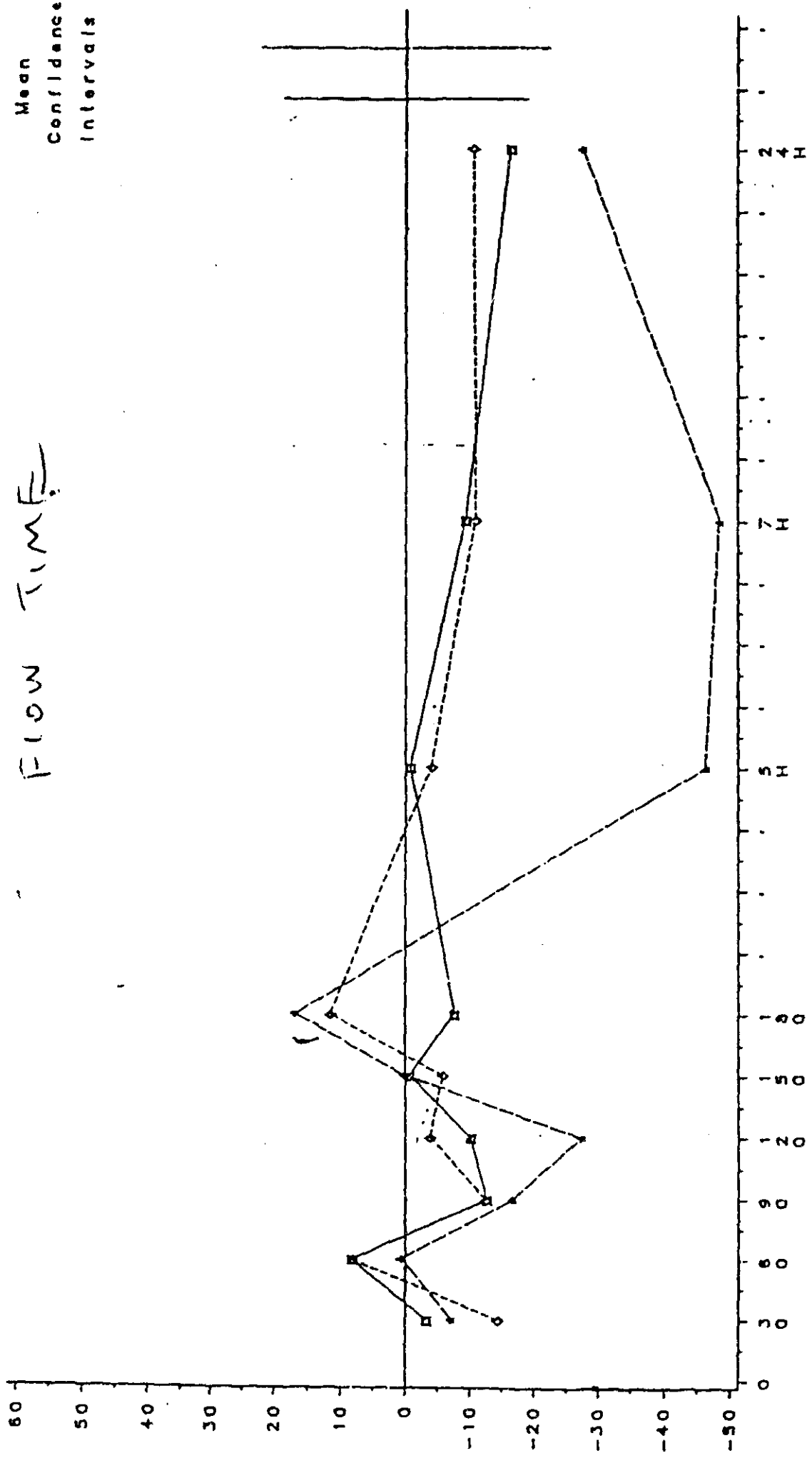
C47

FLOW T CORRECTED
(Changes from Baseline)

FLOW TIME

Mean
Confidence
Intervals

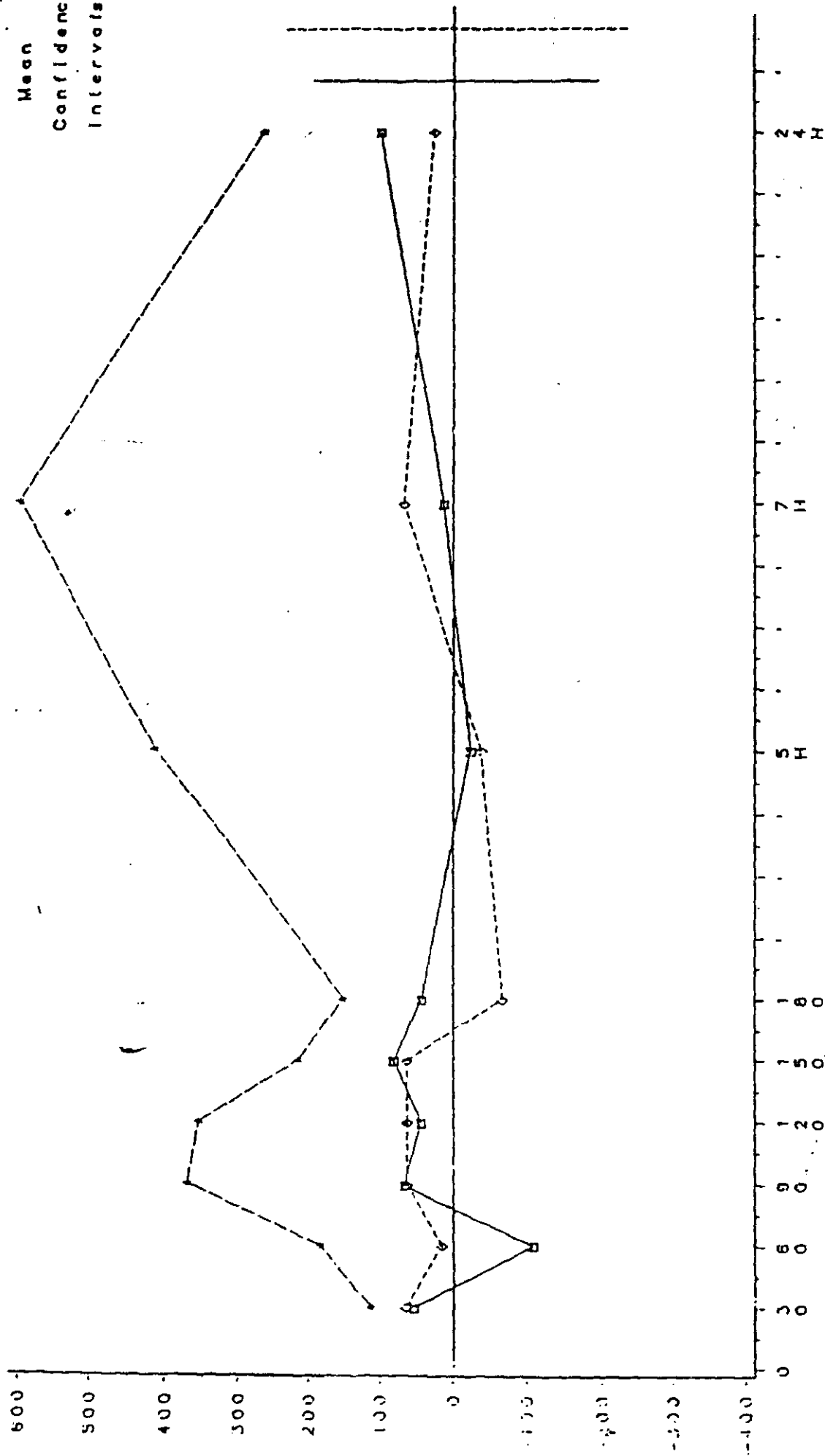
FIGURE 12



-□- 12.5MG CARVEDILOL - PLACEBO
 -◇- 25MG CARVEDILOL - PLACEBO
 -△- 50MG CARVEDILOL - PLACEBO

INDEX OF SYSTEMIC VASCULAR RESISTANCE
 (Changes from Baseline)

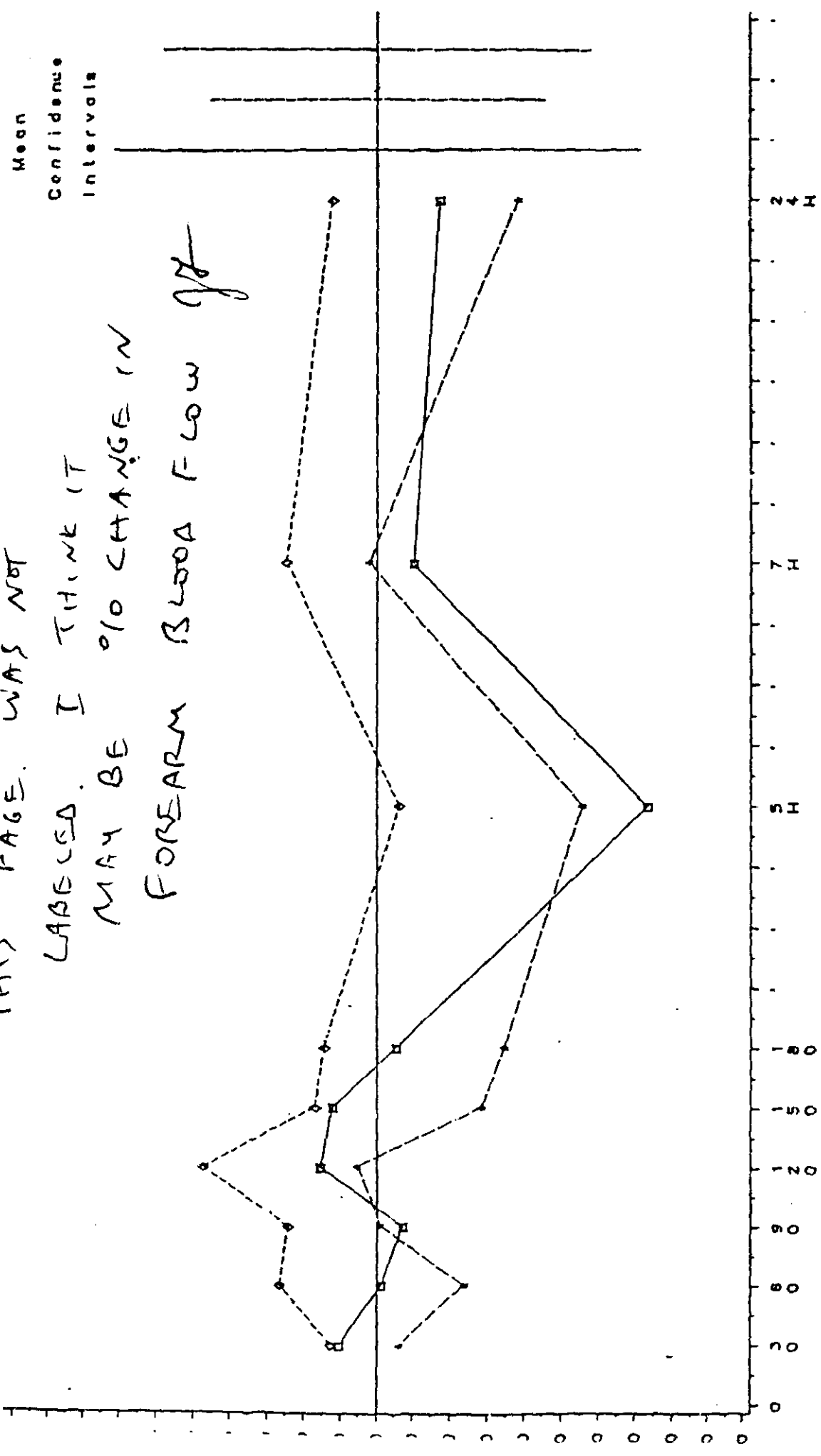
FIGURE 13



—□— 12.5MG CARVEDILOL - PLACEBO
 —○— 25MG CARVEDILOL - PLACEBO
 —△— 50MG CARVEDILOL - PLACEBO

TIME

THIS PAGE WAS NOT
 LABELED. I THINK IT
 MAY BE 0% CHANGE IN
 FOREARM BLOOD FLOW *of*



TIME

-O- 12.5MG CARVEDILOL - PLACEBO
 -□- 25MG CARVEDILOL - PLACEBO
 -△- 50MG CARVEDILOL - PLACEBO

Reviewer: James F. Graumlich

CAR-UK-110 is an in vitro study using venous blood from 8 healthy volunteers. The volunteers had normal coagulation tests and they were prohibited from using other drugs that might influence platelet function. Test drugs were propranolol, carvedilol, and verapamil. Platelet aggregation was induced by ADP, adrenaline and collagen. Figures 1-3 on pages 138-140, volume 1.114, show inhibition of platelet aggregation by the test drugs.

In most humans receiving carvedilol 25 mg po, carvedilol plasma concentrations range up to 208 ng/mL = 0.5 μ M (molecular weight of carvedilol = 406.5). The lowest concentration of carvedilol used in this in vitro study was 1.0 μ M. The lowest IC50 for carvedilol determined in this study was 54 μ M = 21951 ng/mL.

Background information: Alpha 2 receptors on platelets mediate platelet aggregation. Beta 2 receptors mediate inhibition of platelet activation. However, beta blockers do not block the inhibition of platelet activation. Beta blockers inhibit platelet aggregation by stabilizing platelet membranes.

Conclusions: Carvedilol acts like propranolol and inhibits platelet aggregation. The IC50 for inhibition by carvedilol occurs at concentrations higher than plasma levels usually achieved in humans.

INHIBITION OF ADP-INDUCED AGGREGATION

Inhibition (%)

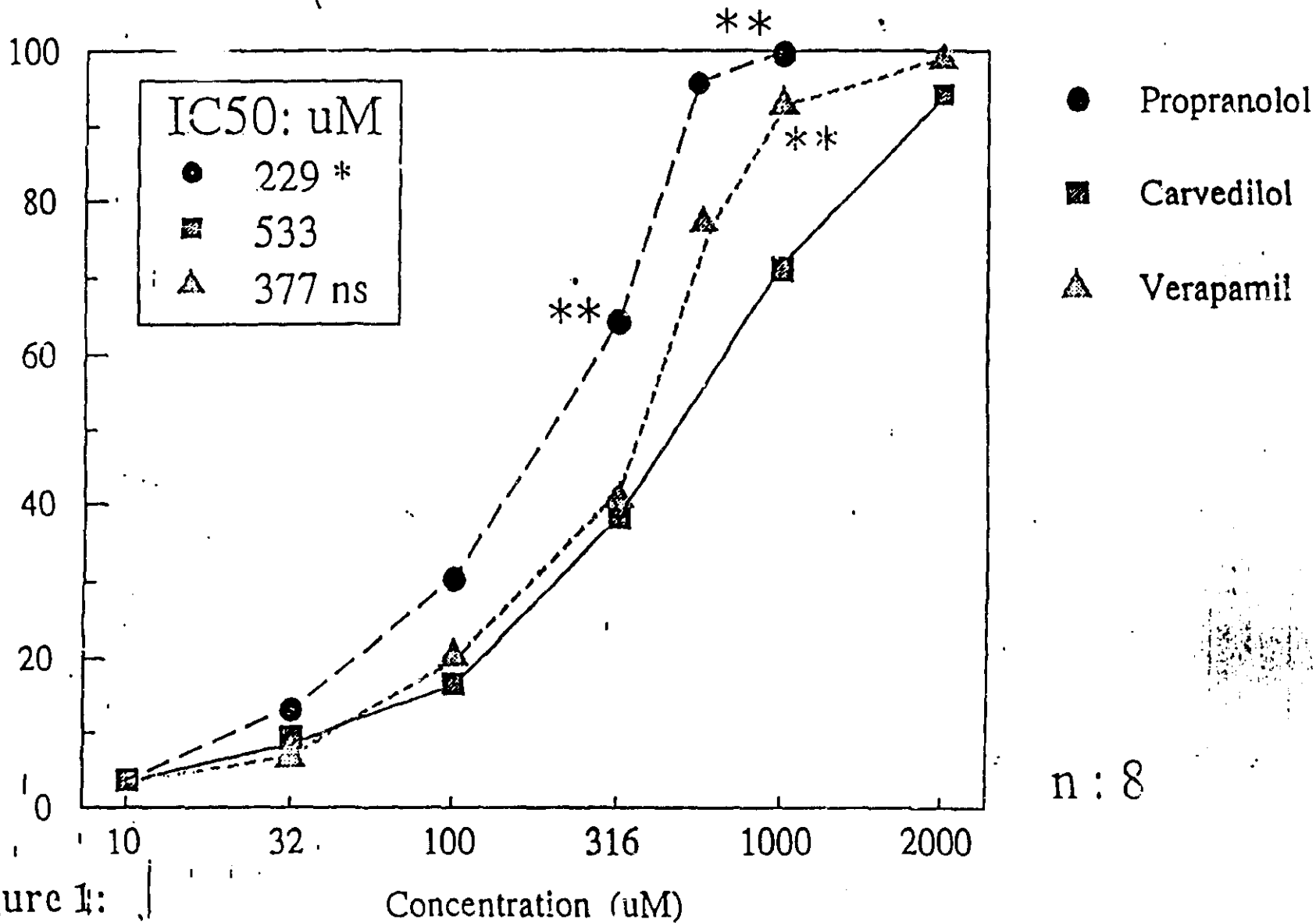


Figure 1:

Concentration (uM)

000138

INHIBITION OF ADRENALINE 10 μ M INDUCED PLATELET AGGREGATION

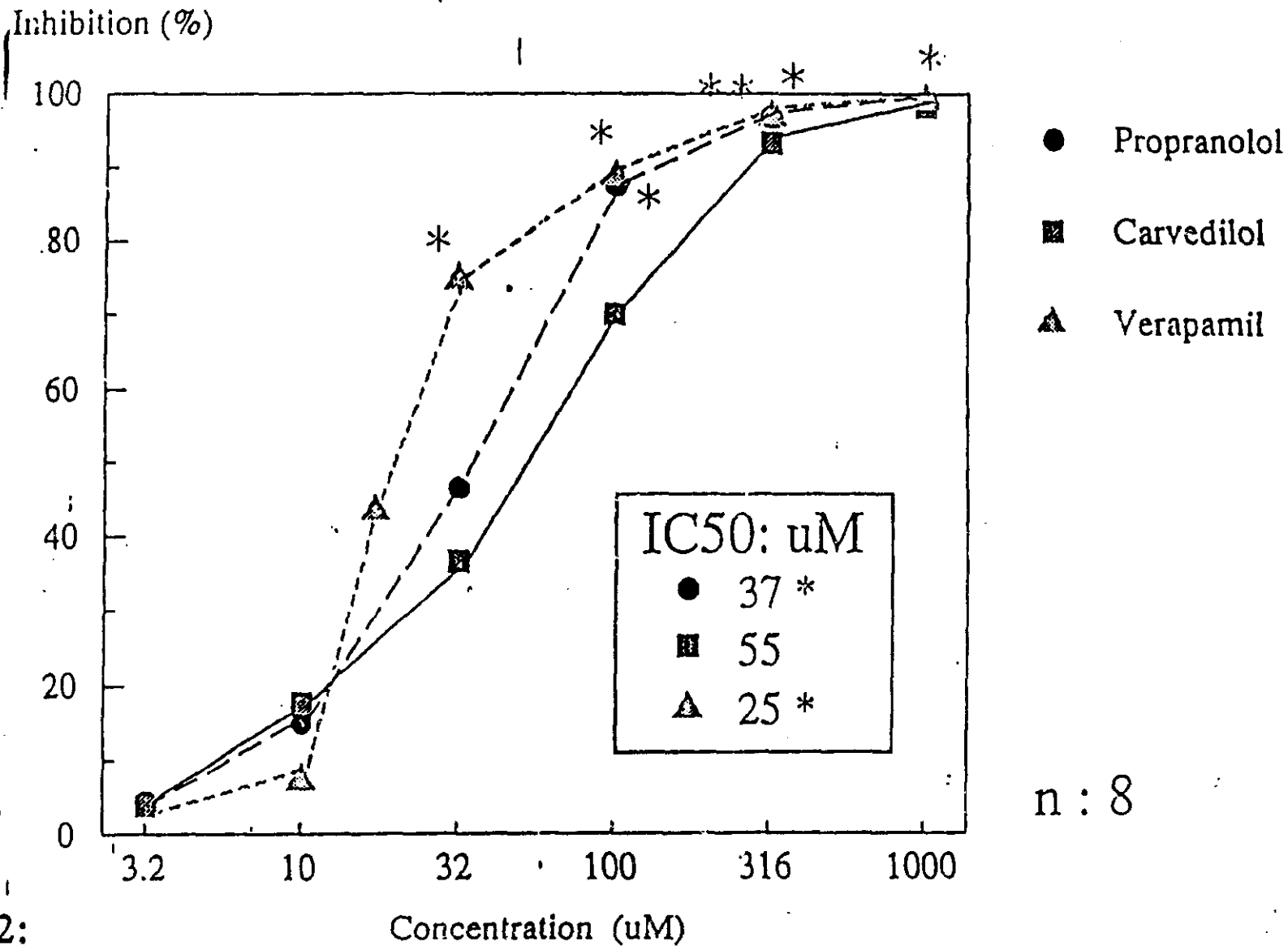


Figure 2:

000139

INHIBITION OF COLLAGEN 1ug/ml INDUCED PLATELET AGGREGATION

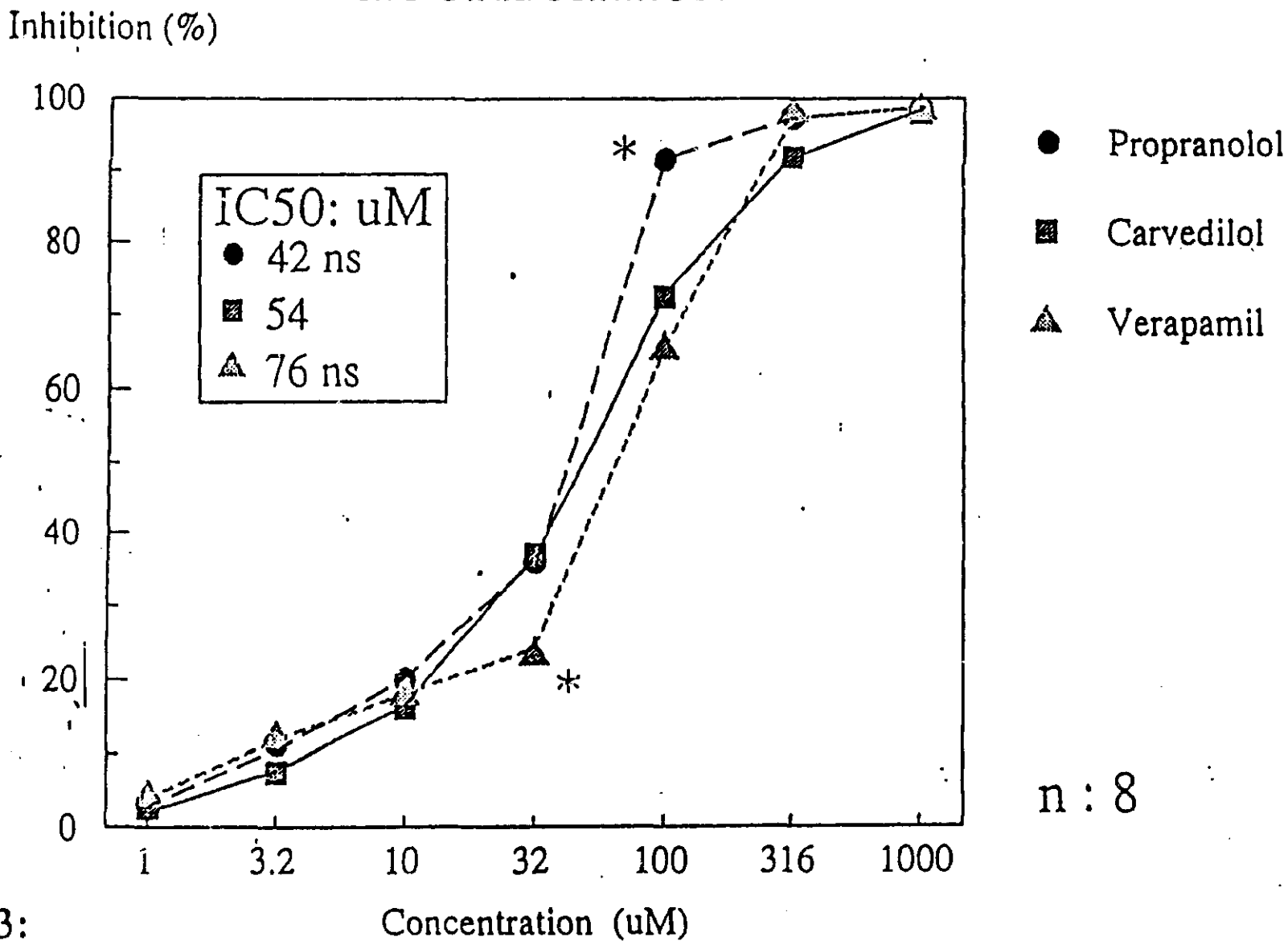


Figure 3:

000140

CSA

NDA 20-297 CARVEDILOL, Protocol CARV0001, Vol 1.74 and 1.82
Reviewer: James F. Graumlich

Publication: Cubeddu et al. Clinical pharmacology of carvedilol in normal volunteers. Clin Pharmacol Ther 1987; 41:31-44. Vol 1.82 page 12.

Design: single-blind, placebo-controlled, parallel group design in healthy men. There was random assignment to carvedilol, labetalol, or placebo.

Treatments were infusions of antagonists over 15 minutes:

IV carvedilol 1 mg/min, total 15 mg (n=8), lot number 818651A (Boehringer Mannheim)

IV labetalol HCl 1.33 mg/min, total 20 mg (n=1)

IV labetalol HCl 2.67 mg/min, total 40 mg (n=4)

IV labetalol HCl 5.3 mg/min, total 80 mg (n=3)

placebo 1 mL/min (n=9)

Before receiving treatments, each subject had infusions of agonists (angiotensin II, isoproterenol and phenylephrine) at various doses to produce a dose-response curve. Doses of agonists producing defined responses (changes in pulse and blood pressure) were extrapolated from the dose-response curve and were used to measure baseline responses pre-antagonist. After antagonist treatment, response to agonists was recorded at 5 minutes and 1, 2, 3, 4, 6, 8 hours. Response variables were heart rate, diastolic blood pressure, and carvedilol concentration in plasma.

Results: Subjects were healthy men (age range 21 to 37 years, mean weight of 170 lbs was similar in the placebo, carvedilol and labetalol groups). Only one subject (# 18) withdrew due to an adverse event. He developed unifocal ventricular ectopy 6 hours after carvedilol infusion. At the time of the ectopy, the plasma carvedilol concentration, 11.09 ng/mL, was decreased from Cmax of 74 ng/mL at Tmax 15 minutes after the end of the infusion. During the ectopy, all of the following were normal: symptoms, blood pressure, heart rate, electrolytes, calcium, magnesium. Six days after discharge from the study, a holter monitor was normal except for 4 premature atrial beats.

The first labetalol subject had no blood pressure or pulse response to 20 mg so the next 4 subjects received labetalol 40 mg. The blood pressure response to labetalol 40 mg was thought to be inadequate so the last 3 subjects received labetalol 80 mg.

At baseline before antagonist therapy, there were differences in the placebo and carvedilol groups in the responses to angiotensin II and phenylephrine. Adjustments for baseline differences were made in the analysis of endpoints measured after antagonist therapy.

Antagonist response (mean ± SD)

Antagonist	Measurement	n	pre-infusion	end of infusion
carvedilol 15 mg	dias BP	8	61.2 ± 6.5	50.2 ± 5.3
	syst BP	8	137.4 ± 17.1	105.5 ± 6.6
	heart rate	8	57.2 ± 12.4	59.0 ± 10.0
labetalol 80 mg	dias BP	3	67.7 ± 7.1	58.0 ± 4.0
	syst BP	3	138.0 ± 7.2	120.3 ± 9.0
	heart rate	3	61.3 ± 16.0	66.7 ± 12.1
placebo	dias BP	9	56.2 ± 6.7	56.4 ± 6.6
	syst BP	9	128.2 ± 13.2	129.8 ± 12.2
	heart rate	9	57.0 ± 12.8	57.8 ± 11.3

Beta effect: See Figures 6 and 7 (pages C57, C58). When compared with placebo, intravenous carvedilol blocked isoproterenol-induced increases in pulse for up to 8 hours after carvedilol infusion. Intravenous carvedilol blocked

isoproterenol-induced (1.4 μg) decreases in supine DBP. The extent of blockade of isoproterenol-induced effects remained unchanged during the 8-hour experiment. Consequently, the carvedilol concentration-response relationship was flat.

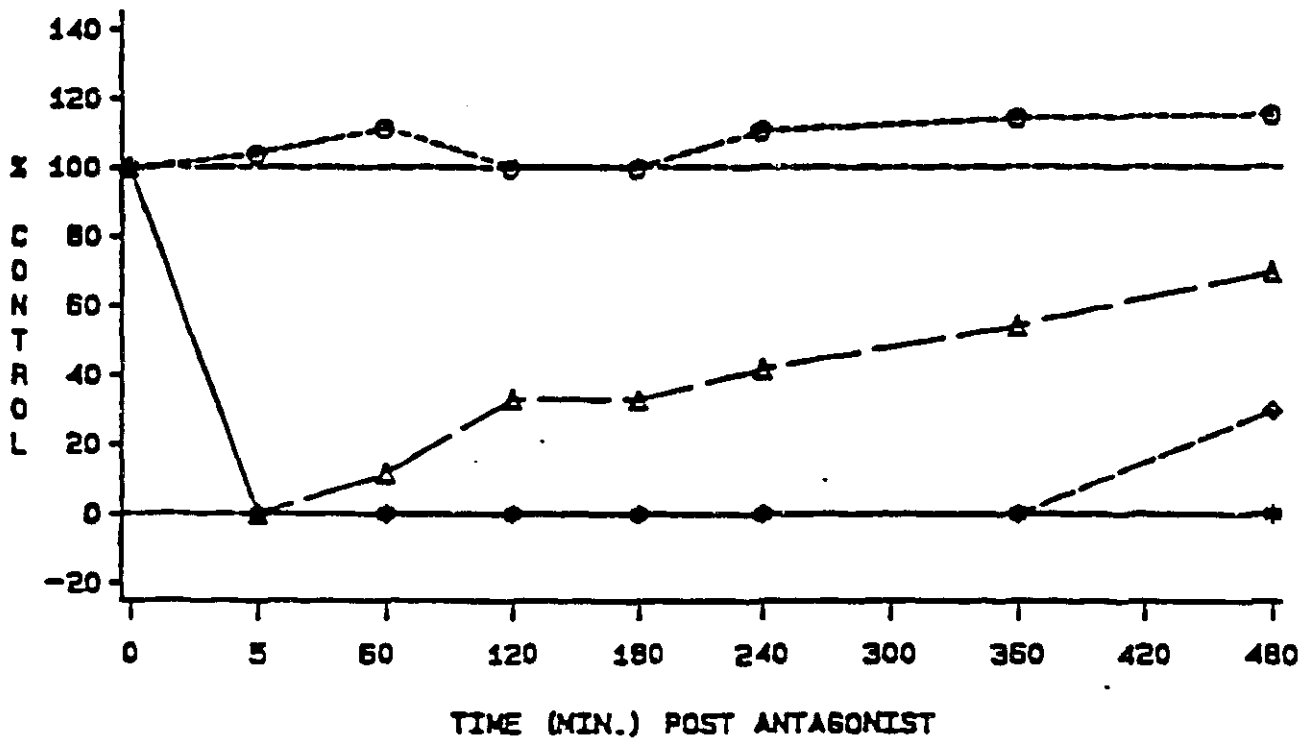
Alpha effect: See Figure 8 (page C59). Phenylephrine (mean dose 0.58 mg in a 2-minute infusion) produced an approximate 25 mm Hg increase in SBP and DBP and an average 18 BPM decrease in heart rate. Intravenous carvedilol blocked phenylephrine-induced increases in SBP and DBP for up to 4 hours. Carvedilol serum concentrations correlated with percent inhibition of phenylephrine effects. The smallest detectable difference between placebo and carvedilol blockade of phenylephrine-induced effects occurred at 4 hours after the end of the carvedilol infusion when the carvedilol serum concentration was approximately 28 ng/mL.

Intravenous carvedilol did not block the pressor effects of intravenous angiotensin II (mean 2.96 μg). See Figure 9 (page C60). Serum concentrations as high as 150 ng/mL failed to block angiotensin II-induced effects.

Adverse events: Ventricular ectopy is described above. There were no clinically significant changes in mean laboratory values or ECG intervals.

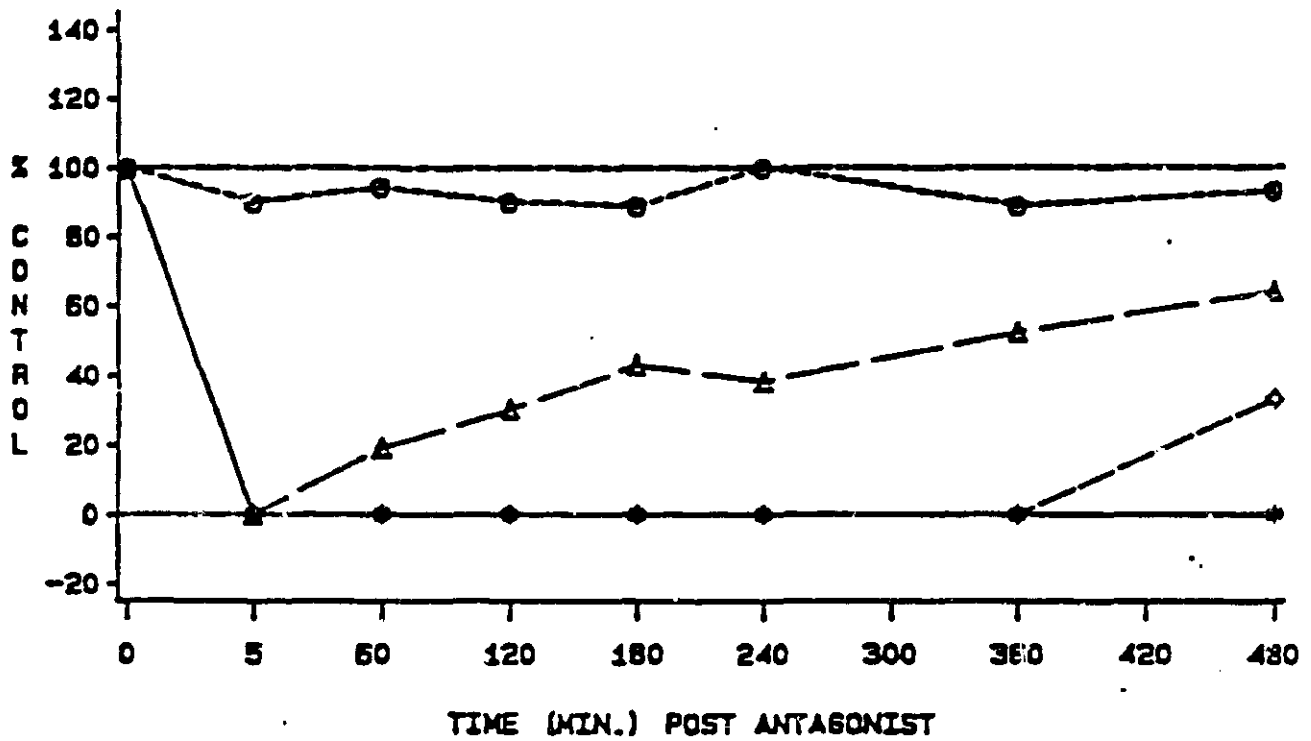
Conclusion: This study demonstrates the non-selective beta and alpha blockade by intravenous carvedilol in healthy men.

FIGURE 6
MEDIAN CHANGE IN HEART RATE (PERCENT OF CONTROL)
ISOPROTERENOL



SYMBOL ◆◆◆ CARVEDILOL ○○○ PLACEBO
 ▲▲▲ LABETALOL-40 ◇◇◇ LABETALOL-80

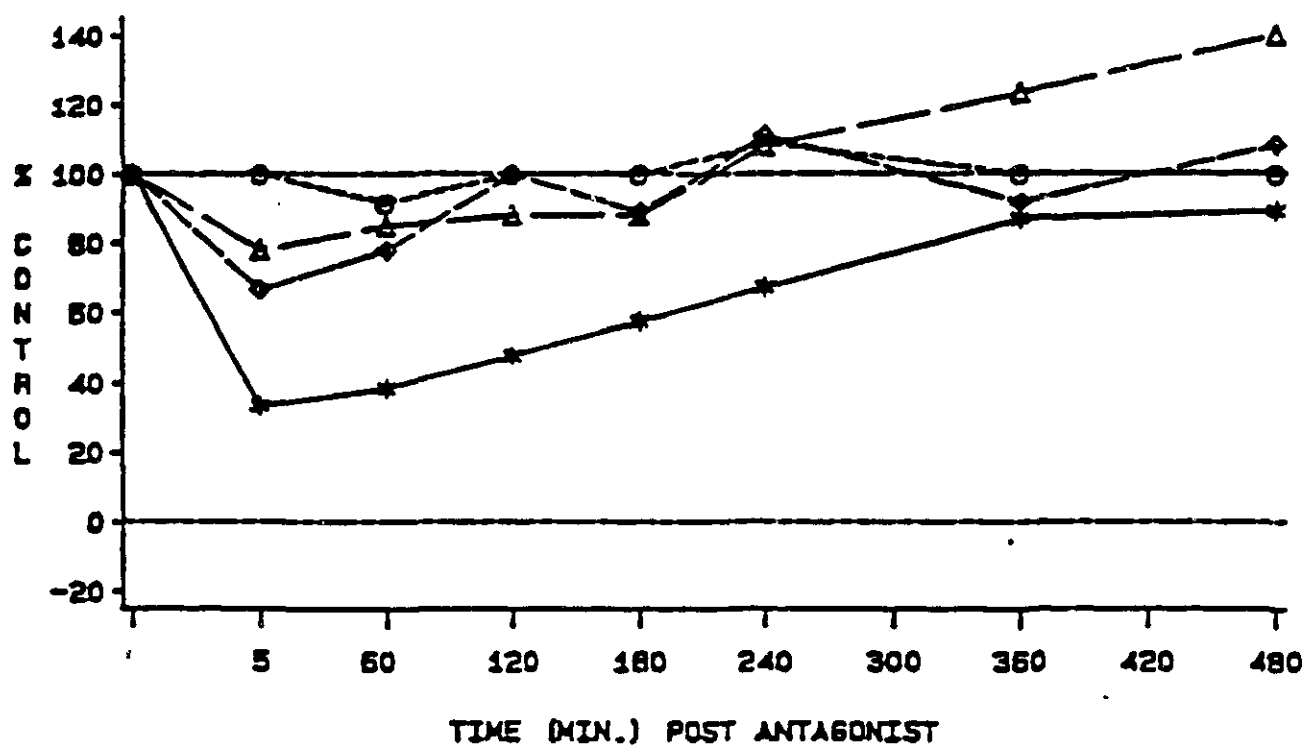
FIGURE 7
MEDIAN CHANGE IN DIASTOLIC BLOOD PRESSURE (PERCENT OF CONTROL)
ISOPROTERENOL



SYMBOL ●-●-● CARVEDILOL ○-○-○ PLACEBO
 ▲-▲-▲ LABETALOL-40 ◆-◆-◆ LABETALOL-50

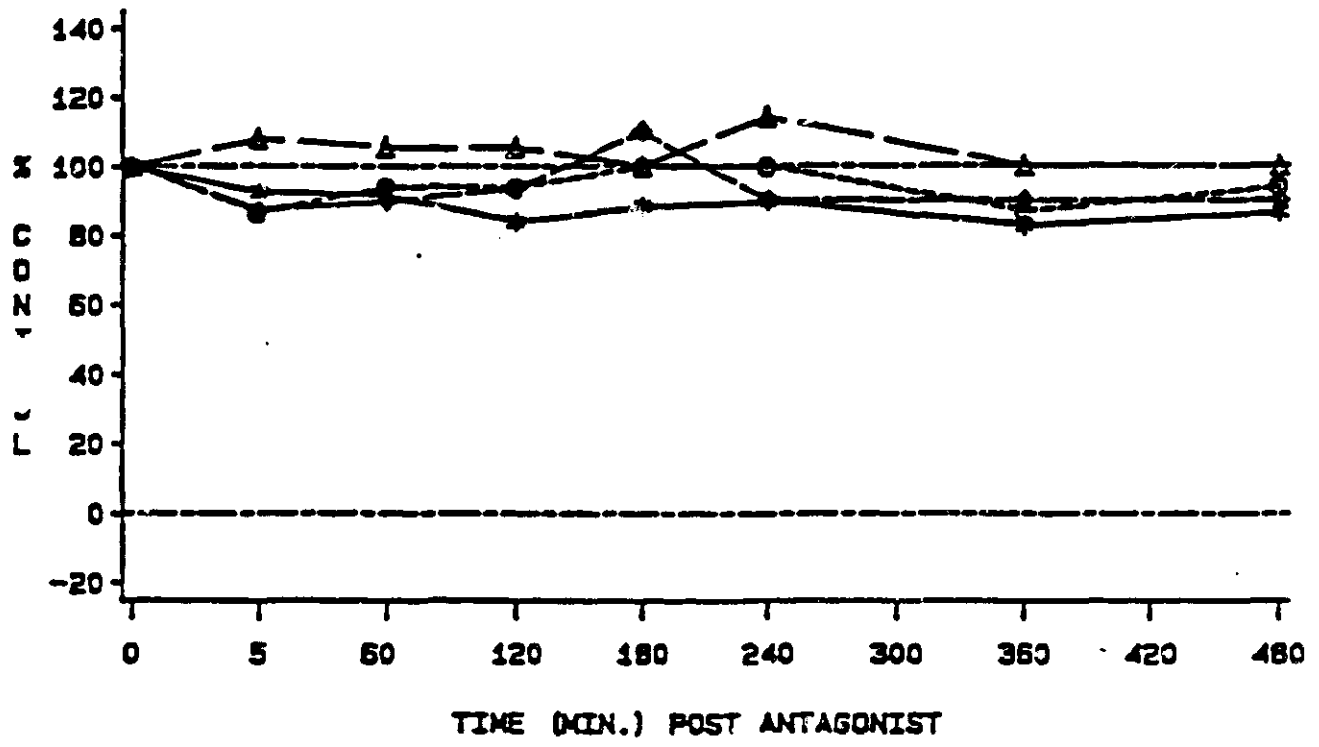
FIGURE .8

MEDIAN CHANGE IN DIASTOLIC BLOOD PRESSURE (PERCENT OF CONTROL)
 PHENYLEPHRINE



SYMBOL ◆◆◆ CARVEDILOL ○○○ PLACEBO
 ▲▲▲ LABETALOL-40 ◆◆◆ LABETALOL-80

FIGURE .9
MEDIAN CHANGE IN DIASTOLIC BLOOD PRESSURE (PERCENT OF CONTROL)
ANGIOTENSIN II



SYMBOL ◆◆◆ CARVEDILOL ○○○ PLACEBO
 ▲▲▲ LABETALOL-40 ◆◆◆ LABETALOL-80

CARVEDILOL NDA 20-297

PROTOCOL CARV0002 VOL 1.75

Reviewer: James F. Graumlich
PK, metabolites

CARV0002 was an open-label, uncontrolled, non-randomized, study of IV carvedilol 0.042 mg/kg and 0.084 mg/kg in 6 healthy men. Endpoints were plasma carvedilol concentration, urine carvedilol, desmethylcarvedilol, and carvedilol conjugates; blood pressure; pulse. PK sampling occurred for 32 hours after the infusion.

Results: 11 healthy men enrolled (age range 22 - 33 years, weight range 140 - 193 lbs). 6 completed. Subject 5 received carvedilol 10 mg IV and had a sinus arrest, junctional escape rhythm, hypotension (BP not reported), syncope, seizure, carvedilol plasma concentration $C_{max} = 308.3$ ng/mL. The C_{max} in Subject 5 was lower than C_{max} recorded in other subjects. Subject 5 had the lowest body weight (140 lbs). The subject recovered after treatment with atropine 1.0 mg. There were no reported residual deficits. Calculated PK parameters for subjects 1-5 were not reported. Blood pressure and pulse were not reported for subjects 1-5. Calculated PK parameters for subjects 6-11 are in Table 2 from page 36 volume 1.75. Urinary elimination of carvedilol and desmethylcarvedilol are listed in Table 3 from page 37 volume 1.75. Mean systolic and diastolic BP fell 8 - 10 mm Hg. The significance of this change in BP is unknown since there is no placebo comparison. Heart rate did not decrease or increase during 12 hours of observation after the dose. Orthostatic vital signs were not reported. There were no clinically significant laboratory safety abnormalities as a result of treatment in subjects 1-11.

Conclusion: Intravenous carvedilol 10 mg caused a serious adverse event in one healthy man. Carvedilol did not decrease heart rate in this study. The small number of subjects and the lack of placebo comparison prevent interpretation of the clinical significance of BP changes.



Table 2

Pharmacokinetic Data Analysis of
Subjects 6-11

Subject	AUC _{0-∞} (hr x ng/ml)	CL _t (ml/hr/kg)	CL _r (ml/hr/kg)	V _{ss} (L/kg)	t _{1/2β} (hr)	C _{max} (ng/ml)
0.042 mg/kg						
6						
7						
8						
9						
10						
11						
Mean	113.9	394	5.9	1.41	6.0	125
S.D.	31.4	113	1.9	0.50	4.0	28
0.084 mg/kg						
6						
7						
8						
9						
10						
11						
Mean	232.2	368	6.1	1.46	6.0	253
S.D.	32.7	50	2.5	0.36	2.0	40

Carvedilol was infused intravenously over 15 minutes. Each subject received 0.042 mg/kg as the first treatment followed one week later by 0.084 mg/kg.

Statistical analyses were not applied to the pharmacokinetic data. The data were summarized as means and standard deviations.



Table 3

Elimination of Carvedilol and Desmethylcarvedilol in the Urine

Subject	Carvedilol				Desmethylcarvedilol			
	Unconjugated		Conjugated		Unconjugated		Conjugated	
	μg	% Dose	μg	% Dose	μg	% Dose	μg	% Dose
0.042 mg/kg								
6								
7								
8								
9*								
10								
11								
Mean		1.5		7.7		0.10		2.2
S.D.		0.7		3.6		0.06		0.6
0.084 mg/kg								
6								
7								
8								
9*								
10								
11								
Mean		1.7		8.2		0.09		2.2
S.D.		0.7		4.0		0.08		0.5

* Urine collection was incomplete for Subject 9 at both doses.

Reviewer: James F. Graulich

CARV0011 is a double-blind, placebo-controlled, randomized-sequence, two-period crossover study of a single oral dose of carvedilol 25 mg in patients with coronary artery disease. Patients were included if they had "suspected or established diagnosis of coronary artery disease" and if they could exercise on a bicycle ergometer. The endpoints, measured by MUGA, were left ventricular ejection fraction at rest, LV EF during exercise. Concomitant beta blocker and calcium channel blocker therapies were prohibited for specified times prior to the first MUGA.

Baseline screening MUGA was not done at the request of the FDA. Rest and exercise MUGA were not done at the same time relative to the dose. The design did not account for potential bias due to training effect.

20 patients were screened. 5 did not qualify for randomization for the following reasons: 1 had a low ejection fraction, 1 had pain with exercise, and 3 had family conflicts or inconveniences. Of the 15 randomized patients (aged 41 to 74 years), 2 were withdrawn for the following reasons: one had a low ejection fraction after placebo treatment, one had total knee arthroplasty that prevented exercise. Of the 13 remaining randomized patients, one was excluded from analysis of efficacy because the treatment sequence was uncertain.

Results are shown in Table 2 from page 40, volume 1.115. Carvedilol did not affect ejection fraction at rest or with exercise. Carvedilol blocked exercise-induced tachycardia and exercise-induced increases in systolic blood pressure. Exercise duration was significantly shorter after carvedilol. The report does not contain information on baseline differences in the efficacy parameters between carvedilol and placebo. The statistical analysis reported "the observed sequence effects were very small, with only one F-statistic greater than 1.0." I assume any baseline effects would be manifest as a sequence effect in this 2 x 2 design.

Treatment-emergent symptoms dizziness (4 carvedilol and 3 placebo), back pain (1 carvedilol and 0 placebo), hypotension (1 carvedilol and 0 placebo), nausea (1 carvedilol and 0 placebo). One patient had a decrease in WBC from 5900 to 3400.

Conclusion: In this group of patients with a history of coronary artery disease, carvedilol did not affect cardiac ejection fraction at rest or with exercise. Carvedilol acted as a beta blocker by blocking exercise-induced increases in heart rate and systolic blood pressure. Exercise time was significantly shorter by 0.9 minutes after carvedilol.

TABLE 2
 MUGA RESULTS

MEASUREMENT	PLACEBO	CARVEDILOL	DIFFERENCE ¹	P-VALUE
EJECTION FRACTION AT REST (%)				
MEAN	49.2	49.7	1.0	.61
S.D. ²	5.0	6.8	1.8	
N	12	12		
EJECTION FRACTION ON EXERCISE (%)				
MEAN	57.3	57.5	0.7	.67
S.D. ²	7.0	6.5	1.6	
N	12	12		
EJECTION FRACTION EXERCISE-REST (%)				
MEAN	8.2	7.8	-0.3	.84
S.D. ²	2.6	4.1	1.2	
N	12	12		
DIASTOLIC BP AT MAX. EXERCISE (MM.HG.)				
MEAN	93.6	87.6	-6.3	.01**
S.D. ²	8.4	7.6	2.0	
N	12	12		
SYSTOLIC BP AT MAX. EXERCISE (MM.HG.)				
MEAN	172.3	148.5	-23.0	<.001***
S.D. ²	21.3	18.0	4.6	
N	12	12		
HEART RATE AT MAX. EXERCISE (BPM)				
MEAN	107.0	88.4	-18.6	<.001***
S.D. ²	11.5	8.9	3.3	
N	12	12		
RATE PRESSURE PRODUCT AT MAX (BPM X MMHG)				
MEAN	18489.1	13098.7	-5311.0	<.001***
S.D. ²	3407.2	1729.0	861.6	
N	12	12		
EXERCISE DURATION (MINUTES)				
MEAN	10.6	9.0	-0.9	.03*
S.D. ²	3.3	3.0	0.4	
N	12	12		
WORKLOAD AT MAXIMUM EXERCISE (KPM/MIN)				
MEAN	575.0	537.5	-45.0	.10
S.D. ²	167.2	149.4	24.8	
N	12	12		

*: p < .05
 **: p < .01
 ***: p < .001

1: Estimated from Analysis of Variance

2: Standard Error is given for estimated mean difference

CARVEDILOL NDA 20-297

PROTOCOL F-30 VOL 1.44

STEREOSELECTIVE PK

Reviewer: James F. Graumlich

Objectives: To examine the pharmacokinetic parameters of R(+) and S(-)carvedilol after single oral doses of carvedilol to humans.

Study design: Open label, uncontrolled, prospective study in 5 healthy men. All subjects are presumed to be Japanese. Subjects received breakfast 30 minutes after the dose. Subjects again received food 4 hours after the dose.

Intervention: Humans received 20 mg carvedilol tablet po as a single dose after an overnight fast.

Response variables: Primary outcome: AUC (trapezoidal)
Secondary outcome: Cmax, Tmax, half-life, F, Vd, CLtot

Blood sampling times were at baseline then 0.5, 1, 2, 3, 4, 6, 8, 10, 24 hours after dose administration.

Materials: racemic carvedilol 20 mg tablet, formulation not specified, batch not specified

Assay: R(+) and S(-)carvedilol assay involved liquid-liquid extraction from plasma, chiral derivatization with GFTC, then HPLC with fluorescence detection. The lower limit of quantification for R(+) and S(-)carvedilol was not specified.

Results: 5 male healthy subjects between 32 and 42 years of age completed the study. Weights of subjects were between 67 and 80 kg.

The attached figure 3 from protocol F-30 (page C68) shows the mean plasma concentration vs time for R(+) and S(-)carvedilol. N = 5 subjects. The table on the next page has the pharmacokinetic parameters for the two enantiomers.

Pharmacodynamic response: None recorded

Adverse events: None recorded

Conclusions: The study used a single dose of carvedilol in healthy Japanese men. Potential distribution differences in hepatic oxidative metabolism between Japanese and American populations limit the generalization of the results.

The distribution of the data was not analyzed. Therefore, statistical comparisons in the report are not reliable due to the small sample size.

The PK analysis assumes absorption of carvedilol from the GI tract is complete. This assumption remains to be proven. Since there was no intravenous dose given, F was calculated using assumptions regarding hepatic blood flow. Since these assumptions are not proven in this sample, the validity of the F calculation is questioned. The Vd and CLtot were calculated using the calculated value of F. Therefore, Vd and CLtot may not be reliable estimates.

The results suggest stereoselective, hepatic first-pass metabolism. S(-) carvedilol is metabolized to a greater extent than R(+) carvedilol.

CARVEDILOL NDA 20-297

PROTOCOL F-30 VOL 1.44

Pharmacokinetic parameters in 5 healthy Japanese men after oral dose

Parameter		R(+) carvedilol	S (-) carvedilol
C _{max} (ng/mL)	mean	25.3	9.8
	SD	15.6	6.8
	min		
	max		
T _{max} (hours)	mean	0.9	0.7
	SD	0.2	0.3
	min		
	max		
AUC _∞ (ng*hr/mL)	mean	105.01	37.95
	SD	58.7	19.59
	min		
	max		
half-life (hours)	mean	5.33	5.05
	SD	1.91	1.8
	min		
	max		
F	mean	0.45	0.24
	SD	0.17	0.1
	min		
	max		
V _d (L)	mean	362	498
	SD	101	188
	min		
	max		
CL _{tot} (L/hr)	mean	49.58	68.48
	SD	15.15	10.29
	min		
	max		

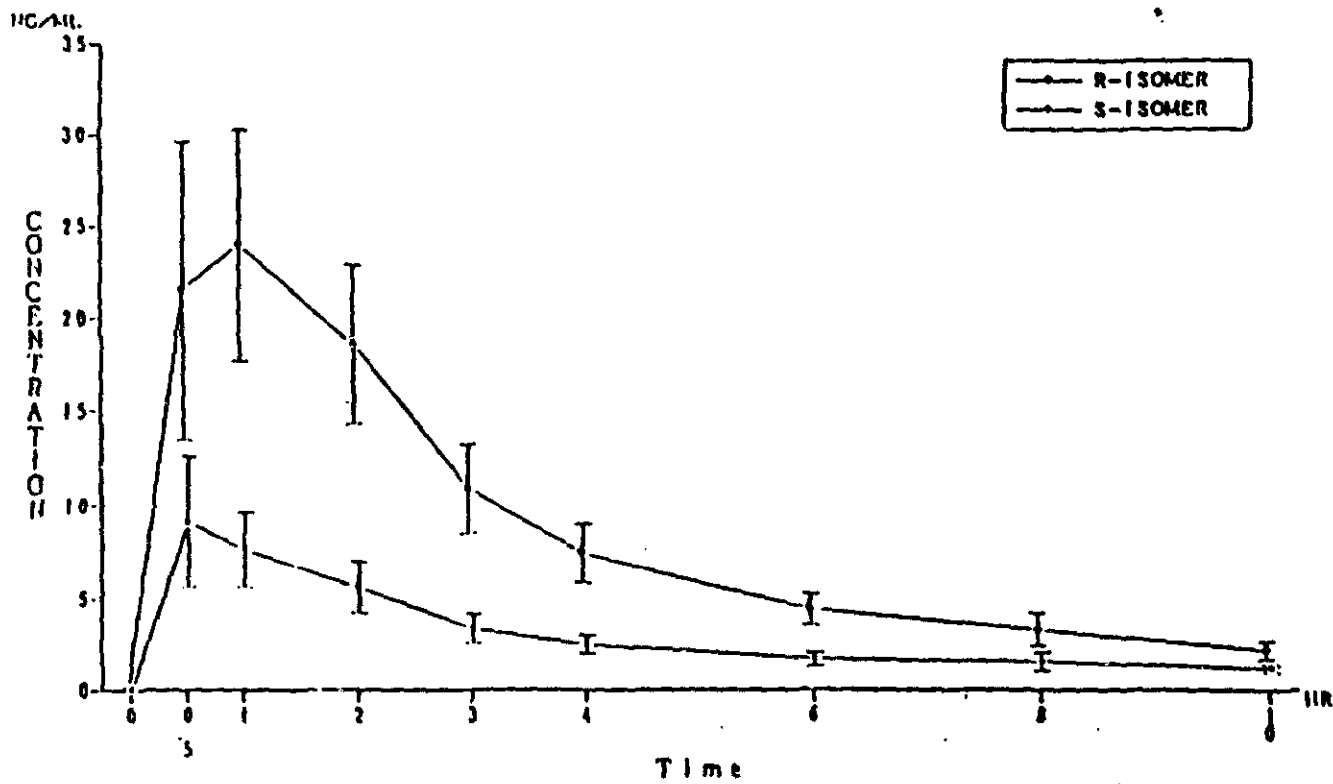


Fig. 3 Mean plasma concentrations of (R)- and (S)-enantiomer after oral administration of racemic DQ-2465 at a dose of 20 mg to healthy volunteers.

F30
000276
Vol. 1, 1994

PHARMACODYNAMIC EFFECT

Reviewer: James F. Graumlich

Name of study: Effect of carvedilol on haemodynamic and performance parameters at rest, during and post exercise testing in healthy volunteers: an open uncontrolled pilot study**Objectives:** To investigate the tolerance to and influence of carvedilol at peak and trough concentrations, on central and peripheral hemodynamics as well as on performance parameters in healthy subject at rest and during exercise testing.**Study design:** Open label, uncontrolled, prospective, 3 week study in 10 well-trained, healthy male subjects. There was forced dose escalation: 12.5 mg po q day for 7 days then 25 mg po q day for 14 days. Analgesic use by subjects was permitted. The definition of well-trained athlete was not provided. Exercise tolerance was measured on a bicycle ergometer. Workload was increased continuously by 30 watts/minute from 50 watts to 320 watts. Exercise duration was 10 minutes or until the subject achieved 17 on the Borg scale.**Intervention:** All subjects exercised (bicycle ergometry) at baseline on day 0.
4 subjects exercised 2 hours after the dose on day 21
6 subjects exercised 8 hours after the dose on day 21**Response variables:** Primary outcome: change in heart rate before and after exercise
Secondary outcome: change in respiratory rate, change in blood pressure, workload (watts), oxygen consumption, carbon dioxide production, minute exercise ventilation, respiratory quotient, orthostatic vital signs, trough plasma carvedilol concentration on day 21**Materials:** carvedilol 12.5 mg tablet, formulation 2, batch 2
carvedilol 25 mg tablet formulation 1/25, batch 6**Assay:** R(+) and S(-)carvedilol assay involved liquid-liquid extraction from plasma then HPLC with fluorescence detection. The lower limit of quantification for R(+) and S(-)carvedilol was 0.3 ng/mL.**Results:** 12 evaluated, 10 enrolled male healthy subjects between 27 and 53 years of age completed the study. Weights of subjects are not reported. One subject ran a marathon race during the study.subject 7 acetaminophen, oxymetazoline (adrenergic vasoconstrictor)
subject 9 acetaminophen + caffeine
subject 10 aspirin + caffeine**Pharmacodynamic response:**

There was no placebo response to compare in this study.

Figures 4 and 5 (vol 1.53 pages 293-294) show trends suggesting blockade of exercise-induced increases in heart rate and systolic blood pressure. In the figures, responses are recorded at rest, 1/2 AT (anaerobic threshold), AT, and WLmax (maximum workload).

The sponsor claims there was no difference between baseline and end-of-study with regard to

exercise-induced changes in diastolic blood pressure, respiratory rate, workload (watts/kg), oxygen consumption VO₂ (mL/min/kg)

Orthostatic changes in vital signs during the course of carvedilol maintenance therapy are summarized in Table 1.

Table 1

Number of subjects with orthostatic changes on carvedilol therapy (N=10)

Parameter measured supine to standing	Number with fall > 10 mm Hg			
	Pretreatment baseline	12.5 mg/d x 1 week	25 mg/d x 1 week	25 mg/d x 2 weeks
DBP	0	0	0	0
SBP	0	1	0	3
	Number with increase > 20 beats per minute			
Pulse	3	0	3	2

SBP = systolic blood pressure. DBP = diastolic blood pressure.

Adverse events:

- tiredness 6/10 subjects
- common cold 4/10
- headache 1/10
- dizzy 1/10
- nocturia 1/10
- weight gain 1/10
- increased sleep 1/10
- swollen feeling 1/10

decreased platelets (normal 150-400): 1/10 fell to 130, 1/10 fell to 106

Conclusions:

The protocol claims to measure exercise tolerance at "peak (2 hours post-dose) or trough (8 hours post-dose)." Neither the protocol nor the study report indicate (1) if peak refers to peak plasma carvedilol concentration or to E_{max}, (2) if trough refers to trough plasma carvedilol concentration or time of least effect. Other studies suggest T_{max} is 1.5 hours. Time to E_{max} varies depending on the parameter being measured. Since 8 hours represents about one-half life of carvedilol, the trough plasma carvedilol concentration cannot occur at 8 hours. Since time to E_{max} is up to 6 hours for some parameters, e.g., diastolic blood pressure, the time of least effect is unlikely at 8 hours after dose administration. The study report indicates overlap of responses measured 2 and 8 hours after the dose on day 21.

No statistical comparisons were attempted in this study due to small sample size. There is an

unexplained problem with missing data from subjects exercised 2 hours after dose administration at the end of the study.

When results are combined for subjects exercised 2 and 8 hours after dose administration on the last study day, there appears to be a trend suggesting carvedilol's effect on reduction of exercise-induced increases in heart rate and systolic blood pressure.

I do not feel this study can support the following claims:

- (1) that there is no difference between baseline and treatment effects for any of the other response variables.
- (2) that there is no difference between peak and trough effects for any of the other response variables.

There was no method for assessment of compliance.

The study reported carvedilol concentrations obtained after 2 weeks of dosing. Assessment of concentration effect relationships is difficult because there is no placebo-corrected effect to correlate with concentration.

There is no report of R(+) and S(-)carvedilol concentrations.

Although the report and the protocol claim the subjects exercised either 2 or 8 hours after dose administration on the last day of the study, the tables in Appendices 1.1, 1.2, 1.3, 1.4, 1.5, and 1.6 claim subjects were exercised either 2 or 6 hours after dose administration.

Side effects are listed above.

The time of analgesic use with relation to exercise is unknown. The confounding effect of analgesic use on exercise performance is unknown.

There is no placebo group with which to compare pharmacodynamic effects. Therefore, I do not feel this study can support a claim that there is a significant difference between baseline and treatment for any of the response variables.

Figure 4 Effects of Carvedilol on Blood Pressure

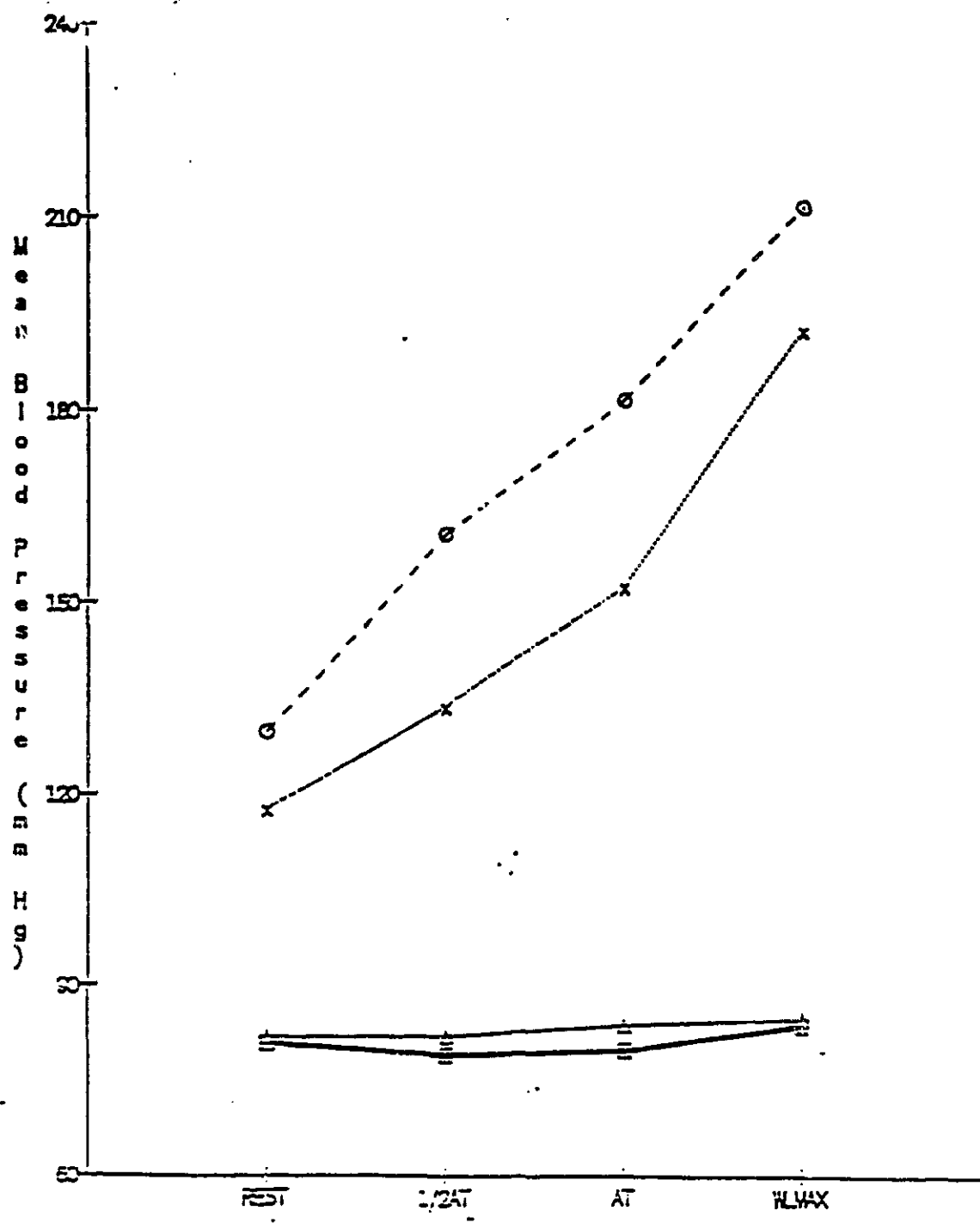


Figure 4. Mean systolic blood pressure immediately before exercise and at 1/2 anaerobic threshold, anaerobic threshold, and maximal workload (X; n=10, 10, 10, 9, respectively) and after three weeks of carvedilol treatment (CIRCLE; n=10, 10, 10, 10, respectively).

Mean diastolic blood pressure immediately before exercise and at 1/2 anaerobic threshold, anaerobic threshold, and maximal workload prior to first dose (TRIANGLE; n=10, 10, 10, 10, respectively) and after three weeks of carvedilol treatment (SQUARE; n=10, 9, 9, 8, respectively).

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Figure 5 Effect of Carvedilol on Heart Rate

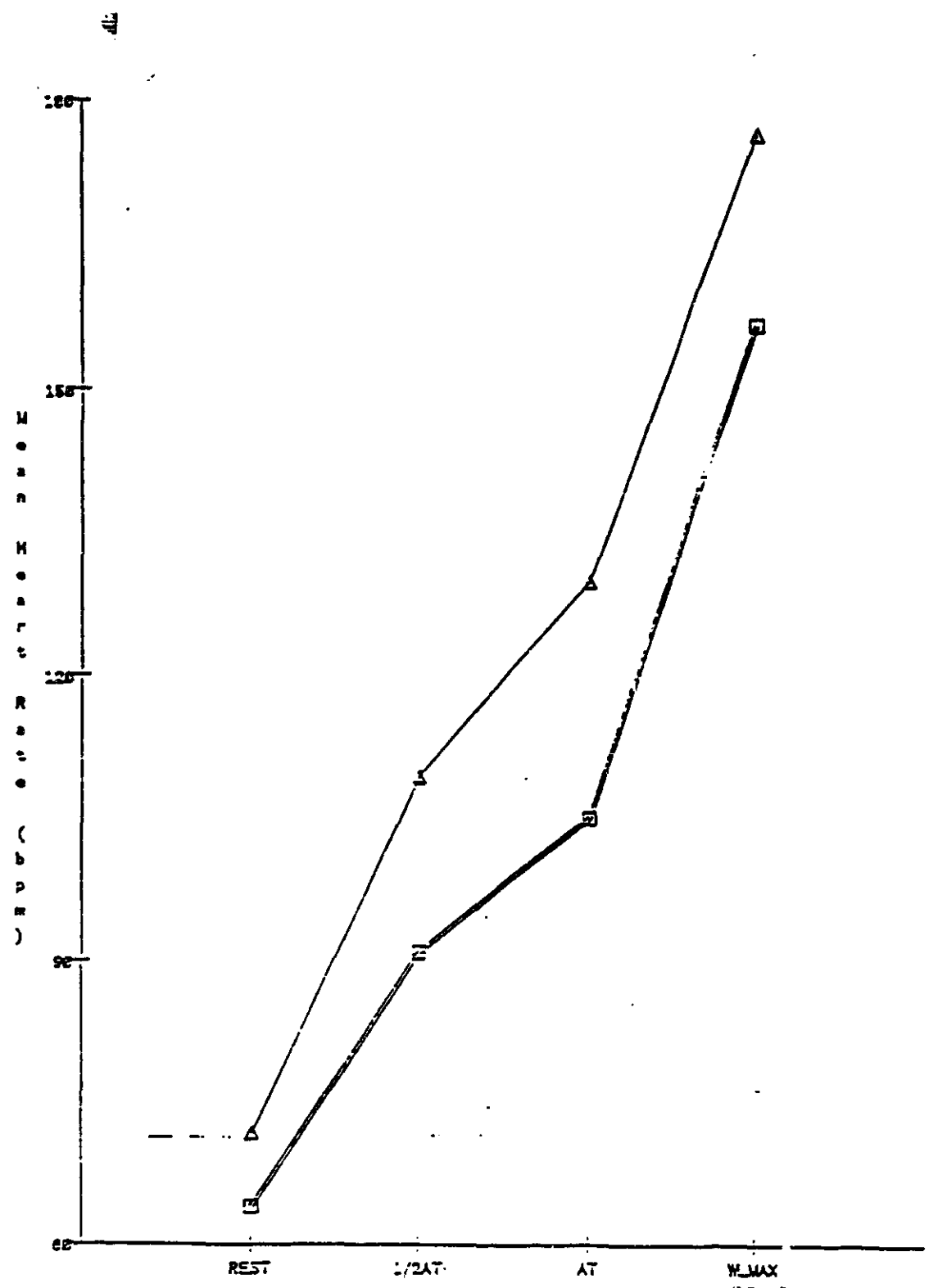


Figure 5. Mean heart rate (bpm) immediately before and during exercise (at 1/2 anaerobic threshold, anaerobic threshold, and maximal workload) prior to first dose (TRIANGLE) and after three weeks of carvedilol treatment (SQUARE); n = 10.

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INT-CAR-225CA
PAGE 000294

Reviewer: James F. Graumlich

INT-CAR-30A is a double-blind, placebo-controlled, 4-period crossover study of single doses of carvedilol 6.25 mg, 12.5 mg, 25 mg, and 50 mg in 7 healthy men. The sequence for carvedilol treatments was ascending in dose strength. Placebo sequence was random. Treatment periods were separated by one week. The objective was to measure beta-blockade by carvedilol using the exercise step test. An additional objective was to determine the lowest dose causing an acute decrease in systolic blood pressure. The subjects (aged 21 - 31 years) had a mean weight of 77.6 kg. There were no clinically significant lab abnormalities related to treatment. There were 2 drop-outs. One subject had symptomatic orthostatic hypotension (supine BP 112/68, standing BP 68/58) 2 hours after carvedilol 25 mg po. Another subject was withdrawn because he had asthma during childhood and because he was drunk on one of the treatment days. Another subject, who completed the study, had symptomatic orthostatic hypotension (supine BP 108/72, standing BP 42/0) one hour after carvedilol 25 mg po. Other symptoms associated with carvedilol were lightheadedness in 6 of 7, headache in 3 of 7, nausea in 2 of 7, sweating in 1 of 7, and chest tightness in 1 of 7. Most of these symptoms occurred in subjects receiving carvedilol 50 mg. There were no symptoms reported in subjects receiving placebo. Beta blockade was determined based on carvedilol's blockade of exercise-induced increases in heart rate (see Figure 2 from page 147, volume 1.113). The maximum reduction in exercise-induced increases in heart rate occurred 2 hours after the dose. The following table shows the effect on exercise heart rate at 2 hours after the dose (from page 144, volume 1.113). Volume 1.113 contains no information on minimum or maximum values for individuals.

Dose	Exercise heart rate beats/min (mean ± SD)	reduction compared to baseline %
placebo	164.5 ± 15.8	+ 1.2
6.25 mg	153.2 ± 10.3	- 5.9
12.5 mg	150.8 ± 4.7	- 8.7
25 mg	141.2 ± 5.4	- 14
50 mg	136.0 ± 13.7	- 14.9

The sponsor does not offer statistical comparisons between the means for the dose groups. It appears the 95% confidence intervals for the various means overlap. Therefore, the various carvedilol group means are not statistically, significantly different from the placebo group mean. There is a trend suggesting a dose-response relationship for carvedilol doses and reductions in exercise-induced tachycardia.

Carvedilol did not cause significant changes in supine heart rate during the 24 hours of observation after the dose (see Figure 8, page 153, volume 1.113). It is unknown if the sample size was adequate to detect a difference. Carvedilol did not cause significant changes in standing heart rate (see Figure 7, page 152, volume 1.113). It is unknown if the sample size was adequate to detect a difference. The effect of carvedilol on supine and standing systolic and diastolic blood pressure are shown in Figures 4 (page 149), Figure 6 (page 151), Figure 10 (page 155), and Figure 12 (page 157). Means for carvedilol groups were not significantly different from the mean for placebo for each response.

Conclusions: This cross-over study was not randomized with respect to the sequence of carvedilol treatments. The sample size was small. The study may not have had adequate power to detect differences if present. The study did not demonstrate significant beta-blocker effect when compared to placebo although there were trends suggesting treatment effect. Vasodilation (as measured by changes from baseline in mean standing diastolic blood pressure) was not statistically, significantly different in any of the treatment groups when compared to placebo.

INTCAR30

Exercise H.R.-Mean Change from Baseline

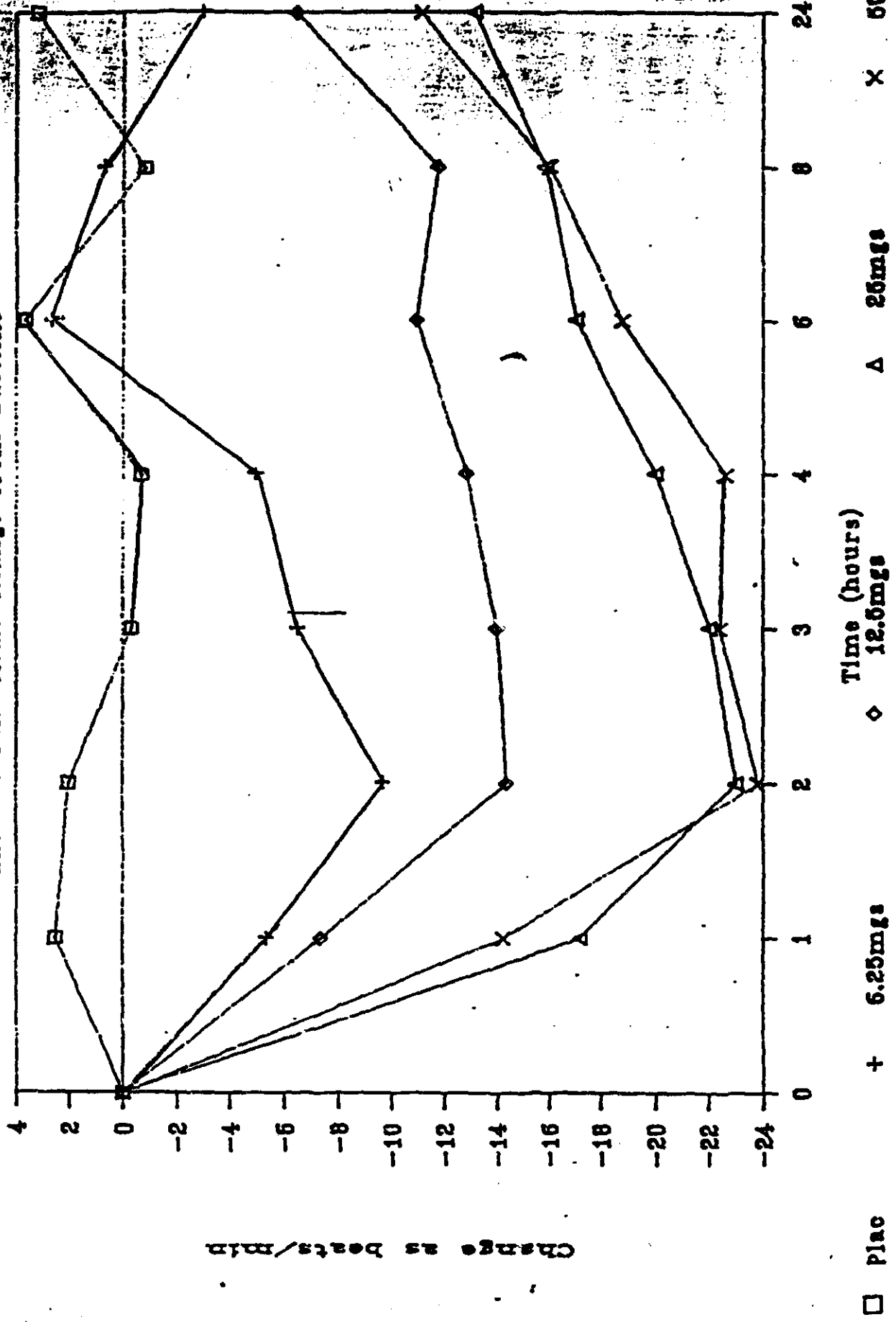
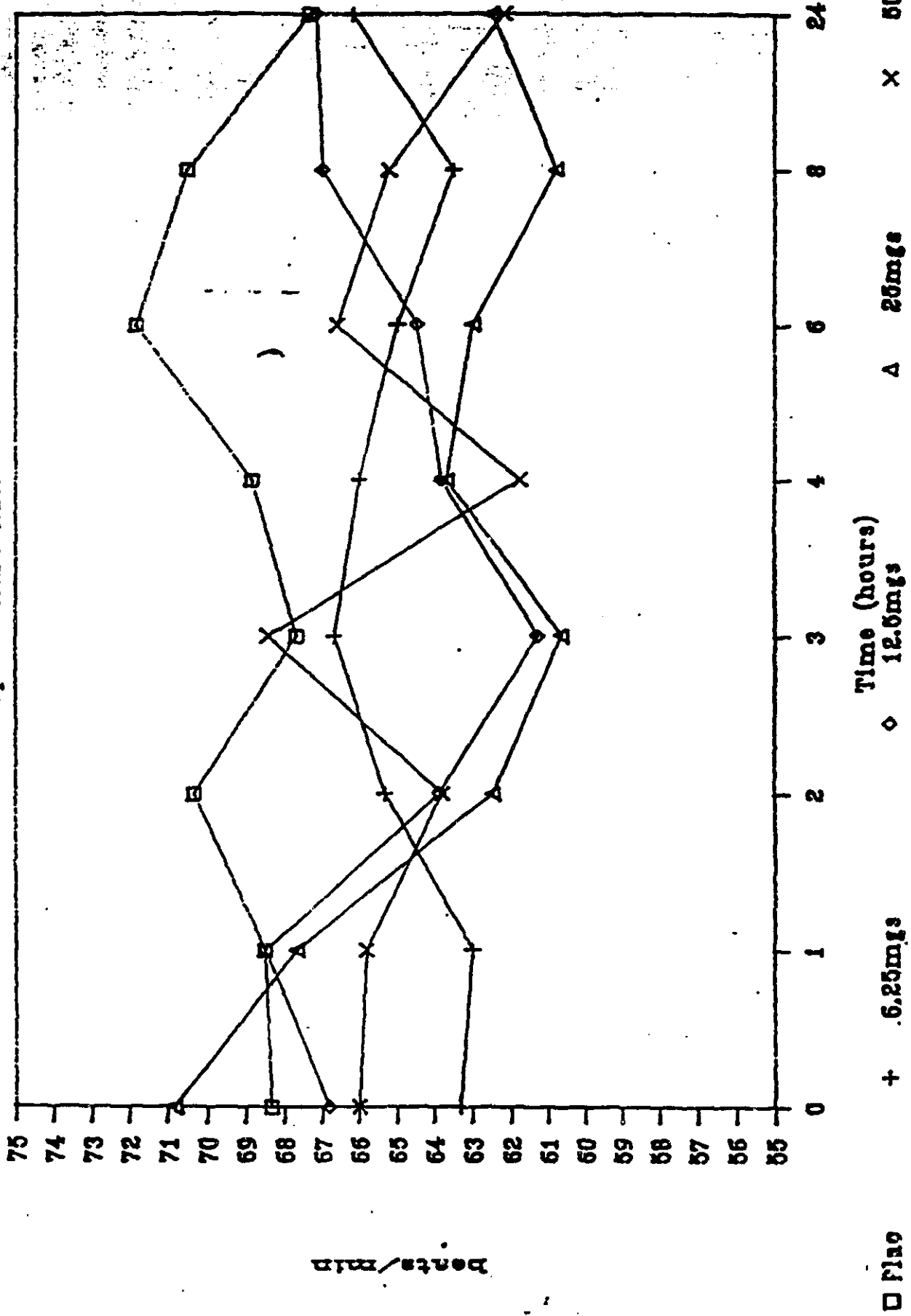


FIGURE 2

INTCAR30

Supine Heart Rate

FIGURE 8



C76

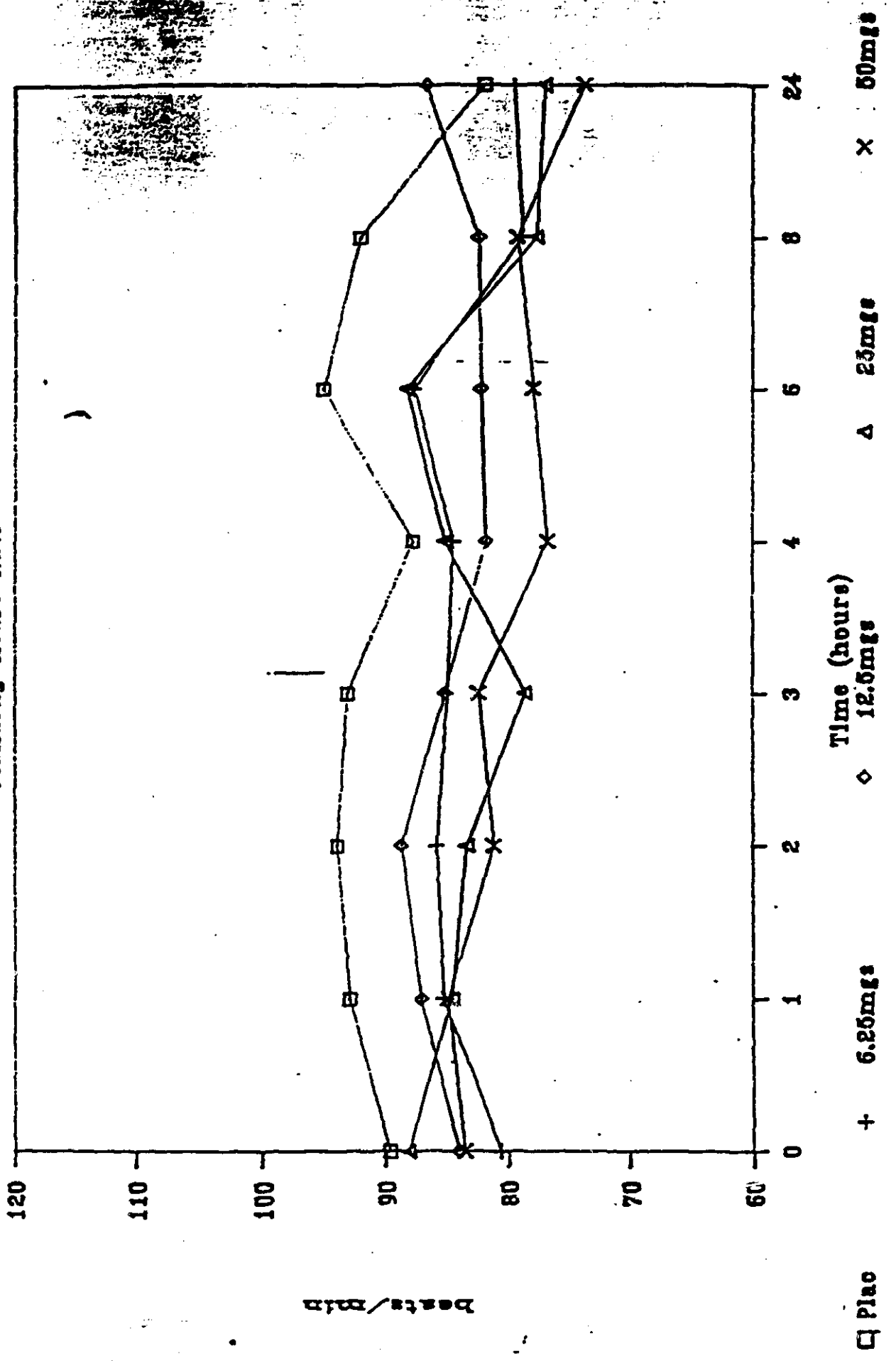
□ Place

FIGURE 7

30

INTCAR30

Standing Heart Rate



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INT'CAR30

Standing DBP -- Change from Baseline

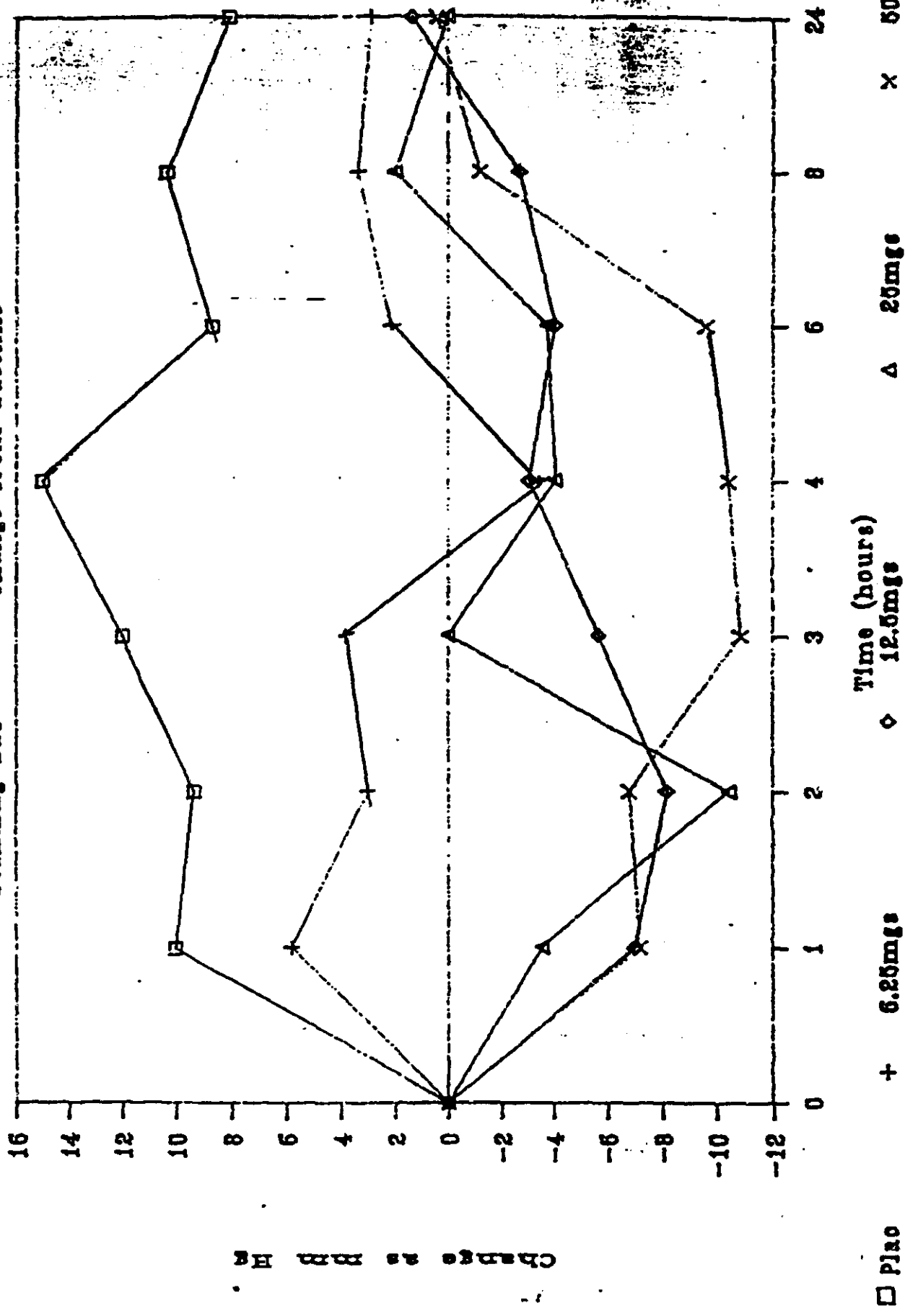


FIGURE 4

Change in mm Hg

□ Placebo

+ 6.25mg

◇ 12.5mg

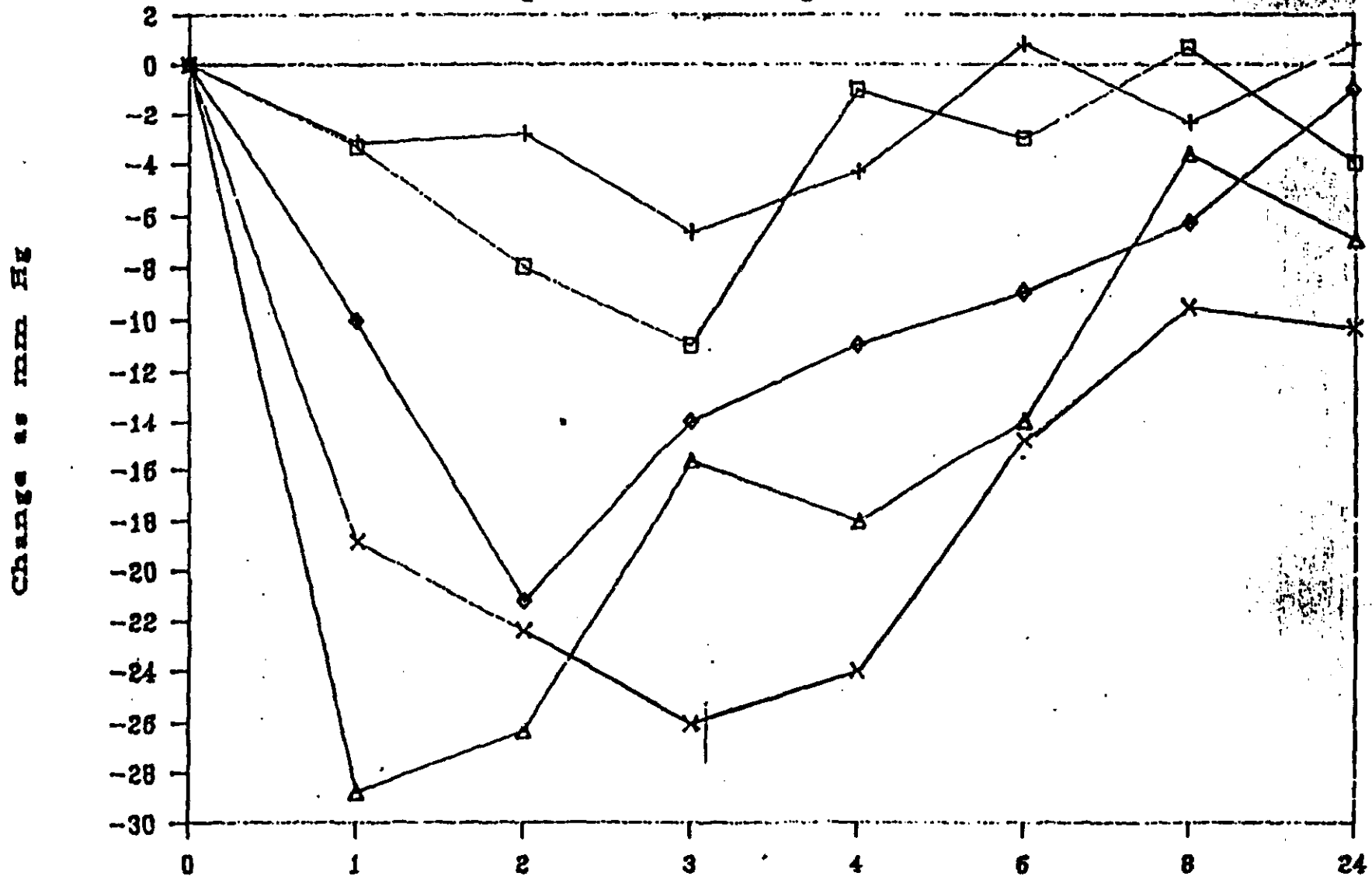
△ 25mg

x 50mg

FIGURE 6

INTCAR30

Standing SBP --- Change from Baseline



□ Place

+ 6.25mg

◇ 12.5mg

△ 25mg

× 50mg

000151

C79

INTCAR30

Supine SBP - - - Change from Baseline

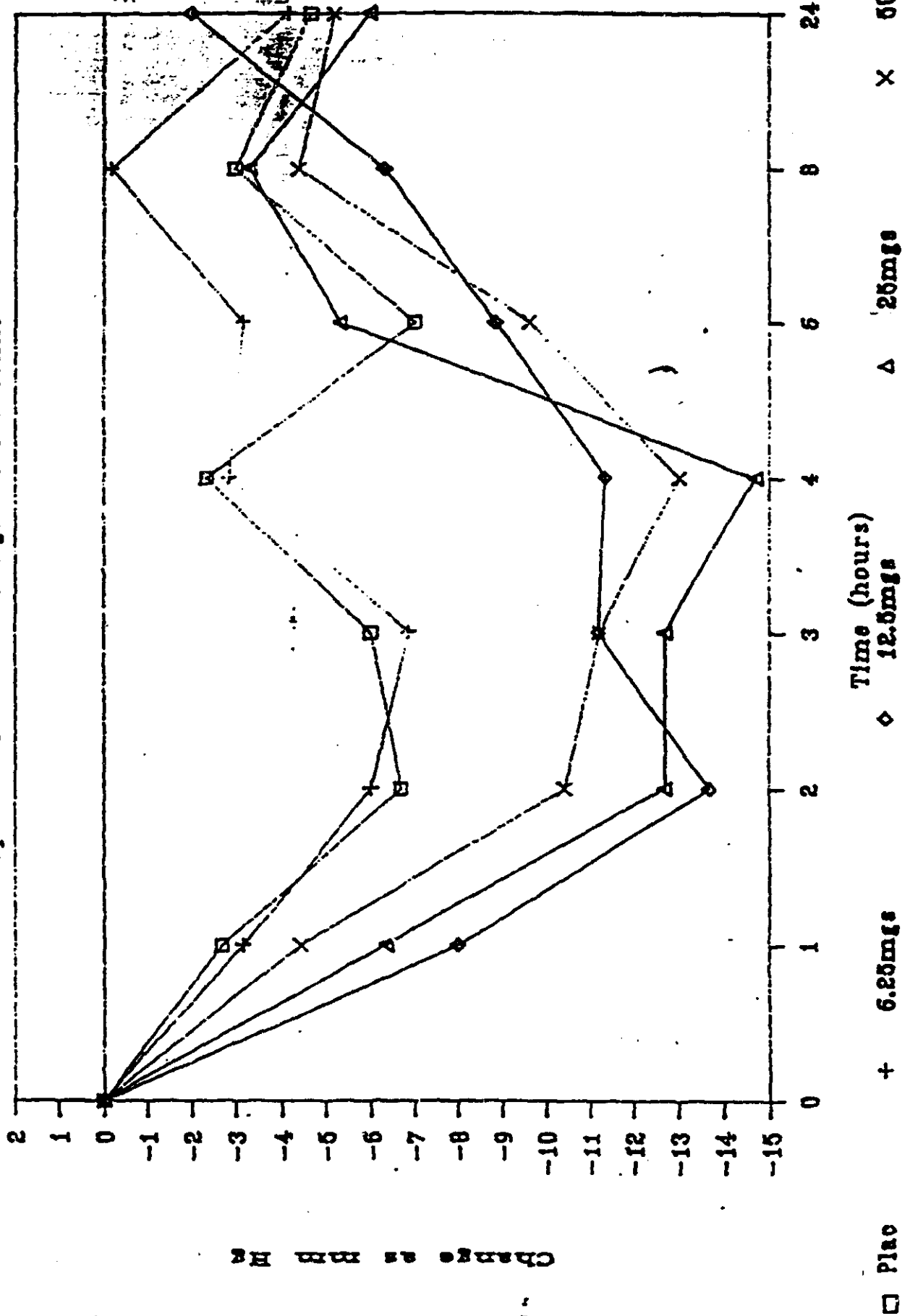


FIGURE 10

: 35 :

INTCAR30

Supine DBP - Change from Baseline

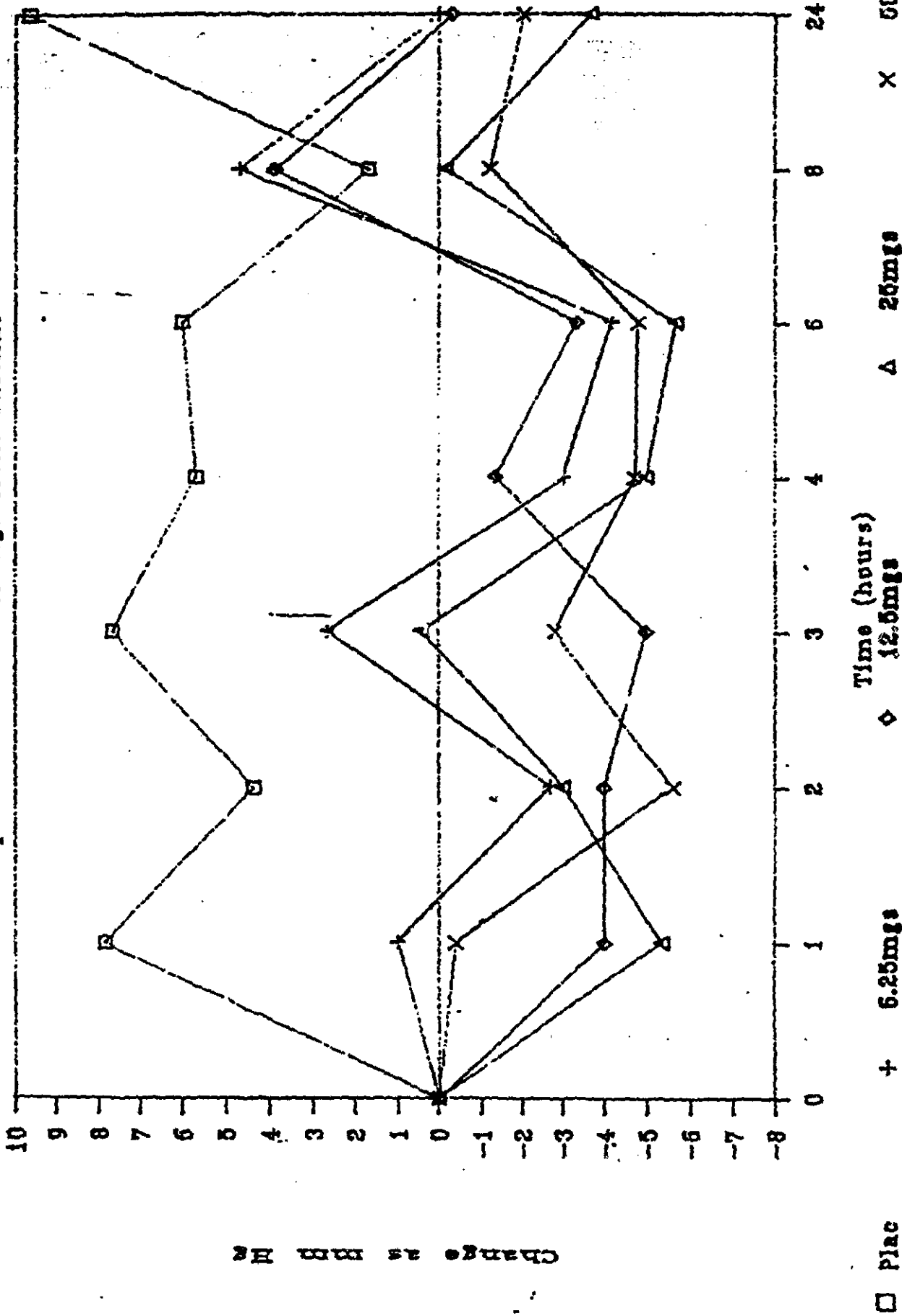


FIGURE 12

Change as mm Hg

PROTOCOL INT.CAR.30B VOL 1.113

Reviewer: James F. Graumlich, Carvedilol NDA 20-297

INT-CAR-30B is a double-blind, placebo-controlled, partially-randomized, 5-period crossover study comparing single doses of study medication: placebo, labetalol 400 mg, and carvedilol 6.25 mg, 12.5 mg, 25 mg. The study was partially-randomized because carvedilol 6.25 mg, labetalol and placebo were presented in random sequence while, for safety reasons, carvedilol 25 mg was always preceded by carvedilol 12.5 mg. Treatments were separated by a week. Subjects were 10 healthy men, aged 19 - 32 years, median weight 73 kg. The objective was to determine the threshold oral dose of carvedilol for alpha blockade as assessed by the effect of carvedilol on phenylephrine (alpha 1 receptor stimulant) -induced elevations in blood pressure, to determine the threshold oral dose of carvedilol for beta blockade as assessed by the effect of carvedilol on isoproterenol (isoproterenol, non-selective beta receptor stimulant) -induced changes in heart rate and blood pressure, and to compare the effects on the above parameters caused by various doses of carvedilol, labetalol and placebo. On each study day, measurements were made before and 2 hours after the dose of study drug for the following response variables: phenylephrine-induced elevations in blood pressure, isoproterenol-induced changes in heart rate, exercise-induced (step test) changes in heart rate. The step test was 30 minutes after the last infusion of phenylephrine or isoproterenol. However, the timing of the step test was not standardized with respect to the time of the dose of study medication. The endpoint for statistical analysis was not prospectively defined. Post hoc, ED50 was defined for SBP as the dose of infusion producing an increase of 15 mm Hg in SBP. Post hoc, ED 50 for heart rate was defined as the dose of infusion producing an increase of 25 beats/min in heart rate. Dose-response curves were drawn for phenylephrine and isoproterenol pre- and post-dose of study medication. ED50 was extrapolated from the dose-response curves.

There were no drop-outs. Other than the usual symptoms of lightheadedness, headache, and nausea, no other clinically significant adverse events were reported.

Hypoglycemia occurred in 4 of 10 subjects (normal glucose 3.5 - 7.0): glucose 1.4 after carvedilol 6.25, glucose 1.6 after carvedilol 6.25, glucose 3.2 after carvedilol 25 mg, and glucose 3.2 after labetalol 400 mg. See Conclusions (page C83) for a potential explanation of the hypoglycemia.

One of 10 subjects had serum sodium 153 (normal 135 - 145) after carvedilol 25 mg. No data were reported from the phenylephrine, isoproterenol, and step-test studies done before the dose of study medication.

The mean % response in SBP versus log-dose of phenylephrine is displayed on the top graph, Figure 1a, page C86. At the ED50, SBP responses to phenylephrine were not statistically different for carvedilol 6.25 mg vs placebo and carvedilol 25 mg vs placebo. Although carvedilol 12.5 mg was statistically different from placebo at the ED50 (ratio of ED50 = 1.33, 95% confidence interval 1.07 to 1.65, $p = 0.013$), the clinical significance of this difference is questionable. Labetalol was a positive control and was significantly different from placebo at the ED50 (ratio of ED50 = 2.05, 95% confidence interval 1.66 to 2.54, $p < 0.001$). When reviewing the ED50 for individual subjects, only 2 of 10 had ascending ED50 values correlating with ascending doses of carvedilol. The data do not suggest carvedilol behaves as an alpha blocker.

The mean % response in SBP versus log-dose of isoproterenol is displayed on the bottom graph, Figure 1b, page C86. Subject 10 was able to increase SBP by 15 mm Hg after carvedilol 12.5 mg and labetalol. However, Subject 10 was excluded from analysis because he did not increase SBP by 15 mm Hg while on placebo, carvedilol 6.25 mg or carvedilol 25 mg. The report does not state if Subject 10 increased SBP by 15 mm Hg when tested pre-dose. In the other 9 subjects at the ED50, carvedilol 12.5, carvedilol 25 mg, and labetalol caused significant reduction in SBP changes induced by isoproterenol.

The mean % response in heart rate versus log-dose of isoproterenol is displayed on the bottom graph, Figure 2b, page C87. Subjects 5, 7, and 9 did not achieve 50% increases in heart rate while on some doses of carvedilol or labetalol. ED50 values for subjects 5, 7, and 9 were extrapolated from the fitted curve of heart rate versus log-dose of isoproterenol. ANOVA revealed a significant interaction due to order of infusion of isoproterenol and phenylephrine.

CARVEDILOL NDA 20-297

PROTOCOL INT.CAR.30B VOL 1.113

At the ED50, each of the doses of carvedilol, as well as labetalol, was different from placebo. Although there are problems with the post hoc analysis, carvedilol did appear to have an effect as a beta-blocker with respect to suppression of tachycardia induced by isoproterenol.

The pulse rate post exercise is shown (C84, C85). All doses of carvedilol and labetalol, when compared to placebo, produced statistically significant decreases in post exercise heart rate.

Conclusions: The results of the phenylephrine and isoproterenol portions of the study may be biased by the post hoc analysis and the exclusion (post hoc) of a non-responder. In this study of healthy men, carvedilol has an effect as a beta blocker because it blocks exercise-induced increases in heart rate. Hypoglycemia was more common in this sample than in other studies I have reviewed. Alpha 2 stimulation of pancreatic beta cells results in decreased insulin secretion. Beta 2 stimulation causes increased insulin secretion. Non-specific alpha blockade with phentolamine with concomitant beta stimulation with isoproterenol increases insulin secretion (Exp-Pathol 1991; 43 (1-2):57-61). In theory, alpha blockade by carvedilol and beta stimulation by isoproterenol could produce hypoglycemia. Neither phenylephrine nor isoproterenol, when given alone, are associated with hypoglycemia.

CARVEDILOL NDA 20-297

PROTOCOL INT.CAR.30B VOL 1.113

and phenylephrine. At the ED50, each of the doses of carvedilol, as well as labetalol, was different from placebo. Although there are problems with the post hoc analysis, carvedilol did appear to have an effect as a beta-blocker with respect to suppression of tachycardia induced by isoproterenol.

The pulse rate post exercise is shown in Appendix 8 (page 238, volume 1.113) and Table 8 (page 211, volume 1.113). All doses of carvedilol and labetalol, when compared to placebo, produced statistically significant decreases in post exercise heart rate.

Conclusions: The results of the phenylephrine and isoproterenol portions of the study may be biased by the post hoc analysis and the exclusion (post hoc) of a non-responder. In this study of healthy men, carvedilol has an effect as a beta blocker because it blocks exercise-induced increases in heart rate. Hypoglycemia was more common in this sample than in other studies I have reviewed. Alpha 2 stimulation of pancreatic beta cells results in decreased insulin secretion. Beta 2 stimulation causes increased insulin secretion. Non-specific alpha blockade with phentolamine with concomitant beta stimulation with isoproterenol increases insulin secretion (Exp-Pathol 1991; 43 (1-2):57-61). In theory, alpha blockade by carvedilol and beta stimulation by isoproterenol could produce hypoglycemia. Neither phenylephrine nor isoproterenol, when given alone, are associated with hypoglycemia.

α_2 stim $\rightarrow$ $\downarrow$ insulin
 β_2 stim $\rightarrow$ $\uparrow$ insulin secretion
 isoproterenol $\rightarrow$ $\uparrow$ insulin secretion

TABLE 8

PROTOCOL INT-CAR 30B
PULSE RATE (bts/min) POST EXERCISE

(a) ANOVA on Pulse Rate

SOURCE	df	SS	F-Value	Sign.
SUBJECT	9	4728.400		
DAY	4	121.000		
TREAT	4	1983.486	10.77	<0.001
ERROR	32	1473.114		
TOTAL	49	8306.000		

(b) Estimated Treatment Differences

Contrast	Diff.	95% Conf. Interval		Sign.
		Lower	Upper	
6.25mg - Plac.	-8.9	-15.1	-2.7	0.006
12.5mg - Plac.	-10.7	-17.1	-4.4	0.002
25.0mg - Plac.	-17.4	-23.7	-11.0	<0.001
Labet. - Plac.	-17.0	-23.2	-10.8	<0.001
6.25mg - Labet.	8.1	1.9	14.3	0.012
12.5mg - Labet.	5.3	-0.1	12.6	0.052
25.0mg - Labet.	-0.4	-6.7	6.0	0.906

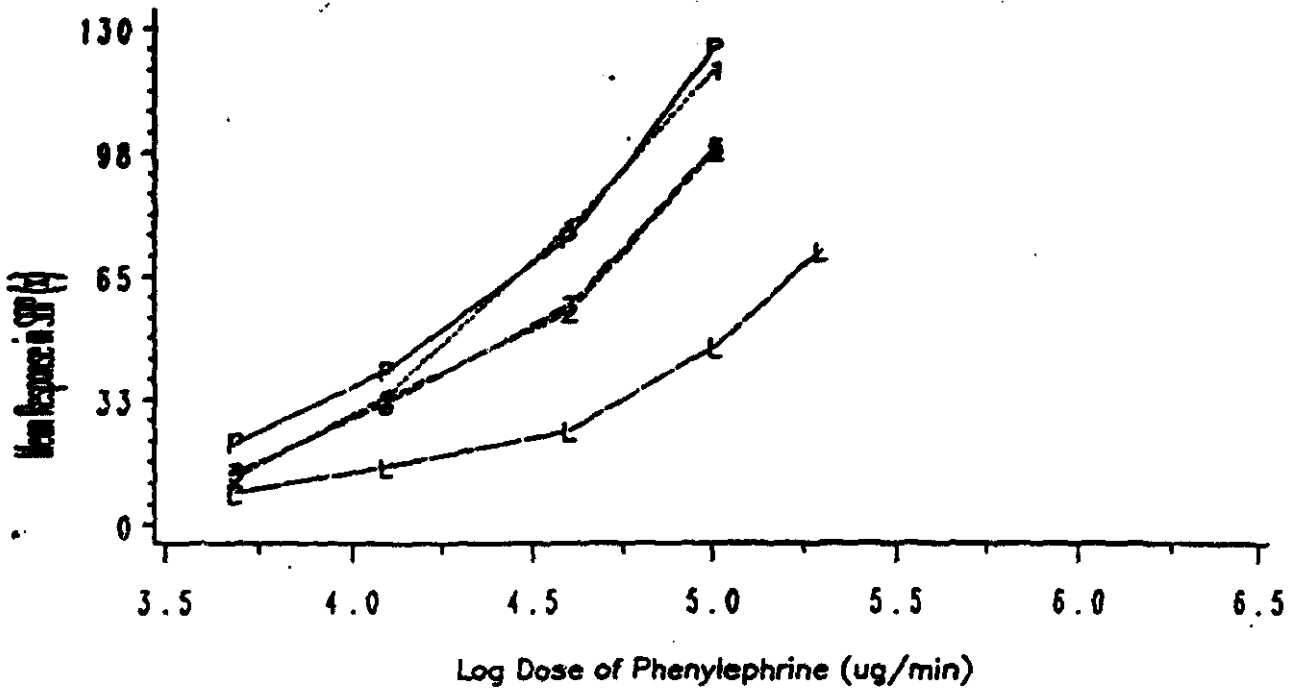
APPENDIX 8

PROTOCOL INT-CAR 30B
PULSE RATE (bts/min) POST EXERCISE

Subject	Carvedilol			Labetalol	Placebo
	6.25mg	12.5mg	25.0mg		
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
No.	10	10	10	10	10
Mean	153	151	144	145	162
SD	13	9	10	11	14

Fig. 1a

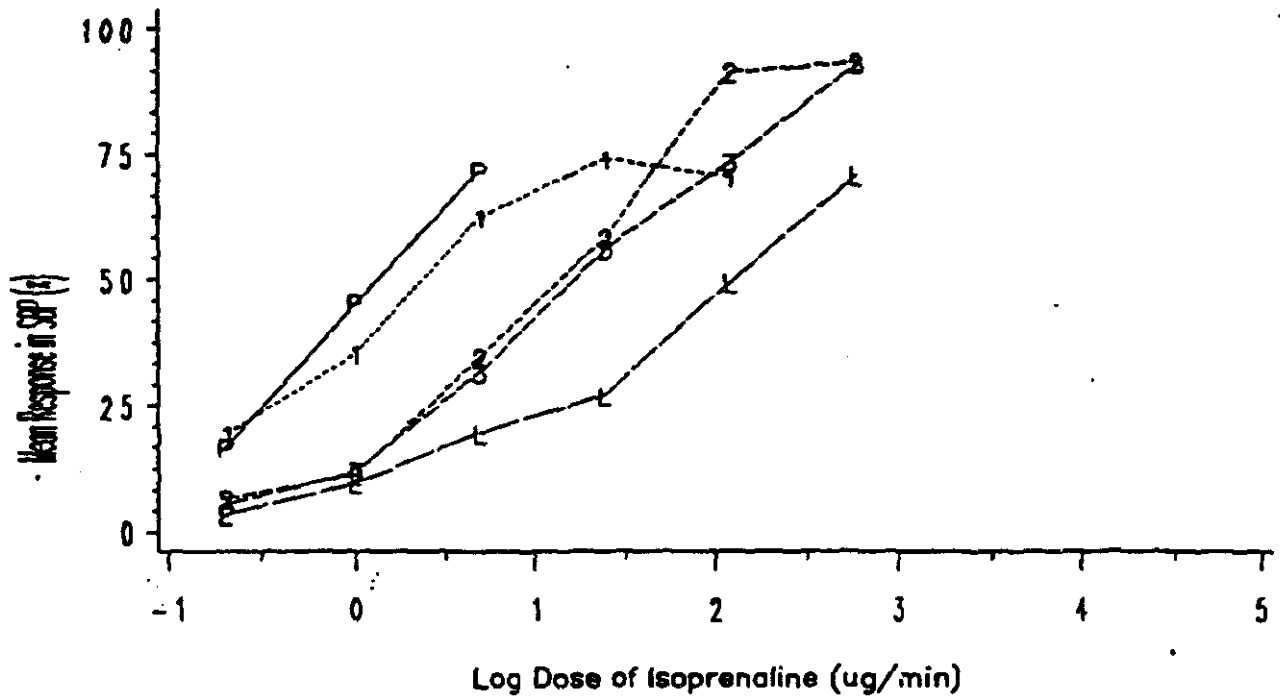
MEAN RESPONSE IN SBP VERSUS LOG-DOSE OF PHENYLEPHRINE



Treatment 1-1-1 6.25mg 2-2-2 12.5mg 3-3-3 25.0mg
 L-L-L Labelalol P-P-P Placebo

Fig. 1b

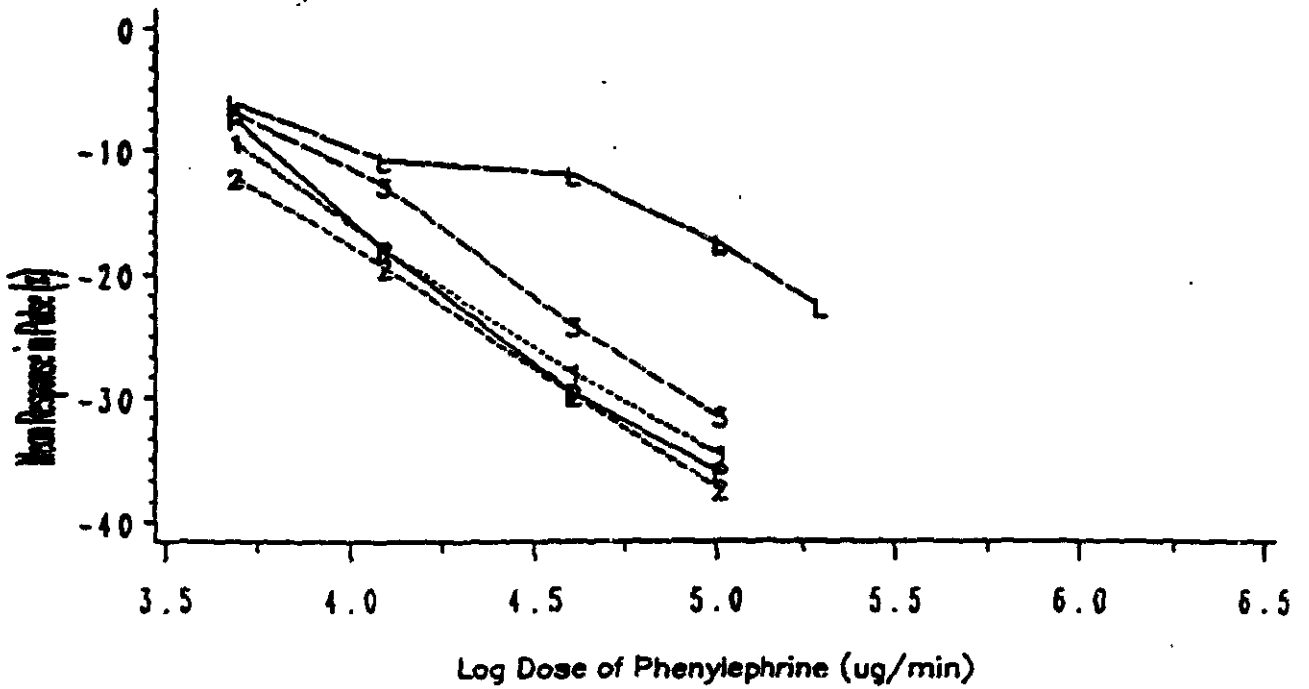
MEAN RESPONSE IN SBP VERSUS LOG-DOSE OF ISOPRENALINE



Treatment 1-1-1 6.25mg 2-2-2 12.5mg 3-3-3 25.0mg
 L-L-L Labelalol P-P-P Placebo

Fig. 2a

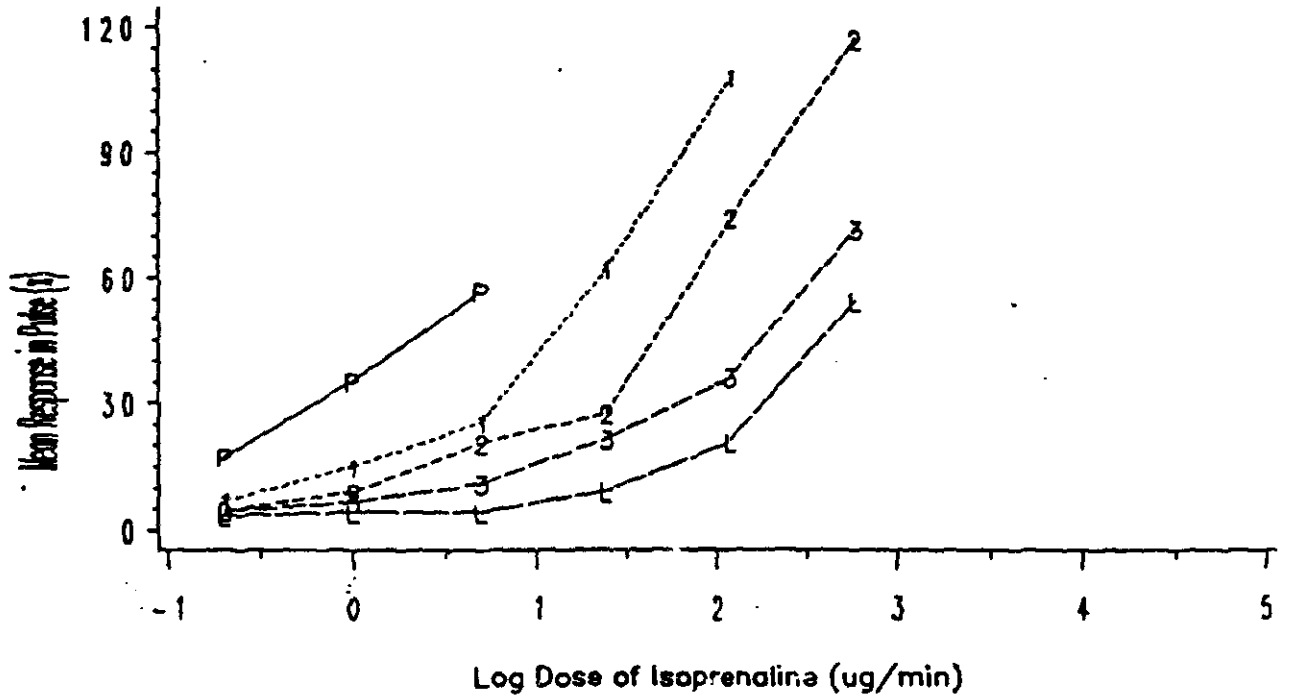
MEAN RESPONSE IN PULSE VERSUS LOG-DOSE OF PHENYLEPHRINE



Treatment 4-4-4 6.25mg 2-2-2 12.5mg 3-3-3 25.0mg
 Δ-Δ-Δ Labeletalol P-P-P Placebo

Fig. 2b

MEAN RESPONSE IN PULSE VERSUS LOG-DOSE OF ISOPRENALINE



Treatment 4-4-4 6.25mg 2-2-2 12.5mg 3-3-3 25.0mg
 Δ-Δ-Δ Labeletalol P-P-P Placebo

CARVEDILOL NDA 20-297

PROTOCOL MF2971 VOL 1.56

PD

Reviewer: James F. Graumlich

Name of study: The efficacy, safety and tolerance of carvedilol in incrementing doses with observations on haemodynamic parameters in healthy volunteers

Objectives: To study the tolerance and safety of carvedilol following single oral doses and to determine the effects of these doses on heart rate and blood pressure at rest and under dynamic exercise

Study design: 2 phase study. Phase 1 was double-blind, randomized sequence, placebo controlled, 3 period crossover phase in 6 healthy men using single oral doses of placebo, carvedilol 50 mg, and carvedilol 100 mg. Phase 2 was single-blind, uncontrolled dose escalation phase using single oral doses of 200, 300, 400, 600, and 800 mg of carvedilol per period. Periods were separated by at least 5 days.

Intervention: placebo and various doses of racemic carvedilol

Response variables: Primary outcome: heart rate and blood pressure before, during, and after exercise, supine and standing

Secondary outcome: carvedilol concentrations in plasma, Cmax, Tmax, AUC, lab safety tests

Bicycle ergometry to standardized workload was used during this study. Hemodynamic responses were measured and plasma samples were collected at baseline then 0.5, 1, 2, 4, 6, 8, and 24 hours after carvedilol administration.

Materials: carvedilol capsules (50, 100, 200, 300, 400, 600, and 800 mg) lot number 814966 Ab

Assay: Plasma assay of carvedilol involved liquid/liquid extraction, HPLC with fluorometric detection. Propranolol was the internal standard. The lower limit of quantification was 1 ng/mL.

Results: 6 healthy men between 23 and 42 years of age completed the phase 1 of the study. There were no dropouts. Weights of subjects were between 70.6 and 93.7 kg. 5 subjects took 200 mg. Orthostatic hypotension was the dose-limiting side effect that prevented 4 of 6 subjects from tolerating more than 200 mg of carvedilol.

Maximum tolerated dose (mg) based on orthostatic symptoms	Number of subjects
100	1
200	3
400	1
800	1

Pharmacodynamic response: n = 6 unless otherwise specified.

Supine systolic blood pressure after 50 mg: When comparing the means, there was no significant decrease compared to placebo during 24 hours of observation.

Supine systolic blood pressure after 100 mg: onset of effect was at 2 hours, Emax was at 4 hours (-12 mm Hg compared to placebo). After 8 hours, there was no effect when compared to placebo.

Supine systolic blood pressure after 200 mg (n = 5): onset of effect was at 2 hours, Emax was at 2 hours (-13 mm Hg compared to placebo). After 8 hours, there was no effect when compared to baseline.

Supine diastolic blood pressure after 50 mg: there was no significant decrease compared to placebo during 24 hours.

Supine diastolic blood pressure after 100 mg: onset of effect was at 4 hours, Emax was at 4 hours (-10 mm Hg compared to placebo). After 4 hours, there was no effect when compared to placebo.

Supine diastolic blood pressure after 200 mg (n = 5): onset of effect was at 2 hours, Emax was at 2 hours (-9 mm Hg compared to placebo). After 2 hours, there was no effect when compared to baseline.

Supine heart rate after 50 mg: there was a statistically significant increase (+4 beats per minute) 30 minutes after the dose. The clinical significance of this difference is questionable. There was no significant change in heart rate at the corresponding time after the 100 mg dose.

Supine heart rate after 100 mg: onset of effect was at 4 hours, Emax was at 4 hours (-4 beats per minute compared to placebo). After 8 hours, there was no effect when compared to placebo.

Supine heart rate after 200 mg (n = 5): onset of effect was at 6 hours, Emax was at 8 hours (-10 beats per minute compared to placebo). After 8 hours, there was no effect when compared to baseline.

Standing systolic blood pressure after 50 mg: onset of effect was at 2 hours, Emax was at 2 hours (-10 mm Hg compared to placebo). After 8 hours, there was no effect when compared to placebo.

Standing systolic blood pressure after 100 mg: onset of effect was at 1 hour, Emax was at 2 hours (-21 mm Hg compared to placebo). After 8 hours, there was no effect when compared to placebo.

Standing systolic blood pressure after 200 mg (n = 5): onset of effect was at 1 hour, Emax was at 2 hours (-32 mm Hg compared to placebo). After 8 hours, there was no effect when compared to baseline.

Standing diastolic blood pressure after 50 mg: there was no significant difference when compared to placebo.

Standing diastolic blood pressure after 100 mg: onset of effect was at 4 hours, Emax was at 4 hours (-17 mm Hg compared to placebo). After 6 hours, there was no effect when compared to placebo.

Standing diastolic blood pressure after 200 mg (n = 5): onset of effect was at 2 hour, Emax was at 2 hours (-25 mm Hg compared to placebo). Blood pressure was decreased from baseline at 24 hours after the dose.

Standing heart rate after 50 mg was complex: 1 hour after the dose, mean heart rate increased significantly (+14 beats per minute compared to placebo). There was no significant difference from placebo until 24 hours after the dose when mean heart rate decreased (-7 beats per minute). No other significant differences from placebo were noted.

Standing heart rate after 100 mg was complex, too. 30 minutes after the dose, mean heart rate increased (+11 beats per minute compared to placebo). At 6 and 24 hours after the dose (but not at 8 hours after the dose), there were significant decreases. Emax was at 6 hours (-10 beats per minute compared to placebo).

Standing heart rate after 200 mg (n = 5): onset of effect was at 4 hours, Emax was at 6 hours (-15 beats per minute compared to placebo). When compared to baseline, decreased heart rate continued to 24 hours.

Effects on exercise parameters: end exercise hemodynamics - pre exercise hemodynamics were compared to placebo.

Exercise-induced increases in systolic blood pressure were blunted by 50 mg (-24 mm Hg compared to placebo). Onset of effect was at 2 hours. Emax was at 4 hours. After 4 hours, there was no effect when compared to placebo.

Exercise-induced increases in systolic blood pressure were blunted by 100 mg (-33 mm Hg compared to placebo). Onset of effect was at 1 hour. Emax was at 2 hours. After 8 hours, there was no effect when compared to placebo.

In 5 subjects, exercise-induced increases in systolic blood pressure were blunted by 200 mg. Onset of effect was at 1 hour. Emax was at 2 hours. After 8 hours, there was no effect when compared to baseline.

Exercise-induced decreases in diastolic blood pressure after 50 mg were not statistically different from placebo responses.

Exercise-induced decreases in diastolic blood pressure were blunted by 100 mg (+21 mm Hg compared to placebo). Effect was significant only at 6 hours after the dose.

Exercise-induced increases in heart rate were blunted by 50 mg: Onset of effect was at 1 hour. Emax was at 2 hours (-20 beats per minute compared to placebo). After 8 hours, there was no effect when compared to placebo.

Exercise-induced increases in heart rate were blunted by 100 mg: Onset of effect was at 1 hour. Emax was at 2 hours (-29 beats per minute compared to placebo). When compared to placebo, decreases in heart rate were present 24 hours after the dose.

Exercise-induced increases in heart rate were blunted by 200 mg. Onset of effect was at 1 hour. Emax was at 2 hours (-40 beats per minute compared to placebo). When compared to baseline, decreases in heart rate were present 24 hours after the dose.

There are no tables or figures demonstrating an attempt to correlate plasma concentrations of carvedilol with hemodynamic variables.

PK parameters for carvedilol are in table 18 (attached).

Subject 5 tolerated doses of carvedilol up to 800 mg. When compared to the other subjects, subject 5 had the lowest AUCs for the 50, 100, and 200 mg doses.

Adverse events: There were no deaths nor withdrawals.

Treatment emergent symptoms and signs were

headache 5/6 nausea 3/6
vomit 1/6 orthostatic faintness 6/6

Only one subject, subject 5, had prolongation of QTc. His QTc change was from 0.41 on placebo to 0.46 sec on 800 mg.

Conclusions:

In healthy men, single oral doses of carvedilol cause beta blockade by blocking exercise-induced tachycardia.

Carvedilol 50 mg did not significantly effect supine blood pressure. However, carvedilol 50 mg significantly decreased standing and exercising blood pressure. The duration of effect was less than 8 hours.

There appears to be dose-proportionality of AUC for single doses between 50 and 200 mg of oral carvedilol.

Orthostatic hypotension was the dose-limiting side effect that prevented 1 of 6 subjects from tolerating more than 100 mg of carvedilol.

Orthostatic hypotension was the dose-limiting side effect that prevented 4 of 6 subjects from tolerating more than 200 mg of carvedilol.

Concentration-effect relationships were not analyzed.

There was no placebo group with which to compare pharmacodynamic responses for carvedilol doses greater than 100 mg.

Doses of carvedilol less than 100 mg did not have an effect on supine systolic or diastolic blood pressure in this study.

The results of this study must be interpreted in the context of a single dose study in healthy men.

Table 10

Pharmacokinetic parameters.

$$\text{Conc} = -A e^{-bt} + C e^{-dt} + F e^{-gt}$$

	50 mg	100 mg	200 mg.	
A	126.62	255.20	2232.44	
b	3.465	2.924	0.790	
C	104.63	232.07	2154.63	
d	0.361	0.343	0.559	
F	21.97	23.21	47.02	
g	0.067	0.040	0.045	
$t_{1/2}$ (b)	0.20	0.27	0.80	Hours
(d)	1.92	2.02	1.20	Hours.
(g)	7.96	14.40	15.40	Hours.
Delay	0.331	0.132	0.319	Hours.
r_2	0.9597	0.9270	0.9509	
A.U.C.	305.88	1050.99	2060.35	ng/ml . h
Peak Conc.	91.5	166.5	282.3	ng/ml
Time to peak	1.10	1.00	1.07	Hours.

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MF 2971
VOL 1.56
000126

CARVEDILOL NDA 20-297

PROTOCOL MF3132I VOL 1.125

Reviewer: James F. Graumlich

MF3132I is a double-blind, placebo-controlled, randomized-sequence, 5-period crossover study in 6 healthy men. The objective was to determine the tolerance, time course and peak effect of single doses of carvedilol 100 mg, labetalol 200 mg, propranolol 160 mg, pindolol 10 mg and placebo. The randomized crossover phase was preceded by measurement of exercise load then exercise training to achieve maximum load in a reproducible manner. During the randomized treatment phase, treatments were separated by at least 5 days. Response endpoints were systolic and diastolic blood pressure in supine and standing positions at rest and during exercise, heart rate PR interval, QT interval, ventricular extra-systoles/min, norepinephrine concentrations, and lab safety tests. Serial observations occurred up to 4 hours after the dose.

Subjects were 6 healthy men (aged 25 - 43 years) who weighed 62.8 - 93.7 kg. Subject #3 withdrew due to a scheduling conflict and another subject replaced Subject #3.

There were four observations of effect at 1, 2, 3, and 4 hours after the dose. The pre-dose baseline measurements appear to be comparable between treatments for the following endpoints: supine and standing SBP, supine and standing DBP, supine and standing pulse, exercise SBP, exercise DBP, exercise pulse, plasma norepinephrine concentration. The time course of the effect is shown in Figures 1 - 4, pages C94-C97. The maximum effect of carvedilol 100 mg occurs at 1 - 2 hours for the following endpoints: supine and standing BP, resting and exercising BP. Propranolol, pindolol, and labetalol served as positive controls. Figure 4 shows little change in pulse over 4 hours of observation for all 5 treatments. Neither the maximum effect of carvedilol 100 mg on pulse nor the time to maximum effect on pulse can be determined from this study.

Figures 7 - 8 (C98, C99) show blood pressure and heart rate 2 hours after the dose and the comparisons to the pre-dose baseline. Carvedilol 100 mg acted like the other beta blockers to block exercise-induced increases in systolic blood pressure and pulse. Carvedilol 100 mg also caused significant decrease in supine SBP but no significant change in supine DBP. The difference of the placebo mean minus the carvedilol mean is 16.6 mm Hg. Carvedilol 100 mg caused significant decrease in orthostatic SBP and DBP. Supine and orthostatic pulse were not affected by carvedilol in this study. As noted in the paragraph above, the observation time may not have been long enough to detect a maximum effect on pulse.

Changes in norepinephrine concentration are shown in Figures 5, 6, and 9 (pages C100-C102). When compared to pre-dose baseline concentrations, carvedilol 100 mg increased norepinephrine concentrations in supine, standing, and exercising subjects. However, when compared to placebo, the increases in norepinephrine concentrations were not significant.

PR and QTc results were not subjected to statistical analysis. There was no trend suggesting treatment-emergent, clinically-relevant, prolongation of PR or QTc. There are no tables in the report showing ventricular extra-systoles.

Adverse events: headaches, tiredness, dyspnea on exertion, dreams, faintness on exertion, orthostatic faintness.

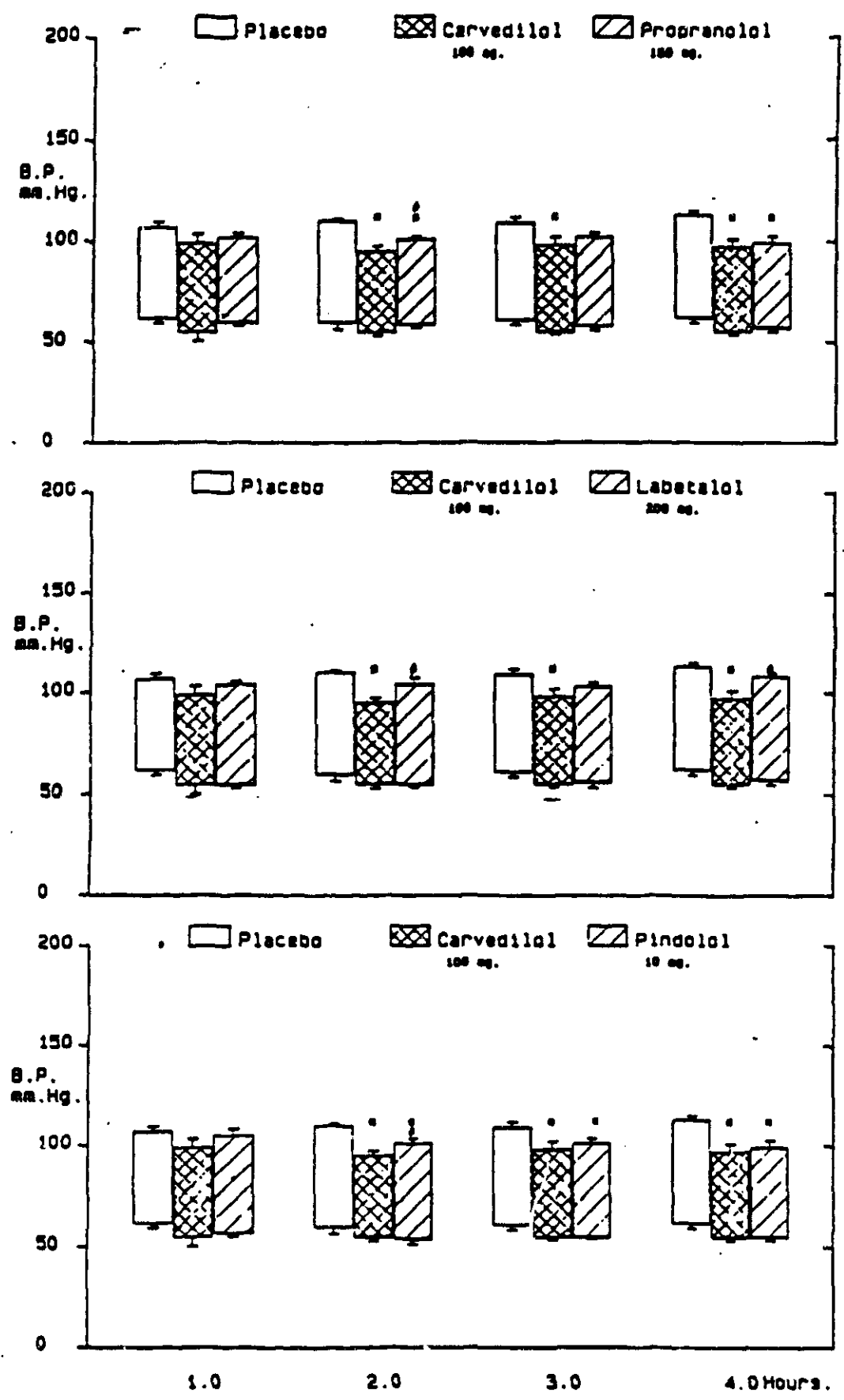
Conclusions: The maximum effect of carvedilol 100 mg on SBP and DBP occurs at 1 - 2 hours after the dose. Carvedilol 100 mg acted like the other beta blockers to block exercise-induced increases in systolic blood pressure and pulse. Carvedilol 100 mg also caused significant decrease in supine SBP but no significant change in supine DBP. Carvedilol 100 mg caused significant decrease in orthostatic SBP and DBP. Supine and orthostatic pulse were not affected by carvedilol in this study.

When compared to placebo, increases in norepinephrine concentrations were not significant.

Figure 1
Supine Blood Pressure with Carvedilol compared to
Placebo, Propranolol, Labetalol and Pindolol (n=6).

M9 - 45

C94



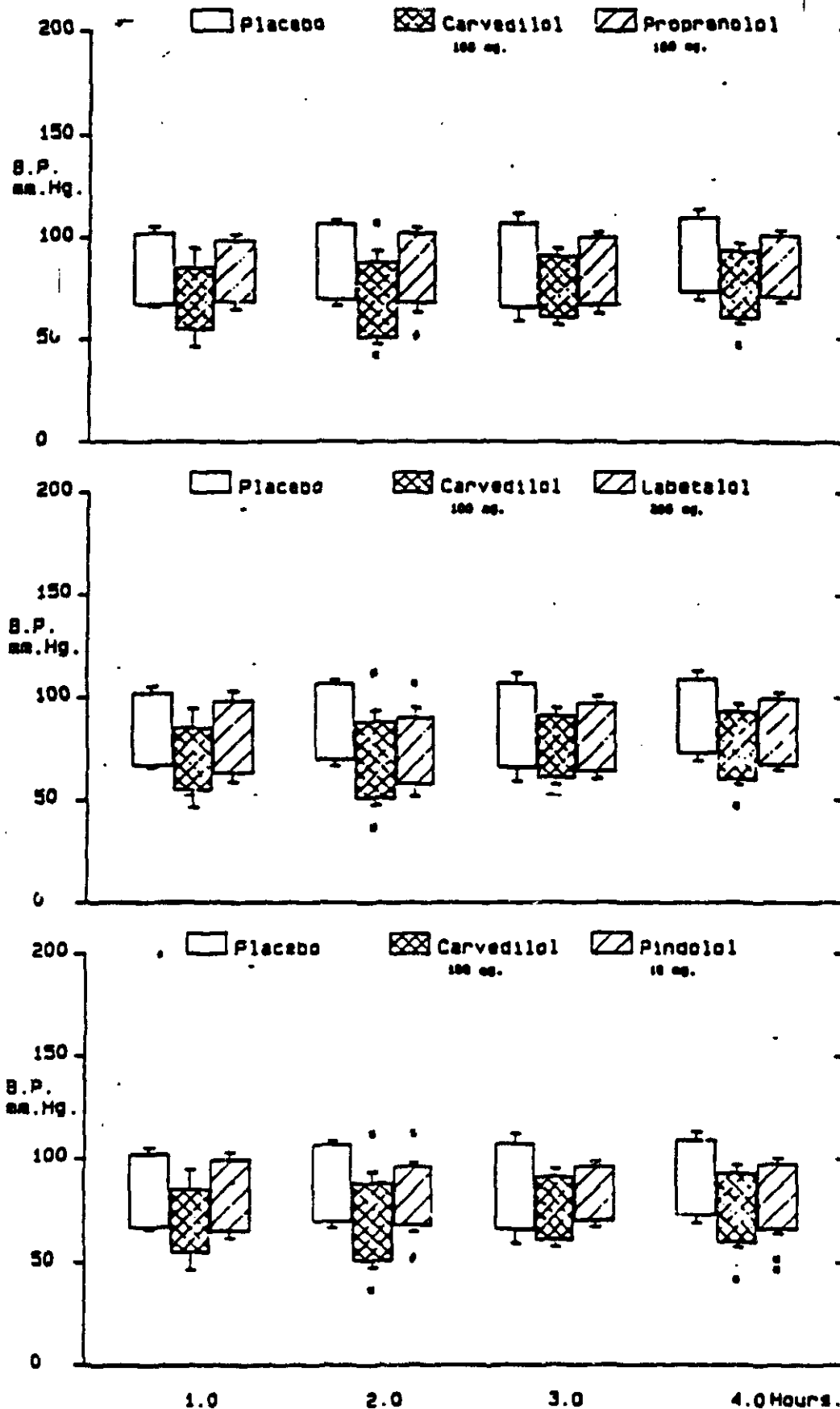
* p < 0.05 compared with Placebo.
p < 0.05 compared with Carvedilol.

Figure 2

M9 - 45

C95

Erect Blood Pressure with Carvedilol compared to Placebo, Propranolol, Labetalol and Pindolol (n=6), except for Car. at 2h. (n=5)



• $p < 0.05$ compared with Placebo.
 ◊ $p < 0.05$ compared with Carvedilol.

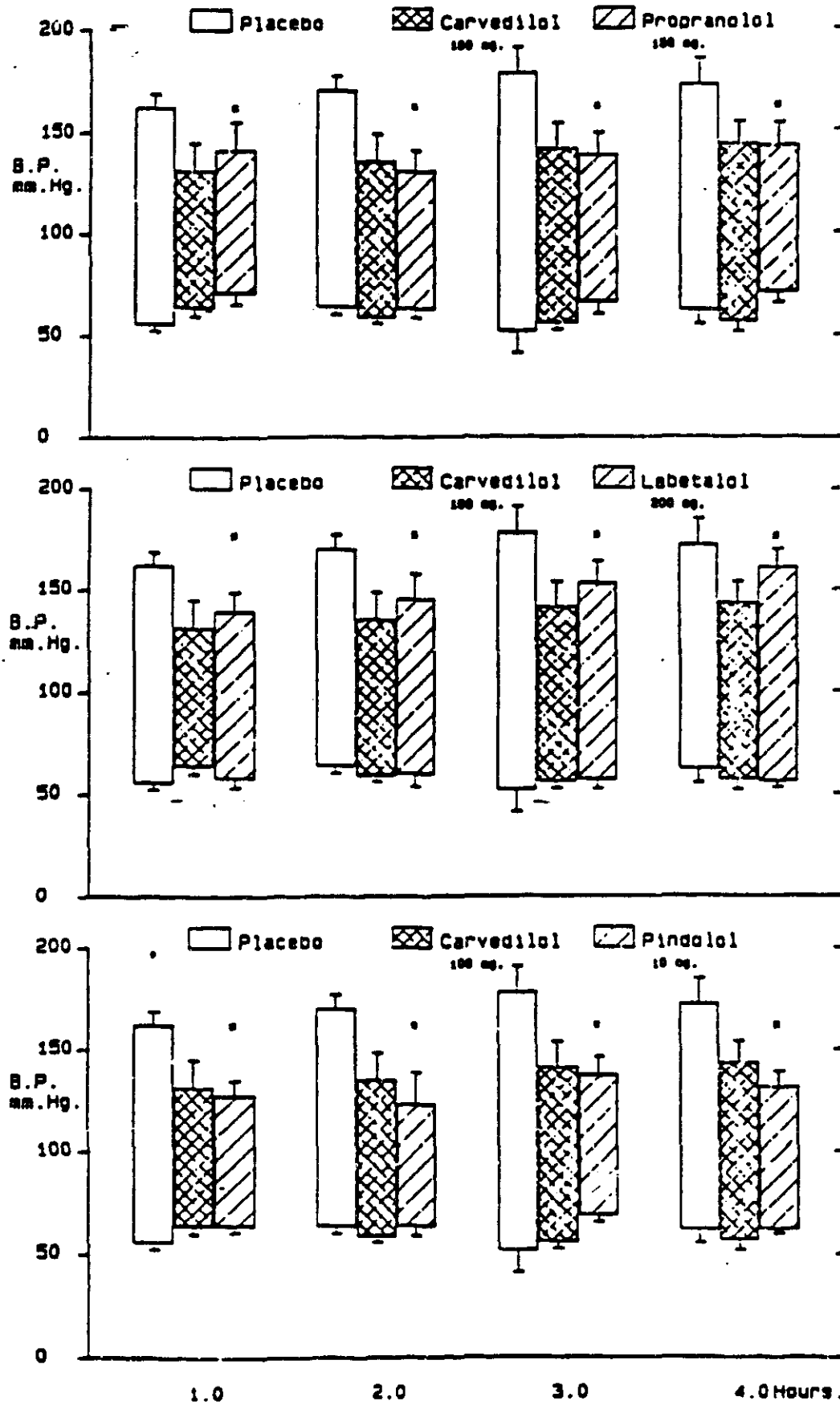
000049

Figure 3

Exercise Blood Pressure with Carvedilol compared to Placebo, Propranolol, Labetalol and Pindolol (n=6).

M9 - 47

C96

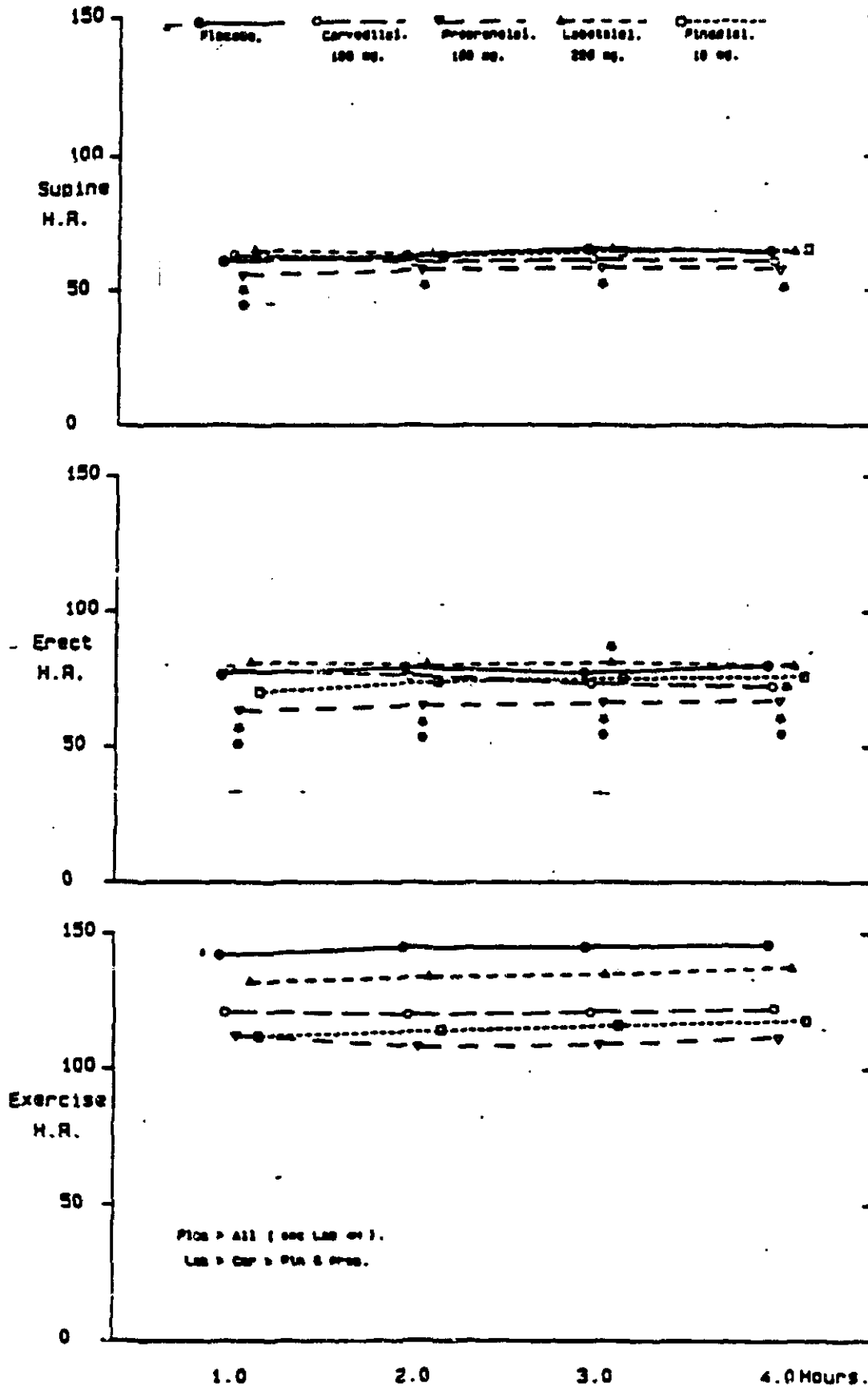


* p < 0.05 compared with Placebo.
 * p < 0.05 compared with Carvedilol.

Figure 4
Heart Rates with Carvedilol compared to Placebo,
Propranolol, Labetalol and Pindolol (n=6).

M9 - 48

C97



Place > All (see Lab on 1).
Lab > Car > Pla & Prop.

● p < 0.05 compared with Placebo.
□ p < 0.05 compared with Carvedilol.

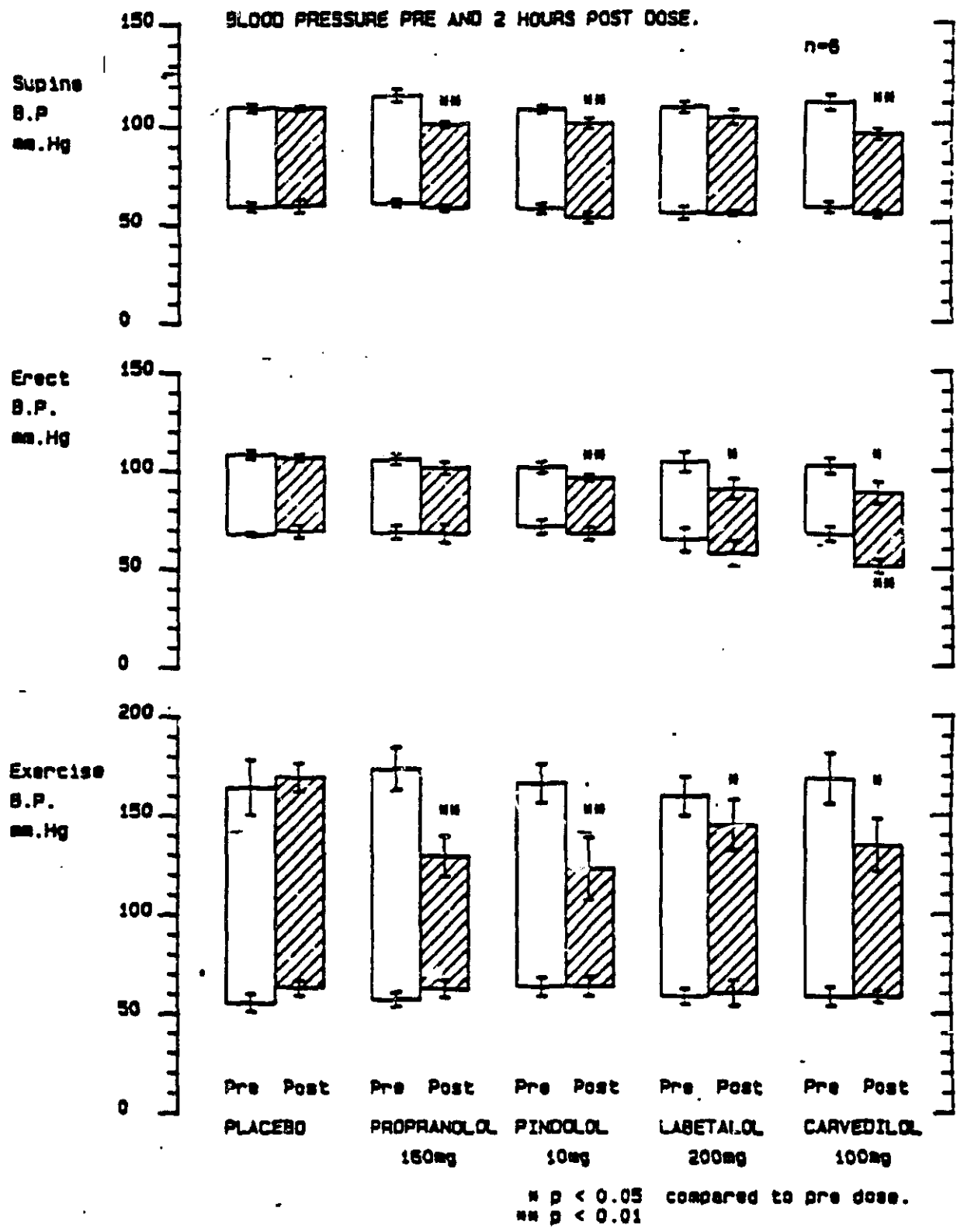
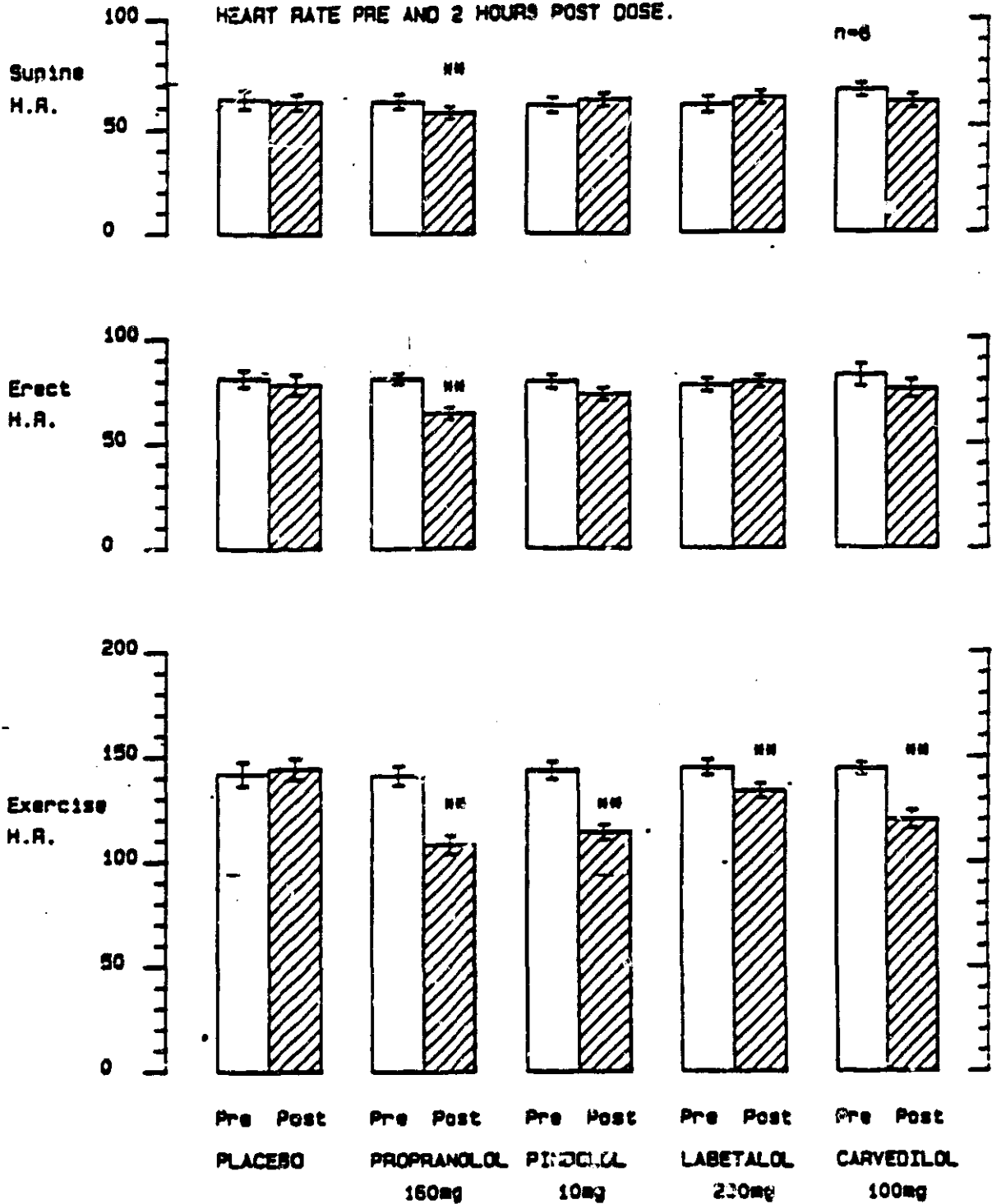


Figure 3

HEART RATE PRE AND 2 HOURS POST DOSE.

n=6

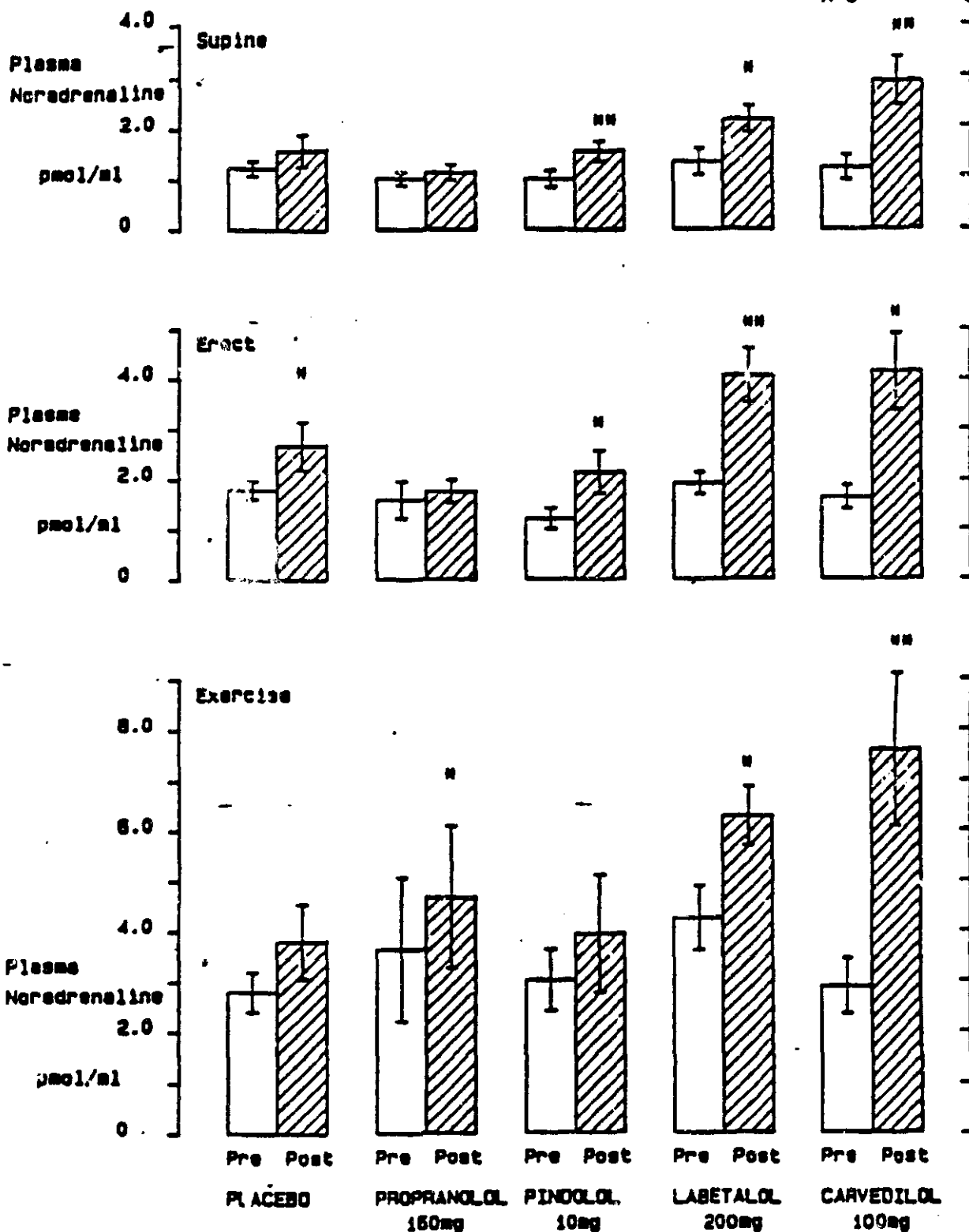
C99



NS p < 0.01 compared to pre dose.

C.100

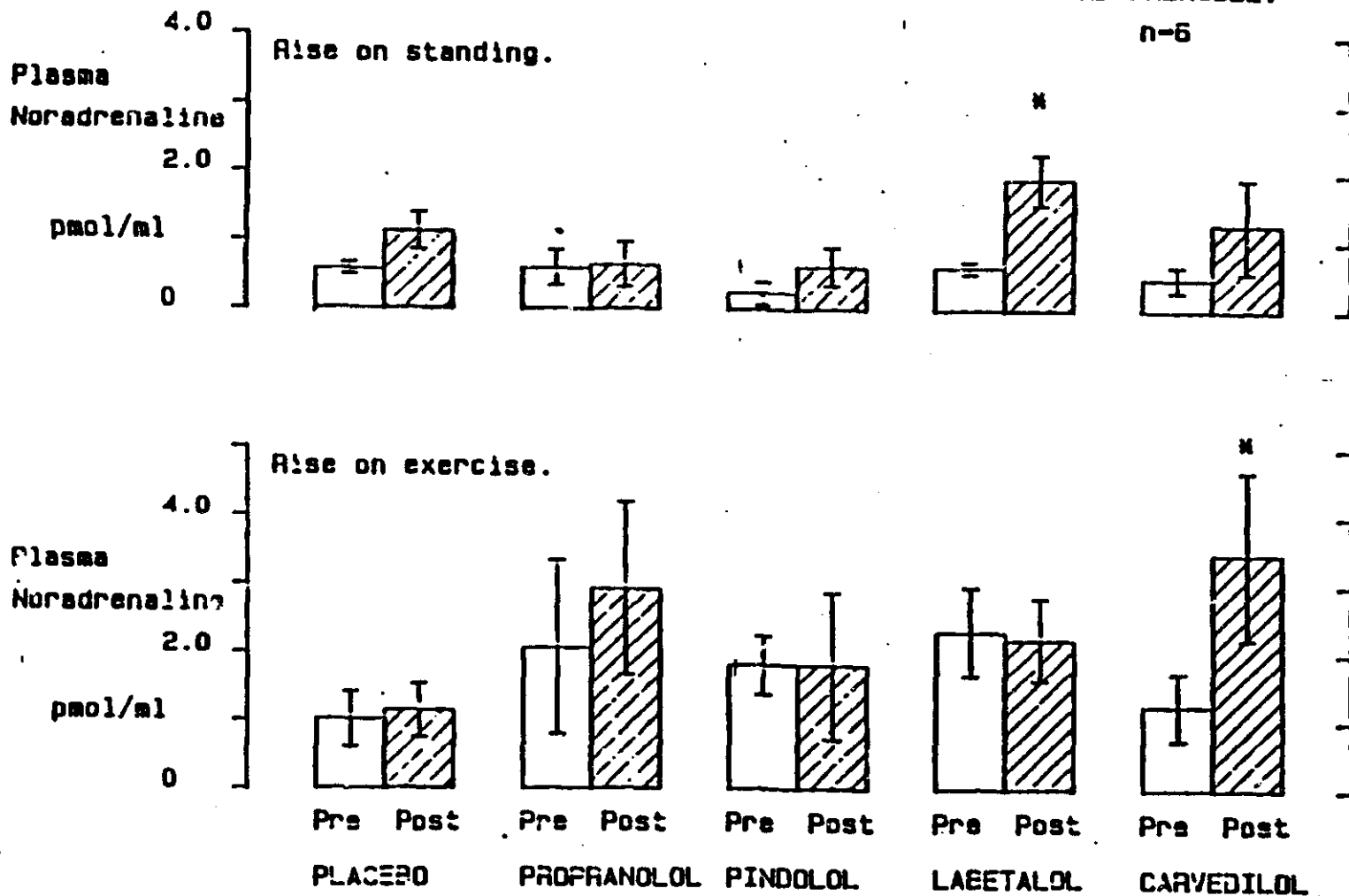
PLASMA NORADRENALINE LEVELS PRE AND 2 HOURS POST DOSE. n=6



* p < 0.05 compared to pre dose.
 ** p < 0.01

Figure 6

CHANGE IN NORADRENALINE LEVELS WITH STANDING AND EXERCISE.



* p < 0.05 compared to pre dose.

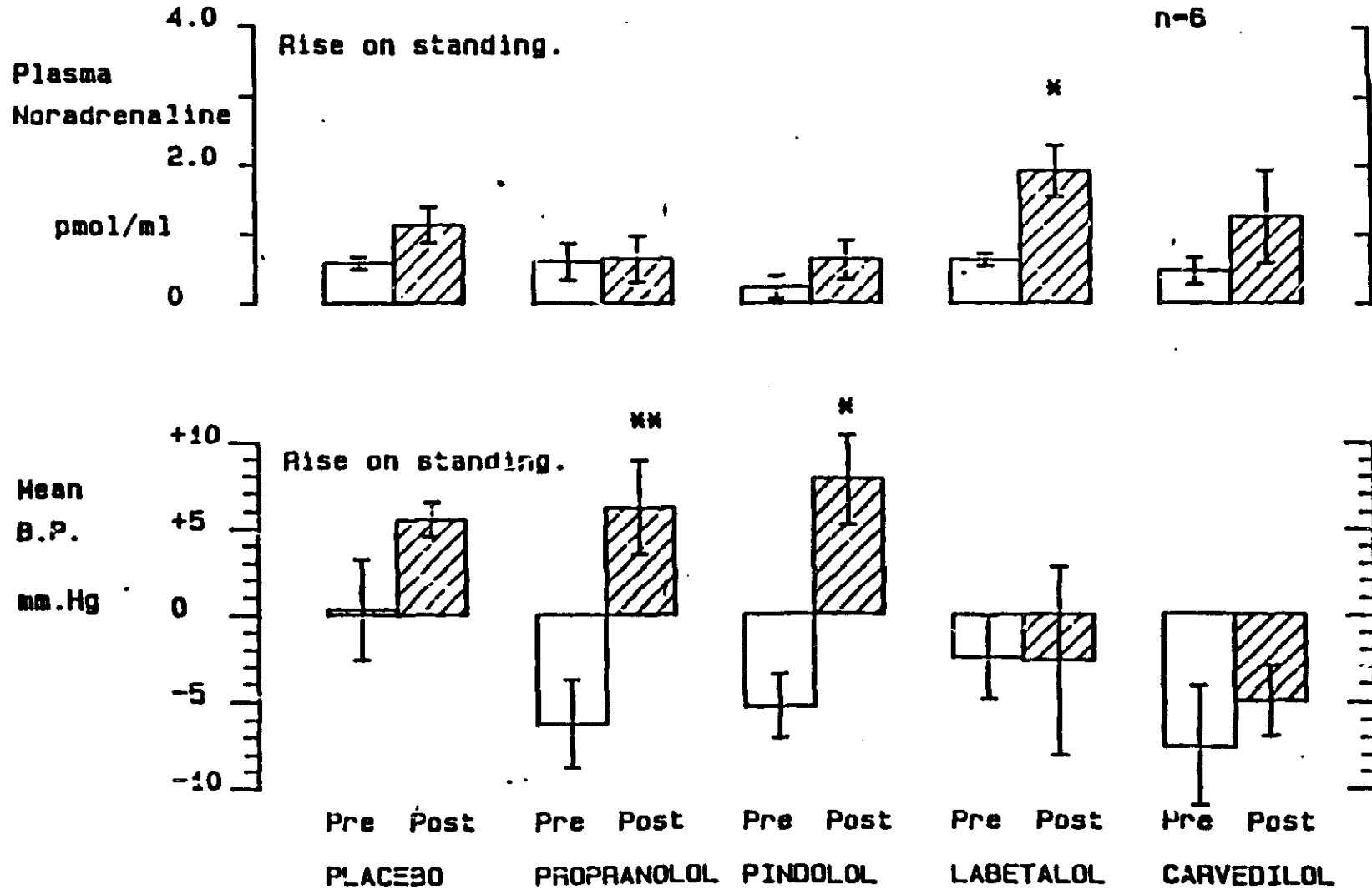
000053

M9 - 59

C101

Figure 9

CHANGE IN NORADRENALINE AND MEAN BLOOD PRESSURE LEVELS WITH STANDING.



* p < 0.05 compared to pre dose.
 ** p < 0.01

000056

M9 - 53

C102

CARVEDILOL NDA 20-297

PROTOCOL MF3132II VOL 1.125

Reviewer: James F. Graumlich

MF3132II is a double-blind, placebo-controlled, randomized-sequence, 2-treatment crossover study of carvedilol 100 mg single dose po and placebo single dose po. This study has the same design and endpoints as MF3132I with the following exceptions: there were only 2 treatments, subjects were a different set of 6 healthy men (aged 20 - 42 years with weights 69.6 - 82.4 kg).

The report displays results for the six subjects in MF3132II by themselves. The report also displays the results of the six subjects in MF3132II combined with the 6 subjects in MF3132I who received carvedilol 100 mg and placebo. Table 9.C from page 35, volume 1.125 shows the results of the 12 subjects from the combined trials. I believe combining the trials is appropriate because I do not perceive systematic biases with regard to the conduct of the two trials.

During the 4 hours of observation, the maximum effect of carvedilol occurred 1 - 2 hours after dose administration. When compared to pre-dose baseline and when compared to placebo, carvedilol 100 mg caused the following clinically relevant changes:

decreased	increased	no significant change
		sup DBP
sup SBP		
sup HR		
stand SBP		
stand DBP		
stand HR		
ex SBP		ex DBP
ex HR		

Abbreviations: sup = supine, ex = exercise, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate.

PR and QTc results were not subjected to statistical analysis. There was no trend suggesting treatment-emergent, clinically-relevant, prolongation of PR or QTc. There are no tables in the report showing ventricular extra-systoles.

Adverse events: 4 of 6 had orthostatic faintness that prevented completion of exercise at one or more time points. Other complaints included dreams, nausea, dyspnea on exertion, headaches, lack of energy, difficulty concentrating, dry mouth, visual disturbance, myalgia, palpitation. There were no clinically relevant laboratory safety abnormalities.

Conclusions: In healthy men, carvedilol 100 mg po acted as a beta blocker to block exercise-induced increases in systolic blood pressure and heart rate.

CARVEDILOL NDA 20-297

PROTOCOL MF3223.I and MF3223.II VOL 1.125

Reviewer: James F. Graumlich

MF3223.I is a double-blind, placebo-controlled, randomized-sequence, 18-period crossover study of healthy men. The treatments were carvedilol 12.5 mg, 25 mg, 50 mg, 100 mg, 200 mg; labetalol 50 mg, 100 mg, 200 mg, 400 mg; propranolol 40 mg, 80 mg, 160 mg, 320 mg; pindolol 2.5 mg, 5 mg, 10 mg, 20 mg; placebo. Treatments were separated by at least 5 days. Using a bicycle ergometer, subjects were exercised and trained to a standardized workload. Blood samples for PK were collected but not reported. Other endpoints were blood pressure and pulse at rest, during exercise, and after exercise. Endpoints were measured pre-dose then 1 and 2 hours after the dose. The same six healthy men studied in MF3132.I participated in MF3223.I (ages 25 - 43, weights 62.8 - 93.7). Subject #3 had an elevation of alkaline phosphatase up to 494 noted at treatment 7 (placebo) after receiving pindolol (various doses), carvedilol 100 mg, and labetalol (various doses) during treatments 1 - 6. In Subject #3, ALT rose from 46 to 113, ALT rose from 35 to 212, gamma GT rose from 17 to 28. The crossover design makes it difficult to determine which one of 5 drugs was associated with the LFT abnormalities.

MF3223.II is a double-blind, placebo-controlled, randomized-sequence, 6-period crossover study in 6 healthy men. The design was similar to MF3223.I with the following exception: the treatments were carvedilol 12.5 mg, 25 mg, 50 mg, 100 mg, 200 mg and placebo. The six healthy men in MF3223.II are the same subjects who participated in MF3132.II (ages 20 - 47 and weights 69.6 - 82.4 kg).

Results: Tables 10.1 and 10.2 (pages C106-C107) show results for MF3223.I only. Propranolol, pindolol, and labetalol served as positive controls by blocking exercise-induced increases in pulse and systolic blood pressure.

It appears to be reasonable to combine the results of MF3223.I and MF3223.II when looking at the effects of carvedilol 12.5 mg, 25 mg, 50 mg, 100 mg, 200 mg and placebo (see Table 9.0, page C108). All doses of carvedilol caused significant reduction in exercise-induced increases in systolic blood pressure and pulse. There are trends showing a dose-response relationship for systolic blood pressure and pulse.

Adverse events were discussed in the reports for MF3132.I and MF3132.II.

Conclusions: In these healthy men, carvedilol doses from 12.5 mg to 200 mg showed beta blocker effects on exercise-induced changes in systolic blood pressure and pulse.

TABLE 10.1

	% Reduction in Exercise Heart Rate				Mean Exercise Tachycardia				% Inhibition of Exercise Tachycardia			
	+1H		+2H		+1H		+2H		+1H		+2H	
PLACEBO					67.3	3.9	69.5	3.9				
CAR12.5	-0.6	1.7	5.4	-1.6	64.7	5.2	56.0	3.4	4.3	3.6	19.2	2.8
25	0.5	1.3	6.3	2.8	64.5	4.8	58.8	5.7	4.1	4.5	15.6	5.6
50	2.2	2.7	7.3	2.1	64.3	5.5	59.2	5.7	4.9	4.5	15.6	3.8
100	7.1	2.9	13.9	2.3	55.7	6.9	51.7	7.0	18.6	6.5	26.9	6.0
200	5.3	3.7	14.4	2.1	55.5	5.8	45.7	3.8	17.5	7.7	33.3	7.0
PROP 40	11.5	2.2	15.0	1.9	56.7	2.8	55.7	2.4	15.0	5.7	19.4	2.5
80	15.7	1.0	18.7	1.0	52.0	3.7	48.7	2.6	22.3	4.9	29.1	4.9
160	17.7	2.2	19.3	3.1	51.0	4.3	50.8	3.6	23.3	7.3	25.5	7.7
320*	20.7	4.2	26.0	1.5	47.2	3.2	39.6	0.5	26.9	3.9	41.4	3.6
PIN 2.5	10.4	3.4	17.2	1.5	56.3	5.1	46.0	2.3	16.8	4.5	33.3	3.4
5	18.4	0.8	18.4	1.4	52.2	3.0	50.2	2.8	22.2	2.6	27.4	3.4
10	18.5	1.1	19.3	1.5	47.7	2.1	48.3	3.1	28.9	1.2	30.5	1.7
20	20.8	1.4	20.4	1.5	45.3	2.8	45.3	3.0	32.7	1.5	34.8	1.4
LAB 50	5.1	4.6	-1.8	1.9	59.7	5.5	67.5	3.6	10.0	8.7	2.5	3.8
100	1.6	1.9	3.5	1.1	63.0	5.1	60.3	2.9	6.9	4.0	12.7	3.4
200	7.9	3.3	5.7	1.4	54.7	4.4	56.7	2.8	18.2	6.1	17.8	4.4
400	10.0	1.2	12.5	1.2	55.5	4.1	49.8	1.5	17.3	5.3	27.6	3.1
Anova P	<0.0001		<0.0001		<0.0001		<0.0001		<0.0001		<0.0001	
L.S.D (5%)	7.5		5.2		9.6		8.1		14.4		11.9	
*n=5												

000044

M9 - 41

C106

TABLE 10.2

	Mean Rise in EXERCISE Systolic Blood Pressure				% Reduction in Exercise Systolic B.P.				% Reduction in Exercise Double Product.			
	+1H		+2H		+1H		+2H		+1H		+2H	
PLACEBO	70.0	5.2	65.7	6.2								
CAR12.5	59.8	9.4	56.7	11.0	8.5	2.0	8.2	4.8	7.9	2.8	12.9	5.3
25	54.3	8.7	54.8	9.6	10.6	5.8	11.4	4.2	10.8	6.6	16.7	5.7
50	51.2	6.8	48.3	8.3	12.4	1.8	14.5	3.2	14.2	3.5	20.6	3.9
100	47.8	9.9	45.2	7.8	20.6	3.0	25.1	3.2	26.1	3.8	35.3	4.0
200	53.7	10.9	47.0	7.1	12.3	3.9	20.5	3.4	16.5	6.1	31.8	4.0
PROP 40	48.2	9.0	42.3	6.4	14.0	3.1	17.3	2.6	23.5	4.7	29.6	3.1
80	39.7	6.5	44.0	7.2	18.6	2.3	16.2	3.7	31.3	2.3	31.9	3.3
160	39.7	7.7	31.8	6.5	16.8	2.0	21.9	2.6	31.4	3.4	36.7	4.3
320*	31.6	8.0	17.2	13.2	24.4	2.1	32.1	6.5	39.8	4.6	49.7	4.9
PIN 2.5	48.3	5.1	41.5	7.7	12.7	0.8	17.8	3.3	21.7	3.4	32.1	2.4
5	34.2	5.5	44.7	10.5	22.1	3.3	18.9	4.6	36.5	2.8	33.9	3.4
10	38.3	6.0	40.2	4.3	20.5	1.0	18.6	1.1	35.2	1.5	34.3	1.0
20	38.8	7.3	42.8	6.9	21.2	1.7	19.9	2.4	37.7	1.4	36.4	1.9
LAP 50	53.8	9.0	64.8	10.2	10.8	4.1	2.2	3.7	15.3	5.9	0.4	4.2
100	58.3	7.9	50.5	9.8	7.6	1.8	12.9	4.5	9.1	2.8	15.9	4.5
200	49.5	10.5	54.5	10.2	11.0	3.6	11.8	5.9	17.6	5.9	16.6	6.2
400	39.7	10.7	44.5	10.4	17.4	4.0	16.9	4.5	25.4	4.4	27.1	4.6
Anova F	<0.0001		<0.0001		<0.0001		<0.0001		<0.0001		<0.0001	
L.S.D. (5%)	14.3		12.5		8.4		7.0		12.1		9.3	
n=5												

000045

M9 - 42

C107

Reviewer: James F. Graumlich

MF3270 is a single-blind, placebo-controlled, non-randomized, 4-period crossover study of patients with chronic, stable angina pectoris. Angina was reproducible on a treadmill exercise test. Patients with hypertension were not excluded. Wash-out (10 days) preceded the first treatment period. Treatments were placebo bid for 2 weeks, carvedilol 25 mg po bid for 2 weeks, carvedilol 50 mg po bid for 2 weeks, and placebo bid for 2 weeks. At the end of each treatment period, the following endpoints were measured: 24-hour ambulatory ST-segment monitoring, maximal symptom-limited graded treadmill exercise test 2 hours after the dose (ETT), resting and exercising radionuclide MUGA ventriculography.

Results: 20 patients entered the study (15 men and 5 women, mean age 62 years, age range 52 - 72 years, 4 of 20 with previous MI, radionuclide ejection fraction 35 - 67%, 9 of 20 with coronary artery disease documented by angiography). Weights were not reported.

3 patients withdrew during the placebo phase for unstable angina and 2 patients withdrew during the carvedilol 25 mg po bid phase for adverse events (unstable angina, lightheadedness). Details about the withdrawn patients are not in the report. Results are depicted in the attached figures: pages 206 - 212 and 228 - 232 from volume 1.125.

Conclusions:

The study was not adequately blinded so bias may influence results.

None of the tables and figures in the report indicate the sample size used to calculate means.

The maximum total daily dose, 100 mg per day, used in this study is twice the maximum total daily dose recommended in the proposed label.

Carvedilol 25 mg po bid and 50 mg po bid decreased resting heart rate when compared to placebo.

There was no difference between carvedilol 25 mg po bid and 50 mg po bid in maximum, minimum, and mean heart rate measured hourly with holter monitor.

Carvedilol 25 mg po bid and 50 mg po bid blocked exercise-induced increases in heart rate at peak exercise.

Carvedilol 50 mg po bid but not carvedilol 25 mg po bid decreased systolic blood pressure at rest. Carvedilol 50 mg po bid but not carvedilol 25 mg po bid blocked exercise-induced increases in systolic blood pressure at peak exercise.

Carvedilol 25 mg po bid and 50 mg po bid appeared to prolong exercise time and prolong time to 1 mm ST segment depression during ETT.

The maximum number of millimeters of ST depression at each stage of exercise was not significantly influenced by carvedilol.

Carvedilol 25 mg po bid and 50 mg po bid appeared to decrease the rate-pressure product.

Carvedilol 25 mg po bid and 50 mg po bid did not cause significant decreases in exercise EF. There was a trend toward decrease in exercise EF. The power of the study to detect a difference is unknown.

Although carvedilol concentrations were measured, no concentration results were reported.

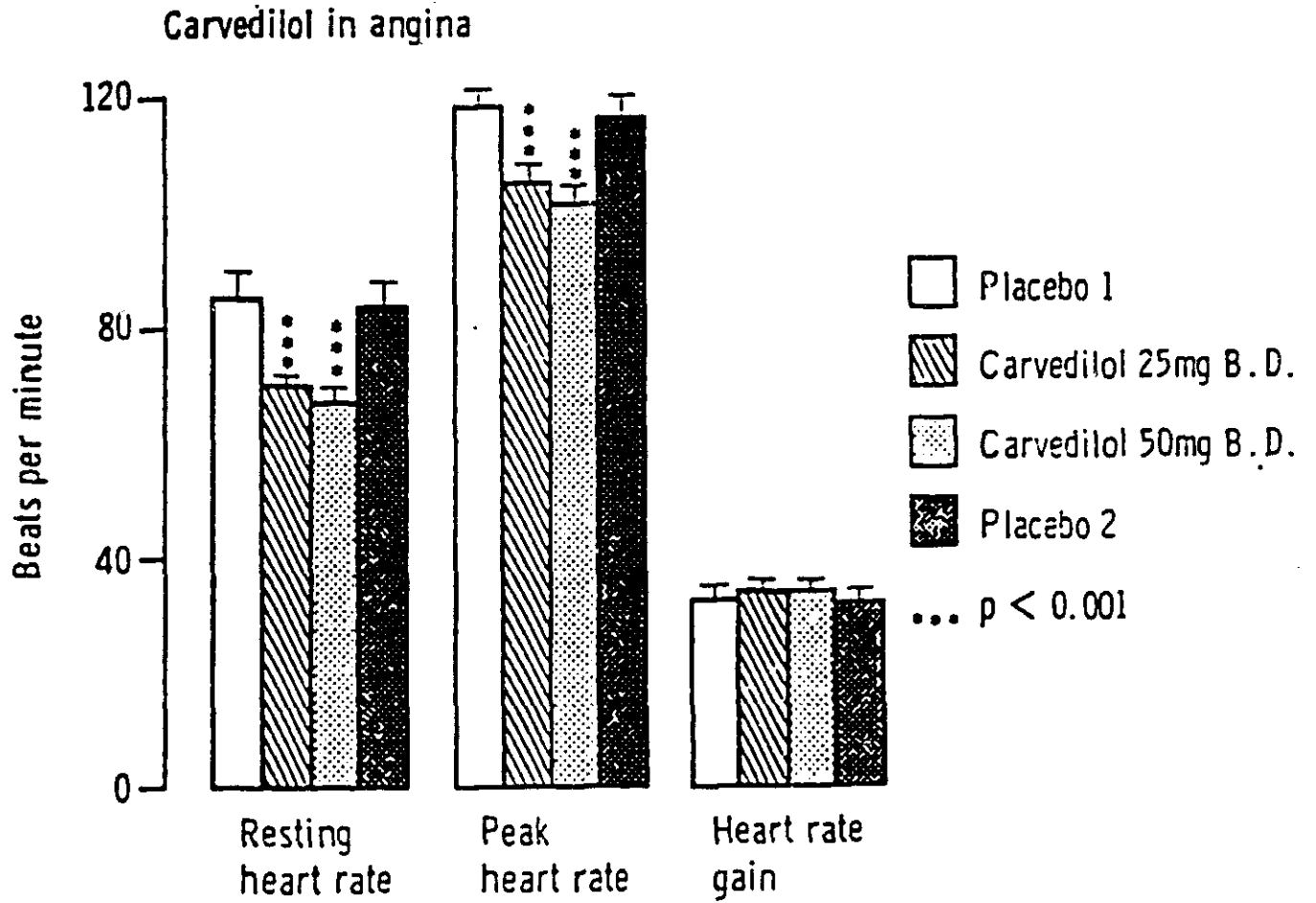


Figure 1 Rest and peak exercise heart rate and exercise heart rate gain on placebo and on Carvedilol.

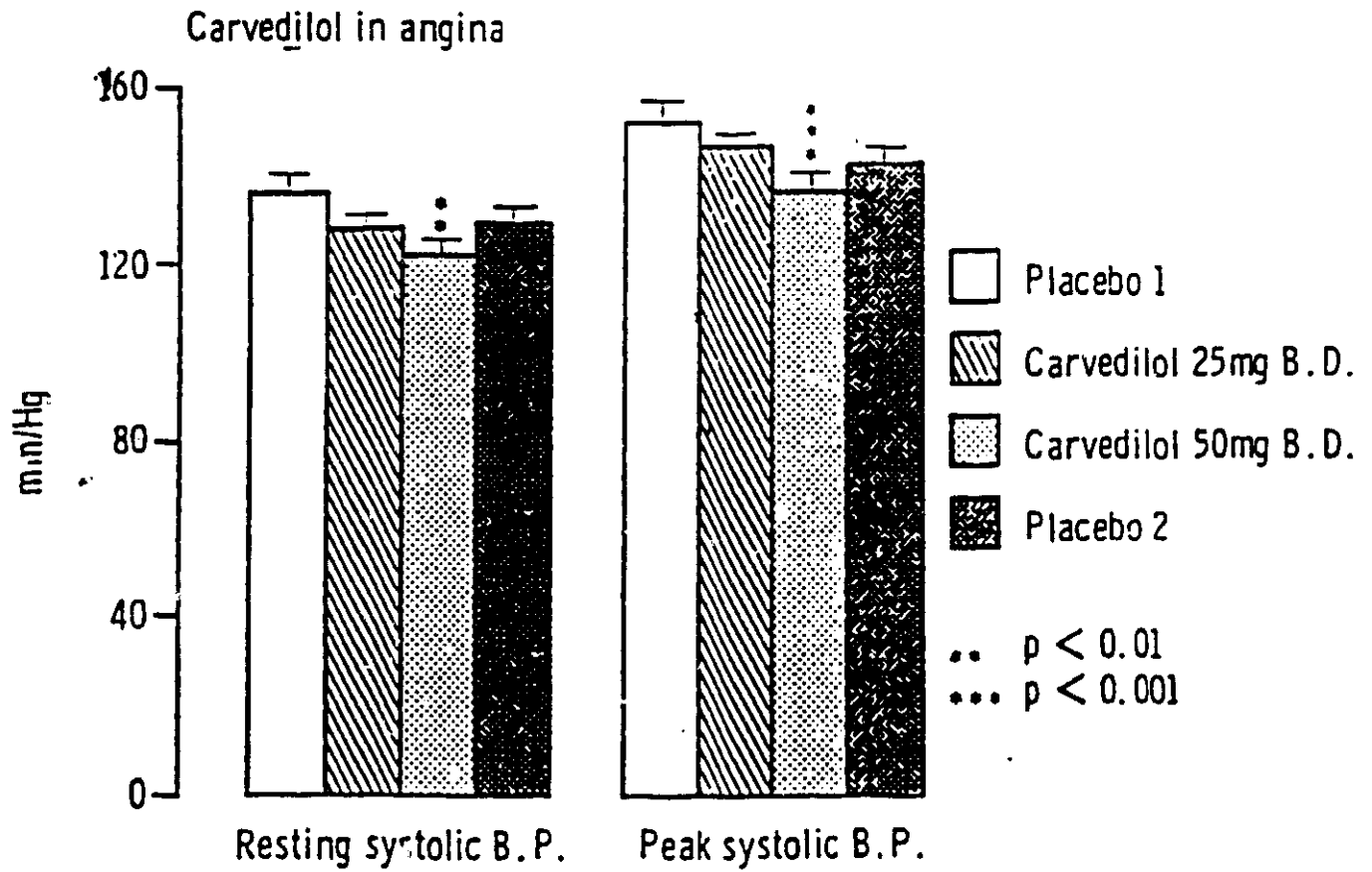


Figure 2 Rest and peak exercise systolic blood pressure on placebo and on Carvedilol.

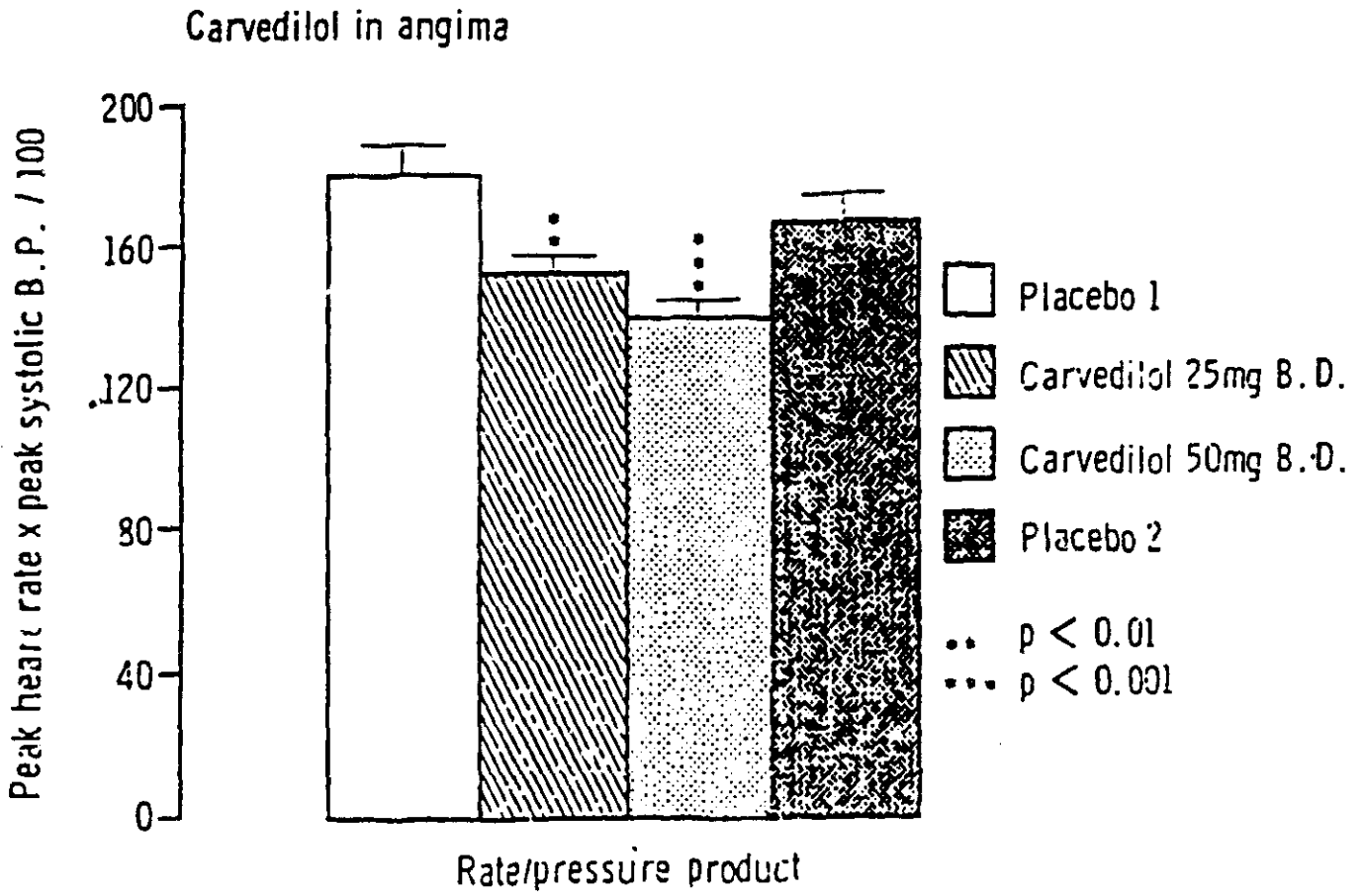


Figure 3 Rate-pressure product on exercise with placebo and Carvedilol.

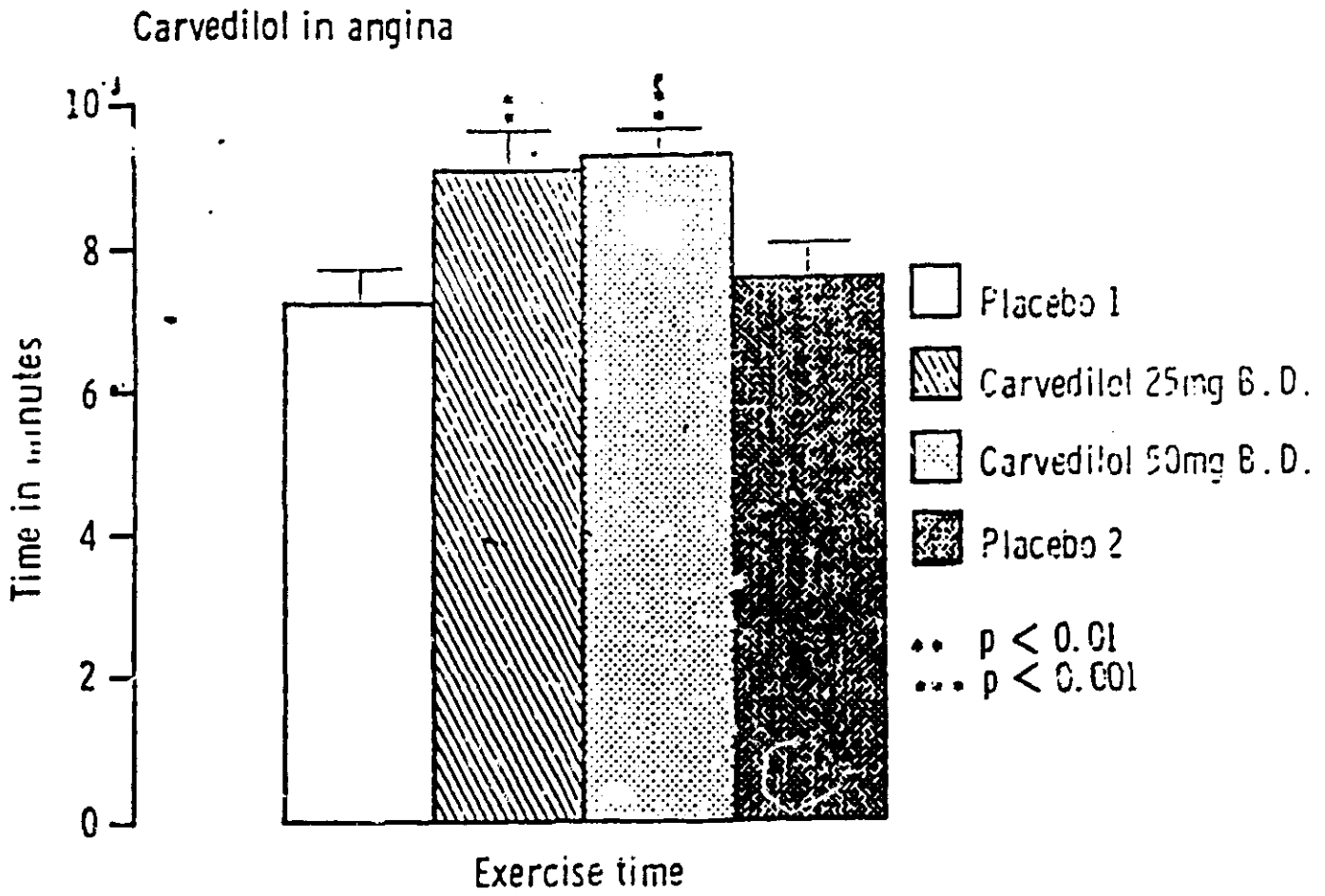


Figure 4 Exercise time on placebo and on Carvedilol.

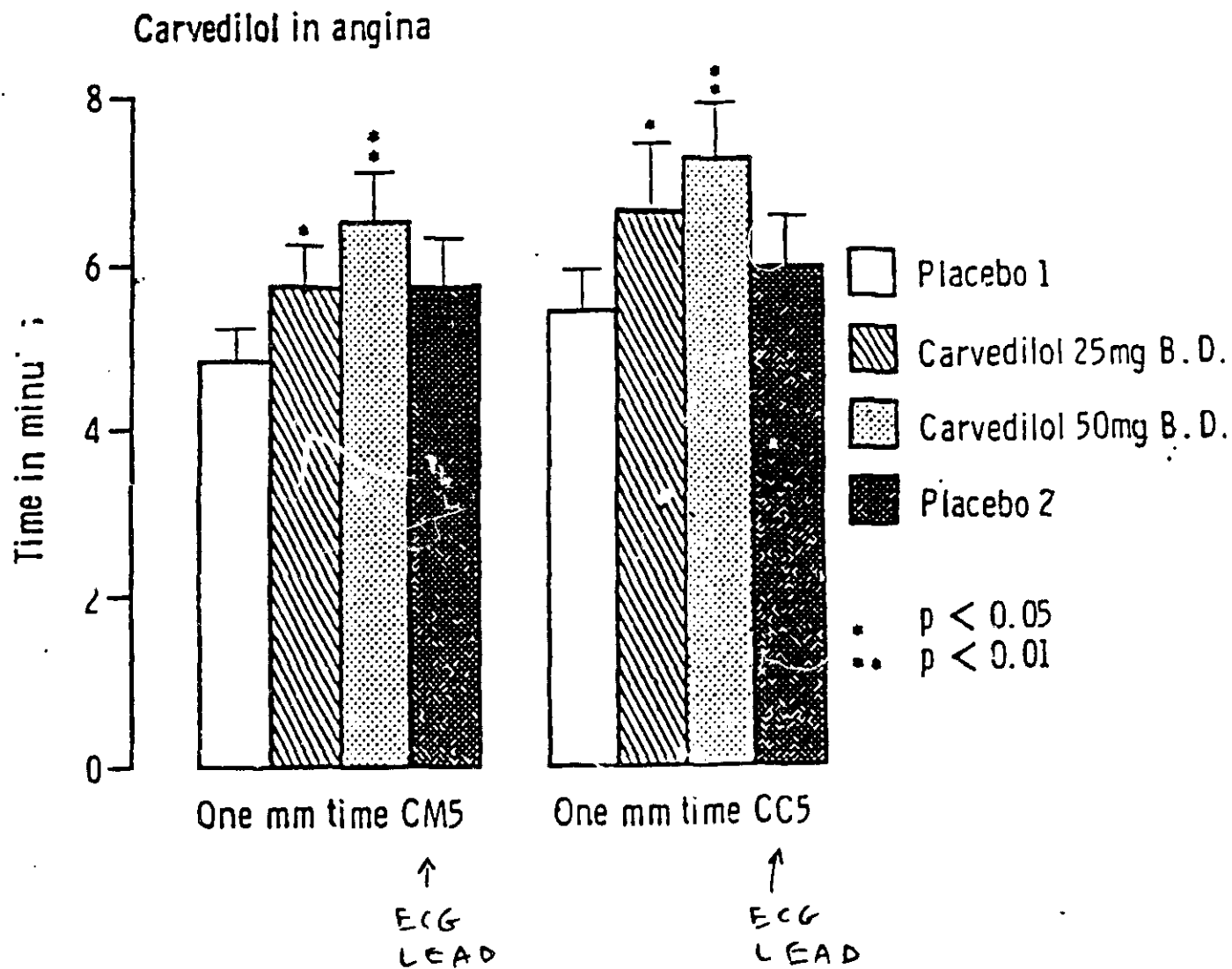


Figure 5 Time to 1 mm ST-depression on placebo and on Carvedilol.

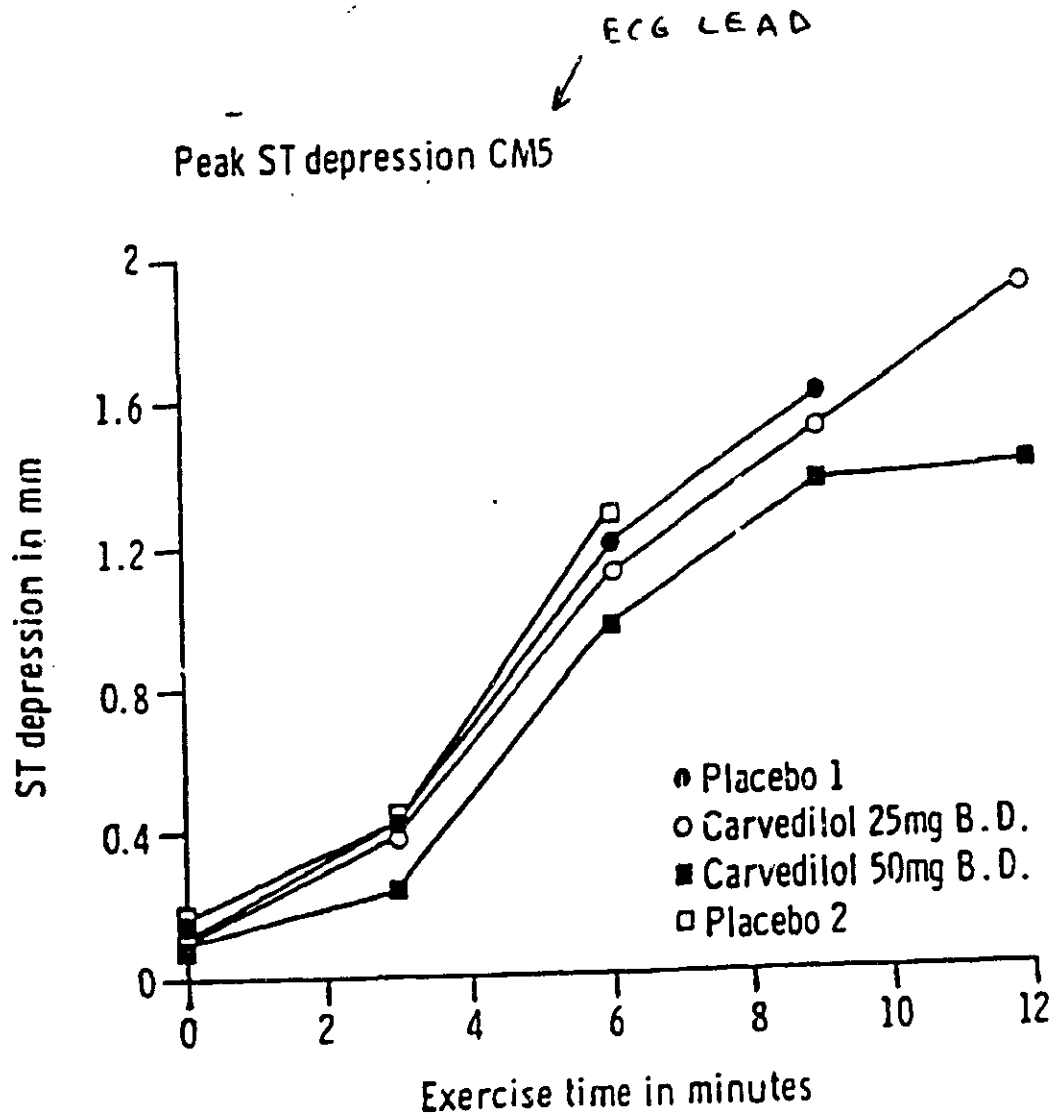


Figure 6 Peak ST-depression at each stage of exercise on placebo and on Carvedilol.

015- 25

Carvedilol in Angina

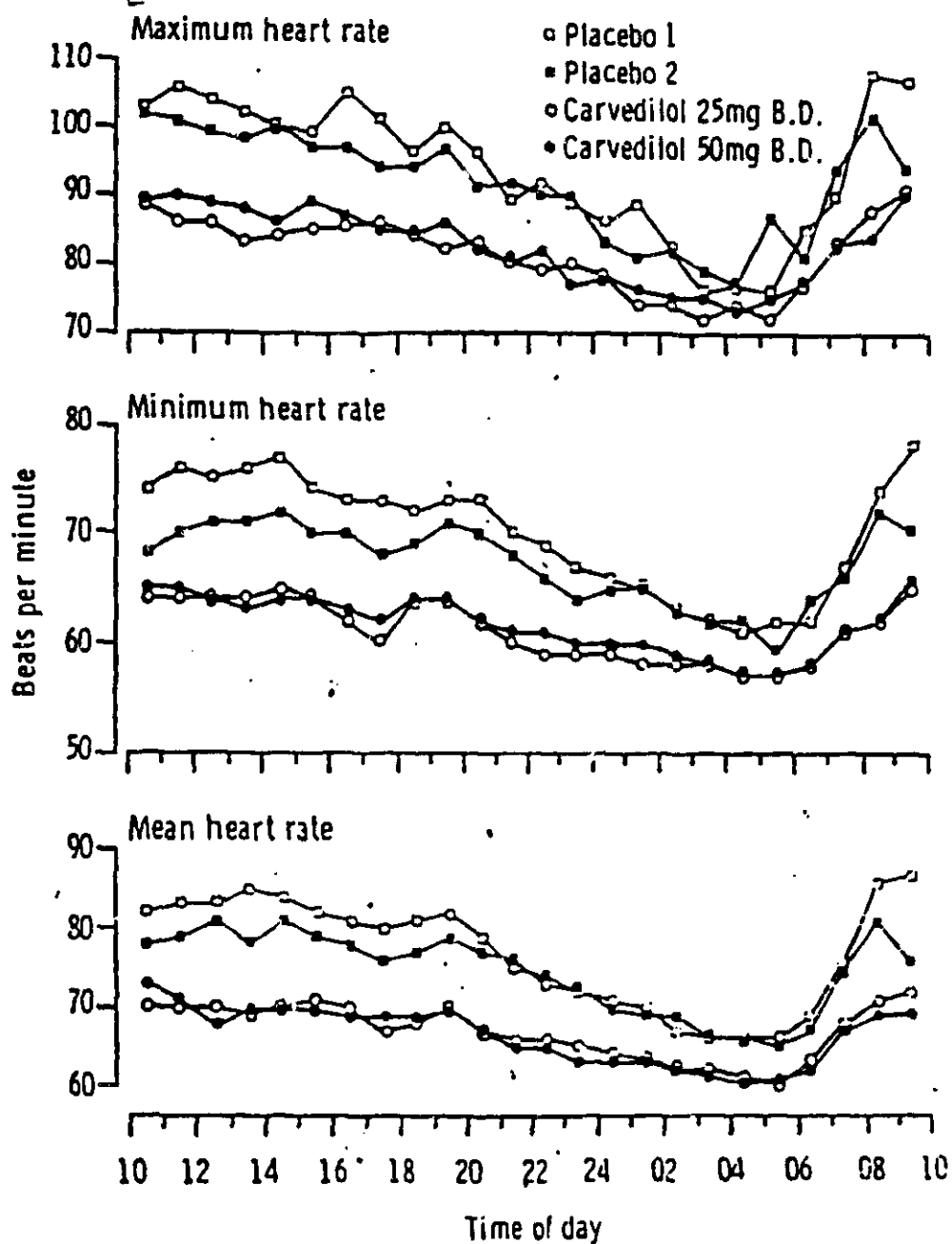


Figure 7 Minimum, maximum and mean hourly heart rates recorded by Holter monitoring on placebo and on Carvedilol.

heart rate and ST change

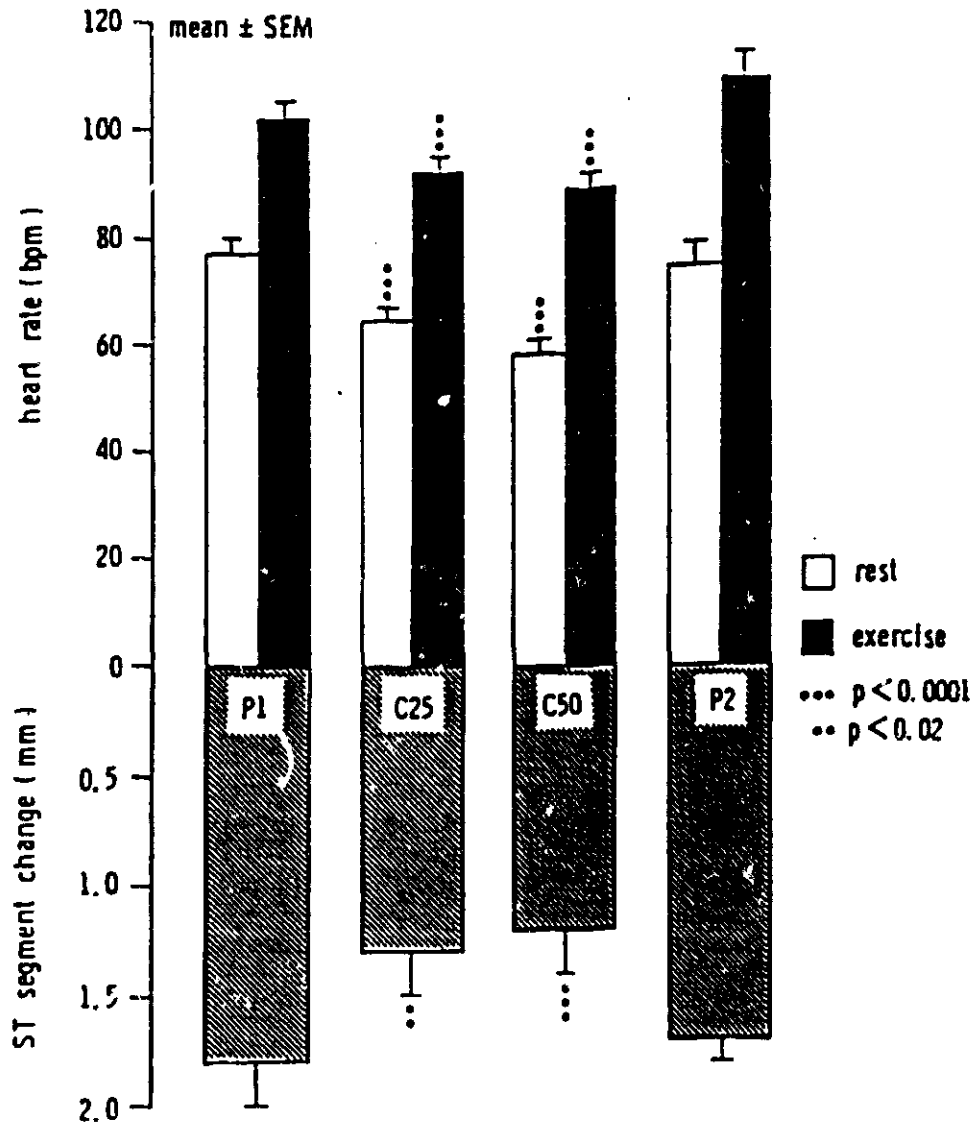


Figure 1

Change in heart rate and ST-segment depression on placebo and on the two doses of carvedilol are shown to highlight the effect of reducing myocardial oxygen demand on ST changes. P1 and P2 = placebo 1 and 2; C25 and C50 = Carvedilol 25 mg and 50 mg twice daily.

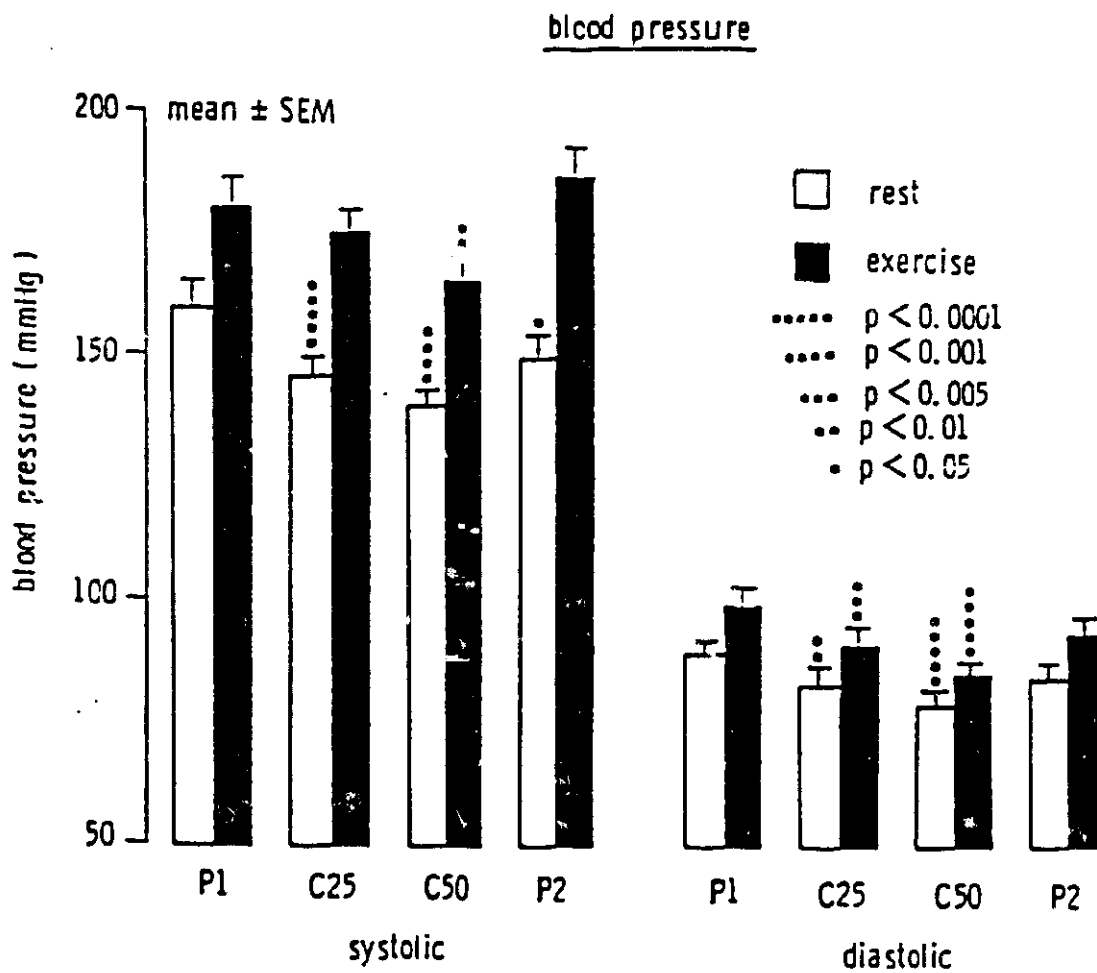


Figure 2

Rest and exercise blood pressure changes on placebo and on carvedilol. BP = blood pressure; C25 and C 50 = carvedilol 25mg and 50 mg twice daily; P1 and P2 = placebo 1 and 2.

~~C118~~
C119

015 - 43 a

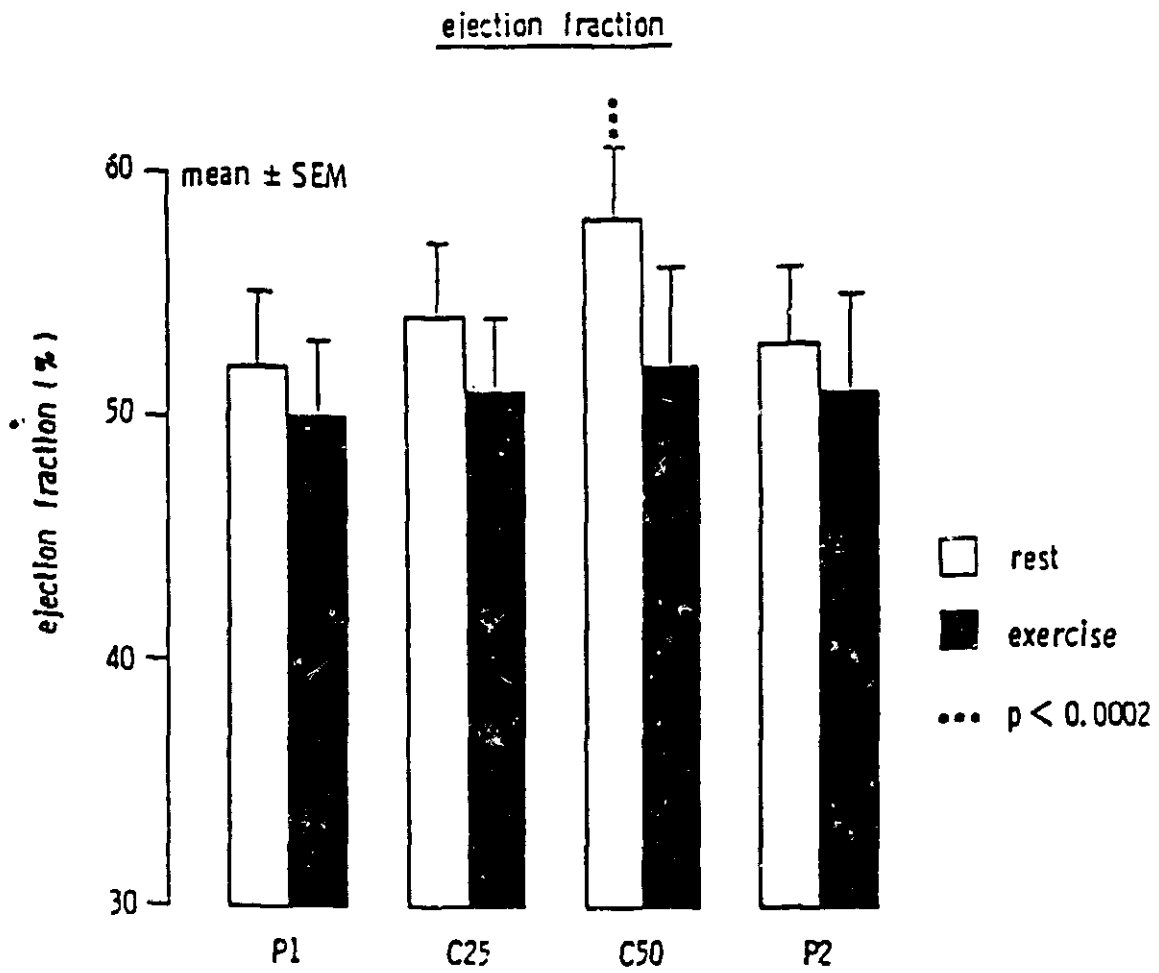


Figure 3

Resting and exercise ejection fraction values on placebo and on carvedilol.

P1 and P2 = placebo 1 and 2; C25 and C50 = carvedilol 25 and 50 mg twice daily.

MF 3070
000220

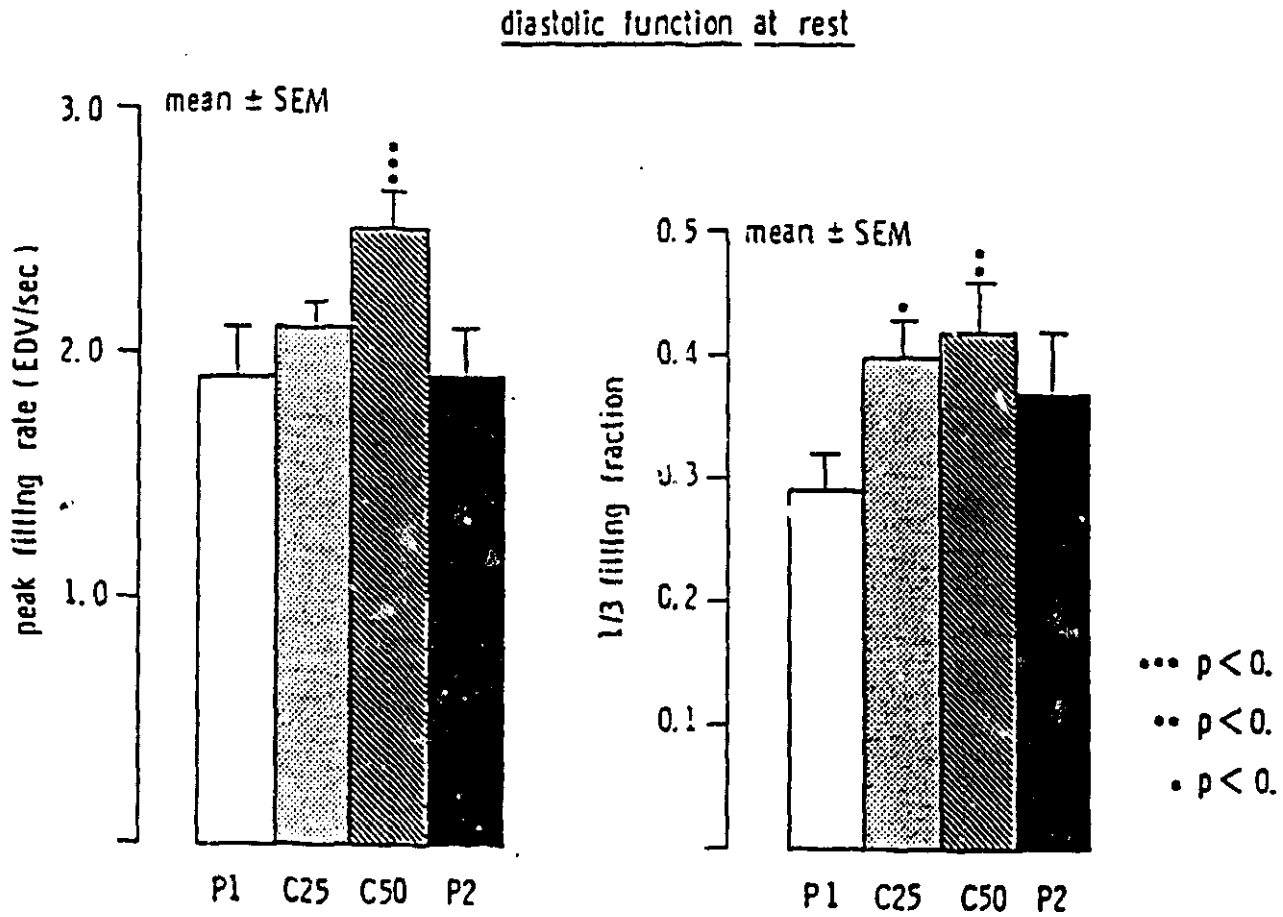


Figure 4

Peak filling rate and first one-third filling fraction values on placebo and on carvedilol at rest. 1/3 filling fraction = first one-third filling fraction; P1 and P2 = placebo 1 and 2; C25 and 50 = carvedilol 25 mg and 50 mg twice daily.

MC 3220

000231

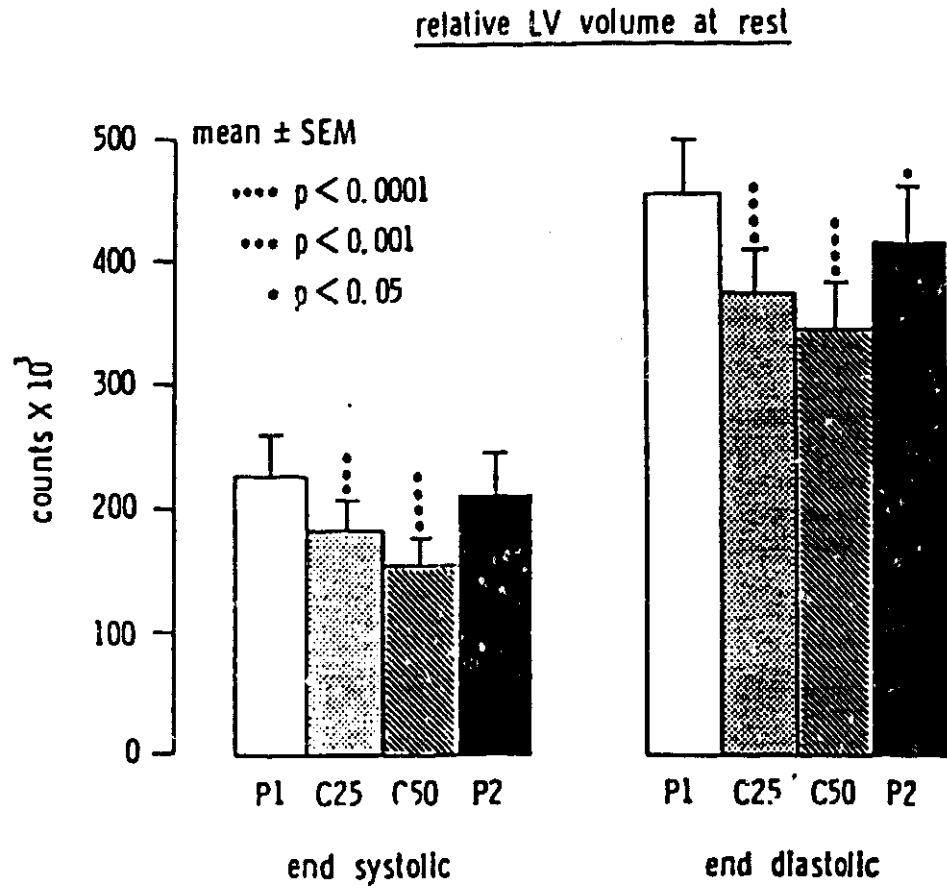


Figure 5

Relative LV volumes are represented by end-systolic and end-diastolic counts. C25 and C50 = Carvedilol 25 mg and 50 mg twice daily; P1 and P2 = placebo 1 and 2.

CARVEDILOL NDA 20-297

PROTOCOL MF3413 VOL 1.57

PK and PD in ELDERLY

Reviewer: James F. Graumlich

Name of study: Single dose pharmacokinetic and pharmacodynamic study of BM 14.190 in young and old healthy volunteers

Objectives: To determine the pharmacokinetics and haemodynamic effects of 5 mg intravenous and 25 mg and 50 mg oral doses of carvedilol, to compare the hypotensive effects of these single oral doses of carvedilol with a single oral dose of labetalol 200 mg, to determine whether the PK of carvedilol is influenced by food ingestion, to examine the conversion of carvedilol to its active desmethyl metabolite in 10 healthy young men and 9 older healthy men and 1 older healthy woman.

Study design: Study in 3 phases. Phase 1 was double-blind, non-randomized sequence, placebo-controlled, 5 period crossover phase in 10 healthy young men and 10 healthy older subjects using single oral doses of placebo, carvedilol 25 mg, carvedilol 50 mg, labetalol 200 mg, and carvedilol 50 mg + food. Periods were separated by at least 14 days. Phase 2 was open, uncontrolled phase using single intravenous doses of 5 mg of carvedilol. Phase 3 was open, uncontrolled phase using single oral doses of 12.5 mg carvedilol.

Intervention: placebo
carvedilol 12.5 mg, 25 mg, 50 mg
carvedilol 50 mg + food (toast, orange juice, 1-2 eggs)
labetalol 200 mg
carvedilol 5 mg intravenous infusion over 5 minutes

Response variables: Primary outcome: carvedilol concentrations in plasma, C_{max}, T_{max}, AUC
Secondary outcome: heart rate and blood pressure before, during, and after exercise, supine and standing; other PK parameters; lab safety tests

Bicycle ergometry to standardized workload was used during this study. BP, pulse, plasma concentration were measured at baseline then 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, 30, and 48 hours after carvedilol administration. BP and pulse after exercise were measured at 13 of the times listed above. Urine was collected for 48 hours. Additional early blood samples were obtained after the IV dose of carvedilol. Symptoms were elicited by questionnaire.

Materials: not specified

Assay: Plasma assay of carvedilol involved liquid/liquid extraction, HPLC with fluorometric detection. Propranolol was the internal standard. The lower limit of quantification was not specified.

Results: 10 healthy young men between 20 and 40 years of age completed phase 1 of the study. Weights of young subjects were between 59 and 87 kg (mean ± SE = 78 ± 3). 9 healthy older men between 57 and 66 years of age and one woman aged 63 years completed phase 1 of the study. Weights of older subjects were between 74 and 89 kg (mean ± SE = 79 ± 2). One elderly subject (#19) experienced hypotension after carvedilol 50 mg po (supine BP 105/72, standing BP 74/70 with documented absence of orthostatic hypotension prior to dose) and was withdrawn from the study and replaced by subject #1. 7 of 20 subjects (5 young and 2 old) were lost to followup and did not complete phase 2 (carvedilol 5 mg IV). 5 of 20 subjects (1 young and 4 old) were lost to followup and did not complete phase 3 (carvedilol 12.5 mg po).

Protocol violations included subject 2 who took penicillin while taking labetalol.
5 of 14 subjects had fewer blood samples collected during the distribution phase after the IV dose.

Carvedilol Pharmacokinetics

A two-compartment open model with a lag time of approximately 0.3 hours described the kinetics in most subjects.

C_{max} was not affected by age or food (see table A, page C126). There appeared to be dose-proportionality of C_{max} in the range of 12.5 to 50 mg (single dose). Dose-proportionality was not addressed statistically in this study. There was a four-fold range of minimum to maximum concentrations.

AUC was increased about 50% in elderly subjects after the 25 and 50 mg doses (page C127). Food caused a small increase in AUC for young and elderly although the differences were not statistically significant. The AUCs were roughly dose-proportional in the range of 12.5 to 50 mg. Dose-proportionality was not addressed statistically in this study.

Bioavailability was increased in older subjects (see table 10, page C128).

Total clearance and renal clearance were decreased in older subjects (see table 10 and 12, pages C128-C129).

Volume of distribution was increased in older subjects (see table 10, page C128).

T_{max} was not affected by age. Food prolonged T_{max} in young and old subjects.

Half-life was longer in younger subjects. The longer half-life may be partially explained by the wider range of variability in younger subjects. Food decreased half-life in young subjects.

Metabolite BM14,242 was not detectable in some subjects. In subjects with detectable BM14,242, C_{max} was approximately 10% of parent carvedilol, T_{max} was 1.2 ± 0.1 hours, n=12.

Pharmacodynamic response:

Maximum fall in resting blood pressure is summarized in table 15 (area under the blood pressure versus time curve, page C130). After carvedilol 12.5 mg, significant decreases in blood pressure occurred only for supine resting blood pressure. After carvedilol 25 and 50 mg, there were significant decreases in supine and standing blood pressure for young and old subjects. The older subjects had twice the effect seen in younger subjects after carvedilol 25 and 50 mg. Labetalol served as a positive control.

The time to maximal fall in resting blood pressure is summarized in table 16 (page C131). The range is 2-4 hours. Older subjects show a trend toward later times to E_{max}.

There were trends suggesting an increased effect on resting blood pressure associated with food (see table 15, page C130).

Duration of effect was not tabulated for fall in resting blood pressure.

The correlation between plasma concentration and PD is summarized in table iii (page C132). The only significant correlation coefficients occurred with standing blood pressure.

Reduction in exercise-induced tachycardia is biased by subjects who failed to exercise secondary to orthostatic blood pressure deterioration.

Carvedilol 12.5 mg did not produce an effect in young subjects. In older subjects, carvedilol 12.5 caused a decrease of 10 beats per minute in exercise-induced tachycardia. Onset of effect was 1 hour. Duration of effect was from 1 to 2

hours.

Carvedilol 25 mg caused a decrease of approximately 12 BPM. Onset of effect was 1-2 hours. Duration of effect was from 2 to 3 hours after the dose in young and old subjects. There were no significant differences between young and old subjects

Carvedilol 50 mg caused a decrease of approximately 30 BPM. Onset of effect was at 1 hour after the dose. Emax was at 3 hours after the dose. Duration of effect was from 1 to 12 hours after the dose. There was no difference in response between young and old subjects except a trend toward a longer duration of effect in older subjects.

Carvedilol 50 mg with food caused a decrease of approximately 20 BPM. Onset of effect was at 1 hour after the dose. Duration of effect was from 1 to 12 hours after the dose. There was no difference in response between young and old subjects except a trend toward a longer duration of effect in older subjects.

Noradrenaline concentrations in plasma showed inconsistent results and large variability. I could not perceive meaningful trends in the data when comparing dose, age, or time after dose.

Adverse events: There were no deaths.

Number of subjects unable to stand for blood pressure determination after doses of carvedilol

	12.5 mg	25 mg	50 mg	50 mg + food
young	0/9	3/10	4/10	3/10
older	1/6	3/10	3/10	5/10

Treatment emergent symptoms and signs were
headache 4/10 young, 4/10 older
nausea 5/10 young, 5/10 older
dizzy/faint 20/20
felt sleepy 8/10 young, 8/10 older

Other events that occurred more often after carvedilol than after placebo
short of breath palpitations indigestion
cold extremities stuffy nose dry mouth
heart burn confusion depression pressure/pain behind eyes

Lab safety changes from pre-study normal values
1/10 decreased potassium
3/10 young, 6/10 older decreased hematocrit
1/10 young, 1/10 older prolonged QT to 0.44 sec

Conclusions:

In phase 1, most subjects received treatments in chronological sequence and not in random sequence. The analysis did not consider sequence effects on results. The importance of sequence effects to the results of this study is unknown.

The statistical rationale for the sample size was not discussed. It is unknown if the sample size was sufficient to detect a difference if present.

Single doses of carvedilol from 12.5 to 50 mg cause dose-dependent increases in beta blockade of exercise-induced tachycardia in healthy volunteers.

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PROTOCOL MF3413 VOL 1.57

There is a problem with orthostatic hypotension after carvedilol 25 and 50 mg.

E_{max} occurs about 1-2 hours after C_{max}.

There were trends suggesting an increased effect on resting blood pressure associated with food. Food was also associated with PK effects.

There were significant PK and PK changes associated with age.

The duration of effect in this study would not support a regimen of once-per-day doses.

The results of this study must be interpreted in the context of a single dose study in a small number of healthy subjects.

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6 OF 11

N24- 67

AUC (0-∞) ng hr.ml⁻¹

Subj. No.	12.5mg	25mg	50mg	50mg+Food	5mg iV
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
$\bar{x} \pm SD$	156±108	226±131	496±343	585±259	144±91
median	149	194	432	515	108
11					
12					
13					
14					
15					
16					
17					
18					
20					
21					
$\bar{x} \pm SD$	166±42	385±188	717±242	810±425	233±155
median	162	320	739	721	176

YOUNGER

OLDER

* The percentage of the AUC extrapolated beyond the last measured data point was less than 20% except where indicated in brackets.

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Pharmacokinetic parameters calculated
using 5mg intravenous data

Subj.No.	Bioavailability*	Clearance mls/min	Volume of
2			
3			
4			
5			
7			
$\bar{x} \pm SE$	34 ± 6.6	718 ± 129	189 ± 32
median	30	772	174
11			
12			
13			
14			
15			
16			
17			
20			
$\bar{x} \pm SE$	44 ± 7.6	503 ± 108	317 ± 96
median	48	474	253

* based on comparison with 50mg dose

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Renal Clearance* [ml/min] BM 14.190

Subj.	12.5mg	25mg	50mg	50mg+ Food	5mg iv

1					
2					
3					
4					
5					
6					
7					
8					
9					
10					

N	7.0	9.0	10.0	10.0	5.0
Mean	2.4	3.3	2.2	1.6	1.9
Stdv	2.9	2.5	2.5	1.6	1.8
Sen	1.1	0.8	0.8	0.5	0.8
Median	1.6	2.2	1.1	1.1	1.0
Minimum					
Maximum					

YOUNGER

Subj.	12.5mg	25mg	50mg	50mg+ Food	5mg iv

11					
12					
13					
14					
15					
16					
17					
18					
20					
21					

N	6.0	10.0	10.0	10.0	6.0
Mean	0.7	0.6	0.7	1.7	1.4
Stdv	0.9	0.5	0.6	3.3	1.3
Sen	0.4	0.2	0.2	2.0	0.5
Median	0.3	0.4	0.5	0.5	1.4
Minimum					
Maximum					

OLDER

* calculated using the data from tables 9 and 11

Table 15

Maximal fall in resting blood pressure (mmHg)

	<u>PLACEBO</u>	<u>12.5mg</u>	<u>25mg</u>	<u>50mg</u>	<u>50mg + F.</u>	<u>LABETALOL</u>
Young Supine	15±2/12±2(10)	11±3/10±1(9) ¹	17±1/15±2(10)	19±14/12±1(10)	21±4/16±2(10)	18±3/17±3(10)
Young standing	16±4/14±3(10)	14±2/10±1(9) ²	19±2/15±1(7)	23±3/10±2(6)	22±3/21±1(7)	23±6/22±5(10)
Old Supine	20±3/14±2(10)	36±2/25±4(6) ³	32±4/22±2(10)	37±2/23±2(10)	40±4/27±3(10)	35±3/19±2(10)
Old Standing	25±3/18±3(10)	39±10/19±5(5) ⁴	46±6/29±4(7)	48±3/35±2(7)	55±9/35±3(5)	47±3/29±3(10)

paired t-test: 12.5 mg vs placebo

- 1 p = .64 p = 0.80
 2 p = .54 p = 0.58
 3 p = 0.007 p = 0.02
 4 p = 0.36 p = 0.81

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Time of Maximal fall in resting blood pressure (h)

	PLACEBO	12.5mg	25mg	50mg	50mg + P.	LABETALOL
Young Supine	2.7±0.6/2.7±0.5	2.6±0.6/3.5±0.6	1.9±0.2/3.5±0.4	2.4±0.4/2.8±0.7	2.7±0.3/3.4±0.5	3.1±0.5/3.2±0.4
Young standing	2.7±0.4/3.4±0.7	1.9±0.5/2.8±0.5	3.1±0.9/3.3±0.8	2.3±0.6/2.7±0.7	3.3±0.6/3.4±0.9	2.5±0.5/2.7±0.5
Old Supine	3.0±0.8/4.0±0.6	4.5±0.5/4.8±0.2	2.9±0.5/4.4±0.3	3.9±0.4/4.6±0.3	2.4±0.4/2.8±0.6	4.6±0.6/4.4±0.4
Old Standing	4.0±0.5/4.7±0.4	4.1±0.8/4.1±0.9	2.5±0.6/4.4±0.5	3.1±0.6/2.8±0.5	2.5±0.4/2.5±0.4	3.1±0.5/3.1±0.5

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C131

4.2.3 Correlation between pharmacokinetic parameters and pharmacodynamic response

The relationship between the pharmacokinetics and pharmacodynamics of BM14,190 were examined by correlating the Cmax of the plasma level data with the maximal fall in blood pressure and the AUC of the plasma level data with the AUC of the blood pressure response. This was done in each age group for supine systolic and diastolic blood pressure and for standing systolic and diastolic blood pressure. The results are shown in Table (iii) below.

Table (iii) Correlation between pharmacokinetic parameters and pharmacodynamic response to BM14,190

	Supine		Standing	
	Sys	Dia	Sys	Dia
<u>Cmax vs blood pressure fall (max)</u>				
Young	0.18	0.08	0.54*	0.61*
Old	0.10	0.12	0.18	0.41*
<u>Plasma AUC vs blood pressure AUC</u>				
Young	0.11	0.18	0.36*	0.33*
Old	0.06	0.12	0.13	0.15

* p < 0.05

There tended to be a significant correlation between the pharmacokinetic parameters and standing blood pressure, particularly in the young subjects.

4.3 Exercise-induced tachycardia

The pulse rates determined immediately after exercise while the subjects were still sitting on the bike are presented in tables 81-86.

CARVEDILOL NDA 20-297

PROTOCOL MF3459 VOL 1.58

PK and RENAL FAILURE

Reviewer: James F. Graumlich

Name of study: Clinical study of the pharmacokinetics of carvedilol after acute administration of 50 mg to patients with chronic renal failure. An open, non-controlled study.

Objectives: To determine the pharmacokinetics of carvedilol, M2, M4, and M5 after single oral doses of carvedilol 50 mg in patients with chronic renal failure and hypertension.

Study design: Open-label, non-controlled, non-randomized prospective study of single oral doses of carvedilol 50 mg given to patients with diastolic blood pressure between 95 and 115 mm Hg. Patients were stratified into 3 groups based on creatinine clearance: group I = CCr > 50 mL/min, group II = CCr 25-50 mL/min, group III = CCr < 25 mL/min. There were 4 study centers.

Intervention: carvedilol 50 mg

Response variables: Primary outcome: carvedilol and metabolite concentrations in plasma, C_{max}, T_{max}, AUC

Secondary outcome: heart rate and blood pressure, supine and standing BP after the first 6 hours supine; other PK parameters; creatinine clearance; lab safety tests

BP, pulse, plasma concentration were measured at baseline then 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 48, 72 hours after carvedilol administration. Urine collection was from 0-4, 4-8, 8-12, 12-24, and 24-48 hours after the dose.

Materials: carvedilol 50 mg capsule batch 819 787 40 LD

Assay: Plasma assay of carvedilol and metabolites involved HPLC with fluorometric detection. The lower limit of quantification was 0.5-1.0 ng/mL.

Results: 25 men and women enrolled and 24 completed the study. Ages ranged between 20 and 69 years of age. Weights of subjects were between 47 and 100 kg. The creatinine clearance groups were not balanced at baseline: Group I = 3 patients, Group II = 9 patients, Group III = 13 patients. The creatinine clearance groups were not comparable with regard to age, sex, weight, blood pressure, pulse.

Protocol violations included 2 patients below 80% of ideal body weight and 1 patient above 130% ideal body weight. Patient 3 (Group II) ingested a concomitant medication (name of medication not stated) that violated the protocol. The blood pressure and heart rate of patient 3 did not appear to be different from other patients in Group II. Medications in the exclusion criteria included psychotropic drugs, aluminum hydroxide, cimetidine, antiarrhythmic, analgesics.

PK data from patient 24 in Group III is not included in the analysis. Patient 24 was lost to follow up after the first 3 measurements of blood pressure and heart rate. Baseline blood pressure and heart rate for patient 24 were similar to other patients in Group III.

Patient 23 (Group II) had small concentrations of carvedilol (C_{max} 5 ng/mL) and no quantifiable metabolites in plasma.

Carvedilol Pharmacokinetics PK parameters for carvedilol, M2, M4, and M5 are included in attached tables 1 - 4 (pages C136-C139). Two patients with the lowest AUCs were taking concomitant vitamin D3. Six of 12 patients in Group III had an additional hump in the curve of plasma concentration vs time. The plasma

concentrations of carvedilol, M2, M4, and M5 showed the extra hump at 6 - 8 hours after the dose. The extra hump is compatible with entero-hepatic circulation of carvedilol and metabolites M2, M4, and M5.

Pharmacodynamic response: The following table (page C135) shows the effect of carvedilol 50 mg po on supine blood pressure and heart rate. Abbreviations include Emax = maximum effect when compared to baseline. T,Emax = time of maximum effect. Duration = time from onset to end of effect. Since there is no placebo group, the duration of effect is arbitrarily defined as the approximate time during which a significant decrease from baseline occurred. There is no information available to suggest Emax exceeded placebo effect.

Adverse events: There were no deaths.

Treatment emergent symptoms and signs were

orthostatic dizziness in patient 33, group I

supraventricular tachycardia, nausea, dizziness in patient 34, Group I

headache in patient 35, Group I

Patient 3 (Group II) developed generalized exanthem and hemoglobin fell from 12.4 to 9.3, WBC fell from 5500 to 2400, and platelets fell from 124000 to 68000.

Patient 31 (Group II) had an increase in uric acid from 6.8 to 10.2 mg/dL.

Means of lab safety variables 72 hours after carvedilol did not change significantly from pre-study values except for total protein in Group I. Total protein pre-study mean of 23.9 g/dL fell to 6.57 at 72 hours. The pre-study mean of 3 patients was influenced by a patient with pre-study total protein of 57 g/dL which may be a decimal place error. The small number of patients and the lack of placebo control prevents assessment of causality.

Conclusions:

The numerous differences between the three creatinine clearance groups confound comparisons of PK and efficacy parameters between groups. The study might not be able to detect differences in PK parameters, e.g., AUC and half-life, due to renal failure even if differences existed.

The study showed significantly less renal clearance of carvedilol, M2, M4, and M5 in severe renal failure vs moderate renal failure. However, the amount of carvedilol, M2, M4, and M5 excreted in the urine is a small percentage of total dose for all groups of creatinine clearance. In this study, the decreases in renal clearance of carvedilol and metabolites in patients with renal failure are not clinically meaningful.

Two patients with the lowest AUCs were taking concomitant vitamin D3. There may be a pharmacokinetic drug interaction between carvedilol and vitamin D3.

In patients with renal failure, there is a delayed peak in the curve of plasma concentration vs time that is compatible with entero-hepatic circulation of carvedilol and metabolites M2, M4, and M5.

Orthostatic vital signs were not reported.

This study should be interpreted in the context of a single dose study without a placebo control.

Systolic blood pressure and heart rate after carvedilol 50 mg po

	Creatinine Clearance, mL/min		
	>50	25 - 50	<25
Systolic BP			
Emax (mm Hg)	-20	-30	-45
T,Emax (hours)	1	1.5	4
Duration (hours)	3	8	8
Diastolic BP			
Emax (mm Hg)	-15	-20	-25
T,Emax (hours)	3	3	3
Duration (hours)	12	12	12
Heart rate			
Emax (beats per min)	-20	-14	-8
T,Emax (hours)	2	3	1.5
Duration (hours)	2.5	6	2.5

BOEHRINGER MANNHEIM GMBH KLINISCHE PHARMAKOLOGIE - KINETIK
 PROGRAM: KRO DATE OF COMPUTATION: 12-DEC-85
 (RAW DATA EVALUATION; LOG.-LIN.REGR. BEGINNING AT 11.9 (h))
 PROJECT : BM 14.190 ; MF 3459
 PATIENTS WITH CHRONIC RENAL INSUFFICIENCY
 LOT : 819 787 40 LD ; DOSE : 50 mg BM 14.190 , PERORAL
 ASSAY : BM 14.190 IN PLASMA; METHOD : HPLC-FLUOROMETRY
 * 1 * : == GROUP I (CREAT-CL > 50 ml/min) ==
 * 2 * : == GROUP II (CREAT-CL 26 - 50 ml/min) ==
 * 3 * : == GROUP III (CREAT-CL 3 - 25 ml/min) ==

Tab. 1

PARENT
 CARVEDILOL

MANN - WHITNEY "U" - TEST P [TWO SIDED APPROX.]

PARAMETER (RAW - DATA)	UNIT		"1"	"2"	"3"	P 1:2	P 1:3	P 2:3
A U C	[ng*h/ml]	N	3.	8.	11.			
		MEAN	1480.63	1342.43	1054.41			0.509
		C.V. (%)	24.58	58.24	51.47			
		MEDIAN	1323.94	1110.42	1063.86			
		MINIM. MAXIM.						
A U C (0 - 72 h)	[ng*h/ml]	N	3.	9.	12.			
		MEAN	1429.39	1156.58	979.55			0.670
		C.V. (%)	25.86	71.29	53.68			
		MEDIAN	1261.98	938.90	946.14			
		MINIM. MAXIM.						
C max	[ng/ml]	N	3.	9.	12.			
		MEAN	321.79	230.10	165.64			0.831
		C.V. (%)	10.14	80.86	44.86			
		MEDIAN	318.29	179.76	173.57			
		MINIM. MAXIM.						
t max	[h]	N	3.	9.	12.			
		MEAN	1.333	1.167	1.590			
		C.V. (%)	108.25	42.86	67.23			
		MEDIAN	0.500	1.000	1.250			
		MINIM. MAXIM.						
t 1/2	[h]	N	3.	8.	11.			
		MEAN	22.377	14.473	14.645			0.741
		C.V. (%)	20.79	63.77	54.29			
		MEDIAN	21.934	12.753	13.394			
		MINIM. MAXIM.						
CL / f	[ml/min]	N	3.	8.	11.			
		MEAN	583.72	788.34	1327.24			0.509
		C.V. (%)	21.89	45.82	119.07			
		MEDIAN	629.64	764.27	783.31			
		MINIM. MAXIM.						
A e (0 - 48 h)	[%]	N	3.	9.	12.			
		MEAN	0.6210	0.2625	0.1107			0.033
		C.V. (%)	17.97	86.71	77.11			
		MEDIAN	0.6551	0.2012	0.0993			
		MINIM. MAXIM.						
CL R	[ml/min]	N	3.	9.	12.			
		MEAN	4.04	2.44	0.98			0.009
		C.V. (%)	37.13	65.69	80.22			
		MEDIAN	4.88	1.85	0.79			
		MINIM. MAXIM.						

MF 3459
 VOL 1.58
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BOEHRINGER MANNHEIM GMBH KLINISCHE PHARMAKOLOGIE - KINETIK
 PROGRAM: KRO_U DATE OF COMPUTATION: 15-DEC-89

(RAW DATA EVALUATION)

PROJECT : BM 14.190 ; MF 3459
 PATIENTS WITH CHRONIC RENAL INSUFFICIENCY
 LOT : 819 787 40 LD ; DOSE : 50 mg BM 14.190 , PERORAL
 ASSAY : M2 (BM 14.262) IN PLASMA; METHOD : HPLC-FLUOROMETRY

M2

- * 1 * : == GROUP I (CREAT-CL > 50 ml/min) ==
- * 2 * : == GROUP II (CREAT-CL 26 - 50 ml/min) ==
- * 3 * : == GROUP III (CREAT-CL 3 - 25 ml/min) ==

VALUES GIVEN IN EQUIVALENTS OF PARENT COMPOUND (factor = 1.0357)

MANN - WHITNEY "U" - TEST P [TWO SIDED APPROX.]

PARAMETER (RAW - DATA)	UNIT		"1"	"2"	"3"	P 1:2	P 1:3	P 2:3
A U C (0 - 72 h)	[ng*h/ml]	N	3.	8.	12.			
		MEAN	89.41	72.05	63.58			0.643
		C.V. (%)	55.51	62.38	63.42			
		MEDIAN	77.10	57.08	62.31			
		MINIM. MAXIM.						
C max	[ng/ml]	N	3.	8.	12.			
		MEAN	16.24	13.23	11.08			0.217
		C.V. (%)	25.54	39.97	52.11			
		MEDIAN	18.23	13.22	10.74			
		MINIM. MAXIM.						
t max	[h]	N	3.	8.	12.			
		MEAN	1.833	1.438	1.757			
		C.V. (%)	56.77	29.03	54.17			
		MEDIAN	1.500	1.500	1.500			
		MINIM. MAXIM.						
A e (0 - 48 h)	[%]	N	3.	9.	12.			
		MEAN	0.0695	0.0162	0.0022			0.014
		C.V. (%)	16.22	145.16	165.43			
		MEDIAN	0.0710	0.0109	0.0006			
		MINIM. MAXIM.						
CL R	[ml/min]	N	3.	8.	12.			
		MEAN	7.49	2.21	0.24			0.002
		C.V. (%)	37.16	87.87	109.88			
		MEDIAN	7.68	1.76	0.11			
		MINIM. MAXIM.						

MF 3459
 VOL 1.58

BOEHRINGER MANNHEIM GMBH KLINISCHE PHARMAKOLOGIE - KINETIK
 PROGRAM: KRO_U DATE OF COMPUTATION: 15-DEC-89

(RAW DATA EVALUATION)

PROJECT : BM 14.190 ; MF 3459
 PATIENTS WITH CHRONIC RENAL INSUFFICIENCY
 LOT : 819 787 40 LD ; DCSE : 50 mg BM 14.190 , PERDRAL
 ASSAY : M4 (BM 14.0686) IN PLASMA; METHOD : HPLC-FLUOROMETRY

M4

- * 1 * : == GROUP I (CREAT-CL > 50 ml/min) ==
- * 2 * : == GROUP II (CREAT-CL 26 - 50 ml/min) ==
- * 3 * : == GROUP III (CREAT-CL 3 - 25 ml/min) ==

VALUES GIVEN IN EQUIVALENTS OF PARENT COMPOUND (factor = 0.9621)

MANN - WHITNEY "U" - TEST P (TWO SIDED APPROX.)

PARAMETER (RAW - DATA)	UNIT		"1"	"2"	"3"	P 1:2	P 1:3	P 2:3
A U C (0 - 72 h)	[ng ^h /ml]	N	3.	8.	12.			
		MEAN	61.74	70.81	60.41			0.589
		C.V. (%)	34.66	53.29	50.28			
		MEDIAN	63.77	62.18	54.32			
		MINIM.						
		MAXIM.						
C MAX	[ng/ml]	N	3.	8.	12.			
		MEAN	14.88	16.90	13.07			0.700
		C.V. (%)	39.61	83.05	49.87			
		MEDIAN	15.31	11.82	13.60			
		MINIM.						
		MAXIM.						
t MAX	[h]	N	3.	8.	12.			
		MEAN	1.333	1.313	1.632			
		C.V. (%)	78.06	60.41	64.79			
		MEDIAN	1.000	1.250	1.250			
		MINIM.						
		MAXIM.						
A e (0 - 48 h)	[%]	N	3.	9.	10.			
		MEAN	0.1231	0.0345	0.0120			0.050
		C.V. (%)	18.98	96.70	84.93			
		MEDIAN	0.1291	0.0284	0.0083			
		MINIM.						
		MAXIM.						
CL R	[ml/min]	N	3.	8.	10.			
		MEAN	18.15	5.77	1.55			0.013
		C.V. (%)	11.71	100.13	68.82			
		MEDIAN	16.96	3.31	1.27			
		MINIM.						
		MAXIM.						

MF 3459
 VOL 1.58
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BOEHRINGER MANNHEIM GMBH KLINISCHE PHARMAKOLOGIE - KINETIK
 PROGRAM: KRO_U DATE OF COMPUTATION: 15-DEC-89

Tab. 4

(RAW DATA EVALUATION)

PROJECT : BM 14.190 ; MF 3459
 PATIENTS WITH CHRONIC RENAL INSUFFICIENCY
 LOT : 819 787 40 LD ; DOSE : 50 mg BM 14.190 , PERORAL
 ASSAY : M5 (BM 14.0830) IN PLASMA; METHOD : HPLC-FLUOROMETRY

M5

- * 1 * : == GROUP I (CREAT-CL > 50 ml/min) ==
- * 2 * : == GROUP II (CREAT-CL 26 - 50 ml/min) ==
- * 3 * : == GROUP III (CREAT-CL 3 - 25 ml/min) ==

VALUES GIVEN IN EQUIVALENTS OF PARENT COMPOUND (factor = 0.9621)

MANN - WHITNEY "U" - TEST P (TWO SIDED APPROX.)

PARAMETER (RAW - DATA)	UNIT		#1	#2	#3	P 1:2	P 1:3	P 2:3
A U C (0 - 72 h)	[ng*h/ml]	N	3.	8.	12.			
		MEAN	62.75	49.15	38.95			0.877
		C.V. [%]	36.71	80.39	54.62			
		MEDIAN	52.56	30.34	32.33			
		MINIM. MAXIM.						
C max	[ng/ml]	N	3.	8.	12.			
		MEAN	14.68	11.62	10.00			0.877
		C.V. [%]	15.93	57.01	43.03			
		MEDIAN	14.16	9.60	10.33			
		MINIM. MAXIM.						
t max	[h]	N	3.	8.	12.			
		MEAN	1.500	1.375	1.632			
		C.V. [%]	57.74	32.23	62.10			
		MEDIAN	1.000	1.250	1.250			
		MINIM. MAXIM.						
A e (0 - 48 h)	[%]	N	3.	9.	11.			
		MEAN	0.1173	0.0336	0.0063			0.025
		C.V. [%]	37.72	156.77	98.24			
		MEDIAN	0.1017	0.0175	0.0034			
		MINIM. MAXIM.						
CL R	[ml/min]	N	3.	8.	11.			
		MEAN	15.54	6.65	1.15			0.002
		C.V. [%]	4.09	75.76	75.54			
		MEDIAN	15.64	6.32	0.88			
		MINIM. MAXIM.						

MF 3459

VOL 1.58

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CARVEDILOL NDA 20-297

PROTOCOL MF3476 VOL 1.60

PK and LIVER INSUFFICIENCY

Reviewer: James F. Graumlich

Name of study: Investigation of the determination of the pharmacokinetics of carvedilol in patients with chronic liver insufficiency.

Objectives: To investigate the pharmacokinetics and the absolute bioavailability of carvedilol after single intravenous and oral doses of carvedilol in patients with chronic liver insufficiency in comparison with healthy volunteers.

Study design: Open-label, non-controlled, randomized sequence, two-period crossover study of single oral doses of carvedilol 25 mg and single intravenous doses of carvedilol 12.5 mg. Patients were classified in 3 groups: Group I had serum cholinesterase 900-1500 U/L and Quick $\geq$ 50%, Group II had serum cholinesterase $<$ 900 U/L and Quick $<$ 50%, Group III had serum cholinesterase $>$ 1500 U/L and Quick 80 - 120%.

Intervention: carvedilol 25 mg capsule po, carvedilol 12.5 mg intravenous infusion over 1 hour. Two patients in group II received carvedilol 12.5 mg po instead of 25 mg po.

Response variables: Primary outcome: carvedilol and BM 14.242 concentrations in plasma and urine, C_{max}, T_{max}, AUC. Plasma concentrations were measured at baseline then 0.17, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 32, and 48 hours after carvedilol administration. Urine collection was from 0-12, 12-24, and 24-48 hours after the dose.

Assay: Plasma assay of carvedilol and BM 14.242 involved HPLC with fluorometric detection. The lower limit of quantification was 1.0 ng/mL in the plasma.

Results: Group I had 13 patients with mild chronic liver insufficiency. Group II had 8 patients with severe chronic liver insufficiency. Group III had 10 patients with normal liver function.

Protocol violations included infusion and measurement of carvedilol through the same central venous catheter in some patients. The investigator could not identify the patients with the protocol violations. Protocol violations included patients from all 3 groups. In patients with the aforementioned protocol violations, the calculated amount of carvedilol in the body exceeded the administered dose.

Subjects 202, 301, and 302 were drop outs. The reason for withdrawal was not stated in the report.

Two patients in group II received their treatments in the wrong sequence. Four patients in group II and one patient in group III did not receive the second treatment.

In vitro protein binding using plasma samples from 8 subjects from Group II was $98.2\% \pm 0.4\%$ (mean $\pm$ SD, minimum 97.6%, maximum 98.6%).

Carvedilol Pharmacokinetics Pk parameters for carvedilol are not meaningful because of the protocol violations.

Pharmacodynamic response: There are no reports of blood pressure or heart rate from this study.

Adverse events: There were no deaths reported.

Patient 202 from Group II (57 year old man) had severe fall in blood pressure (amount not reported) after carvedilol 12.5 mg IV.

Patient 302 from Group III (70 year old man with cecal carcinoma, Billroth I for ulcer and anemia) had severe fall in blood pressure (amount not reported) after carvedilol 25 mg po.

No other adverse events were reported.

Results of lab safety variables were not reported.

Conclusions:

The stratification of patients by level of liver impairment uses tests of liver function that are not commonly used in the United States. There is limited ability to generalize the results of this study to the population of patients with liver insufficiency.

One elderly patient could not tolerate carvedilol 25 mg po.

Protocol violations prevent interpretation of PK data.

Reviewer: James F. Graumlich
PD Study

MF3548 is a double-blind, randomized-sequence, placebo-controlled, 6-period crossover study in 8 healthy men. Response variables were systolic blood pressure, diastolic blood pressure, heart rate, exercise heart rate, carvedilol concentration in serum, impedance cardiography, blood flow, hand tremor. Responses were measured before and after various stimuli: isoprenaline, phenylephrine, isometric exercise, cold stimulus, tilt test, bicycle exercise, angiotensin II. Single oral doses of each treatment were given on 2 separate occasions (at least 5 days apart). Treatments were carvedilol 50 mg, carvedilol 100 mg, propranolol 160 mg, propranolol 80 mg + hydralazine 50 mg, labetalol 400 mg, placebo. Treatment periods were separated by at least 5 days.

Results: All 8 subjects (ages 24 - 45 years, weights 62 - 107.4 kg) completed the study. One subject could not complete exercise due to faintness after carvedilol 100 mg (BP and pulse during faintness not reported). Multiple provocative tests were performed before and 1.5 hours after the dose. There does not appear to be an attempt to perform repeated tests over a dosing interval to correlate concentration with effect. There is no evidence the provocative tests were performed at the time of Emax for any of the treatments.

Response to isometric hand grip exercise: When compared to placebo, none of the treatments influenced the change in SBP, DBP, or heart rate during 2 minutes of hand grip exercise except propranolol 160 mg blocked the increase in heart rate.

Response to cold (foot in 0° water): When compared to placebo, none of the treatments influenced the change in SBP, DBP, or heart rate during 2 minutes of cold exposure except possibly labetalol 400 mg blocked the increase in SBP. Significant differences at baseline make comparisons questionable.

Response to 60° tilt: When compared to placebo, none of the treatments influenced the change in SBP, DBP, or heart rate during 2 minutes of tilt except possibly propranolol 160 mg and propranolol 80 mg + hydralazine 50 mg blocked the increase in SBP. Significant differences at baseline make comparisons questionable.

Response to bicycle exercise: When compared to placebo, all treatments blocked the increase in SBP and heart rate associated with exercise. None of the treatments influenced the change in DBP. Carvedilol 100 mg did not show convincing evidence of increased blockade when compared to carvedilol 50 mg for any response variable. Another problem with the interpretation of the results is the baseline measurements for the carvedilol treatments were lower than placebo.

Heart rate response to isoprenaline: Analysis compared the doses of isoprenaline required to achieve an increase of 25 beats per minute. All treatments demonstrated blockade of isoprenaline's effect on heart rate. There was no difference demonstrated between carvedilol 50 mg and carvedilol 100 mg.

Systolic blood pressure response to isoprenaline: Analysis compared the doses of isoprenaline required to achieve an increase of 20 mm Hg. When compared to placebo, carvedilol 50 mg (not 100 mg) and labetalol demonstrated blockade of isoprenaline's effect on SBP. There was no difference demonstrated between carvedilol 50 mg and carvedilol 100 mg.

Systolic blood pressure response to phenylephrine: Analysis compared the doses of phenylephrine required to achieve an increase of 20 mm Hg. Carvedilol and labetalol demonstrated blockade of phenylephrine's effect on SBP. There was no difference demonstrated between carvedilol 50 mg and carvedilol 100 mg although there was trend suggesting carvedilol 100 mg was more potent.

Diastolic blood pressure response to phenylephrine: Analysis compared the doses of phenylephrine required to achieve an increase of 20 mm Hg. Only labetalol demonstrated blockade of phenylephrine's effect on DBP. There was no difference demonstrated between carvedilol 50 mg and carvedilol 100 mg.

CARVEDILOL NDA 20-297

PROTOCOL MF3548 VOL 1.134

Systolic and diastolic blood pressure response to angiotensin II: None of the treatments demonstrated effect when compared to placebo.

No data were reported for the following response variables: carvedilol concentration in serum, impedance cardiography, blood flow, hand tremor.

There were no clinically significant, treatment emergent, laboratory abnormalities reported.

Conclusion: Carvedilol 50 mg and 100 mg demonstrated effects as a beta blocker and alpha blocker in 8 healthy men.

CARVEDILOL NDA 20-297

PROTOCOL MF3702 VOL 1.61

CARVEDILOL NDA 20-297 PROTOCOL MF3702

Reviewer: James F. Graumlich, MD

29 hypertensive patients (supine DBP $\geq$ 95-115 mm Hg after 2 weeks of placebo therapy) received carvedilol (12.5, 25 and 50 mg po q day) in a dose titration design. There were 8 young and 21 elderly subjects.

Therapy was carvedilol 12.5 mg po q day for 12 weeks. Non-responders at 4 weeks received carvedilol 25 mg po q day. Non-responders at 6 weeks received carvedilol 50 mg po q day. Measurement of BP and HR response was on day 1 at baseline then 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, and 24 hours after dose. The sponsor does not report measurements from 8 hours. Measurement of pre-dose BP and HR occurred on weeks 2, 4, 6, 10, 12. There were pharmacokinetic profiles in week 8 with samples for carvedilol and metabolite concentrations at baseline then 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, and 24 hours after dose. BP and HR were measured at same times as phlebotomy. Subjects received placebo for one week after week 12. BP and HR were measured at the end of placebo wash-out. Placebo wash-out as mentioned in protocol was not done. Non-responders at week 8 were discharged from the study after the PK profile.

Materials: carvedilol 12.5 mg capsule lot number 820 020 40 Jd, 25 mg capsule lot number 819 789 40 Hb (bioequivalence with commercial formulation not established), 50 mg capsule lot number 819 787 40 Ld

32 screened patients entered placebo run-in (8 young, 24 elderly). 29 patients entered and completed active treatment (8 young, 21 elderly). 2 young and 1 elderly did not complete last visit. Prior to treatment, supine and erect systolic BP was significantly greater in the elderly group. There were only men in the young group. 4 of the 21 elderly were women. There were no significant differences at baseline between the young and elderly group with regard to diastolic BP, heart rate, or plasma creatinine.

5 young and 17 elderly had initial PK sampling. After carvedilol 12.5 mg, significant decreases in supine and erect DBP and SBP occurred at 0.5 hours post dose. Peak effect on supine BP occurred at 4 hours (mean SBP fell from 174 mm Hg to 146 mm Hg and mean DBP fell from 101 to 80). There was a significant decrease in mean DBP at 24 hours. Mean supine and erect heart rate did not fall below 60 beats per minute during the first 7 hours nor at the 24th hour. 10 subjects were non-responders at 12.5 and 25 mg. These are the only subjects who received all three doses of carvedilol.

There is no dose response relationship for DBP or SBP.

After 12.5 mg dose, mean plasma concentrations for carvedilol and O-demethylated metabolite for 6 young and 16 elderly patients were not statistically different at any time point (reference vol 1.61 page 97). There was missing data for 2 young and 5 elderly. Effect of missing data is unknown.

After 25 mg dose, mean plasma concentrations of carvedilol for 3 young and 9 elderly are not interpretable due to small numbers of young subjects.

After 50 mg dose, mean plasma concentrations of carvedilol for approximately 6 to 8 young and 16 to 17 elderly patients show significant differences in C_{max} and AUC. C_{max} (carvedilol) was significantly greater in elderly patients vs young patients (220 vs 117 μ g/L). The time to peak carvedilol concentration was between 0.5 and 2 hours. AUC was 49% higher for elderly patients (reference vol 1.61 page 99).

Small n for data from 25 mg (3 young and 9 elderly) result in inconclusive differences. However, there is a trend similar to the 50 mg dose with greater C_{max} and AUC in elderly patients.

For all three doses, the slopes of the terminal elimination phases appear to be the same.

PK-PD DRUG INTERACTION: HYDROCHLOROTHIAZIDE

Reviewer: James F. Graumlich

Name of study: Pharmacodynamic/pharmacokinetic interactions of carvedilol and hydrochlorothiazide.

Objectives: To investigate possible pharmacodynamic/pharmacokinetic interactions of carvedilol and hydrochlorothiazide (HCTZ).

Study design: Double-blind, placebo-controlled, randomized-sequence, 3-period crossover study of single oral doses of carvedilol, HCTZ, and carvedilol + HCTZ given to 12 patients with diastolic blood pressure > 110 mm Hg and systolic blood pressure > 160 mm Hg. Drug administration periods were separated by 4 days. There was a 2-day washout prior to the first treatment period. Upon enrollment, subjects had normal ECG and screening lab tests.

Intervention: carvedilol 25 mg capsule + placebo capsule
HCTZ 25 mg capsule + placebo capsule
carvedilol 25 mg capsule + HCTZ 25 mg capsule

Response variables: Primary outcome: carvedilol and HCTZ concentrations in plasma, Cmax, Tmax, AUC
Secondary outcome: heart rate, blood pressure, respiratory rate, temperature, ECG, pulmonary function tests, other PK parameters; lab safety tests. Reports of adverse events were spontaneous. Measurements of PD variables occurred over 24 hours on study day 1.

Plasma concentrations were measured at baseline then 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 16, and 24 hours after drug administration. Blood pressure and pulse were measured at baseline then 2, 4, 6, 8, 10, 12, 16, and 24 hours after drug administration. The following were measured before the first treatment and after the third treatment: urinalysis, orthostatic vital signs, laboratory safety tests, ECG, and pulmonary function tests.

Assay: The lower limit of quantification of carvedilol was not stated. The lower limit of detection of HCTZ was 7.0 ng/mL

Results: 6 men and 6 women enrolled and all completed the study. Ages ranged between 30 and 69 years of age. Weights of subjects were between 74 and 109.3 kg.

Carvedilol Pharmacokinetics

The attached figure 4 (page 53, volume 1.62) and figure 5 (page 55, volume 1.62) show the means for plasma concentration vs time for carvedilol and HCTZ. The attached tables show the PK parameters for carvedilol and HCTZ. The PK parameters did not change significantly for either drug as a result of combination therapy.

Pharmacodynamic response:

Figure 1, page 45, volume 1.62 displays the systolic blood pressure (sitting). Two hours after combined therapy with carvedilol and HCTZ, 7 of 12 subjects had decreases of systolic blood pressure (compared to pre-dose baseline) in the range of 27 - 54 mm Hg.

Figure 2, page 48, volume 1.62 displays the diastolic blood pressure (sitting). Two hours after combined therapy with carvedilol and HCTZ, 11 of 12 subjects had decreases of diastolic blood pressure (compared to pre-dose baseline) in the range of 3 - 45 mm Hg.

Figure 3, page 51, volume 1.62 displays the heart rate (sitting). Six hours after combined therapy with carvedilol and HCTZ, 10 of 12 subjects had decreases of heart rate (compared to pre-dose baseline) in the range of 4 - 31 beats per minute.

There was no clinically significant difference before or after therapy with combined carvedilol and HCTZ with respect to means of body temperature or respiratory rate.

Orthostatic blood pressure and pulmonary function were not measured before and after each treatment. Consequently, there is no way to distinguish effects of carvedilol, HCTZ, or carvedilol + HCTZ. There was no effect on orthostatic blood pressure or pulmonary function demonstrated. However, treatment effect was measured one day after the third treatment when effects of treatment probably were not demonstrable.

Adverse events: There were no deaths.

Treatment emergent symptoms and signs are in the attached table.

One subject developed an inflammatory lesion on the skin approximately the size of the palm of the hand. The lesion abated with topical antihistamine therapy and did not recur after rechallenge with carvedilol or HCTZ. This skin reaction does not appear to be related to drug therapy.

Lab safety variables were not measured before and after each treatment. Consequently, there is no way to distinguish effects of carvedilol, HCTZ, or carvedilol + HCTZ.

3 of 12 had clinically significant decreases in hemoglobin: 14.3 to 12.2, 15.5 to 13.0, 14.5 to 11.7 g/dL.

1 of 12 had a decrease in WBC from 7.5 to 4.4

1 of 12 had an increase of calcium from 2.27 to 4.28 (normal 2.1 - 2.6)

2 of 12 had a decrease of calcium: 2.26 to 1.7, 2.19 to 1.78.

Conclusions:

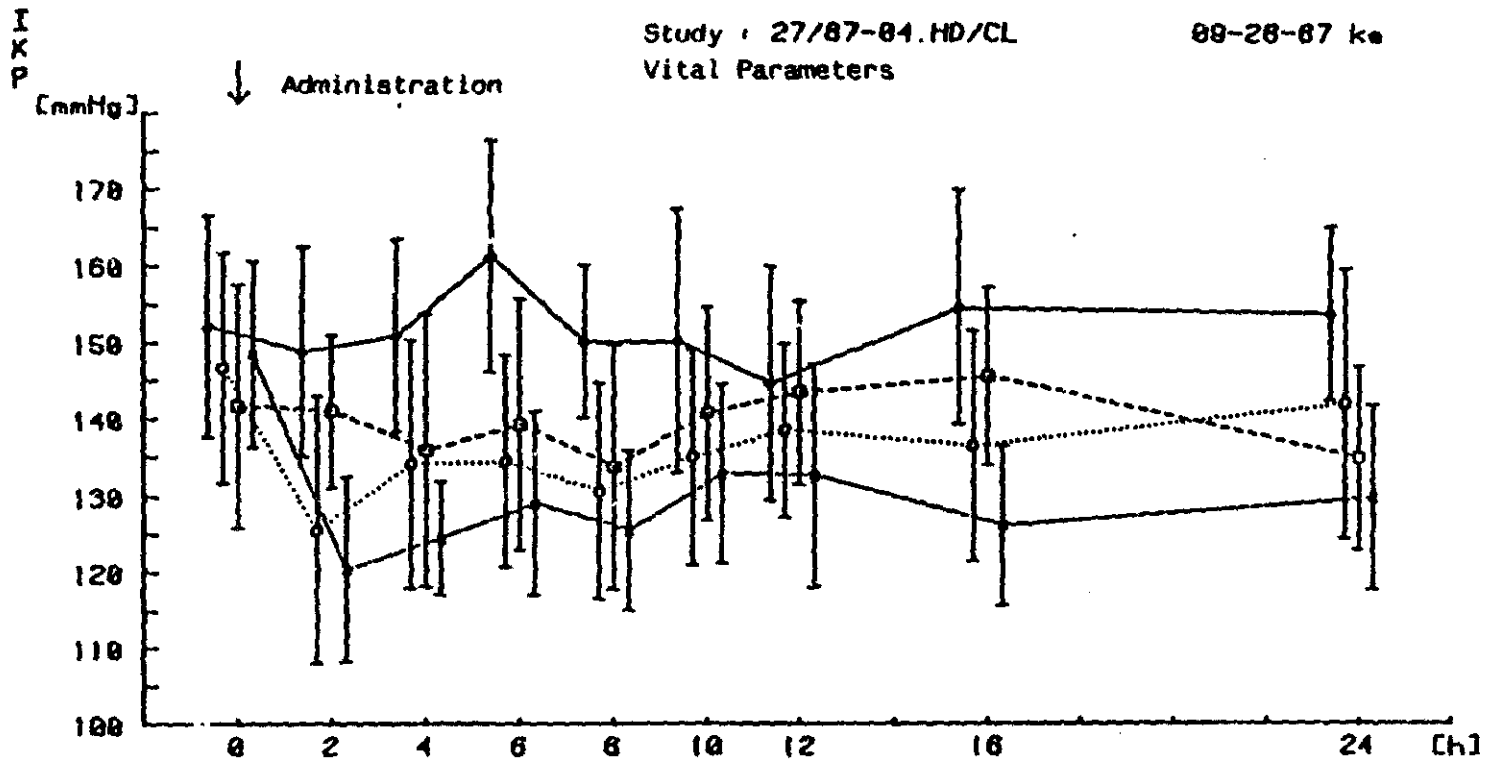
There was no pharmacokinetic interaction between carvedilol and HCTZ.

Lab safety variables, orthostatic vital signs, ECG, and pulmonary function were not measured before and after each treatment. Consequently, there is no way to distinguish effects on these parameters resulting from carvedilol, HCTZ, or carvedilol + HCTZ.

Mean diastolic blood pressure was not significantly different from baseline after any treatment. The sample size may have been too small to detect pharmacodynamic interactions between carvedilol and HCTZ if interactions existed. There was no post hoc power analysis to assess the adequacy of the sample size.

This study should be interpreted in the context of a single dose study in patients with hypertension.

Patients did not receive placebo alone. The effect of placebo on these patients is unknown.



Day 1 - Baseline examination
 Treatment type A: Carvedilol 25 mg
 Treatment type B: Hydrochlorothiazide 25 mg
 Treatment type C: Carvedilol 25 mg + Hydrochlorothiazide 25 mg

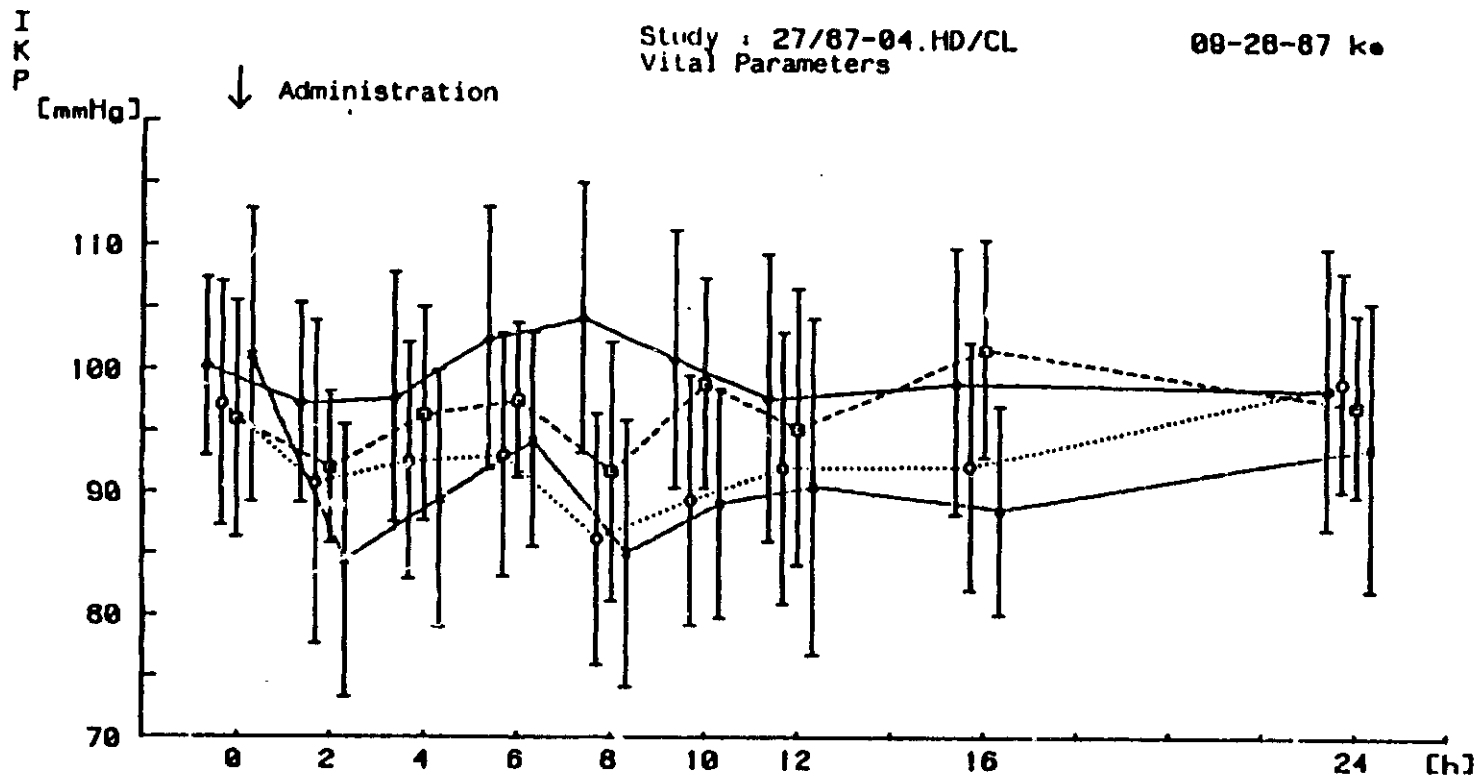
● ———
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Fig. 1: Systolic blood pressure (sitting position) [mmHg]
 Mean ± standard deviation

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C147



Day 1 - Baseline examination
 Treatment type A: Carvedilol 25 mg
 Treatment type B: Hydrochlorothiazide 25 mg
 Treatment type C: Carvedilol 25 mg + Hydrochlorothiazide 25 mg

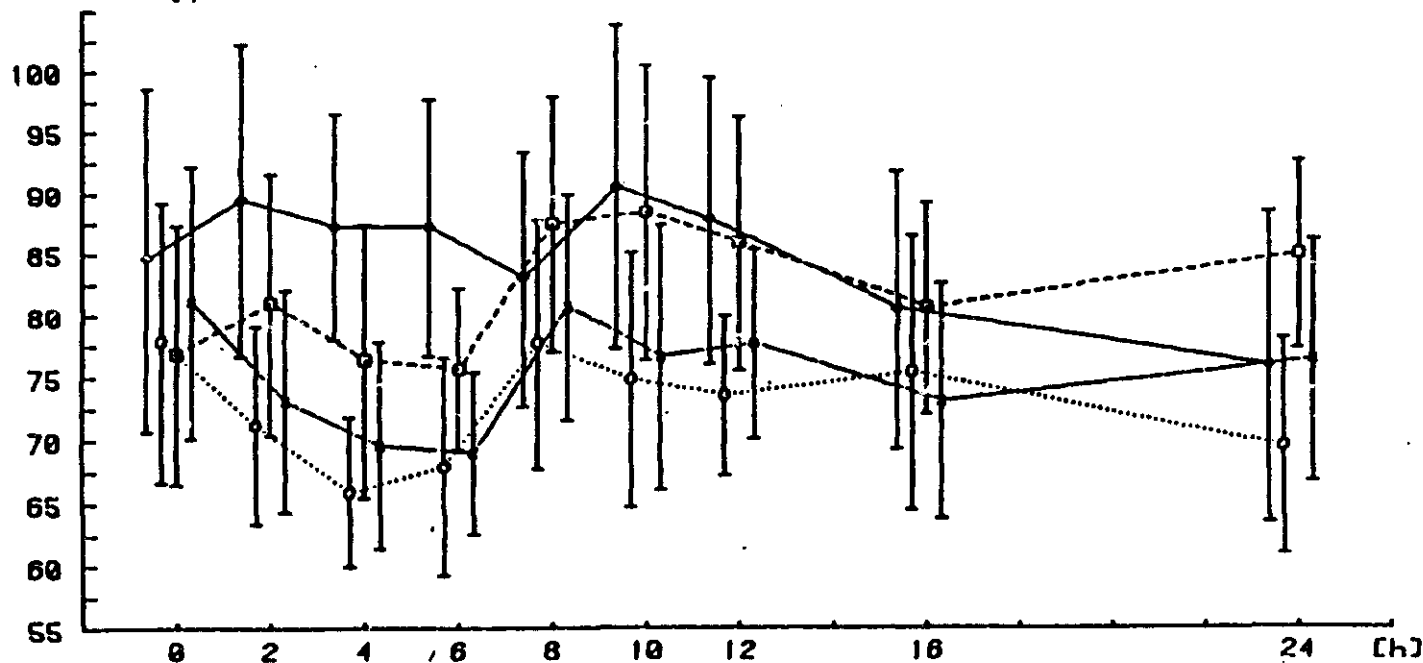
Fig. 2: Diastolic blood pressure (sitting position) [mmHg]
 Mean ± standard deviation

I
K
P (bpm)

Study : 27/87-84.HD/CL
Vital Parameters

09-28-87 ka

↓ Administration



Day 1 - Baseline examination
Treatment type A: Carvedilol 25 mg
Treatment type B: Hydrochlorothiazide 25 mg
Treatment type C: Carvedilol 25 mg + Hydrochlorothiazide 25 mg

Fig. 3: Heart rate (sitting position) [bpm]

MEAN ± SD

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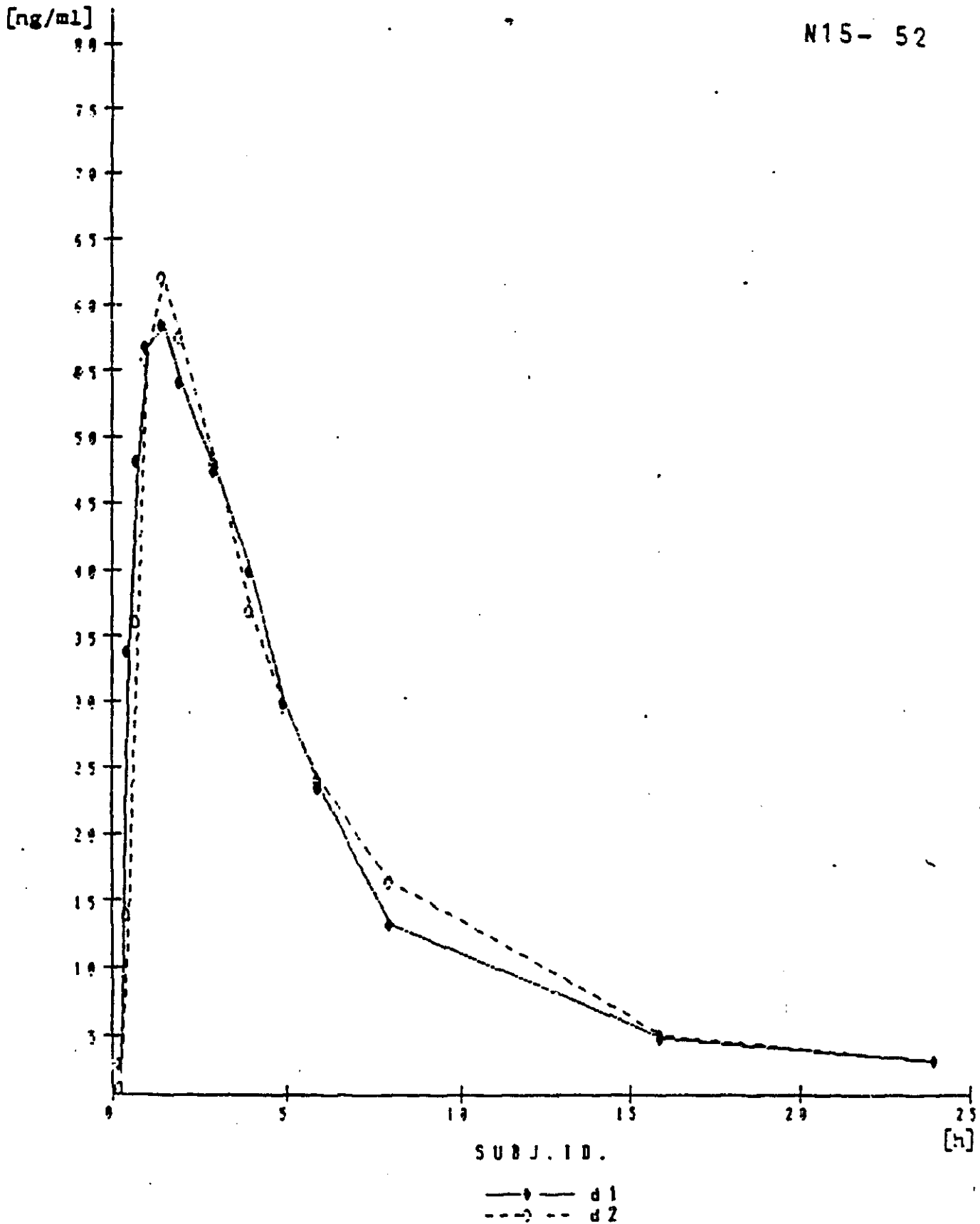


Fig. 4: Synoptic plot of the mean concentration/time curves for carvedilol after single entity administration and combined administration with hydrochlorothiazide (d 1 = carvedilol, d 2 = carvedilol + HCT)

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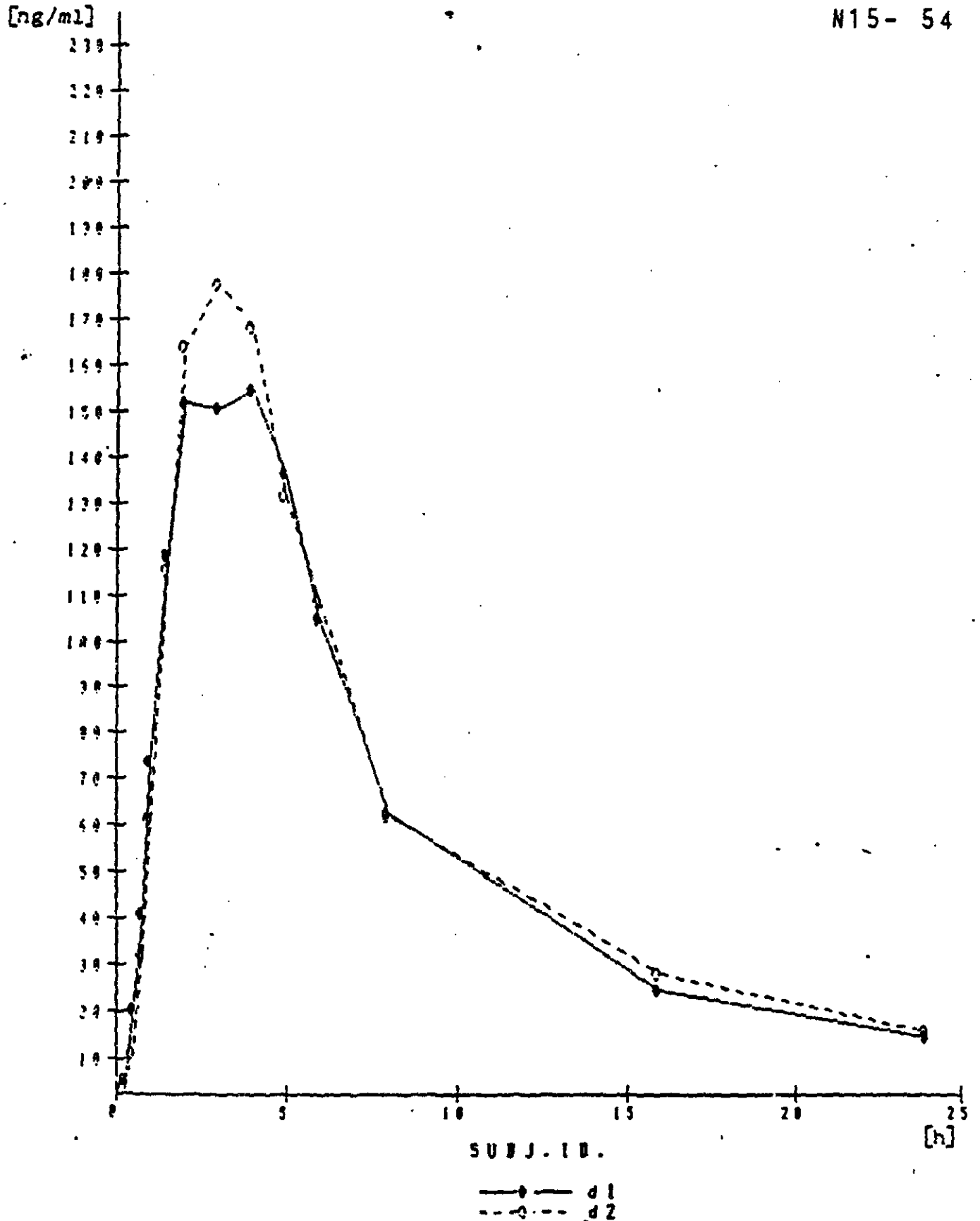


Fig. 5: Synoptic plot of the mean concentration/time curves for hydrochlorothiazide after single entity administration and combined administration with carvedilol (d 1 = HCT, d 2 = HCT + carvedilol)

CARVEDILOL NDA 20-297, PROTOCOL MF3877, VOLUME 1.62

Carvedilol PK N=12 patients			HCTZ PK N=12 patients		
	carvedilol + placebo	carvedilol + HCTZ		HCTZ + placebo	carvedilol + HCTZ
Cmax (ng/mL)			Cmax (ng/mL)		
mean	82.29	77.13	mean	187.9	211.48
SD	73.52	51.91	SD	60.75	92.45
minimum			minimum		
maximum			maximum		
Tmax (hours)			Tmax (hours)		
mean	1.9	1.7	mean	3	2.5
SD	1	0.8	SD	1.5	0.9
minimum			minimum		
maximum			maximum		
AUC (ng*hr/mL)			AUC (ng*hr/mL)		
mean	382.08	393.61	mean	1388.06	1459.28
SD	323.51	293.23	SD	419.78	443.47
minimum			minimum		
maximum			maximum		
half-life (hours)			half-life (hours)		
mean	5.5	5.9	mean	7.7	8.2
SD	2.8	2	SD	2.4	1.3
minimum			minimum		
maximum			maximum		

ADVERSE EVENTS

Number of patients reporting adverse event

N=12 patients

	carvedilol + placebo	HCTZ + placebo	carvedilol + HCTZ
nausea	2	0	1
headache	3	3	3
tired	5	2	5
urinary urgency	1	4	0
dizzy	1	0	1
light headed	1	0	0
nasal congestion	1	0	1
orange urine	0	0	1
muscle cramps	0	1	0
felt cold	0	2	0
stabbing pains	1	0	0

CARVEDILOL NDA 20-297

PROTOCOL MF3950 VOL 1.63

PK IN ELDERLY

Reviewer: James F. Graumlich

Name of study: The pharmacokinetic profile of carvedilol in young and elderly healthy volunteers.**Objectives:** To compare the pharmacokinetic profile and the tolerability of carvedilol 25 mg po once per day for 2 weeks.

Study design: Open, uncontrolled, parallel study of single oral doses of carvedilol 25 mg po every day for 2 weeks in 10 young men (age 20 - 26 years) and 11 old (age $\geq$ 65 years) healthy volunteers. There were 2 study sites: one site enrolled only young volunteers, the other site enrolled only elderly volunteers. PK sampling occurred on days 1 and 14. Upon enrollment, subjects had normal ECG and screening lab tests. The protocol states the inclusion and exclusion criteria were the same for the young and elderly except for age and systolic blood pressure. The study report reveals the young and the elderly had different inclusion and exclusion criteria. Although the differences may have been minor, e.g., positive hepatitis antigen excluded young but not old subjects, the concern exists regarding selection bias. Furthermore, the young were studied at one center and the elderly were studied at another center.

Intervention: carvedilol 25 mg capsule by mouth every day for 2 weeks

Response variables: Primary outcome: carvedilol concentrations in plasma, C_{max} , T_{max} , AUC
Secondary outcome: carvedilol concentration in urine, heart rate, blood pressure, ECG, other PK parameters; lab safety tests. Reports of adverse events were spontaneous. Measurements of sitting and standing BP and pulse occurred over 24 hours on PK sampling days (days 1 and 14).

Plasma concentrations were measured on days 1 and 14 at baseline then 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours after drug administration. The PK sampling after the dose on day 14 included additional samples 36 and 48 hours after dose administration. Beginning on day 2 and continuing approximately every other day thereafter, plasma samples were obtained immediately before and 2 hours after the 8:00 AM dose.

Assay: The lower limit of quantification of carvedilol in plasma and urine was 1.0 ng/mL. The lower limit of quantification of desmethylcarvedilol in plasma and urine was 0.5 - 1.0 ng/mL.

Results: 10 white men (aged 20 - 26 years, weights 59.1 - 85.1 kg) enrolled and completed the study. 11 elderly volunteers (4 men and 7 women), aged between 66 and 71 years of age, enrolled in the study. Weights of 11 elderly subjects were between 51 and 80 kg. 4 of 11 elderly volunteers (1 man and 3 women) withdrew because of symptomatic orthostatic hypotension.

Carvedilol Pharmacokinetics PK parameters for carvedilol and desmethylcarvedilol are listed in the attached tables. Data on desmethylcarvedilol was provided only in summary form. Consequently, data on minimum and maximum values is not in the report.

Pharmacodynamic response: See adverse events. No other BP or pulse data were recorded in volume 1.63.

Adverse events: There were no deaths.
4 of 11 elderly volunteers withdrew because of symptomatic orthostatic hypotension.

Supine BP and pulse for the 4 subjects withdrawn were

BP	Pulse
90/54	73
96/68	not reported
63/51	63
87/54	not reported

Treatment emergent symptoms and signs are in the attached table. Laboratory safety tests for the young and old subjects were analyzed by two different laboratories. The ranges for normal values were not the same in the two laboratories.

Treatment emergent laboratory abnormalities include:

young volunteers

10 of 10 increased phosphorus (normal 0.8 - 1.4):				
1.25 to 1.5	1.16 to 1.6	1.19 to 1.53	1.27 to 1.44	0.9 to 1.55
1.07 to 1.56	1.04 to 1.43	0.96 to 1.42	1.2 to 1.6	0.97 to 1.41

- 1 of 10 decreased neutrophils (normal 2.5 - 7.5): 2.51 to 2.13
- 1 of 10 increased creatinine (normal 45 - 120): 108 to 122
- 1 of 10 increased eosinophils (normal 0.04 - 0.44): 0.19 to 0.57

1 of 11 elderly had increased gamma GT (normal < 35): 25 to 43
Only 1 of 11 elderly subjects had platelet counts done post-study.

Conclusions:

- 1 Four of 11 elderly, normotensive, healthy subjects could not tolerate carvedilol 25 mg po because of orthostatic hypotension. The Cmax and AUC for elderly subjects withdrawn for adverse events were 2 - 3 times greater than the corresponding values for elderly subjects completing the trial.
- 2 In addition to differences regarding age, there were numerous differences between the inclusion and exclusion criteria for the young and elderly subjects. These differences may confound meaningful interpretation of the effect of age on PK and PD outcome. The interaction of center and outcome was not analyzed.
- 3 Based on Cmax and AUC values, carvedilol did not appear to accumulate after 13 days of treatment in 10 healthy young men. Since 4 elderly subjects with elevated Cmax and AUC withdrew, this study should not be used to claim the presence or absence of accumulation in the elderly.
- 4 The young subjects had an unexplained increase in elimination half-life after 13 days of treatment with carvedilol.
- 5 All the young, healthy volunteers in this study developed mild elevations of serum phosphorus while receiving carvedilol. None of the elderly subjects had reports of phosphorus among the data submitted.
- 6 The peak and trough concentrations of carvedilol measured every other day are not reported in volume 1.63.
- 7 The blood pressure and pulse measured at the time of plasma samples are not reported in volume 1.63.
- 8 This study should be interpreted in the context of a multiple dose study in healthy volunteers.
- 9 Patients did not receive placebo. The effect of placebo on these volunteers is unknown.

Table 3 (cont):

Summary of comparison of 10 young and 7 elderly subjects
Desmethylocarvedilol

No. of Subjects	Young		Elderly		SED	P value-	
	10		7				
	Mean	(SD)	Mean	(SD)			
t _{1/2}	Day 1	1.9	(0.40)	2.0	(0.96)	0.33	> 0.2
	Day 14	2.0	(1.06)	2.0	(0.57)	0.44	> 0.2
	P value*	> 0.2		> 0.2			
C _{MAX}	Day 1	3.2	(0.88)	2.6	(0.94)	0.45	0.17
	Day 14	3.2	(1.29)	2.5	(1.48)	0.68	> 0.2
	P value*	> 0.2		> 0.2			
T _{MAX}	Day 1	1.4	(0.34)	1.3	(0.39)	@ -	> 0.2
	Day 14	1.2	(0.34)	1.8	(0.64)	@ -	0.031
	P value*	0.2		0.059			
AUC ₂₄	Day 1	9.40	(3.813)	6.19	(1.787)	1.559	0.057
	Day 14	10.07	(8.928)	6.37	(3.947)	3.623	> 0.2
	P value*	> 0.2		> 0.2			

@ No SED because Mann Whitney test used.

where * = within treatment P value and + = between treatment P value

MF 3950

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Carvedilol PK

	young, day 1 n=10	young, day 14 n=10	all old, day 1 n=11	old, day 14 n=7	old dropouts, day 1 n=4
C_{max} (ng/mL)					
mean	92.9	96.6	79.7	59.8	135.1
SD	37.95	41.04	49.5	33.3	32.16
minimum					
maximum					
T_{max} (hours)					
mean	1.2	1.1	1.3	1.9	1
SD	0.41	0.32	0.7	1	0.41
minimum					
maximum					
AUC 24 (ng*hr/mL)					
mean	381.9	423	396.8	342.5	624.1
SD	219.58	255.83	242.4	110	279.13
minimum					
maximum					
half-life (hours)					
mean	7	13.1	9.1	10.1	8.9
SD	1.33	4.09	4	2.8	5.48
minimum					
maximum					

ADVERSE EVENTS

Number of patients reporting adverse event

	young n=10	old n=11
orthostatic faintness	7	4
headache	3	0
nausea	1	1
chest tightness	0	1
abdominal pain	0	1
lethargy	0	2
diarrhea	1	0

BIOAVAILABILITY

Reviewer: James F. Graumlich

Name of study: Bioavailability of a new carvedilol tablet in comparison with a capsule formulation.**Objectives:** Determination of the relative bioavailability of a new carvedilol tablet in comparison with the known capsule formulation.**Study design:** Open, uncontrolled, randomized-sequence, two-period crossover study of single oral doses of carvedilol 25 mg tablet and carvedilol 25 mg capsule in 20 healthy men. Treatment periods were separated by one week.**Intervention:** test = carvedilol 25 mg tablet (batch 819 896 20 B) by mouth
reference = carvedilol 25 mg capsule (batch 819 291 40 dF) by mouth**Response variables:** Primary outcome: carvedilol concentrations in plasma, C_{max}, T_{max}, AUC
Secondary outcome: carvedilol concentration in urine, heart rate, blood pressure.

Plasma concentrations were measured on days 1 and 8 at baseline then 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 14, and 24 hours after drug administration. Urine was collected 0-6, 6-12, 12-24 hours after dose administration.

Assay: The lower limit of quantification of carvedilol in plasma and urine was 1.0 ng/mL.**Results:** 20 men (aged 20 - 48 years, weights 66 - 98.5 kg) enrolled and completed the study.

Subjects excluded from analysis: The first of 16 plasma concentrations for Subject #8 after the tablet treatment was the highest concentration. Consequently, Subject #8 had no measurements during the increasing phase (absorption phase) of the plasma concentration versus time curve. PK data for tablet treatment for Subject #8 was not reported and was not used in determining mean PK parameters. After capsule treatment, Subject #13 was an outlier with reference to terminal half-life. PK data for capsule treatment for Subject #13 was not reported and was not used in determining mean PK parameters.

Carvedilol Pharmacokinetics PK parameters for carvedilol are listed in the attached table from page 15, volume 1.64.

The 95% confidence interval for the ratio of test and reference AUCs was 88% - 112% (Westlake method).

The 95% confidence interval for the ratio of test and reference C_{max} was 81% - 119% (Westlake method).The volume of distribution was calculated as CL/k_e. Clearance was calculated as Dose/AUC. The reliability of the clearance estimate is unknown because absolute bioavailability was not determined in this study. Consequently, the reliability of the volume estimate is also suspect.

Urine concentrations of carvedilol were not reported.

Pharmacodynamic response: No BP or pulse data were recorded in volume 1.64.

CARVEDILOL NDA 20-297

PROTOCOL MF7008 VOL 1.64

Adverse events: There were no reports of deaths nor adverse events. The protocol did not mention a mechanism for monitoring adverse events or laboratory safety tests.

Conclusions:

The study determined bioequivalence of the tablet and the capsule. The effect of excluding two subjects from the analysis is unknown. I do not know if the exclusion of the two subjects was appropriate. Consequently, I have doubts about the validity of the assertion of bioequivalence.

There is no pharmacodynamic or safety information reported from this study.

This study should be interpreted in the context of a single dose study in healthy volunteers.

BOEHRINGER MANNHEIM GMBH
 KLINISCHE PHARMAKOLOGIE - KINETIK
 PROGRAM: KRO
 DATE OF COMPUTATION: 14-JUL-87

Table :

000015

C159

PART: 1

K I N P A K

GROUP A : MF 7008 - BM 14.190 SER.NO.OF STUDY: 0 7 3 4
 LOT : 819 896 20 B
 DOSE : 25 MG BM 14.190 (= 1 TABL.) PERORAL
 BIOASSAY : BM 14.190 IN PLASMA ; METHOD : HPLC-FLUOROMETRY

GROUP B : MF 7008 - BM 14.190 SER.NO.OF STUDY: 0 7 3 5
 LOT : 819 291 40 D7
 DOSE : 25 MG BM 14.190 (= 1 CAPSULE) PERORAL
 BIOASSAY : BM 14.190 IN PLASMA ; METHOD : HPLC-FLUOROMETRY

PARAMETER (K I N P A K)	UNIT		'A'	'B'
A U C	[ngsh/ml]	N	19.	19.
		MEAN	137.03	136.39
		C.V. [%]	44.49	40.30
		MEDIAN	118.09	126.17
		MINIM. MAXIM.		
A U C (0 - te)	[ngsh/ml]	N	19.	19.
		MEAN	130.73	127.94
		C.V. [%]	44.19	43.04
		MEDIAN	111.30	123.56
		MINIM. MAXIM.		
C max	[ng/ml]	N	19.	19.
		MEAN	41.98	40.02
		C.V. [%]	36.44	49.78
		MEDIAN	40.48	38.42
		MINIM. MAXIM.		
t max	[h]	N	19.	19.
		MEAN	0.916	1.119
		C.V. [%]	43.88	41.44
		MEDIAN	0.931	1.042
		MINIM. MAXIM.		
t 1/2	[h]	N	19.	19.
		MEAN	3.576	5.407
		C.V. [%]	69.59	60.84
		MEDIAN	2.883	4.875
		MINIM. MAXIM.		
t las	[h]	N	19.	19.
		MEAN	0.193	0.302
		C.V. [%]	39.95	35.42
		MEDIAN	0.212	0.269
		MINIM. MAXIM.		
INITIAL INCREASE	[ng/ml/h]	N	19.	19.
		MEAN	191.66	121.15
		C.V. [%]	85.39	80.43
		MEDIAN	121.74	82.41
		MINIM. MAXIM.		

MF 7008

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000015

PD

Reviewer: James F. Graumlich

The results of this study were published by Moellendorff E et al. Clin Pharmacol Ther 1986; 39:677-682.

Name of study: Action of BM 14.190 on circulatory parameters of healthy volunteers

Objectives: Assessment of the vasodilating activity of carvedilol after po administration.

Study design: Open, uncontrolled, non-randomized, escalating dose study of single oral doses of carvedilol suspension in healthy men. Each subject received one dose on one day. There were 2 - 4 subjects assigned to each dose. There was no rationale mentioned to explain the number of subjects assigned to a particular dose.

Intervention: carvedilol oral suspension 2.5, 5, 10, 15, 22.5, 30, 34, 51, 76.5 mg by mouth. There was no rationale mentioned to explain the choice of doses to be studied.

Response variables: Primary outcome: amplitude of digital pulse measured with digital plethysmography. Responses are expressed either as systolic baseline amplitude (units = volts) or as area under the curve of systolic baseline amplitude versus time (units = volts x hours). According to the report, "the amplitude of the A-wave of the finger pulse, the systolic baseline amplitude, was used for assessing the vascular activity." No other explanation is given for the rationale for choosing systolic baseline amplitude as an assessment of vasodilatory activity.

Secondary outcome: orthostatic vital signs, heart rate, blood pressure, ECG, laboratory safety tests.

Primary outcome was measured 15 times during the first 3 hours after dose administration.

Assay: HPLC: the lower limit of quantification was not mentioned in report.

Results: 23 healthy men (aged 20 - 42 years, weights 61.5 - 88 kg) enrolled. 15 subjects completed the trial: 2 received 15 mg, 3 received 22.5 mg, 2 received 30 mg, 2 received 34 mg, 4 received 51 mg, and 2 received 76.5 mg. 8 subjects completed all tests except digital plethysmography: 2 received 2.5 mg, 2 received 5.0 mg, 2 received 10 mg, and 2 received 15 mg.

Among the 15 subjects completing the trial, one subject (xv) who received 76.5 mg of carvedilol was excluded from analysis of systolic baseline amplitude because "he spent most of the time in deep sleep." No other explanation for excluding subject xv was provided. In subject xv, the effect of carvedilol 76.5 mg on systolic and diastolic blood pressure was clinically insignificant. Among the 15 subjects completing the trial, the two subjects (xix and xx) who received 30 mg of carvedilol had no measurement of blood pressure because their arms were used for PK sampling. The sponsor claims the sampling of blood may have influenced digital plethysmography of subjects xix and xx.

Carvedilol Pharmacokinetics Only 2 subjects had blood drawn for PK sampling. Cmax was 149 - 296 ng/mL. Tmax was 0.5 - 1.0 hours. AUC, half-life and other PK parameters were not calculated.

Pharmacodynamic response: The vasodilatory effect of carvedilol was measured in 15 subjects using digital plethysmography. Figure 2 shows the plethysmographic results as area under the curve of systolic baseline amplitude versus dose. The correlation coefficient of 0.78 was obtained after excluding the subject who was asleep (xv, dose = 76.5 mg) and the subject who was a "maverick" (ix, dose 22.5 mg). The correlation coefficient of 0.89 was obtained after excluding subjects xv, ix, xix, and xx.

The onset of effect recorded by digital plethysmography was 0.33 hours after the dose. The maximum effect occurred 1-2 hours after the dose.

Systolic and diastolic blood pressure, heart rate, and orthostatic response: There were only 2 - 4 subjects at each dose level. Therefore, the sponsor did not report descriptive statistics. The sponsor did not plot BP versus time. After reviewing the values at each time for each patient, I could not reliably discern the lowest dose at which an effect occurred.

Adverse events: There were no reports of deaths. There were no side effects reported for the 8 subjects receiving 2.5 - 15 mg of carvedilol. 1 of 15 subjects had lethargy with carvedilol 76.5 mg. 2 of 15 subjects could not tolerate the test of orthostatic vital signs (one subject received 30 mg, the other received 76.5 mg). The report does not state the symptoms causing intolerance of the orthostatic test of vital signs.

Lab safety tests were performed at baseline and 24 hours after dose administration. Results are reported for 23 subjects. One of 23 (subject ii on carvedilol 2.5 mg) had elevation of alkaline phosphatase from 105.6 to 957 with no other LFT abnormalities. There were no other clinically significant changes in CBC, LFT, sodium, potassium, glucose, creatinine. No other lab safety results were reported.

Conclusions:

Using plethysmographic recordings of finger pulse, the sponsor claims a vasodilatory effect of carvedilol that is correlated with doses in the range of 15 - 76.5 mg. I do not have confidence in this claim because data is missing from 9 of 23 subjects and one outlier was excluded. Furthermore, I do not know if the amplitude of digital pulse measured with digital plethysmography is a validated surrogate for measuring the vasodilatory response to an antihypertensive drug.

This study should be interpreted in the context of a single dose study in healthy volunteers.

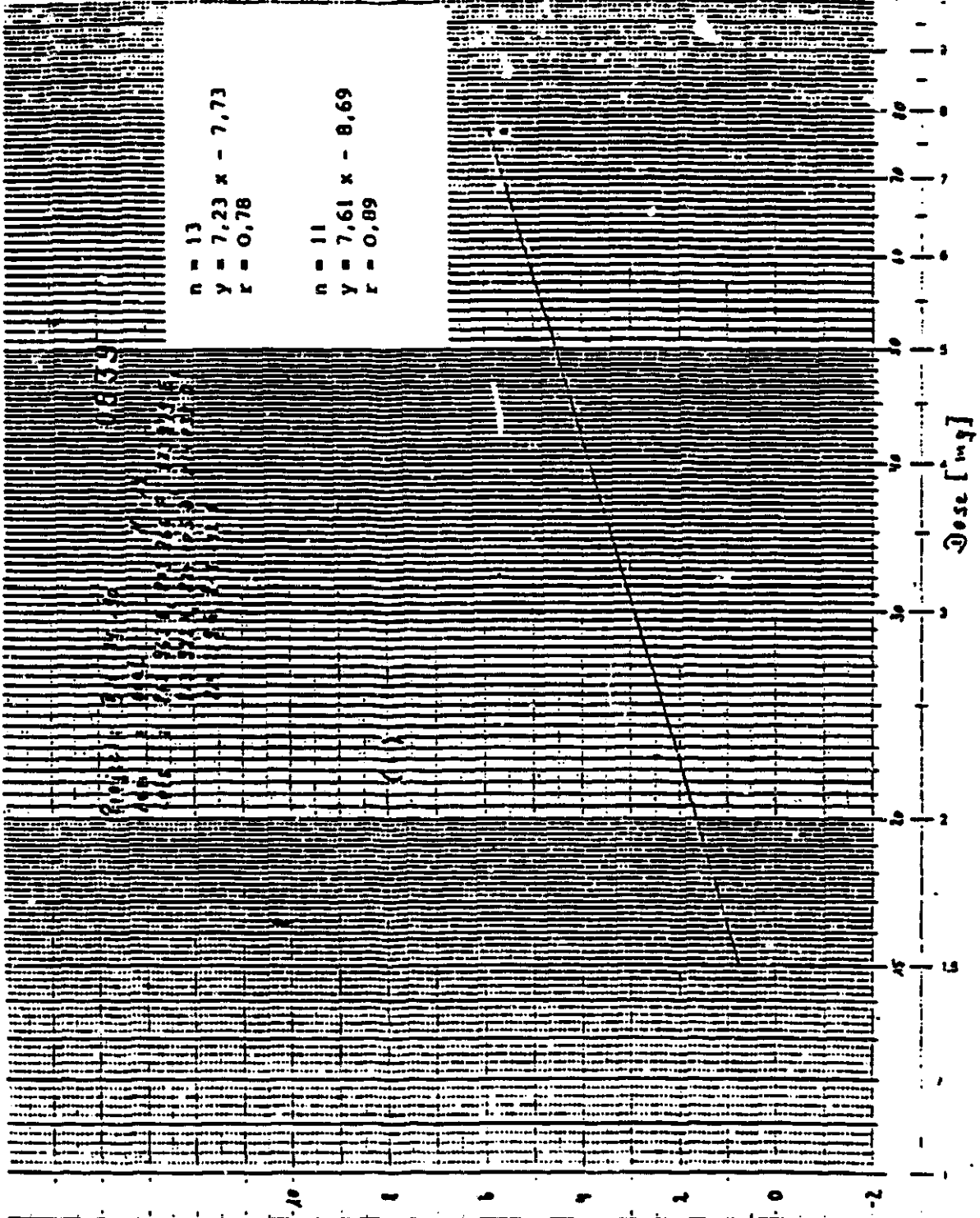


Fig. 2

AUC [VOLT * HOURS] Systolic Baseline Amplitude

PD

Reviewer: James F. Graumlich

The results of this study were published by Moellendorff E et al. Clin Pharmacol Ther 1986; 39:677-682.

Name of study: Action of BM 14.190 on circulatory parameters of healthy volunteers

Objectives: Comparison of the beta blockade caused by carvedilol and metipranolol. The non-selective beta blocker, metipranolol, is used in Europe as an eye drop to treat glaucoma.

Study design: The study occurred in two phases. The first phase (MF7016.0540) was an open, non-randomized study of 3 different doses of carvedilol in 6 healthy men. The second phase was a single-blind study with placebo solution followed by double-blind, non-randomized sequence, 3-period crossover of single oral doses of carvedilol 50 mg, metipranolol 5 mg, metipranolol 10 mg in 6 healthy men. The 50 mg dose of carvedilol was chosen after reviewing results of phase one. The subjects were not the same in phases I and II. Each subject received one dose on one day. Treatment periods were separated by at least one week.

Intervention: phase I: carvedilol oral suspension 30, 45, and 60 mg
phase II: metipranolol 5 mg oral suspension, metipranolol 10 mg oral suspension, carvedilol 50 mg oral suspension, placebo oral suspension

Response variables: Primary outcome: blood pressure and heart rate before and during ergometric exercise, % inhibition of the exercise-induced tachycardia and blood pressure elevation
Secondary outcome: orthostatic vital signs, heart rate, blood pressure, laboratory safety tests.

Measurement of primary outcome used a bicycle ergometer with exercise to a standardized workload. In phase I, bicycle ergometry occurred 5 or 6 times during the first 24 hours after dose administration. In phase II, bicycle ergometry occurred 8 times during the first 10 hours after dose administration.

Assay: The assay was not mentioned in the report.

Results: 7 healthy men (aged 25 - 42 years, weights 64 - 89 kg) enrolled and completed phase I: 2 received carvedilol 30 mg, 3 received carvedilol 45 mg, 2 received carvedilol 60 mg. 6 healthy men (aged 24 - 31 years, weights 62 - 95 kg) enrolled and completed phase II.

Carvedilol Pharmacokinetics PK results were not reported.

Pharmacodynamic response: In phase I, the ergometric measurements after the 30 mg dose were at baseline then 1, 3, 4.5, 6, and 8 hours after dose administration. In contrast, the ergometric measurements after the 45 and 60 mg doses were at baseline then 1.5, 3, 5, 8, 12 and 24 hours after dose administration.

Decreases in blood pressure and heart rate after carvedilol are depicted in the attached table. The results of phase II are shown in Figures 18, 19, and 20 from pages 175, 176, 177 of volume 1.64. Measurements of primary outcome after placebo were not reported.

Adverse events: There were no reports of deaths. During phase I, one subject reported giddiness during orthostatic test (BP not reported) 3 hours after carvedilol 60 mg. Two of 6 subjects reported orthostatic giddiness (BP 125/85 and 130/85) after carvedilol 50 mg. One subject had a headache with metipranolol 10 mg and

the same subject had a headache with carvedilol 50 mg.

Lab safety tests were performed at baseline and 24 hours after dose administration. CBC, creatinine, LFT, glucose, sodium, potassium, urine dipstick, creatinine clearance had no clinically significant changes during phases I and II.

Conclusions:

This study shows that carvedilol 50 mg blocks exercise-induced increases in heart rate and systolic blood pressure as much as metipranolol 5 mg and 10 mg. The study does not show that either carvedilol or metipranolol block exercise-induced cardiovascular changes more than placebo.

This study should be interpreted in the context of a single dose study in healthy volunteers.

Table: Exercise-induced changes in vital signs after carvedilol dose (mean values)

Table

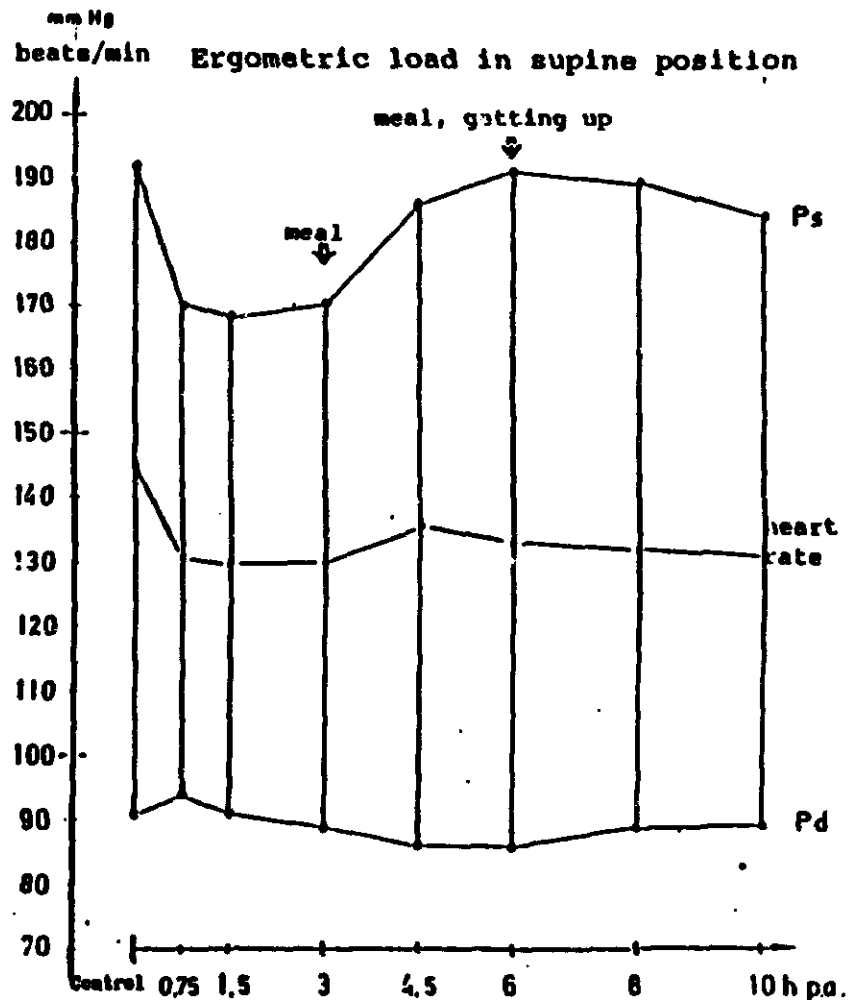
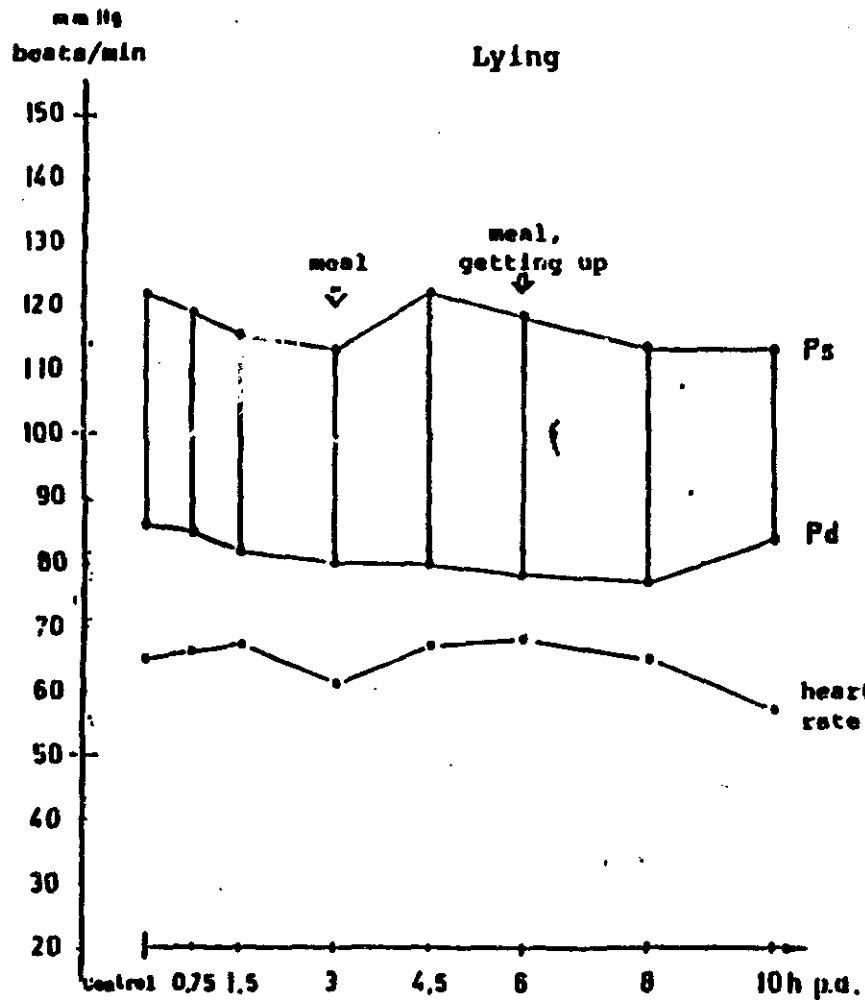
	Carvedilol 30 mg n=2	Carvedilol 45 mg n=3	Carvedilol 60 mg n=2
Systolic blood pressure			
Emax (mm Hg)*	25	25	16
Time to Emax (hrs)	2	1	1
Diastolic blood pressure			
Emax (mm Hg)*	2.5	6	5
Time to Emax (hrs)	4.5	4.5	5.5
Heart rate			
Emax (beats per min)*	12	25	12
Time to Emax (hrs)	3	1.5	1

*predose exercise value - postdose exercise value
Emax= maximum effect

Fig. 18

ERGOMETRY INVESTIGATION: DETERMINATION OF EQUIEFFECTIVE DOSES OF BM 14.190
AND METIPRANOLOL

Course of the blood pressure and heart rate after administration of 50 mg BM 14.190 p.o. ($\bar{x}$)



Short title and project name
Page

ACTION OF BM 14.190 ON CIRCULATORY
PARAMETERS IN HEALTHY VOLUNTEERS

M 1 - 57

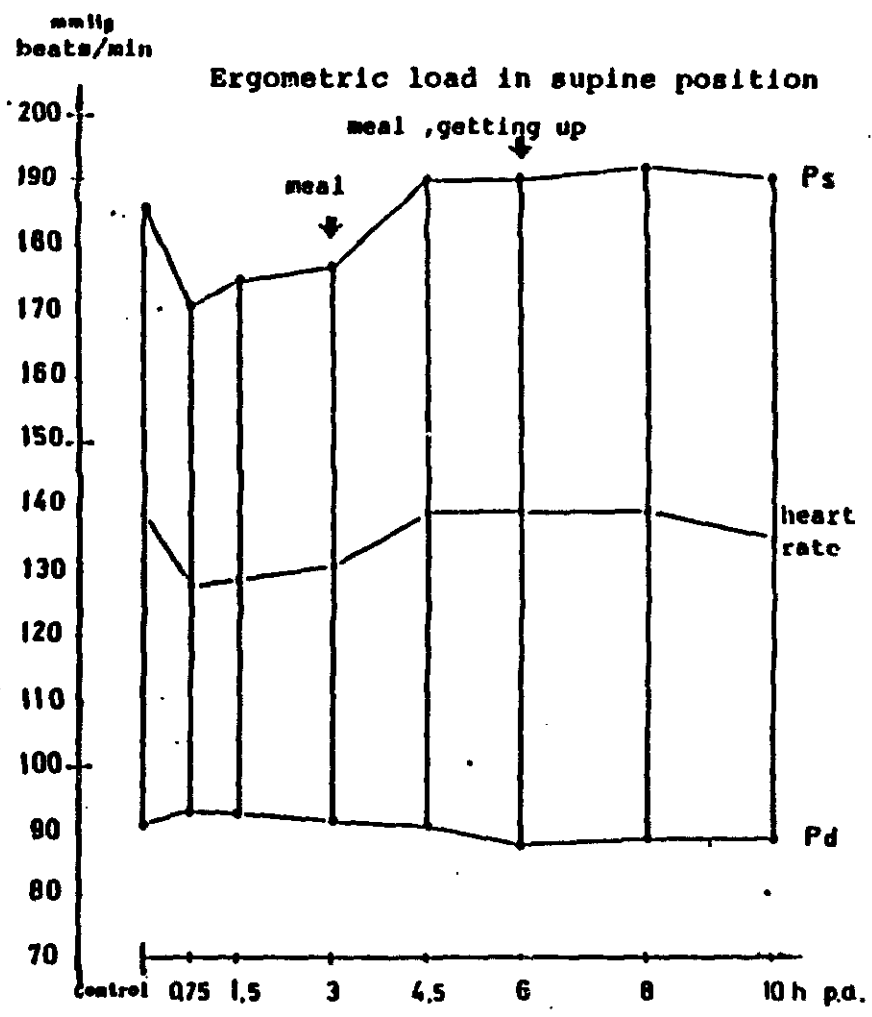
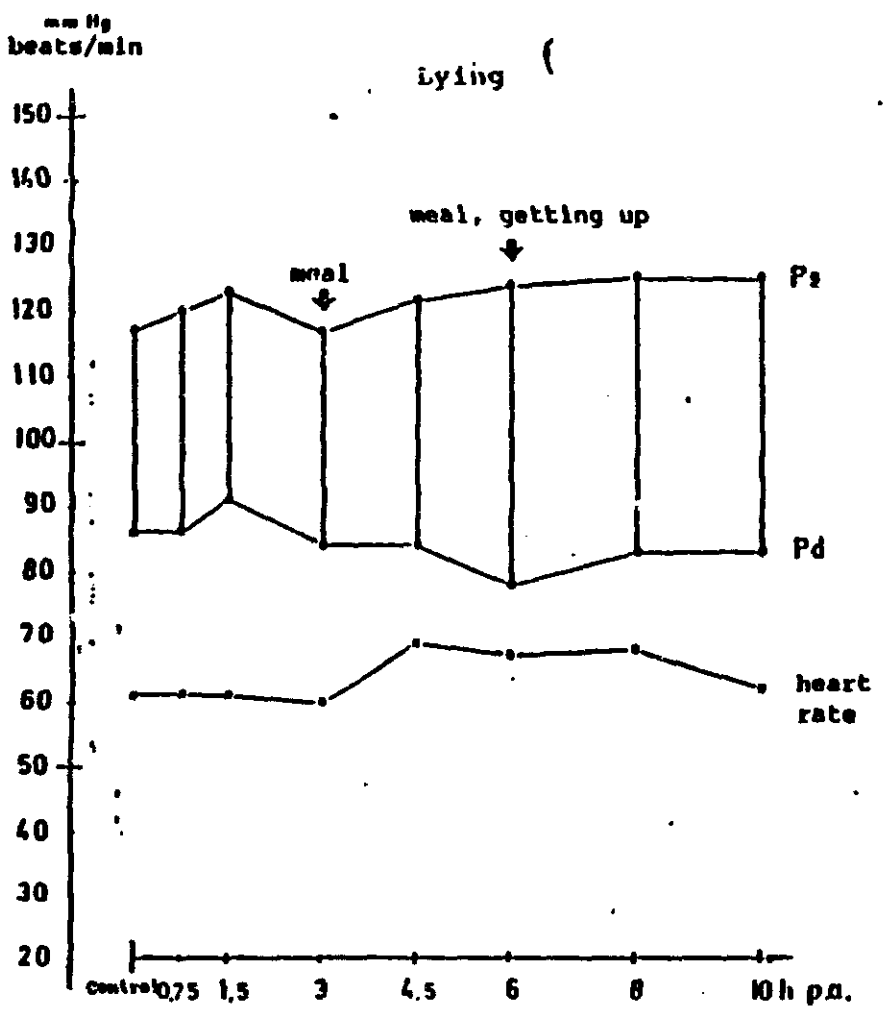
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Fig. 19

ERGOMETRY INVESTIGATION: DETERMINATION OF EQUIEFFECTIVE DOSES OF BM 14.190 AND METIPRANOLOL

Course of the blood pressure and heart rate after administration of 5 mg Metipranolol p.o. ($\bar{x}$)



Short name and project name
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 11-58

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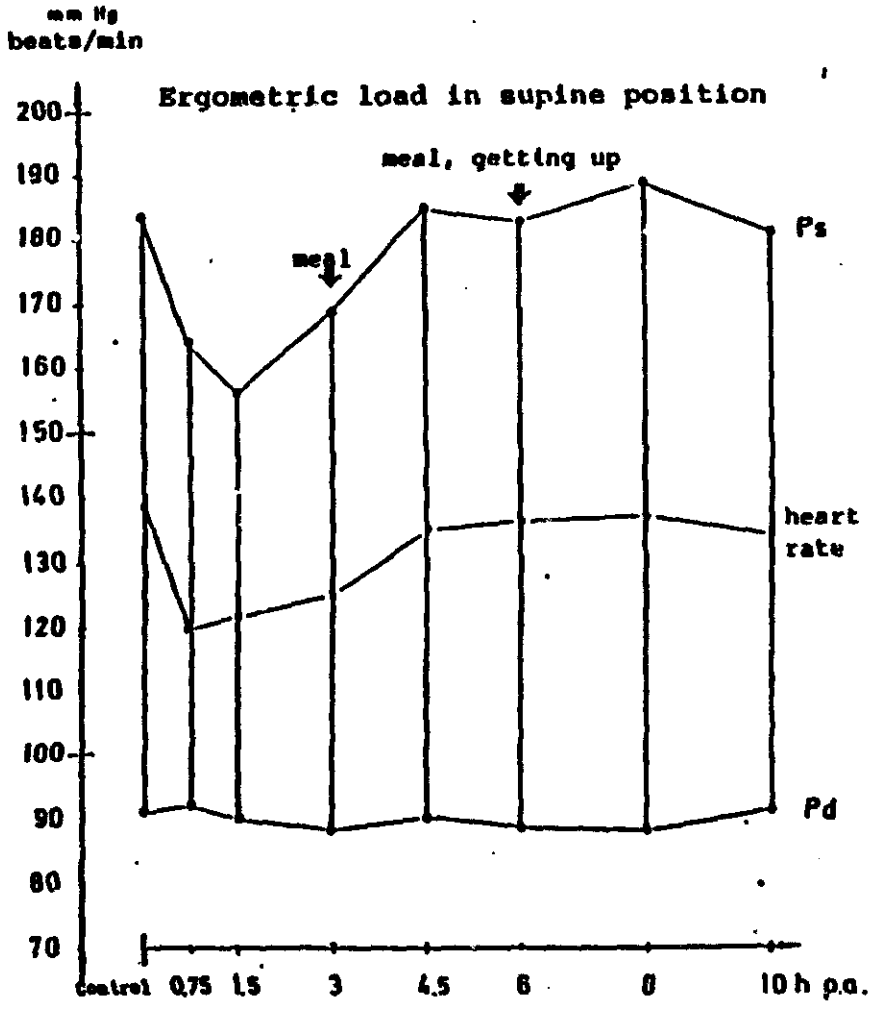
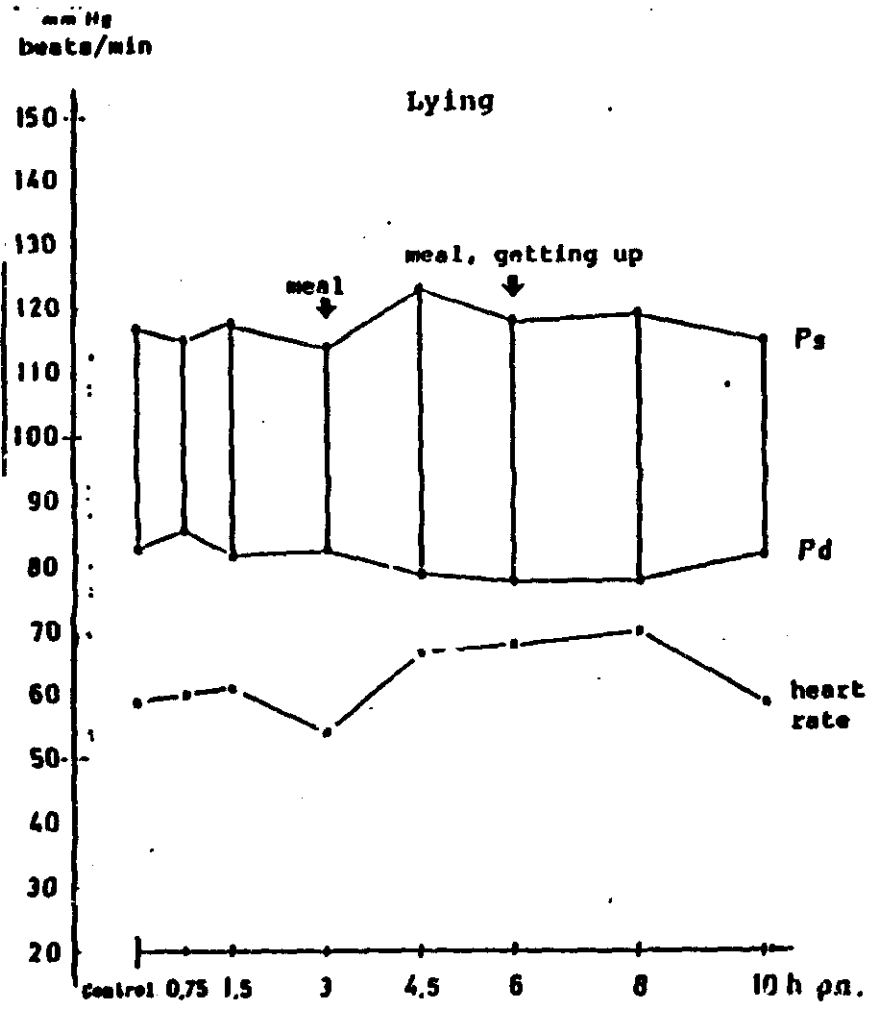
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000171

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Fig. 20

ERGOMETRY INVESTIGATION: DETERMINATION OF EQUIEFFECTIVE DOSES OF BM 14.190 AND METIPRANOLOL

Course of the blood pressure and heart rate after administration of 10 mg metipranolol p.o. ($\bar{x}$)



Action of BM 14.190 on circulatory parameters in healthy volunteers
 M 1-59

AN 11033 (1) 6/1/64

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VOL 1.64

2168

METABOLISM

Reviewer: James F. Graulich

Name of study: Study of the metabolism of BM 14.190 (carvedilol) following the oral administration of 50 mg 14C-labelled substance

Objectives: To study carvedilol metabolism in healthy volunteers.

Study design: Open label, uncontrolled, prospective study of oral single doses of radioactive carvedilol in 6 healthy male volunteers aged 50 years and older. Blood, urine, and feces were collected for 96 up to 336 hours after the dose.

Intervention: 50 mg 14C-labelled carvedilol suspension po as a single dose

Response variables: total radioactivity, carvedilol and metabolite concentrations

Blood sampling times were at baseline then 0.25, 0.5, 1, 1.5, 2, 3, 4, 8, 12, 16, 24, 32, 36, 48, 56, 72, 96, and 168 hours after dose administration. Urine sampling times were at baseline then 0.25, 0.5, 1, 1.5, 12-24, 24-36, 36-48, 48-72, 72-96, 96-120, 120-144, 144-168 hours after dose administration. Feces collected daily. Saliva collected once at 1.5 hours after the dose. Sampling times were changed after the first three subjects and again after the fourth subject.

Materials: 50 mg 14C-labelled carvedilol suspension containing 96.5 µCi. Three different batches of carvedilol were used.

Assay: Blood, urine, and feces were assayed with HPLC, LC/MS. Radioactivity was measured by liquid scintillation. The lower limit of quantification was not specified.

Results: 6 male healthy subjects between 50 and 59 years of age completed the study. Weights of subjects were between 65 and 99 kg. The first 3 subjects were studied in 1985. The results of the first 3 subjects were reported by the sponsor as a reprinted article (Neugebauer G, Akpan V, Moellendorff E, et al. Pharmacokinetics and disposition of carvedilol in humans. J Cardiovasc Pharmacol 1987; 10:S85-S88). The 4th subject was studied in 1989 and the last two subjects were studied in 1991.

Over 7-8 days, subjects 1-3 excreted 76% of ingested radioactivity: 15-17% was excreted in the urine and 56-64% was excreted in the feces. The elimination half-life for total radioactivity was median 39 hours

Over 264 hours (11 days), subject 4 excreted 72% of the ingested radioactivity: 20% was excreted in the urine and 52% was excreted in the feces.

A dosing error occurred with subjects 5 and 6 because the total radioactivity excreted exceeded the dose administered.

Carvedilol and 16 carvedilol metabolites were identified in the plasma.

Carvedilol and 26 metabolites were identified in the urine.

Carvedilol and 7 metabolites were identified in the feces.

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Data for the first 3 subjects appear in the table below (data from Neugebauer et al. 1987).

Carvedilol and its metabolites	Symbol	% of plasma radioactivity	% of urine radioactivity
Carvedilol	M0	9	2
R and S-carvedilol-O-glucuronide	M1	22	32
side chain cleavage products (right side)		20	13
ring hydroxylated and conjugated products		NR	18
des-methyl-carvedilol	M2	NR	NR

Notes: NR=not reported. Fecal metabolites were not characterized.

Data for the last 3 subjects appear in the table below. The following table shows metabolites accounting for more than 5% of the radioactivity in plasma, urine, or feces. The plasma samples were drawn 1.5-3 hours after dose administration. Urine samples were collected either 0-24 hours or 0-36 hours after the dose. Fecal samples were collected either 0-72 or 12-84 hours after the dose.

Carvedilol and its metabolites	Symbol	% of plasma radioactivity	% of urine radioactivity	% of fecal radioactivity
Carvedilol	M0	4 - 8	1 - 2	14 - 10
R-carvedilol-O-glucuronide	M1	7 - 12	9 - 15	NR - NR
S-carvedilol-O-glucuronide	M1	4 - 9	9 - 10	NR - NR
des-methyl-carvedilol	M2	1 - 6	0.3 - 0.6	8 - 10
Hydroxy-phenyl-carvedilol-glucuronide	H35	4 - 23	4 - 9	NR - NR
Hydroxy-phenyl-carvedilol-glucuronide	H39	2 - 3	1 - 10	- NR
1-hydroxy-carbazoyl-carvedilol	M14	2 - 2	0.4 - 0.7	14 - 15
1-hydroxy-carbazoyl-carvedilol-glucuronide	M15	6 - 8	7 - 12	NR - NR
hydroxy-phenyl-carvedilol-sulfate	H42	6 - 8	3 - 7	NR - NR
des-carbazoyl-carvedilol	M8	1 - 3	4 - 7	2 - 3
hydroxy-carbazoyl-N-glucuronide	H14	NR - NR	3 - 10	NR - NR
8'-hydroxy-carbazoyl-carvedilol	M16	NR - NR	NR - NR	14 - 14
4'-hydroxy-phenyl-carvedilol	M4	NR - NR	NR - NR	* - *
5'-hydroxy-phenyl-carvedilol	M5	NR - NR	NR - NR	15 - 15
structure not determined	H46	NR - NR	NR - NR	4 - 9

Notes: NR=not reported, *=coeluted with M16

The primary biotransformation steps consist of phase-I and phase-II reactions. Among phase-I reactions, aromatic ring oxidation and aliphatic side-chain oxidation predominate. Another major initial phase-II reaction is conjugation of carvedilol to glucuronide. The steps of carvedilol metabolism are found in Figure 1 Metabolic Profile of Carvedilol in Man from page 276.

The mean blood/plasma ratio of radioactivity ranged from 0.573 to 0.653 during the first 24 hours.

Pharmacodynamic response: No data were reported for the first 3 subjects.

Table of responses (mean of last 3 subjects) to 50 mg carvedilol suspension

	Heart rate	SBP	DBP
	beat/min	mm Hg	mm Hg
baseline	72	126	81
E _{max}	56	106	71
base-E _{max}	16	20	10
T _{E_{max}}	3	4	3
E, 6hr	59	124	78

SBP=systolic blood pressure, DBP=diastolic blood pressure, E_{max}=maximum effect, T_{E_{max}}=time from dose to maximum effect in hours, E, 6hr= effect at 6 hours after dose

Adverse events:

No data were reported for the first 3 subjects. Among the last 3 subjects, 1/3 had headache, 1/3 had orthostatic dizziness (E_{max}: BP=98/62, pulse 52). There were no significant lab abnormalities among the last 3 subjects.

Conclusions:

Subjects were enrolled from 1985 to 1991 and were dosed with different batches of labelled carvedilol. The metabolites were not characterized completely for the first 3 subjects. Data from the last 3 subjects should form the basis for any claims regarding metabolism.

In the 4 subjects receiving the correct dose, only 71.5-78.1% of ingested radioactivity was recovered. The fate of the remaining radioactivity is unknown.

Hepatic biotransformation and fecal excretion play major roles in the metabolism of carvedilol after oral administration.

The long half-life of radioactivity suggests the possibility of accumulation of metabolites with chronic multi-dose regimens.

MF3459 contains PK data on 4'-hydroxyphenol carvedilol, 5'-hydroxyphenol carvedilol, and des-methyl carvedilol for comparison with this study.

There was no placebo group with which to compare pharmacodynamic responses.

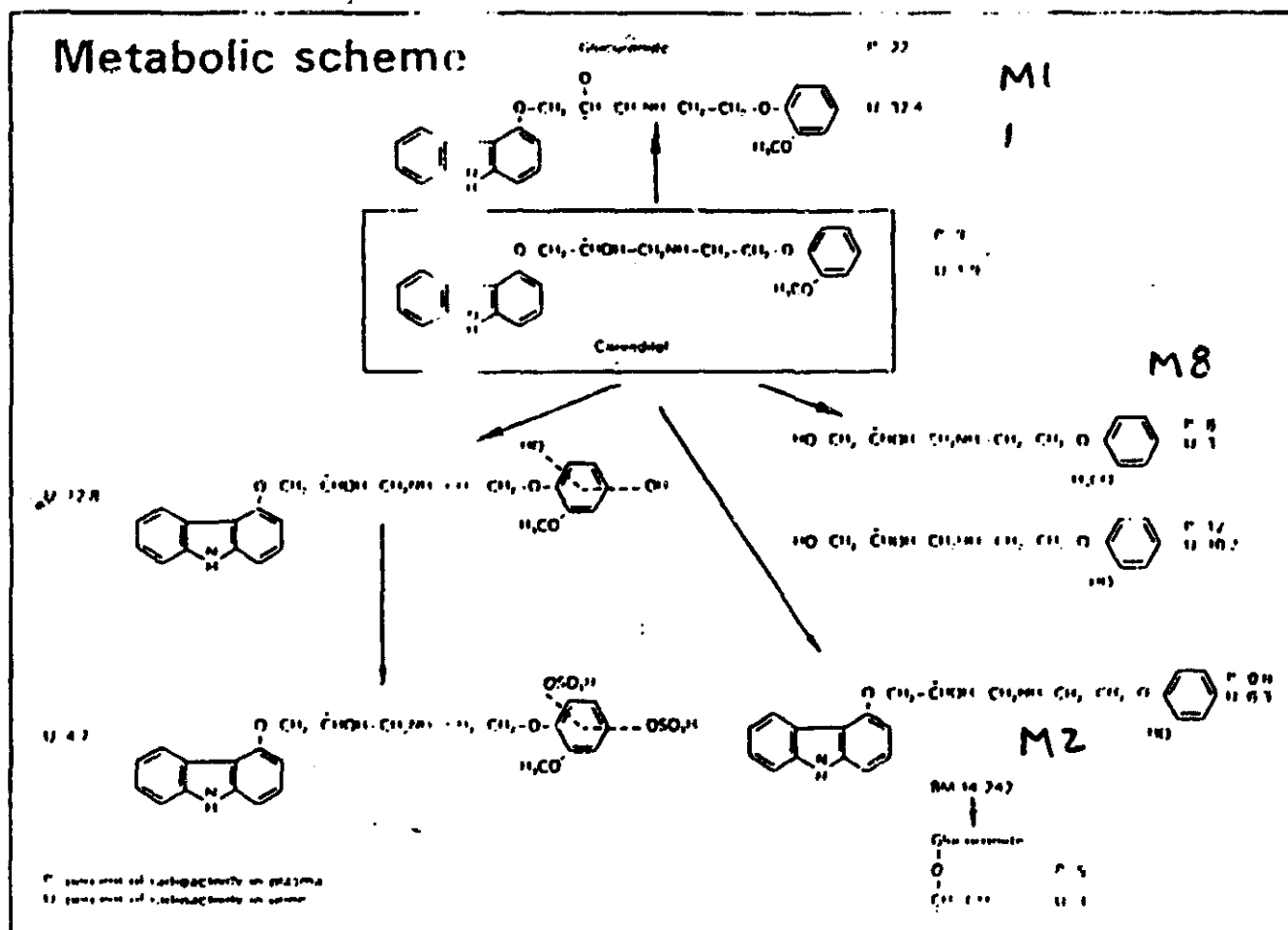


FIG. 3. Scheme of carvedilol biotransformation in man and relative amounts (concentrations) found in urine (U) and plasma (P).

sively eliminated by metabolism. About 16% of the metabolites were cleared renally, the major portion (up to 60%) was eliminated via the fecal route. Some metabolites probably exhibit a longer half-life than the parent compound, since total radioactivity declined with a half-life of 39 h.

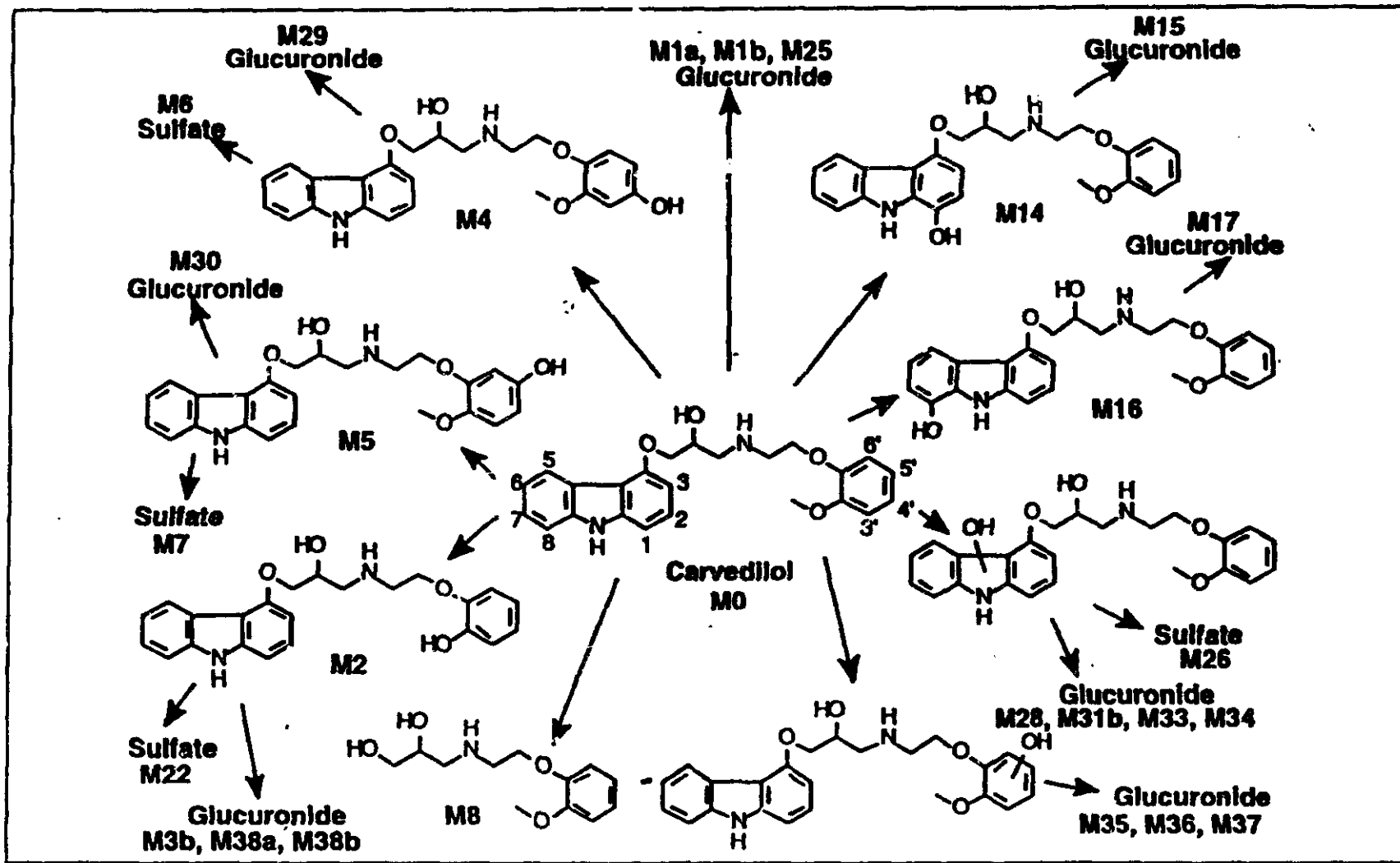
The primary biotransformation steps of carvedilol consist of phase-I and phase-II reactions. Among phase-I reactions, aromatic ring oxidation and aliphatic side-chain oxidation predominate. In a main initial phase-II reaction, carvedilol is conjugated to glucuronide.

REFERENCES

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Figure 1. Metabolic Profile of Carvedilol in Man

(Data from Protocol MF-7029 Addendum)



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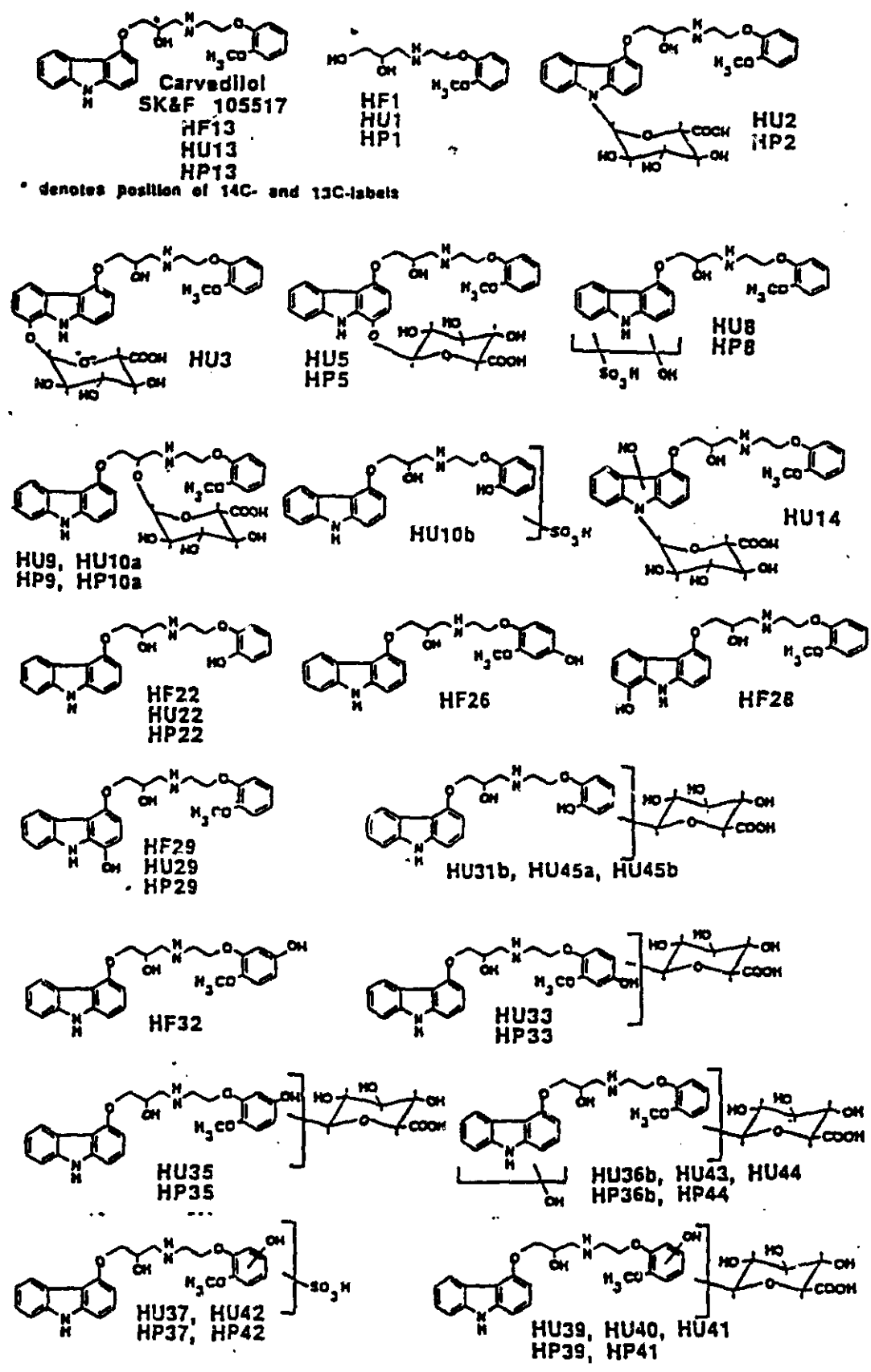


Figure 1. Summary of the fecal, urinary, and plasma metabolites of carvedilol in male human subjects. (HF, human fecal metabolite; HU, human urinary metabolite; HP, human plasma metabolite)

STEREOSELECTIVE PK

Reviewer: James F. Graumlich

The sponsor did not provide a technical report for this study. Instead, a reprint was submitted: Neugebauer G, Akpan W, Kaufmann B, Reiff K. Stereoselective disposition of carvedilol in man after intravenous and oral administration of the racemic compound. Eur J Clin Pharmacol 1990; 38:S108-S111. The study protocol was not included with the reprint.

Objectives: To describe the pharmacokinetics of R-carvedilol and S-carvedilol in 10 healthy volunteers.

Study design: Open label, uncontrolled, randomized sequence, two-period crossover study of oral and intravenous single doses of racemic carvedilol in 10 healthy male volunteers. Treatment periods were separated by one week.

Intervention: 12.5 mg racemic carvedilol intravenous infusion within 1 hour
50 mg racemic carvedilol (2 tablets @ 25 mg) po as a single dose

Response variables: Primary outcome: AUC
Secondary outcome: Cmax, half-life, CL, Vd, F

Blood sampling times were at baseline then multiple times up to 24 hours after dose administration.

Materials: racemic carvedilol 5 mg ampules, batch 819845 59D
racemic carvedilol 25 mg tablet, batch 819896 20B

Assay: Plasma R-carvedilol and S-carvedilol assay involved liquid-liquid extraction, GITC derivatization, HPLC with fluorometric detection. The lower limit of quantification was 1 ng/mL for both S-carvedilol and racemic carvedilol and about 2 ng/mL for R-carvedilol.

Results: 10 male healthy subjects between 21 and 39 years of age completed the study. Weights of subjects were between 56.5 and 98 kg. 4 subjects had concentrations of S-carvedilol below the level of quantification during the elimination phase.

Figure 2 from page 164, vol 1.71 shows the concentration vs time profile for R-carvedilol and S-carvedilol after an intravenous dose of racemic 12.5 mg carvedilol.

Figure 3 from page 164, vol 1.71 shows the concentration vs time profile for R-carvedilol and S-carvedilol after an oral dose of racemic 50 mg carvedilol.

Table 1 from page 163A, vol 1.71 shows the PK parameters for R-carvedilol and S-carvedilol after an intravenous and oral doses.

Pharmacodynamic response: None reported

Adverse events: None reported

Conclusions:

Systemic bioavailability after an oral dose racemic carvedilol is greater for R-carvedilol than for S-carvedilol.

CARVEDILOL NDA 20-297

PROTOCOL M7034 VOL 1.71

The differences in AUC are consistent with stereoselective first-pass metabolism in the liver.

The elimination half-life is significantly longer for S-carvedilol than for R-carvedilol in this study.

This study does not address the claim that R-carvedilol acts solely as a vasodilator and S-carvedilol exhibits activity as a vasodilator and non-selective beta blocker.

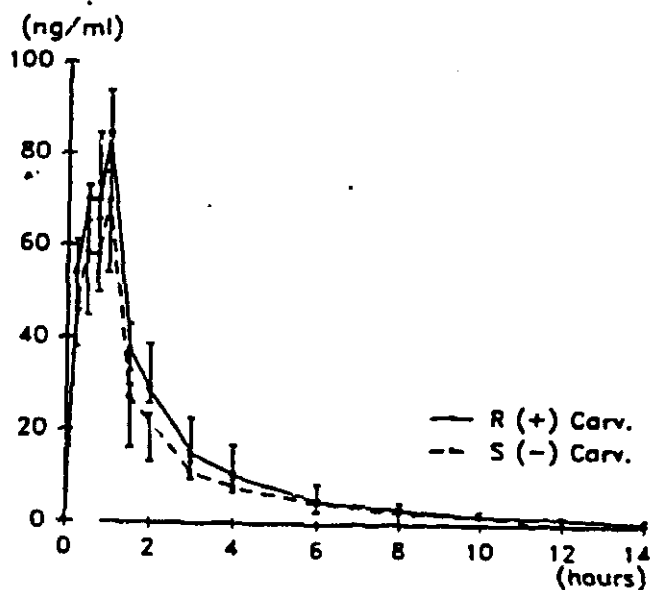


Fig. 2. Concentration-time course of R(+)- and S(-)-carvedilol (Carv.) after a 1-h infusion of 12.5 mg racemic carvedilol in ten healthy male subjects (medians and quartiles)

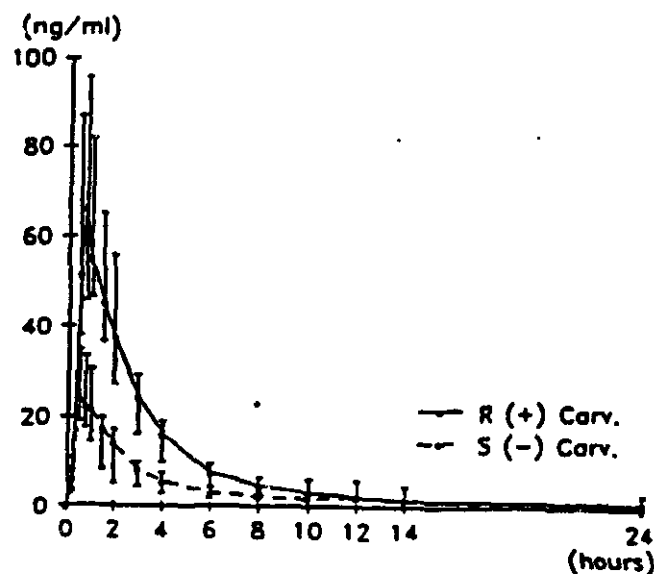


Fig. 3. Concentration-time course of R(+)- and S(-)-carvedilol after 50 mg oral racemic carvedilol (Carv.) in ten healthy male subjects (medians and quartiles)

S 110

G. Neugebauer et al.: Stereoselective disposition of carvedilol

Table 1. Pharmacokinetic parameters of R(+)- and S(-)-carvedilol following i.v. administration of 12.5 mg and p.o. administration of 50 mg racemic carvedilol and enantiomeric ratios [R(+)/S(-)] in 10 subjects (median values with ranges in parentheses)

Route of administration	Enantiomer	AUC ₀₋₂₄ (ng·h·ml ⁻¹)	t _{1/2} (h)	C _{max} (ng·ml ⁻¹)	CVI ^a (ml·min ⁻¹)	V _Z (l)	f (%)
i.v.	R(+)	172 ^b (139-325)	3.5 (2.0-7.1)	85 ^b (65-107)	615 ^b (310-747)	170 (103-251)	100
	S(-)	129 (76-178)	3.2 [6] ^b (2.1-3.8)	70 (51-85)	662 [6] (582-858)	188 [6] (105-284)	100
p.o.	R(+)	214 ^b (138-605)	9.6 ^b (4.1-19.4)	74 ^b (46-138)	1791 (648-2867)	-	31.1 (20.2-46.5)
	S(-)	78 (32-163)	22.1 [7] (4.7-72.5)	29 (11-48)	2439 [7] (1601-6256)	-	15.1 (10.4-24.4)
i.v.	R(+)/S(-)	1.3 (1.0-1.9)	1.1 (0.6-3.5)	1.2 (1.1-1.4)	0.9 (0.5-1.0)	0.9 (0.7-1.8)	-
p.o.	R(+)/S(-)	2.7 (1.6-4.4)	0.4 (0.2-1.6)	2.6 (1.7-4.3)	0.7 (0.3-1.7)	-	2.0 (1.5-2.4)

^a $P < 0.05$ [Wilcoxon test for paired data, R(+)- vs S(-)]

^b After i.v. administration $f = 1$

^c Numbers of evaluable subjects are shown in square brackets

CARVEDILOL NDA 20-297

PROTOCOL MF7038 VOL 1.71

BIOAVAILABILITY

Reviewer: James F. Graumlich

Name of study: Pilot study to determine the absolute bioavailability of carvedilol on simultaneous oral administration of D3-carvedilol and intravenous infusion of carvedilol in one experiment

Objectives: To determine whether plasma concentration of D3-carvedilol and D3-carvedilol-glucuronide (metabolite M1) concurrently with the unlabelled compounds can be performed accurately in human material by means of combined gas chromatography and mass spectrometry.

Study design: Open label, uncontrolled, pilot study of a single oral dose of labelled carvedilol and simultaneous intravenous infusion of unlabelled carvedilol in ONE healthy man.

Intervention: 25 mg deuterium-labelled carvedilol suspension po as a single dose
10 mg unlabelled carvedilol via 2-hour intravenous infusion

Response variables: Primary outcome: AUC
Secondary outcome: C_{max}, T_{max}, half-life, F, CL, V_c

Blood sampling times were at baseline then 0.25, 0.5, 0.75, 1, 1.5, 2, 2.25, 2.5, 3, 4, 6, 8, 10, 12, 24 hours after dose administration. Blood pressure and pulse were measured hourly for 6 hours.

Materials: 25 mg deuterium-labelled carvedilol suspension, batch not specified.
The deuterium label was at the oxymethyl side group of the benzene ring.
Ampoule 5 mg carvedilol in 5 mL, batch 819845 59D

Assay: Plasma D3-carvedilol, D3-carvedilol-glucuronide, carvedilol, and carvedilol-glucuronide assay involved GC/MS. Assay was repeated using HPLC. HPLC does not distinguish between carvedilol and carvedilol-glucuronide. The lower limit of quantification was not specified.

Results: One 33 year old male healthy subject (63 kg) completed the study. The following table (vol 1.71 page 170) shows the PK parameters for the subject. During the elimination phase, concentrations fell below the limit of quantification. Therefore, some calculations could not be made.

The pharmacokinetic data determined are compiled in the following table.

		carvedilol	D3-carvedilol	D3-M1	D3-M1
C _{max}	[ng/ml]	88	43	37.1	92
t _{max}	[h]	-	0.25	2.0	0.75
t _{1/2}	[h]	2.2	2.1	-	-
AUC _{0-24 h}	[ng • h/ml]	-	-	62	137
AUC	[ng • h/ml]	270	57	-	-
Clearance	[ml/min]	618	-	-	-
V _z	[l]	116	-	-	-
f	[%]	-	8.4	-	-

CARVEDILOL NDA 20-297

PROTOCOL MF7038 VOL 1.71

Pharmacodynamic response:

	Heart rate beat/min	SBP mm Hg	DBP mm Hg
baseline	68	115	80
Emax	58	95	70
base-Emax	10	20	10
T,Emax	1.5	2	3
E, 6hr	74	120	75

SBP=systolic blood pressure, DBP=diastolic blood pressure, Emax=maximum effect,
T,Emax=time from dose to maximum effect in hours, E, 6hr= effect at 6 hours after dose

Adverse events:

There were no adverse events reported. There were no significant lab abnormalities.

Conclusions:

The PK parameter values in this subject are low compared to values reported in MF7020.

Generalizations from this study of one healthy man are not possible.

C179

CARVEDILOL NDA 20-297

PROTOCOL MF7097 VOL 1.71

PK and CIMETIDINE

Reviewer: James F. Graumlich

Name of study: Steady state kinetics of the racemic compound and the enantiomers of carvedilol before and after cimetidine administration.

Objectives: Compare steady-state kinetics of racemic carvedilol and the enantiomers of carvedilol before and after concomitant cimetidine administration in 10 healthy men.

Study design: Open label, uncontrolled

Intervention: carvedilol 12.5 mg (half of a 25 mg tablet) po on day 1 then carvedilol 25 mg po every day from day 2 through day 9
cimetidine 200 mg po tid plus 400 mg po at hs (1000 mg per day) on days 7 through 9.

Response variables: Primary outcome: AUC racemic carvedilol
Secondary outcome: R(+) and S(-) carvedilol and metabolite concentrations in plasma and urine, PK parameters, blood pressure, ECG

Blood sampling times were at baseline then 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 24 hours after dose administration on day 6 and day 9. Urine collection (0-24 hours) was on day 6 and day 9. BP and ECG were measured 2 hours after dose administration.

Materials: 25 mg carvedilol tablet, cimetidine 200 mg tablet

Assay: Liquid/liquid extraction, re-extraction, reversed-phase HPLC with fluorometric detection. The lower limit of quantification was 1 ng/mL for racemic carvedilol, 1 ng/mL for S(-) carvedilol, and 2 ng/mL for R(+) carvedilol.

Results: 10 healthy men between 24 and 33 years of age completed the study. There were no dropouts. Weights of subjects were between 74 and 94 kg.

PK parameters for racemic carvedilol, R(+) carvedilol, S(-) carvedilol, metabolite M2, metabolite M4, and metabolite M5 are found in the attached tables.

Pharmacodynamic response:

There was a trend toward increased heart rate (6 BPM above baseline) on day 9.
Systolic blood pressure tended downward (from 128 to 110 mm Hg) during the first 2 days of carvedilol therapy then drifted toward baseline (122 mm Hg) on day 9.
Diastolic blood pressure tended downward (from 70 to 61 mm Hg) throughout treatment with carvedilol and cimetidine.
ECG intervals did not show clinically significant changes during the study.

Adverse events:

1/10 increased bilirubin
4/10 increased creatinine (day 9 only). This is an expected result of cimetidine administration
4/10 increased triglycerides
2/10 decreased chloride

Conclusions:

The sponsor designed the study with a half-dose of carvedilol on the first day to improve tolerance of first dose effects.

Only oral racemic carvedilol was used in this study. Therefore, no information is available from this study to answer questions about the interconversion of enantiomers of carvedilol.

Cimetidine caused a 30% increase in racemic carvedilol AUC and 27% increase in the amount of racemic carvedilol excreted in the urine.

Cimetidine caused a 25% increase in R(+) carvedilol AUC and 39% increase in the amount of R(+) carvedilol AUC excreted in the urine.

Cimetidine caused a 15% increase in S(-) carvedilol AUC and 20% decrease in C_{max} for S(-) carvedilol.

The differences in A_e (%) and CL_{renal} between R(+) carvedilol and S(-) carvedilol suggest differences in stereoselective renal elimination of carvedilol.

The enantiomers of the metabolites were not assayed in this study. The AUCs for M2, M4, and M5 are all less than 4% of the AUC of racemic carvedilol. The renal clearance of the M2, M4, and M5 is approximately 5 times greater than the renal clearance of racemic carvedilol. ~~These data raise a concern regarding accumulation of metabolites during renal failure.~~ *qs*

The mechanism for cimetidine's effect on carvedilol kinetics is unknown. Cimetidine may cause an increase in carvedilol oral bioavailability perhaps through a change in gastric pH. The more likely explanation is cimetidine inhibits first-pass hepatic clearance by CYP450. Cimetidine does not appear to decrease the tubular secretion of carvedilol, carvedilol enantiomers, or carvedilol metabolites.

There was no placebo group with which to compare pharmacodynamic responses. In this small group of healthy men, the pharmacokinetic interaction between cimetidine and carvedilol did not cause a clinically significant pharmacodynamic interaction.

NAME OF COMPANY
Boehringer Mannheim GmbH

INDIVIDUAL STUDY TABLE
IV / V

(FOR NATIONAL AUTHORITY
USE ONLY)

NAME OF FINISHED PRODUCT
Dilatrend®

**REF. TO PART IV
OF THE DOSSIER**

C181

NAME OF ACTIVE INGREDIENT
Carvedilol (= BM 14.190)

Report No.: N 29
Volume:
Page:

SUMMARY/CONCLUSIONS

10 healthy volunteers participated in the study and were evaluated. They received after a standard breakfast once 12.5 mg carvedilol, then 25 mg until day 9, orally as tablets. From day 7 to 9 additionally 5 tablets per day of cimetidine (Tagamet®) were given: every time 200 mg at about 8.30 h, 12.30 h, 16.30 h and 400 mg at about 20.30 h. The study lasted for 9 days. In addition to the pharmacokinetics, evaluation of the tolerability of both drugs was done.

Carvedilol was demonstrated to be well-tolerated in all subjects, cimetidine as well.

The comedication of cimetidine induces some changes of the kinetics of carvedilol in comparison with that without cimetidine. The AUC of racemic carvedilol is significantly increased by 30 %, consequently Cl/f is decreased and Ae increased (the latter by 27 %).

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Kinetic parameters of racemic carvedilol (median, minimum, maximum)

Cimeti- dine	AUC ₀₋₂₄ (ng·h·ml ⁻¹)	C _{max} (ng·ml ⁻¹)	t _{max} (h)	t _{1/2} (h)	Cl/f (ml·min ⁻¹)	Ae (%)	Cl _R (ml·min ⁻¹)
before	211	49	1.25	4.8	2011	0.51	10.5
after	275*	45	1.75	5.1	1526°	0.65*	11.4

* = p < 0.05

° no statistical comparison

* % of dose given

The increase of the AUC is caused by an increase of the AUC of R(+)-carvedilol (+ 25 %) and additionally of the S(-)-carvedilol-AUC (+ 15 %). Consecutively, the R/S-ratios of AUC and Ae increase from 2.76 to 3.01 and from 4.16 to 4.44 respectively.

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NAME OF COMPANY
Boehringer Mannheim GmbH

INDIVIDUAL STUDY TABLE

(FOR NATIONAL AUTHORITY
USE ONLY)

C182

NAME OF FINISHED PRODUCT
Dilatrend®

REFERENCE PART IV
OF THE MONOGRAPH

NAME OF ACTIVE INGREDIENT
Carvedilol (= BM 14.190)

Report No.: 29
Volume:
Page:

VOL 1.71

Kinetic data of R(+)-carvedilol (median, minimum, maximum)

Cimetidine	AUC ₀₋₂₄ (ng·h·ml ⁻¹)	C _{max} (ng·ml ⁻¹)	t _{max} (h)	t _{1/2} (h)	Cl/f (ml·min ⁻¹)	Ae (%) ^a	Cl _R (ml·min ⁻¹)
before	155	34	1.25	4.2	1361	0.72	10.9
after	194*	34	2.00	5.6	1075 ^b	1.00*	11.6

* = p < 0.05 ° no statistical comparison ° % of respective enantiomer

Kinetic data of S(-)-carvedilol (median, minimum, maximum)

Cimetidine	AUC ₀₋₂₄ (ng·h·ml ⁻¹)	C _{max} (ng·ml ⁻¹)	t _{max} (h)	t _{1/2} (h)	Cl/f (ml·min ⁻¹)	Ae (%) ^a	Cl _R (ml·min ⁻¹)
before	68	13.7	1.00	9.2	3053	0.22	6.9
after	79*	10.9*	1.50	6.7	2655 ^b	0.23	7.6

* = p < 0.05 ° no statistical comparison ° % of respective enantiomer

The changes of the metabolites analyzed, M2, M4 and M5, are of minor relevance.

The results demonstrate that carvedilol is in part metabolized by cytochrome P450 enzymes which can be inhibited by cimetidine.

Because of the increase of the AUC, patients should be carefully monitored during the first days of combined treatment with carvedilol and cimetidine.

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C183

7.3.5 R(+)/S(-) ratio

The R/S ratios of some kinetic parameters are listed below.

R/S ratios (median)

Cimetidine	AUC _{0-∞}	C _{max}	t _{1/2}	Ae	Cl _R
before	2.76	3.06	0.50	4.16	1.58
after	3.01	3.15	0.78	4.44	1.45

The R/S ratio for the AUCs is clearly greater than 1, it increases under the comedication of cimetidine still a little bit from 2.76 to 3.01, i.e. + 9 %. The ratio for C_{max}, with 3.06 also clearly greater than 1, does not change very much after cimetidine. The ratio for t_{1/2}, with 0.5 smaller than 1, increases after cimetidine (+ 56 %).

The ratio for Ae, again clearly greater than 1, increases from 4.16 by about 7 %. The ratio for Cl_R, being 1.58, decreases by 8 %.

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1.006 508 111 70 11 01 20



7.3.5

Metabolite M2 (SM 14.242)

1001.71
C184

The kinetic data of metabolite M2 are listed below.

Kinetic parameters of metabolite M2 (SM 14.242)
(median, minimum, maximum)

Cime- tidine	AUC _{0-∞} (ng·h·ml ⁻¹)	C _{max} (ng·ml ⁻¹)	t _{1/2} (h)	Ae (%)	Cl _r (ml·min ⁻¹)
before	7.9	3.3	1.00	0.09	50
after	7.6	3.4	2.00	0.11	50

* % of carvedilol dose given

The C_{max} values reached 3.3 and 3.4 ng·ml⁻¹ at 1.0 and 2.0 h respectively; the corresponding AUC values were 7.9 and 7.6 ng·h·ml⁻¹ before and after cimetidine coadministration respectively. The calculation of the t_{1/2} values was not possible because of the fast decline of the concentration values.

Amounts excreted were 0.09 and 0.11 % respectively, the corresponding Cl_r values are 50 ml·min⁻¹ under both conditions.

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7.3.7

Metabolite M4 (BM 14.0686)

CIBS
VOL 1.7:

The kinetic data of metabolite M4 are listed below.

Kinetic parameters of metabolite M4 (BM 14.0686)
(median, minimum, maximum)

Cime- tidine	AUC ₀₋₂₄ (ng·h·ml ⁻¹)	C _{max} (ng·ml ⁻¹)	t _{max} (h)	Ae (%) [*]	Cl _R (ml·min ⁻¹)
before	6.6	4.1	1.00	0.11	57
after	6.4	3.1	1.75	0.13	81

* % of carvedilol dose given

C_{max} values were 4.1 and 3.1 ng·ml⁻¹, this is a decrease of about 24 %. They were reached at 1.00 and 1.75 h respectively. AUC values were 6.6 and 6.4 ng·h·ml⁻¹ respectively.

Amounts excreted were 0.11 and 0.13 %.

The Cl_R were calculated as 57 and 81 ml·min⁻¹; this is an increase of 42 %.

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7.3.8 Metabolite M5 (BM 14.0830)

C186
VOL 1.71

The kinetic data of metabolite M5 are listed below.

Kinetic parameters of metabolite M5 (BM 14.0830)
(median, minimum, maximum)

Time-tidine	AUC ₀₋₂₄ (ng·h·ml ⁻¹)	C _{max} (ng·ml ⁻¹)	t _{1/2} (h)	Ae (%)	Cl _R (ml·min ⁻¹)
before	4.6	3.3	1.00	0.08	62
after	4.4	2.8	2.00	0.08	75

* % of carvedilol dose given

Metabolite M5 reached C_{max} values of 3.3 and 2.8 ng·ml⁻¹ at 1 and 2 h respectively; this is a decrease of about 15 %. AUC values were 4.6 and 4.4 ng·h·ml⁻¹ respectively.

Amounts excreted were 0.08 % under both conditions; the renal clearance reached 62 and 75 ml·min⁻¹ respectively (increase of 21 %).

**NDA 20-297 CARVEDILOL
Protocol 020, Vol 1.49
Bioequivalence**

Design: open label, replicate design, randomized, period balanced, 4 way crossover with all combinations of test, test, reference, reference. Study periods were separated by one week.

**Reference drug: 25 mg carvedilol capsule, lot number 82152240Lh
Test drug: 25 mg tablet (Tiltab®), lot number x2051CV2**

Blood sampling times: baseline then 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3, 4, 6, 8, 10, 12, and 24 hours after dose administration. Supine blood pressure and pulse will be measured at the same time as blood samples except at the 24 hour sample.

Assay: liquid/liquid cartridge extraction with HPLC and fluorescence detection.

**Results: 39 screened - 5 excluded = 34 received carvedilol - 2 withdrawals
J-230-91 withdrawn for adverse event, syncope
J-257-91 withdrawn for adverse event
BP and concentration data not provided for the 2 withdrawn subjects**

AUC 0-infinity (ng*hr/mL) after po dose, mean of 32 healthy subjects

form	mean	range
capsule 1st	368.38	
capsule repeat	364.32	
tab 1st	340.87	
tab repeat	328.96	

Cmax (ng/mL) after po dose, mean of 32 healthy subjects

form	mean	range
capsule avg	76.82	
tab avg	69.93	

Tmax (hours) after po dose, mean of 32 healthy subjects

form	mean	range
capsule avg	1.37	
tab avg	1.35	

Half-life (hours) after po dose, mean of 32 healthy subjects

form	mean	range
capsule 1st	10.84	
capsule repeat	8.87	
tab 1st	9.26	
tab repeat	10.42	

Supine blood pressure and pulse after carvedilol, n = 32

Form	effect	baseline mean $\pm$ SD	E _{max} mean $\pm$ SD	T _{E_{max}} hours	E _{12hr} mean $\pm$ SD
cap 1st	sup SBP	112 $\pm$ 8	106 $\pm$ 12	1.75	112 $\pm$ 11
	sup DBP	62 $\pm$ 8	56 $\pm$ 7	6	61 $\pm$ 8
	pulse	62 $\pm$ 8	57 $\pm$ 8	2.5	64 $\pm$ 7
cap 2nd	sup SBP	113 $\pm$ 9	105 $\pm$ 8	2	115 $\pm$ 10
	sup DBP	63 $\pm$ 8	56 $\pm$ 7	2	62 $\pm$ 8
	pulse	60 $\pm$ 8	57 $\pm$ 6	1.5	65 $\pm$ 9

Adverse events

J-230-91 syncope withdrawn from study

J-232-91 transitional cell carcinoma of the bladder unrelated to drug.

Other symptoms associated with drug treatment: headache, lightheadedness, pyuria, hematuria, elevated total bilirubin, elevated AST, elevated ALT, elevated glucose

Assessment:

Bioequivalence demonstrated for 25 mg carvedilol capsule, lot number 82152240Lh, and 25 mg tablet (Tiltab®), lot number x2051CV2.

PK parameters in healthy volunteers defined after po dose of 25 mg

PD response not clinically meaningful in this group of healthy volunteers with no placebo control.

11-20-1994
KMP

APR 28 1994

**ORIGINAL PHARMACOLOGY REVIEW AND EVALUATION
of
NDA 20-297
KREDEX (Carvedilol-SKF 105517*)**

Estela A. Gonzalez Barry, M.S.
Pharmacologist
Division of Cardio-Renal Drugs
(HFD-110)

* BM 14.190 and DQ 2466

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* BM 14.190 and DQ 2466

NDA 20-297

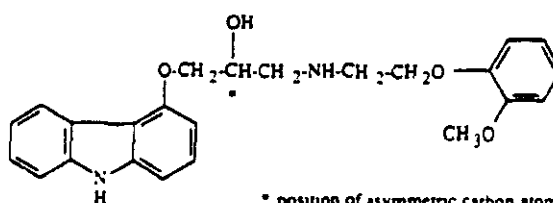
**REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
(Original Summary)**

Reviewer: E. Gonzalez Barry, M.Sc.

ORIGINAL NDA DATED: 03-31-93**AMENDMENTS DATED: 03-28-94; 03-30-94****RECEIVED AT CENTER: 03-31-93****REVIEWER RECEIPT DATE: 04-08-93; 03-30,31-94****SPONSOR: SmithKline Beecham Pharmaceuticals****DRUG: Proprietary Name- Kredex (Carvedilol) Tiltab.**

Generic Name- Carvedilol.

Code Names- SK&F 105517; BM 14.190.

Chemical name- ($\pm$)-1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-2-propanol.

MW: 406.5

S(-)-carvedilol and R(+)-carvedilol.

FORMULATION: Carvedilol will be supplied in film-coated Tiltab tablets containing 12.5 and 25 mg strengths for oral administration. The tablets contain the following inactive ingredients: Lactose, sucrose, Croscavidone, Colloidal Silicon Dioxide, Croscavidone, Magnesium Stearate, Purified Water, USP and in the tablet coating-

The drug is manufactured in

HARMACOLOGICAL CLASS: Vasodilator with non-selective combined β and α_1 -adrenergic receptor blocking activity.

PROPOSED INDICATION: Essential hypertension.

PROPOSED DOSAGE: Orally, 12.5 mg once daily. Dosage may be doubled, up to a maximum total daily dose of 50 mg.

*Position of asymmetric carbon atom.

INDs UNDER WHICH CLINICAL TRIALS WERE CONDUCTED:

o for carvedilol i.v. injection [Boehringer Mannheim Pharmaceutical Corporation (BMP Corp.)]

‡ for capsules and tablets (BMP Corp.)

INDs were transferred from BMP Corp to SmithKline Beecham on June 24, 1987.

BACKGROUND:

Carvedilol, a vasodilator drug, is being developed by SmithKline Beecham (SK&F 105517) and Boehringer Mannheim GmbH (BM 14.190) for the treatment of hypertension. The drug molecule contains a chiral center (asymmetric carbon atom) which results in a pair of enantiomers [S(-) and R(+)] enantiomers. Each enantiomer is pharmacologically active but with different affinity for α - and β -adrenergic receptors. The drug sponsor proposes to market carvedilol as a racemate mixture as a once-a-day oral treatment of mild to moderate hypertension. In this review the term carvedilol always refers to the racemic mixture while each enantiomer of the drug is clearly identified by the prefixes S(-) or R(+).

Sponsor submitted 46 volumes of nonclinical data for review. Many reports were poor English translations of original reports in German. Poor copies of data and untranslated data impeded the review, suggesting that the documentation had not been edited before submission to the FDA.

Numerous studies were previously submitted to the above mentioned INDs and were reviewed by 2 previous pharmacologists (Drs. Gordon Johnson and Martin Winbury) and have undergone a secondary review by their supervisor Charles A. Resnick, Ph.D. Some portions of previous reviews have been edited and incorporated in the present review. Some nonclinical studies submitted in this NDA are new and are so identified.

In the PHARMACOLOGY portion of present review, selected studies are summarized to show dose-related effects when the data were available in the submission. TOXICOLOGY reports of single and multidose studies as well as SPECIAL TOXICITY and MUTAGENICITY STUDIES contained detailed summary tables prepared by sponsor. Portions of these tables were extracted and editorialized versions are used in this review. Portions of the FERTILITY/REPRODUCTION STUDIES reviewed by M. Winbury, Ph.D. are incorporated in the review also with editorial changes. The PHARMACOKINETICS AND METABOLISM section is essentially that of the sponsor but also contain numerous editorial changes. Although CARCINOGENICITY STUDIES were previously reviewed, the data had not been evaluated by FDA's Division of Biometrics. Thus, a brief summary was prepared by the present reviewer to reflect Biometrics' evaluation.

Editorial changes were introduced by this reviewer to reflect her reviewing style and not because of disagreements with previously revised summaries.

INTRODUCTION:

The following briefly overviews the nonclinical pharmacology and pharmacokinetics of carvedilol.

Carvedilol is a chiral drug which possesses one asymmetric carbon which gives rise to 2 enantiomers (see chemical structure and position of asymmetric carbon above.) Sponsor proposes to market carvedilol as a racemate mixture of the single pair of enantiomers- S(-) and R(+) enantiomers. Sponsor asserts that the development of the racemate mixture is designed to produce two complimentary pharmacologic actions of the drug: vasodilation and non-selective β -adrenergic receptor blockade.

The activity of each of the enantiomers was examined in in vitro and in vivo preparations. Studies show that the S(-)-enantiomer of carvedilol exerts a non-cardioselective β_1 -receptor blocking action while the α_1 -adrenergic receptor blocking activity appears to be similar for both R(+) and S(-)-enantiomers. In the guinea pig atria, the S(-)-enantiomer is a potent, competitive blocker of the β_1 -adrenoceptor-mediated positive chronotropic response to isoproterenol in guinea pig atria, with an apparent dissociation constant (K_B) of 0.4nM. The R(+)-enantiomer was more than 100 fold less potent than the S(-)-enantiomer as a blocker of β -adrenoceptors with a K_B of about 45 nM.

In pithed rat, S(-)-enantiomer (0.1 mg/kg i.v.) produced a 25-fold right shift in the β_1 -adrenoceptor-mediated positive chronotropic response to isoproterenol, whereas the R(+)-enantiomer had no β_1 -adrenoceptor blocking activity at this dose in this in vivo model.

In rabbit aorta, both enantiomers produced equal antagonism of the α_1 -adrenoceptor-mediated vasoconstrictor response to norepinephrine with K_B values of 14 and 16 nM, respectively, for the S(-) and R(+) enantiomers. In the pithed rat, the α_1 -adrenoceptor-mediated pressor dose-response curve to cirazoline was shifted to the right by both enantiomers at similar dose of 1 mg/kg i.v.

In anesthetized spontaneous hypertensive rats (SHR), the S(-)-enantiomer was 6-fold more potent as an antihypertensive than the R (+)-enantiomer. The vasodilator and acute antihypertensive effect of carvedilol is considered to be the results from α_1 -adrenoceptor blockade produced by both R(+) and S(-) enantiomers and a concomitant β_1 -blockade is produced by the S(-)-enantiomer (preventing reflex tachycardia). This action leads to a greater overall antihypertensive potency for the S(-)-enantiomer compared to the R(+)-enantiomer.

Carvedilol exhibits no intrinsic sympathomimetic activity (ISA). In SHR given repeated doses, the drug showed no evidence of tachyphylaxis. Although, the vasodilatory action of carvedilol is considered to result primarily from α_1 -adrenoceptor blockade, some studies indicate that at high concentrations of the drug, there is suggestion of Ca^{2+} channel blockade

which may also contribute to vasodilation. Vasorelaxation does not appear to be mediated by intracellular changes of cAMP or cGMP.

Carvedilol reduced the arterial blood pressure (BP) in several animal species and in both normotensive and hypertensive models. The antihypertensive response produced by racemic carvedilol is associated with a decrease in total peripheral vascular resistance (TPVR) (indicative of arterial vasodilation) and either no change or moderate decrease in heart rate (HR) considered to be a consequence of β -receptor blockade. In anesthetized dog, cardiac output (CO) and HR were reduced by the drug and maximum speed of pressure rise (dp/dt) in the left ventricle fell dose-dependently. Carvedilol potentiated the BP fall in response to an orthostatic stimulus (tilt phenomena).

In SHR and dog, carvedilol exhibited renal vasodilator responses with increased renal blood flow and no Na⁺ retention. No synergistic effect on hypertension was noted with diuretic drugs. In the dog, glomerular filtration rate, urine flow, K⁺ excretion, and renal venous plasma-renin activity appeared not to be affected by carvedilol. Carvedilol showed no inhibition on the pressor response to stimulation of the renin-angiotensin II system.

Other pharmacologic activities reported for carvedilol include antiproliferative (anti-mitogenic) effect (both *in vivo* and *in vitro*) against a diverse group of vascular smooth muscle mitogens; antioxidant activity by preventing low density lipoprotein (LDL) oxidation considered due to scavenging free radicals by the drug; increased survival of stroke prone rats and neuroprotection of rat cerebral granule cells against glutamate mediated neuronal death. Limited studies in minipigs reported that carvedilol limits myocardial infarct size in an experimental model of acute infarction and reperfusion. Other studies showed a reduction in the size of infarcted areas in the hearts of rat and dog models of myocardial infarction.

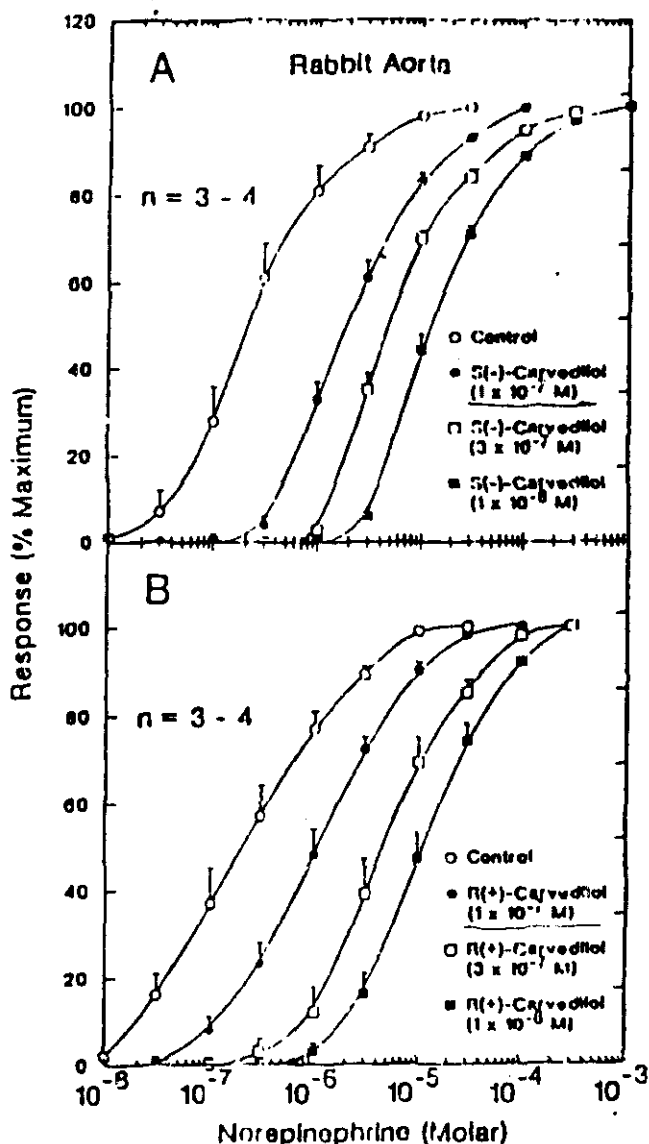
Carvedilol is lipophilic. After oral administration the drug is absorbed and distributed relatively well in all organ tissues. In human the bioavailability was reported to be about 24% and elimination half-life ($T_{1/2}$) after single oral doses ranged from 6-7 h. The drug is highly bound to plasma proteins, primarily albumin (98-99%) in animals and humans. Carvedilol is principally metabolized via hydroxylation and conjugation (glucuronidation and sulfation) pathways and more than a dozen metabolite products have been reported which are mainly excreted via bile into feces. Only 2 metabolites possess any marked β -receptor blocking activity but this action is considered less than that of the parent drug. In SHR, no lowering of BP activity was found with the metabolites tested (MS, MF and MF- See Fig.).

SELECTED PHARMACOLOGY STUDIES SUMMARIZED:

The following are brief summaries of a small number of studies selected to exemplify the pharmacology of carvedilol with special emphasis on studies submitted showing dose-response curves.

Although the racemic carvedilol is proposed for marketing, it is now recognized that the pharmacology and toxicology of each enantiomer could be different. Pharmacology studies reported showed that the 2 enantiomers show marked stereoselective antagonism of β_1 -adrenoceptors, but no stereo-chemical difference at α_1 -adrenoceptors. The most active enantiomer with β_1 -adrenoceptor antagonist properties is the S(-)-carvedilol; this enantiomer contributes to the reduced heart rate.

The R(+)-enantiomer contributes to the vasodilating effects of carvedilol through α_1 -adrenoceptor blockade. S(-)- and R(+)-carvedilol are equipotent as α_1 -adrenoceptor blockers in rat and rabbit aorta; the dissociation constants (K_D) values against norepinephrine calculated by sponsor were to be 16 and 14 nM, respectively.*



The α_1 -adrenoceptor antagonist activity of (-)-S-carvedilol (A) and (+)-R-carvedilol (B) in rabbit isolated aorta.

* AJ Nichols, et al in "The Interaction of the Enantiomers of Carvedilol with α_1 - and β_1 -Adrenoceptors", in Chirality, Vol. 1:265-270, 1989. NDA Vol. 12, p 168

Consistent with the observation that both enantiomers are equipotent in their affinity for α_1 -receptors, in pithed rat the dose-response curve for the α_1 -adrenoceptor mediated pressor effects of cirazoline is shifted in parallel to the right (about 6-fold) by either the S(-)- and R(+)-enantiomers (at 1 mg/kg, i.v.) (Fig. 1).

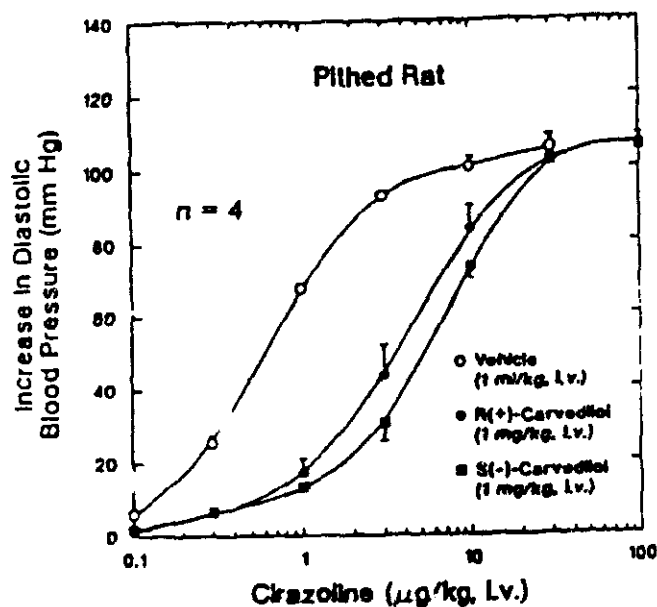


Fig. 1 The α_1 -adrenoceptor antagonist activity of (-)-S- and (+)-R-carvedilol (1 mg/kg, i.v., -15 min) in pithed rats.*

The enantiomers of carvedilol show marked stereoselective antagonism for the β_1 receptors but not for α_1 -adrenoceptors. The S (-)-enantiomer is the most active as a β_1 -adrenoceptor antagonist. The S (-)-enantiomer is considered by sponsor as a pharmacologically distinct entity from the mixture because it is the R(+)-enantiomer that contributes to the vasodilating effect through α_1 -adrenoceptor blockade.

* A. Nichols, et al in Chirality, Vol 1:265-279, 1989

Report 88/00116/SKF 105517 Nov. 5, 1991 in Vol. 12 of this NDA, p. 167

In vitro studies with isolated rat atria and rabbit aorta showed that in this preparation carvedilol caused a competitive antagonism to isoproterenol- and norepinephrine-induced chronotropic effect and contraction (Fig. 2). In the case of isolated rat atria, the β -blocking activity of carvedilol was more potent than propranolol (6X) and labetalol (28X). As for rabbit aorta, the vascular α_1 -blocking activity of carvedilol was equipotent with phentolamine and more potent (16X and 4X, respectively) than labetalol and prazosin.

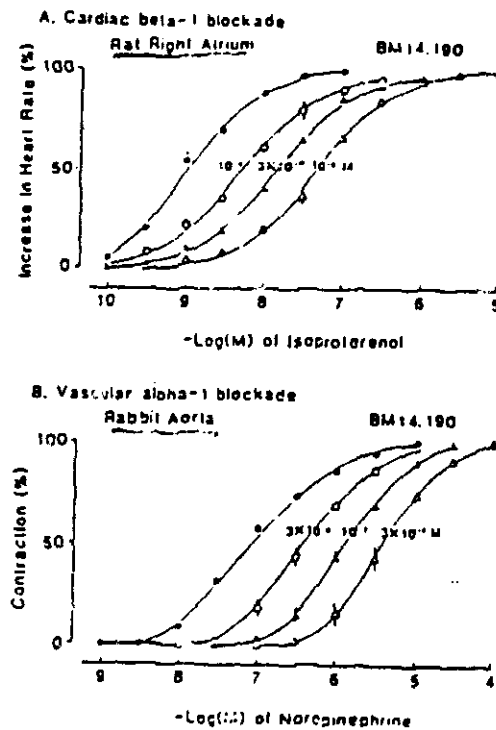


Fig. 2. Antagonism by BM 14,190 of positive chronotropic responses to isoproterenol in rat right atria (A) and of contractile responses to norepinephrine in rabbit aorta (B). Each point represents the mean $\pm$ S.E.M. of 6 experiments.

In SHR, both S(-) and R(+) carvedilol lowered arterial BP in a dose-dependent fashion.

In conscious SHR, the S(-)-enantiomer is about 10-fold more potent than the R(+)-carvedilol in lowering BP.

In the anesthetized SHR, the S(-)-enantiomer was about 6-fold more potent than R(+)-carvedilol (Fig. 3) in lowering BP. The difference in hypotensive potency between the two enantiomers may be explained by the β -adrenoceptor blocking activity of S(-)-carvedilol which inhibits the counterregulatory effects (i.e., tachycardia) to the hypotensive effect of the drug.

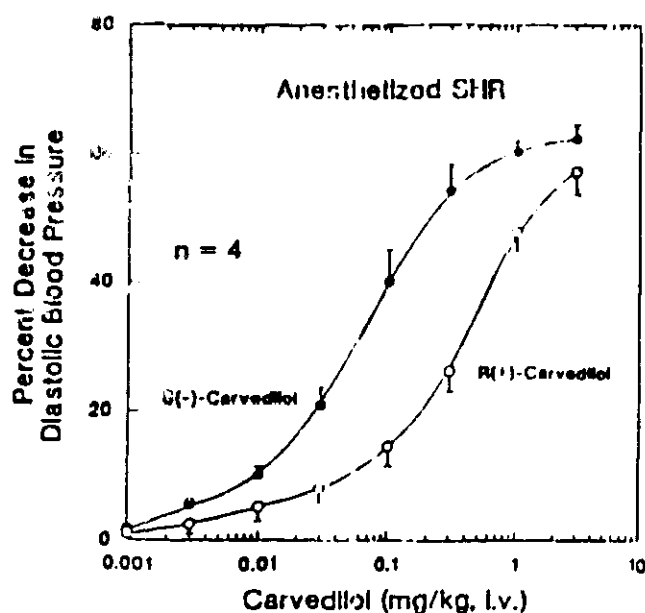


Fig. 3 The hypotensive activity of (-) (S) and (+) (R)-carvedilol in anesthetized spontaneously hypertensive rats.

**SOME STUDIES RELATED TO THE PROPOSED THERAPEUTIC INDICATION
(ANTIHYPERTENSION) OF THE RACEMATE MIXTURE- CARVEDILOL**

Cardiovascular Effects

In conscious SHR and normotensive rats, studies reported show that carvedilol produces an antihypertensive action following oral and i.v. dosing. At effective antihypertensive doses (1-10 mg/kg, p.o.), reduction in mean arterial pressure (MAP) is not associated with reflex tachycardia, as seen with commonly used vasodilators. (Figs. 4, 5, and 6 below.)

The hemodynamic effects of carvedilol appear to be consistent with two primary mechanisms of action, namely β -adrenoceptor blockade and vasodilation. Reduction in MAP results largely from direct arterial vasodilation since cardiac output (CO) and heart rate (HR) remain unchanged. In SHR treated rats, total peripheral vascular resistance (PVR) declines in parallel with BP. This hemodynamic profile of carvedilol is distinct from that of a β -adrenoceptor antagonist which decreases both HR and CO and increases total PVR. Likewise, the antihypertensive profile of carvedilol differs from pure vasodilator agents which produces as a counter effect, reflex tachycardia and therefore an increase in myocardial work.

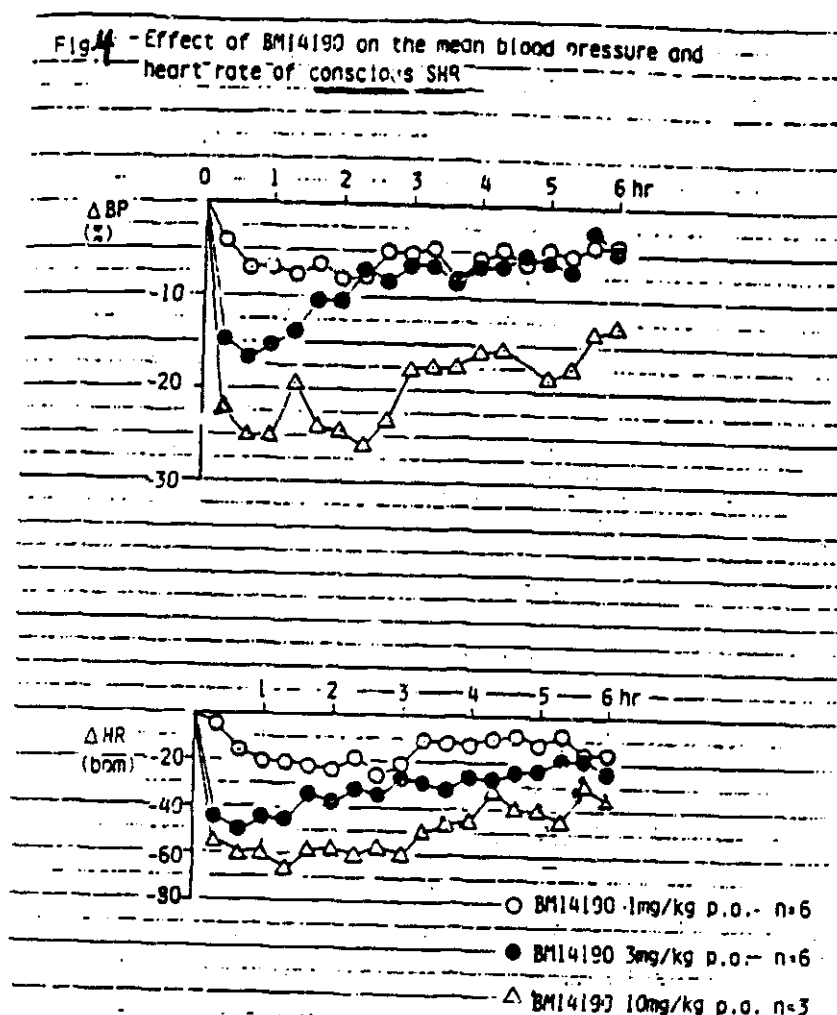


Figure 5

Dose-response relationship for the hypotensive action of BM 14,190 or dihydralazine on the blood pressure in conscious genetically hypertensive rats

Abscissa: Dose of the test substance in mg/kg p.o.

Ordinate: Fall in arterial blood pressure 3 hours after oral administration in mmHg

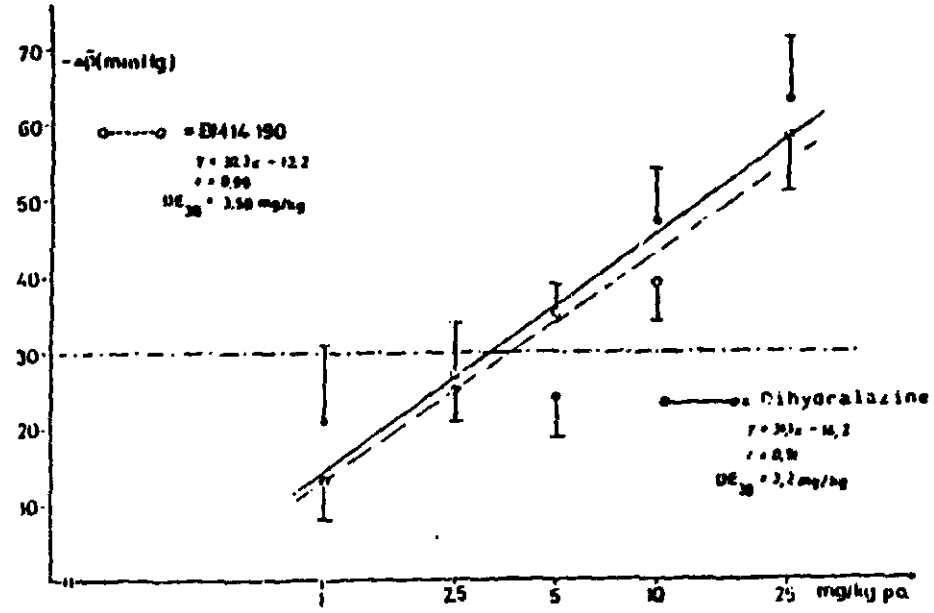
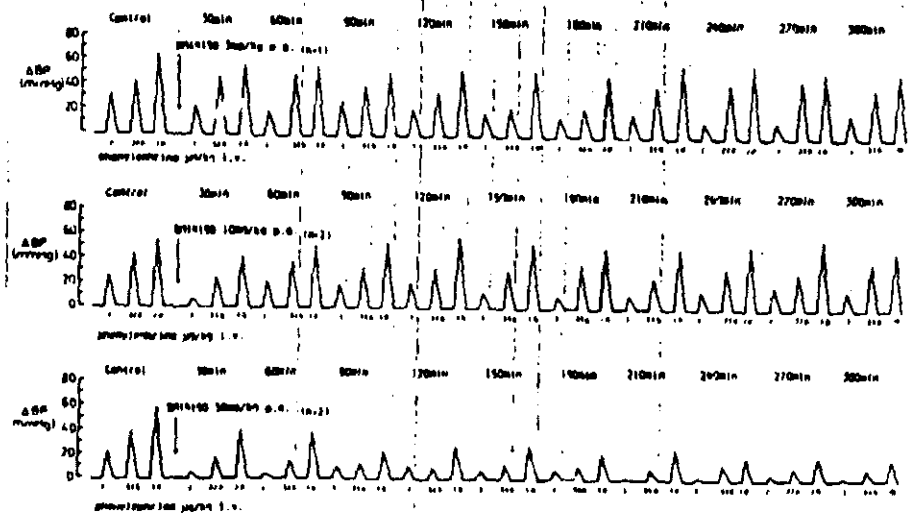


Fig 6 Effect of BM14190 oral administration on thepressor response to phenylephrine (α₁-adrenalin agonist) in conscious normotensive rats



Conscious rats were injected with carvedilol (1 mg/kg, i.v.) twice day for 8 days. The drug continued to block both α - and β -adrenergic hemodynamic responses after dosing for 8 days suggesting the absence of development of tachyphylaxis. (Tables 1 and 2 below.)

Table 1. Effects of carvedilol, prazosin or propranolol on baseline sympathetic arterial blood pressure and heart rate in conscious normotensive rats.

Treatment	n	Blood Pressure (mmHg)		Heart Rate (beats/min)	
		Pre-drug	Post-drug	Pre-drug	Post-drug
Vehicle	7	103 $\pm$ 4	99 $\pm$ 3	382 $\pm$ 14	374 $\pm$ 10
Carvedilol	6	104 $\pm$ 3	↓89 $\pm$ 2**	368 $\pm$ 13	360 $\pm$ 8
Prazosin	5	103 $\pm$ 3	↓80 $\pm$ 3**, †	401 $\pm$ 11	↑466 $\pm$ 14**, ††
Propranolol	5	110 $\pm$ 3	113 $\pm$ 5	411 $\pm$ 11	347 $\pm$ 6*

Values are the mean and SEM of (n) animals within the group. Baseline hemodynamic parameters, obtained on day 1 and day 8 before and after drug administration, were pooled, as were the baseline hemodynamic values obtained after drug administration. Pre-drug refers to baseline hemodynamic parameters before the administration of drug or vehicle, and post-drug refers to hemodynamic parameters after the administration of drug or vehicle. *, p < 0.05; ** p < 0.01, compared to the pre-drug value; †, p < 0.05; †† p < 0.01, compared to the corresponding value of the vehicle-treated group.

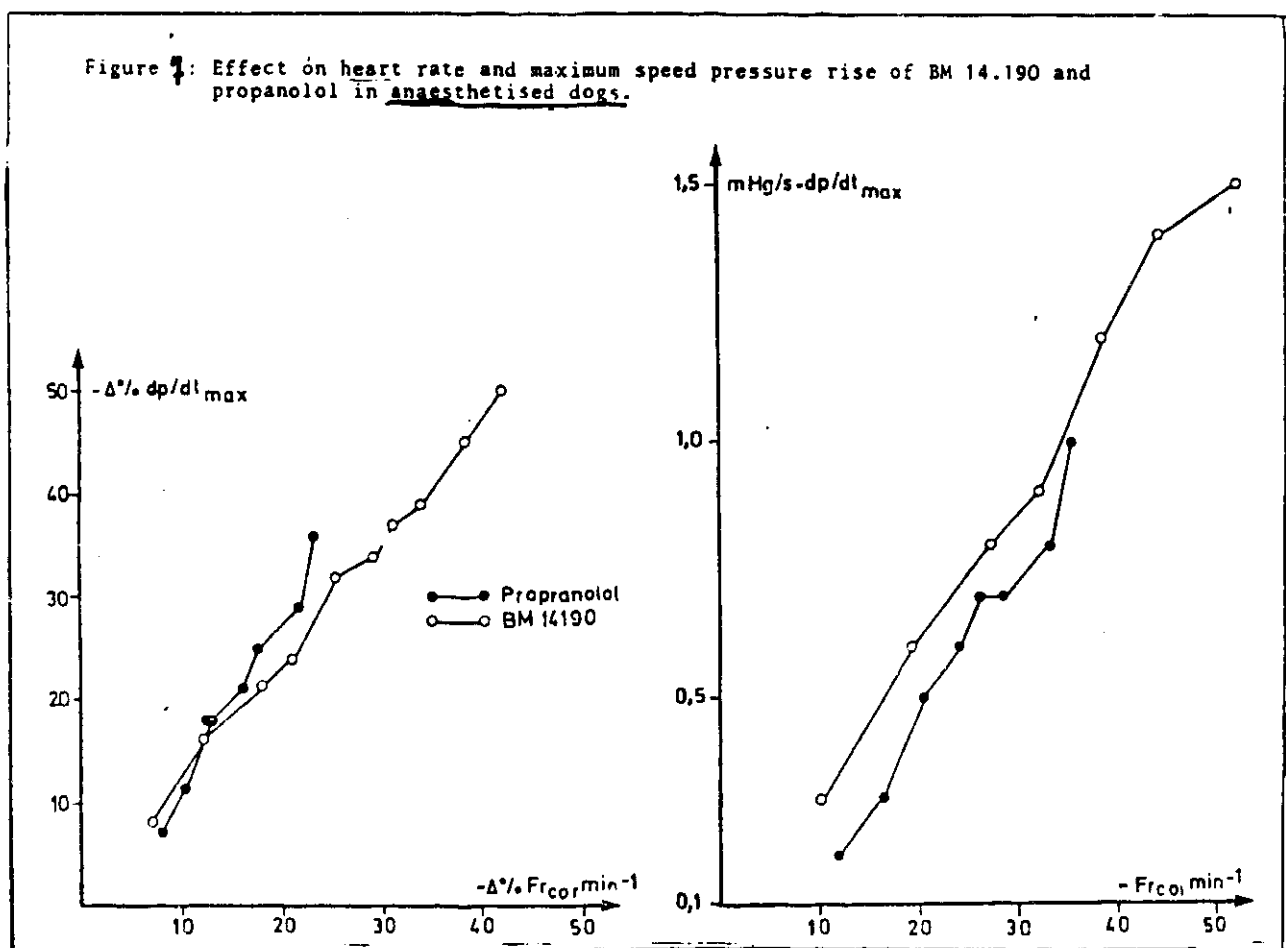
Table 2. Effects of carvedilol, prazosin or propranolol on the maximal heart response following the injection of 100 μ g/ml isoproterenol (an adrenergic receptor agonist)

Treatment	n	Maximal Heart Rate Response (beats/min)			
		Day 1		Day 8	
		Pre-drug	Post-drug	Pre-drug	Post-drug
Vehicle	7	499 $\pm$ 13	502 $\pm$ 13	514 $\pm$ 5	507 $\pm$ 6
Carvedilol	6	497 $\pm$ 12	↓353 $\pm$ 5**, ††	471 $\pm$ 16	↓361 $\pm$ 10**, ††
Prazosin	5	529 $\pm$ 6	555 $\pm$ 9	520 $\pm$ 7	531 $\pm$ 7
Propranolol	5	537 $\pm$ 9	↓371 $\pm$ 10**, ††	496 $\pm$ 8	↓371 $\pm$ 5**, ††

Values are the mean and SEM of (n) animals within the group. The maximal heart rate response is the peak heart rate occurring after the injection of carvedilol, prazosin or propranolol followed by isoproterenol. **, p < 0.01, compared to the pre-drug value; †† p < 0.01, compared to the corresponding value of the vehicle-treated group.

In anesthetized and conscious mongrel dogs, following infusion of cumulative doses of carvedilol (0.01-5.1 mg/kg) sponsor reported a dose-dependent fall in arterial BP and HR from 119 ± 5 to 87 ± 8 bpm. With both propranolol and carvedilol, the dose-dependent fall in HR was attributable to the β -blocking property of the drugs. Simultaneously the maximum speed of pressure rise in the left ventricle fell. In the anesthetized dog, the fall in dp/dt_{max} decreased from 3.8 ± 0.2 to 1.9 ± 0.1 . When dp/dt_{max} is plotted in absolute and relative terms against the reduction in HR, similar behavior was found for both drugs in these dogs (Fig.7 below.) CO was reduced about $70 \pm 4\%$ of control at maximum dose. Total peripheral resistance was also reduced from 117 ± 7 to $82 \pm 8\%$ of control suggesting peripheral vasodilatation.

Sponsor indicated that in this study in conscious dog, it was found that lowering arterial BP took place essentially via reduction of the CO and reduction of HR.



In anesthetized rats, i.v. administration of carvedilol (0.3 mg/kg), labetalol (0.6 mg/kg), prazosin (0.2 mg/kg), hydralazine (0.2 mg/kg) or nitroprusside Na (0.005 mg/kg) caused decreased arterial BP. After i.v. administration of the α_1 - blocker phentolamine (1 mg/kg) and infusion of prostaglandin_{2 α} (40-100 μ g/kg/min) to restore BP to control levels, the hypotensive actions of carvedilol, labetalol and prazosin were almost completely blocked while those of nitroprusside Na and hydralazine were only reduced. These findings suggest that the α_1 blocking action of carvedilol plays a role in the acute hypotensive action of carvedilol (Figs. 8 and 9 below).

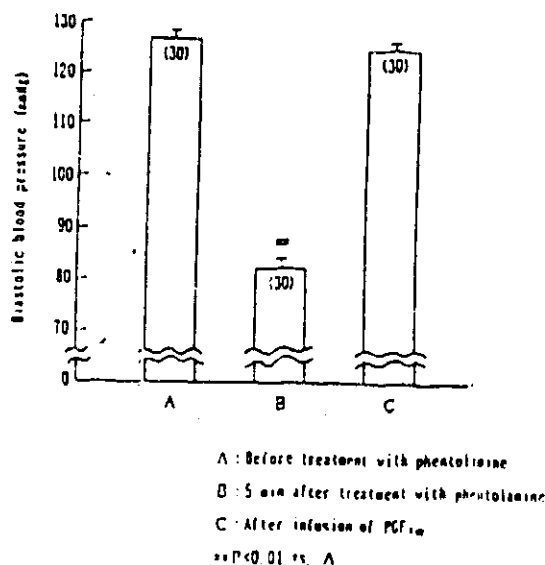


Fig 8 Decrease in diastolic blood pressure by phentolamine (1 mg, kg, i.v.) and its recovery by PGF_{2 α} (40-100 μ g/kg/min for 20 min) in anesthetized rats. Number of experiments are shown in parentheses.

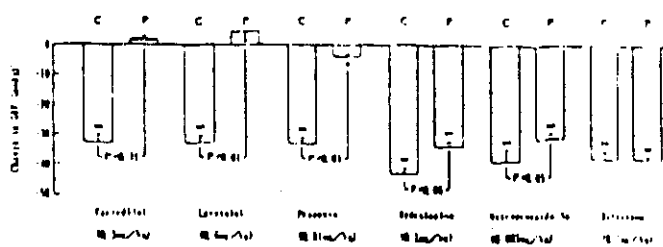


Fig 9 Hypotensive action of 6 vasodilator drugs in control (C) and rats pretreated with phentolamine and PGF_{2 α} (P). Each bar is the mean of 5 animals and vertical line represents the standard error. * P<0.05. ** P<0.01 vs. initial level

In anesthetized rats, carvedilol antagonized both isoproterenol-induced tachycardia and phenylephrine-induced vasopressor response. The cardiac selective β_1 -adrenergic receptor blocking activity of carvedilol was equipotent with the non-selective β -adrenergic receptor blocker propranolol and, more potent (2 to 3X) than labetalol.

In a model of orthostatic stress using conscious normotensive rabbit, successive i.v. injections of carvedilol (ranging from 0.01 to 0.1 mg/kg) lowered resting BP in a dose-dependent manner without producing reflex tachycardia. Based on the doses of carvedilol injected, the hypotensive effect of the drug was calculated as being 15 and 22 times more potent than labetalol and propranolol, respectively, but 3 times less potent than prazosin (Fig. 10). At doses that produced hypotension by 20 to 25 mmHg, carvedilol, labetalol (α_1 - and β -adrenergic blocker) and prazosin (pure α_1 -adrenergic blocker), impaired the BP response to upward tilt of 60° (sudden fall followed by compensatory recovery to pretilt level), whereas propranolol (pure β -adrenergic receptor blocker) did not impair the BP response (Table 3).

Results from these and other studies, suggest that carvedilol exhibits a combined α_1 and β adrenergic receptor antagonist effect as does labetalol.

TABLE 3. Comparison of orthostatic response of E1 14,190 with other adrenoceptor antagonists at equipotent hypotensive doses in conscious normotensive rabbits.

Drug	Dose mg/kg i.v.	n	Change in mean blood pressure (mmHg)	
			Resting	Tilt
E1 14,190	0.3	4	-23±2	-24±7
Labetalol	3	7	-23±3	-21±7
W-09538	1	6	-22±3	-15±7
Propranolol	3	6	-21±1	1±2
Prazosin	0.1	6	-23±2	-46±9

a) Values are mean ± S.E.M. of 4 to 7 experiments.

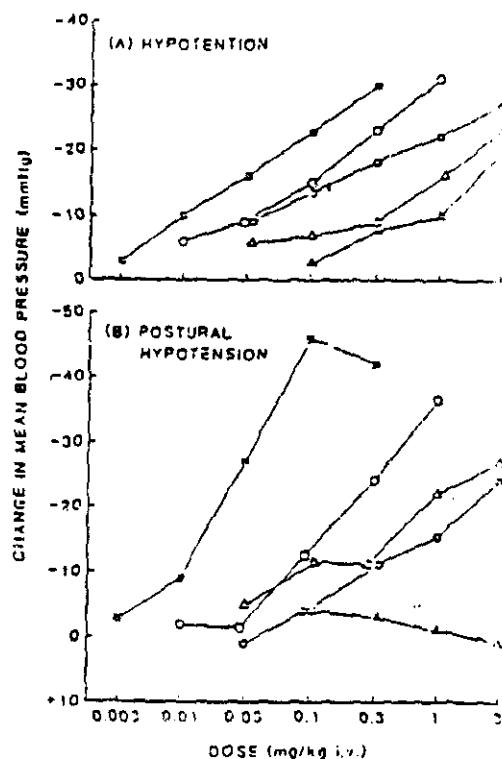


Fig. 10. Effects of E1 14,190 (O-O), prazosin (□-□), labetalol (Δ-Δ), W-09538 (◇-◇) and propranolol (▲-▲) on resting blood pressure (A) and blood pressure responses to 1-min 60° upright tilt (B) in conscious normotensive rabbits.

Postural hypotension is a common side effect in the treatment of hypertension with various drugs. The ability of carvedilol to lower baroreceptor reflex hypertension (cardiovascular changes induced by 90° tilt) was studied in anesthetized normotensive rat. In baseline studies, when compared to vehicle, changes induced by carvedilol (0.3 mg/kg i.v.) consisted in decreased systolic BP (by 12%) and diastolic BP (by 13%), 2 min after dosing; and heart rate decrease (8%). Following this hypotensive dose of carvedilol, the drug enhanced the tilt-induced reduction in BP and inhibited the tilt-induced increase in HR compared to the responses in vehicle treated rats. The potentiation of tilt-induced hypotension by carvedilol is considered a consequence of α_1 adrenoceptor blockade (Figs. 11, 12, and 13 below). This pharmacologic effect may be considered a potential clinical adverse effect of the drug.

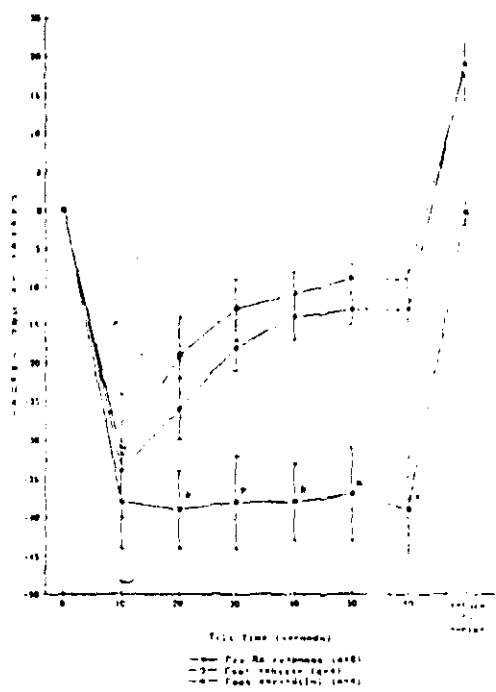


FIGURE 11 Effect of carvedilol (0.3 mg/kg i.v.) on changes in systolic blood pressure induced by vertical tilt in the anesthetized rat. Each point represents the mean $\pm$ S.E.M. * p<0.05.

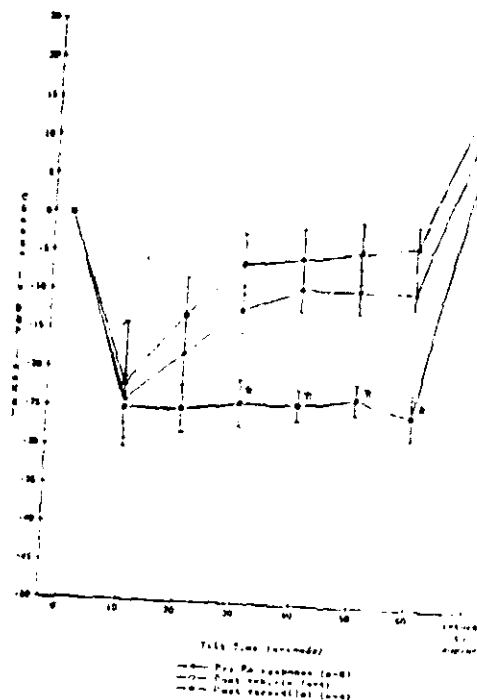


FIGURE 12 Effect of carvedilol (0.3 mg/kg i.v.) on changes in diastolic blood pressure induced by vertical tilt in the anesthetized rat. Each point represents the mean $\pm$ S.E.M. * p<0.05.

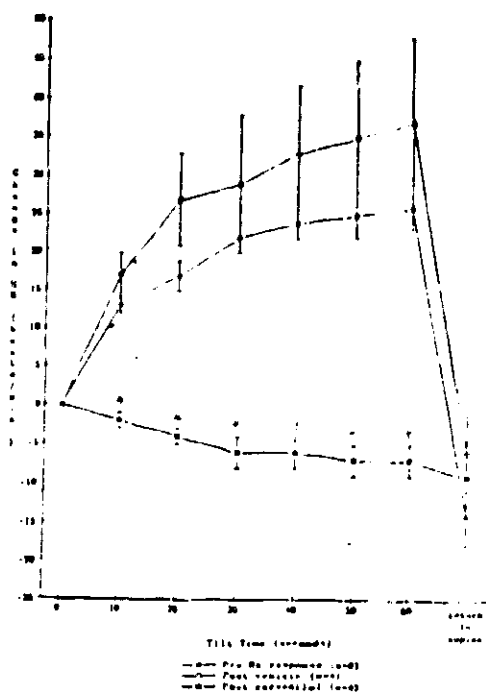


FIGURE 3: Effect of carvedilol (0.3 mg/kg iv) on changes in heart rate induced by vertical tilt in the anesthetized rat. Each point represents the mean $\pm$ s.e. * $p < 0.05$.

Sponsor asserts that reflex tachycardia in response to antihypertensive therapy with vasodilators is a major limitation to the clinical use of these drugs. Further, that unlike clinically used vasodilators (e.g., prazosin, hydralazine or nitrates), the antihypertensive response to carvedilol is not associated with increase in HR because of the concomitant β -adrenoceptor blockade. Thus, the hemodynamic effects of carvedilol and other vasodilators were examined in conscious chronically instrumented normotensive rats and dogs.

Sponsor compared the α_1 - and β -adrenergic blocking activity of carvedilol following acute and chronic administration to these 2 species. Hemodynamic effects to carvedilol were compared to those of the α_1 - blocker prazosin and β -blocker propranolol. The extent of acute and chronic blockade of the adrenergic receptors by these drugs were determined by measuring hemodynamic responses to the effects of the selective α_1 -adrenergic agonist cirazoline (vasopressor), and to the non-selective β -adrenergic agonist isoproterenol (tachycardia).

Briefly, the rats were treated with i.v. doses of carvedilol (1 mg/kg), prazosin (0.3 mg/kg), or propranolol (1 mg/kg) BID for 8 days. Before drug treatments, baseline values for arterial BP and HR were determined. In these rats, acute administration of carvedilol significantly decreased arterial BP but did not cause an increase in HR, prazosin produced significant decrease in BP and increased in HR, and propranolol had no effect on BP but significantly increased HR.

On day 1, after the first dose of carvedilol, the vasopressor response to cirazoline and tachycardia response to isoproterenol were blocked. On day 8, after repeated doses of

carvedilol, the vasopressor effect of cirazoline and isoproterenol tachycardia were significantly reduced suggesting α_1 - and β -adrenergic blockade after chronic dosing of carvedilol. As expected, the α_1 -blocker prazosin antagonized cirazoline-induced acute/chronic vasopressor response and had no effect on the isoproterenol β -receptor-mediated tachycardia. Further, propranolol blocked the acute/chronic effects of isoproterenol-induced tachycardia and had no effect on vasopressor effect of cirazoline.

The effects of acute/chronic administration of carvedilol and, of prazosin or propranolol on the cirazoline/isoproterenol-mediated hemodynamic responses are depicted below in Figures 14-17 below provided by sponsor.

Sponsor asserts that results show that only carvedilol blocked both α_1 - and β -adrenergic hemodynamic responses, respectively, of cirazoline and isoproterenol. Further, that antagonism by carvedilol to those effects was not diminished even after dosing BID for 8 days.

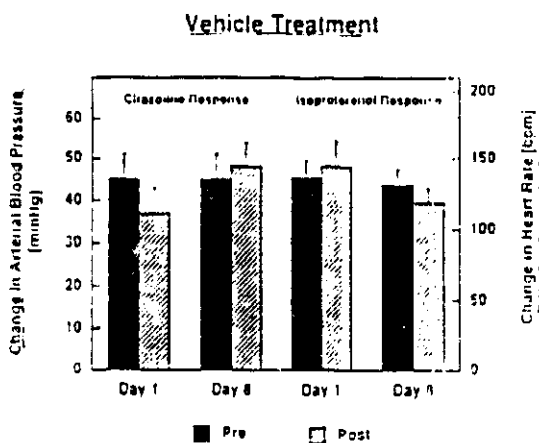


Figure 14 Effect of vehicle treatment for 1 day or 8 days on the cirazoline-induced vasopressor response and isoproterenol-induced tachycardia. Vehicle treatment had no effect on either the cirazoline or isoproterenol hemodynamic responses.

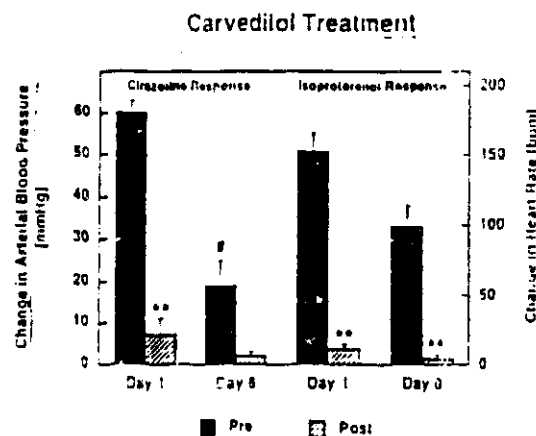


Figure 15 Effect of carvedilol treatment for 1 day or 8 days on the cirazoline-induced vasopressor response and isoproterenol-induced tachycardia. Carvedilol blocked the cirazoline and isoproterenol hemodynamic responses after the first dose and to a similar extent following 8 days of twice daily dosing (1.5 mg/kg, b.i.d.). (** p < 0.01, compared to the pre-dose value of the same day; * p < 0.05, compared to the pre-dose value of Day 1)

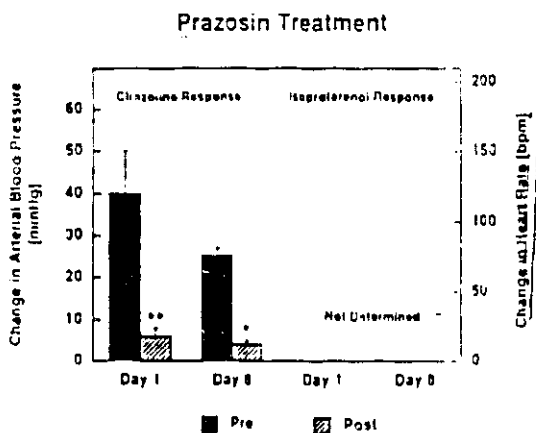


Figure 16 Effect of prazosin treatment for 1 day or 8 days on the cirazoline-induced vasopressor response and isoproterenol-induced tachycardia. Prazosin blocked the cirazoline vasopressor response after the first dose but to a similar extent following 8 days of twice daily dosing (1.5 mg/kg, b.i.d.). The effect of prazosin on the isoproterenol response could not be determined since prazosin caused a significant elevation of heart rate, thereby precluding the determination of heart rate. (** p < 0.01, compared to the pre-dose value of the same day)

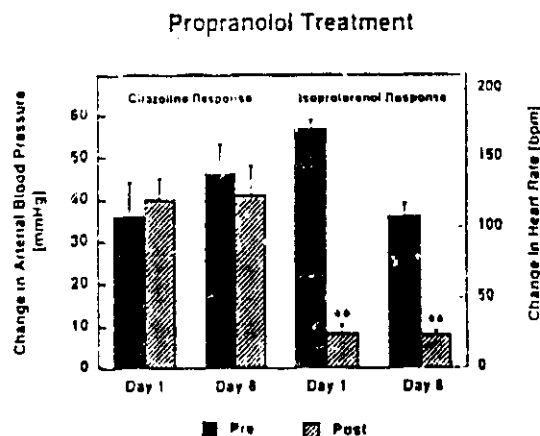


Figure 17 Effect of propranolol treatment for 1 day or 8 days on the cirazoline-induced vasopressor response and isoproterenol-induced tachycardia. Propranolol blocked the isoproterenol hemodynamic responses after the first dose but to a similar extent following 8 days of twice daily dosing (1.5 mg/kg, b.i.d.). Propranolol had no effect on the cirazoline hemodynamic responses. (** p < 0.01, compared to the pre-dose value of the same day; * p < 0.05, compared to the pre-dose value of Day 1)

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In untreated and reserpinized rats, the intrinsic sympathomimetic activity (ISA) of carvedilol was assessed as the percentage (%) increase in HR frequencies produced by effective β -blocking doses.

In normal rat, sponsor indicates that the HR (average of 10 animals) is between 370 and 420 bpm. Reserpine treatment led to a decrease of about 260 bpm (220-283 bpm). In these reserpinized rats, isoprenaline (1 mg/kg i.p.) increased the HR frequency on the average of 189 bpm within 3 min.

Sponsor reports that in the reserpinized rat, doses of carvedilol (0.01-1 mg/kg, i.p.) had no effect on the HR, suggesting that the drug has no positive chronotropic activity when compared to pindolol (a β -blocker) which is known to possess ISA.

Sponsor asserts that the predominant tone of the cerebral vasculature is not mediated by adrenoreceptors. In conscious and anesthetized rats, effects of cumulative hypotensive doses of carvedilol and labetalol (0.1, 0.3 and 1.0 mg/kg i.v. for each drug) on local cortical microvascular perfusion (CP) and (apparent) cerebralvascular resistance (CVR) was examined.

Method used for the determinations of local CP was fully described in the NDA. Hemodynamic parameters [mean arterial BP, CP and CVR (calculated as MAP/CP)] were monitored for up to 30 min during post-drug treatment (Fig. 18).

Sponsor reports that carvedilol and labetalol caused equipotent, mild to moderate dose-dependent reductions in CP, but did not significantly alter local CVR at the 3 hypotensive doses tested. The maximal effect was noted at the highest dose (1.0 mg/kg for both drugs); percent (%) reductions in CP were about $-24 \pm 6\%$ for carvedilol and $-20 \pm 6\%$ for labetalol (Fig. 19).

Sponsor suggests that the % reductions in CP observed represent a passive response to the hypotensive effects of both drugs.

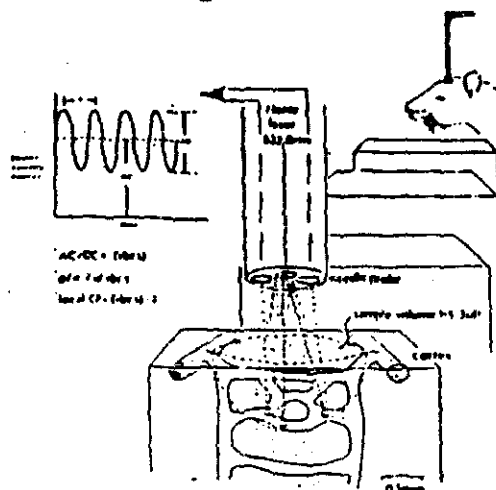


Fig. 18 This schematic diagram illustrates the basic principles of laser-Doppler flowmetry used for measuring local cerebral microvascular perfusion.

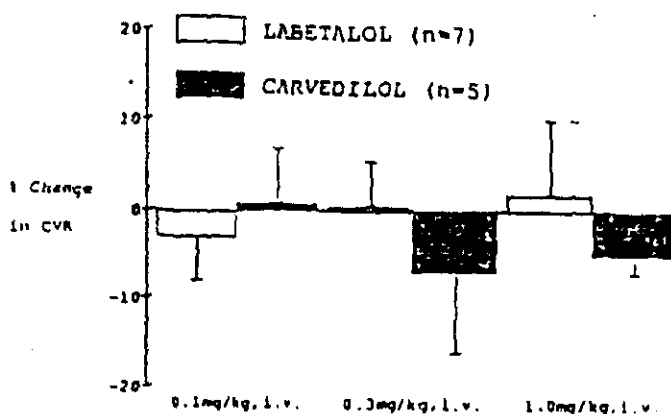


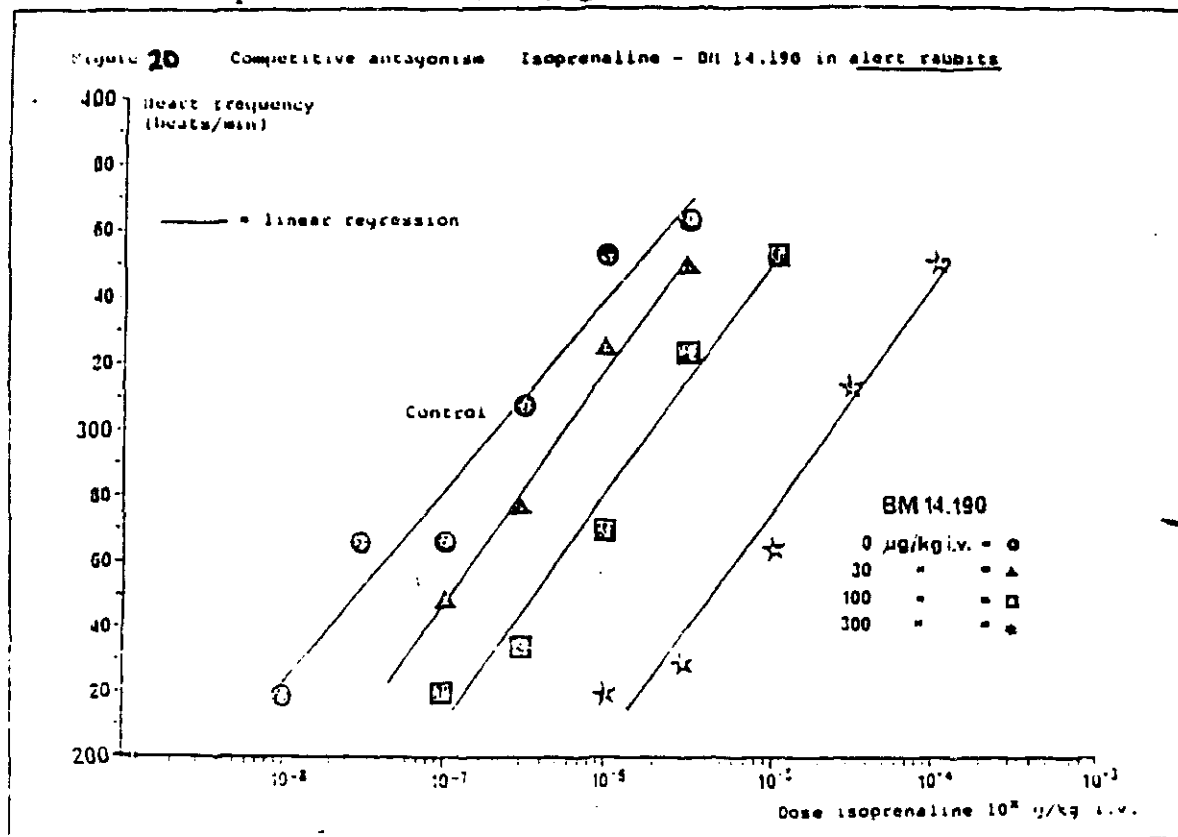
Fig. 19 This bar graph summarizes the maximum steady-state effects of labetalol and carvedilol on local cerebral microvascular resistance (CVR). Doses (0.1, 0.3 and 1.0 mg/kg, i.v.) were administered in a cumulative fashion.

The β -blocking effects oral carvedilol (1, 3 and 10 mg/kg) was investigated in conscious rabbits.

Carvedilol produced a dose-related decrease in the magnitude of isoprenaline-induced (1 μ g/kg i.v.) tachycardia. At a low dose (1 mg/kg), the effects began 120 min and lasted for 30 min. At the 3 and 10 mg/kg doses the effects began at about 60 min post-treatment and lasted for 2 hrs. The slowing down of isoprenaline-induced tachycardia in conscious rabbits indicated that carvedilol also has a β -blocking action in rabbit.

Sponsor considered that since the chemical structure of carvedilol does not resemble other β -blockers, the slowing down of the heart rate could also be due to other mechanisms. Studies to investigate if carvedilol caused a shift to the right in the dose-response curve of isoprenaline would demonstrate competitive antagonism against isoprenaline.

In conscious rabbits, results suggest that the β -blocking effect of carvedilol may be characterized as competitive because doses of 30, 100 or 300 $\mu\text{g}/\text{kg}$ i.v. clearly shifted the dose-effect curve of isoprenaline to the right. (Fig. 20)



In anesthetized rabbits in which carotid sinus pressor reflex had been elicited, carvedilol dose-dependently reduced BP. At doses known to reduced BP by 30 mmHg, when carvedilol (0.11 mg/kg) was compared to hydralazine (0.18 mg/kg) and labetalol (0.95 mg/kg), the test drug appeared to be somewhat more active than hydralazine and 9X more active than labetalol.

After receiving logarithmically increasing dosages of carvedilol, the rabbits died under administration of a mean dose of 5.04 mg carvedilol/kg; the corresponding lethal dose for labetalol was 35.9 mg/kg. All rabbits in the study survived a dosage of hydralazine of 32 mg/kg. Sponsor attributed the poorer tolerance (lethal dose) to carvedilol and labetalol to a quinidine-like effect of β -blockers when these drugs are administered rapidly (30 seconds).

Sponsor described a rabbit model of orthostatic stress (postural hypotension). Briefly, sponsor states that immobilized conscious rabbits subjected to sudden body change from horizontal to vertical position (tilt) will normally (within 5 sec) show brief fall in arterial BP* which regains a value which is generally higher than before the tilt. However, BP remains constant during the period the body is held in the vertical position (about 1 min). This regulatory process to body tilting is affected by hypotensive drugs.

*Fall in carotid pressure.

Using a rabbit model of orthostatic stress, carvedilol (0.12, 1.2, and 6 mg/kg, i.v.) and hypotensive drugs known to produce orthostatic side effects in humans (labetalol, and prazosin and guanethidine) were tested. Low doses prazosin and guanethidine (known to reduce BP 30 mmHg and trigger baroreceptor reflex in anesthetized rabbit), hardly affected the raise in BP effect to the orthostatic stress. When the doses of these hypotensive drugs were increased by 10% (exact doses used could not be clearly determined), the orthostatic reaction was reported as statistically significantly reduced (about 24 and 30%, respectively) by prazosin and guanethidine. Although this response was only moderately reduced by labetalol (about 15%), it was significantly less affected by carvedilol (about 13% at the highest dose tested) suggesting a lesser effect by the test drug on the regulatory process. Sponsor considered that this finding suggest that there would be lower risk of postural hypotension in human to be expected after carvedilol treatment.

In anesthetized rabbit, carvedilol (doses ranging from 0.01 up to 3.0 mg/kg i.v.) dose-dependently reduced mean arterial BP from 101 ± 4 (at the lowest dose) down to 54 ± 3 mmHg at the highest dose tested. Although right atrial pressure dose-dependently slightly increased, the change was not statistically significant and was less than following propranolol. (Table 5)*

Table 5: Effect to arterial blood pressure, heart rate, pressure in the right atrium, respiratory volume, respiratory rate and PQ- and QRS-times in ECG

Experimental animals: mixed-race rabbits of both sexes (Grimm, Erasmus-LA, FRG) anesthetised with urethane, 25 % solution; about 1.5 g/kg

Food: Kaninchen-Alleinfutter, Type 50, 4 mm Pellets (Zahn II, Hockenheim, FRG)

Substances: BM 14.190 (batch Zi 38/2 A₁) dissolved in 10 % DMF-isotonic saline solution.
Propranolol batch LJ 22 87 2) dissolved in isotonic saline solution
 $\bar{x} \pm s_x$

Substance	Parameter	Initial value	Total injected dose in mg/kg					
			0.01	0.02	0.1	0.3	1.0	3.0
BM 14.190 n = 6	MA (mmHg)	106 ± 4	101 ± 4	93 ± 5	81 ± 5	70 ± 4	57 ± 3	54 ± 3
	FR (min ⁻¹)	220 ± 7	211 ± 10	205 ± 13	211 ± 18	213 ± 21	212 ± 19	208 ± 22
	PA (mmHg)	39 ± 4	38 ± 4	37 ± 4	41 ± 5	42 ± 5	48 ± 8	50 ± 9
	Resp. vol. (ml)	12.7 ± 0.6	12.6 ± 0.5	11.9 ± 0.8	10.4 ± 0.7	10.5 ± 0.7	10.8 ± 0.8	10.6 ± 0.7
	Resp. rate (min ⁻¹)	87 ± 3	84 ± 3	100 ± 9	101 ± 10	118 ± 7	110 ± 8	121 ± 9
	PQ-time (msec)	63 ± 3	63 ± 3	66 ± 3	68 ± 3	70 ± 3	72 ± 2	74 ± 4
	QRS-time (msec)	31 ± 1	30 ± 1	30 ± 1	30 ± 1	33 ± 1	33 ± 1	35 ± 4
Propranolol n = 6	MA (mmHg)	108 ± 5	—	—	103 ± 4	121 ± 4	97 ± 5	88 ± 6
	FR (min ⁻¹)	228 ± 13	—	—	226 ± 15	231 ± 17	273 ± 25	266 ± 23
	PA (mmHg)	33 ± 5	—	—	41 ± 5	46 ± 7	53 ± 9	73 ± 6
	Resp. vol. (ml)	12.7 ± 0.7	—	—	12.6 ± 0.9	12.2 ± 1.1	10.9 ± 1.1	10.3 ± 1.2
	Resp. rate (min ⁻¹)	92 ± 5	—	—	95 ± 7	105 ± 10	126 ± 12	133 ± 14
	PQ-time (msec)	59 ± 4	—	—	64 ± 4	67 ± 3	67 ± 3	73 ± 7
	QRS-time (msec)	27 ± 2	—	—	28 ± 2	28 ± 2	28 ± 2	28 ± 2
Carvedilol n = 6	MA (mmHg)	109 ± 5	—	—	100 ± 4	103 ± 5	102 ± 6	97 ± 7
	FR (min ⁻¹)	212 ± 13	—	—	222 ± 14	228 ± 12	231 ± 13	229 ± 15
	PA (mmHg)	32 ± 3	—	—	30 ± 3	27 ± 3	26 ± 3	24 ± 3
	Resp. vol. (ml)	12.7 ± 0.6	—	—	12.1 ± 0.8	12.0 ± 1.0	11.1 ± 0.9	11.4 ± 0.8
	Resp. rate (min ⁻¹)	87 ± 3	—	—	92 ± 6	104 ± 10	108 ± 9	109 ± 9
	PQ-time (msec)	58 ± 2	—	—	59 ± 2	58 ± 2	57 ± 2	58 ± 2
	QRS-time (msec)	25 ± 1	—	—	26 ± 1	26 ± 1	26 ± 1	26 ± 1

* There is no Table 4.

In these rabbits, following carvedilol, the respiratory volumes showed a tendency to fall while respiratory rate increased slightly; these effects were not considered drug related because they were also seen with the vehicle and propranolol. Like propranolol, carvedilol prolonged the PQ time as a result of reduction in HR, an expression of β -adrenergic receptor blockade. Other ECG were not considered significant by sponsor.

In mongrel dog, studies were conducted to determine hemodynamics and regional blood distribution effects of carvedilol compared to propranolol.

Following i.v. infusion of carvedilol, there was a dose-dependent fall in arterial BP in both the anesthetized and unanesthetized dog. However, in the anesthetized dog the lowering of BP took place essentially via a reduction of CO. Sponsor stated that the total PR was not increased to the same degree as the reduction of the CO (which is the result of a reduced HR, to keep the arterial BP constant). However, investigators pointed out that the fall in perfusion pressure of the hind limbs of the dogs under carvedilol was to the same degree as the CO.

In this dog study, HR was dose-dependently reduced following administration of carvedilol and propranolol attributable to the β -blocking property of both drugs. Simultaneously, the maximum rate of ventricular pressure rise (dP/dt_{max}) fell dose-dependently. When the fall in dP/dt_{max} was plotted in absolute and relative terms against the reduction in HR, similar effects were found for carvedilol and propranolol. (Fig. 7, page 14 above).

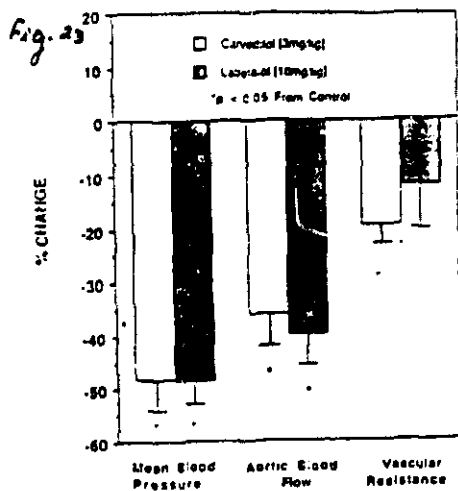
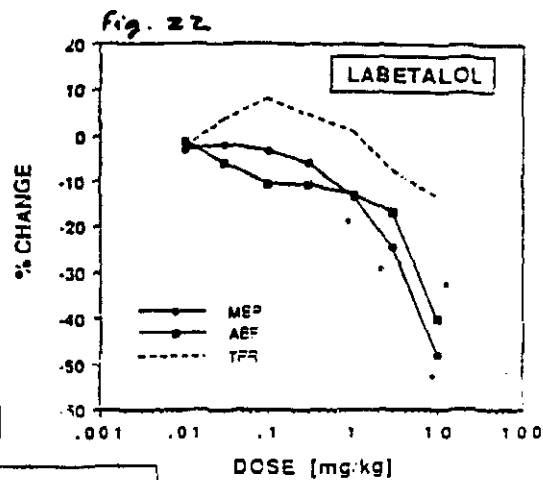
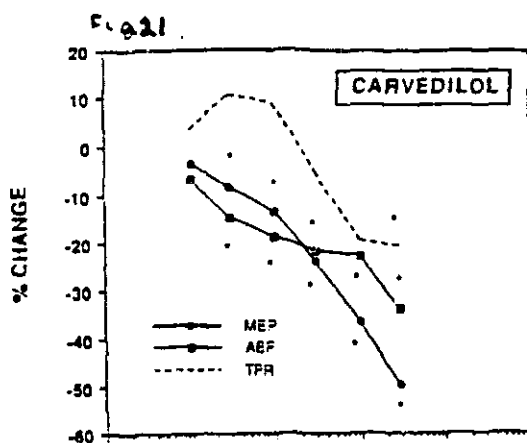
Investigators interpreted the findings in these rabbit and dog studies as suggesting that in the clinics typical β -blocker side effects might be expected from carvedilol. Sponsor further considered that as with propranolol, reduced blood supply of the extremities (Raynaud syndrome) could also occur as a side effect of carvedilol.

Although data were not provided in this dog study, sponsor asserts that the autoregulatory system for perfusion of the kidneys is apparently maintained with both carvedilol and propranolol.

In pentobarbital anesthetized dogs, the hemodynamic actions of carvedilol were compared with those of labetalol. Animals received serially increasing doses of either carvedilol (0.01-3.0 mg/kg, i.v.), labetalol (0.01-10.0 mg/kg, i.v.) or vehicle. Both carvedilol and labetalol produced dose-related reductions in HR, MBP, left ventricular systolic pressure, LV dP/dt , aortic blood flow (ABF), coronary blood flow and coronary resistance. Dose-response noted for each parameter examined indicates that carvedilol is approximately 3-10 fold more potent than labetalol in altering these hemodynamic parameters studied.

Carvedilol produced a significant reduction ($p < 0.05$) in total vascular resistance (TPR) at the highest dose (3 mg/kg, i.v.) while a similar effect was not observed with doses of labetalol (Fig. 2). Compared to control, carvedilol at 3 mg/kg i.v., reduced- mean BP about 50%, HR 17%, LV systolic pressure 43%, LV dP/dt 51% and coronary blood flow 36%, and ABF about 39.5% (Fig. 1). Sponsor asserted that β -adrenoceptor blockade/vasodilation with both

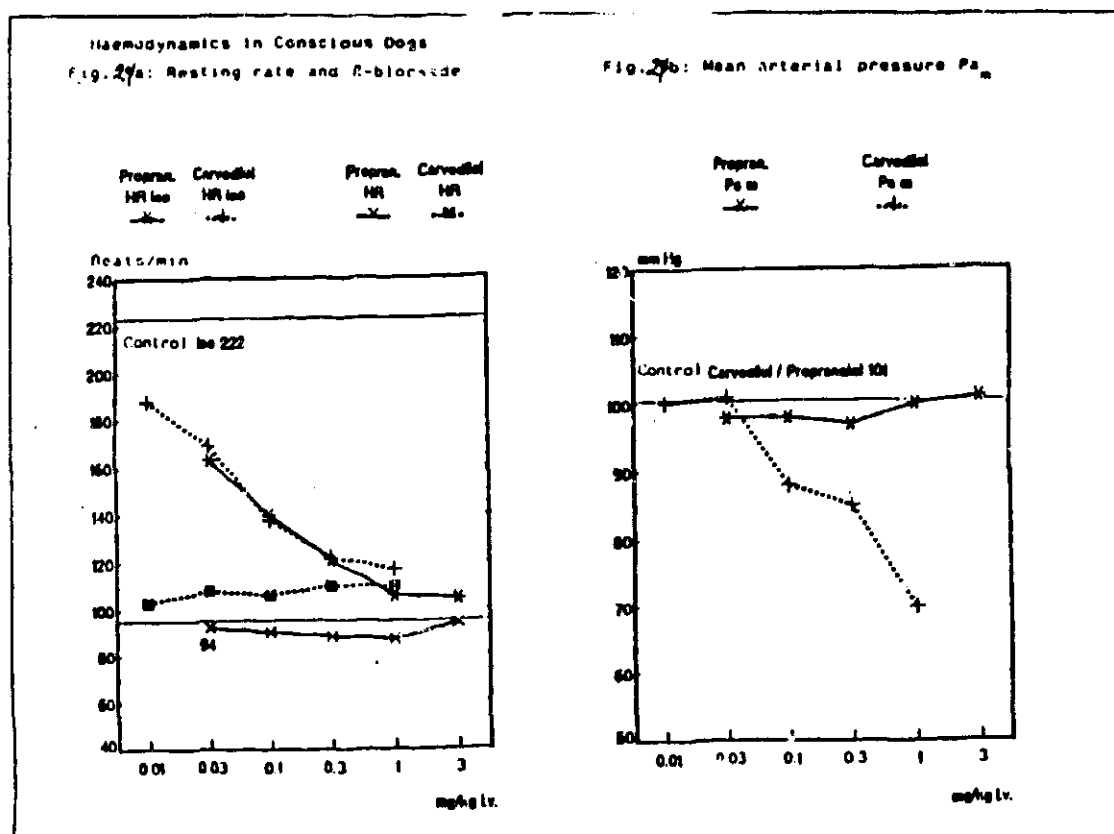
carvedilol and labetalol result in dose-related reductions in arterial BP but only carvedilol decreases TPR perhaps related to α_1 -adrenoceptor blockade (Figs. 21, 22 and 23).



In conscious dogs (chronically instrumented for observing hemodynamic changes), the hemodynamic effects of carvedilol were compared to propranolol. In these studies, the following parameters were examined or calculated: aortal flow (as a measure of CO), MAP, HR, SV, right atrial pressure, coronary flow, and TPR.

In these dogs, isoprenaline-induced tachycardia was inhibited dose-dependently by carvedilol and propranolol (both drugs tested at 0.01 up to 1 mg/kg, i.v.; Fig. 24a). Carvedilol reduced MAP dose-dependently which was attributed to reduction in TPR; with propranolol the MAP remained almost constant as a result of slight rise in TPR (Figs. 24b and 25b following page.) Aortal blood flow (expression on CO) was unchanged by carvedilol (Fig. 25a). Carvedilol only slightly reduced coronary flow (Fig. 26b) and myocardial oxygen requirement (calculated as the product of systolic blood pressure x HR) suggesting no impairment of myocardial oxygen balance (Fig. 26a). Effects of propranolol on these hemodynamic parameters showed no change in the measure for oxygen requirement and a tendency for coronary blood flow to fall indicating an increase in coronary resistance.

Carvedilol did not affect right atrial pressure. Investigators interpreted the absence of an effect on the right atrial pressure to carvedilol producing dilatation by a precapillary action.



Haemodynamics in Conscious Dogs

Fig. 25: Aortal flow (V_{aorta})

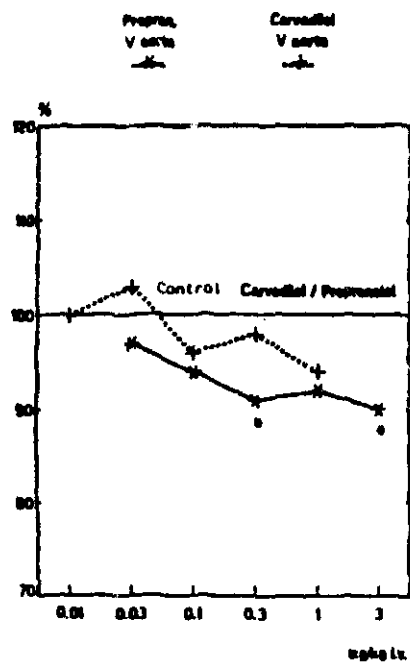
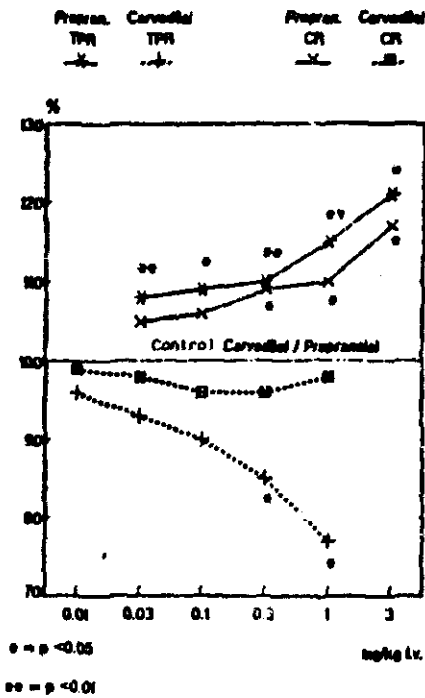


Fig. 26: Vascular resistance (TPR and CR)



Haemodynamics in Conscious Dogs

Fig. 27: Pressure-rate product ($P_a \times HR$)

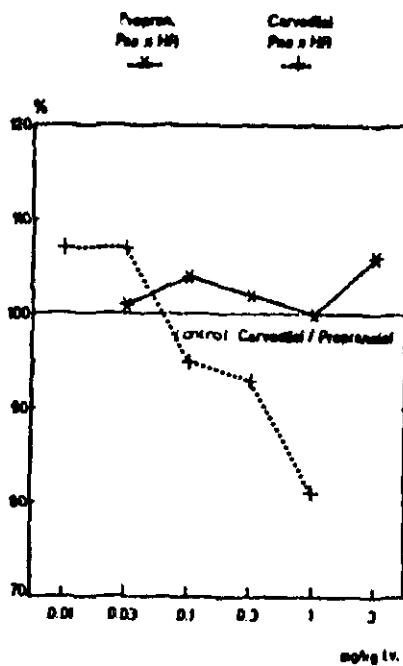
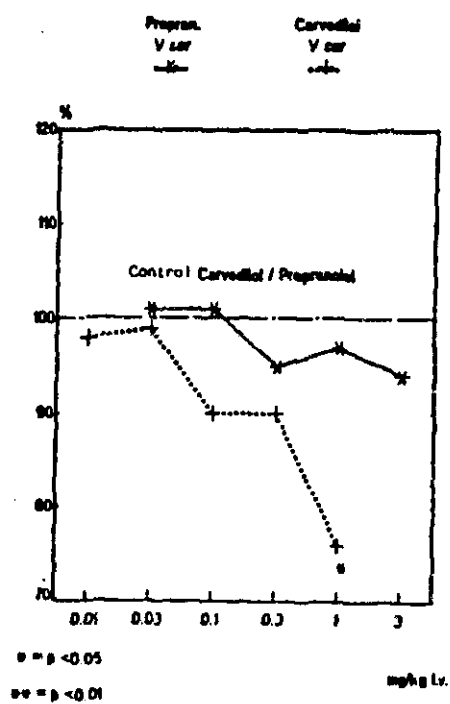


Fig. 28: Coronary flow (V_{cor})



The metabolism of carvedilol (see OVERVIEW OF ADME STUDIES) was examined in 4 animal species (mouse, rat, dog, and monkey), and activity of several metabolites assessed in rabbits and rats.

Studies submitted report that carvedilol is extensively metabolized via aromatic ring oxidation, aliphatic side-chain oxidation and configuration pathways (Fig. 27.) Data reviewed does not indicate if there is a stereoselective metabolism for carvedilol.

To characterize the pharmacologic action of some metabolites with respect to β -blockade and vascular action, these were tested in SHR, conscious rabbits and isolated aortic strips. In conscious rabbits with isoprenaline (1 $\mu\text{g}/\text{kg}$ i.v.) induced tachycardia, cumulative doses of carvedilol and metabolites blocked the tachycardia (reported as 9-100% but no data provided); metabolites BM 14.242 (M-2) and BM 14.686 (M-4) were 2 and 13 X more potent than carvedilol in this preparation. (Table 6, following page.) Sponsor stated that metabolites M-2 (at 1.9 - 125 $\mu\text{g}/\text{kg}$), and M-4 (at 0.98 - 125 $\mu\text{g}/\text{kg}$) blocked isoprenaline-induced tachycardia with ED_{50} = 30 $\mu\text{g}/\text{kg}$ for M-2 and 29 $\mu\text{g}/\text{kg}$ for M-4. Other metabolites tested (e.g. M8, M9, M10, M10), even at high doses showed no indication of β -blockade.

In SHR male rats, carvedilol blocked isoprenaline-induced hypotension (from about 40 to 100%) with an ED_{50} = 112 $\mu\text{g}/\text{kg}$. M-2 and M-4 blocked isoprenaline-induced hypotension (from about 20 up to 100%) with ED_{50} of 45 $\mu\text{g}/\text{kg}$ and 8.6 $\mu\text{g}/\text{kg}$, respectively (Table 6)

The antihypertensive effect of carvedilol in SHR was about 9 times more potent than the metabolites tested (e.g., M2, M4, M8 and M9) (Table 6)

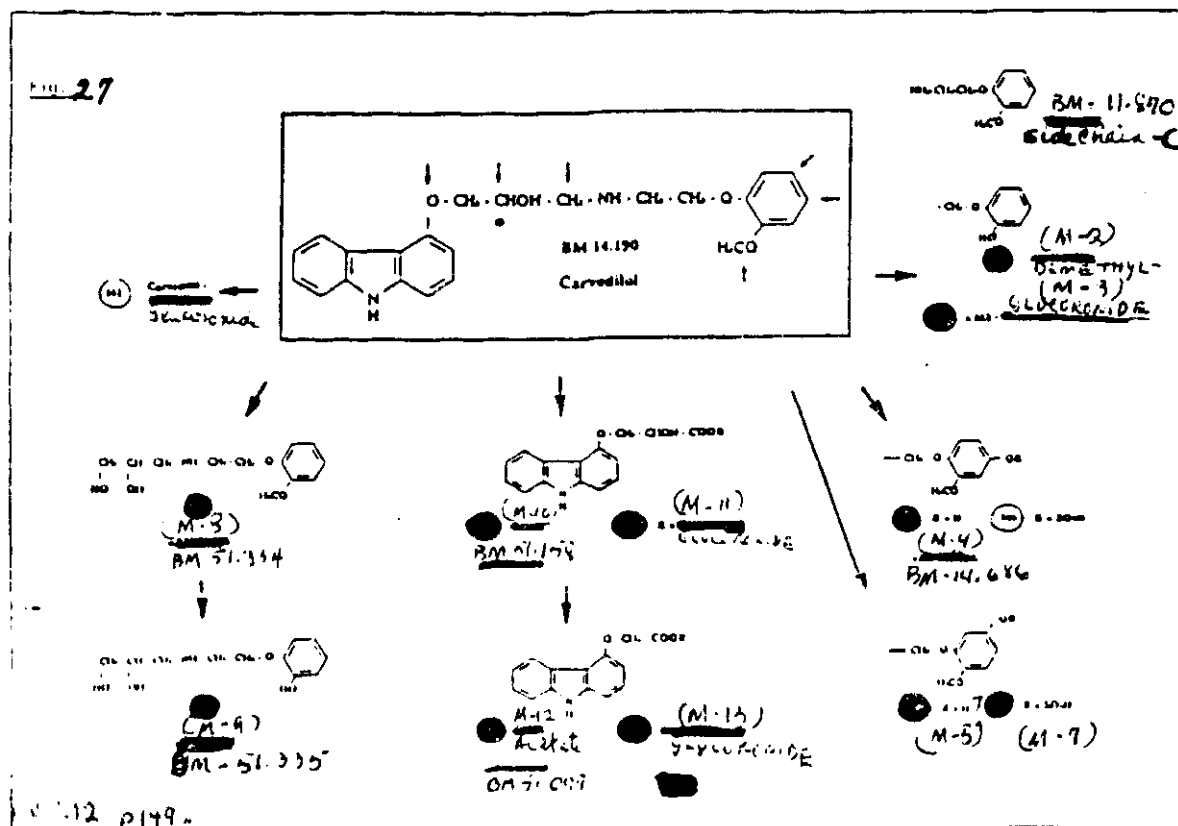


Table 6
Metabolites of 14C-Carvedilol
(for details see part of documentation T9, N8, D38)

No	Name	Code	% of total radioactivity				β-Blockade (rabbit) ED50 % (µg/kg i.v.)	Relaxation 10 ⁻⁵ M rat aortic rings vs NA (10 ⁻⁵ M) (%)	Hypotensive effect SHR ED ₃₀ mmHg (µg/kg i.v.)
			Plasma		Urine				
			Human 1.5 h	Dog 2 h	Human 12 h	Dog 48 h			
	Carvedilol (C)	BM 14.190	9	26	1.9	0.2	112	95	370
M 1	C-glucor.	-	22	8.4	32.4	1	n.d.	n.d.	n.d.
M 2	O-demethyl-C	BM 14.242 (M3)	0.8	0.1	0.3	b.d.l.	45	30	* 3000
M 3	M2-glucor.	-	5	n.d.	3	n.d.	n.d.	n.d.	n.d.
M 4	para-OH-C	BM 14.686 (M4)	n.d.	n.d.	6.4	n.d.	8.6	29	* 3000
	meta-OH-C	-	n.d.	n.d.	6.4	n.d.	n.d.	n.d.	n.d.
M 6	M4-sulfate	-	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
M 7	M5-sulfate	-	n.d.	n.d.	4.7	n.d.	n.d.	n.d.	n.d.
M 8	Oe-carbazoyl-C	BM 51.334 (M8)	12	15.5	10.2	25	* 8000	13	* 3000
M 9	O-demethyl	BM 51.335 (M9)	8	5.2	3	.51	* 8000	0	* 3000
M10	C-lactate	BM 51.158	n.d.	n.d.	n.d.	8	* 2000	n.d.	n.d.
M11	M10-glucor.	-	n.d.	n.d.	12	n.d.	n.d.	n.d.	n.d.
M12	C-acetate	BM 51.097	n.d.	n.d.	n.d.	2	* 6000	n.d.	n.d.
M13	M12-glucor.	-	n.d.	n.d.	1.6	n.d.	n.d.	n.d.	n.d.
	Side chain-C	BM 11.870	Not detectable				* 4000	0	* 3000

n.d. = not determined; b.d.l. = below detection limit; u.i. = under investigation; * = dose higher than

Cardiac Electrophysiologic Studies

High concentrations of certain β -blockers have quinidine-like membrane stabilizing activity (MSA) on the action potential.

In anesthetized rabbits, the MSA of carvedilol was compared to propranolol and quinidine. In sponsor's experience, ventricular flutter (VF) is induced in these animals with an electrical stimulus intensity within the range of 200 and 1300 μ A applied by square wave at a frequency of 50/sec for 0.8 sec. Drugs with MSA increase the strength of current needed to initiate VF.

Doses of propranolol 0.91 mg/kg i.v., quinidine 2.12 mg/kg i.v. and carvedilol 1.9 mg/kg i.v. were found to increase the electrical threshold for initiating VF by 100 μ A in the anesthetized rabbits. Sponsor reported that the MSA of carvedilol is about 6 X less than propranolol when one relates this to the β -blocking potency (Table 7).

Table 7: Shift in the electrical threshold for initiation of ventricular flutter in rabbits by DM 14.190 in comparison with propranolol and quinidine

Experimental animals: Male and female mongrel rabbits
Supplier: Versuchstierzucht Dr. Erich Zimmermann, Schweizerhof, 7001 Abtgemund 2, FRG

Food: Rabbit "Alleinfutter" type Kanin 2, pellets 4 mm
Manufacturer: Hefft Kraftfutterwerk, 6520 Worms/Rhein, FRG

ED₅₀ 100 μ A: Shift in the electrical threshold for initiating ventricular flutter by 100 μ A

ID₅₀: Dose required to inhibit the increase of rate following 1 μ g/kg isoprenaline i.v. by 50 %

M: SEM or M (f)

Substance	n	Control μ A	Dose mg/kg i.v.: μ A threshold 10 min after admin. (accumulated)										ED ₅₀ 100 μ A mg/kg i.v. M (f)	ID ₅₀ mg/kg i.v.	ED ₅₀ 100 μ A
			S	μ A	S	μ A	S	μ A	S	μ A	S	μ A			
Quinidine (C)	6	414 ±51	0,5 ±33	399 ±33	1,5 ±60	463 ±60	3,5 ±68	540 ±68	7,5 ±83	652 ±83	15,5 ±61	678 ±61	2,12 (1,13)	-	-
Propranolol	6	417 ±32	0,4 ±20	496 ±20	1,2 ±35	563 ±35	2,8 ±61	702 ±61	6,0 ±975	>975			0,91 (1,20)	0,3:1	2,7
DM 14.190	6	421 ±37	0,5 ±30	440 ±30	1,0 ±30	452 ±30	2,0 ±35	629 ±35	4,0 -	>778			1,90 (1,22)	0,1:2	17

Electrophysiologic Studies (cont'd)

Groups of anesthetized mongrel dog were studied to determine any significant interaction of carvedilol and the calcium channel antagonist diltiazem. In one group of dogs, interaction of serially increasing doses of carvedilol (0.03 up to 1 mg/kg, i.v. over 10 min with 20 min allowed before giving the next higher dose) and calcium channel antagonist diltiazem (15 μ g/kg/min i.v.), on systemic hemodynamic and electrophysiologic effects. Briefly, increasing doses of carvedilol produced dose-related decreases in systemic mean BP, HR, left ventricular systolic pressure and left ventricular dP/dt_{max} . Dogs receiving only diltiazem infusion demonstrated initial decreases in mean BP and LV systolic pressure but no further significant changes during administration of vehicle; HR declined over time and LV dP/dt was changed over the duration of diltiazem administration. Combined administration of carvedilol and diltiazem resulted in dose-related decreases in mean BP and left ventricular systolic pressure; these effects were not significantly greater than those which occurred with carvedilol alone. HR and left ventricular dP/dt decreased to a greater degree with the combined treatments when compared to either treatment alone.

Sponsor reported that the magnitude of the hemodynamic changes were related to carvedilol plasma levels; these ranged from about 19 ng/ml after carvedilol dose of 0.03 mg/kg i.v. to about 473 ng/ml after 1 mg/kg i.v. dose. (Table 8 below.)

As for electrophysiologic effects, carvedilol alone produced in the ECG dose-related increases in R-R and QT intervals consistent with the observed decrease in HR. When QT was corrected for the decrease in HR (increase in R-R interval), no change was reported in QTc interval (no dose related change in repolarization) for any dose of carvedilol. QRS duration and PR interval were also unaltered by carvedilol. Diltiazem alone caused increases in R-R and QT intervals while QRS duration was unchanged; when QT interval was corrected for the decrease in HR, there was no change in the QTc.

In these anesthetized dogs, combined administration of carvedilol and diltiazem resulted in dose-related prolongation in P-R, QT, R-R intervals were greater (simple additive) than those changes which occurred with either treatment alone. There was no dose-related change in QTc interval (or no dose-related change in repolarization time), considered by sponsor a demonstration of "the dependence of carvedilol-mediated change in repolarization on the level of heart rate." Changes which occurred in systemic BP, HR (and R-R interval) left ventricular systolic pressure and QT interval after combined carvedilol and diltiazem treatment were equivalent to the sum of the responses to the individual agents.

Carvedilol treatment alone produced no significant increase in PR interval while diltiazem alone increased PR interval (Figs. 28 and 29.) Combined treatment with carvedilol and diltiazem resulted in decreases in PR interval and left ventricular dP/dt which were greater than those changes which occurred with either treatment alone.

Sponsor suggests that the mechanism for the effects on PR interval and left ventricular dP/dT are most likely due to inhibition by carvedilol of reflex sympathetic nervous system activity.

Studies were conducted in a separate group of dogs treated with same doses of carvedilol (0.03 up to 1 mg/kg i.v.), while some dogs also received a continuous infusion of diltiazem (15µg/kg/min). Plasma analysis showed that equivalent plasma levels of carvedilol were achieved in both groups; diltiazem infusion did not affect the level of carvedilol in plasma. Peak plasma concentration of carvedilol was not determined. Drug plasma levels reported below were those present 10 min after termination of the infusion; these values represent plasma concentrations of carvedilol present at the time when hemodynamic measurements were made (Table 8).

FIGURE 8 Effect of carvedilol, diltiazem, and carvedilol + diltiazem on R-R interval and Q-T duration. *, p<0.05 from CONTROL value, a, p<0.05 from both Carvedilol and Diltiazem groups

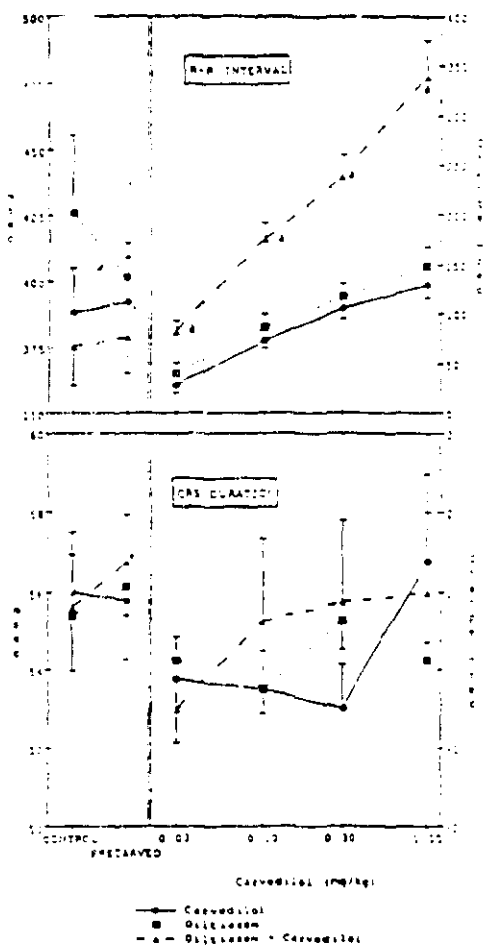


FIGURE 9 Effect of carvedilol, diltiazem, and carvedilol + diltiazem on PR interval. *, p<0.05 from CONTROL value, a, p<0.05 from Carvedilol group, b, p<0.05 from both Carvedilol and Diltiazem groups

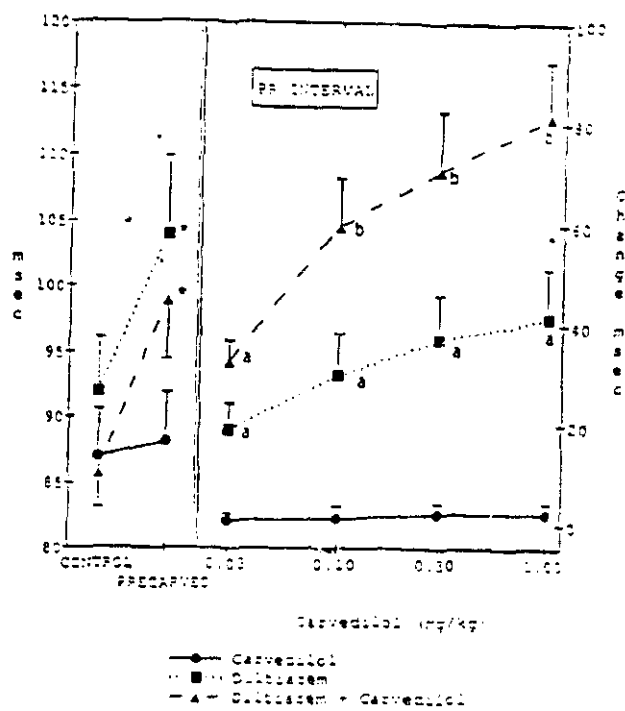


Table 8

Carvedilol plasma levels (In ng/ml)

Treatment	0.03	0.10	0.30	1.00
Carvedilol (n=4)	19.6±4.2	58.2±7.8	242.7±91.3	472.9±57.7
Carvedilol + Diltiazem (n=4)	16.1±2.9	57.8±9.5	210.6±33.0	681.2±76.8
Combined (n=8)	17.9±2.4	58.0±5.7	226.6±45.3	577.0±59.4

Values are mean±sem. There are no differences between the Carvedilol and Carvedilol + Diltiazem plasma concentrations by non-paired t test. Data were therefore combined

Some Effects on Peripheral Blood Flow of Some Organs

Several studies were reported in which single and repeated doses of carvedilol were injected in rat, rabbit and dogs to determine effects on peripheral organ blood flow. The data provided was difficult to interpret because poor copies were submitted, or poor study design. Therefore, only two studies are reported here in which the vasodilatory action of carvedilol is compared to standard vasodilators.

In anesthetized rabbits, constant volume injections of adenosine (at doses of 0.625 up to 20 ug) or carvedilol (0.625 up to 2.50 ug) caused reduction in peripheral vascular resistance (maximum fall in perfusion pressure was taken as the measure of vasodilation). The maximum fall in perfusion pressure for carvedilol and adenosine were reported as -38 mmHg for carvedilol (at the highest dose tested) and that -51 mmHg for 10 ug adenosine. Sponsor calculated that from the dosages of these drugs given in this study, the vasodilatory activity of carvedilol may be considered to be twice as great as that of adenosine.

The α - and β - blocking activities of carvedilol in vasculature of the hind limb of the anesthetized dog were investigated. In mongrel dog, carvedilol (1-30 ug i.a.) and standard drugs (propranolol, papaverine, isoproterenol) produced a dose-dependent increase in femoral artery blood flow (FAF) (Fig. 29a). The vasoconstriction produced by the α -agonist norepinephrine was not remarkably affected by carvedilol while the vasodilation produced by the β -agonist isoproterenol was completely inhibited by carvedilol (Fig. 29b).

Doses causing an increase in FAF by 50% of control values (ED_{50}) were as follows: carvedilol (4.1 mg), propranolol (68 μ g), papaverine (11 μ g). The relative potencies were calculated by: carvedilol, propranolol and papaverine = 2:7:1/62:1 (Figs. 30a and 30b next page).

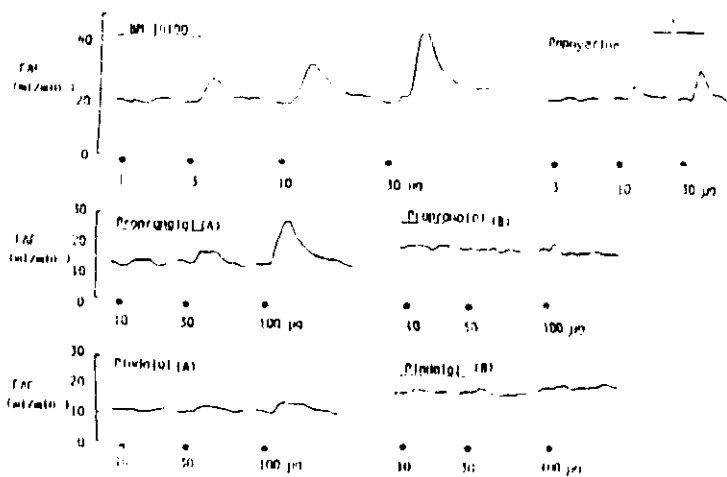


Fig. 29a Effects of carvedilol, propranolol, and papaverine on blood flow through the femoral artery (FAF) of the dog. The drugs were intravenously administered. Results after propranolol and papaverine in the last 18 and 30 sec. (mean).

0.01-0.06

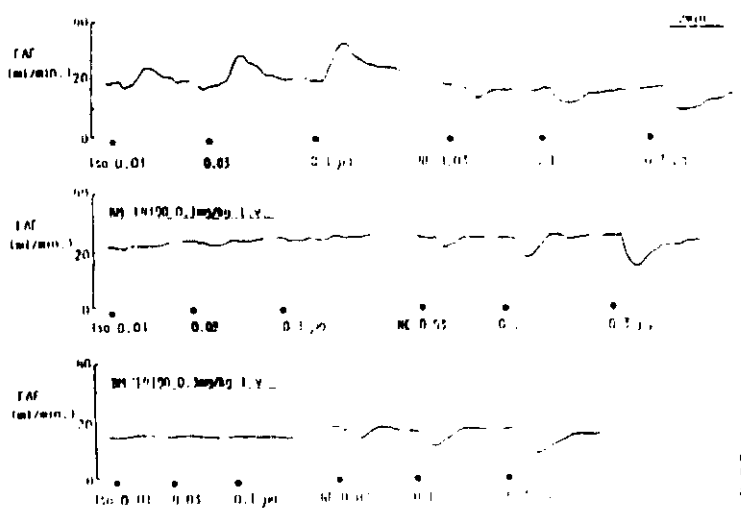
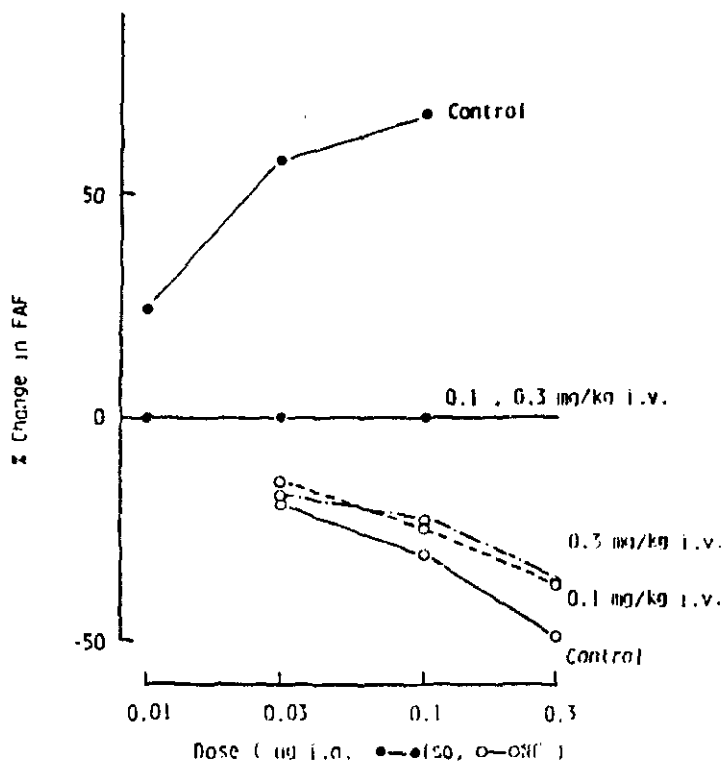


Fig. 29b Influence of carvedilol on vasodilator effect of isoproterenol. Also on vasoconstriction effect of norepinephrine (NE) in the anesthetized dog.

0.01-0.06



30a
 Fig. 4. Dose-response curves of isoproterenol (Iso) and norepinephrine (NE) for the change in FAF before (—) and after (----) administration of IM 15190 (n=2).

DE 4-07

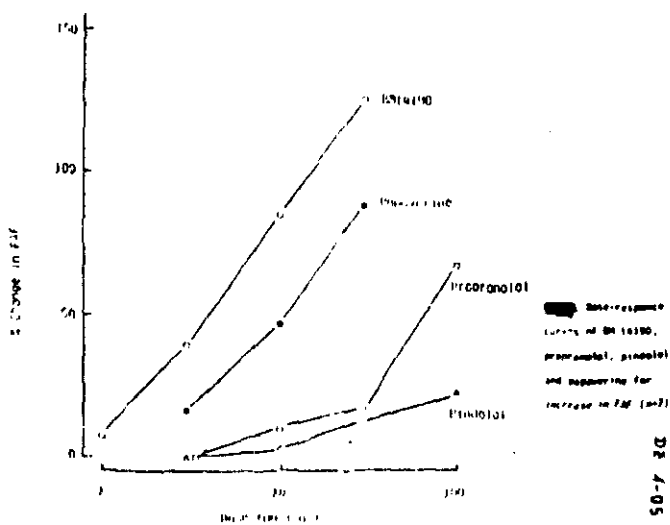


Fig. 30 b.

DE 4-05

SOME STUDIES TO ELUCIDATE MECHANISMS OF ACTION

1. To Test for Beta-adrenergic Receptor Blockade.

a) β_1 -Adrenoceptor blockade

In guinea pig atrium, carvedilol antagonized the β_1 -adrenoceptor mediated positive chronotropic effects of isoproterenol. Analysis of these data suggest that blockade of β_1 -adrenoceptors by carvedilol is considered competitive in nature. The pA_2 value (i.e., negative logarithm of the dissociation constant) for carvedilol is 9.03 ± 0.17 , corresponding an apparent dissociation constant (K_B) of 0.9 nM at β_1 -adrenoceptors (Fig. 31a).

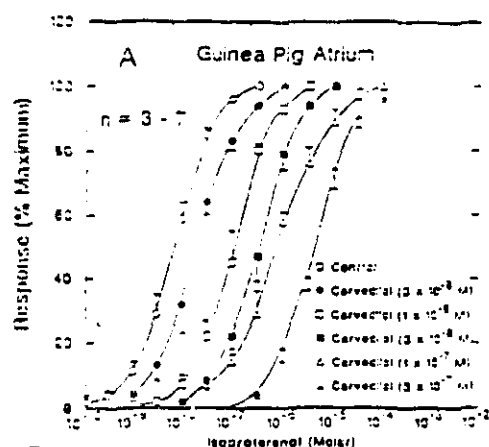


Fig. 31a

In pithed normotensive rats, carvedilol (0.3 mg/kg, i.v.) competitively inhibits the β_1 -adrenoceptor mediated positive chronotropic response to isoproterenol. This dose was associated with a significant reduction in mean arterial BP and inhibition of the chronotropic response of isoproterenol (approximately 100-fold), demonstrating α_1 -adrenoceptor blockade *in vivo* at antihypertensive doses (Fig. 31b).

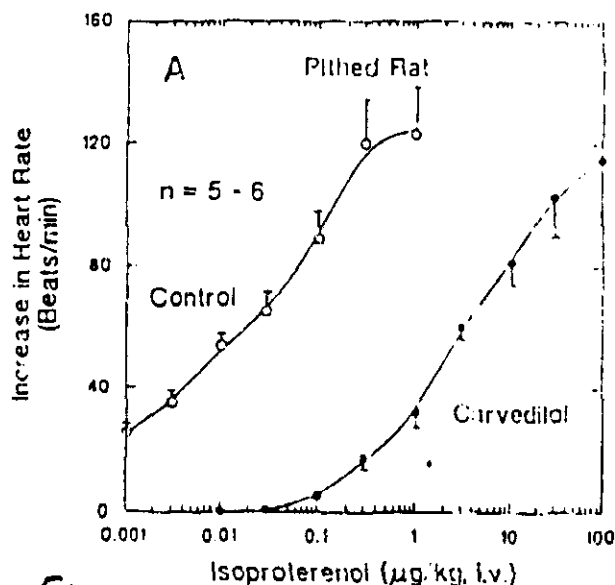


Fig. 31b

b) β_2 -Adrenoceptor Blockade

Carvedilol produces a concentration-dependent inhibition of the β_2 -adrenoceptor mediated relaxation induced by isoproterenol in guinea pig trachea. The antagonism of isoproterenol by carvedilol is considered competitive in nature and suggests a nonselective β -adrenergic antagonism. (Fig. 32a).

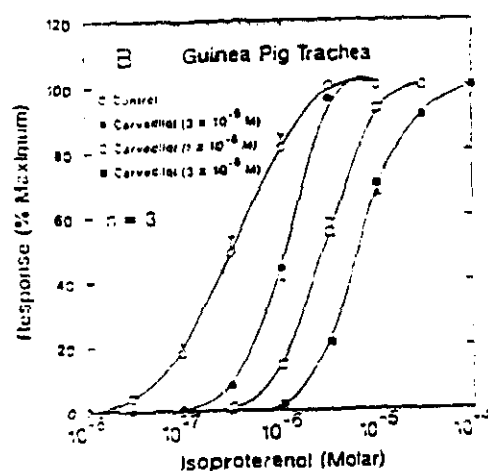


Figure 32a. The β_2 -adrenoceptor antagonist activity of carvedilol against (A) β_1 -adrenoceptors in the guinea pig atrium and (B) against β_2 -adrenoceptors in the guinea pig trachea.

In the pithed rat, the same dose of carvedilol significantly inhibited the β_2 -adrenoceptor mediated vasodilator response of salbutamol (a selective β_2 -agonist used as a bronchodilator), confirming the β_2 -adrenoceptor blocking activity of the drug *in vivo*. The degree of inhibition of the salbutamol effect was slightly less than that observed for β_1 -adrenoceptors in the pithed rat, indicating that carvedilol blocks both β_1 - and β_2 -adrenoceptors *in vivo* with selectivity for beta-1 adrenoceptors (Fig. 32b).

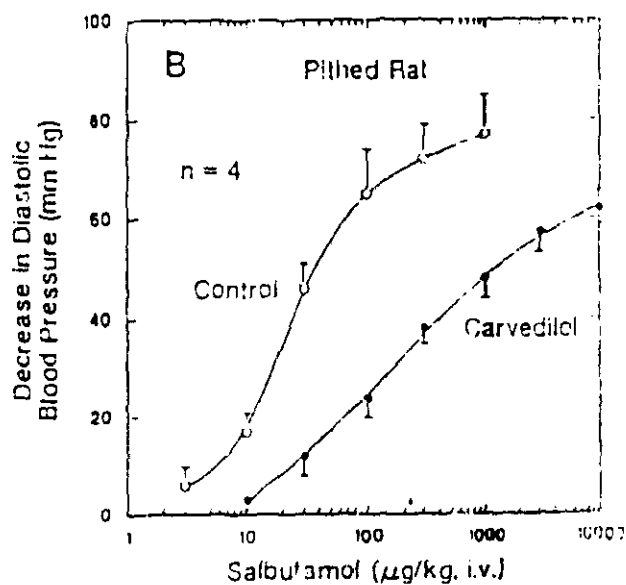


Fig. 32b.

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2. To Test for Alpha-adrenergic Receptor Blockade.

a) α_1 -Adrenoceptor Blockade

Carvedilol is a competitive antagonist of α_1 -adrenoceptors *in vivo* and *in vitro*. In isolated rabbit aorta, the α_1 -adrenoceptor mediated vasoconstrictor effects of norepinephrine are antagonized in a competitive manner with a pA₂ value of 7.97 ± 0.11 , which corresponds to an apparent K_B of 11 nM at α_1 -adrenoceptors. These results indicate that carvedilol is about 10-fold less potent as an α_1 -adrenoceptor antagonist than as a β_1 - or β_2 -adrenoceptor antagonist (Fig. 33).

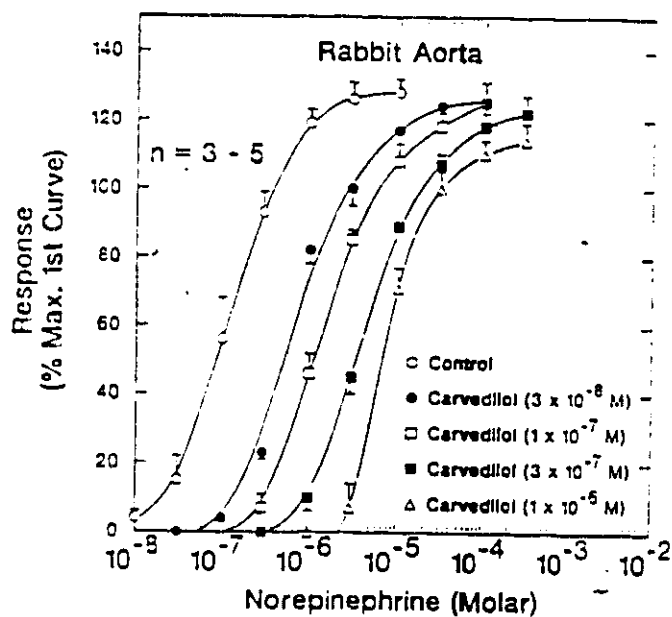


Figure 33 The α_1 -adrenoceptor antagonist activity of carvedilol in rabbit aorta.

b) α_2 -Adrenoceptor Blockade

Carvedilol ($1 \mu\text{M}$) inhibits the α_2 -adrenoceptor mediated vasoconstrictor response of B-HT 920 (an α_2 -adrenoceptor agonist) in the isolated canine saphenous vein. However, this inhibition is noncompetitive, suggesting that carvedilol may inhibit some other component of the α_2 -adrenoceptor effector system (Fig. 34 below).

Electrically stimulated isolated vas deferens of the rat showed that carvedilol had almost no α_2 -adrenoceptor blocking properties.

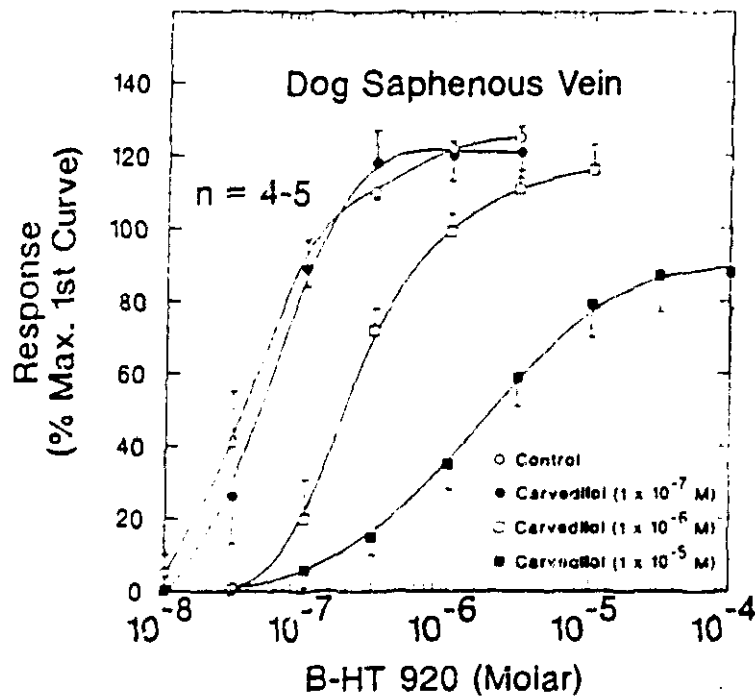


Figure 34. The effect of carvedilol on the contractile response to B-HT 920 in the canine saphenous vein.

3. Test for Calcium Channel Blocking Activity

Sponsor asserts that α_2 -adrenoceptor mediated vasoconstriction in the dog saphenous vein is dependent upon the translocation of extracellular calcium. Since no compelling evidence exists to suggest that carvedilol interacts competitively with α_2 -adrenoceptors, sponsor hypothesized that carvedilol may have calcium channel blocker activity.

A series of experiments were performed to elucidate whether or not there is a calcium channel antagonist effect of the drug. Depolarization of the rat uterus by KCl (70 μ M) produces a nifedipine-sensitive contractile response which results from opening of calcium channels. In this KCl precontracted rat uterus, carvedilol produced a concentration-dependent relaxation with an ED₅₀ of 7.65 $\pm$ 0.62 μ M, consistent with the notion of that of calcium channel blockade (Fig. 35a).

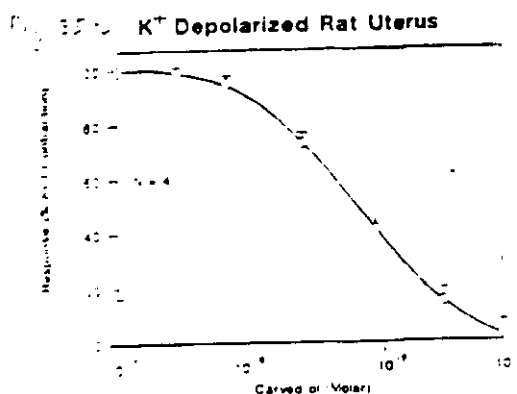


Figure 35a. Dose-response curve for the relaxant effect of carvedilol on K⁺ depolarized rat uterus.

Support for the above results were obtained with the potassium-depolarized rabbit aorta. In rabbit aorta incubated with calcium-free buffer, and subsequently depolarized with KCl (70 mM), a response to exogenously administered calcium can be observed that is sensitive to inhibition by calcium channel blockers. Carvedilol, at concentrations from about 1 μ M, and above, significantly inhibits (parallel shift to the right), the concentration-response curve of calcium-induced contractile response in this tissue (Fig. 35b).

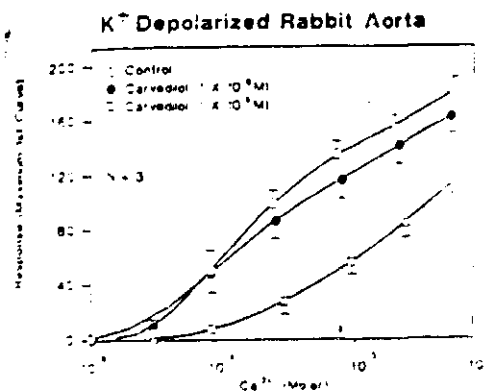


Figure 35b. Effect of carvedilol on the concentration-response curve of calcium-induced contractile response in K⁺ depolarized rabbit aorta.

The apparent calcium channel blocking activity of carvedilol was also seen *in vivo*. In the pithed rat, the direct calcium channel activator, Bay K-8644, produces a dose-dependent vasoconstrictor response that is inhibited by calcium channel antagonists. Carvedilol, at a dose of 1 mg/kg, i.v., which represents the higher portion of the antihypertensive dose-response curve, significantly inhibits the vasoconstrictor response of Bay K-8644, thereby suggesting that *in vivo* carvedilol has some calcium channel antagonist activity (Fig. 36).

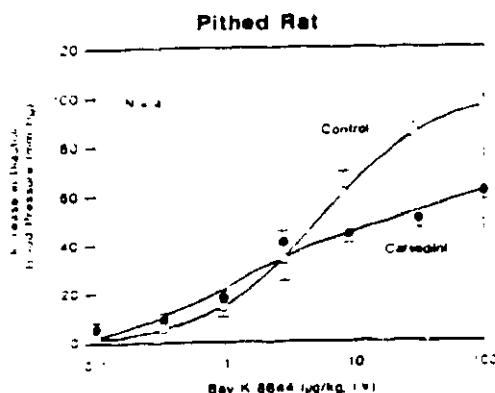


Fig. 36 The effect of carvedilol on the vasoconstrictor response of Bay K-8644 in the pithed rat.

Sponsor considers that studies do not demonstrate a prominent role for this calcium channel antagonistic activity in the overall antihypertensive response of the carvedilol. This is observed in SHR pretreated with propranolol and prazosin to block β - and α_1 -adrenoceptors, respectively, carvedilol does not produce an additional reduction in blood pressure, whereas the potent calcium channel antagonist, nifedipine, still does. The calcium channel blocking activity of carvedilol may be of importance in increasing blood flow in specific regional vascular beds that are highly sensitive to calcium channel antagonists, such as the cutaneous circulation. Sponsor states that the effectiveness of calcium channel blockers in the treatment of peripheral vascular disease suggests the involvement of extracellular calcium in the regulation of cutaneous blood flow.

To determine whether the calcium channel blocking activity of carvedilol, or some other unidentified activity, is relevant to pharmacologic action of the drug, carvedilol was compared to labetalol (a drug with combined β - and α_1 -adrenoceptor antagonist properties), on cutaneous circulation.

At doses of carvedilol and labetalol that produce equivalent reductions in mean arterial BP and HR, labetalol significantly reduced cutaneous blood flow by over 20% with no change in cutaneous vascular resistance being observed. In contrast, carvedilol increased cutaneous blood flow by over 60%, and this effect resulted from a reduction in cutaneous vascular resistance. Because the cutaneous circulation is highly sensitive to calcium channel

antagonists, sponsor speculated that the decrease in cutaneous vascular resistance produced by carvedilol (but not labetalol), results from calcium channel blockade.

The table below was prepared by sponsor summarizing the an overall adrenergic receptor activity profile of carvedilol.

ADRENERGIC RECEPTOR SELECTIVITY OF CARVEDILOL

RECEPTOR	TISSUE	K _B or K _i (nM)
β	Guinea Pig Ventricle ([³ H]DHA)	1.5
β ₁	Guinea Pig Atrium	0.8
		5.8
		0.9
		1.0
	Right	1.8
	Left	2.2
		0.4*
		45+
	Rat Atrium	0.3
	Right	0.9
Left	2.0	
β ₂	Guinea Pig Trachea	1.3
		37
		1.2
α ₁	Rabbit Aorta	10
		6.3
		56
		16*
		14+
	Rat Aorta	0.6
	Guinea Pig Aorta	10
	Rat Vas Deferens	20
Rat Cortex ([³ H]-Prazosin)	9.4	
α ₂	Canine Saphenous Vein	100
	Rat Vas Deferens	10,000

* Data obtained with S(-)Carvedilol

+ Data obtained with R(+)Carvedilol

BRIEF OVERVIEW OF NONCLINICAL RENAL EFFECTS

In conscious SHR, intragastric (i.g.) administration of carvedilol (10 mg/kg) is associated with dose-dependent antihypertensive activity. The hypotension is rapid in onset, lasting 4-8 hrs depending on the dose: the maximal decreases in BP exceeded 35 mm Hg (Fig 37a). Repeated administration of the drug over 3 days is not associated with tachyphylaxis. No synergistic effect was noted with low (hydrochlorothiazide 50 mg/kg i.g.) or high ceiling (furosemide) diuretics (Fig. 38b).

In these rats, administration of carvedilol or labetalol was associated with reductions in urine volume and urinary electrolyte, urea and creatinine excretion rates when given alone or in association with diuretics. Sponsor considers these effects are due to reductions in renal perfusion pressure associated with the antihypertensive activities of these agents and combinations.

FIGURE 37a. CARVEDILOL DOSE RESPONSE. (MMV)

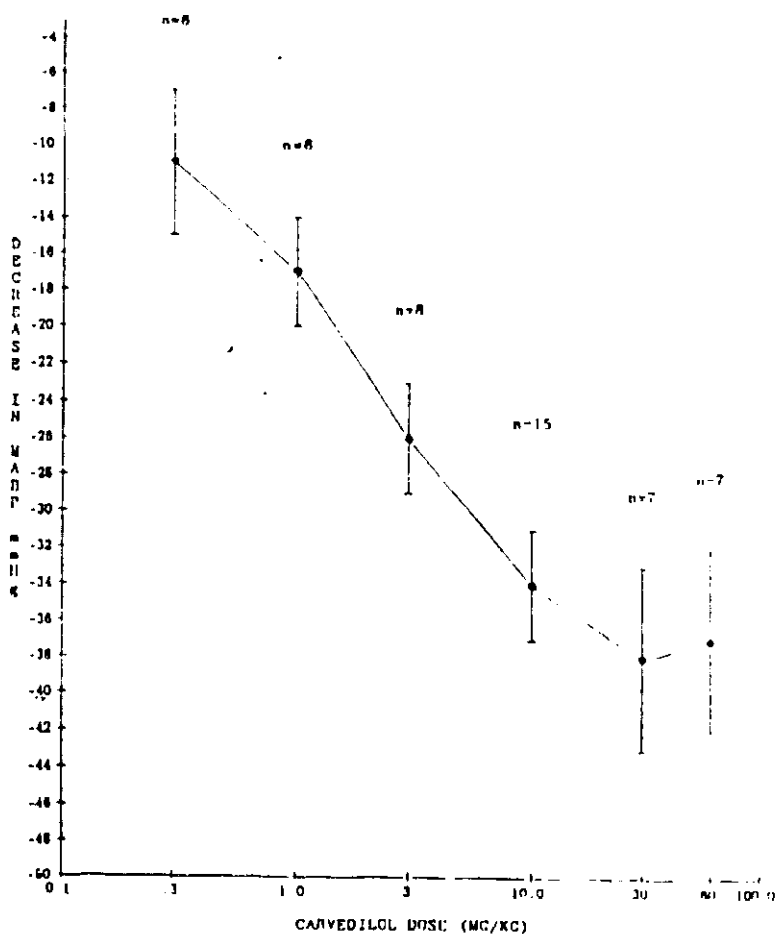
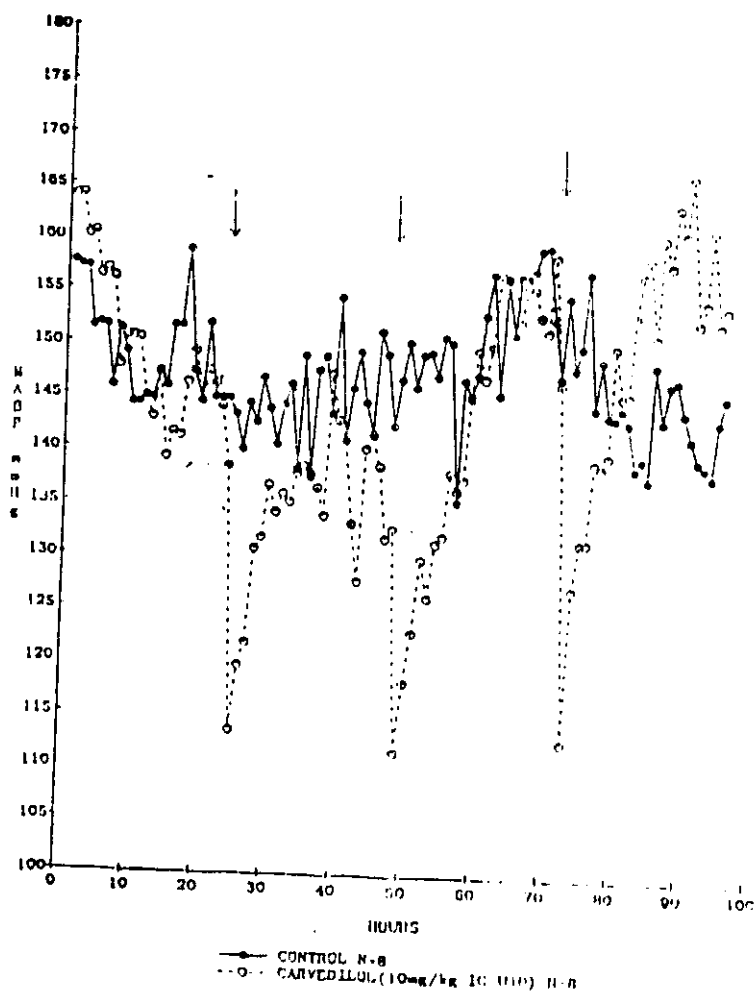


FIGURE 37b. EFFECT OF CARVEDILOL ON MEAN ARTERIAL BLOOD PRESSURE IN SHR. (MMV)



In SHR and normotensive WKY rats, the effects of carvedilol on renal hemodynamics and excretory functions were compared to those of labetalol. In conscious SHR, dose-dependent decreases of BP were recorded when carvedilol was given as i.v. bolus, sustained i.v. infusion (10 $\mu\text{g}/\text{kg}$ min for 80 min). Cardiac performance remained unchanged, thus the hypotensive effect was considered due to a decrease of systemic vascular resistance (VR) (Fig. 38b). In SHR, regardless of the route of administration, carvedilol and labetalol were equipotent in lowering the BP of SHR (Fig. 38a).

Renal VR (calculated as MAP/ERBF^*) was also decreased by carvedilol in both strains of rats and with labetalol in the SHR (only group studied.) A 14% decrease in GFR was observed with carvedilol in WKY and with labetalol in SHR. In the SHR, autoregulation of GFR and renal blood flow was maintained during carvedilol infusion (Fig. 38c). Fall in BP was associated with a decrease in urine excretion, electrolytes and urea, with the exception NA^+ excretion which was unchanged in the SHR receiving carvedilol. Inasmuch as carvedilol reduces BP while maintaining renal blood flow, GFR and sodium excretion in SHR, sponsor suggests that carvedilol possesses renal sparing effect (Table 9 below).

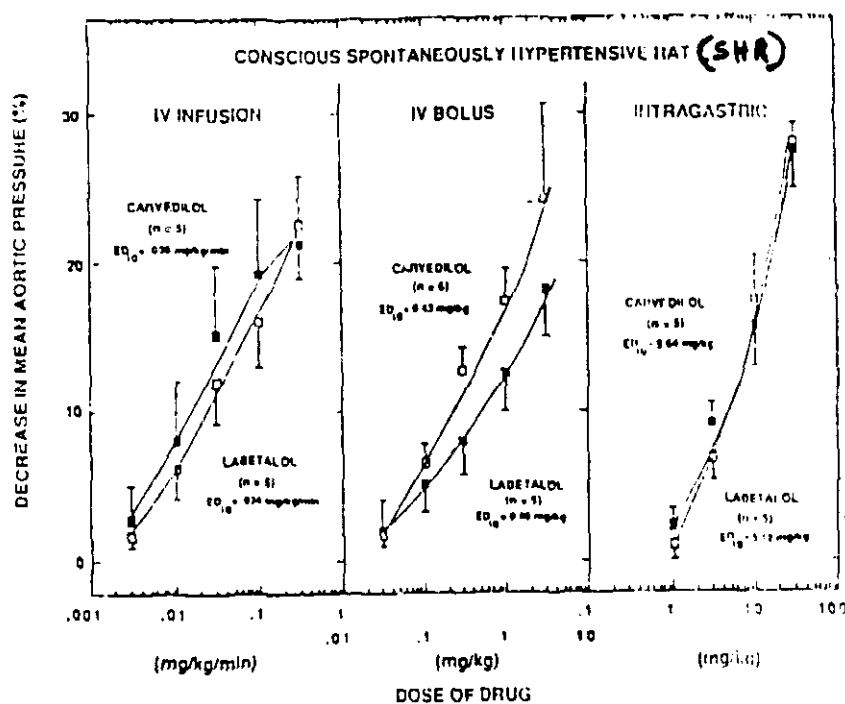


Figure 39a. Dose-response curves for the depressor effects of carvedilol (open squares) and labetalol (solid squares) in conscious spontaneously hypertensive rats. ED₅₀ denotes 50% decrease in blood pressure.

*Effective Renal Blood Flow

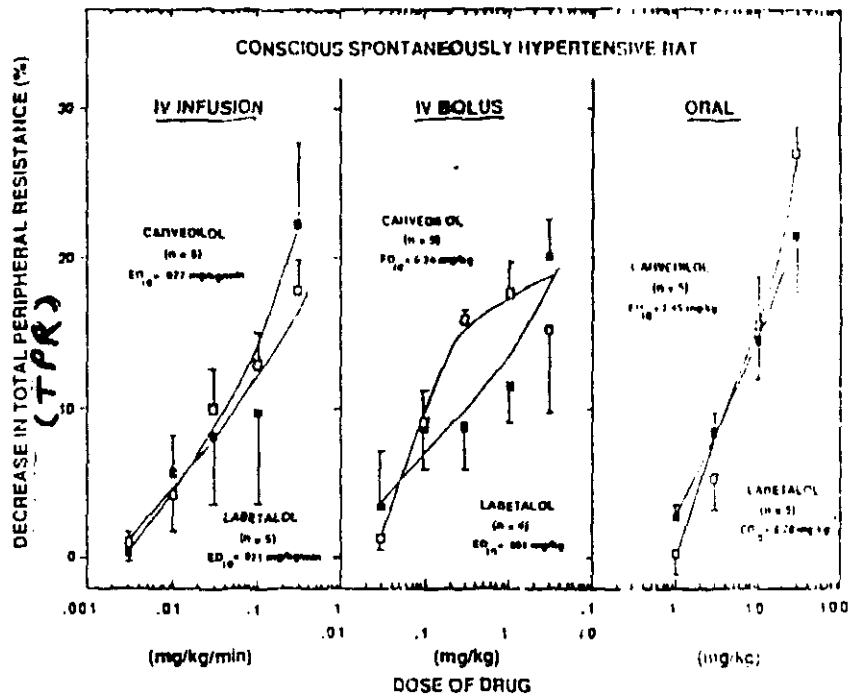


Figure 38. Effects of carvedilol (open squares) and labetalol (solid squares) on systemic peripheral resistance in conscious spontaneously hypertensive rats.

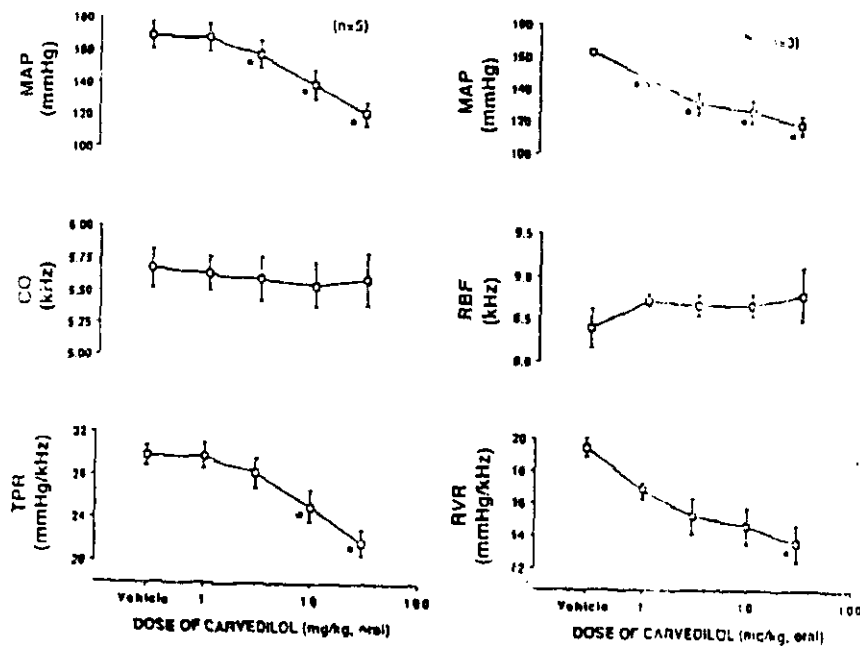


Figure 38C. Comparison of systemic and renal hemodynamic effects of orally administered carvedilol in conscious spontaneously hypertensive rats. Symbols and bars represent means $\pm$ SEM of maximum changes following drug administration. *Significantly different from vehicle-induced changes.

TABLE 4
Summary of Renal Effects of Carvedilol and Labetalol

	CARVEDILOL				LABETALOL	
	WKY (n=5)		SHR (n=6)		SHR (n=6)	
	Control	Exptl.	Control	Exptl.	Control	Exptl.
A. Renal Hemodynamics						
MAP (mm Hg)	113 ± 2.4	98 ± 2.8*	176 ± 5.3	160 ± 4.7*	176 ± 3.9	157 ± 3.0*
GFR (ml/min·100g)	731 ± 58	628 ± 39*	647 ± 90	636 ± 93	772 ± 32	673 ± 28*
ERBF (μl/min·100g)	5366 ± 488	5490 ± 437	4211 ± 404	4372 ± 387	4817 ± 223	4765 ± 219
RVR (MAP/ERBF)	21.0 ± 2.4	17.3 ± 1.4*	42.3 ± 3.6	36.5 ± 2.7*	36.1 ± 1.9	32.4 ± 1.4*
FF (%)	23.9 ± 2.2	19.9 ± 2.2*	28.5 ± 3.9	26.6 ± 4.8	28.1 ± 1.1	24.8 ± 1.2*
B. Handling of Electrolytes and Urea						
Urine flow (μl/min·100g)	33.3 ± 7.6	20.8 ± 3.6*	9.5 ± 1.8	5.5 ± 0.9*	11.8 ± 1.2	5.04 ± 0.7*
V·U _{Na} (μEq/min·100g)	0.45 ± 0.11	0.19 ± 0.06*	0.92 ± 0.18	0.95 ± 0.25	.98 ± 0.14	0.54 ± 0.12*
C _{Na} /C _{in} (%)	0.46 ± 0.12	0.22 ± 0.07*	1.01 ± 0.16	1.24 ± 0.36	0.88 ± 0.18	0.55 ± 0.12*
V·U _K (μEq/min·100g)	1.16 ± 0.22	0.73 ± 0.09*	0.98 ± 0.08	0.72 ± 0.05	1.09 ± 0.11	0.66 ± 0.04*
C _K /C _{in} (%)	40.3 ± 6.7	31.5 ± 4.76*	41.7 ± 7.19	34.3 ± 5.6*	37.18 ± 5.5	27.33 ± 2.54*
V·U _{urea} (μmoles/min·100g)	3.44 ± 0.32	2.09 ± 0.11*	3.16 ± 0.19	2.39 ± 0.21*	3.72 ± 0.16	2.34 ± 0.12*

Values listed under "control" are the means ± SEM of two control clearance periods; those under "Exptl." are the means ± SE of two 30 min measurements during infusion of carvedilol. MAP, mean aortic pressure; GFR, glomerular filtration rate; ERBF, effective renal blood flow; FF, filtration fraction; U_{osm}, urine osmolality; V·U_X, excretion of X; C_X/C_{in}, fractional excretion of X. *significantly different from control (p<0.05).

In female beagles, carvedilol administered as an oral suspension at doses of 1, 3, 10 and 30 mg/kg caused a decrease only on the volume of urine excreted up to 2 hrs after drug administration. Electrolyte excretion was not affected. The oral "no-effect" dose in these dogs was 1 mg/kg. In this study, carvedilol 3 mg/kg, p.o. and above, the dogs showed a dose-dependent relaxation of the nictitating membrane demonstrating postganglionic α_1 -adrenergic blockade and not ganglionic blockade. The absence of ganglionic blocking effect was also demonstrated in anesthetized cats in which carvedilol reduced the contraction of the nictitating membrane brought on by pre- and postganglionic stimulation of the cervical sympathetic ganglia.

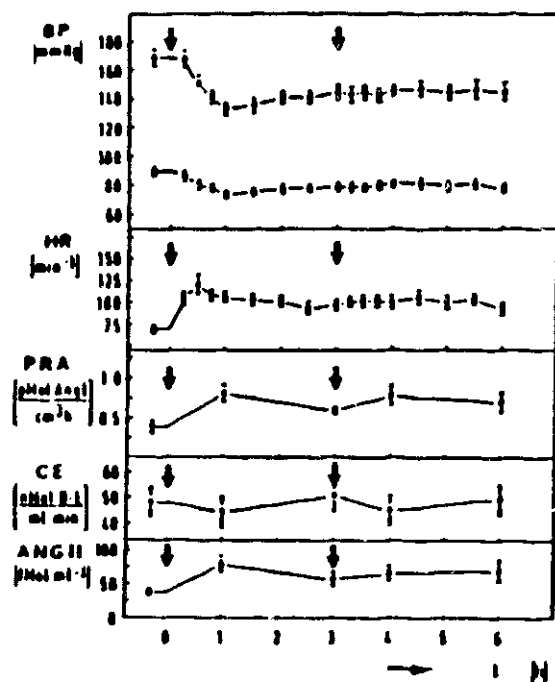
In beagles, carvedilol (6 mg/kg, p.o.) given as a suspension for 5 days, was associated with an increase in HR, slight increase in plasma-renin activity and plasma-angiotensin II concentration on the first day only. By the 5th day, BP was clearly lowered and increase in HR was only slightly detectable. These findings suggest that counter-regulatory mechanisms (increased HR, stimulation of renin-angiotensin system) were only activated during the acute phase of the study and that the ACE-inhibition is not involved in the antihypertensive effect of the drug (Fig. 39, next page.)

Studies reported in the dog show that in spite of reductions in mean arterial BP with carvedilol, the drug increased renal blood flow indicating renal vasodilatation while glomerular filtration rate urine flow, Na^+ and K^+ urinary excretion and venous plasma-renin activity were unaffected.

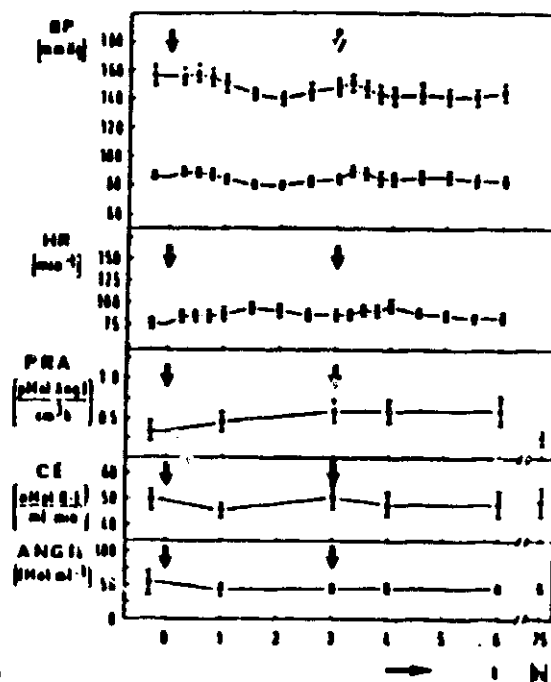
Beagles

Fig. 39 Responses of arterial blood pressure (BP), heart rate (HR), and renin-angiotensin system to oral administration of different vasodilating drugs. The arrows indicate the drug administration. PRA = plasma renin activity; ANG II = plasma angiotensin II concentration; CE = converting-enzyme-activity

carvedilol: 6 mg/kg



1st day



5th day

SOME STUDIES TO TEST FOR POTENTIAL ORGAN PROTECTIVE EFFECTS

Cardioprotection in Experimental Models of Myocardial Infarction

Sponsor states that many marketed β -blockers (except those with intrinsic sympathomimetic activity) possess cardioprotective properties. Sponsor indicates that it is commonly accepted that cardioprotection provided by β -blockers may result of improvement in the balance between myocardial oxygen supply/demand by reducing myocardial work (secondary to reductions in HR and myocardial contractility.)

The literature reports that HR reduction is required for infarct size limitation. (Kjekshus JK: Am J Cardiology 57: 43F, 1986.) Since the hypotensive activity of carvedilol occurs without reflex tachycardia (due to β -blockade), sponsor investigated the potential cardioprotective action of the drug in several different models of myocardial infarction. Four experimental models of acute myocardial infarction in 3 animals species (rat, dog and minipig) were described in the NDA.

Briefly, in anesthetized rat, the left main coronary artery was ligated for 30 min and then reperfused for 24 hours. Carvedilol (0.3 or 1 mg/kg i.v.) or vehicle was administered 15 min before acute ischemia and again 4 hours after the onset of reperfusion (post-ischemia) period. Twenty-four hours after reperfusion, the rats were killed, hearts removed, sliced, fixed and stained. The infarct size was then evaluated.

Compared to the vehicle treated rats, carvedilol (at 1 mg/kg) reduced the infarct size from $14.2 \pm 1.0\%$ to $7.5 \pm 1.0\%$ ($p < 0.01$) of the left ventricle mass. This protective effect of carvedilol was calculated by sponsor to represent 47% reduction of the infarct zone (Table 11). Although actual data was not submitted in this report, sponsor stated that in this rat model, propranolol showed no cardioprotective effect (Smith EF II, et al, "Effect of Propranolol on Ischemic Myocardial Damage and Left Ventricular Hypertrophy following Permanent Coronary Artery Occlusion or Occlusion Followed by Reperfusion" in Pharmacol 38: 298-309, 1989.)

Briefly, the left anterior descending (LAD) coronary artery of Yucatan minipigs were isolated. After a period of stabilization, bolus injections of carvedilol (0.3 and 1 mg/kg, i.v.), propranolol (1 mg/kg, i.v.) or vehicle were given to the animals. After 15 min the LAD was occluded with a microaneurysm clip for 45 min. When the clip was removed, reperfusion was maintained for 4 hrs. Following the reperfusion period, the hearts were removed, treated with buffer solutions, dyed, rinsed, sliced, photographed, weighed, infarcted areas identified and quantified. Pretreatment with carvedilol, produced a dose-dependent reduction in infarct size in the pig model of coronary artery occlusion. Compared to the vehicle treated control pigs, the two doses of carvedilol tested reduced dose-dependently the infarct size (46% and 89%, $p < 0.01$). The reduction in infarct size produced by carvedilol was greater than the reduction produced by propranolol at an equivalent β -adrenoceptor blocking dose (Table 1).

In anesthetized mongrel dogs subjected to 1 hr of transient myocardial ischemia by left circumflex coronary artery followed by 24 hr reperfusion, carvedilol (1 mg/kg i.v.) reduced the infarct size by 78% ($p < 0.05$), compared to a 64% reduction produced by propranolol. In a canine model of permanent LAD coronary artery occlusion (6 Hr), pretreatment with carvedilol (0.3 or 1 mg/kg i.v.) produced dose-dependent reductions in infarct size of 45% and 63%, respectively, compared to propranolol which did not reduce infarct size in this model (Table 11).

The following is a summary table of findings prepared by sponsor for the above studies.

Table 11

Cardioprotection by Carvedilol (1 mg/kg, i.v.) and Propranolol (1 mg/kg, i.v.) in Experimental Models of Acute Myocardial Infarction in Several Species

Species	Treatment with Carvedilol or Propranolol	Duration of Occlusion	Period of Reperfusion	Percent Reduction in Infarct Size ^a		Reference
				Propranolol	Carvedilol	
Rat	Pre-occlusion (15 min) and post-occlusion (4 hr)	30 min	24 hr	NE ^b	47 ± 12% ^c	68
Pig	Pre-occlusion (15 min)	45 min	4 hr	49 ± 17% ^c	90 ± 6% ^{c,d}	68
Dog	Pre-occlusion (15 min)	60 min	24 hr	64 ± 10% ^c	78 ± 8% ^c	68
Dog	Post-occlusion (15 min)	360 min	None	20 ± 10%	63 ± 9% ^{c,d}	68

^aCompared to vehicle control

NE: Not Estimated.

^bPropranolol has been shown to have no effect on infarct size in the rat model of acute myocardial infarction (Ref. 68)

^c $p < 0.05$ vs vehicle

^d $p < 0.05$ vs propranolol

Sponsor reports that abnormal cell growth and proliferation of vascular smooth muscle play a fundamental role in advancing lesions of atherosclerosis in hypertensive patients and experimental animals*.

Studies submitted show that carvedilol produced anti-mitogenic effects against a diverse group of vascular smooth muscle mitogens (e.g., endothelin-1, epidermal growth factor, platelet-derived growth factor A/B, etc.)

Carvedilol (at 10^{-7} to 10^{-5} M) inhibited dose-dependently both basal (control) and endothelin-1-stimulated [^{3} H]thymidine incorporation (measure of DNA synthesis) in rat aortic vascular smooth muscle cultured cells. The IC_{50} for inhibition of [^{3} H]thymidine incorporation by carvedilol was about 1 μ M (Figs. 40a, 40b, and 40c). This inhibitory effect is not considered by sponsor to be due to a cytotoxic effect of carvedilol.

Carvedilol (1-10 μ M) also produced significant concentration-dependent inhibition of the mitogenic response mediated by endothelin-1, angiotensin II, EGF, PDGF_{AB}, TGF α and thrombin. Although PDGF_{AB}-induced rat aortic vascular smooth muscle cell mitogenesis, this was not significantly reduced by 1 μ M carvedilol, however, mitogenesis was inhibited by higher doses of the drug (10 μ M) (Fig. 40d).

This anti-mitogenic effect of carvedilol on rat aortic vascular smooth muscle was not shared by other β -adrenoceptor antagonists. At equimolar concentrations only carvedilol and propranol (non-selective β -adrenoceptor antagonist) inhibited both basal (Fig. 40e) and endothelin 1-stimulated (Fig 40f) mitogenesis. Labetalol (α -1, β 1-, β 2- adrenoceptor antagonist) and sotalol (non-selective β -adrenoceptor antagonist) did not affect either basal or endothelin-1 stimulated mitogenesis in this preparation.

Nifedipine did not significantly affect basal [^{3} H]thymidine incorporation in rat vascular smooth muscle cells (Fig. 7a). Nifedipine (1 μ M) did inhibit endothelin-1-mediated muscle cell mitogenesis by about 36% and at a higher concentration (10 μ M) nifedipine inhibited both basal and endothelin-1- stimulated mitogenesis about 58% and 72%, respectively (Figs. 40g and 40h).

Since carvedilol produced an antimitogenic effect against a diverse group of vascular smooth muscle mitogens, the mechanism of this action is not clear. This relatively high-concentration effect does not appear to be mediated simply through α - or β -adrenoceptor antagonism or calcium channel blockade.

*Ross, R. and Glomset JA, "The Pathogenesis of Atherosclerosis" in NEJM 295: 369, 1976

Ross, R. "The Pathogenesis of Atherosclerosis- An Update" in NEJM 314: 488, 1986.

CARVEDILOL AND VASCULAR PROLIFERATION INDUCED BY MITOGENS

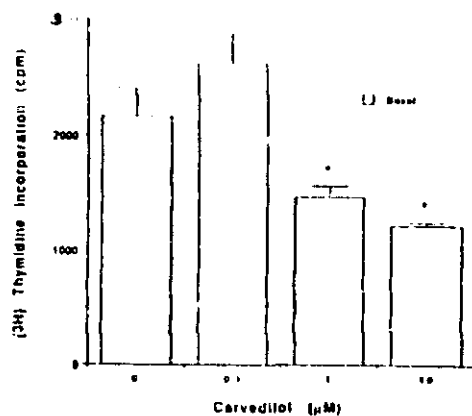


Figure 2

Figure 2. Effect of carvedilol on unstimulated (basal) rat aortic vascular smooth muscle cell proliferation. A typical experiment with triplicate determination. The basal $[^3\text{H}]$ thymidine incorporation was 2159 ± 344 cpm.

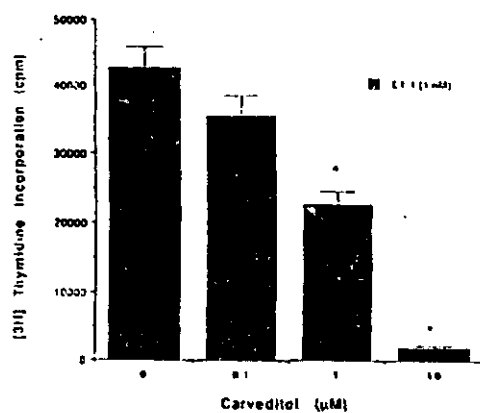


Figure 4. Effect of carvedilol on endothelin-1-stimulated rat aortic vascular smooth muscle cell proliferation. A typical experiment with triplicate determination. ET-1-stimulated $[^3\text{H}]$ thymidine incorporation was 42652 ± 3307 cpm.

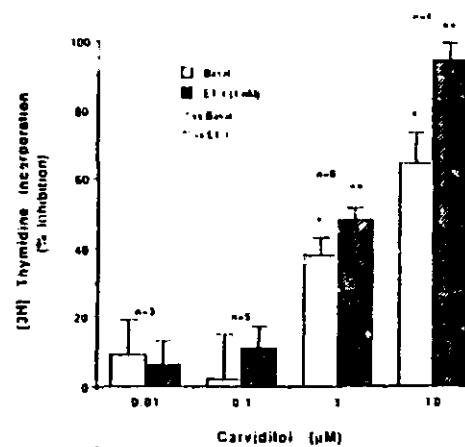


Figure 4b. The percent inhibition of basal and endothelin-1-stimulated vascular smooth muscle cell proliferation. Data are from 3-8 experiments with triplicate determinations in each experiment.

CARVEDILOL AND VASCULAR PROLIFERATION INDUCED BY MITOGEN (Cont a.)

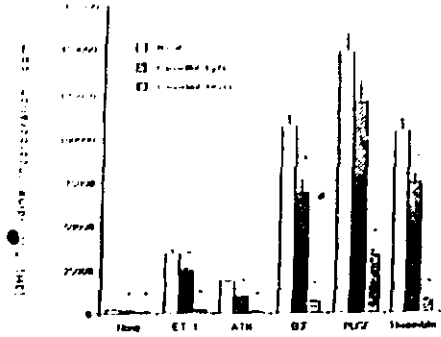


Figure 40d

Effect of carvedilol on different mitogen-stimulated rat aortic vascular smooth muscle cell proliferation. Quiescent rat aortic vascular smooth muscle cells were treated with and without mitogen in the absence and presence of 1- 10 μM carvedilol for 24 hr. The concentrations of mitogen used was predetermined to give maximal mitogenic effect on rat aortic vascular smooth muscle cells : endothelin-1 (1 nM), PDGF A/B (1 nM), EGF(1 nM); TGFα (2 nM); AII (5 nM); thrombin (0.5 U/ml). The results were from three experiments with triplicate determinations in each experiment

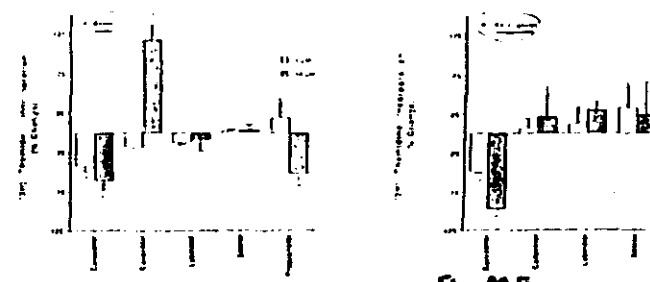


Fig. 40f

Effects of various β-adrenoceptor antagonists on the mitogenesis of endothelin-stimulated rat aortic vascular smooth muscle cells. Quiescent rat aortic vascular smooth muscle cells were pretreated with β-blocker for 10 min followed by the addition of A medium (basal), or B endothelin-1 (1 nM) for additional 24 hr incubation. ³H-thymidine incorporation into TCA insoluble fraction was determined as described in the Method. Data was expressed as % change ± SEM from corresponding controls

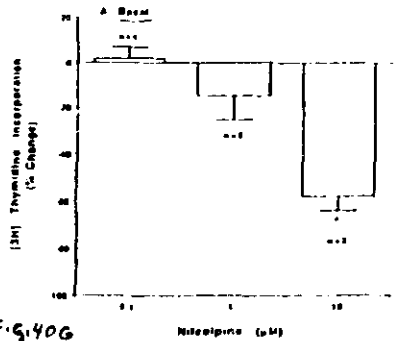


Fig. 40g

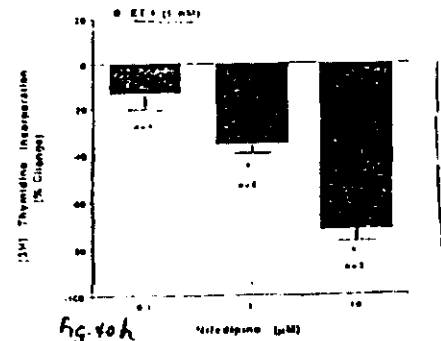


Fig. 40h

Effect of nifedipine on basal and endothelin-1-stimulated mitogenesis of vascular smooth muscle cells. Quiescent rat aortic vascular smooth muscle cells were pretreated with nifedipine for 10 min followed by the addition of A medium (basal), or B endothelin-1 (1 nM) for additional 24 hr incubation. Data was expressed as % change ± SEM from corresponding control from 3-5 experiments with triplicate determinations in each experiment.

Experimental Stroke Studies

Stroke-prone (SP) strain of SHR are inbred to develop/exhibit severe hypertension and very high (80%) incidence of strokes. Sponsor reports that the strokes are considered to be similar to human strokes. SHR-SP were fed a high salt (8%) diet containing carvedilol for 94 days. The drug concentrations administered in diet were 300 ppm for 50 days and raised to 600 ppm for the remaining last 44 days of study. The mean daily intake of carvedilol was reported as 19.5 mg/kg/day at the lower dose (300 ppm) and 46.2 mg/kg/day at the high (600 ppm) in diet.

All carvedilol treated AHR-SP survived the study while 20.8% (5) of the controls died. Compared to controls, the carvedilol treated rats did not differ in their systolic blood pressure, food intake, body weight or motor/neurologic status except for a decreased heart rate. Blood analyses indicated that compared to the controls, the carvedilol treated rats had a significantly higher plasma levels of potassium and alkaline-phosphatase and potassium. Significantly lower mean blood cell volume, glucose, gamma glutamyl transferase, total bilirubin and triglycerides were also reported in drug treated animals.

In a separate group of SHR-SP fed same carvedilol diets, the blood levels of the drug were about 133.9 ng/ml and about 1507 ng/ml for the 300 ppm and 600 ppm carvedilol treatment.

The Table 12 below, prepared by sponsor, summarizes significant changes associated with the treatment of carvedilol.

Table 12

Summary of Significant Differences Observed in Blood Studies Between Carvedilol Treated Rats and Control Rats

Major Changes

- Blood Lipids
 - Triglycerides significantly lower in carvedilol fed rats as compared to the controls

Minor Changes

- Blood Chemistry
 - Potassium significantly higher in carvedilol fed rats as compared to the controls
 - Alkaline Phosphatase significantly higher than controls
 - MCV significantly lower than controls
 - Glucose significantly lower than controls
 - Gamma Glutamyl transferase significantly lower than controls
- Liver Function
 - Total bilirubin significantly lower than controls
 - Direct bilirubin significantly lower than controls

Neuroprotective Properties of Carvedilol

Sponsor states that brain ischemia is known to be accompanied by lipid peroxidation following oxygen free radical formation.* Further, that free radical formation may mediate part of the ischemic neuronal damage caused by the excitatory amino acid glutamate.

Sponsor cites investigations (unpublished reports) that claim that carvedilol is an inhibitor of lipid peroxidation in swine heart** and rat*** brain homogenate exposed to different free-radical generating systems. Thus, the neuroprotective potential of carvedilol (oxygen free radical scavenging) was also tested in an *in vitro* model of cultured rat cerebral neurons (exposed to glutamate or an oxygen free radical generating system) and, in an *in vivo* model of global forebrain ischemic stroke in Mongolian gerbils induced by a 6 min bilateral carotid artery occlusion and 7 days reperfusion. These methodologies are fully reported in the NDA. Neuroprotective mechanism or prevention of lipid peroxidation was determined by measuring the formation of thiobarbituric acid-reactive substances (TBARS).

Briefly, results reported suggested that carvedilol ($IC_{50} = 1.1 \mu M$) protected rat cerebral granule cells against glutamate-mediated neuronal death (Fig. 41 below). To determine if the apparent neuroprotection was due to an oxygen free radical scavenging property by carvedilol, neurons were exposed for 60 min to an hydroxyl radical generating system- DHF- Fe^{3+} /ADP. Cell mortality (in this study >95%) was assessed by staining with fluorescein diacetate dye. In this study, the time required for 50% cell killing time (ET_{50}) with this hydroxyl radical generating system was reported to be 25.3 min. By incubating the neurons with $10 \mu M$ carvedilol 15 min prior to the addition of DHF- Fe^{3+} /ADP system, there was evidence of protection with an increased ET_{50} to 42.7 min. Despite the 17 min protection time, this neuroprotection by carvedilol was not total because when the exposure time to DHF- Fe^{3+} /ADP was reduced from 60 min to 20 min in the presence of glucose (considered the primary substrate in brain), cells were also resistant to damage from free radicals for at least 4 hrs (Fig. 42). Cell mortality was nearly complete at 50 min after replacement of the free radical generating system with the glucose-free buffer. However, carvedilol ($IC_{50} = 5 \mu M$) still protected dose-dependently against the 20 min oxidative challenge. Growing rat cerebral cells in the presence of the lipophilic carvedilol augmented the neuroprotection of the 20 min challenge with free radicals generating system by reducing the IC_{50} from $5 \mu M$ to $1.3 \mu M$ (Fig. 43).

* Braugher JM, Hall ED et al in "Central nervous system trauma and stroke. I Biochemical considerations for oxygen radical formation and lipid peroxidation." and, Part II."...Physiological and pharmacological evidence for involvement of oxygen radicals and lipid peroxidation" in *Biol Med* 6:289-301, 1989 and 6:303-313, 1989, respectively.

** Yue T-L et al in "Carvedilol, a new vasodilator and Beta-adrenoceptor antagonist, inhibits oxygen-radical-mediated lipid peroxidation in swine" (in press)

*** Yue T-L et al in "Carvedilol, a new vasodilator and beta adrenoceptor antagonist, is an antioxidant and free radical scavenger." *JPET* (in press)

The potential of carvedilol for preventing lipid peroxidation, induced by the free radical generating system DHF-Fe³⁺/ADP, was also tested on rat cultured neurons by measuring the amount of TBARS produced 50 min after washout of the free radical generating system. In this assay, pretreatment with carvedilol (10 μM) for 15 min resulted in 50% reduction of the levels of TBARS produced by a 20 min challenge of DHF-Fe³⁺/ADP (Fig. 44).

Even when using a different free radical generating system (Fe²⁺/vitamin C), carvedilol was still neuroprotective against continuous exposure to this system. Pretreatment with carvedilol (10 μM) for 15 min prior to addition of this radical generating system provided a 73% reduction in TBARS production (Fig. 45).

In vivo hippocampal neurons in gerbils exposed to 6 min bilateral carotid artery occlusion were reported as protected 7 days after ischemic insult (Fig 46).

Sponsor considers that these findings suggest a free-radical scavenging mechanism for carvedilol.

Although no data was submitted, sponsor reported that when each of the carvedilol enantiomers were tested separately, and no difference in neuroprotective ability was noted. Thus, sponsor considered that protection from lipid peroxidation was not enantiomer selective.

POTENTIAL NEUROPROTECTIVE PROPERTIES OF CARVEDILOL (In vivo and in vitro studies)

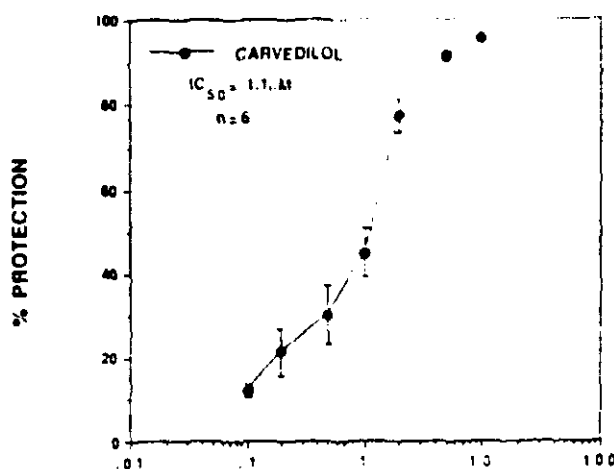


FIGURE LEGENDS

FIGURE 4 Carvedilol protects against glutamate-mediated neuronal death.

Cerebellar granule cells grown in 35mm dishes were incubated in the absence of glucose for 40 minutes prior to the addition of 20μM glutamate. Carvedilol was incubated with the cells for 15 minutes prior to the addition of glutamate, and toxicity was assessed 30 minutes later by staining with fluorescein diacetate. Protection of neurons was determined by counting cells and expressing the percent viability.

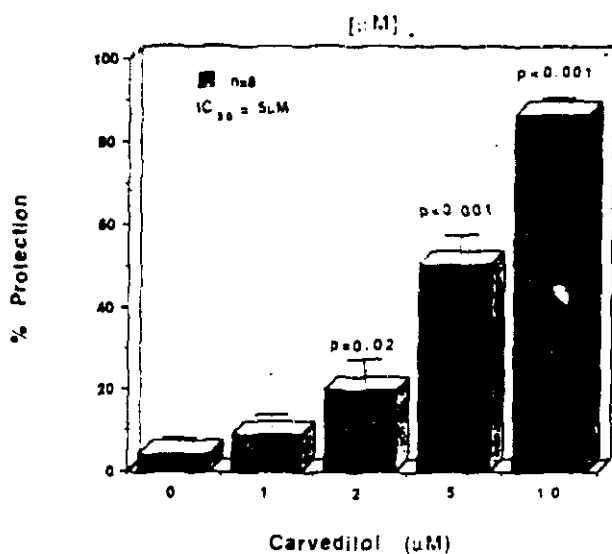


FIGURE 5 Carvedilol protects against hydroxyl radical-mediated neuronal death.

Cerebellar granule cells grown in 35mm dishes were incubated in the absence of glucose for 40 minutes prior to the addition of the DMF-Fe³⁺/ADP free radical generating system. Carvedilol was incubated with the cells for 15 minutes prior to a 20 min exposure to DMF-Fe³⁺/ADP. Contents of the dishes were then removed, replaced with buffer, and toxicity was assessed 50 minutes later by staining with fluorescein diacetate. Protection of neurons was determined by counting cells and expressing the percent viability. Significance was determined with Student's unpaired t-test.

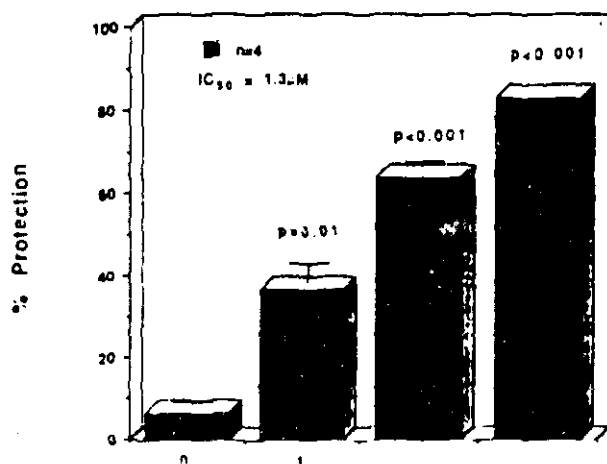


FIGURE 6 Carvedilol protection is augmented by growing cells in the presence of the drug for 24 hours.

Cerebellar granule cells were grown with the indicated concentration of carvedilol for 24 hours prior to removal of the growth medium and duplication of the experiments shown in Figure 2. Significance was determined with Student's unpaired t-test.

POTENTIAL NEUROPROTECTIVE PROPERTIES OF CARVEDILOL. (Cont'd)

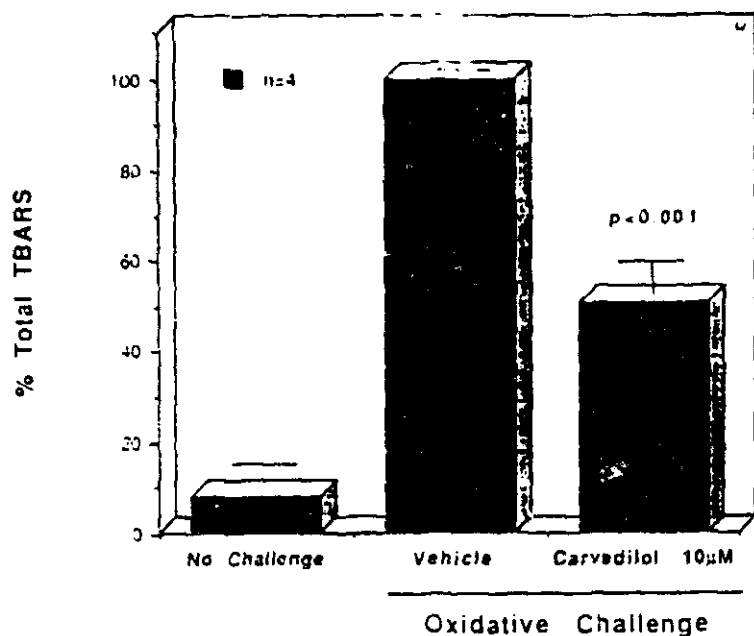


FIGURE 4. Carvedilol inhibits DHF-Fe³⁺/ADP-catalyzed lipid peroxidation.

Cerebellar granule cells grown in 60 mm dishes were incubated in the absence of glucose for 40 minutes prior to the addition of the DHF-Fe³⁺/ADP free radical generating system. Carvedilol was incubated with the cells in a total volume of 3 ml for 15 minutes prior to a 20 minute exposure to DHF-Fe³⁺/ADP. Contents of the dishes were then removed, replaced with 3 ml buffer, and after 50 minutes, the reaction was stopped by adding 0.3 ml of 0.2% butylated hydroxytoluene. Samples were then assayed for TBARS as described in Methods. Significance was determined with Student's unpaired t-test.

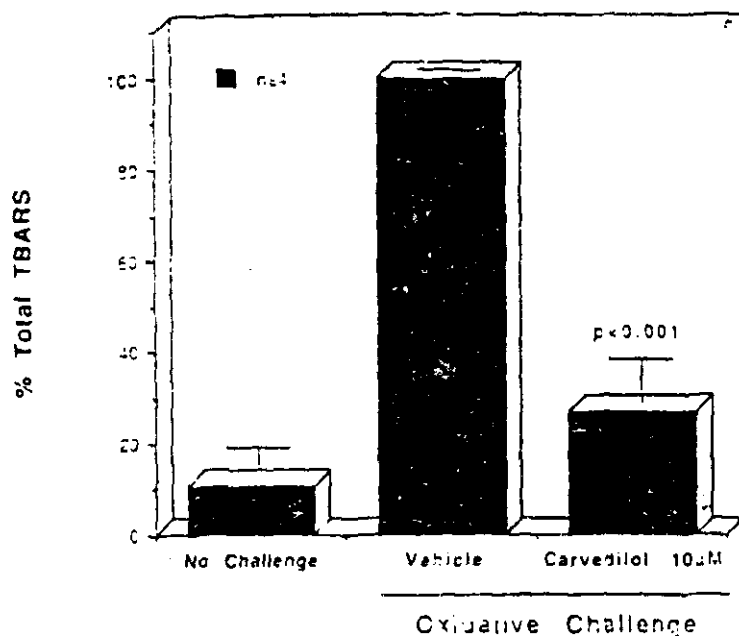


FIGURE 5. Carvedilol inhibits Fe²⁺/vitamin C-catalyzed lipid peroxidation.

Cerebellar granule cells grown in 60 mm dishes were incubated in the absence of glucose for 40 minutes prior to the addition of the Fe²⁺/vitamin C free radical generating system. Carvedilol was incubated with the cells in a total volume of 3 ml for 15 minutes prior to a 120 minute exposure to Fe²⁺/vitamin C. The reaction was stopped by adding 0.3 ml of 0.2% butylated hydroxytoluene, and samples were then assayed for TBARS as described in Methods. Significance was determined with Student's unpaired t-test.

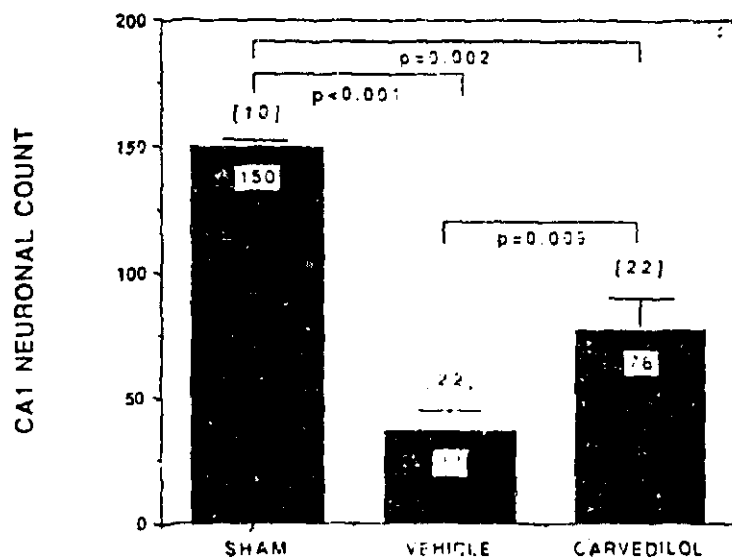


FIGURE 6. In vivo protective effects of carvedilol 7 days after 5-minute ischemia. Carvedilol was given as pretreatment with a bolus of 3 mg/kg s.c. BID for 4 days prior to ischemia and as posttreatment with the same dosing regimen for 3 days thereafter. The number of animals used is indicated over each bar. Data were analyzed by the Kruskal-Wallis procedure, and p values are given for each set of animals. Protection by carvedilol was highly significant as compared to vehicle-treated gerbils (p=0.009).

Vascular Protection

The antiproliferative effects of carvedilol was tested in cultured vascular smooth muscle cells exposed to various mitogens. Carvedilol ($IC_{50} = 1 \mu M$) produced a dose-dependent decrease in basal or endothelin-stimulated ^3H -thymidine incorporation in rat aortic vascular smooth muscle cells. To test the potential of the drug in blocking neointimal growth in response to angioplasty, rats were treated for 3 days with carvedilol (1 mg/kg i.p., BID) and then subjected to left carotid artery balloon angioplasty. Sponsor reported that balloon angioplasty of the left common carotid artery was shown to produce profound intimal thickening in the vehicle-treated rats resulting in a significant (20-fold) increase in the intima:media ratio. The rats were then followed for 14 days with/without treatment with carvedilol, and then sacrificed. Quantitative image analysis of stained cross sections of the carotid vessels revealed profound neointimal growth in the injured vessels of vehicle treated rats; carvedilol treatment caused 80% decrease in the intimal cross-sectional area and intima:media ratio.

These studies suggested to sponsor that in vivo the carvedilol treatment afforded protection from the myointimal proliferation that usually results from vascular wall injury following balloon angioplasty. Further, sponsor considered that an antihypertensive regimen with carvedilol might protect against vascular re-stenosis in the clinic following balloon angioplasty injury.

Antioxidant Activity in Heart.

In addition to apparent high-concentration neuroprotective properties of carvedilol (e.g., inhibition of lipid peroxidation inhibition in rat brain homogenates exposed to oxygen free radical generating systems), sponsor reported that lipid peroxidation was also prevented in swine ventricular membranes and rat cardiac microsomes preparations (pre-incubated with carvedilol or several β -blocking agents for comparison, and exposed to 2 oxygen free radical generating systems- Fe^{2+} -Vit. C and/or DHF/ Fe^{3+} -ADF). As in the nervous tissues/cell preparations, the rate of swine heart membranes lipid peroxidation was measured by the formation of thiobarbituric acid reactive substances (TBARS). Carvedilol inhibited TBARS formation dose-dependently (Fig. 47 and Table 13 below).

The antioxidant activity of carvedilol was calculated by sponsor as percent (%) inhibition of the lipid peroxidation elevation obtained in the absence of the inhibitor; this is assumed to be 100%. A 50% inhibition of lipid peroxidation was expressed as IC_{50} value.

The EC_{50} values for carvedilol and other β -blockers and a reported inhibitor of lipid peroxidation U74500A are seen below in Table 13 prepared by sponsor. The S(-) and R(+)-enantiomers were equally effective inhibiting lipid peroxidase formation in this preparation (Fig 48 below).

Sponsor considers that the antioxidant activity exhibited by carvedilol is likely through some free radical scavenging mechanism.

ANTIOXIDANT ACTIVITY OF CARVEDILOL IN HEART

Fig. 47

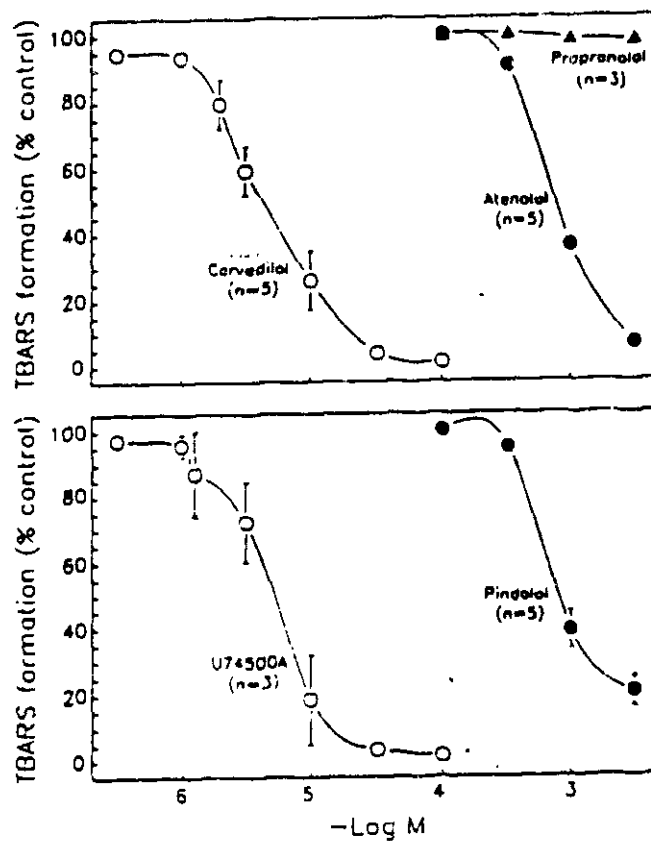


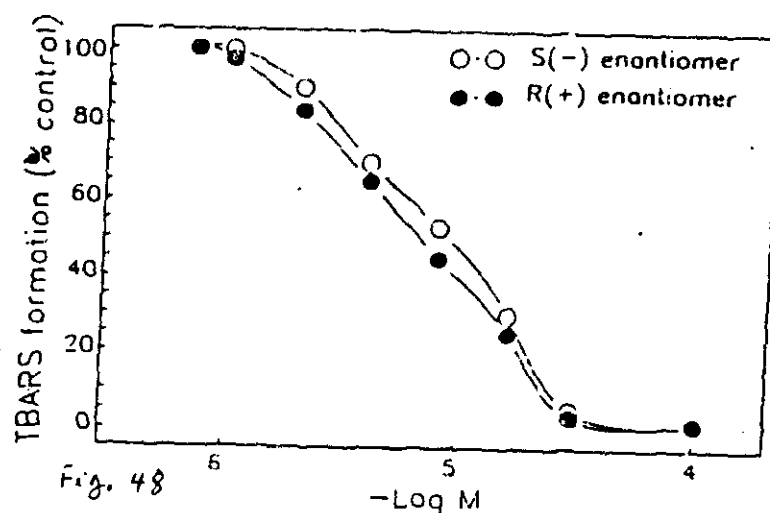
Table 13

IC₅₀ VALUES FOR INHIBITION OF LIPID PEROXIDATION INITIATED BY Fe²⁺-VIT C or DHF/Fe²⁺-ADP IN SWINE VENTRICULAR MEMBRANES

Agent	Fe ²⁺ -Vit C		DHF/Fe ²⁺ -ADP	
	IC ₅₀ (M)	Potency	IC ₅₀ (M)	Potency
Carvedilol	5.1 ± 0.9 × 10 ⁻⁶	100	1.4 ± 0.1 × 10 ⁻³	100
Pindolol	1.3 ± 0.1 × 10 ⁻³	0.4	4.1 ± 0.8 × 10 ⁻³	0.3
Atenolol	9.4 ± 0.1 × 10 ⁻⁴	0.5	2.2 ± 0.2 × 10 ⁻³	0.6
Propranolol	>3.2 × 10 ⁻³		3.8 ± 1.3 × 10 ⁻³	0.4
Celiprolol	>1.0 × 10 ⁻³		ND	
Labetolol	>1.0 × 10 ⁻³		ND	
U74500A	4.6 ± 1.8 × 10 ⁻⁶	111	3.5 ± 0.5 × 10 ⁻⁴	400

Values are the mean ± S.E. (n=4-5). ND: not determined

ANTIOXIDANT PROPERTIES OF THE S(-) AND R(+) ENANTIOMERS OF CARVEDILOL



The following table was provided by sponsor summarizing findings of all studies reported in the NDA examining the antioxidant properties of carvedilol.

Table 14

SUMMARY OF ANTIOXIDANT PROPERTIES OF CARVEDILOL

SYSTEM FOR STUDY OF LIPID PEROXIDATION	CARVEDILOL	IC ₅₀ PROPRANOLOL
Swine ventricular membranes		
Fe ²⁺ -Vit. C-induced	5.1 μM	> 3 mM
DHF/Fe ³⁺ -ADP-induced	14 μM	> 3 mM
Rat Cardiac Microsomes	3.9 μM	170 μM
Rat Brain Homogenates	8.1 μM	> 3 mM
Human LDL Oxidation		
Macrophage-induced	4 μM	> 100 μM
Cu ²⁺ -induced	17 μM	> 300 μM
Rat Cerebellar Neurons		
Fe ²⁺ -Vit. C-induced	<10 μM	Not Determined
DHF/Fe ³⁺ -ADP-induced	10 μM	Not Determined
Human Neutrophils	28 μM	> 100 μM
EPR	25 μM	No effect >(0.5 mM)
DHF Autooxidation (NBT Test)	41 μM	No effect >(0.3 mM)

BRIEF OVERVIEW OF NONCLINICAL NEUROPHARMACOLOGIC EFFECTS

In mice, carvedilol (30 - 300 mg/kg p.o) had no effect on the tonic hindlimb extension induced by maximal electroshock. Propranolol (10 to 100 mg/kg p.o) blocked the convulsion completely. Carvedilol (30-300 mg/kg p.o.) failed to show anticonvulsant effect.

In mice, carvedilol, p.o., one hour prior to i.p. injection with phenyl-p-benzoquinone to induce abdominal constriction, the drug dose-dependently produced an analgesic effect (ED-50 14 mg/kg). The analgesia was time dependent. Analgesic activity of carvedilol could not be detected after 8 hours of treatment.

In mice, doses ranging from 1 up to 10 mg/kg p.o. had little or no analgesic effect against acetic acid writhing; at higher doses (30 to 300 mg/kg p.o. the number of writhing significantly decreased. Propranolol (10 mg/kg p.o.) did not influence writhing.

In a journal article submitted by sponsor, compared to propranolol, carvedilol (30 mg/kg p.o) had little or no effect on the spontaneous motor activity of mice. A slight dose-dependent decrease in the activity was observed after dosing with higher doses of carvedilol (100-300 mg/kg). Propranolol also showed similar but stronger decrease in the same doses.

Carvedilol (3 mg/kg p.o.) was without effect on sleeping time induced by hexobarbital. The drug dose-dependently increased in the sleeping time at higher doses. Propranolol (10-100 mg/kg) also tended to potentiate the anesthesia.

In cats, the drug (0.06 mg/kg i.v.) had little effect on spontaneous EEG activity. At higher doses the drug produced a slight arousal patterns in all cats tested: the EEG pattern returned to normal within 60 min in most of the cats. Propranolol (0.04- 0.4 mg/kg) produced similar but stronger changes in the EEG.

In rabbits, carvedilol (30-300 mg/kg p.o.) had inconsistent effects on body temperature.

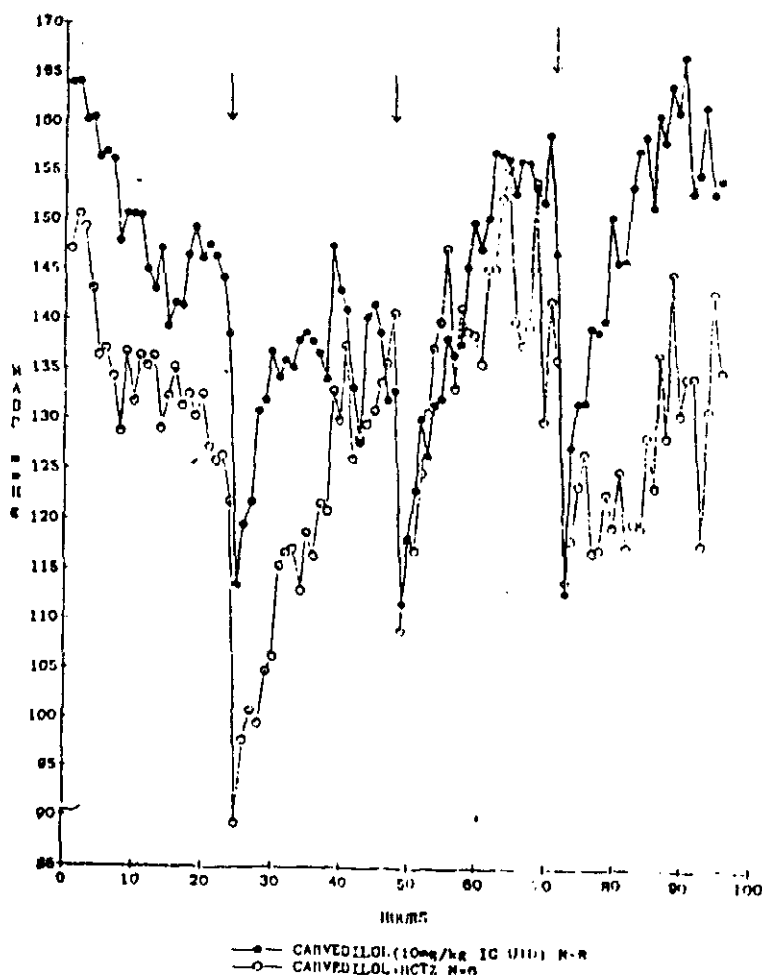
SOME DRUG INTERACTIONS STUDIES

Although not statistically significant, in the rabbit the combination of carvedilol (5 mg/kg i.v. infusion) and the diuretic tor[s]emide (0.5 mg/kg i.v. injection) produced a fall in rectal temperature (up to 1.8°C at this high dose) and increase blood glucose concentrations; the fall in body temperature was completed in about 90 min after treatment and remained at this level. At a lower dose of 1.25 carvedilol and 0.125 mg/kg tor[s]emide, blood sugar decreases occurred within one hour after administration of the combination of drugs. BP effects were not reported.

In conscious SHR, carvedilol, i.g., was associated with rapid dose-dependent decreases in arterial BP (lasting 4-8 hr dependent on the dose). There was no evidence of tachyphylaxis or drug accumulation when the drug was given repeatedly for 3 days. When the drug was given in combination with 50 mg/kg i.g. of each diuretic hydrochlorothiazide (Fig. 49) or furosemide, there was no clear evidence of synergistic antihypertensive response over 3 days of dosing.

Combinations of carvedilol and labetalol with hydrochlorothiazide were associated with acute hemodynamic responses not substantially different than those associated with carvedilol or labetalol alone (no synergistic effect was noted). However, in SHR, carvedilol when given in combination with low or high ceiling diuretics was associated with reductions in urine volume.

FIGURE 49. EFFECT OF CARVEDILOL AND CARVEDILOL/HCTZ ON MEAN ARTERIAL BLOOD PRESSURE IN SH RATS



SOME GASTROINTESTINAL STUDIES

In anesthetized rat, the action of carvedilol on gastric secretion was investigated in comparison with cimetidine, carbachol and propranolol. In these animals, carvedilol (5 or 0.8 mg/kg i.v. infusion) had no effect on gastric secretion. At the higher dose, there was a clear reduction of gastric acid secretion to about the same level as the cimetidine. Propranolol (5 mg/kg i.v.) also showed a reduction of gastric acid production. In this preparation, carbachol (9 μ /kg i.v.) caused as expected a promotion of gastric acid (reduction of the $p_i^{(1)}$) and the H_2 -antagonists cimetidine (8 mg/kg i.v.) caused a reduction of the gastric acid production.

Sponsor asserts that the reduction in gastric acid produced by carvedilol in the rat does not arise via H_2 -antagonistic activity. Sponsor bases this assertion on the results from studies using the isolated guinea pig atria. In this preparation, histamine (concentration of 0.13 μ g/ml in bath) produces a moderate rise in atrial rate; the effects of histamine were not affected by carvedilol up to the highest tolerated dose of 1×10^{-5} M (the β -blocking concentration lie in the range of 10^{-9} - 10^{-8} M.), while H_2 -cimetidine dose-dependently inhibited the histamine-induced rate increase in guinea pig atria.

In a journal article supplied by sponsor, it was reported that carvedilol (4×10^{-6} - 7 g/ml and propranolol 8×10^{-4} - 7) had little or no effect on tonus of isolated rat stomach. At higher concentrations, propranolol increased the tonus of the stomach in the preparation.

Carvedilol (30-300 mg/kg p.o.) and propranolol (10 to 100 mg/kg p.o.) showed little or no effect on the gastrointestinal transit in mice.

In rats, carvedilol (10 mg/kg i.g.) had little or no effect on gastric pH and acidity of gastric juice or acid and pepsin output. A rise in pH of gastric juice was reported for a dose of 300 mg/kg carvedilol. Propranolol (10 mg/kg i.g.) was without any effect.

In rats, carvedilol (3 - 10 mg/kg p.o.) did not induce gastric mucosal lesions (length of lesions were measured and lesion index reported). At higher doses (30 to 300 mg/kg, gastric lesion of the mucosa by carvedilol was dose-dependent. Propranolol (10 to 300 mg/k p.o.) caused a slight lesion of gastric mucosa in the rat.

In rabbits, carvedilol (0.6 - 2 mg/kg i.v.) produced no appreciable change in gastric motility. Propranolol increased the gastric motility and tonus in some rabbits at 1.2 mg/kg and in all at 4 mg/kg.

SUMMARY TABLE 15
(Provided by the sponsor)

**EFFECT OF CARVEDILOL ON ARTERIAL BLOOD PRESSURE IN
SPONTANEOUSLY HYPERTENSIVE RATS**

<u>Preparation (Reference)</u>	<u>Route</u>	<u>n</u>	<u>Dose</u>	<u>Maximum % Change</u>	
				<u>MAP</u>	<u>HR</u>
Conscious SHR SK&F Report #PC002BS	p.o.	8-14	1-25 mg/kg	-35%	-11%
Conscious SHR SK&F Report #PC036BS	p.o.	3-6	1-10 mg/kg	-25%	
Conscious SHR, chronic dosing SK&F Report #PP1001BS	p.o.	22	20 mg/kg/d	-9%	-13%
Conscious SHR SK&F Report #PP003BS	i.g.	7-15	0.3-60 mg/kg	-27%	
Conscious SHR SK&F Report #PP004BS	i.g.	5	1-30 mg/kg	-28%	
Conscious SHR SK&F Report #PP004BS	i.v.	5	0.03-3 mg/kg	-25%	-22%
Conscious SHR SK&F Report #PP004BS	i.v.	5	0.003-0.3 mg/kg/min (30 min)	-22%	-11%
Conscious SHR SK&F Report #PC002BS	i.v.	12	0.03-1 mg/kg	-35%	-15%
Conscious SHR SK&F Report #PC055BS	i.v.	12	0.03-1 mg/kg	-22%	
Conscious SHR SK&F Report #PC036BS	i.v.	3-6	0.03-1 mg/kg	-25%	
Anesthetized SHR SK&F Report #PP009BS	i.v.	4	0.03-1 mg/kg	-34%	-13%
Anesthetized SHR SK&F Report #PP016BS	i.v.	1	0.001-3 mg/kg	-29%	-25%

TOXICOLOGY:**ACUTE (SINGLE DOSE) TOXICITY STUDIES**

The acute toxicity of carvedilol, its enantiomer and four metabolites were studied in 3 animal species. The results of these studies were described in detail in summary tables prepared by sponsor. Although sponsor has submitted in depth summary tables of acute toxicity in mouse, rat and dog given carvedilol by the oral, i.v., and i.p. routes, this reviewer has extracted only oral and i.v. data to prepare the summary tables presented below.

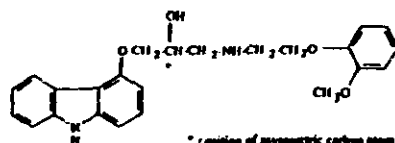
The approximate LD-50 values for the different species and routes of administration appear below.

Species	Duration (days)	Doses (mg/kg)	Report No. Location in NDA IND Submission	Approximate LD-50 values and Drug-Related Observations
Mouse	14	8000 oral	TC004BS (Boehringer Mannheim report F1) Ref. 1 Location: Vol. 1.15 Page 000003 Submitted to IND on 2/15/85	Oral LD ₅₀ >8000 mg/kg in males and females. Apart from hair loss, no other clinical signs were observed. Two animals died and showed macroscopically, lung edema and hemorrhage.
Mouse	14	4000, 8000 oral	TC0031/SKF-105517 (Daiichi report D-1-1) Ref. 2 Location: Vol. 1.15 Page 000044	Oral LD ₅₀ >8000 mg/kg in males and females. Clinical signs consisted of decreased body weight or body weight gain during the first 2 to 4 days, blepharoptosis, decreased motor activity, depressed respiration, soiling of the fur and wasting. Animals that died showed congestion of various organs and microhemorrhages in the brain. Animals that were killed at the end of the study showed splenic congestion and increased extramedullary hematopoiesis. Absolute and relative spleen weights were increased.
Rat	14	500, 1000, 2000, 3200, 4000, 8000 oral	TC004BS (Boehringer Mannheim report F2) Ref. 1 Location: Vol. 1.15 Page 000003 Submitted to IND on 2/15/85	Oral LD ₅₀ >8000 mg/kg in males and females after 1-14 days. Slight hair loss was the only clinical sign observed.
Rat	14	4000, 8000 oral	TC0031/SKF-105517 (Daiichi report D-1-1) Ref. 2 Location: Vol. 1.15 Page 000044	Oral LD ₅₀ >8000 mg/kg in males and females. Clinical signs consisted of decreased body weight or body weight gain during the first 2 to 4 days, blepharoptosis, decreased motor activity, suppressed respiration, soiling of the fur and wasting. Animals that died showed congestion of various organs and microhemorrhages in the brain. Animals that were killed at the end of the study showed splenic congestion and increased extramedullary hematopoiesis. Relative spleen weights were increased.

**ACUTE (SINGLE DOSE) TOXICITY STUDIES OF CARVEDILOL'S
METABOLITES**

Species	Duration (days)	Doses (mg/kg)	Report No. Ref. No. Location in NDA IND Submission	Drug-Related Observations
Rat	14	30, 50 ^② i.v.	TC0024/SKF-105517 (Boehringer Mannheim report F0011) Location: Vol. 1.15 Page 000168	I.V. LD ₅₀ of metabolite M2 > 50 mg/kg. At 30 mg/kg, apathy (0-45') and ptosis (5-60'). At 50 mg/kg, severe apathy (2-60') and clonic spasms (2-10'). <i>No animals died.</i>
Rat	14	30, 40, 50 ^① i.v.	TC0025/SKF-105517 (Boehringer Mannheim report F0012) Location: Vol. 1.15 Page 000185	Approximate I.V. LD ₅₀ > 40 mg/kg. At 30 mg/kg, slight apathy (2-60'); at 40 mg/kg, clonic spasm (0-5'), moderate apathy and staggering (up to 120' or death), ptosis in survivors (20-120') and at 50 mg/kg, clonic spasms (0-1'), severe apathy (1-2') and death within 2 minutes (<i>2/2 F tested</i>). Macroscopic findings at 40 and 50 mg/kg: red marbled and slightly swollen liver. <i>Survivors at LD and MD showed no liver pathology.</i>
Rat	14	30, 50 ^① i.v.	TC0026/SKF-105517 (Boehringer Mannheim report F0013) Location: Vol. 1.15 Page 000203	Approximate I.V. LD ₅₀ > 50 mg/kg. At 30 mg/kg, trembling (5') and slight apathy (15-25'). At 50 mg/kg, apathy (60-90'), clonic spasm (5') and bristling of the fur (30'). One female at 50 mg/kg died 3 minutes after dosing. <i>Postmortem examination showed no pathology.</i>

Chemical structure of carvedilol (SKF 105517, BM 14 190, DQ 2066)



- ① M2 metabolite (BM 14.242)
② M4 metabolite (BM 14.0686)
③ M5 metabolite (BM 14.0830)

Structure	M2 Metabolite Number	M5 Metabolite Number	Species
	M2	22	Major Drug Metabolite
	M4	26	Major Drug Metabolite
	M5	32	" "

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Acute Toxicity (Cont'd.)

ACUTE (SINGLE DOSE) TOXICITY STUDIES OF CARYTECAL (MAY 1982)

Report No.

Species	Sexes (n)	Dose (mg/kg)	Location in FDA IND Submission	Summary of Observations
M Dog (Beagle)	14	500, 1000, 2000 oral	TC0012/MSKF-105517 (Daiichi report D-1-3) Location: Vol. 1.15 Page 000262	Oral LD ₅₀ ≥ 1000 mg/kg. One of the 2 dogs at 1000 mg/kg and 2 of 2 at 2000 mg/kg vomited. Other clinical signs consisted of blepharoptosis, reduced locomotor activity and unsteady gait. Transient changes in clinico-pathology parameters were observed. No macroscopic or microscopic changes were found.

Intravenous Route

Mouse	14	32, 40, 50 i.v.	TC004BS (Boehringer Mannheim report F7) Location: Vol. 1.15 Page 000003 Submitted to IND on 2/15/85	I.V. LD ₅₀ : 41.1 (35.9-47.9) mg/kg after 1-14 days. Clinical signs: apathy and convulsions. No macroscopic findings.
Mouse	14	males: 10, 20, 30, 40, 50, 100 females: 10, 20, 30, 35, 40, 50, 100 i.v.	TC004BS (Boehringer Mannheim report F5) Location: Vol. 1.15 Page 000003 Submitted to IND on 2/15/85	I.V. LD ₅₀ : females: 36 (31-40) mg/kg after 1-14 days; males: 31 (26-36) mg/kg after 1 day and 27 (21-33) mg/kg after 7-14 days. Apathy only clinical sign observed. Macroscopic findings: lung edema (20, 50, 100 mg/kg), discolored liver (40, 50, 100 mg/kg), light red spleen (30, 40 mg/kg) and watery gastrointestinal contents (30, 40 mg/kg).
Rat	14	males: 22, 25, 27, 30 females: 15, 20, 22, 23, 25, 30 i.v.	TC004BS (Boehringer Mannheim report F6) Location: Vol. 1.15 Page 000003 Submitted to IND on 2/15/85	I.V. LD ₅₀ : females: 25 (24-26) mg/kg after 1-14 days; males: 27 (26-28) mg/kg after 1-14 days. Clinical signs: ptosis and apathy. No dose free of signs. Macroscopic findings: lung edema and hemorrhage.

SYNOPSIS OF ACUTE TOXICITY STUDIES WITH CARVEDILOL

The drug sponsor reported estimated median lethal doses for carvedilol and related compounds in mouse, rat and dog. The calculated median lethal oral doses in both rodent species was above 8000 mg/kg and for dog above 1000 mg/kg. In the rodents, toxic signs reported after receiving a range of large oral doses of the drug included- hair loss, decreased motor activity, blepharoptosis, depressed respiration and microhemorrhages in the brain (mouse) and, in dog- decreased motor activity and, unsteady gait.

The estimated median lethal dose for carvedilol by the i.v. route, was not significantly different among the rodents tested. Estimated values in 2 mouse i.v. studies were 36 mg/kg in females and, 27 mg/kg i.v. in males. Remarkable toxic signs in these mice treated with carvedilol i.v. included apathy, convulsions and, macroscopic signs in the second mouse study included lung edema and discolored liver. In male rats the estimated median lethal dose for carvedilol was 27 mg/kg i.v. The median i.v. lethal dose in the dog was not calculated.

Limited studies were conducted to characterize the toxic profile of S(-) and R(+)- enantiomers of carvedilol. Acute toxic signs reported for both enantiomers given by i.v. to mouse were apathy and convulsions; macroscopic findings reported consisted in pulmonary edema. In these mice, the mean lethal doses were estimated as 43.4 mg/kg for S(-)-enantiomer and 30.8 mg/kg i.v., for R(-)-enantiomer. In mouse the overt toxic signs for the enantiomers were no different that for the racemic mixture given i.v.

Acute i.v. toxicity in rat of 3 of the major (and pharmacologic active*) metabolites of carvedilol in mouse and rat was calculated. The metabolites tested were the hydroxy-metabolites M2 (BM 14.242), M4 (BM 14.0686) and M5 (BM 14.0830). In mouse, the median acute dose for M2 was 38 mg/kg i.v. In rat, the estimated value for M2 was above 50 mg/kg (at 30 mg/kg i.v. apathy occurred and, at 50 mg/kg severe apathy and clonic spasms), but no rats died. The mean lethal i.v. dose for M4 and M5 is estimated to be about 40 mg/kg and 50 mg/kg i.v., and greater, respectively. Toxic signs were similar to that of the M2 metabolite and included in common- apathy and clonic spasms. Rat given the M4 metabolite, macroscopic examination in one rat study showed red marbled and slightly swollen liver at 40 and 50 mg/kg i.v. Other postmortem observations, including survivors, were unremarkable.

Data submitted indicate that the estimated mean lethal oral doses of the drug for rodents and dogs of 8000 and 1000 mg/kg, respectively, represent about 8000 and 1000 times the maximum recommended human oral dose of 1 mg/kg carvedilol, assuming a 50 Kg patient.

In dog, limiting toxicities studies with carvedilol (15 mg/kg i.v.), were convulsions and alterations in the ECG (prolongation of P wave, PR and QRS intervals).

* In separate studies the metabolites M2, M4 and M5 showed some β -blocking activity.

SUMMARY OF MULTIDOSE TOXICITY STUDIES

The following tables are the extracted portions of tables submitted by drug sponsor. Footnotes have been added to these new tables where added information was considered needed.

Species	Duration (weeks)	Doses (mg/kg)	Report No. Location in NDA (ND Submission)	Drug-Related Observations
* 1 - Mouse	13	20, 60, 200, 600, 800 diet	TPXXX05/SKF-105517 (Boehringer Mannheim report J6) Location: Vol. 1.15 Page 000289	Body weight was lower (-11 and -17%) in males of the 2 highest dose groups. Hemoglobin was significantly increased in drug-treated males without a dose response being evident. Increases (<2x control) in alkaline phosphatase values were present in males of the 2 highest dose groups. sGPT was increased (max. 2x control) in all drug-treated males and females with exception of high-dose females. Serum total protein was decreased (-10%) in males of the 2 highest dose groups. Liver weights were increased in females at dosages ≥200 mg/kg (up to 30%) and only relative liver weight was increased in high-dose males (20%). Histopathology was not performed. <i>The "No-Adverse-Effect" dose is considered 60 mg/kg/day in this mouse study.</i>
* 2 - Rat	13	30, 100, 300 oral	TC007BS (Boehringer Mannheim report H2) Location: Vol. 1.16 Page 000002 Submitted to IND on 2/15/85	Hair loss was observed in 8/40 high-dose animals and blepharophimosis in the majority of mid- and high-dose animals. sGPT was increased (<2.5x control) in high-dose females with value returning to normal in off-dose period. Relative liver weight was increased in drug-treated animals (up to 25% in high-dose males and up to 50% in high-dose females). Light microscopic examination revealed exacerbation of spontaneous cardiomyopathy in mid- and high-dose animals. Regenerative hepatocellular hyperplasia was observed in 1 high-dose male, nodular hepatocellular hyperplasia in 1 high-dose male and 2 high-dose female and minimal pericholangitis in 3 high-dose males and 3 high-dose females. Furthermore, high-dose animals showed splenic congestion.

* 1.- Sixteen (16) mice (NMRI)/sex/group were used; animals were housed individually. Although alkaline phosphatase was increased in drug treated males, only HD females (800 mg carvedilol/kg/day in diet) a slight increase in this enzyme levels. Toxicokinetic studies revealed that carvedilol was detected in the serum of all drug treated mice with the exception of a few treated with 20 mg/kg/day in diet. Based on the findings in this 13-week study, sponsor considered that the MTD (see toxic signs above) for the mice was 200 mg/kg/day, thus the doses selected for the mouse carcinogenicity study were 20, 65 and 200 mg/kg/day.

* 2.-Twelve (12) rats (Sprague-Dawley, Caw-Ico-Wiga)/sex/group were used. In this study, the NOAEL for carvedilol was estimated as 30 mg/kg/day. Blepharophimosis appeared within 2 hours after treatment with the MD and HD. Although reversible, early in the study elevations of hemoglobin, hematocrit and sGPT were seen at MD and HD. Remarkable histopathologic changes reported included cell infiltrates in the myocardium and inflammatory changes in peripheral biliary tract.

REDACTIONS MADE BY APPLICANT

Multidose rat (Cont'd)

Species	Duration (weeks)	Doses (mg/kg)	Report No. Ref. No. Location in NDA IND Submission	Drug-Related Observations
3) Rat	13	30, 100, 300 oral	TC0029/SKF-105517 (Daiichi report D-4-1) Location: Vol. 1.17 Page 000002	Salivation, lacrimation and blepharoptosis were observed in mid- and high-dose animals. Three high-dose females died as a result of respiratory/cardiac failure. Less body weight gain associated with less food intake were noted in mid- and high-dose males and high-dose females. Blood pressure was increased in high-dose animals (~13%) and heart rate was decreased in drug-treated animals. Slight increases in serum alkaline phosphatase, leucine aminopeptidase, bilirubin, cholesterol, uric acid, CPK, potassium, phosphorous and calcium concentrations were observed in mid- and/or high-dose animals. Decreases were observed for cholinesterase, creatinine, triglycerides, total protein, albumin and chlorine concentrations. Various organ weight increases (adrenal, liver, spleen) and decreases (uterus, thymus, pituitary) were observed in mid- and/or high-dose animals. Dark spleen and dilation of the common bile duct were macroscopic observations in high-dose animals whereas bile duct hyperplasia, biliary ductular dilation, centrilobular hepatocellular hypertrophy, adrenal cortical hypertrophy, uterine atrophy and exacerbation of spontaneous cardiomyopathy were observed microscopically in mid- and/or high-dose animals. Most changes appeared to be reversible after a 5-week drug-free period.
4) Rat	15 (200 ppm) - 11(M), 13(F); (600 ppm) - 33(M), 42(F); (2000 ppm) - 100(M), 126(F); (6000 ppm) - 385(M), 413(F); (20000 ppm) - 532(M), 486(F) diet	TP-0004/SKF-105517 (Boehringer Mannheim report J5) Location: Vol. 1.16 Page 000333	Rough pelt was observed in animals of the highest dose groups. Animals of the 2 highest dose groups consumed less food (down to 17% in males and 30% in females). Body weight was decreased accordingly in these animals. Erythrocyte parameters (Hgb, PCV, MCV) were slightly decreased in animals of the 2 highest dose groups. Significant increase in leukocyte count was observed in high-dose animals (29% and 94% in males and females, respectively). Alkaline phosphatase values did not decrease with age in animals of the 2 highest dose groups. There was no consistent pattern in organ weight changes compared to controls in both sexes. Drug-related macroscopic findings were dilated bile ducts and concretion formation. Histopathology was not performed. <i>The "no-adverse-effect" dose may be considered 200 ppm (11-13 mg/kg/day)</i>	

* 4.- Twelve (Sprague Dawley, Caw-Ico-Wiga) rats/sex/group used. Carvedilol was fed in the diet at concentrations ranging from 200 up to 6000 ppm (see above the calculated drug intake by end of study). Remarkable findings reported, not included above summary, included dose-related increases in liver weight (absolute/relative; significant at the 3 highest doses tested); testicular atrophy and edema in some males at the 2 highest doses, and in both sexes some rats had dilated ductus choledochus/punctate stone formation. Present reviewer's calculations of final body weights showed a decrement of more than 10% at the 2 highest doses compared to controls. Sponsor estimated from this study the MTD and selected a "... dose of 4000 ppm based on effects on body weight development, absolute and relative organ weights, haematological and biochemical parameters." Sponsor also stated that "Based on body weight, food consumption and clinical pathology dosages of $\geq$ 6000 ppm exceeded the maximally tolerated dose in a carcinogenicity study." Toxicokinetic data for this 15-week rat study showed animals were exposed to the drug; compared to week 1, serum concentrations of carvedilol were higher at the end of the study suggesting a decrease in clearance after repeated administration (Table 30 under Overview of ADME Studies)

Multidose rat (Cont'd)

Species	Duration (weeks)	Doses (mg/kg)	Report No. Ref. No. Location in NDA IND Submission
Rat	52	(600 ppm) - 33(M), 38(F); (2000 ppm) - 106(M), 128(F); (6000 ppm) - 333(M), 354(F) ^② diet	TC008BS (Boehringer Mannheim report 114) Location: Vol. 1.18 Page 000002 Submitted to IND on 2/14/86
Rat	78 (19 mo)	31, 89, 261 ^③ diet (600, 1700 and 5000 ppm)	TC/0003/SKF-105517 (Boehringer Mannheim report 116) Location: Vol. 1.19 Page 000002

Drug-Related Observations

The mid- and high-dose animals showed narrowing of the eyelids, slightly encrusted snout, apathy and rough pelt. Food intake was decreased in high-dose females and varied between -24 and -59%. Drug-treated females gained less body weight in a dose-related fashion (-3 to -27%). High-dose males also gained less weight (-14%). A control male and female, 3 mid- and 2 high-dose males and 1 high-dose female died during the study. Death of the control female and 1 mid-dose male was considered accidental. Alkaline phosphatase values were higher in high-dose animals (<3.5x control value). Liver weights were increased in females in a dose-related fashion. Mid- and high-dose animals showed exacerbation of spontaneous cardiomyopathy. Biliary hyperplasia occurred in a higher incidence in drug-treated animals, particularly in high-dose animals. The liver also showed a higher incidence of proliferative liver lesions (altered foci) compared to other groups.
The No. adverse effects could not be determined.

Only during the first 4 weeks, high-dose animals showed sticky eyes, unkempt fur and apathy. Food intake was less in mid- and high-dose animals (down to -6 and -26%, respectively). Drug-treated animals showed a dose-related decrease in body weight (-23% and -43% in high-dose males and females, respectively). Mortality was lower in the mid- and high-dose animals than in the control and low-dose animals. A slight increase in cholesterol and triglyceride serum values was seen in high-dose females. A minimal chronic inflammatory cell infiltrate and fatty infiltration were observed in the hearts of drug-treated animals. A dose-dependent increase in incidence of biliary hyperplasia with all high-dose animals affected was observed. The hyperplastic change was associated with a mixed inflammatory cell infiltrate. Liver cell hyperplasia (altered foci) was also increased dose-dependently. Two high-dose males and 3 high-dose females had developed a hepatocellular adenoma.

② Mean daily drug intake over study period
③ Actual drug intake at end of study period

Multidose rat (Cont'd)

Species	Duration (weeks)	Doses (mg/kg)	Report No. Ref. No. Location in NDA IND Submission	Drug-Related Observations
Rat	78	10 <i>in diet</i>	TC/0003/SKF-105517 (Boehringer Mannheim report H6) (supplement) Location: Vol. 1.19 Page 000002	No differences between control and drug-treated animals were observed.
Rat	4	2.5, 5, 10 i.v.	TP/0003/SKF-105517 (Boehringer Mannheim report G3) Location: Vol. 1.23 Page 000002	Blepharospasm and apathy were observed in mid- and high-dose animals. Tail vein changes precluded further dosing of high-dose animals after 16 days. High-dose females showed decreased food consumption at end of study (~10%). High-dose animals showed decreased body weight from 3 weeks onward (down to -8%). Grossly, tails of the high-dose animals showed subcutaneous hemorrhage, brownish discoloration of the liver in mid- and high-dose males and females and enlargement of the spleen in some high-dose animals. Mid-dose females showed an increase in heart and spleen weights (up to 14 and 28%, respectively). Perivascular inflammation was evident at the injection site. Severity was dose-related. Fatty infiltration of the liver was observed in mid- and high-dose females. Intravenous no effect dose was 2.5 mg/kg.

Multidose dog (beagle)

Species	Duration (weeks)	Doses (mg/kg)	Report No. Ref. No. Location in NDA IND Submission	Drug-Related Observations
* 1) - Dog	13	15, 50, 150 oral	TC009BS (Boehringer Mannheim report 111) Location: Vol. 1.24 Page 000002 Submitted to IND in 2/15/85	An episode of vomiting was seen in high-dose females during the 9th week of treatment. ECG recordings demonstrated a decrease in heart rate and a prolonged PQ interval in drug-treated dogs (due to β -blocking activity of carvedilol). A transient decrease in hemoglobin value was observed in the first week of the study. Relative liver weights were increased in mid- and high-dose male dogs. A dose-dependent increase in relative spleen weight was noted in female dogs; mid-dose male dogs also showed an increase. One low- and one mid-dose male showed fatty infiltration of the heart muscle. Fatty infiltration of the liver was seen in a mid-dose male and female. Iron negative pigmentation was seen in the spleen of one low-dose male and one mid-dose female.
* 2) Dog	13	10, 50, 250 oral	TC/0032/SKF-105517 (Daiichi report D-5-1) Location: Vol. 1.24 Page 000325	High-dose animals showed vomiting, blepharoptosis, protrusion of the membrane nictitans, decreased motor activity and less weight gain. One high-dose female died and showed drug-related pulmonary congestion, hemorrhage and edema. Blepharoptosis was also observed in mid-dose animals. The liver function test showed a significant increase in low-dose females only. A prolonged mean PQ-interval was noted in mid-dose males. Serum potassium concentrations ($\leq 21\%$) were increased in mid- and high-dose animals. Liver weights were increased in high-dose animals ($\leq 41\%$), adrenal weights in low- and high-dose males ($\leq 40\%$), thyroid weights in high-dose females (25%) and pituitary weights in high-dose females (29%). However, thyroid weights were decreased in low-dose females (down to 38%). Splenic congestion was common in high-dose animals. The no effect dose was considered to be 10 mg/kg/day.

* 1- Three beagles/sex/group were used; 3 dogs of the same sex/dose were housed together. Drug doses used in this 13-week study were based on multiples of the effective pharmacologic dose of 3 mg carvedilol/kg p.o. for inhibition of isoprenaline tachycardia in dogs. In these dogs, carvedilol (15, 50 and 150 mg/kg p.o.) was given in capsules.

* 2- In this 2nd dog study, the doses of carvedilol tested were based on a previous study. (See that study below as #3 in which a "no-effect" dose could not be determined because all carvedilol- 30 up to 300 mg/kg p.o., dogs showed bile duct proliferation.) In the present study (# 2 above), a remarkable effect not included consisted in decreased in spontaneous activity at HD. The no effect dose was 10 carvedilol/kg. In a separate subchronic study with beagles, i.v. treatment with carvedilol (0.2, 1.0 and 5.0 mg/kg for 4 weeks), resulted in no biological arrhythmias or extrasystoles, and no dose-dependent changes in QRS-complex.

Multidose beagle (Cont'd)

Species	Duration (weeks)	Doses (mg/kg)	Report No. Ref. No. Location in NDA IND Submission	Drug-Related Observations
*3) - Dog	26	30, 100, 300 oral	TC010BS (Boehringer Mannheim report 113) Location: Vol. 1.25 Page 000002 Submitted to IND on 3/17/90	Transient clinical signs in high-dose animals were lacrimation, swollen eyes, ptosis, slight apathy and respiratory problems. Most of these signs were also seen in one mid-dose male in week 21 of the study. One mid- and one high-dose male died during the study. The mid-dose male showed the clinical signs mentioned above before he died. The other had not shown any signs before death. ECG recordings showed prolongation of the PQ-interval in low- and mid-dose animals but not in high-dose animals. White blood cell counts were up 1.3x in high-dose females but not in high-dose males. Serum alkaline phosphatase values were higher in high-dose animals (up to 1.7x) than in controls. sGPT was increased up to 1.5x in high-dose males during the last 6 weeks of the study. Congestion of various organs was the only drug-related macroscopic finding. Relative liver (up to 1.5x) and spleen (up to 4x) weights were increased in high-dose males. Mid- and high-dose females also showed an increase in relative spleen weight (up to 1.7x). Bronchopneumonia was observed in control and drug-treated animals but was more common in the latter ones. Minimal biliary hyperplasia ^{duct} was only observed in drug-treated animals.

*3) - In this study, 5 beagles/sex/group were used. Carvedilol was administered in capsules. Although this study was designed to last for more than 26 weeks, the duration was reduced to according to drug sponsor to be in "line with European Economic European regulations." NB- To date the FDA has not agreed comply with these EEC guidelines.

In addition to listed toxic signs in the sponsor's summary table above, transient reduction in food intake at HD and, decrease in Hbg in some drug-treated dogs were seen (reversible only in females). Sponsor concludes that the minimal biliary duct hyperplasia in drug-treated animals is of "limited toxicologic importance." (NB- This effect was also reported in a second species treated with carvedilol; in long-term studies hyperplasia of bile duct was also reported.)

A table entitled was provided ("Table 150 "Determination of drug level" in vol 25, p. 250) with no explanation as to what these "drug levels" refer to. Protocol was or sponsor's summary of study was helpful in clarifying the significance of this table.

Multidose beagle (Cont'd.)

Species	Duration (weeks)	Doses (mg/kg)	Report No. Ref. No. Location in NDA IND Submission	Drug-Related Observations
4- Dog	52	10 oral	TC011BS (Boehringer Mannheim report 115) Location: Vol. 1.26 Page 000002 Submitted to IND IND on 6/3/87	Infrequent vomiting and diarrhea and a slight increase in the number of erythrocytes were the only observations made.
4- Dog	52	30, 100, 300 oral	TC011BS (Boehringer Mannheim report 115) Location: Vol. 1.26 Page 000002 Submitted to IND on 6/3/87	lethargy, slight ataxia and blepharostenosis were observed in high-dose animals in the first week of the study. From week 5 onward, vomiting and diarrhea were common observations in mid- and high-dose animals and were seen infrequently in low-dose animals. Heart rate was decreased in high-dose females only. ECG recordings showed prolonged PQ-intervals in the drug-treated animals, particularly in the low-dose group. A dose-related increase in relative liver weight was observed in both sexes (up to 18% in males and 43% in females). Biliary hyperplasia occurred more frequently in mid- and high-dose animals and was graded as more severe than in the controls. <i>The "no-adverse effect" dose could not be determined.</i>

*4 - In the 52-week dog study, 5 beagles/sex/group were used. Study was divided in 2 sections (listed as 8a and 8b above), each with its own control group. Doses of carvedilol were given in 2 daily oral portions for the 52 weeks and then, 1 dog/sex/group were placed on a drug free schedule for 17 weeks for observation.

-a) In the 10 mg/kg/day group, no remarkable histopathologic changes were reported.

-b) Although controls beagles (1M, 1F) and at LD (1M and 1F) exhibited minimal bile duct hyperplasia, this pathologic change (severity minimal to moderate) was mainly observed in drug-treated beagles at MD (2F and 4M) and HD (4M and 5 F). Sponsor explains the bile duct epithelial hyperplasia as "an expression of regeneration of a drug-induced minimal damage and the balance between local damage and its repair remain stationary over 12 months." No remarkable findings were reported in beagles from drug-free portion of the study. Excitability was noted at the beginning of the study in some dogs at 10 mg/kg/day considered due to excitement from manipulation.

ORGAN TOXICITY REPORTED IN VARIOUS STUDIES WITH CARVEDILOL

The primary targets of organ toxicity were liver and heart in mouse, rat and dog treated with repeated doses of carvedilol by oral route. In these 3 species, repeated doses of the drug were associated with liver changes (increase liver weights and unremarkable increases in liver enzymes); rats and dogs also showed biliary hyperplasia. In the heart histopathologic changes were reported as "exacerbated spontaneous cardiomyopathy" or "minimal chronic inflammatory cell infiltrate and fatty infiltration" for rat, and fatty infiltration in dog.

In the 12-month study in rats with carvedilol (LD-600, MD- 2000 and HD- 6000 ppm with with an average daily intake of LD-35.5, MD-117 and HD- 343.5 mg/k), compared to controls there was a higher incidence of bile duct hyperplasia in all carvedilol treated groups. In these rats, the combined (males and females) bile duct hyperplastic findings were reported as C-0, LD- 30, MD- 28 and HD- 59 by one pathologist vs C-5, LD- 9, MD- 43 and HD- 56 by a second pathologist. (Slides were reported as read blindly. No statistical analyses were found for the biliary duct hyperplasia findings.) Also reported in these rats were focal liver hyperplasia, and increase in myocardium interstitial infiltrates and occasionally swelling of the myocardial fibers (See Table 16a below) In this rat study, the apparent "no-effect" level for carvedilol was at the LD (35.5 mg/kg daily p.o.) In the 18-month rat study with carvedilol (LD- 200, MD- 600, HD-1 1700 and HD-2 5000 ppm), liver hyperplasia was reported by sponsor to be an expression of metabolic overload of the liver; hepatomas also were reported in 5 animals at HD (261 mg/kg daily intake at the end of the study). Since some of these rats were allowed to be drug-free for 3 months, and scar formation and telangiectases were later observed, sponsor interpreted these findings as signs of regressive changes. Although in these rats biliary hyperplasia was dose-dependent compared to control, no dose-dependent changes were found in the heart histopathologic changes.

Biliary hyperplasia in the rat was reported as resembling the "type of biliary epithelial hyperplasia seen spontaneously in the rat" and that seen in the dog as being minimal to mild and mostly within the range of untreated controls.

In the dog, heart histopathologic changes consisted of fatty infiltration of the heart muscle; but since these changes were also noted in the control dogs, sponsor did not consider them drug related.

Heart and liver histopathologic changes are summarized by sponsor in Tables 16a, b, c and d.

Table 16a Incidence of Cardiomyopathy in the Rat as Observed in Various Toxicity Studies of Carvedilol

16a)

Dosegroup (ppm)	Males			Females		
	12-Month	18-Month	18-Month	12-Month	18-Month	18-Month
0	0/30	3/30	23/30	0/30	0/30	10/30
200			7/30			7/30
600	3/30	18/30		1/30	6/30	
1700		10/30				
2000	10/30			13/30	10/30	
5000		21/30				
6000	27/30			25/30	8/30	

Organ Toxicity (Cont'd)

Table 16 (Cont'd)

Incidence of Hepatocellular Adenomas in the Rat as Observed
in 18-Month Toxicity and 24-Month Carcinogenicity Studies of Carvedilol

16c)

Dose (ppm)	Males		Females	
	18-Month	24-Month	18-Month	24-Month
0	0/30	1/100	0/30	1/100
200	1/30	2/90	0/30	0/30
400		1/30		0/30
600	0/30		0/30	
800		3/30		0/30
1600		2/30		1/30
3200	0/30		0/30	
5000	2/30		3/30	

Incidence of Fatty Change in Heart Muscle of Dogs as Observed in Various
Toxicity Studies of Carvedilol

16c)

Dose (mg/kg)	Duration of Study			
	3-Month	6-Month	12-Month	12-Month
0	0/6	1/10	5/10	3/10
10				1/10
15	1/6			
30		0/10	3/10	
50	1/6			
100		5/10	2/10	
150	0/6			
300		0/10	6/10	

Incidence of Biliary Hyperplasia in the Dog as Observed
in 6- and 12-Month Toxicity Studies of Carvedilol

16d)

Dose (mg/kg)	Males		Females	
	6-Month	12-Month	6-Month	12-Month
0	0/5	1/10	0/5	1/10
10		0/5		0/5
30	3/5	1/5	1/5	1/5
100	4/5	4/5	5/5	3/5
300	4/5	4/5	3/5	5/5

CARCINOGENICITY STUDIES

The carcinogenicity studies were previously submitted in IND _____ reviewed by consultant pharmacologist M. Winbury, Ph.D. (Final reviews are in Division files dated April 1993.) Previous reviews have undergone a secondary review by supervisory pharmacologist Charles Resnick, Ph.D.

The following is the summary table prepared by the drug sponsor. This table is followed by present reviewer's brief overview of the mouse carcinogenicity study.

MOUSE (SPF-NMRI-HAN-WIGA)

SUMMARY

CARCINOGENICITY STUDIES OF CARVEDILOL (SK&F 105517)

Species	Duration (weeks)	Doses (mg/kg)	Report No. Ref. No. ⁶⁸ Location in NDA IND Submission	Drug-Related Observations
*1) Mouse	97 (females) 114 (males)	20, 65, 200 diet	TC002BS (Boehringer Mannheim report 14) Location: Vol. 1.29 Page 000002 Submitted to IND n 8/11/89	Drug-related clinical signs were apathy, cold skin and ptosis. Mean cumulative food consumption was significantly decreased in mid- and high-dose males and high-dose females. A significant decrease in median body weight gain was seen in high-dose males (-13%). High-dose females showed a non-significant decrease (-6%). The mortality for control, low-, mid- and high-dose males at 114 weeks was 58%, 38%, 56% and 56%, respectively. The respective values for females at week 97 were 73%, 80%, 78% and 80%. Urea nitrogen values were higher in the high-dose males and mid- and high-dose females. sGPT values were significantly higher in low- and high-dose males. Single cell hepatocellular necrosis occurred with a slightly higher incidence in high-dose females than in controls (22% vs 14%). Overall tumor incidence and per cent of tumor bearing animals decreased with dose.

*1.- In the mouse (NMRI) study, 100 animals/sex were used in the controls and 50/animals/sex in drug treated groups. No interim sacrifice was performed. No remarkable changes were reported for macroscopic examinations. Microscopic findings reported was a decrease in the number of HD males with tumors (controls 83% vs HD males 68%) and female tumor carriers at HD (controls 62% vs HD 26%). Study was terminated in males in September 1986 because of sudden death of animals with no previous signs of sickness. Sudden deaths reported: controls- 2M, 7F; LD- 3F; MD- 3M, 2F; HD- 4M, 3F; the total number of drug treated mice dying in the study were 15 animals. Study revealed no carcinogenic effect associated with the doses of carvedilol tested.

Brief overview mouse study.

Oral Carcinogenicity Study: Life-time Application to Mice [TC002BS (Boehringer Mannheim report J4; Vol. 29. Dosing dates: 17-07-84 up to 21-05-86 (for females- week 97), and, up to 16-Sep-86 (for males- week 114).]

Dose selection for the mouse carcinogenicity study was based on the results of a mouse 13-week dose-ranging study (J6 above) at doses from 20 to 800 mg/kg carvedilol. Based on body weight, food consumption and clinical pathology of the mice in this study, sponsor considered that carvedilol at 200 mg/kg/day is the MTD.

Animals: Two hundred and fifty (250) NMRI mice, 5-week old, from Charles River Wiga, Sulzfeld, Germany were used in this study. Animals were randomized to obtain 3 treatment groups of 50 animals per sex and a control group of 100 per sex. Animals were housed individually in type II macrolon cages in an environmentally controlled room ($\approx 23^{\circ}\text{C}$ and 55% relative humidity with a 12-hour light/dark cycle). Tap water was provided in bottles and the animals were fed *ad libitum* standard double-ground SSNIFF R meal with 1% soy bean oil added.

Methods: Groups of 50 males and 50 females each received carvedilol* in the diet for their life-time and a group of 100 mice per sex received the diet only and served as controls.

Daily drug intake for the respective groups was 0, LD-20, MD-65 and HD-200 mg/kg for 97 and 114 weeks for females and males, respectively. Drug concentration in the diet was adjusted according to body weight weekly for the first 2 mo. and at 4 week intervals thereafter. Food consumption was recorded weekly for the first 2 months and monthly thereafter. Body weight was determined weekly. Animals were checked twice daily for clinical status and mortality. Although drug exposure could only be determined (detection limit 20 ng/ml) in serum of LD mice at 1, 6 and 13 weeks, sponsor reported carvedilol exposure in other mice treated for 13 weeks at doses ranging from 60 up 800 mg/kg/day.

At 1-year on study, mice were examined monthly for palpable masses. Blood was collected from 10 males and 10 females of each group at the end of the study. A blood smear was prepared from all animals killed during the study.

Statistical analysis (Kruskal-Wallis Anova and/or Mann-Whitney tests) of food consumption, body weight, clinical pathology and tumor data was performed.

Results:

Except were noted, tables below were extracted from IND review prepared by previous pharmacologist and incorporated in the present NDA review.

*Drug in micronized form ($< \mu 20$ particle size) from Batch No. 814396A

Clinical Signs: Most remarkable signs considered to be drug-related signs were apathy, cold skin and ptosis. Cold skin and ptosis were seen in control and drug-treated animals but more frequently in the treated animals. Apathy was seen in HD males and in a few females of all groups.

Food Consumption: Food consumption was significantly decreased in drug treated mice at certain time intervals; HD mice consumed less feed compared to controls. Mean cumulative food consumption was significantly decreased in MD and HD males (3% and 7%, respectively) and high-dose females (5%) (See table below labeled FOOD CONSUMPTION.)

FOOD CONSUMPTION

Dose (mg/kg/day)		0	20	65	200
START	Male	5.00/144.7 ^W	5.00/141.8	5.00/141.4	4.80/146.0
	Female	4.50/179.3	4.40/173.7	4.50/173.4	4.30/173.3
END	Male	4.50/101.2	4.50/100.1	4.50/100.0	4.50/107.1
	Female	4.50/121.2	4.50/125.0	4.30/121.7	4.30/118.7

^W gm/day - Median Values

^Z gm/day/kg body weight

Source: Vol. 1, 000064, 000065, 000165, 000166

Drug Intake: This parameter was calculated on the basis of the animals's body weight and re-adjusted food consumption during the study at 1 to 4 weeks intervals. (See table below labeled DRUG INTAKE.)

DRUG INTAKE (mg/kg/day)

Dose (mg/kg/day)		20	65	200
START	Male	19.4 ^W	64.2	202.1
	Female	19.0	65.0	201.3
END	Male	17.9	61.3	189.7
	Female	17.8	57.1	175.3

^W Median Values

Source: Vol. 1, 000013, 000069

Levels of carvedilol in serum (mean values reported for several mice after 1, 6 and 13 weeks of treatment) could only be determined in mice treated at 20 mg/kg/day using an HPLC fluorometric method which gave variable results (Vol. 29, p.278).

Body Weight: A significant decrease in median body weight gain was seen in HD males (-13% at end of study). HD females also showed a lower median body weight gain (-6%) than controls but that difference was not statistically significant. (See table below labeled BODY WEIGHT.)

BODY WEIGHT (G)

Dose (mg/kg/day)		0	20	65	200
START	Male	14.0 [∇]	15.0	15.5	13.5
	Female	6.5	6.0	6.5	6.5
END	Male	27.0	25.0	26.0	23.5
	Female	17.0	16.5	17.0	16.0

[∇]/ Median Values

Source: Vol. 1, 000062, 000063, 000163, 000164

Pathology and Clinical Chemistry: These parameter were examined in 10 mice/sex/group. The differential blood count did not reveal differences between control and treated animals. Urea nitrogen values were higher in the HD males and MD and HD females. sGPT values were higher in all male treatment groups but were only significantly higher in the LD and HD groups. (See table labeled BIOCHEMICAL CHANGES.)

BIOCHEMICAL CHANGES

Dose (mg/kg/day)		0	20	65	200
Blood Urea Nitrogen mM/L	M	6.3 [∇]	7.7	8.6	9.5
	F	5.4	7.1	8.5	9.5
GPT μM/L	M	24.5	52.6	33.4	41.2
	F	28.0	29.5	39.0	38.5

[∇]/ Median Values

Source: Vol. 1, 000070, 000071

Mortality: Sponsor reports that in the month that the study was to end (undetermined days), there were some sudden deaths with no previous signs of illness in controls (2M, 7F) and drug treated mice, LD (3F), MD (3M, 2F) and HD (4M, 3F). Overall mortality rates were not significantly affected by carvedilol. The mortality for control, LD, MD and HD males at the end of the study (week 114) was 58%, 38%, 56% and 56%, respectively; the respective values for females (study termination was week 97) were 73%, 80%, 78% and 80%. Overall a higher mortality was noted in all groups of females in this study. With the exception of LD males, mortality rate in control and treatment groups was comparable. (See MORTALITY tables below.)

OVERALL MORTALITY - ALL CAUSES

Dose (mg/kg/day)		0	20	65	200
MALE	Animals per Group	100	50	50	50
	Total Dead	58 (58) ^{1/}	19 (38)	28 (56)	28 (56)
	Tumor Present	46 (79) ^{2/}	13 (68)	21 (75)	17 (61)
	No Tumor	12 (21)	6 (32)	7 (25)	11 (39)
FEMALE	Animals per Group	100	50	50	50
	Total Dead	73 (73) ^{1/}	40 (80)	39 (78)	40 (80)
	Tumor Present	39 (53) ^{2/}	23 (58)	19 (49)	19 (48)
	No Tumor	34 (47)	17 (42)	20 (51)	21 (52)

^{1/} No. Dead (%)

^{2/} No. Event (% of No. Dead)

Source: Vol. 1, 000026-27, 000095-112

MORTALITY RATE (%) AT 18 MONTHS

Dose (mg/kg/day)		0	20	65	200
MALE	Fatal Tumor	3	0	2	2
	Except Fatal Tumor	3	8	10	16
FEMALE	Fatal Tumor	12	12	14	6
	Except Fatal Tumor	31	32	38	36

Source: Vol. 3, 000373-377

ADJUSTED MORTALITY - FREQUENCY OF ANIMALS WITH FATAL TUMORS^{1/}

Dose (mg/kg/day)		0	20	65	200
MALE	Animals per Group	100	50	50	50
	Total	58 (58) ^{2/}	19 (38)	28 (56)	28 (56)
	Fatal Tumor ^{1/}	28 (28)	8 (16)	16 (32)	9 (18)
	Without Fatal Tumor	30 (30)	11 (22)	12 (24)	19 (38)
FEMALE	Animals per Group	100	50	50	50
	Total	73 (73)	40 (80)	39 (78)	40 (80)
	Fatal Tumor ^{1/}	36 (36)	13 (26)	15 (30)	13 (26)
	Without Fatal Tumor	37 (37)	27 (54)	24 (48)	27 (54)

^{1/} Includes fatal tumors according to context 3 and 4 of Proto.

^{2/} No. and (%)

Source: Vol. 1, 000026-27, 000143-146

Gross Pathology: Sponsor stated that no drug-related effects were identified because most observations were considered related to poor body condition.

Histopathology: Non-neoplastic changes reported consisted of single cell hepatocellular necrosis occurring a slightly higher incidence in high-dose females than in controls (14% versus 22%). All other histopathologic changes noted were regarded by sponsor as spontaneous, incidental or infectious in nature.

Compared to controls, the total number of tumor carriers decreased as the dose of carvedilol increased for either sex. The number of animals with tumors with the highest frequencies are presented in table below provided by investigators in the study report.

		Carcinogenicity Study with Carvedilol in mice						J 4 - 67
Table 7: Number of animals with tumors of the organs with the highest frequencies (100 mice per control and 50 mice/dose/sex)								
male mice								
Organs								
Dosage Group	Lungs	Adrenal cortex	Harder. gland	Liver	lymphat. system	Pituitary	Testes	
Control	46	26	25	16	9	6	0	
20 mg/kg	22	4	13	9	10	2	1	
65 mg/kg	17	6	14	7	7	1	3	
200 mg/kg	18	11	11	2	6	2	1	
female mice								
Organs								
Dosage Group	Pituitary	lymphat. system	Lungs	Ovary	Uterus	Harder. gland	Mamm. gland	
Control	25	25	16	15	10	9	4	
20 mg/kg	7	14	4	3	5	3	2	
65 mg/kg	11	15	6	0	3	4	1	
200 mg/kg	5	13	3	1	2	8	0	

NB. The following table was extracted from previous reviews which shows a breakdown of lung tumors and repeats some of the data from the above table.

ORGANS WITH GREATEST TUMOR FREQUENCY

Dose (mg/kg/day)		0	20	65	200
No. Per Group		100	50	50	50
Lung [∇]	M	46 (27+19) [∞]	22 (16+6)	17 (11+6)	18 (14+4)
	F	16 (13+3)	4 (4+0)	6 (4+2)	3 (3+0)
Pituitary [∇]	F	25	7	11	5
Lymphatic Tissue [∇]	F	25	14	15	13

[∇] Broncho-alveolar cell tumor

[∇] Adenoma

[∇] Leucosis

[∞] n (n benign + n malignant)

Source: Vol. 1, 000038-43, 000073

Tables were extracted from previous reviews to show the absence of dose-dependency in the decrease in frequency of- with malignant tumors, and the analysis of tumor severity.

FREQUENCY OF ANIMALS WITH TUMORS

Dose (mg/kg/day)	0	20	65	200
No. Per Group	100	50	50	50
MALE	√/46+37 (83)√2/	13+25 (76)	21+19 (80)	17+17 (68)
FEMALE	39+23 (62)	23+6 (58)	19+9 (56)	19+7 (52)

√/ n unscheduled killed or died with tumor + n scheduled killed with tumor

√2/ % tumor

Source: Vol. 1, 000026-27

FREQUENCY OF ANIMALS WITH MALIGNANT TUMORS

Dose (mg/kg/day)		0	20	65	200
MALE	Animals Per Group	100	50	50	50
	No. with tumor	83	38	40	34
	No. with malignant tumor	40	17	23	16
	No. with metastasizing tumor	1	1	1	2
FEMALE	Animals Per Group	100	50	50	50
	No. with tumor	62	29	28	26
	No. with malignant tumor	37	20	18	16
	No. with metastasizing tumor	5	1	0	2

Source: Vol. 1, 000044-45, 000072

ANALYSIS OF TUMOR SEVERITY - ACCORDING TO PETO

Dose (mg/kg/day)		0	20	65	200
MALE	Animals per Group	100	50	50	50
	Total	83	38	40	34
	Fatal Tumor (3,4)√2/	28 (34)√1/	8 (21)	16 (40)	9 (26)
	Incidental Tumor (1,2)√2/	55 (66)	30 (79)	24 (60)	25 (74)
FEMALE	Animals per Group	100	50	50	50
	Total	62	29	28	26
	Fatal Tumor (3,4)	36 (58)	13 (45)	15 (54)	13 (50)
	Incidental Tumor (1,2)	26 (42)	16 (55)	13 (46)	13 (50)

√1/ No. and (% of Total)

√2/ Context of Peto

Source: Vol. 1, 000143-46

These neoplastic lesions occurring with an incidence of 5% or greater in any dose group are listed in table below prepared by sponsor.

Table 18

Neoplastic Lesions in Mouse Carcinogenicity Study of Carvedilol
Occurring with an Incidence $\geq 5\%$ in any Dose Group

Lesion	Sex	Control	20 mg/kg	65 mg/kg	200 mg/kg
Liver cell adenoma	M	12/100	6/50	5/50	1/50
	F	1/100	0/50	0/50	0/50
Liver cell carcinoma	M	4/100	3/50	2/50	1/50
	F	0/100	0/50	0/50	0/50
Adrenal cortical adenoma	M	18/100	4/50	6/50	10/50
	F	1/100	1/50	0/50	0/50
Adrenal cortical carcinoma	M	8/100	0/50	1/50	1/50
	F	1/100	1/50	0/50	0/50
Bronchoalveolar adenoma	M	27/100	16/50	11/50	14/50
	F	13/100	4/50	4/50	3/50
Bronchoalveolar carcinoma	M	19/100	6/50	6/50	4/50
	F	3/100	0/50	2/50	0/50
Testicular interstitial cell tumor	M	0/100	1/50	3/50	1/50
Uterine stromal polyp	F	5/100	2/50	0/50	0/50
Ovarian granulosa cell tumor	F	10/100	1/50	0/50	1/50
Malignant lymphoma	M	9/100	10/50	7/50	6/50
	F	25/100	14/50	15/50	13/50
Pituitary adenoma	M	6/100	2/50	1/50	2/50
	F	25/100	7/50	11/50	5/50
Lacrimal gland adenoma	M	27/100	13/50	15/50	11/50
	F	10/100	3/50	4/50	6/50
Lacrimal gland carcinoma	M	0/100	0/50	2/50	1/50
	F	0/100	0/50	0/50	2/50
Mammary gland carcinoma	F	6/100	2/50	1/50	0/50

Sponsor asserts that the number of tumor carriers, counting all tumors and the number of carriers with malignant tumors did not show any increase with dose for either sex.

Table 19									
BM 14.190									
SURVEY OF TUMOR FREQUENCY IN MALE MICE									
Dose	n	unscheduled killed or died	with tumors	without tumors	scheduled killed	with tumors	without tumors	total with tumors	total without tumors
Control	100	58-58%	46-79,3%	12-20,7%	42-42%	37-68,1%	5-11,9%	83-83%	17-17%
20 mg/kg	50	19-38%	13-68,4%	6-31,6%	31-62%	25-80,6%	6-19,4%	38-76%	12-24%
65 mg/kg	50	28-56%	21-75%	7-25%	22-44%	19-86,4%	3-13,6%	40-80%	10-20%
200 mg/kg	50	28-56%	17-60,7%	11-39,3%	22-44%	17-77,3%	5-22,7%	34-68%	16-32%

Table 2									
BM 14.190									
SURVEY OF TUMOR FREQUENCY IN FEMALE MICE									
Dose	n	unscheduled killed or died	with tumors	without tumors	scheduled killed	with tumors	without tumors	total with tumors	total without tumors
Control	100	73-73%	39-53,4%	34-46,6%	27-27%	23-85,2%	4-14,8%	62-62%	38-38%
20 mg/kg	50	40-80%	23-57,5%	17-42,5%	10-20%	6-60%	4-40%	29-58%	21-42%
65 mg/kg	50	39-78%	19-48,7%	20-51,3%	11-22%	9-81,8%	2-18,2%	28-56%	22-44%
200 mg/kg	50	40-80%	19-47,5%	21-52,5%	10-20%	7-70%	3-30%	26-52%	24-48%

Carcinogenicity study with BM 14.190

Carcinogenicity study with BM 14.190 in mice

Division of Biometrics evaluation reports that in female mice there was a marginally significant positive linear trend in harderian gland carcinoma ($p= 0.052$) and harderian gland carcinoma and adenoma combined ($p= 0.06$); no trend was found in males. (N.B. The total number of harderian gland tumors reported by sponsor for both sexes does not agree with the numbers reported by Biometrics. However, both reports shows the incidence of these tumors was not dose-related.) (See Table 19 above prepared by investigators.)

In addition, the Biometrics' report expresses concern about the number of surviving female mice and their body weight data. Even when Biometrics recognizes that at HD the MTD had been reached in the mouse carcinogenicity study, the reports stated- "It seems that there were not sufficient female mice in the control and treated groups living long enough to get an adequate exposure to the chemical....." Biometrics considers that because the survival rates in mice the study in the control, LD, MD and HD groups was 42%, 62%, 44% and 44%, respectively for males, and 27%, 20%, 22%, and 20%, respectively for females, there "were not sufficient females mice" in these groups living long enough to get an adequate exposure to carvedilol and to be at risk of forming late-developing tumors. This concern by Biometrics is based on a personal communication between JK Haseman and KK Lin at FDA.

This reviewer considers the low survival and the lack of remarkable effect on body weight uninterpretable in the absence of toxicokinetic data collected during this carcinogenicity study in mice. However, limited pharmacokinetic data with ^{14}C -carvedilol (100 mg/kg p.o. single dose) given the NMRI mice showed no significant different metabolic profile of the drug among the two sexes (about 25 were identified in urine and feces). Unchanged carvedilol was a minor component in urine while being the most abundant component in plasma in both male and female mice determined up to 6 hrs post dosing. Although qualitatively the plasma metabolic profile carvedilol was similar in both sexes, there quantitative differences. The most remarkable pharmacokinetic finding reported was that plasma from female mice contained higher concentrations of carvedilol metabolites, relative to unchanged carvedilol, than found in the plasma from male mice. The unchanged carvedilol concentrations in male mice plasma were 3-4 fold higher than in female mice.

This reviewer concludes that the data submitted show that long-term administration of carvedilol in feed to mouse showed no clear evidence of carcinogenic activity when males received median oral doses ranging from 202 to 189 mg/kg/day for 114 weeks and, females 201 to 175 mg/kg/day for 97 weeks. An interesting finding was that although not dose-related, carvedilol-treated mice showed testicular tumors (C-0, LD-1; MD-3, HD-1) drug-treated male showed a few testicular tumors.(See Table 19 above.)

CARCINOGENICITY STUDIES (Cont'd)

The following is the sponsor's summary tables of an aborted and a definitive carcinogenicity studies, followed by a brief overview of these studies.

RAT (SPRAGUE-DAWLEY, CAW-ICO-WIGA)

Drug-Related Observations

Species	Duration (weeks)	Doses (mg/kg)	Report No. Ref. No. Location in NDA IND Submission
1) Rat	28 (early termination)	(600 ppm) 30(M), 35(F); (2000 ppm) 98(M), 124(F); (4000 ppm) 199(M), 250(F) diet	TP/0006/SKF-105517 (Boehringer Mannheim report J7) Location: Vol. 1.33 Page 000002

Mortality was observed around the occurrence of a steep decrease in body weight. One female died in the low-dose group, 1 male and 1 female in the mid-dose group and 11 females of the high-dose group died between days 81 and 115. Animals that died during the study showed weight loss, slow movement, cool skin, apathy, blepharostenosis and marked emaciation. Although these symptoms were considered to be excessive pharmacological actions, it is more likely that they resulted from a combination of drug treatment and water deprivation. High-dose males and females showed a lower body weight gain from the start of the study. A steep decrease in body weight was observed around day 112 in high-dose males and in mid- and high-dose females. At this time point, the automatic drinking water system was replaced by glass bottles. This resulted in a return to the original body weights as present before the steep decrease. At day 182 of the study, high-dose males and females showed a lower body weight than the controls, 11 and 14%, respectively. A dose-related decrease in hemoglobin was observed in both sexes (approx. 10% in high-dose). All drug-treated males showed an increase in lymphocyte count; the increase was significant in the low- and mid-dose males but not in high-dose males. BUN was significantly increased in high-dose females and serum creatinine and glucose values were significantly decreased in mid-dose females. A variety of macroscopic observations were made in the animals that died and was related to poor condition (fat and lymphoid atrophy, empty GI tract). Main lesions observed light microscopically in these animals were slight biliary hyperplasia (treatment-related) and atrophy of lymphoid tissues. Based on body weight depression prior to and after a technical failure of the automatic drinking water system and the occurrence of deaths due to the technical failure, the study was terminated on day 199.

- 1. Doses of carvedilol (600, 2000 and 4000 ppm in diet) were selected on the basis of a 13-weeks study (J5 above). In present study, 50 rats/sex/groups were used. Drug intake diminished up to the end of the study; doses reported above represent the drug intake by the end of the study, when the study was stopped (10-06-93) after 6 months of treatment (28-07-83.)

Rat carcinogenicity (Cont'd.)

Species	Duration (weeks)	Doses (mg/kg)	Report No. Ref. No. Location in NDA IND Submission	Drug-Related Observations
Rat	104	(200 ppm) 8(M), 10(F); (400 ppm) 16(M), 19(F); (800 ppm) 31(M), 38(F); (1600 ppm) 62(M), 75(F) diet	TC001BS (Boehringer Mannheim report J2) Location: Vol. 1.34 Page 000302 Submitted to IND 8/26/88	Swollen eyelids, cold to touch and a distended abdomen were observed in drug-treated females. Light and touch sensitivity and chromodacryorrhea were more common in drug-treated females than in controls. Food intake was less in high-dose animals (up to 5% in males and 11% in females). At various intervals, median body weight in mid- and high-dose males was approx. 5% higher than controls. Mid- and high-dose females showed a lower median body weight of approximately 8%. A statistically significant increase in unscheduled deaths without a fatal tumor occurred in high-dose animals. This was not associated with any statistically significant changes in the mean life span. Macroscopically, there were less masses observed in the drug-treated animals than in the controls. Drug-treated males showed a higher incidence of lung edema and hemorrhage than the controls. A rounded apex of the heart and ventricular dilation were more common in drug-treated animals than in controls. Liver enlargement, discoloration and congestion and splenic enlargement were observed more frequently in high-dose males than in controls. Adrenal and splenic enlargement were more common in high-dose females than in controls and discoloration of the pituitary was seen more frequently in mid- and high-dose females than in controls. A slightly higher incidence of thyroid adenoma/carcinoma was observed in drug-treated females (4 to 12%) than in controls (2%). Since there was no dose response relationship, the highest incidence being within the expected range for SD rats and the absence of a positive response in males, the thyroid tumor response was not considered to be treatment-related. The number of benign and malignant mammary tumors were greater in females at 200 and 400 ppm than in the controls but the number in females at 800 and 1600 ppm was lower than in the controls. Therefore, the increased number in the low, and mid-low dose groups were considered to be normal variations, particularly since the number of malignant tumors were the greatest in controls. No other significant effect on tumor formation was observed other than the total number of tumor bearing males and females with malignant tumors decreased with increasing dose.

Brief overview of rat studies.

Oral Carcinogenicity Study of Carvedilol in Rats (stopped after 6 months).

[TP/0006/SKF-105517 (Boehringer Mannheim report J7) Vol. 33; This study started on 18-Jan-83 and was aborted by 28-July-83].

Dose selection was based on the results of a rat (Sprague-Dawley, Caw-Ico-Wiga) 3-month dose-ranging study from 200 ppm up to 8,000 ppm carvedilol (TP-0004/SKF-105517 summarized above by sponsor, Boehringer Mannheim report J5). In that rat study the MTD was determined to be 4000 ppm.

Same strain of rats were used. Methods used in the conduct of the study were reported in the NDA and essentially similar to those used in the actual rat carcinogenicity study described below. Carvedilol (batch no. 814936A) was incorporated in the diet at concentrations of 600, 2000 and 4000 ppm and 2 controls groups of 50 animals per sex received the diet only.

At the start of the study, drug intake in the various male groups was reported as approximately 83, 281, and 579 mg/kg and 76, 276 and 545 mg/kg for females. At termination of the study (day 199), drug intake in males was 30, 98 and 199 mg/kg and 35, 124 and 250 mg/kg in females.

Necropsy was performed and the following organs from 10 animals per group were weighed: heart, liver, spleen, kidneys, adrenals, thyroid, testes or ovaries, pituitary and brain. Only tissues from animals that died during the study were examined light microscopically.

Results

Clinical signs: Animals that died during the study showed weight loss, slow movement, cool skin, apathy, blepharostenosis and marked emaciation. Although these symptoms were considered to be excessive pharmacological actions, it is more likely that they were the results of a combination of drug treatment and water deprivation.

Mortality was observed around the occurrence of the steep decrease in body weight. One female died in the LD group, 1 male and 1 female in the MD group and 11 females of the HD group died between days 81 and 115.

Body weights of HD group showed a lower body weight gain from the start of the study. A steep decrease in body weight was reported for day 112 in HD males and, in MD and HD females; this observation was completely reversed when the automatic drinking water system was replaced by glass bottles. However, at day 182 of study, HD rats showed about 13% lower body weight than the controls.

A dose-related decrease in hemoglobin was observed in both sexes, decrease in HD animals was approximately 10%. Both, MD and HD rats showed lower hematocrit values. All drug-treated males showed an increase in lymphocyte count; the increase was statistically significant ($p < 0.05$)* in the LD and MD males but not in the HD group. Blood urea nitrogen was significantly increased ($p < 0.05$) in HD females and serum creatinine and glucose values were significantly decreased ($p < 0.05$) in MD females.

Necropsy was performed. Most animals that died showed poor condition (i.e., atrophy of various tissues, such as fat and lymphoid and an empty gastro-intestinal tract). Absolute spleen weight was increased in MD and HD males, absolute adrenal and liver weights were decreased in HD males and absolute adrenal, ovary, liver, kidney, and brain weights were decreased in HD females. When compared to body weight, relative spleen weight was increased in HD males and MD and HD females, relative liver weight decreased in HD males and relative heart weight increased in all drug-treated females. When compared to brain weight, relative spleen weight was increased in MD and HD males, relative pituitary and liver weights were decreased in HD males and relative pituitary, liver and kidney weights were decreased in HD females.

The LD female that died during the study was diagnosed with a malignant lymphoma, lesion was considered to be spontaneous. Although the rest of the deaths were attributed to drug treatment, the data suggest that water deprivation was at least a contributing factor. The main lesions found in these animals were slight biliary hyperplasia (treatment-related) and atrophy of lymphoid tissues.

Sponsor concludes that the marked body weight depression resulted from too high dosages used. Thus, the study was terminated at day 199.

*Kruskal-Wallis Anova and/or Mann-Whitney tests, $p < 0.05$.

Definitive Oral Carcinogenicity Test of Carvedilol. 2-Year Rat Study (Sprague-Dawley, Caw-Ico-Wiga). (TC001BS; Boehringer Mannheim report J2 in Vol. 34. Dosing dates: 01-06-83 and 10-06-85)

Dose Selection: Although the previous attempt to perform a carcinogenicity study was based on a 3-month dose-range, doses used were found to be too high based because of the marked body weight depression that resulted. The study had to be aborted after 6 months of animal dosing (see above), and this second rat carcinogenicity study was started using lower doses of carvedilol- 200, 400, 800 and 1600 ppm in diet.

Animals: In this study, 250 rats (5 week old)/sex were used. Rats were randomly assigned to 4 treatment groups of 50 animals per sex and 1 control group of 50 per sex. A second control group was taken from a parallel running carcinogenicity study. Rats were housed in pairs in wire cages H3 (V2A-4301) in an environmentally controlled room ($\approx 23^{\circ}\text{C}$ and 55% relative humidity with a 12 hours light/dark cycle). Initially, rats received distilled water via an automatic drinking tap water system. This system was replaced by glass bottles after 6 to 7 months in the study. The animals were fed *ad libitum* standard double milled meal with 1% soy bean oil added.

Methods: Groups of 50 males and 50 females each received carvedilol* in the diet at concentrations of 200, 400, 800 and 1600 ppm and 1 group of 50 rats/sex received the diet only and served as controls.

Drug concentrations in the diet were kept constant during the course of the study and were calculated in mg/kg/day from food consumption. Animals were checked twice daily for clinical status and mortality. Food consumption over a 2-day period was recorded biweekly and expressed as mean per day up to 14 months and monthly thereafter. Body weights were recorded once a week.

After one-year on study, animals were examined monthly for palpable masses. At the termination of the study, clinical pathology parameters were determined in 10 males and 10 females from each group. Necropsy was performed on all animals. Tissues from all animals were examined light microscopically.

Results

Except were noted, tables below were extracted from IND review prepared by previous pharmacologist and incorporated in the present NDA review.

Clinical Signs: HD rats appeared leaner than controls. Swollen eyelids, cold to touch and a distended abdomen were only observed in drug-treated females. Light and touch sensitivity and chromadacryorrhea were more commonly observed in drug-treated females than in controls. All these signs were neither severe nor life-threatening.

*Batch nos. 814 396A and 814 723A

Food Consumption: Food intake in HD males was between 0 and 5% less than the controls during the study. The percentage range for HD females was 3 to 11%. (See Table labeled FOOD CONSUMPTION.)

FOOD CONSUMPTION

ppm		0	200	400	800	1600
START	Male	^W /26.8/107 ^W	26.0/107	25.3/102	27.5/107	26.0/106
	Female	18.8/107	18.5/109	18.3/108	19.3/108	18.0/103
END	Male	26.1/39.6	25.8/38.5	25.8/40.5	26.5/39.2	25.3/38.8
	Female	19.6/48.3	20.5/47.7	20.1/46.9	18.8/47.6	18.8/46.7

^W/ gm/day - Median Values

^Z/ gm/day/kg body weight

Source: Vol 1, 000107, 108, 109, 110

Drug Intake: This parameter varied during the study. At the start of the study, drug intake in the various male groups was approximately 21, 41, 86 and 169 mg/kg and 22, 43, 81 and 165 mg/kg in females. At the end of the study, drug intake had decreased in males to 8, 16, 31 and 62 mg/kg and in females to 10, 19, 38 and 75 mg/kg. (See DRUG INTAKE table.)

DRUG INTAKE (mg/kg/day)

ppm		200	400	800	1600
START	Male	21.3 ^W	40.8	85.5	169.3
	Female	21.7	43.0	86.7	165.3
END	Male	7.7	16.2	31.4	62.1
	Female	9.5	18.8	37.1	74.7

^W/ Median Values

Source: Vol. 1, 000022; Table 5, 000112

Body Weight: At various intervals, median body weight in MD and HD males was 4 to 6% higher than controls. Remarkable body weight increases in males were seen particularly at the beginning of the study from day 84 to 181. Overall the body weight of the males was reported as not affected by the treatment with carvedilol. (See BODY WEIGHT table below). Females showed a dose-related reduction in body weight gain; the difference in medians between the HD and control was about 8% between days 427 and 727 of study.

BODY WEIGHT (g)

ppm		0	200	400	800	1600
START	Male	171 ^{AJ}	175	175	176	170
	Female	110	113	109	118	114
END	Male	568	598	593	596	577
	Female	344	349	353	318	318

^{AJ}/ Median Values

Source: Vol. 1, 000105, 106

Based on body weight findings, Division of Biometrics evaluation considered that it was important to check the toxic signs of the HD rats to determine the adequacy of this for males in this carcinogenicity study. This reviewer considers that since at the 2 highest doses of carvedilol, the males had a higher death rate compared to the other groups as well as lower glucose values (not seen in other studies) at the 3 highest doses, the HD intake (about 169 mg/kg/day at the start of the study later reduced to about 62 mg/kg/day by the end of the study) may be considered adequate for the males. Further, in the previous attempt by sponsor to conduct a oral carcinogenicity study in rat at the determined MTD of 4000 ppm animals that died showed weight lost and marked emaciation.

Hematology and Clinical Chemistry: Data were collected from selected survivors as a single determination at the end of the study. The data showed marked variation and a correlation with drug treatment was not apparent.

Mortality: The overall mortality appears in a table below. Male mortality was dose dependent; higher percentage of males died compared to females.

OVERALL MORTALITY - ALL CAUSES

ppm		0	200	400	800	1600
Male	Total	32 (64) ^{11/}	35 (70)	35 (70)	39 (78)	42 (84)
	Tumor Present	25 (78) ^{12/}	24 (69)	16 (46)	24 (62)	14 (33)
	No Tumor	7 (22) ^{12/}	11 (31)	19 (54)	15 (38)	28 (67)
Female	Total	27 (54)	27 (54)	28 (56)	26 (52)	21 (42)
	Tumor Present	27 (100)	26 (96)	28 (100)	23 (89)	20 (95)
	No Tumor	0 (0)	1 (4)	0 (0)	3 (11)	1 (5)

^{11/} No. Dead (%);

^{12/} No. Event (% of No. Dead)

Source: Vol 1, 000032-33, 000132-150

A statistically significant increase (Kaplan-Meier and Mantel-Cox or Breslow tests, $p < 0.05$) in unscheduled deaths without a fatal tumor occurred in animals receiving the highest dose of carvedilol. The unscheduled deaths without a fatal tumor were not associated with any statistically significant changes in mean life span (Table 20 extracted from previous review.)

Table 20

Total Unscheduled Deaths and Unscheduled Deaths without Fatal Tumor
in Male Rats from the Carcinogenicity Study of Carvedilol

Dose (ppm)	Total Unscheduled Deaths	Unscheduled Deaths without Fatal Tumor	Mean Life span
0	32 (64%)	12	608 ± 33
200	35 (70%)	21	587 ± 30
400	35 (70%)	22	543 ± 32
800	39 (78%)	22	555 ± 28
1600	42 (84%)	30	569 ± 22

Gross Pathology: The liver was the target organ of toxicity. Liver enlargement, discoloration and congestion and splenic enlargement were observed more frequently in high-dose males than in controls.

There were less masses observed in the drug-treated animals than in the controls. Drug-treated males showed a higher incidence of lung edema and hemorrhage than the controls. A rounded apex of the heart and ventricular dilation were more common in drug-treated animals than in controls. Adrenal and splenic enlargement were more common in HD females than in controls and discoloration of the pituitary was seen more frequently in mid- and high-dose females than in controls.

Histopathology: Males showed dose-related focal hyperplasia in liver. Occasional benign hepatoma were found in all drug treated males. In female rats, there was marginally statistically significant linear trend in thyroid adenoma ($p = 0.054$). In females, pairwise comparison of HD vs. controls showed that the increase in thyroid adenomas was statistically significant ($p = 0.0457$). When thyroid adenomas/carcinomas were combined, there was no dose-related trend found in either sex, although females did show a higher incidence of the combined tumors over controls. Also in females, although when compared to controls the number of mammary adenomas in groups treated with 200 ppm, 400 ppm and 1600 ppm were increased, the incidence of these tumors was not dose related.

Of the non-neoplastic lesions, liver cell hyperplasia with/without angiectasis, chronic nephropathy and an inflammatory cell infiltrate in the heart were more common in HD males than in controls whereas the opposite was the case in females. Splenic congestion occurred more frequently in drug-treated animals than in controls. Lung edema was more common in drug-treated males than in controls and angiectasis of the adrenal cortex was observed more frequently in HD males and MD and HD females than in controls.

The frequency of tumor bearing rats declined with drug treatment appeared in tables below extracted from previous pharmacologist's review.

FREQUENCY OF ANIMALS WITH TUMORS

ppm	0	200	400	800	1600
Male	√/25 + 16 (82)√/	24 + 9 (66)	16 + 8 (48)	24 + 8 (64)	14 + 5 (38)
Female	27 + 21 (96)	26 + 22 (96)	28 + 21 (98)	23 + 22 (90)	20 + 26 (92)

√/ n unscheduled killed or died with tumor + n scheduled killed with tumors.
 √/ % tumors

Source: Vol 1, Table 1.2, 000032-33, 000167-170

FREQUENCY OF ANIMALS WITH MALIGNANT TUMORS

ppm	0	200	400	800	1600	
M 50	No. With Tumor	41	33	24	32	19
	No. With Malignant Tumor	14	8	8	11	5
	No. with Metastasizing Tumor	12	0	12	6	12
F 50	No. With Tumor	48	48	49	45	46
	No. With Malignant Tumor	17	14	9	7	11
	No. with Metastasizing Tumor	6	12	12	12	6

Source: Vol. 1, STAT, Table 7, 000117, Table 18, 000049-50, Vol. 1, 000151-170

When deaths caused by tumors were excluded data showed that the mortality in males was higher than females and controls. Based on these finding Division of Biometrics asserted in its evaluation that "There were not sufficient males in the control and treated groups living long enough to get an adequate exposure to the chemical and to be at risk of forming late-developing tumors based on Haseman's proposition," personally communicated to Dr. Karl K. Lin at FDA.

ADJUSTED MORTALITY - FREQUENCY OF ANIMALS WITH FATAL TUMORS^{√/}

ppm	0	200	400	800	1600
Male Total	33 (66) √/	36 (72)	35 (70)	39 (78)	42 (84)
Fatal Tumor ^{√/}	21 (42)	15 (30)	13 (26)	17 (34)	12 (24)
Without Fatal Tumor	12 (24)	21 (42)	22 (44)	22 (44)	30 (60)
Female Total	34 (68)	31 (62)	28 (56)	27 (54)	21 (42)
Fatal Tumor ^{√/}	34 (68)	29 (58)	28 (56)	22 (44)	20 (40)
Without Fatal Tumor	0 (0)	2 (4)	0 (0)	5 (10)	1 (2)

√/ Includes fatal tumors according to context 3 and 4 of Peto
 √/ No. and (%)

Source: Vol 1, 0000132-150, 000151-166, 000167-170, 000171-187; Vol. 4, 000282-283.

The following Table 21 was prepared by sponsor.

NEOPLASTIC LESIONS OCCURRING IN RAT CARCINOGENICITY STUDY OF CARVEDILOL WITH AN INCIDENCE $\geq 5\%$ IN ANY DOSE GROUP.

Lesion	Sex	Control	200 ppm	400 ppm	800 ppm	1600 ppm
Liver cell adenoma	M	0/50	2/50	1/50	3/50	2/50
	F	0/50	0/50	0/50	0/50	1/50
Skin, fibroma	M	3/50	3/50	2/50	4/50	1/50
	F	1/50	0/50	0/50	0/50	0/50
Skin, (neuro-) fibrosarcoma	M	1/50	0/50	2/50	2/50	1/50
	F	0/50	0/50	0/50	0/50	0/50
Pituitary adenoma	M	17/50	15/50	7/50	14/50	10/50
	F	4/50	31/50	29/50	34/50	30/50
Thyroid adenoma	M	4/50	2/50	4/50	2/50	0/50
	F	0/50	6/50	2/50	4/50	5/50
Thyroid carcinoma	M	4/50	0/50	1/50	0/50	0/50
	F	1/50	0/50	0/50	0/50	0/50
Mammary adenoma	M	1/50	0/50	0/50	1/50	0/50
	F	37/50	53/50	65/50	37/50	45/50
Mammary carcinoma	M	0/50	0/50	0/50	0/50	0/50
	F	16/50	13/50	6/50	6/50	5/50

NB.- The following table, on 2 specific tumors, was extracted from data submitted in NDA Amendment From the response to FDA request for historical control tumor data for the strain of rats used in the carcinogenicity study with carvedilol, the following table on 2 specific tumors was prepared with data extracted from sponsor's response in NDA Amendment dated 03-29-94.

Historical Control Tumor Data from
Sprague-Dawley rats (Caw-Leo-Wiga) during the period 1983-1985.

Number of tumors occurring in 100 animals are provided in the table below:

Organ System/ Lesion	Males	Females
Thyroid gland		
Follicular cell adenoma	5/100	3/100
Follicular cell carcinoma	1/100	
C cell tumor	2/100	5/100
Liver		
Liver cell adenoma	1/100	3/100

The following Table 22, submitted by sponsor, shows a survey of tumor frequency in rats for the oral carcinogenicity study.

Table 22

SURVEY OF TUMOR FREQUENCY IN MALE RATS

Dose	n	unscheduled killed or died	with tumors	without tumors	scheduled killed (SURVIVAL)	with tumors	without tumors	total with tumors	total without tumors
Control I	50	32-64%	25-78%	7-21,8%	18-36%	16-88,9%	2-11,1%	41-82%	9-18%
Control II	50	26-52%	21-80,8%	5-19,2%	24-48%	16-66,7%	8-33,3%	37-74%	13-26%
100 ppm	50	35-70%	24-68,6%	11-31,4%	15-30%	9-60%	6-40%	33-66%	17-34%
400 ppm	50	35-70%	16-45,7%	19-54,3%	15-30%	8-53,3%	7-46,6%	24-48%	26-52%
800 ppm	50	39-78%	24-61,5%	15-38,5%	11-22%	8-72,7%	3-27,3%	32-64%	18-36%
1600 ppm	50	42-84%	14-35,3%	28-66,6%	8-16%	5-62,5%	3-37,5%	19-38%	31-62%

SURVEY OF TUMOR FREQUENCY IN FEMALE RATS

Dose	n	unscheduled killed or died	with tumors	without tumors	scheduled killed (SURVIVAL)	with tumors	without tumors	total with tumors	total without tumors
Control I	50	27-54%	27-100%	-	23-46%	21-93,3%	2- 8,7%	48-96%	2- 4%
Control II	50	23-46%	23-100%	-	27-54%	26-96,3%	1- 3,7%	49-98%	1- 2%
200 ppm	50	27-54%	26-93,3%	1- 3,7%	23-46%	22-95,6%	1- 4,3%	48-96%	2- 4%
400 ppm	50	28-56%	28-100%	-	22-44%	21-95,4%	1- 4,5%	49-98%	1- 2%
800 ppm	50	26-52%	23-88,5%	3-11,5%	24-48%	22-91,6%	2- 8,3%	45-90%	5-10%
1600 ppm	50	21-42%	20-95,2%	1- 4,8%	29-58%	26-89,6%	3-10,3%	46-92%	4- 8%

From the data submitted, it may be concluded that in the 2-year feed study, there was no evidence of carcinogenic activity with carvedilol in rats receiving median doses ranging in the male from 169 down to 62 mg/kg/day and, in females 165 down to 75 mg/kg/day. Although not dose-related, when compared to control carvedilol intake was associated with slightly higher incidence of thyroid tumors in all drug-treated females and, mammary tumors in LD and MD females (Table 23). Division of Biometrics analysis of the tumor data reported that there was a significant positive linear trend in stomach papilloma ($p=0.049$) and, marginally significant trend in liver hepatocellular adenoma ($p=0.057$) in male rats.

E		Carcinogenicity Study with Carvedilol in Rats					J2 -113	
Table 23: Number of animals with tumors of the organs with the highest frequencies								
male rats								
Organs								
Dosage Group	Pituitary	Urinary bladder	Pancreas	Skin + Subcutis	Thyroid			
Control 1	17	8	8	11	6			
Control 2s	17	9	10	11	4			
200 ppm	15	8	5	8	2			
400 ppm	7	3	5	7	5			
800 ppm	14	2	3	11	2			
1600 ppm	10	0	2	7	0			
female rats								
Organs								
Dosage Group	Pituitary	Urinary bladder	Pancreas	Skin + Subcutis	Thyroid	Mamma. gland	Uterus	
Control 1	41	0	3	3	1	35	7	
Control 2s	36	3	3	2	2	41	6	
200 ppm	31	0	2	2	6	37	5	
400 ppm	29	0	0	2	2	36	5	
800 ppm	35	0	0	0	4	30	5	
1600 ppm	30	0	1	0	5	36	5	
At begin of study there were 50 animals per dosage and sex.								
s = Control 2 were the controls of a parallel study with another substance. Their results were not used for statistical comparisons in this study.								

SPECIAL TOXICITY STUDIES

Special toxicity studies were performed to detecting the potential of carvedilol to produce adverse reactions on an immunological basis, and limiting toxicity studies.

Immunologic effects associated with the exposure to drugs may result in increased susceptibility to pathologic conditions or diseases. All of the immunotoxicologic tests reported by sponsor were *in vivo* models. The following summary tables were prepared by the sponsor. Brief overview of the studies follows the tables.

SUMMARY

SPECIAL TOXICITY STUDIES OF CARVEDILOL (SK&F 105517)

Species	Dose	Type of Study	Report No. Ref. No.⁷⁵ Location in NDA IND Submission	Methods and Results
Mouse	10, 100 mg/animal i.p.	Antigenicity	TC-0021/SKF-105517 (Daiichi report D-14) Location: Vol. 1.38 Page 000002	Carvedilol mixed with alum gel was given to male BALB/c mice twice intraperitoneally. Six days later, blood was collected and serum separated. Sera was injected i.c. on the dorsum of rats to passively sensitize them. Twenty-four hours later, the rats were challenged intravenously with carvedilol (3 mg/kg) to evoke a passive cutaneous anaphylaxis reaction. No reaction was observed and no IgE antibodies were found.
Guinea Pig	0.2, 2 mg/animal s.c.	Antigenicity	TC-0021/SKF-105517 (Daiichi report D-14) Location: Vol. 1.38 Page 000002	Carvedilol plus Freund's complete adjuvant was given thrice subcutaneously to guinea pigs. Eleven days later, blood was collected and serum separated. Serum was given i.c. to naive guinea pigs. Four hours or 8 days later, these sensitized animals were challenged intravenously with 3 mg/kg carvedilol. One animal (0.2 mg/animal) challenged after 4 hours showed a positive reaction. All other animals, also those challenged after 8 days, showed a negative reaction. In addition, no systemic anaphylaxis could be evoked in all animals tested. Carvedilol-specific antibodies were determined in sera by RIA employing Protein-A-Sepharose-CL-4B. Serum that had given a positive PCA reaction showed a reading about twice as that of normal serum. All other serum samples were comparable with readings of normal serum.
Guinea Pig	0.2, 2 mg/animal oral & s.c.	Antigenicity	TC-0020/SKF-105517 (Daiichi report D-15) Location: Vol. 1.38 Page 000 Submitted to IND	Guinea pigs were given carvedilol orally 3/week for 3 weeks. Other groups were given carvedilol with Freund's complete adjuvant with and without ovalbumin. Twelve days later, blood was collected and serum separated. Serum was given i.c. to guinea pigs and animals were challenged with carvedilol (3 mg/kg) or ovalbumin intravenously 4 hours later. Except for the positive controls, no passive cutaneous anaphylaxis reaction was evoked.

Special Toxicity Studies (Cont'd.)

Species	Dose	Type of Study	Report No. Ref. No. ⁷⁶ Location in NDA IND Submission	Methods and Results
Guinea Pig	0.5, 5 s.c.	Delayed Hypersensi- tivity	TC/0018/SKF-105517 (Daiichi report D-R-11) Location: Vol. 1.38 Page 000231	Guinea pigs were twice sensitized by subcutaneous injection with carvedilol plus Freund's complete adjuvant. Seven days later, the animals were challenged with 30 mg carvedilol/site. Twenty-four and 48 hours later, skin sites were examined. There was no evidence of a delayed type hypersensitivity reaction.
Rabbit	1, 2, 10 mg/animal oral & s.c.	Antigenicity	TC-0020/SKF-105517 (Daiichi report D-15) Location: Vol. 1.38 Page 000131	Male NZ White rabbits were given carvedilol orally 3/week for 3 weeks. Other groups were given carvedilol with Freund's complete adjuvant with and without ovalbumin. Eleven days later, blood was collected and serum separated. Serum was given i.c. to guinea pigs and animals were challenged intravenously with carvedilol (3 mg/kg) 4 hours later. Except for the positive controls, no positive passive cutaneous anaphylaxis reaction was observed. Carvedilol-specific antibodies were determined in sera by RIA employing Protein-A-Sepharose-CL-4B. Except positive controls, all other serum samples were comparable with readings of normal serum.
Dog	12.6, 54 mg/kg i.v. infusion & 7.5, 15, 30 mg/kg i.v. bolus	Limiting toxicity	TI002BS Location: Vol. 1.38 Page 000246 Submitted to IND on 8/18/88	In the conscious dog, limiting toxicity was produced by 15 mg/kg (i.v. bolus) and consisted of convulsions and alterations of the ECG, including prolongation of the P-wave, PR and QRS intervals. In the anesthetized dog, the limiting toxic dosage was 30 mg/kg (i.v. bolus) which produced death of the animals within 5 minutes. Widening of the P-wave and the QRS and QT intervals were typical events. Blood pressure reduction, possibly resulting from a cardiac depressant action of the compound, was the cause of death. Carvedilol may produce alterations in blood pressure and heart rate by exerting a direct depressant effect on cardiac tissue. The cardiac depressant effect is most likely due to the membrane-stabilizing activity of carvedilol.

Brief overview of the special toxicity studies with carvedilol.

1.-Antigenicity and Delayed Hypersensitivity to Carvedilol

The potential for carvedilol to affect the immune system was examined in male species- (BALB/c), guinea pig (Hartley) and rabbit (NZ White). Various antigenicity studies were performed which included determinations of the possibility of the development of passive cutaneous anaphylaxis reaction (PCA), delayed type hypersensitivity reaction, anti-carvedilol antibodies, or carvedilol-induced anti-erythrocyte antibodies.

All studies were conducted in Japan and translations submitted in the NDA. Sponsor prepared detailed summary tables of these studies (see above.) The following overview of the findings is extracted from English translations of the Japanese studies and from the sponsor's summary.

The rationale for doses of carvedilol used is unclear. Reports included results of determination of PCA reaction using the mouse-rat, guinea pig-guinea pig, and rabbit-guinea pig models. The active systemic anaphylaxis reaction (instantaneous type allergy) was measured in guinea pig. Measurement of carvedilol-specific antibody formation was performed in guinea pig and rabbit sera by means of radio-immunoassay (RIA). Delayed type hypersensitivity reaction was determined in guinea pigs sensitized with subcutaneous injections of carvedilol with/without Freund's complete adjuvant (FCA) and ovalbumin.

Briefly, male mice (BALB/c) were treated with carvedilol (10 or 100 mg/animal i.p. twice). Days after the second sensitization, blood was collected and serum separated. Rats were then passively sensitized with this serum by intracutaneous injection. Twenty four hours later, the rats were challenged with carvedilol (3 mg/kg i.v.) to examine the potential of evoking PCA. No PCA reactions was observed and no IgE antibodies were found.

Guinea pigs were treated 3 times at 2 weeks intervals with carvedilol (0.2 or 2 mg emulsified with FCA.) Days after the last injection, blood was collected, serum separated and injected intracutaneously to naive guinea pigs. Hours or days later, these passively sensitized guinea pigs were challenged with carvedilol (3 mg/kg i.v.) to examine the potential of evoking PCA. Only one animal treated with the LD carvedilol showed PCA; all other guinea pigs were PCA negative. Serum from the one positive guinea pig showed a higher binding rate as normal serum in a RIA suggesting the presence of IgE antibodies. When all animals were rechallenged with i.v. carvedilol, no systemic anaphylaxis was observed even in the guinea pig that had shown PCA positive.

In a rabbit-guinea pig model, carvedilol was first given to rabbits (1 or 10 mg/animal p.o. 3 times a week for 3 weeks). Different rabbits were injected with carvedilol (1 or 10 mg/animal) plus FCA, or 2 mg/animal carvedilol plus FCA and ovalbumin, or 2 mg/animal FCA. Days after the final sensitization, blood was collected, serum separated and guinea pigs were passively sensitized with i.c. injection of the rabbit's sera. Four hrs later the guinea pigs

were challenged with carvedilol (3 mg/kg or 1 mg/kg ovalbumin.) All guinea pigs treated with carvedilol were PCA negative except for the positive controls.

Similar procedures as the above were used in a guinea pig-guinea pig model with the exception that the animals were treated with lower doses of carvedilol (0.2 or 2 mg/animal.) Again all guinea pigs tested were PCA negative.

Systemic anaphylaxis was determined in guinea pigs previously sensitized in the manner described above. The animals were later challenged with i.v. doses of carvedilol to determine the potential for evoking system anaphylaxis. None of the guinea pigs tested exhibited symptoms of active systemic anaphylaxis.

Guinea pigs were twice sensitized by subcutaneous injection of carvedilol (0.5 or 5 mg/kg) and FCA. Days after the second sensitization, guinea pigs were challenged with 30 mg carvedilol/site. to evoke a skin reaction. Twenty four to 48 hours later, skin sites were examined, and there was no evidence of a delayed type hypersensitivity reaction.

In a direct Coomb's test, no agglutination occurred with carvedilol at concentrations of 0.63 and lower.

The sera of animals used in these studies was tested to determine antibody formation. Using a RIA, no difference in binding rate was found compared to normal rabbit and guinea pig demonstrating that no antibody was formed against carvedilol.

2. Limiting Toxicity Studies.

Studies were conducted to determine the i.v. dose of carvedilol that would produce "limiting toxicity" in conscious and anesthetized dog. In conscious dog, limiting toxicity for carvedilol, produced by 15 mg/kg i.v. (bolus), was intermittent convulsions prior to the end of the dosing and alterations of the ECG (prolongation of the P-wave, PR and QRS intervals.) In anesthetized dogs, the limiting toxic dose of the drug was 30 mg/kg i.v. (bolus) which produced widening of P-wave and increases QRS and QT intervals occurring simultaneously with the fall in BP and HR; this effect was considered to be a direct cardiodepressant action giving rise to an apparent cardiogenic hypotension.

Most dogs receiving i.v. infusions of 225 ug carvedilol/kg/min for 4 hr or 450 ug/kg/min for 28 min showed very little change in the ECG. An initial fall in systolic BP was seen within 15 min of treatment of dogs. Intermittent convulsions began just minutes prior to the end of 4 hr infusion. Some other remarkable observations included rapid onset of action in conscious dogs on ECG, BP and HR changes; these observations were followed by the convulsions with no recovery of BP (no convulsions were seen at 7.5 mg/kg and only slight/transient changes in ECG.) Investigators pointed out that β -blocking agents at clinical doses would also show P wave widening; at higher doses some drugs (e.g. propranolol) produce prolongation of the PR and QRS intervals produced by a direct depression of A-V

transmission. Investigators considered that this depression may be the result of membrane stabilizing activity (MSA) because β -blockers that do not possess MSA have been reported as not producing this change. It was concluded that carvedilol "may produce alterations in BP and HR by exerting a depressant effect directly on cardiac tissue.....The cardiac depressant effect of carvedilol likely is due to its MSA."

REPRODUCTION STUDIES

Oral reproduction studies with carvedilol were performed following the FDA guidelines in 2 animal species (rats and rabbits). Only the teratology studies (FDA Seg.II) were reviewed in IND by previous pharmacologist N. Winbury, Ph.D. These reviews are reproduced/included below in the appropriate section of this document because N. Winbury's summaries had undergone secondary review by his supervisor C.Resnick, Ph.D., and the evaluations were found adequate.

Detailed summary tables of the reproduction studies (preliminary and definitive) conducted with carvedilol were prepared by sponsor are reproduced below with minor editorial changes. These summary tables are followed by FDA evaluations of all 3 segments of the reproduction studies.

SPONSOR'S SUMMARY TABLE OF REPRODUCTION TOXICITY STUDIES WITH CARVEDILOL

Species	Type of Study	Doses (mg/kg)	Report No. Ref. No. Location in NDA IND Submission	Drug-Related Observations
Rat	Dose Range Segment I/A	300, 400 pre- mating oral	TC015BS (Boehringer Mannheim report K4) Location: Vol. 1.39 Page 000043 Submitted to IND on 6/3/87	Both dosages were associated with less or no body weight gain during the first 4 to 5 days of drug administration. Sedation, red-stained nose and hair loss occurred during the first 2 weeks of the 64-day drug administration period.
Rat	Dose Range Segment I/B	200, 300 oral	TC015BS (Boehringer Mannheim report K4) Location: Vol. 1.39 Page 000043 Submitted to IND on 6/3/87	Sedation and hair loss were seen at 300 mg/kg. Most females at 200 mg/kg showed hair loss. During the first 5 days of drug administration, the high-dose females showed a marked decrease in body weight (approx. 20 g) followed by less weight gain during the 15-day drug administration period. Females at 200 mg/kg showed less weight gain during the first 8 days.
Rat	Segment I/A-I/B	12, 60, 300 oral	TC015BS (Boehringer Mannheim report K4) Location: Vol. 1.39 Page 000043 Submitted to IND on 6/3/87	Sedation, hair loss and less body weight gain were noted in high-dose animals. Forty-three % of high-dose females did not become pregnant versus 0 in controls. Days taken for successful mating were significantly increased in high-dose females. Median uterine weight of full-term high-dose females was lower than controls (70 vs 108 g). The median number of corpora lutea and infants were lower than controls. Developmental delays (stunted or missing 13th ribs) were observed more frequently in fetuses from mid- and high-dose females than from controls. Pup mortality was also increased in offspring of high-dose females. Underdevelopment of offspring of the high-dose group was observed (less weight, delay in pinna detachment, hair coat development, incisor eruption, eyelid separation and grip strength and decreased performance in the swimming maze). Lowest observable effect levels were 300 mg/kg for paternal toxicity and impairment of fertility and 60 mg/kg for developmental effects, and the no observable effect level was 12 mg/kg.
Rat	Food Intake and Pregnancy/ Lactation	12, 60, 200 oral	TC-0019/SKF105517 (Daichi report D-13)	Food intake of the high-dose females was significantly less on gestation days 0-7 and 7-14. Less body weight gain was observed in high-dose females during gestation and lactation.

Sponsor's Summary Table of Reproduction Toxicity with Carvedilol (Cont'd.)

Species	Type of Study	Doses (mg/kg)	Report No. Ref. No. Location in NDA IND Submission	Drug-Related Observations
Rat	Dose- Range Segment II	Non-pregnant: 100, 200, 300, 400, 500, 1000, 1500 Pregnant: 50, 100, 200, 400 oral	TC012BS (Boehringer Mannheim report K1) Location: Vol. 1.39 Page 000176 Submitted to IND on 2/15/85	First study in non-pregnant animals consisted of a dose of 1000 mg/kg. Two of 4 animals showed marked weight loss at days 3 and 4. The animals were weak, the eyelids and nose had a bloody appearance and the urogenital area was brown-stained. Dosages of 500, 1000 and 1500 mg/kg were used in the 2nd study. The high-dose was only administered once due to the development of severe toxic signs, such as apathy, ataxia and low cutaneous temperature. High-dose also showed a steep fall in body weight. One of 2 animals in the mid-dose group showed a decrease in body weight. Animals also exhibited signs as observed in the first study. The low-dose animals behaved as the controls. In the 3rd study, the 100 and 200 mg/kg dose groups gained more weight than the controls in the 1st week, the 300 mg/kg group was not different from controls and the 400 and 500 mg/kg groups lost weight. In the 2nd week, the weight loss was abolished in the 400 and 500 mg/kg dose groups. Food intake was increased at 100 mg/kg in the 1st week and was decreased at 200 mg/kg and greater. In the 2nd week, no difference in food intake was observed. The 400 and 500 mg/kg animals showed signs of toxicity. In pregnant animals, less weight gain or a decrease in body weight was observed at 200 mg/kg and above. Food intake was less at 400 mg/kg. A dosage of 100 mg/kg or above was associated with impairment of general well being, including sedation.
Rat	Segment II	12, 60, 300 oral	TC012BS (Boehringer Mannheim report K1) Location: Vol. 1.39 Page 000176 Submitted to IND on 2/15/85	One high-dose animal died. Sedation, hair loss and red stained eyelids were observed in mid- and high-dose animals. High-dose animals showed less and mid-dose animals more body weight gain than controls. Median full-term uterine weight was lower and post-implantation losses higher in high-dose animals. The latter also implied that there were less live fetuses in the high-dose group. Fetal and placental weights were lower in the high-dose group. Developmental delays were seen in the high-dose group. The lowest observable effect levels were 100 mg/kg for maternal effects and 300 mg/kg for developmental toxicity, and the no observed effect levels were 12 and 60 mg/kg, respectively.

Sponsor's Summary Table of Reproduction Toxicity with Carvedilol (Cont'd.)

Species	Type of Study	Doses (mg/kg)	Report No. Ref. No. Location in NDA IND Submission	
Rabbit	Dose Range Segment II	Non-pregnant: 100, 200 Pregnant: 150 oral	TC013BS (Boehringer Mannheim report K2) Location: Vol. 1.39 Page 000225 Submitted to IND on 2/15/85	At 200 mg/kg, non-pregnant animals showed a decrease in body weight compared to controls during a 12-day period (approx. 100 to 250 g). No other signs were noted. Pregnant animals at 150 mg/kg showed less food intake and marked body weight loss (approx. 250 g) during the period of drug administration (days 7-19 of gestation). There was an increase in post-implantation loss.
Rabbit	Segment II	3, 15, 75 oral	TC0135S (Boehringer Mannheim report K2) Location: Vol. 1.39 Page 000225 Submitted to IND on 2/15/85	A slight increase in median post-implantation loss and consequently less live fetuses were seen in the high-dose group. Fetal and placental weights were higher in drug-treated groups than in controls. The lowest observable effect level was 75 mg/kg for developmental toxicity, and the no observed effect levels were 75 mg/kg for maternal effects and 15 mg/kg for developmental toxicity.
<u>Drug-Related Observations</u>				
Rat	Segment III	12, 60, 200 oral	TC014BS (Boehringer Mannheim report K3) Location: Vol. 1.39 Page 000270 Submitted to IND on 10/3/89	Hair loss was seen at all doses. Sedation occurred in high-dose animals. In the last week of gestation, high-dose females gained less weight. However, the mid- and high-dose females showed more weight gain than the controls during lactation. Pups from mid- and high-dose females showed a higher mortality rate during the first 2 days postpartum. Reduced body weight of pups from the mid- and high-dose groups remained detectable into adulthood. Pups of these dose groups also showed delayed pinna detachment and it took them longer to fulfill the criteria for the grip strength test. The lowest observable effect levels were 60 mg/kg for maternal effects and for developmental toxicity, and the no observed effect level was 12 mg/kg.

Summary of Fertility and General Reproductive Performance in Rat (Seg. I)

(SK&F Report No. TC015BS. Boehringer Mannheim: GMH, Germany.

Study Dates: 08-08-84 until 03-22-85. Report date: November 1986)

No./Dose/Level/Strain: 24 M, 24 F, Sprague-Dawley (CrI:CD(SD)BR)

Route: Orally by gavage

Dose Levels: 0 (vehicle - 1% methylcellulose), 12, 60 or 300 mg carvedilol suspension as 10 ml/kg/day. Doses were based on preliminary studies.

Treatment Schedule and Synopsis of Procedures:

Males (F_0) were treated daily at least 62 days before mating, dosing continued up until successful mating. Body weight was recorded daily for the first 80 days of study, then once weekly until day 129 of study. Females (F_0) were treated daily for 15 days prior to mating and treatment continued through and up to day 21 of lactation. Body weights were determined daily. All rats were observed daily for clinical signs.

Caesarian Group: Groups of dams were killed and laparotomized on 22 p.c. The uteri were removed and weighed before and after the removal of the fetuses, placenta, dead implants and fetal membranes. The fetuses were counted in situ, removed, examined for signs of life and their position in the uterine horns recorded. Observations included: counting of the resorption sites, early resorptions, and corpora lutea, as well as weighing of the placenta, fetuses, inspection of each fetus for externally visible malformations, and sex determination.

Malformations of the skeleton were sought in at least 50% of each litter of caesarian-delivered fetuses. The detection of the skeleton malformations was by means of alizarin staining. Examination for internal organ malformations and determination of sex was carried out in situ after fixation in Bouin's solution.

Examination of F_1 Generation: The litter size of F_1 generation was determined daily until weaning took place; their body weights were recorded once a week. In selected F_1 pups, physical parameters were recorded (pinna detachment, down, full coat of hair, incisor eruption, eye opening, grip strength). At protocol specified times, tests were carried to check the neuromuscular coordination and reflexes (cliff avoidance, air righting, corneal, pupillary and auditory startle reflexes). After that, selected F_1 pups (3 M and 3 F) per litter were subjected to a combined learning and behavior test. All other F_1 pups were sacrificed.

Weaning Groups (rats allowed to litter): Dams that were allowed to litter, their litters (F_1 generation) underwent similar examinations as described above for the "caesarian group."

Selected F_1 males and females from treatment group were allowed to mate. All dams were allowed to deliver spontaneously. F_2 generation pups were observed for physical development, neuromuscular coordination, reflexes and behavior as done for the F_1 generation.

F_1 and F_2 generation were examined for visceral and skeletal abnormalities.

Results:

Parenteral (F_0 generation) Observations:

Remarkable effects were reported at MD and HD. At HD, caesarian group rats showed loss of hair and sedation for both male and female rats; sedation was not long lasting. Body weight gain was also reduced at HD. Compared to control, at MD and HD showed significantly less corpora lutea. Fewer uterine implants were noted at HD compared to controls. On the fetuses, no notable effects of carvedilol were reported on pre- and post-implantation losses, live/dead fetuses, sex ratio or placental weights. The findings in the fetal weight were variable. Compared to controls, fetal weight at LD and HD showed slight dose-related increases and, at HD a slight decrease.

In F_0 generation allowed to litter, loss of hair and delayed body weight gain was also seen at HD; body weight was significantly lower than controls. Compared to controls, drug related effects at HD included decreased uterine implants and live pups.

Litter Observations (F_1 generation):

More malformations in caesarian delivered fetuses were found in the MD and HD dams. Malformations consisted of slight increase in the number of short 13th ribs; however, this malformation was also observed in controls.

F_1 pups from HD group allowed to litter were always lighter in weight than those from other treated groups.

The physical development of F_1 generation was slightly, but persistently retarded. Fertility in this generation exposed in utero to HD could not be reliably evaluated because of the apparently small number of HD offspring that could be reared to sexual maturity.

No adverse effects on development, behavior or fertility was reported for the F_1 generation or development/behavior effects on their F_2 generation.

OVERVIEW OF ADME STUDIES

The drug sponsor has submitted 52 nonclinical ADME and toxicokinetics reports on carvedilol (labelled and unlabelled) administered to whole animals by various routes and, miscellaneous types of studies. Breakdown of studies according to species is as follows: mouse- 2, rat- 25 (11 conducted in Japan), rabbit- 1, dog-10, monkey- 3 conducted in Japan, the remaining 12 (3 conducted in Japan) studies included in vitro studies. Numerous of these studies were conducted in Japan. The following overview is essentially that submitted by the sponsor with editorial changes.

In rat and dog, oral doses of carvedilol are rapidly and extensively absorbed. The absolute bioavailability of the drug in these species is low, 20-25% for rat and 10-30% for dog considered the result of first-pass metabolism and only minor sex differences were noted. In rat, following single dose oral administration of pharmacological active dose of ^{14}C -carvedilol, within 1 hour peak levels of carvedilol were detected in serum samples (138 ng/ml in males and 200 ng/ml in females, Table 28). By 24 hr serum concentrations of the drug were below the limit of quantitation (2 ng/ml). The median AUC_{0-8} values for carvedilol were 587 and 608 ng.hr/ml in male and female rats, respectively. Also, following oral administration of ^{14}C -labeled carvedilol, serum concentrations of radioactivity at all sampling times were significantly higher than those observed for non-labeled carvedilol. In rat and dog, slow terminal elimination $T_{1/2}$ for radioactivity in serum were observed (about 60 hours) and $T_{1/2}$ of carvedilol was about 5 and 7 hours, respectively.

Male beagles, treated with 150 mg/kg ^{14}C -carvedilol showed peak serum concentration of the parent compound (2.8 ug/ml) and radioactivity (11.9 ug equiv. hr/ml) at 1.75 hrs indicating a median rate of absorption at this dose. The median AUC_{0-144} for carvedilol was 40.7.hr/ml compared to 213 ug-equiv.-hr/ml for radioactivity (Table 28). The median terminal elimination $T_{1/2}$ for radioactivity in serum was 75 hrs.

In rat and dog, following i.v. administration of carvedilol, concentrations of the drug declined rapidly with a terminal elimination $T_{1/2}$ of about 1 hour for both species. Plasma clearance of carvedilol (determined on serum) was 45-60 ml/min/kg in rat and 22 ml/min/kg in dog. The volume of distribution (V_d) in the dog was 1.7 L/kg showing that there is substantial distribution into extravascular tissues.

In rat (Sprague-Dawley) and monkey, carvedilol exhibited stereoselective pharmacokinetics when single doses of carvedilol were tested (2 mg/kg i.v. or 10 mg/kg p.o.). The lower limit of quantitation for both enantiomers was 1.55 ng/ml in plasma. In rat, following oral administration, plasma levels of R(+)-carvedilol were higher than the S(-)-carvedilol up to 6 hrs postdose. The R/S enantiomeric ratios for C_{max} and AUC were 2.5 and 2.2, respectively. The absolute bioavailability for R(+)-carvedilol (5.9%) was 40% greater than that of the S(-)-carvedilol (4.2%) (Table 29)

In the cynomolgus monkey, following 10 mg/kg carvedilol p.o., plasma concentration of the R(+)-carvedilol were higher than those of the S(-)-carvedilol up to 6 hrs after dosing. The T_{max} was about 2.5 hrs post dose for both enantiomers. The C_{max} for R(+)-carvedilol was

38.3 ng/ml and for the S(-)-carvedilol 25.1 ng/ml. The R/S enantiomeric ratios for C_{max} and AUC were 2.5 and 1.2, respectively. (Table 29) Following i.v. administration of racemic carvedilol in the rat, mean plasma clearance of R(+)-carvedilol was 20 ml/min/kg vs 33 ml/min/kg for S(-)-carvedilol. The mean volume of distribution (V_d) for R(+)-carvedilol was 1.9 L/kg compared to 3.9 L/kg for S(-)-carvedilol. In both rat and monkey, terminal elimination T_{1/2} for R(+)-carvedilol was slightly faster than that observed for the S(-)-enantiomer.

Table 28
Pharmacokinetic parameters for parent and radioactivity following single doses of ¹⁴C-carvedilol in animals.*

Species	Dose (mg/kg)	Dose Route	No./Sex of animals	Parent Compound			Radioactivity in Serum		
				T _{max} (hr)	C _{max} (ng/ml)	AUC _{0-∞} [†] (ng*hr/ml)	T _{max} (hr)	C _{max} [‡] (ng/ml)	AUC _{0-∞} [‡] (ng*hr/ml)
Rat	10	p.o.	6M	1.0 [§] (1.0-1.0)	* 138 (68-173)	587 [†] (397-726) (0-8 hr)	1.0 [§] (1.0-2.0)	420 (190-447)	664 [†] (6227-8722) (0-48 hr)
	10	p.o.	6F	1.0 [§] (1.0-1.0)	* 200 (128-254)	680 (538-889) (0-8 hr)	1.0 [§] (1.0-1.0)	427 (321-501)	4648 (3899-5275) (0-48 hr)
Dog	0.25	i.v.	4M	0.083 [§]	492 (139-1335)	198 (103-226) (0-8 hr)	0.083 [§]	616 (172-1863)	1592 (2149-1910) (0-48 hr)
	5	p.o.	4M	0.5 (0.25-1.0)	123 (75-1563)	324 (157-2244) (0-24 hr)	0.5 (0.5-1.5)	578 (303-1721)	8552 (7979-10888) (0-144 hr)
	150	p.o.	3M/3F	1.75 (1.0-2.0)	* 2.82 [§] (1.03-4.97)	* 40.7 [†] (32.9-139.8) (0-144 hr)	1.75 (1.5-3.0)	* 11.9 [§] (7.2-45.8)	* 213 [†] (153-451) (0-144 hr)

* data presented as median and range.

[†] sampling interval noted in brackets.

[‡] expressed in ng equivalents of carvedilol.

[§] time of first sample.

[†] n=5; data from one male rat excluded due to incomplete sampling.

[‡] units are ug/ml for C_{max} and ug*hr/ml for AUC_{0-∞}.

Pharmacokinetics Parameters of Enantiomers

24.29 Pharmacokinetic parameters for carvedilol enantiomers following single dose administration of racemic carvedilol in the rat and mon

Species	Dose (mg/kg)	Dose Route	No./Sex of animals	Pharmacokinetic Parameters (mean $\pm$ SD)				
				Enantiomer	T _{max} (hr)	C _{max} (ng/ml)	AUC _{0-∞} (ng $\cdot$ hr/ml)	T _{1/2} (hr)
Rat	2	i.v.	3M	• R(+)	0.083 ^h	814 $\pm$ 36	848 $\pm$ 184	1.09 $\pm$ 0.03
				• S(-)	0.083 ^h	446 $\pm$ 16	544 $\pm$ 158	1.46 $\pm$ 0.50
	10	p.o.	4M	• R(+)	0.5 ^f	110 ^f	251 ^f	4.3 ^f
				• S(-)	0.5 ^f	44 ^f	116 ^f	5.6 ^f
Monkey	10	p.o.	3F	• R(+)	2.7 $\pm$ 0.6	38.3 $\pm$ 13.7	160 $\pm$ 49	2.8 $\pm$ 0.8
				• S(-)	2.3 $\pm$ 1.2	25.1 $\pm$ 8.4	129 $\pm$ 41	3.9 $\pm$ 0.9

time of first sample.

pharmacokinetic analysis performed on mean plasma concentration-time data.

Toxicokinetics.

In a 3-mo dose-range study in mice (NMRI) given carvedilol (20, 60, 200, 600 or 800 mg/kg in diet), a single point measurement (at the end of study for the LD alone) showed serum ranges of the drug from 22 up to 685 ng/ml. Sponsor asserts, but no data were provided, that qualitatively concentrations of the drug increased with the dose showing that the mice were exposed to carvedilol. Sponsor again asserts, without providing data, that systemic exposure to the drug increased with increasing doses when determined for single-point measurements of serum at the end of the 2-year mouse carcinogenicity study.

In a 3-mo rat toxicokinetic study, rats treated with carvedilol (90 and 300 mg/kg/day), C_{max} and AUC $0-24$ values for carvedilol increased about 2 to 3 fold after dosing 1-week suggesting a decrease in the metabolic clearance of the drug with chronic dosing. At the end of the study serum concentrations of the drug in the 90 mg/kg/day more than 10 to 20-fold greater than those reported in hypertensive patients receiving 50 mg once a day (the maximum recommended daily therapeutic dose assuming a 50 kg patient.)

In the 3-month dose-ranging study in rat, carvedilol was administered in the diet at concentrations of 200, 600, 2000, 6000 and 8000 ppm. Drug intake was determined after 1, 6 and 15 weeks of drug treatment. Compared to week 1 of treatment the median intake of the drug was decreased (Table 30) Serum concentrations of the drug were determined at the same time intervals; however, despite the decrease of drug intake between weeks 1 and 15 of study, serum concentrations of drug were higher at week 15 suggesting a decrease in the clearance of carvedilol after repeated administration.

Table 30 SUBSTANCE INTAKE IN THE 3-MONTH DOSE-RANGING STUDY IN RATS FOR THE CARCINOGENICITY STUDY WITH BM 14 190

Dose	Substance intake median (mg/kg)				Blood levels mean value (ng/ml)					
	after 1 week	6 weeks	15 weeks	n	after 1 week	n=4	6 weeks	n=2	15 weeks	n=6
<u>MALE</u>										
200 ppm	27.27	15.85	11.19	6	17		22		26.8	
600 ppm	85.7	46.64	32.52	6	40		44.5		55.3	
2000 ppm	293.13	152.32	100.42	6	605.25		457.5		324.3	
6000 ppm	862.86	498.66	384.88	6	1814		2878		3890.3	
8000 ppm	1268.96	789.36	531.63	6	2929		5925		6409.3	
<u>FEMALE</u>										
200 ppm	27.25	14.94	13.13	6	16.5		33.5		18.6	
600 ppm	79.61	43.40	42.25	6	55.5		141		75.6	
2000 ppm	316.1	155.48	126.08	6	539.75		1071		865.16	
6000 ppm	971.4	508.03	412.79	6	2091.75		4684		6328.8	
8000 ppm	1062.1	654.24	486.24	6	2424.25		8260.5		6282.5	

In a separate study, serum concentrations of carvedilol were determined in rats receiving carvedilol 400 and 1600 ppm in the diet for 28 weeks. At 6 months the mean daily drug intake in the LD group was about 14 mg/kg (equivalent to about the "no-effect" dose in a 18-month study) (Table 31) Sponsor states that mean C_{max} values for carvedilol in this dose group (about 14 mg/kg/day) was close to that seen in hypertensive patients receiving carvedilol 50 mg once daily but this was the result of limited sampling in rat. Mean AUC₀₋₂₄ values for carvedilol in rats receiving the LD were roughly 2-fold higher than that observed in patients administered carvedilol 50 mg once daily.

In the 2-year carcinogenicity study in the rat, 4 doses of carvedilol were administered in the diet (summary above shows that mean daily intake ranged from 8 up to 75 mg/kg at the end of the study.) Serum concentrations of the drug determined at one time point in all dose groups showed mean plasma concentrations of carvedilol in males of 21, 31, 94 and 215 ng/ml and, in females 18, 39, 94 and 354 ng/ml. These results show that the rats used in the carcinogenicity study were exposed to carvedilol and that systemic exposure increase with dose.*

In the 12-month chronic toxicity study in the dog, carvedilol was administered orally at doses of 10, 30, 100, and 300 mg/kg/day. The "no effect" dose in this study was considered to be around 30 mg/kg/day. Based on mean C_{max} and AUC data, serum concentrations of carvedilol were approximately 6-fold higher in these dogs (30 mg/kg/day) compared to that observed in hypertensive patients receiving 50 mg once daily. (Tables 31a and 31b)

With the exception of metabolite M5 (barely quantifiable in rat and dog), plasma levels of the active metabolites in the rat and dog were comparable to those observed in man. In conscious rabbits, the M2 (desmethyl), M4 (4¹-hydroxyphenyl), and M5 (5¹-hydroxyphenyl) metabolites exhibited β-adrenoceptor blocking activity. Compared to carvedilol, metabolites M2, M4 and M5 possess only weak vasodilating activity. In both healthy volunteers and in patients with renal dysfunction, plasma concentrations of these metabolites are less than 10% of those observed for carvedilol and follow a similar time course with parent.

* These data were not submitted in the Original NDA. Data were requested and were submitted by sponsor in NDA Amendment dated 03-29-94.

PHARMACOKINETIC PARAMETERS FOR CARVEDILOL FOLLOWING CHRONIC ORAL DOSING IN RAT AND HYPERTENSIVE (HTN) PATIENTS

<u>Table 31a</u>				Pharmacokinetic Parameters (mean ± standard deviation)			
Species	Dose (mg/kg/day)	Study Day	No./Sex of animals	T _{max} (hr)	C _{max} (ng/ml)	AUC ₀₋₂₄ (ng·hr/ml)	CL/F (ml/min/kg)
Rat (average)	90	8	15M	4.9 ± 2.3	1182 ± 301	14771 ± 6018 ^a	115 ± 40 ^a
			15F	4.9 ± 3.0	1256 ± 373	15412 ± 4195	109 ± 48
	300	88	14M	6.9 ± 2.0	1919 ± 685	26108 ± 9203	64 ± 24
			14F	5.5 ± 3.4	2578 ± 565	41340 ± 11898	39 ± 12
	300	8	15M	6.4 ± 2.4	2146 ± 516	33734 ± 10923	140 ± 42
			15F	6.9 ± 2.5	2560 ± 607	40645 ± 14358	135 ± 41
	300	88	14M	7.6 ± 1.3	4417 ± 1087	71994 ± 15283 [†]	72 ± 13 [†]
			15F	7.3 ± 1.9	7393 ± 2014	139631 ± 42398	40 ± 16
Rat (individual)	30 ppm	8	12M	12.0	219 ± 37	2756 ± 472	176 ± 39
			12F	16.0 ± 3.0	249 ± 69	3603 ± 856	143 ± 36
	12	192	12M	15.0 ± 5.4	167 ± 58	1981 ± 384	101 ± 23
			12F	14.5 ± 7.0	170 ± 109	2062 ± 809	128 ± 68
	1600 ppm	8	12M	15.5 ± 3.1	1152 ± 278	18476 ± 3586	102 ± 27
			12F	17.5 ± 1.7	1278 ± 185	19680 ± 3634	76 ± 17
	45	192	12M	18.5 ± 1.7	794 ± 187	10092 ± 1644	77 ± 27
			12F	15.5 ± 7.9	1280 ± 335	17259 ± 5019	79 ± 35

n=6.
n=13.

<u>Table 31b</u>				Pharmacokinetic Parameters (mean ± standard deviation)			
Species	Dose (mg/kg/day)	Study Day	No./Sex of animals	T _{max} (hr)	C _{max} (ng/ml)	AUC ₀₋₂₄ (ng·hr/ml)	CL/F (ml/min/kg)
Dog	30 ^S	343	5M/5F	2.4 ± 0.8	977 ± 654	7340 ± 4406 [†]	96 ± 57
HTN Patients	12.5 mg/day (0.15) [†]	28	7M/2F	1.6 ± 1.1	32 ± 18	184 ± 142	ND
	25 mg/day (0.31) [†]	28	8M/2F	1.0	73 ± 34	343 ± 226	ND
	50 mg/day (0.53) [†]	28	8M/1F	2.7 ± 1.6	167 ± 108	1136 ± 810	ND

administered in two equally divided doses (15 mg/kg every 12 hours).

AUC₀₋₂₄ calculated as 2 times the observed AUC₀₋₁₂.

approximate mg/kg/day.

Protein Binding/RBC Partitioning.

Carvedilol is bound (about 98-99%) to plasma proteins; similar to values observed. Over the range of 50 to 1000 ng/ml, protein binding of carvedilol in human serum has been shown to be independent of concentration. Since carvedilol is lipophilic, it would be expected to readily cross the red blood cell membrane. However, because the drug is extensively bound to plasma protein, partitioning into the red blood cell is limited. At blood concentrations of about 500 ng/ml, the blood to plasma concentration ratios for carvedilol were 0.92, 0.89, 0.83 and 0.69 and 0.83 in mouse, rat, human and guinea pig, respectively.

Tissue Distribution.

In the rat, following oral administration of labelled carvedilol the radioactivity was relatively well distributed in all tissues considered due to the high lipophilicity of the drug. In the rat, following a single oral dose, concentrations of radioactivity were highest in the gastrointestinal tissues, liver, kidneys, Harderian gland, lungs, hypophysis, submaxillary gland and pancreas. In the rat, carvedilol-related material exhibits high affinity for the erythrocyte resulting in a prolonged elimination $T_{1/2}$ (> 200 hours) for radioactivity in blood. As a consequence of the long elimination $T_{1/2}$ in rats, blood concentrations of radioactivity increased about 14-fold after consecutive daily doses of radiolabeled carvedilol p.o. for 21 days.

Radioactivity did not markedly accumulate in plasma upon repeated oral doses of labeled carvedilol. In the rat, following repeated oral doses of the drug, concentrations of radioactivity were highest in the erythrocyte, liver, and Harderian gland but other tissues also showed concentrations of radioactivity (e.g., cecum, kidneys, ileum, and brown fat.)

In rat, placenta transfer of carvedilol and/or its metabolites was low. In pregnant rat, single oral dose of radiolabeled carvedilol showed a $\leq 0.01\%$ of the administered dose distribution of radioactivity on days 12 and 19 of gestation. Studies in lactating rats demonstrate carvedilol and/or its metabolites were excreted into breast milk. After a single oral dose of ^{14}C -carvedilol, concentration radioactivity in breast milk exceeded those observed in plasma at all sampling times; by 24 hrs after dosing the milk to plasma concentration ratio was decreased.

In rabbit, a single oral dose of radiolabeled carvedilol resulted in the highest concentrations of radioactivity in the liver and kidney at 48 hours post-dose.

In the monkey, whole body autoradiography experiments demonstrated that the highest levels of radioactivity were present in the gall bladder 1 hour after both i.v. and oral administration of ^{14}C -carvedilol suggesting that biliary excretion is a major route of elimination in this species. Concentrations of radioactivity following oral administration were considerably lower compared to i.v. administration indicating substantial first-pass clearance in the monkey. By 24 hours after the oral dose, concentrations of radioactivity had declined from all tissues. Carvedilol and its metabolites exhibit affinity for melanin containing tissues (e.g. uvea and hair follicles.)

Enzyme Inhibition/Induction.

In rat, multiple oral dosing of carvedilol had a minimal effect on hepatic P450-dependent enzyme activities. *In vitro* and *in vivo* studies indicate that the drug at high concentrations is an inhibitor of hepatic cytochrome P450-mediated activities. However, at plasma concentrations approximately 2- to 5-fold higher than those observed in hypertensive patients, carvedilol did not inhibit cytochrome P450-dependent clearance of antipyrine in the rat.

In rat, no major differences were found in the pattern of metabolites in the liver after single and multiple dosing with carvedilol suggesting that the drug does not have an inhibitory effect on its own metabolism and that its metabolic pattern does not change during chronic dosing in this species.

Metabolism.

Carvedilol undergoes extensive metabolism via oxidation and conjugations pathways. The biotransformation of carvedilol was characterized and major metabolic pathways fully described for mouse, rat and dog.

In mouse, given ¹⁴C-carvedilol (100 mg/kg p.o. in a suspension), circulating plasma displayed a complex mixture of products, however; unchanged drug was the most abundant plasma component at 2 and 6 hrs postdosing with the females showing higher concentration of carvedilol metabolites relative to unchanged drug. In this study, the drug was excreted primarily in the feces and a small amount in the urine. The profile of urine and fecal radioactive metabolites was complex, not sex difference was reported in the more than 25 metabolites. (Fig. 50 below) Most of these products identified were minor, accounting for <5% of the administered dose. In the mouse and rat, the primary route of metabolism of carvedilol is hydroxylation of the carbazolyl ring with subsequent phenolic glucuronidation. In dog, carbazolyl ring hydroxylation with subsequent glucuronidation and direct glucuronidation of carvedilol were the major metabolic pathways. In species studied, oxidative dealkylation and sulfation were relatively minor metabolic pathways for carvedilol. In each of the animal species and in humans, unchanged carvedilol was identified as a major drug-related component circulating in plasma (Table 32). Sponsor asserts that essentially all the other circulating metabolites identified in plasma were conjugates of carvedilol or hydroxylated carvedilol which were also identified in excreta.

In humans, carvedilol was also metabolized extensively; drug-related products were excreted primarily in feces. Metabolites identified in urine were considered formed primarily via direct glucuronidation, carbazolyl and phenyl ring hydroxylation with subsequent glucuronidation (as in rat, mouse and dog) or sulfation (a minor pathway in animals), and O-demethylation with subsequent glucuronidation or sulfation. Unchanged carvedilol was a major product circulating in plasma; metabolites in plasma were qualitatively similar to those in urine. Fecal analysis showed unchanged carvedilol, O-desmethyl carvedilol and carbazolyl and phenyl ring hydroxylation products. Based on the metabolites identified in urine, sponsor considers that the majority of the metabolites identified in feces were probably excreted into bile as glucuronide and sulfate conjugates which were subsequently hydrolyzed in the gut.

Some Metabolic Parameters (Cont'd.)

STRUCTURES OF CARVEDILOL AND 3 PRINCIPAL METABOLITES

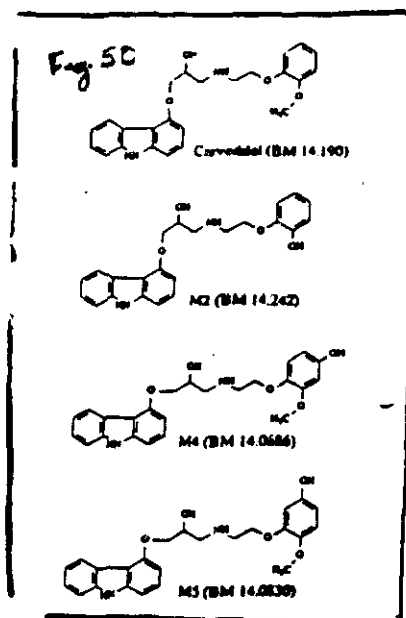


Table 32 Maximum observed plasma concentrations of carvedilol and metabolites M2, M4, and M5 following oral administration of carvedilol in rat, dog, and man.

Species (#/sex)	Dose	Component			
		Carvedilol	Desmethyl (M2)	4'-hydroxy phenyl (M4)	5'-hydroxy phenyl (M5)
Rat (3M/3F)	30 mg/kg ^a	1778 [†] (595-32 ⁵) {3M/2F}	7.2 (3.6-12.5) {1M/3F}	5.1 (2.8-6.7) {1M/2F}	2.6, 2.9 {1M/1F}
Dog (2M/2F)	10 mg/kg ^a	826 [†] (634-1721) {2M/2F}	1.9 (1.8-3.3) {1M/2F}	5.3 (4.1-12.0) {2M/2F}	1.01 {1F}
Man (10M)	25 mg ^S (0.3 mg/kg)	49 (20-84)	3.9 (3.1-6.6)	4.1 (2.4-5.1)	3.3 (2.0-5.8)

^a single dose.

[†] data presented as median and range (units in ng/ml); brackets indicate number and sex of animals with measurable (≥ 1 ng/ml) concentrations.

^S multiple dose (1st dose 12.5 mg, then 25 mg once daily for 6 days).

In conscious rabbits, studies show that the desmethyl (M2), 4'-hydroxyphenyl (M4) and 5'-hydroxyphenyl (M5) metabolites of carvedilol possess β -adrenoceptor blocking activity. Based on dose, the M4 metabolite of carvedilol is about 13 times more potent than carvedilol with respect to β -adrenoceptor blocking activity. The M2 metabolite is about 2.5 fold more potent than carvedilol. The M5 metabolite exhibits the weakest β -adrenoceptor blocking activity, approximately 60% of that observed for carvedilol. In rat and dog, single oral doses of 30 mg/kg or 10 mg/kg of carvedilol, respectively, showed plasma concentrations of metabolites M2 and M4 which were more than 100-fold lower than those observed for parent compound; plasma concentrations of M5 were barely quantifiable in both species. Urinary concentrations of the active metabolites mirrored the plasma concentration. Following enzymatic hydrolysis of the urine of both rat and dog, minor amounts of all three metabolites (M2, M4 and M5) were observed. Results of these studies indicate that both the rat and dog metabolize carvedilol via demethylation and hydroxylation of the phenyl ring. However, these metabolites are primarily present in the rat and dog as conjugates.

Excretion.

Excretion of carvedilol was studied after oral administration of radiolabeled carvedilol in mouse, rat, rabbit, dog, and monkey. Similarly to man, the majority of the radioactivity was excreted in the feces with only a small fraction of the dose excreted in the urine. In bile-duct cannulated rats and dogs, most of the radiolabeled dose was excreted in the bile following both oral and i.v. administration indicating good oral absorption and significant biliary elimination. In both rat and dog, renal elimination of unchanged carvedilol accounts for less than 0.2% of the dose. In the rat, enterohepatic recirculation of carvedilol-related material has been demonstrated; sponsor considered that this finding may explain the slow elimination of radioactivity from the body. (Tables 33a and 33b)

Excretion Parameters (Cont'd.)

Table 33a

Excretion of radioactivity following single doses of ^{14}C -carvedilol in animals and man.

Species	Dose (mg/kg)	Dose Route	No./Sex of animals	Time Period (h.)	Percent of dose recovered (mean $\pm$ SD)			
					Urine	Feces	Bile	Total
Mouse	100	p.o.	18M	0-24	1.7 $\pm$ 0.7	66.1 $\pm$ 22.7	ND	68.1 $\pm$ 23.3 ^a
				0-96	3.2 $\pm$ 0.5	92.9 $\pm$ 5.8	ND	97.1 $\pm$ 5.6 ^f
	100	p.o.	18F	0-24	8.1 $\pm$ 3.3	61.2 $\pm$ 8.8	ND	69.9 $\pm$ 7.1 ^a
				0-96	10.3 $\pm$ 3.5	79.6 $\pm$ 2.3	ND	91.5 $\pm$ 1.9 ^f
Rat	10	p.o.	5M ⁵	0-24	2.5 $\pm$ 0.6	69.2 $\pm$ 12.3	ND	71.7 $\pm$ 12.1
				0-48	2.8 $\pm$ 0.7	87.0 $\pm$ 23.2	ND	89.8 $\pm$ 23.2
	10	p.o.	6F	0-24	1.9 $\pm$ 0.5	48.4 $\pm$ 9.0	ND	50.3 $\pm$ 9.0
				0-48	2.2 $\pm$ 0.5	53.2 $\pm$ 7.6	ND	55.4 $\pm$ 7.7
	10	p.o.	3M	0-24	4.4 $\pm$ 0.9	83.0 $\pm$ 3.3	ND	87.4 $\pm$ 4.2
				0-72	4.5 $\pm$ 0.9	90.8 $\pm$ 0.5	ND	95.4 $\pm$ 1.4
	2.5	i.v.	5M	0-48	12.0 $\pm$ 11.8	1.0 $\pm$ 0.4	81.1 $\pm$ 11.4	98.2 $\pm$ 2.2 ^f
				30	p.o.	6M	0-48	3.5 $\pm$ 2.9
	2.5	i.v.	6F	0-48	5.8 $\pm$ 4.3	1.4 $\pm$ 0.5	92.9 $\pm$ 7.6	102.0 $\pm$ 3.7 ^f
				30	p.o.	6F	0-48	1.6 $\pm$ 1.2
	1.26	i.v.	6M	0-48	8.1 $\pm$ 7.3	2.2 $\pm$ 0.7	89.9 $\pm$ 5.6	100.5 $\pm$ 3.7 ^g
				10	p.o.	6M	0-48	2.9 $\pm$ 0.5
Rabbit	5	p.o.	3M	0-24	3.8 $\pm$ 3.2	24.8 $\pm$ 28.7	ND	28.6 $\pm$ 30.3
				0-48	6.1 $\pm$ 3.6	33.6 $\pm$ 34.6	ND	39.7 $\pm$ 36.3
	5	p.o.	3F	0-24	6.0 $\pm$ 5.5	44.2 $\pm$ 34.9	ND	50.2 $\pm$ 39.9
				0-48	9.2 $\pm$ 2.3	56.1 $\pm$ 31.2	ND	65.3 $\pm$ 32.2

Excretion Parameters (Cont'd.)

Table 33 b
Excretion of radioactivity following single doses of ¹⁴C-carvedilol in animals and man.

Species	Dose (mg/kg)	Dose Route	No./Sex of animals	Time Period (hr)	Percent of dose recovered (mean ± SD)			
					Urine	Feces	Bile	Total
Dog	0.25	i.v.	3F	0-96	14.6 ± 2.0	64.9 ± 3.5	ND	80.2 ± 1.7 ^o
	5	p.o.	3F	0-96	11.9 ± 3.2	66.2 ± 7.1	ND	79.0 ± 6.6 ^o
	0.25	i.v.	4M	0-144	16.2 ± 2.5	53.5 ± 9.8	ND	69.7 ± 11.5
	5	p.o.	4M	0-144	9.2 ± 0.6	48.4 ± 36.1	ND	57.7 ± 36.7
	<u>150</u>	p.o.	3M/3F	0-144	4.6 ± 2.3	41.8 ± 16.5 ^o	ND	46.1 ± 18.3 ^o
	10	p.o.	2F	0-96	8.4, 8.6 ^o	73.1, 74.2	ND	82.0, 82.8 ^o
	10	p.o.	2F	0-96	6.6, 9.0 ^o	21.0, 44.2	35.4, 60.2	87.8, 88.5 ^o
Monkey	10	p.o.	3F	0-240	15.7 ^v	64.5 ^v	ND	80.2 ^v
Man	50 mg	p.o.	3M	0-192 ^{**}	15.9 ± 1.0	59.6 ± 2.9	ND	75.5 ± 3.5

^o includes cage debris.

¹ includes cage debris and carcass.

^{\$} mean data recalculated from data included in report - 1 male rat excluded due to incomplete urine and feces collection.

[†] includes carcass.

^o includes gastrointestinal contents.

^o data from one dog excluded due to lack of defaecation on last study day.

^v mean data only presented in report.

^{**} urine collection period from 0-168 hours.

ND: not determined.

LABELING:

The following minor changes in language are recommended with respect to the sponsor's proposed text.

■ Under the section heading **CLINICAL PHARMACOLOGY**, subsection **Pharmacodynamics** is interpreted by this reviewer as promotional. Thus, if this subsection is allowed in the label the following wording is suggested:

- 4th paragraph, please state- "In animal models of acute myocardial infarction, carvedilol doses up to 1 mg/kg i.v. reduced myocardial infarct size by 47% in rats, 78% in dogs and 89% in minipigs."

-5th paragraph, "In a gerbil model of brain ischemia, subcutaneous doses of carvedilol of 3 mg/kg improved the survival of neurons compared to vehicle treated gerbils. In studies with stroke-prone spontaneously hypertensive rats, repeated oral doses of carvedilol demonstrated a protective effect against lethal strokes compared to controls."

-6th paragraph, " In rat smooth muscle cultured cell preparations, carvedilol exhibited an antiproliferative effect against various smooth muscle mitogens such as angiotensin II, and, a variety of growth factors."

■ Under the section heading **OVERDOSAGE**:

-1st paragraph, "Single oral doses of 8000 mg/kg and higher were lethal to mice and rats. Toxic signs in these species consisted of blepharoptosis, decreased motor activity and depressed respiration."

-2nd paragraph should clearly state that the toxic signs reported to "overdosage" with carvedilol refer to humans, if so.

■ Under the section heading **PRECAUTIONS**, subsection "CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY.":

-1st paragraph, "In 2-year mouse study in which carvedilol was administered in the feed at concentrations providing up to approximately 200 mg/kg/day, i.e., up to 18 times the maximum recommended human dose (MRHD) as mg/M² of body surface area for a 50 kg patient, marginally significant harderian gland carcinomas occurred in females treated at the two highest doses of the drug. In a 2-year rat study in which carvedilol was administered in feed at concentrations providing doses up to approximately 75 mg/kg/day (up to 13 times the MRHD as mg/M²), carvedilol showed no statistically significant tumorigenic effect."

-2nd paragraph. "Carvedilol was not mutagenic when tested for genotoxicity in a variety of assays including *in vitro* bacterial (Ames test) and mammalian (Chinese hamster ovary/hypoxanthine-guanine phosphoribosyl transferase, sister chromatic exchange, human lymphocytes) cell systems or, *in vivo* mammalian system (Chinese hamster bone marrow, mouse host-mediated, mouse micronucleus, DNA synthesis inhibition, and DNA repair by unscheduled DNA synthesis in mouse testicular cells).

-3rd paragraph. "A general reproduction and fertility study in rats was conducted with carvedilol administered at oral doses of 12, 60 and 300 mg/kg/day (up to 52 times the MRHD as mg/M² of body surface area for a 50 kg patient). The high-dose was associated with loss of hair, delayed body weight gain, delayed mating, and reduced fertility when compared to controls. In this study, the no-observed adverse effect level on fertility was estimated to be about 60 mg/kg/day (up to 10 times the MRHD as mg/M²).

■ Under the subsection **Pregnancy: Teratogenic Effects, Pregnancy Category C:**

"Teratology studies were conducted with rats and rabbits given oral doses of carvedilol of 12, 60 and 300 mg/kg/day and, 3, 15 and 75 mg/kg/day, respectively. In rats, carvedilol at 300 mg/kg/day (up to 52 times the MRHD as mg/M²), was associated with maternal sedation, hair loss, decreased body weight gain, and increased post-implantation loss, and significantly fewer fetuses, lower fetal weight, and retarded skeletal development but no increase in skeletal malformations. In these rats, the no-observed adverse effect was estimated as 12 mg/kg/day (2 times the MRHD as mg/M²). In rabbits, carvedilol at 75 mg/kg/day (27 times the MRHD as mg/M²), was associated with increased post-implantation loss, and reduced number of fetuses; however, no malformations were observed. In these rabbits, the no-observed adverse effect was estimated to be below 3 mg/kg/day (about equal to the MRHD as mg/M²). There are no adequate and well-controlled studies in pregnant women. Since animal reproductive studies are not always predictive of human response, carvedilol should be used in pregnancy only if the potential benefit justifies the risk to the fetus."

■ We suggest you consider additional information under the subsection **Nursing Mothers.** Such information would appear under the heading "Non-Teratogenic effects" and would read "A study was conducted in pregnant rats orally dosed with carvedilol at 6, 60 and 200 mg/kg/day during day 16 of pregnancy through day 22 of lactation. The offspring of dams treated with carvedilol at 60 mg/kg/day (10 times the MRHD as mg/M²) and above showed reduced body weight, increased number of deaths during the first of week post-partum, and reduced early physical development. However, mating ability of offspring did not appear to be significantly affected by parental treatment with carvedilol."

EVALUATION

Carvedilol is a chiral compound with one asymmetric carbon atom which gives rise to 2 enantiomers. The drug sponsor proposes to market carvedilol as a racemic mixture of the R(+) and S(-)- enantiomers to treat hypertension.

The sponsor asserts that carvedilol was "designed" to produce 2 complimentary pharmacologic actions- vasodilation that leads to lower BP and a non-selective β -adrenergic receptor blockade without intrinsic sympathomimetic activity. Sufficient nonclinical studies were submitted to characterize the principal pharmacologic effects of a racemic mixture carvedilol, and for each of the 2 enantiomers.

Studies conducted with reliable animal models (conscious or anesthetized) show that carvedilol given as single or repeated doses, by i.v. or oral routes, lowers blood pressure (BP). Animal models used in these studies included spontaneously hypertensive rat (SHR), normotensive or pithed rat, rabbit, cat and dog. In conscious SHR, the effective oral hypotensive dose of carvedilol is in the range of 1-10 mg/kg. In numerous studies, the hypotensive effect of the drug was compared to several clinically effective antihypertensive drugs such as prazosin, labetalol, hydralazine, nitroprusside and propranolol, used as standards. The mechanism for the hypotensive action of carvedilol was studied by using numerous in vitro and in vivo assays. Although the mechanism of action is not completely elucidated, the drug displays non-selective β -adrenoceptor and, at approximately 10x higher concentrations, α_1 -adrenoceptor blocking activities.

The following is a brief overview of some remarkable findings in nonclinical pharmacology, toxicology and pharmacokinetics:

A. PHARMACOLOGY

In anesthetized rats, carvedilol (0.3 mg/kg i.v.) reduced arterial BP. In SHR, repeated administration of carvedilol (1 mg/kg i.v. for 8 days), was not associated with tachyphylaxis. In whole animal preparations, decreases in BP activate baroreflexes producing an increase in sympathetic activity which leads to an increased force and rate of heart contraction, rise in total peripheral resistance (TPR) and retention of Na^+ . However, during the hypotensive action of carvedilol in whole animals, cardiac output (CO) and heart rate (HR) are unchanged and TPR declines in parallel with BP. Since the decrease in BP produced by carvedilol is not associated with reflex tachycardia, the action of carvedilol appears to differ from that of pure vasodilators without sympatholytic activity. The hemodynamic profile of carvedilol is distinct from that of β -adrenoceptor blockers which decrease both HR and CO, and increase TPR.

In conscious dogs, i.v. infusion of carvedilol (0.01 - 5.1 mg/kg) or propranolol caused a dose-related fall in HR attributed to β -blockade, with a simultaneous fall in left ventricle maximum speed of pressure rise ($\text{dP}/\text{dt}_{\text{max}}$); lowering of BP took place via reduction of both CO and HR.

Diuretics are often used with antihypertensive drugs to prevent fluid retention and potentiate their hypotensive effect. In conscious SHR, i.g. carvedilol (10 mg/kg), the fall in BP was associated with reductions in glomerular filtration rate (GFR) and, in urea and urine volume; levels of electrolytes (Na^+ , K^+ and Cl^-) were unaffected. The combination of carvedilol and diuretics (hydrochlorothiazide or furosemide) showed no synergistic hypotensive effect. Compared to carvedilol alone, the combinations of carvedilol with each of the diuretics, caused higher urine volumes and electrolytes excretion. However, when the effects of each of the diuretics alone were compared to the drug combinations, there were dose-related decreases in urine volumes, electrolytes and urea excretion. In separate studies using normotensive WKY and SH rats, again dose-related decreases in BP were reported with carvedilol alone regardless of the routes of administration (i.v. or oral.) In both strains of rats, i.v. infusion of carvedilol reduced renal vascular resistance and GFR without affecting effective renal blood flow suggesting that renal autoregulation was unaffected by carvedilol. In both strains of rats, urine flow decreased significantly ($p < 0.05$) during the infusion of carvedilol; this finding was accompanied with decreases in the excretion of electrolytes and urea in WKY rats. However, in the SHR rats, the infusion of carvedilol was associated with a decrease in K^+ and urea excretion while Na^+ excretion was unaffected. These findings in SHR suggest a "renal sparing" effect for carvedilol since antinatriuretic activity might have been expected.

In female beagles, carvedilol (1, 3, 10 and 30 mg/kg in oral suspension) caused only reduction in urine volume during the first 2 hrs of study. Electrolyte excretion was not affected, again indicating renal sparing. In these dogs the "no-effect" dose was 1 mg/kg p.o.

In beagles, repeated oral doses of carvedilol (6 mg/kg for 5 days), was associated with an increase in HR, and slight increase in plasma-renin activity and plasma-angiotensin II concentration on the first day only; by 5th day BP was clearly lowered and increase in HR was only slightly detectable.

In anesthetized rabbits, carvedilol (0.01- 3.0 mg/kg i.v.) dose-dependently reduced BP from 101 mmHg down to approximately 54 mmHg at the highest dose tested. In conscious rabbits, oral doses of the drug (1, 3 and 10 mg/kg), dose-dependently antagonized isoprenaline induced tachycardia.

The vasodilatory action of carvedilol appears to result from its blocking action on the postjunctional α_1 -adrenoceptor blockade because in isolated aortic rings of the rabbit, the α_1 -adrenoceptor-mediated vasoconstrictor effect of norepinephrine (NE) is competitively antagonized by carvedilol with a K_B of 11 nM. Studies show that the drug is about 10-fold less potent as an α_1 -adrenoceptor antagonist than as a β_1 or β_2 -adrenoceptor antagonist.

In dog isolated saphenous vein, carvedilol produced non-competitive blockade of α_2 -adrenoceptor mediated vasoconstrictor response to B-HT 920 suggesting some activity at these receptors sites. Electrophysiologic studies suggest only very weak interaction of carvedilol with presynaptic α_2 -adrenoceptors. Because α_2 -adrenoceptor mediated vasoconstriction in this tissue is dependent upon the translocation of extracellular calcium, and since there was a lack of clear evidence that carvedilol interacts directly with α_2 -adrenoceptors, studies were conducted to determine if carvedilol was acting as a calcium

channel blocker. The literature reports that some Ca^{2+} channel blockers are effective in the treatment of peripheral vascular diseases because extracellular calcium is involved in the regulation of cutaneous blood flow. To investigate whether or not carvedilol may have a Ca^{2+} channel blocking action on the voltage-dependent Ca^{2+} channels, studies were conducted using rat uterus depolarized by potassium (which produces a nifedipine-sensitive contractile response resulting from opening of Ca^{2+} channels). In this preparation, carvedilol (at ED_{50} of about $7.65 \mu\text{M}$) produced a concentration-dependent relaxation of the potassium-depolarized tissue consistent with Ca^{2+} channel blockade. In potassium-depolarized rabbit aorta, similar results were noted. Further, also in rabbit aorta incubated with calcium-free buffer, and subsequently depolarized with potassium, a contractile response to administration of calcium was seen; this effect is sensitive to inhibition by Ca^{2+} channel blockers and in the case of carvedilol ($1 \mu\text{M}$), this drug inhibited the calcium-induced contractile response. In *in vivo* preparation using the pithed rat, the direct Ca^{2+} channel activator Bay-K-8644 produced a dose-dependent vasoconstrictor response that is inhibited by Ca^{2+} channel antagonists. In this preparation, carvedilol (at a high dose of 1 mg/kg i.v.), significantly inhibited the vasoconstrictor effect induced by Bay-K-8644 further suggesting that carvedilol exhibits some Ca^{2+} channel antagonism, but at several orders of magnitude higher concentrations than those for sympatholytic activity.

In pithed rat, effects of carvedilol on cutaneous circulation were compared, not to Ca^{2+} channel blockers but to labetalol- the 1st drug marketed known to exhibit combined β and α_1 -adrenoceptor antagonism. In this model, the drug and labetalol (both at 1 mg/kg i.v.) caused equivalent reduction in mean arterial BP and HR, carvedilol increased cutaneous blood flow (CBF) by over 60% and reduced cutaneous vascular resistance (CVR). Labetalol reduced CBF by only 20% with no change in CVR. Although in some studies there is suggestion of Ca^{2+} channel antagonism with carvedilol, this activity appears not to be prominent in animals. That is, in SHR pretreated with propranolol and prazosin to block the β - and α_1 -adrenoceptors, respectively, carvedilol did not cause additional reduction in BP unlike nifedipine, evidence of indirect sympatholytic vasodilating activity.

In guinea pig heart, carvedilol showed competitive β_1 -adrenoceptor antagonism to the positive chronotropic effect of isoproterenol (ISO). Sponsor's analysis of the data indicated that the blockade of β_1 -adrenoceptors by carvedilol binding with an apparent equilibrium dissociation constant (K_B) of 0.9 nM at this receptor.

In pithed normotensive rat, the hypotensive dose of carvedilol (0.3 mg/kg i.v.) competitively inhibits the β_1 -adrenoceptor mediated positive chronotropic response to ISO. This dose of carvedilol inhibited the chronotropic response of ISO by 100-fold, indicating β_1 -adrenoceptor blockade *in vivo* at antihypertensive doses.

In the guinea pig trachea, carvedilol dose-dependently inhibited the β_2 -adrenoceptor mediated relaxation induced by ISO; the inhibition was competitive with a K_B of 0.9 nM at the β_2 -adrenoceptors. This K_B value is the same as that calculated for the β_1 -adrenoceptors indicating that the drug is a nonselective β -adrenoceptor antagonist.

In pithed rat, the hypotensive dose of carvedilol (0.3 mg/kg i.v.) inhibited the β_2 -adrenoceptor mediated vasodilator response of the selective β_2 -agonist salbutamol demonstrating the β_2 -blocking effect of carvedilol in vivo. The degree of inhibition was reported to be similar to that observed for β_1 -adrenoceptors in this preparation indicating a non-selective blockade for β_1 - and β_2 -adrenoceptors in vivo.

Each enantiomer of carvedilol was also evaluated in in vitro and in vivo preparations to determine the stereoselectivity for α_1 -adrenoceptor and β_1 -antagonism. Studies show that the β -adrenoceptor blocking effect of the drug is attributed alone to the levo isomer S(-)-carvedilol; this is considered a non-selective β -adrenoceptor blocking activity.

Both the R(+)- and S(-)-enantiomers possess hypotensive activity in vivo, and vasorelaxant activity in in vitro. While the R(+)-enantiomer is an hypotensive agent without β -adrenoceptor blockade, the hypotensive effect of S(-)-carvedilol may be mainly attributed to β -adrenoceptor blockade which inhibits counter-regulatory mechanism provoked by vasodilatation.

In the guinea pig atrium, the S(-)-enantiomer demonstrates β_1 -adrenoceptor antagonism with a K_B of 0.4 nM (about 2-fold more potent than the racemic mixture.) R(+)-enantiomer is about 100-fold weaker than the S(-)-enantiomer as a β_1 -adrenoceptor blocker with a K_B of 45nM.

In anesthetized SHR, the S(-)-enantiomer was 6-fold more potent as an antihypertensive than the R(+)-enantiomer. Studies show that the vasodilator and acute antihypertensive effect of carvedilol is considered to result from α_1 -adrenoceptor blockade produced by both enantiomers, the concomitant β_1 -adrenoceptor blockade produced by the S(-)-enantiomer (preventing reflex tachycardia) apparently enhancing the antihypertensive potency of carvedilol. The drug sponsor speculates that the clinical use of the S(-)-enantiomer alone could lead to relatively strong β -blockade with weak vasodilating effect while the use of the R(+)-enantiomer alone would result in hypotensive effects without β -blockade.

In the pithed rat, S(-)-enantiomer (0.1 mg/kg, i.v.) produced a 25-fold rightward shift in the positive chronotropic dose-response curve of ISO. In this model, R(+)-enantiomer, even at a 10-fold higher i.v. dose showed had no antagonistic activity on the positive chronotropic effect.

In conscious rabbits, the ED-50 for inhibition of ISO tachycardia was 0.025 mg/kg/i.v. for the S(-)-enantiomer, and 4 mg/kg i.v. for the R(+)-enantiomer; the S(-)-enantiomer being over 100 times more potent the R(+)-enantiomer. These findings indicate that the β_1 -adrenoceptor blocking activity of carvedilol (the racemic mixture) results predominantly from the S(-)-enantiomer. Further, that the greater hypotensive activity of S(-)-enantiomer may be attributed to β -adrenoceptor blockade, which inhibits the counter-regulatory mechanisms (tachycardia) provoked by vasodilation.

In isolated rabbit aorta, as stated above, carvedilol showed competitive antagonism at α_1 -adrenoceptors (K_B value of 10 nM); the K_B values for the S(-)- and R(+)-enantiomers at α_1 are equipotent with values of 16 and 14 nM, respectively.

The α - and β -blocking activities of carvedilol, compared to other drugs, on vasculature of the hind limb were investigated. In rabbit and mongrel dog, maximum fall in perfusion pressure of hind limb induced with a drug was taken as a measure of vasodilation.

In rabbit hind limb, carvedilol (at the highest- 2.5 ug i.v.), was reported to cause a -32 mmHg fall in perfusion pressure, while the vasodilator adenosine (at 10 ug) caused a -51 mm Hg fall (the highest fall with that dose.) Sponsor's calculations of the dosages in the study, indicated that the vasodilatory activity of carvedilol could be considered to be approximately twice as great as that of adenosine. And, in mongrel dog, carvedilol (1-30 ug i.a.) and standard vasodilator drugs (i.e., papaverine, ISO), produced a dose-dependent increase in femoral artery blood flow. In this model, the vasoconstrictor effect of norepinephrine (NE) and the vasodilator effect of isoproterenol were tested before and after i.v. doses of carvedilol; after carvedilol, the vasoconstriction by NE was inhibited in a dose-related fashion while the vasodilation of ISO was completely inhibited.

In conscious SHR, intragastric doses of carvedilol (10 mg/kg) were associated with dose-dependent antihypertensive activity which was rapid in onset and long lasting (4-8 hrs). Repeated administration of the drug in this model was not associated with tachyphylaxis. No synergism for the hypotensive effect was noted with diuretics (HCTZ or furosemide).

Other general cardiovascular effects and their duration were reported for carvedilol. In reserpinized rats, no intrinsic sympathomimetic activity was noted with carvedilol. In rats there was no tolerance or tachyphylaxis to the hypotension and lack of reflex tachycardia with repeated i.v. doses of the drug (1 mg/kg). Carvedilol potentiated the BP fall in response to an orthostatic (tilt) stimulus, reflecting α -blockade. In dogs, i.v. doses of carvedilol (0.03 - 1.0 mg/kg) produced hypotension but did not change QTc, PR or QRS intervals; oral doses did not affect coronary blood flow in dogs. Also in dogs, BP reduction after repeated oral doses of carvedilol (6 mg/kg/5 days) were not associated with remarkable increases in HR, or plasma-renin (PRA) activity or angiotensin II concentrations by the end of the study, however some increases in PRA and AII were seen with the first dose of the drug. In anesthetized rabbits, when compared to control values, doses of carvedilol (1 - 3 mg/kg i.v.) were associated with slight decreases in HR and slight increases in PQ and QRS intervals.

The drug sponsor notes that some patients surviving an acute myocardial infarction are at risk for reinfarction and/or sudden cardiac death. In some of these patients, the cardioprotective effect provided by β -antagonists is generally believed to result from an improvement in the balance between myocardial oxygen demand by reduced myocardial work which occurs secondary to reductions in heart rate and contractility. Thus, the potential cardioprotective effect of carvedilol was investigated in several animal models of acute myocardial infarction. In dogs subjected to 1 hr. of left ventricular cardiac ischemia followed by 24 hr reperfusion, carvedilol (1 mg/kg i.v.) significantly ($p < 0.05$) reduced the left ventricular the infarct size by 78% when compared to control; propranolol (1 mg/kg i.v.) reduced the infarcted size by 64%. In dogs subjected to occlusion of the left anterior descending coronary artery for 6 hrs (permanent), compared to controls, carvedilol (0.3 and 1.0 mg/kg i.v.) significantly ($p < 0.05$) reduced the infarcted area size by 46% and 63% and propranolol reduced the infarct size only

by 20%. Cardioprotective effects of carvedilol were also reported in other experimental models of acute myocardial infarction in the rat and pig.

Based on findings in models of orthostatic stress using anesthetized rat and rabbit, in which i.v. doses of carvedilol impaired the compensatory recovery of BP to pretit level (similar to labetalol and prazosin), investigators considered that in the clinics typical α and β -blocker side effects might be expected from carvedilol. The sponsor further considered that as with propranolol, reduced blood supply of the extremities (Raynaud syndrome) could also occur as a side effect of carvedilol.

Cytoprotective actions reported for the drug included increasing the survival of stroke prone rats; reducing lipid peroxidation (measured by the formation of thiobarbituric acid reactive substances) in rat brain mainly by scavenging free radicals. The reported free radicals scavenging activity and anti-mitogenic effect (against a group of vascular smooth muscle mitogens) of carvedilol were considered to be potential cardiovascular protective effect.

Briefly, neuropharmacologic effects reported with carvedilol included: in mice, reduced spontaneous motor activity, ptosis, some analgesic effect against chemically induced spinal constriction, but no prolongation on hexobarbital sleeping time or antagonism against electroshock convulsion; in rabbit, inconsistent effects on body temperature (in combination with a diuretic a fall in body temperature was reported as well as increase in blood sugar); in cat little effect on EEC activity.

In rat, except for decrease in gastric acid with carvedilol (5 mg/kg i.v.), gastrointestinal effects of the drug were unremarkable in mice and rat.

It may be concluded from the studies described above, that carvedilol produces vasodilation by α_1 -adrenoceptor blockade and antagonizes reflex tachycardia through B_1 -adrenoceptor antagonism. Mechanism of action studies show that cGMP is not associated with the vasorelaxation induced by the drug. At doses higher than those needed for α_1 and β blocking activity, carvedilol shows some evidence of Ca^{2+} channel blockade, however; this action is not predominant. There was no evidence of inhibition of angiotensin converting enzyme activity with carvedilol.

B. TOXICOLOGY

Toxicity studies were performed with carvedilol administered by i.v., i.p. and oral routes. Mutagenicity studies were conducted in vitro and in vivo. Except for mutagenicity studies, this evaluation mainly discusses oral dosing studies because this is the proposed route of administration of carvedilol. Drug sponsor reports that toxicity studies were conducted in accordance with GLP practices.

1. Single Dose

Single oral dose toxicity studies (acute toxicity) with carvedilol were conducted in mouse, rat and male beagles. For both the mouse and rat, the median lethal doses were estimated to be 8000 mg/kg p.o. and above and, for dog above 1000 mg/kg p.o (although no beagles died when treated with 2000 mg/kg p.o., the dogs vomited and vomitus contained a substance believed to be carvedilol). Remarkable acute toxic signs in both rodent species included hair loss, blepharoptosis, reduced spontaneous activity and, depressed respiration. Necropsy of mouse and rat that died showed congestion of various internal organs and, in addition rats killed showed micro-hemorrhages in the brain. Remarkable acute toxic signs in the dog included decreased locomotor activity, unsteady gait, blepharoptosis, and transient pathologic changes but no histopathologic changes. A remarkable toxic sign in beagles was a slight increase in blood glucose, 1 day after the drug treatment. However, blood glucose level changes were not noted in a rabbit study in which carvedilol was given 3 mg/kg, i.v. to examine its effect on this parameter.

Except for an acute i.v. study in mouse, the toxicity profile of each enantiomer was not studied to a great extent. In mouse, remarkable signs of toxicity to i.v. doses of the enantiomers were within the range of the racemic mixture (41.1 mg/kg i.v.). Other acute i.v. toxicity in rat included administration of several major and pharmacologically active metabolites of carvedilol (M2, M4 and M5, See Fig. 27 and Table 33). Remarkable toxic signs reported included clonic spasms with all 3 metabolites lasting 2-10 min, apathy lasting up to 45 min and deaths with M4 and M5 metabolites. The calculated median lethal doses were about 50 mg/kg i.v.

In the acute toxicity studies with carvedilol, the calculated median lethal dose for rodents and non-rodents are above 8000 and 1000 mg/kg, respectively. These values represent about 8,000 and 1,000 times, respectively, the maximum recommended therapeutic dose of carvedilol assuming a 50 Kg patient.

In one special study in dog to determine limiting toxicity of i.v. doses of carvedilol. Data show that the drug at 15 to 30 mg/kg i.v., provoked intermittent convulsions and ECG changes (prolongation of P-wave, increases in PR and QRS intervals). However, no convulsions and only slight ECG changes were reported at 7.5 mg carvedilol/kg i.v. From these dog studies with i.v. doses of the drug, investigators considered that the cardiac depression seen is due to a membrane stabilizing activity of carvedilol drug because some B-blockers at high doses produce direct depression of A-V transmission of the drug. The literature reports that such activity is not relevant to clinical practice, but in overdose, this property is potentially dangerous.

2. Multidose

In a 4-week rat i.v. study of carvedilol at 2.5, 5 and 10 mg/kg day, ECG tracings revealed no anomalies. Blepharospasm and apathy as well fatty infiltration of liver in females were reported at the 2 highest doses. The NOAEL for the drug was estimated as 2.5 mg/kg, i.v.

Since it is expected that carvedilol will be taken chronically by hypertensive patients, sponsor has conducted several multidose oral toxicity studies with the drug in rodent and non-rodent species. Briefly, in subchronic studies the drug was administered daily to mice (NMRI) up to 13 weeks in the diet, to rats (Sprague-Dawley) up to 15 weeks given by gavage or in diet, and to beagles up to 26 months in capsules. In chronic and 2-year carcinogenicity studies, carvedilol was administered in diet to mouse and rat for up to 78 weeks, and in capsules to beagles for up to 52 weeks.

In a 13-week study, mice treated with carvedilol (20 up to 800 mg/kg in diet) showed at the 2 highest doses (600 and 800 mg/kg/day) increases in alkaline phosphatase in males and sGPT values in both sexes and decreases in total serum proteins. Body weights in males were reduced > 10% at 600 and 800 mg/kg/day; in females the body weight reduction was >10% only at 20 mg/kg/day dose, and remained fairly constant at the higher doses of carvedilol. Although a NOAEL was not determined, the dose of 200 mg/kg/day was selected by sponsor as the MTD based on the elevation of the relative liver weights of the females which was 9% (at the two highest doses the increases were >20%, respectively, $p < 0.05$) when compared to controls. Although males at 200 mg/kg/day, the elevation in relative liver weight over control was about 4%, the increase was 12 and 20% at the two highest doses, respectively. No histopathology was done. In toxicokinetic studies, serum samples obtained at 1, 5 and 13 weeks of the study from the LD (20 mg/kg/day) showed that levels of carvedilol ranged from 22 to 96 ng/ml. Quantification of carvedilol in serum at the higher dose levels was not possible due to technical difficulties. However, qualitatively determinations reported that carvedilol was detected in all samples and concentrations of the drug increased with dose.

In one 13-week rat study with carvedilol at 30, 100 and 300 mg/kg/day p.o., remarkable toxic signs (reversible after 5 week drug-free period), included blepharoptosis, decreased food intake, increases in BP at HD, bile duct hyperplasia, myocardium cell infiltrates and inflammatory changes in biliary tract. Lethal respiratory/cardiac failure occurred in 3 HD rats. Other remarkable toxic signs in rat and mouse were decreases in total serum protein and (rat only) albumin. In a separate 13-week rat study, in which rats were treated with similar oral doses of carvedilol (up to 300 mg/kg), HD rats had mild hepatic changes described as pericholangitis and single small hyperplastic nodules. The NOAEL for the drug was estimated to be 30 mg/kg/day and below (or 30 X the maximum recommended therapeutic human dose in a 50 kg patient.)

From the 13-week oral dose studies, the accepted MTDs for carvedilol in mouse was 200 mg/kg/day and in rat- 4,000 ppm in diet (actual intake 486-532 mg/kg/day.) These MTDs were based on dose-related increases in liver weights in mouse (no histopathology performed) and, multiple biologic changes in rat which included reduced body weight, reduced erythrocyte parameters, increased leukocyte counts and dilated bile ducts (no histopathology was performed). Based on these studies, drug doses selected for the oral carcinogenicity studies were for the mouse 20, 65 and 200 mg/kg/day and, for the rat 600, 2,000 and 4,000 ppm (in diet). These MTDs range from about 200 to 500 times, respectively, the maximum recommended human therapeutic dose of carvedilol.

In the rat chronic toxicity study (3 doses of carvedilol in diet for up to 52 weeks), remarkable toxic signs in drug-treated rats included decreased food intake (at HD of about 343 mg/kg/day), dose-related decrease of body weight gain, increase alkaline phosphatase for HD rats, exacerbation of spontaneous cardiomyopathy (at MD of about 117 mg/kg/day and at HD), biliary hyperplasia and, increased incidence of proliferative liver lesions.

In a separate rat study (3 doses of carvedilol in diet for up to 78 weeks), remarkable toxic signs were similar to those reported in the 52-week rat study. Other toxic signs reported included a slight increase in cholesterol/triglycerides serum values in females (at HD-5000 ppm in diet with an actual intake determined at the end of the study of 261 mg/kg p.o.). Changes in lipid values were not present at the end of the study in HD females who had an off-drug phase following carvedilol administration. Minimal chronic inflammatory cell infiltrate and fatty infiltration in hearts and dose-dependent liver cell hyperplasia (5 HD rat had developed a hepatocellular adenoma) were noted. Hepatocellular effects were considered to reflect the consequence of excretion of carvedilol and a functional adaptation to hepatic metabolism.

Two 13-week dog studies were conducted with 3 doses of carvedilol ranging from 15 up to 150 mg/kg/day (drug sponsor's labs.) and, from 10 up to 250 mg/kg/day p.o. (conducted in Japan). Remarkable toxic signs noted in some drug-treated dogs in both studies included vomiting and blepharoptosis. Some LD and MD dogs showed fatty infiltration of liver and heart. Serum K^+ was increased at MD and at 250 mg/kg/day. Although not dose-related, absolute weight in some organs (liver, adrenals and thyroid) were increased at 250 mg/kg/day. ECG tracings showed decrease heart rate and prolonged PQ interval in dogs treated with carvedilol doses of 15, 50 and 150 mg/kg/day p.o.

In a 52-week study, beagles were treated with carvedilol (0, 10, 30, 100 and 300 mg/kg/day p.o.) in capsules given in 2 divided doses. Drug effects were compared to controls and, signs noted after a 17-week drug free period. After weeks of dosing with the drug, at the 2 highest doses vomiting and diarrhea occurred. ECG tracings in drug-treated dogs showed prolonged PQ-intervals. Compared to controls, dose-related increases were reported for relative liver weight. Minimal to moderate bile duct hyperplasia was reported at the 3 highest doses, but also in controls; none were reported for dogs treated with carvedilol at 10 mg/kg/day group. NOAEL is estimated to be around 10 mg carvedilol/kg/day p.o. and below (equivalent to about 10 times the maximum recommended therapeutic dose assuming a 50 kg patient). At the beginning of study, toxic signs included ataxia, apathy and blepharostenosis. Treated dogs were unremarkable during the drug-free period. Toxicokinetic reports show that in these beagles, at about week 49 of study, the MD dogs (15 mg/kg/day in 2 divided doses), peak serum concentration of carvedilol were reached at about 2 hrs post-dose. Values for median serum C_{max} were 277 ng/ml for males and 153 ng/ml for females, suggesting sex difference in this study. At 11 months (343 days) of treatment with carvedilol (30 mg/kg/p.o. 2 divided doses), the C_{max} (at about 2 hrs) and AUC_{0-24} values for the drug were about 6 X higher than that reported in hypertensive patients treated for once a day for 28 days with 50 mg/kg/day p.o. carvedilol.

In a 2nd repeat oral dose study with beagles, doses of 30, 100 and 300 mg/kg/day p.o., at 21 weeks of treatment 2 males died (1MD, 1HD). Signs before death included swollen eyes, ptosis, apathy and respiratory problems. During the study, ECG recordings showed prolongation of the PQ-intervals at LD and MD only. At HD, clinical chemistry showed increased levels of serum alkaline phosphatase and, sGPT during the last months of the study. Study was terminated at 26 weeks because investigators wanted "to be in line with EEC regulations." Histopathologic examination for both dog studies showed mild biliary hyperplasia, as seen in previous 52-wk dog study, which drug sponsor considers to be of "limited toxicologic importance" since there is "no known correlation to any human disease.....and this lesion has been reported in animals exposed to marketed beta-adrenergic blocking agent, metoprolol.*" Reviewer notes that hyperplasia of bile duct also reported in rat after long term treatment with carvedilol.

Beagles treated with carvedilol (0.2, 1.0 and 5.0 mg/kg for 4 weeks), no evidence of adverse effects on heart as reported as determined by ECG.

3. Carcinogenicity

Dietary carcinogenicity studies were conducted with 2 rodent species- NMPI mouse (3 drug doses and 1 control) and Sprague-Dawley, CAW-Ico-Wiga rat (4 drug doses and 1 concurrent control and 1 control from another study). The HDs selected for the carcinogenicity studies were based on MTDs (200mg/kg/day p.o. for mouse and 4000 ppm in diet for rat) determined in 13-week studies in the same species/strains.

In this mouse carcinogenicity study, the 3 groups of animals were administered the following daily doses of carvedilol in diet- LD-20, MD-65 and HD-200 mg/kg; the females were dosed for 97 weeks and males for 114 weeks. By the end of the mouse carcinogenicity study, the average drug intake at the HD (182.5 mg/kg/day) represents about 182 X the maximum recommended daily human therapeutic dose for carvedilol. At the end of the study, the survival rates of control, LD, MD and HD mice were 42%, 62%, 44% and, 44% for males, respectively, and 27%, 20%, 22%, and, 20%, respectively, for females. The only clinical chemistry disturbances reported were significantly higher urea nitrogen and, SGOT at the highest doses tested. No remarkable drug-related macroscopic changes were noted. Histopathologic examination of HD mice revealed a higher incidence of single cell hepatocellular necrosis (females) and, an overall lower tumor incidence as well as lower percentage of tumor bearing mice. Accordingly, no evidence of carcinogenicity with carvedilol was noted after dietary administration for 97 to 114 weeks.

Division of Biometrics concluded from the evaluation of data provided by sponsor for the mouse carcinogenicity study with carvedilol, that in both sexes there was no statistically significant difference ($p=0.05$) in the survival distribution, intercurrent mortality rate or linear trend in tumor incidence rates. However, Biometrics asserts that although the survival rates of the HD mice at 1-year satisfied a criterion**, it seems that there were not

* INT Annual Report received at CDER on December 12, 1993 (page 142).

** "Factors in the evaluation of 200 NCI carcinogen bioassays." Chu, et al. J Tox and Environ Health 8:251-80, '81

sufficient female mice in the control and treated groups living long enough to get adequate exposure to carvedilol and to be at risk for forming late-developing tumors as FK Haseman* proposes.

For the rat carcinogenicity study, sponsor attempted to conduct a study using the selected MTD of 4000 ppm carvedilol in diet as the HD. The study was stopped after 6 months for various reasons which included steep decrease in body weight of treated rats (considered by sponsor to be due to too high doses of carvedilol), water deprivation (failure of automatic drinking water system) and, increased mortality. A remarkable histopathologic lesion observed in the rats that died was slight biliary hyperplasia. Biliary hyperplasia associated with long term administration of carvedilol was reported in 2 species (1 rodent and 1 non-rodent.)

A second rat carcinogenicity study was started. This was the definitive carcinogenicity study conducted with 4 doses of carvedilol in diet at LD-200 ppm, MDs- 400 and 800 ppm and HD-1600 ppm. The actual drug intake varied but by the end of study the mean daily drug intake values were for males 8, 16, 31 and 62 mg/kg and, for females 10, 19, 38 and 75 mg/kg for 2-years. By the end of the study, the average drug intake at HD (68.4 mg/kg/day) represents about 68 X the maximum recommended daily human therapeutic dose for

carvedilol. Serum concentrations of carvedilol were determined at one time point (sampled at about 9:00 AM) in all 4 dose groups at the end of the study. The mean concentrations of the drug reported were for male rats- 21, 31, 94 and 215 ng/ml, respectively, and in females- 18, 39, 94 and 354 ng/ml, respectively, for the LD, 2- MDs and HD carvedilol.** Male mortality was dose-dependent and unscheduled deaths without fatal tumors occurred in rats at HD. Although some remarkable histopathologic non-neoplastic findings were also noted in controls, these included liver hyperplasia, chronic nephropathy, cell infiltrates in the heart (in males), splenic congestion and lung edema.

No clear evidence of tumorigenicity was noted in rats treated with daily doses of carvedilol up to MTD given in diet for 104 weeks. Although not-dose related, neoplastic lesions included thyroid adenomas/carcinomas, mammary adenomas/carcinomas, and liver cell adenomas. In female rats at HD-1600 (calculated intake of 75 mg carvedilol/kg/day), there were thyroid and liver cell adenomas; neither of which were reported in controls.

Regarding thyroid adenomas, this reviewer notes that C. Gopinath reports that "... Certain pharmaceutical drugs are known to affect thyroid gland through adrenergic mechanisms.....some....cardiovascular drugs of adrenergic class influence thyroid follicular growth and function, increase TSH secretion and modify iodine organification....The mechanism underlying thyroid lesions are complex"***

* Biometrics evaluation states that JK Haseman personally communicated to Dr.KLin, FDA that a 50% survival rate of the initial animals in HD group between weeks 80-90 will be considered a sufficient number animals and an adequate exposure. But, the percentage can be lower or higher if the number of animals used in each treatment/sex is larger or smaller than 50 as long as there are between 20 to 30 animals still alive during these weeks.

** These data were requested and later submitted as " Best Copy Available" by sponsor in NDA Amendment dated 03-29-94.

*** "Causes and interpretation of thyroid tumors in rodent Bioassays" by C. Gopinath, Chapter 3, p. 19, in *Current Issues in Drug Development*, Huntington Research Center Limited, UK 1991

NDA 28297

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4. Special Studies

Immunologic effects may be associated with the exposure to drugs. Drug sponsor has submitted numerous studies performed in Japan in which guinea pigs showed no evidence of a delayed type hypersensitivity or passive cutaneous anaphylaxis reaction to carvedilol.

5. Reproductive Toxicology

Reproductive toxicity studies included the customary Segments I, II and III in 2 animal species (1 rodent and 1 nonrodent) given orally carvedilol suspended in 1% methylcellulose. In rats, fertility and general reproductive performance studies (Seg. I) included dose-ranging studies with carvedilol (200 up to 400 mg/kg/day in rats prior to mating), and the definitive study where 12, 60 and 300 mg/kg/day p.o. was administered daily prior to mating to males and females for 62 and 15 days, respectively, but continued through day 21 of lactation in the females. Impaired fertility was reported at 300 mg/kg/day and developmental effects in offspring (F₁ generation) of HD parents. Overall the NOAEL on reproductive performance and fertility in both sexes was considered to be 12 mg/kg/day p.o. In a separate rat study performed in Japan) designed to evaluate the effect of carvedilol (12 up to 300 mg/kg/day on days 0 up to 21 days postpartum) on food intake/body weight on dams, these two parameters were significantly decreased at the HD.

Teratology studies (Seg. II), conducted in 2 species (rat and Himalaya rabbit), consisted of preliminary studies in pregnant and non-pregnant rats at doses ranging from 50 up to 400 mg/kg/day and 100 up to 1500 mg/kg/day, respectively. The definitive study, using pregnant rats treated at 3 dose levels 12, 60 and 300 mg/kg/day during the period of organogenesis (days 7-16 postconception), showed sedation, hair loss, and reduced body weight gain at 60 and 300 mg/kg/day. Compared to control, dams from the 300 mg/kg/day groups showed increase in post-implantation losses and decrease in number of live fetuses. Offspring from the 300 mg/kg groups showed developmental delays (missing of stunted 13th rib) but, no malformations were reported. In this study, the NOAEL for dams was considered to be 12 mg/kg/day, and for F₁ developmental toxicity to be 60 mg/kg/day carvedilol.

The rabbit Seg. II studies consisted also of dose-range studies in pregnant and non-pregnant rabbits. For the definitive study in pregnant rabbits the 3 doses tested were 3, 15 and 75 mg/kg/day given during the period of organogenesis (days 7-19 postconception). At 75 mg/kg/day, compared to controls there was an increase in post-implantation losses and decrease in live fetuses. The weights of the live fetuses and the placentas from drug treated animals were heavier than those from the controls. No drug-related malformations were reported in offspring of treated rabbits. The NOAEL for maternal toxicity may be considered to be below 3 mg/kg/day.

In rats, peri- and postnatal toxicity studies (Seg. III) were conducted with carvedilol (12, 60 and 200 mg/kg/day p.o. (on days 16 of gestation to day 22 end of lactation)). Remarkable effects noted in dams (F₀ generation) included decreased body weight gain and mild sedation in some dams at HD and hair-loss in drug-treated. At the HD, dams showed increased intrauterine embryo losses and, reduced rearing activity. Carvedilol did not significantly affect

the gestation duration and, the number of uterine implants and number of live pups (F_1 generation). Offspring (F_1 generation) from MD and HD F_0 dams showed a slight decrease in body weight and early deaths (2 days post-partum) as well as retarded development of pinna detachment and grip strength. There were no significant effects of carvedilol on the mating behavior of the F_1 generation or on the parturition and development of the F_2 generation. From this study, the oral NOAEL of carvedilol on dams (F_0 generation) and offspring (F_1 generation) may be considered to be 12 mg/kg/day.

6. Mutagenicity and Clastogenicity

Numerous genotoxicity assays (*in vitro* and *in vivo*) were reported examining the potential for carvedilol, its metabolites and an intermediate to adversely affect bacterial, yeast and mammalian cell genes.

Prokaryotic cells systems used included 5 strains of *Salmonella typhimurium*, *Escherichia Coli*, *Serratia marcescens* and *Saccharomyces cerevisiae*. Based of the results in the Ames test, compared to appropriate controls, carvedilol (5 to 5000 ug/plate) produced no significant increase in revertant frequencies in any of the 5 appropriate tester strains of *S. typhimurium* and either in the presence or absence of microsomal activation (S9 fraction from rat liver induced with Aroclor or other enzyme inducing chemicals.) An intermediate compound in the synthesis of carvedilol (n-benzyl carvedilol) was assayed in the same 5 strains of *S. typhimurium*. Except for one strain (TA1535), all test strains gave equivocal results with n-benzyl carvedilol. Since this assay showed a limited increase in revertant frequency in microsomal activated TA 1535 strain, the finding was not considered to be significant to human safety. The potential of carvedilol to induce reverse mutation in *E. coli* was studied. Results submitted indicate that in this bacterial assay, with/without S9 activation, carvedilol had no mutation inducing activity. Carvedilol was tested in the mouse host-mediated assay (mouse dosed with 200 or 2000 mg/kg carvedilol, p.o. and injected i.p. with *S. typhimurium* G 46 or *S. marcescens*) to determine the drug's potential for inducing revertants strains of these microorganisms. Results reported from this assay did not indicate that carvedilol at the HD had antibacterial activity and LD was not mutagenic. Results from the assay to detect potential of carvedilol for inducing yeast genetic toxicity were inconclusive.

Mammalian test systems used to examine genotoxicity potential of carvedilol included Chinese hamster ovary (CHO), hamster and mice and bone marrow cells, human lymphocytes lymphocyte cultures, and mouse testicular cells. In a gene mutation test using somatic mammalian cells, carvedilol at concentrations up to 33 ug/ml (with and without S9 liver fraction) showed no evidence of mutagenic activity in the HGPRT locus of the CHO cells when compared to positive controls.

When studies were conducted to examine the potential of carvedilol, with and without microsomal activation, to cause chromosomal aberration *in vitro* and *in vivo* preparations, carvedilol (8 to 80 ug/ml) caused no chromosomal damage in cultured human lymphocytes. However, in separate studies carvedilol concentrations of 70 ug/ml, there was a 25% reduction in mitotic index and, at 200 ug/ml and above the drug was highly toxic to cultured human lymphocytes compared to positive controls. At lower doses tested carvedilol was not

clastogenic in this *in vitro* test. In an *in vivo* chromosome aberration test in bone marrow using Chinese hamster, the animal was dose with the maximally tolerated dose of carvedilol (2000 mg/kg, p.o.), and prior to sacrifice the animal was treated with demecolcine to arrest the cells in metaphase. When bone marrow cells were removed from their femurs, stained and scored, there was no evidence of chromosomal damage; carvedilol was not clastogenic. *In vivo*, using the Chinese hamster micronucleus tests, animals were dosed orally with carvedilol (1500 mg/kg for 2 days). Mean number of micronuclei in bone marrow samples (formed from chromosome or chromosome fractions left behind during anaphase) from carvedilol-treated animals were not significantly different from vehicle treated controls.

Additional tests were also conducted to assess interaction of carvedilol with DNA. They included determination of primary DNA damage by using a sister chromatic exchange (SCE) assay in the Chinese hamster, determination of DNA covalent binding by applying a DNA synthesis inhibition test, and measurement of DNA repair by unscheduled DNA synthesis in mouse testicular cells. Results of all these tests were considered negative for carvedilol when compared to controls because the drug (at 1000 mg/kg p.o.) did not increase the mean numbers of SCE in hamsters and, at doses ranging from 50 up to 100 mg/kg, had no effect on DNA replication in mice or unscheduled DNA synthesis in their testicular cells. Carvedilol doses of 50, 100 and 200 mg/kg produced a significant reduction in body temperature.

C. PHARMACOKINETICS

Carvedilol is extensively metabolized via both oxidation/conjugation pathways. Following oral administration of the drug more than 20 major and minor metabolites have been identified among the 5 species studied. The metabolite profiles for male and female animals appeared qualitatively similar. Usual pharmacokinetics parameters examined showed that oral doses of the drug are rapidly absorbed, undergo first-pass metabolism in the liver, resulting in an estimated low bioavailability for carvedilol (below 30% in rat and dog). The drug binds to blood albumin, peak levels are seen within 1 hr post dosing and elimination $T_{1/2}$ is about 5 hrs (rat). Stereoselective pharmacokinetics was reported in rat and monkey after single oral doses of carvedilol; R/S enantiomeric ratios for C_{max} and AUC were 2.5 and 2.2, respectively, in rat and, in monkey C_{max} and AUC were 1.5 and 1.5, respectively. The oral administration of 10 mg/kg to rat of R(+)- and S(-)-enantiomers led to the excretion of M1 and M2 metabolites, respectively, in bile.

In conclusion, drug sponsor has submitted nonclinical pharmacologic and safety data on carvedilol (a racemic mixture of 2 enantiomers). Nonclinical pharmacology studies show that carvedilol reduces mean arterial blood pressure and peripheral vascular resistance. Absence of reflex tachycardia is considered to be due to inhibition of β_1 -adrenoceptors. Carvedilol showed no intrinsic sympathomimetic activity in the models tested. Studies to elucidate the mechanism of action of carvedilol in *in vivo* and *in vitro* models show that the drug is a competitive antagonist at β_1 , β_2 and, α_1 -adrenoceptors. Studies show that the S(-)-enantiomer is the most active as a β_1 -adrenoceptor and both S(-)- and R(+)- contribute to the vasodilating

effects of the drug through α_1 -adrenoceptor blockade. Electrophysiologic studies suggest only a weak interaction with α_2 -adrenoceptors. Studies suggest that at high doses carvedilol may have some Ca^{2+} channel blocking activity. In appropriate animal models of orthostatic stress, carvedilol interfered with the orthostatic response to tilt suggesting that the drug might exhibit this activity in humans. In contrast with other vasodilators, carvedilol did not diminish kidney function; glomerular filtration and Na^+ excretion are maintained at vasodepressor dosages. Other potential activities of carvedilol suggested from nonclinical studies included cardioprotection based on reductions in infarct size in models of acute myocardial infarction, protection against mortality in stroke-prone SHR, antiproliferative effect in cultured vascular smooth muscle cells exposed to various mitogens, antioxidant activity by inhibition of lipid peroxidation in swine cardiac membranes, inhibition of superoxide release from phorbol ester-activated human neutrophils exposed to oxygen radical generating system, and protection against glutamate-induced neurotoxicity of cultured rat cerebral granule cells.

Safety studies with the drug appear to have been conducted in appropriate animal models. Although most toxicity data reported are said to have been obtained in accordance with GLP regulations, some studies predate these regulations and were poorly organized and not properly edited before submitting to FDA. Nonclinical toxicity studies reviewed/evaluated include short-term, long-term toxicity and special toxicity studies in up to 5 animal species. In 2 animal species (both sexes of rats and dogs), the target organs for chronic toxicity were liver and heart. In rat, after 1 year administration of carvedilol (LD- 600, MD- 2000 and HD- 6000 ppm in diet corresponding to a mean daily intake of 35.4, 117 and 343.5 mg/kg, respectively), the apparent "no-adverse effect" dose for heart histopathologic findings was 35.4 mg/kg (or 209 mg/M² in rat which is equivalent to 5.6X the maximum recommended dose for carvedilol of 37 mg/M² in human); however, this dose in rats was associated with increases in bile duct hyperplasia when compared to controls.

In the dog, after 1 year administration of carvedilol (LD- 10, MD- 30, HD-1 100 and HD-2 300 mg/kg/po), the apparent "no-adverse effect" dose may be considered 10 mg/kg/po for both liver and heart histopathologic findings; this "no-adverse effect" dose represents 200 mg/M² kg for the dog and 5.4X the maximum recommended dose for carvedilol of 37mg/M² in humans.

Results of nonclinical studies submitted in this NDA appear acceptable to support the safe use of carvedilol for the intended therapeutic indication as an oral antihypertensive drug. Although extrapolation of findings with carvedilol across species could be unreliable, adverse effects reported for marketed nonselective β -adrenoceptor antagonists and vasodilator drugs might be expected in humans treated with carvedilol such as bronchospasm, cold extremities, hyperlipidemia, and fatigue particularly in severely ill patients. Remarkable findings in the toxicity studies which are associated with or caused by the administration of carvedilol to mice and rats in the carcinogenicity, to rat and rabbit in the reproduction studies and, in the genotoxicity assays are recommended for inclusion in the appropriate sections and subsections of the sponsor's proposed label for this drug. (See LABELING in the present report for language).

RECOMMENDATIONS:

1. NDA 20,297 is approvable from the standpoint of PHARMACOLOGY.
2. Suggested language changes for subsections in proposed label appear above under LABELING.

Barry 1-21-94
Estela Gonzalez Barry, M.S.
Pharmacologist
02-02-94/04-04-94

cc:
HFD-502/ATaylor
HFD-345/GJames
HFD-110
HFD-110/CSO
HFD-110/EBarry
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MB
4/24/94

MINUTES OF THE EXECUTIVE CARCINOGENICITY ASSESSMENT COMMITTEE
(ECAC) MEETING ON CARVEDILOL (3-22-94)

TO: ALAN TAYLOR

CC: JOSEPH CONTRERA
CC: CHARLES RESNICK
CC: ALBERT F. DEFELICE

SUBJECT: RODENT DOSE-RANGE AND CARCINOGENICITY STUDIES WITH
CARVEDILOL IN DIET. (NDA 20-297)

FROM: ESTELA BARRY 

PREVIOUS TO THE MEETING, MEMBERS OF THE ECAC REVIEWED A BRIEF OVERVIEW OF FINDINGS FROM THE DOSE-RANGING AND CARCINOGENICITY STUDIES WITH CARVEDILOL FED TO MICE AND RATS. THE STATISTICAL ANALYSES OF THE CARCINOGENICITY DATA ESTIMATED THAT THERE WERE NO STATISTICALLY SIGNIFICANT (AT 0.05 LEVEL) TREND IN THE TUMOR INCIDENCE RATES OF THE TUMOR TYPES TESTED. ALTHOUGH THERE WERE MARGINALLY SIGNIFICANT POSITIVE LINEAR TRENDS REPORTED FOR A SMALL NUMBER OF TUMORS IN BOTH RODENT STUDIES, ONLY THE THYROID GLAND ADENOMAS IN DRUG TREATED FEMALE RATS WERE OF CONCERN BECAUSE OF THE $P=0.0504$ VALUES APPROACHED SIGNIFICANCE. NO HISTORICAL CONTROL DATA HAD BEEN PROVIDED BY THE SPONSOR IN THE NDA 20-297 TO HELP WITH THE OVERALL ASSESSMENT OF THESE THYROID TUMOR FINDINGS.

ALTHOUGH ECAC AGREED THAT THE STUDIES WERE ADEQUATE, IT RECOMMENDED THAT A PAIRWISE COMPARISON ON THE THYROID GLAND ADENOMAS WOULD BE AN APPROPRIATE STATISTICAL ANALYSES TO BE CONDUCTED.

THE PAIRWISE COMPARISON (AGE-ADJUSTED METHOD USED) WAS PERFORMED BY DIV. OF BIOMETRICS WITH THE FOLLOWING RESULTS:

"Thyroid Gland Adenoma in Female Rats:

Control vs. High-1: $p = 0.0535$

Control vs. High-2: $p = 0.0457.....$ "*

CONSIDERING THIS TUMOR FINDING IS STATISTICALLY SIGNIFICANT AT THE HIGHEST DOSE OF CARVEDILOL TESTED AND IN THE ABSENCE OF HISTORICAL CONTROLS, ALL THOSE PRESENT AT THE MEETING HAD PREVIOUSLY AGREED THAT IN SUCH A CASE ONLY THIS TUMOR FINDING WOULD BE LISTED ON THE LABEL OF CARVEDILOL.

* Carvedilol intake (mg/kg/day) at end of study: Females: LD- 9.5, MD- 18.8, HD-1 38.1, HD-2 74.7. Males: LD- 7.7, MD- 16.2, HD-1 31.4, HD-2 62.1 RD: EBARRY B:\WP51\FILES\CAC-MEET. MIN. A DeF:off-3-25-94

DATE: 04-13-95

FROM: Estela A. Gonzalez Barry, M.S., Pharmacologist. *EB 4-17-95*

SUBJECT: NDA 20-297, Carvedilol Tablets, SmithKline Beecham Pharmaceuticals.

TO: File through Albert DeFelice, Ph.D., Supervisor. *ADF 4/14/95*

Carvedilol is proposed by sponsor as an antihypertensive agent.

Oral carcinogenicity studies with carvedilol were conducted using mice and rats, and the data submitted revealed no clear evidence of carcinogenicity.

Briefly, labeling recommendations that appeared in the Pharmacology review (04-22-94) of this NDA, suggested the inclusion of some tumor data under the subsection "Carcinogenesis, Mutagenesis, Impairment of Fertility".

The carcinogenicity data had been previously presented to the Executive Carcinogenicity Assessment Committee (ECAC) on 03-22-94. At the meeting, ECAC recommended some additional (pairwise) analyses of the data.

MICE

Prior to ECAC meeting and reanalyses of the data, Pharmacology had recommended including the harderian tumor findings in mice on the label because the drug sponsoring firm was unable to provide FDA with historical control data on the strain of mice used. Tumor findings reported in the harderian glands of treated mice in the carcinogenicity study, underwent several additional statistical analyses by the Division of Biometrics as recommended by ECAC. At this time, Pharmacology concluded that since the combination of harderian gland adenomas and carcinomas (the tumors of Pharmacology concern) did not show a significant positive linear trend, thus these tumors might not need to be listed in the label. At the time of the original presentation to ECAC, the Committee did not appear to be unduly concerned about harderian tumors in mice.

RAT

As for thyroid tumors (tumors of concern by Pharmacology and ECAC) reported in treated rats in the carcinogenicity study, although reanalyses found that there was a marginally statistically significant ($p=0.0504$) linear trend in thyroid gland adenomas in female rats, when the number of thyroid adenomas and carcinomas was combined (as is customarily done), there was no significant positive trend ($p=0.199$) noted.

The above results of the statistical reanalyses were discussed/reviewed, and the final version of the minutes of the ECAC meeting, which included the results of the Division of Biometrics reanalyses recommended by ECAC, were finally issued on 05-05-94.

Subsequent to the Pharmacology final review of NDA 20-297 (04-22-94) with labeling recommendations and the release of the Minutes of the ECAC meeting (05-05-94), a labeling markup version was issued (= March '95). In this labeling version, the subsection under "Carcinogenesis..." did not include references to the above mentioned tumors. This decision was based on further consideration of the Biometrics additional analyses of the carcinogenicity data.

Attachment: Minutes of the ECAC meeting of 03-22-94

cc: Z. McDonald, CSO
Orig. NDA
HFD-110
HFD-110/ADeFelice
HFD-110/EBarry

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Mc Donald

MAY - 5 1994

**Minutes of the Executive Carcinogenicity Assessment Committee
(ECAC) Meeting on Carvedilol (3-22-94)**

To: Alan Taylor

Through: A.F. DeFelice



CC: Joseph Contrera

CC: Charles Resnick

**Subject: Rodent Dose-Range and Carcinogenicity Studies with
Carvedilol in Diet (NDA 20-297)**

From: Estela González Barry -94

Prior to the meeting, members of the ECAC reviewed a brief overview of findings from the dose-range and carcinogenicity studies with carvedilol fed to mice and rats.

1. MICE STUDIES

The dosage level for carvedilol selected for the 2-year carcinogenicity study (20, 65 and 200 mg/kg/day) were based on the results of the 13-week mouse study (at 20 up to 800 mg/kg/day.)

At the meeting, discussions on the adequacy of dose-selection for the 2-year study included particular concerns about the doses tested because of the unremarkable effect reported on the bodyweights of female mice.

The data provided showed that at the end of the dose-range study, male mice at the 2 highest doses (600 and 800 mg/kg/day) showed >10% decrement in bodyweight relative to controls, however; the bodyweights of drug treated females had been minimally affected. Remarkable clinical chemistry findings reported consisted of statistically significant increases in both serum alkaline phosphatase values in males at the 2 highest doses, and increased sGPT values (not significant) in all drug treated mice except for HD females. Absolute liver weights

changes were unremarkable in males but elevated in females [dose-related at 60 mg/kg/day and above and, statistically significant ($p < 0.05$) at the 2 highest doses of carvedilol.] Although relative body weights in treated mice showed dose-related increases (at 60 mg/kg/day and above), the increases were statistically significant only at 800 mg/kg/day for males, and at 200 mg/kg/day and above for females. Based on these findings, drug sponsor selected the 200 mg/kg/day dose as the MTD for purposes of the 2-year carcinogenicity study.

ECAC considered that although these data appear to support the choice of 200 mg/kg/day as MTD for male mice, there were concerns about whether or not this dose approached the MTD in females in light of the unremarkable effect on bodyweight of the females relative to the controls during the dose-range study and, also during the carcinogenicity study.

Although no histopathology was conducted on tissues from mice in dose-range study, data showed that histopathology of livers for the 2-year mouse study revealed a higher incidence of single cell hepatocellular necrosis in these HD females compared to controls. This histopathologic finding suggests that the 200 mg/kg/day dose was close to the MTD in females. Thus, majority of members of **ECAC** agreed that the 3 doses selected/used in the mouse carcinogenicity study were considered acceptable.

Division of Biometrics analysis of the 2-year mice carcinogenicity reported "no statistically significant (at 0.05 level) linear trend in the tumor incidence rates of tumor types tested in both sexes. However, there was a marginally significant positive linear trend in harder's gland carcinoma ($p = 0.0523$) and harder's gland carcinoma and adenoma combined ($p = 0.0663$) in female mice." Pursuant to repeated requests from FDA for historical controls tumor data on this strain of mice, drug sponsor finally confirmed that these data are not unavailable for the SPF-NMRI-HAN-WIGA mice. (NDA Amendment dated 3-30-94.

2. RAT STUDIES

Based on the results of the 15-week dose-range study (at 200 ppm up to 8,000 ppm carvedilol); levels of 600 ppm up to 4,000 ppm in diet were selected for a 2-year rat carcinogenicity study. The 2-year study was started and the HD proved to be toxic, and the study was stopped after 6 months.

Based on the same 15-week study, 4 levels of carvedilol (LD-200, MD-400, HD-1 1,800 and HD-2 1,600 ppm) were tested in a second 2-year carcinogenicity*. The HD in the definitive study was 2.5 X lower than HD used in the aborted 2-year rat study. ECAC considered the 15-week dose-ranging study and the selected MTD as adequate.

Division of Biometrics analyses of the tumor data 2-year rat carcinogenicity study showed "that there was a significant (at 0.05 level) positive linear trend in stomach papilloma ($p = 0.0494$) and skin subcutis sebaceous adenoma ($p = 0.0414$) in male rats. There were marginally statistically significant linear trends in thyroid gland adenoma ($p = 0.0504$)....in female rats + and in liver hepatocellular adenoma ($p = 0.0579$) in male rats." Although the thyroid adenomas in female rats were not dose-related, ECAC was concerned because the linear trend analysis approached statistical significance.

*Carvedilol intake (mg/kg/day) at end of rat carcinogenicity study: **Females:** LD- 9.5, MD- 18.8, HD-1 38.1 and, HD-2 74.7. **Males:** LD- 7.7, MD- 16.2, HD-1 31.4 and, HD-2 62.1

+Thyroid adenoma plus adenocarcinoma combined in carvedilol treated rats (50/sex/group):
Females- C- 1, LD- 6, MD- 2, HD-1 4, HD- 5. **Males-** C- 6, LD- 2, MD- 6, HD-1 2 and HD-2 0.

Since at the time of the **ECAC** meeting, no historical control tumor data had been submitted for the strain of rats used in the 2-year carcinogenicity study (even after repeated requests by FDA), **ECAC** recommended that a pairwise analysis be conducted and if the results of the analysis were statistically significant, the thyroid adenoma findings would be included on the label with the proviso that the findings were marginally significant, if that were the case. In another comment, **ECAC** pointed out that statistical analysis of thyroid adenomas are usually performed on the combination of adenomas and thyroid carcinomas. Although stomach papilloma and skin subcutis sebaceous adenomas were only found in some drug-treated male rats (stomach papilloma, HD-1 1/50 and HD-2 1/50, at the 2 highest doses of the drug and, skin subcutis sebaceous adenomas, HD-2 2/50, only at the highest dose), **ECAC** recommended that concerns over statistically significant increases in these 2 tumors should be noted in the minutes.

About the thyroid tumors, as suggested by **ECAC**, Biometrics performed all of the suggested analysis (age-adjusted pairwise comparisons, and trend test on the combined thyroid adenomas and carcinomas). The following results were extracted from a brief report from Biometrics.

● "... Thyroid Gland Adenoma In Female Rats:

Control vs. High-1: P = 0.0535

Control vs. High-2: P = 0.0457...

● ...[T]rend test on thyroid gland adenoma and adenocarcinoma combined.

Male rats: C, L, M, H1, H2

6 2 5 2 0 P= 0.0173 (sign. negative)

Female rats: C, L, M, H1, H2

1, 6, 2, 4, 5 P= 0.199... "

Regarding the increases in stomach papilloma and subcutis sebaceous adenoma in male rats, the following was extracted from the Biometrics' report:

- "...pairwise comparison on stomach papilloma in male rats...

C, H-1: P = 0.3793

C, H-2: P = 0.307'...

- ...pairwise comparison on skin subcutis sebaceous adenoma in male rats,

C, H-2: P = 0.2347..."

N.B. Pharmacology considers that the biological significance to humans of the tumors described above is uncertain. However, in the absence of historical control tumor data for mice, Pharmacology recommends the inclusion on the label of carvedilol the harderian gland tumors reported for females treated with the 2 highest doses of carvedilol in the 2-year mouse carcinogenicity study.

As for tumors reported for the rat 2-year carcinogenicity study, Pharmacology considers that since the statistical analysis of the data did not show a trend or clear evidence of tumorigenicity induced by carvedilol, the tumors reported might not be included in the label of carvedilol. As for the thyroid tumors in rat, C. Gopinath reports in "**Causes and Interpretation of Thyroid Tumors in Rodent Bioassay**" Chapter 3, p. 19 in Current Issues in Drug Development, Huntingdon Research Center Limited, UK, 1991 that "...Certain pharmaceutical drugs are known to affect thyroid gland through adrenergic mechanisms....cardiovascular drugs of adrenergic class influence thyroid follicular growth and function.....The mechanism underlying thyroid lesions are complex"

R/D EBarry: 3-25-94/4-25-94 B:\ECAC-MTG.MIN

310

AUG 15 1995

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-297

CHEM.REVIEW #: 5

REVIEW DATE: 8 Aug 95

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	31 Mar 93		
AMENDMENT BC	20 Jul 95	20 Jul 95	24 Jul 95

NAME & ADDRESS OF APPLICANT: SmithKline Beecham Pharmaceuticals
Four Falls Corporate Center
Route 23 & Woodmont Avenue
King of Prussia, PA 19406

DRUG PRODUCT NAME:

Proprietary:	Coreg, Covrim or Proreg
Nonproprietary/USAN:	Carvedilol
Code Name/#:	SK&F 105517, BM 14.190
Chem.Type/Ther.Class:	1 S

PATENT STATUS: US 4,503,067, expires 5 March 02

PHARMACOL.CATEGORY/INDICATION: Antihypertensive

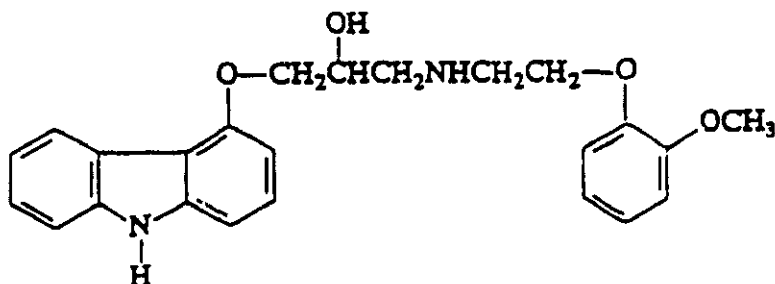
DOSAGE FORM: TCM

STRENGTHS: 6.25, 12.5 and 25 mg

ROUTE OF ADMINISTRATION: Oral

DISPENSED: Rx OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:



(R,S)-1-(Carbazol-4-yloxy)-3-[[2-(o-methoxyphenoxy)ethyl]amino]-2-propanol

C₂₄H₂₆N₂O₄

406.5

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS (if applicable): None

CONSULTS: None

REMARKS/COMMENTS:

The applicant has requested that the Agency consider Proreg as a possible tradename for the drug product in case the Patents and Trademark Office does not find Coreg or Covrim acceptable. A Request for Trademark Review, dated 15 May 95, was sent to the Labeling and Nomenclature Committee requesting review of the proposed tradename. Response, dated 20 Jul 95, was received on 4 Aug 95. The committee found the name acceptable, but with reservations. Some members of the committee thought that the name could be considered to be fanciful. There was also concern that the name could be confused with Prorex, but, since the latter product is for injection, the feeling was that there would be no danger of confusion as long as the product in question was not made available in injection form.

The amendment of 20 Jul 95 provides for the manufacture of a 6.25 mg tablet. This tablet is manufactured from the same granulation as is used for the other strengths, but a proportionally smaller amount of material is used for the new tablet. I noted a number of discrepancies and ambiguities during my review of this amendment. These matters were discussed and satisfactorily resolved, as noted below, with Mr. Peter Kitz by telephone on 8 Aug 95.

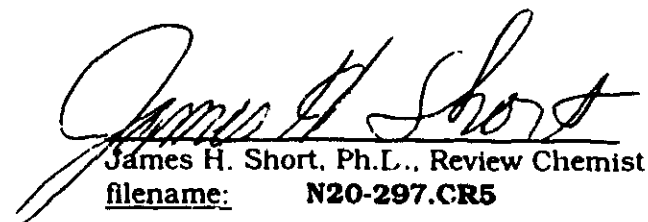
CC INCLUSIONS & RECOMMENDATIONS:

The information provided for the manufacture of a 6.25 mg tablet is satisfactory.

APPROVABLE in regard to the chemistry, manufacturing and controls portion of the application at the present time. Trademark, MV, EER (29 Mar 95) and EA are acceptable.

FUR, dated 31 Jul 95, was sent to HFD-320.

cc:
Orig. NDA
HFD-110/Division File
HFD-110/Short/7/20/95
HFD-110/CSO
District
R/D Init by: RWolters/8/11/95


James H. Short, Ph.L., Review Chemist
filename: N20-297.CR5

STATISTICAL REVIEW AND EVALUATION

NDA #: 20-297 Drug Class: 1S
Applicant: SmithKline Beecham Pharmaceuticals
Drug Name: Kredex (Carvedilol)
Indication: Hypertension
Document Reviewed:

Vols. 1.1, 1.2, 1.504, 1.505, 1.506, 1.521, 1.549, 1.581,
1.594, 1.605, 1.630

Diskettes for datasets

This review was completed after discussion with Dr. Knudson, medical reviewer for the efficacy.

1. INTRODUCTION

The NDA contains numerous volumes. This review pertains to six main Phase III clinical studies for efficacy and dose-effect relationship submitted for supporting the proposed indication that carvedilol is an antihypertensive agent.

2. STUDY OVERVIEW AND REVIEWER'S EVALUATION

In some studies the sponsor attempted to adjust p-value for multiple comparisons in analysis of weekly visit data. In my view such practice is unnecessary since weekly visit analysis is secondary and exploratory.

In the sponsor's subgroup analysis, p value was constantly used to determine whether drug effect is significant in subpopulation. In this review the subgroup p-value will not be reported since it is often misleading in assessing statistical significance.

A few errors were found in some of the key tables in the NDA documents. This review will not report these errors; instead, it will present correct numbers, based on the SAS database provided by the sponsor.

Study B100

This 33-center US study was conducted to assess the antihypertensive effect of carvedilol (CARVDL) 6.25 mg, 12.5 mg, 25 mg administered twice daily as compared to placebo, in patients with mild to moderate hypertension (baseline sitting DBP of 95 to 115 mm Hg inclusive) treated for eight weeks.

After a single-blind placebo baseline phase of up to eight weeks, a total of 480 patients were randomly allocated to receive placebo, CARVDL 6.25 mg, CARVDL 12.5 mg, or CARVDL 25 mg for eight weeks. There were 36% protocol violators that were

believed to affect the evaluability of data; thus, 306 of the 480 patients were included in the per-protocol analysis and were evenly distributed to the four treatment groups. The four treatment groups were comparable at baseline characteristics and vital signs in both intent-to-treat and per-protocol patients, except a possible difference in standing DBP between CARVDL 25 mg and placebo in per-protocol cohort. Of the 480 patients, 419 completed eight-week treatment phase. The percentage of withdrawals due to adverse experience seemed to increase as the CARVDL dosage increases (CARVDL 6.25 mg - 3.4%, CARVDL 12.5 mg - 4.0%, CARVDL 25 mg - 6.0%, placebo - 8.4%), whereas the percentage of withdrawals due to insufficient therapeutic response seemed to decrease in dosage of CARVDL (CARVDL 6.25 mg - 5.9%, CARVDL 12.5 mg - 5.6%, CARVDL 25 mg - 3.4%, placebo - 7.6%).

As seen in Table S, a 4 mm Hg greater reduction in sitting DBP at endpoint was observed in the 12.5 mg group and a 5.2 mm Hg greater reduction in the 25 mg group, as compared to placebo; the differences were statistically significant. A similar trend was observed on other blood pressures (Table 1). CARVDL 6.25 mg seemed to yield a 2.1 mm Hg greater reduction in sitting DBP than placebo; the difference was marginally significant (after adjustment based on Dunnett's procedure). The effect of this dose on DBP in supine or standing position seemed minimal; the effect on SBP was significant (Table 1).

There was a strong trend of positive dose-response ($p < 0.0001$ for slope); no evidence of a leveling-off with dose-response curve was found.

The CARVDL 12.5 mg and 25 mg groups had a 16%-23% higher rate in normalized sitting DBP and a 21%-28% higher rate of responders (those whose sitting DBP $\leq$ 90 mm Hg and/or decreased by at least 10 mm Hg) than the placebo group ($p < 0.005$). Mean decreases in heart rate of 3 to 8 bpm from baseline greater than placebo were observed with each of carvedilol doses (almost all $p < 0.05$, Table 2).

Trough/peak ratio ([mean decrease of active - mean decrease of placebo at trough]/[mean decrease of active - mean decrease of placebo at peak]) for sitting DBP/SBP was 47%/85% for CARVDL 6.25 mg, 66%/63% for CARVDL 12.5 mg, and 55%/67% for CARVDL 25 mg. For standing DBP/SBP, they were 94%/127%, 10%/63%, and 55%/58%, for CARVDL 6.25 mg, 12.5 mg and 25 mg, respectively.

On average black patients did not seem to respond to any one of the study doses of carvedilol (Table 3).

Reviewer's Evaluation

Carvedilol 12.5 mg and 25 mg administered twice daily significantly decreased blood pressure, as compared to placebo. The effect of the 6.25 mg dose on DBP appeared only marginal.

This study does not provide sufficient information to tell how far one may increase the dosage of carvedilol before the effect levels off. The percentage of withdrawals due to adverse experience tends to increase as the carvedilol dosage increases.

Study B101

This 47-center US+CANADA placebo-controlled trial was carried out to evaluate the antihypertensive effect of CARVDL 6.25, 12.5, 25, or 50 mg administered once daily compared to placebo, in patients with mild to moderate hypertension (sitting DBP between 95 and 115 mm Hg inclusive) treated for eight weeks.

Following the initiation of the study, the protocol was amended to eliminate the 50 mg group due to the concern regarding the potential incidence of postural hypotension. After a placebo washout period of up to eight weeks, 520 patients were randomized into one of the five treatment groups for eight weeks. The 50 mg group had 6% of the total randomized population. There were 46% protocol violators; thus, 281 of the 520 patients were included in the per-protocol analysis. The five treatment groups appeared comparable in baseline characteristics and vital signs in both intent-to-treat and per-protocol patients. Of the 520 patients, 384 completed eight-week treatment phase. The percentage of withdrawals due to adverse experience seemed to increase as the CARVDL dosage increases (CARVDL 6.25 mg - 3.3%, CARVDL 12.5 mg - 3.9%, CARVDL 25 mg - 8.7%, CARVDL 50 mg - 13.8%, placebo - 6.0%), whereas the percentage of withdrawals due to insufficient therapeutic response seemed to decrease in dosage of CARVDL (CARVDL 6.25 mg - 14.0%, CARVDL 12.5 mg - 13%, CARVDL 25 mg - 13%, CARVDL 50 mg - 0%, placebo - 16%).

When compared to placebo, a 2.5 mm Hg greater reduction in sitting DBP at endpoint was observed in the 12.5 mg group and a 2.1 mm Hg greater reduction in the 25 mg group; these differences were statistically significant (Table S). Similar observations were made on supine and standing DBP (Table 4), but their performance on SBP was not clear (Table 4). The effect of CARVDL 6.25 mg was found little. CARVDL 50 mg seemed to have a greater effect on all blood pressures than other doses; statistical significance was inconclusive because of the small number of patients.

There was a significant trend of positive dose-response ($p < 0.05$).

The carvedilol 12.5-50 mg doses had a 10%-17% higher rate of responders than placebo. Mean decreases in heart rate of about 1 to 3.5 bpm greater than placebo were observed with each of carvedilol doses (Table 5).

The ratio of the mean change in trough sitting DBP to mean change in peak sitting DBP was 45% for CARVDL 6.25 mg, 49% for CARVDL

12.5 mg, 41% for CARVDL 25 mg, and 59% for placebo. Trough/peak ratio (as defined in Study B100) for sitting DBP was 533% for CARVDL 6.25 mg, 33% for CARVDL 12.5 mg, and 15% for CARVDL 25 mg. The mean of the individual trough/peak ratio for those patients whose response led to a determinate ratio between 0 and 100% was 56% for CARVDL 6.25 mg, 52% for CARVDL 12.5 mg, 44% for CARVDL 25 mg, and 57% for placebo.

Females seemed to respond less well than males. Patients with moderate hypertension seemed to respond better than patients with mild hypertension. No pattern was observed to suggest that blacks respond less well than nonblacks.

Reviewer's Evaluation

Carvedilol 12.5 mg and 25 mg given once daily are significantly different from placebo, but the magnitude of their effects (about 2.1-2.9 mm Hg greater reduction in sitting and supine DBP than placebo) is not impressive. Clinical significance needs to be determined. The 6.25 mg dose qd had little effect. With or without placebo being included, dose-response analysis performed by this reviewer suggests that the positive slope for the decrease in sitting/standing DBP and SBP versus dosage is at borderline significance ($p = 0.02$ to 0.07 for slopes). Thus the positive trend suggests that the 50 mg dose have a significant effect, though it is not quite significant according to Table S and Table 4 due to small sample size. The data is not able to tell how far one may increase dosage to see the effect level off.

With or without placebo being included, logistic analysis done by this reviewer suggests that the percentage of withdrawals due to adverse experience increases as the carvedilol dosage increases (p -value for slope is between 0.01 and 0.05).

Study C1106

This 13-center US study was carried out to compare the antihypertensive effect of titrated doses of carvedilol administered once daily to carvedilol administered twice daily (total daily doses of 6.25-50 mg for either regimen) and to placebo. The BP criteria for entry to treatment phase were: mean sitting DBP and standing DBP were 95-115 mm Hg with the highest to the lowest mean not varying by more than 10 mm Hg, the mean sitting DBP did not vary by more than 5 mm Hg at the last two placebo baseline visits, and the mean standing DBP did not vary by more than 5 mm Hg at the the last two placebo baseline visits.

After a five- to six-week placebo baseline period, 280 patients were randomized to one of three treatment groups: carvedilol once daily with placebo once daily, carvedilol twice-daily, or placebo twice-daily for a 2 to 12 week up-titrated treatment period, followed by a four week fixed-dose maintenance period. Initial doses were CARVDL 6.25 mg and placebo one capsule once daily,

carvedilol 3.125 mg twice daily, and placebo one capsule twice daily. The dose of study medication was increased until the mean sitting DBP was less than 90 mm Hg at two consecutive weekly visits or until the highest allowable dose level (equivalent to a total daily dose of carvedilol 50 mg) had been prescribed for two consecutive weeks.

There were 279 patients in the intent-to-treat sample. About 14% of the patients in each treatment group had protocol violations for which data were completely excluded from the per-protocol analysis; the most common reason for complete exclusion was failure to meet baseline BP data (about 7%). The intent-to-treat sample and the per-protocol sample were similar in baseline characteristics; the three treatment groups were also comparable.

Of the 280 patients randomized, 55% completed the study (25% for placebo, 64% for carvedilol qd; 77% for carvedilol bid); insufficient therapeutic effect was the most common reason for early withdrawal (69% for placebo, 28% for carvedilol qd, 15% for carvedilol bid). A higher percentage of black patients were withdrawn for insufficient therapeutic effect than nonblack patients (77% vs. 64% for placebo, 35% vs. 23% for carvedilol qd, 19% vs. 12% for carvedilol bid). About 3% of the withdrawals were due to adverse experiences.

As said in the study report, evidence of possible deviations in the treatment effects across centers was found. One source of deviation comes from data of the investigator (Dr. Gray), which showed the large decrease in BP in both carvedilol regimens as compared to placebo. Some directional interaction was observed. Three of the 13 investigators observed a smaller decrease in sitting DBP for carvedilol qd than for placebo; only one investigator observed a smaller decrease for carvedilol bid than for placebo. In eleven centers carvedilol bid regimen had a numerically larger decrease in sitting DBP than qd regimen. Thus the rank of performance seemed to indicate that the bid regimen work better, on average, than the qd regimen.

A number of analyses were performed to see the potential impact of possible directional treatment by center interactions. It was explained in the sponsor's report that treatment by center interactions were attributed to Dr. Gray's data and a few possible directional interactions. By pooling all centers, the analysis including the treatment-by-center term in the ANOVA model indicated that both carvedilol regimens yielded a significantly greater reduction in sitting and standing DBP and heart rate ($p < 0.001$) than placebo. The bid regimen also yielded a significantly greater decrease in sitting and standing SBP ($p < 0.001$) than placebo, whereas the qd regimen resulted in a marginally significantly greater decrease. The bid regimen group had a significantly greater reduction in sitting and standing DBP than the qd regimen group ($p < 0.02$). Summary statistics of the study endpoint analysis are displayed in Table S and Table 7. The results of titration phase endpoint analysis and the results

of study endpoint analysis were very similar; so were the results of intent-to-treat analysis and per-protocol analysis. There was a significantly ($p < 0.001$) larger normalized (sitting DBP < 90 mm Hg) rate in both carvedilol groups than in the placebo group (55% for CARVDL bid, 43% for CARVDL qd, 18% for placebo). Response (sitting DBP normalized or decreased by ≥ 10 mm Hg) rates in both carvedilol groups were also significantly ($p < 0.001$) greater (66% for CARVDL bid, 51% for CARVDL qd, 19% for placebo); the difference between qd and bid was statistically significant ($p = 0.024$).

The criterion for entering fixed-dose maintenance period was that the patient had either achieved a mean sitting DBP < 90 mm Hg for two consecutive weeks or had received the highest dose for two weeks during the up-titration period. Only 57% (158/279) had maintenance period data and the number or percentage of patients with maintenance period data differed among the treatment groups: 64% (58/90) for carvedilol qd, 80% (77/96) for carvedilol bid, and 25% (23/93) for placebo. Among these patients, mean decrease in sitting/standing DBP from baseline at titration endpoint was 11.5/12.2 mm Hg for placebo, 13.4/13.0 mm Hg for carvedilol qd, and 13.9/13.8 mm Hg for carvedilol bid. At maintenance endpoint, mean sitting/standing DBP increased from titration endpoint for all three treatment groups: 1.3/3.8 mm Hg for placebo, 1.8/1.4 mm Hg for carvedilol qd, and 1.1/1.9 mm Hg for carvedilol bid.

At study endpoint, the placebo adjusted trough/peak ratio was 47% for the qd regimen and 66% for the bid regimen.

Both carvedilol regimens appeared to be effective in all subgroups by sex, age, race or severity of hypertension (Table 8).

Reviewer's Evaluation

Treatment by center interactions are investigated further. There are 15 centers in total, based on the SAS database provided by the sponsor. In Center 016 only two patients were randomized (one in qd, one in placebo, none in bid). In Center 028 only three patients were randomized (one per treatment group). In 13 of the 15 centers carvedilol bid was numerically superior (i.e., greater decrease in sitting DBP) to placebo, whereas carvedilol qd was numerically superior to placebo in 11 centers. Carvedilol bid was numerically superior to carvedilol qd in 10 centers. The sponsor thought that treatment by center interactions were partly attributed to the data of Dr. Gray (Center 010). Excluding Dr. Gray, analysis still shows a significant treatment by center interaction ($p < 0.02$). Pooling the remaining centers, analysis shows that carvedilol bid yields a 6.5 mm Hg greater decrease in sitting DBP and the qd regimen yields a 2.8 mm Hg greater decrease, than placebo; these differences are statistically significant ($p < 0.03$). Further analysis with Center 016 and Center 028 being also excluded produces very similar result. Based on overall evidence presented by this study, it is clear that the bid regimen is

superior to the qd regimen.

Data suggests that the effect of carvedilol given either once-daily or twice-daily may be maintained for four weeks in patients who had their blood pressure controlled via dose titration.

Study C1109

This 13-center US study was carried out to compare the efficacy of carvedilol (12.5 mg, 25 mg and 50 mg) and atenolol (50 mg, 100 mg) with placebo, administered once daily, for the treatment of patients with mild to moderate essential hypertension. The BP entry criteria were: mean sitting and standing DBP was 95 to 115 mm Hg at each of the last three placebo baseline period visits, the highest to the lowest mean sitting DBP and the highest to the lowest mean standing DBP of the last three placebo baseline visits did not vary by more than 10 mm Hg, and the mean sitting DBP and the mean standing DBP did not vary by more than 5 mm Hg between the last two placebo baseline visits.

After a 5-6 weeks placebo baseline period, a total of 258 patients were randomized to receive once daily regimens of either carvedilol 12.5 mg, atenolol 50 mg, or placebo. After one week, coded medication was titrated upward if mean sitting DBP was ≥ 90 mm Hg (unless mean standing SBP was ≤ 120 mm Hg or mean standing DBP was ≤ 80 mm Hg). At this titration step, eligible patients in the atenolol group remained on an actual dose of 50 mg. In further weekly visits, patients could be titrated to carvedilol 50 mg, atenolol 100 mg, or placebo. The dose was maintained and fixed-dose maintenance period was begun if the mean sitting DBP was < 90 mm Hg for two consecutive weekly visits, or if the patient had received the highest dose level for two consecutive visits. There were a total of 231 patients in the per protocol sample (about 88%-92% of the randomized patients in each treatment group were included in the per protocol sample). The three treatment groups were comparable in baseline characteristics and vital signs in both the intent-to-treat and the per protocol samples.

Among the 258 patients entering treatment phase, completion rates were 86% (87/101) for the atenolol treatment group, 62% (65/105) for the carvedilol group, and 35% (18/52) for the placebo group. Thirty (60%) placebo patients, 31 (30%) carvedilol patients, and 9 (9%) atenolol patients were discontinued for insufficient therapeutic effect (p-value for every pairwise difference < 0.001).

Statistically significant treatment by center interaction terms were detected for sitting and standing blood pressures only at titration endpoint. The sponsor found virtually no difference in the results of analyses using either the model with interaction terms or the model without interaction terms; thus, they considered that the interactions had no effect on the conclusions

of the study. As shown in Tables 8 and 9, at study endpoint, both carvedilol and atenolol regimens reduced sitting and standing diastolic blood pressures and sitting SBP significantly greater than placebo ($p < 0.005$). Atenolol decreased systolic blood pressures significantly greater than placebo ($p < 0.05$), whereas carvedilol seemed to have little effect. Atenolol decreased blood pressures significantly greater than carvedilol ($p < 0.05$). Both atenolol and carvedilol slowed heart beat. Analysis of percent of patients normalized and responders showed similar results.

Change from titration endpoint to maintenance endpoint was calculated for the subset of patients who had maintenance endpoint data: 19 patients receiving placebo, 91 patients receiving atenolol, and 69 patients receiving carvedilol. At maintenance endpoint, mean sitting/standing DBP increased slightly from titration endpoint for all three regimens: 2.8/2.5 mm Hg for placebo, 1.9/1.9 mm Hg for atenolol, 2.3/2.2 mm Hg for carvedilol.

Placebo adjusted trough/peak ratio at study endpoint was 68% for atenolol and 32% for carvedilol. Unadjusted ratio was 87% for atenolol and 53% for carvedilol.

Both carvedilol regimens appeared to be effective in all subgroups by sex, age, race or severity of hypertension (Table 10).

Reviewer's Evaluation

Atenolol yields a significantly greater reduction in blood pressure than carvedilol; both are effective. Atenolol seems to maintain its effect slightly better than carvedilol.

Study C1107

This 12-center US study was conducted to assess the effect of carvedilol 6.25 to 25 mg once daily when added to the treatment regimen of patients whose sitting and standing DBP was uncontrolled (≥ 90 mm Hg) by treatment with hydrochlorothiazide (HCTZ) 25 mg once daily. The EP criteria for entry to treatment phase were: mean sitting and standing DBP were 90-115 mm Hg, and the mean sitting DBP and mean standing DBP did not vary by more than 5 mm Hg between the last two baseline visits.

After a four-week baseline phase during which they took HCTZ 25 mg once daily, a total of 266 patients were randomized to receive once daily regimens: placebo, CARVDL 6.25 mg, CARVDL 12.5 mg, or CARVDL 12.5 mg for one week with possible increase to 25 mg later (the criteria to increase dose were the same as those used in Study C1109). Of them, 243 (91%) completed the four-week treatment phase. Eleven of the 23 dropouts withdrew due to an adverse experience; the percentage of adverse event related dropouts seemed to increase as CARVDL dosage increases (CARVDL

6.25 mg - 1.5%, CARVDL 12.5 mg - 3.8%, CARVDL 25 mg - 6.1%, placebo - 4.5%). There were 239 patients in the per protocol sample. The four treatment groups were comparable in baseline characteristics and vital signs.

The same titration was used for all patients in each treatment group to maintain the blind, but actual dose increase occurred only in the carvedilol 12.5/25 mg group. The carvedilol 12.5/25 mg group showed a statistically significantly greater decrease in sitting DBP than the placebo group; the difference was 3.0 mm Hg (Table S). The following table summarized the mean decrease in sitting DBP at study endpoint for those who underwent the titration step and for those who did not (intent-to-treat patients).

Patients who underwent titration step:

	Baseline		Decrease from baseline	
	n	Mean	n	Mean (s.e.)
Placebo	40	100.7	40	3.0 (1.0)
CARVDL-6.25	39	99.8	39	3.2 (1.2)
CARVDL-12.5	38	98.0	38	3.4 (1.0)
CARVDL-25	32	99.8	32	6.6 (1.1)

Patients who did not undergo titration step:

	Baseline		Decrease from baseline	
	n	Mean	n	Mean (s.e.)
Placebo	26	94.2	26	3.7 (1.3)
CARVDL-6.25	28	94.5	28	6.7 (1.6)
CARVDL-12.5	29	96.0	27	7.0 (1.8)
CARVDL-12.5	34	96.9	34	6.1 (1.3)

As shown in the above table, 32 (48%) patients in the carvedilol 12.5/25 mg group were titrated to 25 mg dose; the mean decrease in sitting DBP was 6.6 mm Hg. The mean decrease of the remaining 34 patients staying on 12.5 mg was 6.1 mm Hg. The mean decrease of the 65 patients originally randomized to carvedilol 12.5 mg dose was 4.9 mm Hg at study endpoint. For the combined 12.5 mg set, the mean decrease was 5.3 mm Hg. With or without including those who remained on the 12.5 mg dose in the carvedilol 12.5/25 mg group, the sponsor's dose response analysis found a statistically significant linear relationship between actual dosing level and mean sitting DBP decrease ($p < 0.01$) and no indication of leveling-off. The per protocol analysis showed a similar numerical trend. The linear trend was marginally significant ($p = 0.076$) and there was no evidence of a quadratic

trend.

Ordering of treatment groups by magnitude of decrease in standing DBP, sitting and standing S3P was consistent with that seen in sitting DBP; the numerical difference between each carvedilol group and placebo was not statistically significant. The three carvedilol groups showed a significantly greater decrease in heart rate than the placebo group. Summary statistics are provided in Table 11.

The three carvedilol groups had a similar rate (30%) of responders and rate (26-30%) of patient normalized; numerically, they were about 10-12% greater than the rates of the placebo group.

Black patients seemed to need high dose of carvedilol. Patients with moderate hypertension also seemed to need high dose of carvedilol (Table 12).

Reviewer's Evaluation

The percentage of adverse event related dropouts tend to increase as carvedilol dosage increases. Data clearly suggests that when their blood pressures are not properly controlled with HCTZ 25 mg, patients with relatively high blood pressure need a higher dose (e.g. only the 25 mg dose of carvedilol appears effective, see the tables on page 9) whereas those with relatively low blood pressure may start with the 6.25 mg dose. There is no evidence of leveling-off in this dose range, 6.25-25 mg/day.

Study B104

This 23-center US study was conducted to study the antihypertensive effects of carvedilol 6.25 to 25 mg twice daily and labetalol 100 to 400 mg twice daily, as compared to placebo, in black patients with mild to moderate hypertension (baseline mean sitting DBP of 95-115 mm Hg inclusive) treated for eight weeks.

After a 2-8 weeks placebo baseline period, a total of 246 patients were randomized to receive either carvedilol 6.25 mg twice daily, labetalol 100 mg twice daily, or placebo twice daily. Patients were seen at the end of Weeks 2, 4, 6, and 8 from randomization. The dose of double-blind medication was increased until the mean sitting DBP was ≤ 90 mm Hg. The patient was maintained at that dose as long as the mean sitting DBP < 95 mm Hg at subsequent visits. If the mean sitting DBP was ≥ 95 mm Hg at subsequent visits, the dose was increased. The increases in study medication dose were made incrementally during regularly scheduled visits. If the patient's medication had been titrated to the highest dose level, that dose was maintained until the end of the treatment phase or until any criterion for discontinuing treatment was met. Patients were then seen at a follow-up visit

scheduled 7-10 days after the last treatment period visit. Study medication was gradually down-titrated during the follow-up period.

There were a total of 210 patients in the per protocol sample (about 83%-90% of the randomized patients in each treatment group). The three treatment groups were comparable in baseline characteristics and vital signs in both the intent-to-treat and the per protocol samples. Distribution of intent-to-treat patients according to type of pre-trial antihypertensive medication also appeared comparable. A total of 56 patients withdrew from the study after randomization; the placebo group had a largest percentage of dropouts (29%), followed by the carvedilol group (21%) and then by the labetalol group (18%). The percentage of dropouts due to adverse events was similar in the three treatment groups. Sixteen percents of the placebo patients, 8% of the carvedilol patients and 4% of the labetalol patients withdrew due to insufficient therapeutic effect.

For endpoint analysis, six (two per treatment group) of the 246 patients in the intent-to-treat sample did not have vital sign measurements. A Bonferroni adjustment made by the sponsor's analysis showed that only the difference between labetalol and placebo in mean change of sitting DBP was significant. The per-protocol analysis also supported this conclusion. The difference between carvedilol and placebo was marginally significant. Analysis of secondary blood pressures showed that carvedilol had a significant effect in reducing blood pressure. Numerically, labetalol seemed to have a larger effect than carvedilol, though the difference was only at best marginally significant; see Table S and Table 13. Both carvedilol and labetalol decrease heart rate in black patients.

Labetalol appeared more effective than carvedilol. Both seemed to be more effective in elderly black patients (Table 14).

Reviewer's Evaluation

Both carvedilol 6.25-25 mg and labetalol 100-400 mg given twice daily significantly decrease blood pressure, as compared to placebo. The mean effect of carvedilol is about 2-3 mm Hg in DBP in black patients, whereas the effect of labetalol is 4.5 to 5.6 mm Hg; the latter is marginally significantly greater than the former.

3. SUMMARY OF REVIEWER'S EVALUATION

Carvedilol given once-daily is studied in four (B101, C1106, C1109 and C1107) of the six studies reviewed. Carvedilol bid administration is studied in B100 and C1106, and B104 specifically in black population. The dose range under study is 6.25 to 50 mg/day.

Once-daily administration

The 6.25 mg dose has little effect. Both the 12.5 and 25 mg

doses show a significantly greater decrease in DBP than placebo; the effect is not impressive (2.1-2.9 mm Hg greater in sitting/standing DBP); see Tables S and 4. Two titration studies (C1106 and C1109) show that carvedilol 6.25-50 mg could yield a 4-6 mm Hg greater reduction in sitting/standing DBP than placebo (Tables S, 7 and 9).

Based on C1107, when their blood pressures are not properly controlled with HCTZ 25 mg, patients with relatively high blood pressure at baseline need a higher dose (only the 25 mg dose appears effective, see the tables on page 9) whereas those with relatively low blood pressure may start with the 6.25 mg dose.

Twice-daily administration

The effect of the 6.25 mg dose (i.e., 12.5 mg/day) on DBP appears only marginal (Tables S and 1). The 12.5 mg and 25 mg doses yield a significant greater reduction in blood pressures than placebo. The effect of the 12.5 dose is 4.0 mm Hg in sitting DBP and about 2.5 mm Hg in supine/standing DBP; the effect of the 25 mg dose is about 5 mm Hg in DBP; see Tables S and 1. The titration study, C1106, shows that the bid administration of carvedilol 6.25-50 mg/day could have an effect of 7.6 mm Hg in sitting/standing DBP.

Dose response

There was a positive trend indicating an increase in BP reduction effect as carvedilol dosage increases in the dose range of 6.25 to 50 mg per day, based on the data of two parallel-group trials (B100 and B101) and one titration study (C1107). None of these studies are able to tell how far one may increase dosage to see the effect level off.

QD vs. BID

Based on C1106, carvedilol 6.25-50 mg/day when given twice daily shows a significantly greater decrease in DBP than carvedilol given once-daily. Data also suggests that the effect of carvedilol may be maintained for four weeks in patients who had blood pressure controlled via dose titration in this dose range.

Atenolol vs. Carvedilol

Atenolol 50-100 mg/day qd yields a significantly greater reduction in blood pressure than carvedilol 12.5-50 mg/day qd. Atenolol seems to maintain its effect slightly better than carvedilol.

Effect on black population

Based on B104, carvedilol 12.5-50 mg/day bid yields a significantly greater decrease in DBP than placebo in black patients; the mean effect is not impressive (about 2 mm Hg in

sitting/supine DBP and 3 mm Hg in supine DBP). Labetalol 200-800 mg/day bid shows a significantly greater reduction in DBP than carvedilol.

Sex and Age

There is no evidence that carvedilol is not effective in a subgroup by sex or age.

Adverse event related withdrawals

B100, B101 and C1107 suggest that the percentage of withdrawals due to adverse experience increases as carvedilol dosage increases.

4. CONCLUSION (MAY BE CONVEYED TO THE SPONSOR)

Main statistics are presented in Table S and summary of my evaluation is given in last section. When given once daily, the 6.25 mg dose of carvedilol has little effect. Both the 12.5 and 25 mg doses show a significantly greater decrease in DBP than placebo; the size of their effects is not impressive. Carvedilol 6.25-50 mg given in the upward-titration-to-effect fashion could, on average, yield a 4-6 mm Hg greater reduction in sitting/standing DBP than placebo. When their blood pressures are not properly controlled with HCTZ 25 mg, patients with relatively high blood pressure at baseline need a higher dose whereas those with relatively low blood pressure may start with the 6.25 mg dose.

When given twice daily, the effect of the 6.25 mg (i.e. 12.5 mg/day) dose on DBP appears only marginal. The 12.5 mg and 25 mg doses yield a significant greater reduction in blood pressures than placebo. The bid administration of carvedilol 6.25-50 mg/day given in the upward-titration-to-effect fashion could have an effect of 7.6 mm Hg in sitting/standing DBP.

There is a positive trend indicating an increase in BP reduction effect as carvedilol dosage increases in the dose range of 6.25 to 50 mg per day. There is no information in these studies reviewed to tell how far one may increase dosage to see the effect level off.

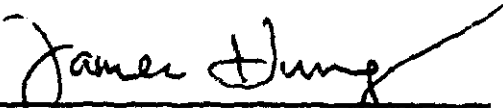
Carvedilol 6.25-50 mg/day when given twice daily shows a significantly greater decrease in DBP than carvedilol given once-daily. Data also suggests that the effect of carvedilol may be maintained in patients who had blood pressure controlled via dose titration in this dose range.

Atenolol 50-100 mg/day qd yields a significantly greater reduction in blood pressure than carvedilol 12.5-50 mg/day qd. Atenolol seems to maintain its effect slightly better than carvedilol.

Carvedilol 12.5-50 mg/day bid yields a significantly greater decrease in DBP than placebo in black patients; the effect is not impressive. Labetalol 200-800 mg/day bid shows a significantly greater reduction in DBP than carvedilol in black patients.

There is no evidence that carvedilol is not effective in a subgroup by sex or age.

The percentage of withdrawals due to adverse experience increases as carvedilol dosage increases.


H.M. James Hung, Ph.D.
Mathematical Statistician

This review consists of 14 pages of text and 15 tables.

Concur:

Dr. Chi

Chi
10/26/93

Dr. Dubey

8/11-1-93

cc: Orig. NDA
HFD-110
HFD-110/Dr. Lipicky
HFD-110/Dr. Knudsen
✓ HFD-110/Ms. Morgenstern
HFD-344/Dr. Lisook
HFD-713/Dr. Dubey [File: DRU 1.3.2 NDA]
HFD-713/Dr. Chi
HFD-713/Dr. Hung

JHung/443-4594/SERB/KREDEX.*/08-25-93

Table 8. Mean decrease from baseline in sitting DBP (mm Hg) - intent-to-treat study endpoint analysis

Treatment Group	N	Mean Decrease (S.E.)	Trtment minus Placebo	95% C.I.	p-value*
STUDY B100 (BID regimen)					
CARVDL-6.25	117	5.4 (0.7)	2.1	(-0.1, 4.2) [#]	0.027
CARVDL-12.5	125	7.3 (0.8)	4.0	(1.9, 6.1) [#]	0.0001
CARVDL-25	114	8.5 (0.8)	5.2	(3.1, 7.4) [#]	0.0001
Placebo	117	3.3 (0.8)			
STUDY B101 (QD regimen)					
CARVDL-6.25	121	4.4 (0.7)	0.7	(-1.3, 2.7) [#]	0.39
CARVDL-12.5	126	6.3 (0.7)	2.6	(0.5, 4.5) [#]	0.004
CARVDL-25	126	5.8 (0.7)	2.1	(0.1, 4.1) [#]	0.016
CARVDL-50	28	8.0 (1.3)	4.3	(1.0, 7.5) [#]	0.083
Placebo	115	3.7 (0.7)			
STUDY C1106 (QD VS. BID, 6.25-50 mg/day)^{\$\$\$}					
CARVDL BID	96	10.9 (0.8)	7.6 [@]	(5.4, 9.8)	0.0001
CARVDL QD	90	7.9 (0.8)	4.6	(2.4, 6.8)	0.0009
Placebo	93	3.3 (0.8)			
STUDY C1109 (CARVDL 12.5-50 mg QD VS. ATENOLOL 50-100 mg QD)					
CARVDL	105	7.5 (0.8)	4.0	(1.5, 6.3)	0.002
ATENOLOL	100	11.3 (0.6)	7.8 ⁺⁺	(5.3, 10.1)	<0.001
Placebo	52	3.5 (0.9)			
STUDY C1107 (QD, HCTZ ADDED)					
CARVDL-6.25	67	4.7 (1.0)	1.4	(-1.2, 4.0) [#]	NS
CARVDL-12.5	65	4.9 (1.0)	1.6	(-1.0, 4.2) [#]	NS
CARVDL-12.5/25	66	6.3 (0.9)	3.0	(0.5, 5.7) [#]	< 0.02
PLACEBO	66	3.3 (0.8)			
STUDY B104 (mg/day BID, BLACK PATIENTS only)					
CARVDL 12.5-50	83	6.3 (0.9)	2.2	(0.1, 4.9)	0.040
LABTLOL 200-800	77	8.6 (0.8)	4.5 ⁺	(2.2, 7.1)	0.0002
PLACEBO	80	4.1 (1.0)			

[#] adjusted based on Dunnett's one-sided procedure

* two-sided p-value not yet adjusted for multiple comparisons

@ p < 0.01 between BID and QD

+ p = 0.080 between carvedilol and labetalol

++ p < 0.001 between carvedilol and atenolol

\$\$\$ unadjusted means are reported (see Reviewer's Evaluation of Study C1106)

Table 1. Mean decrease from baseline at study endpoint in Secondary blood pressure (mm Hg) - intent-to-treat Study B100

Treatment Group	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	95% C.I. #	unadjusted p-value*
Supine DBP					
CARVDL-6.25	117	4.2 (0.8)	1.5	(-1.0, 4.0)	0.15
CARVDL-12.5	125	5.1 (1.0)	2.4	(-0.1, 4.9)	0.0020
CARVDL-25	114	8.1 (0.9)	5.4	(2.9, 7.8)	0.0001
Placebo	116	2.7 (0.9)			
Standing DBP (3 min)					
CARVDL-6.25	117	4.3 (0.8)	1.0	(-1.5, 3.5)	0.24
CARVDL-12.5	125	5.8 (0.8)	2.5	(0.0, 5.0)	0.021
CARVDL-25	114	8.1 (1.0)	4.8	(2.3, 7.3)	0.0001
Placebo	116	3.3 (0.9)			
Sitting SBP					
CARVDL-6.25	117	6.0 (1.2)	4.9	(0.9, 8.8)	0.0044
CARVDL-12.5	125	7.8 (1.3)	6.7	(2.8, 10.6)	0.0001
CARVDL-25	114	8.4 (1.6)	7.3	(3.3, 11.2)	0.0001
Placebo	117	1.1 (1.4)			
Supine SBP					
CARVDL-6.25	117	4.6 (1.3)	3.9	(-0.4, 8.2)	0.053
CARVDL-12.5	125	6.8 (1.5)	6.1	(1.9, 10.4)	0.0020
CARVDL-25	114	6.5 (1.7)	5.8	(1.5, 10.2)	0.0033
Placebo	117	0.7 (1.5)			
Standing SBP (3 min)					
CARVDL-6.25	117	4.2 (1.5)	3.8	(1.0, 8.6)	0.055
CARVDL-12.5	125	7.5 (1.7)	7.1	(2.4, 11.9)	0.0009
CARVDL-25	114	7.5 (1.8)	7.1	(2.3, 12.0)	0.0010
Placebo	117	0.4 (1.6)			

adjusted confidence interval based on Dunnett's one-sided multiple comparison procedure

* two-sided p-value not yet adjusted for multiple comparisons

Table 2. Mean decrease from baseline at study endpoint in Heart rate (bpm) - intent-to-treat Study B100

Treatment Group	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	95% C.I. #	unadjusted p-value*
Sitting HR					
CARVDL-6.25	117	3.4 (0.7)	2.6	(0.4, 4.7)	0.029
CARVDL-12.5	125	6.6 (0.7)	5.8	(3.6, 7.9)	0.0001
CARVDL-25	114	8.2 (0.9)	7.4	(5.2, 9.6)	0.0001
Placebo	117	0.8 (0.7)			
Supine HR					
CARVDL-6.25	117	2.9 (0.8)	2.0	(-0.3, 4.3)	0.11
CARVDL-12.5	125	5.5 (0.7)	4.7	(2.4, 6.9)	0.0001
CARVDL-25	114	7.1 (0.9)	6.2	(3.9, 8.5)	0.0001
Placebo	116	0.9 (0.8)			
Standing HR					
CARVDL-6.25	117	3.4 (0.9)	3.6	(1.2, 6.1)	0.0047
CARVDL-12.5	125	6.8 (0.8)	7.0	(4.5, 9.3)	0.0001
CARVDL-25	114	8.8 (0.7)	9.0	(6.5, 11.4)	0.0001
Placebo	116	-0.2 (0.9)			
Standing HR (3 min)					
CARVDL-6.25	117	3.6 (0.7)	3.7	(1.2, 6.1)	0.0035
CARVDL-12.5	125	6.9 (0.8)	7.0	(4.6, 9.4)	0.0001
CARVDL-25	114	8.8 (0.9)	8.9	(6.4, 11.3)	0.0001
Placebo	117	-0.1 (0.9)			

adjusted confidence interval based on Dunnett's one-sided multiple comparison procedure

* two-sided p-value not yet adjusted for multiple comparisons

Table 3. Mean decrease from baseline in sitting DBP (mm Hg) at study endpoint by subgroup - intent-to-treat Study B100

Treatment Group	Males			Females		
	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO
CARVDL-6.25	84	5.9 (0.8)	2.8	33	4.0 (1.3)	0.4
CARVDL-12.5	79	6.5 (0.9)	3.4	46	8.6 (1.3)	5.0
CARVDL-25	75	8.5 (1.0)	5.4	39	8.6 (1.3)	5.0
Placebo	69	3.1 (1.0)		48	3.6 (1.2)	

Treatment Group	Age ≤ 64 years			Age > 64 years		
	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO
CARVDL-6.25	89	5.5 (0.8)	2.1	28	5.1 (1.3)	2.5
CARVDL-12.5	92	7.8 (0.9)	4.4	33	5.8 (1.5)	3.2
CARVDL-25	84	8.3 (0.9)	4.9	30	9.1 (1.4)	6.5
Placebo	100	3.4 (0.8)		17	2.6 (2.3)	

Treatment Group	Blacks			Non-blacks		
	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO
CARVDL-6.25	19	2.6 (1.9)	-5.2	98	5.9 (0.7)	3.2
CARVDL-12.5	23	8.7 (2.3)	0.9	102	6.9 (0.8)	4.2
CARVDL-25	13	8.3 (2.6)	0.5	101	8.6 (0.8)	5.9
Placebo	15	7.8 (2.1)		102	2.7 (0.8)	

Treatment Group	Mild hypertension [#]			Moderate hypertension [#]		
	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO
CARVDL-6.25	85	4.2 (0.8)	0.8	26	9.7 (0.7)	5.1
CARVDL-12.5	90	6.5 (0.9)	3.1	32	9.9 (0.8)	5.3
CARVDL-25	82	7.7 (0.8)	4.3	29	10.5 (2.1)	5.9
Placebo	84	3.4 (0.9)		27	4.6 (0.9)	

[#] Mild hypertension: baseline sitting DBP 95-105 mm Hg

Moderate hypertension: baseline sitting DBP 106-115 mm Hg

Table 4. Mean decrease from baseline at endpoint in Secondary blood pressure (mm Hg) - intent-to-treat Study B101

Treatment Group	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	95% C.I. #	unadjusted p-value*
Supine DBP					
CARVDL-6.25	121	3.3 (0.8)	1.0	(-1.4, 3.4)	0.26
CARVDL-12.5	126	4.9 (0.9)	2.6	(0.2, 5.0)	0.011
CARVDL-25	125	5.2 (0.8)	2.9	(0.5, 5.3)	0.005
CARVDL-50	28	5.9 (1.4)	3.6	(-0.4, 7.5)	0.19
Placebo	115	2.3 (0.8)			
Standing DBP					
CARVDL-6.25	121	3.0 (0.9)	0.7	(-1.8, 3.2)	0.46
CARVDL-12.5	126	5.1 (0.9)	2.8	(0.3, 5.2)	0.006
CARVDL-25	126	6.0 (0.8)	3.7	(1.2, 6.2)	0.001
CARVDL-50	28	7.5 (1.8)	5.2	(1.1, 9.2)	0.019
Placebo	115	2.3 (0.8)			
Sitting SBP					
CARVDL-6.25	121	4.8 (1.3)	1.9	(-1.9, 5.7)	0.24
CARVDL-12.5	126	7.1 (1.2)	4.2	(0.4, 8.0)	0.012
CARVDL-25	126	4.7 (1.2)	1.8	(-2.0, 5.6)	0.23
CARVDL-50	28	7.9 (5.0)	5.0	(-1.2, 11.2)	0.16
Placebo	115	2.9 (1.2)			
Supine SBP					
CARVDL-6.25	121	3.6 (1.5)	2.4	(-1.9, 6.6)	0.25
CARVDL-12.5	126	4.9 (1.3)	3.7	(-0.5, 7.9)	0.053
CARVDL-25	126	5.7 (1.4)	4.5	(0.3, 8.7)	0.021
CARVDL-50	28	7.3 (2.5)	6.1	(-0.8, 12.9)	0.32
Placebo	115	1.2 (1.5)			
Standing SBP					
CARVDL-6.25	121	3.6 (1.6)	0.9	(-3.6, 5.3)	0.62
CARVDL-12.5	126	4.8 (1.4)	2.1	(-2.4, 6.4)	0.25
CARVDL-25	125	5.7 (1.4)	3.0	(-1.5, 7.3)	0.14
CARVDL-50	28	6.8 (2.5)	4.1	(-3.1, 11.3)	0.40
Placebo	115	2.7 (1.5)			

adjusted confidence interval based on Dunnett's one-sided multiple comparison procedure

* two-sided p-value not yet adjusted for multiple comparisons

Table 5. Mean decrease from baseline at endpoint in Heart rate (bpm) - intent-to-treat Study B101

Treatment Group	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	95% C.I. #	unadjusted p-value*
Sitting HR					
CARVDL-6.25	121	2.7 (0.7)	0.4	(-2.0, 2.9)	0.77
CARVDL-12.5	126	3.5 (0.8)	1.2	(-1.2, 3.6)	0.26
CARVDL-25	126	5.6 (0.8)	3.3	(1.0, 5.8)	0.002
CARVDL-50	28	4.6 (1.6)	2.3	(-1.6, 6.3)	0.31
PLacebo	115	2.3 (0.9)			
Supine HR					
CARVDL-6.25	120	2.1 (0.7)	0.7	(-1.5, 2.9)	0.61
CARVDL-12.5	126	2.6 (0.7)	1.2	(-1.0, 3.4)	0.23
CARVDL-25	126	4.5 (0.7)	3.1	(0.9, 5.3)	0.002
CARVDL-50	28	4.6 (1.6)	3.2	(-0.4, 6.8)	0.079
Placebo	115	1.4 (0.8)			
Standing HR					
CARVDL-6.25	120	3.0 (0.9)	1.4	(-1.2, 4.1)	0.30
CARVDL-12.5	126	2.8 (0.8)	1.2	(-1.4, 3.8)	0.34
CARVDL-25	125	5.3 (0.7)	3.7	(1.1, 6.3)	0.002
CARVDL-50	28	4.9 (1.9)	3.3	(-1.0, 7.6)	0.12
Placebo	115	1.6 (0.9)			

adjusted confidence interval based on Dunnett's one-sided multiple comparison procedure

* two-sided p-value not yet adjusted for multiple comparisons

Table 6. Mean decrease from baseline in sitting DBP (mm Hg) at study endpoint by subgroup - intent-to-treat Study B101

Treatment Group	Males			Females		
	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO
CARVDL-6.25	76	2.9 (0.9)	0.3	45	6.9 (1.2)	1.3
CARVDL-12.5	77	5.6 (1.0)	3.0	47	7.4 (1.0)	1.8
CARVDL-25	81	5.5 (0.8)	2.9	45	6.3 (1.1)	0.7
CARVDL-50	19	8.2 (1.6)	5.6	9	7.6 (2.8)	2.0
Placebo	73	2.6 (0.8)		42	5.6 (1.1)	

Treatment Group	Age ≤ 64 years			Age > 64 years		
	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO
CARVDL-6.25	100	4.4 (0.8)	1.0	21	4.5 (1.7)	-0.3
CARVDL-12.5	100	6.3 (0.8)	2.9	26	6.3 (1.7)	1.5
CARVDL-25	98	6.4 (0.7)	3.0	28	3.8 (1.6)	-1.0
CARVDL-50	24	7.1 (1.4)	3.7	4	13.0 (3.5)	8.2
Placebo	91	3.4 (0.7)		24	4.8 (1.3)	

Treatment Group	Blacks			Non-blacks		
	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO
CARVDL-6.25	19	4.9 (1.9)	3.2	102	4.3 (0.7)	0.2
CARVDL-12.5	17	9.1 (2.3)	7.4	109	5.8 (0.7)	1.7
CARVDL-25	20	3.6 (1.8)	1.9	106	6.2 (0.7)	2.1
CARVDL-50	5	7.4 (2.8)	5.7	23	8.1 (1.5)	4.0
Placebo	18	1.7 (1.7)		97	4.1 (0.7)	

Treatment Group	Mild hypertension [#]			Moderate hypertension [#]		
	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO
CARVDL-6.25	86	4.6 (0.8)	0.9	33	4.0 (1.4)	0.2
CARVDL-12.5	89	5.6 (0.7)	1.9	37	8.0 (1.6)	4.2
CARVDL-25	92	5.2 (0.8)	1.5	32	7.8 (1.2)	4.0
CARVDL-50	20	6.6 (1.4)	2.9	8	11.4 (2.9)	7.6
Placebo	80	3.7 (0.7)		33	3.8 (1.4)	

[#] Mild hypertension: baseline sitting DBP 95-105 mm Hg

Moderate hypertension: baseline sitting DBP 106-115 mm Hg

Table 7. Mean decrease from baseline at endpoint in Secondary blood pressure (mmHg) and Heart rate (bpm) Study C1106 (Intent-to-treat analysis)

Treatment Group	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	95% C.I.	unadjusted p-value
Standing DBP					
CARVDL BID	96	9.3 (0.8)	7.6 ^e	(5.0, 9.2)	0.0001
CARVDL QD	90	7.6 (0.9)	5.3	(2.4, 6.7)	0.0001
Placebo	93	2.3 (0.8)			
Sitting SBP					
CARVDL BID	96	10.9 (1.3)	6.8	(2.4, 9.9)	0.0013
CARVDL QD	90	7.2 (1.3)	3.1	(-0.5, 7.2)	0.084
Placebo	93	4.1 (1.2)			
Standing SBP					
CARVDL BID	96	11.3 (1.3)	8.1 ^e	(3.9, 11.5)	0.0001
CARVDL QD	90	6.5 (1.4)	3.3	(-0.5, 7.3)	0.086
Placebo	93	3.2 (1.3)			
Sitting HR					
CARVDL BID	96	8.1 (0.8)	7.7	(4.6, 10.0)	0.0001
CARVDL QD	90	5.4 (0.9)	5.0	(3.2, 8.7)	0.0001
Placebo	93	0.4 (1.0)			
Standing HR					
CARVDL BID	96	9.0 (0.9)	8.8	(6.2, 12.0)	0.0001
CARVDL QD	90	5.8 (1.0)	5.6	(3.9, 9.9)	0.0001
Placebo	93	0.2 (1.0)			

^e p < 0.03 between QD and BID

Table 8. Mean decrease from baseline in sitting DBP (mm Hg) at study endpoint by subgroup - intent-to-treat Study C1106

Treatment Group	Males			Females		
	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO
CARVDL BID	53	10.3 (1.2)	8.3	43	11.5 (1.1)	6.1
CARVDL QD	58	6.5 (1.0)	4.5	32	10.5 (1.5)	5.1
Placebo	57	2.0 (0.9)		36	5.4 (1.5)	

Treatment Group	Age ≤ 64 years			Age > 64 years		
	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO
CARVDL BID	82	10.8 (0.8)	7.0	14	11.4 (2.6)	11.0
CARVDL QD	76	7.7 (0.9)	3.9	14	9.4 (2.2)	9.0
Placebo	80	3.8 (0.8)		13	0.4 (2.2)	

Treatment Group	Blacks			Non-blacks		
	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO
CARVDL BID	36	11.3 (1.3)	9.0	60	10.6 (1.0)	6.7
CARVDL QD	33	6.5 (1.7)	4.2	57	8.8 (0.8)	4.9
Placebo	35	2.3 (1.2)		58	3.9 (1.0)	

Treatment Group	Mild hypertension [#]			Moderate hypertension [#]		
	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO
CARVDL BID	81	9.9 (0.9)	6.7	15	16.3 (1.7)	12.8
CARVDL QD	75	7.8 (0.9)	4.6	15	8.8 (2.1)	5.3
Placebo	72	3.2 (0.8)		21	3.5 (2.2)	

[#] Mild hypertension: baseline sitting DBP 95-105 mm Hg

Moderate hypertension: baseline sitting DBP 106-115 mm Hg

Table 9. Mean decrease from baseline at study endpoint in Secondary blood pressure (mmHg) and Heart rate (bpm) Study C1109 (Intent-to-treat analysis)

Treatment Group	N	Mean Decrease (S.E.)	Trtment minus PLACEBO	95% C.I.	unadjusted p-value
Standing DBP					
CARVDL	105	6.4 (0.9)	4.1	(1.5, 6.7)	0.002
ATENOLOL	100	9.9 (0.7)	7.6 ⁺	(5.0, 10.2)	<0.001
Placebo	52	2.3 (1.0)			
Sitting SBP					
CARVDL	105	6.1 (1.3)	1.4	(-2.7, 5.7)	0.47
ATENOLOL	100	11.4 (1.2)	6.7 ⁺	(2.5, 10.9)	<0.001
Placebo	52	4.7 (1.7)			
Standing SBP					
CARVDL	105	7.3 (1.4)	2.7	(-1.7, 7.1)	0.23
ATENOLOL.	100	9.6 (1.3)	5.0	(0.7, 9.6)	0.023
Placebo	52	4.6 (1.6)			
Sitting HR					
CARVDL	105	8.4 (0.8)	7.5	(4.9, 10.0)	<0.001
ATENOLOL	100	9.8 (0.7)	8.9	(6.3, 11.5)	<0.001
Placebo	52	0.9 (1.2)			
Standing HR					
CARVDL	105	8.4 (0.8)	7.8	(4.9, 10.4)	<0.001
ATENOLOL	100	10.7 (0.8)	10.1 ⁺	(7.3, 12.8)	<0.001
Placebo	52	0.6 (1.2)			

⁺ p < 0.05 between carvedilol and atenolol, based on modified Bonferroni procedure

Table 10. Mean decrease from baseline in sitting DBP (mm Hg) at study endpoint by subgroup - intent-to-treat Study C1169

Treatment Group	Males			Females		
	N	Mean Decrease (S.E.)	Trtment minus PLACEBO	N	Mean Decrease (S.E.)	Trtment minus PLACEBO
CARVDL	78	7.4 (0.9)	3.9	27	7.6 (1.4)	3.9
ATENOLOL	66	11.2 (0.9)	7.7	34	11.5 (0.9)	7.8
Placebo	36	3.5 (1.0)		16	3.7 (1.8)	

Treatment Group	Blacks			Non-blacks		
	N	Mean Decrease (S.E.)	Trtment minus PLACEBO	N	Mean Decrease (S.E.)	Trtment minus PLACEBO
CARVDL	80	8.1 (0.7)	4.5	25	5.5 (1.9)	2.1
ATENOLOL	76	11.8 (0.7)	8.2	24	9.8 (1.3)	6.4
Placebo	40	3.6 (1.0)		12	3.4 (1.8)	

Treatment Group	Age ≤ 64 years			Age > 64 years		
	N	Mean Decrease (S.E.)	Trtment minus PLACEBO	N	Mean Decrease (S.E.)	Trtment minus PLACEBO
CARVDL	81	7.1 (0.9)	3.7	24	8.8 (1.4)	4.8
ATENOLOL	82	11.3 (0.7)	7.9	18	11.6 (1.8)	7.6
Placebo	41	3.4 (1.1)		11	4.0 (1.5)	

Treatment Group	Mild hypertension [‡]			Moderate hypertension [‡]		
	N	Mean Decrease (S.E.)	Trtment minus PLACEBO	N	Mean Decrease (S.E.)	Trtment minus PLACEBO
CARVDL	87	6.9 (0.9)	3.5	18	10.1 (1.8)	5.3
ATENOLOL	87	11.3 (0.6)	7.9	13	11.6 (2.5)	6.8
Placebo	48	3.4 (0.9)		4	4.8 (3.3)	

[‡] Mild hypertension: baseline sitting DBP 95-105 mm Hg
 Moderate hypertension: baseline sitting DBP 106-115 mm Hg

--- mean decrease from baseline at study endpoint in
 Secondary blood pressure (mmHg) and Heart rate (b/min)
 Study C1107 (Intent-to-treat analysis)

Treatment Group	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	95% C.I. [†]	unadjusted p-value
Standing DBP					
CARVDL 6.25	66	4.1 (0.9)	0.9	(-1.7, 3.6)	NS
CARVDL 12.5	65	4.7 (0.9)	1.5	(-1.1, 4.2)	NS
CARVDL 12.5/25	66	5.6 (0.9)	2.4	(-0.2, 5.1)	0.074
Placebo	66	3.2 (1.0)			
Sitting SBP					
CARVDL 6.25	67	3.5 (1.5)	1.5	(-2.9, 5.7)	NS
CARVDL 12.5	65	4.4 (1.6)	2.4	(-2.0, 6.7)	NS
CARVDL 12.5/25	66	4.5 (1.4)	2.5	(-1.9, 6.7)	NS
Placebo	66	2.0 (1.4)			
Standing SBP					
CARVDL 6.25	66	2.4 (1.4)	-0.2	(-4.5, 4.1)	NS
CARVDL 12.5	65	3.4 (1.5)	0.8	(-3.6, 5.0)	NS
CARVDL 12.5/25	66	4.0 (1.5)	1.4	(-2.9, 5.7)	NS
Placebo	66	2.6 (1.5)			
Sitting HR					
CARVDL 6.25	67	4.7 (1.1)	5.0	(2.2, 7.8)	<0.001
CARVDL 12.5	65	3.3 (1.0)	3.6	(0.8, 6.3)	<0.02
CARVDL 12.5/25	66	6.3 (1.1)	6.6	(3.8, 9.3)	<0.001
Placebo	66	-0.3 (0.9)			
Standing HR					
CARVDL 6.25	66	3.8 (1.1)	3.0	(-0.0, 5.9)	0.024
CARVDL 12.5	65	3.4 (1.2)	2.6	(-0.4, 5.6)	0.048
CARVDL 12.5/25	66	7.0 (1.1)	6.2	(3.3, 9.2)	<0.0001
Placebo	66	0.8 (0.7)			

[†] adjusted based on Dunnett's one-sided procedure

Table 12. Mean decrease from baseline in sitting DBP (mm Hg) at study endpoint by subgroup - intent-to-treat Study C1107

Treatment Group	Males			Females		
	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO
CARVDL-6.25	43	4.3 (1.2)	2.1	24	5.4 (1.6)	0.3
CARVDL-12.5	42	3.8 (1.2)	1.6	23	6.7 (1.6)	1.6
CARV-12.5/25	44	5.3 (1.0)	3.1	22	8.5 (1.5)	3.4
Placebo	42	2.2 (1.0)		24	5.1 (1.2)	

Treatment Group	Age ≤ 64 years			Age > 64 years		
	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO
CARVDL-6.25	58	4.2 (1.0)	0.7	9	7.7 (2.4)	5.0
CARVDL-12.5	50	4.8 (1.1)	1.3	15	5.2 (1.9)	2.5
CARV-12.5/25	58	6.1 (0.9)	2.6	8	8.3 (2.0)	5.6
Placebo	51	3.5 (0.9)		15	2.7 (1.7)	

Treatment Group	Blacks			Non-blacks		
	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO
CARVDL-6.25	22	3.8 (2.1)	0.2	45	5.1 (1.0)	2.0
CARVDL-12.5	25	4.1 (1.8)	0.5	40	5.3 (1.2)	2.2
CARV-12.5/25	21	6.1 (1.8)	2.5	45	6.4 (0.9)	3.3
Placebo	21	3.6 (1.5)		45	3.1 (1.0)	

Treatment Group	Mild hypertension [#]			Moderate hypertension [#]		
	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO
CARVDL-6.25	59	4.6 (1.1)	1.7	8	5.3 (2.4)	-1.0
CARVDL-12.5	62	4.7 (1.0)	1.8	3	8.0 (1.5)	1.7
CARV-12.5/25	58	6.1 (0.9)	3.2	8	8.5 (2.8)	2.2
Placebo	58	2.9 (0.9)		8	6.3 (1.6)	

[#] Mild hypertension: baseline sitting DBP 95-105 mm Hg

Moderate hypertension: baseline sitting DBP 106-115 mm Hg

Duplicate

Z. MELINA

Statistical Review and Evaluation

NDA #: 20-297

Date:

Applicant: SmithKline Beecham Pharmaceuticals

Name of Drug: Kredex (Carvedilol - SKF 105517)

Documents Reviewed:

1. NDA Submission, Volumes 1.34 - 1.37, "Chronic Oral Carcinogenicity Test of BM 14.190 2-Year Experiment in Rats" SK&F Report No. TC001BS, BM Report No. J2, May 1986.
2. NDA Submission, Volumes 1.29 - 1.32, "Chronic Oral Carcinogenicity Study of BM 14.190 Life-Time Application To Mice", SK&F Report No. TC002BS, BM Report No. J4, June 1987.
3. NDA special submission, Data Diskettes and Hardcopy of the Animal Data, Date of Document, April 30, 1993, and May 24, 1993.

I. Background

Two animal carcinogenicity studies (one in rats and one in mice) were included in this NDA submission. The purpose of these two-year studies was to examine whether the oral application of BM 14.190, a vasodilating beta-blocker, to rats and mice has a tumorigenic or carcinogenic effect. Ms. Estela Barry, HFD-110, who is the reviewing pharmacologist of this NDA has requested the Division of Biometrics to perform the statistical review and evaluation of these two studies. The data submitted on computer floppy diskettes were used in the reviewer's independent analyses.

II. The Rat Study

II. a. Design

In this study, 250 male and 250 female white Sprague-Dawley rats of the Caw-Ico-Wiga strain were randomly and equally distributed to four treated and one control groups. A second control group was taken from a parallel study of another drug (BM 11.332) that ran at the same time as this experiment. Carvedilol was administered to rats at the following feed concentrations: 200, 400, 800, and 1600 ppm for two years. Since relative food consumption declined with age and with weight increase, drug dosage declined during the experimental period. The decline in dosage in males was greater than that in females. The group median drug intakes were listed in Table 1. The drug was administered in the period from June 1, 1983 to June 10, 1985 inclusively. Final killings began in May 1985. Initially food consumption was measured for 2 consecutive days at 2 week intervals but from August 2, 1984 on, it was determined once a month. Body

weight was measured weekly. All rats were observed twice daily for mortality and moribundity. At the end of the study, 10 males and 10 females in good health were killed and the blood was submitted to hematological and clinical chemical investigations. After one year the animals were examined at 4-weekly intervals for palpable and suspected tumors. Living animals were anesthetized with pentobarbital and then bled. Animals that died spontaneously were autopsied immediately after they were found. The animals and organs were studied macroscopically as well as microscopically.

II. b. Sponsor's Analyses

Survival data were analyzed by the National Cancer Institute life table analysis (Thomas, Breslow and Gart, "Trend and Homogeneity Analyses of Proportions and Life Table Data", Computers and Biomedical Research, 10, 373-381, 1977) and CARTEST ("A Program for Simple, Sensitive Significance Tests for Carcinogenic Effects in Long-term Animal Experiments", International Agency for Research on Cancer, Lyon, 1981). These packages used the following three methods: Kaplan-Meier product limit estimates of survival data, Cox-Tarone logistic tests and Gehan-Breslow generalized Kruskal-Wallis tests on life table data. Results of the statistical analyses showed that there was a significant negative linear trend in survival time in male rats ($p = 0.01$ for non-time-adjusted evaluation and $p = 0.003$ for time-adjusted evaluation). The female rats in all dose groups lived equally long. For the heterogeneity test, no significant difference in survival distribution was detected in males ($p = 0.18$ for non-time-adjusted and $p = 0.07$ for time-adjusted evaluation). No trend with dose can be seen in the females. The Kaplan-Meier estimates of survival data are presented in Figures 1 and 2 for males and females, respectively. When deaths caused by tumors are excluded, the results show that the males have a higher mortality with increase in dose. This trend is very marked with $p = 0.0006$. For the females no trend with dose is detectable.

The methods described in Peto et al. ("Guidelines for Simple, Sensitive Significance Tests for Carcinogenic Effects in Long-Term Animal Experiments", In Long-Term and Short-Term Screening Assays for Carcinogens: A Critical Appraisal, International Agency for Research on Cancer Monographs, Annex to Supplement 2, World Health Organization, 311-426, 1980) were used to test the linear trend in the tumor data. For small tumor incidence cases, the number of tumor-bearers in the highest dose group was compared with tumor-bearers in the control group by means of the Fisher-Exact test for chance occurrence. The sponsor summarized tumor frequencies in Tables 2 and 3 for males and females, respectively. Based on the results in Tables 2 and 3, the sponsor indicated that "on the basis of the ratio of observed tumor events/expected tumor events, one can see that there is a negative trend with dose for the male animals. For females the groups do not show any trend behavior with dosage." Table 4 lists the total numbers of all tumor-bearers and those with malignant tumors. Table 5 lists numbers of animals with tumors on

the organs with the highest frequencies. No statistical analyses were performed on these tumor data.

Based on the above summaries, the sponsor concluded that "the administration of BM 14.190 at feed concentrations of 200 ppm, 400 ppm, 800 ppm and 1600 ppm over a period of 2 year to growing Sprague-Dawley rats did not provide any indication of tumorigenic or carcinogenic action of the substance."

II.c. Reviewer's Analyses and Comments

The sponsor indicated that there are 50 animals/sex/group in the study, however, the sponsor's submitted diskettes has 51 animals recorded in female low dose group. The reviewer found a mis-coding in animal number 1318, it should be coded as animal number 318. The following analyses are based on 50 animals/sex/group. In addition, the sponsor indicated that a second control group was taken from a parallel study of another drug (BM 41.332) that ran at the same time as this experiment. However, these data were not included in sponsor's submitted diskettes and hence were not included in the following analyses.

The Cox test and the generalized Wilcoxon test described in the paper of Thomas, Breslow, and Gart (1977) were used to test for heterogeneity in survival distribution. The p-values of the Cox test were 0.1095 and 0.8928 for males and females, respectively. Hence, No significant difference in the survival distribution was detected in both sexes. A similar conclusion was obtained in the generalized Wilcoxon test. The p-values of the test were 0.1044 and 0.7704 for males and females, respectively.

The intercurrent mortality rates for both male and female rats (see Table 6) were tested for linear trend according to the death rate method described in the paper of Peto et al. (1980) using the time intervals 0-50, 51-80, and 81-105 weeks. The actual dose levels 0, 200, 400, 800, and 1600 ppm were the scores assigned to the control, low, medium, high-1, and high-2 dose groups, respectively. The results of the analyses showed that there was no significant (at 0.05 level) linear trend in the intercurrent mortality rate in female rats ($p = 0.1625$). However, there was a significant (at 0.05 level) linear trend in the intercurrent mortality rate in male rats ($p = 0.0017$).

The methods described in Peto et al. (1980) and the methods of age-adjusted exact permutation trend test were used to test the linear trend in the tumor data. The results of the above analyses showed that there were significant (at 0.05 level) positive linear trends in stomach papilloma ($p = 0.0494$) and skin subcutis sebaceous adenoma ($p = 0.0414$) in male rats. There were marginally statistically significant linear trends in thyroid gland adenoma ($p = 0.0504$) and brain oligodendroglioma ($p = 0.0852$) in female rats and in liver hepatocellular adenoma ($p = 0.0579$) in male rats. The incidence

rates of stomach papilloma, skin subcutis sebaceous adenoma, and liver hepatocellular adenoma in male rats and thyroid gland adenoma and brain oligodendroglioma in female rats are given in Tables 7 to 11.

Ms. Barry raised the question "Were the doses of Carvedilol proposed in the study-protocol significantly affected by food intake, age, or weight of the animals?" Since the concentration of the drug in the feed was kept constant throughout the entire study period, there is a reduction in dose concentration ppm/kg/day as the age of the animals increases. Tables 12 to 13 show the median body weights of male and female rats, respectively, grouped by time intervals. Tables 14 to 15 listed the food consumptions of male and female rats, respectively. Apparently, food consumption did not increase with the increase in body weight. There was a decline in relative food consumption over the course of the study. As a result, there is a decline in drug intake over the course of the study. This is consistent with the findings of the reviewing pharmacologist, Dr. Martin Winbury, a FDA consultant on this NDA.

The reviewer also evaluated the validity of the experiment. The following two issues are important in determining the validity of an experiment: (1) The numbers of animals alive over the course of the study to get an adequate exposure to the chemical and to be at risk of forming late-developing tumors. (2) If the doses are high enough to present a reasonable tumor challenge to the animals.

With regard to the first issue, the following criteria or rules of thumb have been proposed by some experts in the field:

(A) Haseman proposes (through personal communication with Dr. Karl Lin) that a 50% survival rate of the 50 initial animals in the high dose group between weeks 80-90 will be considered as a sufficient number and an adequate exposure. However, the percentage can be lower or higher if the number of animals used in each treatment/sex is larger or smaller than 50 as long as there will be between 20 to 30 animals still alive during these weeks.

(B) Chu, Ceuto, and Ward ("Factors in the Evaluation of 200 National Cancer Institute Carcinogen Bioassays", Journal of Toxicology and Environmental Health, 8, 1981, pp. 251-280) propose that an experiment that has not shown a chemical to be carcinogenic should have (high dose) groups of animals with greater than 50% survival at one year (52 weeks).

In this study, the survival rates of the 1600 ppm dose group at one-year were 96% and 100% for males and females, respectively. These one-year survival rates satisfied the criterion of Chu et al. (1981). The survival rates of the control, 200, 400, 800, and 1600 ppm dose groups at the terminal sacrifice were 36%, 30%, 34%, 22%, and 16%, respectively, for males, and 46%, 46%, 44%, 48%, and 58%, respectively, for females. There were not sufficient male rats in

the control and treated groups living long enough to get an adequate exposure to the chemical and to be at risk of forming late-developing tumors based on Haseman's proposition.

With regard to the second issue, in the paper of Chu, Ceuto and Ward (1981), the following criteria for dose adequacy are mentioned.

(A) "A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls."

(B) "The administered dose is also considered an MTD (Maximum Tolerated Dose) if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."

(C) "In addition, doses are considered adequate if the dosed animals show a slightly increased mortality compared to the controls."

Figures 3-6 are the median body weight curves of control and treated groups of male and female rats. In Tables 12-13, median body weights of the male and female rats grouped by time intervals are given. All male treated rats gained more body weight than their counterparts in the control groups. Different from the male rats, the female high dose groups gained less body weight than the female control group did. The weight gains in the female low and median dose groups are greater than that of the female control group. The high dose is close to MTD for female rats but not for male rats using the above mentioned criteria. However, it is important to check the clinical and toxic signs of the animals in the male high dose group in the final determination of the adequacy of the high dose for male rats.

III. The Mouse Study

III. a. Design

In this study, 250 male and 250 female Charles River (SPF-NMRI-HAN-WIGA strain) mice were randomly assigned into three treated groups and one control groups. The control group was made up of 100 animals of each sex and the dosed groups were made up of 50 animals of each sex. Carvedilol (BM 14.190) was administered in food with concentration adjusted at 1-4 week intervals to maintain constant doses of 20, 65, and 200 mg/kg/day. The substance was applied in the period from July 17, 1984 to May 21, 1986 (97th week) for the female animals and to September 16, 1986 (114th week) for the male animals. Feed consumption was determined on 2 consecutive days at weekly intervals and the average value for 1 day was recorded. Starting on September 11, 1984, food intake was ascertained at 4-week intervals. Body weight was determined once a week. All animals were checked twice daily for morbidity and mortality. After a running time of 1 year, the animals were examined at 4-week intervals for palpable and presumed tumors. At the end of the study during the terminal sacrifice, 10 males and 10 females in good health were killed and

blood submitted to hematological and clinical chemical investigations. Living animals were anesthetized with pentobarbital and then bled. Animals that died spontaneously were autopsied immediately after they were found. The animals and organs were studied macroscopically as well as microscopically.

III. b. Sponsor's Analyses

Survival data were analyzed by the National Cancer Institute life table analysis (Thomas, Breslow and Gart, 1977) and CARTEST (1981). The results showed there was no difference in overall mortality among the groups for both sexes. The probabilities of survival for animals which died of tumors were approximately constant with dose for both sexes. The Kaplan-Meier estimates of survival data are presented in Figures 7 and 8 for males and females, respectively.

The procedure of Peto et al. was used to test any dose-dependent trend in the number of tumor carriers. The sponsor summarized tumor frequencies for each group/sex and listed them in Tables 16 and 17 for males and females, respectively. The total numbers of animals with tumors and malignant tumors are listed in Table 18. The sponsor indicated that "the total number of tumors remained approximately the same with dose in the two sexes. Nor did adjusted analysis show any differences in the rate of occurrence of tumors as a function of dosage." Table 19 listed the organs which have higher tumor incidence rates. However, no statistical analyses were performed on these tumor data.

Based on the above analyses, the sponsor stated that "life-long application of BM 14.190 to NMRI mice in the doses of 20, 65, and 200 mg/kg/day revealed no tumorigenic or carcinogenic effect."

III.c. Reviewer's analyses and Comments

The Cox test and the generalized Wilcoxon test described in the paper of Thomas et al. (1977) were used to test for heterogeneity in survival distribution. The p-values of the Cox test were 0.2841 and 0.6980 for males and females, respectively. Hence, no statistically significant difference (at 0.05 level) in the survival distribution was detected in both sexes. A similar conclusion was obtained in the generalized Wilcoxon test. The p-values were 0.4450 and 0.5736 for males and females, respectively.

The intercurrent mortality rates for both male and female mice (see Table 20) were tested for linear trend according to the death rate method described in the paper of Peto et al. (1980) using the time intervals 0-50, 51-80, and 81-97 weeks for female mice and 0-50, 51-80, and 81-113 weeks for male mice. The actual dose levels 0, 20, 65, and 200 mg/kg/day were the scores assigned to the control, low, medium, and high dose groups, respectively. The results of the analyses showed that there was no significant (at 0.05 level) linear trend in the intercurrent mortality rate in male ($p = 0.1319$) and

female mice ($p = 0.3866$).

The methods described in Peto et al. (1980) and the methods of age-adjusted exact permutation trend test were used to test the linear trend in the tumor data. The results of the above analyses showed that there was no statistically significant (at 0.05 level) linear trend in the tumor incidence rates of the tumor types tested in both sexes. However, there was a marginally significant positive linear trend in harder's gland carcinoma ($p = 0.0523$) and harder's gland carcinoma and adenoma combined ($p = 0.0663$) in female mice. The incidence rates of harder's gland carcinoma in female mice are 0/100, 0/50, 0/50, and 2/50. The incidence rates of harder's gland carcinoma and adenoma combined in female mice are 9/100, 3/50, 4/50, and 8/50. Although there was no significant linear trend in harder's gland carcinoma ($p = 0.1072$) in male mice, the incidence rates of harder's gland carcinoma in male mice are higher in the treated groups than in the control group (0/100, 0/50, 2/50, and 1/50).

Similar to the rat study, the validity of this mouse experiment has been evaluated. In this study, the survival rates of the high dose mice at one-year were 98% and 92% for males and females, respectively. These one-year survival rates satisfied the criterion of Chu et al. (1981). The survival rates of the control, low, medium, and high dose mice at the terminal sacrifice were 42%, 62%, 44%, and 44%, respectively, for males, and 27%, 20%, 22%, and 20%, respectively, for females. There were not sufficient female mice in the control and treated groups living long enough to get an adequate exposure to the chemical and to be at risk of forming late-developing tumors basing on Haseman's proposition.

Figures 9-10 contain the median body weight curves of control and treated groups of male and female mice, respectively. In Tables 21-22, the median body weights of the male and female mice grouped by time intervals are given. All treated male mice gained less body weight than their counterparts in the control group. Different from the male mice, the female low and medium dose groups had the same body weight gains as the female control group. The female high dose group gained less body weight than the female control group did. The body weight gain data suggest that the high dose is over MTD for both male and female mice using the above mentioned criteria. However, it is important to check the clinical and toxic signs of the animals in the female high dose group in the final determination of the adequacy of the high dose for female mice.

IV. Summary

IV. a. The Rat Study

The oncogenic potential of carvedilol was evaluated in this rat study when administered to rats at the following feed concentrations: 0, 200, 400, 800, and 1600 ppm for two years. A second control group was taken from a parallel study of another drug (BM 41.332) that ran

at the same time as this experiment.

The Cox and the generalized Wilcoxon methods were used to test the heterogeneity in survival distribution. The test results revealed that there was no significant difference in the survival distribution in both sexes.

The statistical methods given in the paper of Peto et al. (1980) and an exact permutation trend test were used to test the positive linear trend in intercurrent mortality and incidental tumor rates. The results of the analyses showed that there was no significant (at 0.05 level) linear trend in the intercurrent mortality rate in female rats ($p = 0.1625$). However, there was a significant (at 0.05 level) linear trend in the intercurrent mortality rate in male rats ($p = 0.0017$). Results of tumor data analyses showed that there was a significant (at 0.05 level) positive linear trend in stomach papilloma ($p = 0.0494$) and skin subcutis sebaceous adenoma ($p = 0.0414$) in male rats. There were marginally statistically significant linear trends in thyroid gland adenoma ($p = 0.0504$) and brain oligodendroglioma ($p = 0.0852$) in female rats and in liver hepatocellular adenoma ($p = 0.0579$) in male rats.

With regard to the questions raised by Ms. Barry: "if the doses of Carvedilol proposed in the study protocol were significantly affected by food intake, age, or weight of the animals?" Since the concentration of the drug in the feed was kept constant throughout the entire study period, there is a reduction in dose concentration as the age of the animals increases. This is consistent with the findings of the reviewing pharmacologist, Dr. Martin Winbury, a FDA consultant on this NDA.

The validity of the experiment has been evaluated. As mentioned previously, the numbers of animals alive over the course of the study and the adequacy of dose levels are the two important factors considered in the evaluation.

In this study, the survival rates of the 1600 ppm dose group at one-year were 96% and 100% for males and females, respectively. These one-year survival rates satisfied the criterion of Chu et al. (1981). The survival rates of the control, 200, 400, 800, and 1600 ppm dose groups at the terminal sacrifice were 36%, 30%, 34%, 22%, and 16%, respectively, for males, and 46%, 46%, 44%, 48%, and 58%, respectively, for females. There were not sufficient male rats in the control and treated groups living long enough to get an adequate exposure to the chemical and to be at risk of forming late-developing tumors based on Haseman's proposition.

The weight gain data show that the high dose is close to MTD for female rats but not for male rats. However, it is important to check the clinical and toxic signs of the animals in the male high dose group in the final determination of the adequacy of the high dose for male rats.

IV. b. The Mouse study

The oncogenic potential of carvedilol was evaluated in this mouse study when administered in food with concentration adjusted at 1-4 week intervals to maintain a constant dose of 20, 65, and 200 mg/kg/day for 97 weeks for the females and 114 weeks for the males. One control group was made up of 100 animals of each sex and the dosed groups were made up of 50 animals of each sex.

The Cox and the generalized Wilcoxon methods were used to test the heterogeneity in survival distribution. No statistically significant difference (at 0.05 level) in the survival distribution was detected in both sexes in both tests.

The statistical methods given in the paper of Peto et al. (1980) and an exact permutation trend test were used to test the positive linear trend in intercurrent mortality and incidental tumor rates. Applying the above methods to the data on sponsor's computer diskettes, the results of the analyses showed that there was no significant (at 0.05 level) linear trend in the intercurrent mortality rate in male ($p = 0.1819$) and female mice ($p = 0.3866$).

Results of tumor data analyses showed that there was no statistically significant (at 0.05 level) linear trend in the tumor incidence rates of tumor types tested in both sexes. However, there was a marginally significant positive linear trend in harder's gland carcinoma ($p = 0.052$) and harder's gland carcinoma and adenoma combined ($p = 0.0663$) in female mice. The incidence rates of harder's gland carcinoma in female mice are 0/100, 0/50, 0/50, and 2/50. The incidence rates of harder's gland carcinoma and adenoma combined in female mice are 9/100, 3/50, 4/50, and 8/50. Although there was no significant linear trend in harder's gland carcinoma ($p = 0.1072$) in male mice, the incidence rates of harder's gland carcinoma in male mice are higher in the treated groups than in the control group (0/100, 0/50, 2/50, and 1/50).

However, before drawing the final conclusion that the chemical is not carcinogenic, the validity of the experiment has been evaluated. The survival rates of the high dose mice at one-year were 98% and 92% for males and females, respectively. These one-year survival rates satisfied the criterion of Chu et al. (1981). The survival rates of the control, low, medium, and high dose mice at the terminal sacrifice were 42%, 62%, 44%, and 44%, respectively, for males, and 27%, 20%, 22%, and 20%, respectively, for females. It seems that there were not sufficient female mice in the control and treated groups living long enough to get an adequate exposure to the chemical and to be at risk of forming late-developing tumors basing on Haseman's proposition.

The weight gain data show that the high dose is over MTD for both male and female mice. However, it is important to check the clinical and toxic signs of the animals in the female high dose group in

the final determination of the adequacy of the high dose for female mice.

Daphne Lin

Daphne Lin, Ph.D.
Mathematical Statistician

Concur:

Karl K. Lin 6/30/93
Karl K. Lin, Ph.D., Group Leader, SARB

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HFD-715/Dr. Daphne Lin
HFD-715/Chron (SARB)
HFD-502/Assistant Director (Pharmacology)
HFD-715/DRU 2.1.1, Carvedilol, SmithKline Beecham

Fig. 7a. PROPORTION SURVIVING - MALE
(Kaplan Meier)

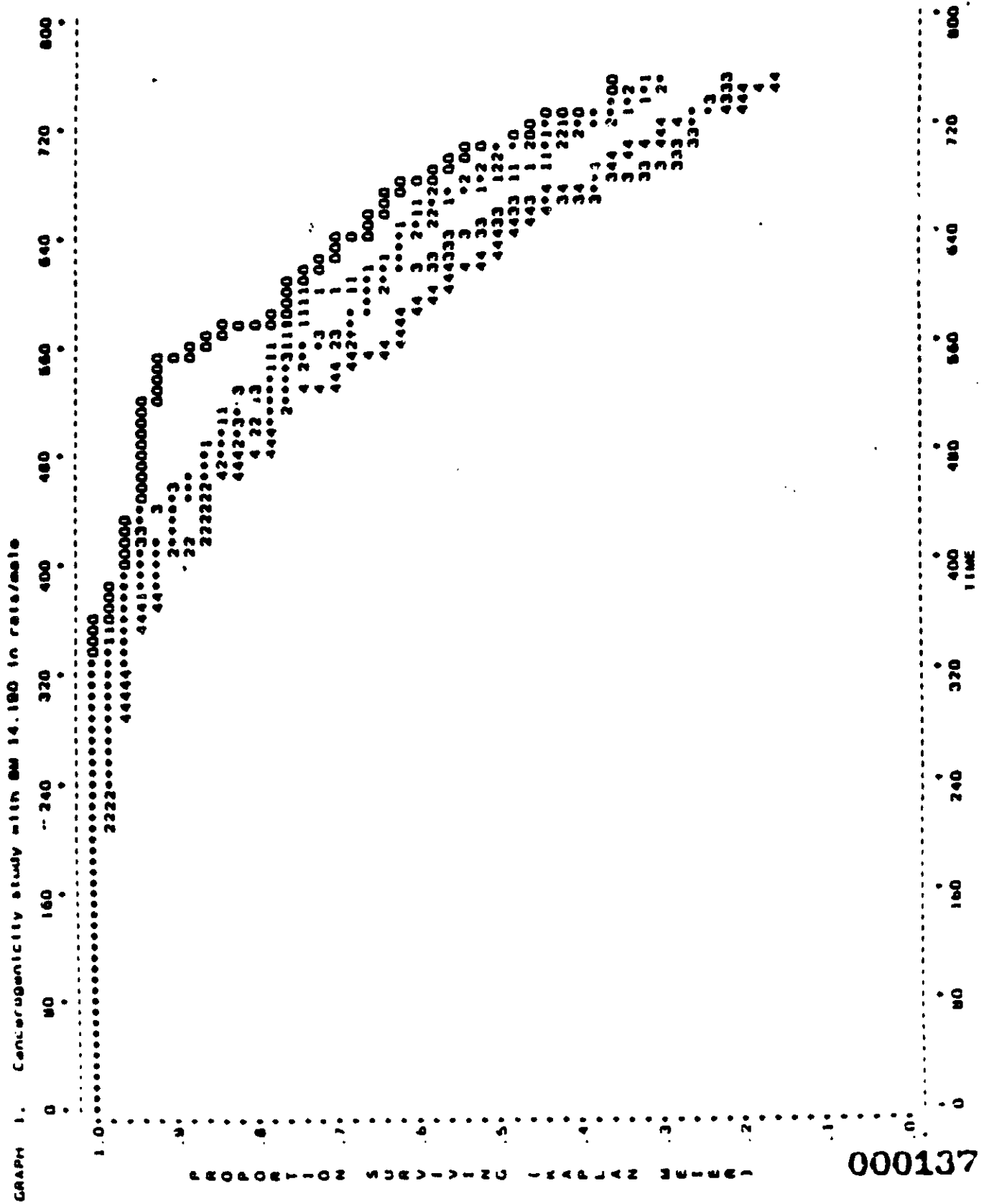


Fig. 8a. PROPORTION SURVIVING - FEMALE
(Kaplan Meier)

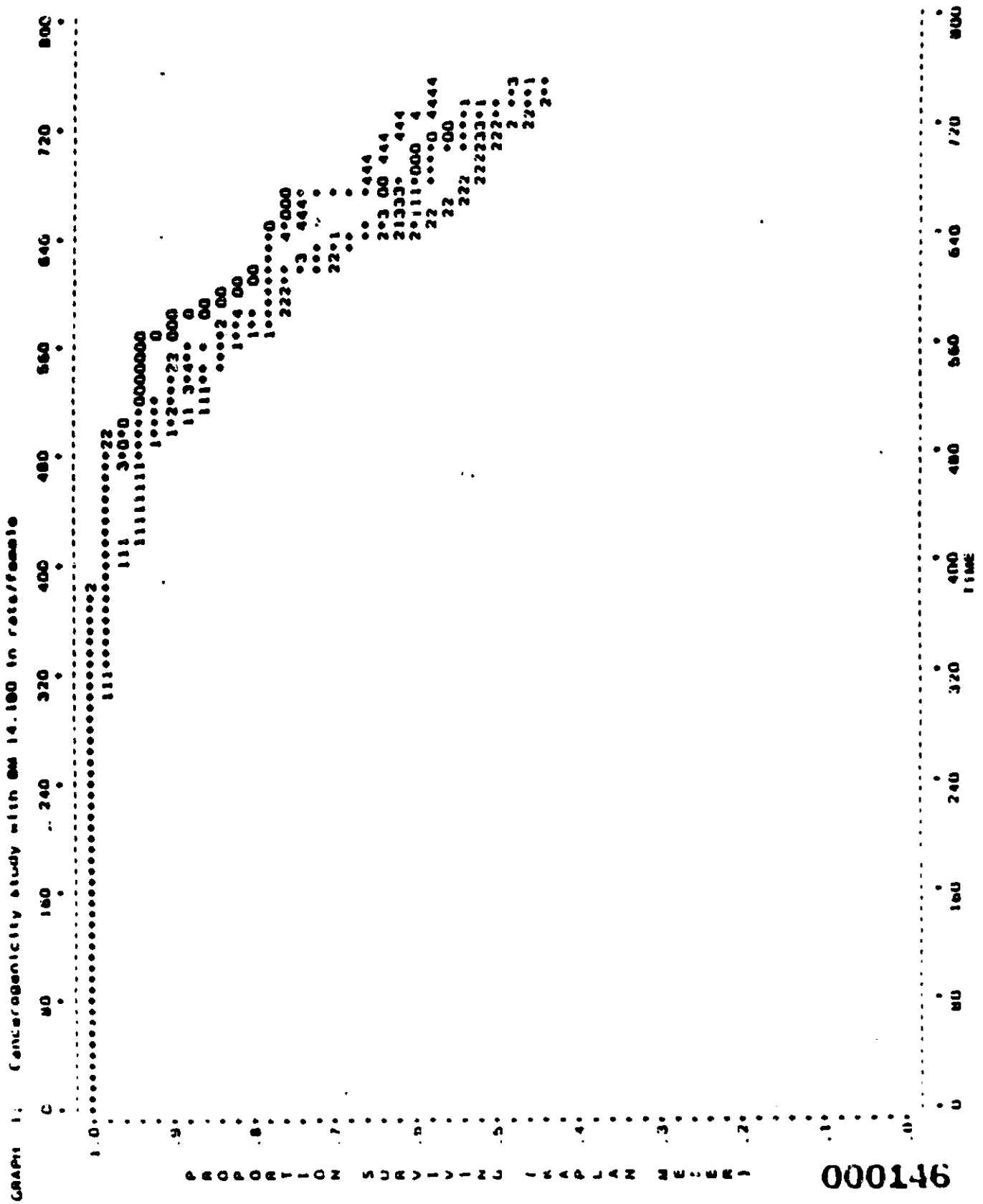
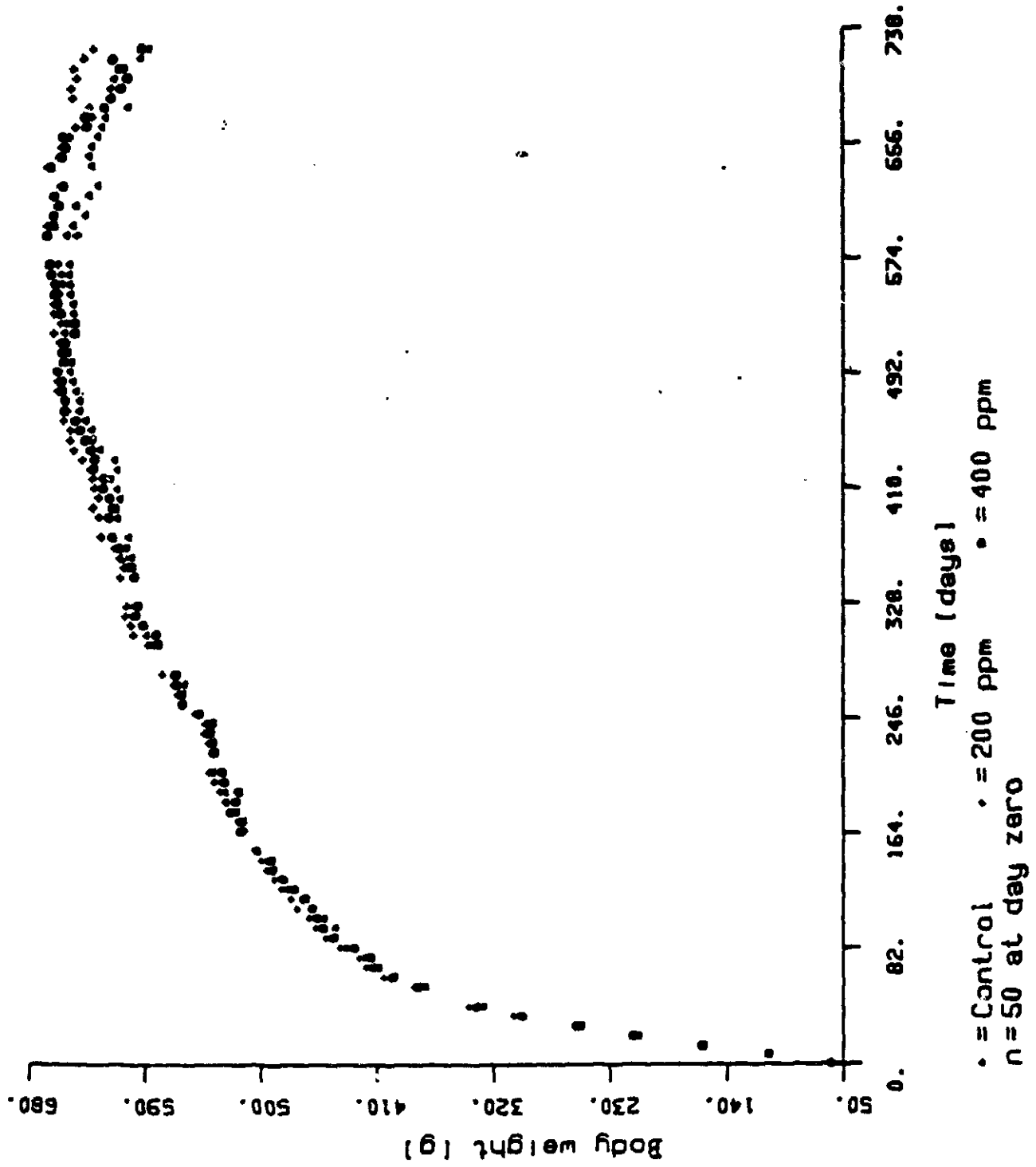




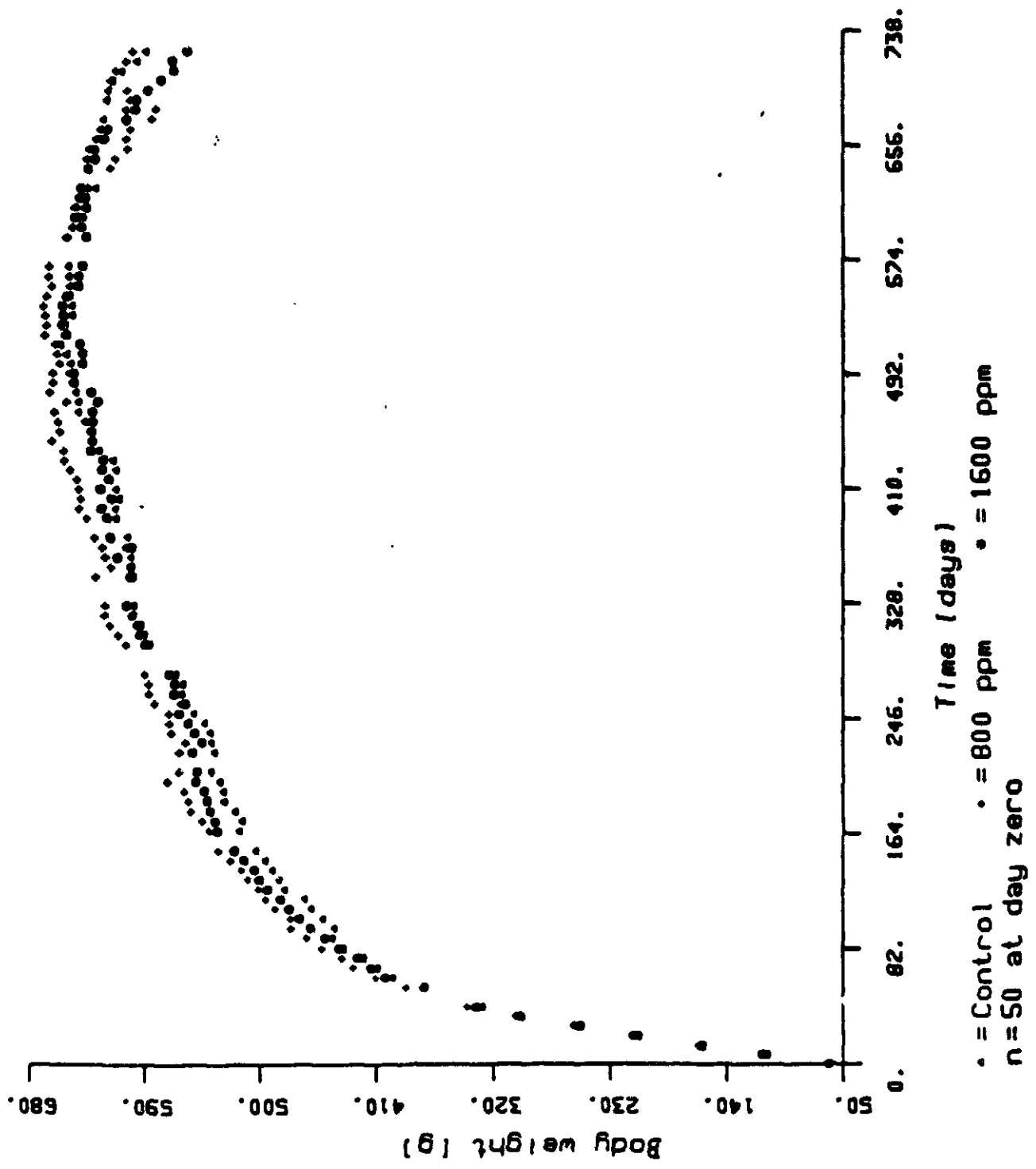
Fig. 1a CARCINOGENICITY STUDY WITH BM 14.190 IN RATS
Body weight of male rats (median) for low
dose groups



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Fig. 1b CARCINOGENICITY STUDY WITH BM 14.190 IN RATS
 Body weight of male rats (median) for high dose groups



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Fig.2a CARCINOGENICITY STUDY WITH BM 14.190 IN RATS
Body weight of female rats (median) for low dose groups

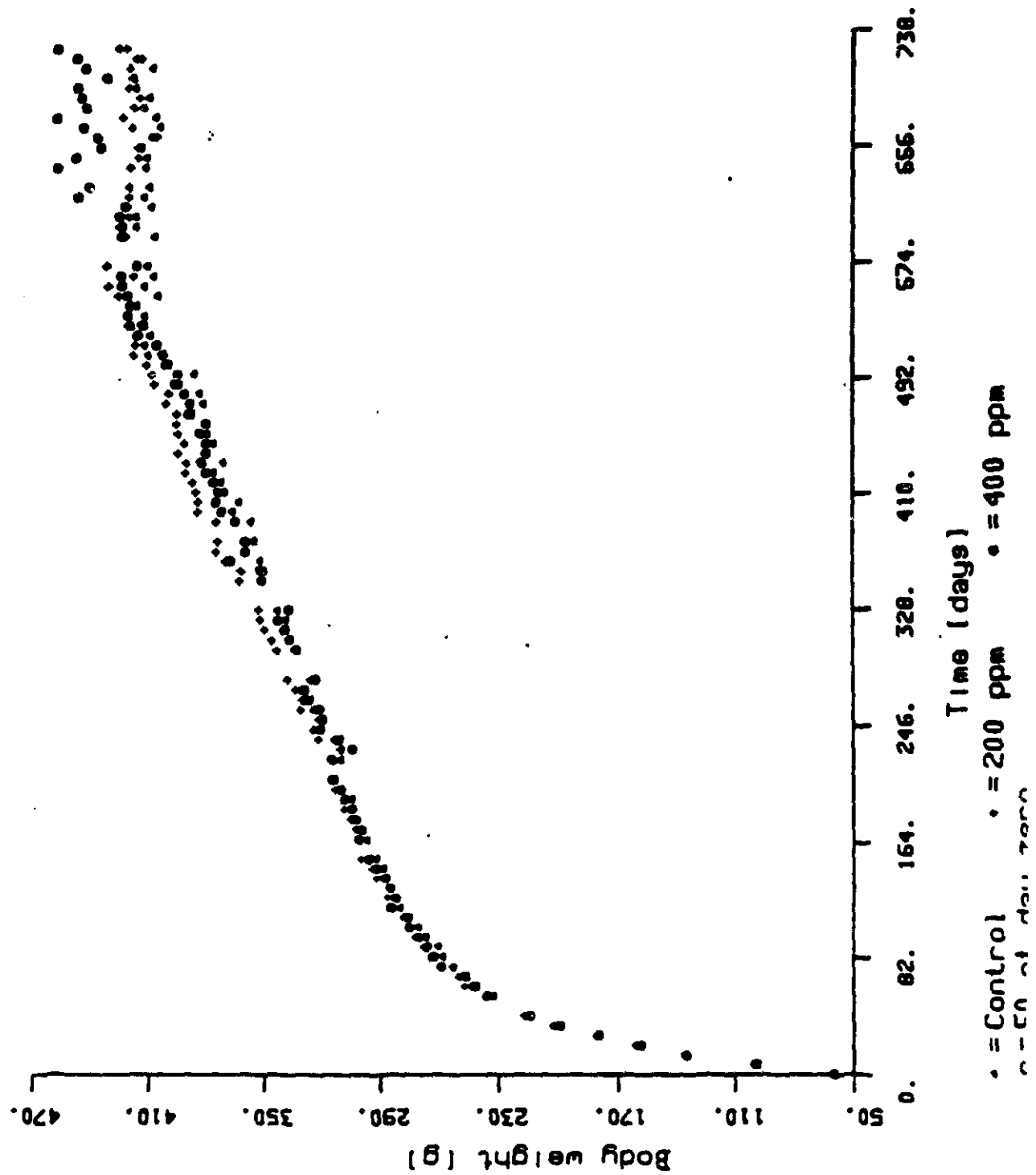
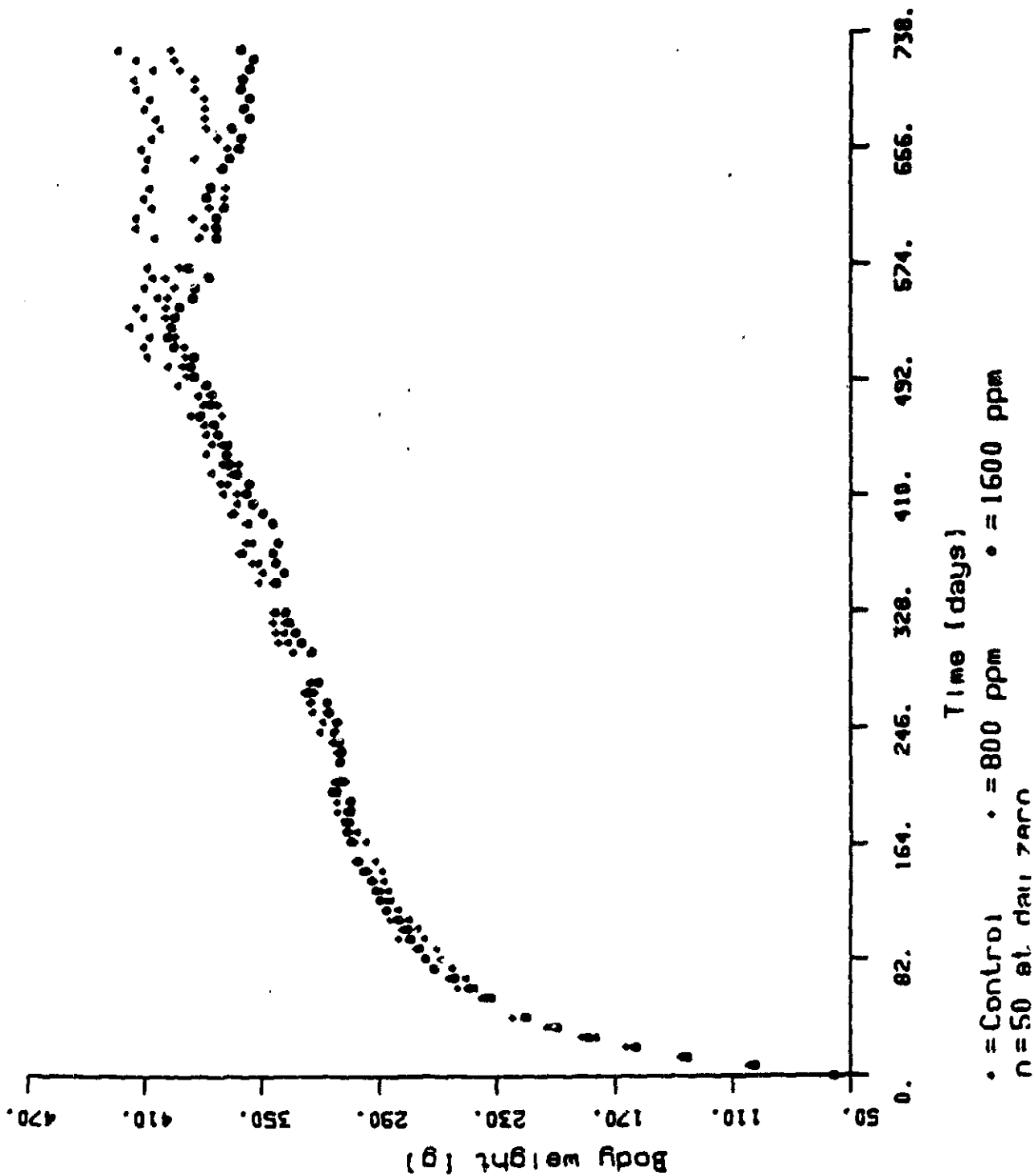


Fig. 2b CARCINOGENICITY STUDY WITH DM 14.190 IN RATS
Body weight of female rats (median) for high dose groups



000121

Fig. 4a. PROPORTION SURVIVING - MALE (Kaplan Meier)

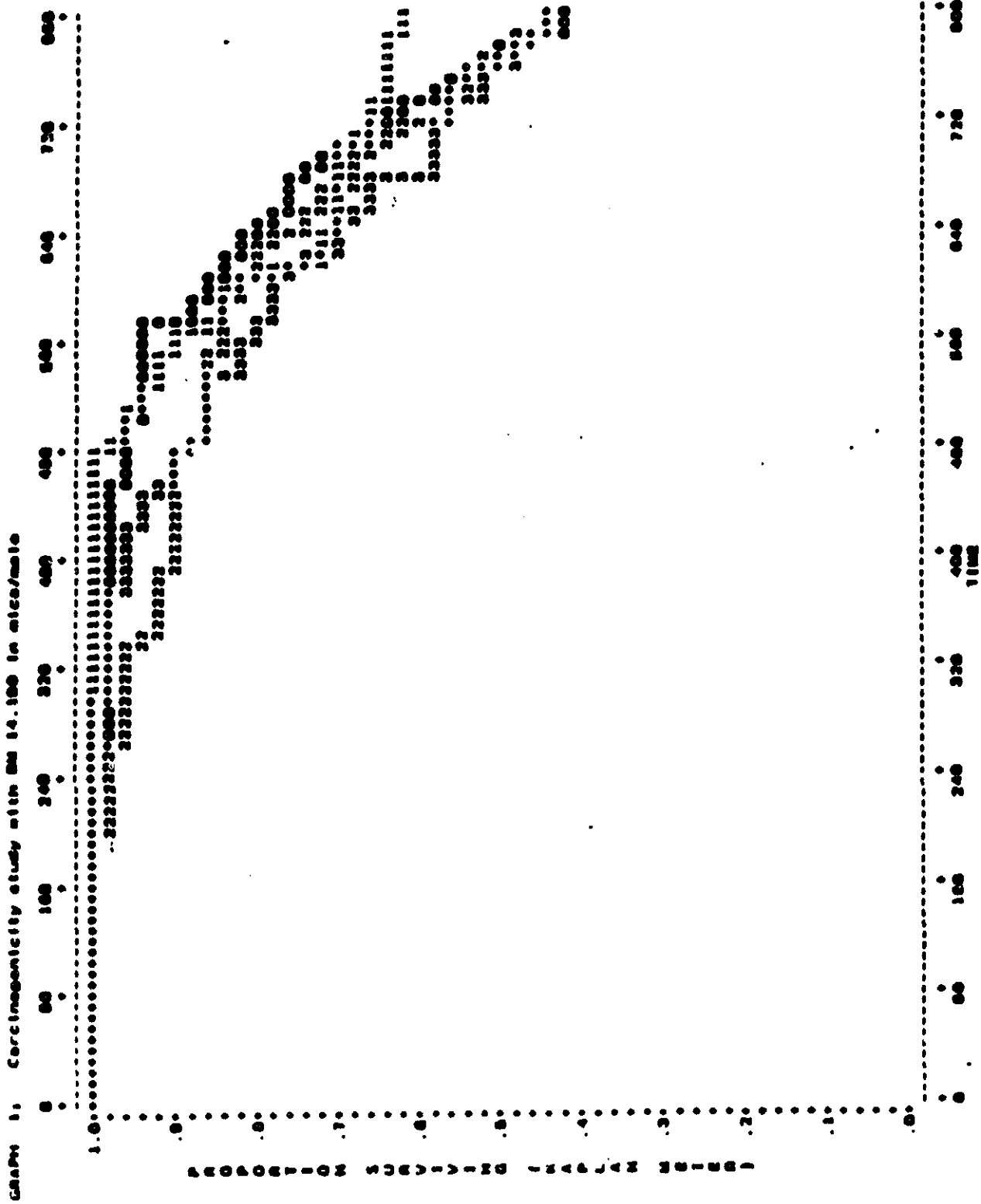


Fig. 5a. PROPORTION SURVIVING - FEMALE (Kaplan Meier)

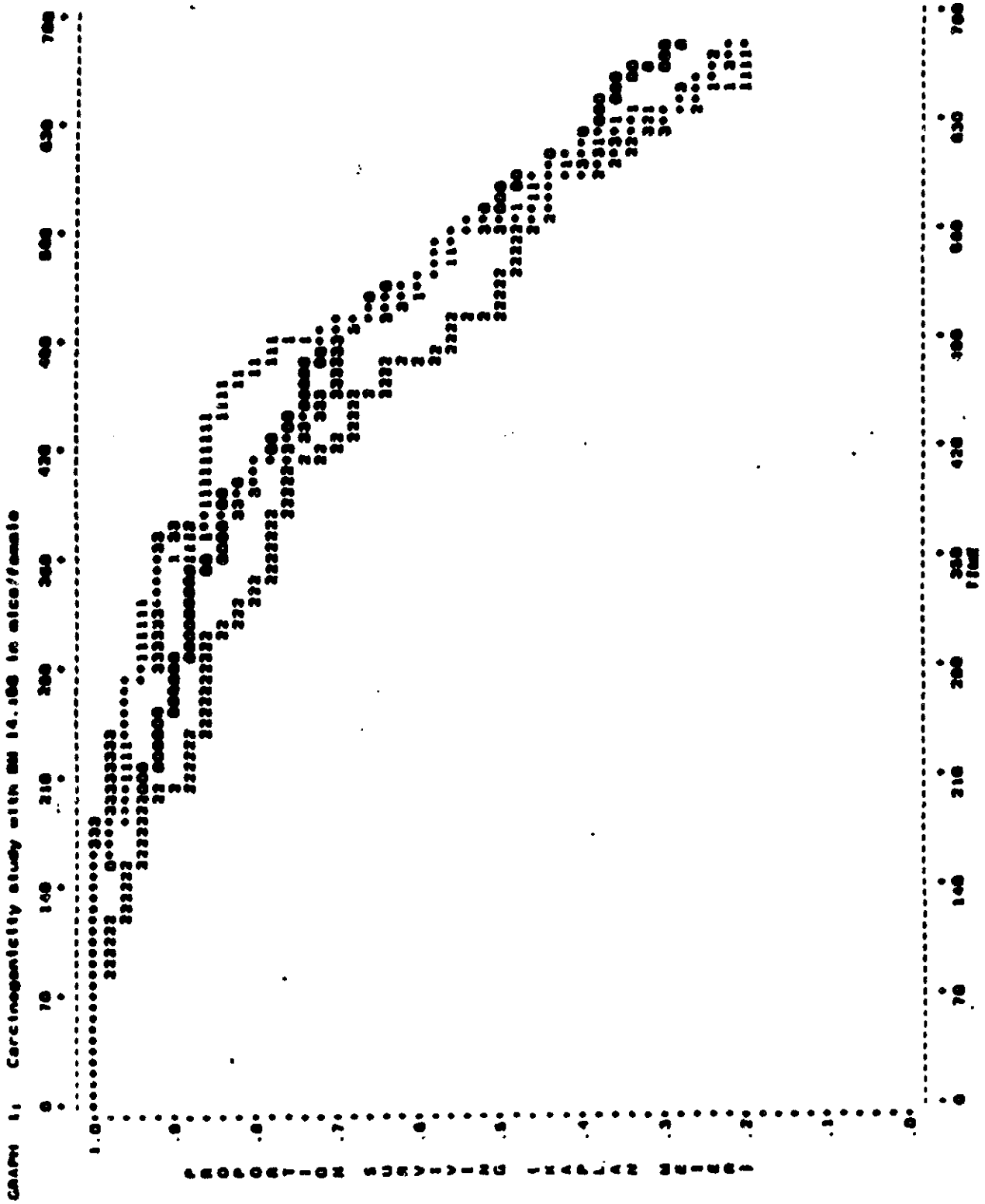
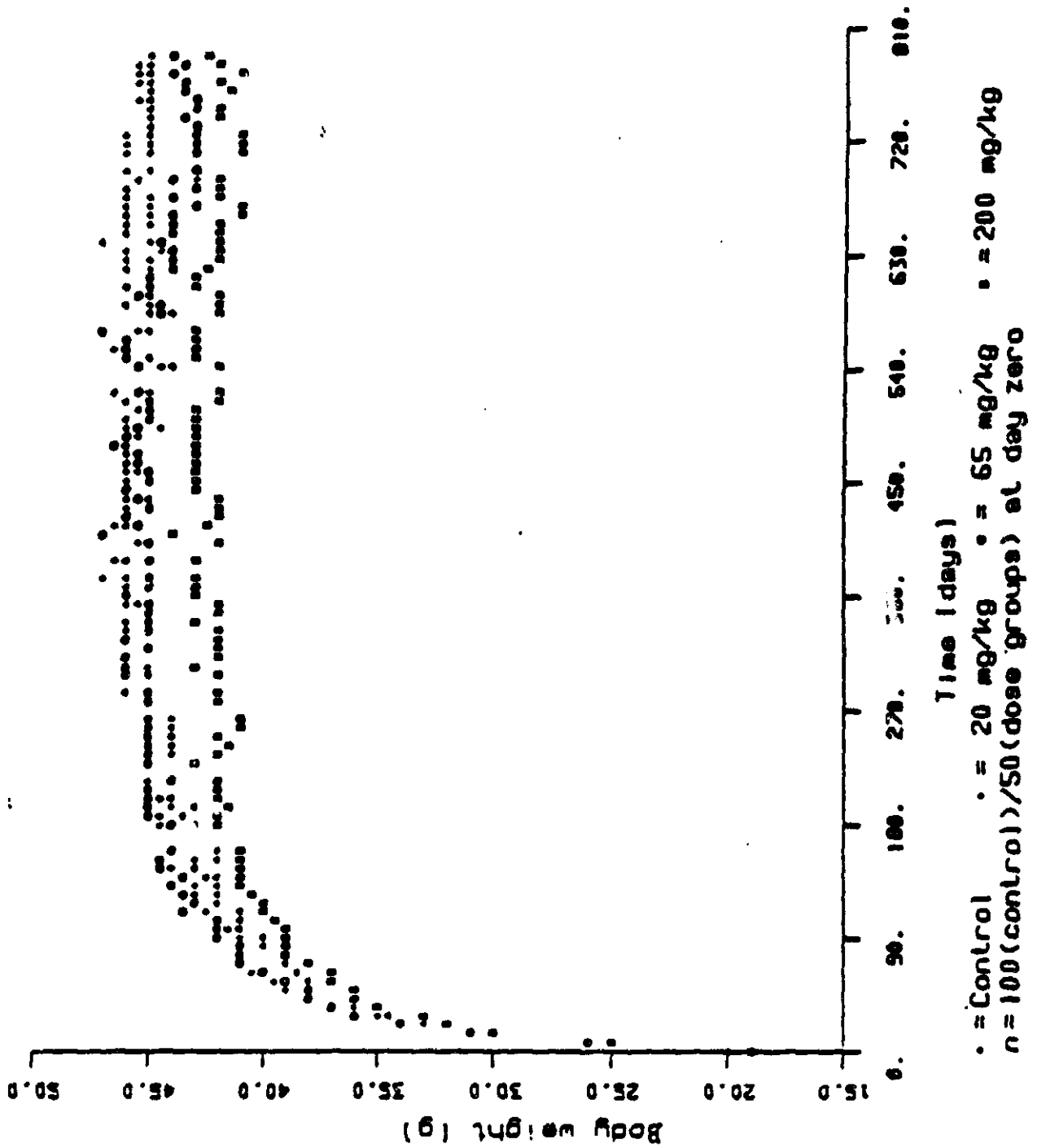


Figure 9

Fig. 1a. CARCINOGENICITY STUDY WITH CARVEDILOL IN MICE
Body weight of male mice (median)



000163

Fig. 1b. CARCINOGENICITY STUDY WITH CARVEDILOL IN MICE
Body weight of female mice (median)

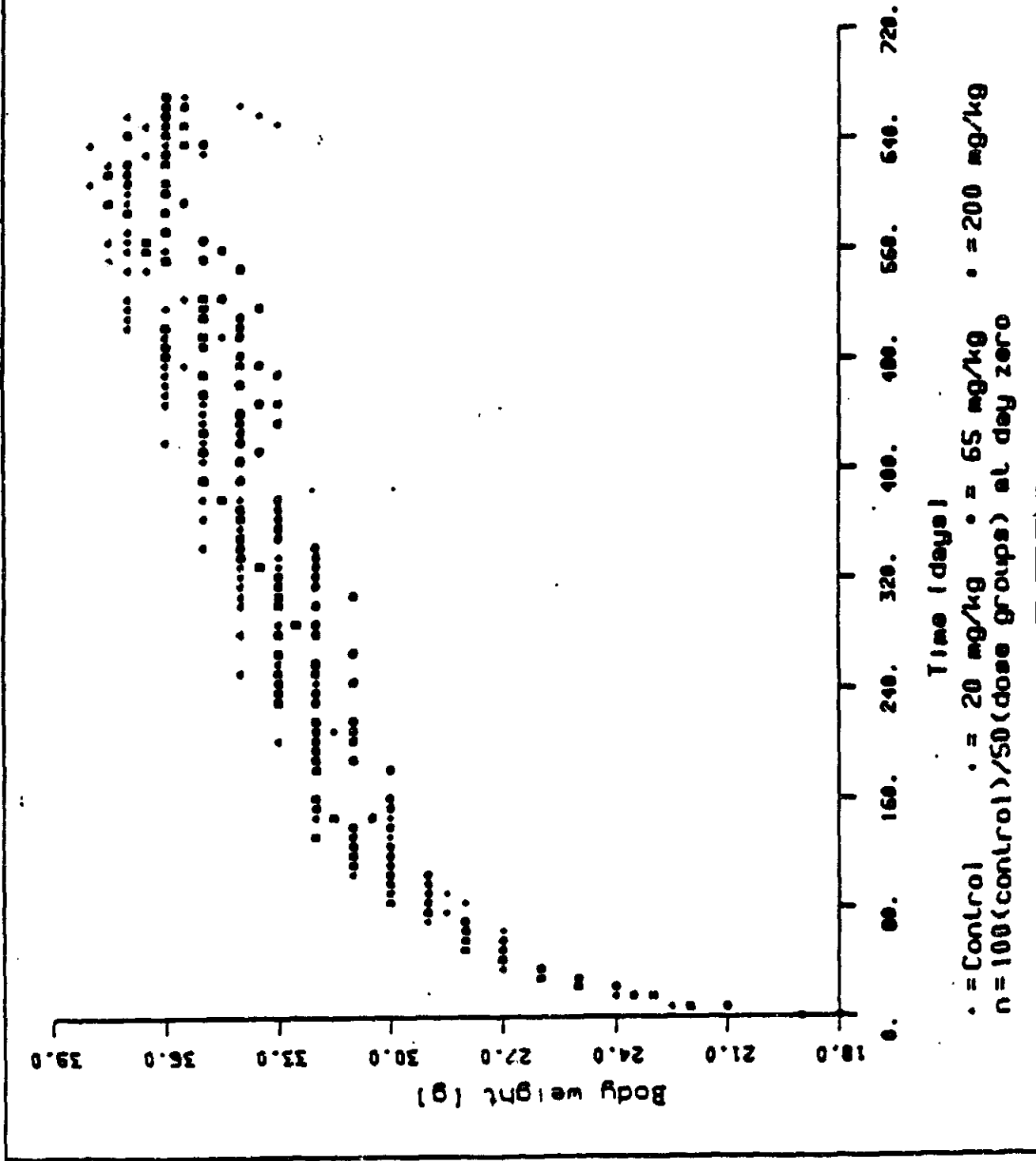


Table 1

Short title and project name		Page 18 Carcinogenicity Study with Carvedilol in Rats			J2 -107
Table 5: Drug intake per day of male and female rats in mg/kg body weight, grouped by time intervals. median; n = sample size (1st quartile; 3rd quartile)					
first day - last day	Group 2 200 ppm	Group 3 400 ppm	Group 4 800 ppm	Group 5 1600 ppm	
0 - 41 male	21.30;n=50 (20.05; 21.85)	40.80;n=50 (38.38; 42.33)	85.50;n=50 (83.40; 90.65)	169.30;n=50 (162.95;175.22)	
female	21.70;n=50 (20.13; 22.60)	43.00;n=50 (40.35; 45.63)	86.70;n=50 (81.48; 94.68)	165.30;n=50 (153.52;174.75)	
42 - 83 male	12.40;n=50 (11.95; 12.75)	24.90;n=50 (24.20; 25.88)	50.10;n=50 (48.38; 51.78)	98.40;n=50 (96.40;102.13)	
female	14.80;n=50 (14.00; 15.73)	30.50;n=50 (29.08; 32.18)	61.00;n=50 (57.78; 64.35)	121.00;n=50 (110.05;127.52)	
84 - 118 male	10.70;n=50 (10.45; 10.90)	21.60;n=50 (20.55; 22.05)	42.70;n=50 (41.38; 43.73)	85.60;n=50 (83.50; 88.25)	
female	13.40;n=50 (12.85; 14.00)	27.50;n=50 (26.43; 29.53)	51.10;n=50 (49.60; 54.65)	102.80;n=50 (96.18;113.00)	
119 - 181 male	10.10;n=50 (9.90; 10.33)	20.10;n=50 (19.38; 20.80)	39.10;n=50 (37.08; 40.10)	77.20;n=50 (75.30; 80.98)	
female	12.30;n=50 (11.68; 12.98)	24.60;n=50 (23.48; 25.38)	48.20;n=50 (46.65; 50.03)	93.40;n=50 (90.45; 96.80)	
182 - 279 male	9.60;n=50 (9.20; 9.83)	19.20;n=49 (18.20; 20.60)	37.80;n=49 (37.00; 39.00)	73.30;n=50 (68.68; 75.90)	
female	11.60;n=50 (11.40; 12.15)	23.50;n=50 (22.50; 24.30)	43.30;n=50 (41.53; 45.35)	84.30;n=50 (81.28; 89.38)	
280 - 426 male	8.30;n=47 (8.10; 8.60)	16.65;n=48 (16.13; 17.80)	31.80;n=46 (31.18; 33.80)	64.60;n=47 (60.30; 67.70)	
female	11.30;n=49 (10.80; 11.70)	21.70;n=50 (20.75; 22.85)	44.00;n=49 (41.20; 46.25)	90.70;n=50 (85.33; 92.33)	
427 - 727 male	7.70;n=37 (7.40; 8.35)	16.20;n=39 (15.00; 17.30)	31.40;n=39 (29.60; 34.00)	62.10;n=35 (59.00; 67.30)	
female	9.50;n=43 (8.90; 10.50)	18.80;n=45 (17.70; 19.95)	38.10;n=44 (35.20; 41.28)	74.70;n=43 (70.60; 81.40)	

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Table 1
BM 14.190

SURVEY OF TUMOR FREQUENCY IN MALE RATS

Dose	n	unscheduled killed or died	with tumors	without tumors	scheduled killed	with tumors	without tumors	total with tumors	total without tumors
Control I	50	32-64%	25-78%	7-21,8%	18-36%	16-88,9%	2-11,1%	41-82%	9-18%
Control II	50	26-52%	21-80,8%	5-19,2%	24-48%	16-66,7%	8-33,3%	37-74%	13-26%
200 ppm	50	35-70%	24-60,6%	11-31,4%	15-30%	9-60%	6-40%	33-66%	17-34%
400 ppm	50	35-70%	16-45,7%	19-54,3%	15-30%	8-53,3%	7-46,6%	24-48%	26-52%
800 ppm	50	39-78%	24-61,5%	15-38,5%	11-22%	8-72,7%	3-27,3%	32-64%	18-36%
1600 ppm	50	42-84%	14-33,3%	28-66,6%	8-16%	5-62,5%	3-37,5%	19-38%	31-62%

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 Start date and protocol number
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 J2

Table 2

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Table 2
BM 14.190

SURVEY OF TUMOR FREQUENCY IN FEMALE RATS

Dose	n	unscheduled killed or died	with tumors	without tumors	scheduled killed	with tumors	without tumors	total with tumors	total without tumors
Control I	50	27=54%	27=100%	-	23=46%	21=93,3%	2= 8,7%	48=96%	2= 4%
Control II	50	23=46%	23=100%	-	27=54%	26=96,3%	1= 3,7%	49=98%	1= 2%
200 ppm	50	27=54%	26=93,3%	1= 3,7%	23=46%	22=95,6%	1= 4,3%	48=96%	2= 4%
400 ppm	50	28=56%	28=100%	-	22=44%	21=95,4%	1= 4,5%	49=98%	1= 2%
800 ppm	50	26=52%	23=88,5%	3=11,5%	24=48%	22=91,6%	2= 8,3%	45=90%	5=10%
1600 ppm	50	21=42%	20=95,2%	1= 4,8%	29=58%	26=89,6%	3=10,3%	46=92%	4= 8%

Short term and project name
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Carcinogenicity-study with BM 14.190
J2 - 2

000032

TABLE 2

Table 4

Short title and protocol name		Page 23 Carcinogenicity Study with Carvedilol in Rats					J2 -112
Table 7: Frequencies of animals with tumors respective malignant tumors							
male rats							
Dosage	Group 1 Control 1	Control 2s	Group 2 200 ppm	Group 3 400 ppm	Group 4 800 ppm	Group 5 1600 ppm	
Number of animals with a tumor	41	37	33	24	32	19	
Number of animals with a malignant tumor	14	10	8	8	11	5	
female rats							
Dosage	Group 1 Control 1	Control 2s	Group 2 200 ppm	Group 3 400 ppm	Group 4 800 ppm	Group 5 1600 ppm	
Number of animals with a tumor	48	49	48	49	45	46	
Number of animals with a malignant tumor	17	22	14	9	7	11	
At begin of study there were 50 animals per dosage and sex.							
s. = Control 2 were the controls of a parallel study with another substance. Their results were not used for statistical comparisons in this study.							

Table 5

Table 8: Number of animals with tumors of the organs with the highest frequencies

male rats

Organs

Dosage Group	Pituitary	Urinary bladder	Pancreas	Skin + Subcutis	Thyroid
Control 1	17	8	8	11	6
Control 2s	17	9	10	11	4
200 ppm	15	8	5	8	2
400 ppm	7	3	5	7	5
800 ppm	14	2	3	11	2
1600 ppm	10	0	2	7	0

female rats

Organs

Dosage Group	Pituitary	Urinary bladder	Pancreas	Skin + Subcutis	Thyroid	Mamma. gland	Uteru
Control 1	41	0	3	3	1	35	7
Control 2s	36	3	3	2	2	41	6
200 ppm	31	0	2	2	6	37	5
400 ppm	29	0	0	2	2	36	5
800 ppm	35	0	0	0	4	30	5
1600 ppm	30	0	1	0	5	36	5

At begin of study there were 50 animals per dosage and sex.

§ = Control 2 were the controls of a parallel study with another substance. Their results were not used for statistical comparisons in this study.

Table 6
Intercurrent Mortality Rates
Male Rats

Weeks	Control			Low			Medium			High-1			High-2		
	S	D	%	S	D	%	S	D	%	S	D	%	S	D	%
0-50	50	0	0	50	1	2	50	2	4	50	3	6	50	2	4
51-80	50	7	14	49	10	20.4	48	14	29.1	47	10	21.3	48	16	33.3
81-105	43	25	58.1	39	24	61.5	34	17	50.0	37	26	70.3	32	24	75
Term.	18			15			17			11			8		

Female Rats

Weeks	Control			Low			Medium			High-1			High-2		
	S	D	%	S	D	%	S	D	%	S	D	%	S	D	%
0-50	50	1	2	50	1	2	50	0	0	50	1	2	50	0	0
51-80	49	2	4.1	49	7	14.3	50	7	14	49	7	14.3	50	8	16
81-105	47	24	51.1	42	19	45.2	43	21	48.8	42	18	42.8	42	13	30.9
Term.	23			23			22			24			29		

Notes: S: Number of animals starting during the period
D: Deaths
%: Percent of death during the period

Table 7
Tumor Incidence Rates
Male Rats, Stomach Papilloma

Weeks	Control		Low		Medium		High-1		High-2	
	T	N	T	N	T	N	T	N	T	N
0-50	0	0	0	1	0	2	0	3	0	2
51-80	0	7	0	10	0	14	0	10	0	16
81-105	0	25	0	24	0	17	0	26	0	24
terminal	0	18	0	15	0	17	1	11	1	8
Total	0	50	0	50	0	50	1	50	1	50

Table 8
Tumor Incidence Rates
Male Rats, Skin Subcutis Sebaceous Adenoma

Weeks	Control		Low		Medium		High-1		High-2	
	T	N	T	N	T	N	T	N	T	N
0-50	0	0	0	1	0	2	0	3	0	2
51-80	0	7	0	10	0	14	0	10	0	16
81-105	0	25	0	24	0	17	0	26	2	24
terminal	0	18	0	15	0	17	0	11	0	8
Total	0	50	0	50	0	50	0	50	2	50

Notes: T: Number of necropsies with the above tumor.
N: Number of necropsies.

Table 9
Tumor Incidence Rates
Male Rats, Liver Hepatocellular Adenoma

Weeks	Control		Low		Medium		High-1		High-2	
	T	N	T	N	T	N	T	N	T	N
0-50	0	0	0	1	0	2	0	3	0	2
51-80	0	7	0	10	0	14	0	10	0	16
81-105	0	25	0	24	0	17	2	26	0	24
terminal	0	18	2	15	1	17	1	11	2	8
Total	0	50	2	50	1	50	3	50	2	50

Notes: T: Number of necropsies with the above tumor.
N: Number of necropsies.

Table 10
Tumor Incidence Rates
Female Rats, Thyroid Gland Adenoma

Weeks	Control		Low		Medium		High-1		High-2	
	T	N	T	N	T	N	T	N	T	N
0-50	0	1	0	1	0	0	0	1	0	0
51-80	0	2	0	7	0	7	0	7	0	8
81-105	0	24	3	19	0	21	1	18	0	13
terminal	0	23	3	23	2	22	3	24	5	29
Total	0	50	6	50	2	50	4	50	5	50

Table 11
Tumor Incidence Rates
Female Rats, Brain Oligodendroglioma

Weeks	Control		Low		Medium		High-1		High-2	
	T	N	T	N	T	N	T	N	T	N
0-50	0	1	0	1	0	0	0	1	0	0
51-80	0	2	0	7	0	7	0	7	2	8
81-105	0	24	0	19	0	21	0	18	0	13
terminal	0	23	0	23	0	22	0	24	0	29
Total	0	50	0	50	0	50	0	50	2	50

Notes: T: Number of necropsies with the above tumor.
N: Number of necropsies.

Table 12

Short title and project name		Page 11 Carcinogenicity Study with Carvedilol in Rats					J2 -10
Table 1a: Difference of body weights of male rats in grams, grouped by time intervals.							
median 1st quartile; 3rd quartile n = sample size							
first day - last day	Group 1 Control 1	Control 2 [§]	Group 2 200 ppm	Group 3 400 ppm	Group 4 800 ppm	Group 5 1600 ppm	
0 - 41	171.25 162.0;181.6 n = 50	190.00 182.9;196.6 n = 50	174.50 169.9;184.6 n = 50	175.25 166.8;184.6 n = 50	175.50 167.0;181.5 n = 50	170.25 159.0;183.1 n = 50	
42 - 83	350.50 320.5;375.5 n = 50	348.75 333.3;368.9 n = 50	358.50 339.5;370.8 n = 50	351.50 331.8;376.3 n = 50	366.50 345.3;393.5 n = 50	356.50 331.0;379.5 n = 50	
84 - 118	393.50 358.5;422.0 n = 50	401.50 383.0;442.0 n = 50	401.50 381.0;417.8 n = 50	398.00 373.0;418.0 n = 50	417.50 [*] 387.0;444.3 n = 50	410.00 [*] 376.5;444.0 n = 50	
119 - 181	440.50 396.5;474.4 n = 50	444.50 421.4;490.4 n = 50	441.80 421.8;471.1 n = 50	437.30 404.5;471.9 n = 50	465.00 [*] 427.5;499.9 n = 50	457.30 417.8;494.1 n = 50	
182 - 279	481.50 438.3;522.8 n = 50	481.00 456.0;531.5 n = 49	484.50 467.5;516.5 n = 50	476.00 450.5;528.0 n = 49	510.00 473.5;547.0 n = 49	494.00 451.5;542.0 n = 50	
280 - 426	546.50 505.3;584.0 n = 49	553.00 515.5;602.0 n = 47	553.00 517.5;577.9 n = 48	540.50 507.0;612.8 n = 48	583.50 521.5;619.0 n = 47	551.50 505.0;609.6 n = 48	
427 - 727	568.00 538.0;612.0 n = 37	584.50 552.0;633.0 n = 40	598.00 546.8;626.8 n = 33	592.50 555.4;645.4 n = 32	595.50 547.3;632.8 n = 32	576.50 538.0;633.1 n = 28	
1 = Kruskal-Wallis-Test: no significance, alpha = 0.05 1+ = Kruskal-Wallis-Test: significance, alpha = 0.05 * = Mann-Whitney-Test: significantly different from group 1, alpha = 0.05 § = Control 2 were the controls of a parallel study with another substance. Their results were not used for statistical comparisons in this study.							

Table 13

Short title and project name		Page 12 Carcinogenicity Study with Carvedilol in Rats					J2 -10
Table 1b: Difference of body weights of female rats in grams, grouped by time intervals.							
Median 1st quartile; 3rd quartile n = sample size							
First day - Last day	Group 1 Control 1	Control 2 ³	Group 2 200 ppm	Group 3 400 ppm	Group 4 800 ppm	Group 5 1600 ppm	
0 - 41	110.25 102.0;123.5 n = 50	110.50 102.6;114.3 n = 50	113.25 106.9;119.0 n = 50	108.75 103.9;117.8 n = 50	118.00 107.9;123.8 n = 50	114.25 106.3;119.5 n = 50	
42 - 83	187.50 177.8;206.3 n = 50	190.00 179.9;202.6 n = 50	190.50 178.0;209.5 n = 50	188.50 175.8;205.0 n = 50	196.00 181.8;214.5 n = 50	195.50 184.8;207.3 n = 50	
84 - 118	211.00 196.8;235.0 n = 50	218.00 204.8;232.3 n = 50	216.00 202.0;236.8 n = 50	215.00 198.0;231.3 n = 50	219.50 203.0;241.0 n = 50	218.00 207.0;232.5 n = 50	
119 - 181	231.25 216.3;257.0 n = 50	237.00 226.8;252.9 n = 50	236.50 219.4;261.3 n = 50	229.50 214.0;254.8 n = 50	237.25 221.4;258.1 n = 50	240.50 228.9;254.1 n = 50	
182 - 279	254.50 233.8;287.8 n = 50	258.50 245.8;278.0 n = 50	258.50 240.5;287.3 n = 50	251.50 236.0;281.5 n = 50	255.50 233.8;271.3 n = 50	253.00 ~~242.2;288.5~~ n = 50	
280 - 426	293.50 266.5;338.0 n = 49	314.00 277.6;337.8 n = 50	311.00 273.5;347.3 n = 49	293.75 270.8;351.4 n = 50	292.50 262.5;318.8 n = 49	286.25 270.9;305.9 n = 50	
427 - 727	344.00 298.4;389.1 n = 40	362.00 319.5;396.0 n = 43	348.50 326.0;413.0 n = 39	352.75 307.8;425.9 n = 38	318.00 289.0;379.0 n = 39	318.00 293.5;349.5 n = 39	
1 = Kruskal-Wallis-Test: no significance, alpha = 0.05 1+ = Kruskal-Wallis-Test: significance, alpha = 0.05 3 = Control 2 were the controls of a parallel study with another substance. Their results were not used for statistical comparisons in this study.							

Table 14

Short title and project name		Page 13 Carcinogenicity Study with Carvedilol in Rats					J2 -10
Table 2a: Food consumption of male rats in grams per day, grouped by time interval							
median 1st quartile; 3rd quartile n = sample size							
first day - last day	Group 1 Control 1	Control 2 [§]	Group 2 200 ppm	Group 3 400 ppm	Group 4 800 ppm	Group 5 1600 ppm	
0 - 41	26.80 26.3; 28.5 n = 50	26.00 25.3; 26.6 n = 50	26.00 ¹ 25.2; 27.5 n = 50	25.30 ² 24.5; 27.5 n = 50	27.50 25.3; 29.1 n = 50	26.00 ³ 24.7; 27.0 n = 50	
42 - 83	26.50 25.0; 28.3 n = 50	26.30 24.5; 28.0 n = 50	26.00 24.5; 27.6 n = 50	25.80 25.2; 27.5 n = 50	27.00 25.0; 29.0 n = 50	26.50 25.5; 27.0 n = 50	
84 - 118	25.10 23.3; 26.6 n = 50	26.10 24.5; 26.8 n = 50	24.40 23.5; 26.3 n = 50	24.30 23.3; 25.7 n = 50	25.50 23.8; 26.9 n = 50	25.10 24.1; 26.5 n = 50	
119 - 181	25.50 23.7; 27.2 n = 50	25.10 23.8; 26.7 n = 50	24.90 24.1; 25.7 n = 50	24.30 24.0; 25.9 n = 50	24.90 23.7; 26.9 n = 50	25.00 24.1; 26.3 n = 50	
182 - 279	26.60 25.0; 27.8 n = 50	25.30 24.3; 26.7 n = 49	25.90 25.2; 27.0 n = 50	26.00 25.2; 28.0 n = 49	27.30 25.0; 28.9 n = 49	25.40 ² 24.8; 26.7 n = 50	
280 - 426	26.40 24.5; 27.5 n = 48	25.50 24.8; 27.8 n = 47	26.00 25.3; 27.0 n = 47	25.80 24.8; 26.8 n = 48	26.00 24.9; 28.0 n = 46	25.30 24.0; 26.0 n = 47	
427 - 727	26.10 23.4; 27.3 n = 45	24.90 23.3; 25.9 n = 45	25.80 25.0; 26.8 n = 37	25.80 25.0; 27.8 n = 39	26.50 25.3; 27.8 n = 39	25.30 24.0; 27.2 n = 35	
¹ = Kruskal-Wallis-Test: no significance, alpha = 0.05 ² = Kruskal-Wallis-Test: significance, alpha = 0.05 ³ = Mann-Whitney-Test: significantly different from group 1, alpha = 0.05 [§] = Control 2 were the controls of a parallel study with another substance. Their results were not used for statistical comparisons in this study.							

Table 15

E	Short title and project name	J2 - 1
	Page 14 Carcinogenicity Study with Carvedilol in Rats	

Table 2b: Food consumption of female rats in grams per day, grouped by time inter

First day - last day	median 1st quartile; 3rd quartile n = sample size					
	Group 1 Control 1	Control 2s	Group 2 200 ppm	Group 3 400 ppm	Group 4 800 ppm	Group 5 1600 ppm
0 - 41	18.80 18.0; 20.3 n = 50	20.00 18.7; 20.4 n = 50	18.50 17.7; 19.6 n = 50	18.30 17.7; 19.5 n = 50	19.30 18.6; 20.4 n = 50	18.00 [*] 17.5; 19. n = 50
42 - 83	19.80 18.5; 21.5 n = 50	19.00 18.5; 21.1 n = 50	19.30 18.2; 20.1 n = 50	19.30 18.0; 20.4 n = 50	19.30 19.0; 19.9 n = 50	18.80 [*] 17.8; 19. n = 50
84 - 118	19.50 18.3; 20.6 n = 50	19.10 18.3; 20.4 n = 50	18.90 [*] 18.0; 19.3 n = 50	19.10 18.3; 19.8 n = 50	18.50 [*] 17.9; 19.4 n = 50	18.10 [*] 17.2; 19. n = 50
119 - 181	19.00 18.0; 20.3 n = 50	19.60 18.6; 20.5 n = 50	18.00 [*] 17.0; 19.2 n = 50	18.30 [*] 17.0; 18.8 n = 50	18.30 [*] 17.3; 18.9 n = 50	17.80 [*] 17.1; 18. n = 50
182 - 279	18.90 18.1; 20.6 n = 50	18.80 18.0; 19.9 n = 50	19.10 18.1; 19.8 n = 50	18.40 [*] 17.5; 19.5 n = 50	17.00 [*] 16.5; 17.4 n = 50	16.80 [*] 16.2; 17. n = 50
280 - 426	19.80 18.8; 21.5 n = 49	19.00 18.5; 20.5 n = 50	20.50 [*] 19.8; 21.3 n = 49	20.00 19.0; 21.8 n = 50	19.00 [*] 18.3; 20.3 n = 49	19.30 18.5; 20. n = 50
427 - 727	19.60 18.6; 20.6 n = 47	20.00 19.0; 21.1 n = 46	20.50 [*] 19.1; 21.5 n = 43	20.10 18.4; 21.3 n = 45	18.75 [*] 17.6; 19.5 n = 44	18.80 [*] 17.3; 20. n = 43

- 1 = Kruskal-Wallis-Test: no significance, alpha = 0.05
 1* = Kruskal-Wallis-Test: significance, alpha = 0.05
 ° = Mann-Whitney-Test: significantly different from group 1, alpha = 0.05
 s = Control 2 were the controls of a parallel study with another substance.
 Their results were not used for statistical comparisons in this study.

The following summary tables were submitted by sponsor. Table 24 shows that in fetuses from dams sacrificed on day 22 of pregnancy (caesarean group), variations occurred in all groups; these variations were not dose-dependent. As for skeletal abnormalities, these were also found in all treated groups, except for malformations of the 13th rib which occurred at the MD and HD. Sponsor considered that 13th-rib malformations as spontaneous malformations "which also occurred with varying frequency in the control group." Sponsor does not consider that these findings are teratogenic because in the rat teratology study (see below review by previous pharmacologist N. Winbury, Ph.D.), there was no indication of an increase in these anomalies, even the same doses tested in the fertility and general reproduction study.

Table 24

VISCERAL AND SKELETAL ABNORMALITIES
IN CAESAREAN FETUSES/DAM

F0-generation, caesarean group -

Median (1st and 3rd quartiles in case of
statistical evaluation)

	Group 1 Control	Group 2 12 mg/kg	Group 3 60 mg/kg	Group 4 300 mg/kg	stat. test
VISCERAL ABNORMALITIES	n=9	n=9	n=11	n=6	-
Retardations x 100 no. fetuses examined	0.0	0.0	0.0	0.0	-
Variations x 100 no. fetuses examined	11.1 0.0;33.0	12.2 0.0;66.6	0.0 0.0;16.3	0.0 0.0;3.6	2
Malformations x 100 no. fetuses examined	0.0	0.0	0.0	0.0	-
SKELETAL ABNORMALITIES	n=9	n=9	n=11	n=6	
Retardations x 100 no. fetuses examined	77.0 69.3;85.7	28.6 20.0;76.6	62.3 50.0;65.7	83.3 55.7;100.0	2
Variations x 100 no. fetuses examined	18.7 0.0;33.0	25.0 5.0;63.9	16.3 0.0;25.0	28.3 0.0;32.9	2
Malformations x 100 no. fetuses examined	0.0 0.0;0.0	0.0 0.0;0.0	0.0 * 0.0;26.6	30.0 * 12.5;64.7	2-

1 = Jonckheere-Test: no significance (alpha = 0.05)

2 = Jonckheere-Test: significance (alpha = 0.05)

* = Wilcoxon-U-Test: significantly different from group 1 (alpha = 0.05)

- = no statistical test was performed

Sponsor provided the following tables (25a and b below) showing the frequency of visceral and skeletal abnormalities found in the fetuses of the F₀ dams on day 22 of pregnancy.

Table 25a FREQUENCIES OF VISCERAL ABNORMALITIES IN CAESAREAN FETUSES

	Group 1 Control	Group 2 12 mg/kg	Group 3 60 mg/kg	Group 4 300 mg/kg
Nb. Fetuses examined	68	62	74	33
Viscerations (V)				
RPU syndrome	0	14	11	1
Thyroid enlarged	1	1	0	0
Thyroid enlarged	4	0	0	1
Thyroid and thyroid enlarged	1	0	0	0
RPU-syndrome and thyroid enl.	1	0	0	0

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Table 25b

FREQUENCIES OF SKELETAL ABNORMALITIES IN CAESAREAN FETUSES

	Group 1 Control	Group 2 12 mg/kg	Group 3 60 mg/kg	Group 4 300 mg/kg
Nb. Fetuses examined	66	62	73	33
Retardations (R)				
Stavrus	2	3	3	2
Hiraklinus	3	6	8	2
Paralimus	6	4	11	2
Thoracic vertebral centers	4	2	2	0
Cervical vertebral centers	1	0	0	0
Center of hyoid bone	1	0	0	0
More than one bone retarded	18	6	10	9
Viscerations (V)				
Stavrus	2	3	1	1
Scapula	2	3	1	0
Ribs	0	2	1	0
Malformations (M)				
Ribs	0	0	3	1
Combinations				
R + V	0	6	4	4
R + M	1	1	6	4
R + V + M	0	0	3	1
V + M	0	0	1	2
O + R	0	0	1	0

NB- RPU (Dilated renal pelvis and/or ureter.)

For further clarification of type of skeletal anomalies reported above as found in the fetuses of the F₀ dams, the following table submitted by the sponsor is provided below.

SKELETAL ANOMALITIES ("COMBINATIONS") IN CAESAREAN FETUSES			
Group 1 Control	Group 2 12 mg/kg	Group 3 60 mg/kg	Group 4 300 mg/kg
Skf phalange (fingers) partly ossified; thumb distal phalanx un- ossified (bilat.); sternura VI asym- -etric Skf IV I unossified (bilat.); cervical rib (bilat.); sternura IV asymmetric; sternura V unossified Skf IV I unossified (bilat.); 12th thorac- al vertebral center absent; rudimentary rib (right) Skf bilat.; 12th thorac- al vertebral center absent; sternura VI asymmetric Skf IV I unossified (bilat.); sternura IV and V asymmetric; sternura VI asym- -metric; stapes asymmetric (bilat.) Skf IV I unossified (right); thumb: distal phalanx unossified (bilat.); stapes asym- -metric (left); center of hyoid bone un- ossified; interparietal bone partly ossified	Skf IV I unossified (right); stapes asymmetric (bilat.) Skf IV I unossified (right) stapes asymmetric (bilat.) Skf thumb: distal phalanx unossified (left); sternura VI asym- -etric Skf IV I unossid ed (bilat.); sternura VI asymmetric Skf sternura IV and VI asymmetric; stapes asymmetric (left) Skf stapes asymmetric (right); 12th thorac- al vertebral center absent Skf sternura IV and VI asymmetric; 12th rib short (right)	Skf IV I unossified (bilat.); thumb: distal phalanx unossified (bilat.); sternura VI asymmetric Skf IV I unossified (bilat.); thumb: distal phalanx unossified (bilat.); sternura VI asymmetric; center of hyoid bone, inter- parietal bone and stapylal ossus partly ossified Skf thumb: distal phalanx unossified (right); rudimentary rib (bilat.) Skf thumb: distal phalanx unossified (left); sternura VI asym. Skf 12th thoracal vertebral center absent; 12th rib short (bilat.); sternura IV asymmetric Skf IV I unossified (right); 12th rib short (bilat.) Skf IV I unossif. (bilat.); 12th thoracal vertebral center fragmented Skf 12th rib missing (left); sternura V unossified	Skf stapes asymmetric (bilat.); sternura IV and VI asymmetric Skf IV I unossified (bilat.) sternura VI asymmetric Skf IV I unossified (bilat.); sternura asymmetric Skf IV I unossified (bilat.); sternura asymmetric Skf bilat.; sternura asymmetric Skf 12th rib short (right); sternura V unossified Skf IV I unossified (bilat.); thumb: distal phalanx unossified (bilat.); 12th thoracal vertebral center absent; 12th rib short (bilat.) Skf IV I unossified (bilat.); 12th rib missing (left) Skf 12th rib short (left); center right; focus with 3 lumbar vertebrae; sternura V unossified Skf Cervical rib (bilat.); 12th rib short (bilat.); focus with 3 lumbar vertebrae; sternura V unossified

SKELETAL ANOMALITIES ("COMBINATIONS") IN CAESAREAN FETUSES (CONT'D.)			
Group 1 Control	Group 2 12 mg/kg	Group 3 60 mg/kg	Group 4 300 mg/kg
Skf IV I unossified (bilat.); phalange (fingers) partly ossified; thumb distal phalanx unossified (bilat.); 12th thoracal vertebral center absent; sternura IV asym.; sternura V unossified (left); inter- parietal bone partly ossified Skf phalange (fingers) partly ossified; thumb: distal phalanx unossif. (bilat.); 12th thoracal vertebral center absent; sternura VI asym.; phalange (thumb) partly ossified Skf thumb: distal phalanx unossified (bilat.); 12th rib short (bilat.); sternura VI asymmetric; center of hyoid bone partly ossified Skf IV I unossified (bilat.); 12th rib short (bilat.); sternura VI asymmetric; center of hyoid bone partly ossified Skf IV I unossified (right); 12th rib short (bilat.); sternura VI asymmetric Skf phalange (fingers): partly ossified; thumb: distal phalanx unossif. (bilat.); 12th rib short (bilat.); sternura V unossified, VI asym. 12th rib short (right); sternura VI asymmetric Skf phalange (thumb) partly ossified; thumb: distal phalanx unossified (bilat.); very ribs (right); interparietal bone partly ossified		Skf thumb: distal phalanx unossified (bilat.); phalange (fingers) partly ossified; 12th thoracal vertebral center absent; 12th rib short (right) Skf IV I unossif. (bilat.); thumb: distal phalanx unossif. (bilat.); 12th rib short (bilat.); focus with 3 lumbar vertebrae; sternura V unossified, VI asym.; center of hyoid bone partly ossified Skf IV I unossified (bilat.); 12th rib short (bilat.); sternura VI asymmetric; center of hyoid bone partly ossified Skf IV I unossified (right); 12th rib short (bilat.); sternura VI asymmetric	Skf 12th rib short (bilat.); sternura VI asymmetric Skf 12th rib short (left); sternura VI asymmetric

When F₀ dams were allowed to litter, although there were no external malformations reported, there were a small number of visceral variations and skeletal retardations and malformations reported (Tables 26a and b below). However, none of these histopathologic findings in F₁ animals were dose-related.

Table 26a FREQUENCIES OF VISCERAL ABNORMALITIES IN RAISED F₁-ANIMALS

	Group 1 Control	Group 2 12 mg/kg	Group 3 60 mg/kg	Group 4 300 mg/kg
No. fetuses examined	168	99	142	28
Variations (V)				
Thyroid enlarged	15	3	11	1
Truncus brachiocephalic, short or missing	2	2	3	0
APU syndrome	1	3	3	0
APU syndrome; truncus brachiocephalic short	0	0	1	0
Malformations (M)				
retarded testicle descent;	1	0	0	0
additional liver lobe	1	0	0	0
additional liver lobe situm liverum	0	2	0	0
hypoplasia of left kidney with hyperplasia of right kidney	0	1	0	0

Table 26b SKELETAL ABNORMALITIES IN PREMATURELY SIZED PUPS OF F₁-GENERATION

	Group 1 Control	Group 2 12 mg/kg	Group 3 60 mg/kg	Group 4 300 mg/kg
No. fetuses examined (F ₁)	5	3	4	13
Retardations (R)				
MT I unossified	1	0	0	0
more than one bone with retarded ossification	0	1	0	1
thoracic vertebral centers retarded	0	0	0	2
Variations (V)				
scapula asymmetric	1	0	0	1
sternum asymmetric	0	1	0	2
Combinations				
R + V	0	1	0	1
R + M	0	0	0	2
Explanation of Combinations:				
Group 2, 11A/11	asymmetric scapula + notched thoracic vertebral centers + asymmetric sternal center			
Group 4, 10B/10	asymmetric scapula + sternal center No. V unossified			
323/ 2	13th rib short (unilateral) + only 3 lumbar vertebrae + sternal center No. IV asymmetric			
323/ 3	13th rib short (bilateral) + sternal center No. V unossified			
MT = metatarsal bone				

The offspring of F₁ generation (that is F₂ generation), showed a small number of abnormalities. Tables 27a and 27b below were provided by sponsor and show the actual number of visceral and skeletal changes in the animals examined. No dose-relation was found in small number of changes reported, but there were only 8 HD pups available.

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Table 27a FREQUENCIES OF VISCERAL ABNORMALITIES IN F ₂ -PUPS					
	Group 1 Control n = 135	Group 2 12 mg/kg n = 104	Group 3 60 mg/kg n = 103	Group 4 300 mg/kg n = 8	
APU-syndrom	1	0	9	0	
thymus enlarged	3	0	3	0	
hydrometra	0	1	0	0	
transverse bronchospasmodic short	0	0	1	0	
unionition of right A. subclavia	0	1	0	0	

FEDERAL BUREAU OF INVESTIGATION DEPARTMENT OF JUSTICE WASHINGTON, D. C.		N4 -113			
Table 27b FREQUENCIES OF SKELETAL ABNORMALITIES IN PRENATALLY DIED F ₂ -PUPS					
	Group 1 Control	Group 2 12 mg/kg	Group 3 60 mg/kg	Group 4 300 mg/kg	
No. fetuses examined	10	15	15	0	
Retardations (R)					
thoracal vertebral centers retarded	0	1	1	0	
sternum unossified	0	1	0	0	
more than one bone retarded	0	3	1	0	
Violations (V)					
sternum asymmetric	1	0	1	0	
Malformations (M)					
thoracal vertebral fragmented centers	1	0	0	0	
ribs thickened	0	1	0	0	
multiple malformations	1	0	0	0	
Combinations					
R + D	0	1	0	0	
V + M	0	1	0	0	
R + V	0	0	1	0	

Explanation of Combinations:

Group 2, 117/11 unossified anlagen (phalanges, metacarpal and metatarsal bone, cervical vertebral centers, sternal centers) hyoid bone and calvaria poorly ossified, wavy ribs bilateral

119/ 4 9th and 11th thoracal vertebral centers fragmented; sternum VI retarded

Group 3, 201/12 sternum VI asymmetric; parietal bone poorly ossified

Data provided indicate that the HD (300 mg/kg/day oral carvedilol) reduced fertility in the parental generation, caused high post-natal mortality in the F₁-generation and some delay in some parameters of the physical/mental development of surviving offspring. A remarkable finding was hair loss in some HD rats.

Teratology Studies in Rats and Rabbits:

The following 2 reviews/evaluations of rat oral teratology studies (Seg. II) with carvedilol were prepared by previous pharmacologist M. Winbury, Ph.D. when submitted to the IND, and have received a secondary review by C. Resnick, Ph.D.

Report No. K 1. Reproduction Toxicology Study (Teratogenicity) with BM 14,190 in Rats. Drug Administration per os. (Boehringer

Mannheim, Germany; Report dated Nov. 8, 1982, vol. 1.7, p. 06 001454; Study Director's statement of compliance with GLP dated Nov. 8, 1982, p. 06 001502; Quality Assurance Unit Statement of Compliance dated Jan. 24, 1983, p. 06 001501)

Report No. K 2. Reproductive Toxicology Study (Teratogenicity) with BM 14,190 in Rabbits. Drug Administration per os. (Boehringer Mannheim, Germany; Report dated Nov. 29, 1982, vol. 1.7, p 06 001503; Study Director's statement of compliance with GLP dated Nov. 29, 1982, p. 06 001547; Quality Assurance Unit Statement of Compliance dated Jan. 24, 1983, p. 06 001546)

Report No. K 1: Oral Teratology Study - Rat:

Species/Strain: Rat/Sprague-Dawley.

Study Dates: July 1 to July 29, 1980.

Test Substance: Micronized Carvedilol, batch No. 812755 A, suspended in 1% methylcellulose; prepared fresh daily. A suspension of 200 mg in 10 ml MC was stable for 4 hrs.

Route/Schedule of Administration: Oral by gavage on days 7 through 16 of pregnancy. Day sperm detected in vaginal smear = day 1.

Doses: 0 (methylcellulose), 12, 60 and 300 mg/kg/day. Each dose was administered in a volume of 10 ml/kg.

Rationale For Doses: Based on results of 3 experiments in non-pregnant female rats and 1 experiment in pregnant rats 300 mg/kg was expected to cause adverse but tolerated maternal effects. The 12 mg/kg dose was selected as a low multiple of a pharmacodynamically active dose (in SH rats 3.5 mg/kg, p.o., reduced blood pressure 30 mmHg). The mid-dose was selected as a high multiple of the pharmacodynamic dose but probably a non-toxic dose.

Number of Animals: 112 mated females divided into 28/dose group. In the control, low-, mid-, and high-dose groups, 2, 4, 3 and 5 rats, respectively, were not pregnant and 1 high-dose rat died. Therefore, 26 control, 24 low-dose, 25 mid-dose and 22 high-dose rats reached study termination.

Caesarean Section: Day 22.

(Cont'd. Rat Teratology-MWinbury's review)

Results: Maternal Effects: Mortalities: 1 high-dose Day 17. Body weight (Days 1, 6, 17 & 22): High-dose dams not only failed to gain weight during drug administration they in fact lost weight; from day 16 to 22 (i.e. after drug administration) they gained significantly less weight (about 1/2) than controls. During drug administration the low- and mid-dose groups tended to gain more weight than controls; this was statistically significant for only the mid-dose group. Clinical Signs of Toxicity: There was a dose-related increase in the incidence of hair loss (1/26 control, 4/24 low-dose, 9/25 mid-dose, and 15/22 high-dose), sedation (14/22 mid-dose, 22/22 high-dose) and blood covered eye (1 mid-dose), nose (6 high-dose) and/or vulva (1 high-dose). Implantation Sites: There was no differences between groups in the median number of

implantation sites/dam. Resorptions: The median number of resorptions as a % of implantation sites was significantly higher in the 300 mg/kg group than controls. In fact, there was 100% resorptions in 9 out of 22 dams; all were early resorptions in 7 dams, late in 1 dam, and both early and late in 1 dam. Thus, certain observations refer to 13, not 22, animals. Uterine Weight both full and empty was reduced in the high-dose group. Fetal Effects. Dead Fetuses: There were no dead fetuses in any of the treatment groups. Relative to the control group the following differences were seen in the 300 mg/kg group: decreased median number of live fetuses (as a % of implantation sites), median Fetal Weight/Dam, and median Placental Weight/Dam; increased median number of Skeletal Retardations/Dam (due to retardations in the paws). The low- and mid-doses had no apparent effect on these parameters and none of the doses of carvedilol affected the Sex Ratio of fetuses, caused Visceral Abnormalities (variations or malformations) or Skeletal Variations and/or malformations.

Conclusion: Carvedilol, 12, 60 or 300 mg/kg/day (suspended in 1% methylcellulose), was administered orally to pregnant Sprague-Dawley rats on days 7 through 16 of pregnancy. None of the doses were teratogenic and the 12 and 60 mg/kg/day doses were also not embryotoxic or fetotoxic. While 12 mg/kg/day had no clear maternal effects it is about 4 times the dose shown to lower blood pressure in hypertensive rats. The 60 mg/kg/day dose caused sedation in the dams and the 300 mg/kg/day dose was clearly toxic to the dams (causing death of one animal and weight loss in the others) and was also embryotoxic, fetotoxic and retarded skeletal growth of the paws. The fetal effects of the high-dose could be related to maternal effects.

The following is the review by previous pharmacologist of rabbit Seg. II study which has been also reviewed by C. Resnick and found adequate.

Report No. K 2: Oral Teratology Study - Rabbit:

Species/Strain: Himalaya rabbits/Chhb:HI

Study Dates: Sept. 23, 1980 to Oct. 29, 1980

Test Substance: Micronized carvedilol, batch No. 812 755A, suspended in 1% methylcellulose. Prepared fresh daily. A suspension of 200 mg in 10 ml MC was stable for 4 hours.

Route/Schedule of Administration: Oral by gavage on day 7 to 19 of pregnancy. Day 1 was the day of artificial insemination.

Doses: 0 (1% methylcellulose), 3, 15 and 75 mg/kg/day. Doses were administered in a volume of 5 ml/kg.

Rationale For Doses: Preliminary studies in non-pregnant rabbit: indicated 1) a dose of 200 mg/kg, but not 100 mg/kg, administered daily for 10 days reduced body weights, and 2) that beta-receptor antagonism occurred at an oral dose of 1 mg/kg and increased dose-dependently at 3 and 10 mg/kg. A preliminary study in pregnant rabbits indicated that 150 mg/kg/day on days 7 to 19 of pregnancy caused a marked reduction of body weight and increased post implantation losses. Therefore, the high dose of 75 mg/kg/day

was selected for the present study since this dose was considered to be at the lower limit for maternal toxicity. The low dose of 3 mg/kg was selected because it was above the beta-blocking dose in the rabbit.

Number of Animals: 17/dose group. At study termination there were 15 control animals, 17 low-dose animals, and 16 mid- and high-dose animals (1 animal each in the control, mid- and high-dose groups was non-pregnant; 1 control animal aborted).

Caesarean Section: Day 30 of pregnancy (15 controls, 17 low-dose, 16 mid-dose and 16 high-dose).

Results: Maternal Effects: Mortalities: None. Clinical Signs: None.

Body Weight: No significant differences between groups either overall or during the period of drug administration. Food

Consumption: Unremarkable except for a reduction in controls on day

14 to 17. There were no significant differences between groups in the median Uterine Weight (full or empty) or median number of

Implantation Sites. Fetal Effects: There was a tendency for

increased resorptions in the high-dose group (expressed as a % of implantation sites, total # of resorptions, # dams with

resorptions, or average # resorptions/dam) but this was not

statistically significant. There was 100 % resorptions in 1

low-dose, 2 mid-dose and 1 high-dose dams. Therefore, fetuses were obtained from 15 control, 16 low-dose, 14 mid-dose and 15 high-dose

rabbits. Dead Fetuses: There were none in any group. Live Fetuses:

The number of live fetuses as a % of implantation sites tended to be lower in the high-dose group but this was not statistically

significant. Sex Ratio: The median number of males at the low-dose

was significantly lower than controls. This was not seen with the

other doses. The median Placental Weight/dam was higher in all drug

groups than in controls but was statistically significant for the low- and high-dose groups.

(Cont'd. Rabbit teratology- MWinbury's review)

Fetal Weight: The median fetal weight/dam was significantly higher in the low-dose group than in controls. Visceral and Skeletal Abnormalities: There were no significant differences between drug and vehicle treated groups in terms of visceral malformations or skeletal retardations, variations or malformations.

Conclusions: Carvedilol, 3, 15 or 75 mg/kg/day (suspended in 1% methylcellulose), was administered orally to Himalayan rabbits on days 7 to 19 of pregnancy. The doses used in this study were all higher than the oral dose shown to have significant but sub-maximal beta blocking activity (1 mg/kg) in the rabbit. None of the doses were teratogenic. The 75 mg/kg dose was slightly embryotoxic/fetotoxic but this effect was not statistically significant. A preliminary study in pregnant rabbits indicated that twice this dose (150 mg/kg/day) was embryotoxic/fetotoxic (increased number of resorptions) and toxic to the dams (marked decreases in body weight). In the present study, there was no indication of maternal toxicity at the 75 mg/kg/day dose. The increased placental weights in all dose groups, the increased fetal

weight in in the low-dose group, and the tendency for increased resorptions in the high-dose group were considered by the Sponsor as being secondary to the pharmacodynamic (beta-blockade/vasodilation) effects of the compound.

Perinatal and Postnatal Studies in Rats.

(SK&F Report No. TCO14BS Boehringer Mannheim GmbH, Germany. Study dates: March 25-26, 1985 to September 16, 1985. Report date: November 1986)

No./Dose Level and Strain: About 23 pregnant rats [Sprague-Dawley, Crl:CD(SD)BR].

Route: Orally, by gavage.

Dose Levels and Treatment Schedule: 0 (vehicle - 1% methycellulose), LD-12, MD-60 and HD-200 mg carvedilol in a 10 ml suspension/body weight on day 16 of gestation and continued up to the end (day 22) of lactation phase.

Synopsis of Procedures: Observations of F₀ females included mortality, body weight, appearance/behavior, pregnancy rate, duration of gestation, number of uterine implants/dam, number of live neonates/dam, fetotoxic effects and sex distribution of the F₁ pups. Observations in F₁ generation included body weights of individuals, and per litter, physical development and behavior. Numerous tests were listed in the NDA that were conducted on selected F₁ pups to determine the development of physical characteristics of F₁ generation. F₁ animals were mated (no sibling pairing), observed/weighed and allowed to litter and rear F₂ pups. F₁ dams and their pups who died prematurely were necropsied. F₂ pups were observed through developmental stages, reflexes tested and sacrificed/necropsied at the end of lactation.

Results:

Maternal (F₀ generation) Observations:

Remarkable toxic signs seen during treatment period were reported mainly for HD; these consisted of narrowing of palpebral fissures suggesting sedation. Hair loss was noted in all treated groups including controls. At sacrifice time, necropsy findings in treated rats were similar to those seen in controls. A significant resorption of 5 litters was noted at HD compared to controls. Compared to controls, treated dams were reported as showing no significant changes in implantation sites, onset/course of parturition, live pups/dam or reproductive indices per litter (birth index or viability indices) and no significant differences in sex ratio of pups.

Litter Observations:

F₁ Generation: Body weight of F₁ pups was determined about once a week starting on day 1 after birth up to day 43 of study. Except for a significantly lower median body weight in F₁ pup from the HD F₀ dams, no remarkable toxic effects were reported for the F₁ pups. The body weight of neonates was dose-dependently depressed and body weights continued this way until the end of study (day 43 after birth). Starting in the 1st week post partum, at MD and HD groups, more pups were found dead or cannibalized by the dams than in the controls. This effect was also dose-dependent but is regarded as a drug effect deriving both from

unspecific retardation of the fetuses and deficient rearing activity by the dams treated with a toxic dose of carvedilol. Except for pinna detachment and grip strength, all other parameter of physical development (e.g., testicular descent into scrotum, vaginal opening, incisor eruption) as well as reflexes test (e.g., auditory startle, corneal and pupillary), and behavior (e.g., learning and memory) were unaffected. The necropsy findings of the F₀ and F₁ animals revealed no drug-related effects.

F₂ Generation: Although there were some differences in the median weight of groups in this F₂ generation the number of F₂ pups born alive (derived from HD F₀ dams), there were no remarkable observations in these animals regarding the number of pups born alive or their physical development of reflexes or learning and memorizing capacity. These did not differ from the control group. The necropsy findings at the end of the study did not reveal any possible drug effects in the F₂ pups.

Sponsor concluded that 200 mg carvedilol/kg p.o. caused increased intrauterine embryo losses in the F₀ dams, reduced their rearing activity, and retarded physical development of the F₁ generation. This dosage also had a slight influence on the number of F₂ pups born live, the development of some reflexes and behavioral parameters.

60 mg/kg) had only a marginal effect on the rearing activity of the F₀ generation and on the physical development of the F₁ generation.

Sponsor provided necropsy of findings of F₁ pups dying prematurely, F₁ dams and F₂ pups; findings reported did not reveal any drug effects.

Overall, the data presented above indicate that in the definitive Segment I rat study the "no-observed-effect level" (NOEL) for overt toxicity and impairment of fertility may be considered 60 mg/kg/p.o., and that for developmental retardation of offspring was 12 mg/kg/p.o. Further, for the rat and rabbit Segment II studies, for the rat the NOEL for maternal toxicity is considered 12 mg/kg/p.o. and 60 mg/kg/p.o. for developmental toxicity; in the rabbit the NOEL for maternal toxicity, 75 mg/kg/day and 15 mg/kg/day for developmental toxicity. In the rat Segment III studies, the NOEL is considered to be 12 mg/kg/day.

GENOTOXICITY STUDIES

Carvedilol was tested for genotoxic potential using various non-mammalian and mammalian cell systems. Except where indicated for new studies below (i, ii, -iv, Bi, -ii, -vii), results of assays were previously reported and submitted to the injectable carvedilol application (IND). These reports were reviewed/evaluated by previous pharmacologist M. Winbury, Ph.D.; portion of the reviews are reproduced below. The reviews/evaluations were secondarily reviewed by supervisory pharmacologist C. Resnick, Ph.D. and were found acceptable. In the present NDA, sponsor has submitted numerous summary tables of the assays. Pertinent portions of these summaries have been extracted, edited and presented below, followed by a brief overview of new studies not previously evaluated. Some studies were conducted prior to implementation of GLP regulations.

MUTAGENICITY STUDIES OF CARVEDILOL (SK&F 105517) AND ITS INTERMEDIATE (SK&F 105569)

Study	Concentrations Tested	Report No. Ref. No. Location in NDA IND Submission	Drug-Related Observations
A - IN VITRO NON-MAMMALIAN SYSTEMS			
i) Ames test (Salmonella) * (Detects gene re-use mutation)	1, 10, 50, 100, 500, and 1000 µg/plate w/w/DS9 (1st test) 10, 50, 100, 500 µg/plate w/w/ S9 (2nd test)	TC016BS (Boehringer Mannheim report J1) Location: Vol. 1.40 Page 000004 Submitted to IND on 2/15/85	First test: Not assessed since concentrations above 100 µg/test plate were bactericidal. Second test: No increase in revertant frequencies in any strain tested.
ii) Ames test (Salmonella) **	50, 150, 500, 1500, and 5000 µg/plate w/w/ S9 (initial experiment); 5, 15, 50, 150, and 500 µg/plate (repeat experiment) Positive controls without S9: 2-nitro- fluorene and 1-ethyl-2-nitro-3- nitrosourea Positive control with S9: 2-amino- anthracene.	TC017BS (Boehringer Mannheim report J3) Location: Vol. 1.40 Page 000090 Submitted to IND on 2/15/85 (Report states that studies were conducted in 1986)	Initial experiment: Concentrations of 1500 µg/plate and greater resulted in precipitation of carvedilol. A mild precipitation was also seen at 500 µg/plate. Repeat experiment: No statistically significant increases in revertant frequencies over the negative controls were observed in 2 independent experiments.
iii) Ames test (Salmonella)	n-Benzyl Carvedilol (intermediate) 50, 167, 500, 1670, 3330, and 5000 µg/plate w/w/ S9	TP001BS Location: Vol. 1.40 Page 000269 Submitted to IND on 10/3/89	The intermediate was minimally positive (2-fold elevation) in strain TA1535 without S9 mix and an equivocal response was observed in strain TA1537 with S9 mix. All other 4 test strains (w/w/ S9) were negative. The observed difference was considered of limited biological significance and of no significance relative to safety. (Complies with GLP)
* n-Benzyl carvedilol is less than 0.02% of the drug. 1) w/w/ = with/without S9 from rat liver induced with phenobarbital+ methylcholanthrene. ** S. typhimurium strains TA TA 100, TA 1535, TA 1537 and TA 1538.			

Genotoxicity (Cont'd)

A- IN VITRO NON-MAMMALIAN CELL SYSTEMS (Cont'd.)

Study	Concentrations Tested	Report No. Ref. No. Location in NDA IND Submission	Drug-Related Observations
iV) <i>E. coli</i> WP2 <i>uvrA</i> (Reverse Mutation Assay)	5, 15, 50, 150, 500, 1500 and 5000 µg/plate w/w S9* DMSO used as negative control and 2AA and ENU as positive controls.**	TC0030/SKF-105517 (Daiichi report D-17) Location: Vol. 1.40 Page 000298	Toxic effects and precipitation were noted at dosages ≥500 mg/plate w/w activation. Dosages below 500 mg/plate were negative. Carvedilol was considered negative in this assay. Positive controls showed increases in mutations.
v) Mouse host mediated assay (Reverse Mutation Assay)	200, and 2000 mg/kg p.o. Saline appears to have been used as control.	TC016BS (Boehringer Mannheim report J1) Location: Vol. 1.40 Page 000004 Submitted to IND on 2/15/85	At 2000 mg/kg, bactericidal effects were seen in both <i>S. typhimurium</i> and <i>S. marcescens</i> but were absent at 200 mg/kg. There were no compound- related relevant significant increases in gene mutation in any of these tests.
vi) <i>Saccharomyces cerevisiae</i> MP-1 (Defects gene forward mutation and other genetic changes)	0.01, 0.1, 1, 10, and 50 mg/ml w/w S9* Solvent was used as the control.	TC016BS (Boehringer Mannheim report J1) (supplement) Location: Vol. 1.50 Page 000004 Submitted to IND on 2/15/85	No yeast growth at concentrations of 0.1 mg/kg or greater. Therefore, the results of this assay were not taken into account.

* S9 mix prepared from liver fraction of phenobarbital and 5,6-benzoflavone induced male Sprague Dawley rats.
** 2-aminoanthracene and n-ethyl-N-nitrosoguanidine.

Genotoxicity (Cont'd)

Study	Concentrations Tested	Report No. Ref. No. Location in NDA IND Submission	Drug-Related Observations
β- IN VITRO MAMMALIAN CELL SYSTEMS			
i) Chinese Hamster Ovary Cell Mutation Assay (Detects forward mutation at the hprt locus)	8, 9, 12, 15, 16, 18, 20, 2, and 24 µg/ml without S9 mutation assay 16, 20, 21, 24, 28, 30, 32, and 33 µg/ml with S9 <i>Positive results with ethyl methanesulphonate and 3-methylcholanthrene.</i>	TC017BS (Boehringer Mannheim report J3) Location: Vol. 1.40 Page 000090 Submitted to IND on 2/15/85 (Report prepared in 1986, data from study with carvedilol not directly related.)	In the absence of S9 mix, small increases in mutation frequency over vehicle control values were obtained in the cultures treated only with 15 µg/ml of carvedilol. This isolated incidence was not regarded as significant. In the presence of S9 mix, no evidence of mutagenic activity was obtained in carvedilol-treated cultures. This mutagenicity assay was considered to be negative. (Under S9 conditions)
ii) Chromosome aberration test with human lymphocytes	8, 40, and 80 µg/l w/o S9 <i>Positive results with phenytoin, p.o. and methylcellulose, p.o.</i>	TC017BS (Boehringer Mannheim report J3) Location: Vol. 1.40 Page 000090 Submitted to IND on 2/15/85 (Report states that studies were conducted in 1986)	There was no significant increase either in damage to chromosome structure or in numerical changes at dosages tested. Thus, carvedilol did not cause significant chromosomal damage in this test. (Under S9 conditions)
iii) DNA synthesis inhibition test (Detects damage to normal testicular DNA replication)	Mouse given 50, 100, and 200 mg/kg p.o.	TC016BS (Boehringer Mannheim report J1) Location: Vol. 1.40 Page 000004 Submitted to IND on 2/15/85	Lowering of the body temperature by 10°C occurred by using the 200 mg/kg solution (2 of 3 experiments). One of 2 experiments showing a lower body temperature demonstrated a decrease in thymidine incorporation. This effect was related to the body temperature change and not considered a primary DNA damaging effect. It was concluded that carvedilol did not affect DNA replication. (Not under S9 conditions)

*S9 mix obtained from liver fraction of Aroclor induced male Fisher 344 rats.

** S9 mix obtained from liver fraction of phenobarbital and 3-methylcholanthrene induced male Sprague Dawley rats.

Genotoxicity (Cont'd)

B- IN VITRO MAMMALIAN CELL SYSTEM (cont'd.)

Study	Concentrations Tested	Report No. Ref. No. Location in NDA IND Submission	Drug-Related Observations
iv) <i>Unscheduled DNA synthesis test (Detects repair of DNA damage.)</i>	<i>Mouse given</i> 200 mg/kg p.o.	TC016BS (Boehringer Mannheim report J1) Location: Vol. 1.40 Page 000004 Submitted to IND on 2/15/85	There was no difference in % UDS between control and drug-treated animals. Thus, carvedilol did not induce unscheduled DNA synthesis in mouse testicular cells in this system.
v) <i>Micronucleus test in Chinese hamster (Detects chromosomal aberrations.)</i>	1500 mg/kg p.o.	TC016BS (Boehringer Mannheim report J1) Location: Vol. 1.40 Page 000004 Submitted to IND on 2/15/85	The mean number of micronuclei in control and drug-treated animals was 13.90 and 20.67, respectively. Since these numbers represented less than a doubling in the micronucleus rate, the test was considered negative.
vi) <i>Sister Chromatid exchanges in Chinese hamster (Detects chromosome breaking (clastogenic) chemicals)</i>	1000 mg/kg p.o.	TC016BS (Boehringer Mannheim report J1) Location: Vol. 1.40 Page 000004 Submitted to IND on 2/15/85	The mean number of sister chromatid exchanges in cells of control and drug-treated animals was 85.16 and 70.83, respectively. Carvedilol did not enhance sister chromatid exchange <i>in vivo</i> .
vii) <i>Chromosome aberration test in bone marrow of Chinese hamster</i>	2000 mg/kg p.o.	TC016BS (Boehringer Mannheim report J1) Location: Vol. 1.40 Page 000004 Submitted to IND on 2/15/85 TC017BS (Not under GCP conditions) (Boehringer Mannheim report J3) Location: Vol. 1.40 Page 000090 Submitted to IND on 2/15/85 <i>(Report states that studies were conducted in 1986)</i>	* <i>First study:</i> Three gaps and one fracture were observed in 3200 metaphase nuclei of drug-treated animals. These numbers corresponded to past observations in nuclei of control animals. Therefore, the control animals were <i>not</i> examined and the test was considered to be negative. <i>Second study:</i> Not any drug-related increase in either structural or numerical changes compared to the negative control. Thus, carvedilol has no effect on chromosomal aberrations <i>in vivo</i> . <i>(Complies with GCP)</i>

Genotoxicity Studies (Cont'd)

OVERVIEW OF GENOTOXICITY STUDIES NOT PREVIOUSLY REVIEWED

(Identification symbols refer to studies listed above in Table submitted by drug sponsor and edited by present reviewer.) All studies submitted in Vol. 40 of this NDA.

A.iii) **Mutagenicity Evaluation of n-Benzyl Carvedilol (Intermediate [SK&F 105569]) in the Ames Salmonella/Microsome Plate Test [TP001BS].** Submitted to IND on 10/3/89, Study Dates: 15-Apr-87 and 5-May-87).

n-Benzyl carvedilol is an intermediate in the synthesis of carvedilol and is not found in the finished drug substance.

n-Benzyl carvedilol was tested for its ability to cause gene mutation (reverse mutation at selected histidine loci) in *S. typhimurium* tester strains TA98, TA100, TA1535, TA1537 and TA1538, both in the absence and presence of microsomal activation system (S9). The tests were performed at 6 concentrations of n-benzyl carvedilol: 50, 167, 500, 1670, 3330 and 5000 µg/plate (lot no. AC10368). n-Benzyl carvedilol precipitated out at the highest concentration tested.

Statistically significant, dose-dependent increases in revertant frequencies were seen with n-benzyl carvedilol (2-fold elevation) in strain TA1535 without S9 mix, and an equivocal response was observed at 500 µg/plate in strain TA1537 with S9 mix. All other strains were negative. Although n-benzyl carvedilol was considered to have produced a positive response in strain TA1535 with S9 and equivocal response in strain TA1537 with S9, these were considered by sponsor to be of "uncertain biological significance" and of no significance relative to safety.

The negative and positive and negative control values were reported as within historical limits and all positive controls produced positive responses under the plating conditions.

A.iv) **Study of Mutagenicity of Carvedilol (DQ-2466): Reverse Mutation Assay using Escherichia Coli [TC/0030/SKF-105517 (Daiichi report D-17)].** Test Dates: 11-Apr-88 - 26-May-88). Carvedilol Lot no. 437265 was tested

Carvedilol was tested for its ability to cause gene mutation in *E. coli* WP2uvrA, a strain sensitive to a wide range of mutagens. Carvedilol was tested both with and without microsomal activation in *E. coli* WP2uvrA at 7 concentrations: 5, 15, 50, 150, 500, 1500 and 5000 µg/plate. DMSO was used as negative control and 2-aminoanthracene and n-ethyl-n-nitrosoguanidine as positive controls.

Toxic effects and precipitation were noted at concentrations of 500 µg/plate and above with and without metabolic activation. Levels below 500 µg/plate did not show an increase in revertant frequency with and without S. Thus, sponsor considered that the drug did not demonstrate gene mutation activity in this test.

B.i) Carvedilol (BM14.190): Chinese Hamster Ovary Cell (CHO) Mutation Assay [TC017BS (Boehringer Mannheim report J3)] Submitted to IND on 2/15/85; Study Dates: Apr-86 and Oct-86. Carvedilol batch no. 815164A was tested.

Carvedilol was tested to determine its potential to induce mutation in cultured CHO cells at the sex-linked hypoxanthine-guanine-phosphoribosyl transferase (hgp_rt) locus, from hgp_rt⁺ to hgp_rt⁻. This forward mutation results in colony growth in agar containing 6-thioguanine which is cytotoxic to cells possessing hgp_rt and less toxic to the mutants.

In preliminary toxicity tests CHO cell cultures exposed to the drug at concentrations ranging from 0.03 up to 300 µg/ml; at 30 µg/ml in the presence of S9 there was reduced cell growth to 7% of vehicle control value, and in the absence of S9 total cell death.

After preliminary tests to determine adequate concentrations of carvedilol to be tested for mutagenic potential, the final concentrations selected were 8-9, 12, 15-16, 18-20 and 21-24 µg/ml in the absence of S9 mix, and 16-21, 20-24, 27-28 and 30-32 or 33 µg/ml in the presence of S9 mix; assays were repeated 4 times. Concurrent positive controls were ethyl methanesulphonate (EMS) and 3-methylcholanthrene (3-MC) and vehicle used DMSO.

In this assay, sponsor reported that mutant fractions obtained with the positive control and vehicle controls were within the normal ranges of the testing laboratory.

In the absence of S9 mix, a small increase in mutation frequency over vehicle control values was obtained only in the cultures treated with 15 µg/ml of carvedilol. This isolated incidence was not regarded as significant by sponsor. In the presence of S9 mix, no evidence of mutagenic activity was obtained in carvedilol-treated cultures.

Data suggest that carvedilol is not mutagenic in Chinese hamster ovary cells, in the presence or absence of S9 mix, when tested in DMSO at close to toxic concentrations.

B.ii) Chromosome Aberration Test with Human Lymphocytes *in vitro* [TC017BS (BM/J3)] Submitted to IND on 2/15/85; Study Dates: 17-Mar-86 and 17-Apr-86). Carvedilol batch no. 815164A was tested.

Carvedilol was tested to determine its potential to cause chromosomal damage in human lymphocytes cell cultures. The drug was tested, both with and without microsomal activation, by metaphase analysis of the cultured human lymphocytes.

In a preliminary assay, carvedilol was highly toxic to the lymphocytes at concentrations of 200 µg/ml and above; 25% reduction in mitotic index was obtained at 70 µg/ml. The definitive assays were performed with carvedilol at concentrations of 8, 40 and 80 µg/ml in the absence/presence of S9. The positive controls were bleomycin 10 µg/ml and cyclophosphamide 100 µg/ml. All treatments were in duplicate cultures.

No significant damage in chromosome structure or numerical changes were reported for this assay with carvedilol.

B.iv) DNA-Synthesis Inhibition Test [TC]16 BS (BM/J1) submitted to IND on 2/15/85; Study Dates: 13-Jan-82 and 11-Feb-82)

Carvedilol was tested for its ability to detect covalent binding to testicular DNA which interferes with normal DNA replication synthesis. This effect is measured as a reduction in uptake of radio-labeled thymidine.

ICR mice were administered carvedilol (batch no. 811012A), orally by gavage, at dosages of 50, 100 and 200 mg/kg dissolved in 10% DMSO/90% PEG 400.

Lowering of the animal's body temperature by 10°C using this solution was found in 2 of 3 experiments at a dosage of 200 mg/kg. At this dose, one of the two experiments showed a decrease in thymidine incorporation. This finding was related to the extreme decrease in body temperature and was not considered to be due to damage to DNA. Thus, it may be concluded that carvedilol had no effect on DNA replication in this *in vivo* DNA test.

The following are the summaries/evaluations of mutagenicity studies (J series) are reproduction of previously submitted to FDA and that have undergone a secondary review by supervisory pharmacologist Charles Resnick, Ph.D. Thus, since they were found to be adequate, these are incorporated in this document unedited.

Report No. J1. Mutagenicity of BM 14,190. (Boehringer Mannheim, Germany; Dated March 26, 1979. vol. 1.7, p 06 001371): Quality Assurance Unit statement for this report dated Nov. 18, 1983, concerns only the report and not the study conduct. Statement of Compliance with GLP dated Dec. 10, 1984 (p. 06 0014248) indicates that studies in Part 1 of Report J1 were performed prior to GLP regulations. Deviations from GLP are stated. Studies described in Part 2, i.e., "Supplement to the Report of March 26, 1979" were conducted according to GLP except: 1) "The protocol did not meet all formal requirements of the GLP regulation", and 2) "The conduct of the tests was not inspected by the quality assurance unit. The final report however, was completely audited by the quality assurance unit."

- o Host-Mediated Assay in the Mouse with Salmonella typhimurium G 46 and Serratia marcescens a 21. (A test for substance-induced revertants). Doses: 200 and 2000 mg/kg, p.o. With Salmonella typhimurium G 46, Carvedilol at 2000 mg/kg was too antibacterial to determine mutagenicity; at 200 mg/kg the compound was neither antibacterial or mutagenic. With Serratia marcescens a 21 carvedilol at 2000 mg/kg (but not 200 mg/kg) was both antibacterial and mutagenic. No positive control.

Mutagenicity studies (Cont'd.)

- In vitro test with Multiple Purpose Strain *Saccaromyces cerevisiae* RP-1 with and without Liver Homogenate. (A test for substance-induced gene conversion, forward mutation and recombinations). Concentrations: 0.01 to 50 mg/ml with and without liver homogenate (S9 mix from rat liver induced with phenobarbital and methylcholanthrene). Carvedilol was toxic to the organism at 0.1 mg/ml and above without the liver homogenate and at concentrations of 1 mg/ml and above with the liver homogenate. There was no indication that 0.01 mg/ml with or without the S9 mix or 0.1 mg/ml with the S9 mix was mutagenic. Conclusions with this test are, therefore, limited since only low concentrations were not lethal to the yeast. No positive control.
- Micronucleus Test in the Chinese Hamster (A test for chromosome breaking). Dose: 1500 mg/kg. Bone marrow obtained at 24 hrs. The increase of micronuclei per 10,000 RBCs from 13.5 ± 6.1 in controls to 20.7 ± 4.6 in treated hamsters was less than the doubling considered by the Sponsor to be necessary for the test to be positive. No positive control.
- Test for Sister Chromatid Exchange (SCE) in the SCE-test in Chinese Hamster. Dose: 1000 mg/kg p.o. Carvedilol did not induce sister chromatid exchange. No positive control.
- Ames Test with and without Liver Homogenate using the Test Strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 (A test for substance-induced revertants). Concentration: 1 to 5000 mcg/plate with or without liver homogenate (S9 fraction of homogenized liver from Sprague Dawley rats treated with phenobarbital and methylcholanthrene). This study was done twice. Carvedilol was markedly antibacterial at concentrations above 100 mcg/plate, therefore, only the mutagenic potential of carvedilol at low concentrations (100 mcg/plate or less) could be assessed. Carvedilol was not mutagenic based on the criteria of a concentration-response relationship and/or at least a 2 fold increase in the number of revertants. There were, however, statistically significant increases in the number of revertants in some strains. The statistics applied consisted of an overall one-way analysis of variance (ANOVA) and a multiple comparison of each concentration with vehicle. Consistency between studies occurred only with strain TA 1535 in which, without metabolic activation, a statistically significant increase in revertants was seen by ANOVA and at 100 mcg/plate. Occasional significant (by ANOVA or at 100 mcg/plate) increases in the number of revertants were seen with strains TA 98, TA 100, TA 1537 and TA 1538. In conclusion, the results of the Ames test were inconclusive since, although not clearly mutagenic, carvedilol tended to be mutagenic at 100 mcg/plate. Higher concentrations could not be tested because of the marked antibacterial activity of the compound. No positive controls.

Mutagenicity studies (Cont'd.)

- Bone Marrow Test in the Chinese Hamster (*Cricetus griseus*) (A test for substance-induced chromosome aberrations). Dose: 2000 mg/kg, p.o., single dose. Sponsor refers to data presented in Table 29 but no such table found. Sponsor's description of results: "the three gaps (holes in the staining) and one fracture found in the 3200 metaphase nuclei examined correspond to our control values. We therefore omitted the further examination of the control group that was also included in the test." No positive control.

Summary and Conclusions: Failure to use positive controls in any of these studies lessens their value.

Carvedilol at oral doses of from 1000 to 2000 mg/kg did not show any effects in mammalian tests in which chromosome-breaking activity was tested directly (bone marrow test, micronucleus test) or indirectly (SCE).

In non-mammalian tests for substance-induced gene mutation (Ames test, *Saccharomyces cerevisiae* MP-I test, and host-mediated assay with *Salmonella typhimurium* G and *Serratia marcescens*). Carvedilol was mutagenic in the host-mediated assay with *Serratia marcescens* at 2000 mg/kg (this dose was also antibacterial). The results of all the other tests are inconclusive since the marked antibacterial activity of carvedilol prevented testing high doses and/or concentrations. Although not satisfying strict criteria for positivity, carvedilol did tend to be mutagenic in the Ames test at 100 mcg/plate. The highest concentrations of carvedilol that could be tested in the *Saccharomyces cerevisiae* MP-I test (10 mcg/ml without the S9 mix and 100 mcg/ml with the S9 mix) were negative.

BfI 14,190 - Mutagenicity. Supplement to Report of March 26, 1979 (report dated August 10, 1983, vol 1.7, p. 06 001418.) This supplement was included in Report J1 but not summarized. Three studies are presented:

1. DNA-Synthesis Inhibition (DSI) Test (mouse)
2. Unscheduled DNA-Synthesis (UDS) Test
3. Ames Test

The first two tests were performed in Dr. Seiler's laboratory at the Wädenswil Federal Research Institute, Switzerland while the last test was carried out by Boehringer Mannheim, Germany.

- DNA-Synthesis Inhibition (DSI) Test. Mouse testes. Doses: 50, 100 and 200 mg/kg, p.o. given as single doses. Rationale for doses not presented. Dr. Seiler's general methods indicate the high dose is usually the established LD50. This is clearly not the case for carvedilol (oral LD50 in mouse is in excess of 8000 mg/kg). Test drug is administered to mice prebled with 14C-thymidine; Three

Mutagenicity studies (Cont'd.)

hours post-test drug, 3H-thymidine is administered and 45 minutes later the incorporation of 3H-thymidine into the testes is determined. The test was repeated twice at 50 and 100 mg/kg and in both tests carvedilol failed to inhibit DNA synthesis. The 100 mg/kg dose reduced rectal temperature 2-3 degrees C. Three tests were performed at 200 mg/kg and in one of these tests DNA synthesis was inhibited by 54% and rectal temperature fell by 12 degrees C. DNA synthesis was not significantly inhibited (-12 and -18%) in the other two tests and rectal temperature was not reduced (-40 and -100, respectively) less markedly.

- Unscheduled DNA Synthesis (UDS) Test. Mouse. Dose: 200 mg/kg three hours prior to removal of testes to measure, in vitro, DNA synthesis and repair. This test was in fact performed by Dr Seiler as a part of the above report. The experiment was performed twice and in neither test was there a significant change in unscheduled DNA synthesis. In the absence of statements to the contrary, it is assumed that these UDS studies used testicular preparations from different mice than used for DSI test at 200 mg/kg. It is also not known what effect the compound had on rectal temperature or on DNA synthesis in these animals. The table presented in Dr. Seiler's report combines the data and suggests that the UDS data were from testicular preparations from the two studies in which carvedilol did not inhibit DNA synthesis.

Conclusion: Dr. Seiler concluded that the reduced DNA synthesis associated with carvedilol in 1 out of 3 studies at 200 mg/kg, p.o., was secondary to the drug-induced fall in body temperature and not due to a direct effect of the compound on DNA synthesis. This dose of carvedilol did not affect unscheduled DNA synthesis.

- Ames Test: Test strains: TA 98, TA 100, TA 1535, TA 1537 and TA 1538. Concentrations: 10 to 500 mcg/plate with and without liver homogenate (S-9 mix from Sprague Dawley rats induced with phenobarbital and methyholanthrene). Carvedilol at up to 500 mcg/plate was not mutagenic in any of the test strains. The significantly (statistically) higher number of revertants seen with the S-9 mix in TA 98 at 10 & 100 mcg/plate (but not at 50 or 500 mcg/plate) and in TA 100 at 50 & 100 mcg/plate (but not at 10 or 500 mcg/plate) was less than twice the number of revertants seen with vehicle.

		Short title and project name						J 4 - 21	
		Page						Carcinogenicity study with BM 14.190 in mice	
SURVEY OF TUMOR FREQUENCY IN MALE MICE									
Table 1									
BM 14.190									
Dose	n	unscheduled killed or died	with tumors	without tumors	scheduled killed	with tumors	without tumors	total with tumors	total without tumors
Control	100	58-581	46-79,38	12-20,78	42-428	37-88,18	5-11,98	83-838	17-178
20 mg/kg	50	19-381	13-68,48	6-31,68	31-628	25-88,68	6-19,48	38-768	12-248
65 mg/kg	50	28-561	21-751	7-251	22-441	19-86,41	3-13,61	40-801	10-201
200 mg/kg	50	28-561	17-60,71	11-39,31	22-441	17-77,31	5-22,71	34-681	16-321

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Table 2

BM 14.190

SURVEY OF TUMOR FREQUENCY IN FEMALE MICE

Dose	n	unscheduled killed or died	with tumors	without tumors	scheduled killed	with tumors	without tumors	total with tumors	total without tumors
Control	100	73-738	39-53,48	34-46,68	27-278	23-85,28	4-14,88	62-628	38-388
20 mg/kg	50	40-808	23-57,58	17-42,58	18-208	6-608	4-408	29-588	21-428
65 mg/kg	50	39-788	19-48,78	20-51,38	11-228	9-81,88	2-18,28	28-568	22-448
200 mg/kg	50	40-808	19-47,58	21-52,58	10-208	7-708	3-308	26-528	24-488



Page 4

Carcinogenicity study with BM 14.190 in mice

J 4 - 22

Table 17

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Table 18

Sponsor and project name		Page 21 Carcinogen city Study with Carvedilol in mice			J 4 - 60																														
Table 7: Frequencies of animals with tumors respective malignant tumors male mice <table border="1"> <thead> <tr> <th>Dosage</th> <th>Group 1 Control</th> <th>Group 2 20 mg/kg</th> <th>Group 3 65 mg/kg</th> <th>Group 4 200 mg/kg</th> </tr> </thead> <tbody> <tr> <td>Number of animals with a tumor</td> <td>83</td> <td>38</td> <td>40</td> <td>34</td> </tr> <tr> <td>Number of animals with a malignant¹⁾ tumor</td> <td>40</td> <td>17</td> <td>23</td> <td>16</td> </tr> </tbody> </table> female mice <table border="1"> <thead> <tr> <th>Dosage</th> <th>Group 1 Control</th> <th>Group 2 20 mg/kg</th> <th>Group 3 65 mg/kg</th> <th>Group 4 200 mg/kg</th> </tr> </thead> <tbody> <tr> <td>Number of animals with a tumor</td> <td>62</td> <td>29</td> <td>28</td> <td>26</td> </tr> <tr> <td>Number of animals with a malignant¹⁾ tumor</td> <td>37</td> <td>20</td> <td>18</td> <td>16</td> </tr> </tbody> </table> At begin of study there were 100 animals per Control and 50 animals per dosage and sex. ¹⁾ - malignant is not the same as fatal						Dosage	Group 1 Control	Group 2 20 mg/kg	Group 3 65 mg/kg	Group 4 200 mg/kg	Number of animals with a tumor	83	38	40	34	Number of animals with a malignant ¹⁾ tumor	40	17	23	16	Dosage	Group 1 Control	Group 2 20 mg/kg	Group 3 65 mg/kg	Group 4 200 mg/kg	Number of animals with a tumor	62	29	28	26	Number of animals with a malignant ¹⁾ tumor	37	20	18	16
Dosage	Group 1 Control	Group 2 20 mg/kg	Group 3 65 mg/kg	Group 4 200 mg/kg																															
Number of animals with a tumor	83	38	40	34																															
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Number of animals with a malignant ¹⁾ tumor	37	20	18	16																															

NDA 20297

9 OF 11

Short title and project name		Page 22					J 4 - 67	
Carcinogenicity Study with Carvedilol in mice								
Table 8: Number of animals with tumors of the organs with the highest frequencies								
male mice								
Organs								
Dosage Group	Lungs	Adrenal cortex	Harder. gland	Liver	lymphat. system	Pituitary	Testes	
Control	46	26	25	16	9	6	0	
20 mg/kg	22	4	13	9	10	2	1	
65 mg/kg	17	6	14	7	7	1	3	
200 mg/kg	18	11	11	2	6	2	1	
female mice								
Organs								
Dosage Group	Pituitary	lymphat. system	Lungs	Ovary	Uterus	Harder. gland	Mamm. gland	
Control	25	25	16	15	10	9	4	
20 mg/kg	7	14	4	3	5	3	2	
65 mg/kg	11	15	6	0	3	4	1	
200 mg/kg	5	13	3	1	2	8	0	
At begin of study there were 100 animals per Control and 50 animals per dosage and sex.								

Table 20
Intercurrent Mortality Rates
Male Mice

Weeks	Control			Low			Medium			High		
	S	D	%	S	D	%	S	D	%	S	D	%
0-50	100	3	3	50	0	0	50	3	6	50	1	2
51-80	97	3	3.1	50	5	10	47	4	8.5	49	8	16.3
81-113	94	52	55.3	45	14	31.1	43	21	48.8	41	19	46.3
Term.	42			31			22			22		

Female Mice

Weeks	Control			Low			Medium			High		
	S	D	%	S	D	%	S	D	%	S	D	%
0-50	100	15	15	50	5	10	50	11	22	50	4	8
51-80	85	30	35.3	45	17	37.7	39	15	38.4	46	18	39.1
81-97	55	28	50.9	28	18	64.3	24	13	54.1	28	18	64.3
Term.	27			10			11			10		

Notes: S: Number of animals starting during the period
D: Deaths
%: Percent of death during the period

Table 21

first day - last day		Group 1 Control	Group 2 20 mg/kg	Group 3 65 mg/kg	Group 4 200 mg/kg	
0 - 42	14.00 (13.00;15.50) n = 100	15.00* (13.88;16.50) n = 50	15.50* (13.38;17.13) n = 50	13.50* (12.00;14.50) n = 50	1+	
43 - 84	19.50 (17.63;21.50) n = 100	20.50* (19.00;22.50) n = 50	21.25* (17.88;24.00) n = 50	19.00 (18.00;20.00) n = 50	1+	
85 - 119	22.00 (20.00;24.00) n = 100	23.00 (20.75;24.25) n = 50	23.00 (19.00;25.25) n = 50	21.00* (19.00;22.00) n = 50	1+	
120 - 182	23.00 (21.00;26.00) n = 100	24.00 (22.00;26.00) n = 50	24.00 (21.00;28.00) n = 50	22.00* (20.00;23.25) n = 50	1+	
183 - 280	25.00 (22.00;28.00) n = 99	25.00 (23.00;27.00) n = 50	26.00 (22.50;29.00) n = 49	23.00* (21.00;25.00) n = 50	1+	
281 - 427	26.00 (23.75;29.50) n = 97	26.25 (24.00;29.00) n = 50	26.00 (24.00;29.50) n = 47	24.00* (21.50;25.00) n = 49	1+	
428 - 791	27.00 (24.00;29.13) n = 78	25.00 (24.00;28.00) n = 35	26.00 (23.00;29.00) n = 38	23.50* (22.00;25.00) n = 35	1+	

1 = Kruskal-Wallis-Test: no significance (alpha = 0.05)
 1+ = Kruskal-Wallis-Test: significance (alpha = 0.05)
 * = Mann-Whitney-test: significantly different from group 1 (alpha = 0.05)

Table 22

Short title and project name		Page 12 Carcinogenicity Study with Carvedilol in mice			J 4 - 57	
Table 1b: Difference of body weight of female mice in grams, grouped by time intervals.						
median (1st quartile; 3rd quartile) n = sample size						
first day - last day	Group 1 Control	Group 2 20 mg/kg	Group 3 65 mg/kg	Group 4 200 mg/kg		
0 - 42	6.50 (5.50; 7.50) n = 100	6.00 (5.00; 7.50) n = 50	6.50 (5.50; 7.50) n = 50	6.50 (5.50; 7.13) n = 50	1	
43 - 84	9.50 (8.00;10.50) n = 100	9.00 (7.50;10.00) n = 50	9.50 (8.00;10.63) n = 50	9.00 (8.50;11.00) n = 50	1	
85 - 119	12.00 (10.00;13.00) n = 100	11.00* (9.00;12.00) n = 50	11.00 (9.00;12.00) n = 49	11.00 (10.00;13.00) n = 50	1+	
120 - 182	13.00 (11.00;14.00) n = 99	11.00* (10.00;12.25) n = 50	12.00 (10.25;14.00) n = 48	12.50 (11.00;14.25) n = 50	1+	
183 - 280	14.00 (12.00;16.00) n = 91	13.00 (12.00;14.00) n = 48	13.00 (11.50;15.00) n = 43	13.25 (12.00;15.00) n = 48	1	
281 - 427	15.25 (13.00;17.00) n = 84	14.00 (13.00;15.88) n = 44	14.50 (12.00;16.00) n = 39	14.50 (13.50;16.13) n = 46	1	
428 - 672	17.00 (15.00;19.00) n = 51	16.50 (15.25;19.38) n = 24	17.00 (13.00;19.25) n = 22	16.00 (15.00;19.00) n = 23	1	
1 = Kruskal-Wallis-Test: no significance (alpha = 0.05) 1+ = Kruskal-Wallis-Test: significance (alpha = 0.05) * = Mann-Whitney-Test: significantly different from group 1 (alpha = 0.05)						

000060

FEB -7 1995

NDA 20-297/Amendment (BZ)
Carvedilol Tablets, 12.5 and 25 mg.
Brand Name: Kredex[®]

Submission Date: 3-22-94 and 5-9-94

Sponsor: Smith Kline Beecham

Reviewer: Rajendra S. Pradhan

Type of Submission: Response to FDA Comments

Priority: 1S

Background: The sponsor has requested for an approval of Kredex[®] tablets, 12.5 and 25 mg. In the original NDA review (11-16-93), several comments were conveyed to the sponsor. In these amendments the sponsor is addressing these comments. A copy of Div. of Biopharmaceutics' comments is attached in Appendix I along with sponsors' response. There were six incomplete studies that the sponsor had submitted partial reports on, in the original NDA submission. Study A9911 was of significant importance but rest of the studies were of secondary importance as similar studies addressing similar issues were included in the original submission. A completed study report of study A9911 was received by the Division of Biopharmaceutics and was reviewed on 10-13-94. Other issues/comments raised by the Division in the original review (11-16-93) are addressed satisfactorily by the sponsor.

Recommendation: The sponsor's response to the Division of Biopharmaceutics comments is satisfactory.

Comments to the Sponsor: The sponsor should submit a complete study report of the following studies.

Studies: B1103, B1104, 177, 224, CARV0020



Rajendra S. Pradhan, Ph.D.
Division of Biopharmaceutics

RD Initialed by Ameeta Parekh, Ph.D. Ameeta Parekh 2/7/95

cc NDA 20-297, HFD-110, HFD-426 (Fleischer), HFD-427 (Pradhan) Reviewer, Chron, Drug, FOI (HFD-19), HFD-340 (Viswanathan)

Appendix I

SB
SmithKline Beecham
Pharmaceuticals

March 22, 1994

NDA 20-297

Kredex[®] (carvedilol) 12.5 mg and 25 mg Tablets

Raymond J. Lipicky, M.D., Director
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products (HFD-110)
Document Control Room 16B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Dear Dr. Lipicky:

Reference is made to our New Drug Application for Kredex[®] (carvedilol) Tablets, NDA 20-297.

Additional reference is made to the Agency's letter of November 29, 1993, which provided questions from the Statistics and Biopharmaceutics reviewers.

Submitted herewith, in duplicate, are responses to the questions provided within the aforementioned correspondence. For your convenience, the questions precede the SmithKline Beecham responses and are presented in bold-face type.

- 1. The firm should submit the report on all the studies which were listed in the application as on-going studies.**

Protocol A9911:

A study to investigate the pharmacokinetics of carvedilol enantiomers and the metabolites of carvedilol in poor and extensive metabolizers of debrisoquin.

Protocol B1103:

A study to investigate the effect of renal insufficiency on the pharmacokinetics of carvedilol and the metabolites of carvedilol after single and multiple dose administration in patients with hypertension.

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Doctor Lipicky
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March 22, 1994

Protocol B1104:

A study to assess the effects of chronic oral carvedilol on the steady-state pharmacokinetics of oral digoxin in patients with mild to moderate hypertension.

Protocol 177:

A pharmacokinetic study of a single oral dose of carvedilol 25 mg administered to healthy elderly males compared to the same dose given to healthy young males.

Protocol 224:

An *in vitro* study to assess plasma protein binding of the enantiomers of carvedilol (SK&F 105517) in blood from patients with renal insufficiency and liver disease.

Protocol CARV0020:

A study of the relationship between the dose and antihypertensive effect of carvedilol when administered orally twice a day for two weeks to patients with mild to moderate hypertension (OU-006).

Reports for on-going studies included in Item 6 of the NDA for Kredex® are in preparation and will be submitted when available.

2. In Vitro Dissolution:

- a. The Division of Biopharmaceutics recommends a Q specification of not less than at 30 minutes.

The dissolution specification has been changed to "Q value of in 30 minutes" from "Q value of . 30 minutes".

- b. Please submit the in-vitro dissolution data on whole Kredex® 12.5 mg tablets and half Kredex® tablets (12.5 and 25 mg/broken at the score) using the same dissolution method.

Refer to Table I on page 000003.

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Table 1
In-Vitro Dissolution Data
(Method DI-105517-F-20)
on Whole and Half Kredex[®] Tablets (12.5 and 25mg)

Time	One-half* 12.5mg Tablet Lot U-92100		Whole 12.5mg Tablet Lot U-92100		One-half* 25mg Tablet Lot U-93062		Whole 25mg Tablet Lot U-93062	
	15 min	30 min	15 min	30 min	15 min	30 min	15 min	30 min
Percent dissolved								
Mean	99	102	95	99	96	98	93	96
High								
Low								
R.S.D.	1.94%	2.43%	2.8%	2.6%	3.27%	3.50%	0.90%	0.79%

* broken at the score

000003

Doctor Lipicky
Page 4
March 22, 1994

- c. Please clarify whether the dissolution medium is the same as the simulated gastric fluid as defined in USP XXII.

The composition of the simulated gastric fluid used for dissolution testing of the carvedilol tablets is identical to that defined in the USP, except for pH. While the USP states the pH should be about 1.2, the pH of the dissolution medium used for carvedilol tablets is 1.45 ± 0.2 units.

The lot of pepsin used during the validation of the analytical method resulted in a solution of pH 1.45. Different lots of pepsin were used to prepare subsequent batches of simulated gastric fluid which were closer to the pH stated in the USP (pH 1.2). In order to maintain consistency with the data already reported, a decision was made to adjust the pH of the simulated gastric fluid to a range similar to that used in the validation and early testing. It was felt that this pH change would have no effect on the dissolution results for carvedilol tablets, as the ruggedness results obtained during validation indicate there is no change in dissolution rate when pepsin and sodium chloride are removed from the medium.

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Doctor Lipicky
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March 22, 1994

3. The relative steady-state AUCs for the free fraction of carvedilol enantiomers and each active metabolites were estimated from Study 7097 by the reviewer. The following table was generated:

	Steady-state AUC (ng*hr/ml)	Free Fraction	Steady-state AUC _f (ng*hr/ml)	β-Blocking potency
R(+) carvedilol	166.75	0.6%	1.00	0.01
S(-)-carvedilol	62.99	1.2%	0.76	1
M2	3.80	1.1%	0.097	2.5
M4	7.47	3.3%	0.25	13
M5	5.11	3.4%	0.17	0.6

Although the steady-state AUC for M4 metabolite is about 10-12% of S(-)-carvedilol, due to its higher potency (based on preclinical data) and higher free fraction in plasma, the contribution to the β-blocking activity may be about the same or higher than S(-)-carvedilol. Specific calculation cannot be made because potency relative to free drug is apparently unknown. Such metabolites should be monitored in bio-studies and used in establishing pharmacokinetic-pharmacodynamic link.

Metabolite concentrations are being monitored in all recent studies for hypertension and congestive heart failure.

Please do not hesitate to contact me at (215) 832-3714 should you have any questions regarding this submission.

Sincerely,

Linda Rebar

Linda Rebar
Manager
U.S. Regulatory Affairs

Desk Copy: Ms. Z. McDonald (Cardio - Renal Division, FDA)
Dr. S. Pradhan (Biopharmaceutics Division, FDA)

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Dup

OCT 13 1994

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NDA No. 20-297
 Submission Dates: 3/31/93, 8/15/94
 Generic Name: Carvedilol
 Brand Name: Kredex
 Formulation: Tablets 12.5 and 25 mg
 Sponsor: Smith Kline Beecham,
 King of Prussia, PA 19406
 Type of submission: Amendment to NDA
 Reviewer: O. Borga, Ph.D.

Status: 18

BACKGROUND:

On the request of the Agency, the Sponsor has submitted additional information pertinent to the ongoing review by the Division of Cardio-Renal Drug Products. A report of the pharmacokinetic Protocol A9911, entitled "A study to investigate the pharmacokinetics of carvedilol enantiomers and the metabolites of carvedilol in poor and extensive metabolizers of debrisoquin" was submitted.

LABELING COMMENTS:

(Appendix I)

The following changes of the Package Insert need to be done to accommodate the new data. Under the heading "Pharmacokinetics" the paragraph beginning "Carvedilol undergoes stereoselective first-pass metabolism..." needs to be reworded as follows (the modified portion has been highlighted):

"Carvedilol undergoes stereoselective metabolism with plasma levels of R(+)-carvedilol approximately twice those of S(-)-carvedilol following oral administration in healthy subjects. Kredex is subject to genetic polymorphism with poor metabolizers of debrisoquin (a marker for cytochrome P450 2D6) exhibiting 2- to 3-fold higher plasma concentrations of the R(+)-carvedilol compared to extensive metabolizers. In contrast, plasma levels of S(-)-carvedilol are increased only about 25% in poor metabolizers. Thus, the ratio of R(+)- to S(-)-carvedilol is further increased (to approximately 4) in poor metabolizers of debrisoquin.

Carvedilol is greater than 98% bound..."

The paragraph Drug Interactions should be modified to read as follows, the changed portion being highlighted:

"No pharmacokinetic interaction was observed between single oral doses of Kredex and hydrochlorothiazide in patients with hypertension. Combined administration of Kredex and torasemide in healthy subjects did not result in any significant differences in the pharmacokinetics of either compound. Since carvedilol

undergoes substantial oxidative metabolism, even in patients receiving inducers or inhibitors of cytochrome P-450 enzymes. In particular, drugs able to inhibit CYP2D6-mediated metabolism, e.g., quinidine, may potentiate the plasma levels of R(+)-carvedilol, presumably leading to increased alpha adrenoceptor blockade. Following concomitant administration of Kredex and digoxin, ..."

The new data necessitates no action other than the suggested changes of the labeling.

Olof Borga
.....
Olof Borga, Ph.D.
Pharmacokinetics Review Branch

10/12/94
.....
Date

FT Initialed by Ameeta Parekh, Ph.D. *Ameeta Parekh*
..... 10/13/94

cc: NDA 20-297, HFD-110, HFD-426 (Fleischer, Borga), Drug, FOI (HFD-19), Chron, HFD-340 (Vishwanathan).

This is a review of the preliminary report submitted by the Sponsor. A full report is being prepared by the Sponsor and will be submitted later. Since all pertinent data were presented in the preliminary report, it was judged to be reviewable by the Agency in its present format.

Study Title: A study to investigate the pharmacokinetics of carvedilol enantiomers and the metabolites of carvedilol in poor and extensive metabolizers of debrisoquin.

Protocol number: 105517/A991-US

Report Number: DR94141

Investigators:

Study Site:

Objectives: To determine the metabolism of carvedilol in poor and extensive metabolizers of debrisoquin, and determine the role of CYP2D6 and investigate whether stereoselective metabolism of carvedilol occurs.

Treatments: Subjects received 25 mg of racemic carvedilol orally after an overnight fast.

Design: Open single dose study.

Study Subjects: Nine extensive metabolizers of both debrisoquin and mephenytoin, 7 poor metabolizers of debrisoquin but extensive metabolizers of mephenytoin, and 3 poor metabolizers of mephenytoin but extensive metabolizers of debrisoquin. No demographic data on the subjects were presented in the report.

Blood sampling: Plasma samples were taken at 0, 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours after dosing. All urine up to 72 hours was collected in 24-hr fractions. Plasma and urine was stored at -20°C until analyzed.

Assay of carvedilol and metabolites: Carvedilol and its three metabolites, M2 (desmethyl carvedilol), M4 (4'-hydroxyphenyl carvedilol), and M5 (5'-hydroxyphenyl carvedilol), were determined by one single assay. Plasma with internal standard added was alkalinized and extracted with diethyl ether, and then back-extracted into dilute aqueous acid. HPLC was then performed isocratically using a C-18 base-deactivated column. The compounds were detected by a fluorescence detector set to activate at 285 nm and detect at 350 nm. The lower limit of quantitation was 0.31 ng/ml. Over a concentration range of 0.31 to 64 ng/mL, the

interday precision ranged from 3.8 to 7.1% for the four analytes. Urine concentrations were analyzed by a similar procedure before and after an overnight incubation with Glucuronase to liberate the aglycones. Overall interassay variability was less than 6% for the four analytes.

Carvedilol enantiomer concentrations in plasma were determined by solid phase extraction and subsequent derivatization with GITC to form the diastereoisomers. These were separated on HPLC with fluorescence detection. The lower limit of quantitation for this assay was 0.5 ng/mL and the overall interassay CV less than 4%.

Pharmacokinetic evaluation: A standard noncompartmental analysis was undertaken to determine $AUC_{0-\infty}$, CL/F, K_{el} (terminal elimination rate constant), and terminal half-life. The total 72-hr excretion of conjugated carvedilol (presumably the glucuronide), M2, M4, and M5 were determined as well as their partial metabolic formation clearances.

Data on poor metabolizers of mephenytoin were also reported, but because of their small number, this reviewer considers the data obtained in these individuals inconclusive. Hence they will not be discussed in this review.

STUDY RESULTS:

The means $\pm$ SEM of the pharmacokinetic parameters for the R- and S-enantiomers of carvedilol in poor and extensive metabolizers of debrisoquin are presented in Table 1.

TABLE 1
Area under the plasma concentration/time curve and apparent oral clearance for the R and S enantiomers of carvedilol.

	R-Isomer			S-Isomer			Total Cl (L/h)	S/R Cl Ratio
	AUC (ng.lh/mL)	Cl (L/h)	$t_{1/2}$ (h)	AUC (ng.lh/mL)	Cl (L/h)	$t_{1/2}$ (h)		
<u>Debriso-</u> <u>quin</u>								
EMs (n=9)	159.4 ± 38.3	119.2 ± 26.9	2.68 ± 0.25	72.7** ± 11.4	215.4+++ ± 40.0	4.03** ± 0.52	156.57 ± 31.74	2.03 ± 0.19
PMs (n=7)	408.9*** ± 72.2	38.9* ± 8.6	4.71**** ± 0.51	104.04++ ± 19.9	163.6** ± 43.1	5.70 ± 1.49	65.99* ± 14.54	4.06**** ± 0.16

* $p < 0.05$; *** $p < 0.01$; **** $p < 0.002$ vs EMs
** $p < 0.05$; ++ $p < 0.005$; +++ $p < 0.0005$ vs R

The mean $\pm$ SEM of the corresponding plasma concentration curves is presented in Figure 1. Both R- and S-carvedilol plasma levels are higher in poor metabolizers of debrisoquin. The apparent oral clearance of the two enantiomers was reduced accordingly as shown in Figure 2, which presents mean $\pm$ SEM data.

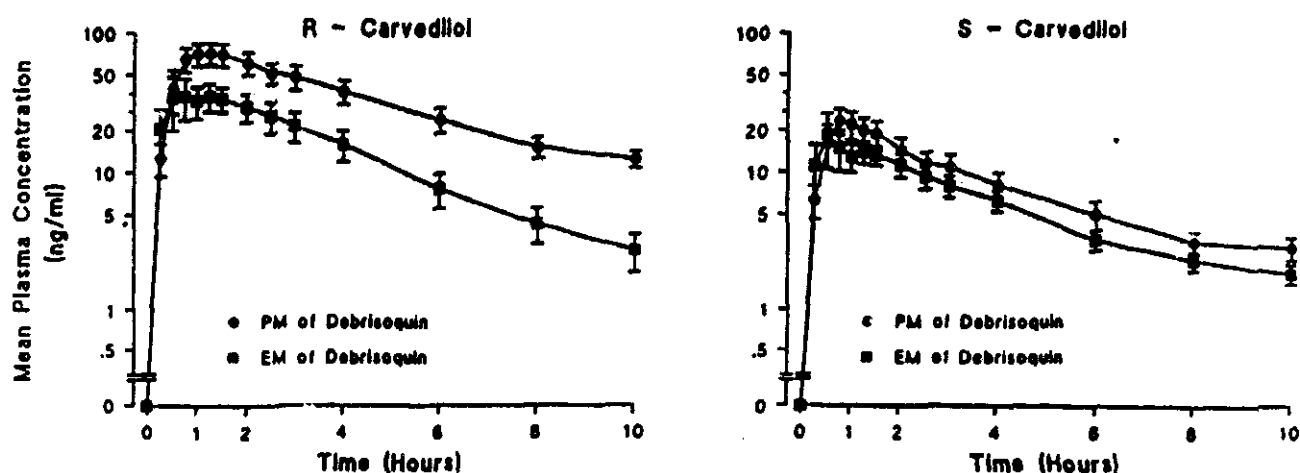


Figure 1 - Plasma R and S carvedilol concentrations in EMs (n = 9) and PMs (n = 7) of debrisoquin.

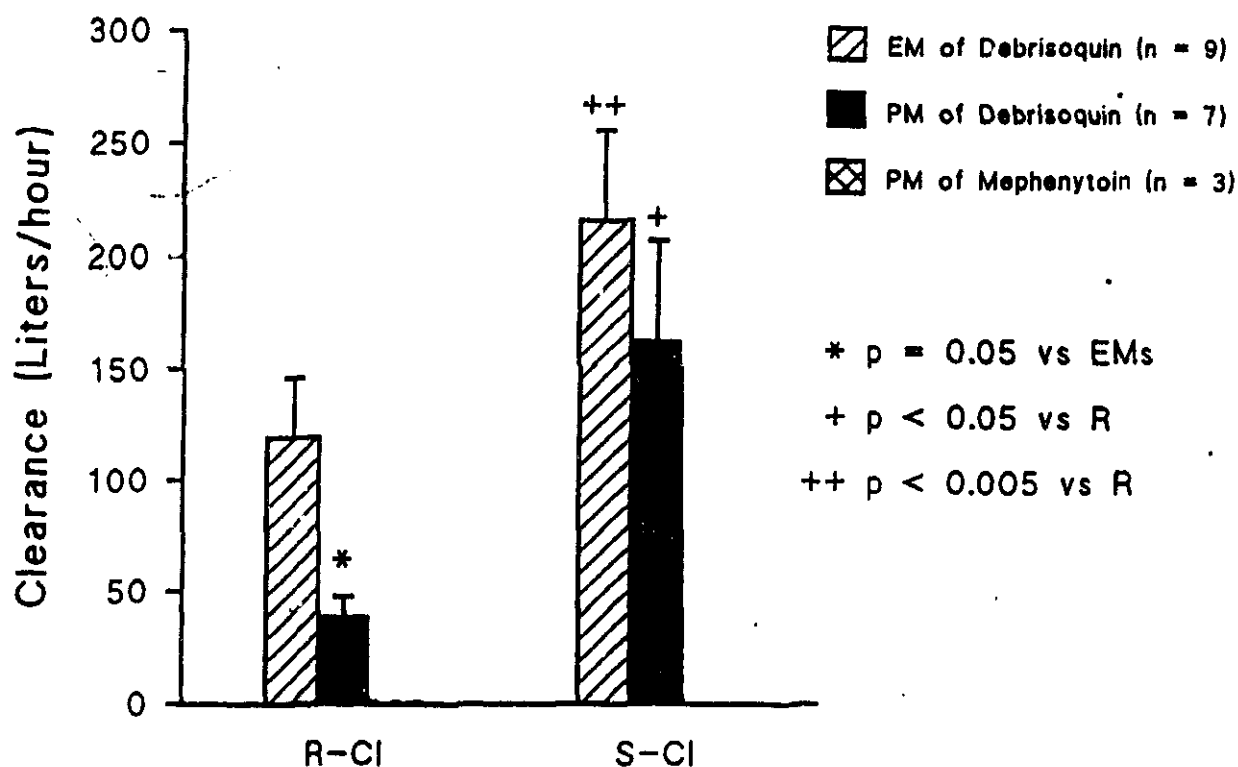


Figure 2 - Clearance of R and S carvedilol in EMs and PMs of debrisoquin

The S/R clearance ratios in poor and extensive metabolizers of debrisoquin are presented in Figure 3. As shown in the Figure, the clearance of the S-enantiomer is approximately 2 in extensive metabolizers of debrisoquin. This ratio is increased to approximately 4 in the poor metabolizers.

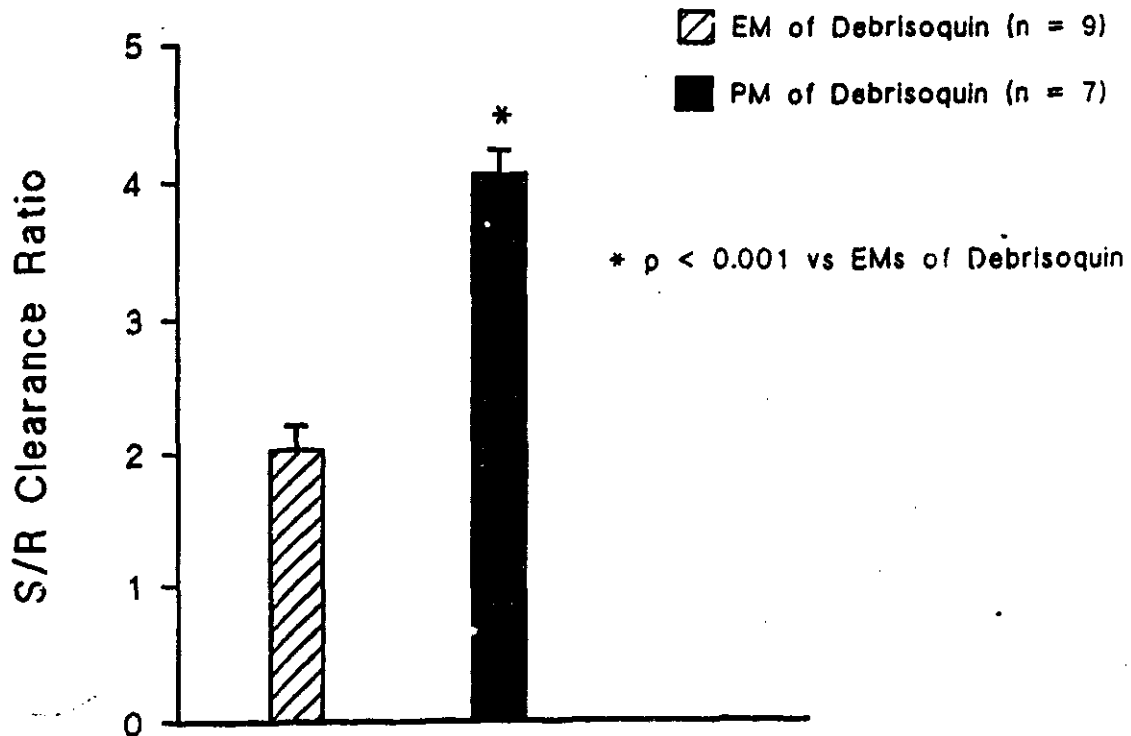


Figure 3 - S/R clearance ratio in EMs and PMs of debrisoquin.

The partial metabolic clearances of carvedilol to its metabolites showed a dramatic difference in poor metabolizers of debrisoquin. Mainly, the M4 and M5 pathway clearances were reduced to approximately 25% of those in extensive metabolizers of debrisoquin, while direct conjugation of carvedilol and formation of metabolite M2 were unchanged.

For completeness, the data obtained in the three poor metabolizers of mephenytoin is presented in Table 2 below.

Table 2. Areas under the plasma concentration-time curve and apparent oral clearance for the R- and S-enantiomers of carvedilol in poor metabolizers of mephenytoin.

R-isomer			S-isomer			Total CL (L/hr)	S/R CL Ratio
AUC (ng*hr/mL)	CL (L/hr)	t1/2 (hr)	AUC (ng*hr/mL)	CL (L/hr)	t1/2 (hr)		
213.8 ±138	118.6 ±46.6	2.97 ±0.38	90.6 ±42.3	197.9 ±64.8	3.83 ±0.18	144.3 ±51.3	1.99 ±0.42

DISCUSSION: The present data demonstrate large differences in plasma levels and apparent oral clearances of carvedilol in poor and extensive metabolizers of debrisoquin. This is not caused by differences in absorption of carvedilol between these two groups, but are due to different metabolism rates as demonstrated by reduced clearances of two particular metabolic pathways: formation of metabolites M4, 4'-hydroxyphenyl carvedilol, and M5, 5'-hydroxyphenyl carvedilol.

CONCLUSIONS: The relatively increased plasma levels of R-carvedilol in the poor as opposed to the extensive metabolizers of debrisoquin may lead to increased alpha adrenoceptor blockade. The same effect might be obtained in patients that are extensive metabolizers of debrisoquin, when treated with drugs able to inhibit CYP2D6, e.g. quinidine.

*Discussed c
Olog, there
was no differ
in M4, M5, M2, 1
this group
Amount*

KREDEX (carvedilol) Tablets
ITEM 4.C.1 Draft Labeling

	<u>Volume</u>	<u>Page</u>
a. Draft Package Insert	1.2	000551
b. Immediate Container Labels		
12.5 mg Tiltab® Tablet.....	1.2	000570
25 mg Tiltab® Tablet.....	1.2	000571

h181awdn

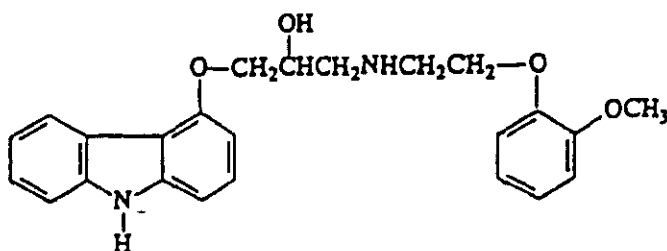
March 5, 1993

**KR:L1 PRESCRIBING
INFORMATION**

KREDEX®
brand of
carvedilol
Tablets

DESCRIPTION

Kredex (carvedilol) is (±)-1-Carbazol-4-yloxy)-3-[[2-(o-methoxyphenoxy)ethyl]amino]-2-propanol. It is a racemic mixture with the following structure:



carvedilol

Carvedilol is a white to off-white powder with a molecular weight of 406.5 and a molecular formula of C₂₄H₂₆N₂O₄. It is freely soluble in dimethylsulfoxide; soluble in methylene chloride and methanol; sparingly soluble in 95% ethanol and isopropanol; slightly soluble in ethyl ether; and practically insoluble in water, gastric fluid (simulated, TS, pH 1.1) and intestinal fluid (simulated, TS without pancreatin, pH 7.5).

Tablets for Oral Administration:

Each white, scored, oval, film-coated Tiltab® tablet contains 12.5 mg or 25 mg

of carvedilol. Inactive ingredients consist of crospovidone, hydroxypropyl methyl cellulose, lactose, magnesium stearate, polyethylene glycol, polysorbate 80, povidone, colloidal silicon dioxide, sucrose and titanium dioxide.

CLINICAL PHARMACOLOGY

Kredex combines effective nonselective β -adrenoreceptor-blocking activity with significant peripheral vasodilating activity in a single substance. The vasodilation is primarily related to α_1 -blockade. Through these effects, *Kredex* significantly reduces blood pressure in hypertensive patients. Both enantiomers possess vasodilating activity; the S(-) enantiomer produces β -blockade. *Kredex* has no intrinsic sympathomimetic activity.

Pharmacodynamics

β -adrenoreceptor blocking activity has been demonstrated in animal and human studies showing that carvedilol 1) reduces systolic and diastolic blood pressure at rest and during exercise; 2) reduces cardiac output; 3) reduces exercise- and/or isoproterenol-induced tachycardia and 4) reduces reflex orthostatic tachycardia. Significant β -adrenoreceptor-blocking effect is usually seen within 1 hour of drug administration and is still present at 24 hours.

Vasodilation has been demonstrated in animal and human studies showing that carvedilol significantly reduces peripheral vascular resistance which, in turn, contributes to the reduction of blood pressure. This effect, which also helps reduce some of the unwanted effects usually associated with β -blockade (e.g., cold extremities,

bradycardia and myocardial depression), is usually seen within 30 minutes of drug administration. Calcium-channel-blocking activity has been demonstrated in animal models (*in vivo* and *in vitro*); however, this effect has only been demonstrated at concentrations higher than those observed within the therapeutic antihypertensive dosage range.

With chronic once-daily administration, antihypertensive effectiveness is maintained over 24 hours. Steady-state plasma concentrations appear to correlate with therapeutic response.

By balancing vasodilation and β -adrenoreceptor blockade, *Kredex* maintains myocardial function without significantly affecting left ventricular ejection fraction. Heart rate is generally unchanged or slightly decreased.

In patients with exertional angina, *Kredex* reduces the rate pressure product and increases stroke volume index. Thus, myocardial oxygen demand is reduced at any given exercise level.

In 2 double-blind, placebo-controlled clinical trials involving patients with well-compensated congestive heart failure (NYHA Class II and Class III), *Kredex* therapy improved submaximal exercise tolerance, left ventricular ejection fraction and clinical symptomatology. Studies in patients with NYHA Class IV heart failure have not been performed and, generally, β -blockers should be used cautiously in any patient with compensated heart failure.

Kredex has no adverse effect on peripheral blood flow, or excretion of

sodium, potassium, chloride, uric acid, calcium or phosphorous. *Kredex* did not affect spirometry, with or without histamine challenge, in normal volunteers or hypertensive patients without known bronchospastic pulmonary disease. In hypertensive patients with normal renal function, therapeutic doses of *Kredex* decreased renal vascular resistance with no change in glomerular filtration rate or renal plasma flow.

Additionally, *Kredex* has little effect on plasma catecholamines, plasma aldosterone or electrolyte levels, but it does significantly reduce plasma renin activity when given for at least 4 weeks. It also increases levels of atrial natriuretic peptide.

In animal models carvedilol reduced myocardial infarct size--47% in rats, 63% to 79% in dogs and 89% in pigs.

In a gerbil stroke model, carvedilol improved survival of neurons. Furthermore, chronic carvedilol treatment of hypertensive rats prone to develop stroke significantly reduced mortality.

In vitro, carvedilol reduced basal and stimulated mitogenic activity in vascular smooth muscle cells. In particular, carvedilol inhibited smooth muscle cell proliferation in response to diverse growth factors, hormones and modulators such as angiotensin II.

Pharmacokinetics

Kredex is rapidly and extensively absorbed following oral administration. The absolute bioavailability is approximately 25% to 35% due to a significant degree of first-pass

metabolism (approximately 50% to 70%). Following oral administration of the 25 mg Tiltab® tablets in healthy subjects, maximum plasma concentrations were observed between 0.5 and 3.3 hours (median 1.1 hours), and ranged from 28 to 208 ng/mL (mean: 70 ng/mL). Plasma concentrations increased in a dose-proportional manner. In general, mean-terminal elimination half-lives range from 7 to 10 hours after oral administration. There is no unexpected accumulation following once-daily dosing of *Kredex*. When administered with food, the time to reach peak-plasma levels is prolonged, with no significant difference in extent of bioavailability.

Carvedilol undergoes stereoselective first-pass metabolism with plasma levels of R(+)-carvedilol approximately 2- to 3-fold higher than S(-)-carvedilol following oral administration in healthy subjects. *Kredex* is subject to genetic polymorphism with poor metabolizers of debrisoquin exhibiting 2- to 3-fold higher plasma concentrations of the R(+)-carvedilol compared to extensive metabolizers. In contrast, plasma levels of S(-)-carvedilol are increased only about 20% to 25% in poor metabolizers. The pharmacokinetics of carvedilol enantiomers do not appear to be different in poor metabolizers of S-mephenytoin.

Carvedilol is greater than 98% bound to plasma proteins, primarily with albumin. The plasma-protein binding is independent of concentration over the therapeutic range. Carvedilol is a basic, lipophilic compound with a steady-state volume of distribution of approximately 115 L, indicating substantial distribution

into extravascular tissues. Plasma clearance ranges from 500 to 700 mL/min. Carvedilol is extensively metabolized with less than 2% of the dose excreted unchanged in the urine. Carvedilol is metabolized primarily by aromatic ring oxidation and glucuronidation. The oxidative metabolites are further metabolized by conjugation via glucuronidation and sulfation. The metabolites of carvedilol are excreted primarily via the bile into the feces. Demethylation and hydroxylation at the phenol ring produce 3 active metabolites with β -receptor-blocking activity. Based on preclinical studies, the 4'-hydroxyphenyl metabolite is approximately 13 times more potent than carvedilol. Compared to carvedilol, the 3 active metabolites exhibit weak vasodilating activity. Plasma concentrations of the active metabolites are about 10 times lower than those observed for carvedilol and follow a similar time course with the parent.

Elderly: Plasma levels of carvedilol are generally higher in the elderly population compared to young subjects, although the difference appears to fall within the range of intersubject variability.

Hepatic Impairment: Compared to healthy subjects, patients with cirrhotic liver disease exhibit significantly higher concentrations of carvedilol (approximately 4- to 7-fold) following single-dose therapy.

Renal Insufficiency: Since carvedilol is metabolized primarily by the liver, it is unlikely that the pharmacokinetics will be altered in patients with renal disease. Data from studies in hypertensive patients with varying degrees of renal

impairment suggest no significant effect of renal dysfunction on plasma concentrations of carvedilol and its active metabolites. Consistent with its high degree of plasma protein-binding, carvedilol does not appear to be significantly cleared by hemodialysis.

CLINICAL TRIALS

Hypertension

Kredex has been shown to be an effective antihypertensive agent, providing consistent 24-hour reduction of blood pressure. The antihypertensive efficacy of once-daily *Kredex* therapy has been demonstrated in double-blind, placebo-controlled studies ranging in length from 8 to 16 weeks. These studies involved patients with mild-to-moderate essential hypertension of whom 692 were on *Kredex* (23.2% >64 years of age) and 260 were on placebo (18.3% >64 years of age).

Kredex produced significant blood pressure reduction within 2 weeks of initiating therapy. At 8 to 16 weeks, *Kredex* produced statistically significant reductions in sitting and standing diastolic blood pressure at 24 hours post-dose, averaging about 7 mmHg in the standing position and 6 mmHg in the sitting position. Blood-pressure effect is maintained over the 24-hour dosing interval. Tolerance to the antihypertensive effect of *Kredex* was not observed in over 200 patients in U.S. clinical trials studied for up to 1 year. The reduction in sitting and standing blood pressure is dose related within the recommended range of 12.5 mg to 50 mg once daily. Effects on diastolic blood pressure and response rates were similar in younger and older patients.

Chronic Stable Angina

The effectiveness of *Kredex* therapy in chronic exercise-induced angina has been evaluated in a double-blind comparative trial of 4 weeks' duration involving 163 patients (84 *Kredex*, 79 sustained release nifedipine). The increase in total exercise work averaged 34.6% (121 W sec) for *Kredex* and 21.7% (84 W sec) for nifedipine.

Kredex also increased time to angina and time to 1 mm ST segment depression, and decreased angina attack rate.

INDICATIONS AND USAGE

Kredex (carvedilol) is indicated for the management of essential hypertension. It can be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics. (See PRECAUTIONS, Drug Interactions.)

CONTRAINDICATIONS

Kredex is contraindicated in patients with uncontrolled cardiac failure, bronchial asthma or related bronchospastic conditions, second- or third-degree AV block, cardiogenic shock or severe bradycardia.

Kredex is contraindicated in patients with hypersensitivity to the drug.

PRECAUTIONS

General

Since *Kredex* has β -blocking activity, it should not be discontinued abruptly, particularly in patients with ischemic heart disease. Instead, it should be discontinued over 1 to 2 weeks.

Kredex may cause bradycardia. If pulse rate drops below 55 beats/min., the dosage must be reduced.

Caution should be exercised when administering agents with β -blocking activity to diabetic patients since early signs of acute hypoglycemia may be obscured.

Agents with β -blocking activity may obscure symptoms of thyrotoxicosis.

Patients with psoriasis or a family history of psoriasis should receive drugs with β -blocking properties only if the benefit outweighs the risk.

Wearers of contact lenses should bear in mind the possibility of reduced lacrimation.

Patients with Hepatic Dysfunction:
Use of *Kredex* in patients with clinically manifest hepatic impairment is not recommended since bioavailability increases in patients with hepatic cirrhosis.

Anesthesia and Major Surgery:
The necessity or desirability of withdrawing a β -blocker before major surgery is controversial. β -adrenergic receptor blockade impairs the ability of the heart to respond to β -adrenergically mediated reflex stimuli. While this might be of benefit in preventing arrhythmic response, the risk of excessive myocardial depression during general anesthesia may be increased, and difficulty in restarting and maintaining the heart beat has been reported with β -blockers. If treatment is continued, particular care should be taken when using anesthetic agents that depress the myocardium (e.g., ether, cyclopropane and trichloroethylene), and it is prudent to use the lowest possible dose of *Kredex*. *Kredex*, like other β -blockers, is a competitive

inhibitor of β -receptor agonists and its effect on the heart can be reversed by cautious administration of such agents (e.g., dobutamine or isoproterenol--see OVERDOSAGE). Manifestations of excessive vagal tone (e.g., profound bradycardia, hypotension) may be corrected with atropine 1 to 3 mg IV in divided doses.

Information for Patients

Patients should know how they react to this medication before they operate automobiles and machinery, or engage in other tasks requiring alertness.

Drug Interactions

No pharmacokinetic interaction was observed between single oral doses of *Kredex* and hydrochlorothiazide in patients with hypertension. Combined administration of *Kredex* and torasemide in healthy subjects did not result in any significant differences in the pharmacokinetics of either compound. Since carvedilol undergoes substantial oxidative metabolism, care may be required in patients receiving inducers or inhibitors of mixed function oxidases, as carvedilol plasma concentrations may be altered.

Following concomitant administration of *Kredex* and digoxin, steady-state trough concentrations of digoxin were increased by 16% in hypertensive patients. Although this is of uncertain clinical significance, increased monitoring of digoxin is recommended when initiating, adjusting or discontinuing *Kredex*. Carvedilol has been shown not to alter the *in vitro* plasma-protein binding of racemic warfarin.

A 12-day study involving 28 hypertensive patients showed that the

combination of *Kredex* and captopril resulted in at least an additive antihypertensive effect and was generally well tolerated.

The potential for a pharmacokinetic interaction between carvedilol and calcium channel blocking agents has not been explored. Literature reports suggest that oral calcium antagonists may be used in combination with agents with β -blocking activity when heart function is normal, but should be avoided in patients with impaired cardiac function. Hypotension, AV conduction disturbances and left ventricular failure have been reported in some patients when an oral calcium antagonist was added to treatment with a β -blocking agent. Hypotension was more likely to occur when the calcium antagonist was a dihydropyridine derivative, while left ventricular conduction disturbances, including AV block, were more likely to occur with verapamil or diltiazem. With *Kredex*, isolated cases of conduction disturbance (rarely with hemodynamic compromise) have been observed when co-administered orally with diltiazem. As with other agents with β -blocking properties, if *Kredex* is to be administered orally with calcium channel blockers of the verapamil or diltiazem type, it is recommended that ECG and blood pressure be monitored.

Patients taking both agents with β -blocking properties and a drug that can deplete catecholamines (e.g., reserpine and monoamine oxidase inhibitors) should be observed closely for signs of hypotension and/or severe bradycardia. Concomitant administration of clonidine with agents with β -blocking properties may potentiate blood-pressure- and

heart-rate-lowering effects. When concomitant treatment with agents with β -blocking properties and clonidine is to be terminated, the β -blocking agent should be discontinued first. Clonidine therapy can then be discontinued several days later by gradually decreasing the dosage. Agents with β -blocking properties may enhance the blood-sugar-reducing effect of insulin and oral hypoglycemics. The signs of hypoglycemia (especially tachycardia) may be obscured or attenuated. Therefore, regular monitoring of blood glucose is recommended.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In 2-year studies conducted in rats given carvedilol at doses up to 75 mg/kg/day (75 times the maximum human dose) or in mice given up to 200 mg/kg/day (200 times the maximum human dose), carvedilol had no carcinogenic effect.

Carvedilol was not mutagenic in *in vitro* or *in vivo* nonmammalian and mammalian tests.

At doses $\geq$ 200 mg/kg/day ($\geq$ 200 times the maximum human dose) carvedilol was toxic to adult rats (sedation, reduced weight gain) and was associated with a reduced number of successful matings, prolonged mating time, significantly fewer corpora lutea and implants per dam and complete resorption of 18% of the litters. The no-observed-effect dose level for overt toxicity and impairment of fertility was 60 mg/kg/day (60 times the maximum human dose).

Pregnancy: Teratogenic Effects, Pregnancy Category C.

Studies performed in pregnant rats and rabbits given carvedilol revealed increased post-implantation loss in rats at doses of 300 mg/kg/day (300 times the maximum human dose) and in rabbits at doses of 75 mg/kg/day (75 times the maximum human dose). In the rats, there was also a decrease in fetal body weight at the maternally toxic dose of 300 mg/kg/day (300 times the maximum human dose), which was accompanied by an elevation in the frequency of fetuses with delayed skeletal development (missing or stunted 13th rib). In rats the no-observed-effect level for developmental toxicity was 60 mg/kg/day (60 times the maximum human dose); in rabbits it was 15 mg/kg/day (15 times the maximum human dose). There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Studies in rats have shown that carvedilol and/or its metabolites (as well as other β -blockers) cross the placental barrier and are excreted in breast milk. Therefore, the possibility of the consequences of α - and β -blockade in the human fetus and neonates should be borne in mind. With the other α - and β -blocking agents effects have included perinatal and neonatal distress.

Pediatric Use

Safety and efficacy in children have not been established.

Geriatric Use

Of the 1,921 patients in U.S. clinical trials of efficacy or safety who were treated with *Kredex*, 22% (415) were 65

years of age or older. Of 3,722 patients receiving *Kredex* in hypertension clinical trials conducted worldwide, 24% were 65 years of age or older. There were no notable differences in efficacy or the incidence of adverse events between older and younger patients. With the exception of dizziness (incidence 8.8% in the elderly vs. 6% in younger patients), there were no events for which the incidence in the elderly exceeded that in the younger population by greater than 2.0%.

Similar results were observed in a postmarketing surveillance study of 3,328 *Kredex* patients, of whom approximately 20% were 65 years of age or older.

ADVERSE REACTIONS

Kredex has been evaluated for safety in hypertension in more than 2,153 patients in U.S. clinical trials and in 2,976 patients in international clinical trials. Approximately 25% of the total treated population received *Kredex* for at least 6 months. In general, *Kredex* was well tolerated at doses up to 100 mg daily. Most adverse events reported during *Kredex* therapy were of mild to moderate severity. In U.S. controlled clinical trials directly comparing *Kredex* monotherapy in doses up to 50 mg (n=1,142) to placebo (n=462), 4.9% of *Kredex* patients discontinued for adverse events vs. 5.2% of placebo patients; the difference was not statistically significant.

Table 1 shows adverse events in U.S. placebo-controlled clinical trials that were possibly or probably related to treatment and occurred with an incidence of greater than 1%.

Table 1

**Adverse Events in U.S. Placebo-Controlled Trials
Incidence $\geq 1\%$**

	<i>Kredex</i> (n=1,142) (%)	Placebo (n=462) (%)
Headache	6.4	10.6
Dizziness	5.0*	4.3
Fatigue	3.6	2.8
Bradycardia	2.1	0.2
Postural hypotension	1.8	0.0
Edema	1.6	1.5
Diarrhea	1.4	0.6
Somnolence	1.3	1.3

* Only dizziness appeared to be dose related.

The following adverse events were reported as possibly or probably related in worldwide open or controlled trials with *Kredex*.

- Incidence $>0.1\%$ to $\leq 1\%$

Cardiovascular: Abnormal ECG, AV block, extrasystoles, heart disorder, hypertension, hypotension, palpitations, peripheral ischemia, syncope.

Central and Peripheral Nervous System: Ataxia, hypesthesia, paresthesia, vertigo.

Gastrointestinal: Abdominal pain, bilirubinemia, constipation, dyspepsia, flatulence, increased hepatic enzymes, nausea, vomiting.

General: Asthenia, chest pain, hot flushes, leg cramp, malaise, pain.

Musculoskeletal System: Back pain, myalgia.

Psychiatric: Decreased libido (male), depression, impotence, insomnia, nervousness.

Respiratory System: Asthma, cough, dyspnea, rhinitis, sinusitis.

Skin and Appendages: Pruritus, rash, rash erythematous, rash maculopapular, rash psoriaform.

Special Senses: Abnormal vision, tinnitus.

Urinary System: Albuminuria, hematuria, micturition frequency.

Autonomic Nervous System: Dry mouth, sweating increased.

Metabolic and Nutritional: Hypercholesterolemia, hyperglycemia, hypertriglyceridemia, hyperuricemia.

Hematologic: Anemia, leukopenia, thrombocytopenia.

The following events were reported in $\leq 0.1\%$ of patients: angina, arrhythmia, atrial fibrillation, bundle branch block, cardiac failure, myocardial ischemia, tachycardia, cerebrovascular disorder, hypertonia, migraine, neuralgia, paresis, speech disorder, tremor, flushing, allergy, skin disorder, alopecia, muscle weakness, arthralgia, arthrosis, agitation, anxiety, amnesia, impaired concentration, confusion, abnormal dreaming, sleep disorder, abnormal thinking, anorexia, gastroenteritis, nonspecific gastrointestinal disorder, bronchitis, bronchospasm, epistaxis, pleurisy, respiratory disorder, nocturia,

micturition disorder, decreased hearing, conjunctivitis, retinal disorder, respiratory alkalosis, increased BUN, glycosuria, decreased HDL, hyperkalemia, hypokalemia, hyperlipidemia, increased NPN, increased alkaline phosphatase, thirst, increased weight, thrombocytopenia, eosinophilia and atypical lymphocytes.

Other reactions occurred sporadically in single patients and cannot be distinguished from concurrent disease states or medications.

Kredex therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, fasting serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, creatinine or liver function tests.

OVERDOSAGE

The acute oral LD₅₀s in male and female mice and male and female rats are over 8000 mg/kg.

Overdosage may cause severe hypotension, bradycardia, cardiac insufficiency, cardiogenic shock and cardiac arrest. Respiratory problems, bronchospasms, vomiting, lapses of consciousness and generalized seizures may also occur.

The patient should be placed in a supine position and, where necessary, kept under observation and treated under intensive-care conditions. Gastric lavage or pharmacologically induced emesis may be used shortly after

ingestion. The following agents may be administered:

for excessive bradycardia: atropine, 2 mg IV.

to support cardiovascular function: glucagon, 5 to 10 mg IV rapidly over 30 seconds, followed by a continuous infusion of 5 mg/hour; sympathomimetics (dobutamine, isoprenaline, adrenaline) at doses according to body weight and effect.

If peripheral vasodilation dominates, it may be necessary to administer adrenaline or noradrenaline with continuous monitoring of circulatory conditions. For therapy-resistant bradycardia, pacemaker therapy should be performed. For bronchospasm, β -sympathomimetics (as aerosol or IV) or aminophylline IV should be given. In the event of seizures, slow IV injection of diazepam or clonazepam is recommended.

NOTE: In the event of severe intoxication where there are symptoms of shock, treatment with antidotes must be continued for a sufficiently long period of time consistent with the 7- to 10-hour half-life of carvedilol.

Three cases of overdose have been reported. A 59-year-old male who ingested 200 mg experienced severe chest pain but recovered completely. A 2-year-old child who ingested an unknown quantity suffered no adverse effects following induced vomiting and observation. A 39-year-old female ingested 400 mg with an unknown amount of benzodiazepine. She was hospitalized in a state of stupor and hypotension, but recovered completely following supportive measures.

DOSAGE AND ADMINISTRATION

Dosage should be individualized. For all patients, the recommended starting dose is 12.5 mg once daily. The full antihypertensive effect is usually seen within 7 to 14 days; after this time if the response is inadequate, the dosage can be doubled, up to a maximum total daily dose of 50 mg.

HOW SUPPLIED

Tablets: 12.5 mg and 25 mg--white, scored, oval, film-coated Tiltab® tablets, in bottles of 100.

Store at controlled room temperature (15° to 30°C; 59° to 86°F). Protect from moisture. Dispense in a tight, light-resistant container.

12.5 mg 100's: NDC 0007-4141-20

25 mg 100's: NDC 0007-4142-20

DATE OF ISSUANCE _____

© SmithKline Beecham, 199-

**SmithKline Beecham
Pharmaceuticals
Philadelphia, PA 19101**

KR:L1

Printed in U.S.A.

LOT
EXP.
05382-A



Store at controlled room temperature (20° to 25°).
Dispense in a tight, light-resistant container.
Each Tiltab[®] tablet contains carvedilol, 12.5 mg.
Dosage: See accompanying prescribing information.
Important: Use safety closures when dispensing
this product unless otherwise directed by
physician or requested by purchaser.
Caution: Federal law prohibits dispensing
without prescription.
SmithKline Beecham Pharmaceuticals
Philadelphia, PA 19101

12.5mg
NDC 0027-4131-20

KREDEX[®]
CARVEDILOL TABLETS

100 TILTAB[®] Tablets

SB SmithKline Beecham



LOT
EXP.



3 0007-4142-20 1

Store at controlled room temperature
(20° to 25°).
Dispense in a light, light-resistant metal or
Each TILTAB® tablet contains carvedilol, 25 mg.
Dosage: See accompanying prescribing
information.
Important: Use safety closures when
dispensing this product unless otherwise
directed by physician or requested by purchaser.
Caution: Federal law prohibits dispensing
without prescription.
SmithKline Beecham Pharmaceuticals
Philadelphia, PA 19101

25mg

NDC 6307-4142-20

KREDEX
CARVEDILOL TABLETS

100 TILTAB® Tablets

SB SmithKline Beecham



000571

NOV 16 1993

NDA 20-297

Submission Date: 10-29-93

Carvedilol Tablets, 12.5 and 25 mg.

Brand Name: Kredex[®]

Sponsor: Smith Kline Beecham

Reviewer: Rajendra S. Pradhan

Type of Submission: Amendment

Priority: 1S

Background: The sponsor has requested for an approval of Kredex[®] tablets, 12.5 and 25 mg. In the original NDA submission (04-30-93), the firm had submitted a pivotal bioequivalency study (#020). In the report of this study, bioequivalence was assessed using AUC_{0-24} and C_{max} as the primary parameters. The firm had tried to justify the use of AUC_{0-24} instead of $AUC_{0-\infty}$, since the percent of $AUC_{0-\infty}$ which was extrapolated was greater than 20% in number of subjects. The Division of Biopharmaceutics had requested the firm to reanalyze the bioequivalence using $AUC_{0-\infty}$. In this submission the firm is amending the results of study #020 by submitting the point estimate for the true ratio (tablet/capsule) for $AUC_{0-\infty}$ and its 90% confidence limits.

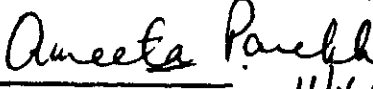
Comments: Despite the fact that the percent of $AUC_{0-\infty}$ which was extrapolated was greater than 20% in number of subjects, the point estimate and 90% confidence intervals for the true ratio (tablet/capsule) for $AUC_{0-\infty}$ were almost identical to those presented for AUC_{0-24} . Thus to be marketed tablet can be considered to be bioequivalent to capsule in terms of AUC_{0-24} , $AUC_{0-\infty}$ and C_{max} .

(log-transformed)	Mean Ratio	90% CI
$AUC_{0-\infty}$	0.92	(0.88, 0.97)
AUC_{0-24}	0.93	(0.89, 0.97)
C_{max}	0.90	(0.81, 1.01)

Recommendation: The firm has appropriately addressed the concerns raised by the Division of Biopharmaceutics.


11/16/93

Rajendra S. Pradhan, Ph.D.
Division of Biopharmaceutics

RD Initialed by Ameeta Parekh, Ph.D. 

11/16/93

cc NDA 20-297, HFD-110, HFD-426 (Fleischer/Pradhan)
FOI (HFD-19), HFD-340 (Viswanathan)

Reviewer, Chron, Drug,

NOV 16 1993

NDA: 20-297

Carvedilol, 12.5 & 25 mg tablets
Kredex®
SmithKline Beecham Pharmaceuticals
Four Falls Corporate Center
King of Prussia, PA 19406

SUBMISSION DATE: Mar. 31, 1993
Apr. 30, 1993, Sept. 14, 1993
Oct. 4, 1993

REVIEWERS: Hae-Ryun Choi, Ph.D.
Rajendra Pradhan, Ph.D.

TYPE OF SUBMISSION: Original NME

PRIORITY: 1 S

SYNOPSIS:

The sponsor has adequately studied the pharmacokinetics (single and multiple dose), metabolism and excretion of carvedilol and has established the dose proportionality of carvedilol to include the dose range covered in the package insert. Acceptable studies have been performed in elderly population, hypertensive patients, renally impaired patients, and patients with hepatic diseases. The sponsor has adequately studied the bioequivalency of 25 mg carvedilol capsule formulation used in US clinical trials to the 25 mg tablet formulation of carvedilol to be marketed. Drug interactions between carvedilol and hydrochlorothiazide, torsemide, digoxin, cimetidine, and rifampin were studied. The sponsor has adequately validated the assay methods for carvedilol, carvedilol enantiomers, and its metabolites. The sponsor provided adequate in-vitro dissolution information on the bio-batch tablets and capsule formulations used in pivotal clinical trials. Kredex® 12.5 mg tablets are compositionally proportional to Kredex® 25 mg tablets. The sponsor has attempted to correlate the plasma carvedilol level to the pharmacological effects.

RECOMMENDATION:

The sponsor's NDA 20-297 appears to be acceptable for meeting the biopharmaceutics requirements, provided that comments are addressed satisfactorily by the sponsor.

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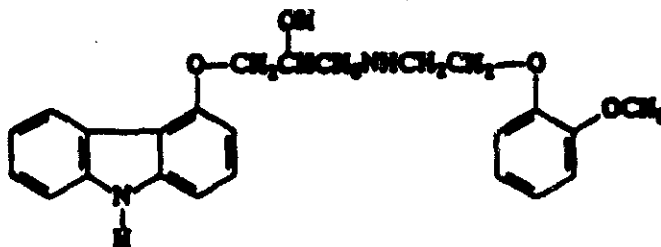
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BACKGROUND:

Carvedilol is a multiple-action cardiovascular agent that was designed to produce two complementary pharmacological actions: combined venous and arterial vasodilation and non-cardioselective, β -adrenergic blockade. Carvedilol is indicated for the treatment of essential hypertension. Carvedilol is ($\pm$)-1-Carbazol-4-yloxy-3-[2-(o-methoxyphenoxy)ethyl]amino-2-propanol. It is a racemic mixture of two isomers, R(+)- and S(-)-carvedilol with the following structure:



Carvedilol is a white to off-white powder with a molecular weight of 406.5 and a molecular formula of $C_{24}H_{28}N_2O_4$. It is practically insoluble in water (solubility: 10 mcg/ml), simulated gastric fluid (USP XXII, solubility: 50 mcg/ml) and simulated intestinal fluid (without pancreatin, pH 7.5, USP XXII, solubility: 3 mcg/ml). The pKa of the secondary amine of carvedilol is 7.8. The carbazole NH is amphoteric and its pKa's were not determined. The partition coefficient of carvedilol is approximately 2000 (octanol/pH 7.4 buffer).

Clinical evaluation of carvedilol was initiated by Boehringer Mannheim during 1981 in West Germany and is being co-developed by SmithKline Beecham and Boehringer Mannheim GmbH. In addition, carvedilol is being developed by As of August 1992, carvedilol has been approved for marketing and launched in four countries: Argentina, Belgium, Germany and South Africa. Technical approvals have been granted in ten additional countries. IND IND for carvedilol injection and IND IND for capsules and tablets were originally submitted by Boehringer Mannheim Pharmaceutical Corporation on Feb. 15, 1985 and Sept. 13, 1985, respectively and were transferred to SmithKline Beecham on June 24, 1987.

The firm has submitted 57 studies in support of NDA 20-297. Twenty-five studies listed in Appendix I are considered as important studies while others as supportive information.

From preclinical and clinical data, both the R(+)- and S(-)-carvedilol possess similar α_1 -adrenoceptor blocking activity. In contrast, only S(-)-carvedilol exhibits β_1 -adrenoceptor blocking activity. Preclinical studies demonstrate that the des-methyl, 4'-hydroxyphenyl and 5'-hydroxyphenyl metabolites of carvedilol possess β -adrenoceptor blocking activity. Based on comparison of ED_{50} values (effective dose that reduced isoprenaline induced tachycardia by 50%), the 4'-hydroxyphenyl metabolite is approximately 13 times more potent than carvedilol. The des-methyl metabolite is 2.5 fold more potent and 5'-hydroxyphenyl exhibits the weakest activity (60%). Compared to carvedilol these three metabolites possess only weak vasodilating activity (based on degree of relaxation of rat aortic strips precontracted with norepinephrine). The plasma levels of these three metabolites were less than 10% of carvedilol based on mean C_{max} and AUC data.

The recommended starting dose is 12.5 mg once daily and can be increased up to a maximum daily dose of 50 mg. Dosage should be individualized. It can be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

SUMMARY OF BIOAVAILABILITY/PHARMACOKINETICS/PHARMACODYNAMICS:

I. BIOAVAILABILITY AND BIOEQUIVALENCE:

The absolute bioavailability of carvedilol was approximately 30% for both the capsule and solution formulation.

The firm has established bioequivalence between 25 mg Tiltab® (immediate release, film-coated tablet formulation to be marketed) and 25 mg capsule (capsule batch used in bioequivalency study was pharmaceutically equivalent to capsule used in clinical trial i.e. same formulations but different batches). Upon this reviewer's request the firm submitted an in vitro dissolution profile comparing capsule batches used in pivotal clinical studies and capsule batch used in this bioequivalence study. It was seen that more than 90% drug was dissolved in 15 min for all capsule batches. This in vitro dissolution information was used to link capsule batch used in this bioequivalence study and other capsule batches used in pivotal clinical study. Carvedilol is metabolized into active metabolites in vivo. Bioequivalence of active metabolites from capsule and Tiltab® formulation was not addressed.

II. PHARMACOKINETICS:

A. Absorption: The absorption of carvedilol from tablet or capsule formulation was rapid. After an oral dose of ¹⁴C-carvedilol, the majority of the dose (about 60%) was recovered in feces. Since data was not available following iv administration of ¹⁴C-carvedilol, it was not possible to determine if this represents unabsorbed drug or drug which has been absorbed and subsequently excreted in bile either as parent or metabolites. About 10 - 20% of radioactivity in feces was unchanged drug. For fasting conditions, the mean (SD) T_{max} occurred at 1.35 ± 0.8 hr. The rate but not the extent of absorption was decreased when carvedilol was administered after breakfast. The T_{max} for carvedilol increased significantly after postprandial administration.

B. Distribution: The mean (SD) volume of distribution at steady state of carvedilol, in young healthy volunteers was 113 ± 38 liters. This indicates substantial distribution into extravascular tissue. The percent carvedilol bound was ≈ 95%, which was independent over 50 to 1000 ng/ml concentration range (upper limit of C_{max} at steady state for 50 mg QD, the maximum dose, was 417 ng/ml). Carvedilol binds to serum albumin and α₁-acid glycoprotein, but it has significantly higher affinity to serum albumin. At a blood concentration of 100 ng/ml, the blood to plasma concentration ratio for carvedilol was 0.69.

The active metabolites of carvedilol viz. des-methyl, 4'-hydroxyphenyl and 5'-hydroxyphenyl have been shown to be highly bound to plasma proteins. However the free fractions for 4'-hydroxyphenyl (3.3%) and 5'-hydroxyphenyl (3.4%) were 2 to 3 times that of des-methyl (1.1%) and carvedilol.

C. Metabolism: The metabolite profiles in plasma and urine were determined by administering ¹⁴C-carvedilol orally as a single dose. Mean excretion of radioactivity was 16% in urine and 60% in faeces within 7 to 8 days (total recovery = 76%). The radioactivity was eliminated

from plasma with $t_{1/2} = 38$ hr. The $t_{1/2}$ of unchanged carvedilol was 5 hr. Carvedilol was extensively metabolized to polar water soluble metabolites. At 1.5 hr, 9% of total radioactivity in plasma was accounted for by unchanged drug, 22% by carvedilol glucuronide and another 20% by oxidative cleavage products of the beta-blocking side chain. Out of 16% of total radioactivity dose excreted in urine 2% represented unchanged drug, 32% carvedilol glucuronide and about 25% side chain oxidation products. Ring-hydroxylated metabolites of carvedilol accounted for 18% of the radioactive compounds in the urine. Of the 60% dose excreted fecally, 71.1% could be accounted for. The most abundant were unchanged carvedilol, 4'-hydroxyphenyl carvedilol, 5'-hydroxyphenyl carvedilol and 1-hydroxycarbazolyl carvedilol.

D. Elimination: The mean serum clearance of carvedilol in healthy volunteers was 547 (range 288 - 838) ml/min following intravenous administration of carvedilol. Based on a blood to plasma concentration ratio of 0.69 for carvedilol, the blood clearance ranged from 720 to 1040 ml/min. Therefore, the estimated hepatic extraction ratio of carvedilol is between 0.5 to 0.7, assuming normal hepatic blood flow (1500 ml/min) and negligible renal clearance of carvedilol. The plasma concentration of carvedilol declined in a biexponential manner following iv administration in healthy volunteers. The mean terminal half life ranged from 1.5 to 6 hr for iv route and ranged from 7 to 11 hr for single dose oral administration.

E. Stereoselective Pharmacokinetics of Carvedilol: The postoral mean C_{max} and AUC_{0-t} values for R(+) carvedilol were two to four times greater than those observed for S(-) carvedilol (R/S ratio for AUC_{0-t} ranging from 1.6 to 4.4). The C_{max} s of S(-)carvedilol were observed earlier than for R(+)carvedilol. Following the intravenous dose of racemic carvedilol, stereoselective differences were less marked (R/S ratio for AUC_{0-t} ranging from 1.04 to 1.9).

Route		Cl_p (ml/min)	$V_{d\text{ area}}$ (L)	$t_{1/2}$ (hr)	F
Oral	R			9.6	31.1%
	S			22.1	15.1%
IV	R	605	170	3.5	
	S	662	188	3.2	

The values reported are medians. (Eur. J. Clin. Pharmacol, 1990, 38:S108-S111)

The stereoselective pharmacokinetics of carvedilol may be related, at least partly, to the differences in the plasma protein binding of the enantiomers. The free fraction for S(-)-carvedilol (1.2%) was approximately 2 fold higher than that observed for R(+)-carvedilol (0.6%). The protein binding for both enantiomers was independent over the concentration 0.3 to 300 ng/ml. The higher free fraction for S(-)-carvedilol could explain in part, the higher plasma clearance for this isomer.

F. Multiple-Dose Kinetics: The multiple oral dose kinetics were investigated in hypertensive patients at QD for four weeks and BID for two weeks. Based on C_{max} and AUC data, there was minimal accumulation of carvedilol at steady state (for QD doses 12.5, 25 and 50 mg). There was approximately 10-40% increase in C_{max} and AUC on multiple dosing with BID doses

of 6.25 and 12.5 mg (morning doses: mean (range) 6.25/day 1: Cmax = 17.6 (8.4 - 33.3) and AUC = 52.2 (23.8 - 95.2) 6.25/day 14: Cmax = 21.8 (3.5 -32.9) and AUC = 73.0 (14.7 - 164.3) 12.5/day 1: Cmax = 27.5 (11.2 - 50.7) and AUC = 127.5 (55.7 - 226.5) 12.5/day 14: Cmax = 43 (25 - 80.5) and AUC = 178.7 (62.1 - 334)). Carvedilol showed diurnal variation. The BID administration (3.125, 6.25 and 12.5 mg) of carvedilol showed significantly lower Cmax (100%) and AUC (30-40%) after evening doses.

Comparison of single dose to multiple dose was not carried out for carvedilol active metabolites viz. des-methyl, 4'-hydroxyphenyl and 5'-hydroxyphenyl carvedilol. However in a drug interaction study it was observed that following carvedilol administration 25 mg QD for 6 days, Cmax and AUC for these metabolites were less than 10% that of carvedilol at steady state.

III. DOSE AND DOSAGE FORM PROPORTIONALITY:

The dose proportionality was investigated in two different studies viz. a. single dose (6.25, 12.5, 25 and 37.5 mg) and b. single dose (12.5, 25 and 50 mg). The study 'a' showed that R(+) and S(-) carvedilol appear to be dose proportional over 6.25 to 37.5 mg dose range. The slight disproportionality seen in dose normalized AUC values could be due to under-estimation of AUC at 6.25 mg dose. The study 'b' showed dose-proportionality for carvedilol over 12.5 to 50 mg dose range.

IV. PHARMACOGENETICS:

In an ongoing study, subjects were grouped in three based on, 1. extensive metabolizers of debrisoquin and mephenytoin, (EM) 2. poor metabolizers of debrisoquin (PM_D) and 3. poor metabolizers of mephenytoin (PM_M). The following table summarizes mean Cmax and AUC for these three groups.

		EM	PM _D	PM _M
AUC _{0-∞} ng*hr/ml	R	115(42-367)	338 (148-635)	74 (72-481)
	S	61 (22-123)	77 (31-175)	51 (39-172)
Cmax ng/ml	R	33.4 (19.8-111.8)	71.4 (36-120.7)	46 (22.4-75)
	S	18.1 (9-62.1)	22.7 (9.6-44.9)	28.7 (12.6-30.3)

Mean Cmax and AUC of R(+) carvedilol for group 2 (PM_D) were higher (2 times) than group 1 (EM). In contrast, mean Cmax and AUC of S(-) carvedilol for group 2 (PM_D) increased only slightly. Since this study is ongoing, the review will be completed when firm submits complete data on the study. The observation stated above is made based on just the study summary which was submitted to the Division of Biopharmaceutics. From these preliminary findings, it can be concluded that cytochrome P450/2D6 is one of the metabolizing coenzymes for R(+)-carvedilol.

V. INFLUENCE OF FOOD ON PHARMACOKINETICS:

When the 25 mg carvedilol tablet formulation (to-be-marketed) was administered in healthy volunteers with about 750 Calories meal, there was a significant increase in median T_{max} (135 minutes in the fed state compared to 60 minutes in the fasted state). There was a minimal effect of meals on AUC and C_{max} of carvedilol.

VI. SPECIAL POPULATIONS:

A. Hypertensive Patients: Following both single and multiple administration of 12.5, 25, and 50 mg carvedilol, mean C_{max} for carvedilol appeared to increase in a dose-proportional manner. Mean AUC(0-∞) values following single and multiple doses of carvedilol appeared to increase in a dose-proportional manner between 12.5 and 25 mg carvedilol. However, following 50 mg carvedilol mean AUC(0-∞) increased more than proportionality (65%). In comparison with the values in young healthy volunteers, dose-normalized mean C_{max} and AUC(0-∞) values for carvedilol appeared to be higher and showed an increase in variability in hypertensive patients.

B. Patients with Renal Impairment: The renal excretion of unchanged carvedilol accounts for less than 2% of the administered dose. Renal impairment in hypertensive subjects led to a proportional decrease in renal clearance of carvedilol and its metabolites but not to a corresponding increase in plasma C_{max} and AUC values. Consistent with high degree of plasma protein binding carvedilol was not significantly cleared by hemodialysis.

C. Patients with Hepatic Impairment: The pharmacokinetics and absolute bioavailability of carvedilol were studied in six patients with liver cirrhosis following both intravenous and oral administrations. Following intravenous administration of 12.5 mg carvedilol infused over 1 hour, median systemic clearance was significantly reduced by 36% in patients with liver cirrhosis while median V_d at steady-state was significantly increased by 280% compared to that in historical healthy controls. Elimination half-life was about 3-fold longer in patients with liver cirrhosis than that in healthy controls (7.1 hrs vs. 2.5 hrs). After 25 mg carvedilol oral administration, median C_{max} and AUC (0-∞) values were increased by 4- and 7-fold in these patients, respectively, compared to healthy controls. Terminal half-life did not differ significantly. Oral clearance was decreased by 85% in patients. The median absolute bioavailability increased from 19% in historical controls to 83% in patients with liver cirrhosis.

D. Elderly: After single oral doses of 12.5 mg, 25 mg, and 50 mg carvedilol in young (20-40 yrs) and elderly (57-66 yrs) healthy subjects, mean C_{max} and AUC(0-∞) values in both groups increased linearly over the dose range of 12.5 - 50 mg. In elderly subjects, at 25 mg and 50 mg doses, mean AUC(0-∞) values were significantly higher (about 50%) compared to the young subjects. Mean C_{max} values were 3-40% higher in the elderly, but the difference was not statistically significant. There was a trend, a decrease in systemic clearance, and an increase in volume of distribution in the elderly subjects after administration of 5 mg carvedilol intravenously.

In a dose titration study in young (39-47 yrs) and elderly (63-79 yrs) hypertensive patients, after single oral dose of 12.5 mg carvedilol, there were no significant differences in C_{max}, T_{max}, AUC(0-24), and t_{1/2} values between two age groups. After multiple oral administration of carvedilol once daily, there was a tendency for C_{max} values to be increased by 44% and 33% in the elderly and AUC(0-24) values to be increased by 66% and 49% in the elderly after administrations of 25 and 50 mg carvedilol, respectively. The half-life values were similar between two age groups.

E. Gender Analysis: The firm did not submit any gender analysis. Data obtained following single oral administration of 25 mg carvedilol tablet in 6 male and 6 female young healthy volunteers (Study 9907) were reanalyzed by the reviewer for gender differences and no striking differences were observed. The following table was generated:

Parameter	Males (n=6) Mean ± SD	Females (n=6) Mean ± SD	% Difference
C _{max} (ng/ml)	54.64 ± 31.73	52.48 ± 26.32	-3.95
AUC(0-24) (ng*min/ml*kg)	159.3 ± 114.8	133.4 ± 51.9	-16.3
AUC(0-∞) (ng*min/ml*kg)	167.2 ± 121.3	140.4 ± 50.5	-16.0
T _{max} (min)	60.0 ± 21.2	77.5 ± 46.9	29.2
t _{1/2} (min)	431 ± 118	414 ± 128	3.9

In addition to the above analysis, data from a multiple dose, b.i.d. administration study in mild to moderate hypertensive patients was also evaluated by the Division to assess gender differences. Of the 41 patients in this study, 12 were females. Examination of individual demographic characteristics showed no gender related pharmacokinetic differences.

VII. DRUG INTERACTIONS:

A. Hydrochlorothiazide: Combined single oral administration of 25 mg carvedilol and 25 mg HCTZ in hypertensive patients did not result in any differences in their pharmacokinetics in comparison with drugs administered alone. Concomitant administration of carvedilol and HCTZ has little effect on HCTZ absorption and disposition.

B. Torsemide: Combined multiple oral administration of 25 mg carvedilol and 5 mg torsemide once daily for 5 days in healthy volunteers did not result in any significant differences in the pharmacokinetics of either compound.

C. Cimetidine: Concomitant oral administration of carvedilol (25 mg once daily) and cimetidine (200 mg t.i.d., 400 mg h.s.) for three days caused a significant increase in mean AUC(0-24)

(approximately 17%) and Ae (amount of unchanged carvedilol excreted in urine) (approximately 22%) for carvedilol. There was a significant stereoselective increase in mean AUC(0-24) (21%) and Ae (24%) for R(+)-carvedilol in combined administration. For S(-)-carvedilol, there was a significant decrease in mean Cmax (14%) with an increase in AUC(0-24) in combined administration. There were no major changes in the kinetic parameters of the M2, M4, and M5 metabolites of carvedilol following with cimetidine.

D. Rifampin: There was a significant reduction in mean Cmax and AUC(0-∞) (approximately 70%) for carvedilol when a single oral dose of 25 mg carvedilol was administered after pre-treatment with the enzyme inducer, rifampin (600 mg daily for 12 days).

E. Digoxin: Following co-administration of single oral doses of 25 mg carvedilol and 0.5 mg digoxin in healthy subjects, there were statistically significant increases in mean Cmax (about 60%), AUC(0-48) (19%), and C24 (digoxin level measured at 24 hours)(19%) values of digoxin compared to administration of digoxin alone.

In an interim report, following concomitant oral administration of carvedilol (12.5 mg once daily for 2 days, then 25 mg once daily for 12 days) with digoxin (0.25 mg once daily for 14 days) in hypertensive patients, mean steady-state AUC(0-24) and trough concentration (C24) of digoxin were significantly increased by 14% and 16%, respectively. The mean steady-state Cmax for digoxin were approximately 30% higher when digoxin was dosed with carvedilol. There was no change in Tmax. This study is ongoing and review will be completed when firm submits complete data on the study.

E. Warfarin: Four carvedilol concentrations (300, 100, 17.4, and 3 ng/ml) and two warfarin concentrations (1.8 and 5.4 ug/ml) were studied to assess the effect of carvedilol on the in-vitro plasma binding of warfarin. The warfarin free fraction was not significantly changed at the four concentrations studied.

VIII. PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS:

In a study investigating the efficacy of carvedilol in hypertensive patients, percent decreases in diastolic blood pressure were plotted as a function of carvedilol concentrations. There appeared to be no correlation between individual trough concentration and reduction in supine diastolic blood pressure. There appears to be a correlation between steady-state concentrations of carvedilol and therapeutic response.

IX. FORMULATION:

The tablet formulations of carvedilol to be marketed (12.5 mg and 25 mg) are compositionally proportional.

X. DISSOLUTION:

The firm proposed a dissolution method using USP Apparatus II at 50 rpm in 900 ml simulated gastric fluid (USP XXII) at 37°C and a specification of at least in 30 minutes. The dissolution data and profiles for the bio-batch tablet and capsule formulations used in pivotal clinical trials are located in Appendix I. The dissolution was rapid and almost complete at 15 minutes.

XI. ASSAY:

The sponsor used several HPLC methods with fluorescence detection, to measure the concentrations of carvedilol and its metabolites, desmethylcarvedilol, 4'-hydroxyphenylcarvedilol and 5'-hydroxyphenylcarvedilol in plasma and urine samples.

Overall, the assay validations for carvedilol and its metabolites were acceptable.

General Comments (need not be sent to the firm):

1. The ¹⁴C-carvedilol given orally showed high $t_{1/2}$ for the radioactivity (38 hr). It is important to note that even though this was not due to carvedilol or the active metabolites, there were other metabolites with high $t_{1/2}$. It is not known how much of these metabolites would accumulate at steady state and would that be a safety concern.

2. In Study MF 3702, mean C_{max} values of 189 ng/ml (younger hypertensive patients) and 252 ng/ml (older hypertensive patients) were observed after multiple oral administration of 50 mg carvedilol. Plasma concentrations of carvedilol were about 2-3 times higher in both groups of patients as compared to those observed in normal healthy volunteers.

3. In Study MF 3459, median C_{max} value of carvedilol was 318 ng/ml after single oral administration of 50 mg carvedilol to hypertensive patients (n=3) with chronic renal failure (Cl_{cr}: 51-90 ml/min). An unexplained finding in this investigation is the approximately 2 to 3 fold higher concentrations of carvedilol than those observed in normal healthy volunteers (MF 7034).

Comments to the Pharmacologist: Under Carcinogenesis, Mutagenesis, Impairment of Fertility section of labeling, the firm claims that mice and rats were exposed to doses 200 and 75 times higher than human dose respectively. Based on a comparison between rats and humans and using area under radioactivity versus time curve as an exposure parameter and considering 50 mg as highest human dose, the use of mg/kg dose to animals is overestimating exposure.

Comments (to be sent to the firm):

1. The firm should submit the reports on all the studies which were listed in this application as on-going studies.

2. In Vitro Dissolution:

a. The Division of Biopharmaceutics recommends a Q specification of not less than at 30 minutes.

b. Please submit the in-vitro dissolution data on whole Kredex® 12.5 mg tablets and half Kredex® tablets (12.5 and 25 mg/broken at the score) using the same dissolution method.

c. Please clarify whether the dissolution medium is same as the simulated gastric fluid, as defined in USP XXII.

3. The relative steady-state AUCs for the free fraction of carvedilol enantiomers and each active metabolites were estimated from Study 7097 by this reviewer. The following table was generated:

	Steady-state AUC (ng*hr/ml)	Free fraction	Steady-state AUC _f (ng*hr/ml)	β-Blocking potency
R(+)-carvedilol	166.75	0.6%	1.00	0.01
S(-)-carvedilol	62.99	1.2%	0.76	1
M2	8.80	1.1%	0.097	2.5
M4	7.47	3.3%	0.25	13
M5	5.11	3.4%	0.17	0.6

Although the steady-state AUC for M4 metabolite is about 10-12% of S(-)-carvedilol, due to its higher potency (based on preclinical data) and higher free fraction in plasma, the contribution to the β-blocking activity may be about the same or higher than S(-)-carvedilol. Specific calculation cannot be made because potency relative to free drug is apparently unknown. Such metabolites should be monitored in bio-studies and used in establishing pharmacokinetic-pharmacodynamic link.

Labelling Comments:

1. The following information expressing pharmacokinetic characterization of the carvedilol enantiomers 'carvedilol undergoes stereoselective first-pass.....in healthy subjects' should be replaced by:

'Stereoselective differences were seen in pharmacokinetics of carvedilol enantiomers following oral and intravenous administration. The plasma concentrations of R(+) carvedilol were greater than S(-) carvedilol. After an oral administration of racemic carvedilol, R(+) carvedilol showed higher bioavailability and lower elimination half life than S(-) carvedilol, thus indicating stereo-selective first-pass metabolism'.

It is recommended that the firm incorporate mean pharmacokinetic parameters in the statement above.

2. The statement 'Kredex is subject to genetic polymorphism not appear to be different in poor metabolizers of S-mephenytoin' should be replaced by the following information, since the study supporting this statement is ongoing and was not reviewed.

Kredex may be subject to genetic polymorphism. Poor metabolizers of debrisoquin (low cytochrome P450/2D6) exhibited two to three fold higher plasma concentrations of R(+) carvedilol compared to extensive metabolizers. In contrast, plasma levels of S(-) carvedilol are increased by only about 20% to 25% in poor metabolizers. The pharmacokinetics of carvedilol enantiomers do not appear to be different in poor metabolizers of S-mephenytoin (low cytochrome P450/2C9).

3. The following information should be included in the labelling:

'Following administration of radiolabelled carvedilol to healthy volunteers, carvedilol AUC accounted for only about 7% of the total radioactivity in plasma'.

4. The following information should be included in the labelling:

'Renal impairment in hypertensive subjects led to a decrease in renal clearance of carvedilol and its metabolites but not to a corresponding increase in plasma Cmax and AUC values. Caution should be exercised in dosing renally impaired hypertensive patients'.

5. The following information should be included in the labelling:

'After single oral doses of 12.5 mg, 25 mg, and 50 mg carvedilol in young (20-40 yrs) and elderly (57-66 yrs) healthy subjects, at 25 mg and 50 mg doses, mean AUC(0-∞) values were significantly higher in the elderly (about 50%) compared to the young subjects'.

6. The statement 'Following concomitant administration of Kredex and digoxin, steady-state trough concentrations of digoxin were increased by 16% in hypertensive patients.' should be replaced by the following statement.

'Preliminary findings from an on-going study indicate that following concomitant
.....in hypertensive patients'.

7. The following information should be included in the labelling:

'There was a statistically significant reduction in Cmax and AUC(0-∞) values (approximately 70%) for carvedilol when a single oral dose of 25 mg carvedilol was administered after a pre-treatment with the enzyme inducer, rifampin (600 mg daily for 12 days)'.

8. Dosing of animals in pre-clinical pharmacology should be expressed relative to human exposure i.e. AUC ratios instead of just based on dose in mg/kg.

Hae-Ryun Choi

**Hae-Ryun Choi, Ph.D.
Pharmacokinetic Review Branch**

Rajendra Pradhan

**Rajendra Pradhan, Ph.D.
Pharmacokinetic Review Branch**

Biopharm day on 10/19/93 (Collins, Fleischer, Parekh, Malinowski, Choi, and Pradhan)

FT initialed by Ameeta Parekh, Ph.D. Ameeta Parekh 11/16/93

**cc: NDA 20-297, HFD 110, HFD 426 (Fleischer, Choi, Pradhan), HFD 340 (Viswanathan),
Chron, Drug, DI, REPLICATE, FOI (HFD 19), F, M.**

APPENDIX I

Pivotal Bioequivalence Study

Vol. 1.49 Page 000002

Title: A study in healthy male volunteers to assess the in-vivo bioequivalence of two 25 mg carvedilol (SK&F 105517) formulations (25 mg capsule compared to 25 mg 'Tiltab' tablet)

Investigator: Bernard Ilson, M.D.

Study Center: SmithKline Beecham Clinical Research Unit, Presbyterian Medical Center of Philadelphia, Philadelphia, Pennsylvania, USA

Objective: To determine, in healthy volunteers, if a 25 mg carvedilol 'Tiltab' formulation and a 25 mg carvedilol capsule formulation are bioequivalent

Study Design: The pharmacokinetic profile of carvedilol was determined in thirty-two healthy male volunteers (age 21 to 47 years; weight 62 to 95 kg) after administration of the following formulations:

Regimen A: 25 mg carvedilol capsule (821522 40Lh). Formulation used in SmithKline Beecham clinical trials conducted in the United States. The batch of capsules used in this study is pharmaceutically equivalent to those lots used in the pivotal clinical trials for hypertension

Regimen B: 25 mg carvedilol 'Tiltab' tablet (X205-1CV2). SmithKline Beecham Tiltab formulation to be marketed within the United States. This lot is one of three validation batches manufactured at Cidra, Puerto Rico.

Each regimen was administered twice to each subject with subjects randomized to either the ABBA, BBAA, AABB, or BAAB treatment sequence. On each occasion, carvedilol was administered after an overnight fast. Blood samples were drawn just before the dose (0 time) and at 15, 30, 45 minutes and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12, and 24 hours after dosing. Pharmacokinetic parameters were determined by noncompartmental methods.

90% confidence intervals were computed for the point estimates of the true ratio (tablet/capsule) for both AUC_{0-24} and C_{max} by back-transforming the point estimates and confidence intervals from the log scale. In order to demonstrate bioequivalence, the 90% confidence intervals for AUC_{0-24} and C_{max} must fall within the 80% to 125% range. The $AUC_{0-\infty}$ was not used for bioequivalence assessment since a few individuals had greater than 20% of the AUC extrapolated.

Since the values taken by the parameter T_{max} are restricted to values determined by the study design, non-parametric analysis was used. A mean was calculated of the two observations on each formulation on each subject. These means were analyzed using a Wilcoxon signed-rank statistic. The 90% confidence interval for the median difference in formulations (tablet-capsule) was calculated.

Assay: HPLC with fluorescence detection.

Carvedilol:

Linearity: Satisfactory (0.3 to 160 ng/ml).

Precision: Within-day ranged from 3.8 to 9.5% and between day ranged from 6.2 to 12.1%, over the concentration range (2 to 80 ng/ml). The assay precision at the LQL was 25.1% (n=6).

Accuracy: Ranged from 3 to 8%, over the concentration range (2 to 80 ng/ml). The assay accuracy at the LQL was 13% (n=6).

The firm did not submit any data on assay quality control samples.

Result and Discussion: The mean plasma concentration versus time profiles for capsule and tablet treatments are shown in fig 1. The mean, median and range of the pharmacokinetic parameters for carvedilol following administration of each formulation are shown in table 1.

The mean ratios and 90% confidence intervals for AUC_{0-24} and C_{max} are shown in table 2. The median difference (tablet-capsule) for T_{max} was -0.13 hours (table 2). The mean apparent terminal half-life values for carvedilol ranged from 9-11 hours with no apparent difference between formulations.

Conclusions and Comments: The mean ratios (tablet/capsule) and 90% confidence intervals for log transformed AUC_{0-24} and log transformed C_{max} were within the accepted 80% to 125% range.

The 25 mg capsule used in this study was pharmaceutical equivalent to capsule formulations used in clinical trials. Upon this reviewer's request the firm submitted an in vitro dissolution profile comparing capsule batches used in pivotal clinical studies and capsule batch used in this bioequivalence study. As shown in table 3, more than 90% drug was dissolved in 15 min for all capsule batches. This in vitro dissolution information was used to link capsule batch used in this bioequivalence study and other capsule batches used in pivotal clinical study.

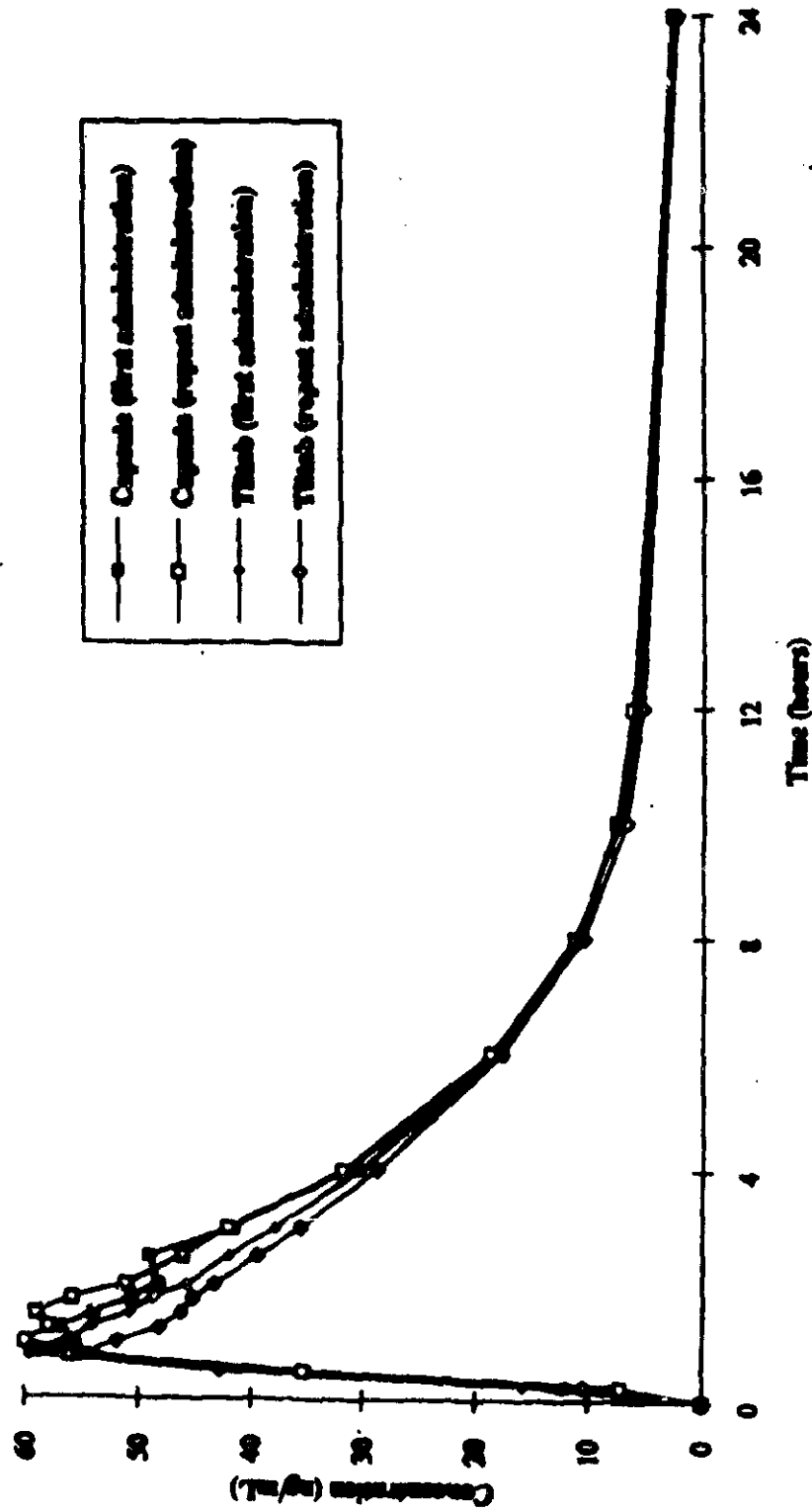
However following questions are unanswered.

Whether QC samples were run during the assay of carvedilol. (In a correspondence dated 09-14-1993, firm has made a commitment to provide this information in near future)

Truncated AUCs and not the $AUC_{0-\infty}$ were used for establishing bioequivalence. What will be the result if $AUC_{0-\infty}$ are used or if subjects showing more than 20% extrapolated AUCs are excluded from the analysis and $AUC_{0-\infty}$ for rest of the subjects are used.

Protocol MMS17/009

Fig 1. Mean plasma concentration-time profiles for carvedilol following single dose administration of 25 mg capsules and 25 mg TlTab in 32 healthy male volunteers.



Note: Non-quantifiable values (< 0.3 ng/ml) were not included in the calculation of mean data.

81-0000

Table 1 Pharmacokinetic Parameters of Carvedilol
(Protocol 105517/030-US)

	Mean	Median	Range
Regimen A (capsule)			
First Administration			
AUC ₀₋₈ (ng*hr/ml)	322	302	
AUC _{0-∞} (ng*hr/ml)	360	325	
C _{max} (ng/ml)	74.0	65.3	
T _{max} (hr)	1.3	1.3	
T _{1/2} (hr)	10.0	8.6	
Second Administration			
AUC ₀₋₈ (ng*hr/ml)	330	293	
AUC _{0-∞} (ng*hr/ml)	364	310	
C _{max} (ng/ml)	79.6	75.5	
T _{max} (hr)	1.3	1.0	
T _{1/2} (hr)	8.9	8.11	
Regimen B (tablet)			
First Administration			
AUC ₀₋₈ (ng*hr/ml)	310	309	
AUC _{0-∞} (ng*hr/ml)	341	304	
C _{max} (ng/ml)	72.6	59.9	
T _{max} (hr)	1.3	1.0	
T _{1/2} (hr)	9.3	7.9	
Second Administration			
AUC ₀₋₈ (ng*hr/ml)	292	242	
AUC _{0-∞} (ng*hr/ml)	329	253	
C _{max} (ng/ml)	67.3	63.0	
T _{max} (hr)	1.4	0.9	
T _{1/2} (hr)	10.4	9.3	

Table 2 Point Estimates and 90% Confidence Intervals
(Protocol 105517/030-US)

AUC₀₋₂₄ (log-transformed)	
Mean ratio	900
90% confidence interval	800 to 970
C_{max} (log-transformed)	
Mean ratio	900
90% confidence interval	810 to 1010
T_{max} (non-parametric)	
Median of difference	-0.13 hr
90% confidence interval	-0.31 to 0.13 hr

SD Reference No.	383	% Dissolved - (Avg.)				
Method Reference No.	DI-105517-B-0					
Lot 820-354-40Aa	Interval - minutes	0	15	30	45	60
	Initial	0	94	97	97	97
SD383/chart1	36 mo 30°C	0	94	98	98	99
Capsule 6.25 mg *		% Dissolved - (Avg.)				
SD Reference No.	355					
Method Reference No.	DI-105517-B					
Lot 820-169-40Cc	Interval - minutes	0	15	30	45	60
	Initial	0	97	100	102	
SD355Chart2	36 mo 30°C	0	94	97	98	
Capsule 12.5 mg *		% Dissolved - (Avg.)				
SD Reference No.	354					
Method Reference No.	DI-105517-A					
Lot 820-173-40Lg	Interval - minutes	0	15	30	45	60
	Initial	0	98	102	103	
SD354Chart3	48 mo 30°C	0	90	97	98	
Capsule 12.5 mg *		% Dissolved - (Avg.)				
SD Reference No.	419					
Method Reference No.	DI-105517-A					
820-468-40Lg	Interval - minutes	0	15	30	45	60
	Initial	0	101	100	101	
SD419chart6	48 mo 30°C	0	91	94	107	
Capsule 25 mg *		% Dissolved - (Avg.)				
SD Reference No.	353					
Method Reference No.	DI-105517-A					
Lot 820-176-40Lh	Interval - minutes	0	15	30	45	60
	Initial	0	88	97	96	
SD353Chart4	12 mo 30°C	0	88	100	102	
Capsule 25 mg *		% Dissolved - (Avg.)				
SD Reference No.	418					
Method Reference No.	DI-105517-A					
Lot 820-469-40Lh	Interval - minutes	0	15	30	45	60
	Initial	0	82	91	93	
SD418chart7	48 mo 30°C	0	79	93	99	
Capsule 25 mg		% Dissolved - (Avg.)				
SD Reference No.	NP					
Method Reference No.	DI-105517-F					
Lot 821-522-40Lh	Interval - minutes	0	15	30	45	60
		0	98	102	102	102
chart8						

* Capsule batches used in Pivotal clinical trials.

000038

Drug Disposition Study of ¹⁴C-Labelled Carvedilol

Study: MF 7029 and MF 7029 (Addendum) Volume: 1.70 and 71

These two studies addresses the metabolic profile of carvedilol. Each study has 3 normal subjects, the route of administration was post-oral and the same dosage form was used. The reason for reviewing these two studies together is that, the first study addresses plasma pharmacokinetic profile of radioactivity, carvedilol and O-desmethyl metabolite where as the second study addresses total urinary and fecal excretion of several carvedilol metabolites.

Study MF 7029

Vol. 1.70 Page 000115

Title: Metabolism of carvedilol in man

Investigator: Dr. G. Neugebauer, Prof. Dr. U. Abshagen

Study Center: Department of Clinical Pharmacology, Boehringer Mannheim GmbH, Federal Republic of Germany

Objectives: Determine the metabolism of carvedilol after oral administration of 50 mg of ¹⁴C-carvedilol.

Study Design: Three healthy male volunteers (age: 50 to 58 years; weight: 65 to 85 kg) participated in the study. After an overnight fast, subjects received a single oral dose of 50 mg of ¹⁴C-carvedilol in suspension (lot no. 819022 A). After ingestion of the suspension, the vial was rinsed twice with water and the water was swallowed. The vials were examined for residual radioactivity to guarantee that 100% of the dose was ingested. Ten ml of blood were obtained at 0, 15, and 30 minutes and 1, 2, 3, 4, 8, 12, 16, 24, 32, 36, 48, 56, 72, 96, and 168 hours after the dose to determine concentrations of total radioactivity, carvedilol, and the O-desmethyl metabolite. At 1.5 hours a 60 ml blood sample was obtained to detect metabolites of carvedilol and to measure radioactivity in red blood cells:

Radioactivity in saliva was measured at 0 and 1.5 hours. Urine was collected at 0-2, 2-4, 4-8, 8-12, 12-24, 24-36, 36-48, 48-72, 72-96, 96-120, 120-168 (subjects 2 and 3) hours time intervals. After measuring radioactivity in each urine collection period, each subject had their 0-12 hour urine collections pooled for the determination of metabolites. Feces were gathered every day (if possible) up to day 8 for determination of total radioactivity, carvedilol, and O-desmethylcarvedilol. Pharmacokinetic parameters for total radioactivity, carvedilol, and the O-desmethyl metabolite were determined using noncompartmental analysis.

Analytical Methods: Plasma and urine concentrations of carvedilol and O-desmethylcarvedilol (BM 14.242) were determined by HPLC with fluorescence detection (~~and radioactivity in urine~~). The lower limit of quantitation was 2 ng/ml. Radioactivity was measured by liquid scintillation spectrometry [51]. The isolation of the metabolites was performed by stepwise extraction procedures (solvent extraction, separation, and purification by LC and HPLC) and identification achieved by spectroscopic (LC/MS) and chromatographic (TLC, HPLC) techniques. Known metabolites from the dog and synthesized compounds were used as reference.

Results: Carvedilol is extensively metabolized to polar and mostly water soluble compounds (Fig. 1). Pharmacokinetic parameters determined for total radioactivity, carvedilol and O-desmethylcarvedilol are shown in table 1. Fig 2 shows mean plasma profile of radioactivity and carvedilol - O-desmethylcarvedilol concentration time profile. The following table shows total urinary and fecal excretion (% of administered dose) for total radioactivity, carvedilol and O-desmethylcarvedilol.

	TUE	TFE
Radioactivity	15.89 ± 0.97	59.57 ± 2.92
Carvedilol	0.37 ± 0.2	14.02 ± 5.04
O-desmethylcarvedilol	0.04 ± 0.01	4.07 ± 0.32

Measurement of radioactivity in plasma and red blood cells (1.5 hr post-dose) showed preferential distribution within the plasma. Saliva samples (1.5 hr post-distribution) showed high concentration of radioactivity.

Figure 1. Metabolic Profile of Carvedilol in Man
(Data from Protocol MF-7029 Addendum)

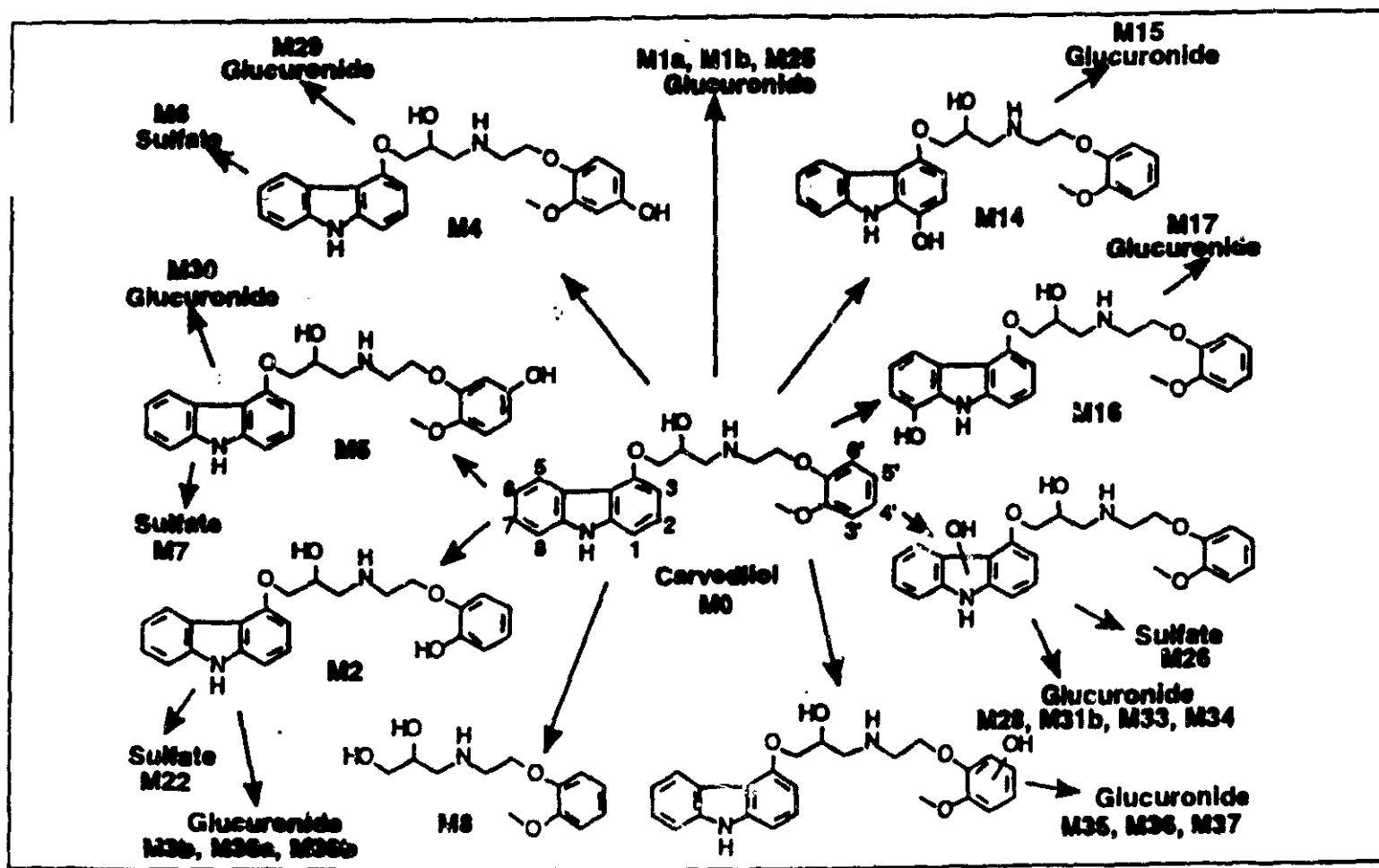


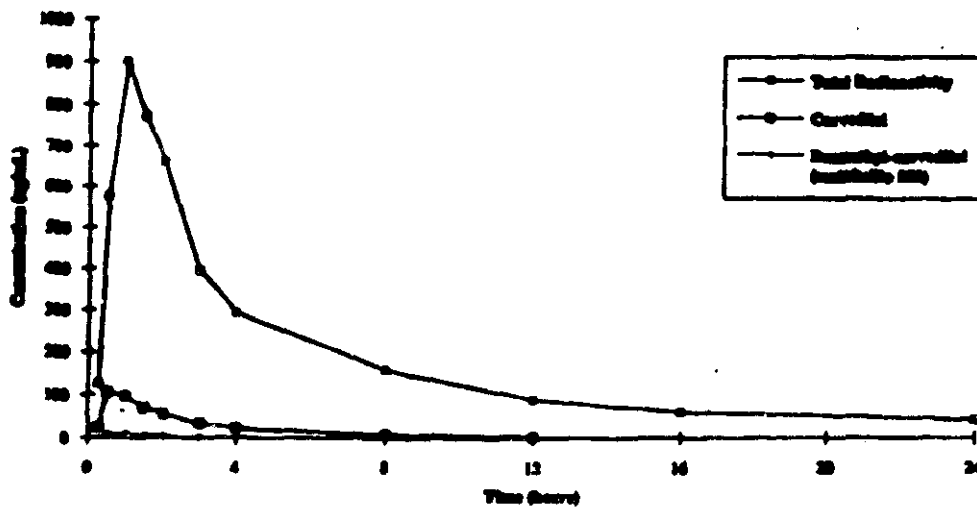
Table 1
Pharmacokinetic Parameters for Total Radioactivity, Carvedilol,
and O-desmethylcarvedilol
(Protocol MF 7009)

Parameter	Total radioactivity	carvedilol	o-desmethyl carvedilol
C _{max} (ng/ml)	901 763 - 1019	106 50 - 166	19 7 - 11
T _{max} (hr)	1.00 1.00	0.50 0.50	0.03 0.00 - 1.00
AUC _{0-∞} (ng·hr/ml)	5627 4312 - 6334	319 150 - 521	19 7 - 19
AUC ₀₋₂₄ (ng·hr/ml)	5763 4300 - 6600	319 150 - 521	ND [†]
t _{1/2} (hr)	30.2 22.0 - 52.4	4.0 3.2 - 7.6	ND

^{*} Data are presented as mean and range.
[†] ND = Not Determined

Protocol MF-7009 / Figure 3

Mean plasma concentration-time profiles following a single oral dose of
¹⁴C-carvedilol 50mg, compared to three healthy male volunteers.
(Dose rate, 0.05 hours per dose)



Note: As per report, non-quantifiable values (< 2 ng/ml) were not added to zero in the calculation of mean data; mean data are not presented if 2 or more subjects exhibited non-quantifiable values.

Study MF 7029 (Addendum)

Vol. 1.71 Page 000002

Title: Metabolism of carvedilol (SK&F 105517) in male human subjects after single dose p.o. administration of ^{14}C -carvedilol (target dose, 50 mg in suspension)

Investigators: F. Dixon, J.F. Politowski, A. Goalwin, K. Anderson, W.H. Schaefer, J.P. Holck, R. Endele, P. Neubert, E. von Mollendorf, and G. Neugebauer.

Study Center: The Department of Drug Metabolism and Pharmacokinetics, SmithKline Beecham Pharmaceuticals, Upper Merion, Pennsylvania, USA and the Department of Clinical Pharmacology, Boehringer Mannheim GmbH, Federal Republic of Germany

Objectives: The excretion of ^{14}C -carvedilol, and the profiling and characterization of carvedilol metabolites excreted in urine and circulating in plasma have been previously investigated in three normal male volunteers (Protocol MF 7029). The purpose of this additional biotransformation study was to investigate the metabolism of carvedilol in three additional normal male volunteers after oral administration of ^{14}C -carvedilol, and in particular, to profile and characterize fecal metabolites of carvedilol.

Study Design: Three healthy male volunteers (age: 50 to 52 years; weight: 94 to 99 kg) participated in the study. Subject #4 was dosed in August 1989 and subjects #5 and #6 were dosed in February 1991. The same formulation was used for each subject in this study and in the three subjects previously investigated (Protocol MF 7029). After an overnight fast, subjects received a single oral dose of 50 mg of ^{14}C -carvedilol in suspension (lot no. 91/0144 and 91/0145). After ingestion of the suspension, the vial was rinsed twice with water and the water was swallowed. The vials were examined for residual radioactivity to guarantee that 100% of the dose was ingested. Following dose administration, heparinized blood samples were obtained at 1.5, 3, 8, 24, 48, 96, 168, 216, 264, and 336 hours for measurements of total radioactivity. At 1.5, 3, and 8 hours, a 60 ml blood sample was obtained for determination of metabolite profiles. Urine was collected over 12 hour intervals out to 264 hours post-dose. Feces samples were collected over 12 hour intervals for 216 hours and in one final collection period from 216-264 hours.

Analytical Methods: Radiometabolites in both feces and urine were separated, quantified, and characterized structurally using a combination of high performance liquid chromatographic (HPLC) and mass spectral techniques (methods described in report). The metabolites circulating in plasma were also separated chromatographically and identified based on HPLC retention times (method described in report). Sample analysis was performed at the Department of Drug Metabolism and Pharmacokinetics, SmithKline Beecham Pharmaceuticals, USA.

Table 2-

Summary of Carvedilol Metabolites Excreted in Feces Following Single Dose
 P.O. Administration (50 mg) of 14C-Carvedilol to Normal Male Volunteers
 (Expressed as % of Fecal Radioactivity)

Peak Name	Subject 04 0-72 h	Subject 05 12-84 h	Subject 06 0-72 h	Mean	Structure
MF1 (M8) (a)				1.93	des-carbamoyl-carvedilol
MF46				6.38	not determined
MF26 (M4) (b)				14.09	4'-hydroxyphenyl-glucuronide
MF28 (M16) (b)					0-hydroxycarbonyl-carvedilol
MF32 (M5)				15.05	5'-hydroxyphenyl-carvedilol
MF29 (M14)				14.71	1-hydroxycarbonyl-carvedilol
MF22 (M2)				9.21	des-methyl-carvedilol
MF13 (M9)				16.10	Carvedilol
9 Identified				71.10	

ND not detectable

(a) nomenclature used by Boehringer Mannheim

(b) metabolites MF26 and MF28 analyzed on HPLC and the quantitation represents the sum

000273

Table 3

Summary of Carvedilol Metabolites Excreted in Urine Following Single Dose P.O. Administration (target dose - 50 mg) of ¹⁴C-Carvedilol to Normal Male Volunteers (Expressed as % of Urinary Radioactivity)

Peak Name	Subject 04 0-24 h	Subject 05 0-26 h	Subject 06 0-26 h	Mean	Structure
MU16				2.02	not determined
MU17				3.49	not determined
MU1	(M0)(a)			5.21	des-carbasoyl-carvedilol
MU14	(M20)			6.40	hydroxycarbasoyl-β-glucuronide
MU2	(M25)			1.72	carbasoyl-β-glucuronide
MU3	(M17)			3.90	β-hydroxycarbasoyl-glucuronide
MU22	(M20)			4.62	hydroxyphenyl-glucuronide
MU39	(M30)			5.26	hydroxyphenyl-glucuronide
MU35	(M30)			4.45	hydroxyphenyl-glucuronide
MU5	(M30)(b)			9.37	1-hydroxycarbasoyl-glucuronide
MU60	(M26)(b)				hydroxyphenyl-glucuronide
MU41	(M37)			3.16	hydroxyphenyl-glucuronide
MU34b	(M31b)(c)			3.42	hydroxycarbasoyl-glucuronide
MU1b	(M2b)(c)			5.32	des-methyl-glucuronide
MU42	(M6/7)(d)				hydroxyphenyl-sulfate
MU43	(M33)(d)			3.44	hydroxycarbasoyl-glucuronide
MU44	(M36)(e)				hydroxycarbasoyl-glucuronide
MU37	(M6/7)(e)				hydroxyphenyl-sulfate
MU45a	(M30a)(e)			1.19	des-methyl-glucuronide
MU6	(M26)(f)				hydroxycarbasoyl-sulfate
MU45b	(M30b)(f)			11.19	des-methyl-glucuronide
MU9	(M1a)			9.40	β-carvedilol-0-glucuronide
MU10a	(M1b)(g)			0.39	β-carvedilol-0-glucuronide
MU10b	(M22)(g)			0.46	des-methyl-sulfate
MU19	(M1c)			1.40	1-hydroxycarbasoyl-carvedilol
MU22	(M2)				des-methyl-carvedilol
MU13	(M0)			78.31	Carvedilol

Identified

- NU not detectable
- (a) nomenclature used by Boehringer Mannheim
- (b) metabolites NU5 and NU6 excreted on HPLC and the quantitation represents the sum
- (c) metabolites NU3b and NU1b excreted on HPLC and the quantitation represents the sum
- (d) metabolites NU42 and NU3 excreted on HPLC and the quantitation represents the sum
- (e) metabolites NU44, NU37 and NU3a excreted on HPLC and the quantitation represents the sum
- (f) metabolites NU8 and NU45b excreted on HPLC and the quantitation represents the sum
- (g) metabolites NU10a and NU10b excreted on HPLC and the quantitation represents the sum

not detectable on HPLC

000274

Table 4

Summary of Carvedilol Metabolites in Plasma following Single Dose P.O. Administration (target dose - 50 mg) of 14C-Carvedilol to Normal Male Volunteers (Expressed as % of Plasma Radioactivity)

Peak Name	Subject 04 1.5 h	Subject 05 1.5 h	Subject 05 3 h	Subject 06 1.5 h	Subject 06 3 h	Structure
MP1 (M1) (a)						des-carbamoyl-carvedilol
MP2 (M2)						carbamoyl-β-glucuronide
MP3 (M3)						hydroxyphenyl-glucuronide
MP39 (M39)						hydroxyphenyl-glucuronide
MP35 (M35)						hydroxyphenyl-glucuronide
MP5 (M5)						1-hydroxyacarbonyl-glucuronide
MP41 (M41)						hydroxyphenyl-glucuronide
MP36 (M36)						hydroxyacarbonyl-glucuronide
MP42 (M42)						hydroxyphenyl-sulfate
MP44 (M44) (b)						hydroxyacarbonyl-glucuronide
MP37 (M37) (b)						hydroxyphenyl-sulfate
MP9 (M9)						β-carvedilol-O-glucuronide
MP10a (M10a)						β-carvedilol-O-glucuronide
MP29 (M29)						1-hydroxyacarbonyl-carvedilol
MP67						not determined
MP22 (M22)						des-methyl-carvedilol
MP13 (M13)						Carvedilol
% Identified	59.76	83.67	73.33	86.07	73.76	
% Column Recovery	98.79	96.33	95.07	94.52	97.17	

ND not detectable

(a) nomenclature used by Beechinger Mannheim

(b) metabolites MP4 and MP37 coeluted on HPLC and the quantitation represents the sum

000275

Results: The fecal metabolites of carvedilol observed in this study included unchanged carvedilol and several oxidation products (table 2). In total, the metabolites identified in feces represented 71.1% of the fecal radioactivity. The profile of urinary metabolites displayed a very complex pattern of more than 26 components (table 3). In total, the metabolites identified in urine represented 81.3% of the urinary radioactivity. Unchanged carvedilol was an abundant radioactive component in plasma at 1.5 and 3 hr (table 4).

Conclusions and Comments:

In pharmacokinetic and metabolic study with 3 subjects at 50 mg ¹⁴C carvedilol (MF 7029), C_{max} for total radioactivity was 9 times higher than for C_{max} for carvedilol, demonstrating that large portion of the radioactivity could be accounted for by metabolism. A longer elimination half-life and larger AUC for total radioactivity as compared to carvedilol indicate a lower plasma clearance for at least some metabolites.

The primary metabolic pathway for carvedilol include glucoronidation, aromatic ring oxidation and aliphatic side chain oxidation. The major route of elimination for carvedilol metabolites is via the bile into the feces (Urinary: 16% of total radioactivity, Fecal: 60% of total radioactivity over 7 to 8 days). The mean total recovery amounted to 76%.

O-desmethylcarvedilol, one of the active metabolites looked at, showed 10 fold lower plasma concentrations than those for carvedilol.

In an additional metabolic study with 3 subjects at 50 mg ¹⁴C carvedilol (MF 7029 Addendum), fecal metabolites included products of oxidation pathway, while urinary metabolites included products of both oxidation and conjugation pathways.

The assay validation data was not provided with the studies.

Title: A pharmacokinetic study of carvedilol, 25 mg orally, (SK&F 105517) to study the intra-subject variability and stereoselectivity of the pharmacokinetics in healthy subjects

Investigator: Robert M. Stote, M.D.

Study Center: SmithKline & French Laboratories Clinical Research Unit, Presbyterian-University of Pennsylvania Medical Center, Philadelphia, Pennsylvania, USA

Objectives: 1) Estimate the intrasubject variability in the pharmacokinetic parameters of carvedilol after oral administration; 2) Determine the pharmacokinetics of the enantiomers of carvedilol following oral administration of 25 mg racemic carvedilol.

Study Design: Twelve healthy male subjects (age 22 to 33 years; weight 70 to 86 kg) received a single oral dose of carvedilol (25 mg capsule, lot no. 820176 40L5) on three separate occasions separated by at least one week. On each occasion, carvedilol was given after an overnight fast. Blood samples were obtained prior to dosing (0 time) and then at 10, 20, 30, 45, 60, 75, and 90 minutes and at 2, 2.5, 3, 4, 6, 8, 10, 12, 14, and 24 hours after the dose. Data were analyzed using traditional model-independent methods.

same lot as clinical trials

To estimate the intersubject and intrasubject variability of carvedilol, an analysis of variance (ANOVA) model with linear effects due to subject (period effects were not significant) was used. The ANOVA tested for systematic differences between C_{max} , T_{max} , and AUC_{0-t} measurements for the carvedilol data obtained on Study Days 1, 2, and 3. These pharmacokinetic parameters were chosen since these parameters have been used to estimate the rate and extent of absorption for carvedilol in previous bioequivalence studies. Intrasubject variance (α^2_w) and intersubject variance ($\alpha^2_w + \alpha^2_b$) were computed for these pharmacokinetic parameters for carvedilol. The percent coefficient of variation (CV) and the percent of total variation (PTV) attributable to intrasubject and intersubject variability were also calculated.

The calculations for the % CV and the % total variation (PTV) attributable to intra-subject and inter-subject variability are shown in Appendix II.

Assay: Plasma concentrations of carvedilol and O-desmethyl carvedilol were determined using HPLC with fluorescence detection.

Carvedilol:

Linearity: Satisfactory (0.3 to 160 ng/ml).

Precision: Within-day ranged from 3.8 to 9.5% and between day ranged from 6.2 to 12.1%, over the concentration range (2 to 80 ng/ml). The assay precision at the LQL was 25.1% (n=6).

Accuracy: Ranged from 3 to 8%, over the concentration range (2 to 80 ng/ml). The assay accuracy at the LQL was 13% (n=6).

O-desmethylcarvedilol:

Linearity: Satisfactory (0.3 to 160 ng/ml).

Precision: Within-day ranged from 3.1 to 5.5% and between day ranged from 5.8 to 9.8%, over the concentration range (2 to 80 ng/ml). The assay precision at the LQL was 30.5% (n=6).

Accuracy: Ranged from 4 to 8%, over the concentration range (2 to 80 ng/ml). The assay accuracy at the LQL was 14% (n=6).

Plasma concentrations of R(+)-carvedilol, S(-)-carvedilol, R(+)-O-desmethylcarvedilol and S(-)-O-desmethylcarvedilol were determined from samples obtained on day 3. The procedure involved derivatization with a chiral reagent 2,3,4,6 tetra-O-acetyl- β -D-glucopyranosylisothiocyanate (GITC), followed by HPLC with fluorescence detection.

Carvedilol:

Linearity: Satisfactory (1.25 to 80 ng/ml).

Precision: Within-day ranged from 1.33 to 10.5% for R(+)-carvedilol and 1.29 to 6.53% for S(-)-carvedilol, over the concentration range (1.25 to 80 ng/ml).

Accuracy: (Max. deviation) Within-day was 3% for R(+)-carvedilol 1.9% for S(-)-carvedilol, over the concentration range (1.25 to 80 ng/ml).

O-desmethylcarvedilol:

Linearity: Satisfactory (1.25 to 80 ng/ml).

Precision: Within-day ranged from 1.29 to 6.75% for R(+)-O-desmethylcarvedilol and 1.08 to 6.19% for S(-)-O-desmethylcarvedilol, over the concentration range (1.25 to 80 ng/ml).

Accuracy: (Max. deviation) Within-day was 2.9% for R(+)-O-desmethylcarvedilol 2.3% for S(-)-O-desmethylcarvedilol, over the concentration range (1.25 to 80 ng/ml).

Results:

The pharmacokinetic parameters for carvedilol obtained from the data are summarized in table 1. Estimates of intrasubject and intersubject variability are presented in table 2. Fig 1 summarizes mean plasma concentration versus time profiles following oral administration of 25 mg carvedilol on three separate occasions.

Individual C_{max} values were highly variable and ranged from 12.5 to 117.7 ng/ml for the entire study with a mean of 59.6 ng/ml on Study Day 1, 46.5 ng/ml on Study Day 2, and 59.5 ng/ml on Study Day 3. Peak concentrations were achieved approximately one hour after drug administration on all three study days. As seen for C_{max} , individual AUC_{0-t} values were highly variable with an overall range from 41.9 to 521.1 ng*hr/ml. Mean AUC_{0-t} were similar on the three study days (222.6, 205.7, and 217.7 ng*hr/ml, respectively). The mean apparent terminal elimination half-life was about 10 hours after each treatment with a range of 6.4 to 14.9 hours for the entire study.

Intersubject variability for AUC_{0-t} was large (58.4%) and was greater than intrasubject variability (17.5%). Similarly, the intersubject variability observed for C_{max} was large (53.2%). In contrast, intrasubject variability for C_{max} contributed more to the total variation observed. The percent of total variation for intrasubject variability was 30.7% for C_{max} as compared to 6.5% for AUC_{0-t} . A negative estimate of intersubject variance for T_{max} was obtained from the analysis of variance. Obtaining a negative estimate from the analysis of variance method is solely a consequence of the data (i.e. discrete sampling schedule), and it does not imply that the true estimate of variance is zero or the data are erroneous.

Plasma concentrations of O-desmethylcarvedilol were less than 10% of those observed for carvedilol on all three study days based on C_{max} and AUC_{0-t} data. Although the source of variability for O-desmethylcarvedilol was not estimated, the magnitude of the overall variability appears similar to that observed with carvedilol. The mean (range) AUC_{0-t} (ng*hr/ml) for O-desmethylcarvedilol were 12.5 (2.0 - 26.3), 15.3 (2.4 - 24.7), and 13.9 (3.2 - 27.9) on Study Day 1, Study Day 2, and Study Day 3, respectively. The mean (range) C_{max} (ng/ml) were 3.7 (2.2 - 6.1), 3.2 (1.8 - 5.2), and 4.6 (2.1 - 7.7) on the individual study days. The mean T_{max} were approximately 1.0 hour on each study day.

The time courses of the plasma concentrations were similar for R(+)-carvedilol and S(-)-carvedilol following oral administration of racemic carvedilol. The pharmacokinetic parameters for R(+)-carvedilol and S(-)-carvedilol are presented in Table 3. The mean T_{max} were approximately 1.0 hour for each enantiomer. Mean C_{max} and AUC_{0-t} values for R(+)-carvedilol were two to four times greater than those observed for S(-)-carvedilol. The mean (range) AUC_{0-t} (ng*hr/ml) were 156.7 (23.2 - 343.7) for R(+)-carvedilol and 43.9 (7.8 - 83.2) for S(-)-carvedilol. The mean (range) C_{max} (ng/ml) were 44.3 (8.3 - 92.2) and 16.7 (4.8 - 37.9) for R(+)-carvedilol and S(-)-carvedilol, respectively. The enantiomeric ratios (R/S) of carvedilol for AUC_{0-t} and C_{max} are shown in Table 4. This ratio showed wide intersubject variability, ranging from 1.7 to 8.1 (geometric mean 3.6) for AUC_{0-t} and 1.7 to 3.9 (geometric mean 2.6) for C_{max} . Because of the higher limit of quantification and the lower concentrations of the enantiomers relative to carvedilol, the terminal half-life (λ_3) could only be estimated in a small number of individuals. The mean (range) terminal elimination half-life ($t_{1/2\lambda_3}$) of R(+)-carvedilol, measurable in three subjects, was 8.3 hours (5.7 - 11.2 hours). This was similar to the mean terminal half-life of 9.0 hours (6.4 - 12.2 hours) seen for carvedilol on Study Day 3. The terminal elimination half-life ($t_{1/2\lambda_3}$) of S(-)-carvedilol could only be determined in one subject and was 17.9 hours. The mean $t_{1/2\lambda_2}$ were similar for R(+)-carvedilol and S(-)-carvedilol, 2.8 and 2.7 hours, respectively.

For R(+)-O-desmethylocarvedilol, the mean (range) AUC_{0-t} , C_{max} , and T_{max} were 7.2 (2.2 - 18.5) ng*hr/ml, 4.2 (2.0 - 6.6) ng/ml, and 1.3 (0.8 - 2.5) hr, respectively. Since plasma concentrations of S(-)-O-desmethylocarvedilol were below the limit of quantification at almost every time point in all subjects, pharmacokinetic analysis was not conducted for this isomer.

Table 1 Summary of Pharmacokinetic Parameters for Carvedilol*
(Protocol 105517/A9901-US)

<u>Parameter</u>	<u>Study Day 1</u>	<u>Study Day 2</u>	<u>Study Day 3</u>
C_{max} (ng/ml)	59.6 ± 31.5	46.5 ± 22.0	59.5 ± 32.5
T_{max} (hr)	0.93 ± 0.28	1.60 ± 0.94	1.10 ± 0.70
AUC_{0-T} (ng*hr/ml)	212.6 ± 147.4	205.7 ± 111.8	217.7 ± 115.7
$AUC_{0-\infty}$ (ng*hr/ml)	278.5 ± 158.2	329.2 ± 128.7	236.0 ± 125.7
$t_{1/2}$ (hr)	9.7 ± 1.7	10.0 ± 2.4	9.0 ± 1.7

* Mean ± SD

Table 2 The Percent Coefficient of Variation (CV) and Percent of Total Variation (PTV) For Carvedilol Attributable to Intrasubject and Intersubject Variability

	<u>AUC_{0-T}</u>		<u>C_{max}</u>		<u>T_{max}</u>	
	CV	PTV	CV	PTV	CV	PTV
Intrasubject	17.5%	6.5%	35.0%	30.7%	60.9%	68.9%
Intersubject	58.4%	93.5%	53.2%	69.3%	0.0%	31.1%

Conclusion and Comments:

Following oral administration of carvedilol, intersubject variability for C_{max} and AUC_{0-t} was greater than the intrasubject variability. The contribution of intrasubject variability to total variation was greater for C_{max} .

Mean C_{max} and AUC_{0-t} values for R(+)-carvedilol were two to four times greater than those observed for S(-)-carvedilol.

Plasma concentrations of O-desmethylocarvedilol were less than 10% of those of carvedilol based on AUC_{0-t} and C_{max} data.

The study is acceptable, however it is unclear that lower levels seen for S(-)-carvedilol are due to selective higher S(-)-carvedilol clearance, difference in plasma protein binding or interconversion of enantiomers.

Following Oral Administration of 25 mg of Racemic Carvedilol
(Protocol 105517/A9901-US)

	Mean	Median	Range
R(+)-carvedilol			
Tmax (hr)	1.1	0.8	
Cmax (ng/ml)	44.3	39.3	
AUC _{0-t} (ng*hr/ml)	156.7	122.3	
AUC _{0-∞} (ng*hr/ml)	169.3	129.1	
t/12λ ₂ (hr)	2.8	2.7	
S(-)-carvedilol			
Tmax (hr)	1.0	0.8	
Cmax (ng/ml)	16.7	13.2	
AUC _{0-t} (ng*hr/ml)	43.9	35.7	
AUC _{0-∞} (ng*hr/ml)	51.2	41.9	

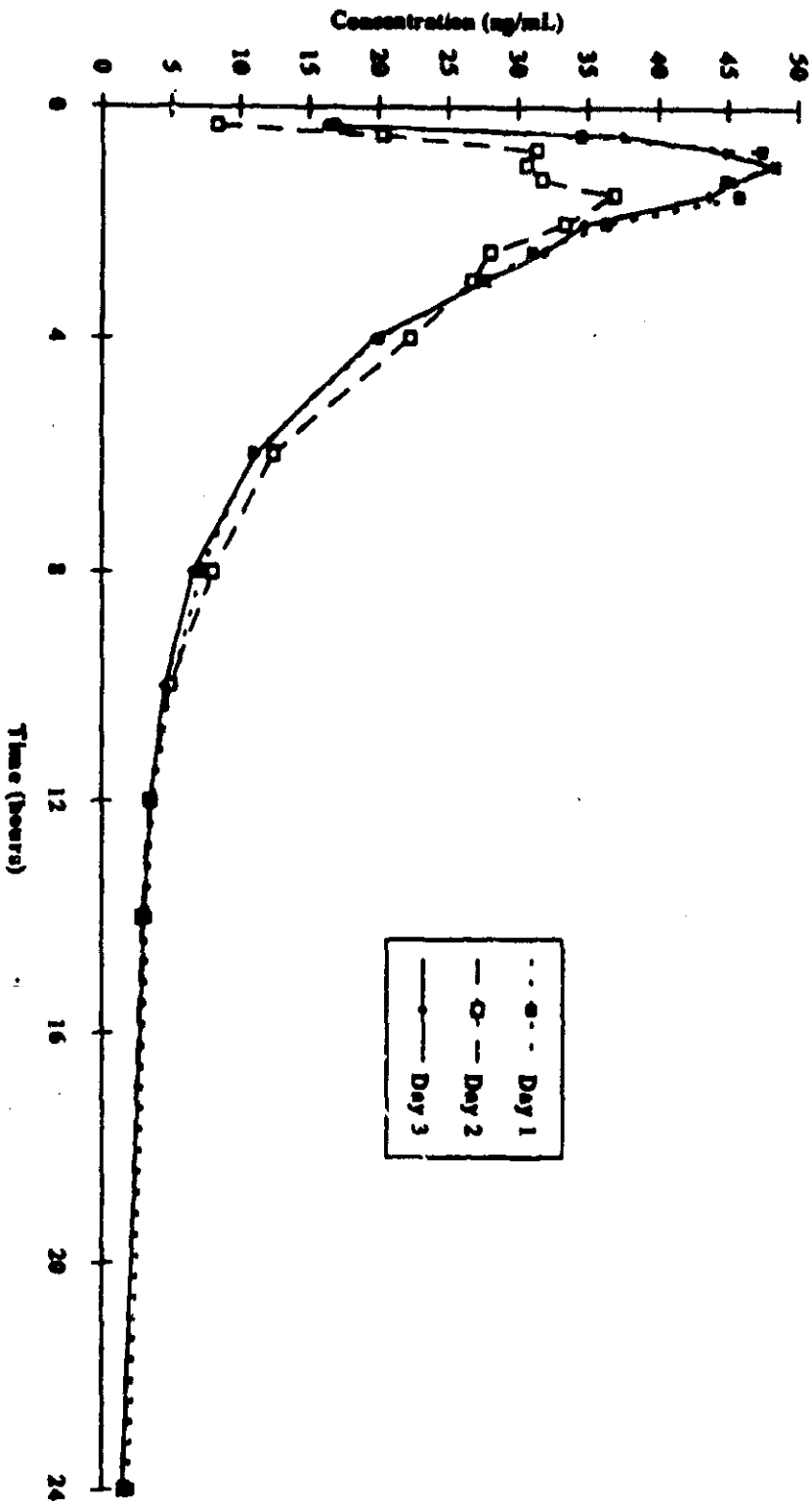
**Table 4 Enantiomeric Ratio (R/S) of Carvedilol for AUC_{0-t} and Cmax
(Protocol 105517/A9901-US)**

Subject No	AUC _{0-t}	Cmax
S-78-88	3.18	2.55
S-79-88	1.71	1.82
S-80-88	2.32	2.01
S-81-88	4.09	3.93
S-82-88	2.02	1.78
S-83-88	3.61	2.67
S-84-88	4.37	2.73
S-85-88	4.94	3.30
S-86-88	2.98	1.72
S-87-88	3.54	3.53
S-88-88	8.11	3.41
S-89-88	6.23	3.21
Geometric Mean	3.57	2.62
Minimum	1.71	1.72
Maximum	8.11	3.93

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Protocol A5901/Figure 1

Mean plasma concentration-time profiles for corrected following a single oral dose of 25 mg corrected on three separate occasions (same formulation) to healthy male volunteers.



Note: Non-quantifiable values (< 0.3 ng/mL) were not included in the calculation of mean data; mean data are not presented if more than one-half of the subjects exhibited non-quantifiable values.

Absolute Bioavailability of Carvedilol Enantiomers

Report of this study was not submitted. The reviewer has evaluated the reference cited by the sponsor (Eur. J. Clin. Pharmacol, 1990, 38: S108 - S111).

Objectives: To investigate the enantiomers of carvedilol in man after intravenous and oral dosing of racemic carvedilol.

Study Design: Ten healthy male subjects (age: 21 to 39 years; weight: 57 to 98 kg) participated in the study. In an open, randomized, two-period, crossover study, the subjects received either 12.5 mg racemic carvedilol (lot no. 819845 59D) infused intravenously within 1 hour or 50 mg racemic carvedilol (25 mg tablets, lot no. 819896 20B) orally. The treatments were repeated after a 1 week washout period. Serial blood samples were obtained at intervals up to 24 hours after the start of the infusion or after oral administration.

Pharmacokinetic parameters were determined using non-compartmental methods. The Wilcoxon test for paired data was used for statistical comparisons.

Analytical Methods: Plasma concentrations of racemic carvedilol were determined using HPLC with fluorescence detection. The lower limit of quantification was 1 ng/ml for racemic carvedilol.

Plasma concentrations of R(+)-carvedilol and S(-)-carvedilol were determined. The procedure involved derivatization of racemic carvedilol with the chiral reagent 2,3,4,6-tetra-O-acetyl- β -D-glucopyranosylisothiocyanate (GITC). The resulting diastereomers were resolved and quantified using HPLC with fluorescence detection.

The lower limit of quantification was 2 ng/ml for R(+)-carvedilol and 1 ng/ml S(-)-carvedilol.

Results and Discussion: An excellent correlation ($r = 0.99$) existed between the racemic carvedilol concentrations and the sum of the enantiomer concentrations over the whole range of plasma concentrations. Median (range) pharmacokinetic parameters for R(+)- and S(-)-carvedilol and enantiomeric ratios (R/S) are shown in Table 1

The median C_{max} and AUC_{0-24} values for S(-)-carvedilol were significantly lower than those for R(+)-carvedilol after both i.v. and p.o. administration. Differences in the enantiomeric ratio were wider after oral administration. The median (range) R/S enantiomeric ratios were 1.3 (1.04 - 1.9) and 1.2 (1.1 - 1.4) for AUC_{0-24} and C_{max} , respectively, after intravenous administration, and 2.7 (1.6 - 4.4) and 2.6 (1.4 - 4.3) for AUC_{0-24} and C_{max} , respectively, after oral administration. A close correlation ($r = 0.93$) existed between enantiomeric ratios after i.v. and p.o. administration, demonstrating slight intraindividual variability. (Fig 1)

The median $t_{1/2}$ value for S(-)-carvedilol was significantly longer than that for R(+)-carvedilol after oral administration, 22.1 hours ($n = 7$) versus 9.6 hours, respectively. Following intravenous administration, median $t_{1/2}$ values S(-)- and R(+)-carvedilol were similar, 3.2 hours ($n = 6$) and 3.5 hours, respectively. Median systemic clearance for S(-)-carvedilol was higher than that observed for R(+)-carvedilol, 662 ml/min ($n = 6$) and 605 ml/min, respectively. The median volume of distribution ($V_{d_{area}}$) was for S(-)-carvedilol was 188 L ($n = 6$) compared to 170 L for R(+)-carvedilol. The median absolute bioavailability of R(+)-carvedilol was twice that of S(-)-carvedilol, 31% and 15%, respectively.

Comments and Conclusion:

The firm has not provided assay validation for this study. The firm has reported median and range instead of mean and standard deviation for all the pharmacokinetic parameters. The R(+) enantiomer has shown twice the bioavailability as S(-) enantiomer. Interestingly, for other β -blockers e.g. propranolol R(+) enantiomer has shown higher oral clearance (Silber et al., 1982, J.Pharm.Sci., 71:699-703).

Following both oral and intravenous administration of carvedilol, there were stereoselective differences in the pharmacokinetics of the enantiomers of carvedilol with plasma concentrations of R(+) carvedilol greater than S(-) carvedilol. The R/S enantiomeric ratios following oral administration were greater than after intravenous administration suggesting that carvedilol exhibits stereoselective first pass metabolism.

Table 1. Pharmacokinetic parameters of *R*(+)- and *S*(-)-carvedilol following i.v. administration of 12.5 mg and p.o. administration of 50 mg racemic carvedilol and enantiomeric ratios [*R*(+) / *S*(-)] in 10 subjects (median values with ranges in parentheses)

Route of administration	Enantiomer	AUC 0-24 (ng·h·ml ⁻¹)	t _{1/2} (h)	C _{max} (ng·ml ⁻¹)	Cl/P ^a (ml·min ⁻¹)	V _z (l)	f (%)
i.v.	<i>R</i> (+)	172* (139-325)	3.5 (2.0-7.1)	85* (65-107)	605* (310-747)	170 (103-251)	100
	<i>S</i> (-)	129 (76-178)	3.2 (2.1-3.8)	70 (51-85)	662 (582-858)	188 (105-284)	100
p.o.	<i>R</i> (+)	214* (138-605)	9.6* (4.1-19.4)	74* (46-138)	1791 (648-2867)	-	31.1 (20.2-46.5)
	<i>S</i> (-)	78 (32-163)	22.1 (4.7-72.5)	29 (11-48)	2439 (1601-6256)	-	15.1 (10.4-24.4)
i.v.	<i>R</i> (+)/ <i>S</i> (-)	1.3 (1.0-1.9)	1.1 (0.6-3.5)	1.2 (1.1-1.4)	0.9 (0.5-1.0)	0.9 (0.7-1.8)	-
p.o.	<i>R</i> (+)/ <i>S</i> (-)	2.7 (1.6-4.4)	0.4 (0.2-1.6)	2.6 (1.7-4.3)	0.7 (0.3-1.7)	-	2.0 (1.5-2.4)

* $P < 0.05$ [Wilcoxon test for paired data, *R*(+) vs *S*(-)]

^a After i.v. administration $f = 1$

^b Numbers of evaluable subjects are shown in square brackets

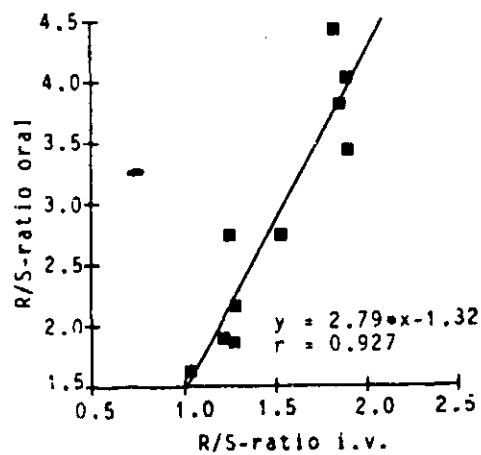


Fig. 1. Correlation between the AUC enantiomer ratios after i.v. and oral administration of carvedilol in ten subjects

Title: A study of the bioavailability and pharmacokinetics of carvedilol in healthy subjects

Investigator:

Study Center:

Objective: Determine the systemic bioavailability of carvedilol following oral and intravenous administration.

Study Design: The pharmacokinetic profile of carvedilol was determined in a group of twelve healthy male volunteers (age: 19 - 31 years; weight: 142 - 210 pounds). Each subject received the following formulations of carvedilol in randomized order: 0.094 mg/kg intravenously infused over 15 minutes (lot no. 818651 59A), 50 mg oral solution (lot no. 818651 59A), 50 mg capsule (size 0; lot no. 819178 40Ge). All treatments were administered under fasting conditions. Blood samples were obtained prior to administration of the oral formulations of carvedilol and at 15, 30, and 45 minutes and 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 16, and 24 hours post-dose. For the intravenous preparation, blood samples were obtained before the start of the infusion, immediately post-infusion, 1, 2.5, 5, 7.5, 10, 15, 30, and 45 minutes and 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 16, 20, and 24 hours after the end of the infusion. Total urine volume was collected at the following time intervals: pre-dose, 0-4, 4-8, 8-12, 12-24, and 24-48 hours post-dose. Pharmacokinetic parameters were determined by noncompartmental methods. Data are presented as mean and range. Statistical comparisons were performed using analysis of variance.

Assay: HPLC with fluorometric detection.

Serum: LQL was 2 ng/ml.

Precision: Interday ranged from 13% at 2 ng/ml to 3.2% at 150 ng/ml. Intraday ranged from 11.8% at 3 ng/ml to 4.1% at 125 ng/ml.

Accuracy: Interday ranged from 15% at 2 ng/ml to 0.6% at 150 ng/ml. Intraday ranged from 13.3% at 3 ng/ml to 17.3% at 125 ng/ml.

Urine: LQL was 2.5 ng/ml.

Precision: Interday ranged from 11.5% at 2.5 ng/ml to 0.6% at 1000 ng/ml. Intraday ranged from 4.2% at 3 ng/ml to 1.43% at 600 ng/ml.

Accuracy: Interday ranged from 4% at 2.5 ng/ml to 0.56% at 1000 ng/ml. Intraday ranged from 10% at 3 ng/ml to 9% at 600 ng/ml.

Results and Discussion:

The pharmacokinetic parameters for carvedilol after administration of the different formulations are shown in table 1. The mean plasma concentration versus time profiles are summarized in fig 1.

Following intravenous administration of 0.084 mg/kg of carvedilol, the mean C_{max} was 203.3 ng/ml and ranged from 144.4 to 291.3 ng/ml. Mean C_{max} values were similar following oral administration of the solution and capsule, 120.7 versus 128.0 ng/ml, respectively. Following administration of the oral formulations, T_{max} was reached most rapidly with the solution. The mean T_{max} were 0.85 hours (0.5 - 3.0 hours) and 1.35 hours (0.5 - 3.5 hours) after administration of the 50 mg solution and 50 mg capsule, respectively.

Following intravenous dosing, the mean $AUC_{0-\infty}$ for carvedilol was 228 ng·hr/ml (139 - 421 ng·hr/ml). The mean $AUC_{0-\infty}$ was 519 ng·hr/ml (225 - 1036 ng·hr/ml) following 50 mg of carvedilol in the solution compared to 627 ng·hr/ml (211 - 1518 ng·hr/ml) after the 50 mg carvedilol capsule. The absolute bioavailability of carvedilol from the oral formulations was generally low but highly variable between subjects. The mean absolute bioavailability was 29% (18% - 58%) from the solution and 33% (21% - 67%) from the 50 mg capsule.

Elimination half-life was significantly shorter for the intravenous preparation of carvedilol than the oral formulations. Mean half-lives were 3.22 hours (1.46 - 8.01 hours) following 0.084 mg/kg carvedilol intravenously, 9.06 hours (2.67 - 16.48 hours) after the 50 mg carvedilol solution, and 7.53 hours (4.37 - 13.98 hours) following administration of the 50 mg carvedilol capsule.

There were no statistically significant differences between the capsule formulation and the oral solution with regard to any of the pharmacokinetic parameters.

Following intravenous administration of carvedilol, systemic clearance was 547 ml/min (288 - 838 ml/min). Volume of distribution at steady-state for carvedilol was 114 L (66 - 171 L).

The amount of carvedilol and the percent of the dose which appeared in the urine as unchanged carvedilol was small for each formulation administered. Following both the oral solution and the capsule, 0.37% appeared in the urine as unchanged carvedilol while after intravenous administration, 1.07% appeared in the urine as unchanged carvedilol.

Conclusions and Comments:

The study is acceptable.

The absolute bioavailability of carvedilol was low (approximately 30%) for both the capsule and solution formulation. The solution and capsule (post oral) dosage forms showed significantly higher variability than iv solution in $AUC_{0-\infty}$ and C_{max} .

The clearance and volume of distribution at steady state for carvedilol were about 550 ml/min and 115 L, respectively.

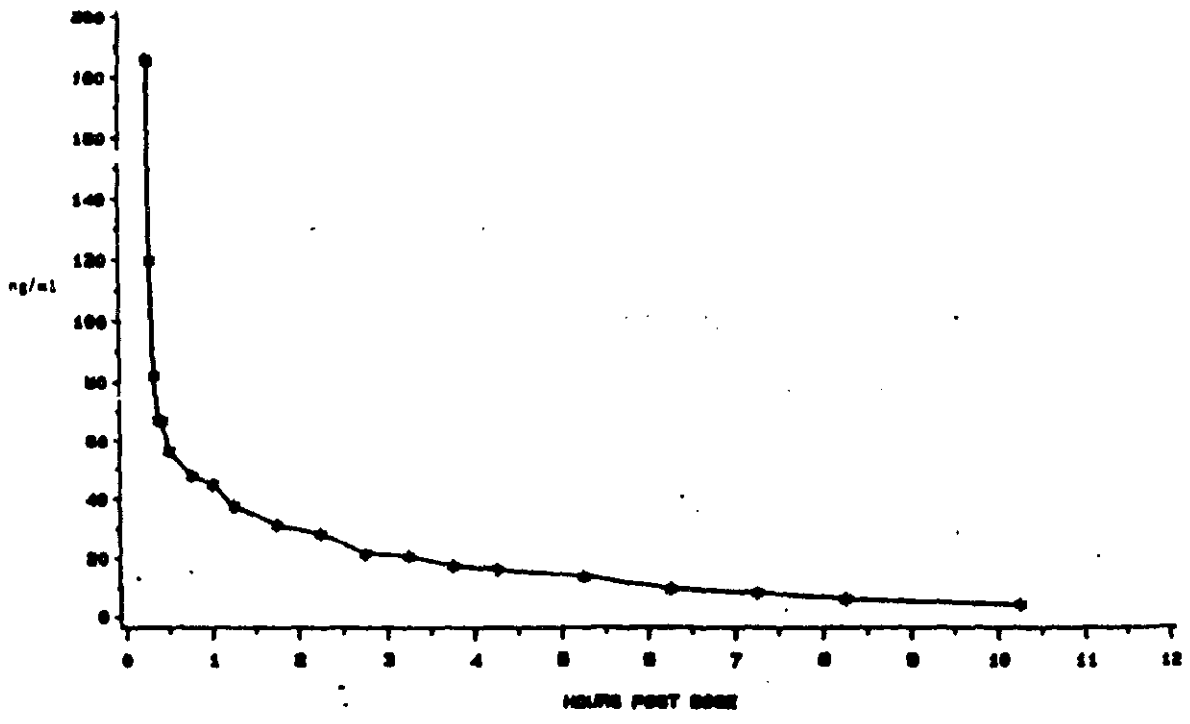
The significant difference seen in case of the $t_{1/2}$ between two routes, is most likely due to slow absorption of carvedilol. The slower absorption in case of solution could be due to drug precipitating in the gut.

	0.084 mg/kg intravenous	50 mg solution	50 mg capsule
C _{max} (ng/ml)	203.3	120.7 [†]	128.0 [†]
T _{max} (hr)		0.85	1.35
AUC _{0-∞} (ng*hr/ml)	228	519 [†]	627 [†]
t _{1/2} (hr)	3.22	9.06 [†]	7.53 [†]
V _{ss} (L)	114		
CL _s ml/min	547		

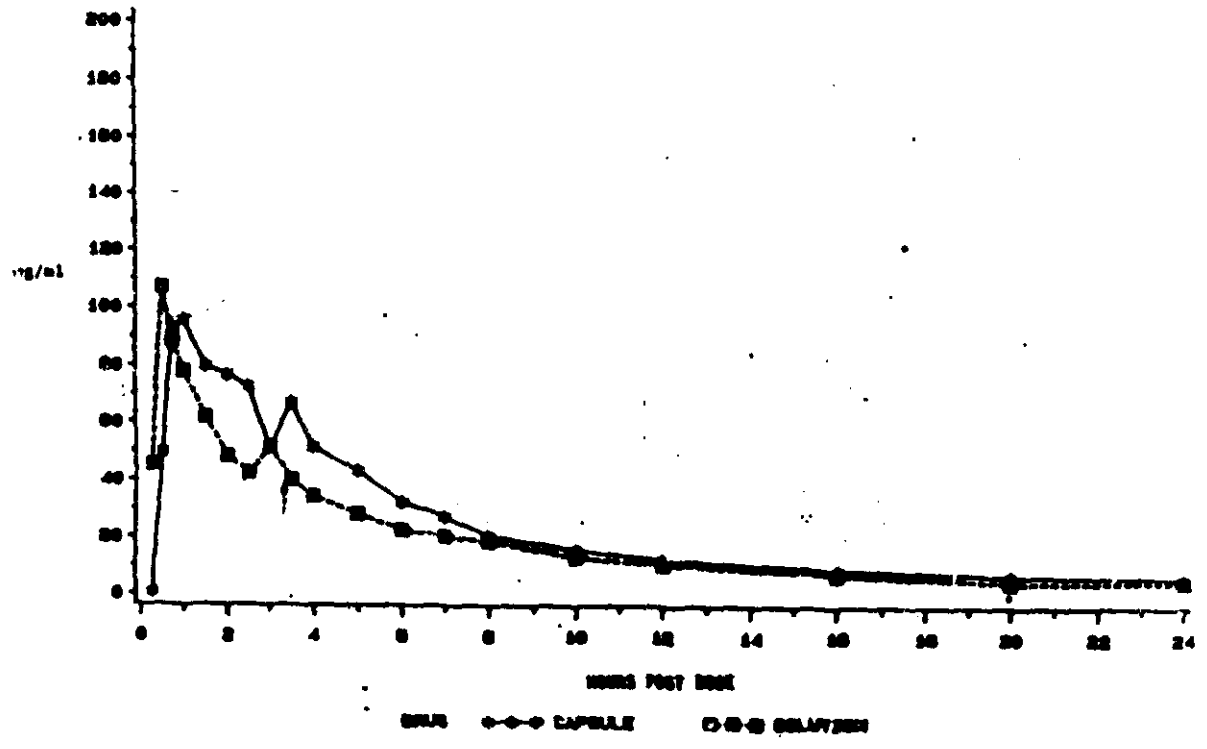
* Data are presented as mean and range.

† p < 0.05, compared to intravenous data.

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Dose Proportionality of Carvedilol

Vol. 1.51 Page 000231

Title: A dose proportionality study of carvedilol enantiomers following doses of racemic carvedilol (SK&F 105517 - capsules) of 6.25, 12.5, 25.0, and 37.5 mg orally in healthy subjects

Investigator: Diane Jorkasky, M.D.

Study Center: SmithKline Beecham Clinical Research Unit, Presbyterian Medical Center of Philadelphia, Philadelphia, Pennsylvania, USA

Objectives: To assess the dose proportionality of plasma concentrations of carvedilol enantiomers following oral doses of 6.25, 12.5, 25, and 37.5 mg of racemic carvedilol.

Study Design: Twelve healthy male subjects (age 23 to 35 years; weight 67 to 91 kg) completed this randomized, crossover study. Each subject received a single oral dose of 6.25 mg (lot no. 820169 40Cc), 12.5 mg (lot no. 820468 40Lg), 25 mg (lot no. 820469 40Lh), and 37.5 mg (administered as one 12.5 and one 25 mg capsule) racemic carvedilol. On each occasion, carvedilol was administered after an overnight fast. Blood samples were collected before the dose (0 time) and at 15, 30, 45 minutes and 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours after dosing on each study day. Pharmacokinetic parameters were determined by noncompartmental methods.

Systematic differences between dose-normalized measurements of C_{max} and AUC_{0-t} for R(+)-carvedilol and S(-)-carvedilol were analyzed using analysis of variance (ANOVA). ~~Scheffe's multiple comparison test at the 5% level of significance was used if the ANOVA showed a significant difference for AUC_{0-t} or C_{max} .~~ Dose proportionality of the pharmacokinetics of each enantiomer was also assessed by calculating dose-normalized C_{max} and AUC_{0-t} ratios using the 12.5 mg dose as the reference dose. Based upon dose proportional pharmacokinetics, the dose-normalized C_{max} and AUC_{0-t} ratios should be equal to unity. Because of the log-normal distribution for these ratios, the geometric mean was calculated as a measure of central tendency.

Assay:

Plasma concentrations of R(+)-carvedilol and S(-)-carvedilol were determined from samples by a procedure involving derivatization with a chiral reagent 2,3,4,6 tetra-O-acetyl- β -D-glucopyranosylisothiocyanate (GITC), followed by HPLC with fluorescence detection.

Carvedilol:

Linearity: Satisfactory (1.25 to 80 ng/ml).

Sensitivity: LQ_L for each the enantiomer was 0.3 ng/ml.

Precision: Within-day ranged from 1.33 to 10.5% for R(+)-carvedilol and 1.29 to 6.53% for S(-)-carvedilol, over the concentration range (1.25 to 80 ng/ml).

Accuracy: (Max. deviation) Within-day was 3% for R(+)-carvedilol 1.9% for S(-)-carvedilol, over the concentration range (1.25 to 80 ng/ml).

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BY APPLICANT

Result and Discussion: The time courses of the plasma concentrations for R(+) carvedilol and S(-) carvedilol were similar following oral administration of 6.25, 12.5, 25 and 37.5 mg racemic carvedilol (fig 1). The pharmacokinetic parameters obtained from the data are shown in table 1. Median T_{max} values were approximately 1 hour for each enantiomer after each treatment. Plasma concentrations of the enantiomers following 6.25 mg racemic carvedilol could only be measured out to 6 to 10 hours for most subjects. Due to the shorter time intervals for calculation of AUC_{0-t} for the 6.25 mg dose, this parameter was underestimated compared to the higher doses.

Mean AUC_{0-t} and C_{max} values for R(+)carvedilol were approximately two to three times greater than those observed for S(-)carvedilol at each dose level and appear to exhibit dose proportionality between dose levels. The geometric mean for the individual ratios (R/S) for AUC_{0-t} were 3.46, 3.01, 2.64, and 2.53, respectively (see Table 1). Similarly, the geometric mean for the individual ratios (R/S) for C_{max} were 2.80, 2.63, 2.57, and 2.30, respectively. Within the same individual, the enantiomer ratio for AUC_{0-t} and C_{max} varied minimally across doses. However, there was considerable variability in the enantiomer ratio for AUC_{0-t} and C_{max} between subjects. In general, at each dose level, there was a 3-4 fold range in individual enantiomer ratios for AUC_{0-t} and C_{max} following racemic carvedilol administration.

Following single dose administration, the R/S ratio for plasma concentrations of carvedilol enantiomers changes over time. The terminal elimination of S enantiomer appeared to be slightly slower than R enantiomer. Following table shows the ANOVA results on the dose normalized values for C_{max} and AUC_{0-t} for each enantiomer.

	Parameters	P
R(+)-Carvedilol	AUC _{0-t}	0.3589
R(+)-Carvedilol	C _{max}	0.5566
S(-)-Carvedilol	AUC _{0-t}	0.0117
S(-)-Carvedilol	C _{max}	0.4473

Fig 2 shows the dose proportionality analysis for each enantiomer using the 12.5 mg dose as the reference dose. The disproportionate increase in AUC_{0-t} for S(-)carvedilol is most likely due to under-estimation of the AUC following 6.25 mg racemic carvedilol.

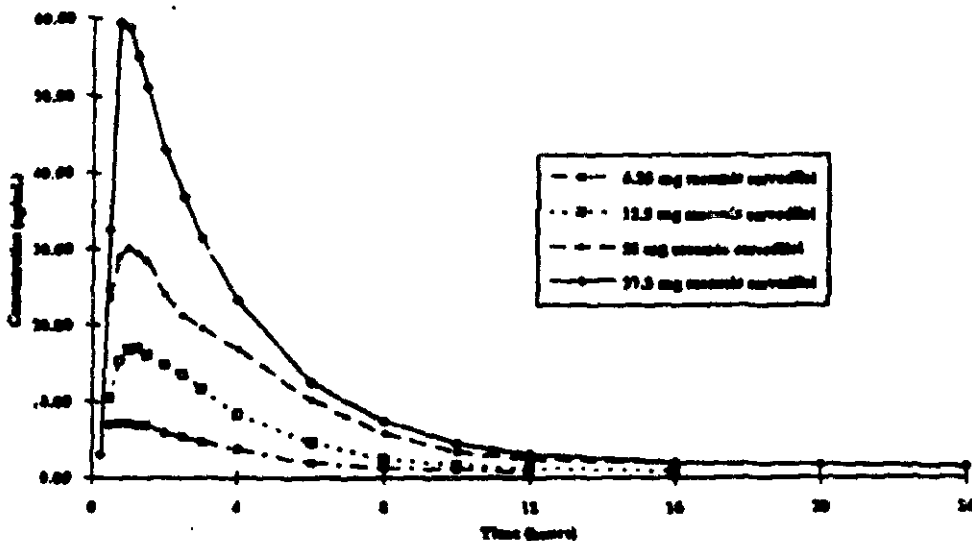
Conclusion and Comments:

The study is acceptable.

Plasma concentrations of R(+)carvedilol and S(-)carvedilol appear to be dose proportional over the dosing range of 6.25 to 37.5 mg. Proportionality of active metabolites of carvedilol was not studied and therefore, following a dose escalation, nothing could be commented on the plasma profiles of the active metabolites.

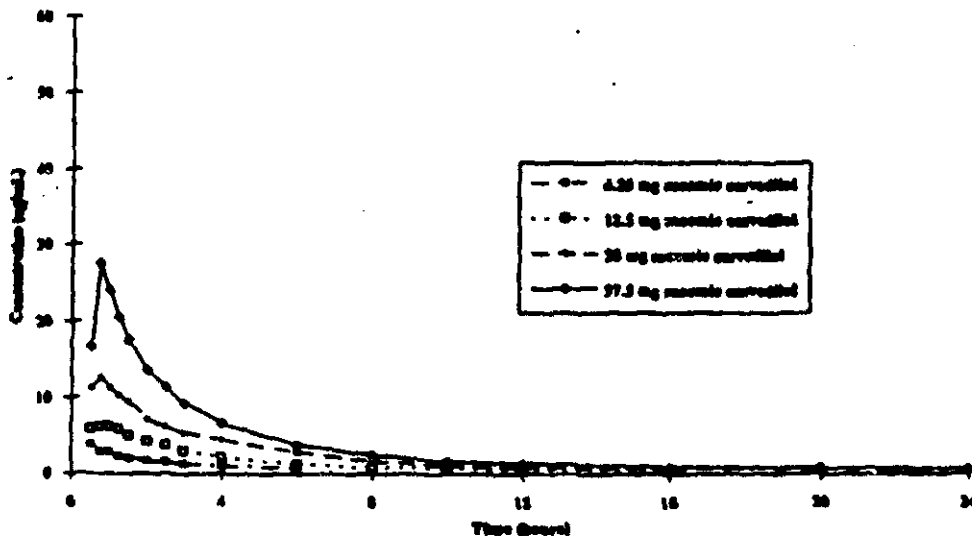
Preced A2007Figure 1

Mean plasma concentration-time profiles for *(R)*-carvedilol following single oral doses of 6.25, 12.5, 25, and 37.5 mg rounded to healthy volunteers.

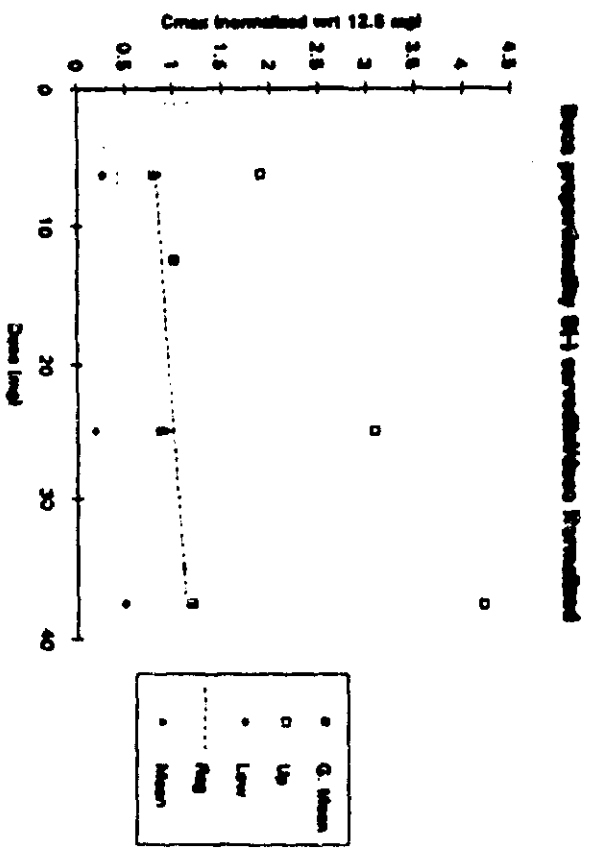
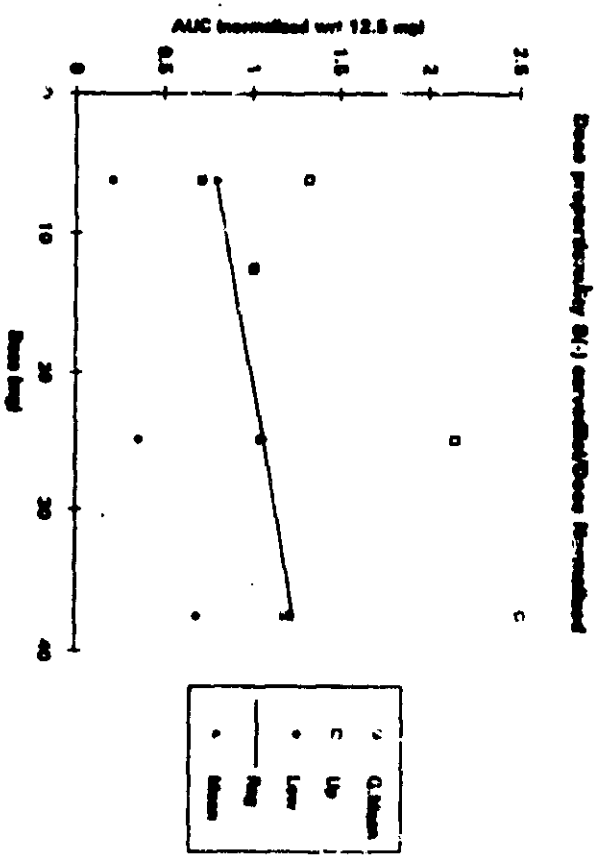
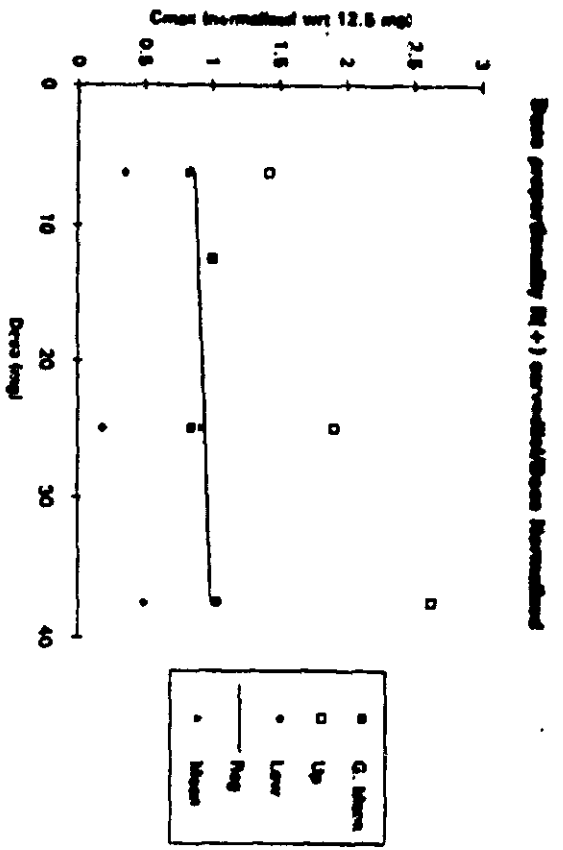
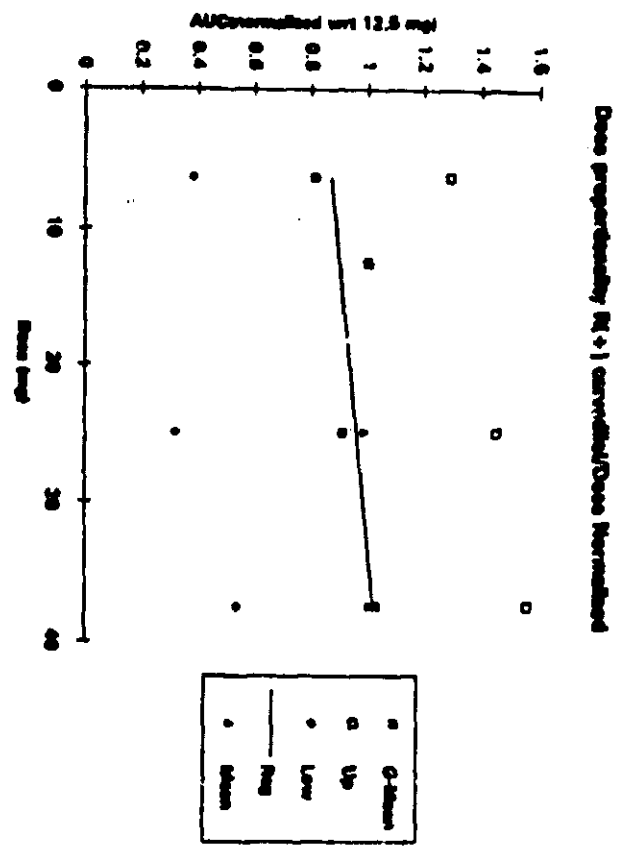


Note: Non-quantifiable values (< 0.3 ng/mL) were not included in the calculation of mean data; mean data are not presented if more than one-half of the subjects exhibited non-quantifiable values.

Mean plasma concentration-time profiles for *(S)*-carvedilol following single oral doses of 6.25, 12.5, 25, and 37.5 mg rounded to healthy volunteers.



Note: Non-quantifiable values (< 0.3 ng/mL) were not included in the calculation of mean data; mean data are not presented if more than one-half of the subjects exhibited non-quantifiable values.



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Table 1 Pharmacokinetic Parameters for R(+)-Carvedilol and S(-)-Carvedilol
Following 6.25, 12.5, 25, and 37.5 mg Racemic Carvedilol*
(Protocol 105517/A9903-US)

	6.25 mg Dose	12.5 mg Dose	25.0 mg Dose	37.5 mg Dose
C_{max}				
R(+)	8.9	21.4	40.1	66.2
S(-)	3.5	8.2	15.6	29.0
T_{max}				
R(+)	1.00	1.25	1.00	1.00
S(-)	0.88	0.75	0.75	0.75
AUC_{0-t}				
R(+)	32.1	78.4	155.9	237.7
S(-)	9.5	23.7	50.4	85.2
t_{1/2}				
R(+)	5.0	<u>6.3</u>	<u>8.1</u>	<u>9.2</u>
	(N = 3)	(N = 7)	(N = 9)	(N = 11)
S(-)	10.5	<u>10.5</u>	<u>10.2</u>	7.4
	(N = 2)	(N = 5)	(N = 6)	(N = 7)
R/S				
C _{max}	2.80	2.63	2.57	2.30
AUC _{0-t}	3.46	3.01	2.64	2.53

* Data presented as mean and range for C_{max} (ng/ml), AUC_{0-t} (ng*hr/ml), and t_{1/2} (hr); as median and range for T_{max} (hr); and as the geometric mean and range for the enantiomeric ratio (R/S); N = 12 except for t_{1/2}, which could not be estimated in a number of subjects, particularly at the low doses.

000156

Multiple Dose Study/BID Administration

Vol. 1.79 Page 000003

Study # CA 020021

Title: A study of the relationship between the dose and antihypertensive effect of carvedilol when administered orally twice a day for two weeks to patients with mild to moderate hypertension

Investigator:

Study Center:

Objectives: Determine the relationship between dose, serum level, magnitude and duration of the antihypertensive action of carvedilol.

Study Design: Seventy-six patients with mild to moderate hypertension were titrated off their antihypertensive medication and entered into a four week placebo period. Forty-one patients qualified for random assignment to one of the following four parallel treatment groups:

- placebo: n = 10 (6 male, 4 female); age: 26 to 59 years; weight: 116 to 255 pounds
- 3.125 mg carvedilol: n = 11 (5 male, 6 female); age: 35 to 67 years; weight: 164 to 239 pounds; lot no. CTM-027
- 6.25 mg carvedilol: n = 10 (10 male); age: 33 to 65 years; weight: 171 to 259 pounds; lot no. CTM-026
- 12.5 mg carvedilol: n = 10 (8 male, 2 female); age: 23 to 66 years; weight: 150 to 275 pounds; lot no. 819176 40Ge

Doses were administered twice a day for two weeks during the treatment phase. Thirty-eight patients completed the two week treatment phase. A study of the pharmacokinetics of carvedilol was undertaken on day 1 after the first (AM) dose (phase 1) and second (PM) dose (phase 2) and on day 14 after the first (AM) dose (phase 3) and second (PM) dose (phase 4). Blood samples were obtained after administration of each dose as follows: 0 (pre-dose), 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 10, and 12 hours after the dose. Pharmacokinetic parameters were determined by noncompartmental analysis.

In the 3.125 mg dose group, one subject dropped out of the study after refusing an indwelling catheter for blood sampling (no data for phase 2, 3, 4), one subject was discharged from the study due to severe systolic hypertension (no data for phase 4), and one subject had samples mislabeled or the dose switched (no data for phase 4). In the 6.25 mg dose group, for one subject, there was a problem with the initial assay and insufficient sample for repeat analysis (no data for phase 1 and 2). In the 12.5 mg dose group, one subject dropped out of the study due to schedule problems (no data for phase 3 and 4).

Assay: HPLC with fluorescence detection.

LQL: 0.38 ng/ml. **Linearity:** 0.078 to 20 ng/ml.

Precision: Interday was 7.52% at 0.078 ng/ml and 5.13% at 20 ng/ml. Intraday was 1.48% at 0.078 ng/ml and 0.57% at 20 ng/ml.

Accuracy: Interday was 0.4% at 0.078 ng/ml and 3.15% at 20 ng/ml. Intraday was 0.6% at 0.156 ng/ml and 1.5% at 20 ng/ml.

Note: Vol. 1.79, 1.80, since this study used a large # of males & females, individual data was examined for possible gender differences. A gender related pharmacokinetic difference was not apparent.

Result and Discussion: The pharmacokinetic parameters for carvedilol obtained from serum concentration data are shown in Table 1 to 3. The firm did not submit any plasma concentration-time figures.

There was a large amount of variability in the data between patients for C_{max} following both single and multiple doses of carvedilol at all dose levels. Mean C_{max} did not appear to change with multiple dosing of carvedilol but tended to be higher following the morning dose of carvedilol than the evening dose. Despite the parallel design and wide interpatient variability, mean C_{max} increased in an approximately dose-proportional manner.

T_{max} was not dependent upon the duration of treatment or the dose administered. The time to peak was longer following the evening dose of carvedilol as compared to the morning dose. The prolongation of T_{max} following the evening dose was most likely due to a decrease in the rate of absorption of carvedilol secondary to administration with food.

As seen for the C_{max} data, there was a large amount of interpatient variability in AUC data for carvedilol. As for C_{max}, mean AUC increased in an approximately dose-proportional manner. Following multiple dosing, mean AUC₀₋₁₂ tended to be higher (30 to 40%) following the morning dose of carvedilol than the evening dose. The median accumulation ratio, defined as the ratio of steady-state (Day 14 morning dose) AUC₀₋₁₂ to single dose (Day 1 morning dose) AUC_{0-∞}, was 1.09 (range 0.73-1.35) for the 3.125 mg regimen, 1.45 (range 0.62-2.13) for the 6.25 mg regimen, and 1.29 (range 0.78-1.67) for the 12.5 mg regimen (Table 4). This degree of accumulation may be artifactual due to the inability to describe the true terminal elimination half-life of carvedilol following single dose administration. In this study, blood sampling was carried out only to 12 hours after the first dose of carvedilol at which time the second dose was administered. The mean half-life used in estimation of single dose AUC_{0-∞} ranged from 3.5 to 4.6 hours compared to the 7 to 10 hour mean terminal elimination half-life typically observed for carvedilol. Therefore, the AUC_{0-∞} following single dose administration was most likely underestimated in this study.

Overall, the elimination half-life tended to be between four and five hours and was independent of the magnitude of the dose. Half-life values should be viewed with some caution as concentrations of carvedilol were only obtained out to 12 hours after a dose.

There was no pharmacokinetic analysis of the data for desmethylcarvedilol because of the incomplete nature of the concentration-time data for the metabolite.

The relationship between average steady-state serum concentration of carvedilol and average decrease in supine diastolic blood pressure was examined (Figure 1). There was a qualitative but variable relationship between concentration and response ($r^2 = 0.30$) with the correlation appearing closer in the higher dose groups.

Conclusions and Comments:

This study is acceptable.

In this parallel study, there was approximately 10-40% increase in C_{max} and AUC_{0-12} on multiple dosing with BID doses of 6.25 and 12.5 mg. The terminal elimination phase was not well described due to BID dosing and this could translate into inaccurate estimation of $AUC_{0-\infty}$.

The mean C_{max} and AUC tended to be lower 100% and 30-40% respectively following evening doses. This partly may be due to food effect as the subjects were told to take evening doses one hr before or 2 hr after evening meal (8:00 pm). However the food effect seen in another study showed only slight decrease in C_{max} , slight increase in AUC and significant increase in T_{max} .

In this study the characteristic fluctuation seen in C_{max} and AUC after morning and evening doses are due to diurnal variation, even though it may be partly confounded with food effect.

It is unclear in PK-PD analysis, whether the average plasma concentration data used is average of morning and evening doses.

Table 1
Pharmacokinetics of Carvedilol 3.125 mg Administered
Twice a Day to Hypertensive Patients*
(Protocol CARV0021)

	Day 1-AM (n = 11)	Day 1-PM (n = 10)	Day 14-AM (n = 10)	Day 14-PM (n = 8)
C _{max} (ng/ml)	13.8	6.8	11.7	5.6
T _{max} (hr)	1.36	3.38	1.05	3.31
AUC (0-12) (ng*hr/ml)	ND [†]	31.3	39.6	28.6
AUC (0-∞) (ng*hr/ml)	39.8	ND	ND	ND
t _{1/2} (hr)	3.5	8.8	3.8	5.9

* Data presented as mean and range
† ND = Not Determined

Table 3
Pharmacokinetics of Carvedilol 12.5 mg Administered
Twice a Day to Hypertensive Patients*
(Protocol CARV0021)

	Day 1-AM (n = 10)	Day 1-PM (n = 10)	Day 14-AM (n = 9)	Day 14-PM (n = 9)
C _{max} (ng/ml)	27.8	18.5	43.0	22.1
T _{max} (hr)	1.00	2.05	1.06	2.96
AUC (0-12) (ng*hr/ml)	ND [†]	101.5	178.7	141.5
AUC (0-∞) (ng*hr/ml)	127.5	ND	ND	ND
t _{1/2} (hr)	4.6	16.5	4.9	4.6

* Data presented as mean and range
† ND = Not Determined

Table 2
Pharmacokinetics of Carvedilol 6.25 mg Administered
Twice a Day to Hypertensive Patients*
(Protocol CARV0021)

	Day 1-AM (n = 9)	Day 1-PM (n = 9)	Day 14-AM (n = 10)	Day 14-PM (n = 10)
C _{max} (ng/ml)	17.6	10.9	21.8	10.4
T _{max} (hr)	1.00	2.11	1.35	2.75
AUC (0-12) (ng*hr/ml)	ND [†]	58.6	73.0	55.6
AUC (0-∞) (ng*hr/ml)	52.2	ND	ND	ND
t _{1/2} (hr)	3.5	6.9	4.2	6.5

* Data presented as mean and range
† ND = Not Determined

Table 4
Accumulation Ratio*
(Protocol CARV0021)

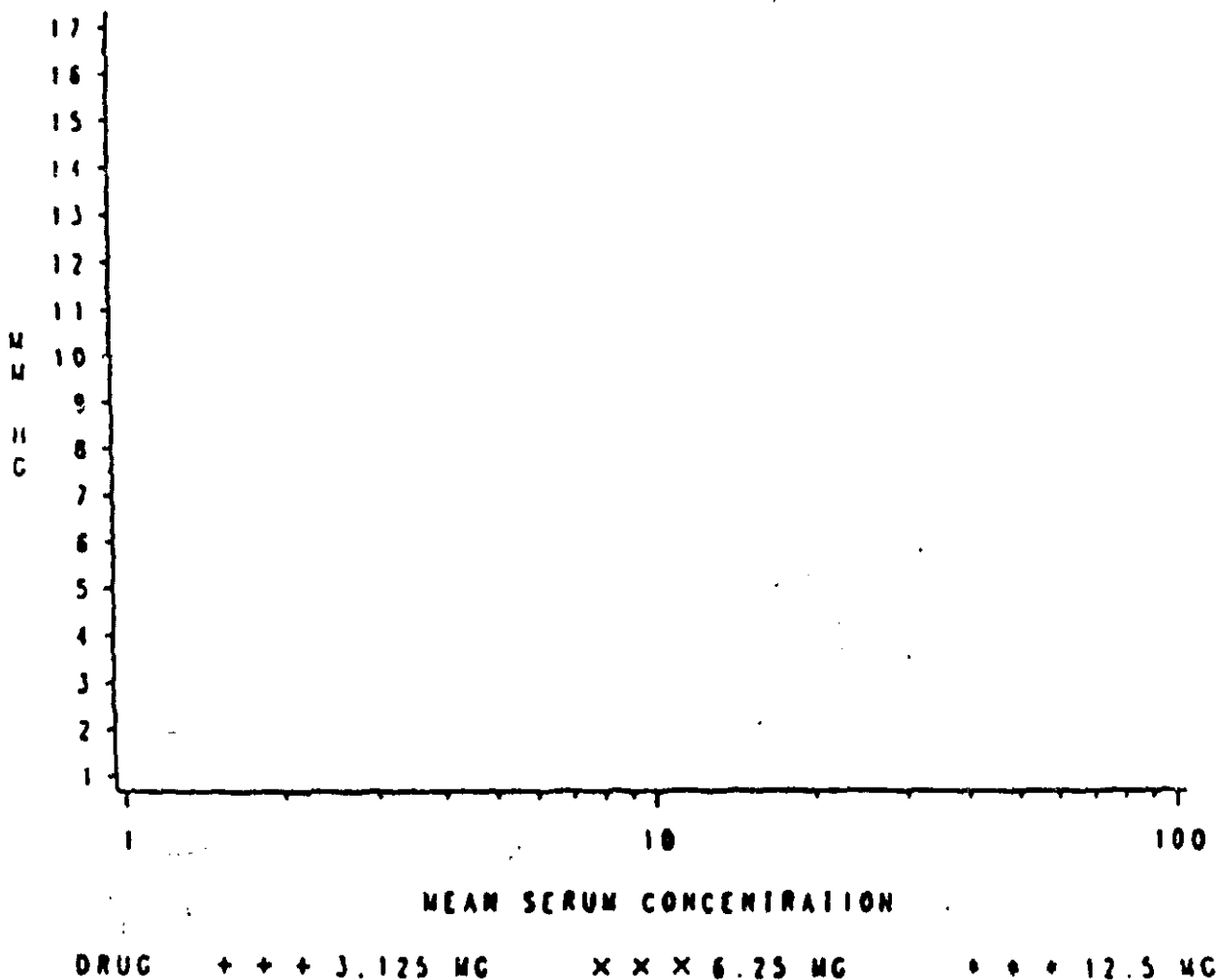
Dose	Accumulation Ratio [†]
3.125 mg (n = 10)	1.09
6.25 mg (n = 9)	1.45
12.5 mg (n = 9)	1.29

* Data are presented as median (range)

† Accumulation ratio defined as the ratio of the steady-state (Day 14 morning dose) AUC_(0,12) to single dose (Day 1 morning dose) AUC_{0-∞}

Figure 1

Relationship between average steady-state concentration (log scale) of carvedilol and average decrease in supine diastolic blood pressure observed after administration of carvedilol in hypertensive patients.



The data in the figure represent means across patients within time points at which blood was drawn for carvedilol measurements. The 0.5 and 1 hour time points were omitted because these times were during the distribution phase. The six data points represent the means of 9-10 patients at each time point.

and 12-hr. time point is also omitted.

IMP: The blood pressure data used is an average of morning ⁷⁸⁹ ~~000330A~~ and evening decrease in blood pressure (from baseline taken prior to treatment was begun) on day 14.

Multiple Dose Study/Pharmacokinetics in Hypertensive Patients

Vol. 1.76 Page 000003

Study # CAAD0003

Title: A dose-finding study for the use of oral carvedilol in the treatment of mild to moderate essential hypertension

Investigator:

Study Center:

Objectives: Determine the pharmacokinetics of 12.5 mg, 25 mg, and 50 mg carvedilol after single dose and multiple dose administration in patients with hypertension.

Study Design: Ninety-two patients with mild to moderate hypertension were weaned from their antihypertensive drugs and entered into a four week placebo period. Forty-four patients qualified for random assignment to one of the following four treatment groups:

placebo:	n = 11 (7 male, 4 female); (age: 42 to 59 years; weight: 125 to 256 lbs)
12.5 mg carvedilol:	n = 10 (8 male, 2 female); (age: 41 to 68 years; weight: 118 to 235 lbs); lot no. 819176 40Ge
25 mg carvedilol:	n = 11 (8 male, 3 female); (age: 36 to 53 years; weight: 144 to 217 lbs); lot no. 819177 40Fe
50 mg carvedilol:	n = 12 (11 male, 1 female); (age: 26 to 60 years; weight: 116 to 265 lbs); lot no. 819178 40Ge

Doses were administered once a day for four weeks during the treatment phase. Thirty-nine patients completed the four week treatment phase. A study of the pharmacokinetics of carvedilol was undertaken after the first treatment dose and at the end of four weeks of treatment. On each study day, blood samples were obtained before the administered dose and 0.25, 0.5, 1, 3, 6, 12, and 24 hours after the dose. Pharmacokinetic parameters were determined by noncompartmental analysis.

Assay: Carvedilol and O-desmethylocarvedilol in serum were analyzed by HPLC with fluorescence detection (LQL = 1.0 and 0.5 ng/ml respectively). Accuracy was not reported. Precision: Intraday ranged from 3.9% at 10 ng/ml to 3.8% at 80 ng/ml for carvedilol and 22.9% at 1 ng/ml to 7.78% at 8 ng/ml for O-desmethylocarvedilol. Interday ranged from 5.4% at 10 ng/ml to 5.06% at 80 ng/ml for carvedilol and 12.7% at 1 ng/ml to 6.8% at 8 ng/ml for O-desmethylocarvedilol. O-desmethylocarvedilol serum concentrations were not provided for review.

Results and Discussion: The pharmacokinetic parameters for carvedilol obtained from the serum concentration time data are shown in table 1. Fig 1 shows mean serum drug concentration after first and last dose. Fig 2 shows relation between first dose AUC_{0-24} and last dose AUC_{0-24} at each dose level.

There was a large amount of variability in the data between patients for C_{max} at each dose level following both single and multiple doses of carvedilol. In general, mean C_{max} values appeared

to increase in a dose proportional manner after both single dose and steady state administration. There was no evidence of an increase in the serum concentrations of carvedilol upon steady state dosing (table 2).

There was no change in median T_{max} upon multiple dosing. T_{max} occurred at one hour for the 12.5 mg and 25 mg regimens and three hours for the 50 mg regimen after both single dose and multiple dose administration. Although T_{max} appeared to be delayed at the highest dose, according to the design of the study, no blood samples were obtained for measurement of carvedilol concentration between one and three hours post study dose administration.

As seen for the C_{max} data, there was a large amount of intersubject variability in the AUC data for carvedilol at each dose level. Mean values for AUC_{0-24} (multiple dose) and $AUC_{0-\infty}$ (single and multiple dose) appeared to increase in an approximate dose-proportional manner between 12.5 and 25 mg of carvedilol. In contrast, mean AUC values following 50 mg of carvedilol increased 34 to 75% more than predicted based on strict dose-proportionality. Due to marked variability in the data, these differences were not statistically significant. In those patients who completed the study, the ratio of mean $AUC_{0-\infty}$ at steady-state versus mean $AUC_{0-\infty}$ after single dose administration ranged from 3-23% demonstrating modest accumulation of carvedilol following multiple dosing (Table 2). The median accumulation ratios, defined as AUC_{0-24} after multiple dosing divided by $AUC_{0-\infty}$ after single dose administration were 1.02 (range 0.66-1.22) for 12.5 mg dosing, 0.96 (range 0.63-1.31) for 25 mg dosing, and 1.01 (range 0.79-1.42) for 50 mg dosing, indicating no unexpected accumulation of carvedilol upon multiple dosing.

Overall, the mean elimination half-life for carvedilol ranged from 6.5 to 7.9 hours after single dose administration of carvedilol and from 7.6 to 8.3 hours after multiple dose administration of carvedilol.

Although serum concentrations were determined for O-desmethylcarvedilol, pharmacokinetic analysis of the metabolite data was not possible due to the limited number of concentrations above the limit of detection.

Since the T_{max} of carvedilol occurred approximately one hour post-dose, the change in supine diastolic blood pressure was plotted against serum levels measured one hour after administration of a single dose of carvedilol (Figure 3). Although there was a significant correlation ($r^2 = 0.13$) between serum concentration and response, there was considerable noise in the data. Removing the data from the two outliers did not effect the overall correlation between concentration and response ($r^2 = 0.17$) (based on reanalysis of data in report). In addition, it should be noted that while peak levels of carvedilol were observed at one hour, maximum decreases in supine diastolic blood pressure occurred between three to seven hours post-dose.

Conclusion and Comments:

The study is acceptable.

Individual plasma concentration-time data was not provided by the firm.

Based on C_{max} and AUC data, there was minimal accumulation of carvedilol at steady state (for 12.5 to 50 mg QD dosing). The accumulation ratios (AR) were expressed as medians. These should have been expressed as mean $\pm$ sd. The calculated mean ($\pm$ sd) AR were 0.97 ± 0.18 ,

1.0 ± 0.2 and 1.06 ± 0.23 for 12.5, 25 and 50 mg doses respectively. Following single and multiple dose administration, mean C_{max} for carvedilol appeared to increase in dose proportional manner. The mean AUC_{0-∞} values following single and multiple dose appeared to increase dose proportional between 12.5 to 25 mg of carvedilol. Following 50 mg carvedilol, the mean AUC_{0-∞} increased 40-70% more than dose proportionality. The terminal elimination half life of carvedilol was approximately 6 to 8 hr in hypertensive patients. Interpatient variability seen in this study was similar to seen in normal individuals.

Table 1
Pharmacokinetic Parameters for Carvedilol*†
(Protocol CARV0003)

	SINGLE DOSE	MULTIPLE DOSE
Cmax (ng/ml)		
12.5 mg carvedilol	38.6	32.4
25 mg carvedilol	75.4	72.9
50 mg carvedilol	160	167.0
Cmax (hr)		
12.5 mg carvedilol	2.0	2.0
25 mg carvedilol	2.0	2.0
50 mg carvedilol	2.0	2.0
AUC₀₋₂₄ (ng*hr/ml)		
12.5 mg carvedilol	306	300
25 mg carvedilol	605	543
50 mg carvedilol	1200	1126
AUC_{0-∞} (ng*hr/ml)		
12.5 mg carvedilol	390	304
25 mg carvedilol	416	306
50 mg carvedilol	1097	1242
t_{1/2} (hr)		
12.5 mg carvedilol	6.5	6.3
25 mg carvedilol	7.9	7.6
50 mg carvedilol	7.0	7.6

* Data are presented as mean (range) except Tmax which is median (range)

Number of Subjects	Single Dose		Multiple Dose	
	12.5 mg	25 mg	25 mg	50 mg
	10	11	11	9

† Not Determined

Table 2
Comparison of Single and Multiple Dose Pharmacokinetics
(Protocol CARV0003)

	Single Dose*	Multiple Dose*	Ratio†
Cmax (ng/ml)			
12.5 mg carvedilol	41.4	22.4	0.78
25 mg carvedilol	72.1	72.9	2.01
50 mg carvedilol	152.7	167.0	1.09
AUC_{0-∞} (ng*hr/ml)			
12.5 mg carvedilol	390	304	1.07
25 mg carvedilol	375	306	1.03
50 mg carvedilol	1093	1242	1.23

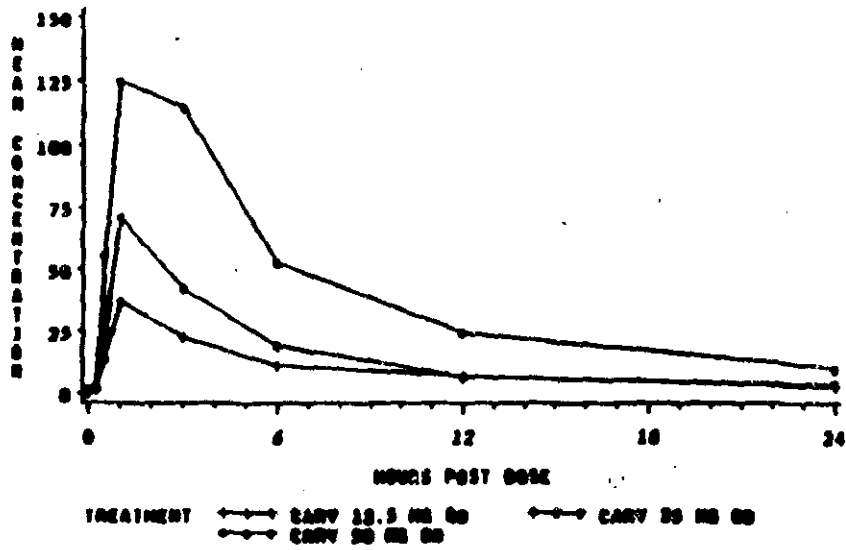
* Data are presented as mean for those patients who completed the study

† Ratio calculated as mean AUC_{0-∞} or Cmax after multiple dosing divided by mean AUC_{0-∞} or Cmax after a single dose

Fig 1

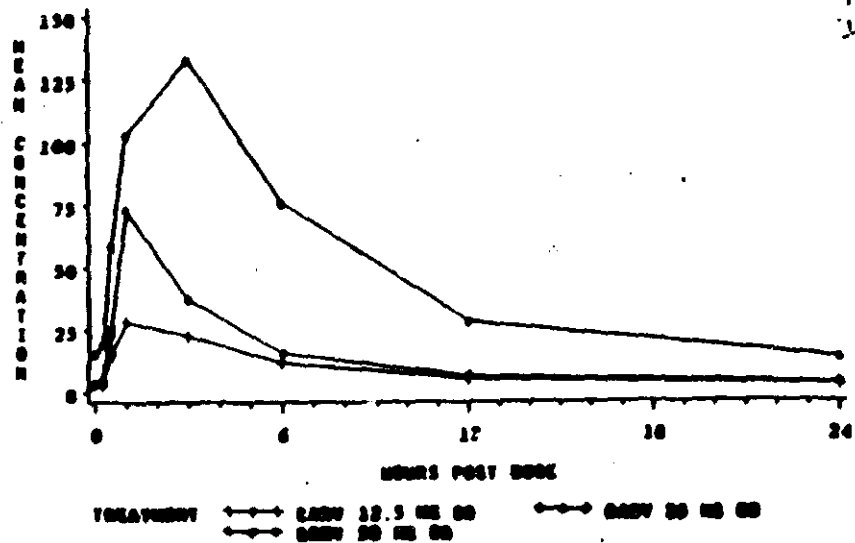
MEAN SERUM CARVEDILOL CONCENTRATION VS HOURS POST DOSE
Visit Number-004 (ACUTE)

150
Dose



MEAN SERUM CARVEDILOL CONCENTRATION VS HOURS POST DOSE
Visit Number-005 (CHRONIC)

150
Dose



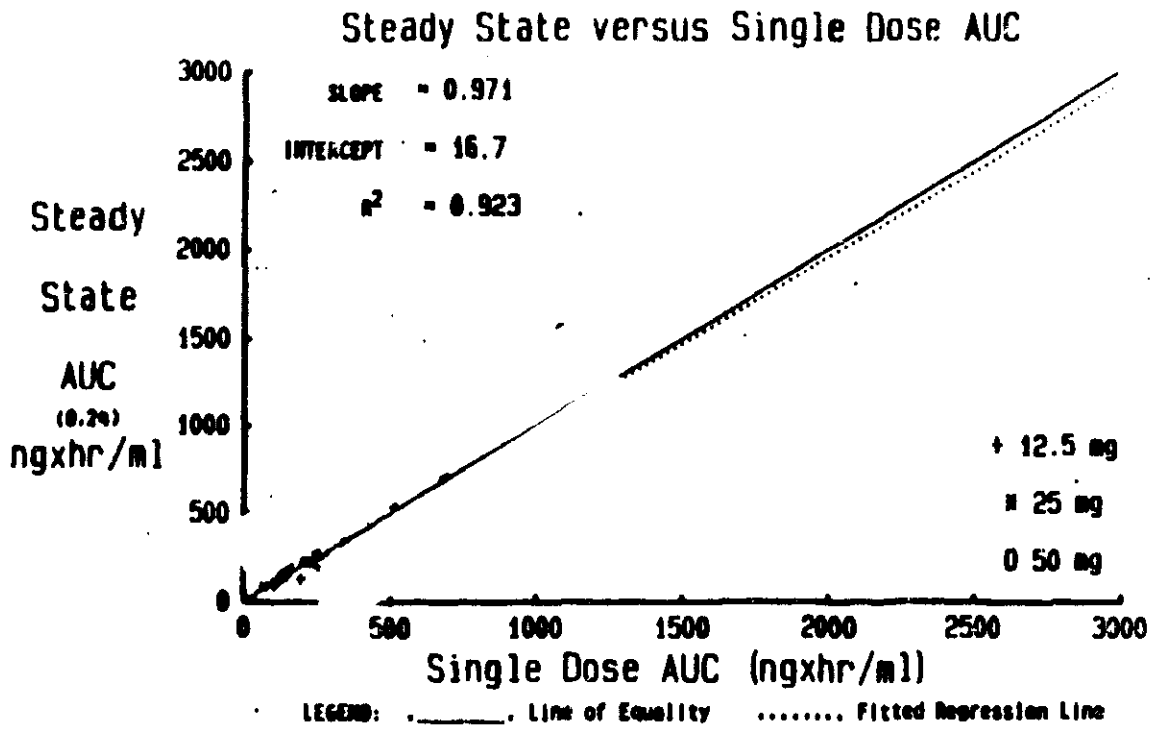
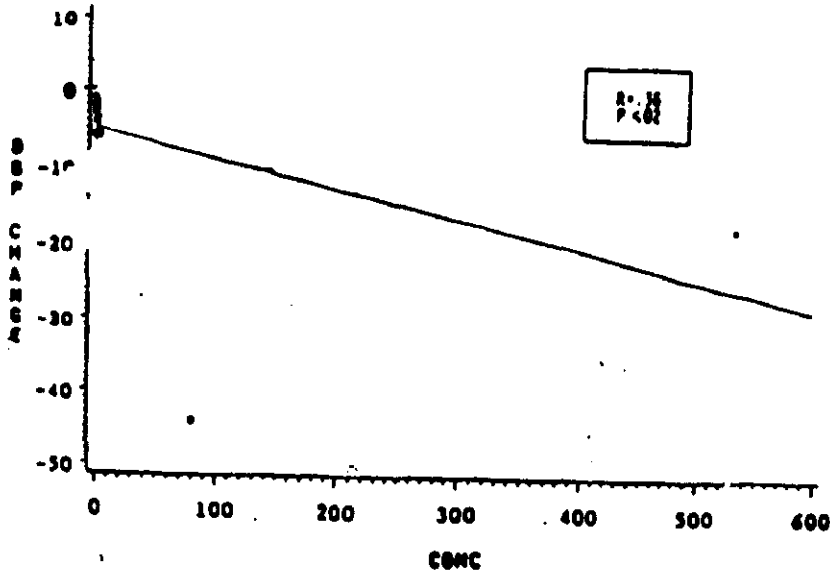


Fig 3.

Relationship between serum concentration of carvedilol and change in supine diastolic blood pressure observed one hour post-dose after single dose administration of carvedilol in hypertensive patients.



Influence of Food on Pharmacokinetics

Study No.: A9907

Volume: 1.52

Pages: 165-313

Investigators and Site: C. de Mey, M.D. and D. Enterling, Ph.D.

Clinical Pharmacology Unit of the SK & F

Institute for Applied Clinical Pharmacology, Goettingen, FRG

Objectives: To describe and compare the pharmacokinetics of carvedilol after administration of a single oral dose of 25 mg carvedilol either in the fasting condition or at the end of a standard meal in healthy volunteers.

Formulation: • Carvedilol 25 mg tablets (Tiltab[®] formulation), batch # CDC 15444-195

Study Design: Period-balanced, two-way cross-over design. Six male and 6 female healthy volunteers (age: 23-32 yrs; weight: 46-85 kg) received the following two treatments in a randomized order separated by at least 1 week:

treatment F: single oral dose of 25 mg carvedilol tablet in the fasting condition

treatment E: 25 mg carvedilol tablet 5 mins after the end of a standard meal

The subjects fasted from 10:00 p.m. the previous evening up to five hours after dosing (treatment F). On the other occasion subjects were also fasted from 10:00 p.m. the previous evening (treatment E).

The meal consisted of 1 boiled egg, 2 bread rolls, 3 teaspoons margarine, 40 g ham, 40 g cheese, and 230 ml orange juice [equivalent with 3100 KJ (750 Cal): approximately 17% protein, 40% fat, and 43% carbohydrate].

Specimens: Plasma samples, at pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, and 24 hours following oral dose.

Assay:

Plasma samples were analyzed for carvedilol by HPLC with fluorescence detection.

Linearity: linear from 0.3 to 160 ng/ml

Precision: Inter CV ranged from 2.1 to 4.5% at concentrations of 6, 30, and 100 ng/ml. Intra CV ranged from 2.3 to 5.6% at those same concentrations.

Accuracy: range 96-108%

Specificity: satisfactory

Sensitivity: LLQ=0.3 ng/ml

Data Analysis: Pharmacokinetic parameters were determined by noncompartmental methods. The 90% confidence intervals based on the two one-sided tests were calculated. Data for

NDA 20297

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AUC(0-24) and AUC(0-∞) were log-transformed, and data for t_{1/2} and C_{max} were untransformed. These parameters were analyzed using ANOVA model with linear effects for group, sequence, period, and treatment.

Results: Mean (range) pharmacokinetic parameters, point estimates, and 90% CI for carvedilol are shown in Table 1. Individual subject data and statistical analysis for parameters are listed in Appendix II.

Table 1
Mean (Range) Pharmacokinetic Parameters, Point Estimates,
and 90% Confidence Intervals for Carvedilol
(Protocol 105517/A9907-GER).

	Fasted State	Fed State	Point Estimate	90% CI
C _{max} (ng/ml)	53.6	48.4	E/P [‡] : 0.90	0.62 - 1.29
T _{max} (min)	60 [‡]	135 [‡]	E-P [†] : 90 min	15 - 150 min
AUC _{0-t} (ng·min/ml)	9976	10301	E/P [§] : 1.07	0.89 - 1.30
AUC _{0-∞} (ng·min/ml)	10492	10843	E/P [§] : 1.07	0.90 - 1.28
t _{1/2} (min)	423	355	E-P [‡] : -67 min	-137 - +3 min

* parametric analysis of untransformed data
† non-parametric analysis
§ parametric analysis of log-transformed data
‡ medians

When administered in the fed state, there was a significant increase in median T_{max} (135 mins vs. 60 mins in the fasted state). Also there was overall increase in its variability in the presence of food. In contrast to the change in T_{max}, the extent of bioavailability of carvedilol did not appear to be altered in the presence of food. Compared to the fasted state, only small differences (7-10%) in mean C_{max} and AUC values for carvedilol were observed in the fed state. Although, their 90% CI fell outside the 80% to 120% range normally accepted for bioequivalence because of the large variability, these parameters were not significantly different between two treatments.

Conclusions and Comments: Following an oral dose of 25 mg carvedilol tablet in the presence of food, there was a significant increase in T_{max} as well as increase in variability. Although there was little change in terms of mean C_{max} , $AUC(0-24)$, $AUC(0-\infty)$, and $t_{1/2}$ values, those were not statistically significantly different.

Single-dose PK in Young & Elderly Healthy Volunteers

Study No.: MF 3413

Volume: 1.57

Pages: 2-263

Investigators and Site:

Objectives: To determine the pharmacokinetics of carvedilol in young versus elderly healthy volunteers.

Formulations:

- Carvedilol 5 mg ampoules, batch # 818 651 59 A
- Carvedilol 12.5 mg capsules, batch # 819 155 Fc
- Carvedilol 25 mg capsules, batch # 818 902 Db, 819 561 Ec
- Carvedilol 50 mg capsules, batch # 818 173 Cd, 819 292 Ed
- Placebo capsules, batch # 817 944 40 Ac
- Labetalol 200 mg tablets, batch # 195068, 195177

Study Design: Ten young male subjects (age: 20-40 yrs; weight: 59-87 kg) and 10 elderly subjects (9 M, 1 F; age: 57-66 yrs; weight: 74-89 kg) with a supine DBP between 70 and 100 mm Hg were recruited. Twenty subjects received first 5 treatments (cross-over) in a randomized order (double blinded) after an overnight fast:

1. single oral dose of 25 mg carvedilol
2. single oral dose of 50 mg carvedilol
3. single oral dose of 200 mg labetalol
4. single oral dose of placebo capsule
5. single oral dose of 50 mg carvedilol plus a standard breakfast (2 pieces of toast, 1 drink of orange juice and 1-2 eggs)
6. 5 mg carvedilol iv infusion over 5 mins.
7. single oral dose of 12.5 mg carvedilol

Only 5 young and 8 elderly subjects received carvedilol intravenously. Only 6 elderly and 9 young subjects completed the 7th study. Each treatment was separated by at least 2 weeks.

Specimens: Plasma samples were collected before and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, 30, and 48 hours following oral administration of carvedilol. During i.v. study, additional samples were taken at 4, 10, 20, 30, 40, 50, and 75 mins after cessation of the infusion. In some subjects, additional plasma samples were collected immediately after the infusion ceased and at 2, 6, and 8 mins. Urine was collected over the 0-12, 12-24, and 24-48 hr time periods after oral and intravenous administration.

Assay:

Plasma and urine samples were analyzed for carvedilol and desmethylcarvedilol by HPLC with fluorescence detection.

Linearity: not reported

Precision: not reported

Sensitivity: LLQ for carvedilol: 2-5 ng/ml, for desmethylcarvedilol: 5 ng/ml

Specificity: not reported

Data Analysis: Pharmacokinetic parameters were determined by noncompartmental methods. The data sets relating to the oral doses of carvedilol were analyzed by repeated measures analysis of variance with age as a between subjects factor and dose as a within subjects factor.

Parameters derived from i.v. and 12.5 mg oral doses were compared between young and old groups using a non-paired t-test.

Results: The mean pharmacokinetic parameters for carvedilol derived from the data after oral and intravenous dosing are shown in Tables 1 and 2. Mean plasma profiles for carvedilol are shown in Fig. 1 to 6.

Table 1
Pharmacokinetic Parameters for Carvedilol*
(Protocol MF 3413)

		12.5 mg	25 mg	50 mg	50 mg (+ food)	5 mg (iv)
C _{max} (ng/ml)	Y	74 (N = 9)	94	119	96	
	E	27 (N = 6)	68	122	134	
T _{max} (hr)	Y	1.4 (N = 9)	1.1	1.4	1.8	
	E	1.2 (N = 6)	1.0	1.2	1.4	
AUC _{0-∞} (ng·hr/ml)	Y	156 (N = 9)	226 [†]	496 [†]	585 [†]	144 (N = 5)
	E	166 (N = 6)	385	717	810	233 (N = 8)
t _{1/2β} (hr)	Y	18.5 (N = 9)	14.0	14.7	8.2	4.3 (N = 5)
	E	9.2 (N = 6)	13.3	9.8	9.3	9.8 (N = 8)

* Data are presented as mean and range; Y = young, E = elderly; Number of subjects (N) equals 10 unless otherwise indicated.

[†] p = 0.02 between young and elderly subjects.

[‡] Estimates obtained using the modeling program AUTOAN2.

Table 2. Pharmacokinetic parameters calculated using 3 mg iv BM14,190

	% Bioavailability	Clearance (mls/min)	Volume of distribution (l)
Young	34 ± 7	718 ± 129	189 ± 32
Old	44 ± 7	593 ± 108	317 ± 96

Results are means ± SE

Following oral administration plasma concentrations in the majority of subjects were best described by 2 compartment model. Carvedilol was rapidly absorbed after oral doses. Tmax generally occurred within 2 hours after drug administration. The Cmax and AUC in both groups increased linearly over the dose range 12.5-50 mg in the fasted state (Fig. 7). Mean Tmax and Cmax were similar between two age groups. In the older group, AUC(0-∞) was about 1.5 times larger than that of the young group (p=0.02) after 25 mg and 50 mg carvedilol (both fasting and fed) administration. The AUC(0-∞) was not significantly different between two groups after 12.5 mg dose. Because of the wide variability in elimination half-life there was no significant difference in t1/2 between two groups.

Following i.v. administration, mean t1/2 was approximately 10 hrs in the elderly. In the young group, mean t1/2 was about 4 hrs. Because of the variability in the data and the smaller number of subject, t1/2 was not significantly different between two groups. Mean AUC(0-∞) was 1.6 times larger in the elderly, but was not statistically different between two groups.

Conclusions: Mean Tmax and Cmax values were similar between young and elderly groups. The Cmax and AUC in both groups increased linearly over the dose range 12.5-50 mg in the fasted state. However, at the 25 mg and 50 mg doses AUC(0-∞) was significantly higher in the elderly (approximately 1.5 times higher in the elderly).

The elimination half-life was highly variable and was not different between the young and elderly after oral and intravenous administration and no difference over dose.

There is a trend in increase in bioavailability, decrease in clearance, and increase in volume of distribution after intravenous administration of carvedilol in elderly subjects.

The administration of food with carvedilol did not significantly alter the disposition of the drug.

Comments: The quality control data were not provided.

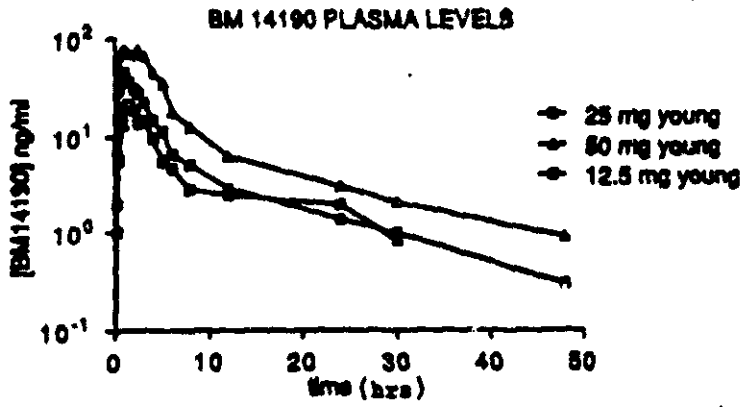


Fig. 1

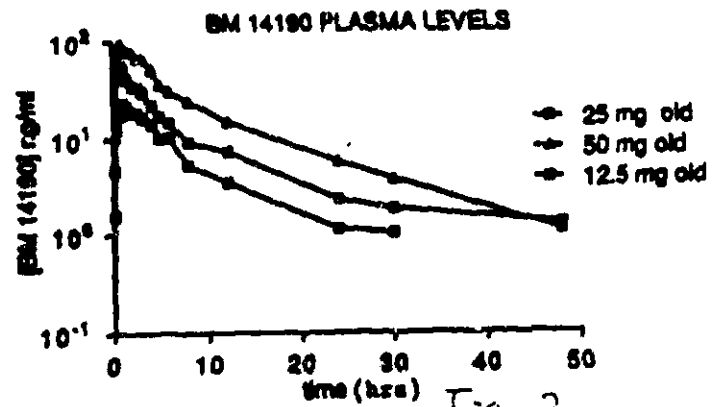


Fig. 2

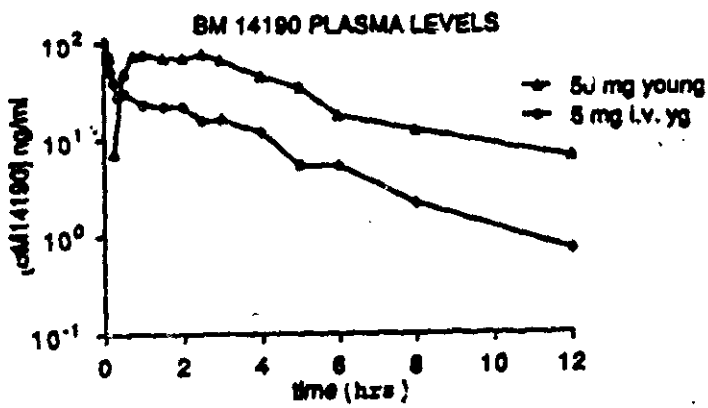


Fig. 3

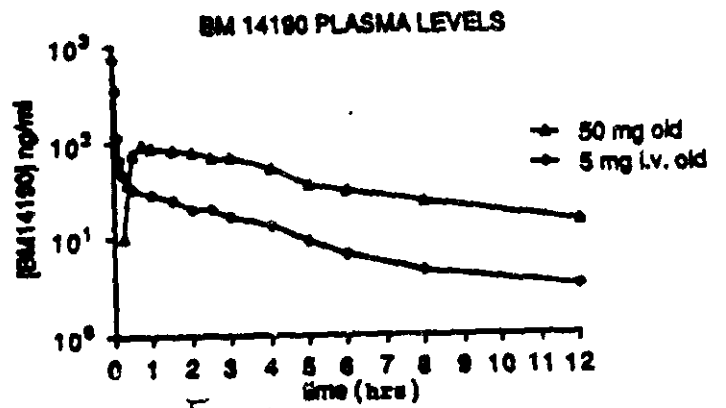


Fig. 4

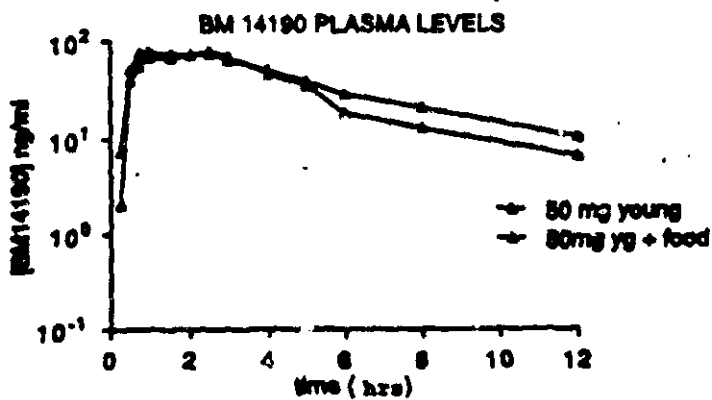


Fig. 5

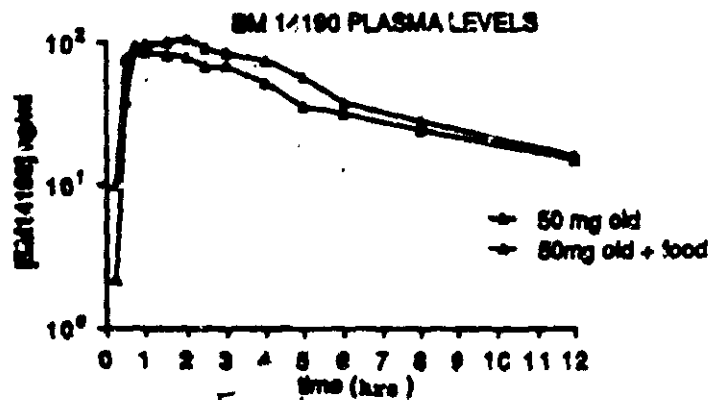
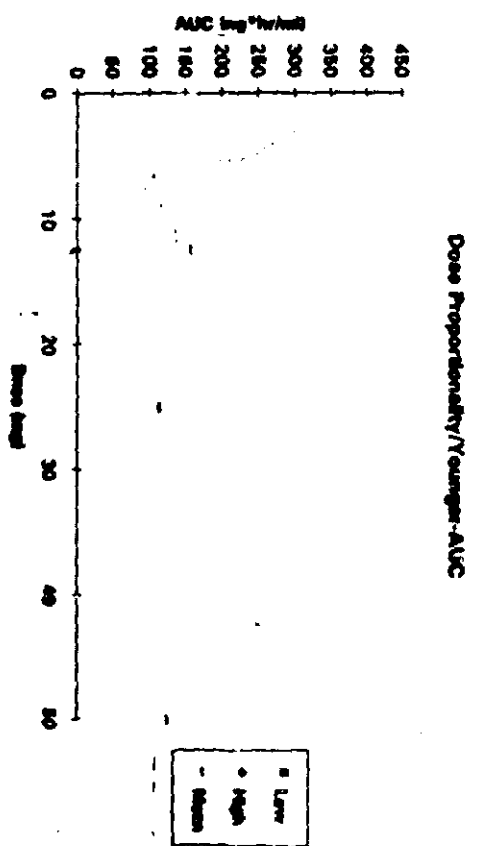
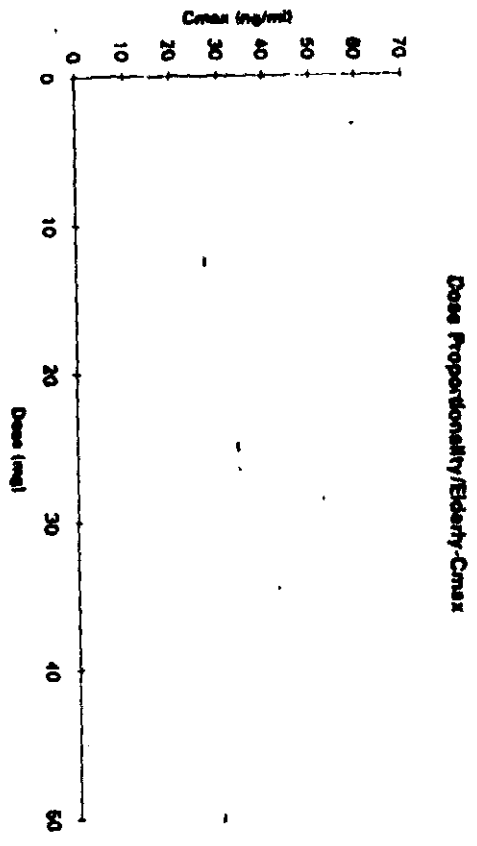
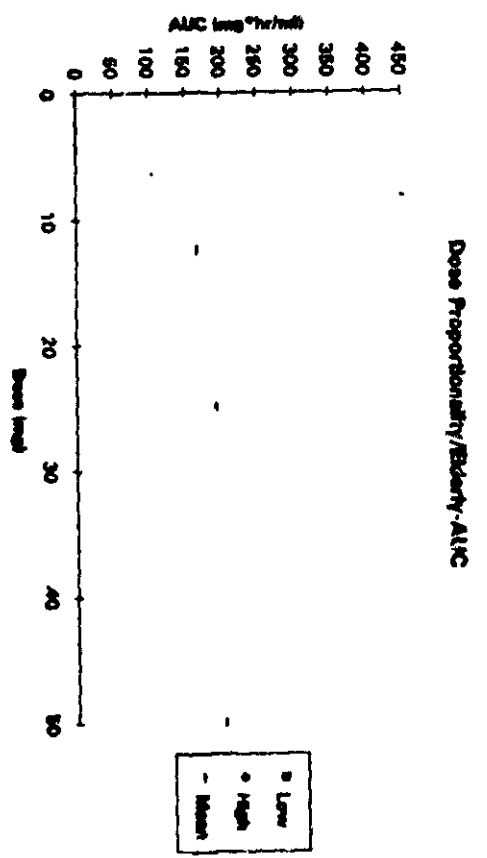
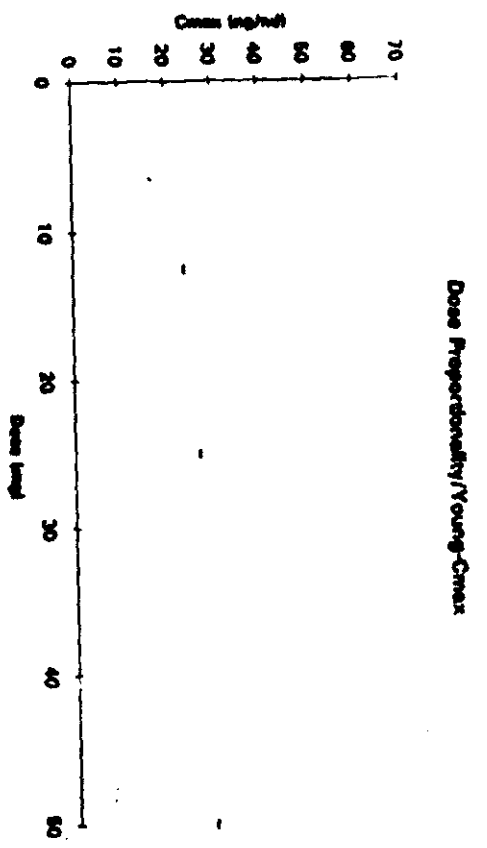


Fig. 6

Fig. 7.



* AUC & Cmax are normalized w/rt 12.5mg dose

Single and Multiple-dose PK in Young & Elderly Healthy Volunteers

Study No.: MF 3950

Volume: 1.63

Pages: 2-253

Investigator and Sites:

Center 1:

Center 2:

Objectives: To determine the pharmacokinetics of carvedilol in young and elderly population after single and multiple oral doses.

Formulations: • Carvedilol 25 mg capsules, batch # 819 156 40 Ec

Study Design: Two-center, open, uncontrolled multiple dose study. Ten young male subjects (age: 20-26 yrs; weight: 59-85 kg) were studied at one center and a parallel study was conducted in 11 elderly male and female subjects (age: 66-71 yrs; weight: 59-85 kg) at a separate geriatric facility. They received 25 mg carvedilol capsules once daily for 2 weeks.

The first evaluation on day 1 could be performed in all 21 subjects. Four of the elderly subjects were withdrawn from the study due to postural hypotension, so only 17 subjects could be included into the second evaluation on day 14.

On days 1 and 14 the drug was administered after overnight fast and no food was given until 4 hours post dose. On the other days subjects were dosed 1 hr prior to a standard breakfast comprising cereal, toast, butter, marmalade, fruit juice, and tea or coffee.

Specimens: Plasma samples, at pre dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours post-dose in the single dose study. Additional samples were obtained at 36 and 48 hours post-dose in the multiple dose study. All urine was collected over 0-24 hour time period on days 1, 14, and 15.

Assay:

Plasma and urine samples were analyzed for carvedilol and desmethylcarvedilol by HPLC with fluorescence detection. Samples were analyzed at

Linearity: satisfactory, calibration curves from 5.0 ng/ml to 200 ng/ml for carvedilol, calibration curves from 5.0 ng/ml to 100 ng/ml for desmethylcarvedilol.

Sensitivity: LLQ in plasma for carvedilol: 1 ng/ml, for desmethylcarvedilol: 0.5 ng/ml

LLQ in urine for carvedilol and desmethylcarvedilol : 1.0 ng/ml

Precision: Interday CV for carvedilol ranged from 6.4% at 10 ng/ml to 4.5% for 150 ng/ml.

Interday CV for desmethylcarvedilol ranged from 7.8% at 5.0 ng/ml to 6.4% at 50 ng/ml.

Specificity: satisfactory

Data Analysis: Pharmacokinetic parameters were determined by noncompartmental methods. The unpaired t-test was also used to compare the pharmacokinetic parameters for carvedilol and ophthalmic carvedilol between the young and elderly. When the residual is not normally distributed, Mann-Whitney and Wilcoxon matched pair tests were used instead of t-test.

Results: The pharmacokinetic parameters for carvedilol in young and elderly subjects are shown in Tables 1 and 2. Figures 1 and 2 show the mean plasma-time profile for carvedilol for both the young and elderly subjects on day 1 and 14.

Table 1
Pharmacokinetic Parameters for Carvedilol*
(Protocol MF 3950)

	SINGLE DOSE		MULTIPLE DOSE	
	Young (n=10)	Elderly (n=11)	Young (n=10)	Elderly (n=7)
AUC ₀₋₂₄ (ng*hr/ml)	382	397 267	423	342
AUC _{0-∞} (ng*hr/ml)	401	462	505	396
C _{max} (ng/ml)	92.9	75.7	96.6	59.8
t _{1/2} (hr)	7.0	9.1	13.1	10.1
T _{max} (hr)	1.2	1.3	1.1	1.9

* Data are presented as mean and range

Table 2
Comparison of Single and Multiple Dose Pharmacokinetics
(Protocol MF 3950)

	Single Dose*	Multiple Dose*	Ratio†
<u>Young (n = 10)</u>			
AUC ₀₋₂₄ (ng*hr/ml)	382 (220)	423 (256)	1.11
C _{max} (ng/ml)	92.9 (38.0)	96.6 (41.0)	1.04
<u>Elderly (n = 7)</u>			
AUC ₀₋₂₄ (ng*hr/ml)	267 (70)	342 (110)	1.28
C _{max} (ng/ml)	40.1 (18.9)	59.8 (33.3)	1.24

* Data are presented as mean (SD)

† Ratio calculated as mean AUC₀₋₂₄ or C_{max} after multiple dosing divided by mean AUC₀₋₂₄ or C_{max} after a single dose

There were no statistically significant differences in the pharmacokinetics of carvedilol between young and elderly subjects after both single and multiple administration of carvedilol. Carvedilol was handled in a similar manner by the two groups after a single oral dose of 25 mg. C_{max} were achieved after about 1 hour, and half-lives were about 7 hours and 9 hours in young and elderly groups, respectively. C_{max} and AUC were significantly greater for the elderly subjects who withdrew than for those elderly subjects who completed the study. However, the PK parameters of the 4 elderly subjects were not different from those of the young subjects.

The comparison of PK parameters obtained on day 1 (young n=10, elderly n=11) and day 14 (young n=10, elderly n=7) showed no significant differences between the young and elderly, except for a slightly longer T_{max} in the elderly.

Conclusions: Compared to young healthy volunteers, the pharmacokinetics of carvedilol appeared to be similar in the elderly, although carvedilol plasma level is lower in the elderly. After 14 days dosing, there was only modest increase in carvedilol plasma levels in elderly group. On average, plasma levels of desmethylcarvedilol was less than 5% of those observed for carvedilol.

MEAN VALUES YOUNG SUBJECTS (n=10): PLASMA CARVEDILOL/TIME CURVE
COMPARISON OF DAY 1 & DAY 14

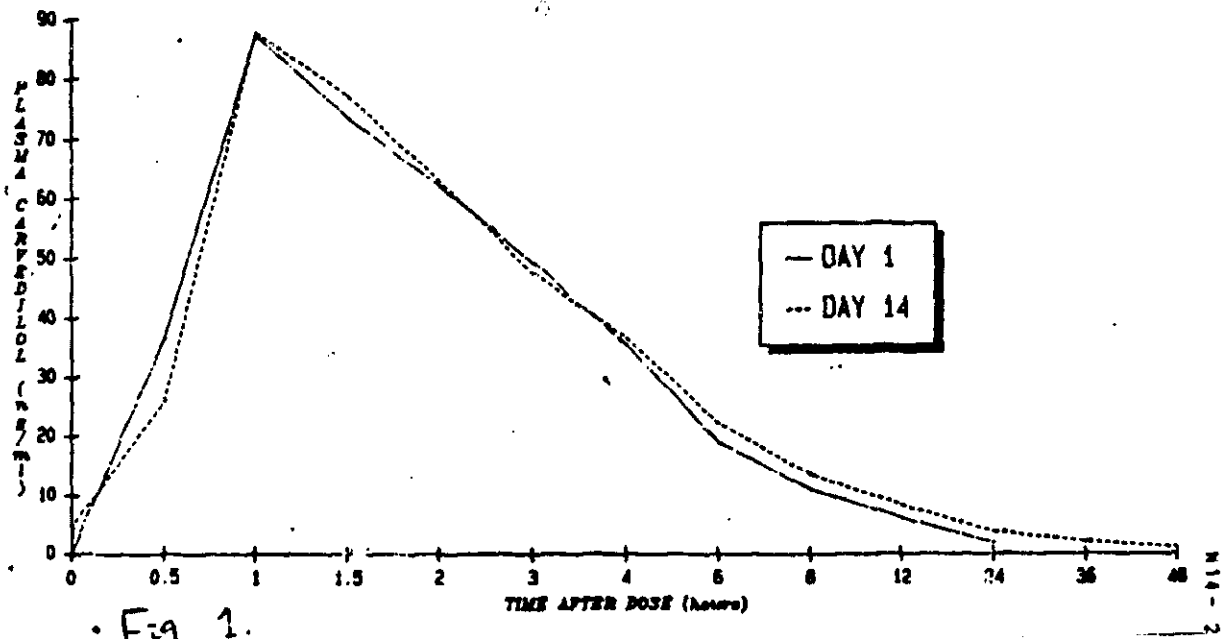


Fig. 1.

MEAN VALUES ELDERLY SUBJECTS (n=7): PLASMA CARVEDILOL/TIME CURVE
COMPARISON OF DAY 1 & DAY 14

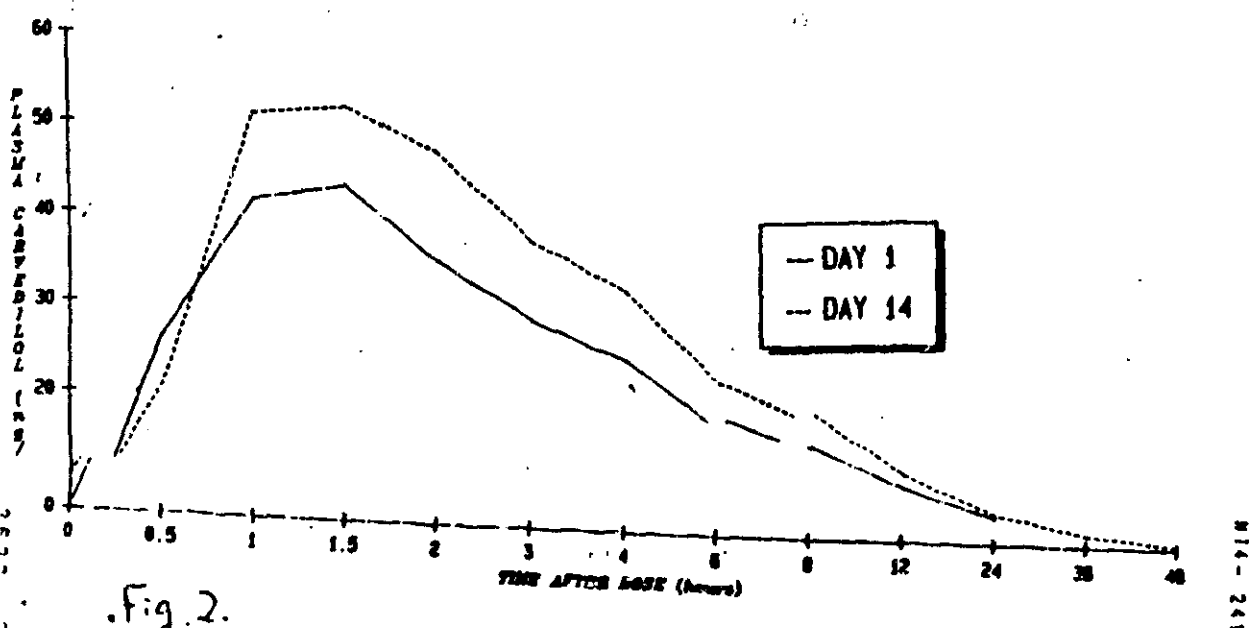


Fig. 2.

Single and Multiple-dose PK in Young & Elderly Hypertensive Patients

Study No.: MF 3702

Volume: 1.61

Pages: 2-263

Investigator and Site:

Objectives: To compare the steady-state pharmacokinetics of carvedilol between young and elderly hypertensive patients.

Formulations: • Carvedilol 12.5 mg capsules, batch # 820 020 40 Jd

- Carvedilol 25 mg capsules, batch # 819 789 40 Hb
- Carvedilol 50 mg capsules, batch # 819 787 40 Ld
- Placebo capsules, batch # 817 944 4G Ac

Study Design: Open, subchronic sequential clinical monocenter trial in two groups of young and elderly hypertensive patients over 12 weeks. Thirty-two patients with essential hypertension entered into a four-week placebo run-in period. Twenty-one older patients (17 M, 4 F: 63-79 yrs) and 8 younger male patients (age 39-47 yrs) with a supine DBP of 95-115 mm Hg qualified for the active drug study. They were initially given 12.5 mg of carvedilol daily as a test dose. The dose of carvedilol was titrated to 25 mg or 50 mg daily according to the patient's blood pressure response. Plasma levels of carvedilol was measured in 5 younger and 17 older patients after single dose of 12.5 mg dose. Plasma levels of carvedilol were measured after patients received 25 mg (3 younger and 3 older patients) or 50 mg (8 younger and 17 older patients) of carvedilol once a day for 14 days. The patients were instructed to take the drug before breakfast.

Specimens: Plasma samples, at pre dose and at 0.5, 1, 1.5, 2, 8, 4, 5, 6, 7 and 24 hours post-dose.

Assay:

Plasma samples were analyzed for carvedilol and desmethylcarvedilol by HPLC with fluorescence detection. Samples were analyzed at the investigational site.

Plasma

Linearity: linear from 0 to 4000 ng/ml

Precision: Inter CV (%) for carvedilol was 6.86% at 50.0 ng/ml.

Intra CV (%) for carvedilol was 10.04% at 50.0 ng/ml.

Sensitivity: LOD, 0.1 ng/ml

Specificity: satisfactory

Data Analysis: Pharmacokinetic parameters were determined by noncompartmental methods. The Wilcoxon test were applied for paired data. Comparisons between the groups were

performed with the Mann-Whitney U-test, $p=0.05$.

Results: Mean pharmacokinetic parameters for carvedilol are shown in Table 1. Figures 1 to 3 show the mean plasma levels of carvedilol in young and elderly patients after administration of 12.5 mg, 25 mg, and 50 mg doses of carvedilol.

Table 1.
Pharmacokinetic Parameters for Carvedilol*
(Protocol MF 3702)

	Younger 12.5 mg [†] (n=5)	Older 12.5 mg [†] (n=17)	Younger 25 mg [‡] (n=3)	Older 25 mg [‡] (n=9)	Younger 50 mg [‡] (n=8)	Older 50 mg [‡] (n=17)
C _{max} (ng/ml)	58 (25)	69 (41)	105 (21)	151 (63)	189 (48)	252 (136)
T _{max} (min)	80 (49)	58 (49)	80 (35)	60 (21)	105 (59)	79 (45)
AUC ₀₋₂₄ (ng*hr/ml)	225 (103)	208 (168)	572 (294)	947 (450)	1073 (571)	1595 (1336)
t _{1/2} (min)	138 (67)	114 (74)	257 (61)	280 (165)	300 (204)	318 (173)

* Data are presented as mean (standard deviation)

† Single dose

‡ Multiple doses

After single dose of 12.5 mg carvedilol, no differences in C_{max}, T_{max}, AUC(0-24), and t_{1/2} were observed between two groups. In contrast, steady-state C_{max} and AUC(0-24) after 25 and 50 mg carvedilol daily for 14 days were higher in the elderly group [C_{max} by 44 % and 33 %, AUC(0-24) by 66% and 49%, respectively] ($p=0.1$). However, these differences were not statistically significant due to large variability and the small number of young patients studied. Half-life values at steady-state were similar between two groups.

A lag-time existed between C_{max} for carvedilol and maximum effect on supine DBP resulting in a hysteresis of mean concentration-effect curve (Figure 4).

After chronic dosing, there was no apparent relationship between individual trough concentration of carvedilol and reduction in supine diastolic blood pressure (Figure 5).

Conclusions: The pharmacokinetics of carvedilol were similar for both groups after single administration of 12.5 mg carvedilol.

After multiple administration of 25 and 50 mg carvedilol daily for 14 days, there was a tendency for C_{max} and AUC(0-24) to be increased (approximately 50%) in the elderly hypertensive patients.

Comments: Plasma concentrations of carvedilol were about 2-3 times higher in both group of patients as compared to those observed in previous study. In the current study, mean C_{max} of 189 ng/ml (younger patients) or 252 ng/ml (older patients) was measured after multiple oral dose of 50 mg carvedilol.

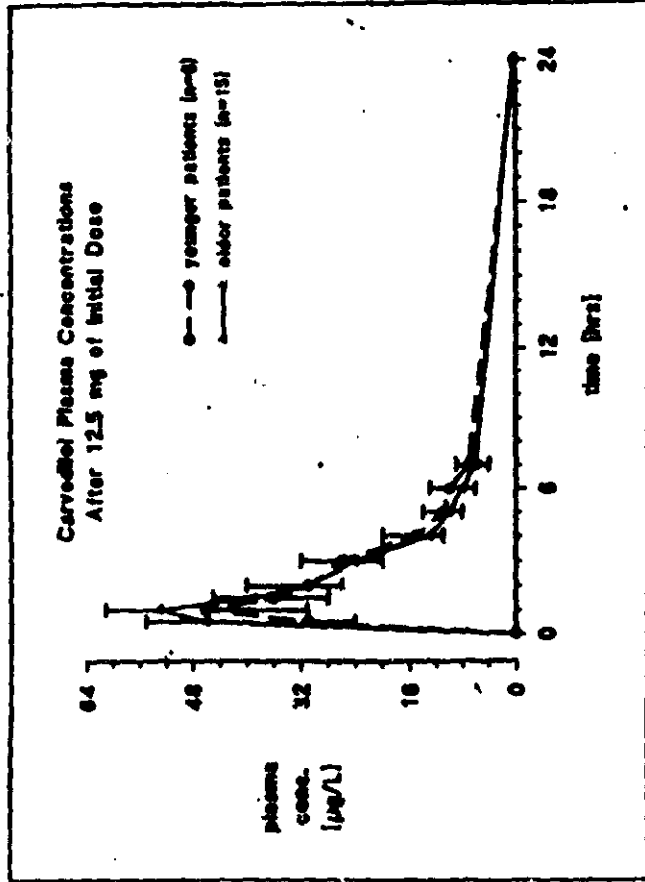


Figure 1: Plasma concentrations obtained with the first dose of 12.5 mg in youngest and older patients. (mean ± SD) See Tab.27 for values

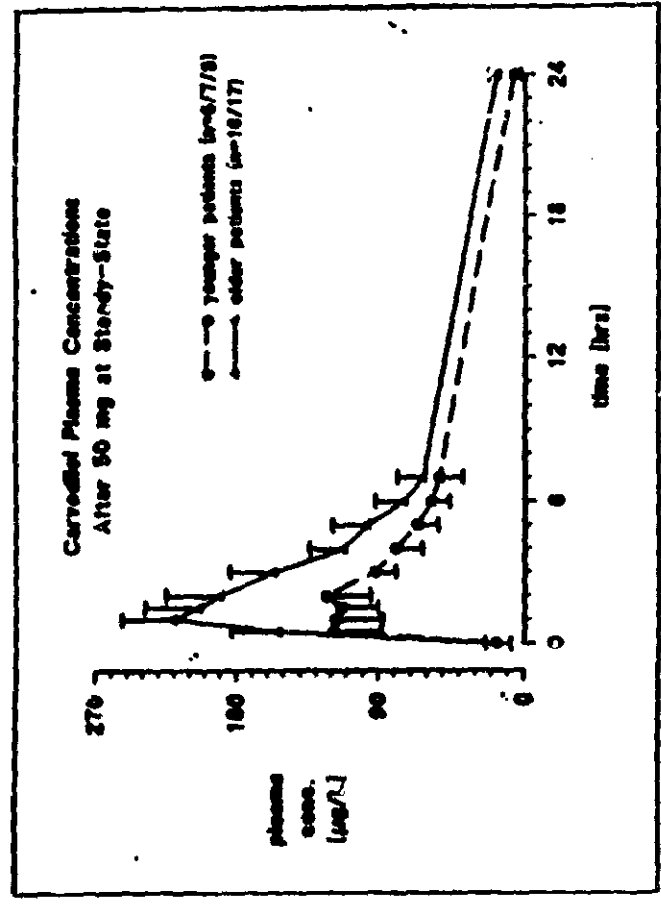


Figure 2: Plasma concentrations obtained in a dose-interval with 50 mg at steady-state. (mean ± SD) See Tab.28 for values

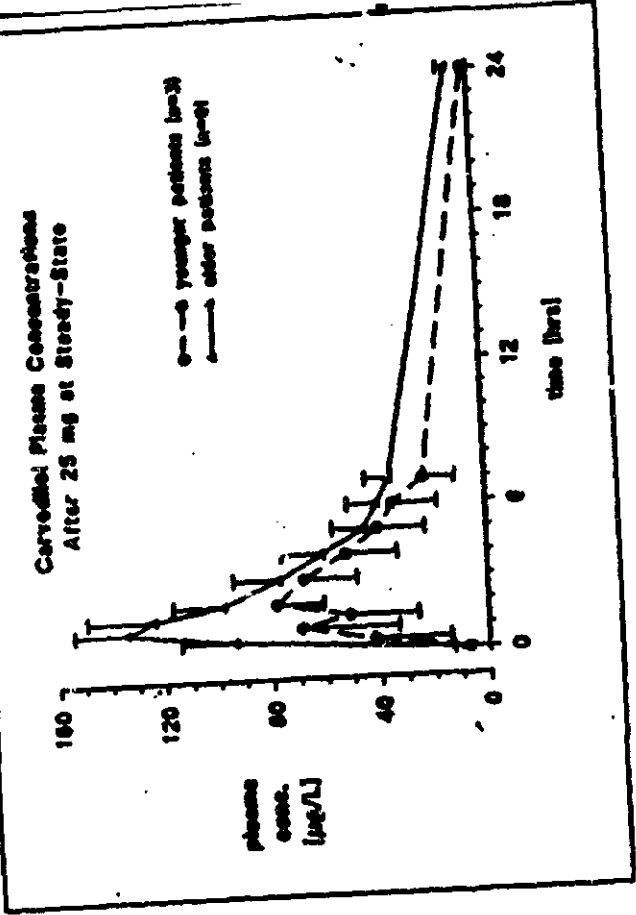


Figure 3: Plasma concentrations obtained in a dose-interval with 25 mg at steady-state. (mean ± SD) See Tab.28 for values

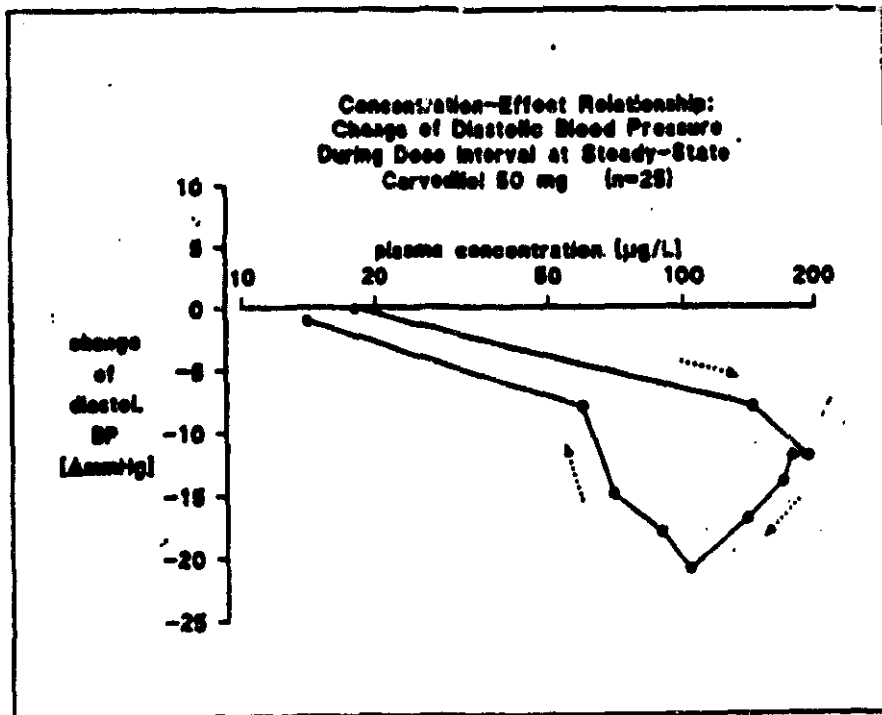


Figure 4: Effect of plasma concentrations (log scale) on BP_{dose} with 50 mg. See Tab.8 for values.

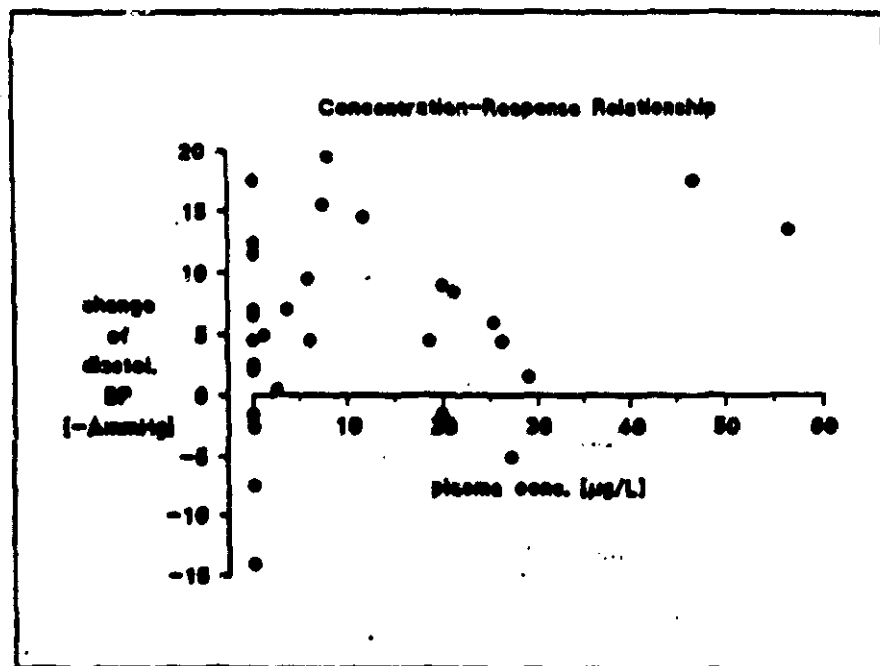


Figure 5: Relationship between plasma concentrations and reduction of mean BP_{dose} at trough levels of diastolic change. Each point = one patient. Concentration of 0 means below limit of quantitation. For values see Tab.31.

PK in Hypertensive Patients with Chronic Renal Failure

Study No.: MF 3459

Volume: 1.58

Investigators and Sites: Multicentre Trial
Centre 1

Centre

Centre

Centre

Objectives: To determine if the pharmacokinetics of carvedilol and its metabolites (M2, M4, and M5) are altered in hypertensive patients with chronic renal failure after single oral administration of 50 mg carvedilol.

Formulations: • Carvedilol 50 mg capsules, batch # 819 789 40 Ld

Study Design: Open, uncontrolled, single-dose multicentre trial. Twenty-five male and female hypertensive patients with chronic renal failure (age: 20-69 yrs, weight: 47-100 kg) were stratified into three groups according to their grade of renal impairment as measured by creatinine clearance (Cl_{cr}):

Group I Cl_{cr} 51-90 ml/min (n=3)

Group II Cl_{cr} 26-50 ml/min (n=9)

Group III Cl_{cr} 4-25 ml/min (n=13)

Each patients received a single dose of 50 mg of carvedilol capsule orally after an overnight fast. Since this dose is not recommended as the starting dose for the treatment of hypertension. The patients were asked to stay in the supine position for the first 6 hours.

Specimens: Blood, at pre dose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 48, and 72 hours post dose. Urine was collected before, and at 0-4, 4-8, 8-12, 12-24, and 24-48 hours post dose.

Assay:

Plasma and urine samples were analyzed for carvedilol and its active metabolites M2, M4, and M5 by HPLC with fluorescence detection. Samples were analyzed at the Dept. of Biochemical Analysis, Boehringer Mannheim GmbH.

Carvedilol (plasma)

Linearity: linear

Precision: Inter CV ranged from 3.0 to 11.8%. Intra CV ranged from 4.4 to 10.9%.

Accuracy: range 96.9-101%

Specificity: satisfactory

Sensitivity: LLQ=0.078 ng/ml

Desmethylcarvedilol (plasma)

Linearity: linear

Precision: Inter CV ranged from 3.0 to 12.1%. Intra CV ranged from 1.2 to 19.3%.

Accuracy: range 105-119%

Specificity: satisfactory

Sensitivity: LLQ=0.078 ng/ml

Data Analysis: Pharmacokinetic parameters were determined by noncompartmental methods. Statistical evaluation was done by means of the Mann-Whitney U-test between Group II and III only, because the limited number of patients (n=3) did not permit statistical analysis.

Results: The pharmacokinetic parameters for carvedilol and the active metabolites M2, M4, and M5 are shown in Tables 1, 2, 3, and 4, respectively.

Table 1
Pharmacokinetic Parameters for Carvedilol*
(Protocol MF 3459)

	Group I (n = 3)	Group II (n = 9)	Group III (n = 12)
C _{max} (ng/ml)	318.3	179.8	173.6
T _{max} (hr)	0.5	1.0	1.25
AUC _{0-∞} (ng*hr/ml)	1324	1110 [†]	1064 [§]
t _{1/2} (hr)	21.9	12.8 [†]	13.4 [§]
Ae ₀₋₆₈ (%)	0.66	0.20	0.10
Cl _r (ml/min)	4.9	1.9	0.9

Table 2
Pharmacokinetic Parameters for Carvedilol Metabolite M2*
(Protocol MF 3459)

	Group I (n = 3)	Group II (n = 9)	Group III (n = 12)
C _{max} (ng/ml)	18.2	13.2	10.7
T _{max} (hr)	1.5	1.5	1.5
AUC _{0-t} (ng*hr/ml)	77	57	62
Ae ₀₋₆₈ (%)	0.07	0.01 [†]	0.001
Cl _r (ml/min)	7.7	1.8	0.1

* Data are presented as median and range.

Group I Cl_r > 30 ml/min, Group II Cl_r 26 - 30 ml/min, and Group III Cl_r < 25 ml/min
[†] n = 9

* Data are presented as median and range.

Group I Cl_r > 30 ml/min, Group II Cl_r 26 - 30 ml/min, and Group III Cl_r < 25 ml/min

[†] n = 8

[§] n = 11

Table 3
Pharmacokinetic Parameters for Carvedilol Metabolite M4*
(Protocol MF 3459)

	Group I (n = 3)	Group II (n = 8)	Group III (n = 12)
C _{max} (ng/ml)	15.3	11.0	13.6
T _{max} (hr)	1.0	1.25	1.25
AUC _{0-t} (ng*hr/ml)	64	62	54
A _{e0-48} (%)	0.13	0.03 [†]	0.01 [§]
Cl _r (ml/min)	17.0	3.5	1.3 [§]

* Data are presented as median and range.

Group I Cl_{cr} > 50 ml/min, Group II Cl_{cr} 26 - 50 ml/min, and Group III Cl_{cr} < 25 ml/min

[†] n = 9

[§] n = 10

Table 4
Pharmacokinetic Parameters for Carvedilol Metabolite M5*
(Protocol MF 3459)

	Group I (n = 3)	Group II (n = 8)	Group III (n = 12)
C _{max} (ng/ml)	14.2	9.6	10.3
T _{max} (hr)	1.0	1.25	1.25
AUC _{0-t} (ng*hr/ml)	53	30	32
A _{e0-48} (%)	0.10	0.02 [†]	0.003 [§]
Cl _r (ml/min)	15.6	6.3	0.9 [§]

* Data are presented as median and range.

Group I Cl_{cr} > 50 ml/min, Group II Cl_{cr} 26 - 50 ml/min, and Group III Cl_{cr} < 25 ml/min

[†] n = 9

[§] n = 11

An unexplained finding in this investigation are the approximately 2 to 3 fold higher concentrations of carvedilol in all three patients groups compared to previous pharmacokinetic studies. The AUC, t_{1/2}, C_{max}, and T_{max} were not significantly different between two groups, whereas the amount of unchanged drug or metabolite excreted in urine (A_e) and the renal clearance of carvedilol and its metabolites (M2, M4 and M5) were significantly decreased in Group III.

Plasma levels of M2, M4, and M5 were approximately ten-fold lower than those observed for carvedilol.

Conclusions: Renal impairment in hypertensive subjects led to a proportional decrease in the renal clearance of carvedilol and its metabolites but not to a corresponding increase in plasma C_{max} and AUC values.

Comments: An unexplained finding in this investigation are the approximately 2 to 3 fold higher concentrations of carvedilol when compared to previous studies. The median C_{max} for carvedilol in Group I was 318.3 ng/ml after single oral dose of 50 mg carvedilol.

Because the dose administered was relatively high, the patients were asked to stay in the supine position for the first 6 hours to prevent the first-dose syncope effect.

PK in Patients with Liver Cirrhosis

Study No.: MF 3837
Investigator and Site:

Volume: 1.61

Pages: 264-403

Objectives: To investigate changes of pharmacokinetics of carvedilol (esp. systemic clearance, half-life, distribution volume, and first pass effect) due to impaired liver function. Historical comparison was made with a similar study in healthy volunteers.

Formulations:

- Carvedilol 5 mg ampules, batch # 819 673 59 D. The infusion solution was prepared by diluting 3 ampoules of 5 ml each with sterile saline solution to 36 ml (15 mg in 36 ml). 30 ml of this solution (12.5 mg) was infused intravenously over 1 hour.
- Carvedilol 25 mg capsules, batch # 819 854 40 Gf

Study Design: Open, non-controlled, randomized two-way cross-over study. Six patients (5 males and 1 female) with liver cirrhosis were included in the study (age: 40-76 yrs; weight: 66-96 kg). Liver cirrhosis was diagnosed according to clinical signs, biopsy, laparoscopy or ultrasonography. Only patients with impaired liver function measured by a diminished serum cholinesterase of less than 1800 U/l and a Quick test of less than 70% were entered the study. They received either 12.5 mg carvedilol infused intravenously within one hour or 25 mg orally after overnight fast which were separated at least 6 to 7 days. Data following i.v. dosing in one patient were excluded from the PK analysis due to erratic plasma level profile. A group of 20 healthy subjects (age: 19-45 yrs; weight: 60-92 kg), who had been studied previously under similar conditions served as historical controls.

Specimens: Plasma samples, at pre dose and at 0.25, 0.5, 1, 2, 4, 8, 12, 24, and 32 hours post dose. During i.v. medication, the plasma samples were collected from the contralateral arm. Urine was collected before drug administration, and at 0-12, 12-24, and 24-32 hours post dose. The plasma samples were collected for 24 hrs after i.v. and oral dosing for healthy controls.

Historical Controls: A group of 20 healthy volunteers who were previously investigated served as a historical control (Study MF 7020). The PK profile of carvedilol was determined in random order following i.v. (12.5 mg infused over one hour) and oral 50 mg suspension (various lots), 50 mg capsule (batch # 815120 40 Ba), and 25 mg capsule (batch # 816034 40 Bb) doses of carvedilol.

Assay (carvedilol):

Plasma and urine samples were analyzed for carvedilol and desmethylcarvedilol by HPLC with fluorescence detection. Samples were analyzed at the Dept. of Biochemical Analysis, Boehringer Mannheim GmbH.

Plasma

Linearity: linear from 0 to 100 ng/ml

Precision: Inter CV (%) for carvedilol and desmethylcarvedilol were 5.6% and 5.35% at 40.0 ng/ml, respectively. Intra CV (%) for carvedilol and desmethylcarvedilol were 6.76% and 6.00% at 50.0 ng/ml, respectively.

Sensitivity: LLQ:1 ng/ml

LODs for carvedilol and desmethylcarvedilol were 0.38 and 0.46 ng/ml

Specificity: satisfactory

Urine

Linearity: linear from 0 to 100 ng/ml

Precision: Inter CV (%) for carvedilol and desmethylcarvedilol were 3.64% and 4.67% at 50.0 ng/ml, respectively. Intra CV (%) for carvedilol and desmethylcarvedilol were 6.59% and 9.06% at 50.0 ng/ml, respectively.

Sensitivity: LLQ: 1 ng/ml

LODs for carvedilol and desmethylcarvedilol were 0.82 and 1.07 ng/ml

Specificity: satisfactory

Data Analysis: Pharmacokinetic parameters were determined by noncompartmental methods. Non-parametric tests were used for statistical comparisons. The Wilcoxon test were applied for paired data. Comparison between the groups were performed with the Mann-Whitney U-test, $p = 0.05$.

Results: The following table summarizes the pharmacokinetic variables in healthy controls and patients with liver cirrhosis. Median time courses of carvedilol levels after i.v. and oral administrations in liver patients and healthy controls are shown in Fig. 1 and 2, respectively.

Table I
Pharmacokinetic Parameters for Carvedilol
in Patients with Liver Cirrhosis and in Healthy Subject
(Protocol MF 3837)*

	12.5 mg IV (Cirrhosis) (n = 5)	12.5 mg IV (Healthy) [†] (n = 20)	25 mg oral (Cirrhosis) (n = 6)	25 mg oral (Healthy) [‡] (n = 20)
C _{max} (ng/ml)	101.1	176.4	104.3	23.7
T _{max} (hr)	1.00	1.00	0.50	1.5
AUC _{0-τ} [†] (ng·hr/ml)	490	340	955	114
AUC _{0-∞} (ng·hr/ml)	535	342	1040	148
				(n = 19)
t _{1/2} (hr)	7.1	2.5	9.0	7.1
				(n = 19)
CL [‡] (ml/min)	389	609	410	2809
				(n = 19)
V _{dβ} (L)	321	125		
V _{dss} (L)	294	77		
F (%)			83	19
			(n = 5)	

* Data are presented as median and range

[†] AUC₀₋₃₂ in patients with liver cirrhosis; AUC₀₋₂₄ in healthy subjects

[‡] CL_T after oral administration

[§] Data from Protocol MF 7020

Compared to historical data in healthy subjects, clearance was reduced by 36% ($p > 0.05$) in the patients with hepatic disease while V_d at steady-state was significantly larger 280% ($p < 0.008$). Elimination half-life was about 3-fold longer in patients after i.v. doses of carvedilol ($p < 0.001$).

After 25 mg carvedilol oral doses, C_{max} was increased by over 4-fold in patients with liver disease. Terminal half-life did not differ between two groups. Oral clearance was decreased by 85% in patients ($p < 0.001$). Mean absolute bioavailability increased from 19% to 83% in patients with liver cirrhosis ($p < 0.01$).

Half-life of carvedilol was dependent on the route of administration in healthy subjects, this difference was absent in the liver patients. This findings were mainly explained by an absorption dependence of half-life after oral doses. Since i.v. half-life increases in liver patients in part to due to reduced clearance, and mainly due to the increase in distribution volume.

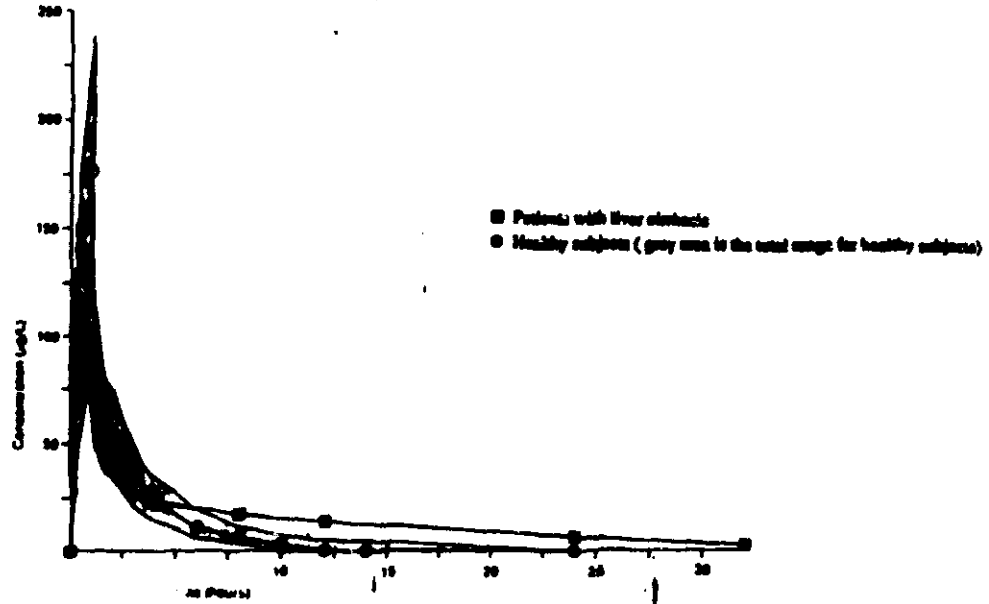
Plasma levels of desmethylcarvedilol were below the detection limit (1 ng/ml) in the majority of subjects after i.v. and oral doses.

Conclusions: After intravenous administration, patients with liver disease exhibited decreased clearance and increased volume of distribution at steady-state compared to healthy volunteers. Following oral administration of 25 mg carvedilol, significant increases in C_{max} (from 31.75 ± 21.33 to 134.64 ± 93.31 ng/ml), $AUC(0-\infty)$ (from 160.17 ± 84.93 to 575.90 ± 276.43 ng*hr/ml), and bioavailability were observed in liver cirrhotic patients.

Comments: The formulations of 25 mg carvedilol used in historical controls and used in patients with liver cirrhosis are not identical. C_{max} and AUC values of the historical controls is relatively small compared to those observed for other 25 mg carvedilol formulations.

Protocol MBF-3959 Figure 1

Median plasma concentration-time profiles for carvedilol following a single intravenous dose of 12.5 mg carvedilol infused over 1 hour in healthy subjects (historical controls from Protocol MBF-7000) and in patients with liver cirrhosis.

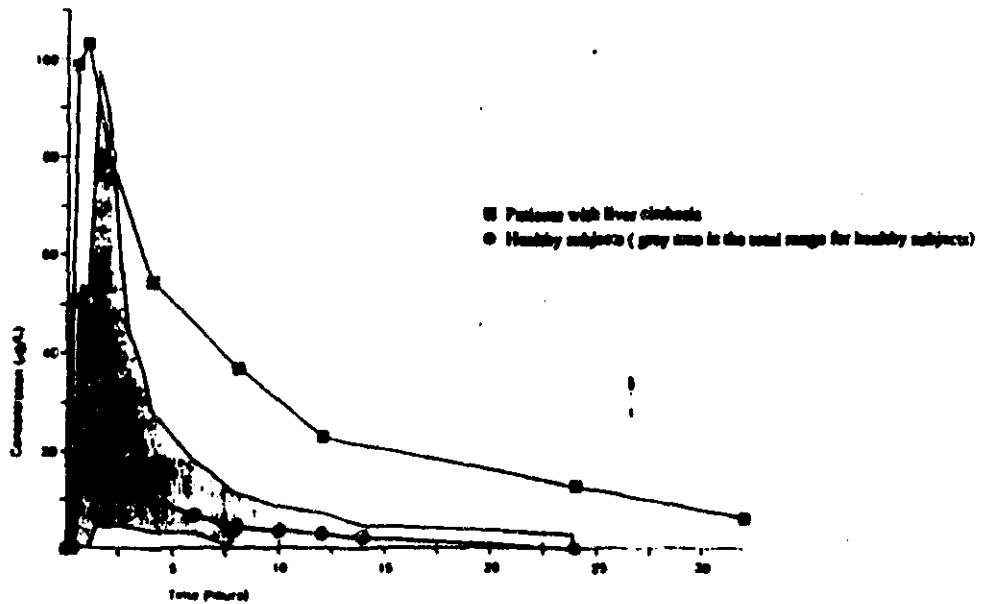


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Figure obtained from: Nongthamer G, Gaber M, Reiff K. Pharmacokinetics and bioavailability of carvedilol in patients with liver cirrhosis. *Drugs* 1988;36(Suppl. 6):146-154.

Protocol MBF-3837 Figure 2

Median plasma concentration-time profiles for carvedilol following a single oral dose of 25 mg carvedilol in healthy subjects (historical controls from Protocol MBF-7000) and in patients with liver cirrhosis.



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Figure obtained from: Nongthamer G, Gaber M, Reiff K. Pharmacokinetics and bioavailability of carvedilol in patients with liver cirrhosis. *Drugs* 1988;36(Suppl. 6):146-154.

PK in Patients with Chronic Liver Insufficiency

Study No: MF 3476
Investigator and Site:

Volume: 1.60

Pages: 2-228

Objectives: To investigate the pharmacokinetics and absolute bioavailability of carvedilol in patients with chronic liver insufficiency in comparison with healthy volunteers.

Formulations: • Carvedilol 5 mg ampules, batch # 818 651 59 A.

The infusion solution was prepared by diluting 3 ampoules of 5 ml each with sterile saline solution to 36 ml (15 mg in 36 ml). 30 ml of this solution (12.5 mg) was infused intravenously over 1 hour.

• Carvedilol 25 mg capsules, batch # 818 902 40 Db

Study Design: Open, randomized, two-way cross-over study. Three groups of patients were enrolled:

Group I: Patients with slight impaired liver function (serum cholinesterase 900-1500 U/I, Quick test $\geq$ 50%, n=13, 5 F/8 M).

Group II: Patients with severe liver impairment (serum cholinesterase < 900 U/I, Quick test < 50%, n=8 all male).

Group III: Healthy subjects (n= 10, 4 F/6 M).

These patients were given carvedilol in randomized sequence at intervals of about 1 week in one of the following modes of administration: 12.5 mg carvedilol i.v. as a 1 hour infusion or 25 mg carvedilol orally. The drug was given at about 8:00 a.m.

Specimens: Plasma samples, at pre dose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 32, and 48 hours post dose. Urine was collected before drug administration, and at 0-12, 12-24, and 24-48 hours post dose.

Assay: Plasma samples were analyzed for carvedilol and desmethylcarvedilol by HPLC with fluorescence detection.

Plasma

Linearity: linear from 0 to 100 ng/ml

Precision: Inter CV (%) for carvedilol and desmethylcarvedilol were 5.6% at 57.78 ng/ml and 5.35% at 48.60 ng/ml, respectively. Intra CV (%) for carvedilol and desmethylcarvedilol were 6.76% at 53.36 ng/ml and 6.00% at 46.53 ng/ml, respectively.

Sensitivity: LLQ:1 ng/ml

LODs for carvedilol and desmethylcarvedilol were 0.38 and 0.46 ng/ml

Specificity: satisfactory

Urine

Linearity: linear from 0 to 100 ng/ml

Precision: Inter CV (%) for carvedilol and desmethylcarvedilol were 3.64% and 4.67% at 50.0 ng/ml, respectively. Intra CV (%) for carvedilol and desmethylcarvedilol were 6.59% and 9.06% at 50.0 ng/ml, respectively.

Sensitivity: LLQ: 1 ng/ml

LODs for carvedilol and desmethylcarvedilol were 0.82 and 1.07 ng/ml

Specificity: satisfactory

Data Analysis: Pharmacokinetic parameters were determined by noncompartmental methods.

Results: The pharmacokinetic parameters for carvedilol after 25 mg oral dose are shown in Table 1.

Table 1
Pharmacokinetic Parameters Following Oral Administration of Carvedilol*
(Protocol MF 3476)

	Group I 25 mg <u>oral</u>	Group II 25 mg <u>oral</u>	Group III† 25 mg <u>oral</u>
C _{max} (ng/ml)	81	92	91
n	13	3	7
T _{max} (hr)	3.9	4.0	1.6
n	13	3	7
AUC ₀₋₄₈ (ng*hr/ml)	720	777	388
n	11	3	7

* Data are presented as mean and range. Group I - slight impaired liver dysfunction;

Group II - severe liver impairment; Group III - normal liver function

† Two patients excluded from statistics due to aberrant or incomplete plasma concentration-time profiles.

Observed C_{max} appeared to be similar between groups. In contrast, AUC(0-48) in both groups of patients with liver disease were higher (about 2-fold) compared to healthy subjects. Based on C_{max} and AUC data, plasma desmethylcarvedilol levels were less than 10% of those observed for carvedilol in all groups.

Some patients in all groups showed unaccountably high plasma levels of carvedilol following i.v. dosing. The intravenous data was not evaluated because of inappropriate blood sampling. The in vitro binding of carvedilol in patients with severe liver dysfunction (Group II) was examined. At a total concentration of 200 ng/ml, carvedilol was approximately 98.2% bound to plasma proteins. This value is similar to that in healthy volunteers, suggesting that protein binding is not altered in patients with liver disease.

Conclusions: Following oral administration of 25 mg carvedilol, observed C_{max} appeared to be similar between groups. AUC(0-48) in both patients with liver disease were approximately 2 times higher than that in healthy subjects. Plasma levels of desmethylcarvedilol were less than 10-fold than those observed for carvedilol in all study groups.

Comments: Two patients with severe liver impairment (Group II) received 12.5 mg single oral dose instead of 25 mg carvedilol. The PK data from these patients were not included in Table 1. The dose was reduced due to preceding severe hypotensive patients.

Evaluation of Drug Interaction of Carvedilol with Hydrochlorothiazide (HCTZ) in Hypertensive Patients

Study No: MF 3877

Volume: 1.62

Pages: 2-382

Investigator and Site:

Objectives: To determine the pharmacokinetic interactions between carvedilol and HCTZ after single oral administration of each drug and in combination.

Formulations:

- Carvedilol 25 mg capsules, batch # 819 776 40 Hc, batch size:
- HCTZ 25 mg capsules, batch # 819 974 40 Aa, batch size: . . . (in-house)
- Placebo capsules, batch # 819 560 Cb, batch size:

Study Design: This was a controlled, randomized, double-blind, three way cross-over study in which 12 patients with mild to moderate hypertension (6 M, 6 F; age 30 - 69 yrs; weight 74 - 109 kg) received single oral doses of each of the following treatments separated by at least 96 hrs:

1. carvedilol 25 mg capsule and placebo capsule
2. HCTZ 25 mg capsule and placebo capsule
3. carvedilol 25 mg capsule and HCTZ 25 mg capsule

Administration was performed in the morning between 8:00 a.m. and 9:00 a.m. together with a standard breakfast comprising one bread roll, 20 g butter, 50 g cottage cheese and 150 ml mineral water.

Specimens: Blood samples were collected before and at 15, 30, 45 min and 1, 1.5, 2, 3, 4, 5, 6, 8, 16, and 24 hrs after dosing.

Assay:

Carvedilol

Plasma samples were analyzed for carvedilol at the Dept. of Biochemical Analysis, Boehringer Mannheim GmbH by means of HPLC with fluorescence detection using in-house standardized methods.

Plasma

Linearity: linear up to 4 ug/ml

Precision: Inter CV (%) was 8.9% at 2 ng/ml.

Sensitivity: LLQ = 1 ng/ml

HCTZ

Plasma samples were analyzed for HCTZ at the

Linearity: linear, from 10 to 60 ng/ml, and from 60 to 400 ng/ml

Precision: Inter CV ranged from 2.6% at 100 ng/ml to 8.3% at 25 ng/ml. Intra CV ranged from 2.8% at 100 ng/ml to 4.5% at 25 ng/ml.

Sensitivity: LOQ was 7 ng/ml (CV 10%)

Accuracy: not reported

Specificity: not reported

Data Analysis: Pharmacokinetic parameters were determined by noncompartmental methods. The parameters were tested for significant differences using ANOVA.

Results: Table 1 shows mean pharmacokinetic parameters for carvedilol when administered alone and in combination with HCTZ. Table 2 shows the mean pharmacokinetic parameters for HCTZ. Table 3 summarized the ANOVA for possible pharmacokinetic interaction between carvedilol and HCTZ. The mean plasma concentration-time profiles for carvedilol and HCTZ, when administered alone and in combination, are shown in Fig. 1 and 2, respectively. Individual data for carvedilol and HCTZ are listed in Appendix II.

Table 1. Mean ($\pm$ SD) pharmacokinetic parameters for carvedilol

Treatment	C _{max} (ng/ml)	T _{max} (hr)	AUC(0- ∞)	t _{1/2} (hr)
carvedilol	82.3 $\pm$ 73.5	1.9 $\pm$ 1.0	420 $\pm$ 397	5.5 $\pm$ 2.8
carvedilol with HCTZ	77.1 $\pm$ 51.9	1.7 $\pm$ 0.8	427 $\pm$ 343	5.9 $\pm$ 2.0

AUC: ng*hr/ml

Table 2. Mean ($\pm$ SD) pharmacokinetic parameters for HCTZ

Treatment	C _{max} (ng/ml)	T _{max} (hr)	AUC(0- ∞)	t _{1/2} (hr)
HCTZ	187.9 $\pm$ 60.8	3.0 $\pm$ 1.5	1564 $\pm$ 480	7.7 $\pm$ 2.4
HCTZ with carvedilol	211.5 $\pm$ 92.5	2.5 $\pm$ 0.9	1653 $\pm$ 521	8.2 $\pm$ 1.3

AUC: ng*hr/ml

Table 3. P values for the unifactorial ANOVA (single vs. combined administration)

Drug	Variable	p-Value
carvedilol	AUC	0.749
	Cmax	0.580
	Tmax	0.605
HCTZ	AUC	0.401
	Cmax	0.244
	Tmax	0.301

Conclusions: Single-dose oral administration of 25 mg carvedilol with 25 mg HCTZ in hypertensive patients did not result in any differences in their pharmacokinetics in comparison with administration of drugs as single entities.

Comments: The firm did not submit the quality control data for carvedilol.

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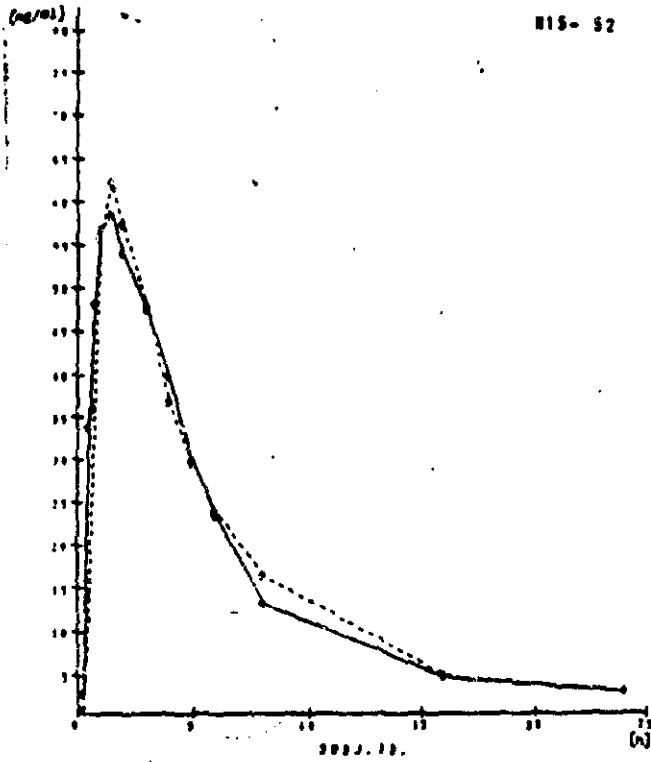


Fig. 1 Synthesis plot of the mean concentration/time curves for carvedilol after single orally administration and combined administration with hydrochlorothiazide
 (1 = carvedilol, 2 = carvedilol + HCT)

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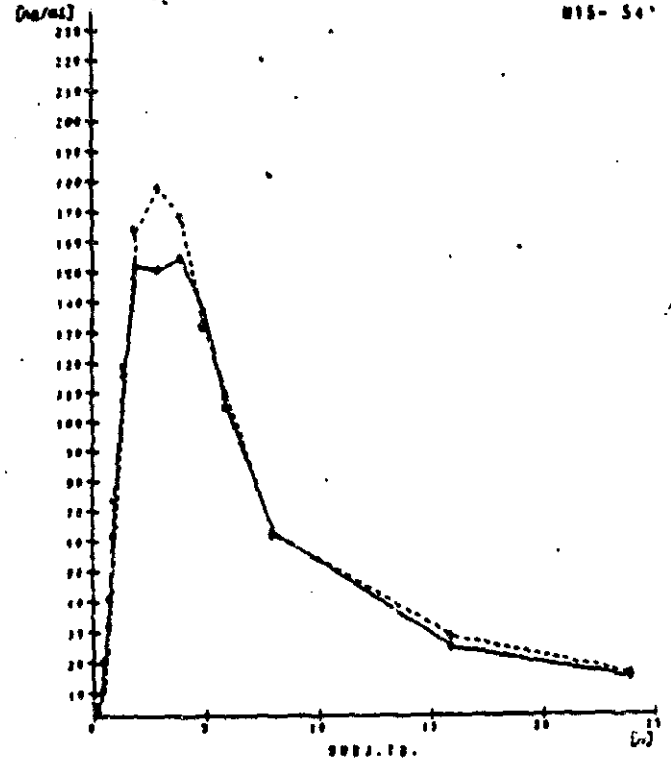


Fig. 2 Synthesis plot of the mean concentration/time curves for hydrochlorothiazide after single orally administration and combined administration with carvedilol
 (1 = HCT, 2 = HCT + carvedilol)

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Evaluation of Steady-state Pharmacokinetic Interaction of Carvedilol with Torsemide

Study No: MF 7024
Investigator and Site:

Volume: 1.68

Pages: 113 - 424

Objectives: To determine the possible drug interaction between carvedilol and torsemide and to determine the steady-state pharmacokinetic profile following oral administration of single entities and their combination after 5 days of administration.

Formulations: • Torsemide 5 mg tablets, batch # 819 018 C (in-house)
• Carvedilol 25 mg capsules, batch # 819 406 40 Df

Study Design: Open, randomized three-way cross-over study in 3 sections each comprising 5 medication days. The washout period between medications was at least 1 week. The pharmacokinetic profiles of carvedilol, torsemide, and torsemide M5 (metabolite) were determined in 12 healthy male volunteers (age: 19-34 yrs; weight: 61-87 kg). The volunteers were hospitalized 36 hrs before the first administration, at which time they were all put on the same diet. The volunteers drank 1.5 l water daily. Each volunteer received following 3 treatments in randomized order:

1. carvedilol 25 mg once daily for 5 days
2. torsemide 5 mg once daily for 5 days
3. carvedilol 25 mg plus torsemide 5 mg once daily for 5 days.

Administration took place in the morning between 8.00 and 9.00 a.m. together with a standard breakfast comprising one bread roll, 20 g butter, 50 g cottage cheese and 150 mg water.

Specimens: Blood, at pre dose and at 10, 30, 40 mins and 1, 1.5, 2, 2.5, 3, 6, 8, 10, 12, 14, and 24 hrs after dosing on study day 5 of each regimen. All urine was collected from 0-24 hrs after dosing.

Assay:

Plasma and urine samples were analyzed for carvedilol, torsemide, and torsemide M5 at the Dept. of Biochemical Analysis, Boehringer Mannheim GmbH by means of HPLC with fluorescence detection.

Carvedilol (Plasma)

Linearity: satisfactory, linear from 0.3 to 160 ng/ml

Precision: Inter-day CV (%) ranged from 3.8 to 9.5% and intra-day CV (%) ranged from 6.2 to 12.1%.

Accuracy: Mean accuracy ranged from 97 to 108%

Sensitivity: LLQ=0.32 ng/ml

Specificity: satisfactory

Torsemide and Torsemide M5

Analytical methods for torsemide and the M5 metabolite were not described in the report.

Data Analysis: Pharmacokinetic parameters were determined by noncompartmental methods. ANOVA was used to test for statistically significant differences of the pharmacokinetic parameters.

Results: Table 1 shows mean pharmacokinetic parameters for carvedilol when administered alone and in combination with torsemide. Tables 2 and 3 show the mean pharmacokinetic parameters for torsemide and torsemide M5, respectively. Individual data for carvedilol in each subject are listed in Appendix II.

Table 1. Mean ($\pm$ SD) steady-state pharmacokinetic parameters for carvedilol

Treatment	C _{max} (ng/ml)	T _{max} (hr)	AUC(0-24)	t _{1/2} (hr)	Ae (%)
carvedilol	43.6 $\pm$ 16.9	1.3 $\pm$ 0.6	168 $\pm$ 58	6.2 $\pm$ 1.9	0.25
carvedilol with torsemide	45.6 $\pm$ 12.2	1.7 $\pm$ 0.4	192 $\pm$ 39	6.4 $\pm$ 3.2	0.29

AUC: ng*hr/ml

Ae (%) : amount of carvedilol excreted in urine as a percentage of the dose

Table 2. Mean ($\pm$ SD) steady-state pharmacokinetic parameters for torsemide

Treatment	C _{max} (ng/ml)	T _{max} (hr)	AUC(0-24)	t _{1/2} (hr)	Ae (%)
torsemide	592.7 $\pm$ 175.0	1.2 $\pm$ 0.5	2132 $\pm$ 571	5.3 $\pm$ 3.7	22.8
torsemide with carvedilol	539.5 $\pm$ 181.8	1.5 $\pm$ 0.6	1998 $\pm$ 656	4.7 $\pm$ 2.4	22.2

AUC: ng*hr/ml

Table 3. Mean ($\pm$ SD) steady-state pharmacokinetic parameters for torsemide M5

Treatment	Cmax (ng/ml)	Tmax (hr)	AUC(0-24)	t1/2 (hr)	Ae (%)
torsemide	83.1 $\pm$ 24.7	2.4 $\pm$ 0.6	412 $\pm$ 153	3.3 $\pm$ 0.9	80.4
torsemide with carvedilol	80.5 $\pm$ 26.6	2.7 $\pm$ 0.	429 $\pm$ 184	3.4 $\pm$ 0.9	82.7

AUC: ng*hr/ml

The pharmacokinetics of carvedilol were not affected by torsemide. The pharmacokinetic parameters for torsemide and torsemide M5 were not changed when torsemide was administered in combination with carvedilol.

Less than 1% of dose of carvedilol was excreted in the urine as unchanged carvedilol. Renal excretion of unchanged torsemide in the 24 h urine is approximately 23% of the dose administered.

Conclusions: The combination of carvedilol and torsemide did not result in any differences in their pharmacokinetics in comparison with administration of the drugs as single entities.

Comments: Volunteer no. 3 did not have any measurable plasma or urine levels and it was suspected that medication was not taken. He was excluded from the evaluations on the PK. He was replaced by volunteer no. 13.

Evaluation of Drug Interaction of Carvedilol with Cimetidine and Rifampin

Study No: CAR 8902
Investigator and Site:

Volume: 1.73

Pages: 2 - 200

Objectives: To investigate the influence of inhibition (cimetidine) and induction (rifampin) of hepatic mixed function oxidase activity on the pharmacokinetics of a single oral dose of 25 mg carvedilol in healthy volunteers.

Formulations:

- Cimetidine (Tagamet®) 400 mg tablets, batch # HL 0059
- Carvedilol 25 mg capsules, batch # 820156 40 Kc
- Rifampin (Rifadin®) 300 mg capsules, batch # 7003

Study Design: Open, non-randomized, three-way cross-over study in 8 healthy male volunteers (age: 19-45 yrs; weight: 57-88 kg). All the volunteers completed following three phases:

Phase 1: single oral dose of 25 mg carvedilol.

Phase 2: cimetidine 400 mg orally every 12 hours for 7 doses. The last dose of cimetidine was co-administered with 25 mg carvedilol.

Phase 3: rifampin 600 mg orally once daily for 12 days. The last dose of rifampin was co-administered with 25 mg carvedilol.

The second phase started 24 hrs after carvedilol dosing in phase 1. There was a wash-out period of 13 days between phase 2 and phase 3.

Subjects were required to fast for at least 10 hours prior to each carvedilol dosing and were not allowed any food until 4 hours after the dose. Each dose was taken orally with 240 ml of water.

Specimens: Blood samples were collected before and at 15, 30, 45 mins and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 hrs after each carvedilol dosing.

Assay (carvedilol and desmethylcarvedilol):

Plasma samples were analyzed for carvedilol and desmethylcarvedilol at the
by means of HPLC with fluorescence
detection.

Data Analysis: Data were analyzed using model-independent methods. C_{max} , AUC_T , AUC_{0-1} , and $T_{1/2}$ for the three doses of carvedilol were analyzed by an ANOVA. T_{max} was analyzed using Wilcoxon matched signed rank test. The Westlake 95% CI and two 1-sided t-test 90% CI were calculated for C_{max} and AUC_{0-1} between Dose 1 and 2 and 1 and 3.

Results: The pharmacokinetic parameters for carvedilol and desmethylcarvedilol when carvedilol was administered alone and in combination with cimetidine and rifampin are shown in Tables 1 and 2. P values are also shown in Tables 1 and 2. The mean plasma levels for carvedilol and desmethylcarvedilol after three separate 25 mg oral administrations are shown in Figs. 1 and 2. Individual data are listed in Appendix II.

Carvedilol PK parameters (C_{max} , $t_{1/2}$, T_{max} , and AUC_0) were not statistically significantly altered following multiple oral administration of cimetidine.

Multiple oral administration of rifampin statistically reduced both carvedilol C_{max} ($p=0.0003$) and AUC_0 ($p=0.0002$) but not T_{max} , compared with the values determined when carvedilol was administered alone.

There was a significant difference in metabolic ratio between carvedilol and carvedilol with rifampin ($p=0.0003$) but not between carvedilol and carvedilol with cimetidine ($p=0.4516$)

Based on mean C_{max} and AUC_0 data, plasma concentration of desmethylcarvedilol were around 10% of those of carvedilol when carvedilol were administered alone or in combination with cimetidine.

Conclusions: Carvedilol (25 mg) administered after multiple oral doses of cimetidine (400 mg, BID for 3 days) expressed a slightly lower C_{max} and later T_{max} although those are not significantly different. The extent of absorption was apparently unchanged. There was a statistically significant reduction in C_{max} and extrapolated AUC_0 (approximately 70%) but not T_{max} when carvedilol was co-administered with the enzyme inducer, rifampin.

Comments: The plasma samples were collected up to 12 hours, the mean elimination half-life (2.46 ± 0.36 hrs) for carvedilol was shorter compared to other studies. Quality control data were not submitted.

From the mean profiles of carvedilol in Fig. 5, the lower C_{max} with cimetidine may be due to the lower solubility of this drug in intestinal fluid.

Table: 1

SUMMARY OF PLASMA CARVEDILOL PHARMACOKINETIC DATA

DOSE 01 : CARVEDILOL 25 mg.

	C _{max} (ng.ml ⁻¹)	T _{max} (h) MEDIAN RANGE	AUC(T) (ng.ml ⁻¹ .h)	AUC(I) (ng.ml ⁻¹ .h)	K _{elim} (h ⁻¹)	T 1/2 (h)	Cl (l/hr)
MEAN	86.5	0.75	202.830	214.392	0.2915	2.43	0.135
S.D.	35.4		86.908	95.748	0.0484	0.36	0.055

DOSE 02 : CARVEDILOL 25mg and CIPROFLOXACIN 400 mg.

	C _{max} (ng.ml ⁻¹)	T _{max} (h) MEDIAN RANGE	AUC(T) (ng.ml ⁻¹ .h)	AUC(I) (ng.ml ⁻¹ .h)	K _{elim} (h ⁻¹)	T 1/2 (h)	Cl (l/hr)
MEAN	71.7	1.50	238.212	252.309	0.2854	2.59	0.111
S.D.	39.1		85.392	83.254	0.0671	0.82	0.044

DOSE 03 : CARVEDILOL 25 mg AND RIFAMPICIN 400 mg.

	C _{max} (ng.ml ⁻¹)	T _{max} (h) MEDIAN RANGE	AUC(T) (ng.ml ⁻¹ .h)	AUC(I) (ng.ml ⁻¹ .h)	K _{elim} (h ⁻¹)	T 1/2 (h)	Cl (l/hr)
MEAN	28.4	0.88	62.947	66.904	0.3503	2.02	0.394
S.D.	14.4		16.905	16.399	0.0532	0.32	0.098

Dose 1 and Dose 2:

	p value	Two one sided t-test lower limit	upper limit	Westlake limits
C _{max}	0.2486	90.4 %	143.8 %	+/- 45.01 %
AUC I	0.2220	53.7 %	109.0 %	+/- 45.80 %
T 1/2	0.5023			
T _{max} *	> 0.05			
R B (1.270)	0.1328			
Metabolic ratio	0.4516			

Dose 1 and Dose 3:

C _{max}	0.0003	140.3 %	193.9 %	+/- 94.65 %
AUC I	0.0002	139.2 %	197.9 %	+/- 98.31 %
T 1/2	0.1042			
T _{max} *	> 0.05			
R B (0.349)	0.0001			
Metabolic ratio	0.0003			

* = Wilcoxon matched signed test.
R B = Relative bioavailability.

SUMMARY OF PLASMA DESMETHYLCARVEDILOL PHARMACOKINETIC DATADOSE 01 : CARVEDILOL 25 mg.

	C _{max} (ng.ml ⁻¹)	T _{max} (h)	AUC(T) (ng.ml ⁻¹ .h)	AUC(I) (ng.ml ⁻¹ .h)	K _{elim} (h ⁻¹)	T 1/2 (h)	Cl (l/hr)
		MEDIAN					
MEAN	8.1	0.88	16.109	19.234	0.7665	1.62	1.702
		RANGE					
S.D.	3.3		9.617	11.623	0.6341	1.19	0.855

DOSE 02 : CARVEDILOL 25mg and CIMETIDINE 400 mg.

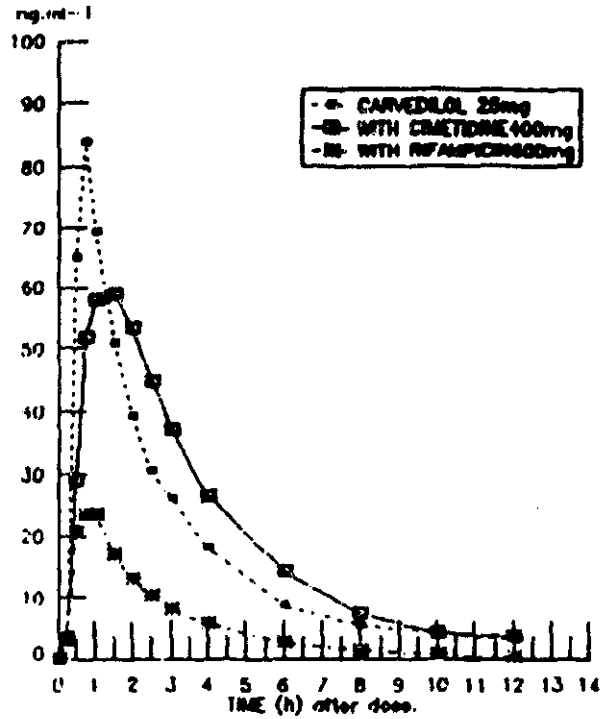
	C _{max} (ng.ml ⁻¹)	T _{max} (h)	AUC(T) (ng.ml ⁻¹ .h)	AUC(I) (ng.ml ⁻¹ .h)	K _{elim} (h ⁻¹)	T 1/2 (h)	Cl (l/hr)
		MEDIAN					
MEAN	8.1	1.50	21.093	24.917	0.4242	2.05	1.164
		RANGE					
S.D.	3.6		8.680	10.161	0.1789	1.30	0.466

DOSE 03 : CARVEDILOL 25 mg AND RIFAMPICIN 400 mg.

	C _{max} (ng.ml ⁻¹)	T _{max} (h)	AUC(T) (ng.ml ⁻¹ .h)	AUC(I) (ng.ml ⁻¹ .h)	K _{elim} (h ⁻¹)	T 1/2 (h)	Cl (l/hr)
		MEDIAN					
MEAN	5.4	1.00	11.750	14.256	0.5517	1.31	1.835
		RANGE					
S.D.	1.2		2.751	3.072	0.1183	0.29	0.447

FIGURE 1

MEAN PLASMA CARVEDILOL LEVELS AFTER THREE SEPARATE 25mg ORAL ADMINISTRATIONS



MEAN PLASMA CARVEDILOL LEVELS AFTER THREE SEPARATE 25mg ORAL ADMINISTRATION

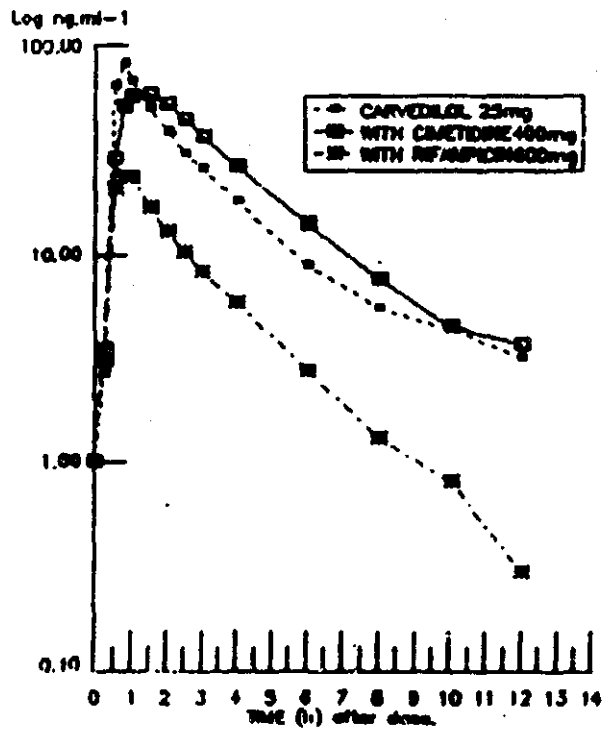
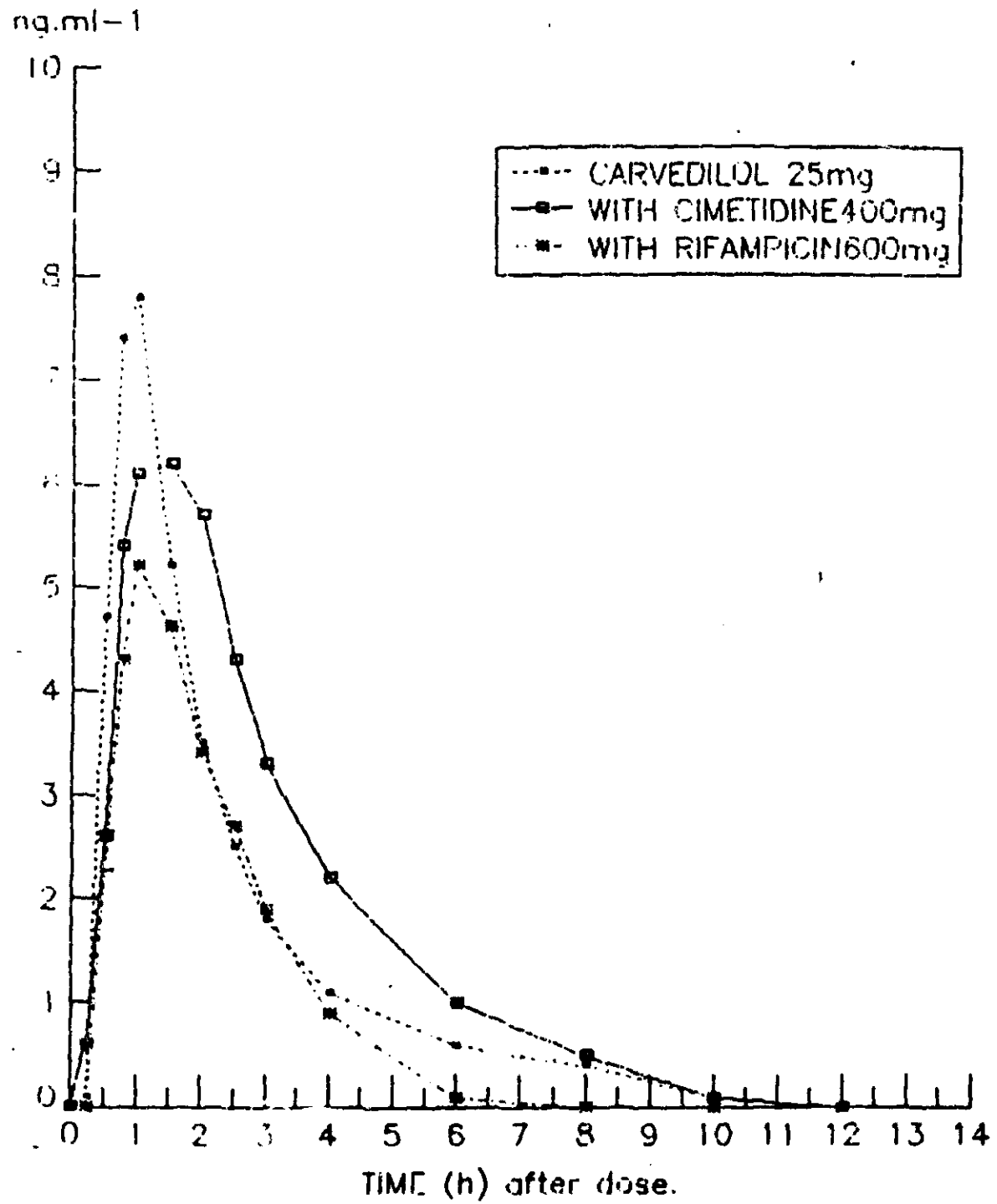


FIGURE 2.

MEAN PLASMA DESMETHYL CARVEDILOL LEVELS AFTER THREE SEPARATE CARVEDILOL DOSES.



Evaluation of Steady-state Kinetics of Carvedilol with Cimetidine

Study No: MF 7097

Volume: 1.71

Pages: 265-432

Investigator and Site: E. v. Möllendorff, M.D., Dept. of Clinical Pharmacology
Boehringer Mannheim GmbH, Sandhofer Str. 116, 6800 Mannheim 31, FRG

Objectives: To determine steady-state kinetics of carvedilol, carvedilol enantiomers, and the desmethyl (M2), 4-hydroxyphenyl (M4), and 5-hydroxyphenyl (M5) metabolites of carvedilol before and after concomitant cimetidine administration.

Formulations:

- Carvedilol 25 mg tablets (Dilatrend®, Boehringer Mannheim GmbH, Mannheim), batch # 746874-01
- Cimetidine 200 mg tablets (Tagamet®, SmithKline Dauelsberg GmbH, Goettingen) batch # 270790K19

Study Design: This was an open, single center study in which 10 healthy male volunteers (age: 24-33 yrs; weight: 74-94 kg) participated. Subjects were administered single oral doses of carvedilol, 12.5 mg on day 1 and then 25 mg on day 2 to day 6 after a standard breakfast. Subjects then continued to receive carvedilol (25 mg per day) along with cimetidine (200 mg at 0830, 1230, and 1630 and 400 mg at 2030) on day 7 to day 9.

Specimens: Blood samples were obtained before and at 0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 6, 8, 10 and 24 hrs after dosing on day 6 and day 9. Urine was collected over 24 hours.

Assay:

Carvedilol and M2 (HPLC with fluorescence detection)

Plasma

Linearity: linear from 0 to 100 ng/ml

Precision: Inter CV (%) for carvedilol and M2 were 5.6% and 5.35% at 50.0 ng/ml, respectively. Intra CV (%) for carvedilol and M2 were 6.76% and 6.00% at 50.0 ng/ml, respectively.

Sensitivity: LLQ for carvedilol and M2: 1.15 ng/ml

Specificity: satisfactory

Urine

Linearity: linear from 0 to 100 ng/ml

Precision: Inter CV (%) for carvedilol and M2 were 3.64% and 4.67% at 50.0 ng/ml, respectively. Intra CV (%) for carvedilol and M2 were 6.59% and 9.06% at 50.0 ng/ml, respectively.

Sensitivity: LLQs in urine for carvedilol and M2: 1.24 ng/ml

Specificity: satisfactory

M4 and M5 (HPLC with fluorescence detection)

Plasma

Linearity: satisfactory

Precision: Inter CV (%) for M4 ranged from 2.4% to 9.5% and intra CV (%) ranged from 5.7% to 9.8%. Inter CV (%) for M5 ranged from 2.2% to 15.9% and intra CV (%) ranged from 7.0% to 12.0%.

Sensitivity: LLQ=1.26 ng/ml

Specificity: satisfactory

Urine

Linearity: satisfactory

Precision: Inter CV (%) for M4 ranged from 1.44% to 5.64% and intra CV (%) ranged from 4.55% to 6.20%. Inter CV (%) for M5 ranged from 2.03% to 13.89% and intra CV (%) ranged from 8.18% to 11.65%.

Sensitivity: LLQ=1.22 ng/ml

Specificity: satisfactory

R(+)- and S(-)-carvedilol (Stereospecific HPLC method)

Linearity: satisfactory

Precision: not reported

Sensitivity: LLQ: 1.0 ng/ml for plasma, 0.5 ng/ml for urine.

Data Analysis: Pharmacokinetic parameters for carvedilol, carvedilol enantiomers, M2, M4, and M5 metabolites were determined using model-independent methods. The Wilcoxon test for paired data was used for statistical comparison, with $\alpha=0.05$.

Results: The steady-state pharmacokinetic parameters for carvedilol, R(+)- and S(-)-carvedilol when administered alone and in combination with cimetidine are shown in Table 1. The pharmacokinetic parameters for M2, M4 and M5 after administration of racemic carvedilol alone and in combination with cimetidine are shown in Table 2. The mean plasma concentration-time profiles for carvedilol, R(+)- and S(-)-carvedilol, M2, M4, and M5 are shown in Figs. 1 to 6.

DEUTSCHE MANNEIN GMBH KLINISCHE PHARMKOLOGIE - KINETIK
 PROGRAM: KPO DATE OF COMPUTATION: 26-FEB-82

025- 77

RAW DATA EVALUATION; LOG.-LIN.SCALE, BEGINNING AT 5.9 DN

PROJECT: EN 14.100 ORNEDILAL ; MF 7007
 DOSE : DAY 1: 12.5 mg DAY 2-9: 25 mg DILATEND(S) ; ONCE DAILY
 DAY 7-9: 1000 mg CONVEDILIN (TABANET(R)) PER DAY, ORAL

- " 1 " : ASSAY: EN 14.100 IN PLASMA AND URINE ; DET. BY HPLC --- DAY 6 ---
- " 2 " : ASSAY: EN 14.100 IN PLASMA AND URINE ; DET. BY HPLC --- DAY 9 ---
- " 3 " : ASSAY: S(+)- EN 14.100 IN PLASMA AND URINE ; DET. BY HPLC --- DAY 6 ---
- " 4 " : ASSAY: S(+)- EN 14.100 IN PLASMA AND URINE ; DET. BY HPLC --- DAY 9 ---
- " 5 " : ASSAY: S(-)- EN 14.100 IN PLASMA AND URINE ; DET. BY HPLC --- DAY 6 ---
- " 6 " : ASSAY: S(-)- EN 14.100 IN PLASMA AND URINE ; DET. BY HPLC --- DAY 9 ---

PARAMETER (RAW - DATA) UNIT

			"1"	"2"	"3"	"4"	"5"	"6"
AUC (0-24)	(ng*hr/ml)	N	10.	10.	10.	10.	10.	10.
		MEAN	221.10	209.40	146.25	201.25	62.99	66.10
		C.V. (%)	67.29	66.75	53.00	51.51	35.89	45.35
		MEDIAN	211.05	276.92	129.00	194.34	67.63	70.16
		MINI-MAXI-M.						
C _{max}	(ng/ml)	N	10.	10.	10.	10.	10.	10.
		MEAN	50.56	47.21	30.10	30.95	12.82	11.06
		C.V. (%)	59.70	45.30	42.61	44.85	34.90	45.84
		MEDIAN	48.68	45.44	23.94	24.22	13.69	10.91
		MINI-MAXI-M.						
t _{max}	(h)	N	10.	10.	10.	10.	10.	10.
		MEAN	1.288	1.435	1.325	1.600	1.175	1.500
		C.V. (%)	38.23	28.32	28.34	37.30	41.42	38.29
		MEDIAN	1.250	1.700	1.250	2.000	1.000	1.500
		MINI-MAXI-M.						
t _{1/2}	(h)	N	10.	10.	10.	10.	9.	10.
		MEAN	5.200	5.135	4.400	5.097	6.400	6.536
		C.V. (%)	55.47	48.79	32.32	42.64	52.90	37.39
		MEDIAN	4.795	5.057	4.156	5.603	9.171	6.086
		MINI-MAXI-M.						
C _l / f	(ml/min)	N	10.	10.	10.	10.	10.	10.
		MEAN	2491.40	2022.64	1710.05	1605.72	3060.34	4254.73
		C.V. (%)	57.33	58.91	77.45	81.00	45.97	64.85
		MEDIAN	2011.00	1529.95	1300.00	1075.27	3082.73	2645.40
		MINI-MAXI-M.						
V _d / f	(l)	N	10.	10.	10.	10.	9.	10.
		MEAN	1088.7	787.3	623.4	486.8	2512.2	1990.7
		C.V. (%)	69.90	38.29	78.59	23.64	73.36	33.53
		MEDIAN	736.2	678.3	430.2	491.6	4245.3	2017.2
		MINI-MAXI-M.						
A ₀	(%)	N	10.	10.	10.	10.	10.	10.
		MEAN	0.34	0.66	0.86	1.06	0.20	3.23
		C.V. (%)	57.29	47.91	57.73	47.77	42.34	7.59
		MEDIAN	0.51	0.65	0.72	1.00	0.22	3.23
		MINI-MAXI-M.						
C _l R	(ml/min)	N	10.	10.	10.	10.	10.	10.
		MEAN	10.40	18.91	11.34	11.98	6.37	7.53
		C.V. (%)	25.50	16.00	37.73	26.84	17.23	23.70
		MEDIAN	10.43	11.44	10.91	11.97	6.86	7.59
		MINI-MAXI-M.						

Carvedilol (R(+)-) (S(-) Carvedilol)

DEPARTMENT OF PHARMACEUTICAL CHEMISTRY
 PROGRAM: MED

CLINICAL PHARMACOLOGY - KINETIC
 DATE OF COMPUTATION: 24-FEB-68

RAW DATA EVALUATION

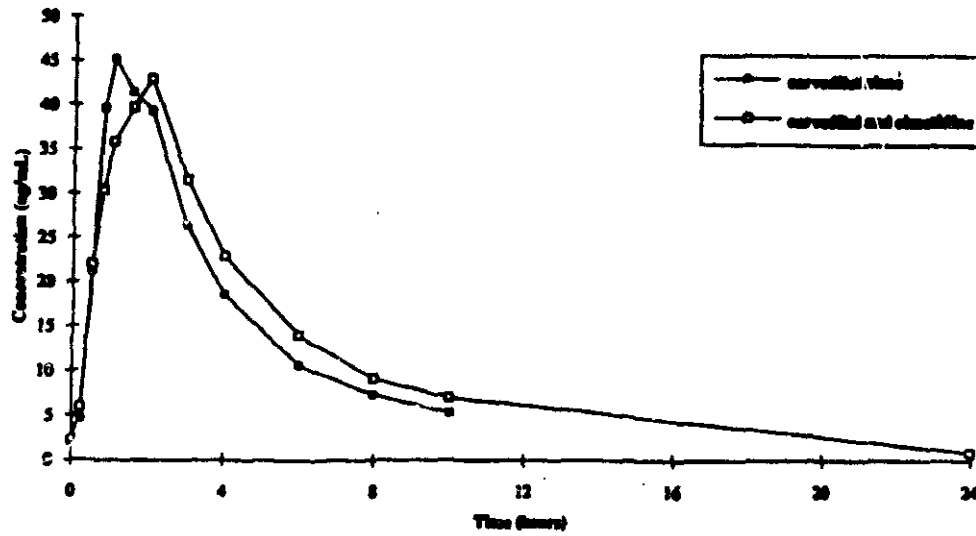
PROJECT: ON 14.900 GRANULES ; IP 7097
 DOSE : DAY 1: 12.5 mg DAY 2-9: 25 mg BILATROND(S) ; ONCE DAILY
 DAY 7-9: 1000 mg CINEPTIDIN (TARGEM(R)) PER DAY, ORAL

- * 1 * : ASSAY: ON 14.242 IN PLASMA AND URINE ; DET. BY HPLC *** DAY 6 ***
- * 2 * : ASSAY: ON 14.242 IN PLASMA AND URINE ; DET. BY HPLC *** DAY 9 ***
- * 3 * : ASSAY: ON 14.0226 IN PLASMA AND URINE ; DET. BY HPLC *** DAY 6 ***
- * 4 * : ASSAY: ON 14.0226 IN PLASMA AND URINE ; DET. BY HPLC *** DAY 9 ***
- * 5 * : ASSAY: ON 14.0226 IN PLASMA AND URINE ; DET. BY HPLC *** DAY 6 ***
- * 6 * : ASSAY: ON 14.0226 IN PLASMA AND URINE ; DET. BY HPLC *** DAY 9 ***

PARAMETER (RAW - DATA)	UNIT	"1"	"2"	"3"	"4"	"5"	"6"
A U C	(mg ² /ml)	10.	10.	10.	10.	10.	10.
	MEAN	8.80	9.53	7.67	7.23	5.11	4.33
	C.V. (%)	<u>54.50</u>	<u>59.90</u>	<u>33.30</u>	<u>44.67</u>	<u>34.77</u>	<u>50.74</u>
	MEDIAN	7.92	7.63	6.64	6.39	4.57	4.35
	MINIM. MAXIM.						
C MAX	(mg/ml)	10.	10.	10.	10.	10.	10.
	MEAN	4.30	3.70	3.00	3.34	3.34	2.70
	C.V. (%)	<u>25.12</u>	<u>27.06</u>	<u>18.33</u>	<u>22.02</u>	<u>30.03</u>	<u>28.32</u>
	MEDIAN	3.04	3.44	4.10	3.17	3.30	2.76
	MINIM. MAXIM.						
T MAX	(h)	10.	10.	10.	10.	10.	10.
	MEAN	1.275	1.425	1.250	1.400	1.225	1.625
	C.V. (%)	<u>33.14</u>	<u>20.19</u>	<u>37.71</u>	<u>26.72</u>	<u>36.37</u>	<u>37.82</u>
	MEDIAN	1.000	2.000	1.000	1.750	1.000	2.000
	MINIM. MAXIM.						
A 0	(%)	10.	10.	10.	10.	10.	10.
	MEAN	0.09	0.10	0.11	0.12	0.08	0.09
	C.V. (%)	31.00	25.00	20.57	21.57	35.14	40.57
	MEDIAN	0.09	0.11	0.11	0.13	0.08	0.08
	MINIM. MAXIM.						
CL R	(ml/min)	10.	10.	10.	10.	10.	10.
	MEAN	49.00	25.40	64.04	85.07	67.44	121.04
	C.V. (%)	32.00	47.90	48.04	42.14	38.14	83.40
	MEDIAN	50.17	50.20	57.07	80.51	62.10	75.03
	MINIM. MAXIM.						

Protocol 107-707 / Figure 1

Mean plasma concentration-time profiles for carvedilol following multiple dose administration of carvedilol alone (25 mg once daily) and in combination with diltiazem (1800 mg/day) in ten healthy male volunteers.

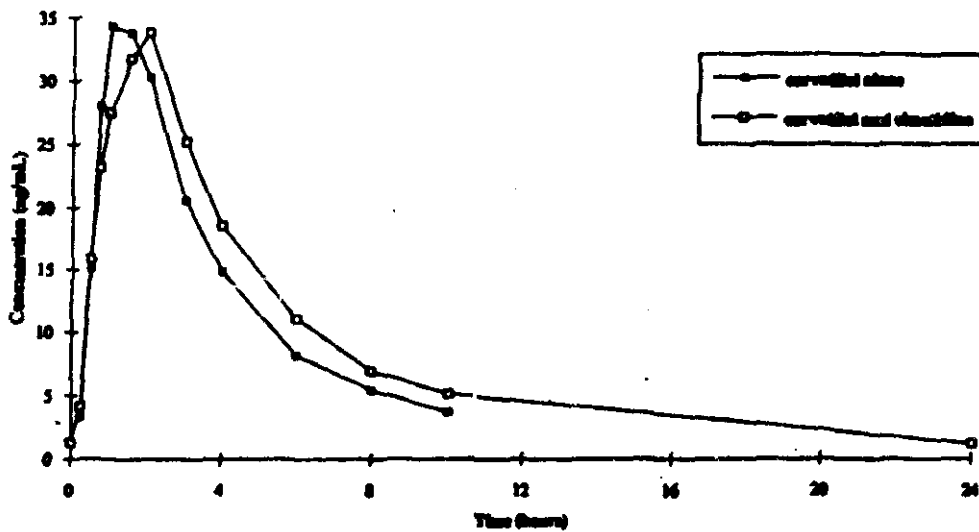


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Note: As per report, non-quantifiable values were not equal to zero in the calculation of mean data; mean data are not presented if more than one-half of the subjects exhibited non-quantifiable values.

Protocol 107-707 / Figure 2

Mean plasma concentration-time profiles for D(+)-carvedilol following multiple dose administration of carvedilol alone (25 mg once daily) and in combination with diltiazem (1800 mg/day) in ten healthy male volunteers.

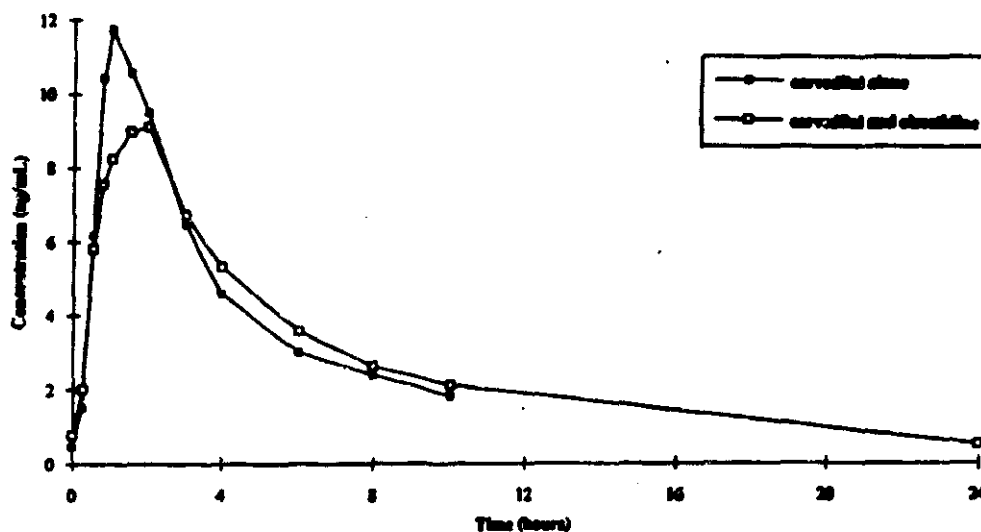


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Note: As per report, non-quantifiable values were not equal to zero in the calculation of mean data; mean data are not presented if more than one-half of the subjects exhibited non-quantifiable values.

Protocol MF-7897 / Figure 3

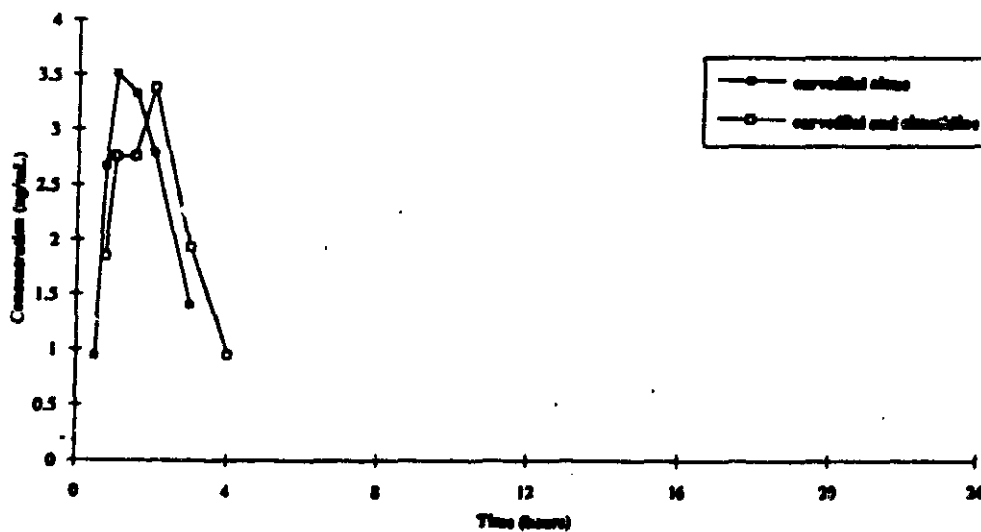
Mean plasma concentration-time profiles for (S)-carvedilol following multiple dose administration of carvedilol alone (25 mg once daily) and in combination with atenolol (1000 mg/day) in ten healthy male volunteers.



Note: As per report, non-quantifiable values were not equal to zero in the calculation of mean data; mean data are not presented if more than one-half of the subjects exhibited non-quantifiable values.

Protocol MF-7897 / Figure 4

Mean plasma concentration-time profiles for desmethyl-carvedilol (metabolite M2) following multiple dose administration of carvedilol alone (25 mg once daily) and in combination with atenolol (1000 mg/day) in ten healthy male volunteers.

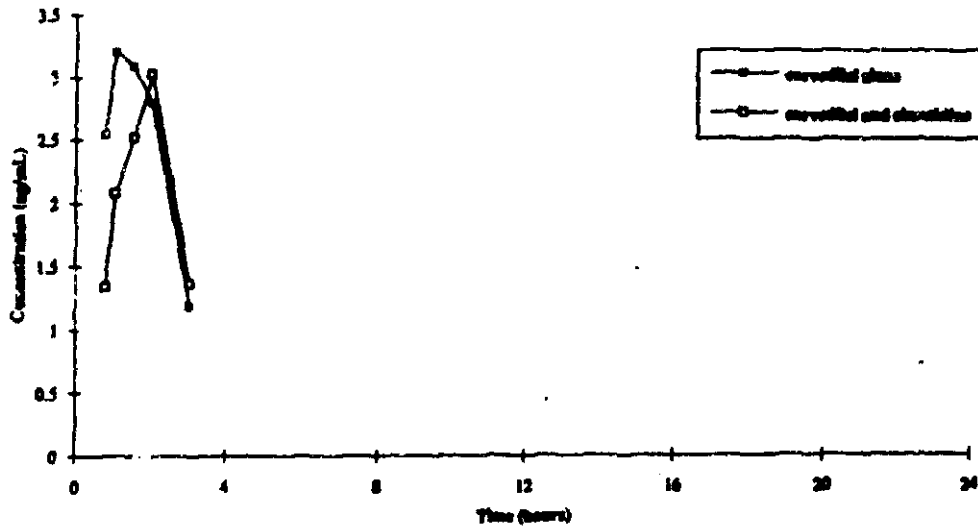


Note: As per report, non-quantifiable values were not equal to zero in the calculation of mean data; mean data are not presented if more than one-half of the subjects exhibited non-quantifiable values.

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Protocol MF-7007 / Figure 5

Mean plasma concentration-time profiles for 4'-hydroxyphenyl-carvedilol (metabolic M4) following multiple dose administration of carvedilol alone (25 mg once daily) and in combination with diltiazem (1800 mg/day) in ten healthy male volunteers.

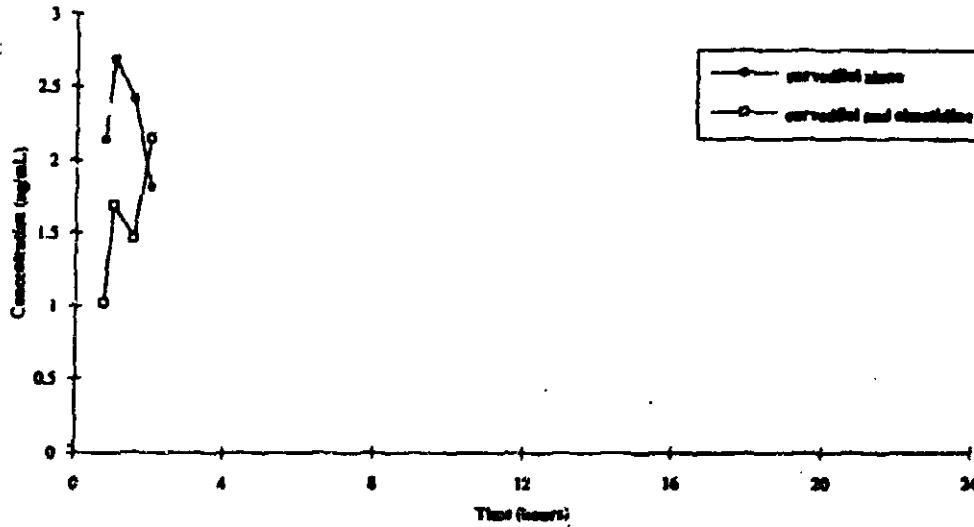


Note: As per report, non-quantifiable values were set equal to zero in the calculation of mean data; mean data are not presented if more than one-half of the subjects exhibited non-quantifiable values.

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Protocol MF-7007 / Figure 6

Mean plasma concentration-time profiles for 3'-hydroxyphenyl-carvedilol (metabolic M5) following multiple dose administration of carvedilol alone (25 mg once daily) and in combination with diltiazem (1800 mg/day) in ten healthy male volunteers.



Note: As per report, non-quantifiable values were set equal to zero in the calculation of mean data; mean data are not presented if more than one-half of the subjects exhibited non-quantifiable values.

There were no statistical differences in C_{max} , T_{max} , $t_{1/2}$, or CL_r for carvedilol when carvedilol was co-administered with cimetidine. Mean $AUC(0-24)$ increased approximately 17% ($p < 0.05$) and mean A_e (amount of carvedilol excreted in urine) increased approximately 22% ($p < 0.05$).

Based on mean C_{max} data, metabolites levels were less than 10% of those of carvedilol when carvedilol was administered alone or in combination.

Mean $AUC(0-t)$ for R(+)-carvedilol was increased approximately 21% ($p < 0.05$) and mean A_e for R(+)-carvedilol increased about 24% ($p < 0.05$) when carvedilol was administered with cimetidine.

Mean C_{max} for S(-)-carvedilol was approximately 14% decreased ($p < 0.05$) when carvedilol was administered with cimetidine.

Conclusions and Comments: Administration of carvedilol with cimetidine caused a moderate increase in mean $AUC(0-24)$ (17%) and mean A_e (22%) of carvedilol. This was reflected by a moderate increase in mean $AUC(0-24)$ (21%) and mean A_e (24%) for R(+)-carvedilol in combined administration. For S(-)-carvedilol, there was a slight decrease in mean C_{max} (14%). There were no major changes in the kinetic parameters of the M2, M4, and M5 metabolites of carvedilol following with cimetidine.

Evaluation of Drug Interaction of Carvedilol with Digoxin (administered orally)

Study No.: A9904

Volume: 1.52

Pages: 2-72

Investigator and Site: Christian de May, M.D.

SK & F Institute for Applied Clinical Pharmacology, Göttingen, FRG

Objectives: To assess the acute effects of the co-administration of a single dose of 25 mg carvedilol on the plasma and urinary pharmacokinetics of digoxin. For the assessment of acute interaction on concomitant administration, relatively high dose of digoxin was administered in order to profile the plasma kinetics in sufficient detail, without however exposing the subjects to undue risk.

Formulations: • Carvedilol 25 mg tablets, batch #: 1/25/B/6

- Matched placebo, formulation: 1/25-P-S, batch #: 2, provided by Dept. of Pharmaceutical Development, SK & F Labs, Welwyn, UK.
- Digoxin 0.25 mg tablets (Lenoxin[®], Wellcome, Ch.B.: M5161A)

Study Design: In a double blind, period-balanced, within-subject cross-over design with randomly allocated sequences, 8 healthy male subjects (age 22 to 27 yrs; weight 65 to 87 kg) received the two study treatments separated by 1 week. On one occasion a single oral dose of 0.5 mg digoxin (two tablets of 0.25 mg digoxin) was administered concomitantly with 25 mg carvedilol, on the other occasion, a single oral dose of 0.5 mg digoxin was administered concomitantly with carvedilol matched placebo. The medications were administered with 150 ml water, then 200 ml of water was given every 2 hrs up to 8 hrs after dosing.

Specimens: Blood samples were collected before and at 15, 30, 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36 and 48 hours after dosing. Urine was collected in 5 fractions: pre-dosing blank, 0-8, 8-24, 24-36 and 36-48 hours after dosing.

Assay (digoxin):

Plasma digoxin levels were determined by radio-immuno assay (Amersham, UK).

Linearity: Calibration curve from 0.09 to 5.40 ng/ml

Precision: 0.7% at 1.0 ng/ml and 6.1% at 5.0 ng/ml

Sensitivity: LL_C=0.07 ng/ml

Specificity: Satisfactory

Digoxin levels in urine were assayed using HPLC with UV detection.

Linearity: Calibration curve from 10 to 400 ng/ml

Precision: 15.6% at 10 ng/ml and 3.0% at 300 ng/ml

Sensitivity: LL_Q=10 ng/ml

Specificity: Satisfactory

These assays were performed by the Bio-Analytical Unit of the SK & F Institute.

Data Analysis: C_{max}, C₂₄ (plasma concentration at 24 hrs after dosing), AUC₀₋₄ (up to the last measurable plasma concentration), AUC_{0-∞} (extrapolated to infinity), K (apparent elimination rate constant), and U₄₈ (48 hours urinary recovery) for digoxin were calculated.

C_{max} and the log-transformed AUC₀₋₄, C₂₄ and K were assessed for subject, treatment and period related variance, with a subplot to assess group and sequence effects. The resulting residual variance was used to calculate the 95% CI. Two-sided 95% confidence intervals were provided for the estimates of the true difference or ratio of the treatment means.

Results: The pharmacokinetic parameters, point estimates, and two-sided 95% CI for digoxin/placebo and digoxin/carvedilol are shown in Table 1. The median plasma concentration-time profiles are shown in Fig. 1.

Table 1. Pharmacokinetic parameters (mean ± SD) for digoxin with point estimates and 95% confidence intervals following administration with placebo and with carvedilol

Parameter	Digoxin and Placebo (R)	Digoxin and Carvedilol (T)	Point Estimate		95% CI
			T - R	T/R	
C _{max} (ng/ml)	1.62 ± 0.56	2.59 ± 1.00	0.97		0.20 - 1.73*
C ₂₄ (ng/ml)	0.23 ± 0.04	0.28 ± 0.05		1.19	1.10 - 1.27*
AUC ₀₋₄ (ng*hr/ml)	15.0 ± 2.7	17.9 ± 2.9		1.19	1.10 - 1.30*
AUC _{0-∞} (ng*hr/ml)	25.6 ± 7.1	30.7 ± 9.6		1.19	0.97 - 1.46
K (hr ⁻¹)	0.017 ± 0.004	0.017 ± 0.006		1.00	0.76 - 1.31
U ₄₈ (ng)	216 ± 116	188 ± 47	-28		-113 - 57

*p < 0.05

Mean C_{max} for digoxin increased from 1.62 to 2.59 ng/ml (60% increase) and mean AUC₀₋₄ increase from 15.0 to 17.9 ng*hr/ml (19% increase). Mean plasma concentration of digoxin at 24 hours was significantly increased from 0.23 to 0.28 ng/ml, for digoxin/placebo versus digoxin/carvedilol, respectively. In contrast, AUC_{0-∞}, K, U₄₈ were not significantly different between treatments.

Conclusions and Comments: Administration of a single oral dose of 25 mg carvedilol with an oral dose of 0.5 mg digoxin in healthy volunteers, caused a significant increase in C_{max} and AUC₀₋₄ of digoxin. The changes were almost entirely confined to the early course of the curves up to 4 hrs after dosing although the effects were evident after 24 hrs after dosing.

105517/A9904-GER : MEDIAN VALUES

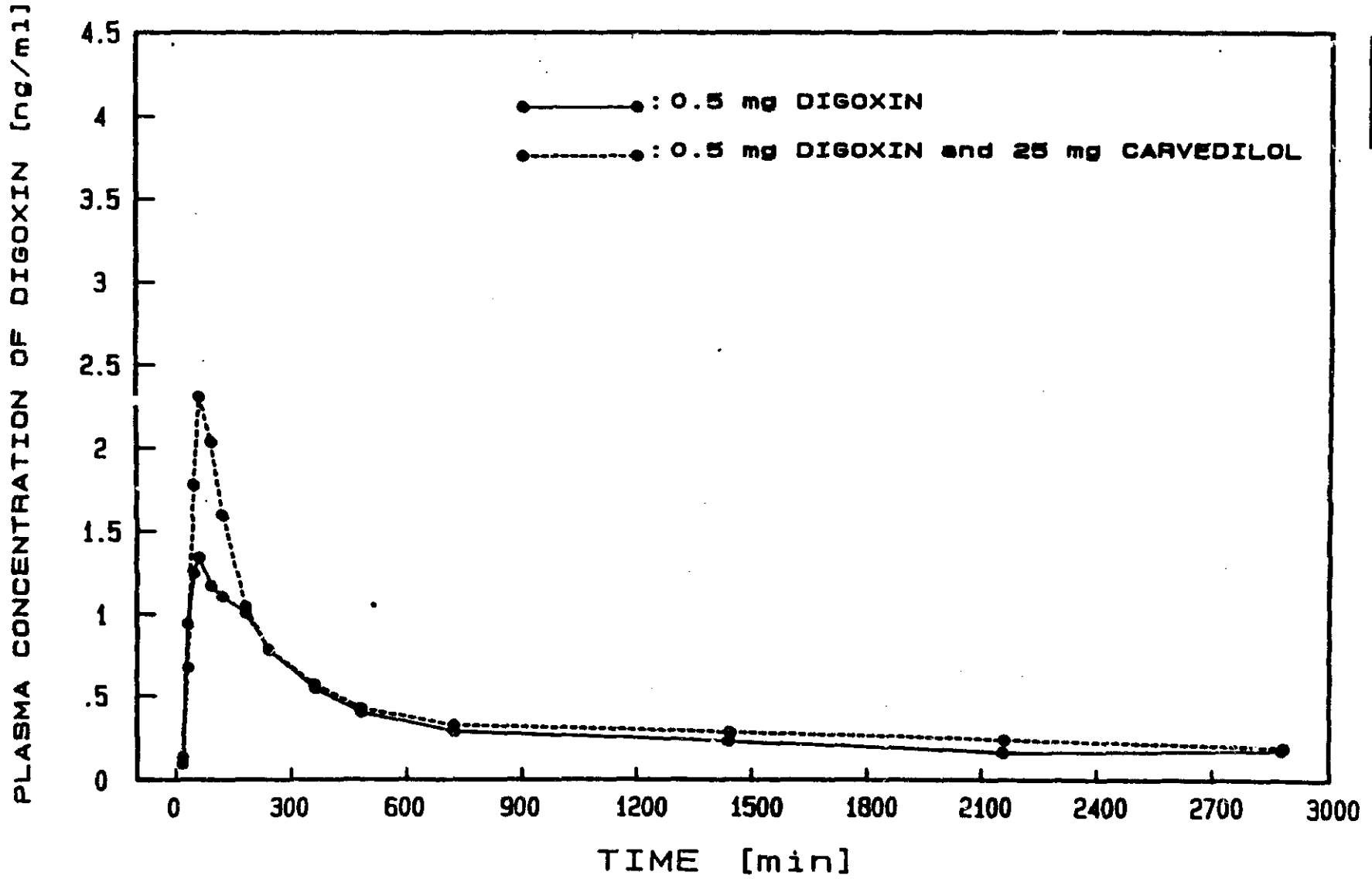


Figure 1:

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Evaluation of Drug Interaction of Carvedilol with Digoxin (administered intravenously)

Study No: A9905

Volume: 1.52

Pages: 73-164

Investigator and Site: Christian de Mey, M.D.

SK & F Institute for Applied Clinical Pharmacology, Göttingen, FRG

Objectives: To assess the acute effects of a single dose of 25 mg carvedilol on the plasma and urinary pharmacokinetics of a single dose of 0.5 mg digoxin administered via constant rate intravenous infusion over 10 minutes.

Formulations: • Carvedilol 25 mg tablets, batch #: 1/25/B/7

- Matched placebo, formulation: 1/25-P-5, batch #: 2, provided by Dept. of Pharmaceutical Development, SK & F Labs, Welwyn, UK.
- Commercially available digoxin solutions for parenteral administration (Lenoxin[®], Wellcome, FRG). Digoxin (0.5 mg) was diluted in isotonic saline and administered as a 10 ml/10 min infusion in sideline to a mainline of isotonic saline at 100 ml/min.

Study Design: In a double blind, period-balanced, within-subject cross-over design with randomly allocated sequences, 8 healthy male subjects (age 23 to 32 yrs; weight 63 to 92 kg) received the two study treatments separated by 2 weeks. On one occasion a single intravenous dose of 0.5 mg digoxin was administered via 10 min iv-infusion, immediately after the administration of a single oral dose of 25 mg carvedilol. On the other occasion digoxin was administered immediately after oral administration of carvedilol matched placebo. The medications were administered with 150 ml water, then 200 ml of water was given every 2 hrs up to 8 hrs after dosing. The subjects remained in bed up to 8 hrs after dosing.

Specimens: Blood samples were collected before and at 2, 5, 10, 15, 20, 30, 45 min and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48 and 72 hrs after dosing. Urine was collected in 5 fractions: pre-dosing blank, 0-8, 8-24, 24-36 and 36-48 hours after dosing.

Assay (digoxin):

Plasma digoxin levels were determined by radio-immuno assay (Amersham, UK).

Linearity: Calibration curve from 0.09 to 5.40 ng/ml

Precision: 0.7% at 1.0 ng/ml and 6.1% at 5.0 ng/ml

Sensitivity: LLQ=0.07 ng/ml

Specificity: Satisfactory

Digoxin levels in urine were assayed using HPLC with UV detection.

Linearity: Calibration curve from 10 to 400 ng/ml

Precision: 15.6% at 10 ng/ml and 3.0% at 3.0%

Sensitivity: LLQ=10 ng/ml

Specificity: Satisfactory

These assays were performed by the Bio-Analytical Unit of the SK & F Institute.

Data Analysis: C_{max} , C_{24} (plasma concentration at 24 hrs after dosing), AUC_{0-t} (up to the last measurable plasma concentration), AUC_{0-24} , K (apparent elimination rate constant), and U_{48} (48 hours urinary recovery) for digoxin were calculated.

C_{max} and the log-transformed AUC_{0-t} , C_{24} and K were assessed for subject, treatment and period related variance, with a subplot to assess group and sequence effects. The resulting residual variance was used to calculate the 95% CI. Two-sided 95% confidence intervals were provided for the estimates of the true difference or ratio of the treatment means.

Results: The pharmacokinetic parameters, point estimates, and two-sided 95% CI for digoxin/placebo and digoxin/carvedilol are shown in Table 1. The median plasma concentration-time profiles are shown in Fig. 1.

Table 1. Pharmacokinetic parameters (mean $\pm$ SD) for digoxin with point estimates and 95% confidence intervals following administration with placebo and with carvedilol

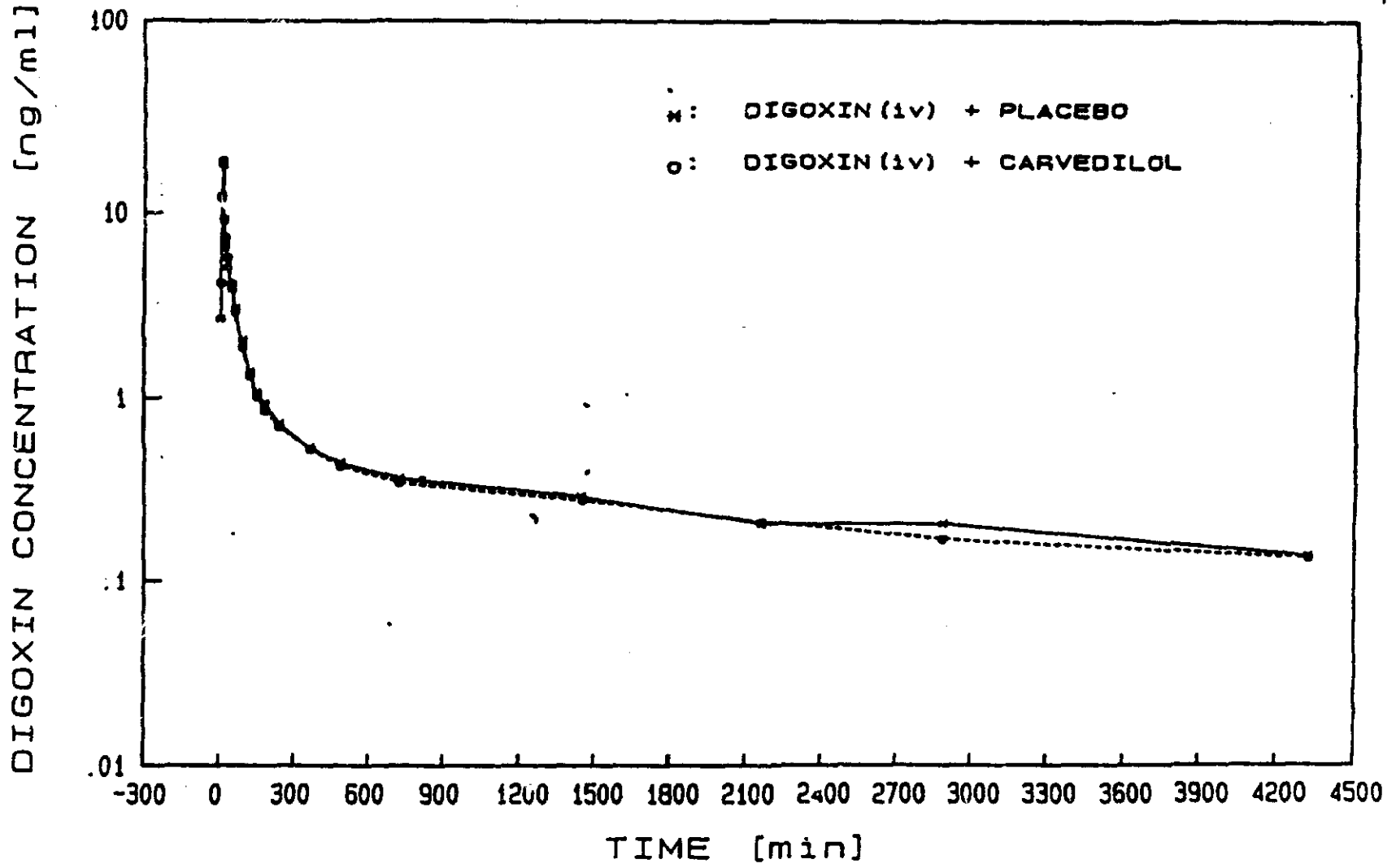
Parameter	Digoxin and Placebo (R)	Digoxin and Carvedilol (T)	Point Estimate		95% CI
			T - R	T/R	
C_{max} (ng/ml)	16.7 $\pm$ 4.3	17.6 $\pm$ 4.2		1.06	0.93 - 1.20
C_{24} (ng/ml)	0.29 $\pm$ 0.07	0.27 $\pm$ 0.06	-0.026		-0.054 - 0.002
AUC_{0-t} (ng*hr/ml)	27.9 $\pm$ 4.1	26.7 $\pm$ 3.9	-1.20		-2.71 - 0.31
AUC_{0-24} (ng*hr/ml)	18.3 $\pm$ 2.2	17.8 $\pm$ 2.2	-0.50		-1.19 - 0.20
K (hr ⁻¹)	0.017 $\pm$ 0.004	0.015 $\pm$ 0.004		0.89	0.73 - 1.10
U_{48} (ng)	258 $\pm$ 18	246 $\pm$ 29		0.95	0.83 - 1.08

There was not a statistically significant difference in the PK parameters of digoxin (C_{max} , C_{24} , AUC_{0-t} , AUC_{0-24} , K , or U_{48}) when the administration of i.v. digoxin (and placebo) was compared with the administration of i.v. digoxin and carvedilol.

Conclusions: Administration of a single oral dose of 25 mg carvedilol with an intravenous dose of 0.5 mg digoxin in healthy volunteers, did not alter the digoxin's PK.

105517/A9905-GER : MEDIAN VALUES

Figure 1:



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-109-

000125

Evaluation of Drug Interaction of Carvedilol with Warfarin (In-Vitro)

Study No: BP006BS

Volume: 1.55

Pages: 2-17

Investigator and Site: Brian R. Smith, Ph.D.

The Department of Drug Metabolism, SK & F Laboratories, Pennsylvania, USA

Objective: To assess the effect of carvedilol on the in-vitro plasma protein binding of warfarin

Study Design and Methods: Four carvedilol concentrations (300, 100, 17.4, and 3 ng/ml) and two warfarin concentrations (1.8 and 5.4 ug/ml) were studied. Bound and free fractions of warfarin were determined in triplicate from pooled plasma of healthy volunteers using equilibrium dialysis and ¹⁴C-warfarin. The warfarin concentrations correspond to the range required to produce a target prothrombin time ratio of 1.5 and 3.5 in human subjects, respectively. Dialysis cells were rotated to equilibrium (3 hrs) at 37°C. Samples were quantitated by determination of radiochemical content using liquid scintillation counting.

Results: The mean $\pm$ SD warfarin free fraction in the absence of carvedilol was $0.677 \pm 0.033\%$ (99.31% bound) and $0.794 \pm 0.148\%$ (99.21% bound) at 1.8 and 5.4 ug/ml, respectively (Table 1). ANOVA showed that the warfarin free fraction was not significantly changed ($p \geq 0.3$) at any of the 4 carvedilol concentrations studied.

Table 1. Effect of carvedilol on the free fraction of warfarin (mean $\pm$ SD, N=3)

Carvedilol (ng/ml)	% Free Fraction	
	1.8 ug/ml	5.4 ug/ml
0.0	0.688 ± 0.033	0.794 ± 0.148
3.0	0.698 ± 0.169	0.685 ± 0.089
17.4	0.554 ± 0.137	0.746 ± 0.093
100	0.698 ± 0.144	0.651 ± 0.025^b
300	0.801 ± 0.113	0.547 ± 0.06

^b N=2

Conclusions: At carvedilol concentrations which occur clinically, the free fraction of warfarin at therapeutic concentrations was not changed in-vitro in pooled plasma from healthy volunteers.

Protein Binding/Carvedilol

Study No: BC019BS

Volume: 1.73

Pages: 201-212

Investigator and Site: A. Haak and Dr. P. Neubert

Boehringer Mannheim GmbH, FRG

Objective: To describe the plasma protein binding of carvedilol in the presence of torsemide and the plasma protein binding of torsemide in the presence of carvedilol.

Study Design and Methods: The plasma protein binding for carvedilol and torsemide were determined in duplicate using equilibrium dialysis. Three radioactive working solutions were made to contain:

1. 200 ng/ml of ^{14}C -carvedilol
2. 1000 ng/ml ^3H -torsemide
3. 200 ng/ml ^{14}C -carvedilol and 1000 ng/ml ^3H -torsemide

Two ml of the working solutions were dialyzed against an equal volume of plasma for 6 hrs at 37°C. Samples were quantified by determination of radiochemical content using liquid scintillation counting.

Results:

Table 1. Percent protein binding of carvedilol in the presence of carvedilol in plasma of three subjects

Compound	Subject 1	Subject 2	Subject 3	Mean $\pm$ SD
Carvedilol	97.8 98.1	98.3 98.4	98.7 98.4	98.3 $\pm$ 0.3
Carvedilol with Torsemide	98.6 98.8	98.5 98.1	98.8 98.6	98.6 $\pm$ 0.3
Torsemide	94.0 94.2	94.2 94.1	92.7 93.9	93.9 $\pm$ 0.6
Torsemide with Carvedilol	94.3 94.5	94.2 93.6	94.1 94.0	94.1 $\pm$ 0.

Conclusions: It was demonstrated that plasma protein binding of carvedilol (98%) was unchanged in the presence of torsemide and the plasma protein binding of torsemide (94%) was unchanged in the presence of carvedilol.

Protein Binding/Carvedilol Enantiomers

Study No: 170

Volume: 1.55

Pages: 18-56

Investigator and Site: R.D. Eckardt, B.S., The Department of Drug Metabolism and Pharmacokinetics, SmithKline Beecham Pharmaceuticals, Upper Merion, Pennsylvania, USA

Background: Carvedilol undergoes stereospecific first-pass metabolism with plasma levels of R-carvedilol approximately 2 to 3 times higher than S-carvedilol following oral dose in healthy volunteers.

Objective: To describe the plasma protein binding of the two enantiomers over a therapeutic range

Methods: Plasma protein binding of ^3H -R- and ^3H -S-carvedilol over a concentration range of 0.3 to 300 ng/ml was carried out by equilibrium dialysis in semi-micro cells at 37°C for 6 hrs. Samples were quantified by determination of radiochemical content using liquid scintillation counting.

Results: The observed percent free fraction of ^3H -R-carvedilol remained constant with a mean value of 0.85% (± 0.13) over the concentration range used in this study. The observed percent free fraction of ^3H -S-carvedilol also remain constant with a mean value of 1.60% (± 0.27) (Fig. 1). After correction of overestimation due to radiochemical impurities, the actual mean free fraction of ^3H -R- and ^3H -S-carvedilol were approximately 0.5 - 0.6% and 1.2 - 1.3%, respectively.

Conclusions: It was demonstrated that plasma protein binding of both ^3H -R- and ^3H -S-carvedilol, was linear over the concentration range of 0.3 to 300 ng/ml. The mean free fraction of ^3H -S-carvedilol was 2-3 fold higher than ^3H -R-carvedilol. However, the correction of overestimation of free fraction due to radiochemical impurities is not well explained.

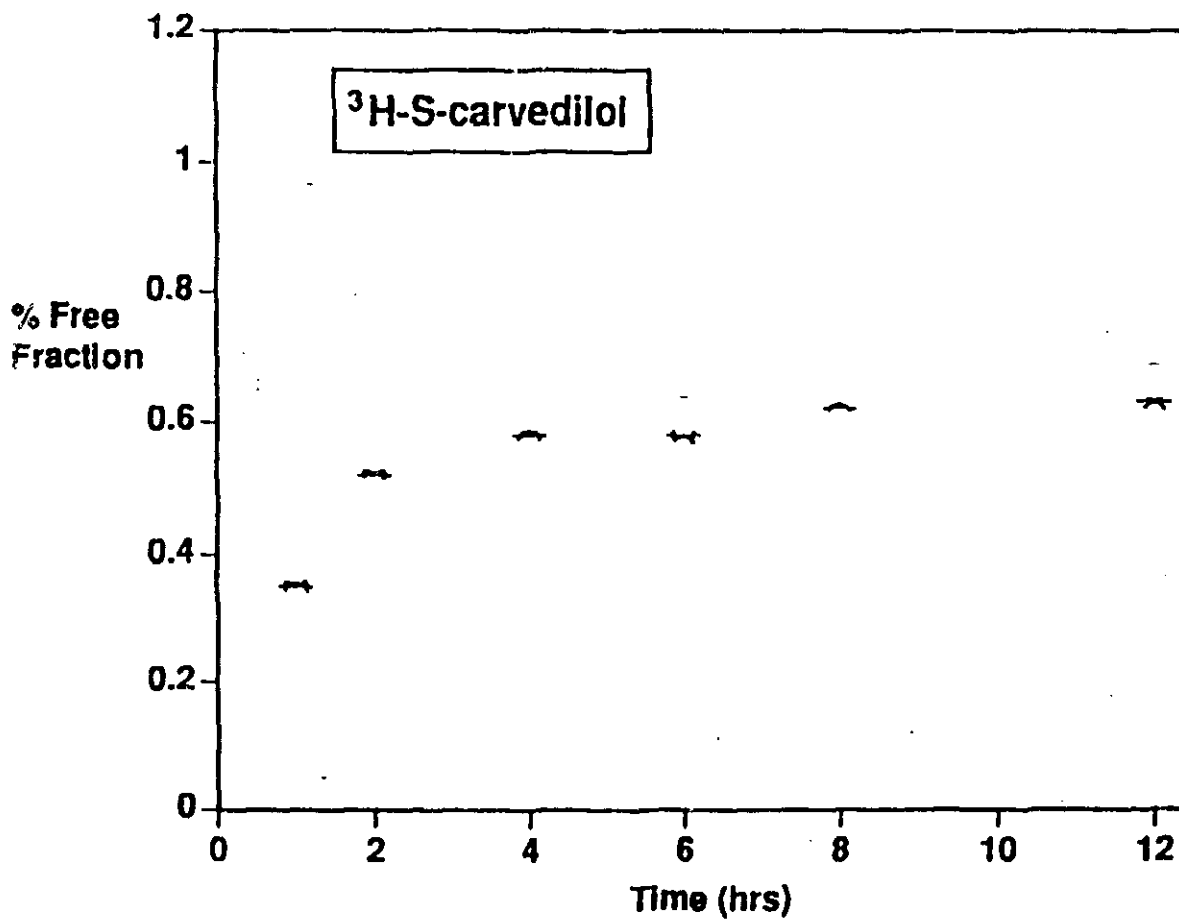
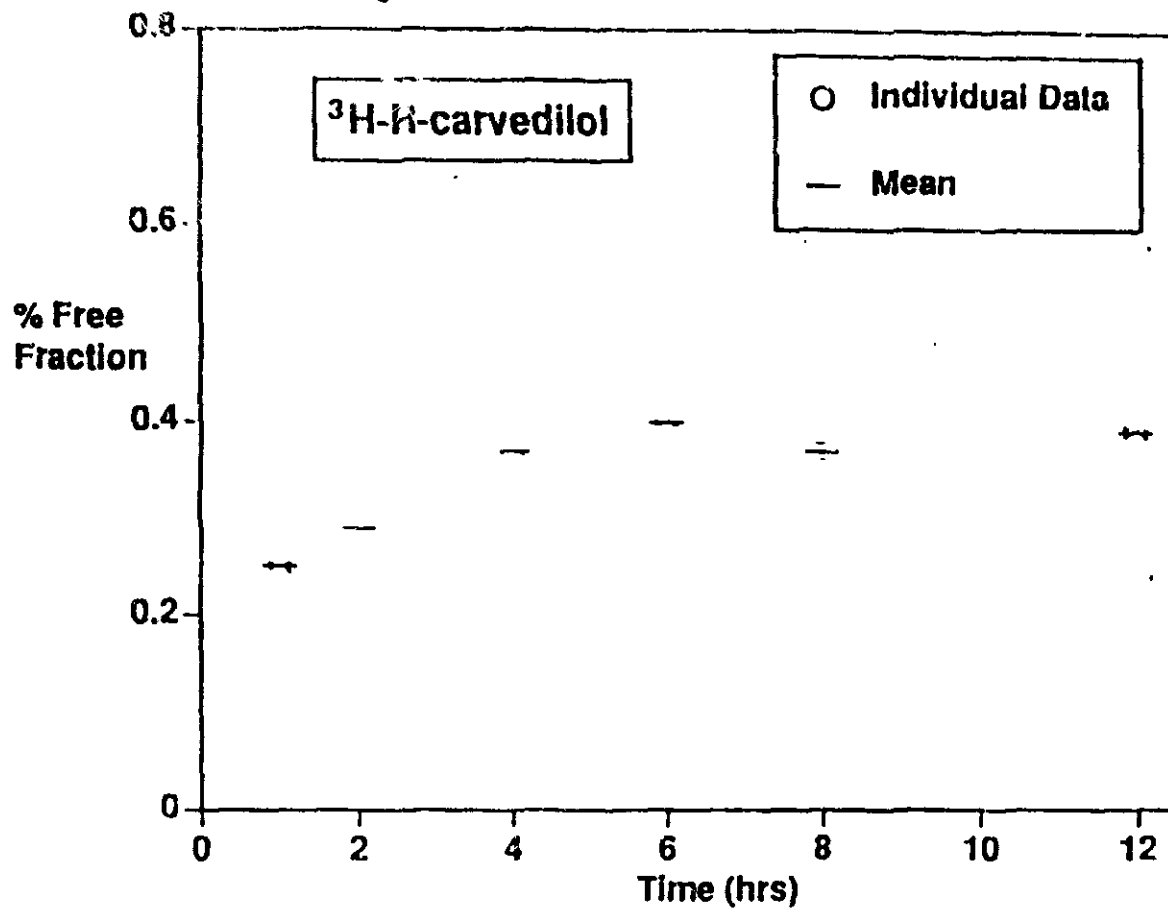


Figure 1. Effect of incubation time on the free (unbound) fraction of $^3\text{H-R}$ or $^3\text{H-S-carvedilol}$ in plasma.

Data points displayed are replicate analyses of pooled heparinized plasma from two subjects.

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Carvedilol Metabolites/Protein Binding

Study: BP-0018/SKF-105517

Volume: 1.55

Page: 57-81

Investigator and Site:

Lee Ann P. Yodis, B.S.

Smith Kline Beecham, Upper Merion

Background: O-desmethyl carvedilol (M2), 4'-hydroxyphenyl carvedilol (M4) and 5'-hydroxyphenyl carvedilol are pharmacologically active metabolites of carvedilol. In human volunteers, these metabolites are observed over a concentration range of 0.3 to 30 ng/ml.

Objectives: To describe the plasma protein binding of the carvedilol metabolites M2, M4 and M5.

Methods

Plasma protein binding of ^3H -M2, ^3H -M4 and ^3H -M5 over a concentration range of 0.3 - 30 ng/ml was carried out by equilibrium dialysis in semi-micro cells at 37°C for 6 hrs. Samples were quantitated by determination of radiochemical content using liquid scintillation counting.

Results

The observed percent free fraction of ^3H -M2 remained constant at a mean value of approximately 1.3% over the concentration range used in this study. Because radiochemical impurities could lead to an overestimation of the free fraction, the contribution of impurities to the estimated free fraction were evaluated by quantitation of the radiochemical species in the dialysate. For ^3H -M2 (approximately 10 ng/ml), impurities represented approximately 17% of the radioactivity in the plasma dialysate suggesting that the actual mean free fraction of ^3H -M2 is approximately 1.0-1.1%. The observed percent free fraction of ^3H -M4 and ^3H -M5 also remained constant over the concentration used in this study but were approximately 3 fold greater than ^3H -M2 at a mean value of 3.3 and 3.4%, respectively. For ^3H -M4 and ^3H -M5 (approximately 10 ng/ml), impurities represented less than 2% of the radioactivity in the plasma dialysate suggesting that the observed free fraction is an appropriate estimate of the actual mean free fraction of ^3H -M4 and ^3H -M5.

Conclusions and Comments: It was demonstrated that the plasma protein binding of the carvedilol metabolites, was linear over concentration range of 0.3 to 30 ng/ml. The mean free fraction of M4 and M5 were 2-3 fold higher than the actual free fraction of M2.

This study is acceptable. However, correction of overestimation of free fraction due to radio-labelled impurities (in case of M2) is not well explained.

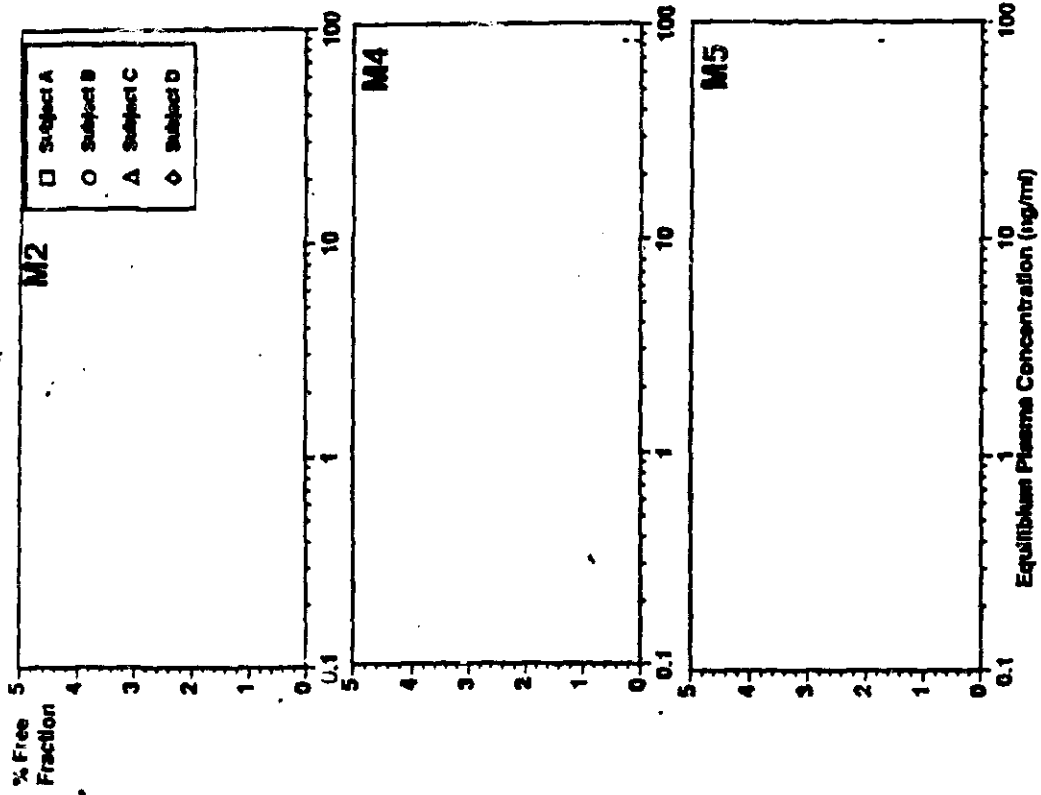


Figure 2. Concentration dependence of the plasma protein binding of ^3H -M2, ^3H -M4 and ^3H -M5 metabolites of SK&F 105517. Data points displayed are analyses of individual blood samples from four normal male volunteers. For actual data see Appendix Table IV-VI.

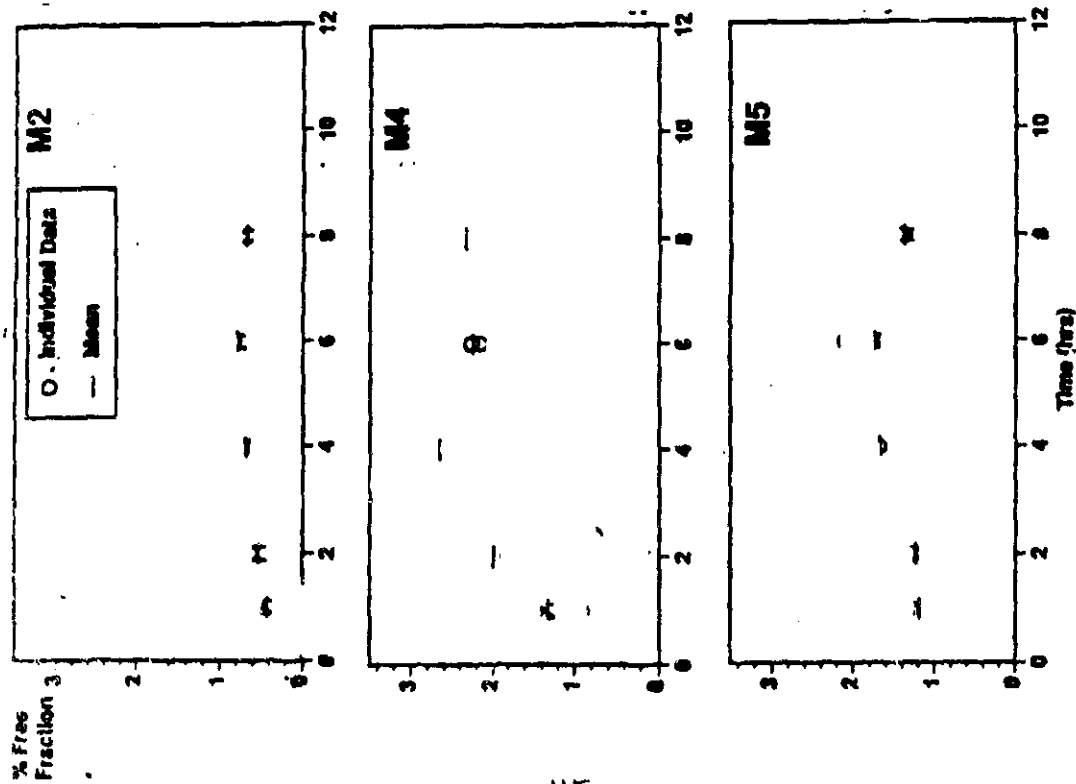


Figure 1. Effect of incubation time on free (unbound) fraction of ^3H -M2, ^3H -M4 and ^3H -M5 metabolites of SK&F 105517. Data points displayed are replicate analyses of blood from pooled heparinized blood from human subjects. For actual data see Appendix Table I-III.

In-Vitro Dissolution

The proposed dissolution method is listed below:

Medium: 900 ml simulated gastric fluid (USP XXII) at 37°C

Apparatus: USP Apparatus II (paddle), 50 rpm

Sampling times: 15, 30, 45, and 60 minutes or as requested

The dissolution samples were analyzed by HPLC using a C-18 column. The detection wavelength was 285 nm. The dissolution was rapid and almost complete at 15 minutes. In-vitro dissolution data for the tablets and capsules used in bio-study (Study 020) and pivotal clinical trials (Studies B100, B101, C1106, C1107 and C1109) are shown in Table 1.

Carvedilol Batches used in Pivotal Clinical Trials and in Bioequivalence Study 020

Dosage Form	Formula	Strength	Batch Lot Number	Protocol Number
Capsule	A	3.125 mg	820-168-40Aa	B101
Capsule	A	3.125 mg	820-354-40Aa	C1106
Capsule	B	6.25 mg	820-169-40Cc	B100, B101, C1106, C1107 -
Capsule	C	12.5mg	820-173-40Lg	B100, B101
Capsule	C	12.5mg	820-468-40Lg	C1106, C1107, C1109 -
Capsule	D	25 mg	820-176-40Lh	B100, B101
Capsule	D	25 mg	820-469-40Lh	C1106, C1107, C1109 -
Capsule	D	25 mg	821-522-40Lh	A9914/020
Tablet	A	25 mg	X205-1CV2	A9914/020

ATTACHMENT 2

Dissolution Profile Data for Biobatch Tablets

Tablet 25 mg						
SD Reference No.	704					
Method Reference No.	DI-105517-F	% Dissolved - (Avg.)				
Lot X205-1CV2	Interval - minutes	0	15	30	45	60
	initial	0	94	94	94	94
SD 704Chart5	12 mo 30°C	0	94	96	96	97

Table 1

Carvedilol Stability Dissolution Profile Data

Capsule 3.125 mg					
SD Reference No.	383				
Method Reference No.	DI-105517-B-0				
Lot 820-354-40Aa	Interval - minutes	0	15	30	45 60
	initial	0	94	97	97 97
SD383/chart1	36 mo 30°C	0	94	98	98 99
Capsule 6.25 mg					
SD Reference No.	355				
Method Reference No.	DI-105517-B				
Lot 820-169-40Cc	Interval - minutes	0	15	30	45 60
	initial	0	97	100	102
SD355Chart2	36 mo 30°C	0	94	97	98
Capsule 12.5 mg					
SD Reference No.	354				
Method Reference No.	DI-105517-A				
Lot 820-173-40Lg	Interval - minutes	0	15	30	45 60
	initial	0	96	102	103
SD354Chart3	48 mo 30°C	0	90	97	98
Capsule 12.5 mg					
SD Reference No.	419				
Method Reference No.	DI-105517-A				
820-468-40Lg	Interval - minutes	0	15	30	45 60
	initial	0	101	100	101
SD419chart6	48 mo 30°C	0	91	104	107
Capsule 25 mg					
SD Reference No.	353				
Method Reference No.	DI-105517-A				
Lot 820-176-40Lh	Interval - minutes	0	15	30	45 60
	initial	0	88	97	96
SD353Chart4	12 mo 30°C	0	88	100	102
Capsule 25 mg					
SD Reference No.	418				
Method Reference No.	DI-105517-A				
Lot 820-469-40Lh	Interval - minutes	0	15	30	45 60
	initial	0	82	91	93
SD418chart7	48 mo 30°C	0	79	93	99
Capsule 25 mg					
SD Reference No.	NP				
Method Reference No.	DI-105517-F				
Lot 821-522-40Lh	Interval- minutes	0	15	30	45 60
		0	96	102	102 102
chart8					

MAY 19 1995

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

KREDEX® TABLETS

(Carvedilol)

12.5 and 25 mg

NDA 20-297

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

(HFD-110)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-297

Kredex® Tablets

(Carvedilol)

The Food and Drug Administration (FDA) recognizes the National Environmental Policy Act of 1969 (NEPA) as the national charter for protection, restoration, and enhancement of the environment. NEPA establishes policy, sets goals (section 101), and provides procedures (section 102) for carrying out the policy.

Environmental information is to be available to the public and the decisionmaker before decisions are made about actions that may significantly affect the quality of the human environment; FDA actions are to be supported by accurate scientific analyses; and environmental documents are to concentrate on timely and significant issues, not to amass needless detail.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for **Kredex® Tablets**, **SmithKline Beecham Pharmaceuticals** has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Carvedilol is administered as an oral tablet in the treatment of essential hypertension. Drug substance intermediates are manufactured by Boehringer Mannheim GmbH, Mannheim, Germany. The drug substance will be manufactured at SmithKline Beecham (Manufacturing) Limited, County Cork, Ireland and the drug product will be manufactured and packaged at SmithKline Beecham Pharmaceuticals Co., Cidra, Puerto Rico. The finished drug product will be used in hospitals, clinics and by patients in their homes.

Chemical and physical test results and information indicate that carvedilol will most likely be restricted to the aquatic and terrestrial environments. A substantial amount of the drug will be removed from the aquatic environment as the compound will adsorb to sludge in waste water treatment plants. The compound degrades rapidly upon exposure to light although this will vary depending on the exposure conditions in the environment and it is also susceptible to aerobic biodegradation. As the compound is expected to persist in the environment for some time, acute toxicity studies were conducted using water fleas (*Daphnia pulex*) and bluegill sunfish (*Lepomis macrochirus*). The studies indicate that the drug would not be expected to exhibit acute toxicity effects to aquatic organisms at concentrations expected to be emitted into and exist in the environment. Carvedilol may enter the terrestrial environment from sludge that is applied to land and will remain tightly bound to soil. The material is not expected to persist in the soil compartment and toxicity to terrestrial organisms is expected to be less than that determined for aquatic organisms due to the decreased exposure pathways.

Microbial inhibition studies indicate that respiration in activated sludge is not inhibited at concentrations several orders of magnitude greater than the maximum expected environmental concentration (MEEC).

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, pharmaceutical processing waste, and user disposal of empty or partly used product and packaging. Waste drug product and pharmaceutical processing waste will be disposed of predominantly at licensed incineration facilities although small quantities may be emitted in effluent waste streams. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system while some unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. A certification has been provided by the German authorities stating that Boehringer Mannheim GmbH is operating in compliance with their environmental laws and regulations.

Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

5/19/95 *[Signature]*
DATE Prepared by
Philip D. Cager
Review Chemist
Center for Drug Evaluation and Research

[Signature]
DATE Approved
Philip C. Vincent, Ph.D.
Technical Assessment Officer
Center for Drug Evaluation and Research

[Signature]
DATE Approved
Thomas A. Jerussi, Ph.D.
Associate Director for Chemistry
Center for Drug Evaluation and Research

Attachments:

- I: Environmental Assessment
- II: Compliance Statements
- III: Compliance Table
- IV: Environmental Safety Data Sheet

CC: Original NDA 20-297/ZMcDonald copy to NDA/HFD-110
FONSI File 20-297/HFD-004
P. Vincent/HFD-004
Docket File 20-387/HFD-004
FOI Copy/HFD-019

20297.FON
F/T by NBS 05/19/1995

ATTACHMENT I

ENVIRONMENTAL ASSESSMENT INFORMATION

Carvedilol

1. DATE: March 17, 1995
2. NAME OF APPLICANT: SmithKline Beecham Pharmaceuticals
3. ADDRESS: Four Falls Corporate Center
Route 23 and Woodmont Avenue
P.O. Box 1510
King of Prussia, PA 19406

4. DESCRIPTION OF THE PROPOSED ACTION:

4.1 Description of the Requested Approval

SmithKline Beecham Pharmaceuticals is requesting approval for use of carvedilol for the treatment of essential hypertension. β -blocking and vasodilator effects occur in the same dosage range; carvedilol thus offers two active mechanisms of value in the management of hypertension. Carvedilol may also be effective in the management of other cardiovascular disorders, such as angina pectoris and/or left ventricular dysfunction.

4.2 Need for the Proposed Action

Carvedilol is a non-selective β -receptor blocking agent with vasodilative properties. It reduces peripheral vascular resistance through vasodilation and suppresses the renin-angiotensin-aldosterone system through β -blockage. Through these effects, carvedilol significantly reduces blood pressure in hypertensive patients. Carvedilol has no intrinsic sympathomimetic activity. By balancing vasodilation and β -adrenoreceptor blockage, carvedilol maintains myocardial function without affecting left ventricular ejection fraction. It causes no significant decrease in heart rate. The multiple actions of carvedilol are responsible for the antihypertensive efficacy of the drug in animals and in humans, and may also provide effective therapy in angina and congestive heart failure.

This Environmental Assessment Information reflects effluent discharges based on estimated fifth year production of drug substance and product, as well as detailed information on the waste treatment and disposal processes at SmithKline Beecham Pharmaceuticals facilities at Cork, Ireland, (drug substance production), and Cidra, Puerto Rico (drug product production), as well as summary information on the production of key drug intermediates at the Boehringer Mannheim facility in Mannheim, Germany (drug intermediate production). Details on the Boehringer Mannheim facility are available in DMF 9502. This report also includes all of the fate and effects data and evaluations which are currently available for carvedilol drug substance.

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ENVIRONMENTAL ASSESSMENT INFORMATION

Carvedilol

The manufacture of carvedilol substance and product will employ the same environments and utilize existing plants that are also currently manufacturing other pharmaceutical products.

4.3 Location where Product will be Produced

Carvedilol drug intermediates, used to produce the product that is the subject of the proposed action, are manufactured at the following facility:

Boehringer Mannheim GmbH
Sandhofer Strasse 116
Postfach 310120
D-6800 Mannheim 31
Federal Republic of Germany

The Boehringer Mannheim facilities used to produce these intermediates are located in Mannheim, Germany.

Carvedilol, the drug substance in the product which is the subject of the proposed action, is manufactured (stages 4-8) at the following facility:

SmithKline Beecham (Manufacturing) Limited
Currabinny, Carrigaline
County Cork
Ireland

SmithKline Beecham (Manufacturing) Limited is located approximately twelve miles south of Cork City on the southern shores of Cork Harbor. There is a total land bank of 130 acres, but the facility occupies only 28 acres. The immediate area is rural, with some farms and dwellings within a half mile radius of the boundary fence. The site discharges an aqueous waste into Cork Harbor after on-site biological treatment.

Carvedilol drug product will be prepared at the following facility:

SmithKline Beecham Pharmaceuticals Co.
Road 172
KM9.1/Bo Certenejas
Cidra, Puerto Rico 00739

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ENVIRONMENTAL ASSESSMENT INFORMATION

Carvedilol

The Cidra facility for the drug product manufacture is a site of approximately 52 acres located in an agricultural/urban/industrial area on the central mountainous ridge of the island of Puerto Rico.

4.4 Locations where Product will be Used

Carvedilol drug product will be used in the United States of America (the subject of this NDA) and world-wide, with predominant use coinciding with areas of greatest population density.

4.5 Locations where Product will be Disposed of

Carvedilol drug product returned goods will be collected at the following site:

Division KENCO Group Inc.
1704 Mid Park Drive
Knoxville, Tennessee 37291

From this site, the materials will be shipped to one or more of the following licensed facility for destruction by high temperature incineration:

SmithKline Beecham Pharmaceuticals
Bristol Industrial Park
Weaver Pike
Bristol, Tennessee 37620

Ogden Martin Systems of Lake, Inc.
3830 Rogers Industrial Park Road
Okahumpka, Florida 34762

Documentation for these disposal facilities is provided in Appendix I.

5. DESCRIPTION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION:

5.1 Complete Nomenclature

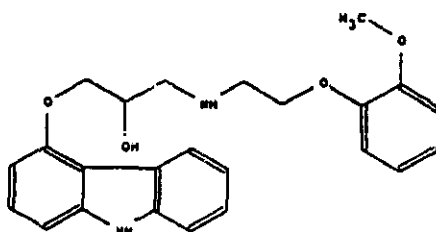
British Adopted Name (BAN):	Carvedilol
INN:	Carvedilol
United States Adopted Name (USAN):	Carvedilol

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ENVIRONMENTAL ASSESSMENT INFORMATION

Carvedilol

Trade Name:	
Chemical Name:	(±)-1-(9H-carbazol-4-yloxy)-3-[(2-(2-methoxy-phenoxy)-ethyl)amino]-2-propanol
5.2 <u>CAS Number:</u>	72956-09-3
5.3 <u>Laboratory Codes:</u>	SK&F 105517; BM 14.190
5.4 <u>Molecular Formula:</u>	C ₂₄ H ₂₆ N ₂ O ₄
5.5 <u>Molecular Weight:</u>	406.5
5.6 <u>Structural Formula:</u>	



5.7 <u>Description:</u>	A white to off-white powder
5.8 <u>Melting Range:</u>	SK&F 105517 typically melts over a 2-3°C range within 113-119°C
5.9 <u>Additives:</u>	Not applicable
5.10 <u>Impurities:</u>	

Organic impurities arising from the synthesis are determined by GC and HPLC. Solvent content is also measured by GC and the inorganic impurities, heavy metals, and sulfated ash are also monitored. Identification is included on the drug substance specification. The compound is stable, and no degradants are likely to arise under normal conditions.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

6.1 Introduction from Production

The production of carvedilol drug substance, intermediates and drug product will utilize the same facilities currently being used for the production of other pharmaceutical products. The following evaluation of the anticipated environmental impact of carvedilol production is based on estimated fifth year production and on existing waste treatment systems at the production facilities. Engineering estimates are used to predict anticipated discharge levels; however, the evaluations do not reflect changes in treatment process operations or technology which might be implemented before actual approval of the carvedilol application.

This Environmental Assessment contains non-confidential information on the control and disposition of gaseous, aqueous, and solid wastes at the production facilities.

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ENVIRONMENTAL ASSESSMENT INFORMATION

Carvedilol

6.1.1 Drug Intermediate Production at Boehringer

The Boehringer Mannheim facilities used to produce the intermediates (2) are located in Mannheim, Germany. One intermediate will be produced at Production Plant HC-B 21, and the second intermediate will be produced at Production Plants HC-B 4, HC-B 10 and HC-B/OB.

6.1.1.1 Introduction from Production of Drug Intermediate at HC-B 21

The following information was provided by Boehringer Mannheim GmbH regarding the introduction of substances into the environment from production of intermediate at Production Plant HC-B 21.

6.1.1.1.1 Emissions as Part of Waste Water

The substances described in the following table are expected to be emitted as part of the wastewater. This wastewater is discharged from the production plants, pretreated in the BM waste water purification plant and then discharged into the community wastewater system/sewage plant, where final treatment takes place.

Substance ^a	CAS Number
Sodium chloride	7647-14-5
Toluene	108-88-3
Organic By-products	NA

^a Substances expected to be emitted during each process step.

6.1.1.1.2 Solid/Liquid Wastes

No other solid or liquid wastes are produced during the production steps of the intermediate.

6.1.1.2 Emissions Requirements at the Boehringer Mannheim Plant

Boehringer Mannheim GmbH reached an agreement on pollution control with Mannheim in the state of Baden-Wurtemberg, where its plant is located. This agreement requires Boehringer Mannheim GmbH to comply with the regulations for environmental protection enacted by the German Federal Government.

6.1.1.2.1 Emission Requirements for Sewage into the Municipal Wastewater System

The following table summarizes the maximum wastewater permit levels established by the government.

ENVIRONMENTAL ASSESSMENT INFORMATION

Carvedilol

Parameter	Value
pH	6.0 - 9.5
Temperature	max. 35°C
COD	700 mg/L
Ratio COD/BOD	< 2.5 :1
Settling substances (solvents)	1 mL/30 minutes
Sulfate (SO ₄)	400 mg/L
Sulfide (S)	10 mg/L
Sulfite (SO ₃)	50 mg/L
Fluoride	50 mg/L
Phenols	20 mg/L
Aromatic Hydrocarbons	30 mg/L
Ammonia as NH ₄	100 mg/L
AOX	0.5 mg/L
Organic solvents miscible with water	3000 mg/L
Organic solvents not miscible with water	According to solubility in water
Cu	1 mg/L
Fe	20 mg/L
Cr (III)	3 mg/L
Cr (VI)	0.1 mg/L
Zn	3 mg/L

6.1.1.2.2 Emission Requirements on Waste Gases

The following table summarizes the permit levels for waste gas emissions, according to the "Technical Directions for Maintaining Clean Air" (TA Luft).

Emission	Value
Ethylene oxide	≤ 5 mg/m ³
Toluene	0.15 g/Nm ³

If more than one substance in the waste gas is classified as carcinogenic III, the total concentration is not allowed to exceed 5 mg/m³ at a mass flow of 25 grams (or more) per hour. If there is more than one organic substance (vapor) in the waste gas, the total concentration is not allowed to exceed 0.15 g/Nm³ at a mass flow of 3 kg (or more) per hour.

ENVIRONMENTAL ASSESSMENT INFORMATION

Carvedilol

Manufacture of the intermediate in the Boehringer Mannheim plant (HC-B 21) will not result in the discharge of any emissions in excess of the amounts allowed by the applicable laws. A citation of and statement of compliance with applicable emissions requirements is provided in Appendix II. In addition, a certification of compliance signed by the appropriate government authority (Regierungsprasidium Karlsruhe) is also included in Appendix II.

6.1.2 Drug Intermediate Production at Boehringer

6.1.2.1 Introduction from Production of Drug Intermediate at HC-B 4, HC-B 10, and HC-B/OB

The following information was provided by Boehringer Mannheim GmbH regarding the introduction of substances into the environment from production of intermediate at Production Plants HC-B 4, HC-B 10 and HC-B/OB.

6.1.2.1.1 Emissions as Part of Wastewater

The substances described in the following table are expected to be emitted as part of the wastewater. This wastewater is discharged from the production plants, pretreated in the BM wastewater purification plant and then discharged into the community wastewater system/sewage plant, where final treatment takes place.

Substance	CAS Number
Acetic acid	64-19-7
Methanol	67-56-1
Organic By-products	NA
Intermediates	NA
Phosphoric acid	7664-38-2
Ethanol	64-17-5
Potassium chloride	7447-40-7

6.1.2.1.2 Solid/Liquid Wastes

The substances listed in the following table are produced as liquid or solid wastes. Solid wastes are disposed of through incineration at a community plant, and liquid wastes are disposed of through incineration at an outside company licensed to dispose of industrial waste products.

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Substance	CAS Number
Resin by-products dissolved in solvent	NA
Activated carbon	7440-44-0
Filter aid	NA
Waste solvents	NA
Alumina	1344-28-1
Solvent/Oil mixture (residue of distillation)	NA

6.1.2.2 Emissions Requirements at the Boehringer Mannheim Plant

Boehringer Mannheim GmbH reached an agreement on pollution control with Mannheim in the state of Baden-Wurtemberg, where its plant is located. This agreement requires Boehringer Mannheim GmbH to comply with the regulations for environmental protection enacted by the German Federal Government.

6.1.2.2.1 Emission Requirements for Sewage into the Municipal Wastewater System

The following table summarizes the wastewater permit levels required by the government.

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Parameter	Value
pH	6.0 - 9.5
Temperature	max. 35°C
COD	700 mg/L
Ratio COD/BOD	< 2.5 :1
Settling substances (solvents)	1 mL/30 minutes
Sulfate (SO ₄)	400 mg/L
Sulfide (S)	10 mg/L
Sulfite (SO ₃)	50 mg/L
Fluoride	50 mg/L
Phenols	20 mg/L
Aromatic Hydrocarbons	30 mg/L
Ammonia as NH ₄	100 mg/L
AOX	0.5 mg/L
Organic solvents miscible with water	3000 mg/L
Organic solvents not miscible with water	According solubility in water
Cu	1 mg/L
Fe	20 mg/L
Cr (III)	3 mg/L
Cr (VI)	0.1 mg/L
Zn	3 mg/L

6.1.2.2.2 Emission Requirements on Waste Gases

The following table summarizes the permit levels for waste gas emissions, according to the "Technical Directions for Maintaining Clean Air" (TA Luft).

Emission	Value
Ethanol	0.15 mg/m ³
Diisopropylether	0.15 g/Nm ³

If more than one of the substances listed in the table above is found in the waste gas, the total concentration is not allowed to exceed 0.15 g/Nm³ at a mass flow of 3 kg (or more) per hour.

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Manufacture of the intermediate in the Boehringer Mannheim plant (HC-B 4, HC-B 10 and HC-B/OB) will not result in the discharge of any pollutants in excess of the amounts allowed by the applicable laws. A citation of and statement of compliance with applicable emissions requirements is provided in Appendix III. In addition, a certification of compliance signed by the appropriate government authority (Regierungsprasidium Karlsruhe) is also included in Appendix III.

6.1.3 Drug Substance Production at Cork

Carvedilol (SK&F 105517) drug substance process stages 4-8 will be performed at SmithKline Beecham (Manufacturing) Limited, a SmithKline Beecham Pharmaceuticals' facility in Cork, Ireland. Environmental evaluations of the impacts from drug substance production at Cork follow.

SmithKline Beecham (Manufacturing) Limited, Cork, Ireland is expected to remain in compliance with applicable waste effluent permits throughout the production of carvedilol drug substance. The Cork facility is regulated under an Integrated Pollution Control (IPC) license (Reference Number in Register of Licenses: 4; Date of Notification: October 28, 1994), under authority of the Environmental Protection Agency and the Environmental Protection Agency Act, 1992. This license contains permit levels and monitoring procedures for all plant emissions (wastewater, air, incinerators, etc.), as well as guidelines for the establishment of an Environment Management Programme, to assess all operations for the use of cleaner technology and the minimization of waste.

6.1.3.1 Waste Stream Summary and Disposition

The types of waste streams generated at SmithKline Beecham (Manufacturing) Limited will be disposed of such that release into the environment (gaseous and aqueous waste) will not exceed SmithKline Beecham (Manufacturing) Limited' plant permit levels (Appendix III).

6.1.3.2 Material Balance

Material balance information for the chemical inputs, process intermediates and effluents was determined for stages 4-8, thus accounting for all materials and amounts used in or produced by these stages. Waste outputs include leftover material resulting from production, inspection operations, assay solutions sampled before and after filtration, and floor and equipment washings.

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6.1.3.3 Controls Exercised on Wastes

6.1.3.3.1 Air and Fugitive Emissions

Hydrogen, the only off-gas produced, is vented directly to the atmosphere through a flame arrestor. Fugitive emissions are monitored if there is reason to suspect a gaseous leak. Air from the buildings where chemical processes are performed is filtered through two chemical absorbers. Air is automatically monitored every half hour by gas chromatography for several compounds, depending on the processes being performed, as it is discharged to the atmosphere.

6.1.3.3.2 Incinerated Wastes

Most process waste streams produced during carvedilol production at SmithKline Beecham (Manufacturing) Limited are incinerated at 1000°C. Process effluents are stored prior to incineration, and approximately 200 L of waste per hour are burned in each of two incinerators. After incineration, the effluent gas is passed through an absorber for the scrubbing of acidic compounds before discharge to the environment through a stack. This scrubber unit consists of a caustic solution circulating through a packed bed. Scrubber liquors are sent to the on-site wastewater treatment facility.

At discharge, incinerator gases are continuously monitored for carbon monoxide, sulphur dioxide and total organic carbon (TOC). The amount of organic material remaining after incineration is calculated using a 99.99% incineration destruction efficiency, based upon the known removal efficiencies for mercaptan and methylethyl ketone (MEK). The Cork facility is regulated under an Integrated Pollution Control (IPC) license (Reference Number in Register of Licenses: 4; Date of Notification: October 28, 1994), under authority of the Environmental Protection Agency and the Environmental Protection Agency Act, 1992.

6.1.3.3.3 Biotreatment System

Several of the carvedilol process wastestreams are treated in the on-site wastewater biotreatment facility. Scrubber liquors from the incinerators are sent for aerobic biological treatment before being discharged.

The treatment facility incorporates a basin of activated sludge, which has a retention time of 10 days. The biotreated waste (including domestic effluents and mutrators, floor washes, incinerator quench streams, and scrubber and environmental spent liquors) is sent to a balancing tank prior to neutralization in a second tank. The wastes are then sent to a stripping tank, prior to passing to an aeration tank to reduce biological oxygen demand (BOD). After aeration, some of the waste is aerated a second time in another tank, while the remaining waste is sent to a clarifier. The twice-aerated effluent is passed to another

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clarifier. Both clarifiers are dosed with polyelectrolytes, and effluent wastes are sent to the final holding tank prior to discharge.

Several parameters of the effluent are monitored on a daily basis at three stages of the treatment process. The flow rate, pH, COD, total dissolved solids and load (kg of COD per day) are monitored at the input stage, and the pH, dissolved oxygen, MLSS and F/M are monitored at the sludge plant. At the final holding tank, the pH, COD, suspended solids, ammonia and flow rate are also monitored. In addition to normal testing, effluent liquors are sampled if a problem (e.g., equipment malfunction) is discovered.

Treatment of effluents results in >80% reduction in BOD. Review of the measured (confidential) and calculated concentrations of affected aqueous effluent components and a comparison with their permit levels resulted in the determination that the SmithKline Beecham (Manufacturing) Limited facility is in compliance with their aqueous effluent permits.

6.1.3.3.4 Solid Waste

Solid wastes produced during Cork carvedilol substance production process are sent off-site for disposal.

All treatment plant sludge is mechanically dewatered to approximately 15% solids prior to off-site disposal, with the extracted liquid returned to the effluent treatment plant. The Cork facility is regulated under an Integrated Pollution Control (IPC) license (Reference Number in Register of Licenses: 4; Date of Notification: October 28, 1994), under authority of the Environmental Protection Agency and the Environmental Protection Agency Act, 1992. Wastes and leachate will be tested for the presence of heavy metals, organohalogens and other micropollutants; solid waste regarded as non-hazardous will then be disposed of in a lined landfill designated for non-hazardous materials, with leachate monitoring. There are currently no limits as to the amount of solid wastes disposed of off-site.

6.1.3.4 Certification of Compliance

SmithKline Beecham Pharmaceuticals Co. (SmithKline Beecham (Manufacturing) Limited) is committed to environmental control and will operate within its permit during the production of carvedilol drug substance. A citation of and statement of compliance with applicable emissions requirements is provided in Appendix III.

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6.1.4 Introduction from Production of Drug Product

Carvedilol (SK&F 105517) drug product will be produced in a continuous process, consisting of granulation, drying and blending, compression and coating, and printing and packaging at SmithKline Beecham Pharmaceuticals Co. in Cidra, Puerto Rico. The manufacture of carvedilol will employ the same environment and utilize the existing plants that are currently used to manufacture other pharmaceutical products. Carvedilol will be prepared as 12.5 and 25 mg tablets. Environmental evaluations of the impacts from drug product production follow.

6.1.4.1 Waste Stream Summary and Disposition

The waste streams generated at the Cidra facility will be disposed of using appropriate procedures, such that release into the environment (gaseous and aqueous waste) will not exceed Cidra permit levels (Appendix IV) and off-site disposal of solid wastes will not violate applicable regulations.

6.1.4.2 Material Balance

Material balance information for the chemical inputs, process intermediates and effluents was determined, thus accounting for all materials and amounts used in or produced during the drug product process. Waste outputs include leftover material resulting from production, inspection operations (rejects are discarded), assay solutions sampled before and after filtration, and floor and equipment washings.

For the purposes of this evaluation, the production campaign is assumed to use all of the drug substance, which is based on the projected fifth year of carvedilol production for the U.S. Market.

6.1.4.3 Controls Exercised on Wastes

6.1.4.3.1 Dryer Water Vapor

Two waste streams consist of water evaporated during drying processes. These streams are filtered before venting to the environment and should contain no hydrocarbons or particulates. The water collected is sent to the on-site wastewater treatment facility for biotreatment.

Air emissions from the process fall under the State Rules and Regulations for Air Pollution Control. The regulations are administered by the Environmental Quality Board of the Commonwealth of Puerto Rico. Currently, the facility is operating under Permit No. PFE-21-

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0590-0477-I-III-0 and PFE-21-1089-0929-I-II-III-0, and is not considered to be a major pollutant source; thus, a PSD review (under the EPA program) will not be necessary.

6.1.4.3.2 Solvent Vapor

The incinerator at the Cidra facility is expected to burn only four solvent vapors, none of which are produced during the carvedilol production process. The scrubber blowdown liquors from the incinerator are sent to the SmithKline Beecham Pharmaceuticals Co. facility in Guayama, Puerto Rico for treatment and disposal.

6.1.4.3.3 Aqueous Wastes Disposed Of Through Biotreatment

The aqueous waste streams (1-4) are sent to the wastewater treatment facility. The streams are first pumped through a series of sand filters and an activated carbon adsorption system. The waste streams are then discharged into an equalization holding tank for aeration. Sanitary waste bypasses sand and carbon columns and goes directly to the equalization basin. The pH of the influent stream is adjusted with sodium hydroxide or carbon dioxide prior to entering the activated sludge system. The residence time of effluent in the activated sludge basin is 24 hours, and the average volume maintained is 80,000 gallons. The treatment facility is designed for a 85,000 gallon per day flow, with a maximum capacity of 127,000 gallons per day. The biotreatment waste stream then enters a clarifier, where the sludge is allowed to settle and separate from the biotreated aqueous effluent as supernatant.

The pH of the aqueous effluent is adjusted to 11.0 with hydrated lime and sent to a second clarifier, where solids are precipitated out of solution and removed by flocculation. The clarifier's precipitated solids are sent to the aerobic digester for further processing. The wastewater effluent is recarbonated and neutralized with carbon dioxide prior to passing through a second series of sand and carbon filters. Filtered effluent is collected in a filter effluent sump. This filtered effluent then passes through a Reverse Osmosis (RO) module for total dissolved solids and organic removal. Reverse Osmosis (RO) Permeate is collected in a 100,000 gallon effluent storage tank and Reverse Osmosis (RO) reject is disposed off to PRASA (Permit Number GDC-94-505-032). A copy of the permit is attached in Appendix V. The effluent is then chlorinated, aerated and monitored for pH, temperature and dissolved oxygen before entering Quebrada Las Quebradillas (Las Quebradillas Creek). After aeration in the biotreatment facility, 55,000 gallons per day of final effluent is recycled to cooling and quench towers and 25,000 gallons per day of final effluent is discharged. Rainwater runoff from the grounds of the Cidra facility are also discharged to this creek, which empties into the Turabo River and flows into Carraizo Lake (the water source for the metropolitan area of San Juan).

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For the purpose of this environmental assessment, the total quantity of drug product components expected to be emitted into the site biotreatment facility is estimated at 3% of the total batch.

Final effluent levels from biotreatment were calculated using the following equation:

$$(A \times 10^6 \text{ mg/kg} / B/C)D = E$$

where: A = total quantity of component to waste per day (kg/day);
B = number of days over which discharge is made (1);
C = site effluent discharge rate (240,175 L/day);
D = removal efficiency;
E = concentration of component in effluent in mg/L.

For developing the discharge level data, it is assumed that no volatilization or bioadsorption of these materials occurs during treatment, and that biodegradation is the only operative removal mechanism for some of the effluent compounds. Review of the measured (confidential) and calculated concentrations of affected aqueous effluent components and a comparison with their permit levels resulted in the determination that the Cidra facility is in compliance with their aqueous effluent permits.

The contributions of the compounds used in the tablet formulation of carvedilol (SK&F 105517) to the total quantity of regulated components in the effluent will not cause total effluent concentrations to exceed the permit levels, assuming complete removal of carvedilol by the wastewater treatment facility. The quality of the effluent discharge meets Puerto Rico's water quality standards. The treatment facility operates under National Pollutant Discharge Elimination System (NPDES) Permit PR 0021997. In Puerto Rico, the NPDES Permit Program is administered by the Federal Environmental Protection Agency.

The facility is also regulated by the Puerto Rico Water Pollution Law, which is administered by the Assistant Secretary of Health for Environmental Health and Consumer Protection. Additional regulations are the Puerto Rico Harmful Soils Law, the Puerto Rico Public Policy Environmental Act, and the Puerto Rico Water Quality Standards, each administered by the Board of Environmental Quality. Permit limits for the wastewater discharge are stated in the NPDES permit. The discharge limits are presented in Appendix IV.

6.1.4.3.4 Solid Wastes

The activated carbon (granular Calgon AC, 8 X 30 mesh) from the biotreatment filters is replaced every three months. Settled sludge from the first clarifier in the biotreatment process is divided into two streams: sludge waste to an aerobic digester and sludge returned to the system. Within the digester the sludge waste is concentrated by settling and decanting the water. More water is then removed from the concentrated sludge slurry

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by means of a wedge filtration system and solar drying beds. The decanted water is recycled back to the feed of the wastewater treatment system. Sludge is maintained in the drying beds at a depth of two feet, and the waste volume is reduced by at least 92% during the drying period of two weeks. The dried sludge, and the spent carbon are disposed of as non-hazardous material at a municipal landfill, after testing using the Toxicity Characteristic Leaching Procedure (TCLP). Other solid wastes containing drug product (rejects, protective clothing, drums, filters, collected dust) are disposed of off-site to Ogden Martin Systems of Lake, Inc., Okahumpka, Florida, US (see Appendix I). There are no limits or restrictions placed on the quantities of materials that may be sent to the licensed disposal facilities.

6.1.4.4 Environmental Legislation

The following partial list of federal legislation may affect operation of the wastewater treatment facility.

- Federal Water Pollution Control Act, as amended
- Clean Water Act, as amended
- Resource Conservation and Recovery Act
- Safe Drinking Water Act
- Toxic Substances Control Act
- National Environmental Policy Act

6.1.4.5 Safety

The Cidra facility has adopted personnel safety procedures in all areas of plant activity, including procedures and information on electrical hazards, tool use, fire hazards, chemical handling and first aid.

6.1.4.6 Certification of Compliance

SmithKline Beecham Pharmaceuticals Co., Cidra, Puerto Rico, will operate within its permits during the production of carvedilol drug product. A citation of and statement of compliance with applicable emissions requirements is provided in Appendix IV.

6.2 Introduction from Use of Drug Product

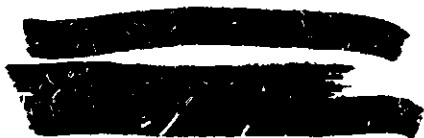
Estimates of the maximum expected emitted concentrations (MEEC) from use of carvedilol tablets were calculated in part using data from reference [1]. At concentrations expected to be emitted into and exist in the environment, carvedilol is expected to exhibit no toxicity to aquatic organisms.

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6.3 Introduction from Disposal of Drug Product

Carvedilol drug product returned goods will be collected at the following site:



From this site, the materials will be shipped to the following licensed facilities for disposal (e.g., destruction by high temperature incineration).

SmithKline Beecham Pharmaceuticals
Bristol Industrial Park
Weaver Pike
Bristol, Tennessee 37620



Documentation for these disposal facilities is provided in Appendix 1. Based on the controlled and highly efficient thermal destruction of unused drug substance and product, no material should be introduced into the environment from disposal.

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

7.1 Metab m

The biotransformation and excretion of carvedilol in normal male human volunteers following single oral administration of ¹⁴C-carvedilol was investigated [2]. Radiometabolites in both feces and urine were separated, quantified, and characterized structurally using a combination of HPLC and mass spectral techniques. The majority of the radiolabeled dose was found to be excreted in the feces (52%), with a lesser amount excreted in the urine (20%). The carvedilol-related products observed in the feces in this study included unchanged carvedilol and several oxidation products. Carvedilol-related products identified in feces represented 71% of the fecal radioactivity, with all of the products each accounting for more than 6.4% of the fecal radioactivity characterized.

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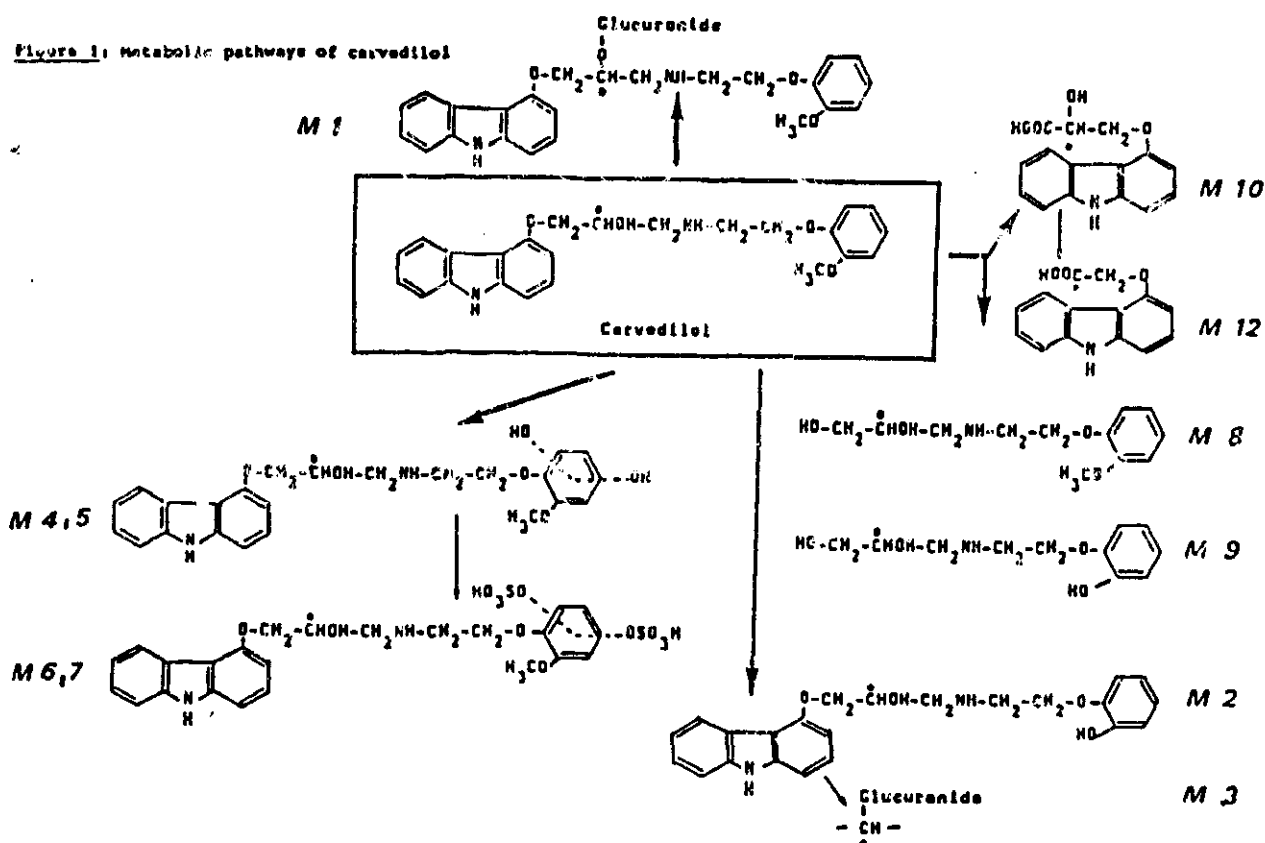
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The profile of urinary metabolites was much more complex, containing more than 26 compounds. The most abundant urinary metabolites were glucuronide derivatives of carvedilol. While the majority of the carvedilol metabolites excreted in feces were products of oxidation pathways, urinary metabolites included products of both oxidation and conjugation pathways. In general, all of the major metabolites structurally related to carvedilol are more polar analogs, and for the purposes of this environmental assessment, assessment of the fate and effects of carvedilol itself may be taken to represent a worst-case scenario.

The reported percent of an administered radioactive dose (range) recovered in the urine and feces is 15.29% - 20.00% and 52.12% - 61.40% respectively [31, 32]. The percent dose representing drug substance which was excreted unmetabolized was 0.21% - 0.28% for urine and 8.39% - 9.89% for feces [32].

A summary of the fecal, urinary and plasma metabolites of carvedilol in male human subjects is presented in Figure 1.

Figure 1



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7.2 Physical Properties

Physical properties were determined for carvedilol in-house, at the Environmental Research Laboratory. Several detailed reports are given in Appendix VI and summarized below.

7.2.1 Water Solubility

The water solubility of carvedilol as a function of pH was determined at 25°C. The results are given below and detailed in reference [3].

pH	Water Solubility (mg/L)			95% Confidence Range	
	mean	stdev	%RSD	low	high
5.04	434	46.3	10.7	416	452
7.09	30.8	3.66	11.9	29.4	32.2
9.04	1.61	0.356	22.1	1.46	1.76
8.43(DI H ₂ O)	5.46	1.88	34.3	4.72	6.20

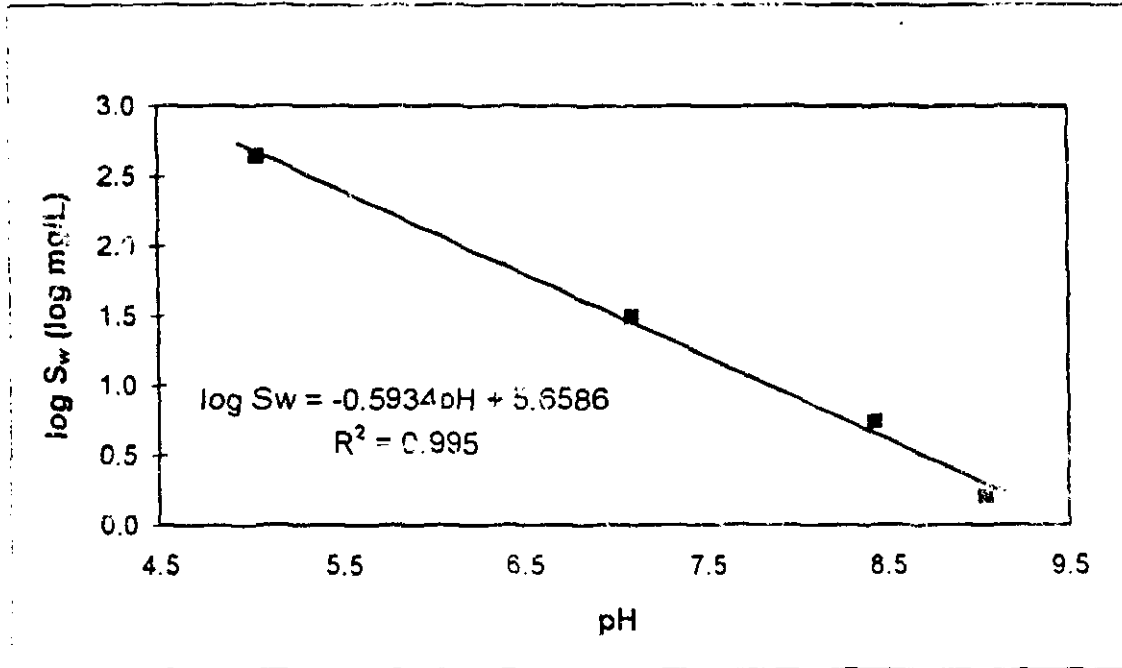
A log transformation of the solubility data plotted against pH shows a linear relationship, as illustrated in Figure 2 below.

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Figure 2

Aqueous Solubility of SK&F 105517.



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7.2.2 Dissociation Constant

Because of its low water solubility, the pK_a for carvedilol was determined by preparing methanol-water solutions of carvedilol containing 45, 50, 57, 66 and 71 v/v% methanol and then titrating these solutions with 0.1N HCl. The apparent pK_a was plotted versus concentration of methanol, resulting in a straight line whose intercept is the value of pK_a in water. A pK_a of 7.8 was obtained for the secondary amine group. The pK_a 's of the -NH- group in the carbazole ring, which is amphoteric, were not determined. According to published data, the pK_a 's of carbazole are 16.7 [4] (proton lost) and -5.7 [5] (proton gained). This suggests that the acidity or basicity of the carbazole in SK&F 105517 is extremely weak. The experiment is detailed in SB report code CSL-14467-250 which is included in Appendix VI; see reference [6].

7.2.3 Octanol/Water Distribution Coefficient

The octanol/water distribution coefficients (K_{ow}) for carvedilol were determined at two concentrations in triplicate test systems consisting of pH 5, 7 and 9 buffers and high-purity n-octanol. The results are reported in reference [7] and summarized below.

Solvent	26.3 mg/L		263 mg/L	
	K_{ow}	log K_{ow}	K_{ow}	log K_{ow}
Octanol/pH 5 buffer	106	2.02	35.7	1.93
Octanol/pH 7 buffer	528	2.72	549	2.74
Octanol/pH 9 buffer	1040	3.01	1260	3.10

7.2.4 Vapor Pressure, Volatilization, Henry's Law Constant

The vapor pressure of a substance is the property governing the tendency of a chemical substance to be transported into and in air and is thus an important parameter for predicting the distribution of chemicals into environmental compartments. For non-ionizable organic compounds, measurement of the vapor pressure is straightforward, and the value obtained is meaningful in environmental predictions. However, for compounds such as carvedilol, which will be ionized in solution at environmental pHs, the vapor pressure of the free base of the compound alone is less useful for predicting air-water partitioning. Vapor pressure may over-predict volatilization of chemicals which are partially ionized in aqueous solution. Since carvedilol has a basic pK_a of 7.8, approximately 86% of dissolved carvedilol species (ionized) will exist as the protonated base at pH 7. Therefore, only 14% (neutral) of dissolved species are available for volatilization.

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A more useful parameter for estimating the air-water partition coefficient for a chemical, and thus the likelihood of its entering into and being transported by the atmosphere, is Henry's law constant. The apparent Henry's law constant, H_L , represents the ratio of the equilibrium concentration of a chemical substance in air to its corresponding concentration in water in a closed system. It can be used to estimate the tendency of a chemical to volatilize from aqueous solution at a given pH. H_L is related to vapor pressure (VP) and aqueous solubility (S_w) as follows:

$$H_L = VP/S_w$$

Since carvedilol exists primarily as a protonated base at environmental pH levels, the Henry's law constant was measured directly experimentally. Values of $< 2.66 \times 10^{-7} \text{ m}^3 \text{ atm/mol}$ at pH 6.7 and $3.93 \times 10^{-7} \text{ m}^3 \text{ atm/mol}$ at pH 6.55 were obtained. The results are detailed in reference [9].

Lyman et al. in reference [10] provides the following interpretation of H_L values:

H_L ($\text{m}^3 \cdot \text{atm/mol}$)	Aquatic Volatility
1E-5 to 1E-7	"volatilizes slowly"
1E-7 to 3E-7	"essentially non-volatile"
< 1E-7	"less volatile than water"

With an H_L of $3.93 \times 10^{-7} \text{ m}^3 \cdot \text{atm/mol}$, the aquatic volatility of carvedilol may be characterized as a very slow process. In the presence of any significant depletion mechanism, mass transfer to the atmospheric compartment over time would be negligible.

7.2.5 UV/Vis Spectrum

The UV/Vis spectra of aqueous solutions of carvedilol were determined at pH 5, 7 and 9. The detailed study report is given in reference [11]. The experimental results indicate that the UV/Vis absorption spectrum of carvedilol is not affected by solution pH. In addition, significant absorbance at wavelengths greater than 290 nm was found, which suggests that carvedilol is likely to be susceptible to direct photochemical degradation in the environment.

7.2.6 Soil Sorption/Desorption (K_{oc}) and K_d

Soil sorption/desorption isotherms are carried out in order to generate a water-soil partitioning coefficient (K_{oc}) for use in predicting the mobility of a chemical in the terrestrial

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environmental compartment. For human drugs, however, the majority of users will discharge into municipal wastewater treatment systems [1]. As a result, a more meaningful partitioning coefficient to predict initial sorption to biomass or sludge is K_p , a measure of the partitioning between the aqueous phase and the biosolids phase in a wastewater treatment plant (WWTP).

From preliminary experiments, a mean K_p was determined to be 5500 ($\log K_p = 3.74$). From definitive equilibrium Freundlich isotherm data with active sludge, the sludge adsorption isotherm constant K was determined to be 20,400 ($\log K = 4.31$). The difference between these results may be due to different sludge sources and treatments. Standardized methodology for sludge adsorption studies has not yet been established. Details of the studies are given in reference [12]. The use of this constant to predict environmental partitioning is shown in section 7.3 below.

A soil sorption/desorption isotherm study was also carried out to generate a K_{oc} value for carvedilol. The detailed study report is given in reference [13] and summarized below.

Soil	%TOC	Solvent	K_{oc}	$\log K_{oc}$
Kansas	2.06	H ₂ O	23500	4.37
California	1.59	H ₂ O	40900	4.61
Iowa	1.53	H ₂ O	<u>36900</u>	<u>4.57</u>
Average			33800	4.53
Kansas	0.8	CaCl ₂	143000	5.16
California	1.59	CaCl ₂	530000	5.72
Iowa	1.53	CaCl ₂	<u>227000</u>	<u>6.36</u>
Average			300,000	5.47

The average K_{oc} from studies in water was 33,800; from studies in CaCl₂, a value of 300,000 was determined. Usually, if a lower K_{oc} is determined in the CaCl₂ solvent system, this is taken as indicating a significant amount of ion-exchange character in the sorption process, since the calcium ions would compete with the carvedilol protonated free base ions for ion-exchange sites, resulting in less carvedilol partitioning into the soil organic carbon phase. However, for carvedilol, the CaCl₂ studies gave a higher value. This may be due to a "salting out" effect of the CaCl₂, decreasing the water solubility of the carvedilol and resulting in stronger hydrophobic interactions with the soil organic carbon. Thus the

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sorption appears to be a more complex function of the chemical nature of the carvedilol and of the soil organic carbon. The usual name given to this complex phenomenon is chemisorption. It is interesting to note that correction of the sludge partition coefficient, $\log K_p = 4.31$, for organic carbon content (assumed to be approximately 50% (reference [14])), yields a $\log K_{OC}$ for sludge of 4.61. This is essentially the same as the $\log K_{OC}$ obtained for soils using water as the solvent.

Carvedilol exhibited very little desorption from soil. The percent desorbed from the soil systems tested ranged from only 0.34-2.36%.

In summary, the sludge and soil adsorption studies indicate that carvedilol will adsorb strongly to particulate organic materials and that once adsorbed it will be relatively immobile in the environment.

7.3 Environmental Partitioning Estimates for Carvedilol

Since the majority of carvedilol used in the United States will be introduced into the environment through Wastewater Treatment Plants (WWTPs), the partitioning of carvedilol in that system must first be considered. Taking total production as unity, the maximum fraction of drug entering the aquatic and terrestrial compartments after discharge from the WWTPs can be calculated as follows:

CALCULATION OF MAXIMUM EXPECTED EMITTED CONCENTRATION

Carvedilol

Given the following assumptions:

Total annual market volume (5th year)(MV_{total})	=	1
Fraction of US population using WWTP($F_{sewered}$)	=	0.74 [1]
Fraction of Drug Substance not excreted(F_m)	=	0
Annual US Sewage Flow(SF_{annual})	=	3.7×10^{13} L/yr [1]
Annual Yield of Dry Sludge from WWTPs(DS_{annual})	=	5.9×10^9 kg/yr [1]
Dilution rate from Application of Sludge to Agricultural Land (DR_{annual})	=	0.025 [1]
K_p (carvedilol)	=	

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Then the maximum expected emitted concentration (MEEC) into the environment of carvedilol from use of the drug product is calculated as follows, assuming 100% excretion of carvedilol and its metabolites in one day:

$$\begin{aligned} \text{Fraction emitted into WWTPs} &= MV_{\text{total}} \times F_{\text{sewered}} \\ &= \\ &= \end{aligned}$$

Based on the distribution of carvedilol between sludge and water,

$$\begin{aligned} K_p &= \frac{\text{Concentration in sludge } (C_2)}{\text{Concentration in sewer effluent } (C_1)} \\ 2.04 \times 10^4 &= \frac{C_2}{C_1} \\ C_2 &= \text{(equation 1)} \end{aligned}$$

Since the fraction emitted (0.74) will be distributed between the sludge and the sewer effluent, the balance around the WWTP is

$$C_1 \times SF_{\text{annual}} + C_2 \times DS_{\text{annual}} = \text{(equation 2)}$$

Substitution of the equation for C_2 (equation 1) into equation 2 gives

$$\begin{aligned} (3.7E13C_1) + (5.9E09)(2.04E04C_1) &= \\ (3.7E13C_1) + (1.20E14C_1) &= \\ 1.57E14C_1 &= \\ C_1 &= \\ C_2 &= \\ C_2 &= \\ C_2 &= \end{aligned}$$

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Using the relationships of equation 2 gives:

$$\begin{aligned} (3.7E13C_1) &= \\ &= \\ (5.9E09)(C_2) &= \\ &= \end{aligned}$$

Thus, [] of the carvedilol emitted to wastewater treatment plants from use will distribute into the aqueous phase, with [] sorbing to the sludge and entering the terrestrial compartment. Given the high soil sorption and very low desorption of carvedilol, very little migration of carvedilol through the terrestrial compartment is likely to occur.

7.4 Transformation and Depletion Mechanisms of Carvedilol

7.4.1 Hydrolysis

The hydrolytic stability of carvedilol was determined in deionized water and in pH 5, 7 and 9 buffers. The results indicated that carvedilol is hydrolytically stable under the conditions tested, and has an estimated hydrolytic half-life ≥ 1 year [15]. The study is detailed in reference [16].

7.4.2 Aqueous Photolysis

Given carvedilol's significant absorption of light at wavelengths > 290 nm, the photolysis study on carvedilol was carried out at pH 7 in natural sunlight. The first-order direct aqueous photoreaction rate constant was determined to be 0.468 hr^{-1} , giving a half-life of 1.48 hours. The detailed study report is given in reference [17].

7.4.3 Aerobic Biodegradation

Aerobic biodegradability studies were carried out on carvedilol using a modification of standard methodology. The analytical method validation study is given in reference [18]. The definitive aerobic biodegradation study is detailed in references [19] and [33]. ERL study 92-021, reference [19], determined that biotransformation of carvedilol was detected after ~ 40 days with a first-order rate constant of 0.03 day^{-1} giving a half-life of 26.2 days. Another study, ERL Study 92-050, used methanol as a carrier to facilitate carvedilol bioavailability in the biodegradation test systems. For comparison it also contained treatments that added carvedilol to the test system without methanol carrier.

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The two treatment groups that used methanol had first-order rate constants of 0.1 and 0.05 day⁻¹ at 5 and 10 mg/L carvedilol concentration, respectively. This corresponds to respective half-lives of 6.9 and 13.9 days. The no methanol treatments had first-order rate constants of 0.02 and 0.01 day⁻¹ at 5 and 10 mg/L carvedilol concentration, respectively. This corresponds to respective half-lives of 34.6 and 69.3 days. The presence of a carrier solvent appears to significantly enhance the biodegradation kinetics in the test systems employed for the study probably as a direct consequence of increased bioavailability to the degrading microorganisms.

In addition to carvedilol itself, biodegradation/biotransformation studies were carried out on 4-hydroxycarbazole and carbazole, substructures of the carvedilol molecule likely to be the most recalcitrant to biotransformation. The half-lives for these two compounds were 21.8 days and 0.39 days, respectively. This may be taken as indicative of the eventual mineralization of the carvedilol molecule once the initial acclimation is accomplished. Interestingly, the two replicate experiments for the biodegradation studies showed different HPLC profiles, indicating that carvedilol in the different flasks was undergoing biotransformation by two different pathways. The details of these studies are given in references [20] and [21]. See also aquatic toxicity evaluations in Section 8.2.3.

It is clear from these data that carvedilol is indeed susceptible to biodegradation in aerobic compartments and should not persist in the environment. Given the high biomass concentrations in activated sludge systems, the likely presence of surface-active agents which may facilitate bioavailability, and higher levels of dissolved organics which would enhance the solubility of carvedilol, the degradation of carvedilol in unacclimated waste water treatment plant systems would be expected to be more rapid than the conservative kinetics presented in typical biodegradation test systems.

7.4.4 Fate Summary

From the data presented above, the following are predictions concerning the environmental fate of carvedilol from use:

1. Based on environmental partitioning estimates presented in section 7.3, approximately 77% of carvedilol introduced into WWTPs is expected to distribute into the sludge phase. Biotransformation may occur during the solids retention, which may reduce sludge concentrations considerably. Due to the high turbidity of activated sludge mixed liquor, little photolysis is expected to occur during aeration. During secondary settling, dissolved carvedilol may be more susceptible to photodegradation in the clarified secondary effluent.
2. Carvedilol discharged into the aquatic environmental compartment will not likely persist based on photolysis and slow biotransformation depletion mechanisms. An

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overall depletion rate may be estimated from the individual depletion rate constants. An estimation of half-life in the aquatic compartment may range from 1.5 hours to 40-50 days based on the dominant active depletion mechanism.

3. Carvedilol entering the terrestrial compartment by land application of sludge would likely remain sorbed, immobile and undergo, under aerobic conditions, slow biotransformation. It would not be expected to persist in the soil compartment.
4. The very low Henry's constant suggests that transport of carvedilol to the atmosphere by volatilization from either the treatment plant or the terrestrial compartment will be insignificant.
5. Given that the log of the octanol/water distribution coefficient varies from 2 to 3 at environmental pH levels, little bioconcentration of carvedilol is likely to occur. This prediction is further supported by the metabolism studies, which indicate that carvedilol is biotransformed by a variety of mechanisms into more polar materials, which are excreted.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES:

8.1 Human and Mammalian Health Effects Summary [22]

8.1.1 Acute Toxicity Studies

8.1.1.1 Oral Toxicity

No lethality occurred in rats after administration of a single oral dose of 8000 mg/kg. The oral LD₅₀ in rats was greater than 8000 mg/kg.

8.1.1.2 Inhalation Toxicity

Inhalation toxicity was not determined. However, symptoms after exposure to dust might include slow pulse, dizziness, fainting, difficult or irregular breathing or bluish colored fingernails or palms.

8.1.1.3 Skin Irritation

Skin irritation potential was not determined. We can assume that direct contact can produce irritation or allergic skin reaction. Symptoms such as itching, redness or swelling might be immediate or delayed.

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8.1.1.4 Eye Irritation

Eye irritation potential was not determined. Assume that direct contact can produce irritation. Symptoms might include redness or swelling.

8.1.1.5 Sensitization

The sensitization potential of carvedilol has not been determined.

8.1.2 Chronic Toxicity Studies

8.1.2.1 Reproduction Toxicology

Carvedilol did not produce adverse effects on male or female reproduction in studies with rats.

8.1.2.2 Teratogenicity

Carvedilol did not produce teratogenic effects in studies with rats.

8.1.2.3 Genetic Toxicology

Carvedilol was not found to be mutagenic in bacteria (Ames test) or other genotoxicity tests. It is not listed as a carcinogen by IARC, NTP, or US OSHA. There was no evidence of a carcinogenic effect in chronic studies with rats or mice.

8.1.2.4 Other Effects

Carvedilol exhibits an effect on the cardiovascular system by lowering blood pressure.

8.2 Aquatic Toxicity Studies

8.2.1 Acute Aquatic Toxicities of Carvedilol

Acute aquatic toxicity studies were carried out on microorganisms (Microtox[®] and Microbial Respiration Inhibition), *Daphnia magna*, and bluegill sunfish (*Lepomis macrochirus*) using carvedilol. The detailed reports on the Microtox[®] studies for carvedilol, 4-hydroxycarbazole, and carbazole are given in references [23,24,25]. The reports of the contract study of the activated sludge respiration inhibition of carvedilol is given in reference [26]. Reports of the contract studies on the acute toxicities of carvedilol to *Daphnia pulex* and bluegill sunfish (*Lepomis macrochirus*) are given in references [27] and [28], respectively. The results are summarized below.

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Toxicity Test	Carvedilol (mg/L)
Microtox [®] - EC ₅₀	5.43 ± 0.25 6.71 ± 1.87 (4-OH carbazole) 0.26 ± 0.031 (carbazole)
Respiration Inhibition - EC ₅₀	98.4
<i>Daphnia pulex</i> - ^{EL} LC ₅₀ _{1.2/1.45}	> 2.8
<i>Daphnia pulex</i> - NOEL	< 0.37
Bluegill Sunfish - LC ₅₀	0.99 (95% CI = 0.87-1.1)
Bluegill Sunfish - NOEL	< 0.43

8.2.2 Acute Aquatic Toxicity of Carvedilol Photolysis By-Products

Since carvedilol was found to degrade in the presence of sunlight, the relative toxicity of the photo-degradant(s) compared to carvedilol itself was determined using the Microtox[®] test carried out on samples of carvedilol solutions that had been exposed to sunlight. No EC₅₀ could be determined for the degraded solutions because of a lack of toxic effect. Based on these results, any compounds entering the environment from the photolysis of carvedilol would not be expected to exert toxic effects on aquatic organisms. Details of the study are given in reference [29].

8.2.3 Acute Aquatic Toxicity of Carvedilol Biodegradation By-Products

The relative acute aquatic toxicity of carvedilol biodegradation by-products was also determined by a Microtox[®] test carried out on samples of carvedilol solutions after laboratory biodegradation experiments. For one sample of biodegradants, no EC₅₀ could be determined for the degraded solutions because of a lack of toxic effect. For the "replicate" sample, an EC₅₀ of 15.4% was calculated. See reference [30] in Appendix VII. However, as noted in Section 7, the carvedilol in the two samples appeared to be biotransformed by two different pathways, and by consortia of apparently different microorganisms. However, even though minimal toxic effect was observed, the unknown biodegradants responsible were derived from carvedilol at a concentration far in excess of what could be emitted into the environment from use.

From the data above, carvedilol and its degradants would not be expected to exhibit acute toxic effects to aquatic organisms at concentrations expected to be emitted into and exist in the environment.

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9. USE OF RESOURCES AND ENERGY

9.1 Use of Resources and Energy at Boehringer

9.1.1 Use of Resources and Energy at Plant HC-B 21

The following tables summarize the known amounts of energy and resources utilized during intermediate production at the production plant HC-B 21.

**Percent of Energy and Resources Utilized at Boehringer Mannheim
for Production of Intermediate in 1990
HC-B 21 Plant**

Consumption	Electricity (kw-hour)	Steam / 2.5 bar (t)	Tap Water (m ³)	Cooling Water (m ³)	Demineralized Water (m ³)
Percent of Total Consumption at Boehringer Mannheim	0.02	0.005	0.006	0.06	0.05

9.1.2 Use of Resources and Energy at Plants HC-B 4, HC-B 10 and HC-B/OB

The following tables summarize the known amounts of energy and resources utilized during intermediate production at production plants HC-B 4, HC-B 10 and HC-B/OB.

**Percent of Energy and Resources Utilized at Boehringer Mannheim
for Production of Intermediate in 1990
HC-B 4, HC-B 10 & HC-B/OB Plants**

Process Step	Electricity (kw-hour)	Steam / 2.5 bar (t)	Tap Water (m ³)	Cooling Water (m ³)	Demineralized Water (m ³)
Percent of Total Consumption at Boehringer Mannheim	0.13	0.08	0.13	0.38	0.36

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9.1.3 Effect Upon Endangered Species And Historic Places

The production of carvedilol intermediates and the disposal of associated wastes at the Boehringer Mannheim production facilities should have no impact on threatened or endangered species. Property listed in or eligible for listing in the National Register of Historic Places will not be impacted by intermediate production or waste disposal activities since the production is taking place outside of the United States and the Boehringer-Mannheim facility is not a designated historic site.

9.2 Use of Resources And Energy At Cork

The effects on the use of resources and land for the production of carvedilol drug substance are minimal because of the low production volumes and associated wastes, and the existing treatments units that will be used.

The following table summarizes the percent of energy and resources utilized during carvedilol substance production stages at the SmithKline Beecham (Manufacturing) Limited facility, based on the projected 5th year of production and current use.

Consumption	Electricity (kw-hour)	Fuel Therms	Water (m ³)
Percent of Total Consumption	0.05	4.2	0.07

9.2.1 Effect Upon Endangered Species And Historic Places

The production of carvedilol substance and the disposal of associated wastes should have no impact on threatened or endangered species. Property listed in or eligible for listing in the National Register of Historic Places will not be impacted by carvedilol substance production or waste disposal activities since the production is taking place outside of the United States and the SmithKline Beecham (Manufacturing) Limited facility is not a designated historic site.

9.3 Use of Resources and Energy to Produce Drug Product at Cidra

The Cidra facility for carvedilol product manufacture is a 52 acre site located in an agricultural/urban/industrial area on the central mountainous ridge of the island of Puerto Rico. The effects on the use of resources and land for the production of carvedilol drug

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product are minimal because of the low production volumes and associated wastes, and the existing treatments units which will be used. Manufacture of this product uses only a small percentage of the resources and energy available at this site and of resources and energy required for transport.

The following table summarizes the total known amounts of energy and resources used at the Cidra plant.

Consumption	Electricity (kw-hour)	Fuel Oil (gallons)	Water (gallons)
Percent of Total Consumption	4%	4%	4%

To produce the carvedilol drug product at maximum yearly production levels at Cidra, it is estimated that 4% of total yearly Cidra plant usage of electricity, fuel and water will be used.

9.3.1 Effect Upon Endangered Species And Historic Places

The production of carvedilol product and the disposal of associated wastes should have no effect on threatened or endangered species. Property listed in or eligible for listing in the National Register of Historic Places will also not be impacted by carvedilol product production or waste disposal activities since the Cidra facility is not a designated historic site.

10. MITIGATION MEASURES

10.1 Mitigation Measures at Boehringer

Potential adverse environmental impacts associated with drug intermediate production at Boehringer Mannheim are minimized by the following:

No waste or exhaust streams are directly discharged, but are directed to major treatment units;

Treated effluent streams are checked before discharge, with ample capacity for emergency storage in the event that effluent criteria are not met;

Floor spills are swept and incinerated;

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Off-spec or rejected materials are returned to the supplier or are incinerated in an outside incineration plant for industrial wastes;

Accidental introductions of bulk product into the environment during storage is mitigated by controlled packaging and storage operations. Bulk drug product is packaged in new corrugated cardboard boxes lined with two polyethylene bags. These boxes are heat-sealed, sealed with plastic tape, properly labeled, and stored in a secured bulk storage area of the plant warehouse.

Storage facilities are designed to allow for the capture and treatment of any spills before any major environmental effects could result. Also, the adopted spills prevention, control and contingency plans have been demonstrated to be effective in the prevention of such emergencies.

The plant personnel are well-trained and follow written instructions when performing their work.

The site is audited regularly by the Boehringer Mannheim central Environment Department, to assist in the identification and implementation of any additional mitigation measures as circumstances warrant.

10.2 Mitigation Measures At Cork

Plans to minimize waste output were considered and implemented at the outset of carvedilol development, as well as during substance production. The Integrated Pollution Control (IPC) license contains guidelines for the establishment of an Environment Management Programme to assess all operations for the use of cleaner technology and the minimization of waste. Potential environmental impacts associated with production at Cork are also minimized by the following:

Most waste streams are incinerated, and the gases scrubbed before being discharged. Scrubber liquors are biotreated in the on-site wastewater treatment facility before discharge.

Biotreated effluent streams are checked before discharge, with ample capacity for emergency storage in the event that effluent criteria are not met

Airstreams from the process buildings are filtered prior to venting to the atmosphere.

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10.3 Mitigation Measures at Cidra

Potential adverse environmental impacts associated with the proposed action are minimized at the Cidra facility by the following:

10.3.1 General

The proposed formulation process involves small production lots, which will generate very small quantities of waste;

No waste or exhaust streams are directly discharged. All streams are directed to major treatment units. Treated effluent streams are checked before discharge, with ample capacity for emergency storage in the event that effluent criteria are not met;

Airstreams from the process are small and directed to dust collectors, which minimize the effects of the emissions by at least 99.9%;

Storage facilities are designed to allow for the capture and treatment of any spills before any major environmental effects could result. Also, the adopted spills prevention, control and contingency plans have been demonstrated to be effective in the prevention of such emergencies.

10.3.2 Energy and Resources

A thermal oxidizer with a regenerative heat recovery system is used to incinerate gaseous waste streams produced during tablet coating operations. The heat recovery system is operated to recover at least 85% of the heat generated, for use in continual incineration of the gases. After aeration in the biotreatment facility, 55,000 gallons per day of final effluent is recycled to cooling and quench towers and 25,000 gallons per day of final effluent is discharged.

10.4 Mitigation from Use

The potential environmental risk from carvedilol centers on the aquatic and terrestrial compartments. Carvedilol will not be directly discharged into the environment from use, but instead most will be subjected to depletion mechanisms found in wastewater treatment plants (WWTP).

Two mechanisms at the plants will decrease environmental concentrations of carvedilol: sorption and biodegradation. Approximately 77% of carvedilol in WWTP influent will be sorbed onto plant biomass solids, thus dramatically decreasing carvedilol concentrations in WWTP effluent. Carvedilol in solution will likely be at least partially biotransformed based

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upon data described in ERL Report 9501. Any carvedilol that is released from the WWTP into surface waters will be subjected to aqueous photolysis. Since the carvedilol photolysis rate constant was determined to be approximately 0.47 hr^{-1} , photolysis will serve as a significant depletion mechanism in the aquatic compartment.

Carvedilol sorbed onto sludge biomass will be ultimately disposed of, in some cases, by incineration or placed into secure landfills. Those WWTPs that do dispose of sludge via landfarming or distribution and marketing could serve to release carvedilol into the terrestrial compartment. However, carvedilol in sludge-amended soil will be subjected to aerobic biodegradation, albeit at slower rates than those determined in aqueous matrices. Finally, carvedilol in sludge-amended soil will be tightly bound to organic matter and not bioavailable.

In conclusion, predicted environmental concentrations of carvedilol are well below predicted toxicity concentrations and carvedilol will not require any additional mitigation actions.

11. ALTERNATIVE TO THE PROPOSED ACTION

No potential adverse environmental impacts have been identified for the proposed action. The approval of carvedilol will provide an important benefit to patients requiring its administration with no adverse environmental risk. The only alternative to the proposed action is that of no action, thus depriving patients an important therapy.

12. LIST OF PREPARERS

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13. CERTIFICATION:

The undersigned official certifies that the information presented is true, accurate, and complete to the best knowledge of the Environmental Research Laboratory.

Date:

March 17, 1995

Signature:

James Hagan

James R. Hagan, P.E.
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ATTACHMENT II

Note: The current name for Penn Chemicals (Cork, Ireland)
is SmithKline Beecham (Manufacturing) Limited

GENERAL COMPLIANCE STATEMENT

Boehringer Mannheim GmbH states that it is in compliance with all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of Guaiacol-O-ethyltosylate at its facilities in Mannheim, Federal Republic of Germany.

February 14, 1992

Date



Dr. G. Lettenbauer

Senior Vice President
of
Chemical Production and
Development Department

February 14, 1992

Date



Dr. W. Wäble

Vice President
of
Safety and Environmental Department

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GENERAL COMPLIANCE STATEMENT

Boehringer Mannheim GmbH states that it is in compliance with all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of 4-Hydroxycarbazole at its facilities in Mannheim, Federal Republic of Germany.

February 14, 1992

Date



Dr. G. Lettenbauer

Senior Vice President
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February 14, 1992

Date



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BOEHRINGER
MANNHEIM

February 3, 1994



TO WHOM IT MAY CONCERN

"ENVIRONMENTAL ASSESSMENT"

Boehringer Mannheim GmbH, as the manufacturer of various pharmaceutical active ingredients (drug substances) and finished medicinal products (drug products), having the official address

Boehringer Mannheim GmbH
Sandhofer Straße 116
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Federal Republic of Germany,

herewith certifies that the manufacture of active ingredients and finished products in the facilities of the above mentioned plant site is carried out according to the current laws and regulations of the Federal Republic of Germany for purposes of environmental protection.

The construction and the operation of plants for the manufacture of pharmaceutical products is principally subject to approval according to §4 of the Bundesimmissionsschutzgesetz (BImSchG) "Federal Law on Immissions". This requirement is based on the regulations concerning plants subject to approval (4th BImSchV = Regulations on the Federal Law on Immissions), which are given in the enclosures under subparagraph

4.1: Plants for the manufacture of products by chemical conversion ...

and under subparagraph

4.3: Plants for the manufacture of medicinal products or medicinal-product intermediates ...

Approval for these plants is to be obtained by submitting a detailed written application to the relevant authorizing body. Only after thorough inspection is a notice of approval conferred by the authorizing body (for Boehringer Mannheim GmbH, the Regierungspräsidium Karlsruhe = Directorate of the Administrative District, Karlsruhe). This notice may only be conferred if the relevant permit requirements have been satisfied according to §6 BImSchG (see enclosure).

It is therefore essential to guarantee the fulfillment of the obligations in §5 BImSchG which are incumbent on the operator of plants subject to approval. In addition, the construction and operation of the plants should not contravene further regulations under public law and the interest of industrial safety.

... 2

Deutsche Bank AG, Mannheim
BLZ: 670 700 10 - Konto 07/02 832
 Dresdner Bank AG, Mannheim
BLZ: 670 800 50 - Konto 6 608 231

Registernummer Mannheim HRB 1962
Gesellschaftsführung: Bernhard Kubitz (Vorst.), Prof. Dr. rer. nat. Dr. med. Uwe Dicker (Stellv.),
Dr. Ing. Fried. Heintzer (Stellv.), Gernold Metzger, Hans Schmidt,
Vorsitzender des Aufsichtsrates: Curt Engelen

In accordance with §5 BImSchG plants subject to approval are to be constructed and operated in such a manner that

1. harmful environmental effects and other hazards, considerable disturbance and considerable inconvenience to the community and vicinity cannot be evoked,
2. provisions are made against harmful environmental effects, in particular through the use of state-of-the-art measures for the limitation of emissions.
3. residues are avoided where possible, or are processed and rendered harmless according to regulations, or, where avoidance and processing is not technically feasible or is unreasonable, they are removed as waste without harm to the well-being of the community, and
4. any resulting heat is used in the operator's plant or transferred to a third party that has declared itself as willing to accept, provided that the process involved is technically possible and acceptable, and that it is compatible with the obligations according to subparagraphs 1 to 3.

However, where plants not subject to approval with respect to the BImSchG, approvals according to other laws may be binding (e.g. according to building regulations, according to industrial code and others). Moreover, §22 and §23 of the BImSchG lay down the obligations for the operator and also the requirements for the construction and the operation of such plants (see enclosure). Accordingly, such plants are to be constructed and operated so that

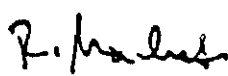
1. harmful environmental effects are prevented through the use of state-of-the-art technology,
2. unavoidable harmful effects on the environment are minimized through the use of state-of-the-art technology, and
3. waste arising from the operation of the plants can be removed according to regulations.

We are obliged to comply strictly with such legal regulations. This is being controlled by the responsible administration.

Additionally, we draw attention to the fact that we are subject to the constant supervision of the civil Industrial Inspection Board.

Yours faithfully,

BOEHRINGER MANNHEIM GMBH
ppa. l.v.



Dr. Machat



Dr. Oehmichen

7 Enclosures

Karlsruhe, 2-21-1994

Regierungspräsidium Karlsruhe
Agreed:



Hoffmann

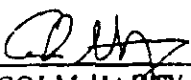
Oberregierungsrat



GENERAL COMPLIANCE STATEMENT

PENN CHEMICALS B.V. states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of Carvedilol at its facilities in Currabinny, Carrigaline, Co. Cork, Ireland as well as emission requirements set forth in applicable federal state, and local statutes and regulations applicable to the production of Carvedilol at its facilities in Currabinny, Carrigaline, Co. Cork


DECLAN RYAN
MANAGER ENGINEERING/ENVIRONMENTAL


COLM HARTY
DIRECTOR FINANCE & ADMINISTRATION

PENN CHEMICALS B.V., Currabinny, Carrigaline, Co. Cork, Ireland.

Tel. 021-371201, Fax 021-372383, Telex 75869 Int. Dialing +353-21-371201



000053



SmithKline Beecham
Pharmaceuticals

GENERAL COMPLIANCE STATEMENT

SmithKline Beecham Pharmaceuticals Co. states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of CARVEDILOL (KREDEX) at its facilities in Cidra, Puerto Rico as well as emission requirements set forth in applicable federal, state, and local statutes and regulations applicable to the production of CARVEDILOL at its facilities in Cidra, Puerto Rico.

Jose L. Rosado

4-13-92

JOSE L. ROSADO
PRESIDENT & GENERAL MANAGER

DATE

Antonio Garcia

4-13-92

ANTONIO GARCIA
ENVIRONMENTAL & PLANT
SERVICES LEADER

DATE

ATTACHMENT III

**SMITHKLINE BEECHAM ENVIRONMENTAL RESEARCH LABORATORY
SUMMARY OF ENVIRONMENTAL FATE AND EFFECT STUDIES**

compound - SK&F 105517 (CARVEDILOL)

summary prepared by - Scott Ziegenfuss

revised as of 3/17/95

ENVIRONMENTAL FATE

		pH 5	pH 7	pH 9	DI H2O (pH 8.4)	
Water Solubility	definitive data - mean	434	30.8	1.61	5.46	(mg/L)
	stdev	46.3	3.66	0.356	1.88	
Octanol/Water Distribution Coefficient (Kow) *				pH 5	pH 7	pH 9
			C1 (28.3 ug/L)	106	528	1040
			C2 (263 ug/L)	85.7	549	1260
Sludge Adsorption	preliminary experiment - mean Kp = 5500, log mean Kp = 3.74					
	factorial experiment - 19 hour equilibration Freundlich isotherm data					
	active sludge - log K = 2.76			poisoned sludge - log K = 3.64		
	1/n = 0.713			1/n = 0.999		
	R^2 = 0.993			R^2 = 0.964		
	log Kp = 3.37			log Kp = 3.65		
	definitive isotherm experiment - 19 hour equilibration					
	log K = 4.31	mean Kp = 10800				
	1/n = 1.1	log Kp = 4.03				
	R^2 = 0.931	stdev = 2400				
Soil Adsorption						
			H2O	CaCl2		
	soil	TOC (%)	log K	log Koc	log K	log Koc
	Kansas	2.06	2.69	4.37	3.47	5.16
	Calif.	1.59	2.81	4.61	3.93	5.72
	Iowa	1.53	2.75	4.57	4.54	6.36
Henry's Constant	< 2.66E-7 m ³ ·atm/mol @ pH 6.70, 3.93E-7 m ³ ·atm/mol @ pH 6.55					
UV/vis Spectrum	in 10% water in methanol		lambda		E (M·1·cm ⁻¹)	
			204		34200	
			224		36900	
			242		50200	
			286		14500	
			320		4610	
			332		6040	
Dissociation Constant (pKa)	7.8 (from SB Analytical Chemistry report #3077)					
Aerobic Biodegradation	carvedilol				k = 0.03 /day, t1/2 = 26.2 days	
	carbazole				k = 1.76 /day, t1/2 = 0.39 days	
	4-hydroxycarbazole				k = 0.03 /day, t1/2 = 21.8 days	
Photolysis	k = 0.4679 /hr, t1/2 = 1.5 hrs					

ENVIRONMENTAL EFFECTS

D. pulex 48-hr acute		EC50 -	> 2.8 mg/L	(95% c.i. - N/A)
		NOEC -	< 0.37 mg/L	
Bluegill 96-hr acute		L.C. EC50 -	0.99 mg/L	(95% c.i. = 0.87 to 1.1)
		NOEC -	< 0.43 mg/L	
Microbia Microtox	carvedilol	EC50-15 -	5.43	mg/L (stdev = 0.25)
	carbazole	EC50-15 -	0.26	mg/L (stdev = 0.031)
	4-hydroxycarbazole	EC50-15 -	6.71	mg/L (stdev = 1.87)
	biologically-degraded solution - #1 - EC50 at 15.4%, #3 - non-toxic			
	photolytically-degraded solution - 0 and 5 hours exposure: non-toxic			
	1.5 hours exposure: EC50-5 = 41.0 +/- 11.9 % (SD)			
Activated Sludge Respiration Inhibition (OECD 209)		EC50 -	98.4 mg/L	

ATTACHMENT IV

MATERIAL SAFETY DATA SHEET

1. IDENTIFICATION OF THE SUBSTANCE/PREPARATION
AND OF THE COMPANY/UNDERTAKING

SUBSTANCE\PREPARATION:

CARVEDILOL

TRADE NAMES/SYNONYMS:

1-(9H-CARBAZOL-4-YLOXY)-3-[[2-(2-METHOXYPHENOXY)ETHYL]AMINO]-2-PROPANO
L * SK&F 105517 * BM 14.190 * SKF 105517 * KREDEX * 105517 (SK&F) *
105517 (SKF)

CHEMICAL FAMILY:

Substituted carbazole.

MOLECULAR FORMULA:

C24-H26-N2-O4

MOLECULAR WEIGHT:

406.481

EINECS NUMBER:

Not Assigned

ELINCS NUMBER:

Not Assigned

COMPANY:

SMITHKLINE BEECHAM, CORPORATE ENVIRONMENT & SAFETY

U.S. OFFICE:

709 SWEDLAND ROAD
KING OF PRUSSIA, PA, 19406
U.S.A.

U.K. OFFICE:

NORFOLK HOUSE, DOWNSBROOK TRADING ESTATE
SOUTHDOWNVIEW WAY, WORTHING
WEST SUSSEX, BN14 8NQ, ENGLAND

PHONE NUMBERS:

++1-610-270-7807

++44-(0)903-822650

EMERGENCY AND AFTER HOURS CONTACT:

++1-800-228-5635 (EXTENSION 157)

2. COMPOSITION/INFORMATION ON INGREDIENTS

INGREDIENTSCAS REGISTRY NOPERCENT

CARVEDILOL

72956-09-3

MORE THAN 99%

CONTAMINANTS:

No significant hazardous contaminants.

3. HAZARDS IDENTIFICATION

PRIMARY ROUTES OF EXPOSURE:

Avoid breathing dust, eye contact, skin contact, ingestion.

CONTACT:

Allergic skin reaction can occur following direct contact with this material.
Symptoms such as itching, redness or swelling might be delayed.

EYE CONTACT:

Irritation can occur following direct contact with this material. Symptoms might
include redness or swelling.

INHALATION:

Symptoms after overexposure to dust might include slow pulse, dizziness,
fainting, difficult or irregular breathing, or bluish colored fingernails or
palms.

INGESTION:

Toxicity is not expected but ingestion should be avoided. Symptoms after
overexposure might include slow pulse, dizziness, fainting, difficult or

MATERIAL SAFETY DATA SHEET

irregular breathing, or bluish colored fingernails or palms.

CONDITIONS AGGRAVATED BY EXPOSURE:

Diabetics or individuals taking cardiovascular medications might be sensitive to the effects of this material. In cases of overexposure, seek medical assistance concerning possible drug interactions.

4. FIRST-AID MEASURES

SKIN CONTACT:

Remove contaminated clothing and flush exposed area with large amounts of water. Obtain medical assistance if skin reaction occurs, which may be delayed.

NOTE TO PHYSICIAN:

None.

EYE CONTACT:

Flush eyes continuously with water for at least 15 minutes. Do not use a chemical neutraliser. Obtain medical assistance if symptoms occur.

NOTE TO PHYSICIAN:

None.

INHALATION:

Move exposed subject to fresh air. Seek medical assistance in case of known or possible overexposure to this material or with symptoms including chest pain, difficulty breathing, loss of consciousness or other adverse effects which may be delayed. IF BREATHING HAS STOPPED, START BASIC LIFE SUPPORT AND SEEK IMMEDIATE MEDICAL ATTENTION.

NOTE TO PHYSICIAN:

For combustion products, refer to section number 5.

INGESTION:

In the event of swallowing this material, seek medical assistance. Do not induce vomiting.

NOTE TO PHYSICIAN:

Medical treatment in cases of overexposure should be treated as an overdose of beta-adrenergic blockers. Gastric lavage is recommended. Refer to current prescribing information or to local poison control information centers. This material is not a corrosive agent.

ANTIDOTES:

None known.

5. FIRE-FIGHTING MEASURES

FIRE CONTROL:

Use water, carbon dioxide, foam or dry chemical extinguishers. Toxic or corrosive gases are expected from fires involving this material.

SPECIAL FIREFIGHTING PROCEDURES:

Toxic or corrosive gases including oxides of carbon and nitrogen are expected in fires involving this material. Self contained breathing apparatus and full protective equipment are recommended for firefighters. Move containers from fire area if possible without increased personal risk. Dike area if possible to contain water for later disposal.

6. ACCIDENTAL RELEASE MEASURES

SPILLS:

Instruct all personnel not involved in clean up operations to keep at a designated, safe distance. Do not allow this material to enter surface drainage systems. Wear protective clothing and equipment consistent with

MATERIAL SAFETY DATA SHEET

the degree of hazard. Carefully scoop up the spillage, avoid dust generation and place in a suitable, properly labeled container for recovery or disposal. Wash down spillage area with copious amounts of water. This must only be undertaken if waste water can be directed to an on-site waste water treatment system.

DECONTAMINATION PROCEDURES:

Detergent solutions can be used for clean-up and decontamination operations. No specific detoxification procedures have been identified for this substance.

7. HANDLING AND STORAGE

HANDLING:

This material has not been tested for its dust explosion properties. However, like most organic dusts, it is expected to explode when ignited as a dust cloud. Care should be taken to avoid dispersion as a dust cloud. Ensure that all items of plant and equipment used for handling this material are bonded and earthed (grounded). The presence of isolated conductors should be avoided. Enclosure is recommended to routinely control airborne dust levels below published exposure limits.

STORAGE:

Avoid prolonged storage at elevated temperatures (greater than room temperature, approximately 20 degrees C). Keep in tightly closed containers or packages away from moisture and away from sources of ignition.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

EXPOSURE CONTROLS:

CARVEDILOL:

SmithKline Beecham (PEL):
0.03 MG/M3 (8 HR TWA)

INDUSTRIAL HYGIENE METHOD:
SB/1210 analytical method.

PERSONAL PROTECTION:

RESPIRATORS:

Respirators are normally not required when handling small quantities. If the airborne dust level is greater than allowable levels, a laboratory fume hood, local exhaust ventilation or an appropriate respirator should be used. The specific type used will be determined by air concentrations present. Follow local regulations for respirator use in the workplace.

GLOVES:

Wear neoprene or other impervious gloves for handling wet or dry powder.

EYE PROTECTION:

In laboratories, wear safety glasses with sideshields when handling this material. In production areas, wear full face respirator for dry powder, goggles for wet powder.

HYGIENE PRACTICES:

Wash hands and arms thoroughly after handling this material.
Clean up spills immediately.

OTHER PROTECTIVE EQUIPMENT:

In laboratories, wear lab coat or other protective clothing with long sleeves. In production areas, wear protective clothing that is laundered or discarded after each use. An eye wash station should be available.

9. PHYSICAL AND CHEMICAL PROPERTIES

MATERIAL SAFETY DATA SHEET

APPEARANCE:

White to off-white crystalline powder.

FLASH POINT:

Expected to be greater than 55 degrees C.

AUTOIGNITION TEMP:

Not determined.

LOWER EXPLOSIVE LIMIT:

Not applicable solids.

UPPER EXPLOSIVE LIMIT:

Not applicable solids.

MELTING POINT:

115 to 117 degrees C.

BOILING POINT:

Not determined.

VAPOUR DENSITY:

Expected to be negligible.

VAPOUR PRESSURE:

Expected to be negligible.

EVAPORATION RATE:

Expected to be negligible.

VOLATILE COMPONENTS (%):

None expected.

VISCOSITY:

Not applicable for solids.

PH OF AQUEOUS SOLUTIONS:

Not determined.

RELATIVE DENSITY:

Not determined.

CONDUCTIVITY:

Not applicable for solids.

OCTANOL/WATER DISTRIBUTION COEFFICIENT:

KOW (26.3 micrograms/l) = 106 (pH 5), 528 (pH 7), 1040 (pH 9)

KOW (263 micrograms/l) = 85.7 (pH 5), 549 (pH 7), 1260 (pH 9)

DISSOCIATION CONSTANT (pKA):

7.8

SOLUBILITY:

Soluble in many polar solvents.

Insoluble in water.

OXYGEN BALANCE:

This material is considered to be of low energy hazard potential based on oxygen balance calculated as minus 224.

TRAIN FIRE TEST:

Since this material has not been train fire tested, it should be assumed to support combustion in bulk quantities.

DUST EXPLOSIVITY:

Classification: Not determined.

Minimum explosive concentration (grams/cubic metre): Not determined.

Minimum ignition temperature - cloud (degrees C): Not determined.

Minimum ignition temperature - layer (degrees C): Not determined.

Minimum oxygen concentration (% v/v): Not determined.

Explosion characteristics:

Pmax (bar): Not determined.

dP/dT (bar/second): Not determined.

Kst (bar metre/second): Not determined.

St class: Not determined.

MATERIAL SAFETY DATA SHEET

DUST ELECTRICAL PROPERTIES:

Minimum ignition energy (mjoules): Not determined.
Resistivity at ambient humidity (ohm meter): Not determined.
Charge decay time at ambient humidity (seconds): Not determined.
Resistivity at low humidity (ohm metre): Not determined.
Charge decay time at low humidity (seconds): Not determined.

10. STABILITY AND REACTIVITY

CONDITIONS TO AVOID:

Avoid direct sunlight, conditions that might generate heat and dispersion as a dust cloud.

INCOMPATIBILITY:

None known.

STABILITY:

This material is expected to be stable.

THERMAL STABILITY:

Capillary tube test:

Thermal degradation can be expected at temperatures greater than 200 degrees C.

Differential scanning calorimetry:

Not determined.

Accelerating rate calorimeter:

Not determined.

HAZARDOUS POLYMERIZATION:

Not expected to occur.

HAZARDOUS DECOMPOSITION PRODUCTS:

Not identified.

FIRE AND EXPLOSION HAZARDS:

Not identified. As with many organic dusts, explosions might result when excessive dust concentrations are present.

11. TOXICOLOGICAL INFORMATION

ORAL TOXICITY:

The oral LD50 in rats was greater than 8000 mg/kg. No lethality occurred in rats after administration of a single oral dose of 8000 mg/kg.

INHALATION TOXICITY:

Not determined for this material.

SKIN IRRITATION:

This material was classified as a non irritant to rabbit skin. No signs of irritation occurred up to 3 days after direct application in rabbits for 4 hours.

EYE IRRITATION:

This mixture was classified as a minimal irritant in rabbit eyes. Conjunctival redness occurred up to 1 day after direct application in rabbits. Eyes appeared normal 2 days after treatment.

SENSITISATION:

This material was classified as a mild sensitiser to guinea pig skin. Adverse skin reactions or irritation occurred in 4 out of 20 guinea pigs used to test for allergic reaction or sensitisation (maximisation test).

MUTAGENICITY:

This material was not mutagenic in bacteria (Ames Test) or other genotoxicity tests.

CARCINOGENICITY:

This material is not listed as a carcinogen by SB, IARC, NTP or US OSHA.

MATERIAL SAFETY DATA SHEET

There was no evidence of a carcinogenic effect in chronic studies with rats or mice.

REPRODUCTIVE EFFECTS:

This material did not produce teratogenic effects (birth defects) or adverse effects on male or female reproduction in studies with rats.

OTHER EFFECTS:

This material exhibits an effect on the cardiovascular system by lowering blood pressure.

12. ECOLOGICAL INFORMATION

ACUTE AQUATIC EFFECTS:

48-hour Daphnia EC50 = greater than 2.8 mg/l.
48-hour Daphnia no-observed-effect-concentration less than 0.37 mg/l.
96-hour Bluegill EC50 = 0.99 mg/l.
96-hour Bluegill no-observed-effect-concentration less than 0.43 mg/l.

BIODEGRADATION:

Not determined.

ACTIVATED SLUDGE RESPIRATION INHIBITION (OECD 209 PROTOCOL):

EC50 = 98.4 mg/l (draft results).

SOIL ADSORPTION:

Not determined.

OTHER EFFECTS:

None.

13. DISPOSAL CONSIDERATIONS

Collect for recycling or recovery, if possible. Dispose of material on site in a licensed chemical incinerator, if allowed by the incinerator license or permit. If no on-site incinerator is available, dispose of material in a licensed commercial chemical incinerator.

14. TRANSPORT INFORMATION

FOR AIR TRANSPORT (IATA REQUIREMENTS):

Proper Shipping Name: NOT RESTRICTED
Technical Name (for n.o.s., not otherwise specified): Not applicable
UN/Identification Number: Not applicable
Class/Division: Not applicable
Sub Risk: Not applicable
Packing Group: Not applicable
RQ (Reportable Quantity): Not applicable
Emergency Response Guide Number: Not applicable

FOR MARITIME TRANSPORT (IMDG REQUIREMENTS):

Proper Shipping Name: NOT RESTRICTED
Technical Name (for n.o.s., not otherwise specified): Not applicable
UN/Identification Number: Not applicable
Class: Not applicable
Sub Risk: Not applicable
Packing group: Not applicable
IMDG page number: Not applicable
MFAG number: Not applicable
EMS number: Not applicable
Marine Pollutant: Not applicable
Emergency Response Guide Number: Not applicable

FOR UNITED STATES GROUND TRANSPORT (DOT REQUIREMENTS):

MATERIAL SAFETY DATA SHEET

Proper Shipping Name: NOT RESTRICTED
Technical Name (for n.o.s., not otherwise specified): Not applicable
UN/Identification Number: Not applicable
Class/Division: Not applicable
Sub Risk: Not applicable
Packing Group: Not applicable
RQ (Reportable Quantity): Not applicable
Emergency Response Guide Number: Not applicable
FCR EUROPEAN GROUND TRANSPORT (ADR/RID/ROAD/RAIL REQUIREMENTS):
Not determined. Hazards according to ADR/RID requirements not identified.
EMERGENCY INFORMATION:
HAZCHEM code: Not applicable.
TREM CARD number: Not applicable.

15. REGULATORY INFORMATION

EUROPEAN UNION CLASSIFICATION AND LABELLING REQUIREMENTS:
No European Union labelling requirements.

16. OTHER INFORMATION

HAZARD LABEL:

**** NOT CLASSIFIED AS A SIGNIFICANT FIRE HAZARD ****
**** NO FIRE HAZARD IDENTIFIED ****
**** NOT CLASSIFIED AS A SIGNIFICANT ENVIRONMENTAL HAZARD ****
** TARGET ORGAN- PHARMACEUTICAL AGENT- MAY REDUCE BLOOD PRESSURE.
** SYMBOL: NOT REQUIRED. (NN)

REFERENCES:

SB HAZARD DETERMINATION

OTHER INFORMATION:

IF HMIS RATINGS ARE USED AT YOUR SITE, USE THE FOLLOWING:
HEALTH = 2 FIRE = U REACTIVITY = U

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13E1

MAY 19 1995

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

KREDEX® TABLETS

(Carvedilol)

12.5 and 25 mg

NDA 20-297

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

(HFD-110)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-297

Kredex® Tablets

(Carvedilol)

The Food and Drug Administration (FDA) recognizes the National Environmental Policy Act of 1969 (NEPA) as the national charter for protection, restoration, and enhancement of the environment. NEPA establishes policy, sets goals (section 101), and provides procedures (section 102) for carrying out the policy.

Environmental information is to be available to the public and the decisionmaker before decisions are made about actions that may significantly affect the quality of the human environment; FDA actions are to be supported by accurate scientific analyses; and environmental documents are to concentrate on timely and significant issues, not to amass needless detail.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Kredex® Tablets, SmithKline Beecham Pharmaceuticals has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Carvedilol is administered as an oral tablet in the treatment of essential hypertension. Drug substance intermediates are manufactured by Boehringer Mannheim GmbH, Mannheim, Germany. The drug substance will be manufactured at SmithKline Beecham (Manufacturing) Limited, County Cork, Ireland and the drug product will be manufactured and packaged at SmithKline Beecham Pharmaceuticals Co., Cidra, Puerto Rico. The finished drug product will be used in hospitals, clinics and by patients in their homes.

Chemical and physical test results and information indicate that carvedilol will most likely be restricted to the aquatic and terrestrial environments. A substantial amount of the drug will be removed from the aquatic environment as the compound will adsorb to sludge in waste water treatment plants. The compound degrades rapidly upon exposure to light although this will vary depending on the exposure conditions in the environment and it is also susceptible to aerobic biodegradation. As the compound is expected to persist in the environment for some time, acute toxicity studies were conducted using water fleas (*Daphnia pulex*) and bluegill sunfish (*Lepomis macrochirus*). The studies indicate that the drug would not be expected to exhibit acute toxicity effects to aquatic organisms at concentrations expected to be emitted into and exist in the environment. Carvedilol may enter the terrestrial environment from sludge that is applied to land and will remain tightly bound to soil. The material is not expected to persist in the soil compartment and toxicity to terrestrial organisms is expected to be less than that determined for aquatic organisms due to the decreased exposure pathways.

Microbial inhibition studies indicate that respiration in activated sludge is not inhibited at concentrations several orders of magnitude greater than the maximum expected environmental concentration (MEEC).

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, pharmaceutical processing waste, and user disposal of empty or partly used product and packaging. Waste drug product and pharmaceutical processing waste will be disposed of predominantly at licensed incineration facilities although small quantities may be emitted in effluent waste streams. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system while some unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. A certification has been provided by the German authorities stating that Boehringer Mannheim GmbH is operating in compliance with their environmental laws and regulations.

Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

5/19/95 *[Signature]*
DATE Prepared by
Fancy B. Sager
Review Chemist
Center for Drug Evaluation and Research

5/19/95 *[Signature]*
DATE Approved
Phillip G. Vincent, Ph.D.
Technical Assessment Officer
Center for Drug Evaluation and Research

5/19/95 *[Signature]*
DATE Approved
Robert L. Terussi, Ph.D.
Associate Director for Chemistry
Center for Drug Evaluation and Research

Attachments:

- I: Environmental Assessment
- II: Compliance Statements
- III: Label Warning Table
- IV: Material Safety Data Sheet

CC: Original NDA 20-297/ZMcDonald copy to NDA/HFD-110
FONSI File 20-297/HFD-004
P. Vincent/HFD-004
Docket File 20-387/HFD-004
FOI Copy/HFD-019

20297.FON
F/T by NBS 05/19/1995

ATTACHMENT I

ENVIRONMENTAL ASSESSMENT INFORMATION

Carvedilol

1. DATE: March 17, 1995
2. NAME OF APPLICANT: SmithKline Beecham Pharmaceuticals
3. ADDRESS: Four Falls Corporate Center
Route 23 and Woodmont Avenue
P.O. Box 1510
King of Prussia, PA 19406

4. DESCRIPTION OF THE PROPOSED ACTION:

4.1 Description of the Requested Approval

SmithKline Beecham Pharmaceuticals is requesting approval for use of carvedilol for the treatment of essential hypertension. β -blocking and vasodilator effects occur in the same dosage range; carvedilol thus offers two active mechanisms of value in the management of hypertension. Carvedilol may also be effective in the management of other cardiovascular disorders, such as angina pectoris and/or left ventricular dysfunction.

4.2 Need for the Proposed Action

Carvedilol is a non-selective β -receptor blocking agent with vasodilative properties. It reduces peripheral vascular resistance through vasodilation and suppresses the renin-angiotensin-aldosterone system through β -blockage. Through these effects, carvedilol significantly reduces blood pressure in hypertensive patients. Carvedilol has no intrinsic sympathomimetic activity. By balancing vasodilation and β -adrenoreceptor blockage, carvedilol maintains myocardial function without affecting left ventricular ejection fraction. It causes no significant decrease in heart rate. The multiple actions of carvedilol are responsible for the antihypertensive efficacy of the drug in animals and in humans, and may also provide effective therapy in angina and congestive heart failure.

This Environmental Assessment Information reflects effluent discharges based on estimated fifth year production of drug substance and product, as well as detailed information on the waste treatment and disposal processes at SmithKline Beecham Pharmaceuticals facilities at Cork, Ireland, (drug substance production), and Cidra, Puerto Rico (drug product production), as well as summary information on the production of key drug intermediates at the Boehringer Mannheim facility in Mannheim, Germany (drug intermediate production). Details on the Boehringer Mannheim facility are available in DMF 9502. This report also includes all of the fate and effects data and evaluations which are currently available for carvedilol drug substance.

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The manufacture of carvedilol substance and product will employ the same environments and utilize existing plants that are also currently manufacturing other pharmaceutical products.

4.3 Location where Product will be Produced

Carvedilol drug intermediates, used to produce the product that is the subject of the proposed action, are manufactured at the following facility:

Boehringer Mannheim GmbH
Sandhofer Strasse 116
Postfach 310120
D-6800 Mannheim 31
Federal Republic of Germany

The Boehringer Mannheim facilities used to produce these intermediates are located in Mannheim, Germany.

Carvedilol, the drug substance in the product which is the subject of the proposed action, is manufactured (stages 4-8) at the following facility:

SmithKline Beecham (Manufacturing) Limited
Currabinny, Carrigaline
County Cork
Ireland

SmithKline Beecham (Manufacturing) Limited is located approximately twelve miles south of Cork City on the southern shores of Cork Harbor. There is a total land bank of 130 acres, but the facility occupies only 28 acres. The immediate area is rural, with some farms and dwellings within a half mile radius of the boundary fence. The site discharges an aqueous waste into Cork Harbor after on-site biological treatment.

Carvedilol drug product will be prepared at the following facility:

SmithKline Beecham Pharmaceuticals Co.
Road 172
KM9.1/Bo Certenejas
Cidra, Puerto Rico 00739

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The Cidra facility for the drug product manufacture is a site of approximately 52 acres located in an agricultural/urban/industrial area on the central mountainous ridge of the island of Puerto Rico.

4.4 Locations where Product will be Used

Carvedilol drug product will be used in the United States of America (the subject of this NDA) and world-wide, with predominant use coinciding with areas of greatest population density.

4.5 Locations where Product will be Disposed of

Carvedilol drug product returned goods will be collected at the following site:

Division KENCO Group Inc.
1704 Mid Park Drive
Knoxville, Tennessee 37291

From this site, the materials will be shipped to one or more of the following licensed facility for destruction by high temperature incineration:

SmithKline Beecham Pharmaceuticals
Bristol Industrial Park
Weaver Pike
Bristol, Tennessee 37620

Ogden Martin Systems of Lake, Inc.
3830 Rogers Industrial Park Road
Okahumpka, Florida 34762

Documentation for these disposal facilities is provided in Appendix I.

5. DESCRIPTION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION:

5.1 Complete Nomenclature

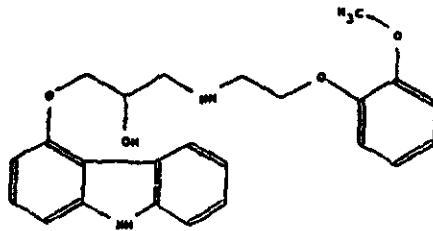
British Adopted Name (BAN):	Carvedilol
INN:	Carvedilol
United States Adopted Name (USAN):	Carvedilol

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Carvedilol

Trade Name:	
Chemical Name:	(±)-1-(9H-carbazol-4-yloxy)-3-[(2-(2-methoxy-phenoxy)-ethyl)amino]-2-propanol
5.2 <u>CAS Number:</u>	72956-09-3
5.3 <u>Laboratory Codes:</u>	SK&F 105517; BM 14.190
5.4 <u>Molecular Formula:</u>	C ₂₄ H ₂₆ N ₂ O ₄
5.5 <u>Molecular Weight:</u>	406.5
5.6 <u>Structural Formula:</u>	



5.7 <u>Description:</u>	A white to off-white powder
5.8 <u>Melting Range:</u>	SK&F 105517 typically melts over a 2-3°C range within 113-119°C
5.9 <u>Additives:</u>	Not applicable
5.10 <u>Impurities:</u>	

Organic impurities arising from the synthesis are determined by GC and HPLC. Solvent content is also measured by GC and the inorganic impurities, heavy metals, and sulfated ash are also monitored. Identification is included on the drug substance specification. The compound is stable, and no degradants are likely to arise under normal conditions.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

6.1 Introduction from Production

The production of carvedilol drug substance, intermediates and drug product will utilize the same facilities currently being used for the production of other pharmaceutical products. The following evaluation of the anticipated environmental impact of carvedilol production is based on estimated fifth year production and on existing waste treatment systems at the production facilities. Engineering estimates are used to predict anticipated discharge levels; however, the evaluations do not reflect changes in treatment process operations or technology which might be implemented before actual approval of the carvedilol application.

This Environmental Assessment contains non-confidential information on the control and disposition of gaseous, aqueous, and solid wastes at the production facilities.

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6.1.1 Drug Intermediate Production at Boehringer

The Boehringer Mannheim facilities used to produce the intermediates (2) are located in Mannheim, Germany. One intermediate will be produced at Production Plant HC-B 21, and the second intermediate will be produced at Production Plants HC-B 4, HC-B 10 and HC-B/OB.

6.1.1.1 Introduction from Production of Drug Intermediate at HC-B 21

The following information was provided by Boehringer Mannheim GmbH regarding the introduction of substances into the environment from production of intermediate at Production Plant HC-B 21.

6.1.1.1.1 Emissions as Part of Waste Water

The substances described in the following table are expected to be emitted as part of the wastewater. This wastewater is discharged from the production plants, pretreated in the BM waste water purification plant and then discharged into the community wastewater system/sewage plant, where final treatment takes place.

Substance ^a	CAS Number
Sodium chloride	7647-14-5
Toluene	108-88-3
Organic By-products	NA

^a Substances expected to be emitted during each process step.

6.1.1.1.2 Solid/Liquid Wastes

No other solid or liquid wastes are produced during the production steps of the intermediate.

6.1.1.2 Emissions Requirements at the Boehringer Mannheim Plant

Boehringer Mannheim GmbH reached an agreement on pollution control with Mannheim in the state of Baden-Wurtemberg, where its plant is located. This agreement requires Boehringer Mannheim GmbH to comply with the regulations for environmental protection enacted by the German Federal Government.

6.1.1.2.1 Emission Requirements for Sewage into the Municipal Wastewater System

The following table summarizes the maximum wastewater permit levels established by the government.

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Parameter	Value
pH	6.0 - 9.5
Temperature	max. 35°C
COD	700 mg/L
Ratio COD/BOD	< 2.5 :1
Settling substances (solvents)	1 mL/30 minutes
Sulfate (SO ₄)	400 mg/L
Sulfide (S)	10 mg/L
Sulfite (SO ₃)	50 mg/L
Fluoride	50 mg/L
Phenols	20 mg/L
Aromatic Hydrocarbons	30 mg/L
Ammonia as NH ₄	100 mg/L
AOX	0.5 mg/L
Organic solvents miscible with water	3000 mg/L
Organic solvents not miscible with water	According to solubility in water
Cu	1 mg/L
Fe	20 mg/L
Cr (III)	3 mg/L
Cr (VI)	0.1 mg/L
Zn	3 mg/L

6.1.1.2.2 Emission Requirements on Waste Gases

The following table summarizes the permit levels for waste gas emissions, according to the "Technical Directions for Maintaining Clean Air" (TA Luft).

Emission	Value
Ethylene oxide	≤ 5 mg/m ³
Toluene	0.15 g/Nm ³

If more than one substance in the waste gas is classified as carcinogenic III, the total concentration is not allowed to exceed 5 mg/m³ at a mass flow of 25 grams (or more) per hour. If there is more than one organic substance (vapor) in the waste gas, the total concentration is not allowed to exceed 0.15 g/Nm³ at a mass flow of 3 kg (or more) per hour.

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Manufacture of the intermediate in the Boehringer Mannheim plant (HC-B 21) will not result in the discharge of any emissions in excess of the amounts allowed by the applicable laws. A citation of and statement of compliance with applicable emissions requirements is provided in Appendix II. In addition, a certification of compliance signed by the appropriate government authority (Regierungsprasidium Karlsruhe) is also included in Appendix II.

6.1.2 Drug Intermediate Production at Boehringer

6.1.2.1 Introduction from Production of Drug Intermediate at HC-B 4, HC-B 10, and HC-B/OB

The following information was provided by Boehringer Mannheim GmbH regarding the introduction of substances into the environment from production of intermediate at Production Plants HC-B 4, HC-B 10 and HC-B/OB.

6.1.2.1.1 Emissions as Part of Wastewater

The substances described in the following table are expected to be emitted as part of the wastewater. This wastewater is discharged from the production plants, pretreated in the BM wastewater purification plant and then discharged into the community wastewater system/sewage plant, where final treatment takes place.

Substance	CAS Number
Acetic acid	64-19-7
Methanol	67-56-1
Organic By-products	NA
Intermediates	NA
Phosphoric acid	7664-38-2
Ethanol	64-17-5
Potassium chloride	7447-40-7

6.1.2.1.2 Solid/Liquid Wastes

The substances listed in the following table are produced as liquid or solid wastes. Solid wastes are disposed of through incineration at a community plant, and liquid wastes are disposed of through incineration at an outside company licensed to dispose of industrial waste products.

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Substance	CAS Number
Resin by-products dissolved in solvent	NA
Activated carbon	7440-44-0
Filter aid	NA
Waste solvents	NA
Alumina	1344-28-1
Solvent/Oil mixture (residue of distillation)	NA

6.1.2.2 Emissions Requirements at the Boehringer Mannheim Plant

Boehringer Mannheim GmbH reached an agreement on pollution control with Mannheim in the state of Baden-Wurtemberg, where its plant is located. This agreement requires Boehringer Mannheim GmbH to comply with the regulations for environmental protection enacted by the German Federal Government.

6.1.2.2.1 Emission Requirements for Sewage into the Municipal Wastewater System

The following table summarizes the wastewater permit levels required by the government.

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Carvedilol

Parameter	Value
pH	6.0 - 9.5
Temperature	max. 35°C
COD	700 mg/L
Ratio COD/BOD	< 2.5 :1
Settling substances (solvents)	1 mL/30 minutes
Sulfate (SO ₄)	400 mg/L
Sulfide (S)	10 mg/L
Sulf (SO ₃)	50 mg/L
Fluoride	50 mg/L
Phenols	20 mg/L
Aromatic Hydrocarbons	30 mg/L
Ammonia as NH ₄	100 mg/L
AOX	0.5 mg/L
Organic solvents miscible with water	3000 mg/L
Organic solvents not miscible with water	According solubility in water
Cu	1 mg/L
Fe	20 mg/L
Cr (III)	3 mg/L
Cr (VI)	0.1 mg/L
Zn	3 mg/L

6.1.2.2.2 Emission Requirements on Waste Gases

The following table summarizes the permit levels for waste gas emissions, according to the "Technical Directions for Maintaining Clean Air" (TA Luft).

Emission	Value
Ethanol	0.15 mg/m ³
Diisopropylether	0.15 g/Nm ³

If more than one of the substances listed in the table above is found in the waste gas, the total concentration is not allowed to exceed 0.15 g/Nm³ at a mass flow of 3 kg (or more) per hour.

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Manufacture of the intermediate in the Boehringer Mannheim plant (HC-B 4, HC-B 10 and HC-B/OB) will not result in the discharge of any pollutants in excess of the amounts allowed by the applicable laws. A citation of and statement of compliance with applicable omissions requirements is provided in Appendix III. In addition, a certification of compliance signed by the appropriate government authority (Regierungsprasidium Karlsruhe) is also included in Appendix III.

6.1.3 Drug Substance Production at Cork

Carvedilol (SK&F 105517) drug substance process stages 4-8 will be performed at SmithKline Beecham (Manufacturing) Limited, a SmithKline Beecham Pharmaceuticals' facility in Cork, Ireland. Environmental evaluations of the impacts from drug substance production at Cork follow.

SmithKline Beecham (Manufacturing) Limited, Cork, Ireland is expected to remain in compliance with applicable waste effluent permits throughout the production of carvedilol drug substance. The Cork facility is regulated under an Integrated Pollution Control (IPC) license (Reference Number in Register of Licenses: 4; Date of Notification: October 28, 1994), under authority of the Environmental Protection Agency and the Environmental Protection Agency Act, 1992. This license contains permit levels and monitoring procedures for all plant emissions (wastewater, air, incinerators, etc.), as well as guidelines for the establishment of an Environment Management Programme, to assess all operations for the use of cleaner technology and the minimization of waste.

6.1.3.1 Waste Stream Summary and Disposition

The types of waste streams generated at SmithKline Beecham (Manufacturing) Limited will be disposed of such that release into the environment (gaseous and aqueous waste) will not exceed SmithKline Beecham (Manufacturing) Limited' plant permit levels (Appendix III).

6.1.3.2 Material Balance

Material balance information for the chemical inputs, process intermediates and effluents was determined for stages 4-8, thus accounting for all materials and amounts used in or produced by these stages. Waste outputs include leftover material resulting from production, inspection operations, assay solutions sampled before and after filtration, and floor and equipment washings.

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6.1.3.3 Controls Exercised on Wastes

6.1.3.3.1 Air and Fugitive Emissions

Hydrogen, the only off-gas produced, is vented directly to the atmosphere through a flame arrestor. Fugitive emissions are monitored if there is reason to suspect a gaseous leak. Air from the buildings where chemical processes are performed is filtered through two chemical absorbers. Air is automatically monitored every half hour by gas chromatography for several compounds, depending on the processes being performed, as it is discharged to the atmosphere.

6.1.3.3.2 Incinerated Wastes

Most process waste streams produced during carvedilol production at SmithKline Beecham (Manufacturing) Limited are incinerated at 1000°C. Process effluents are stored prior to incineration, and approximately 200 L of waste per hour are burned in each of two incinerators. After incineration, the effluent gas is passed through an absorber for the scrubbing of acidic compounds before discharge to the environment through a stack. This scrubber unit consists of a caustic solution circulating through a packed bed. Scrubber liquors are sent to the on-site wastewater treatment facility.

At discharge, incinerator gases are continuously monitored for carbon monoxide, sulphur dioxide and total organic carbon (TOC). The amount of organic material remaining after incineration is calculated using a 99.99% incineration destruction efficiency, based upon the known removal efficiencies for mercaptan and methylethyl ketone (MEK). The Cork facility is regulated under an Integrated Pollution Control (IPC) license (Reference Number in Register of Licenses: 4; Date of Notification: October 28, 1994), under authority of the Environmental Protection Agency and the Environmental Protection Agency Act, 1992.

6.1.3.3.3 Biotreatment System

Several of the carvedilol process wastestreams are treated in the on-site wastewater biotreatment facility. Scrubber liquors from the incinerators are sent for aerobic biological treatment before being discharged.

The treatment facility incorporates a basin of activated sludge, which has a retention time of 10 days. The biotreated waste (including domestic effluents and mutrators, floor washes, incinerator quench streams, and scrubber and environmental spent liquors) is sent to a balancing tank prior to neutralization in a second tank. The wastes are then sent to a stripping tank, prior to passing to an aeration tank to reduce biological oxygen demand (BOD). After aeration, some of the waste is aerated a second time in another tank, while the remaining waste is sent to a clarifier. The twice-aerated effluent is passed to another

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clarifier. Both clarifiers are dosed with polyelectrolytes, and effluent wastes are sent to the final holding tank prior to discharge.

Several parameters of the effluent are monitored on a daily basis at three stages of the treatment process. The flow rate, pH, COD, total dissolved solids and load (kg of COD per day) are monitored at the input stage, and the pH, dissolved oxygen, MLSS and F/M are monitored at the sludge plant. At the final holding tank, the pH, COD, suspended solids, ammonia and flow rate are also monitored. In addition to normal testing, effluent liquors are sampled if a problem (e.g., equipment malfunction) is discovered.

Treatment of effluents results in >80% reduction in BOD. Review of the measured (confidential) and calculated concentrations of affected aqueous effluent components and a comparison with their permit levels resulted in the determination that the SmithKline Beecham (Manufacturing) Limited facility is in compliance with their aqueous effluent permits.

6.1.3.3.4 Solid Waste

Solid wastes produced during Cork carvedilol substance production process are sent off-site for disposal.

All treatment plant sludge is mechanically dewatered to approximately 15% solids prior to off-site disposal, with the extracted liquid returned to the effluent treatment plant. The Cork facility is regulated under an Integrated Pollution Control (IPC) license (Reference Number in Register of Licenses: 4; Date of Notification: October 28, 1994), under authority of the Environmental Protection Agency and the Environmental Protection Agency Act, 1992. Wastes and leachate will be tested for the presence of heavy metals, organohalogens and other micropollutants; solid waste regarded as non-hazardous will then be disposed of in a lined landfill designated for non-hazardous materials, with leachate monitoring. There are currently no limits as to the amount of solid wastes disposed of off-site.

6.1.3.4 Certification of Compliance

SmithKline Beecham Pharmaceuticals Co. (SmithKline Beecham (Manufacturing) Limited) is committed to environmental control and will operate within its permit during the production of carvedilol drug substance. A citation of and statement of compliance with applicable emissions requirements is provided in Appendix III.

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6.1.4 Introduction from Production of Drug Product

Carvedilol (SK&F 105517) drug product will be produced in a continuous process, consisting of granulation, drying and blending, compression and coating, and printing and packaging at SmithKline Beecham Pharmaceuticals Co. in Cidra, Puerto Rico. The manufacture of carvedilol will employ the same environment and utilize the existing plants that are currently used to manufacture other pharmaceutical products. Carvedilol will be prepared as 12.5 and 25 mg tablets. Environmental evaluations of the impacts from drug product production follow.

6.1.4.1 Waste Stream Summary and Disposition

The waste streams generated at the Cidra facility will be disposed of using appropriate procedures, such that release into the environment (gaseous and aqueous waste) will not exceed Cidra permit levels (Appendix IV) and off-site disposal of solid wastes will not violate applicable regulations.

6.1.4.2 Material Balance

Material balance information for the chemical inputs, process intermediates and effluents was determined, thus accounting for all materials and amounts used in or produced during the drug product process. Waste outputs include leftover material resulting from production, inspection operations (rejects are discarded), assay solutions sampled before and after filtration, and floor and equipment washings.

For the purposes of this evaluation, the production campaign is assumed to use all of the drug substance, which is based on the projected fifth year of carvedilol production for the U.S. Market.

6.1.4.3 Controls Exercised on Wastes

6.1.4.3.1 Dryer Water Vapor

Two waste streams consist of water evaporated during drying processes. These streams are filtered before venting to the environment and should contain no hydrocarbons or particulates. The water collected is sent to the on-site wastewater treatment facility for biotreatment.

Air emissions from the process fall under the State Rules and Regulations for Air Pollution Control. The regulations are administered by the Environmental Quality Board of the Commonwealth of Puerto Rico. Currently, the facility is operating under Permit No. PFE-21-

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0590-0477-I-III-0 and PFE-21-1089-0929-I-II-III-0, and is not considered to be a major pollutant source; thus, a PSD review (under the EPA program) will not be necessary.

6.1.4.3.2 Solvent Vapor

The incinerator at the Cidra facility is expected to burn only four solvent vapors, none of which are produced during the carvedilol production process. The scrubber blowdown liquors from the incinerator are sent to the SmithKline Beecham Pharmaceuticals Co. facility in Guayama, Puerto Rico for treatment and disposal.

6.1.4.3.3 Aqueous Wastes Disposed Of Through Biotreatment

The aqueous waste streams (1-4) are sent to the wastewater treatment facility. The streams are first pumped through a series of sand filters and an activated carbon adsorption system. The waste streams are then discharged into an equalization holding tank for aeration. Sanitary waste bypasses sand and carbon columns and goes directly to the equalization basin. The pH of the influent stream is adjusted with sodium hydroxide or carbon dioxide prior to entering the activated sludge system. The residence time of effluent in the activated sludge basin is 24 hours, and the average volume maintained is 80,000 gallons. The treatment facility is designed for a 85,000 gallon per day flow, with a maximum capacity of 127,000 gallons per day. The biotreatment waste stream then enters a clarifier, where the sludge is allowed to settle and separate from the biotreated aqueous effluent as supernatant.

The pH of the aqueous effluent is adjusted to 11.0 with hydrated lime and sent to a second clarifier, where solids are precipitated out of solution and removed by flocculation. The clarifier's precipitated solids are sent to the aerobic digester for further processing. The wastewater effluent is recarbonated and neutralized with carbon dioxide prior to passing through a second series of sand and carbon filters. Filtered effluent is collected in a filter effluent sump. This filtered effluent then passes through a Reverse Osmosis (RO) module for total dissolved solids and organic removal. Reverse Osmosis (RO) Permeate is collected in a 100,000 gallon effluent storage tank and Reverse Osmosis (RO) reject is disposed off to PRASA (Permit Number GDG-94-505-032). A copy of the permit is attached in Appendix V. The effluent is then chlorinated, aerated and monitored for pH, temperature and dissolved oxygen before entering Quebrada Las Quebradillas (Las Quebradillas Creek). After aeration in the biotreatment facility, 55,000 gallons per day of final effluent is recycled to cooling and quench towers and 25,000 gallons per day of final effluent is discharged. Rainwater runoff from the grounds of the Cidra facility are also discharged to this creek, which empties into the Turabo River and flows into Carraizo Lake (the water source for the metropolitan area of San Juan).

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For the purpose of this environmental assessment, the total quantity of drug product components expected to be emitted into the site biotreatment facility is estimated at 3% of the total batch.

Final effluent levels from biotreatment were calculated using the following equation:

$$(A \times 10^6 \text{ mg/kg} / B/C)D = E$$

where: A = total quantity of component to waste per day (kg/day);
B = number of days over which discharge is made (1);
C = site effluent discharge rate (240,175 L/day);
D = removal efficiency;
E = concentration of component in effluent in mg/L.

For developing the discharge level data, it is assumed that no volatilization or bioadsorption of these materials occurs during treatment, and that biodegradation is the only operative removal mechanism for some of the effluent compounds. Review of the measured (confidential) and calculated concentrations of affected aqueous effluent components and a comparison with their permit levels resulted in the determination that the Cidra facility is in compliance with their aqueous effluent permits.

The contributions of the compounds used in the tablet formulation of carvedilol (SK&F 105517) to the total quantity of regulated components in the effluent will not cause total effluent concentrations to exceed the permit levels, assuming complete removal of carvedilol by the wastewater treatment facility. The quality of the effluent discharge meets Puerto Rico's water quality standards. The treatment facility operates under National Pollutant Discharge Elimination System (NPDES) Permit PR 0021997. In Puerto Rico, the NPDES Permit Program is administered by the Federal Environmental Protection Agency.

The facility is also regulated by the Puerto Rico Water Pollution Law, which is administered by the Assistant Secretary of Health for Environmental Health and Consumer Protection. Additional regulations are the Puerto Rico Harmful Spills Law, the Puerto Rico Public Policy Environmental Act, and the Puerto Rico Water Quality Standards, each administered by the Board of Environmental Quality. Permit limits for the wastewater discharge are stated in the NPDES permit. The discharge limits are presented in Appendix IV.

6.1.4.3.4 Solid Wastes

The activated carbon (granular Calgon AC, 8 X 30 mesh) from the biotreatment filters is replaced every three months. Settled sludge from the first clarifier in the biotreatment process is divided into two streams: sludge waste to an aerobic digester and sludge returned to the system. Within the digester the sludge waste is concentrated by settling and decanting the water. More water is then removed from the concentrated sludge slurry

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by means of a wedge filtration system and solar drying beds. The decanted water is recycled back to the feed of the wastewater treatment system. Sludge is maintained in the drying beds at a depth of two feet, and the waste volume is reduced by at least 92% during the drying period of two weeks. The dried sludge, and the spent carbon are disposed of as non-hazardous material at a municipal landfill, after testing using the Toxicity Characteristic Leaching Procedure (TCLP). Other solid wastes containing drug product (rejects, protective clothing, drums, filters, collected dust) are disposed of off-site to Ogden Martin Systems of Lake, Inc., Okahumpka, Florida, US (see Appendix I). There are no limits or restrictions placed on the quantities of materials that may be sent to the licensed disposal facilities.

6.1.4.4 Environmental Legislation

The following partial list of federal legislation may affect operation of the wastewater treatment facility.

Federal Water Pollution Control Act, as amended
Clean Water Act, as amended
Resource Conservation and Recovery Act
Safe Drinking Water Act
Toxic Substances Control Act
National Environmental Policy Act

6.1.4.5 Safety

The Cidra facility has adopted personnel safety procedures in all areas of plant activity, including procedures and information on electrical hazards, tool use, fire hazards, chemical handling and first aid.

6.1.4.6 Certification of Compliance

SmithKline Beecham Pharmaceuticals Co., Cidra, Puerto Rico, will operate within its permits during the production of carvedilol drug product. A citation of and statement of compliance with applicable emissions requirements is provided in Appendix IV.

6.2 Introduction from Use of Drug Product

Estimates of the maximum expected emitted concentrations (MEEC) from use of carvedilol tablets were calculated in part using data from reference [1]. At concentrations expected to be emitted into and exist in the environment, carvedilol is expected to exhibit no toxicity to aquatic organisms.

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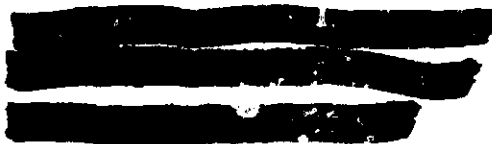
6.3 Introduction from Disposal of Drug Product

Carvedilol drug product returned goods will be collected at the following site:



From this site, the materials will be shipped to the following licensed facilities for disposal (e.g., destruction by high temperature incineration).

SmithKline Beecham Pharmaceuticals
Bristol Industrial Park
Weaver Pike
Bristol, Tennessee 37620



Documentation for these disposal facilities is provided in Appendix I. Based on the controlled and highly efficient thermal destruction of unused drug substance and product, no material should be introduced into the environment from disposal.

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

7.1 Metabolism

The biotransformation and excretion of carvedilol in normal male human volunteers following single oral administration of ^{14}C -carvedilol was investigated [2]. Radiometabolites in both feces and urine were separated, quantified, and characterized structurally using a combination of HPLC and mass spectral techniques. The majority of the radiolabeled dose was found to be excreted in the feces (52%), with a lesser amount excreted in the urine (20%). The carvedilol-related products observed in the feces in this study included unchanged carvedilol and several oxidation products. Carvedilol-related products identified in feces represented 71% of the fecal radioactivity, with all of the products each accounting for more than 6.4% of the fecal radioactivity characterized.

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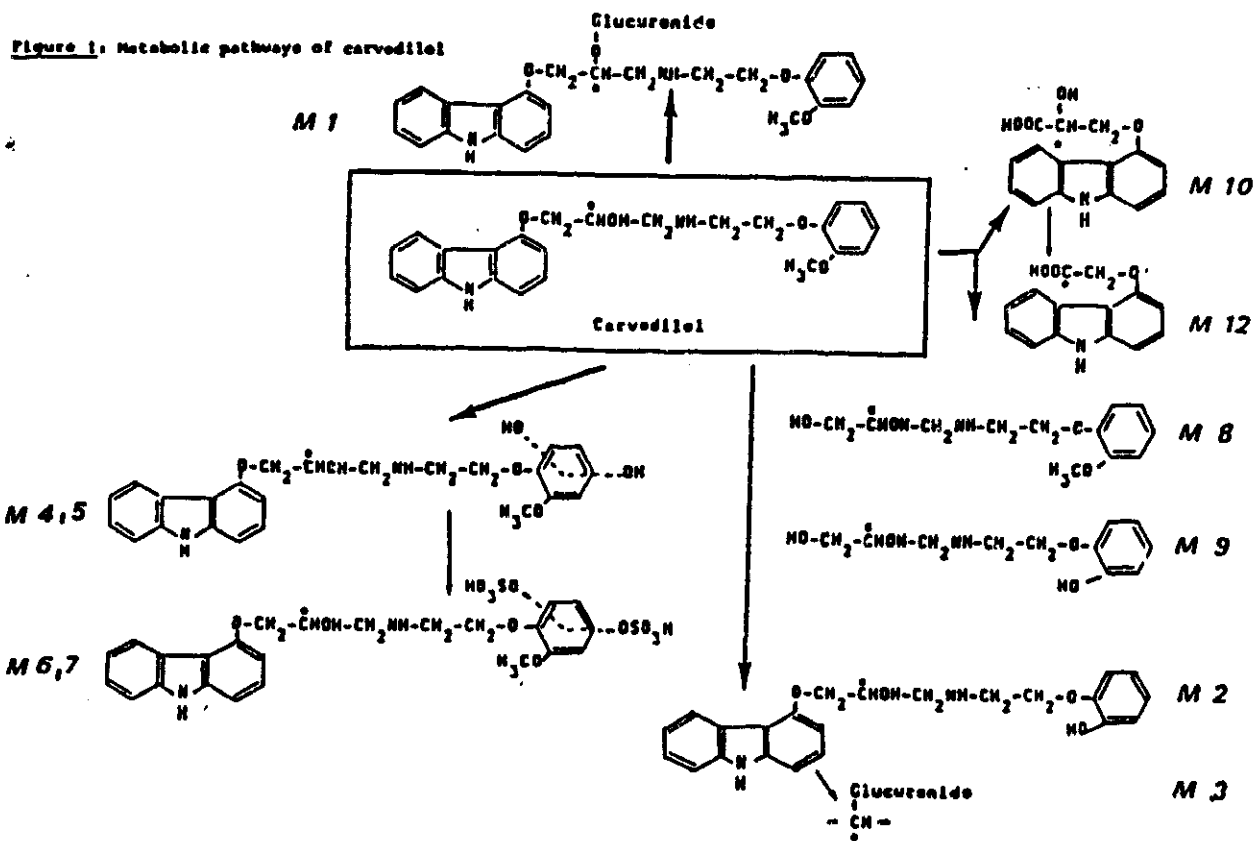
Carvedilol

The profile of urinary metabolites was much more complex, containing more than 26 compounds. The most abundant urinary metabolites were glucuronide derivatives of carvedilol. While the majority of the carvedilol metabolites excreted in feces were products of oxidation pathways, urinary metabolites included products of both oxidation and conjugation pathways. In general, all of the major metabolites structurally related to carvedilol are more polar analogs, and for the purposes of this environmental assessment, assessment of the fate and effects of carvedilol itself may be taken to represent a worst-case scenario.

The reported percent of an administered radioactive dose (range) recovered in the urine and feces is 15.29% - 20.00% and 52.12% - 61.40% respectively [31, 32]. The percent dose representing drug substance which was excreted unmetabolized was 0.21% - 0.28% for urine and 8.39% - 9.89% for feces [32].

A summary of the fecal, urinary and plasma metabolites of carvedilol in male human subjects is presented in Figure 1.

Figure 1



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7.2 Physical Properties

Physical properties were determined for carvedilol in-house, at the Environmental Research Laboratory. Several detailed reports are given in Appendix VI and summarized below.

7.2.1 Water Solubility

The water solubility of carvedilol as a function of pH was determined at 25°C. The results are given below and detailed in reference [3].

pH	Water Solubility (mg/L)			95% Confidence Range	
	mean	stdev	%RSD	low	high
5.04	434	46.3	10.7	416	452
7.09	30.8	3.66	11.9	29.4	32.2
9.04	1.61	0.356	22.1	1.46	1.76
8.43(DI H ₂ O)	5.46	1.88	34.3	4.72	6.20

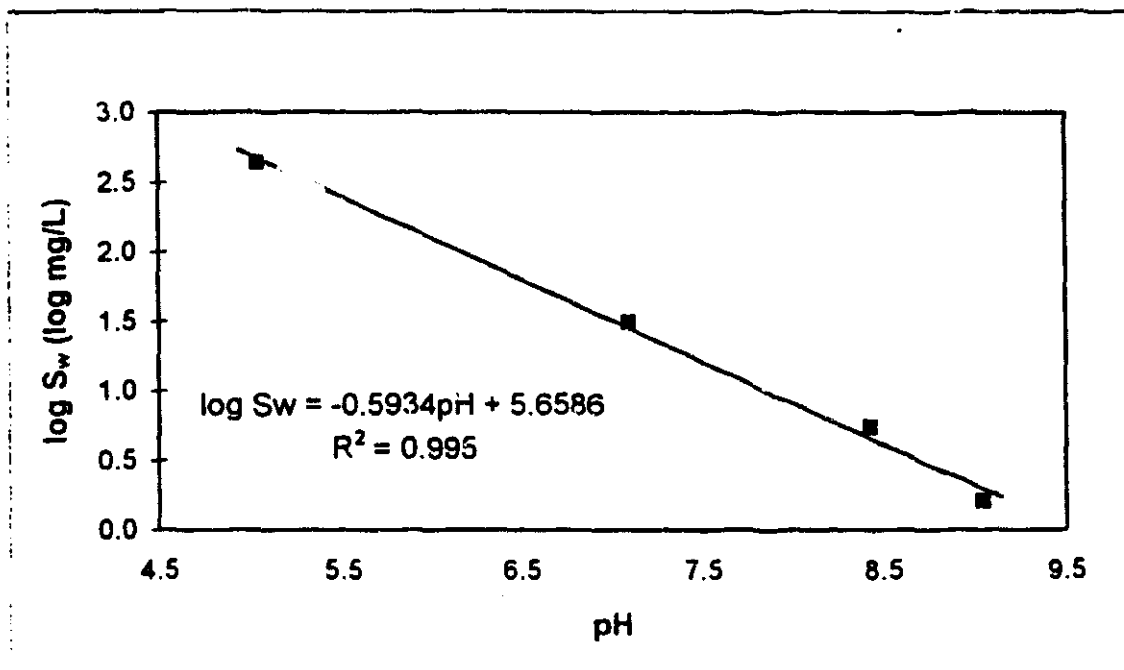
A log transformation of the solubility data plotted against pH shows a linear relationship, as illustrated in Figure 2 below.

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Figure 2

Aqueous Solubility of SK&F 105517.



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7.2.2 Dissociation Constant

Because of its low water solubility, the pK_a for carvedilol was determined by preparing methanol-water solutions of carvedilol containing 45, 50, 57, 66 and 71 v/v% methanol and then titrating these solutions with 0.1N HCl. The apparent pK_a was plotted versus concentration of methanol, resulting in a straight line whose intercept is the value of pK_a in water. A pK_a of 7.8 was obtained for the secondary amine group. The pK_a 's of the -NH- group in the carbazole ring, which is amphoteric, were not determined. According to published data, the pK_a 's of carbazole are 16.7 [4] (proton lost) and -5.7 [5] (proton gained). This suggests that the acidity or basicity of the carbazole in SK&F 105517 is extremely weak. The experiment is detailed in SB report code CSL-14467-250 which is included in Appendix VI; see reference [6].

7.2.3 Octanol/Water Distribution Coefficient

The octanol/water distribution coefficients (K_{ow}) for carvedilol were determined at two concentrations in triplicate test systems consisting of pH 5, 7 and 9 buffers and high-purity n-octanol. The results are reported in reference [7] and summarized below.

Solvent	26.3 mg/L		263 mg/L	
	K_{ow}	log K_{ow}	K_{ow}	log K_{ow}
Octanol/pH 5 buffer	106	2.02	85.7	1.93
Octanol/pH 7 buffer	528	2.72	549	2.74
Octanol/pH 9 buffer	1040	3.01	1260	3.10

7.2.4 Vapor Pressure, Volatilization, Henry's Law Constant

The vapor pressure of a substance is the property governing the tendency of a chemical substance to be transported into and in air and is thus an important parameter for predicting the distribution of chemicals into environmental compartments. For non-ionizable organic compounds, measurement of the vapor pressure is straightforward, and the value obtained is meaningful in environmental predictions. However, for compounds such as carvedilol, which will be ionized in solution at environmental pHs, the vapor pressure of the free base of the compound alone is less useful for predicting air-water partitioning. Vapor pressure may over-predict volatilization of chemicals which are partially ionized in aqueous solution. Since carvedilol has a basic pK_a of 7.8, approximately 86% of dissolved carvedilol species (ionized) will exist as the protonated base at pH 7. Therefore, only 14% (neutral) of dissolved species are available for volatilization.

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A more useful parameter for estimating the air-water partition coefficient for a chemical, and thus the likelihood of its entering into and being transported by the atmosphere, is Henry's law constant. The apparent Henry's law constant, H_L , represents the ratio of the equilibrium concentration of a chemical substance in air to its corresponding concentration in water in a closed system. It can be used to estimate the tendency of a chemical to volatilize from aqueous solution at a given pH. H_L is related to vapor pressure (VP) and aqueous solubility (Sw) as follows:

$$H_L = VP/S_w$$

Since carvedilol exists primarily as a protonated base at environmental pH levels, the Henry's law constant was measured directly experimentally. Values of $<2.66 \times 10^{-7} \text{ m}^3 \text{ atm/mol}$ at pH 6.7 and $3.93 \times 10^{-7} \text{ m}^3 \text{ atm/mol}$ at pH 6.55 were obtained. The results are detailed in reference [9].

Lyman et al. in reference [10] provides the following interpretation of H_L values:

H_L ($\text{m}^3 \cdot \text{atm/mol}$)	Aquatic Volatility
1E-5 to 1E-7	"volatilizes slowly"
1E-7 to 3E-7	"essentially non-volatile"
< 1E-7	"less volatile than water"

With an H_L of $3.93 \times 10^{-7} \text{ m}^3 \cdot \text{atm/mol}$, the aquatic volatility of carvedilol may be characterized as a very slow process. In the presence of any significant depletion mechanism, mass transfer to the atmospheric compartment over time would be negligible.

7.2.5 UV/Vis Spectrum

The UV/Vis spectra of aqueous solutions of carvedilol were determined at pH 5, 7 and 9. The detailed study report is given in reference [11]. The experimental results indicate that the UV/Vis absorption spectrum of carvedilol is not affected by solution pH. In addition, significant absorbance at wavelengths greater than 290 nm was found, which suggests that carvedilol is likely to be susceptible to direct photochemical degradation in the environment.

7.2.6 Soil Sorption/Desorption (K_{oc}) and K_d

Soil sorption/desorption isotherms are carried out in order to generate a water-soil partitioning coefficient (K_{oc}) for use in predicting the mobility of a chemical in the terrestrial

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environmental compartment. For human drugs, however, the majority of users will discharge into municipal wastewater treatment systems [1]. As a result, a more meaningful partitioning coefficient to predict initial sorption to biomass or sludge is K_p , a measure of the partitioning between the aqueous phase and the biosolids phase in a wastewater treatment plant (WWTP).

From preliminary experiments, a mean K_p was determined to be 5500 ($\log K_p = 3.74$). From definitive equilibrium Freundlich isotherm data with active sludge, the sludge adsorption isotherm constant K was determined to be 20,400 ($\log K = 4.31$). The difference between these results may be due to different sludge sources and treatments. Standardized methodology for sludge adsorption studies has not yet been established. Details of the studies are given in reference [12]. The use of this constant to predict environmental partitioning is shown in section 7.3 below.

A soil sorption/desorption isotherm study was also carried out to generate a K_{oc} value for carvedilol. The detailed study report is given in reference [13] and summarized below.

Soil	%TOC	Solvent	K_{oc}	$\log K_{oc}$
Kansas	2.06	H ₂ O	23500	4.37
California	1.59	H ₂ O	40900	4.61
Iowa	1.53	H ₂ O	<u>36900</u>	<u>4.57</u>
Average			33800	4.53
Kansas	0.8	CaCl ₂	143000	5.16
California	1.59	CaCl ₂	530000	5.72
Iowa	1.53	CaCl ₂	<u>227000</u>	<u>6.36</u>
Average			300,000	5.47

The average K_{oc} from studies in water was 33,800; from studies in CaCl₂, a value of 300,000 was determined. Usually, if a lower K_{oc} is determined in the CaCl₂ solvent system, this is taken as indicating a significant amount of ion-exchange character in the sorption process, since the calcium ions would compete with the carvedilol protonated free base ions for ion-exchange sites, resulting in less carvedilol partitioning into the soil organic carbon phase. However, for carvedilol, the CaCl₂ studies gave a higher value. This may be due to a "salting out" effect of the CaCl₂, decreasing the water solubility of the carvedilol and resulting in stronger hydrophobic interactions with the soil organic carbon. Thus the

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sorption appears to be a more complex function of the chemical nature of the carvedilol and of the soil organic carbon. The usual name given to this complex phenomenon is chemisorption. It is interesting to note that correction of the sludge partition coefficient, $\log K_p = 4.31$, for organic carbon content (assumed to be approximately 50% (reference [14]), yields a $\log K_{OC}$ for sludge of 4.61. This is essentially the same as the $\log K_{OC}$ obtained for soils using water as the solvent.

Carvedilol exhibited very little desorption from soil. The percent desorbed from the soil systems tested ranged from only 0.34-2.36%.

In summary, the sludge and soil adsorption studies indicate that carvedilol will adsorb strongly to particulate organic materials and that once adsorbed it will be relatively immobile in the environment.

7.3 Environmental Partitioning Estimates for Carvedilol

Since the majority of carvedilol used in the United States will be introduced into the environment through Wastewater Treatment Plants (WWTPs), the partitioning of carvedilol in that system must first be considered. Taking total production as unity, the maximum fraction of drug entering the aquatic and terrestrial compartments after discharge from the WWTPs can be calculated as follows:

CALCULATION OF MAXIMUM EXPECTED EMITTED CONCENTRATION

Carvedilol

Given the following assumptions:

Total annual market volume (5th year)(MV_{total})	=	1
Fraction of US population using WWTP($F_{sewered}$)	=	0.74 [1]
Fraction of Drug Substance not excreted(F_m)	=	0
Annual US Sewage Flow(SF_{annual})	=	3.7×10^{13} L/yr [1]
Annual Yield of Dry Sludge from WWTPs(DS_{annual})	=	5.9×10^9 kg/yr [1]
Dilution rate from Application of Sludge to Agricultural Land (DR_{annual})	=	0.025 [1]
K_p (carvedilol)	=	

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Then the maximum expected emitted concentration (MEEC) into the environment of carvedilol from use of the drug product is calculated as follows, assuming 100% excretion of carvedilol and its metabolites in one day:

$$\begin{aligned} \text{Fraction emitted into WWTPs} &= MV_{\text{total}} \times F_{\text{sewered}} \\ &= \\ &= \end{aligned}$$

Based on the distribution of carvedilol between sludge and water,

$$\begin{aligned} K_p &= \frac{\text{Concentration in sludge } (C_2)}{\text{Concentration in sewer effluent } (C_1)} \\ 2.04 \times 10^4 &= \frac{C_2}{C_1} \\ C_2 &= \text{ (equation 1)} \end{aligned}$$

Since the fraction emitted (0.74) will be distributed between the sludge and the sewer effluent, the balance around the WWTP is

$$C_1 \times SF_{\text{annual}} + C_2 \times DS_{\text{annual}} = \text{ (equation 2)}$$

Substitution of the equation for C_2 (equation 1) into equation 2 gives

$$\begin{aligned} (3.7E13C_1) + 3.9E09(2.04E04C_1) &= \\ (3.7E13C_1) + (1.20E14C_1) &= \\ 1.57E14C_1 &= \\ C_1 &= \\ C_2 &= \\ C_2 &= \\ C_2 &= \end{aligned}$$

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Using the relationships of equation 2 gives:

$$\begin{aligned} (3.7E13C_1) &= \\ &= \\ (5.9E09)(C_2) &= \\ &= \end{aligned}$$

Thus, $\frac{1}{2}$ of the carvedilol emitted to wastewater treatment plants from use will distribute into the aqueous phase, with $\frac{1}{2}$ sorbing to the sludge and entering the terrestrial compartment. Given the high soil sorption and very low desorption of carvedilol, very little migration of carvedilol through the terrestrial compartment is likely to occur.

7.4 Transformation and Depletion Mechanisms of Carvedilol

7.4.1 Hydrolysis

The hydrolytic stability of carvedilol was determined in deionized water and in pH 5, 7 and 9 buffers. The results indicated that carvedilol is hydrolytically stable under the conditions tested, and has an estimated hydrolytic half-life ≥ 1 year [15]. The study is detailed in reference [16].

7.4.2 Aqueous Photolysis

Given carvedilol's significant absorption of light at wavelengths > 290 nm, the photolysis study on carvedilol was carried out at pH 7 in natural sunlight. The first-order direct aqueous photoreaction rate constant was determined to be 0.468 hr^{-1} , giving a half-life of 1.48 hours. The detailed study report is given in reference [17].

7.4.3 Aerobic Biodegradation

Aerobic biodegradability studies were carried out on carvedilol using a modification of standard methodology. The analytical method validation study is given in reference [18]. The definitive aerobic biodegradation study is detailed in references [19] and [33]. ERL study 92-021, reference [19], determined that biotransformation of carvedilol was detected after ~ 40 days with a first-order rate constant of 0.03 day^{-1} giving a half-life of 26.2 days. Another study, ERL Study 92-050, used methanol as a carrier to facilitate carvedilol bioavailability in the biodegradation test systems. For comparison it also contained treatments that added carvedilol to the test system without methanol carrier.

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The two treatment groups that used methanol had first-order rate constants of 0.1 and 0.05 day⁻¹ at 5 and 10 mg/L carvedilol concentration, respectively. This corresponds to respective half-lives of 6.9 and 13.9 days. The no methanol treatments had first-order rate constants of 0.02 and 0.01 day⁻¹ at 5 and 10 mg/L carvedilol concentration, respectively. This corresponds to respective half-lives of 34.6 and 69.3 days. The presence of a carrier solvent appears to significantly enhance the biodegradation kinetics in the test systems employed for the study probably as a direct consequence of increased bioavailability to the degrading microorganisms.

In addition to carvedilol itself, biodegradation/biotransformation studies were carried out on 4-hydroxycarbazole and carbazole, substructures of the carvedilol molecule likely to be the most recalcitrant to biotransformation. The half-lives for these two compounds were 21.8 days and 0.39 days, respectively. This may be taken as indicative of the eventual mineralization of the carvedilol molecule once the initial acclimation is accomplished. Interestingly, the two replicate experiments for the biodegradation studies showed different HPLC profiles, indicating that carvedilol in the different flasks was undergoing biotransformation by two different pathways. The details of these studies are given in references [20] and [21]. See also aquatic toxicity evaluations in Section 8.2.3.

It is clear from these data that carvedilol is indeed susceptible to biodegradation in aerobic compartments and should not persist in the environment. Given the high biomass concentrations in activated sludge systems, the likely presence of surface-active agents which may facilitate bioavailability, and higher levels of dissolved organics which would enhance the solubility of carvedilol, the degradation of carvedilol in unacclimated waste water treatment plant systems would be expected to be more rapid than the conservative kinetics presented in typical biodegradation test systems.

7.4.4 Fate Summary

From the data presented above, the following are predictions concerning the environmental fate of carvedilol from use:

1. Based on environmental partitioning estimates presented in section 7.3, approximately 77% of carvedilol introduced into WWTPs is expected to distribute into the sludge phase. Biotransformation may occur during the solids retention, which may reduce sludge concentrations considerably. Due to the high turbidity of activated sludge mixed liquor, little photolysis is expected to occur during aeration. During secondary settling, dissolved carvedilol may be more susceptible to photodegradation in the clarified secondary effluent.
2. Carvedilol discharged into the aquatic environmental compartment will not likely persist based on photolysis and slow biotransformation depletion mechanisms. An

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overall depletion rate may be estimated from the individual depletion rate constants. An estimation of half-life in the aquatic compartment may range from 1.5 hours to 40-50 days based on the dominant active depletion mechanism.

3. Carvedilol entering the terrestrial compartment by land application of sludge would likely remain sorbed, immobile and undergo, under aerobic conditions, slow biotransformation. It would not be expected to persist in the soil compartment.
4. The very low Henry's constant suggests that transport of carvedilol to the atmosphere by volatilization from either the treatment plant or the terrestrial compartment will be insignificant.
5. Given that the log of the octanol/water distribution coefficient varies from 2 to 3 at environmental pH levels, little bioconcentration of carvedilol is likely to occur. This prediction is further supported by the metabolism studies, which indicate that carvedilol is biotransformed by a variety of mechanisms into more polar materials, which are excreted.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES:

8.1 Human and Mammalian Health Effects Summary [22]

8.1.1 Acute Toxicity Studies

8.1.1.1 Oral Toxicity

No lethality occurred in rats after administration of a single oral dose of 8000 mg/kg. The oral LD₅₀ in rats was greater than 8000 mg/kg.

8.1.1.2 Inhalation Toxicity

Inhalation toxicity was not determined. However, symptoms after exposure to dust might include slow pulse, dizziness, fainting, difficult or irregular breathing or bluish colored fingernails or palms.

8.1.1.3 Skin Irritation

Skin irritation potential was not determined. We can assume that direct contact can produce irritation or allergic skin reaction. Symptoms such as itching, redness or swelling might be immediate or delayed.

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8.1.1.4 Eye Irritation

Eye irritation potential was not determined. Assume that direct contact can produce irritation. Symptoms might include redness or swelling.

8.1.1.5 Sensitization

The sensitization potential of carvedilol has not been determined.

8.1.2 Chronic Toxicity Studies

8.1.2.1 Reproduction Toxicology

Carvedilol did not produce adverse effects on male or female reproduction in studies with rats.

8.1.2.2 Teratogenicity

Carvedilol did not produce teratogenic effects in studies with rats.

8.1.2.3 Genetic Toxicology

Carvedilol was not found to be mutagenic in bacteria (Ames test) or other genotoxicity tests. It is not listed as a carcinogen by IARC, NTP, or US OSHA. There was no evidence of a carcinogenic effect in chronic studies with rats or mice.

8.1.2.4 Other Effects

Carvedilol exhibits an effect on the cardiovascular system by lowering blood pressure.

8.2 Aquatic Toxicity Studies

8.2.1 Acute Aquatic Toxicities of Carvedilol

Acute aquatic toxicity studies were carried out on microorganisms (Microtox[®] and Microbial Respiration Inhibition), *Daphnia magna*, and bluegill sunfish (*Lepomis macrochirus*) using carvedilol. The detailed reports on the Microtox[®] studies for carvedilol, 4-hydroxycarbazole, and carbazole are given in references [23,24,25]. The reports of the contract study of the activated sludge respiration inhibition of carvedilol is given in reference [26]. Reports of the contract studies on the acute toxicities of carvedilol to *Daphnia pulex* and bluegill sunfish (*Lepomis macrochirus*) are given in references [27] and [28], respectively. The results are summarized below.

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Toxicity Test	Carvedilol (mg/L)
Microtox [®] - EC ₅₀	5.43 ± 0.25 6.71 ± 1.87 (4-OH carbazole) 0.26 ± 0.031 (carbazole)
Respiration Inhibition - EC ₅₀	98.4
<i>Daphnia pulex</i> - EC ₅₀ ^{1.2/45}	> 2.8
<i>Daphnia pulex</i> - NOEL	< 0.37
Bluegill Sunfish - LC ₅₀	0.99 (95% CI = 0.87-1.1)
Bluegill Sunfish - NOEL	< 0.43

8.2.2 Acute Aquatic Toxicity of Carvedilol Photolysis By-Products

Since carvedilol was found to degrade in the presence of sunlight, the relative toxicity of the photo-degradant(s) compared to carvedilol itself was determined using the Microtox[®] test carried out on samples of carvedilol solutions that had been exposed to sunlight. No EC₅₀ could be determined for the degraded solutions because of a lack of toxic effect. Based on these results, any compounds entering the environment from the photolysis of carvedilol would not be expected to exert toxic effects on aquatic organisms. Details of the study are given in reference [29].

8.2.3 Acute Aquatic Toxicity of Carvedilol Biodegradation By-Products

The relative acute aquatic toxicity of carvedilol biodegradation by-products was also determined by a Microtox[®] test carried out on samples of carvedilol solutions after laboratory biodegradation experiments. For one sample of biodegradants, no EC₅₀ could be determined for the degraded solutions because of a lack of toxic effect. For the "replicate" sample, an EC₅₀ of 15.4% was calculated. See reference [30] in Appendix VII. However, as noted in Section 7, the carvedilol in the two samples appeared to be biotransformed by two different pathways, and by consortia of apparently different microorganisms. However, even though minimal toxic effect was observed, the unknown biodegradants responsible were derived from carvedilol at a concentration far in excess of what could be emitted into the environment from use.

From the data above, carvedilol and its degradants would not be expected to exhibit acute toxic effects to aquatic organisms at concentrations expected to be emitted into and exist in the environment.

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9. USE OF RESOURCES AND ENERGY

9.1 Use of Resources and Energy at Boehringer

9.1.1 Use of Resources and Energy at Plant HC-B 21

The following tables summarize the known amounts of energy and resources utilized during intermediate production at the production plant HC-B 21.

Percent of Energy and Resources Utilized at Boehringer Mannheim for Production of Intermediate in 1990 HC-B 21 Plant					
Consumption	Electricity (kw-hour)	Steam / 2.5 bar (t)	Tap Water (m³)	Cooling Water (m³)	Demineralized Water (m³)
Percent of Total Consumption at Boehringer Mannheim	0.02	0.005	0.006	0.08	0.05

9.1.2 Use of Resources and Energy at Plants HC-B 4, HC-B 10 and HC-B/OB

The following tables summarize the known amounts of energy and resources utilized during intermediate production at production plants HC-B 4, HC-B 10 and HC-B/OB.

Percent of Energy and Resources Utilized at Boehringer Mannheim for Production of Intermediate in 1990 HC-B 4, HC-B 10 & HC-B/OB Plants					
Process Step	Electricity (kw-hour)	Steam / 2.5 bar (t)	Tap Water (m³)	Cooling Water (m³)	Demineralized Water (m³)
Percent of Total Consumption at Boehringer Mannheim	0.13	0.08	0.13	0.38	0.36

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9.1.3 Effect Upon Endangered Species And Historic Places

The production of carvedilol intermediates and the disposal of associated wastes at the Boehringer Mannheim production facilities should have no impact on threatened or endangered species. Property listed in or eligible for listing in the National Register of Historic Places will not be impacted by intermediate production or waste disposal activities since the production is taking place outside of the United States and the Boehringer-Mannheim facility is not a designated historic site.

9.2 Use of Resources And Energy At Cork

The effects on the use of resources and land for the production of carvedilol drug substance are minimal because of the low production volumes and associated wastes, and the existing treatments units that will be used.

The following table summarizes the percent of energy and resources utilized during carvedilol substance production stages at the SmithKline Beecham (Manufacturing) Limited facility, based on the projected 5th year of production and current use.

Consumption	Electricity (kw-hour)	Fuel Therms	Water (m ³)
Percent of Total Consumption	0.05	4.2	0.07

9.2.1 Effect Upon Endangered Species And Historic Places

The production of carvedilol substance and the disposal of associated wastes should have no impact on threatened or endangered species. Property listed in or eligible for listing in the National Register of Historic Places will not be impacted by carvedilol substance production or waste disposal activities since the production is taking place outside of the United States and the SmithKline Beecham (Manufacturing) Limited facility is not a designated historic site.

9.3 Use of Resources and Energy to Produce Drug Product at Cidra

The Cidra facility for carvedilol product manufacture is a 52 acre site located in an agricultural/urban/industrial area on the central mountainous ridge of the island of Puerto Rico. The effects on the use of resources and land for the production of carvedilol drug

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product are minimal because of the low production volumes and associated wastes, and the existing treatments units which will be used. Manufacture of this product uses only a small percentage of the resources and energy available at this site and of resources and energy required for transport.

The following table summarizes the total known amounts of energy and resources used at the Cidra plant.

Consumption	Electricity (kw-hour)	Fuel Oil (gallons)	Water (gallons)
Percent of Total Consumption	4%	4%	4%

To produce the carvedilol drug product at maximum yearly production levels at Cidra, it is estimated that 4% of total yearly Cidra plant usage of electricity, fuel and water will be used.

9.3.1 Effect Upon Endangered Species And Historic Places

The production of carvedilol product and the disposal of associated wastes should have no effect on threatened or endangered species. Property listed in or eligible for listing in the National Register of Historic Places will also not be impacted by carvedilol product production or waste disposal activities since the Cidra facility is not a designated historic site.

10. MITIGATION MEASURES

10.1 Mitigation Measures at Boehringer

Potential adverse environmental impacts associated with drug intermediate production at Boehringer Mannheim are minimized by the following:

No waste or exhaust streams are directly discharged, but are directed to major treatment units;

Treated effluent streams are checked before discharge, with ample capacity for emergency storage in the event that effluent criteria are not met;

Floor spills are swept and incinerated;

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Off-spec or rejected materials are returned to the supplier or are incinerated in an outside incineration plant for industrial wastes;

Accidental introductions of bulk product into the environment during storage is mitigated by controlled packaging and storage operations. Bulk drug product is packaged in new corrugated cardboard boxes lined with two polyethylene bags. These boxes are heat-sealed, sealed with plastic tape, properly labeled, and stored in a secured bulk storage area of the plant warehouse.

Storage facilities are designed to allow for the capture and treatment of any spills before any major environmental effects could result. Also, the adopted spills prevention, control and contingency plans have been demonstrated to be effective in the prevention of such emergencies.

The plant personnel are well-trained and follow written instructions when performing their work.

The site is audited regularly by the Boehringer Mannheim central Environment Department, to assist in the identification and implementation of any additional mitigation measures as circumstances warrant.

10.2 Mitigation Measures At Cork

Plans to minimize waste output were considered and implemented at the outset of carvedilol development, as well as during substance production. The Integrated Pollution Control (IPC) license contains guidelines for the establishment of an Environment Management Programme to assess all operations for the use of cleaner technology and the minimization of waste. Potential environmental impacts associated with production at Cork are also minimized by the following:

Most waste streams are incinerated, and the gases scrubbed before being discharged. Scrubber liquors are biotreated in the on-site wastewater treatment facility before discharge.

Biotreated effluent streams are checked before discharge, with ample capacity for emergency storage in the event that effluent criteria are not met.

Airstreams from the process buildings are filtered prior to venting to the atmosphere.

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10.3 Mitigation Measures at Cidra

Potential adverse environmental impacts associated with the proposed action are minimized at the Cidra facility by the following:

10.3.1 General

The proposed formulation process involves small production lots, which will generate very small quantities of waste;

No waste or exhaust streams are directly discharged. All streams are directed to major treatment units. Treated effluent streams are checked before discharge, with ample capacity for emergency storage in the event that effluent criteria are not met;

Airstreams from the process are small and directed to dust collectors, which minimize the effects of the emissions by at least 99.9%;

Storage facilities are designed to allow for the capture and treatment of any spills before any major environmental effects could result. Also, the adopted spills prevention, control and contingency plans have been demonstrated to be effective in the prevention of such emergencies.

10.3.2 Energy and Resources

A thermal oxidizer with a regenerative heat recovery system is used to incinerate gaseous waste streams produced during tablet coating operations. The heat recovery system is operated to recover at least 85% of the heat generated, for use in continual incineration of the gases. After aeration in the biotreatment facility, 55,000 gallons per day of final effluent is recycled to cooling and quench towers and 25,000 gallons per day of final effluent is discharged.

10.4 Mitigation from Use

The potential environmental risk from carvedilol centers on the aquatic and terrestrial compartments. Carvedilol will not be directly discharged into the environment from use, but instead most will be subjected to depletion mechanisms found in wastewater treatment plants (WWTP).

Two mechanisms at the plants will decrease environmental concentrations of carvedilol: sorption and biodegradation. Approximately 77% of carvedilol in WWTP influent will be sorbed onto plant biomass solids, thus dramatically decreasing carvedilol concentrations in WWTP effluent. Carvedilol in solution will likely be at least partially biotransformed based

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Upon data described in ERL Report 9501. Any carvedilol that is released from the WWTP into surface waters will be subjected to aqueous photolysis. Since the carvedilol photolysis rate constant was determined to be approximately 0.47 hr^{-1} , photolysis will serve as a significant depletion mechanism in the aquatic compartment.

Carvedilol sorbed onto sludge biomass will be ultimately disposed of, in some cases, by incineration or placed into secure landfills. Those WWTPs that do dispose of sludge via landfarming or distribution and marketing could serve to release carvedilol into the terrestrial compartment. However, carvedilol in sludge-amended soil will be subjected to aerobic biodegradation, albeit at slower rates than those determined in aqueous matrices. Finally, carvedilol in sludge-amended soil will be tightly bound to organic matter and not bioavailable.

In conclusion, predicted environmental concentrations of carvedilol are well below predicted toxicity concentrations and carvedilol will not require any additional mitigation actions.

11. ALTERNATIVE TO THE PROPOSED ACTION

No potential adverse environmental impacts have been identified for the proposed action. The approval of carvedilol will provide an important benefit to patients requiring its administration with no adverse environmental risk. The only alternative to the proposed action is that of no action, thus depriving patients an important therapy.

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Carvedilol

12.2 List of Preparers:

Virginia L. Cunningham, Ph.D. & ERL Staff
Director
Environmental Research Laboratory (ERL)
SmithKline Beecham
(See Appendix V for Curricula Vitae)

13. CERTIFICATION:

The undersigned official certifies that the information presented is true, accurate, and complete to the best knowledge of the Environmental Research Laboratory.

Date:

March 17, 1995

Signature:

James Hagan

James R. Hagan, P.E.
Vice President
Corporate Environment & Safety
SmithKline Beecham

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ATTACHMENT II

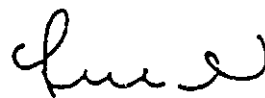
Note: The current name for Penn Chemicals (Cork, Ireland)
is SmithKline Beecham (Manufacturing) Limited

GENERAL COMPLIANCE STATEMENT

Boehringer Mannheim GmbH states that it is in compliance with all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of Guaiacol-O-ethyltosylate at its facilities in Mannheim, Federal Republic of Germany.

February 14, 1992

Date



Dr. G. Lettenbauer

Senior Vice President
of
Chemical Production and
Development Department

February 14, 1992

Date



Dr. W. Wäble

Vice President
of
Safety and Environmental Department

BOEHRINGER
MANNHEIM

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GENERAL COMPLIANCE STATEMENT

Boehringer Mannheim GmbH states that it is in compliance with all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of 4-Hydroxycarbazole at its facilities in Mannheim, Federal Republic of Germany.

February 14, 1992

Date



Dr. G. Lettenbauer

Senior Vice President
of
Chemical Production and
Development Department

February 14, 1992

Date



Dr. W. Wäble

Vice President
of
Safety and Environmental Department

BOEHRINGER
MANNHEIM

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Boehringer Mannheim GmbH
D-68298 Mannheim
Rheinstraße
Sandhofer Straße 116
D-68305 Mannheim

Telefon: (06 21) 7 59-0
Tele: 483193 bmd
Fax: (06 21) 7 59 28 90

BOEHRINGER
MANNHEIM

February 3, 1994



TO WHOM IT MAY CONCERN

"ENVIRONMENTAL ASSESSMENT"

Boehringer Mannheim GmbH, as the manufacturer of various pharmaceutical active ingredients (drug substances) and finished medicinal products (drug products), having the official address

Boehringer Mannheim GmbH
Sandhofer Straße 116
D-68305 Mannheim
Federal Republic of Germany,

herewith certifies that the manufacture of active ingredients and finished products in the facilities of the above mentioned plant site is carried out according to the current laws and regulations of the Federal Republic of Germany for purposes of environmental protection.

The construction and the operation of plants for the manufacture of pharmaceutical products is principally subject to approval according to §4 of the Bundesimmissionschutzgesetz (BImSchG) "Federal Law on Immissions". This requirement is based on the regulations concerning plants subject to approval (4th BImSchV = Regulations on the Federal Law on Immissions), which are given in the enclosures under subparagraph

4.1: Plants for the manufacture of products by chemical conversion ...

and under subparagraph

4.3: Plants for the manufacture of medicinal products or medicinal-product intermediates ...

Approval for these plants is to be obtained by submitting a detailed written application to the relevant authorizing body. Only after thorough inspection is a notice of approval conferred by the authorizing body (for Boehringer Mannheim GmbH, the Regierungspräsidium Karlsruhe = Directorate of the Administrative District, Karlsruhe). This notice may only be conferred if the relevant permit requirements have been satisfied according to §0 BImSchG (see enclosure).

It is therefore essential to guarantee the fulfillment of the obligations in §5 BImSchG which are incumbent on the operator of plants subject to approval. In addition, the construction and operation of the plants should not contravene further regulations under public law and the interest of industrial safety.

... 2

Deutsche Bank AG, Mannheim
BLZ: 670 700 10 - Konto 01/02 832
 Dresdner Bank AG, Mannheim
BLZ: 670 800 50 - Konto 8 608 231

Registergericht Mannheim HRB 2952
Geschäftsführung: Bernhard Kubicek (Vorl.), Prof. Dr. rer. nat. Dr. med. Uwe Ginter (Stellv.),
Dr. Ing. Fritz Schneider (Stellv.), Gernot J. Janderath, Hansjörg Schmitt,
Vorstandsrat: Dr. Arthur Müller, Curt Engstler

To whom it may concern
"Environmental Assessment"

February 3, 1994
Page 2

In accordance with §5 BImSchG plants subject to approval are to be constructed and operated in such a manner that

1. harmful environmental effects and other hazards, considerable disturbance and considerable inconvenience to the community and vicinity cannot be evoked,
2. provisions are made against harmful environmental effects, in particular through the use of state-of-the-art measures for the limitation of emissions,
3. residues are avoided where possible, or are processed and rendered harmless according to regulations, or, where avoidance and processing is not technically feasible or is unreasonable, they are removed as waste without harm to the well-being of the community, and
4. any resulting heat is used in the operator's plant or transferred to a third party that has declared itself as willing to accept, provided that the process involved is technically possible and acceptable, and that it is compatible with the obligations according to subparagraphs 1 to 3.

However, where plants not subject to approval with respect to the BImSchG, approvals according to other laws may be binding (e.g. according to building regulations, according to industrial code and others). Moreover, §22 and §23 of the BImSchG lay down the obligations for the operator and also the requirements for the construction and the operation of such plants (see enclosure). Accordingly, such plants are to be constructed and operated so that

1. harmful environmental effects are prevented through the use of state-of-the-art technology,
2. unavoidable harmful effects on the environment are minimized through the use of state-of-the-art technology, and
3. waste arising from the operation of the plants can be removed according to regulations.

We are obliged to comply strictly with such legal regulations. This is being controlled by the responsible administration.

Additionally, we draw attention to the fact that we are subject to the constant supervision of the civil industrial inspection Board.

Yours faithfully,

DOEHRINGER MANNHEIM GMBH
ppa. i.V.



Dr. Machat



Dr. Ochmichen

7 Enclosures

Karlsruhe, 2-23-1994

Regierungspräsidium Karlsruhe
Agreed:



Hoffmann

Oberregierungsrat

BOEHRINGER
MANNHEIM



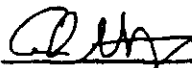
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GENERAL COMPLIANCE STATEMENT

PENN CHEMICALS B.V. states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of Carvedilol at its facilities in Currabinny, Carrigaline, Co. Cork, Ireland as well as emission requirements set forth in applicable federal state, and local statutes and regulations applicable to the production of Carvedilol at its facilities in Currabinny, Carrigaline, Co. Cork


DECLAN RYAN
MANAGER ENGINEERING/ENVIRONMENTAL


COLM HARTY
DIRECTOR FINANCE & ADMINISTRATION

PENN CHEMICALS B.V., Currabinny, Carrigaline, Co. Cork, Ireland.

Tel. 021-371201, Fax 021-372383, Telex 75868 Int Dating +353-21-371201



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SB
SmithKline Beecham
Pharmaceuticals

GENERAL COMPLIANCE STATEMENT

SmithKline Beecham Pharmaceuticals Co. states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of CARVEDILOL (KREDEX) at its facilities in Cidra, Puerto Rico as well as emission requirements set forth in applicable federal, state, and local statutes and regulations applicable to the production of CARVEDILOL at its facilities in Cidra, Puerto Rico.

Jose L. Rosado 4-13-92

JOSE L. ROSADO DATE
PRESIDENT & GENERAL MANAGER

Antonio Garcia 4-13-92

ANTONIO GARCIA DATE
ENVIRONMENTAL & PLANT
SERVICES LEADER

ATTACHMENT III

**SMITHKLINE BEECHAM ENVIRONMENTAL RESEARCH LABORATORY
SUMMARY OF ENVIRONMENTAL FATE AND EFFECT STUDIES**

compound - SK&F 105517 (CARVEDILOL)

summary prepared by - Scott Ziegenfuss

revised as of 3/17/95

ENVIRONMENTAL FATE

		pH 5	pH 7	pH 9	DI H2O (pH 8.4)
Water Solubility	definitive data - mean	434	30.8	1.81	5.46 (mg/L)
	stdev	48.7	3.66	0.356	1.28

Octanol/Water Distribution Coefficient (K _{ow}) *		pH 5	pH 7	pH 9
		C1 (28.3 ug/L)	106	528
	C2 (283 ug/L)	85.7	548	1280

Sludge Adsorption

preliminary experiment - mean K_p - 5500, log mean K_p - 3.74

factorial experiment - 19 hour equilibration Freundlich isotherm data

active sludge - log K - 2.76	poisoned sludge - log K - 3.64
1/n - 0.713	1/n - 0.999
R ² - 0.993	R ² - 0.984
log K _p - 3.37	log K _p - 3.65

definitive isotherm experiment - 19 hour equilibration

log K - 4.31	mean K _p - 10800
1/n - 1.1	log K _p - 4.03
R ² - 0.931	stdev - 2400

Soil Adsorption

soil	TOC (%)	H2O		CaCl2	
		log K	log K _{oc}	log K	log K _{oc}
Kansas	2.06	2.69	4.37	3.47	5.16
Calif.	1.59	2.81	4.81	3.93	5.72
Iowa	1.53	2.75	4.57	4.54	6.38

Henry's Constant < 2.66E-7 m³·atm/mol @ pH 6.70, 3.93E-7 m³·atm/mol @ pH 6.55

UV/vis Spectrum in 10% water in methanol

lambda	E (M-1·cm-1)
204	34200
224	38900
242	50200
286	14500
320	4610
332	6040

Dissociation Constant (pKa) 7.8 (from SB Analytical Chemistry report #3077)

Aerobic Biodegradation

carvedilol	k - 0.03 /day, t1/2 - 26.2 days
carbazole	k - 1.76 /day, t1/2 - 0.39 days
4-hydroxycarbazole	k - 0.03 /day, t1/2 - 21.8 days

Photolysis k - 0.4679 /hr, t1/2 - 1.5 hrs

ENVIRONMENTAL EFFECTS

D. pulex 48-hr acute	EC50 -	> 2.8 mg/L	(95% c.i. - N/A)
	NOEC -	< 0.37 mg/L	
Bluegill 96-hr acute	L.C. EC50 -	0.99 mg/L	(95% c.i. - 0.87 to 1.1)
	NOEC -	< 0.43 mg/L	
Microbio Microtox	carvedilol	EC50-15 - 5.43	mg/L (stdev - 0.25)
	carbazole	EC50-15 - 0.26	mg/L (stdev - 0.031)
	4-hydroxycarbazole	EC50-15 - 8.71	mg/L (stdev - 1.87)
biologically-degraded solution - #1 - EC50 at 15.4%, #3 - non-toxic			
photolytically-degraded solution - 0 and 5 hours exposure: non-toxic			
1.5 hours exposure: EC50-5 - 41.0 +/- 11.9 % (SD)			
Activated Sludge Respiration Inhibition (OECD 209)	EC50 -	98.4 mg/L	

ATTACHMENT IV

MATERIAL SAFETY DATA SHEET

1. IDENTIFICATION OF THE SUBSTANCE/PREPARATION AND OF THE COMPANY/UNDERTAKING

SUBSTANCE/PREPARATION:

CARVEDILOL

TRADE NAMES/SYNONYMS:

1-(9H-CARBAZOL-4-YLOXY)-3-([2-(2-METHOXYPHENOXY)ETHYL]AMINO)-2-PROPANO
L * SK&F 105517 * BM 14.190 * SKF 105517 * KREDEX * 105517 (SK&F) *
105517 (SKF)

CHEMICAL FAMILY:

Substituted carbazole.

MOLECULAR FORMULA:

C24-H26-N2-O4

MOLECULAR WEIGHT:

406.481

EINECS NUMBER:

Not Assigned

ELINCS NUMBER:

Not Assigned

COMPANY:

SMITHKLINE BEECHAM, CORPORATE ENVIRONMENT & SAFETY

U.S. OFFICE:

709 SWEDLAND ROAD
KING OF PRUSSIA, PA, 19406
U.S.A.

U.K. OFFICE:

NORFOLK HOUSE, DOWNSBROOK TRADING ESTATE
SOUTHDOWNVIEW WAY, WORTHING
WEST SUSSEX, BN14 8NQ, ENGLAND

PHONE NUMBERS:

++1-610-270-7807

++44-(0)903-822650

EMERGENCY AND AFTER HOURS CONTACT:

++1-800-228-5635 (EXTENSION 157)

2. COMPOSITION/INFORMATION ON INGREDIENTS

INGREDIENTSCAS REGISTRY NOPERCENT

CARVEDILOL

72956-09-3

MORE THAN 99%

CONTAMINANTS:

No significant hazardous contaminants.

3. HAZARDS IDENTIFICATION

PRIMARY ROUTES OF EXPOSURE:

Avoid breathing dust, eye contact, skin contact, ingestion.

SKIN CONTACT:

Allergic skin reaction can occur following direct contact with this material.
Symptoms such as itching, redness or swelling might be delayed.

EYE CONTACT:

Irritation can occur following direct contact with this material. Symptoms might
include redness or swelling.

INHALATION:

Symptoms after overexposure to dust might include slow pulse, dizziness,
fainting, difficult or irregular breathing, or bluish colored fingernails or
palms.

INGESTION:

Toxicity is not expected but ingestion should be avoided. Symptoms after
overexposure might include slow pulse, dizziness, fainting, difficult or

MATERIAL SAFETY DATA SHEET

irregular breathing, or bluish colored fingernails or palms.
CONDITIONS AGGRAVATED BY EXPOSURE:

Diabetics or individuals taking cardiovascular medications might be sensitive to the effects of this material. In cases of overexposure, seek medical assistance concerning possible drug interactions.

4. FIRST-AID MEASURES**SKIN CONTACT:**

Remove contaminated clothing and flush exposed area with large amounts of water. Obtain medical assistance if skin reaction occurs, which may be delayed.

NOTE TO PHYSICIAN:

None.

EYE CONTACT:

Flush eyes continuously with water for at least 15 minutes. Do not use a chemical neutraliser. Obtain medical assistance if symptoms occur.

NOTE TO PHYSICIAN:

None.

INHALATION:

Move exposed subject to fresh air. Seek medical assistance in case of known or possible overexposure to this material or with symptoms including chest pain, difficulty breathing, loss of consciousness or other adverse effects which may be delayed. IF BREATHING HAS STOPPED, START BASIC LIFE SUPPORT AND SEEK IMMEDIATE MEDICAL ATTENTION.

NOTE TO PHYSICIAN:

For combustion products, refer to section number 5.

INGESTION:

In the event of swallowing this material, seek medical assistance. Do not induce vomiting.

NOTE TO PHYSICIAN:

Medical treatment in cases of overexposure should be treated as an overdose of beta-adrenergic blockers. Gastric lavage is recommended. Refer to current prescribing information or to local poison control information centers. This material is not a corrosive agent.

ANTIDOTES:

None known.

5. FIRE-FIGHTING MEASURES**FIRE CONTROL:**

Use water, carbon dioxide, foam or dry chemical extinguishers. Toxic or corrosive gases are expected from fires involving this material.

SPECIAL FIREFIGHTING PROCEDURES:

Toxic or corrosive gases including oxides of carbon and nitrogen are expected in fires involving this material. Self contained breathing apparatus and full protective equipment are recommended for firefighters. Move containers from fire area if possible without increased personal risk. Dike area if possible to contain water for later disposal.

6. ACCIDENTAL RELEASE MEASURES**SPILLS:**

Instruct all personnel not involved in clean up operations to keep at a designated, safe distance. Do not allow this material to enter surface drainage systems. Wear protective clothing and equipment consistent with

MATERIAL SAFETY DATA SHEET

the degree of hazard. Carefully scoop up the spillage, avoid dust generation and place in a suitable, properly labeled container for recovery or disposal. Wash down spillage area with copious amounts of water. This must only be undertaken if waste water can be directed to an on-site waste water treatment system.

DECONTAMINATION PROCEDURES:

Detergent solutions can be used for clean-up and decontamination operations. No specific detoxification procedures have been identified for this substance.

7. HANDLING AND STORAGE

HANDLING:

This material has not been tested for its dust explosion properties. However, like most organic dusts, it is expected to explode when ignited as a dust cloud. Care should be taken to avoid dispersion as a dust cloud. Ensure that all items of plant and equipment used for handling this material are bonded and earthed (grounded). The presence of isolated conductors should be avoided. Enclosure is recommended to routinely control airborne dust levels below published exposure limits.

STORAGE:

Avoid prolonged storage at elevated temperatures (greater than room temperature, approximately 20 degrees C). Keep in tightly closed containers or packages away from moisture and away from sources of ignition.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

EXPOSURE CONTROLS:

CARVEDILOL:

SmithKline Beecham(PEL):

0.03 MG/M3 (8 HR TWA)

INDUSTRIAL HYGIENE METHOD:

SB/1210 analytical method.

PERSONAL PROTECTION:

RESPIRATORS:

Respirators are normally not required when handling small quantities. If the airborne dust level is greater than allowable levels, a laboratory fume hood, local exhaust ventilation or an appropriate respirator should be used. The specific type used will be determined by air concentrations present. Follow local regulations for respirator use in the workplace.

GLOVES:

Wear neoprene or other impervious gloves for handling wet or dry powder.

EYE PROTECTION:

In laboratories, wear safety glasses with sideshields when handling this material. In production areas, wear full face respirator for dry powder, goggles for wet powder.

HYGIENE PRACTICES:

Wash hands and arms thoroughly after handling this material.

Clean up spills immediately.

OTHER PROTECTIVE EQUIPMENT:

In laboratories, wear lab coat or other protective clothing with long sleeves. In production areas, wear protective clothing that is laundered or discarded after each use. An eye wash station should be available.

9. PHYSICAL AND CHEMICAL PROPERTIES

MATERIAL SAFETY DATA SHEET

APPEARANCE:

White to off-white crystalline powder.

FLASH POINT:

Expected to be greater than 55 degrees C.

AUTOIGNITION TEMP:

Not determined.

LOWER EXPLOSIVE LIMIT:

Not applicable solids.

UPPER EXPLOSIVE LIMIT:

Not applicable solids.

MELTING POINT:

115 to 117 degrees C.

BOILING POINT:

Not determined.

VAPOUR DENSITY:

Expected to be negligible.

VAPOUR PRESSURE:

Expected to be negligible.

EVAPORATION RATE:

Expected to be negligible.

VOLATILE COMPONENTS (%):

None expected.

VISCOSITY:

Not applicable for solids.

PH OF AQUEOUS SOLUTIONS:

Not determined.

RELATIVE DENSITY:

Not determined.

CONDUCTIVITY:

Not applicable for solids.

OCTANOL/WATER DISTRIBUTION COEFFICIENT:

KOW (26.3 micrograms/l) = 106 (pH 5), 528 (pH 7), 1040 (pH 9)

KOW (263 micrograms/l) = 85.7 (pH 5), 549 (pH 7), 1260 (pH 9)

DISSOCIATION CONSTANT (pKA):

7.8

SOLUBILITY:

Soluble in many polar solvents.

Insoluble in water.

OXYGEN BALANCE:

This material is considered to be of low energy hazard potential based on oxygen balance calculated as minus 224.

TRAIN FIRE TEST:

Since this material has not been train fire tested, it should be assumed to support combustion in bulk quantities.

DUST EXPLOSIVITY:

Classification: Not determined.

Minimum explosive concentration (grams/cubic metre): Not determined.

Minimum ignition temperature - cloud (degrees C): Not determined.

Minimum ignition temperature - layer (degrees C): Not determined.

Minimum oxygen concentration (% v/v): Not determined.

Explosion characteristics:

Pmax (bar): Not determined.

dP/dT (bar/second): Not determined.

Kst (bar metre/second): Not determined.

St class: Not determined.

MATERIAL SAFETY DATA SHEET

DUST ELECTRICAL PROPERTIES:

Minimum ignition energy (mjoules): Not determined.
Resistivity at ambient humidity (ohm meter): Not determined.
Charge decay time at ambient humidity (seconds): Not determined.
Resistivity at low humidity (ohm metre): Not determined.
Charge decay time at low humidity (seconds): Not determined.

10. STABILITY AND REACTIVITY

CONDITIONS TO AVOID:

Avoid direct sunlight, conditions that might generate heat and dispersion as a dust cloud.

INCOMPATIBILITY:

None known.

STABILITY:

This material is expected to be stable.

THERMAL STABILITY:

Capillary tube test:

Thermal degradation can be expected at temperatures greater than 200 degrees C.

Differential scanning calorimetry:

Not determined.

Accelerating rate calorimeter:

Not determined.

HAZARDOUS POLYMERIZATION:

Not expected to occur.

HAZARDOUS DECOMPOSITION PRODUCTS:

Not identified.

FIRE AND EXPLOSION HAZARDS:

Not identified. As with many organic dusts, explosions might result when excessive dust concentrations are present.

11. TOXICOLOGICAL INFORMATION

ORAL TOXICITY:

The oral LD50 in rats was greater than 8000 mg/kg. No lethality occurred in rats after administration of a single oral dose of 8000 mg/kg.

INHALATION TOXICITY:

Not determined for this material.

SKIN IRRITATION:

This material was classified as a non irritant to rabbit skin. No signs of irritation occurred up to 3 days after direct application in rabbits for 4 hours.

EYE IRRITATION:

This mixture was classified as a minimal irritant in rabbit eyes. Conjunctival redness occurred up to 1 day after direct application in rabbits. Eyes appeared normal 2 days after treatment.

SENSITISATION:

This material was classified as a mild sensitiser to guinea pig skin. Adverse skin reactions or irritation occurred in 4 out of 20 guinea pigs used to test for allergic reaction or sensitisation (maximisation test).

MUTAGENICITY:

This material was not mutagenic in bacteria (Ames Test) or other genotoxicity tests.

CARCINOGENICITY:

This material is not listed as a carcinogen by SB, IARC, NTP or US OSHA.

MATERIAL SAFETY DATA SHEET

There was no evidence of a carcinogenic effect in chronic studies with rats or mice.

REPRODUCTIVE EFFECTS:

This material did not produce teratogenic effects (birth defects) or adverse effects on male or female reproduction in studies with rats.

OTHER EFFECTS:

This material exhibits an effect on the cardiovascular system by lowering blood pressure.

12. ECOLOGICAL INFORMATION

ACUTE AQUATIC EFFECTS:

48-hour Daphnia EC50 = greater than 2.8 mg/l.

48-hour Daphnia no-observed-effect-concentration less than 0.37 mg/l.

96-hour Bluegill EC50 = 0.99 mg/l.

96-hour Bluegill no-observed-effect-concentration less than 0.43 mg/l.

BIODEGRADATION:

Not determined.

ACTIVATED SLUDGE RESPIRATION INHIBITION (OECD 209 PROTOCOL):

EC50 = 98.4 mg/l (draft results).

SOIL ADSORPTION:

Not determined.

OTHER EFFECTS:

None.

13. DISPOSAL CONSIDERATIONS

Collect for recycling or recovery, if possible. Dispose of material on site in a licensed chemical incinerator, if allowed by the incinerator license or permit. If no on-site incinerator is available, dispose of material in a licensed commercial chemical incinerator.

14. TRANSPORT INFORMATION

FOR AIR TRANSPORT (IATA REQUIREMENTS):

Proper Shipping Name: NOT RESTRICTED

Technical Name (for n.o.s., not otherwise specified): Not applicable

UN/Identification Number: Not applicable

Class/Division: Not applicable

Sub Risk: Not applicable

Packing Group: Not applicable

RQ (Reportable Quantity): Not applicable

Emergency Response Guide Number: Not applicable

FOR MARITIME TRANSPORT (IMDG REQUIREMENTS):

Proper Shipping Name: NOT RESTRICTED

Technical Name (for n.o.s., not otherwise specified): Not applicable

UN/Identification Number: Not applicable

Class: Not applicable

Sub Risk: Not applicable

Packing group: Not applicable

IMDG page number: Not applicable

MFAG number: Not applicable

EMS number: Not applicable

Marine Pollutant: Not applicable

Emergency Response Guide Number: Not applicable

FOR UNITED STATES GROUND TRANSPORT (DOT REQUIREMENTS):

MATERIAL SAFETY DATA SHEET

Proper Shipping Name: NOT RESTRICTED
Technical Name (for n.o.s., not otherwise specified): Not applicable
UN/Identification Number: Not applicable
Class/Division: Not applicable
Sub Risk: Not applicable
Packing Group: Not applicable
RQ (Reportable Quantity): Not applicable
Emergency Response Guide Number: Not applicable
FOR EUROPEAN GROUND TRANSPORT (ADR/RID/ROAD/RAIL REQUIREMENTS):
Not determined. Hazards according to ADR/RID requirements not identified.
EMERGENCY INFORMATION:
HAZCHEM code: Not applicable.
TREM CARD number: Not applicable.

15. REGULATORY INFORMATION

EUROPEAN UNION CLASSIFICATION AND LABELLING REQUIREMENTS:
No European Union labelling requirements.

16. OTHER INFORMATION

HAZARD LABEL:

**** NOT CLASSIFIED AS A SIGNIFICANT FIRE HAZARD ****
**** NO FIRE HAZARD IDENTIFIED ****
**** NOT CLASSIFIED AS A SIGNIFICANT ENVIRONMENTAL HAZARD ****
** TARGET ORGAN- PHARMACEUTICAL AGENT- MAY REDUCE BLOOD PRESSURE.
** SYMBOL: NOT REQUIRED. (NN)

REFERENCES:

SB HAZARD DETERMINATION

OTHER INFORMATION:

IF HMIS RATINGS ARE USED AT YOUR SITE, USE THE FOLLOWING:
HEALTH = 2 FIRE = U REACTIVITY = U

'This information contained herein is based on data considered accurate. However, no warranty is expressed or implied regarding the accuracy of these data or the results to be obtained from the use thereof. The publisher, its parent, subsidiaries and affiliates assume no responsibility for personal injury or property damage to vendees, users or third parties caused by the material. Such persons assume all risks associated with the use of the material.'



Food and Drug Administration
Rockville MD 20857

NDA 20-297

SEP 14 1995

SmithKline Beecham Pharmaceuticals
Attention: Ms. Catherine Clark
Four Falls Corporate Center
Route 23 & Woodmont Avenue
P.O. Box 1510
King of Prussia, PA 19406

Dear Ms. Clark:

Please refer to your March 31, 1993 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Coreg (carvedilol) 6.25, 12.5 and 25 mg tablets.

We acknowledge receipt of your amendments and correspondence dated April 22 and 30 (2), June 9, August 12, September 14, October 4, 25 and 29, November 2 and December 6, 1993; March 15, 22, 28, and 30, April 1 and 29, May 9, July 29, August 3, 4, 8, 9, 25 and 31, September 28, November 3, and December 5, 1994; and February 20, March 16, April 24, May 10 and 12, June 2, July 20, August 18 and September 8 and 12, 1995.

This new drug application provides for the use of carvedilol for the treatment of hypertension.

We have completed the review of this application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed package insert submitted on September 8, 1995 and the draft immediate container labeling submitted on September 12, 1995. Accordingly, the application is approved effective on the date of this letter.

The immediate container final printed labeling must be identical to that contained in the September 12, 1995 submission but please revise it to add the statement, "Protect from moisture." Marketing the product with FPL that is not identical to this draft labeling with the requested change may render the product misbranded and an unapproved new drug.

Please submit fifteen copies of the final printed labeling as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-297. Approval of this labeling by FDA is not required before it is used.

NDA 20297

1 OF 11

ND A 220297

Food and Drug Administration
Rockville MD 20857

NDA 20-297

SEP 14 1995

SmithKline Beecham Pharmaceuticals
Attention: Ms. Catherine Clark
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Please submit fifteen copies of the final printed labeling as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-297. Approval of this labeling by FDA is not required before it is used.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Cardio-Renal Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-240
5600 Fishers Lane
Rockville, Maryland 20857

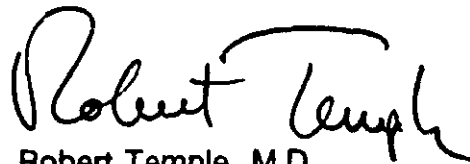
Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Ms. Zeld McDonald
Regulatory Health Project Manager
(301) 594-5300

Sincerely yours,



Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

DEC 21 1993

NDA 20-297 KR[®]DEX[™]

(Carvedilol) SmithKline Beecham

The attached Medical Officer Review does not have continuous page numbering nor continuous dialog. The Medical Officer used the pages from the Sponsors submission as a review and added comments to the original pages.

Carvedilol (KREDEX[®]) is presented as a non-cardio-selective β -blocker and an α_1 adrenergic blocker. In high concentrations it also has some blocking effect on slow calcium channels.

It has been studied as an antihypertensive drug. In addition the sponsor presents it as a protective agent in myocardial infarction, stroke, renal failure and heart failure; as a drug with antioxidant activity and an antiproliferative effect that may result in attenuation of the atherosclerotic process; a drug that prevents platelet aggregation and leads to an improvement in the hemorheologic properties. There is, however, insufficient clinical data to support these additional claims.

Boehringer-Mannheim (BM) submitted the first US IND in 1985. The phase I studies were interrupted when a subject collapsed during an IV infusion and had to be resuscitated. Details of this episode were scarce (no EKG) but there was apparently a cardiac arrest that needed intervention. The sponsor conducted an extensive literature search and a review of BM international safety data. The conclusion was that the episode could be ascribed to an overdose of β -blocker. Clinical trials were resumed with lower maximum doses, explaining why some of the initial protocols failed to explore the full range used in later studies. SmithKline & French (now SmithKline Beecham (SKB)) entered the picture in 1987.

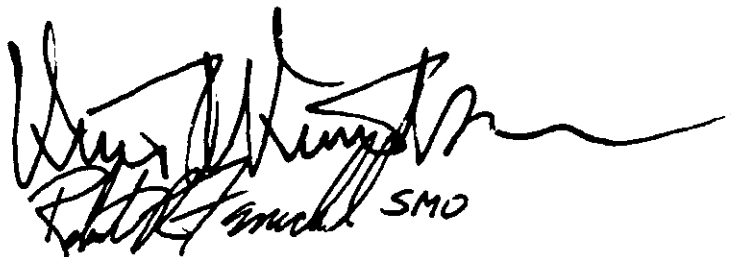
NDA 20-297 for use in hypertension was submitted in March 1993 . The CANDA

NDA 20-297 has been selected by the CardioRenal Division to test if parallel review is feasible. This portion of the team review addresses clinical efficacy, only.

1 Title and General Information

1.1 Medical Officer's Review

Reviewer: Knud Knudsen, M.D.



1.1.1 NDA # 20-297

1.1.2 M.O. Review # 1.

1.1.3 Submitted March 1993

1.1.4 Review Completed December 1993

1.2 Drug Name:

1.2.1 Generic Name: Carvedilol

1.2.2 Proposed Trade Name: KREDEX

1.2.3

The sponsor has submitted reports on 101 controlled clinical studies, conducted under the aegis of SKF or BM; and has filed reprints of a number of published papers relating to efficacy. Six of these studies: protocols B100, B101, B104, C1106, C1107 and C1109, all multicenter trials conducted in USA, carry the burden of showing that the drug works.

The remaining studies are submitted to support the claims and to evaluate safety in numbers. The complete list, compiled by the sponsor, is appended. Most of the studies, taken individually, are small. The well half-dozen sizable studies do not have placebo control but pit Carvedilol against other beta-blockers, calcium blockers ACE inhibitors and diuretica. The list speaks volumes (literally) about the intensive marketing effort all over Europe. The studies lack placebo control and do not provide independent evidence of efficacy.

Controlled Clinical Trials in Mild to Moderate Hypertension.

Carvedilol (KREDEX) NDA 20-297

Protocol #	Ctry	Study Design	Treatments	Doses (mg)	number randomized	n	sex M/F	Race B/NB	Duration	Results
B100	USA	DB, ran, parallel	Carvedilol bid Placebo	6.25 12.5 25	480	118 126 117 119	312/168	71/409	2 Mo	Moderate, dose related reduction of blood pressure. Mild reduction of heart rate. No subgroup effect.
B101	USA	DB, ran, parallel	Carvedilol UID Placebo	6.25 12.5 25 50	520	121 127 127 29 116	328/192	79/441	2 Mo	Moderate dose related reduction in BP at peak. No statistically significant difference at trough. Carvedilol does not appear useful as a once-a-day drug. No subgroup effect.
B104	USA	DB, ran, parallel titration. Black patients, only	Carvedilol BID Labetalol BID Placebo	6.25 12.5 25 100 200 400	85 79 82	(n at endpoint) 26 24 33 25 16 33 75	117/129	246/0	2 Mo	In the intent to treat analysis both Carvedilol and Labetalol lowered sitting diastolic blood pressure more than placebo did. No significant difference between the two active treatments. No convincing effect on several other BP measures.

**Controlled Clinical Trials in Mild to Moderate Hypertension.
(cont.)**

Carvedilol (KREDEX) NDA 20-297

Protocol #	Ctry	Study Design	Treatments	Doses (mg)	number randomized	n	sex M/F	Race B/NB	Duration	Results
C1107	USA	DB, ran, parallel, step II with HCTZ	Carvedilol UID (titrated) w/ HCTZ 25 mg/day Placebo w/HCTZ 25 mg/day	6.25 12.5 25	200 66	67 67 66 66	172/94	89/177	1 Mo	As step II in patients responding poorly to HCTZ 25 mg/day Carvedilol and Placebo were equally effective.
C1109	USA	DB, ran, parallel, titration.	Carvedilol UID (titrated) Atenolol UID Placebo	12.5 25 50 50 100	105 101 52	10 14 81 57 32 48	181/77	61/196	11 Wks	Both drugs beat placebo but atenolol was significantly better than carvedilol Aten vs Plac(-10.9, -5.9) <0.001* Carv vs Plac(-7.2, -2.2) <0.001* Carv vs Aten(1.6, 5.7) <0.001*
C1106	USA	DB, ran, parallel, titration.	Carvedilol UID (titrated) Carvedilol BID (titrated) Placebo	6.25 - 50 mg/day 6.25 - 50 mg/day	280	90 96 93	111/168	105/175	11- 22 wks	Carvedilol BID and UID were better than placebo, and Carvedilol BID was better than UID at endpoint. UID vs PLAC ^c (-5.83, -1.51) p=0.0009* BID vs PLAC ^c (-8.79, -4.57) p=0.0001* UID vs BID ^d (0.87, 5.15) p=0.0060*

**Controlled Clinical Trials in Mild to Moderate Hypertension.
Foreign studies, all with positive control, no placebo arm**

Carvedilol (KREDEX) NDA 20-297

Protocol #	Ctry	Study Design	Treatments	Doses (mg)	n	sex M/F	Duration	Results
CAR-UK-104	UK	DB/RAN/PAR	Carvedilol UID	12.5 - 50	232	89/143	3 Mo	All patients $\geq$ 65. Recommended start dose 12.5 mg
INT/CAR/07	Europe	DB/RAN/PAR	Carvedilol UID Atenolol	12.5 - 25 50	161 104	176/149	2 Mo	No difference between drugs
INT/CAR/08	France	DB/RAN/PAR	Carvedilol UID Acebutolol	12.5 - 25 200	105 112	101/116	2 Mo	No difference between drugs
INT/CAR/10	UK	DB/RAN/PAR	Carvedilol UID Nifedipine bid	25-50 (20-40)x2	103 102	118/87	2 Mo	No difference between drugs
INT/CAR/11	UK	DB/RAN/PAR	Carvedilol UID HCTZ	25-50 25-50	100 100	105/95	2 Mo	No difference between drugs
INT/CAR/12	Europe	DB/RAN/PAR	Carvedilol UID Captopril	12.5 - 50 25 - 50	147 151	140/158	2 Mo	No difference between drugs
MF3460	Europe	DB/RAN/PAR	Carvedilol UID Pindolol {+HCTZ prn}	25 - 50 7.5 - 15	337 165	278/224	3 Mo {1ye}	No difference between drugs
MF3461	Germany Belgium	DB/RAN/PAR	Carvedilol UID Pindolol	25-50-100 15	156 49	102/103	3 Mo	No difference between drugs
MF3948	UK	DB/RAN/PAR	Carvedilol UID Nifedipine bid Atenolol UID	25-50 (20-40)x2 50 - 100	103 102	118/87	3 Mo	Atenolol appeared more effective than either of the other.

ITEM 2 SUMMARY

C. FOREIGN MARKETING HISTORY

Carvedilol (Kredex[®]) was in-licensed from Boehringer Mannheim GmbH and is being co-developed by SmithKline Beecham and Boehringer Mannheim in the United States, Canada, Europe, Australia and New Zealand. Under a separate co-development agreement, carvedilol is being developed in Boehringer Mannheim. Additionally an NDA was filed in

As of August 31, 1992, carvedilol has been approved, and is on the market for the treatment of hypertension in four foreign countries: Germany (approved October 1990; launched January 1991), Belgium (approved November 1990; launched March 1991), South Africa (approved October 1991; launched February 1992), and Argentina (approved September 1991; launched May 1992). Table 2.C.1 provides the labeling information relating to dosage and administration in these countries. The complete text of the approved labeling for each country is provided in Section 8.F.3 (Appendix 1: Vol 1.89 page 0000014).

Carvedilol has not been withdrawn from marketing in any country. There have been no major changes in labeling in any of the foreign countries in which carvedilol has been approved for marketing.

Marketing applications have been filed in 41 foreign countries. Table 2.C.2 provides a summary of the regulatory status of these applications.

000076

Table 2.C.1 Countries in Which Carvedilol Has Been Approved for Marketing

COUNTRY	APPROVAL/LAUNCH	DOSAGE AND ADMINISTRATION
ARGENTINA Dilatrend®	Sep. 1991/May 1992 (Boehringer Mannheim)	Your doctor will decide on the amount of the daily dose and the length of time for which it must be taken. Unless otherwise prescribed, the dose is 1 Dilatrend tablet once daily. Treatment should begin with half a Dilatrend tablet (=12.5 mg) daily for the first two days. After that, treatment can continue with one tablet of Dilatrend once a day. Do not increase the dose unless directed to do so by your doctor. If the effect is insufficient, he may increase the dose to one tablet of Dilatrend twice a day, after 15 days at the earliest. A single dose of 25 mg or the total daily dose of 50 mg must not be exceeded. The tablet should be swallowed whole, without chewing, with sufficient liquid.
BELGIUM Kredex® Dimitone®	Nov. 1990/Mar. 1991 (SmithKline Beecham) Nov. 1990/Mar. 1991 (Boehringer Mannheim)	The recommended dose is 25 mg once daily. The initial dose is 12.5 mg (half a tablet) once a day, during the first two days of treatment. If necessary, the daily dose can be increased to 50 mg administered in one dose or in 2 doses of 25 mg. The daily dose must not exceed 100 mg. No development of tolerance to the therapeutic effect was observed during clinical trials. In the event of moderate hepatic or renal impairment a reduction in dose should be considered. The dose can then be increased gradually according to clinical results. Kredex should be withdrawn gradually in coronary patients.
GERMANY Dilatrend®	Oct. 1990/Jan. 1991 (Boehringer Mannheim)	Generally 1 Dilatrend tablet per day is sufficient. Treatment should be begun with one-half Dilatrend tablet (=12.5 mg) on the first two days. Then treatment may continue with 1 tablet per day. If the effect is insufficient the dose may be increased, not earlier than after 14 days, to 2 x 1 Dilatrend tablets per day, spread over the day. The single dose of 25 mg or daily amount of 50 mg must not be exceeded.
SOUTH AFRICA Kredex® Dilatrend®	Oct. 1991 (SmithKline Beecham) Oct. 1991/Feb. 1992 (Boehringer Mannheim)	The recommended dosage is 25 mg once daily. Combination with a diuretic may give the desired response. It is recommended that treatment is initiated with 12.5 mg (half of one 25 mg tablet) as a single dose for the first two days. At doses higher than 25 mg, the incidence of side-effects increases significantly with only a marginal increase in efficacy. It is not necessary to time the dose in relation to meals.

2200072

Table 2.C.2 Foreign Countries in Which Marketing Applications Have Been Submitted

COUNTRY	SPONSOR	APPLICATION	APPROVAL	LAUNCH
ARGENTINA	Boehringer Mannheim	May 1989	Sep. 1991	May 1992
AUSTRIA	Boehringer Mannheim	Jun. 1989	Dec. 1991	
BELGIUM	SmithKline Beecham Boehringer Mannheim	Oct. 1988 Oct. 1988	Nov. 1990 Nov. 1990	Mar. 1991 Mar. 1991
CHILE	Boehringer Mannheim	Mar. 1989	May 1992	Oct. 1992
FRANCE	SmithKline Beecham Boehringer Mannheim	Nov. 1988 Nov. 1988	Aug. 1991 Aug. 1991	
GERMANY	Boehringer Mannheim	Dec. 1986	Oct. 1990	Jan. 1991

(E)=Expected

000078

Table 2.C.2 (cont.) Foreign Countries in Which Marketing Applications Have Been Submitted

COUNTRY	SPONSOR	APPLICATION	APPROVAL	LAUNCH
GUATEMALA	Boehringer Mannheim	Dec. 1991	Mar. 1992	
IRELAND	SmithKline Beecham	Dec.1988/updated file Dec. 1990	Feb. 1992	
	Boehringer Mannheim	Dec.1988/updated file Dec. 1990	Feb. 1992	
ITALY	SmithKline Beecham	Jul. 1989	Nov. 1990	Mar. 1993 (E)
	Boehringer Mannheim	Jul. 1989	Nov. 1990	Mar. 1993 (E)
LUXEMBOURG	Boehringer Mannheim	Dec. 1990	May 1991	
MEXICO	Farmacéuticos Lakeside	April 1989	Mar. 1992	Oct. 1992

(E) = Expected

000079

Table 2.C.2 (cont.) Foreign Countries in Which Marketing Applications Have Been Submitted

COUNTRY	SPONSOR	APPLICATION	APPROVAL	LAUNCH
SOUTH AFRICA	SmithKline Beecham	Aug. 1989	Oct. 1991	
	Boehringer Mannheim	Aug. 1989	Oct. 1991	Feb. 1992
SPAIN	SmithKline Beecham	Mar. 1988	Oct. 1992	2nd Q 1993
	Boehringer Mannheim	Mar. 1988	Oct. 1992	2nd Q 1993

(E)=Expected

000030

8 Clinical Studies

8.1 Trial #B100

8.1.1 Objectives: Evaluate the safety and antihypertensive efficacy of carvedilol 6.25 mg, 12.5 mg, or 25 mg administered twice daily as compared to placebo, in patients with mild to moderate hypertension treated for eight weeks.

8.1.2 Design: Parallel, DB, placebo control.

n	Single Blind	n	Double Blind		Single Blind
742	Placebo up to 8 weeks	119	Placebo		Placebo for 2 weeks
		118	6.25 mg bid for 8 weeks		
		126	6.25 mg bid for 1 week	12.5 mg bid for 7 weeks	
		117	12.5 mg bid for 1 week	25 mg bid for 7 weeks	
742	8 weeks	480	1 week	7 weeks	419

8.1.3 Protocol

8.1.3.1 Population, procedures:

Males and females between the ages of 21 and 75 years with mild to moderate hypertension (SitDBP greater than or equal to 95 mm Hg and less than or equal to 115 mm Hg) were eligible for enrollment. Eligible female patients were post-menopausal for at least six months, surgically sterilized, or using an intrauterine device or oral contraceptives for at least three months prior to entry into the study.

Exclusion criteria were appropriate to rule out secondary hypertension or concurrent heart, liver or other systemic disorder. Concurrent medication was restricted.

8.1.3.2. Endpoints:

The primary parameter of efficacy in this study was change in mean *sitting Diastolic Blood Pressure (SitDBP)*.

Secondary Efficacy Parameters were Diastolic Pressure (*standing and supine*), Systolic Pressure, Heart Rate, and Response Rates. Patients were considered "responders" if their mean SitDBP was lowered during the study to 90 mm Hg or less and/or if it had decreased from baseline at least 10 mm Hg. (Although categorical endpoints are arbitrary in the evaluation of hypertension, 'response rate' may be a useful indicator for comparison of drugs. The 'and/or' term, however, makes it worthless. A drop from 95 to 89 is hardly a response worth the price in money or misery caused by the drug, nor is a drop from 110 to 100 sufficient unto the goal of treatment. A more meaningful - albeit still arbitrary - definition of response might be 'a lowering to 90 mmHg or below, and a drop of at least 10 mmHg'.)

8.1.3.3. Statistical Considerations:

Thirty-three (33) investigators enrolled 742 patients into the placebo baseline evaluation. *Two hundred sixty-two (262)* were withdrawn during this phase. Of these, 30 were withdrawn for an adverse event, the rest for failure to meet entry criteria. *Four hundred eighty (480)* entered the double blind treatment phase; of these 419 completed the study; a total of 306 were considered to have completed 'per protocol' but of the latter 74 had one or more censored data and additional data were excluded or missing due to the patients' failure to show up at the scheduled time. The main analyses, then, involved the '*intention to treat*' (480 patients) or the '*per protocol*' (306 patients) groups. The numbers raise the perennial issue: Do the weeding out of placebo responders bias the outcome?.

Subgroup analyses by sex, age, and race - according to current agency guidelines - were also performed. These subgroups tend to be too small to yield statistically meaningful data but gross discrepancies are not in evidence.

Summary of Baseline Characteristics

Intent-to-Treat Sample

	Carvedilol <u>6.25 mg</u> (N=118)	Carvedilol <u>12.5 mg</u> (N=126)	Carvedilol <u>25.0 mg</u> (N=117)	Placebo (N=117)	<u>p-value*</u>
Number (%) of Patients					
Age (years):					
≤ 64	90 (76%)	93 (74%)	86 (74%)	101 (85%)	0.125
≥ 65	28 (24%)	33 (26%)	31 (24%)	18 (15%)	
Mean Age ± S.D.	56 ± 11	56 ± 11	57 ± 11	55 ± 10	0.3422
Gender:					
Male	85 (72%)	80 (63%)	77 (66%)	70 (59%)	0.193
Female	33 (28%)	46 (37%)	40 (34%)	49 (41%)	
Race:					
Non-black	99 (84%)	103 (82%)	104 (89%)	103 (87%)	0.426
Black	19 (16%)	23 (18%)	13 (11%)	16 (13%)	
Severity of Hypertension*:					
Normal	6 (5%)	3 (2%)	2 (2%)	5 (4%)	0.914**
Mild	86 (73%)	91 (72%)	83 (71%)	85 (71%)	
Moderate	26 (22%)	32 (25%)	31 (26%)	28 (24%)	
Severe	0	0	1 (1%)	1 (1%)	
Prior Anti-hypertensives:					
No	20 (17%)	24 (19%)	20 (17%)	21 (18%)	0.972
Yes	98 (83%)	102 (81%)	97 (83%)	98 (82%)	
Body Weight (kg):					
≤ 70	9 (8%)	22 (18%)	21 (18%)	22 (18%)	0.261
71-90	57 (48%)	57 (45%)	51 (44%)	49 (41%)	
≥ 91	52 (44%)	47 (37%)	45 (38%)	48 (41%)	
Mean ± S.D.	88 ± 13	87 ± 18	87 ± 17	87 ± 20	0.8704

Summary of Baseline Characteristics

Per-Protocol Sample

	<u>Carvedilol</u> <u>6.25 mg</u> (N=70)	<u>Carvedilol</u> <u>12.5 mg</u> (N=75)	<u>Carvedilol</u> <u>25.0 mg</u> (N=77)	<u>Placebo</u> (N=84)	<u>p-value*</u>
Number (%) of Patients					
Age (years):					
≤ 64	35 (79%)	53 (71%)	55 (71%)	72 (86%)	0.082
≥ 65	15 (21%)	22 (29%)	22 (29%)	12 (14%)	
Mean ± S.D.	56 ± 10	56 ± 12	58 ± 9	54 ± 10	0.1583
Gender:					
Male	51 (73%)	50 (67%)	49 (64%)	53 (63%)	0.576
Female	19 (27%)	25 (33%)	28 (36%)	31 (37%)	
Race:					
Non-black	55 (79%)	62 (83%)	68 (88%)	72 (86%)	0.410
Black	15 (21%)	13 (17%)	9 (12%)	12 (14%)	
Severity of Hypertension*:					
Normal	3 (4%)	0	1 (1%)	3 (4%)	0.660**
Mild	52 (74%)	52 (69%)	55 (71%)	62 (74%)	
Moderate	19 (23%)	15 (21%)	23 (31%)	20 (26%)	
Severe	0	0	1 (1%)	1 (1%)	
Prior Anti-hypertensives:					
No	9 (13%)	17 (23%)	14 (18%)	19 (23%)	0.381
Yes	61 (87%)	58 (77%)	63 (82%)	65 (77%)	
Body Weight (kg):					
≤ 70	2 (3%)	14 (19%)	13 (17%)	13 (15%)	0.055
71-90	37 (53%)	37 (49%)	37 (48%)	33 (39%)	
≥ 91	31 (44%)	24 (32%)	27 (35%)	38 (45%)	
Mean ± S.D.	89 ± 13	85 ± 17	88 ± 18	89 ± 21	0.3244

* p-value of Chi Square test

†

Mean SixDBP prior to receipt of first dose of randomized medication; Normal = < 95 mm Hg, Mild = 95-105 mm Hg, Moderate = 106-115 mm Hg, Severe = ≥ 116 mm Hg
 ** Test based on Mild and Moderate categories only.

**Number and Percentage of Patients with Data Included
and Excluded from the Efficacy Analysis**

	Carvedilol <u>6.25 mg</u>		Carvedilol <u>12.5 mg</u>		Carvedilol <u>25.0 mg</u>		Placebo	
	N		N		N		N	
Included <i>Intent-to Treat</i> analysis	118	100%	126	100%	117	100%	119	100%
Included <i>Per-Protocol</i> analysis	70	59.3%	75	59.5%	77	65.8%	84	70.6%
Completely excluded by protocol violation	48	40.7%	51	40.5%	40	34.2%	35	29.4%
Partially excluded by protocol violation*	17	14.4%	14	11.1%	22	18.8%	21	17.6%
Partially excluded by slotting procedure†	7	5.9%	8	6.3%	6	5.1%	11	9.2%

+

Patients had one or more visits excluded because of a protocol violation that did not cause complete exclusion of data.

† Patients had one or more visits excluded by the slotting procedure.

8.1.4 Results

8.1.4.1. Patient Disposition, procedures

Of the 480 patients who entered the double-blind treatment phase and received at least one dose of active study medication totals of 118, 126, 117, and 119 patients were randomized to carvedilol 6.25 mg, carvedilol 12.5 mg, carvedilol 25 mg, and placebo regimens, respectively.

While there may have been fewer elderly and more women in the placebo group than in the active treatment groups, there is no evidence that the differences have biased the outcome of the trial. Nor was the distribution skewed between the 'per protocol' and the 'intention to treat' populations. Baseline blood pressures and prior exposure to antihypertensive drugs were similar in all groups.

8.1.4.2. Efficacy Endpoint Outcomes

Mean Systolic Blood Pressure (mm Hg) at Baseline

<u>Parameter</u>	<u>Treatment Group (bid)</u>		<u>Intent-to-Treat</u>		<u>Per-Protocol</u>	
			<u>n</u>	<u>Mean ± S.E.</u>	<u>n</u>	<u>Mean ± S.E.</u>
SitSBP	Carvedilol	6.25 mg	118	151 ± 1.5	70	151 ± 1.8
		12.5 mg	126	154 ± 1.6	75	155 ± 2.2
		25.0 mg	117	155 ± 1.5	77	156 ± 1.8
	Placebo	119	153 ± 1.5	84	152 ± 1.8	
SupSBP	Carvedilol	6.25 mg	118	149 ± 1.5	70	150 ± 1.8
		12.5 mg	126	153 ± 1.6	75	155 ± 2.4
		25.0 mg	117	153 ± 1.6	77	155 ± 1.9
	Placebo	119	152 ± 1.8	84	151 ± 2.0	
StaSBP	Carvedilol	6.25 mg	118	147 ± 1.5	70	147 ± 1.9
		12.5 mg	126	150 ± 1.6	75	151 ± 2.3
		25.0 mg	117	150 ± 1.6	77	152 ± 1.8
	Placebo	119	148 ± 1.5	84	147 ± 1.9	
StaSBP (3 min)	Carvedilol	6.25 mg	118	148 ± 1.6	70	149 ± 2.1
		12.5 mg	126	153 ± 1.8	75	154 ± 2.6
		25.0 mg	117	153 ± 1.6	77	154 ± 1.7
	Placebo	119	150 ± 1.5	84	149 ± 1.8	

Mean Diastolic Blood Pressure (mm Hg) at Baseline

<u>Parameter</u>	<u>Treatment Group (bid)</u>		<u>Intent-to-Treat</u>		<u>Per-Protocol</u>	
			<u>n</u>	<u>Mean ± S.E.</u>	<u>n</u>	<u>Mean ± S.E.</u>
SitDBP	Carvedilol	6.25 mg	118	101 ± 0.5	70	101 ± 0.6
		12.5 mg	126	101 ± 0.5	75	102 ± 0.7
		25.0 mg	117	102 ± 0.5	77	102 ± 0.6
	Placebo	119	101 ± 0.5	84	101 ± 0.6	
SupDBP	Carvedilol	6.25 mg	118	97 ± 0.6	70	98 ± 0.8
		12.5 mg	126	99 ± 0.7	75	99 ± 0.9
		25.0 mg	117	99 ± 0.7	77	99 ± 0.8
	Placebo	119	98 ± 0.7	84	97 ± 0.8	
StaDBP	Carvedilol	6.25 mg	118	99 ± 0.7	70	100 ± 0.9
		12.5 mg	126	100 ± 0.7	75	100 ± 0.9
		25.0 mg	117	101 ± 0.8	77	102 ± 1.0
	Placebo	119	100 ± 0.7	84	99 ± 0.8	
StaDBP (3 min)	Carvedilol	6.25 mg	118	101 ± 0.7	70	101 ± 0.9
		12.5 mg	126	101 ± 0.7	75	102 ± 1.0
		25.0 mg	117	103 ± 0.7	77	104 ± 0.9
	Placebo	119	101 ± 0.7	84	101 ± 0.8	

Mean Change from Baseline in Sitting Diastolic Blood Pressure (mm Hg)

<i>Intent-To-Treat Analysis</i>								
<u>Visit</u>	Treatment Group	(bid)	n	Mean	SE	Comparison with Placebo	CI	[*] p-value [‡]
<u>Endpoint</u>	Carvedilol	6.25 mg	117	-5.4	0.7	-2.1	(-4.2, 0.1)	0.0265
		12.5 mg	125	-7.3	0.8	-4.0	(-6.1, -1.9)	0.0001*
		25.0 mg	114	-8.5	0.8	-5.2	(-7.4, -3.1)	0.0001*
	Placebo		117	-3.3	0.8			
<i>Per-Protocol Analysis</i>								
<u>Week 4</u>	Carvedilol	6.25 mg	60	-6.9	1.0	-1.9	(-4.5, 0.7)	0.2190
		12.5 mg	64	-8.0	1.0	-3.0	(-5.6, -0.4)	0.0137*
		25.0 mg	62	-9.6	1.0	-4.6	(-7.2, -2.0)	0.0002*
	Placebo		69	-5.0	0.9			
<u>Week 8</u>	Carvedilol	6.25 mg	56	-5.7	1.0	-0.7	(-3.7, 2.2)	0.5586
		12.5 mg	62	-8.6	1.0	-3.6	(-6.5, -0.8)	0.0108*
		25.0 mg	62	-9.6	1.0	-4.6	(-7.5, -1.7)	0.0005*
	Placebo		62	-5.0	1.1			
<u>Endpoint</u>	Carvedilol	6.25 mg	67	-5.4	0.9	-1.5	(-4.3, 1.2)	0.3218
		12.5 mg	74	-8.0	1.0	-4.1	(-6.7, -1.4)	0.0022*
		25.0 mg	74	-9.3	1.0	-5.4	(-8.1, -2.8)	0.0001*
	Placebo		81	-3.9	1.0			

• Sample sizes differ due to missing vital signs values.

• Simultaneous confidence intervals based on Dunnett's One-sided Test for Multiple Comparisons with Placebo Control, ensuring 0.05 probability of significance. Values which were statistically significant when compared to placebo are indicated by * next to the p-value for that sample.

‡ For two-sided comparisons with placebo of Least Squares Means.

Trough to Peak Ratios of Sitting and Standing Systolic and Diastolic Blood Pressures for Patients Completing Eight Weeks of Treatment

		<u>N</u>	<u>Mean Change ± S.E.</u>		<u>Trough/Peak Ratio</u>
			<u>Trough</u>	<u>Peak</u>	
<i>INTENT-TO-TREAT SAMPLE</i>					
<i>Change in Sitting Diastolic Blood Pressure</i>					
Carvedilol	6.25 mg bid	100	-5.5 ± 0.8	-7.0 ± 1.0	47%
	12.5 mg bid	106	-6.8 ± 0.8	-7.6 ± 0.9	65%
	25.0 mg bid	97	-8.5 ± 0.8	-11.8 ± 0.9	55%
Placebo		91	-3.2 ± 0.9	-2.1 ± 0.9	
<i>Change in Standing Diastolic Blood Pressure</i>					
Carvedilol	6.25 mg bid	100	-5.6 ± 0.9	-6.5 ± 1.0	94%
	12.5 mg bid	106	-2.7 ± 1.1	-7.9 ± 1.0	10%
	25.0 mg bid	97	-7.1 ± 1.0	-11.8 ± 1.0	55%
Placebo		91	-2.2 ± 1.0	-2.9 ± 1.0	
<i>Change in Sitting Systolic Blood Pressure</i>					
Carvedilol	6.25 mg bid	100	-7.4 ± 1.3	-9.4 ± 1.5	85%
	12.5 mg bid	106	-7.8 ± 1.6	-12.9 ± 1.5	63%
	25.0 mg bid	97	-9.5 ± 1.6	-14.8 ± 1.6	67%
Placebo		91	-0.4 ± 1.5	-1.2 ± 1.5	
<i>Change in Standing Systolic Blood Pressure</i>					
Carvedilol	6.25 mg bid	100	-8.2 ± 1.8	-9.1 ± 1.6	127%
	12.5 mg bid	106	-8.0 ± 1.7	-14.0 ± 1.6	63%
	25.0 mg bid	97	-8.8 ± 1.8	-16.4 ± 1.6	58%
Placebo		91	-1.6 ± 1.9	-3.9 ± 1.5	

The 'response' and 'normalization' as defined in this protocol (table below) suggests a dose related improvement of blood pressure values over and above the placebo response.

**Number and Percentage of Patients Responding to Treatment
at Endpoint According to Medication Regimen**

		<u>Normalized*</u>			<u>Responders**</u>		
		<u>Number</u>	<u>(%)</u>	<u>p-value†</u>	<u>Number</u>	<u>(%)</u>	<u>p-value†</u>
<i>Intent-to-Treat</i>							
Carvedilol	6.25 mg bid	32/117	27	0.081	41/117	35	0.077
	12.5 mg bid	44/125	35	0.003**	59/125	47	<0.001**
	25.0 mg bid	48/114	42	<0.001**	62/114	54	<0.001**
Placebo		22/117	19		30/117	26	
p value*	Linear				<0.001		
	Non-Linear				0.419		
<i>Per-Protocol</i>							
Carvedilol	6.25 mg bid	19/67	28	0.252	26/67	39	0.092
	12.5 mg bid	27/74	36	0.038**	37/74	50	0.003**
	25.0 mg bid	32/74	43	0.004**	38/74	51	0.002**
	Placebo	18/81	22		22/81	27	
p value*	Linear				0.002		
	Non-Linear				0.290		

* SitDBP $\leq$ 90 mm Hg.

** SitDBP normalized and/or a decrease from baseline in mean $\geq$ 10 mm Hg.

† For Fisher's Exact two-sided test for multiple comparisons with placebo.

** ChiSquare p-values for significance of Linear Response and Deviation from Linear Response.

** Values are statistically significant.

Mean Change from Baseline at Endpoint in Secondary Blood Pressure (mm Hg) Parameters - Per-Protocol Analysis

	<u>Treatment Group</u> (b/c)	n	<u>Mean ± S.E.</u>	<u>Comparison with Placebo</u>	<u>CI</u>	<u>p-value</u> ^d
<u>SitSBP</u> **	Carvedilol 6.25 mg	67	-5.0 ± 1.5	-2.5	(-7.1, 2.1)	0.3490
	12.5 mg	74	-8.6 ± 1.8	-6.1	(-10.6, -1.6)	0.0050*
	25.0 mg	74	-10.4 ± 1.9	-7.8	(-12.3, -3.3)	0.0008*
	Placebo	81	-2.5 ± 1.5			
<u>SupSBP</u> **	Carvedilol 6.25 mg	67	-3.9 ± 1.6	-4.1	(-9.2, 1.0)	0.1156
	12.5 mg	74	-8.3 ± 1.9	-8.6	(-13.5, -3.6)	0.0010*
	25.0 mg	74	-8.3 ± 2.2	-8.5	(-13.5, -3.6)	0.0008*
	Placebo	81	0.3 ± 1.8			
<u>SupDBP</u> **	Carvedilol 6.25 mg	67	-3.5 ± 1.0	-1.3	(-4.3, 1.6)	0.3422
	12.5 mg	74	-5.9 ± 1.2	-3.7	(-6.6, -0.8)	0.0067*
	25.0 mg	74	-8.7 ± 1.2	-6.3	(-9.2, -3.5)	0.0001*
	Placebo	81	-2.2 ± 1.1			
<u>StaSBP</u> **	Carvedilol 6.25 mg	67	-5.0 ± 1.7	-3.5	(-9.2, 2.1)	0.2896
	12.5 mg	74	-8.1 ± 2.1	-6.6	(-12.1, -0.5)	0.0275*
	25.0 mg	74	-7.4 ± 2.0	-6.0	(-11.5, -1.1)	0.0337*
	Placebo	81	-1.5 ± 2.0			
<u>StaDBP</u> **	Carvedilol 6.25 mg	67	-4.4 ± 1.0	-0.4	(-3.4, 2.5)	0.9229
	12.5 mg	74	-3.7 ± 1.0	0.2	(-2.7, 3.1)	0.9487
	25.0 mg	74	-7.5 ± 1.2	-3.6	(-6.5, -0.7)	0.0117*
	Placebo	81	-3.9 ± 1.2			
<u>StaSBP</u> ** (3 min)	Carvedilol 6.25 mg	67	-2.8 ± 1.9	-2.1	(-8.0, 3.8)	0.5480
	12.5 mg	74	-7.4 ± 2.4	-6.7	(-12.4, -1.0)	0.0164*
	25.0 mg	74	-7.0 ± 2.3	-6.2	(-11.9, -0.5)	0.0194*
	Placebo	81	-0.7 ± 1.8			
<u>StaDBP</u> ** (3 min)	Carvedilol 6.25 mg	67	-3.5 ± 1.1	-0.4	(-3.4, 2.7)	0.8587
	12.5 mg	74	-5.8 ± 1.1	-2.7	(-5.7, 0.3)	0.0303
	25.0 mg	74	-8.5 ± 1.2	-5.3	(-8.3, -2.3)	0.0002*
	Placebo	81	-3.1 ± 1.0			

- * Sample sizes differ due to missing vital sign values.
- * Simultaneous confidence intervals based on Dunnett's One-sided Test for Multiple Comparisons with Placebo Control, ensuring 0.05 probability of significance. Values which were statistically significant when compared to placebo are indicated by * next to the p-value for that sample.
- * For two-sided comparisons with placebo of Least Squares Means.

Subgroup analysis showed no difference of concern. The comparison by race was confounded by small numbers and the high placebo response in the black subgroup.

**Change from Baseline in Sit.DBP (mm Hg) at Endpoint
for the Subgroup Analysis According to Medication Regimen
Intent-to-Treat**

Subgroup = Sex

		Male Patients			Female Patients		
<u>Treatment Group (bid)</u>		<u>n</u>	<u>Mean ± S.E.</u>	<u>p-value^d</u>	<u>n</u>	<u>Mean ± S.E.</u>	<u>p-value^d</u>
Carvedilol	6.25 mg	84	-5.9 ± 0.8	0.0168*	33	-4.0 ± 1.3	0.2360
	12.5 mg	79	-6.5 ± 0.9	0.0117*	46	-8.6 ± 1.3	0.0001*
	25.0 mg	75	-8.3 ± 1.0	0.0001*	39	-8.6 ± 1.3	0.0002*
Placebo		69	-3.1 ± 1.0		48	-3.6 ± 1.2	

Subgroup = Age

		Age < 64 years			Age > 64 years		
<u>Treatment Group (bid)</u>		<u>n</u>	<u>Mean ± S.E.</u>	<u>p-value^d</u>	<u>n</u>	<u>Mean ± S.E.</u>	<u>p-value^d</u>
Carvedilol	6.25 mg	89	-5.5 ± 0.8	0.0338	28	-5.1 ± 1.3	0.0735
	12.5 mg	92	-7.8 ± 0.9	<0.0001*	33	-5.8 ± 1.5	0.0494
	25.0 mg	84	-8.3 ± 0.9	<0.0001*	30	-9.1 ± 1.4	0.0016*
Placebo		100	-3.4 ± 0.8		17	-2.6 ± 2.3	

Subgroup = Race

		Black Patients			Non-Black Patients		
<u>Treatment Group (bid)</u>		<u>n</u>	<u>Mean ± S.E.</u>	<u>p-value^d</u>	<u>n</u>	<u>Mean ± S.E.</u>	<u>p-value^d</u>
Carvedilol	6.25 mg	19	-2.6 ± 1.9	0.0451	98	-5.9 ± 0.7	0.0010*
	12.5 mg	23	-8.7 ± 2.3	0.3482	102	-6.9 ± 0.8	<0.0001*
	25.0 mg	13	-8.3 ± 2.6	0.4248	101	-8.6 ± 0.8	<0.0001*
Placebo		15	-7.8 ± 2.1		102	-2.7 ± 0.8	

Subgroup = Severity of Hypertension

		Mild Hypertension ^e			Moderate Hypertension ^f		
<u>Treatment Group (bid)</u>		<u>n</u>	<u>Mean ± S.E.</u>	<u>p-value^d</u>	<u>n</u>	<u>Mean ± S.E.</u>	<u>p-value^d</u>
Carvedilol	6.25 mg	85	-4.2 ± 0.8	0.1340	26	-9.7 ± 0.7	0.0038*
	12.5 mg	90	-6.5 ± 0.9	0.0041*	32	-9.9 ± 0.8	<0.0039*
	25.0 mg	82	-7.7 ± 0.8	<0.0001*	29	-10.5 ± 2.1	<0.0001*
Placebo		84	-3.4 ± 0.9		27	-4.6 ± 0.9	

* Sample sizes may differ due to missing vital sign values.

^d For one-sided comparisons with placebo of Least Squares Means.

* Simultaneous confidence intervals based on Dunnett's One-tailed T-Test for Multiple Comparisons with Placebo, Control, ensuring 0.05 probability of significance. Values which were statistically significant when compared to placebo are indicated by * next to the p-value for that sample.

^e Mild = Baseline mean sitting DBP 95-105 mm Hg, moderate = baseline mean sitting DBP 106-115 mm Hg [not shown: borderline = ≤ 95 mm Hg or severe = ≥ 115 mm Hg]

8.1.4.3. Safety comparisons

These matters are handled by another member of the team.

8.1.5 Reviewer's Comments/Conclusions of study results.

The above tables are copied from the submission and reflect accurately the information in the detailed listing of results. They show a moderate but statistically significant effect on blood pressure. Maximum effect was probably not achieved in this dose range but maximum dose was limited by concerns about side effects.

The following table shows the effect of this combined alpha and beta blockade on the heart rate.

The study population was shrinking throughout the study. This casts a pall on our efforts to generalize from the trial to a general population. The phenomenon is not specific for this drug or this trial but is a recurring cause of concern. In particular, if one wants to pay attention to the 'responder rate' as defined in this protocol, the response rates would be quite different when one included all the placebo responders that were weeded out.

Mean Change from Baseline at Endpoint in Heart Rate (bpm)

Intent-To-Treat Analysis

	<u>Treatment Group</u> (bid)	n	<u>Mean ± S.E.</u>	<u>Comparison with Placebo</u>	<u>CI*</u>	<u>p-value[‡]</u>
<u>SitHR</u>	Carvedilol 6.25 mg	117	-3.4 ± 0.7	-2.6	(-4.7, -0.4)	0.0287
	12.5 mg	125	-6.6 ± 0.7	-5.7	(-7.9, -3.6)	0.0001
	25.0 mg	114	-8.2 ± 0.9	-7.4	(-9.6, -5.2)	0.0001
	Placebo	117	-0.8 ± 0.7			
<u>SupHR</u>	Carvedilol 6.25 mg	117	-2.9 ± 0.8	-2.0	(-4.3, 0.3)	0.1068
	12.5 mg	125	-5.6 ± 0.7	-4.7	(-6.9, -2.4)	0.0001
	25.0 mg	114	-7.1 ± 0.9	-6.2	(-8.5, -3.9)	0.0001
	Placebo	116	-0.9 ± 0.8			
<u>StaHR</u>	Carvedilol 6.25 mg	117	-3.4 ± 0.9	-3.6	(-6.1, -1.2)	0.0047
	12.5 mg	125	-6.8 ± 0.8	-6.9	(-9.3, -4.5)	0.0001
	25.0 mg	114	-8.8 ± 0.7	-8.9	(-11.4, -6.5)	0.0001
	Placebo	116	-0.2 ± 0.9			
<u>StaHR</u> (3 min)	Carvedilol 6.25 mg	117	-3.6 ± 0.7	-3.7	(-6.1, -1.2)	0.0035
	12.5 mg	125	-6.9 ± 0.8	-7.0	(-9.4, -4.6)	0.0001
	25.0 mg	114	-8.8 ± 0.9	-8.9	(-11.3, -6.4)	0.0001
	Placebo	116	0.1 ± 0.9			

* Sample sizes differ due to missing vital sign values.

† Simultaneous confidence intervals based on Dunnett's One-sided Test for Multiple Comparisons with Placebo Control, ensuring 0.05 probability of significance.

‡ For two-sided comparisons with placebo of Least Squares Means. All comparisons are statistically significant with the exception of supine HR in the carvedilol 6.25 mg group.

8.2 Trial # B101

8.2.1 Objective/Rationale

The purpose of this study was to evaluate the safety and antihypertensive efficacy of carvedilol 6.25, 12.5, 25, or 50 mg administered *once daily* compared to placebo, in patients with mild to moderate hypertension treated for eight weeks.

8.2.2 Design Double blind, Parallel, Placebo Control.

n	Single Blind	n	Double blind Group	Double Blind			Single Blind
				Dose	Dose	Dose	
792	Placebo	116	Placebo	0.0			Placebo
		121	6.25 mg QD	6.25			
		127	12.5 mg QD	6.25	12.5		
		127	25 mg QD	12.5	25		
		29	50 mg QD	12.5	25	50	
up to 8 wks		520		wk 1	wk 2	wk 3-8	2 wks

8.2.3 Protocol

8.2.3.1 Population, Procedures

Males and females between the ages of 21 and 75 years with mild to moderate essential hypertension (SitDBP greater than or equal to 95 mm Hg and less than or equal to 115 mm Hg) were eligible for enrollment.

Exclusion and inclusion criteria were adequate.

8.2.3.2 Endpoints

The primary index of efficacy for comparing the treatment groups was the *mean change from baseline in SitDBP*.

Secondary Indices

- Percentage of patients with SitDBP of 90 mm Hg or less
 - Mean change in standing diastolic blood pressure
 - Mean change in supine diastolic blood pressure
 - Mean change in standing systolic blood pressure
 - Mean change in supine systolic blood pressure
 - Mean change in sitting systolic blood pressure
 - Mean change in standing heart rate
 - Mean change in supine heart rate
 - Mean change in sitting heart rate

8.2.3.3 Statistical Considerations

The target sample size required for this study was a minimum of 224 patients for which procedurally correct case report forms were completed with sufficient information to evaluate efficacy. It was estimated that 30 centers be recruited with each center providing approximately 12 to 48 patients in the Treatment Phase.

In order to determine that the appropriate range of doses was being studied, the Colton and McPherson two-stage plan was implemented, such that after the case report forms for approximately half of the patients who had completed the study were received by the sponsor, an analysis would be done. The purpose of this analysis was administrative, and as such it was not intended as a basis for any decision to terminate the study. Therefore, no adjustment was planned for the significance level of the conclusions of the final analysis.

A more extended analysis than specified in the protocol was done for subgroups. These included comparison of the primary index for subgroups based on the following categories: sex; age(≤ 64 , > 64 years); severity of hypertension at baseline (mild: 95-105 mm Hg;

**moderate: 106-115 mm Hg); and race (black, non-black, including8
caucasian and others races).**

Trough to peak ratio of effects at steady state:

Patients who completed the protocol-specified period of double-blind treatment were used for determination of the trough to peak ratio of effects at steady state. Pulse and blood pressure for these patients were recorded in the doctor's office just before and then at 0.5, 1.0, 1.5 and 2.0 hrs in the doctor's office after dosing.

The submission works through three different methods for estimating trough/peak ratio. Needless to say, the conclusion may depend on which method is chosen, and it illustrates the difficulties of translating a sound idea into policy (*i.e.* for QD dosing a trough effect must be demonstrated; this effect must *not* be bought at the price of overdosing during the peak). The statistician ends the discussion with this Parthian shot:

This estimate of the trough/peak ratio is derived as the mean of the ratio of the Trough(adj)/Peak(adj), effect computed for each patient. With this definition it is possible that this ratio for a particular patient might actually not be determinate because of division by zero (infinite ratio) or increase in steady state trough (negative ratio). Hence, the ratio is not clinically meaningful. Accordingly, this estimate was restricted to the subgroup (S) of patients treated with regimen r and for whom the $0 < \text{Adj\_Ratio} < 1$ (*i.e.*, there was efficacy at steady state and the "placebo adjusted" steady state trough was not greater than the "placebo adjusted" predose peak).

A total of 792 patients from 39 centers in the United States and six centers in Canada were screened for entry into the study. *Two hundred and seventy one (271)* patients were withdrawn during the screening phase and the remaining 521 patients were randomized into the double-blind treatment phase and received at least one dose of active study medication. One patient (patient 602) received randomized treatment, but was not entered into the database. Therefore, this patient was not included in the *intent-to-treat* sample of 520 patients.

The United States contributed the most patients (463 patients; 89%), while Canada contributed 57 patients (11%).

All 520 patients who received at least one dose of randomized treatment were included in the safety analysis and the *intent-to-treat* analysis of efficacy and make up the group hereafter referred to as the *intent-to-treat* sample.

Totals of 121, 127, 127, 29, and 116 patients were randomized to carvedilol 6.25 mg,

carvedilol 12.5 mg, carvedilol 25 mg, carvedilol 50 mg, and placebo, respectively.

The most prevalent protocol violation among the patients excluded was a failure to satisfy the blood pressure criteria for entering the treatment phase. Ninety-three (93) patients were excluded for this violation. (In other words: they had responded to placebo during the screening phase. This number is in addition to the 240, or so, who were excluded *prior* to randomization. This poses the same question that was raised in the discussion of protocol B100: To what extent does this practice bias the outcome of trials? (reviewer's comment)).

8.2.4 Results

8.2.4.1 Patient disposition. Procedures.

Number of Patients Excluded from the Per-Protocol Analysis of Efficacy According to Protocol Violation and Treatment Group

<u>Protocol Violation</u>	<u>Carvedilol 6.25 mg</u>	<u>Carvedilol 12.5 mg</u>	<u>Carvedilol 25 mg</u>	<u>Carvedilol 50 mg</u>	<u>Placebo</u>
<u>Baseline blood pressure criteria not satisfied</u>	15	21	23	13	21
<u>Predose vital signs not taken 22-26 hours after previous dose</u>	19	20	15	1	16
<u>Visit outside specified windows</u>	18	9	13	0	11
<u>Use of prohibited medications</u>	3	3	2	0	2
<u>Patient not withdrawn following protocol- defined insufficient therapeutic effect</u>	3	0	0	0	0
<u>Significant arrhythmias requiring therapy</u>	0	1	0	0	0
<u>WBC count <3500 mm³</u>	0	1	0	0	0
<u>Total Number of Patients Completely Excluded</u>	56	54	53	14	53

Summary of Baseline Characteristics
Intent-to-Treat Sample

	<u>Carvedilol</u> <u>6.25 mg</u> (N=121)	<u>Carvedilol</u> <u>12.5 mg</u> (N=127)	<u>Carvedilol</u> <u>25 mg</u> (N=127)	<u>Carvedilol</u> <u>50 mg</u> (N=29)	<u>Placebo</u> (N=116)	<u>P-value</u>
Number (%) of Patients						
Age (years):						
≤ 64	100 (83%)	101 (80%)	99 (78%)	25 (86%)	92 (79%)	0.784
> 64	21 (17%)	26 (20%)	28 (22%)	4 (14%)	24 (21%)	
Mean Age ± S.E.	54.0 ± 11.4	54.3 ± 10.5	56.6 ± 10.6	52.9 ± 11.6	55.2 ± 10.4	
Gender:						
Male	76 (63%)	78 (61%)	82 (65%)	19 (65%)	73 (63%)	0.876
Female	45 (37%)	49 (39%)	45 (35%)	10 (35%)	43 (37%)	
Race:						
Non-black	102 (84%)	110 (87%)	107 (84%)	24 (83%)	98 (84%)	0.941
Black	19 (16%)	17 (13%)	20 (16%)	5 (17%)	18 (16%)	
Severity of Hypertension:						
Normal	2 (2%)	0	1 (1%)	0	2 (2%)	0.880
Mild	86 (71%)	89 (70%)	93 (73%)	21 (72%)	81 (70%)	
Moderate	33 (27%)	38 (30%)	32 (25%)	8 (28%)	33 (28%)	
Severe	0	0	1 (1%)	0	0	
Mean Body Weight (kg) ± S.E.:						
	86.8 ± 18.8	89.6 ± 19.2	87.5 ± 18.9	86.1 ± 13.7	86.5 ± 21.6	0.502

Mean SitDBP prior to receipt of first dose of randomized medication; Normal = < 95 mm Hg, Mild = 95-105 mm Hg, Moderate = 106-115 mm Hg, Severe = ≥ 116 mm Hg

Summary of Baseline Characteristics
Per-Protocol

	<u>Carvedilol</u> <u>6.25 mg</u> (N=65)	<u>Carvedilol</u> <u>12.5 mg</u> (N=71)*	<u>Carvedilol</u> <u>25.0 mg</u> (N=74)*	<u>Carvedilol</u> <u>50.0 mg</u> (N=12)*	<u>Placebo</u> (N=59)	<u>p-value</u>
Number (%) of Patients						
Age (years):						
≤ 64	53 (82%)	53 (75%)	60 (81%)	10 (83%)	47 (80%)	0.784
> 64	12 (18%)	18 (25%)	14 (19%)	2 (17%)	12 (20%)	
Gender:						
Male	39 (60%)	44 (62%)	45 (61%)	7 (58%)	37 (63%)	0.859
Female	26 (40%)	27 (38%)	29 (39%)	5 (42%)	22 (37%)	
Race:						
Non-black	57 (88%)	62 (87%)	60 (81%)	9 (75%)	49 (83%)	0.784
Black	8 (12%)	9 (13%)	14 (19%)	3 (25%)	10 (17%)	
Severity of Hypertension*:						
Normal	1 (2%)	0	1 (1%)	0	0	
Mild	47 (72%)	46 (65%)	51 (69%)	9 (75%)	40 (6%)	0.436
Moderate	17 (26%)	25 (35%)	22 (30%)	3 (25%)	19 (3%)	
Severe	0	0	0	0	0	
Mean Body Weight (kg) ± S.E.:						
	85.9±19.1	88.9±19.6	87.9±16.7	85.7±17.1	84.7±17.2	0.767

Mean SitDBP prior to receipt of first dose of randomized medication; Normal < 95 mm Hg, Mild = 95-105 mm Hg, Moderate = 106-115 mm Hg, Severe ≥ 116 mm Hg

* Nine patients who did not commit a protocol violation were not included in the *per-protocol* analysis (carvedilol 6.25 mg: 2 patients; carvedilol 50 mg: 3 patients; placebo: 4 patients).

**Number of Patients Withdrawn From Study
by Reason for Withdrawal**

<u>Reason for Withdrawal</u>	<u>Number and Percentage of Patients</u>				
	<u>Carvedilol 6.25 mg (n=121)</u>	<u>Carvedilol 12.5 mg (n=127)</u>	<u>Carvedilol 25 mg (n=127)</u>	<u>Carvedilol 50 mg (n=29)</u>	<u>Placebo (n=116)</u>
Adverse Experience	4 3.3%	5 3.9%	11 8.7%	4 13.8%	7 6.0%
Insufficient Therapeutic Response	17 14.0%	16 12.6%	16 12.6%	0	19 16.4%
Other	5 4.1%	4 3.1%	7 5.5%	18 62.1%	3 2.6%
Total	26 21.5%	25 19.7%	34 26.8%	22 75.9%	29 25.0%

8.2.4.2 Efficacy Endpoint Outcomes.

Mean Diastolic Blood Pressure (mm Hg) at Baseline

Parameter	Treatment Group		Intent-to-Treat		Per-Protocol	
			n	Mean ± S.E.	n	Mean ± S.E.
SitDBP	Carvedilol	6.25	121	102.0 ± 0.5	65	101.9 ± 0.6
		12.5	127	102.4 ± 0.5	71	102.6 ± 0.7
		25	127	102.1 ± 0.5	74	101.6 ± 0.6
		50	29	102.0 ± 1.0	12	102.8 ± 1.7
	Placebo	116	102.0 ± 0.5	59	102.6 ± 0.7	
	SupDBP	Carvedilol	6.25	121	98.8 ± 0.6	65
12.5			127	98.0 ± 0.8	71	98.5 ± 1.0
25			127	98.7 ± 0.7	74	98.7 ± 1.0
50			29	98.4 ± 1.1	12	97.3 ± 2.0
Placebo		116	97.8 ± 0.7	59	97.3 ± 1.0	
StaDBP		Carvedilol	6.25	121	100.6 ± 0.7	65
	12.5		127	100.5 ± 0.7	71	101.0 ± 1.1
	25		126	100.8 ± 0.7	73	100.2 ± 0.9
	50		29	99.8 ± 1.3	12	100.3 ± 2.3
	Placebo	116	100.0 ± 0.7	59	100.0 ± 1.0	
	StaDBP (3 min)	Carvedilol	6.25	121	102.9 ± 0.7	65
12.5			127	102.1 ± 0.7	71	102.7 ± 0.9
25			125	102.2 ± 0.6	72	100.9 ± 0.9
50			29	101.3 ± 1.0	12	101.4 ± 2.1
Placebo		116	101.9 ± 0.6	59	102.4 ± 0.8	

Analysis of variance showed no statistically significant difference ($p > 0.05$) between the regimens in the mean diastolic pressure at any of the positions recorded at baseline

**Mean Change from Baseline
in Sitting Diastolic Blood Pressure (mm Hg)**

<u>Visit</u>	<u>Treatment Group</u>		<u>n</u>	<u>Mean</u>	<u>SE</u>	<u>Comparison with Placebo</u>	<u>CI*</u>	<u>p-value†</u>
<i>Intent-To-Treat Analysis</i>								
<u>Endpoint</u>	Carvedilol	6.25	121	-4.4	0.7	-0.7	(-2.7, 1.3)	0.390
		12.5	126	-6.3	0.7	-2.3	(-4.5, -0.5)	0.004*
		25	126	-5.8	0.7	-2.1	(-4.1, -0.1)	0.016*
		50	28	-8.0	1.3	-4.2	(-7.5, -1.0)	0.083
	Placebo		115	-3.7	0.7			
<i>Per-Protocol Analysis</i>								
<u>Week 4</u>	Carvedilol	6.25	54	-5.0	0.8	0.6	(-1.8, 3.1)	0.843
		12.5	64	-8.0	0.8	-2.4	(-4.7, -0.04)	0.016*
		25	62	-7.2	1.0	-1.5	(-3.9, 0.8)	0.087
		50	4	-11.5	2.2	*		
	Placebo		51	-5.6	0.8			
<u>Week 8</u>	Carvedilol	6.25	47	-5.3	1.0	-0.02	(-2.8, 2.8)	0.934
		12.5	56	-9.0	1.1	-3.8	(-6.5, -1.1)	0.031*
		25	51	-7.3	1.0	-2.0	(-4.8, 0.7)	0.171
		50	2	-14.0	2.0	*		
	Placebo		44	-5.3	0.9			
<u>Endpoint</u>	Carvedilol	6.25	65	-4.3	0.9	0.2	(-2.4, 2.9)	0.862
		12.5	70	-8.2	1.0	-3.6	(-6.2, -1.1)	0.004*
		25	73	-5.7	0.9	-1.2	(-3.7, 1.4)	0.101
		50	12	-9.8	2.2	-5.3	(-9.9, -0.7)	0.115
	Placebo		59	-4.5	0.8			

* 50 mg excluded from analysis of per-protocol sample at Week 4 and Week 8 because of small number of cases.

† Simultaneous confidence intervals based on Dunnett's One-tailed T-Test for Multiple Comparisons with Placebo Control, ensuring 0.05 probability of significance. Values which were statistically significant when compared to placebo are indicated by * next to the p-value for that sample.

‡ For two-sided comparisons of Least Squares Means compared with placebo.

§ Sample sizes differ due to missing vital sign values.

**Mean Change from Baseline at Endpoint in Secondary Blood Pressure (mm Hg) Parameters
Intent-to-Treat Analysis**

	<u>Treatment Group</u>		<u>n</u>	<u>Mean ± S.E.</u>	<u>Comparison with Placebo</u>	<u>CI*</u>	<u>p-value[†]</u>
<u>SisSBP</u>	Carvedilol	6.25	121	-4.8 ± 1.3	-1.9	(-5.7, 1.9)	0.239
		12.5	126	-7.1 ± 1.2	-4.2	(-8.0, -0.4)	0.012*
		25	126	-4.7 ± 1.2	-1.8	(-5.6, 2.0)	0.234
		50	28	-7.9 ± 2.5	-5.0	(-11.2, 1.2)	0.159
	Placebo	115	-2.9 ± 1.2				
<u>SupSBP</u>	Carvedilol	6.25	121	-3.6 ± 1.5	-2.4	(-6.6, 1.9)	0.254
		12.5	126	-4.9 ± 1.3	-3.7	(-7.9, 0.5)	0.053
		25	126	-5.7 ± 1.4	-4.5	(-8.7, -0.3)	0.021*
		50	28	-7.3 ± 2.5	-6.1	(-12.9, 0.8)	0.320
	Placebo	115	-1.2 ± 1.5				
<u>SupDBP</u>	Carvedilol	6.25	121	-3.3 ± 0.8	-1.0	(-3.4, 1.4)	0.259
		12.5	126	-4.9 ± 0.9	-2.6	(-5.0, -0.2)	0.011*
		25	125	-5.2 ± 0.8	-2.9	(-5.3, -0.5)	0.005*
		50	28	-5.9 ± 1.4	-3.6	(-7.5, 0.4)	0.188
	Placebo	115	-2.3 ± 0.8				
<u>StaSBP</u>	Carvedilol	6.25	121	-3.6 ± 1.6	-0.8	(-5.3, 3.6)	0.621
		12.5	126	-4.8 ± 1.4	-2.0	(-6.4, 2.4)	0.247
		25	125	-5.7 ± 1.4	-2.9	(-7.3, 1.5)	0.139
		50	28	-6.8 ± 2.5	-4.1	(-11.3, 3.1)	0.402
	Placebo	115	-2.7 ± 1.5				
<u>StaDBP</u>	Carvedilol	6.25	121	-3.0 ± 0.9	-0.7	(-3.2, 1.8)	0.459
		12.5	126	-5.1 ± 0.9	-2.7	(-5.2, -0.3)	0.006*
		25	126	-6.0 ± 0.8	-3.7	(-6.2, -1.2)	0.001*
		50	28	-7.5 ± 1.8	-5.2	(-9.2, -1.1)	0.019*
	Placebo	115	-2.3 ± 0.8				

* Sample sizes differ due to missing BP and HR values.
† Simultaneous confidence intervals based on Dunnett's One-tailed T-Test for Multiple Comparisons with Placebo Control, ensuring 0.05 probability of significance. Values which were statistically significant when compared to placebo are indicated by * next to the p-value for that sample.
‡ For two-sided comparisons of Least Squares Means with placebo.

Mean Change from Baseline at Endpoint in Heart Rate (bpm)

Intent-To-Treat Analysis

	Treatment Group		n	Mean ± S.E.	Comparison		p-Value*
					with Placebo	CI*	
<u>SitHR</u>	Carvedilol	6.25	121	-2.7 ± 0.7	-0.4	(-2.9, 2.0)	0.774
		12.5	126	-3.5 ± 0.8	-1.2	(-3.6, 1.2)	0.256
		25	126	-5.6 ± 0.8	-3.4	(-5.8, -1.0)	0.002*
		50	28	-4.6 ± 1.6	-2.3	(-6.3, 1.6)	0.309
	Placebo	115	-2.3 ± 0.9				
<u>SupHR</u>	Carvedilol	6.25	120	-2.1 ± 0.7	-0.7	(-2.9, 1.5)	0.606
		12.5	126	-2.6 ± 0.7	-1.2	(-3.4, 1.0)	0.229
		25	126	-4.5 ± 0.7	-3.1	(-5.3, -0.9)	0.002*
		50	28	-4.6 ± 1.6	-3.2	(-6.8, 0.4)	0.079
	Placebo	115	-1.4 ± 0.8				
<u>StaHR</u>	Carvedilol	6.25	120	-3.0 ± 0.9	-1.4	(-4.1, 1.2)	0.300
		12.5	126	-2.8 ± 0.8	-1.2	(-3.8, 1.4)	0.340
		25	125	-5.3 ± 0.7	-3.7	(-6.3, -1.1)	0.002*
		50	28	-4.9 ± 1.9	-3.3	(-7.6, 1.0)	0.119
	Placebo	115	-1.6 ± 0.9				

Per-Protocol Analysis

	Treatment Group		n	Mean ± S.E.	Comparison		p-value*
					with Placebo	CI*	
<u>SitHR</u>	Carvedilol	6.25	65	-4.0 ± 1.0	-0.1	(-3.6, 3.4)	0.948
		12.5	70	-4.7 ± 1.0	-0.8	(-4.2, 2.6)	0.375
		25	73	-6.8 ± 1.0	-2.9	(-6.3, 0.5)	0.053*
		50	12	-4.7 ± 2.8	-0.8	(-6.9, 5.3)	0.978
	Placebo	59	-3.9 ± 1.3				
<u>SupHR</u>	Carvedilol	6.25	65	-2.3 ± 1.0	-0.6	(-3.7, 2.5)	0.473
		12.5	70	-3.4 ± 0.9	-1.7	(-4.9, 1.3)	0.032
		25	72	-5.1 ± 0.9	-3.5	(-6.5, -0.4)	0.003*
		50	12	-5.0 ± 2.8	-3.4	(-8.8, 2.1)	0.269
	Placebo	59	-1.6 ± 1.1				
<u>StaHR</u>	Carvedilol	6.25	64	-4.0 ± 1.2	-1.8	(-4.6, 3.0)	0.375
		12.5	70	-3.1 ± 1.1	-0.8	(-5.7, 2.1)	0.448
		25	72	-5.7 ± 1.0	-3.4	(-7.2, 0.4)	0.071
		50	12	-7.8 ± 4.0	-5.5	(-12.3, 1.4)	0.263
	Placebo	59	-2.3 ± 1.4				

* Sample size

† differ due to missing vital sign values.

* Simultaneous confidence intervals based on Dunnett's One-tailed T-Test for Multiple Comparisons with Placebo Control, ensuring 0.05 probability of significance. Values which were statistically significant when compared to placebo are indicated by * next to the p-value for that sample.

* For two-sided comparisons of Least Squares Means with placebo.

The moderate changes in heart rate suggests either a weak β -blocking effect on the heart or a masking due to the simultaneous α -blockade.

**Proportion and Percentage of Patients
Classified as Responders to
Randomized Treatment at Study Endpoint**

		<u>Intent-To-Treat</u>			<u>Per-Protocol</u>		
		<u>Number</u>	<u>(%)</u>	<u>p-value¹</u>	<u>Number</u>	<u>(%)</u>	<u>p-value</u>
<i>Sitting Diastolic Blood Pressure</i>							
Carvedilol	6.25	39/121	32	0.395	20/65	31	0.846
	12.5	47/126	37	0.099	30/70	43	0.141
	25	55/126	44	0.007**	34/73	47	0.048**
	50	11/28	39	0.248	7/12	58	0.090
Placebo		31/115	27		17/59	29	
p value*	Linear	0.021			0.006		
	Non-Linear	0.409			0.782		
<i>Supine Diastolic Blood Pressure</i>							
Carvedilol	6.25	52/121	43	0.426	28/65	43	0.584
	12.5	60/126	48	0.119	35/70	50	0.159
	25	63/126	50	0.052	38/73	52	0.114
	50	12/28	43	0.667	6/12	50	0.521
Placebo		43/115	37		22/59	37	
p value*	Linear	0.197			0.135		
	Non-Linear	0.412			0.709		
<i>Standing Diastolic Blood Pressure</i>							
Carvedilol	6.25	48/121	40	0.173	26/65	40	0.348
	12.5	54/126	43	0.061	34/70	49	0.048
	25	65/125	52	0.001	36/72	50	0.032
	50	15/28	54	0.027	6/12	50	0.315
Placebo		35/115	30		18/59	31	
p value*	Linear	0.001			0.044		
	Non-Linear	0.467			0.473		

* Diastolic blood pressure normalized (≤ 90 mmHg) and/or decreased from baseline in mean SitDBP ≥ 10 mm Hg.
[†] ChiSquare p-values for significance of Linear Response and Deviation from Linear Response.
¹ Fisher exact test
^{**} Statistically significant when compared to placebo.

A remarkable aspect of the numbers is that even after the intense effort to exclude placebo responders prior to randomization as well as after the fact, there is still a significant response rate in the placebo group. The observed differences between treatments are not statistically significant.

Trough to Peak Ratios of Sitting and Standing Diastolic Blood Pressures for Patients Completing Eight Weeks of Treatment

		Mean Change		Ratio of Means*	Mean Ratio'
		<u>Trough</u>	<u>Peak</u>	% (N)	% (N >)
<i>Change in Sitting Diastolic Blood Pressure</i>					
Carvedilol	6.25	4.7	10.4	45 (33)	56 (24)
	12.5	8.4	17.1	49 (36)	52 (33)
	25	7.4	18.2	41 (26)	44 (19)
Placebo		6.3	10.7	59 (31)	57 (23)
<i>Change in Standing Diastolic Blood Pressure</i>					
Carvedilol	6.25	4.3	10.7	40 (33)	59 (12)
	12.5	7.3	15.4	51 (36)	64 (25)
	25	7.0	18.3	38 (26)	49 (16)
Placebo		4.5	8.9	51 (31)	72 (15)

50 mg group excluded from analysis because of small number of cases.
 * Ratio of means: the ratio of the mean change in trough diastolic pressure to mean change in peak diastolic blood pressure, expressed as a percentage.
 ' Mean ratio: mean of the individual patient peak/trough ratios for those patients whose response led to a determinate (0-1) ratio.

The method used for calculating the above ratios is given as

$$\frac{\text{Mean Trough}_{\text{Active}} - \text{Mean Trough}_{\text{Placebo regimen}}}{\text{Mean Peak}_{\text{Active}} - \text{Mean Peak}_{\text{Placebo regimen}}}$$

In order to make sense of the placebo numbers the term '*placebo regimen*' must mean the value after single blind baseline observation. The ratios presumably show that the mean change in blood pressure at trough is more than half the change seen at peak, (and thus should qualify for QD dosing). What is interesting in the table is that even placebo has a peak and trough, and that at trough the placebo response is not significantly different from the Carvedilol response. The difference between drug and placebo in *peak* effect seems meaningful

and shows a dose response. The drug is clearly not a once-a-day preparation. To quote the sponsor's statistician:

This analysis suggests that the 12.5 mg and 25 mg doses of carvedilol are more effective than the 6.25 mg dose and placebo, but that the effect does not last through the day.

**Change from Baseline in SitDBP (mm Hg) at Endpoint
for the Subgroup Analysis According to Medication Regimen
Intent-to-Treat**

Subgroup - Sex

		Male Patients			Female Patients		
<u>Treatment Group (uid)</u>		<u>n</u>	<u>Mean±S.E.</u>	<u>p-value[†]</u>	<u>n</u>	<u>Mean±S.E.</u>	<u>p-value[†]</u>
Carvedilol	6.25 mg	76	-2.9±0.9	0.3398	45	-6.9±1.2	0.2015
	12.5 mg	77	-5.6±1.0	0.0144*	47	-7.4±1.0	0.0371
	25.0 mg	81	-5.5±0.8	0.0111*	45	-6.3±1.1	0.1717
	50.0 mg	19	-8.2±1.6	0.0342	9	-7.6±2.8	0.2717
Placebo		73	-2.6±0.8		42	-5.6±1.1	

Subgroup - Age

		Age ≤ 64 years			Age > 64 years		
<u>Treatment Group (uid)</u>		<u>n</u>	<u>Mean±S.E.</u>	<u>p-value[†]</u>	<u>n</u>	<u>Mean±S.E.</u>	<u>p-value[†]</u>
Carvedilol	6.25 mg	100	-4.4±0.8	0.1450	21	-4.5±1.7	0.4394
	12.5 mg	100	-6.3±0.8	0.0026*	26	-6.3±1.7	0.2135
	25.0 mg	98	-6.4±0.7	0.0013*	28	-3.8±1.6	0.2780
	50.0 mg	24	-7.1±1.4	0.0907	4	-13.0±3.5	0.0625
Placebo		91	-3.4±0.7		24	-4.8±1.3	

Subgroup - Race

		Black Patients			Non-Black Patients		
<u>Treatment Group (uid)</u>		<u>n</u>	<u>Mean±S.E.</u>	<u>p-value[†]</u>	<u>n</u>	<u>Mean±S.E.</u>	<u>p-value[†]</u>
Carvedilol	6.25 mg	19	-4.9±1.9	0.1619	102	-4.3±0.7	0.3024
	12.5 mg	17	-9.1±2.3	0.0038*	109	-5.8±0.7	0.0264
	25.0 mg	20	-3.6±1.8	0.2430	106	-6.2±0.7	0.0097*
	50.0 mg	5	-7.4±2.8	0.1372	23	-8.1±1.5	0.0721
Placebo		18	-1.7±1.7		97	-4.1±0.7	

* Sample sizes may differ due to missing vital sign values.

† For one-sided comparisons with placebo of Least Squares Means.
* Simultaneous confidence intervals based on Dunnett's One-tailed T-Test for Multiple Comparisons with Placebo Control, ensuring 0.05 probability of significance. Values which were statistically significant when compared to placebo are indicated by * next to the p-value for that sample.

**Change from Baseline in SitDBP (mm Hg) at Endpoint (cont'd)
for the Subgroup Analysis According to Medication Regimen
Intent-to-Treat**

Subgroup - Severity of Hypertension

<u>Treatment Group (uid)</u>	<u>Mild Hypertension*</u>			<u>Moderate Hypertension*</u>			
	<u>n</u>	<u>Mean ± S.E.</u>	<u>p-value[†]</u>	<u>n</u>	<u>Mean ± S.E.</u>	<u>p-value[†]</u>	
Carvedilol	6.25 mg	86	-4.6 ± 0.8	0.2331	33	-4.0 ± 1.4	0.3371
	12.5 mg	89	-5.6 ± 0.7	0.0225	37	-8.0 ± 1.6	0.0155*
	25.0 mg	92	-5.2 ± 0.8	0.0578	32	-7.8 ± 1.2	0.0151*
	50.0 mg	20	-6.6 ± 1.4	0.2307	8	-11.4 ± 2.9	0.0173*
Placebo		80	-3.7 ± 0.7		33	-3.8 ± 1.4	

* Sample sizes may differ due to missing vital sign values.

†

For one-sided comparisons with placebo of Least Squares Means.

* Mild = Baseline mean sitting DBP 95-105 mm Hg, moderate = baseline mean sitting DBP 106-115 mm Hg [not shown: borderline = $\leq$ 95 mm Hg or severe = $\geq$ 115 mm Hg].

† Simultaneous confidence intervals based on Dunnett's One-tailed T-Test for Multiple Comparisons with Placebo Control, ensuring 0.05 probability of significance. Values which were statistically significant when compared to placebo are indicated by * next to the p-value for that sample.

Subgroup Comparison by Age (quoted from submission):

Comparison by age at entry ($\leq$ 64 years versus $>$ 64 years) demonstrated a statistically significant decrease in mean change from baseline at endpoint in SitDBP compared to placebo in non-elderly patients in the carvedilol 12.5 mg uid regimen (D = -6.3 mm Hg, p = 0.0026), and carvedilol 25 mg uid regimen (D = -6.4 mm Hg, p = 0.0013). *In elderly patients, none of the carvedilol regimens demonstrated a statistically significant decrease in SitDBP from baseline compared with placebo. (emphasis added).*

Subgroup Comparison by Race:

Comparison by race (black versus non-black) in mean change in SitDBP at endpoint in *non-black* patients achieved statistical significance (D = -6.2 mm Hg, p = 0.0097) in the carvedilol 25 mg regimen. The carvedilol 12.5 mg regimen demonstrated a statistically significant decrease (D = -9.1 mm Hg, p = 0.0038) from baseline in SitDBP in *black* patients.

Subgroup Comparison by Severity of Hypertension at Baseline:

Comparison by severity of hypertension at baseline was carried out for mild and moderate hypertensives. For the *intent-to-treat* sample of mild hypertensives, none of the

carvedilol regimens demonstrated a statistically significant decrease in SitDBP at endpoint when compared with placebo. All carvedilol treatment groups, with the exception of the carvedilol 6.25 mg group, in the intent-to-treat sample, showed a statistically significant ($p < 0.0173$) decrease from baseline in SitDBP for moderate hypertensives.

8.2.5 Reviewer's Comments:

In the dose range tested, Carvedilol does not appear useful as once-a-day drug.

At the peak there is a moderate blood pressure lowering effect. It is clearly dose related, and it is possible that a maximum effect has not been achieved with a maximum dose of 25 mg/day.

Judged by a clinical evaluation of patient response, as defined by the protocol, the drug could not be differentiated from placebo.

Subgroup analyses by sex, age or race did not indicate any significant difference in response.

The large weeding out of participants during placebo observation is again in evidence. Even the moderate claims that can be made on the basis of this trial are tainted by the large drop-out which makes it difficult to generalize the results of the trial to a general population of hypertensive patients.

PROTOCOL B104:

8.3.1 Objectives:

This study was designed to evaluate the safety and antihypertensive efficacy of carvedilol 6.25 to 25 mg twice daily and labetalol 100 to 400 mg twice daily, as compared to placebo, in *black* patients with mild to moderate hypertension treated for eight weeks.

8.3 Study Design:

Black patients 21 to 75 years of age, with a diagnosis of mild to moderate hypertension entered a two to eight week single-blind placebo run-in phase to confirm diagnosis and establish baseline blood pressure. Patients were then randomized to receive either carvedilol 6.25 mg twice daily, labetalol 100 mg twice daily or placebo twice daily.

Screening	n	Baseline	n	Double blind titration/treatment	Post treatment
Withdrawal from previous medication	315	Single blind placebo bid	246	Labetalol 100 - 400 mg bid	
				Carvedilol 6.25 - 25 mg bid	
				Placebo bid	
2 weeks		2 - 8 weeks		8 weeks	7 - 10 days

Population 3. Procedures.

The number of patients screened is not given. A total of 315 patients entered the single blind baseline phase. Sixty-eight patients were withdrawn during this phase and the remaining 247 patients were randomized into the treatment phase. One of these 247 patients (Pt. 14) was lost to follow-up after dosing day 1 and the inadvertent failure to account for the one dose of randomized during taken in the study medication record resulted in this patient being categorized as not being randomized. Accordingly, this patient was not included in the intent-to-treat sample of 246 patients, to which all tabulations and discussions that follow apply.

Among patients completely excluded from the per-protocol analysis, the most prevalent protocol violation was a failure to satisfy the blood pressure criteria for entering the treatment phase. Twenty-one patients were excluded for this violation.

One-hundred-seventeen (117) males and 129 females received randomized medication. The average age of patients in the study was 54 years (range 25 to 76 years) and the average body weight was 86 kg (range 47 to 159 kg). The sex, age and weight distribution of the patients assigned to the carvedilol (85 patients), labetalol (79 patients) and placebo (82 patients) treatment groups revealed no important differences in demographic characteristics.

Six patients (two in each of the three treatment groups) withdrew from the study, after at least one day of treatment without an evaluation of vital signs at the end of the dosing interval. The intent-to-treat endpoint analysis of predose (trough) vital signs, therefore, included 240 patients (83 in the carvedilol group, 77 in the labetalol group and 80 in the placebo group). From among these patients, 190 were included in the per-protocol endpoint analysis of *trough* vital signs (65 in the carvedilol group, 63 in the labetalol group and 62 in the placebo group), having had at least one set of trough vital signs measured in the treatment phase that was not excluded because of protocol violation.

Intent-to-Treat Sample

	Number (%) of Patients			
	<u>Carvedilol</u> (n = 85)	<u>Labetalol</u> (n = 79)	<u>Placebo</u> (n = 82)	<u>All</u> (n = 246)
Age (years):				
< 40	7 (8%)	6 (8%)	11 (13%)	24 (10%)
40-64	58 (68%)	54 (68%)	50 (61%)	162 (66%)
> 60	20 (24%)	19 (24%)	21 (26%)	60 (24%)
[mean age]	54	54	54	54
Gender:				
Female	50 (59%)	42 (53%)	37 (45%)	129 (52%)
Male	35 (41%)	37 (47%)	45 (55%)	117 (47%)
Severity of Hypertension:				
Mild	60 (71%)	58 (73%)	60 (73%)	178 (72%)
Moderate	24 (28%)	21 (27%)	20 (24%)	65 (26%)
Severe	1 (1%)	0 (0%)	2 (2%)	3 (1%)
Duration of Hypertension:				
≤ 24 months	10 (12%)	12 (15%)	13 (16%)	35 (14%)
> 24 months	75 (88%)	66 (84%)	68 (83%)	209 (85%)
unknown	0 (0%)	1 (1%)	1 (1%)	2 (1%)
Prior Antihypertensive Treatment:				
Yes	68 (80%)	63 (80%)	70 (85%)	201 (82%)
No	17 (20%)	16 (20%)	12 (15%)	45 (18%)
Body Weight (kg):				
≤ 70	14 (17%)	21 (27%)	18 (22%)	40 (16%)
71-90	38 (45%)	28 (35%)	36 (44%)	102 (41%)
> 91	33 (39%)	30 (38%)	28 (34%)	91 (37%)
[mean weight]	87	87	85	86

*Mean SitDBP prior to receipt of first dose of randomized medication; Mild = 95-105 mm Hg, Moderate = 106-115 mm Hg, Severe = > 115 mm Hg

Per-Protocol Sample

Number (%) of Patients

	<u>Carvedilol</u> (n = 71)	<u>Labetalol</u> (n = 71)	<u>Placebo</u> (n = 68)	<u>All</u> (n = 210)
Age (years):				
< 40	6 (8%)	5 (7%)	9 (13%)	20 (10%)
40-64	48 (68%)	48 (68%)	42 (62%)	138 (66%)
> 64	17 (25%)	18 (25%)	17 (25%)	52 (25%)
[mean age]	54	55	54	54
Gender:				
Female	41 (58%)	37 (52%)	29 (43%)	107 (51%)
Male	30 (42%)	34 (48%)	39 (57%)	103 (49%)
Severity of Hypertension:				
Mild	54 (76%)	51 (72%)	51 (75%)	156 (74%)
Moderate	17 (24%)	20 (28%)	17 (25%)	54 (26%)
Severe	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Duration of Hypertension:				
≤ 24 months	9 (17%)	10 (14%)	11 (16%)	30 (14%)
> 24 months	62 (87%)	60 (85%)	56 (82%)	178 (85%)
unknown	0 (0%)	1 (2%)	1 (2%)	2 (1%)
Prior Antihypertensive Treatment:				
Yes	54 (76%)	56 (79%)	58 (85%)	168 (80%)
No	17 (24%)	15 (21%)	10 (15%)	42 (20%)
Body Weight (kg)				
≤ 70	12 (17%)	19 (27%)	16 (24%)	47 (22%)
71-90	31 (44%)	27 (38%)	29 (43%)	87 (41%)
> 91	28 (39%)	25 (35%)	23 (34%)	76 (36%)
[mean Weight]	87	87	84	86

Withdrawals from the Study:

Of the 246 patients who received randomized study medication, 21% (18 of 85) in the carvedilol group, 18% (14 of 79) in the labetalol and 29% (24 of 82) in the placebo group were withdrawn prior to the completion of the study.

Number (%) of Patients Discontinued From the Study *after* Randomization

<u>Reason for Discontinuation</u>	<u>Carvedilol</u> (n=85)	<u>Labetalol</u> (n=79)	<u>Placebo</u> (n=82)
Adverse Experience (6%)	7 (8%)	6 (7%)	5
Insufficient Therapeutic Effect (16%)	7 (8%)	3 (4%)	13
Other (7%)	4 (5%)	5 (7%)	6
<u>Total Patients Discontinued</u> (29%)	18 (21%)	14 (18%)	24

**Distribution of Patients According to Dosage at
Endpoint of the Treatment Phase**

		<u>Number (%) of Patients</u>	
		<u>Intent-to-Treat Analysis</u>	<u>Per-Protocol Analysis</u>
Carvedilol		(n=83)	(n=65)
	6.25 mg bid	26 (31%)	25 (38%)
	12.5 mg bid	24 (29%)	19 (29%)
	25 mg bid	33 (40%)	21 (32%)
Metoprolol		(n=77)	(n=63)
	100 mg bid	25 (32%)	27 (43%)
	200 mg bid	16 (21%)	15 (24%)
	400 mg bid	33 (43%)	21 (24%)
	Off Drug*	3 (4%)	
Placebo		(n=80)	(n=62)
	1 capsule bid	30 (37%)	28 (45%)
	2 capsules bid	13 (16%)	9 (15%)
	4 capsules bid	32 (40%)	25 (40%)
	Off Drug*	5 (6%)	

*Off study medication more than 24 hours prior to visit.

8.3.3.2 Endpoints:

Two categories defining *response* at a given treatment phase visit were used. For both the intent-to-treat and per-protocol samples, no statistically significant difference was detected among the three treatments in either the *normalized* or the *responder* rates at endpoint, which ranged in the three groups from 35% to 44% (normalized) and from 40% to 57% (responders) in the intent-to-treat sample, and from 32% to 40% (normalized) and from 37 to 48% (responders) in the per-protocol sample.

The primary index of efficacy in this study was change from baseline in mean sitting diastolic blood pressure (SitDBP).

The three treatment groups were also compared with regard to the following secondary parameters of efficacy:

- percentage of patients who achieved a mean SitDBP pressure of ≤ 90 mm Hg (normalized)
- percentage of patients who achieved a mean SitDBP of ≤ 90 mm Hg and/or with a decrease in mean SitDBP of ≥ 10 mm Hg (responders)
- change (from baseline) in supine diastolic blood pressure (SupDBP)
- change (from baseline) in mean standing diastolic blood pressure (SupDBP)
- change (from baseline) in mean sitting diastolic blood pressure (StaDBP)
- change (from baseline) in mean sitting systolic blood pressure (SitSBP)
- change (from baseline) in supine systolic blood pressure (SupSBP)
- change (from baseline) in mean systolic blood pressure (StaSBP)
- change (from baseline) in mean sitting heart rate (SitHR)
- change (from baseline) in supine heart rate (SupHR)
- change (from baseline) in mean standing heart rate (StaHR)

8.3.4 Results:

**Mean Baseline Blood Pressure (mm Hg)
and Heart Rate Data (bpm)**

Intent-To-Treat Analysis

<u>Parameter</u>	<u>Regimen</u>	<u>n</u>	<u>mean</u>	<u>SE</u>	<u>Comparison</u> [*]	<u>(CI)</u> [*]	<u>P-value</u> [*]
SitSBP	Carvedilol	85	154	1.7	C vs P	(-3.25, 5.84)	0.5749
	Labetalol	79	152	1.8	L vs P	(-5.15, 4.13)	0.8289
	Placebo	82	153	1.7	C vs L	(-2.78, 6.39)	0.4393
SitDBP	Carvedilol	85	102	0.6	C vs P	(-2.16, 1.17)	0.5584
	Labetalol	79	102	0.6	L vs P	(-2.49, 0.91)	0.3612
	Placebo	82	102	0.7	C vs L	(-1.39, 1.97)	0.7309
SitHR	Carvedilol	85	75	0.9	C vs P	(-1.02, 3.71)	0.2644
	Labetalol	79	75	0.9	L vs P	(-1.43, 3.39)	0.4233
	Placebo	82	74	0.9	C vs L	(-2.03, 2.75)	0.7667
SupSBP	Carvedilol	85	154	1.7	C vs P	(-1.87, 7.49)	0.2377
	Labetalol	79	153	2.0	L vs P	(-2.31, 7.25)	0.3095
	Placebo	82	151	1.7	C vs L	(-4.39, 5.07)	0.8864
SupDBP	Carvedilol	85	100	0.8	C vs P	(-1.90, 2.46)	0.8028
	Labetalol	79	100	0.8	L vs P	(-1.50, 2.95)	0.5226
	Placebo	82	99	0.8	C vs L	(-2.65, 1.76)	0.6898
StaSBP	Carvedilol	85	153	1.6	C vs P	(-3.17, 5.86)	0.5574
	Labetalol	79	152	1.8	L vs P	(-3.61, 5.60)	0.6699
	Placebo	82	151	1.7	C vs L	(-4.21, 4.90)	0.8805
StaDBP	Carvedilol	85	102	0.7	C vs P	(-1.98, 2.29)	0.8856
	Labetalol	79	102	0.8	L vs P	(-1.96, 2.39)	0.8438
	Placebo	82	102	0.9	C vs L	(-2.22, 2.09)	0.9539

**Mean Change from Baseline at Endpoint in
Secondary Blood Pressure (mm Hg) Parameters**

Intent-To-Treat Analysis

<u>Parameter</u>	<u>Regimen</u>	<u>n</u>	<u>mean</u>	<u>SE</u>	<u>Comparison*</u>	<u>CI*</u>	<u>P-value*</u>
<u>SitSBP</u>	Carvedilol	83	-6.1	1.7	C vs P	(-10.12, -1.33)	0.0109 *
	Labetalol	77	-6.5	1.8	L vs P	(-10.45, -1.49)	0.0092 *
	Placebo	80	-0.7	1.4	C vs L	(-4.19, 4.67)	0.9146
<u>SupSBP</u>	Carvedilol	83	-3.9	1.7	C vs P	(-9.12, -0.39)	0.0330
	Labetalol	77	-5.3	1.7	L vs P	(-10.28, -1.38)	0.0104 *
	Placebo	80	0.3	1.4	C vs L	(-3.33, 5.48)	0.6302
<u>SupDBP</u>	Carvedilol	83	-5.0	1.0	C vs P	(-4.94, 0.35)	0.0885
	Labetalol	77	-7.3	0.8	L vs P	(-4.46, -2.08)	0.0006 *
	Placebo	80	-3.0	1.0	C vs L	(-0.19, 5.14)	0.0685
<u>StaSBP</u>	Carvedilol	83	-5.8	1.7	C vs P	(-10.16, -1.28)	0.0118 *
	Labetalol	77	-8.4	1.8	L vs P	(-12.49, -3.44)	0.0006 *
	Placebo	80	-0.5	1.5	C vs L	(-2.23, 6.72)	0.3238
<u>StaDBP</u>	Carvedilol	83	-6.3	1.0	C vs P	(-6.01, -0.73)	0.0127 *
	Labetalol	77	-8.8	1.0	L vs P	(-8.33, -2.95)	0.0001 *
	Placebo	80	-3.2	1.0	C vs L	(-0.39, 4.93)	0.0938

*Least squares 95% comparison-wise confidence interval and P-value of contrast from SAS General Linear Model.

*Comparison between groups significant at alpha = 0.05 using a modified Bonferroni adjustment for the 3 comparisons

**Mean Change from Baseline in
Sitting Diastolic Blood Pressure (mm Hg)**

Per-Protocol Analysis

<u>Visit</u>	<u>Regimen</u>	<u>n</u>	<u>mean</u>	<u>SE</u>	<u>Comparison*</u>	<u>CI*</u>	<u>P-value*</u>
Week 2	Carvedilol	61	-6.2	0.9	C vs P	(-4.62, 0.43)	0.1035
	Labetalol	60	-6.1	0.9	L vs P	(-4.58, 0.56)	0.1236
	Placebo	54	-4.5	1.0	C vs L	(-2.53, 2.37)	0.9483
Week 4	Carvedilol	55	-6.4	0.8	C vs P	(-2.89, 1.72)	0.6188
	Labetalol	47	-8.0	1.0	L vs P	(-4.8, 0.05)	0.0547
	Placebo	48	-5.5	0.8	C vs L	(-0.49, 4.11)	0.1213
Week 6	Carvedilol	45	-8.2	0.9	C vs P	(-6.93, -0.48)	0.0249 *
	Labetalol	43	-10.0	1.2	L vs P	(-9.03, -2.38)	0.0009 *
	Placebo	43	-5.1	1.3	C vs L	(-1.23, 5.24)	0.2224
Week 8	Carvedilol	40	-7.6	1.2	C vs P	(-5.32, 1.91)	0.3504
	Labetalol	34	-9.8	1.3	L vs P	(-7.43, 0.08)	0.0549
	Placebo	30	-7.0	1.1	C vs L	(-1.42, 5.36)	0.2505
Endpoint	Carvedilol	65	-6.3	0.9	C vs P	(-4.70, 0.45)	0.1050
	Labetalol	63	-8.0	0.9	L vs P	(-6.73, -1.48)	0.0023 *
	Placebo	62	-4.2	0.9	C vs L	(-0.58, 4.53)	0.1283

*Least squares 95% comparison-wise confidence interval and P-value of contrast from SAS General Linear Model.

*Comparison between groups significant at alpha = 0.05 using a modified Bonferroni adjustment for the 3 comparisons

**Mean Change from Baseline at Endpoint in
Secondary Blood Pressure (mm Hg) Parameters**

Per-Protocol Analysis

<u>Visit</u>	<u>Regimen</u>	<u>n</u>	<u>mean</u>	<u>SE</u>	<u>Comparison</u> [†]	<u>CI</u> [†]	<u>P-value</u> [†]
SitSBP	Carvedilol	65	-5.5	1.8	C vs P	(-8.01, 1.57)	0.1866
	Labetalol	63	-5.6	1.9	L vs P	(-8.26, 1.49)	0.1723
	Placebo	62	-2.3	1.5	C vs L	(-4.59, 4.92)	0.9451
SupSPB	Carvedilol	65	-3.5	1.9	C vs P	(-7.88, 1.71)	0.2054
	Labetalol	63	-3.0	1.8	L vs P	(-7.54, 2.21)	0.2819
	Placebo	62	-0.5	1.4	C vs L	(-5.17, 4.33)	0.8617
SupDBP	Carvedilol	65	-4.3	1.3	C vs P	(-4.61, 1.36)	0.2839
	Labetalol	63	-6.2	0.9	L vs P	(-6.66, -5.59)	0.0194
	Placebo	62	-2.8	1.1	C vs L	(-0.96, 4.96)	0.1832
SBP	Carvedilol	65	-4.4	1.9	C vs P	(-8.00, 2.06)	0.2450
	Labetalol	63	-6.1	1.9	L vs P	(-9.86, 0.38)	0.0693
	Placebo	62	-1.1	1.7	C vs L	(-3.22, 6.76)	0.4855
StaDBP	Carvedilol	65	-5.8	1.2	C vs P	(-5.51, 0.68)	0.1249
	Labetalol	63	-7.2	1.2	L vs P	(-7.13, -0.84)	0.0133 *
	Placebo	62	-3.5	1.1	C vs L	(-1.49, 4.64)	0.3128

[†]Least squares 95% comparison-wise confidence interval and P-value of contrast from SAS General Linear Model.

*Comparison between groups significant at alpha = 0.05 using a modified Bonferroni adjustment for the 3 comparisons

Response Rates

Two categories defining response at a given treatment phase visit were used in the analysis of antihypertensive efficacy in this study. Patients considered "normalized" were those whose mean SitDBP was lowered during the treatment phase to 90 mm Hg or less. Patients considered "responders" were those who achieved a normalized mean SitDBP and/or demonstrated a decrease from baseline in mean SitDBP of at least 10 mm Hg.

Number and Percent of Patients Normalized* and Responding* to Randomized Treatment at Study Endpoint

Intent-To-Treat Analysis			
	<u>Total n</u>	<u>No. (%) Normalized</u>	<u>No. (%) Responding</u>
Carvedilol	83	34 (41%)	40 (48%)
Labetalol	77	34 (44%)	44 (57%)
Placebo	80	28 (35%)	32 (40%)
<u>P-value</u> [†] :			
	C vs P	0.519	0.345
	L vs P	0.257	0.038
	C vs L	0.750	0.272
Per-Protocol Analysis			
	<u>Total n</u>	<u>No. (%) Normalized</u>	<u>No. (%) Responding</u>
Carvedilol	65	26 (40%)	30 (46%)
Labetalol	63	23 (37%)	30 (48%)
Placebo	62	20 (32%)	23 (37%)
<u>P-value</u> [†] :			
	C vs P	0.460	0.369
	L vs P	0.707	0.279
	C vs L	0.719	1.000

Subgroup efficacy results**Mean Change from Baseline at Endpoint in
Sitting Diastolic Blood Pressure (mm Hg)****Intent-To-Treat Subgroup Analyses^a**

<u>Subgroup</u>	<u>Regimen</u>	<u>n</u>	<u>mean</u>	<u>SE</u>	<u>Comparison^b</u>	<u>CI^c</u>	<u>P-value^d</u>
Age ≤ 64 years	Carvedilol	63	-5.2	1.1	C vs P	-4.62, 1.05)	0.2142
	Labetalol	59	-7.6	0.9	L vs P	(-7.46,-1.67)	0.0022 *
	Placebo	59	-4.0	1.1	C vs L	(-0.07, 5.62)	0.0560
Age > 64 years	Carvedilol	20	-9.9	1.5	C vs P	(-10.70,-1.49)	0.0106 *
	Labetalol	18	-11.6	1.2	L vs P	(-10.85,-1.30)	0.0138 *
	Placebo	21	-4.3	1.7	C vs L	(-5.14, 5.09)	0.9926
Moderate Hyperten- sion	Carvedilol	24	-3.5	2.0	C vs P	(-6.96, 4.46)	0.6607
	Labetalol	21	-10.4	1.7	L vs P	(-14.99,-3.49)	0.0023 *
	Placebo	18	-1.2	1.8	C vs L	(2.75,13.22)	0.0036 *
Weight 71-90 kg	Carvedilol	37	-10.1	1.0	C vs P	(-9.24,-2.56)	0.0007 *
	Labetalol	26	-10.0	1.3	L vs P	(-10.38,-2.93)	0.0006 *
	Placebo	36	-4.9	1.3	C vs L	(-2.85, 4.36)	0.6771
Weight ≥ 91 kg	Carvedilol	33	-4.2	1.6	C vs P	(-6.21, 2.81)	0.4554
	Labetalol	30	-8.0	1.2	L vs P	(-11.53,-2.13)	0.0050 *
	Placebo	27	-2.6	1.6	C vs L	(0.63, 9.64)	0.0262

^aResults are only shown for the subgroups for which between-group comparisons revealed statistically significant differences

^bLeast squares 95% comparison-wise confidence interval and P-value of contrast from SAS General Linear Model. ^cComparison between groups significant at alpha = 0.05 using a modified Bonferroni adjustment for the 3 comparisons

Mean Change from Pre-dose in Blood Pressure (mm Hg) and Heart Rate (bpm) at Peak Post-Dose Effect

Intent-To-Treat Analysis

	<u>n*</u>	<u>Mean Sitting</u>			<u>Supine</u>			<u>Immediate Standing</u>			<u>3 Minute Standing</u>		
		<u>SBP</u>	<u>DPP</u>	<u>HR</u>	<u>SBP</u>	<u>DPP</u>	<u>HR</u>	<u>SBP</u>	<u>DPP</u>	<u>HR</u>	<u>SBP</u>	<u>DPP</u>	<u>HR</u>
		Carvedilol											
6.25 mg	85	-13.8	-9.4	-5.8	-12.0	-8.5	-5.4	-16.0	-10.4	-7.2	-13.8	-9.5	-6.2
12.5 mg	59	-12.5	-8.9	-5.6	-10.8	-8.8	-4.6	-12.6	-9.4	-6.4	-14.0	-9.5	-6.4
25.0 mg	34	-17.0	-9.9	-4.4	-13.7	-8.7	-4.6	-19.3	-11.5	-6.3	-17.1	-10.9	-5.1
Labetalol													
100 mg	77	-15.3	-11.9	-7.1	-15.4	-11.5	-5.8	-18.6	-13.1	-6.5	-18.8	-13.8	-6.0
200 mg	51	-15.3	-9.5	-6.0	-13.1	-8.3	-5.3	-16.3	-10.9	-4.9	-18.0	-10.6	-4.5
400 mg	33	-14.5	-9.2	-5.7	-14.4	-6.7	-3.0	-17.2	-11.6	-4.5	-20.4	-11.1	-5.2
Placebo													
1 cap	81	-11.0	-8.6	-7.1	-8.2	-7.0	-5.9	-10.8	-7.4	-5.8	-8.8	-7.8	-4.4
2 caps	51	-7.4	-5.2	-6.3	-8.3	-5.8	-5.3	-6.3	-4.1	-5.5	-6.6	-5.7	-5.8
4 caps	36	-7.9	-4.7	-6.0	-7.3	-4.8	-5.0	-7.9	-6.2	-5.7	-6.7	-5.8	-6.4

Peak defined as the time at which the lowest SBP, DBP or HR was observed in the post-dose period for a given patient

Postural hypotension was specifically defined in the protocol as a reduction in blood pressure >30 mm Hg systolic and > 15 mm Hg diastolic, concurrent with associated signs and symptoms (e.g., diaphoresis, dizziness, etc), with a change from the supine to standing position. One patient randomized to *labetalol* therapy had a postural hypotensive event so defined:

- Patient 149 (55 years old, female) experienced a fall in BP from 201/105 mm Hg, supine to 120/83, standing, on day 29 of labetalol treatment (approximately 45 minutes after receiving the first dose of 400 mg b.i.d.). Among the blood pressures recorded until the patient recovered after about 1.5 hours, the lowest was 96/56 mm Hg measured in the standing position about 1 hour after the initial event.

Two additional patients, each randomized to *labetalol* had a hypotensive event and additional post-dose vital signs recorded, but the conditions surrounding the event did not meet the protocol definition for postural hypotension:

- Patient 152 (55 years old, female) experienced a fall in BP from 186/105 mm Hg, supine to 156/83, standing (and therefore a fall of 30 mm Hg systolic, but not >30 mm Hg systolic), on day 29 of labetalol treatment (approximately 30 minutes after receiving the first dose of 400 mg b.i.d.). Among the blood pressures recorded until the patient recovered after about 1.5 hours, the lowest was 115/84 mm Hg, measured in the standing position about 1 hour after the initial event.

- Patient 169 (51 years old, female) had a standing blood pressure of 84/54 mm Hg recorded about 30 minutes after dosing on day 50 of labetalol treatment (day 2 of treatment with 200 mg b.i.d., after having previously received 14, 14 and 20 days treatment with 100, 200 and 400 mg b.i.d., consecutively). While a supine blood pressure prior to this reading was not recorded, a reading of 120/94 mm Hg in the sitting position was taken prior to dosing that day.

Finally, Patient 43 experienced a hypotensive adverse experience on day 21 of treatment with 6.25 mg *carvedilol* b.i.d. The event resulted in a fall and injury to the face. Additional details from the serious adverse experience report indicate that the patient actually experienced a temporary loss of consciousness, and the event is therefore considered a "syncope". The patient was withdrawn from the study at that time because of the event.

Vital signs of possible clinical concern were defined as a systolic blood pressure < 100 mm Hg, a diastolic blood pressure of < 80 mm Hg and a heart rate < 50 bpm. Each of the three treatment groups demonstrated isolated cases of patients with vital signs of possible clinical concern within a given period of treatment, very few of which were for systolic blood pressure or heart rate.

DISCUSSION AND CONCLUSIONS (according to the Sponsor)

While beta-blocking agents as a class are generally established as being less effective in black as compared with non-black patients in the treatment of hypertension³, labetalol has been shown, although not in all studies⁴, to be more effective than propranolol^{4,5}. Carvedilol, like labetalol, has the combined pharmacologic activities of alpha- and beta-blockade, although at a different ratio; at dosage levels of equivalent beta-blocking potency, carvedilol is estimated to have approximately half as much alpha-blocking potency as labetalol (data on file). This study was designed to evaluate the antihypertensive efficacy and safety of carvedilol, as compared with placebo, in black patients, utilizing labetalol as a positive control.

The intent-to-treat and per-protocol analyses showed no difference at endpoint between carvedilol and labetalol with regard to the primary parameter of efficacy (mean change from baseline in SitDBP) nor for any of the secondary blood pressure parameters of efficacy. At the intent-to-treat endpoint of the treatment phase, labetalol achieved a statistically significant greater reduction from baseline in mean SitDBP (-8.6 mm Hg), as compared with placebo (-4.1 mm Hg). Carvedilol achieved a significantly greater reduction in mean SitDBP, as compared with placebo, at Week 6 of the per-protocol analysis (-8.2 mm Hg vs -5.1 mm Hg), but not at study endpoint. Both carvedilol and labetalol also achieved at intent-to-treat endpoint a statistically significant reduction from baseline in mean SitSBP, StaSBP and StaDBP, as compared with placebo.

With regard to response rates, there was no significant differences between the carvedilol, labetalol and placebo treatment groups in the percentage of patients normalized (mean SitDBP $\leq$ 90 mm Hg) or in the percentage of patients classified as responders (mean SitDBP $\leq$ 90 mm Hg or decreased from baseline $\geq$ 10 mm Hg).

The failure of this study to demonstrate more significant efficacy results with either active treatment, as compared with placebo, may be related in part to the study methodology. Previous studies demonstrating the efficacy of labetalol in blacks were with dosages up to 800 mg twice daily.⁸ This study may have been improved if an additional titration step to 50 mg carvedilol or 800 mg labetalol twice daily was permitted.

In summary, this clinical trial in black hypertensives demonstrated no statistically significant difference between carvedilol and labetalol, with regard to any of the parameters of efficacy in the overall sample. It did not demonstrate a statistically significant greater reduction in mean SitDBP at endpoint (the primary parameter of efficacy) with carvedilol at the dosage levels studied, as compared with placebo, although significant reductions in secondary assessments of diastolic blood pressure in the supine and standing positions were noted. Additional investigation allowing for the possible titration to 50 mg carvedilol twice daily is required to evaluate the full potential of carvedilol in treating hypertension in blacks.

Reviewer's Comment:

The study as a whole did not suggest that Carvedilol is useful in treatment of hypertension in Blacks, although the p-values reached significance in some subgroups. Labetalol did perform better. The sponsor makes the claim that there was no difference between the two active treatments. It is doubtful that the trial had enough power to warrant this conclusion.

8.4 PROTOCOL C1106:

A MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED TITRATION TRIAL OF CARVEDILOL ADMINISTERED ONCE (QD) OR TWICE (BID) DAILY TO PATIENTS WITH MILD TO MODERATE HYPERTENSION

8.4.1 Objective:

- study and compare the efficacy and safety of *titrated* doses of carvedilol administered once daily (every 24 hours) as compared to carvedilol administered twice daily (every 12 hours) and to placebo
- evaluate whether the antihypertensive effect demonstrated after *one* week of carvedilol is different from that observed after *two* weeks of the same dose of carvedilol
- assess the steady-state *peak* and *trough* effects of carvedilol.

8.4.2 Design:

Single Blind	Double Blind Group	Up titration: dose	Fixed dose	C1111 (open)
Placebo	Carvedilol once daily, Placebo once daily	Carvedilol 6.25 - 50 mg/day	same	optional continuation of maintenance medication
	Carvedilol twice daily	same as above	same	
	Placebo twice daily	0 mg Carvedilol	0 mg Carvedilol	
5 - 6 weeks	randomization	2 - 12 weeks	4 weeks	long term

Multicenter, double-blind, randomized, placebo-controlled, parallel group study. Patient eligibility was established at an initial screening visit. Eligible patients who were already taking antihypertensive medication had those medications withdrawn in a manner deemed appropriate by the investigator. A Placebo Baseline Phase was begun on the day following their last dose of antihypertensive medication

Patients qualified to enter the double-blind Treatment Phase when all of the following criteria were met:

- 1) the mean sitting diastolic blood pressure (SitDBP) and the mean standing diastolic blood pressure (StaDBP) were 95 - 115 mm Hg at the last three Placebo Baseline Phase visits;
- 2) the highest to the lowest mean SitDBP and StaDBP at the last three Placebo Baseline Phase visits did not vary by more than 10 mm Hg;
- 3) the mean SitDBP did not vary by more than 5 mm Hg at the last two Placebo Baseline Phase visits; and,
- 4) the mean StaDBP did not vary by more than 5 mm Hg at the last two Placebo Baseline Phase visits.

Exclusion criteria were adequate. Restrictions on concomitant medication were appropriate.

8.4.3 Protocol:

8.4.3.1 Population, Procedures

A total of 280 patients (169 males and 111 females; 167 Caucasian, 105 Black, and 8 Hispanic) received coded medication.

The average age of the patients in the study was 52.7 years (range: 22 to 84 years) and the average body weight was 89.1 kg (range: 39.1 to 178.8 kg).

The sex, age, weight, and race distributions revealed no important differences in demographic characteristics among the three treatment groups.

There were 57 additional patients who entered the placebo baseline phase and were excluded at randomization. Among them, 30 were excluded for 'failure to meet entry criteria' (n.o.s. but possibly the bulk of them were 'placebo responders').

**Summary of Baseline Characteristics for the *Intent-To-Treat*
Sample According to Regimen**

	Placebo		Carvedilol UID		Carvedilol BID		Total		p-Value*
	N	%	N	%	N	%	N	%	
TOTAL PATIENTS	93	100%	90	100%	96	100%	279	100%	
<u>AGE</u>									
< 40	9	10%	12	13%	14	15%	35	13%	0.862
40-64	71	76%	64	71%	68	71%	203	73%	
> 64	13	14%	14	16%	14	15%	41	15%	
<u>SEX</u>									
FEMALE	36	39%	32	36%	43	45%	111	40%	0.423
MALE	57	61%	58	64%	53	55%	168	60%	
<u>SEVERITY OF HYPERTENSION</u>									
MILD	72	77%	75	83%	81	84%	228	82%	0.415
MODERATE	21	23%	15	17%	15	16%	51	18%	
<u>BLACK</u>									
BLACK	35	38%	33	37%	36	38%	104	37%	0.989
NON-BLACK*	58	62%	57	63%	60	63%	175	63%	
<u>PRIOR ANTI - HYPERTENSIVES</u>									
NO	32	34%	39	43%	33	34%	104	37%	0.353
YES	61	66%	51	57%	63	66%	175	63%	
<u>BODY WEIGHT AT BASELINE</u>									
< 70 Kgs	14	15%	15	17%	20	21%	49	18%	0.872
71-90 Kgs	36	39%	34	38%	36	38%	106	38%	
≥ 91 Kgs	43	46%	41	46%	40	42%	124	44%	
<u>DURATION OF HYPERTENSION†</u>									
< 24 MONTHS	15	16%	11	12%	13	14%	39	14%	0.724
≥ 24 MONTHS	77	83%	79	88%	82	85%	238	85%	
MISSING	1	1%	0	0%	1	1%	2	1%	

	PLACEBO			CARV UID			CARV BID			p-value*
	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	
AGE (yrs)	93	53	11	90	53	11	96	52	11	0.6380
WEIGHT (kgs)	93	90	20	90	89	19	96	89	22	0.8402
DURATION OF HYPERTENSION (mos)	92	117	94	90	112	101	95	128	111	0.5091

* Randomized, received double-blind study medication, and had at least one on-therapy trough vital signs observation, regardless of protocol violations.

† p-Value of Chi-square test
 ‡ See Appendix 3.2.1 for breakdown of non-black category
 § Test excludes missing category for duration of hypertension
 ¶ F-test from SAS General Linear Model.

Primary efficacy index

The primary index of efficacy for comparing the treatment groups was the mean change from baseline SitDBP at endpoint.

Secondary efficacy indices

The treatment groups were compared with regard to the following secondary efficacy indices:

- Percentage of patients with a SitDBP of < 90 mm Hg (normalized SitDBP)
- Percentage of patients with a StaDBP of < 90 mm Hg (normalized StaDBP).
- Mean change in StaDBP and SuDBP.
- Mean change in StaSBP, SitSBP and SuSBP.
- Mean change in StaHR, SitHR and SuHR.

Subgroup analyses

Subgroups of patients in the *per-protocol* and *intent-to-treat* samples were compared, both within a given treatment and between the two treatments, with regard to the mean change from baseline in SitDBP, percentage of patients achieving the primary index of response, and the percentage of patients achieving a normalized ($\leq$ 90 mm Hg) mean SitDBP at endpoint. The subgroups were based on the following categories: sex, age ($\leq$ 64, $>$ 64 years old), severity of hypertension, and race (Black; Non-black, including Caucasian, Hispanic, and Other). The numbers of patients completing the study were also compared between Black and non-Black subgroups.

Reasons for Concluding Study by Medication Regimen
Comparison of Black Versus Non-black Patients
Randomized Sample

<u>Reason for Concluding Study</u>	<u>Placebo</u>		<u>Carvedilol QID</u>		<u>Carvedilol BID</u>	
	<u>Non- Black</u>	<u>Black</u>	<u>Non- Black</u>	<u>Black</u>	<u>Non- Black</u>	<u>Black</u>
<u>N(%)</u>	<u>N(%)</u>	<u>N(%)</u>	<u>N(%)</u>	<u>N(%)</u>	<u>N(%)</u>	<u>N(%)</u>
Insufficient Therapeutic Effect*	37(64)	27(77)	13(23)	12(35)	7(12)	7(19)
Adverse experience	1(1)	0(0)	2(4)	1(3)	3(5)	1(3)
Other*	2(3)	3(9)	4(7)	1(3)	3(5)	1(3)
Completed study	<u>18(31)</u>	<u>5(14)</u>	<u>38(67)</u>	<u>20(59)</u>	<u>47(78)</u>	<u>27(75)</u>
Total Patients	58(62)	35(38)	57(63)	34(37)	60(63)	36(37)

* Two patients (128 and 134) randomized to carvedilol once daily requested to be withdrawn for 'patient perceived' insufficient therapeutic effect.

* "Other" includes the following reasons: non-compliant, unable to keep appointments, or patient decided to stop.

The striking features of this table are the higher fraction of "insufficient therapeutic effect" in the black population, and the high dropout rate among blacks on *placebo* (only 5 of 35 completed the study). Two tentative conclusions might be that 1): The black participants had more intractable hypertension and 2): (the often repeated contention) Black patients with hypertension respond poorly to β -blockers (although in this case the latter observation is confounded by the high placebo response among non-blacks).

Distribution of Patients According to Regimen and Dose Level at Each Endpoint

	Placebo		Carvedilol UID*		Carvedilol BID	
	No.	%	No.	%	No.	%
Total Randomized	93	100.0	91	100.0	96	100.0
<u><i>Intent-to-Treat</i></u>						
Titration Endpoint						
Level 2 (.../6.25/3.125)	11	(11.8)	10	(11.1)	10	(10.4)
Level 3 (.../12.5/6.25)	9	(9.7)	15	(16.7)	6	(6.3)
Level 4 (.../25/12.5)	4	(4.3)	22	(24.4)	27	(28.1)
Level 5 (.../50/25)	67	(72.0)	41	(45.6)	52	(54.2)
Off drug ^a	2	(2.2)	2	(2.2)	1	(1.0)
Regimen total	93	(100.0)	90	(100.0)	96	(100.0)
[Percent of Randomized]		[100.0]	90	[98.9]	96	[100.0]
Maintenance Endpoint						
Level 2 (.../6.25/3.125)	10	(43.5)	5	(8.6)	8	(10.4)
Level 3 (.../12.5/6.25)	1	(4.3)	13	(22.4)	5	(6.3)
Level 4 (.../25/12.5)	2	(8.7)	18	(31.0)	25	(32.5)
Level 5 (.../50/25)	10	(43.5)	21	(36.2)	37	(48.1)
Off drug ^a	0	(0.0)	1	(1.7)	2	(2.6)
Regimen total	23	(100.0)	58	(100.0)	77	(100.0)
[Percent of Randomized]		[24.7]	58	[63.7]	77	[80.2]
Study Endpoint						
Level 2 (.../6.25/3.125)	11	(11.8)	10	(11.1)	9	(9.4)
Level 3 (.../12.5/6.25)	9	(9.7)	14	(15.6)	6	(6.3)
Level 4 (.../25/12.5)	4	(4.3)	22	(24.4)	26	(27.1)
Level 5 (.../50/25)	67	(72.0)	42	(46.7)	52	(54.2)
Off drug ^a	2	(2.2)	2	(2.2)	3	(3.1)
Regimen total	93	(100.0)	90	(100.0)	96	(100.0)
[Percent of Randomized]		[100.0]	90	[98.9]	96	[100.0]

* Study medication was administered by Levels in order to maintain double-blind conditions. The carvedilol doses (mg) for each level are displayed in parentheses, (placebo [...]; carvedilol once daily [mg]; carvedilol twice daily [mg]).

• Patient #164 was withdrawn after receiving the first dose of study medication and is excluded from efficacy analysis.

As in the previous table, the numbers here are confounded by the black/non-black dichotomy. On the face of it a drug effect is shown by the higher number of placebo patients who were titrated to the highest level. Nearly half of them, however, must have been blacks who then dropped out. Another way to look for a drug effect is to note that in the placebo group 3 out of 4 quit before the end of the study; in the UID group 1 out of 3 quit; while in the BID group 4 out of 5 stayed the course. The decision to quit depended on the patient's perception of benefit, as well as on the physician's evaluation. In this sense the drug was judged better than placebo, and BID better than UID.

**Summary of Tabulations and Analysis of Baseline SitDBP
and Change from Baseline at Titration, Maintenance and Study Endpoints
*Intent-to-Treat***

	<u>REGIMEN</u>	<u>N</u>	<u>MEAN*</u>	<u>SE</u>	<u>COMPARISON</u>	<u>ESTIMATE CONFIDENCE INTERVAL</u>	<u>P - VALUE</u>
Baseline	PLACEBO	93	102	0.5			
	CARV UID	90	101	0.4	UID vs PLAC*	(-2.09, 0.50)	0.2288
	CARV BID	96	101	0.4	BID vs PLAC*	(-2.26, 0.27)	0.1225
				UID vs BID *	(-1.08, 1.48)	0.7559	
End Titration	PLACEBO	93	- 3.6	0.8			
	CARV UID	90	- 9.1	0.9	UID vs PLAC*	(-6.34,-2.73)	0.0001*
	CARV BID	96	-11.8	0.7	BID vs PLAC*	(-8.98,-4.87)	0.0001*
				UID vs BID *	(0.00, 4.17)	0.0496*	
End Maintenance	PLACEBO	23	-10.2	1.7			
	CARV UID	58	-11.6	0.7	UID vs PLAC ^y	(-4.10, 1.29)	0.3051
	CARV BID	77	-12.8	0.7	BID vs PLAC ^y	(-5.23,-0.03)	0.0478
				UID vs BID ^y	(-0.68, 3.13)	0.2056	
Study Endpoint	PLACEBO	93	- 3.3	0.8			
	CARV UID	90	- 7.9	0.8	UID vs PLAC*	(-5.83,-1.51)	0.0009*
	CARV BID	96	-10.9	0.8	BID vs PLAC*	(-8.79,-4.57)	0.0001*
				UID vs BID *	(0.87, 5.15)	0.0060*	

* MEAN is the unadjusted mean; units are mm Hg.

* Significant at $\alpha=0.05$ using modified Bonferroni procedure for the three comparisons.

* Least Squares 95% Comparisonwise Confidence Interval & p-value of contrast from SAS General Linear Model.

^y

Fisher's LSD 95% Comparisonwise Confidence Interval & p-value of t-test.

The high dropout rate in the placebo group continues to confound the issue. The average blood pressure results among the *completers* are not different in the 3 groups. Given all the practical problems of a titration study, and acknowledging the philosophical issues surrounding '*per protocol*' vs '*intent-to-treat*' analyses, it is difficult to evaluate a trial where the two analytical methods give such disparate results. There seems to be a drug effect on blood pressure even in this study but the outcome is not confidence-building.

**Mean* Change from Baseline in
Sitting Diastolic Blood Pressure
at Titration, Maintenance, and Study Endpoints
According to Dose*
*Intent-to-Treat***

	<u>Placebo</u>			<u>Carvedilol UTD</u>			<u>Carvedilol BID</u>		
	<u>n</u>	<u>Mean</u>	<u>SE</u>	<u>n</u>	<u>Mean</u>	<u>SE</u>	<u>n</u>	<u>Mean</u>	<u>SE</u>
Baseline SitDBP:	93	102.1	0.5	90	101.3	0.4	96	101.1	0.4
Change from Baseline at Titration Endpoint									
Level 2 (.../6.25/3.125)	11	-11.3	2.6	10	-5.4	3.1	10	-9.5	1.5
Level 3 (.../12.5/6.25)	9	-2.4	4.0	15	-15.3	1.9	6	-14.3	1.3
Level 4 (.../25/12.5)	4	-8.5	2.5	22	-12.3	1.6	27	-15.1	1.3
Level 5 (.../50/25)	67	-2.3	0.7	41	-6.3	1.1	52	-10.1	1.0
Off Drug	2	-2.5	1.5	2	-3.0	3.0	1	-12.0	0
Change from Baseline at Maintenance Endpoint									
Level 2 (.../6.25/3.125)	10	-14.1	1.6	5	-7.8	2.9	8	-8.3	1.7
Level 3 (.../12.5/6.25)	1	-12.0	0	13	-12.8	1.3	5	-13.4	1.1
Level 4 (.../25/12.5)	2	-2.5	4.5	18	-13.3	1.3	25	-15.7	0.9
Level 5 (.../50/25)	10	-7.7	3.1	21	-10.3	1.1	37	-12.4	1.2
Off Drug	0	...	...	1	-12.0	0	2	-1.5	0.5
Change from Baseline at Study Endpoint									
Level 2 (.../6.25/3.125)	11	-11.7	2.8	10	-3.6	2.9	9	-7.2	1.8
Level 3 (.../12.5/6.25)	9	-2.3	4.0	14	-11.7	1.7	6	-14.2	1.2
Level 4 (.../25/12.5)	4	-4.0	2.7	22	-11.2	1.8	26	-14.7	1.4
Level 5 (.../50/25)	67	-2.0	0.7	42	-6.1	1.1	52	-9.6	1.2
Off Drug	2	-2.5	1.5	2	-6.0	6.0	3	-5.0	3.5

* Mean is the unadjusted mean; units are mm Hg.

* Study medication was administered by Levels in order to maintain double-blind conditions. The carvedilol doses (mg) for each level are displayed in parentheses.

This table adds nothing. The numerical distribution of patients between dose levels was presented in a previous table. The BP changes from baseline show, as expected, that those with the poorest response get titrated to the highest level and we get what looks like an inverted dose/response curve. It is not clear why the placebo group at 'level 2' beats the other two groups so handily. (I am sceptical, though, of the level of blinding in trials involving β -blockers. The side effects are too obvious to go unnoticed.)

Number and Percentage of Patients Responding to Treatment at Titration, Maintenance and Study Endpoints

Intent-To-Treat

		<u>Total N</u>	<u>Normalized*</u>		<u>Responder*</u>	
			<u>N (%)</u>	<u>p-value*</u>	<u>N (%)</u>	<u>p-value*</u>
TITRATION ENDPOINT						
PLACEBO	sitting	93	18 (19%)		22 (24%)	
	standing	93	15 (16%)		21 (23%)	
CARV UID	sitting	90	52 (58%)	<0.001*	55 (61%)	<0.001*
	standing	90	32 (36%)	<0.001*	53 (59%)	<0.001*
CARV BID	sitting	96	65 (68%)	<0.001*	73 (76%)	<0.001*
	standing	96	42 (44%)	<0.001*	68 (71%)	<0.001*
CARV UID vs CARV BID		sitting		0.116		0.018*
		standing		0.192		0.067
MAINTENANCE ENDPOINT						
PLACEBO	sitting	23	14 (61%)		14 (61%)	
	standing	23	10 (43%)		13 (57%)	
CARV UID	sitting	58	41 (71%)		43 (74%)	
	standing	58	26 (45%)		39 (67%)	
CARV BID	sitting	77	50 (65%)		59 (77%)	
	standing	77	34 (44%)		55 (71%)	
STUDY ENDPOINT						
PLACEBO	sitting	93	17 (18%)		18 (19%)	
	standing	93	11 (12%)		19 (20%)	
CARV UID	sitting	90	43 (48%)	<0.001*	46 (51%)	<0.001*
	standing	90	28 (31%)	0.001*	43 (48%)	<0.001*
CARV BID	sitting	96	53 (55%)	<0.001*	63 (66%)	<0.001*
	standing	96	35 (36%)	<0.001*	58 (60%)	<0.001*
CARV UID vs BID		sitting		0.260		0.024* CARV
		standing		0.348		0.051

* Normalized is defined as a reduction of mean SitDBP to < 90 mm Hg; a responder is defined as a patient with a reduction of mean SitDBP to < 90 mm Hg patient with and/or a reduction of ≥ 10 mm Hg.
 ; p-value of Paired Comparisons using CMH Chi-square.
 ; Significant at experimentwise alpha = 0.05 using modified Bonferroni procedure.

The different views are consistent. The story, if there is one, is told by the drop-outs.

Peak and trough: (see table on next page)

The following is verbatim from the submission:

Both placebo-adjusted and unadjusted trough to peak ratios were calculated. The placebo adjustment is used to decrease the effect of carvedilol treatment by the amount that could be attributed to placebo treatment. But because of this study design, only patients with at least a minimal response to treatment have had post-dosing data collected. For patients randomized to placebo, this effect is greater at trough than at peak, and cannot be considered a representative peak effect. These placebo results cause the adjusted carvedilol trough to be reduced by a greater amount than the adjusted carvedilol peak for both regimens. Therefore, unadjusted trough to peak ratios are also presented.

Analysis of steady-state sitting diastolic trough and peak measurements for the *intent-to-treat* sample at Study Endpoint showed that 47.1% of the peak effect for carvedilol once daily and 65.5% of the peak effect for carvedilol twice daily is retained at trough, based upon placebo-adjusted trough to peak ratios. In comparison, unadjusted trough to peak ratios at Study Endpoint indicate that 71.6% of the peak effect for carvedilol once daily and 85.4% of the peak effect for carvedilol twice daily is retained at trough.

For patients who demonstrated an adequate response to treatment and therefore have peak data collected at Maintenance Endpoint, analysis of steady-state sitting diastolic trough and peak measurements for the *intent-to-treat* sample at Study Endpoint showed that 31.7% of the peak effect for carvedilol once daily and 39.8% of the peak effect for carvedilol twice daily is retained at trough, based upon placebo-adjusted trough to peak ratios. In comparison, unadjusted trough to peak ratios at Study Endpoint indicate that 76.9% of the peak effect for carvedilol once daily and 90.1% of the peak effect for carvedilol twice daily is retained at trough.

Anything I can add will only tend to magnify the mystery.

**Summary of Mean* Change from Baseline SitDBP at Peak and
Trough at Study Endpoint and According to Phase of Last Visit
Intent-to-Treat**

	REGIMEN	N	MEAN (SE) DIFFERENCE [ENDPOINT-BASELINE]				TROUGH/PEAK*	
			TROUGH: MEAN (SE)		PEAK:		RATIO	
			Mean	(SE)	Mean	(SE)	Placebo Adjusted	Unadjusted
TITRATION ENDPOINT	PLACEBO	54	-1.0	(0.9)	-1.8	(1.1)		
	CARV UID	23	-0.5	(1.3)	-6.9	(1.8)	-9.8%	7.2%
	CARV BID	13	-1.8	(2.2)	-6.8	(2.1)	16.0%	26.5%
MAINTENANCE ENDPOINT	PLACEBO	23	-9.8	(1.8)	-8.9	(1.7)		
	CARV UID	57	-11.3	(0.7)	-14.1	(0.9)	31.7%	76.9%
	CARV BID	74	-12.7	(0.8)	-14.1	(1.0)	39.8%	90.1%
STUDY ENDPOINT	PLACEBO	78	-3.5	(0.9)	-1.4	(1.1)		
	CARV UID	80	-8.3	(0.8)	-11.6	(0.9)	47.1%	71.6%
	CARV BID	87	-11.1	(0.8)	-13.0	(0.9)	65.5%	85.4%

* Mean is the unadjusted mean; units are mm HG.

$$\text{UNADJUSTED TROUGH/PEAK RATIO} = \frac{(\text{MEAN DIF ACTIVE TROUGH})}{(\text{MEAN DIF ACTIVE PEAK})} \times 100\%$$

where DIF = Study Endpoint - Baseline

$$\text{PLACEBO-ADJUSTED TROUGH/PEAK RATIO} = \frac{(\text{MEAN DIF ACTIVE TROUGH}) - (\text{MEAN DIF PLACEBO TROUGH})}{(\text{MEAN DIF ACTIVE PEAK}) - (\text{MEAN DIF PLACEBO PEAK})} \times 100\%$$

where DIF = Study Endpoint - Baseline

Subgroup analyses

A stated object was to compare results after week one and week two on any given dose level. One of the resulting tables is reproduced below. The discussion is not helpful. The concluding paragraphs are reproduced. Although the differences seen hardly are meaningful, it seems as if the initial response gets blunted.

Summary of Tabulations and Analysis of Baseline SitDBP and Change from Baseline at Study Endpoint for Subgroup Analyses Intent-to-Treat

	<u>REGIMEN</u>	<u>N</u>	<u>MEAN*</u>	<u>SE</u>	<u>COMPARISON</u>	<u>ESTIMATE CONFIDENCE INTERVAL *</u>	<u>p-VALUE*</u>
MALE							
Baseline	PLACEBO	57	102.0	0.6			
	CARV UID	58	103.7	0.5	UID vs PLAC	(2.9, 0.3)	0.0493
	CARV BID	53	103.6	0.6	BID vs PLAC	(-3.1, 0.2)	0.0823
					UID vs BID	(-1.5, 1.7)	0.8977
Study Endpoint	PLACEBO	57	-2.0	0.9			
	CARV UID	58	-6.5	1.0	UID vs PLAC	(-7.0, -2.1)	0.0004*
	CARV BID	53	-10.3	1.2	BID vs PLAC	(-10.9, -5.8)	0.0001*
Baseline	PLACEBO	36	102.3	0.7			
	CARV UID	32	102.4	0.8	UID vs PLAC	(-1.8, 2.0)	0.8939
	CARV BID	43	101.8	0.6	BID vs PLAC	(-2.2, 1.3)	0.6230
					UID vs BID	(-1.3, 2.4)	0.5391
Study Endpoint	PLACEBO	36	-5.4	1.5			
	CARV UID	32	-10.5	1.5	UID vs PLAC	(-8.0, -2.1)	0.0010*
	CARV BID	43	-11.5	1.1	BID vs PLAC	(-8.8, -3.4)	0.0001*
					UID vs BID	(1.8, 3.8)	0.4801
BLACK							
Baseline	PLACEBO	35	102.3	0.8			
	CARV UID	33	102.0	0.7	UID vs PLAC	(-2.2, 1.6)	0.7439
	CARV BID	36	101.3	0.7	BID vs PLAC	(-2.9, 0.8)	0.2754
					UID vs BID	(-1.2, 2.6)	0.4544
Study Endpoint	PLACEBO	35	-2.3	1.2			
	CARV UID	33	-6.5	1.7	UID vs PLAC	(-7.4, -1.0)	0.0113*
	CARV BID	36	-11.3	1.3	BID vs PLAC	(-12.2, -5.9)	<0.0001*
					UID vs BID	(1.6, 8.0)	0.0036*
NON-BLACK							
Baseline	PLACEBO	58	102.0	0.6			
	CARV UID	57	100.9	0.6	UID vs PLAC	(-2.6, 0.4)	0.1373
	CARV BID	60	101.1	0.5	BID vs PLAC	(-2.4, 0.5)	0.2020
					UID vs BID	(-1.6, 1.3)	0.8178
Study Endpoint	PLACEBO	58	-3.9	1.0			
	CARV UID	57	-8.8	0.8	UID vs PLAC	(-7.2, -2.5)	0.0001*
	CARV BID	60	-10.6	1.0	BID vs PLAC	(-9.0, -4.4)	<0.0001*
					UID vs BID	(-0.5, 4.4)	0.01196

* MEAN is the unadjusted mean, units are mm Hg.
 * Fisher's Least Significant Difference, 95% Comparisonwise Confidence Interval & p-value of t-test.
 * Significant at $\alpha = 0.05$ using modified Bonferroni procedure for the 3 comparisons.

Reference documentation: Appendixes 8.1.2, 8.1.3, 8.1.4, 8.1.5, 8.2.3, 8.2.5, 8.2.7, 8.2.9, and 8.11.3.

(cont.)

**Summary of Tabulations and Analysis of Baseline SitDBP
and Change from Baseline at Study Endpoint
for Subgroup Analyses
*Intent-to-Treat***

	<u>REGIMEN</u>	<u>N</u>	<u>MEAN*</u>	<u>SE</u>	<u>COMPARISON</u>	<u>ESTIMATE CONFIDENCE INTERVAL *</u>	<u>P-VALUE*</u>
MILD ANTIHYPERTENSIVES							
Baseline	PLACEBO	72	100.3	0.4			
	CARV UID	75	99.9	0.3	UID vs PLAC	(-1.3, 0.4)	0.3464
	CARV BID	81	99.8	0.3	BID vs PLAC	(-1.3, 0.4)	0.2812
				UID vs BID	(-0.9, 0.8)	0.9043	
Study Endpoint	PLACEBO	72	-3.2	0.8			
	CARV UID	75	-7.8	0.9	UID vs PLAC	(-6.6, -2.5)	<0.0001*
	CARV BID	81	-9.9	0.9	BID vs PLAC	(-8.6, -4.6)	<0.0001*
				UID vs BID	(0.1, 4.1)	0.0400	
MODERATE ANTIHYPERTENSIVES							
Baseline	PLACEBO	21	108.5	0.4			
	CARV UID	15	108.5	0.6	UID vs PLAC	(-1.3, 1.3)	0.9884
	CARV BID	15	108.3	0.5	BID vs PLAC	(-1.5, 1.2)	0.8274
				UID vs BID	(-1.6, 1.3)	0.8283	
Study Endpoint	PLACEBO	21	-3.5	2.2			
	CARV UID	15	-8.8	2.1	UID vs PLAC	(-9.9, -0.6)	0.0277*
	CARV BID	15	-16.3	1.7	BID vs PLAC	(-17.7, -8.2)	<0.0001*
				UID vs BID	(2.5, 12.6)	0.0048*	
≤ 64 YEARS OLD							
Baseline	PLACEBO	80	102.7	0.5			
	CARV UID	76	101.2	0.5	UID vs PLAC	(-2.7, -0.2)	0.0208
	CARV BID	82	100.9	0.4	BID vs PLAC	(-3.0, -0.5)	0.0058*
				UID vs BID	(-1.5, 1.0)	0.6825	
Study Endpoint	PLACEBO	80	-3.8	0.8			
	CARV UID	76	-7.7	0.9	UID vs PLAC	(-6.0, -1.8)	0.0004*
	CARV BID	82	-10.8	0.8	BID vs PLAC	(-9.1, -4.9)	<0.0001*
				UID vs BID	(1.0, 5.2)	0.0038*	
> 64 YEARS OLD							
Baseline	PLACEBO	13	98.7	0.6			
	CARV UID	14	101.8	1.1	UID vs PLAC	(0.3, 5.9)	0.3020
	CARV BID	14	102.3	1.4	BID vs PLAC	(0.8, 6.4)	0.0138*
				UID vs BID	(-3.2, 2.2)	0.7018	
Study Endpoint	PLACEBO	13	-0.4	2.2			
	CARV UID	14	-9.4	2.2	UID vs PLAC	(-14.8, -3.30)	0.0041*
	CARV BID	14	-11.4	2.6	BID vs PLAC	(-16.8, -5.30)	0.0008*
				UID vs BID	(-3.64, 7.64)	0.4647	

- * MEAN is unadjusted mean; units are mm Hg.
- * Fisher's Least Significant Difference, 95% Comparisonwise Confidence Interval & p-value of t-test.
- * Significant at $\alpha_{ps} = 0.05$ using modified Bonferroni procedure for the 3 comparisons.

The subgroup analysis does not appear to show any striking difference in response based on sex, age, race, or level of untreated blood pressure, although, as noted before, in the placebo group a larger fraction of black patients was terminated for insufficient response.

The final concerns re efficacy were an investigator-by-treatment interaction (one investigator, -Gray, - was the largest contributor and showed the highest drug effect); and the protocol issue of week 1 vs week 2 results on a constant regimen. The sponsor's discussion of both issues is reproduced below.

**Frequency Distribution of Patients by Investigator
According to Randomization to Regimen**

<u>INVESTIGATOR</u>	<u>Placebo</u>		<u>Carvedilol QID*</u>		<u>Carvedilol BID*</u>		<u>Total</u>	
	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>
Cushman*	8	8.6	6	6.6	8	8.3	22	7.9
Fischer	7	7.5	7	7.7	7	7.3	21	7.5
Fisk-Sander	3	3.2	3	3.3	4	4.2	10	3.6
Gray	14	15.1	14	15.4	14	14.6	42	15.0
Herron	9	9.7	10	11.0	10	10.4	29	10.4
Jenkins	7	7.5	6	6.6	6	6.3	19	6.8
Lonigro	11	11.8	12	13.2	12	12.5	35	12.5
Lucas	8	8.6	7	7.7	8	8.3	23	8.2
Miller	4	4.3	4	4.4	3	3.1	11	3.9
Schoenberger	7	7.5	5	5.5	6	6.3	18	6.4
Synhavsky	6	6.5	7	7.7	8	8.3	21	7.5
Wallin	6	6.5	7	7.7	6	6.3	19	6.8
Zinny	3	3.2	3	3.3	4	4.2	10	3.6
TOTAL	93	100	91*	100	96	100	280	100

* QID = once daily; BID = twice daily.

Evidence of possible investigator-by-regimen interaction ($p \leq 0.1$) was found in the analysis of the mean change from baseline for SBP, DBP, and HR for both *intent-to-treat* and *per-protocol* samples. One investigator's contribution toward the interaction was based on magnitude. At the other investigators, the interaction was directional. With statistical testing based on a model without inclusion of the interactive term, the interaction did not interfere with interpretation of the final results or the conclusions of the study.

The percentages of patients classified as normalized (DBP < 90 mm Hg) and as responders (DBP < 90 mm Hg or decreased by ≥ 10 mm Hg) were significantly greater ($p < 0.001$) for the carvedilol regimens than for placebo in both sitting and standing positions. At both Titration and Study Endpoints the differences between carvedilol regimens in sitting and standing normalized rates and in standing responder rates were not statistically significant. However, at these same endpoints, the difference between carvedilol regimens in sitting responder rates was statistically significant. For all three regimens, there were fewer patients normalized/responding at Study Endpoint than at Titration Endpoint.

Comparison of 1 week vs 2 weeks at the same dose

For patients who received two weeks of treatment with a given dose, the mean (SE) change in DBP from baseline at Week 1 and from the end of the Week 1 to the end of the Week 2 is presented below.

**Mean Change in SitDBP from 1 Week to 2 Weeks
at the Same Dose According to Double-Blind Dose Level
and Normalized Response
*Intent-to-Treat***

<u>Dose Level (mg)</u>	<u>n</u>	<u>Normalized</u>				<u>Not Normalized</u>				
		<u>Change</u> <u>from</u> <u>Baseline</u> <u>at Week 1</u>	<u>SE</u>	<u>Change</u> <u>from</u> <u>Week 1</u> <u>to Week 2</u>	<u>SE</u>	<u>Change</u> <u>from</u> <u>Baseline</u> <u>at Week 1</u>	<u>SE</u>	<u>Change</u> <u>from</u> <u>Week 1</u> <u>to Week 2</u>	<u>SE</u>	
Placebo										
Level 2	11	-13.2	1.5	+4.2	1.8	62	-2.7	0.5	-0.7	0.6
Level 3	7	-14.6	2.1	+5.0	3.3	54	-2.4	0.6	-0.4	0.7
Level 4	9	-10.1	0.7	+7.2	1.6	45	-2.6	0.5	+0.5	0.6
Level 5	4	-11.8	2.1	+4.5	3.8	60	-3.3	0.6	+0.6	0.6
Carvedilol Once Daily Regimen										
Level 2 (6.25)	11	-11.9	1.1	+6.4	2.4	67	-2.2	0.5	-0.6	0.6
Level 3 (12.5)	20	-14.5	0.8	+1.7	1.0	42	-3.4	0.6	-1.0	0.7
Level 4 (25)	20	-14.7	0.9	+2.5	1.0	34	-3.2	0.8	-2.4	1.2
Level 5 (50)	10	-14.3	1.7	+1.7	1.4	29	-3.8	1.1	-1.5	1.0
Carvedilol Twice Daily Regimen										
Level 2 (3.125)	14	-13.1	1.1	+7.9	1.8	71	-3.4	0.5	-0.2	0.6
Level 3 (6.25)	15	-15.3	1.0	+3.7	1.1	63	-4.7	0.7	-0.4	0.6
Level 4 (12.5)	28	-16.5	1.1	+2.7	0.8	40	-5.6	0.9	-1.8	0.9
Level 5 (25)	19	-14.3	0.9	+0.7	1.4	32	-7.6	1.0	-0.8	0.8

Reference documentation: Appendix 8.8.6.

Among patients who normalized after one week of treatment with a given dose, those randomized to placebo had increases from Week 1 to Week 2 that ranged from +4.5 ±

3.8 mm Hg to $+7.2 \pm 1.6$ mm Hg. Similarly, for patients who normalized after one week of treatment with the lowest dose levels of carvedilol, 6.25 mg once daily or 3.125 mg twice daily, mean changes from Week 1 to Week 2 were $+6.4 \pm 2.4$ mm Hg and $+7.9 \pm 1.8$ mm Hg, respectively. Smaller increases from Week 1 to Week 2 were observed for the other dose levels: for the once daily carvedilol regimen, these increases ranged from $+1.7 \pm 1.0$ mm Hg to $+2.5 \pm 1.0$ mm Hg, and for the twice daily regimen, these increases ranged from $+0.7 \pm 1.4$ mm Hg to $+3.7 \pm 1.1$ mm Hg.

For patients who did not normalize after one week of treatment with any given dose, an additional week of treatment at that dose did not produce a further meaningful reduction, regardless of dose or treatment regimen. Among these patients, there was only one dose, carvedilol 25 mg once daily for which an additional week of treatment produced a reduction greater than 2 mm Hg: -2.4 ± 1.2 mm Hg in addition to a change from baseline equal to -3.2 ± 0.8 mm Hg at the end of one week of treatment with this dose.

8.5 PROTOCOL C1107:

**A MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED,
RANDOMIZED ASSESSMENT OF CARVEDILOL IN PATIENTS WHOSE
BLOOD PRESSURE IS UNCONTROLLED ON HYDROCHLOROTHIAZIDE
(HCTZ)**

Investigators: This study was conducted by a total of 12 investigators in the United States of America.

8.5.1 Objective:

To assess the safety and efficacy of carvedilol 6.25 to 25 mg once daily when added to the treatment regimen of patients whose sitting and standing diastolic blood pressure (DBP) was uncontrolled (≥ 90 mm Hg) by treatment with hydrochlorothiazide (HCTZ) 25 mg once daily.

8.5.2 Study Design: This was a multicenter, double-blind, randomized, placebo-controlled, parallel group study. Patients qualified to enter the Treatment Phase when at both the third and fourth weekly baseline visits all of the following conditions were satisfied: the mean Sitting Diastolic Blood Pressure (SitDBP) and the mean Standing Diastolic Blood Pressure (StaDBP) were 90 - 115 mm Hg, and the mean SitDBP and mean StaDBP did not vary by more than 5 mm Hg between Visits 3 and 4.

n	Baseline (open)	n	Treatment Phase (blinded)	
	HCTZ 25 mg once daily	66	HCTZ + Placebo once daily	
		67	HCTZ 25 mg + Carvedilol 6.25 mg once daily	
		67	HCTZ 25 mg + Carvedilol 12.5 mg once daily	
		66	HCTZ 25 mg + Carvedilol 12.5 mg	HCTZ 25 mg + Carvedilol 25 mg once daily (elective)
410	4 weeks	266	1 week	3 weeks

The primary efficacy parameter was change (from baseline) in mean SitDBP.

Upon entry into the Treatment Phase, patients were stratified according to severity of hypertension (mild: SitDBP $\geq$ 90 mm Hg, < 100 mm Hg; moderate: SitDBP > 100 mm Hg, < 115 mm Hg) and randomized in a double-blind fashion.

Response to treatment was evaluated after one week of double blind treatment, and coded medication for all groups was increased if mean SitDBP was $\geq$ 90 mm Hg, (unless the mean StaSBP was $\leq$ 120 mm Hg or the mean StaDBP was $\leq$ 80 mm Hg). Although coded medication was increased for all four treatment groups according to these guidelines, the actual dose of medication increased only for Group 4, for which the initial dose of carvedilol 12.5 mg once daily was doubled to 25 mg once daily. Dose decreases (return to the first level of study medication) were not permitted.

Withdrawals from Study: Of 410 patients who were entered into the Baseline Phase, 35.1% (144/410) were withdrawn during this phase. Of these 144 patients, failure to meet selection criteria was the most common reason for discontinuation, reported for 31.2% (45/144).

Of 266 patients who received randomized medication, 91.3% (243/266) of the patients completed the four-week Treatment Phase.

Efficacy Results: Intent-to-treat sample: Statistically significant ($p \leq 0.05$) differences in mean SitDBP change from baseline were observed at Week 1, Week 4 and at endpoint for Group 4 (carvedilol 12.5/25 mg) compared to Group 1 (placebo). No statistically significant differences between the carvedilol 12.5 mg regimen and placebo or between the carvedilol 6.25 mg regimen and placebo were detected in mean SitDBP change from baseline at endpoint.

Comparisons of all carvedilol randomized groups to the placebo group showed no statistically significant differences in either normal or response rates at endpoint. There were no indications of statistically significant regimen-regimen interactions ($p > 0.1$) in the analysis of mean SitDBP change from baseline at endpoint.

Per protocol sample: No statistically significant differences between any of the carvedilol regimens and placebo were detected for mean SitDBP change from baseline at any of the four weekly visits or at endpoint. There was no evidence of a significant linear or quadratic relationship between dosing level and mean SitDBP change from baseline at endpoint.

CONCLUSIONS: (according to Sponsor) The *intent-to-treat* analysis showed statistically significant differences from baseline at Week 1, at Week 4, and at endpoint between the carvedilol 12.5/25 mg group and the placebo group with regard to the primary parameter of efficacy (change from baseline in SitDBP). The results suggest

that, if a patient has not responded to one week of treatment with carvedilol 12.5 mg, continuation of the same dose for another three weeks results in no additional antihypertensive effect. However, for those patients who did not respond to one week of carvedilol 12.5 mg, doubling the dose of carvedilol to 25 mg produced a reduction in blood pressure comparable to that observed for patients who did respond earlier to treatment with carvedilol 12.5 mg.

The results from this study demonstrated that combined antihypertensive treatment with carvedilol added to pre-existing HCTZ therapy is both efficacious and well tolerated.

Subgroup analyses

Analysis of variance (ANOVA) of baseline and mean SitDBP change from baseline at endpoint according to randomized regimen was performed for five subgroups, defined by sex, age, severity of hypertension at baseline, race, and weight.

8.5.3 Protocol

8.5.3.1 STUDY POPULATION

Number and Percentage of Patients with Data Included and
Excluded from Efficacy Analysis

	<u>Number and Percentage (%) of Patients</u>				<u>Total</u>
	<u>Placebo</u>	<u>Carvedilol</u>			
	<u>N (%)</u>	<u>6.25 mg N (%)</u>	<u>12.5 mg N (%)</u>	<u>12.5/25 mg N (%)</u>	
Included Intent-to-Treat analysis	66 (100.0)	67 (100.0)	67 (100.0)	66 (100.0)	266 (100.0)
Included Per-Protocol analysis	58 (87.9)	62 (92.5)	62 (92.5)	57 (86.4)	239 (89.8)
Completely excluded by protocol violation	8 (12.1)	5 (7.5)	5 (7.5)	9 (13.6)	27 (10.2)
Partially excluded by protocol violation *	8	6	12	6	32
Partially excluded by slotting procedure †	6	3	1	4	14

* Patients had one or more visits excluded because of a protocol violation that did not cause complete exclusion of data.

† Patients had one or more visits excluded by the slotting procedure.

**Summary of Baseline Characteristics According to Regimen
Intent-to-Treat***

	PLACEBO		CARVEDILOL (mg)						TOTAL		P-VALUE†
			6.25		12.5		12.5/25				
	N	%	N	%	N	%	N	%	N	%	
TOTAL PATIENTS	66	100	67	100	67	100	66	100	266	100	
<u>AGE (Yr)</u>											
≤ 64	51	77	58	87	52	78	58	88	219	82	0.221
> 64	15	23	9	13	15	22	8	12	47	18	
<u>SEX</u>											
FEMALE	24	36	24	36	24	36	22	33	94	35	0.984
MALE	42	64	43	64	43	64	44	67	172	65	
<u>RACE</u>											
BLACK	21	32	22	33	25	37	21	32	89	33	0.897
NON-BLACK	45	68	45	67	42	63	45	68	177	67	
<u>SEV. OF HYPERTENSION AT BASELINE</u>											
MILD	46	70	47	70	51	76	46	70	190	71	0.803
MODERATE	20	30	20	30	16	24	20	30	76	29	
<u>PRIOR ANTI- HYPERTENSIVES</u>											
NO	1	27	20	30	13	19	18	27	69	26	0.532
YES	48	73	47	70	54	81	48	73	197	74	
<u>BODY WEIGHT AT BASELINE</u>											
< 70 Kgs	7	11	4	6	10	15	10	15	31	12	0.116
71-90 Kgs	28	42	36	54	31	46	20	30	115	43	
≥ 91 Kgs	31	47	27	40	26	39	36	54	120	45	

	PLACEBO		CARVEDILOL (mg)						TOTAL		P-VALUE#		
			6.25		12.5		12.5/25						
	N	MEAN	STDERR	N	MEAN	STDERR	N	MEAN	STDERR	N		MEAN	STDERR
AGE (Yr)	66	56	1.4	67	54	1.2	67	54	1.4	66	55	1.2	0.7634
WEIGHT (Kg)	66	90	2.4	67	89	2.1	67	88	2.3	66	90	1.9	0.8931

- * Randomized and received active medication, regardless of protocol violations
† P-value of Fisher's Exact Test
P-value of F-test from General Linear Model (section 2.9.2).

Summary of Baseline Characteristics According to Regimen
Per-protocol*

	PLACEBO		CARVEDILOL (mg)						TOTAL	P-VALUE*	
	N	%	6.25		12.5		12.5/25				N
TOTAL PATIENTS	58	100	62	100	62	100	57	100	239	100	
<u>AGE (Yr)</u>											
≤ 64	45	78	55	89	48	77	51	89	199	83	0.129
> 64	13	22	7	11	14	23	6	11	40	17	
<u>SEX</u>											
FEMALE	22	38	22	35	23	37	19	33	86	36	0.958
MALE	36	62	40	65	39	63	38	67	153	64	
<u>RACE</u>											
BLACK	17	29	19	31	22	35	14	25	72	30	0.638
NON-BLACK	41	71	43	69	40	65	43	75	167	70	
<u>SEV. OF HYPERTENSION AT BASELINE</u>											
MILD	38	66	43	69	47	76	39	68	167	70	0.646
MODERATE	20	34	19	31	15	24	18	32	72	30	
<u>PRIOR ANTI-HYPERTENSIVES</u>											
NO	15	26	20	32	13	21	15	26	63	26	0.572
YES	43	74	42	68	49	79	42	74	176	74	
<u>BODY WEIGHT AT BASELINE</u>											
< 70 Kgs	7	12	3	5	10	16	9	16	29	12	0.056
71-90 Kgs	27	46	33	53	29	47	16	28	105	44	
≥ 91 Kgs	24	41	26	42	23	37	32	56	105	44	

	PLACEBO		CARVEDILOL (mg)						TOTAL	P-VALUE#			
	N	MEAN	STDERR	6.		12.5		12.5/25			N	MEAN	STDERR
AGE (Yr)	58	56	1.5	62	54	1.2	62	54	1.5	57	55	1.3	0.6105
WEIGHT (Kg)	58	88	2.5	62	90	2.2	62	88	2.4	57	90	2.1	0.9708

* Randomized and received active medication, with no protocol violations.
 * P-value of Fisher's Exact Test
 * P-value of F-test from General Linear Model(section 2.9.2).

Reference Documentation: Appendix 3.2.1, 3.3.1, 3.4.1, and 8.10.2.

Reason for Discontinuation

A total of 266 patients were randomized into the treatment phase. Overall, 91.5% (183/200) of patients randomized to carvedilol completed the study compared to 90.9% (60/66) of patients randomized to placebo. No deaths were reported on-therapy or within 30 days post-therapy for any of the patients randomized in this study, nor for any of the additional 144 patients treated only in the Baseline Phase. After entering the treatment phase, six patients (9.1%, 6/66) in the placebo group, four patients (6.0%, 4/67) in the carvedilol 6.25 mg group, seven patients (10.4%, 7/67) in the carvedilol 12.5 mg group, and six patients (9.1%, 6/66) in the carvedilol 12.5/25 mg group were withdrawn during the course of the four week period.

Among all patients randomized to treatment, 11 patients were discontinued due to an adverse experience: three received placebo, one received carvedilol 6.25 mg, five received carvedilol 12.5 mg, and two received carvedilol 25 mg (section 4.3.1 and Table 22). Of 200 patients randomized to carvedilol, 4.0% (8/200) were withdrawn from treatment because of an adverse experience. Of 66 patients randomized to placebo, there were 4.5% (3/66) withdrawn from treatment because of an adverse experience. In comparison, during the HCTZ monotherapy phase, 2.0% (8/410) were withdrawn for adverse experiences.

Four patients, one in each of the treatment regimens were discontinued due to insufficient therapeutic effect. Eight patients (two patients each in the placebo and the carvedilol 6.25 mg groups, three in carvedilol 12.5 mg group, and one in carvedilol 12.5/25 mg group) were discontinued for other reasons; none of these patients had the onset of adverse experiences associated with their withdrawal. Of the 266 randomized patients, 133/266 were entered into the long-term, open-label carvedilol protocol (C1111). Of the patients randomized to carvedilol, 50.0% (100/200) continued carvedilol treatment by entering into an open-label extension study; the same percentage of patients randomized to placebo, 50.0% (33/66), entered into the same open-label extension study.

8.5.4 RESULTS

**Distribution of Patients According to Randomized Regimen
at Endpoint of the Treatment Phase**

	<u>Intent-to-Treat</u> <u>Analysis</u> N=264*		<u>Per-Protocol</u> <u>Analysis</u> N=233	
	<u>Number</u>	<u>(%) of</u> <u>Patients</u>	<u>Number</u>	<u>(%) of</u> <u>Patients</u>
Placebo	66	(25.0)	58	(24.9)
Carv* 6.25 mg	67	(25.4)	62	(26.6)
Carv 12.5 mg	65*	(24.6)	57	(24.5)
Carv 12.5/25 mg*	66	(25.0)	56	(24.0)

32 patients in the *intent-to-treat sample* and 28 patients in the *per-protocol sample* had their dose increased from 12.5 mg to 25 mg in Group 4 (carvedilol 12.5/25 mg).

* Carv = carvedilol

* Two patients (85 and 261) had no records after dose-day 1 and therefore have no endpoint data.

Reference documentation: Appendix 8.1.1

**Summary of HCTZ Baseline Phase Vital Signs
According to Randomized Regimen during Treatment Phase
Intent-to-Treat Sample**

	<u>REGIMEN</u> (mg)	<u>N</u>	<u>MEAN</u> SBP/DBP	<u>SE</u> HR SBP/DBP HR
SITTING:				
Screening visit:				
	Placebo	66	153/98	74 2.0/0.90.9
	Carv 6.25	67	151/97	77 2.2/0.71.2
	Carv 12.5	67	148/96	76 1.8/0.71.2
	Carv 12.5/25	66	148/98	74 1.9/0.61.0
Baseline Vital Signs (mean at last two visits of HCTZ Baseline Phase)				
	Placebo	66	150/98	74 1.8/0.71.0
	Carv 6.25	67	148/98	78 2.0/0.71.2
	Carv 12.5	67	148/97	76 1.6/0.61.0
	Carv 12.5/25	66	146/98	76 1.6/0.71.0
3-MINUTE STANDING:				
Screening visit:				
	Placebo	66	153/99	77 2.1/0.91.9
	Carv 6.25	67	150/99	80 2.3/0.82.1
	Carv 12.5	67	148/98	79 2.0/0.81.8
	Carv 12.5/25	66	148/100	77 1.9/0.81.7
Baseline Vital Signs (mean at last two visits of HCTZ Baseline Phase)				
	Placebo	66	150/101	79 1.9/0.81.0
	Carv 6.25	67	146/100	82 2.1/0.81.2
	Carv 12.5	67	147/99	80 1.8/0.71.1
	Carv 12.5/25	66	146/100	80 1.7/0.81.2

**Summary of Tabulations and Analysis of Baseline Sitting DBP (mm Hg)
and Change from Baseline at Each Visit and Endpoint by Randomized Regimen**

	REGIMEN (mg)	N	<i>Intent-to-Treat</i>		95% CONFIDENCE INTERVAL (vs. placebo)
			MEAN	SE	
SITTING: DIASTOLIC					
Baseline	Placebo	66	98	0.7	
	Carv 6.25	67	98	0.7	(-2.68, 1.60)
	Carv 12.5	67	97	0.6	(-3.13, 1.15)
	Carv 12.5/25	66	98	0.7	(-1.96, 2.33)
Week 1* (change)	Placebo	66	-3.7	0.8	
	Carv 6.25	65	-4.9	0.8	(-3.85, 1.30)
	Carv 12.5	63	-4.3	1.0	(-3.28, 1.91)
	Carv 12.5/25	65	-6.3	0.9	(-5.20, -0.50)*
Week 2 (change)	Placebo	60	-4.3	0.8	
	Carv 6.25	63	-5.4	1.0	(-3.59, 1.43)
	Carv 12.5	61	-4.9	0.8	(-3.13, 1.93)
	Carv 12.5/25	61	-6.3	0.9	(-4.49, 0.57)
Week 3 (change)	Placebo	60	-5.8	0.8	
	Carv 6.25	63	-4.8	0.8	(-1.47, 3.35)
	Carv 12.5	59	-4.7	0.7	(-1.38, 3.52)
	Carv 12.5/25	57	-6.6	1.0	(-3.36, 1.59)
Week 4 (change)	Placebo	61	-3.7	0.8	
	Carv 6.25	63	-5.1	1.0	(-3.99, 1.05)
	Carv 12.5	60	-5.3	0.9	(-4.14, 0.95)
	Carv 12.5/25	60	-6.7	0.8	(-5.56, -0.46)*
Endpoint (change)	Placebo	66	-3.3	0.8	
	Carv 6.25	67	-4.7	1.0	(-3.96, 1.22)
	Carv 12.5	65	-4.9	1.0	(-4.20, 1.03)
	Carv 12.5/25	66	-6.3	0.9	(-5.66, -0.46)*

- * Dunnett's 95% Experimentwise Confidence Interval (Two-Tailed for Baseline Visits and One-Tailed for On-Therapy Visits).
- * Change from baseline at Week 1 represents Group 4 prior to any dose change, i.e., at 12.5 mg actual dose.
- * Significant at alpha = 0.05.

Dose-response: The relationship between dose levels and change in sitting DBP at endpoint was examined by analysis of variance according to actual doses rather than randomized regimen. For this analysis, the subset of Group 4 patients who were not titrated were excluded; thus, only the 32 patients for whom study medication was increased to carvedilol 25 mg were included in the analysis of the 25 mg group.

**Summary of Tabulations and Analysis by Dose Received
for Mean Sitting Diastolic Blood Pressure (mm Hg) Change from Baseline
at Endpoint
*Intent-to-treat***

<u>PLACEBO</u>	<u>CARVEDILOL (mg)</u>				<u>P-VALUE*</u>	
	<u>6.25</u>	<u>12.5</u>	<u>25</u>	<u>LINEAR</u>	<u>QUADRATIC</u>	
N	66	67	65	32*		
Mean	-3.3	-4.7	-4.9	-6.6	0.008*	0.504
Standard Deviation	6.5	7.9	7.9	6.3		

* Of 66 patients randomized to Group 4 (12.5/25 mg), the actual dose was increased to 25 mg for 32 patients who had endpoint data. Patient 135 was discontinued after one dose of 25 mg and had no endpoint data. The other 33 patients who remained on 12.5 mg were excluded from this analysis, but data for these patients are presented in Table 11.

In addition to this analysis, mean change from baseline in SitDBP at endpoint was examined for all randomized patients according to actual dose and for the subsets of patients according to study medication level.

**Mean SitDBP (mm Hg) at Baseline and
Change from Baseline at Endpoint
According to Dose Received at Endpoint
*Intent-to-Treat Sample***

	<u>Baseline</u>			<u>Change from Baseline at Endpoint</u>		
	n	Mean	SE	n	Mean	SE
<i>All patients</i>						
Placebo	66	98.1	0.7	66	-3.3	0.8
Carv 6.25 mg	67	97.6	0.7	67	-4.7	1.0
Carv 12.5 mg	101	97.0	0.5	99	-5.3	0.8
Carv 12.5/25 mg	32	99.8	1.1	32	-6.6	1.1
<i>Patients at Level 1</i>						
Placebo	26	94.2	0.5	26	-3.7	1.3
Carv 6.25 mg	28	94.5	0.8	28	-6.7	1.6
Carv 12.5 mg	29	96.0	0.6	27	-7.0	1.8
Carv 12.5 mg*	34	96.9	0.9	34	-6.1	1.3
<i>Patients at Level 2*</i>						
Placebo	40	100.7	1.0	40	-3.0	1.0
Carv 6.25 mg	39	99.8	0.8	39	-3.2	1.2
Carv 12.5 mg	38	98.0	0.9	38	-3.4	1.0
Carv 25 mg	32	99.8	1.1	32	-6.6	1.1

* Group 4 patients for whom dose was not increased.

These patients had not responded to one week of treatment with the initial dose (Level 1) and therefore had study medication increased to Level 2. However, only one treatment group had an actual increase in dose; the dose for Group 4 was increased from carvedilol 12.5 mg to 25 mg.

Dose-response: The relationship between dose levels and change in sitting DBP at endpoint was examined by analysis of variance according to actual doses rather than randomized regimen. For this analysis, the subset of Group 4 patients who were not titrated were excluded; thus, only the 28 patients for whom study medication was increased to carvedilol 25 mg were included. There was no indication of a statistically significant ($p > 0.05$) linear or quadratic relationship between dosing level and mean SitDBP change from baseline at endpoint. Table 13 summarizes the mean changes from baseline and corresponding linear and quadratic p-values.

Summary of Tabulations and Analysis by Dose Received for Mean Sitting Diastolic Blood Pressure (mm Hg) Change from Baseline at Endpoint
Per-protocol

<u>PLACEBO</u>	<u>6.25</u>	<u>CARVEDILOL (mg)</u>			<u>P-VALUE*</u>	
		<u>12.5</u>	<u>25</u>	<u>LINEAR</u>	<u>QUADRATIC</u>	
N	58	62	57	28*		
Mean	-3.8	-4.9	-5.8	-5.5	0.076	0.804
Standard Deviation	6.2	8.3	7.3	5.6		

* Of 56 patients evaluated in Group 4 (12.5/25 mg), the actual dose was increased to 25 mg for 28 patients. The other 28 patients who were not titrated to 25 mg were excluded from this analysis, but data for these patients are presented in Table 14.

Change from baseline mean SitDBP at endpoint did not increase with the increase in actual dose. The change from baseline mean SitDBP at endpoint observed for the lowest and highest doses of carvedilol (6.25 and 25 mg, respectively) were within one SE of that observed for placebo. Therefore, these data are consistent with the analysis of variance findings, which did not show an indication of linear or quadratic dose-response relationships.

**Summary of Tabulations and Analysis of Baseline Sitting DBP (mm Hg) and Change
from Baseline at Each Visit and Endpoint by Randomized Regimen
*Intent-to-Treat***

	<u>REGIMEN</u> (mg)	<u>N</u>	<u>MEAN</u>	<u>SE</u>	<u>95% CONFIDENCE</u> <u>INTERVAL*</u>
(vs. placebo)					
SITTING:					
<u>DIASTOLIC</u>					
Baseline	Placebo	66	98	0.7	
	Carv 6.25	67	98	0.7	(-2.68, 1.60)
	Carv 12.5	67	97	0.6	(-3.13, 1.15)
	Carv 12.5/25	66	98	0.7	(-1.96, 2.33)
Week 1[†] (change)	Placebo	66	-3.7	0.8	
	Carv 6.25	65	-4.9	0.8	(-3.85, 1.30)
	Carv 12.5	63	-4.3	1.0	(-3.28, 1.91)
	Carv 12.5/25	65	-6.3	0.9	(-5.20, -0.50) [‡]
Week 2 (change)	Placebo	60	-4.3	0.8	
	Carv 6.25	63	-5.4	1.0	(-3.59, 1.43)
	Carv 12.5	51	-4.9	0.8	(-3.13, 1.93)
	Carv 12.5/25	61	-6.3	0.9	(-4.49, 0.57)
Week 3 (change)	Placebo	60	-5.8	0.8	
	Carv 6.25	63	-4.8	0.8	(-1.47, 3.35)
	Carv 12.5	59	-4.7	0.7	(-1.38, 3.52)
	Carv 12.5/25	57	-6.6	1.0	(-3.36, 1.59)
Week 4 (change)	Placebo	61	-3.7	0.8	
	Carv 6.25	63	-5.1	1.0	(-3.99, 1.05)
	Carv 12.5	60	-5.3	0.9	(-4.14, 0.95)
	Carv 12.5/25	60	-6.7	0.8	(-5.56, -0.46) [‡]
Endpoint (change)	Placebo	66	-3.3	0.8	
	Carv 6.25	67	-4.7	1.0	(-3.96, 1.22)
	Carv 12.5	65	-4.9	1.0	(-4.20, 1.03)
	Carv 12.5/25	66	-6.3	0.9	(-5.66, -0.46) [‡]

- † Change from baseline at Week 1 represents Group 4 prior to any dose change, i.e., at 12.5 mg actual dose.
- ‡ Significant at alpha = 0.05.

**Mean Change from Baseline at Endpoint in SitDBP and Secondary
Blood Pressure Parameters (mm Hg)
Intent-to-Treat Sample**

<u>PARAMETER/ Regimen (mg)</u>	<u>n</u>	<u>Baseline</u>		<u>Change from Baseline at Endpoint</u>		<u>95% CONFIDENCE INTERVAL</u>	
		<u>Mean</u>	<u>SE</u>	<u>n</u>	<u>Mean</u>		
COMPARISON vs PLACEBO							
Sitting Diastolic Blood Pressure							
Placebo	66	98.1	0.7	66	-3.3	0.8	
Carv 6.25	67	97.6	0.7	67	-4.7	1.0	(-3.96, 1.22)
Carv 12.5	67	97.1	0.6	65	-4.9	1.0	(-4.20, 1.03)
Carv 12.5/25	66	98.3	0.7	66	-6.3	0.9	(-5.66, -0.46)*
Sitting Systolic Blood Pressure							
Placebo	66	150.0	1.8	66	-2.0	1.4	
Carv 6.25	67	147.7	2.0	67	-3.5	1.5	(-5.71, 2.88)
Carv 12.5	67	148.3	1.6	65	-4.4	1.6	(-6.68, 1.97)
Carv 12.5/25	66	146.5	1.6	66	-4.5	1.4	(-6.72, 1.90)
Standing Diastolic Blood Pressure							
Placebo	66	100.6	0.8	66	-3.2	1.0	
Carv 6.25	67	99.5	0.8	66	-4.1	0.9	(-3.6, 1.7)
Carv 12.5	67	99.4	0.7	65	-4.7	0.9	(-4.2, 1.1)
Carv 12.5/25	66	100.1	0.8	66	-5.6	0.9	(-5.1, 0.2)
Standing Systolic Blood Pressure							
Placebo	66	149.8	1.9	66	-2.6	1.5	
Carv 6.25	67	146.4	2.1	66	-2.4	1.4	(-4.10, 4.50)
Carv 12.5	67	146.8	1.8	65	-3.4	1.5	(-5.03, 3.60)
Carv 12.5/25	66	146.0	1.7	66	-4.0	1.5	(-5.69, 2.90)

**Summary of Tabulations and Analysis of Baseline Heart Rate and Change from
Baseline at Each Visit and Endpoint**
Intent-to-Treat

	<u>REGIMEN</u> (mg)	<u>N</u>	<u>MEAN</u>	<u>SE</u>	<u>95% CONFIDENCE</u> <u>INTERVAL*</u>
SITTING:					(vs. placebo)
<u>HEART RATE</u>					
Baseline	Placebo	66	74	1.0	
	Carv 6.25	67	78	1.2	(0.65, 7.53) [#]
	Carv 12.5	67	76	1.0	(-0.94, 5.95)
	Carv 12.5/25	66	76	1.0	(-1.43, 5.49)
Week 1 (change)	Placebo	66	-0.2	0.9	
	Carv 6.25	65	-2.8	1.1	(-5.11, -0.09) [#]
	Carv 12.5	63	-4.3	1.1	(-6.21, -1.18) [#]
	Carv 12.5/25	65	-3.8	0.9	(-6.71, -1.65) [#]
Week 2 (change)	Placebo	60	-0.3	0.9	
	Carv 6.25	63	-3.9	1.2	(-6.21, -0.96) [#]
	Carv 12.5	61	-4.2	1.1	(-6.56, -1.26) [#]
	Carv 12.5/25	61	-4.5	0.9	(-6.77, -1.48) [#]
Week 3 (change)	Placebo	60	1.1	1.0	
	Carv 6.25	63	-1.9	1.1	(-5.85, -0.09) [#]
	Carv 12.5	59	-3.2	1.1	(-7.24, -1.40) [#]
	Carv 12.5/25	57	-5.1	1.2	(-9.21, -3.31) [#]
Week 4 (change)	Placebo	61	0.2	1.1	
	Carv 6.25	63	-4.6	1.1	(-7.07, -1.29) [#]
	Carv 12.5	60	-4.0	1.1	(-7.65, -1.95) [#]
	Carv 12.5/25	60	-6.7	1.1	(-9.70, -3.98) [#]
Endpoint (change)	Placebo	66	0.3	0.9	
	Carv 6.25	67	-4.7	1.1	(-7.75, -2.23) [#]

* Dunnett's 95% Experimentwise Confidence Interval (Two-Tailed for Baseline Visits and One-Tailed for On-Therapy Change from baseline at Week 1 represents Group 4 prior to any dose change, i.e., at 12.5 mg actual dose.
Significant at alpha = 0.05.

NDH 20297

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**Mean Change from Baseline at Endpoint in Sitting and
Standing Heart Rate Parameters (bpm)
*Intent-to-Treat Sample***

<u>PARAMETER/ Regimen (mg)</u>	<u>n</u>	<u>Baseline</u>		<u>n</u>	<u>Change from Baseline at Endpoint</u>		<u>95% CONFIDENCE INTERVAL* (vs. placebo)</u>
		<u>Mean</u>	<u>SE</u>		<u>Mean</u>	<u>SE</u>	
SitHR							
Placebo	66	74.0	1.0	66	0.3	0.9	
Carv 6.25	67	78.1	1.2	67	-4.7	1.1	(-7.75, -2.23)*
Carv 12.5	67	76.5	1.0	65	-3.3	1.0	(-6.34, -0.79)*
Carv 12.5/25	66	76.0	1.0	66	-6.3	1.1	(-9.31, -3.78)*
StaHR							
Placebo	66	78.8	1.0	66	-0.8	0.7	
Carv 6.25	67	81.8	1.2	66	-3.8	1.1	(-5.92, 0.01)
Carv 12.5	67	80.1	1.1	65	-3.4	1.1	(-5.60, 0.35)
Carv 12.5/25	66	80.4	1.2	66	-7.0	1.1	(-9.19, -3.26)*

Dunnett's 95% Experimentwise Confidence Interval (Two-Tailed for Baseline Visits and One-Tailed for On-Therapy visits).

* Significant at alpha = 0.05.

Reference Documentation: Appendixes 8.1.1, 8.2.1, 8.11.1, and 8.12.1

Response rates to treatment

Two categories defining "response" were used in the analysis of antihypertensive efficacy in this study. Patients considered 'normalized' were those whose mean SitDBP was lowered during the treatment phase to less than 90 mm Hg. Patients considered 'responders' were those who achieved a normalized mean SitDBP and/or demonstrated a decrease from baseline in mean SitDBP of at least 10 mm Hg.

**Number and Percentage of Patients Normalized* and
Responding* by Randomized Treatment at Study Endpoint**

Intent-To-Treat Analysis

	<u>Total No.</u>	<u>No. (%) Normalized</u>	<u>No. (%) Responding</u>
Placebo	66	18 (27.3%)	21 (31.8%)
Carv 6.25 mg	67	30 (44.8%)	30 (44.8%)
Carv 12.5 mg	65	26 (40.0%)	30 (46.2%)
Carv 12.5/25 mg	66	27 (40.9%)	31 (47.0%)
<u>P-value[†]</u> :			
Carv 6.25 vs P		0.047	0.154
Carv 12.5 vs P		0.141	0.108
Carv 12.5/25 vs P		0.141	0.108

Per-Protocol Analysis

	<u>Total No.</u>	<u>No. (%) Normalized</u>	<u>No. (%) Responding</u>
Placebo	58	14 (24.1%)	20 (34.5%)
Carv 6.25 mg	62	29 (46.8%)	29 (46.8%)
Carv 12.5 mg	57	23 (40.4%)	27 (47.4%)
Carv 12.5/25 mg	56	23 (41.1%)	25 (44.6%)
<u>P-value[†]</u> :			
Carv 6.25 vs P		0.013 [‡]	0.196
Carv 12.5 vs P		0.074	0.187
Carv 12.5/25 vs P		0.072	0.338

- * Achieving a Mean SitDBP < 90 mm Hg
 † Achieving a Mean SitDBP < 90 mm Hg and/or a decrease from baseline in mean SitDBP ≥ 10 mm Hg

Subgroup comparisons

Analysis of variance of baseline and mean SitDBP change from baseline at endpoint was performed for four subgroups (sex, age-group, severity of hypertension at baseline, and weight group).

Within the non-black sub-group, which included 157 Caucasian and 20 Hispanic patients, statistically significant ($p \leq 0.05$) differences in the mean SitDBP change from baseline at endpoint were observed for carvedilol 25 mg when compared to placebo (*intent-to-treat sample*). However, within the black subgroup, no statistically significant differences were observed (*intent-to-treat sample*). Neither non-black nor black subgroups were found to have statistically significant differences in mean change from baseline SitDBP at endpoint when the *per-protocol sample* was analyzed.

Summary of Tabulations and Analysis of Baseline SitDBP (mm Hg) and Change from Baseline at Endpoint for the Non-black and Black Subgroups According to Randomized Regimen

Intent-to-Treat

95% CONFIDENCE

<u>REGIMEN</u> (mg)	<u>N</u>	<u>MEAN</u>	<u>SE</u>	<u>INTERVAL*</u>

Subgroup: Non-black *(vs. placebo)*

Sitting Diastolic Blood Pressure at Baseline (mm Hg)

Placebo	45	98.1	0.8	
Carv 6.25	45	97.0	0.8	(-1.9, 3.3)
Carv 12.5	42	97.2	0.7	(-3.5, 1.7)
Carv 12.5/25	45	98.8	0.9	(-3.7, 1.5)

Change from Baseline at Endpoint (mm Hg)

Placebo	45	-3.1	1.0	
Carv 6.25	45	-5.1	1.0	(-4.8, 0.9)
Carv 12.5	40	-5.3	1.2	(-5.1, 0.8)
Carv 12.5/25	45	-6.4	0.9	(-6.2, -0.5)*

Subgroup: Black

Sitting Diastolic Blood Pressure at Baseline (mm Hg)

Placebo	21	98.2	1.5	
Carv 6.25	22	98.7	1.1	(-3.1, 4.2)
Carv 12.5	25	97.0	0.9	(-4.7, 2.4)
Carv 12.5/25	21	97.2	1.1	(-4.7, 2.7)

Change from Baseline at Endpoint (mm Hg)

Placebo	21	-3.6	1.5	
Carv 6.25	22	-3.8	2.1	(-5.6, 5.3)
Carv 12.5	25	-4.1	1.8	(-5.8, 4.8)
Carv 12.5/25	21	-6.1	1.8	(-8.0, 3.0)

**Summary of Tabulations and Analysis of Baseline Sitting Diastolic Blood Pressure
and Change from Baseline at Endpoint for the Non-elderly and Elderly Subgroups**

Per-protocol

<u>REGIMEN</u> (mg)	<u>N</u>	<u>MEAN</u>	<u>SE</u>	<u>95% CONFIDENCE INTERVAL*</u> (vs. placebo)

Subgroup: Non-elderly (≤ 64 yrs)

Sitting Diastolic Blood Pressure at Baseline (mm Hg)

Placebo	45	99.0	0.9	
Carv 6.25	55	97.9	0.7	(-3.7, 1.4)
Carv 12.5	48	97.4	0.7	(-4.2, 1.1)
Carv 12.5/25	51	98.5	0.8	(-3.1, 2.2)

Change from Baseline at Endpoint (mm Hg)

Placebo	45	-4.1	0.9	
Carv 6.25	55	-4.3	1.1	(-3.1, 2.8)
Carv 12.5	44	-5.5	1.2	(-4.5, 1.7)
Carv 12.5/25	50	-5.9	0.9	(-4.8, 1.3)

Subgroup: Elderly (> 64 yrs)

Sitting Diastolic Blood Pressure at Baseline (mm Hg)

Placebo	13	97.5	1.4	
Carv 6.25	7	94.4	0.9	(-5.1, 4.7)
Carv 12.5	14	96.2	1.1	(-5.2, 2.5)
Carv 12.5/25	6	97.3	1.4	(-7.8, 1.6)

Change from Baseline at Endpoint (mm Hg)

Placebo	13	-2.5	1.9	
Carv 6.25	7	-10.1	2.1	(-13.4, -1.8) ⁺
Carv 12.5	13	-6.5	1.5	(-8.9, 0.9)
Carv 12.5/25	6	-8.7	1.7	(-12.3, -0.01) ⁺

Within the subgroups defined according to sex, severity of hypertension at baseline, and weight, no statistically significant differences among treatment groups were found in SitDBP change from baseline at endpoint in either the *intent-to-treat* or *per-protocol samples*.

In addition, multiple subgroup analyses of response rates were performed. No significant differences in response rates were observed within or between treatment groups, for the various subgroups tested, including those within the categories of age, sex, and severity of hypertension.

Adverse experiences (postural hypotension) recorded during the assessment of post-dose vital signs

Marked postural hypotension was defined in the protocol as a reduction in blood pressure both of > 30 mm Hg systolic and > 15 mm Hg diastolic, concurrent with associated signs and symptoms (e.g. diaphoresis, dizziness, etc.), upon change from the supine to standing position. One patient randomized to carvedilol therapy had a postural hypotensive event so defined:

- Patient #135 (45 years old, male) experienced a fall in BP from 146/82 mm Hg supine to 85/57 mm Hg standing (and a fall of 61 mm Hg systolic, and 25 mm Hg diastolic), on day 7 of carvedilol treatment (approximately 30 minutes after receiving the first dose of carvedilol 25 mg). Among the blood pressures subsequently recorded until the patient recovered (after about 2 hours), the lowest was 85/57 mm Hg, measured in the standing position about 90 minutes after the initial event. The patient had associated symptoms of diaphoresis, lightheadedness (dizziness), unsteadiness on feet, and headache and was withdrawn from study. Complete vital signs listings for this patient on the day of the hypotensive event can be found in Appendix 16.0.

One additional patient (#112) experienced a "passing out episode," but the conditions surrounding the event did not meet the protocol definition for postural hypotension:

- Patient #112 (43 year old, female) experienced a "passing out episode" on day 13 of treatment with carvedilol 6.25 mg. The investigator considered this adverse experience unrelated to study medication, but related to reactive anxiety secondary to chest pain which she also experienced on Day 13. Both adverse experiences of chest pain and "passing out episode" were of mild severity

and considered by the investigator to be unrelated to study medication. The patient completely recovered on the same day and continued in the study until completion. No vital sign information was obtained since the patient was not treated for the adverse experiences (chest pain, "passing out episode").

Comments:

Apart from isolated (and inconsistent) records, there is no evidence in these data that carvedilol once a day is different from placebo as a second step treatment - - following HCTZ - - in patients with mild or moderate hypertension.

8.6 PROTOCOL C1109:**CARVEDILOL (SK&F 105517) VERSUS ATENOLOL AND PLACEBO IN PATIENTS WITH MILD TO MODERATE ESSENTIAL HYPERTENSION**

8.6.1 Objective: Compare the efficacy and safety of carvedilol (12.5 mg, 25 mg and 50 mg), atenolol (50 mg and 100 mg), and placebo administered *once daily* for the treatment of patients with mild to moderate essential hypertension .

8.6.2 Study Design:

baseline observation	randomization n	up titration	n	fixed dose maintenance	n	down titration
Single blind placebo once daily	52	placebo once daily	48	placebo once daily	19	
	105	carvedilol 12.5 mg/day - 50 mg/day	10	carvedilol 12.5 mg/day	66	
			14	carvedilol 25 mg/day		
			81	carvedilol 50 mg/day		
	101	atenolol 50 mg/day - 100 mg/day	57	atenolol 50 mg/day	89	
			32	atenolol 100 mg/day		
5-6 wks	258	1-6 wks	242	4 wks	174	1 week

This was a multicenter (13 centers), double-blind, double-dummy, randomized, placebo-controlled, parallel group study where patients were titrated to a therapeutic effect. The study consisted of a Screening visit, a single-blind Placebo Baseline Period (5-6 weeks), and a double-blind Treatment Period which included an Up-Titration Period (1-6 weeks), a Fixed-Dose Maintenance Period (4 weeks), and a Down-titration Period (1 week).

The skewed numbers at the different treatment levels indicate that at the doses permitted in the study, atenolol 50 mg/day was perceived by the investigators to be more effective than carvedilol 25 mg/day.

Of 258 patients who received randomized medication, 65.9% (170/258) of the patients completed the study. Also, four additional patients completed all but the Down-Titration Period. It is difficult, if not impossible to decide from the report how many dropped out in each phase on each dose level. The total number entering baseline observation is not given. The number randomized to each drug is given but not the number completing the titration, nor the number completing maintenance. The sponsor has promised to submit precise numbers in a desk copy. (10/1/93).

Reason for Discontinuation

After entering into the treatment phase, 40 patients (38.1%) in the carvedilol group, 34 patients (65.4%) in the placebo group, and 14 patients (13.9%) in the atenolol group were *withdrawn* during the course of the treatment period (Up Titration, Fixed-Dose Maintenance, and Down Titration). Completion rates were 86.1% (87/101) for the atenolol treatment group, 61.9% (65/105) for the carvedilol treatment group, and 34.6% (18/52) for the placebo treatment group.

Safety Results: No deaths were reported on-therapy or within 30 days post-therapy for any of the 258 patients randomized in this study. One of the 52 patients (1.9%) randomized to placebo, two of the 101 patients (2%) randomized to atenolol, and five of the 105 patients (4.8%) randomized to carvedilol were withdrawn from the study because of one or more adverse experiences.

The distribution of patients according to the reason for concluding the study is presented below.

Reasons for Concluding Study by Medication Regimen
Intent-to-Treat Sample

<u>Reasons for Concluding Study</u>	<u>Placebo</u>		<u>Atenolol</u>		<u>Carvedilol</u>	
	n	(%)	n	(%)	n	(%)
Insufficient therapeutic effect* p-value*	31	(59.6)	9	(8.9)	31	(29.5)
Aten vs Plac		<0.0001				
Carv vs Plac		0.0001				
Aten vs Carv		<0.000				
Adverse experience	1	(1.9)	2	(2.0)	5	(4.8)
Other*	1	(1.9)	1	(1.0)	3	(2.9)
Completed study	18	(34.6)	87	(86.1)	65	(61.9)
Patient completed all but Down-Titration Period: AE	0	(0.0)	1	(1.0) ^y	0	(0.0)
Patient completed all but Down-Titration Period: Other	1	(1.9)	1	(1.0)	1	(1.0)

- * Insufficient therapeutic effect includes cases that meet the protocol-specific definition (section 2.6.3); that were perceived by the investigator as insufficient; or, that were perceived by the patient as insufficient.
- * Statistically significant based on Fisher's exact test, two-tailed, and the modified Bonferroni procedure.
- * "Other" includes the following reasons: non-compliant, unable to keep appointments, or patient decided to stop.
- ^y Patient #52 (atenolol 50 mg) was discontinued prior to Down-titration Period due to a nervous condition (self-hospitalization) which was considered by the investigator to be not related to study medication.

Number and Percentage of Patients with Data Included or Excluded from Efficacy Analysis

	<u>Placebo</u> N (%)	<u>Atenolol</u> N (%)	<u>Carvedilol</u> N (%)	<u>Total</u> N (%)
Randomized patients	52 (100.0)	101 (100.0)	105 (100.0)	258 (100.0)
Included Intent-to-Treat analysis	52 (100.0)	100 (99.0)	105 (100.0)	257 (99.6)
Included Per-Protocol analysis	48 (92.3)	90 (88.1)	93 (88.6)	231 (89.5)
Patients with Data Excluded from the Per Protocol Analysis:				
Completely excluded by protocol violation	4 (7.7)	11 (10.9)	12 (11.4)	27 (10.5)
Partially excluded by protocol violation	12	22	28	62
Partially excluded by slotting procedure	3	0	4	7

STUDY POPULATION

A total of 258 patients from 13 centers in the United States entered the double-blind treatment phase and received at least one dose of randomized study medication. A total of 52, 101, and 105 patients were randomized to placebo, atenolol and carvedilol, respectively. Because one patient had no data 257 randomized patients were included in the *intent-to-treat sample*.

3.1 Demographic Characteristics

There were no statistically significant differences between the regimens, in any of the demographic parameters, in either the *intent-to-treat* or *per-protocol* samples. In both samples, the majority of patients were Caucasian, 25 to 80 years, and 80% of the patients had mild essential hypertension, defined as a mean SitDBP 90 - 105 mm Hg at baseline Visit 4.

**Summary of Baseline Characteristics
According to Regimen
Intent-to-Treat**

	<u>Placebo</u>		<u>Atenolol</u>		<u>Carvedilol</u>		<u>Total</u>		<u>P-Value*</u>
	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>	
Total Patients	52	100	100	100	105	100	257	100	
<u>Age</u>									0.716
<u>< 64</u>	41	79	82	82	81	77	204	79	
<u>≥ 64</u>	11	21	18	18	24	23	53	21	
<u>Sex</u>									0.407
Female	16	31	34	34	27	26	77	30	
Male	36	69	66	66	78	74	180	70	
<u>Race</u>									1.000
Black	12	23	24	24	25	24	61	24	
Non-Black	40	77	76	76	80	76	196	76	
<u>Severity of Hypertension</u>									0.277
Mild	48	92	87	87	87	83	222	86	
Moderate	4	8	13	13	18	17	35	14	
<u>Prior Anti-Hypertensives</u>									0.188
No	13	25	34	34	24	23	71	28	
Yes	39	75	66	66	81	77	86	72	
<u>Body Weight At Baseline</u>									0.838
< 70 Kgs	7	13	15	15	14	13	36	14	
71-90 Kgs	25	48	48	48	44	42	117	46	
≥ 91 Kgs	20	38	37	37	47	45	104	40	

	<u>Placebo</u>			<u>Atenolol</u>			<u>Carvedilol</u>			<u>P-Value*</u>
	<u>N</u>	<u>Mean</u>	<u>Std</u>	<u>N</u>	<u>Mean</u>	<u>Std</u>	<u>N</u>	<u>Mean</u>	<u>Std</u>	
Age	52	54.1	11.0	100	53.7	11.4	105	53.6	12.0	0.954
Weight	52	85.7	13.1	100	86.4	17.1	105	91.5	20.7	0.050

* P-value of Fisher's Exact Test

* P-value of F-test from General Linear Model (see statistical methods).

Reference documentation: Appendixes 8.10.1, 8.10.2

**Summary of Baseline Characteristics
According to Regimen
*Per-Protocol***

	<u>Placebo</u>		<u>Atenolol</u>		<u>Carvedilol</u>		<u>Total</u>		<u>P-Value*</u>
	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>	
Total Patients	48	100	89	100	93	100	230	100	
<u>Age</u>									0.749
< 64	37	77	72	81	71	76	180	78	
≥ 64	11	23	17	19	22	24	50	22	
<u>Sex</u>									0.383
Female	16	33	31	35	24	26	71	31	
Male	32	67	58	65	69	74	159	69	
<u>Race</u>									0.884
Black	12	25	23	26	21	23	56	24	
Non-Black	36	75	66	74	72	77	174	76	
<u>Severity of Hypertension at Baseline</u>									0.262
Mild	45	94	77	87	78	84	200	87	
Moderate	3	6	12	13	15	16	30	13	
<u>Prior Anti-Hypertensives</u>									0.230
No	12	25	30	34	21	23	63	27	
Yes	36	75	59	66	72	77	167	73	
<u>Body Weight at Baseline</u>									0.848
< 70 Kgs	7	15	12	13	13	14	32	14	
71-90 Kgs	23	48	43	48	38	41	104	45	
≥ 91 Kgs	18	38	34	38	42	45	94	41	

	<u>Placebo</u>			<u>Atenolol</u>			<u>Carvedilol</u>			<u>P-Value*</u>
	<u>N</u>	<u>Mean</u>	<u>Std</u>	<u>N</u>	<u>Mean</u>	<u>Std</u>	<u>N</u>	<u>Mean</u>	<u>Std</u>	
Age	48	54	11.3	89	53	11.7	93	54	11.8	0.750
Weight	48	86	13.4	89	87	17.4	93	91	20.2	0.114

- * P-value of Fisher's Exact Test
- * P-value of F-test from General Linear Model (see statistical methods).

**Distribution of Patients
According to Type of Pre-trial Antihypertensive Medication
Intent-to-treat Sample**

	Number (%) of Patients			
	<u>Placebo</u> (n=52)	<u>Atenolol</u> (n=100)	<u>Carvedilol</u> (n=105)	<u>Total</u> (n =257*)
No Treatment	13 (25.0)	34 (34.0)	24 (22.9)	71 (27.6)
Treated*	39 (75.0)	66 (66.0)	81 (77.1)	186 (72.4)
Type of Medication				
Diuretic	15 (28.8)	23 (23.0)	36 (34.3)	74 (28.8)
Beta Blocker	9 (17.3)	29 (29.0)	22 (21.0)	60 (23.3)
ACE Inhibitor	13 (25.0)	15 (15.0)	23 (21.9)	51 (19.8)
Peripheral Vasodilators	13 (25.0)	23 (23.0)	25 (23.8)	61 (23.7)
Other	10 (19.2)	30 (30.0)	23 (21.9)	63 (24.5)

- * Patients treated with multiple agents of different pharmacologic actions are tabulated within each of the appropriate categories.
- * Patient #82, who was withdrawn after receiving one dose of atenolol 50 mg, received Corgard 20 mg and Maxzide prior to enrolling in this study.

Evaluation of Efficacy

Primary efficacy results are presented for two analyses, the *intent-to-treat* analysis and the *per-protocol* analysis (Tables 8 to 15). All secondary efficacy results are presented for the *intent-to-treat* sample (Tables 16 to 20).

Baseline demographic characteristics did not differ between regimens for either the *intent-to-treat* sample or *per-protocol* sample. No statistically significant differences among the regimens in any sitting or standing baseline vital sign measurements were found.

Efficacy Results: Statistically significant ($p \leq 0.05$) differences in the mean change from baseline for both SitDBP and StaDBP at Titration and Study Endpoints were observed between carvedilol and placebo, between atenolol and placebo, and between carvedilol and atenolol. The mean $\pm$ SE change from baseline SitDBP at Study Endpoint was: -7.5 ± 0.8 mm Hg for carvedilol, -11.3 ± 0.6 mm Hg for atenolol, and -3.5 ± 0.9 mm Hg for placebo. The mean $\pm$ SE change from baseline StaDBP at Study Endpoint was: -6.4 ± 0.9 mm Hg for carvedilol, -9.9 ± 0.7 mm Hg for atenolol, and -2.3 ± 1.0 mm Hg for placebo.

At Study Endpoint, the percentages of patients normalized were 19% (10/52), 51% (51/100), and 33% (35/105) for placebo, atenolol, and carvedilol, respectively, and statistically significant ($p < 0.05$) differences in SitDBP normalized rates were found for atenolol vs placebo and for atenolol vs carvedilol. Responder rates were 23% (12/52), 63% (63/100), and 45% (47/105) for placebo, atenolol, and carvedilol, respectively, and statistically significant ($p < 0.05$) differences in the percentage of patients who were responders for SitDBP were found for all three comparisons.

Primary efficacy parameters: Mean SitDBP and Mean StaDBP

Results of the *intent-to-treat* and *per protocol* analyses of the change in SitDBP and StaDBP were consistent in that all three comparisons were statistically significant at Titration and Study Endpoints. The changes were similar in magnitude, and the rank order (atenolol > carvedilol > placebo) was the same among regimens.

**Summary of Tabulations and Analysis of Baseline *SitDBP* (mm Hg) and Change from
Baseline at Titration and Study Endpoints
Intent-to-Treat Sample**

	<u>Regimen</u>	<u>N</u>	<u>Mean</u>	<u>SE</u>	<u>Comparison</u>	<u>Estimate Confidence Interval*</u>	<u>P-Value*</u>
<u>Baseline <i>SitDBP</i></u>							
Diastolic	Placebo	52	100	0.6			
	Atenolol	100	100	0.4	Aten vs Plac	(-1.4, 1.1)	0.826
	Carvedilol	105	101	0.4	Carv vs Plac	(-0.8, 1.7)	0.486
					Carv vs Aten	(-0.4, 1.6)	0.265
<u>Change from Baseline at Titration Endpoint</u>							
Diastolic	Placebo	52	-4.6	1.0			
	Atenolol	100	-13.0	0.6	Aten vs Plac	(-10.6, -6.0)	<0.001*
	Carvedilol	105	-9.1	0.7	Carv vs Plac	(-6.6, -2.1)	<0.001*
					Carv vs Aten	(2.0, 5.8)	<0.001*
<u>Change from Baseline at Maintenance Endpoint</u>							
Diastolic	Placebo	19	-8.4	1.2			
	Atenolol	91	-12.0	0.6	Aten vs Plac	(-6.4, 0.5)	0.090
	Carvedilol	69	-9.5	0.9	Carv vs Plac	(-3.9, 3.2)	0.838
					Carv vs Aten	(0.5, 4.7)	0.018
<u>Change from Baseline at Study Endpoint</u>							
Diastolic	Placebo	52	-3.5	0.9			
	Atenolol	100	-11.3	0.6	Aten vs Plac	(-10.1, -5.3)	<0.001*
	Carvedilol	105	-7.5	0.8	Carv vs Plac	(-6.3, -1.5)	0.002*
					Carv vs Aten	(1.8, 5.8)	<0.001*

**Summary of Tabulations and Analysis of
Baseline StaDBP (mm Hg) and Change from Baseline
at Titration, and Study Endpoints
Intent-to-Treat Sample**

<u>Baseline StaDBP</u>	<u>Regimen</u>	<u>N</u>	<u>Mean</u>	<u>SE</u>	<u>Comparison</u>	<u>Estimate Confidence Interval*</u>	<u>P-Value*</u>
Diastolic	Placebo	52	102	0.7			
	Atenolol	100	102	0.5	Aten vs Plac	(-2.0, 1.1)	0.540
	Carvedilol	105	102	0.6	Carv vs Plac	(-1.7, 1.3)	0.757
					Carv vs Aten	(-1.0, 1.5)	0.710
<u>Change from Baseline at Titration Endpoint</u>							
Diastolic	Placebo	52	-3.2	1.1			
	Atenolol	100	-11.6	0.6	Aten vs Plac	(-10.9, -5.9)	<0.001*
	Carvedilol	105	-8.0	0.8	Carv vs Plac	(-7.2, -2.2)	<0.001*
					Carv vs Aten	(1.6, 5.7)	<0.001*
<u>Change from Baseline at Maintenance Endpoint</u>							
	Placebo	19	-8.1	1.3			
	Atenolol	91	-10.6	0.7	Aten vs Plac	(-5.6, 1.8)	0.307
	Carvedilol	69	-8.8	1.0	Carv vs Plac	(-3.9, 3.7)	0.962
					Carv vs Aten	(-0.5, 4.1)	0.119
<u>Change from Baseline at Study Endpoint</u>							
Diastolic	Placebo	52	-2.3	1.0			
	Atenolol	100	-9.9	0.7	Aten vs Plac	(-10.2, -5.0)	<0.001*
	Carvedilol	105	-6.4	0.9	Carv vs Plac	(-6.7, -1.5)	0.002*
					Carv vs Aten	(1.3, 5.6)	0.002*

* Least Squares 95% Comparison-wise Confidence Interval & p-value of contrast from SAS General Model.

* Significant at alpha = 0.05 using modified Bonferroni procedure for the three comparisons.

Comparing the two tables, orthostatic hypotension, at least at trough levels, does not appear to be a major problem.

**Mean (SE) Change from Baseline
in Sitting Diastolic Blood Pressure (mm Hg)
at Titration, Maintenance, and Study Endpoints
According to Dose Level
Intent-to-Treat Sample**

<u>Baseline Sitting DBP</u>	<u>n</u>	<u>Mean</u>	<u>SE</u>						
Placebo	52	100.2	0.6						
Atenolol (50/50/100 mg)	100	100.1	0.4						
Carvedilol (12.5/25/50 mg)	105	100.8	0.4						
				<u>Level 2</u>		<u>Level 3</u>		<u>Level 4</u>	
				<u>n</u>	<u>Mean</u>	<u>SE</u>	<u>n</u>	<u>Mean</u>	<u>SE</u>
<u>Change from Baseline at Titration Endpoint</u>									
Placebo	4	-12.3	2.7	3	-5.3	4.2	45	-3.8	1.1
Atenolol (50/50/100 mg)	35	-16.1	0.9	22	-15.2	0.7	43	-9.5	0.9
Carvedilol (12.5/25/50 mg)	10	-6.9	4.6	14	-11.6	1.4	81	-8.9	0.7
<u>Change from Baseline at Maintenance Endpoint</u>									
Placebo	3	-11.0	3.1	2	-4.0	5.0	14	-8.5	1.4
Atenolol (50/50/100 mg)	35	-13.4	0.9	22	-12.3	1.2	33	-9.7	1.1
Carvedilol (12.5/25/50 mg)	8	-7.4	2.3	11	-9.6	1.9	50	-9.8	1.1
<u>Change from Baseline at Study Endpoint</u>									
Placebo	4	-11.3	2.2	3	-1.7	3.7	45	-3.0	0.9
Atenolol (50/50/100 mg)	35	-13.4	0.9	22	-12.3	1.2	42	-8.6	1.0
Carvedilol (12.5/25/50 mg)	10	-2.9	3.8	14	-9.0	1.7	81	-7.8	0.8

Reference documentation: Appendix 8.1.8, 8.2.15, and 8.2.16

When means $\pm$ standard errors for StaDBP are compared, there are differences in effect among different dose levels. At Study Endpoint, the largest mean changes in StaDBP were observed for the atenolol and carvedilol regimens at the middle dose level (a result not surprising in a titration trial).

**Mean (SE) Change from Baseline
in Standing Diastolic Blood Pressure (mm Hg)
at Titration, Maintenance, and Study Endpoints
According to Dose Level
Intent-to-Treat Sample**

<u>Baseline Standing DBP</u>	<u>n</u>	<u>Mean</u>	<u>SE</u>						
Placebo	52	102.4	0.7						
Atenolol (50/50/100 mg)	100	101.8	0.5						
Carvedilol (12.5/25/50 mg)	103	102.2	0.6						
				<u>Level 2</u>		<u>Level 3</u>		<u>Level 4</u>	
				<u>n</u>	<u>Mean</u>	<u>SE</u>	<u>n</u>	<u>Mean</u>	<u>SE</u>
<u>Change from Baseline at Titration Endpoint</u>									
Placebo	4	-12.0	1.5	3	-4.0	4.2	45	-2.4	1.2
Atenolol (50/50/100 mg)	35	-13.6	1.7	22	-13.9	1.0	43	-8.9	0.9
Carvedilol (12.5/25/50 mg)	10	-3.1	4.2	14	-10.9	2.1	81	-8.1	0.8
<u>Change from Baseline at Maintenance Endpoint</u>									
Placebo	3	-11.0	2.1	2	-3.0	3.0	14	-8.1	1.6
Atenolol (50/50/100 mg)	35	-11.5	1.0	22	-12.5	1.4	33	-8.0	1.1
Carvedilol (12.5/25/50 mg)	8	-8.6	1.6	11	-10.2	1.8	50	-8.6	1.3
<u>Change from Baseline at Study Endpoint</u>									
Placebo	4	-11.3	1.5	3	-0.7	2.9	45	-1.6	1.1
Atenolol (50/50/100 mg)	35	-11.5	1.0	22	-12.5	1.4	42	-7.0	1.0
Carvedilol (12.5/25/50 mg)	10	-3.3	4.3	14	-8.6	2.0	81	-6.4	0.9

Reference documentation: Appendix 8.1.8, 8.2.15, and 8.2.16

Mean SitDBP and mean StaDBP at Baseline and the mean change from baseline at Titration, Maintenance, and Study Endpoints for trough (pre-dose) measurements for the *per-protocol* samples were consistent with the *intent-to-treat* results.

In comparison to SitDBP results, mean changes in mean StaDBP were slightly less for all three regimens at all three endpoints, as was observed for the *intent-to-treat* analysis.

Per-Protocol Sample

	<u>Regimen</u>	<u>N</u>	<u>Mean</u>	<u>SE</u>	<u>Comparison</u>	<u>Estimate Confidence Interval*</u>	<u>P-Value*</u>
<u>Baseline Standing DBP</u>							
Diastolic	Placebo	48	102	0.7			
	Atenolol	89	101	0.5	Aten vs Plac	(-1.8, 1.1)	0.626
	Carvedilol	93	101	0.5	Carv vs Plac	(-2.1, 0.9)	0.407
					Carv vs Aten	(-1.5, 1.0)	0.683
<u>Change from Baseline at Titration Endpoint</u>							
Diastolic	Placebo	48	-2.8	1.1			
	Atenolol	89	-11.1	0.8	Aten vs Plac	(-10.8, -5.7)	<0.001*
	Carvedilol	93	-7.6	0.7	Carv vs Plac	(-7.2, -2.2)	<0.001*
					Carv vs Aten	(1.4, 5.6)	<0.001
<u>Change from Baseline at Maintenance Endpoint</u>							
Diastolic	Placebo	14	-6.4	1.9			
	Atenolol	69	-10.3	0.7	Aten vs Plac	(-7.5, 1.4)	0.174
	Carvedilol	47	-9.0	1.3	Carv vs Plac	(-5.9, 3.4)	0.606
					Carv vs Aten	(-0.9, 4.6)	0.187
<u>Change from Baseline at Study Endpoint</u>							
Diastolic	Placebo	48	-1.8	1.1			
	Atenolol	89	-9.3	0.8	Aten vs Plac	(-10.0, -4.7)	<0.001*
	Carvedilol	93	-6.3	0.8	Carv vs Plac	(-7.0, -1.7)	0.001*
					Carv vs Aten	(0.8, 5.2)	0.008*

* Least Squares 95% Comparison-wise Confidence Interval & p-value of contrast from SAS General Model.

* Significant at alpha = 0.05 using modified Bonferroni procedure for the three comparisons.

**Mean (SE) Change from Baseline
in Sitting Diastolic Blood Pressure (mm Hg)
at Titration, Maintenance, and Study Endpoints
According to Dose
Per-Protocol Sample**

<u>Baseline Sitting DBP</u>	<u>n</u>	<u>Mean</u>	<u>SE</u>						
Placebo	48	99.9	0.6						
Atenolol (50/50/100 mg)	89	100.1	0.4						
Carvedilol (12.5/25/50 mg)	91	100.4	0.4						
				Level 2	Level 3	Level 4			
				<u>n</u>	<u>Mean</u>	<u>SE</u>	<u>n</u>	<u>Mean</u>	<u>SE</u>
<u>Change from Baseline at Titration Endpoint</u>									
Placebo	6	-5.8	4.4	7	-4.7	2.1	35	-3.1	1.1
Atenolol (50/50/100 mg)	33	-15.2	1.3	24	-13.3	1.4	32	-9.7	1.1
Carvedilol (12.5/25/50 mg)	9	-10.3	3.3	23	-7.0	1.4	61	-9.5	0.7
<u>Change from Baseline at Maintenance Endpoint</u>									
Placebo	1	-15.0	0.0	2	-4.0	5.0	11	-7.1	1.1
Atenolol (50/50/100 mg)	28	-13.4	1.0	17	-12.9	1.1	23	-8.7	1.2
Carvedilol (12.5/25/50 mg)	4	-6.0	2.9	7	-10.4	2.6	36	-9.8	1.3
<u>Change from Baseline at Study Endpoint</u>									
Placebo	6	-5.2	4.0	7	-3.1	2.1	35	-2.2	1.0
Atenolol (50/50/100 mg)	33	-12.9	1.2	24	-11.2	1.2	31	-8.4	1.2
Carvedilol (12.5/25/50 mg)	9	-8.2	3.6	23	-5.9	1.3	61	-8.3	0.9

Reference documentation: Appendix 8.1.8, 8.2.15, and 8.2.16

"Responders":

Intent-to-treat analysis: Statistically significant ($p \leq 0.05$) differences in SitDBP *normalized* and *responder* rates were found at Titration Endpoint (all three comparisons for both rates).

At Study Endpoint, statistically significant ($p \leq 0.05$) differences in SitDBP *normalized* and *responder* rates were found for: carvedilol vs atenolol and atenolol vs placebo for *normalized* rates and for all three comparisons for *responder* rates.

**Number and Percent of Patients Normalized* and
Responders* to Randomized Treatment at Study Endpoint:
Sitting Diastolic Blood Pressure**

Intent-To-Treat Sample

	<u>Total No.</u>	<u>No. (%) Normalized</u>	<u>No. (%) Responders</u>
Titration Endpoint			
Placebo	52	13 (25%)	16 (31%)
Atenolol	100	76 (76%)	81 (81%)
Carvedilol	105	48 (46%)	60 (57%)
<u>P-value[†]:</u>	Carv vs Aten	< 0.001 [‡]	< 0.001 [‡]
	Aten vs Plac	< 0.001 [‡]	< 0.001 [‡]
	Carv vs Plac	0.015 [‡]	0.002 [‡]

	<u>Total No.</u>	<u>No. (%) Normalized</u>	<u>No. (%) Responders</u>
Maintenance Endpoint			
Placebo	19	8 (42%)	10 (53%)
Atenolol	91	50 (55%)	61 (67%)
Carvedilol	69	28 (41%)	37 (54%)

	<u>Total No.</u>	<u>No. (%) Normalized</u>	<u>No. (%) Responders</u>
Study Endpoint			
Placebo	52	10 (19%)	12 (23%)
Atenolol	100	51 (51%)	63 (63%)
Carvedilol	105	35 (33%)	47 (45%)
<u>P-value[†]:</u>	Carv vs Aten	0.011 [‡]	< 0.012 [‡]
	Aten vs Plac	< 0.001 [‡]	< 0.001 [‡]
	Carv vs Plac	0.091	0.008 [‡]

- * Normalized: sitting diastolic pressure of less than 90 mm Hg.
- * Responders: sitting diastolic pressure normalized and/or decreased from baseline by 10 mm Hg or more.
- * P-value of Fisher's Exact Test (Two-Tailed) to test differences between active groups versus placebo and carvedilol group versus atenolol.
- † Significant at alpha = 0.05 using modified Bonferroni procedure for the comparisons.

**Number and Percent of Patients Normalized*
and Responders† to Randomized Treatment at Study Endpoint:
Standing Diastolic Blood Pressure**

Intent-to-Treat Sample

	<u>Total No.</u>	<u>No. (%) Normalized</u>	<u>No. (%) Responders</u>
Titration Endpoint			
Placebo	52	11 (21%)	14 (27%)
Atenolol	100	51 (51%)	65 (65%)
Carvedilol	105	31 (30%)	49 (47%)

<u>P-value</u> ‡:	Carv vs Aten	< 0.003 [§]	< 0.011 [§]
	Aten vs Plac	< 0.001 [§]	< 0.001 [§]
	Carv vs Plac	0.339	0.024 [§]

	<u>Total No.</u>	<u>No. (%) Normalized</u>	<u>No. (%) Responders</u>
Maintenance Endpoint			
Placebo	19	6 (32%)	10 (53%)
Atenolol	91	39 (43%)	51 (56%)
Carvedilol	69	30 (43%)	38 (55%)

	<u>Total No.</u>	<u>No. (%) Normalized</u>	<u>No. (%) Responders</u>
Study Endpoint			
Placebo	52	7 (13%)	12 (23%)
Atenolol	100	41 (41%)	55 (55%)
Carvedilol	105	33 (31%)	43 (41%)

<u>P-value</u> ‡:	Carv vs Aten	0.190	0.051
	Aten vs Plac	< 0.001 [§]	< 0.001 [§]
	Carv vs Plac	0.019 [§]	0.033

- * Normalized: sitting diastolic pressure of less than 90 mm Hg.
- † Responders: sitting diastolic pressure normalized and/or decreased from baseline by 10 mm Hg or more.
- ‡ P-value of Fisher's Exact Test (Two-Tailed) to test differences between active group versus placebo and carvedilol group versus atenolol.
- § Significant at alpha = 0.05 using modified Bonferroni procedure for the comparisons.

4.2.3 Maintenance of effect

Change from Titration Endpoint to Maintenance Endpoint was calculated for the subset of patients who had Maintenance Endpoint data: 19 patients receiving placebo, 91 patients receiving atenolol, and 69 patients receiving carvedilol.

**Change in Mean* SitDBP and StaDBP from End-Titration
to End-Maintenance for Patients with Maintenance Endpoint Data According
to Medication Regimen/*Intent-To-Treat* Sample**

	<u>n</u>	<u>Placebo</u> <u>Mean</u>	<u>SE</u>	<u>n</u>	<u>Atenolol</u> <u>Mean</u>	<u>SE</u>	<u>n</u>	<u>Carvedilol</u> <u>Mean</u>	<u>SE</u>
<u>Sitting DBP (mm Hg)</u>									
Baseline	19	100.2	1.1	91	99.7	0.3	69	100.4	0.5
Change from baseline to end-titration	19	-11.3	1.4	91	-13.9	0.6	69	-11.9	0.7
Change from end-titration to end- maintenance	19	+2.8	1.6	91	+1.9	0.7	69	+2.4	0.9
<u>Three Minute Standing DBP (mm Hg)</u>									
Baseline	19	101.1	1.1	91	101.4	0.5	69	101.7	0.7
Change from baseline to end-titration	19	-10.5	1.2	91	-12.5	0.6	69	-11.3	0.8
Change from end-titration to end- maintenance	19	+2.5	1.9	91	+1.9	0.6	69	+2.4	1.0

* Mean is the unadjusted mean.

4.2.4 Subgroup comparisons

Analysis of variance of baseline and mean SitDBP change from baseline at endpoint was performed for four subgroups (sex, age, severity of hypertension at baseline, and race) for both the *intent-to-treat* and *per-protocol* samples.

Analysis of the *intent-to-treat* and *per-protocol* samples found no statistically significant ($p > 0.05$) differences between the regimens at baseline for any category of sex and race subsets.

For the black subgroup, the *change from baseline* at Study Endpoint was less than the corresponding change for the non-black subgroup by more than two standard errors of the mean for both atenolol and carvedilol treatment groups; (Tables 27 and 28). For the placebo treatment group, however, changes from baseline in both SitDBP and StaDBP were similar (within $\pm$ one SE of the mean), although the changes were smaller than those observed for the active treatments.

The black subgroup did not show any statistically significant differences in mean change from baseline for SitDBP and StaDBP, except for the comparison of atenolol to placebo for SitDBP ($p = 0.020$) at Study Endpoint (*intent-to-treat analysis*).

Mean Change from Baseline at Study Endpoint
Intent-to-Treat Sample
FEMALE SUBGROUP

SitDBP (mm Hg)

<u>Regimen</u>	<u>n</u>	<u>Mean</u>	<u>SE</u>
Placebo	16	-3.7	1.8
Atenolol	34	-11.5	0.9
Carvedilol	27	-7.6	1.4

<u>Comparison</u>	<u>CI*</u>	<u>P-Value*</u>
C vs P	(-8.5, 0.5)	0.077
A vs P	(-11.9, -3.2)	0.001*
C vs A	(0.1, 7.0)	0.045

StaDBP (mm Hg)

<u>Regimen</u>	<u>n</u>	<u>Mean</u>	<u>SE</u>
Placebo	16	-1.0	2.0
Atenolol	34	-10.7	1.0
Carvedilol	27	-4.5	1.4

<u>Comparison</u>	<u>CI*</u>	<u>P-Value*</u>
C vs P	(-6.8, 2.5)	0.358
A vs P	(-12.3, -3.2)	0.001*
C vs A	(2.1, 9.2)	0.002*

4.2.5 Analysis of peak and trough sitting DBP

Assessments were taken 30, 60, 90 and 120 minutes post-dosing at Baseline visit 4 as well as the Study Endpoint. Only patients with a set of both trough and peak measurements recorded on the same day and having a set at both the baseline and end-of-study observations were selected for these tabulations.

Analysis of steady-state sitting diastolic peak and trough measurements at Study Endpoint (*intent-to-treat* sample) showed 53.3% of the peak effect for carvedilol and 86.5% of the peak effect for atenolol is retained at trough, based on unadjusted trough/peak ratios. Adjusting these ratios for the placebo response among patients with maintenance data (ie, those patients for whom a placebo effect was observed) resulted in estimates of 32.2% of the peak effect for carvedilol and 67.9% of the peak effect for atenolol is retained at trough.

than those produced by carvedilol, administration of carvedilol once daily was superior to placebo in reducing SitDBP and StaDBP in patients with mild to moderate essential hypertension. At Study Endpoint, the mean change ($\pm$ SE) produced by carvedilol was -7.5 ± 0.8 mm Hg in Sit DBP and -6.4 ± 0.9 mm Hg in StaDBP. Among patients receiving carvedilol during the maintenance period, more than 50% of the peak effect was retained at trough. Also, the safety profile was similar for both atenolol and carvedilol. Most adverse experiences were mild and transient, with the majority (52%) of adverse experiences classified as mild. The results of this study demonstrate that carvedilol once daily is both safe and efficacious.

Reviewer's comments:

In the dose range tested Carvedilol is not a particularly effective drug and can not be recommended for once-a-day dosing. In a direct comparison, Atenolol is clearly more effective. This could be a consequence of dose rather than potency but the study does not address this issue.

The drug does not appear to be effective in black patients.

Age and sex of patients played no significant role in the outcome of this trial.

The drop-out rate is high and may have biased the outcome in favor of both active treatments.

Protocol CAR-UK-104

This multicenter study in UK had an unusual twist. Although the treatment phase lasted 12 weeks, it was unblinded to the investigators after week 4. Its purpose was to establish a dose range and evaluate safety in elderly patients (≥ 65 years old). There was no concurrent placebo arm. Efficacy was estimated by calculating the proportion of 'responders' in each group. Median values and ranges are also presented in the tables together with confidence intervals for the comparisons between treatment groups.

The titration at week 4 was based on efficacy, with the caveat that dose could not be increased if adverse effects were a problem.

Safety issues are discussed in some detail with summaries of individual case histories.

CAR-UK-104										
n	single blind	n	double blind	n	n	single blind	n	n	% response	Δ DBP(sitting) mm Hg (median)
262	Placebo	114	Carvedilol 12.5 mg UID	106	?	carvedilol 12.5 mg UID	56	93	68%	-10
					?	carvedilol 25 mg UID	37			
		118	Carvedilol 25 mg UID	104	?	Carvedilol 25 mg UID	62	90	70%	-12
					?	Carvedilol 50 mg UID	28			
262	3-6 weeks	232	4 weeks	210		8 weeks	183	183		

SUMMARY

This study was conducted as a double-blind, parallel group, multicentre study in hospital and in general practice. 262 elderly hypertensive patients (aged 65 to 89), including 6 protocol violators aged under 65 years, were recruited in order to obtain 183 who completed the protocol. All patients had to have a diastolic blood pressure of between 95 and 115mmHg and a systolic blood pressure of no more than 220mmHg confirmed during the baseline period. Each patient was randomised to receive either carvedilol 12.5mg or carvedilol 25mg at the end of the baseline period. After four weeks of treatment, the dose was titrated to "double dose" if the blood pressure remained uncontrolled (diastolic blood pressure being greater than 90mmHg and had decreased by less than 10mmHg). However, if patients were experiencing side effects which were likely to be exacerbated by increasing the dose then they remained on the lower dose. Following dose titration, if applicable, the patients continued in the study for a further eight weeks making the total study period twelve weeks.

Two statistical analyses were performed: an intention-to-treat analysis which considered all patients present at a particular visit, and a per-protocol analysis which considered only those patients present at a particular visit who were eligible under the terms of the protocol (i.e. non-protocol violators). Three time points were also used: final baseline visit, following four weeks of treatment (before any dose titration) and following twelve weeks of treatment (end of study). The primary efficacy parameter was to show a reduction in mean sitting diastolic blood pressure below 90mmHg and/or a fall of 10mmHg over the study period. The statistical analyses concentrated on the dose as randomised as this eliminates potential bias. However, similar numbers of patients were titrated correctly at week 4 in both treatment groups making it possible and logical to compare dose as randomised without adjustment for dose titration. A total of 114 and 118 patients were randomised to receive carvedilol 12.5mg and 25mg, respectively. At week 4, 106 patients were taking carvedilol 12.5mg and 104 patients were taking carvedilol 25mg. Of these patients 88 in the carvedilol 12.5mg group and 86 in the carvedilol 25mg group were eligible for the per-protocol analysis. By the end of the study 93 patients were remaining in the carvedilol 12.5mg starting dose group (56 patients on 12.5mg, 37 patients titrated up to 25mg at week 4) and 90 patients were remaining in the carvedilol 25mg starting dose group (62 patients on 25mg, 28 patients titrated up to 50mg at week 4). Of these patients 75 in the carvedilol 12.5mg starting dose group (46 patients on 12.5mg, 29 patients on 25mg) and 74 in the carvedilol 25mg starting dose group (52 patients on 25mg, 22 patients on 50mg) were eligible for the per-protocol analysis.

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The following table presents the results of the responders in each treatment group, according to the analysis performed, following four weeks and twelve weeks of treatment.

DOSE	INTENTION-TO-TREAT (all patients present for assessment)		PER-PROTOCOL (eligible patients)	
	Week 4	Week 12	Week 4	Week 12
Carvedilol 12.5mg	63/106 (59%)	63/93 (68%)	52/88 (59%)	50/75 (67%)
Carvedilol 25mg	72/104 (69%)	63/90 (70%)	60/86 (70%)	50/74 (68%)
% difference between groups	10% p=0.14	2% p=1.00	11% p=0.14	1% p=0.83

From this table it would appear that carvedilol 25mg is slightly more effective following four weeks of treatment compared to carvedilol 12.5mg, although this result is not statistically significant. However, following twelve weeks of treatment (post dose titration if applicable) the difference between these two groups narrows.

Safety is another important issue to consider when treating elderly hypertensive patients as they appear to be more prone to side effects than a younger population of patients. The safety section of this report was split into two sections: (a) those adverse events related to dizziness and/or postural hypotension and (b) others. Statistical analyses were only performed on the group of patients that fell into section (a) above. No statistically significant difference was observed between the two treatment group as randomised although almost one and a half times as many adverse events related to dizziness and/or postural hypotension were reported by patients started on carvedilol 25mg compared to 12.5mg. This becomes a little clearer when we split the groups into treatment schedules (i.e. 12.5mg → 12.5mg, 12.5mg → 25mg, 25mg → 25mg, 25mg → 50mg) although these results should be treated with caution as patients involved in treatment schedules that require a dose titration (i.e. 12.5mg → 25mg and 25mg → 50mg) had to have received at least four weeks' treatment before inclusion. Adverse events occurring during the first four weeks of the study tended to appear in the groups where the dose was not subsequently doubled, whereas adverse events occurring at a later stage tended to appear in groups where the dose was doubled.

The following table presents the percentage of patients suffering adverse events related to dizziness and/or postural hypotension in each treatment schedule.

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TREATMENT SCHEDULE	TOTAL REPORTS	TOTAL PATIENTS	% OF PATIENTS
12.5mg → 12.5mg	9	7	10%
12.5mg → 25mg	7	6	14%
25mg → 25mg	21	13	15%
(Total 25mg)	(28)	(19)	(15%)
25mg → 50mg	6	6	19%

Therefore it would appear that the higher the dose of carvedilol, the higher the incidence of adverse events related to dizziness and/or postural hypotension. Increasing the dose from 12.5mg to 25mg does increase the incidence of these adverse events although the incidence is no greater in this group of patients compared to the group who remained on 25mg throughout the study.

Regarding other adverse events a greater number was again reported by the higher dose group (96 reports by 57 patients randomised to carvedilol 12.5mg compared to 104 reports by 63 patients randomised to carvedilol 25mg). Although the total numbers of adverse events reported is high, it is what one might expect from this population of patients. Similarly, many of the laboratory values taken throughout the study were out of the normal range, although not necessarily clinically significant, and reflects the elderly population studied.

In conclusion, carvedilol 12.5mg and carvedilol 25mg have very similar efficacy as starting doses in the elderly hypertensive population, provided titration to a higher dose occurs, if necessary. However, it does appear that the higher the dose of carvedilol the higher the incidence of adverse events related to dizziness and/or postural hypotension which is also true to some extent for all other adverse events. It would therefore seem prudent to initiate treatment in the elderly with 12.5mg once daily and there may be individual patients who can be maintained on this dosage.

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analyse parameters expressed as counts of patients (e.g. number of patients whose dose was increased, number fulfilling the primary efficacy criteria, etc.). All changes or differences described as statistically significant in this report are significant at least at the 5 percent level.

The Mantel-Haenszel Chi-square test was used to compare the starting dose groups with respect to the incidence of adverse events related to dizziness and/or postural hypotension, both overall and during each stage of the study. The Mantel-Haenszel Chi-square test adjusted for whether or not the dose was doubled at week 4 in the analysis of the stage following the dose titration step.

Fisher's Exact test was used to compare these adverse events between the starting dose groups at the increased dose monitoring visit since only a small number of events occurred at this stage. The two-sided p-value was obtained by doubling the one-sided value.

4. RESULTS

4.1 Number of Patients

A total of two hundred and sixty two patients were recruited to take part in the study. Two hundred and thirty two patients entered the active phase of the study. The first dose of study medication was administered in March 1989 and the last dose in February 1991. The thirty patients who did not receive active medication were withdrawn by the investigators for the following reasons: diastolic blood pressure below level for inclusion (13), abnormal renal function (3), standing systolic blood pressure too low (1), concomitant treatment with additional antihypertensive medication (2), patient request (4), adverse event (4), non-compliance with study medication (2) and investigator absence (1).

Of the 232 patients who received active medication 22 patients withdrew during the first 4 weeks, 16 due to adverse events (6 in the carvedilol 12.5mg group, 10 in the carvedilol 25mg group), 1 as he did not meet study eligibility criteria (carvedilol 25mg group), 1 due to non-compliance with study medication (carvedilol 25mg group), 2 requested to withdraw (carvedilol 25mg group) and 2 defaulted (both carvedilol 12.5mg group).

A further 27 patients withdrew before the week 12 visit, 21 due to adverse events (6 taking carvedilol 12.5mg, 11 taking carvedilol 25mg and 4 taking carvedilol 50mg), 2 requested to withdraw (one in each group), 1 had a diastolic pressure greater than 115 mmHg (carvedilol 12.5mg starting dose group), 2 defaulted (one in each group)

and one due to additional antihypertensive treatment being given by his GP (carvedilol 25mg starting dose group).

Forty investigators located within the UK were involved in recruiting patients into the study (Table 1). It was not possible to assess treatment x centre interactions as the numbers of patients recruited by each centre were far too small. This report presents data on two hundred and thirty two patients who were randomised to receive either carvedilol 12.5mg or carvedilol 25mg during the initial period of the active phase of the study. If necessary, dose titration to "double-dose" occurred following four weeks of active treatment according to the criteria detailed in "Procedure, section 3.3.3. Treatment Phase Visits". The safety section of this report will also consider data on those patients who dropped out during the baseline period.

Of the 232 patients who received active medication 14 had all data excluded from the per protocol analysis due to the following reasons: diastolic pressure less than 95mmHg at baseline (7), age under 65 years (6) and emphysema (1). An additional 22 patients had their week 4 data excluded due to a late visit, where the patient would have run out of medication. Twenty patients also had week 12 data excluded for the same reason. Compliance less than 75% affected one patient at week 4 and one patient at week 12. These violations affected 36 patients at week 4 and 34 patients at week 12.

4.2 Demographic Data

No statistical tests were performed on the demographic data at the preliminary examination. Data is presented in terms of median, minimum and maximum values for all demographic parameters for the 232 patients who received active treatment. Table 3 presents the demographic data for all randomised patients (232 patients), table 4 presents the demographic data for all randomised patients that were present at week 12 (183 patients) and table 5 presents the demographic data for all eligible patients present at week 12 (149 patients).

At the preliminary examination, for all patients randomised, there were 48 males and 66 females in the carvedilol 12.5mg group, and 41 males and 77 females in the carvedilol 25mg group, median age and range being 71 (30-87) and 71 (62-86) years, respectively. A qualitative examination of the data presented in table 3 does not reveal any striking differences in any of the demographic parameters, apart from perhaps the male to female proportions (42%:58% carvedilol 12.5mg group, 35%:65% carvedilol 25mg group). 183 of these patients were present at the end of the study and had data available for comparisons on an intention-to-treat basis. Again, table 4 does not appear to reveal any differences in the demographic data of

000015

ALL RANDOMISED PATIENTS PRESENT AT WEEK 12
 CLINICAL EFFICACY DATA
 FINAL PLACEBO BASELINE PERIOD VALUES

		Treatment Group			Comparison of Treatment Groups			
		Carvedilol 12.5mg	Carvedilol 25mg	Overall	Median Difference	95% C.I.		P-value
	Median Min Max N					Lower	Upper	
Mean Systolic BP (mmHg) Sitting		177	182	179	-6	-11	-2	0.01
		93	90	183				
Mean Diastolic BP (mmHg) Sitting		103	102	102	0	-1	2	0.71
		93	90	183				
Systolic BP (mmHg) Immediate Standing		178	188	178	-6	-18	-2	0.01
		93	90	183				
Diastolic BP (mmHg) Immediate Standing		102	102	102	0	-1	2	0.63
		93	90	183				
Postural Drop in Systolic BP (mmHg)		-2	-2	-2	0	-2	1	0.56
		93	90	183				
Postural Drop in Diastolic BP (mmHg)		0	0	0	0	-1	1	0.86
		93	90	183				
Pulse Rate (bpm) Sitting		76	76	76	0	-3	2	0.70
		93	90	183				
Pulse Rate (bpm) Immediate Standing		80	80	80	0	-2	4	0.96
		93	90	183				
Weight (kg)		74	70	71	3	-1	6	0.13
		93	89	182				

**ALL RANDOMISED PATIENTS PRESENT AT WEEK 12
CLINICAL EFFICACY DATA
WEEK 12 VALUES**

		Treatment Group			Comparison of Treatment Groups			
		Carvedilol 12.5mg	Carvedilol 25mg	Overall	Median Difference	95% C.I. Lower	Upper	P-value
Mean Systolic BP (mmHg) Sitting	Median	163	163	163	-1	-8	5	0.62
	Min							
	Max							
	N	93	90	183				
Mean Diastolic BP (mmHg) Sitting	Median	90	89	90	1	-2	3	0.53
	Min							
	Max							
	N	93	90	183				
Systolic BP (mmHg) Immediate Standing	Median	160	160	160	0	-10	5	0.54
	Min							
	Max							
	N	93	89	182				
Diastolic BP (mmHg) Immediate Standing	Median	90	90	90	0	-3	4	0.87
	Min							
	Max							
	N	93	89	182				
Postural Drop in Systolic BP (mmHg)	Median	-1	-1	-1	-1	-3	1	0.38
	Min							
	Max							
	N	93	89	182				
Postural Drop in Diastolic BP (mmHg)	Median	0	0	0	0	-1	1	0.61
	Min							
	Max							
	N	93	89	182				
Pulse Rate (bpm) Sitting	Median	71	72	71	0	-3	2	0.63
	Min							
	Max							
	N	93	90	183				
Pulse Rate (bpm) Immediate Standing	Median	72	72	72	0	-2	2	0.63
	Min							
	Max							
	N	92	88	180				
Weight (kg)	Median	74	70	71	2	-1	5	0.17
	Min							
	Max							
	N	92	89	181				

000099

**ALL RANDOMISED PATIENTS PRESENT AT WEEK 12
CLINICAL EFFICACY DATA
CHANGES (WEEK 12 - BASELINE)**

		Treatment Group			Comparison of Treatment Groups			
		Carvedilol 12.5mg	Carvedilol 25mg	Overall	Median Difference	95% C.I.		P-value
					Lower	Upper		
Mean Systolic BP (mmHg) Sitting	Median	-13	-20	-17	5	0	11	0.07
	Min							
	Max							
	N	93	90	183				
Mean Diastolic BP (mmHg) Sitting	Median	-10	-12	-11	1	-2	4	0.41
	Min							
	Max							
	N	93	90	183				
Systolic BP (mmHg) Immediate Standing	Median	-12	-20	-15	5	-1	10	0.15
	Min							
	Max							
	N	93	89	182				
Diastolic BP (mmHg) Immediate Standing	Median	-10	-10	-10	0	-3	4	0.85
	Min							
	Max							
	N	93	89	182				
Postural Drop in Systolic BP (mmHg)	Median	0	1	1	-1	-3	1	0.33
	Min							
	Max							
	N	93	89	182				
Postural Drop in Diastolic BP (mmHg)	Median	0	1	0	-1	-3	1	0.27
	Min							
	Max							
	N	93	89	182				
Pulse Rate (bpm) Sitting	Median	-6	-6	-6	0	-2	3	0.68
	Min							
	Max							
	N	93	90	183				
Pulse Rate (bpm) Immediate Standing	Median	-7	-7	-7	0	-2	2	0.87
	Min							
	Max							
	N	92	88	180				
Weight (kg)	Median	0	0	0	0	-1	0	0.17
	Min							
	Max							
	N	92	88	180				

Patient 244 had a sudden drop in WBC from 6.59 to $2.18 \times 10^9/L$ between week 2 and week 8 of treatment. This was repeated at week 12 and returned to normal. The patient had no symptoms and the investigator thought that this spurious result was a lab error or maybe due to an old sample (5 days).

Patient 249 was diagnosed as diabetic after the preliminary examination and treated with an oral hypoglycaemic agent. Relationship: not related.

Patient 304 was also diagnosed as mildly diabetic (glucose = 16.3mmol/L) following the preliminary examination and a diet was recommended.

Patient 305 had elevated renal function tests throughout the study. Relationship: not related.

Many patients also had clinically significant abnormal lipids (total cholesterol and triglycerides) which were only analysed at the preliminary examination visit.

There was a relatively high incidence of elevated chloride values and low bicarbonate values both pre- and post-treatment in both dose groups, although these were not statistically or clinically significant.

8. DISCUSSION

The concept of reducing high blood pressure in elderly patients in order to reduce cardiovascular morbidity and non-fatal cerebrovascular incidents is well documented. This study was designed to compare two dosage regimes of carvedilol in elderly hypertensive patients with special reference to any safety issues that may occur.

This report presents the results of 262 patients who were recruited to take part in the study. 30 patients were not randomised, 114 patients received carvedilol 12.5mg as a starting dose and 118 patients received carvedilol 25mg as a starting dose. The response rates at week 4 for carvedilol 12.5mg and 25mg starting doses were 59% and 69% respectively and at week 12 were 68% and 70% respectively. Results were similar from the per protocol analysis and the differences detected were not statistically significant.

Figures 15 and 16 illustrate the falls in median sitting and standing blood pressure in each group over time. Figures 17 and 18 show median postural blood pressure drop during the study. These figures highlight the lack of statistically significant differences between the two groups. However, the 95% confidence intervals suggest

that carvedilol 25mg may be more effective at four weeks compared to carvedilol 12.5mg although at twelve weeks the confidence intervals could favor either treatment.

There was a significant difference between the two groups in standing systolic blood pressure at week 4, carvedilol 25mg producing a median drop 16mmHg, carvedilol 12.5mg producing a median drop of 9mmHg. Sitting systolic blood pressure showed marginal significance ($p=0.07$). These results again suggest that carvedilol 25mg may be more effective at four weeks compared to carvedilol 12.5mg.

Figures 19 and 20 show median falls in pulse rate during the study which seem to be reduced to a similar extent in each treatment group. Finally Figure 21 illustrates the median body weight during the study with minimal changes in each group although patients randomised to carvedilol 12.5mg tended to be heavier than those randomised to carvedilol 25mg.

Approximately 40% of patients receiving carvedilol 12.5mg compared to 30% of patients receiving carvedilol 25mg, had their dose doubled at week 4. This result was not statistically significant but it does suggest that, clinically, more patients will require a titration of their dose if they are started on carvedilol 12.5mg compared to carvedilol 25mg. Similar numbers of patients were titrated correctly at week 4 which rules out the possibility of any bias within treatment groups.

Safety is a very important issue in this population of patients and adverse events are discussed in detail in the main body of this report. All patients included in the study have been considered in this report. In total, 55% of patients designated to receive carvedilol 12.5mg reported a total of 121 adverse events, and 60% of patients designated to receive carvedilol 25mg reported a total of 145 adverse events. The safety section has been split into two sections a) those adverse events relating to dizziness and/or postural hypotension which is what one might expect from an anti-hypertensive agent with alpha blocking activity, and b) any others. Statistical significance tests were performed only on those adverse events relating to dizziness and/or postural hypotension and no significant difference between the two treatment groups was observed.

However, the difference in the incidence of these adverse events between the two groups may have clinical relevance as it appears that almost one and a half times the number of events were reported by patients randomised to carvedilol 25mg (16%) compared to patients randomised to carvedilol 12.5mg (11%). In many cases, these adverse events were recorded after the first dose or any increase in dose and seem to be related to the first dose. This is true in both treatment groups.

Therefore this trend suggests that a starting dose of carvedilol 12.5mg should reduce the incidence of adverse events related to dizziness and/or postural hypotension to a minimum. Increasing the dose to 25mg increases the incidence of adverse events. However this incidence is no higher than that reported by patients who were initially given carvedilol 25mg. These results are illustrative of more potent alpha blocking activity at higher doses of carvedilol.

The most commonly reported "other" adverse event was fatigue which was suffered by a total of 28 patients. Three patients experienced a cerebrovascular incident, one just two days following the first dose of carvedilol 25mg (relationship: not known), one patient suffered a fatal stroke approximately 9 months after the trial period (not related), and the other patient suffered a mild stroke 16 days after he defaulted from the study (not related). Overall the occurrence of these adverse events appear to be what one might expect from this population of patients.

The majority of patients had abnormal laboratory results during the course of the study although not all of these were clinically significant. The main abnormality which was highlighted at the preliminary examination was a high glucose level usually treated by diet or oral hypoglycaemic agents.

The differences between treatment groups in median changes over 12 weeks with respect to creatinine and urea were statistically significant. These results do not suggest clinical significance. A marginally statistically significant difference in the median changes from baseline in white cell count was also observed although this is not clinically relevant.

In conclusion these results suggest that elderly hypertensive patients should start on 12.5mg once daily. This may be an effective dose in some patients and it is likely that individual patients could be maintained on this dosage. However, dose titration to 25mg, and perhaps 50mg, may be necessary to control the blood pressure in the long term, although it is important to note that exacerbation of some side effects may occur on an increased dose.

9. REFERENCES

1. Heber ME et al. (1987) Carvedilol for systemic hypertension. Am. J. Cardiol., 59, 400-405.
2. European Working Party on High Blood Pressure in the Elderly Trial, Lancet 1985; 1: 1349.



**KREDEX (CARVEDILOL - SKF 105517)
NEW DRUG APPLICATION**

Volume 1.336 of 1129

**ITEM 8
CLINICAL DATA SECTION**

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Protocol: INT-CAR-07	Report: MP/0021/SKF-105517	000002
Comparison of carvedilol with atenolol in the treatment of mild to moderate essential hypertension		

000001

Protocol INT-CAR-07

This was a multicenter, multinational trial conducted in Europe. The purpose was to compare carvedilol and atenolol. The study was blinded with random allocation. An up-titration after 4 weeks was outcome dependent. The primary endpoint was the proportion of responders. Blood pressure data as means in several tables.

There was no evidence of difference between treatments, nor in any of the subgroup analyses performed after the fact.

INT-CAR-07								
n	single blind	n	double blind	n	double blind	n	% response	Δ DBP mm Hg (mean)
	Placebo	161	Carvedilol 25 mg UID	110	carvedilol 25 mg UID	161	35%	- 15
				51	carvedilol 50 mg UID			
		164	Atenolol 50mg UID	114	Atenolol 50mg UID	163	43%	-14
				50	Atenolol 100 mg UID			
	3-6 weeks	325	4 weeks	325	4 weeks	324		

CLINICAL REPORT SUMMARY

PROTOCOL INT-CAR-07: COMPARISON OF CARVEDILOL TO ATENOLOL IN THE TREATMENT OF MILD TO MODERATE ESSENTIAL HYPERTENSION

Investigators: This study was conducted by a total of 38 investigators in seven countries: Belgium, Germany, Italy, The Netherlands, Portugal, Spain, and the United Kingdom.

Objective: This study was designed to compare the safety and antihypertensive efficacy of carvedilol 25 to 50 mg once daily with atenolol 50 to 100 mg once daily in patients with mild to moderate essential hypertension over a period of eight weeks.

Study Design: Patients, at least 18 years of age, with a diagnosis of mild to moderate essential hypertension, defined as a mean sitting diastolic blood pressure of 95-115 mm Hg (disappearance of Korotkoff sound-Phase V) entered a single-blind placebo run-in phase to confirm diagnosis and establish baseline blood pressure. At each visit, blood pressure and heart rate were measured three times, at approximately one-minute intervals, in the sitting position. At the final placebo run-in phase visit and at each visit of the treatment phase, single measurements of immediate standing blood pressure and heart rate were also assessed. Patients qualified to enter the Treatment Phase when the three measurements of sitting diastolic blood pressure at each of 3 consecutive weekly visits satisfied the following conditions: 1) the mean of all 9 measurements was 95-115 mm Hg, 2) the range of the individual measurements was not more than 30 mm Hg, and 3) there was an absence of a placebo response, defined as a continuous fall at each visit, with the decline over the last two visits being more than 4 mm Hg. Patients were then randomized in the treatment phase in a double-blind fashion to receive either 25 mg carvedilol once daily or 50 mg atenolol once daily. Carvedilol therapy was initiated with 12.5 mg once daily for two days. Visits were scheduled after 2, 4 and 8 weeks of treatment, at the time of day corresponding to 22-26 hours after the previous day's dosing. After four weeks of treatment, the dosage of study medication was doubled if adequate response to treatment (mean sitting diastolic blood pressure $\leq$ 90 mm Hg or decreased from the baseline value by at least 10 mm Hg) was not achieved. Baseline vital sign values were the means at the final placebo baseline period visit, just prior to the first dosing with active study medication.

The primary index of efficacy was the reduction of mean sitting diastolic blood pressure to 90 mm Hg or less and/or by at least 10 mm Hg from baseline. Secondary efficacy parameters were mean change in blood pressure and heart rate from baseline and achievement of a normalized blood pressure (mean sitting diastolic blood pressure $\leq$ 90 mm Hg). Safety was evaluated by monitoring for adverse events and by comparing clinical laboratory test results obtained at baseline with those obtained during the treatment period.

Demography: A total of 325 patients (176 males and 149 females; 316 Caucasian and 9 other) received coded medication. The average age of the patients in the study was 53.5 years (range:

Additionally, if a patient required concomitant treatment with any antihypertensive medication, had a known hypersensitivity to carvedilol or atenolol, was known to be a non-responder to or intolerant of carvedilol or atenolol at the dosage levels used in this study, had used an investigational drug within 30 days of entry into this study or 5 half-lives of the investigational drug (the longer period applied) or, in the investigator's opinion, was unsuitable to participate in the study for any other reason, then he/she was to be excluded from the study.

2.2 Study Design

The study was conducted in two phases. There was a single-blind Placebo Baseline Period of three to six weeks. The double-blind Treatment Phase then followed, during which patients were randomized to receive either carvedilol or atenolol for a period of eight weeks. Visits were scheduled after two, four and eight weeks of treatment.

2.3 Materials and Dosage Schedule

A complete description of medication supplies used in this study can be found in Appendix 25. Patients were randomized in blocks of two, within each country (see Appendix 26). Each center within a country was initially allocated a sequentially numbered set of an even number of randomized supplies (e.g., supplies 001 to 020). Some supplies were subsequently redistributed among centers in a given country, in cases of under- or extra-enrollment.

Supplies were dispensed at each visit. During the placebo baseline period, all patients took two tablets once daily, consisting of one placebo matching carvedilol 12.5 mg and one placebo matching atenolol 50 mg.

During the treatment phase patients randomized to carvedilol took one 12.5 mg tablet for two days, then one 25 mg tablet until the Week 4 visit (12.5 mg and 25 mg carvedilol tablets, both active and placebo, were of identical appearance). If an upward titration of the dosage was warranted at the Week 4 visit, patients took two 25 mg carvedilol tablets once daily; if the dose was not increased at the Week 4 visit, patients continued with one 25 mg carvedilol tablet once daily. Each carvedilol regimen was provided with placebo matching 50 mg atenolol which was also doubled, if warranted, at the Week 4 visit. Patients randomized to atenolol took one atenolol 50 mg tablet until the Week 4 visit. If an upward titration of the dosage was warranted at the Week 4 visit, patients took two 50 mg tablets once daily; if the dose was not titrated at the Week 4 visit, patients continued with one tablet once daily. Patients randomized to the atenolol treatment group also received an equivalent number of placebo tablets matching carvedilol once daily. In each treatment group, therefore, patients took two tablets once daily prior to a possible upward titration, and four tablets once daily, if the titration was implemented.

Table 3
Summary of Baseline Characteristics

	Intent-to-Treat Sample		Per-Protocol Sample	
	Carvedilol (n=161)	Atenolol (n=164)	Carvedilol (n=150)	Atenolol (n=146)
Number (%) of Patient				
Age (years):				
18-40	15 (9%)	22 (13%)	15 (10%)	20 (14%)
41-64	122 (76%)	120 (73%)	113 (75%)	105 (72%)
≥ 65	24 (15%)	22 (13%)	22 (15%)	21 (14%)
Gender:				
Female	76 (47%)	73 (45%)	70 (47%)	67 (46%)
Male	85 (53%)	91 (55%)	80 (53%)	79 (54%)
Race:				
Caucasian	157 (98%)	159 (97%)	147 (98%)	142 (97%)
Other	4 (2%)	5 (3%)	3 (2%)	4 (3%)
MSDBP^a (mm Hg):				
< 95	3 (2%)	1 (1%)	0 (0%)	0 (0%)
95 - 105	119 (74%)	115 (70%)	114 (76%)	104 (71%)
106 - 115	39 (24%)	48 (29%)	36 (24%)	42 (29%)
Prior Antihypertensive Treatment:				
Yes	94 (58%)	107 (65%)	88 (58%)	96 (66%)
No	67 (42%)	57 (35%)	62 (41%)	50 (34%)
Mean Value				
Age (years)	53.9	53.1	53.7	52.9
Weight (kg)	76.0	77.0	75.7	76.5
MSDBP ^a (mm Hg)	103	104	104	104
Duration of Hypertension (months)	55.3	51.0	56.0	50.8

^a At the final baseline period visit

Reference Documentation: Tables S.2 - S.5.2.

The distribution of patients according to type of pre-trial antihypertensive medication(s) used by 201 of the 325 patients in the intent-to-treat sample are detailed in Table 4. With the exception of one patient in each treatment group, all patients who had been previously treated with antihypertensive medication(s) were reported as not having been adequately controlled by such treatment.

Table 6
Summary of Efficacy Analysis Results

	Intent-to-Treat Analysis			Per-Protocol Analysis		
	Carvedilol (n=161)	Atenolol (n=163)	p-value ^a	Carvedilol (n=150)	Atenolol (n=146)	p-value ^a
Mean Duration of Treatment (Days)	56	55		52	52	
Mean Sitting Systolic BP (mm Hg):						
Baseline	165	167	0.30	165	167	0.36
Endpoint	146	149		147	150	
Change from Baseline	-19 .	-17 .	0.23	-18 .	-17 .	0.61
Mean Sitting Diastolic BP (mm Hg):						
Baseline	104	104	0.60	104	104	0.98
Endpoint	89	89		89	90	
Change from Baseline	-15 .	-14 .	0.39	-14 .	-14 .	0.81
Mean Sitting Heart Rate (bpm):						
Baseline	76	76	0.68	76	76	0.63
Endpoint	70	68		70	68	
Change from Baseline	-6 .	-8 .	0.13	-6 .	-8 .	0.14
Endpoint Response Rates:						
MSDBP $\leq$ 90 mm Hg	66%	63%	0.49	60%	61%	0.91
MSDBP $\leq$ 90 or $\downarrow$ $\geq$ 10 mm Hg	80%	82%	0.57	75%	82%	0.21
Non-responders at Week 4 (thus requiring dose titration)	34%	33%	1.00	33%	33%	1.00
Response Rates After Titration:	(n=51)	(n=51)		(n=39)	(n=38)	
MSDBP $\leq$ 90 mm Hg	36%	43%	0.54	28%	42%	0.15
MSDBP $\leq$ 90 or $\downarrow$ $\geq$ 10 mm Hg	61%	77%	0.14	51%	71%	0.10

Reference Documentation: Tables S.7, S.16.1, S.16.2, and S.19

^aBetween group comparisons.

. Statistically significant reduction from baseline ($p < 0.05$).

Primary Efficacy Parameter

Response was defined as achieving a normalized MSDBP ($\leq$ 90 mm Hg) and/or demonstrating a reduction from baseline in MSDBP by at least 10 mm Hg. Response rates in the carvedilol and atenolol treatment groups were 75% and 82%, respectively, in the per-protocol analysis of efficacy at endpoint. The difference in response between the two regimens (compared at a power of 0.80 to detect a difference of 15%) was not statistically significant. In the per-protocol analysis at endpoint 74% of the responders in the carvedilol group and 71% of the responders in the atenolol group received the once-daily dosage regimen of 25 mg carvedilol or 50 mg atenolol.

normal being 24 U/L) after 58 days of treatment with carvedilol. This event was not considered to be related to study treatment, and the ALAT level returned to normal (14 U/L) 14 days after the study stop date. Finally, hyperglycemia of mild severity and considered by the investigator to be related to study treatment was reported for Patient 8006. This patient's fasting serum glucose level rose from a baseline of 5.9 mmol/L to 6.5 mmol/L after 15 days of treatment with carvedilol. After 58 days of treatment, the fasting serum glucose returned to baseline (5.57 mmol/L).

5.0 DISCUSSION AND CONCLUSIONS

The results of this study demonstrate that carvedilol (25 mg to 50 mg once daily) is as effective as atenolol (50 to 100 mg once daily) in the control of mild to moderate essential hypertension. Both drugs significantly lowered blood pressure at the endpoint of treatment as compared to baseline. There were no statistically or clinically significant differences between the treatment groups in blood pressure response, either at week 4 of treatment (before the titration step) or at endpoint.

For the primary efficacy parameter, data were included from 296 patients in the per-protocol and 324 in the intent to treat analyses. The primary efficacy index (or "response"), defined as a reduction in MSDBP to 90 mmHg or less, or a reduction from baseline of at least 10 mm Hg, was met in the per-protocol analysis by 75% and 82% of the carvedilol and atenolol treatment groups, respectively. More than two-thirds of these responders to treatment at endpoint (74% in the carvedilol group; 71% in the atenolol group) were treated with 25 mg carvedilol once daily or 50 mg atenolol once daily.

A MSDBP of 90 mm Hg or less was achieved at endpoint in 60% of the carvedilol patients in the per protocol analysis, as compared with 61% of patients in the atenolol group. Of these patients achieving a "normalized" MSDBP, 87% in the carvedilol group and 80% in the atenolol group received the once-daily dosage regimen of 25 mg carvedilol or 50 mg atenolol, respectively.

Among the patients included in the per-protocol analysis, one-third in each treatment group were considered non-responders at the Week 4 treatment visit and had their doses doubled. Of these, 51% of those who received carvedilol and 71% of those who received atenolol were classified as responders after four additional weeks of treatment at the higher dosage level. A sitting diastolic blood pressure of 90 mmHg or less was achieved by 26% of the patients titrated to 50 mg carvedilol, and 42% of the patients titrated to 100 mg atenolol.

Multiple subgroup analyses of response were made. No significant differences in response rates were observed within or between treatment groups for the various subgroups tested, including those within the categories of age, gender, baseline and severity of hypertension. It is noteworthy that elderly patients did not appear to have different dosage requirements in either treatment group.



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Protocol: INT-CAR-08

Report: MP/0020/SKF-105517

000002

Comparison of carvedilol with acebutolol in the treatment of mild to moderate essential hypertension

000001

Protocol INT-CAR-08

This trial involved 13 centers in France. The purpose was to compare carvedilol and acebutolol. The study was blinded with random allocation of subjects in each group. The up-titration after week two was, however, result driven. There was no concurrent placebo control. The primary endpoint was, as in most of the European studies, the proportion of patients 'normalized' in each group. Mean blood pressures in each group are also presented in the tables.

The trial is remarkable in that practically every patient accounted for completed the study. The dropout during the baseline is not ascribed to 'placebo response' but to 'failure to meet entry criteria'. Of the 207 patients who completed the study, 148 met all the provisions in the protocol and provided data for the 'per protocol analysis'.

There is no evidence of significant differences in treatment. Subgroup analyses by sex and age showed no differences.

INT-CAR-08								
n	single blind	n	double blind	n	double blind	n	% response	Δ DBP mm Hg (mean)
217	Placebo	100	Carvedilol 25 mg UID	65	carvedilol 25 mg UID	98	67%	- 13
				35	carvedilol 50 mg UID			
		109	Acebutolol 200 mg BID	86	Acebutolol 200 mg BID	109	75%	
				23	Acebutolol 400 mg BID			
217	2-5 weeks	209	2 weeks	209	6 weeks	207		

CLINICAL REPORT SUMMARY

PROTOCOL INT-CAR-08: COMPARISON OF CARVEDILOL TO ACEBUTOLOL IN THE TREATMENT OF MILD TO MODERATE BENIGN ESSENTIAL HYPERTENSION

Investigators: This study was conducted by a total of 13 centers in France.

Objective: This study was designed to compare the safety and antihypertensive efficacy of carvedilol 25 to 50 mg once daily with acebutolol 200 to 400 mg twice daily in patients with mild to moderate essential hypertension over a period of eight weeks.

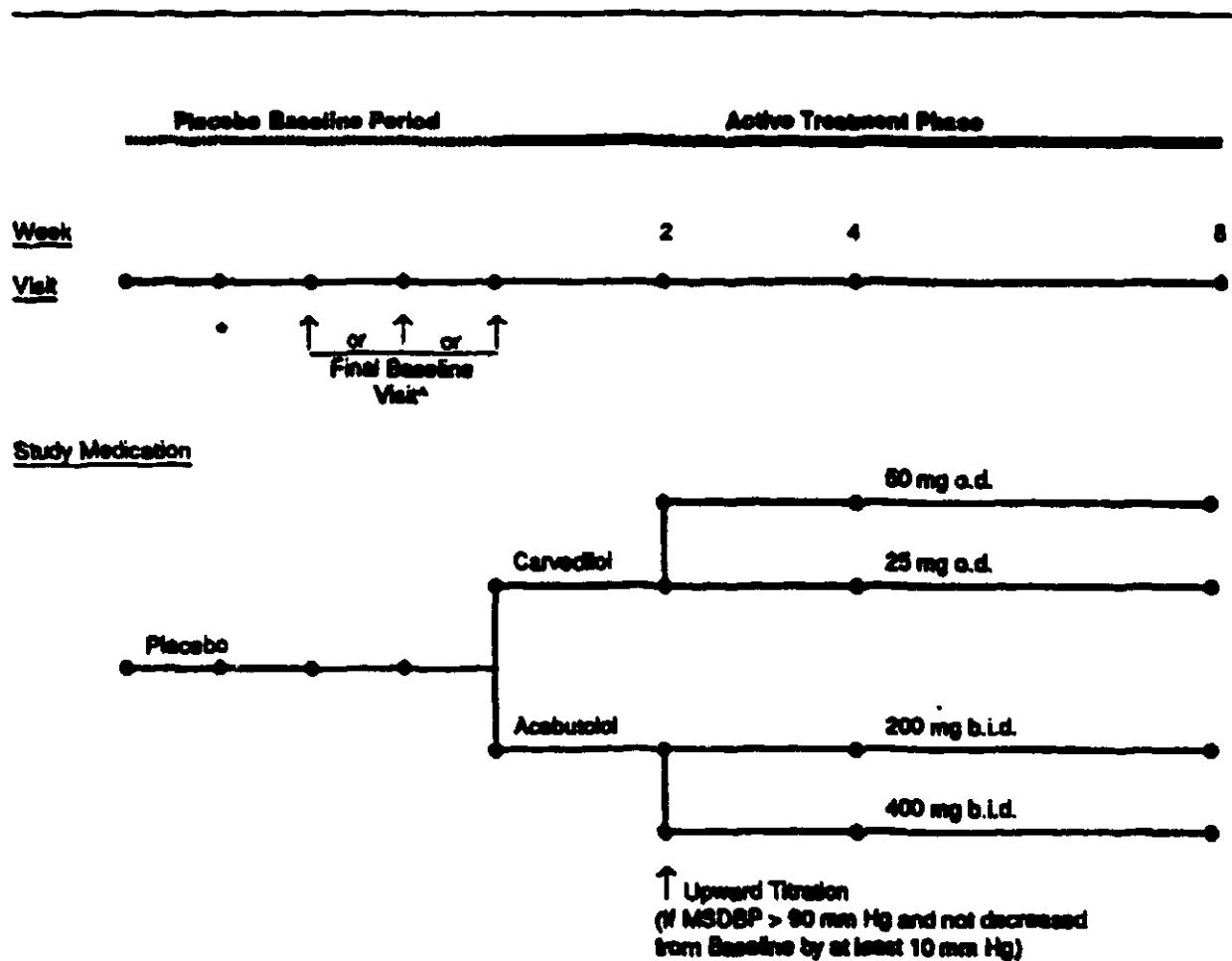
Study Design: Patients, 18 to 70 years of age, with a diagnosis of mild to moderate essential hypertension, defined as a mean supine diastolic blood pressure of 95-115 mm Hg (disappearance of Korotkoff sound-Phase V) entered a single-blind placebo run-in phase to confirm diagnosis and establish baseline blood pressure. At each visit, blood pressure and heart rate were measured three times in the supine position and twice in the standing position. Patients qualified to enter the Treatment Phase when the three measurements of supine diastolic blood pressure at each of two consecutive weekly visits satisfied the following conditions: 1) the mean of the three measurements was 95-115 mm Hg, 2) the range of all six measurements was not more than 30 mm Hg, and 3) there was an absence of a placebo response, defined as a continuous fall in mean supine diastolic pressure at each visit, with the decline over the last two visits being more than 5 mm Hg. Patients were then randomized in the treatment phase in a double-blind fashion to receive either 25 mg carvedilol once daily or 200 mg acebutolol twice daily. Carvedilol therapy was initiated with 12.5 mg for two days. Morning visits were scheduled after 2, 4 and 8 weeks of treatment, at the time of day corresponding to 20 to 24 hours after the previous day's dosing with once-daily study medication, and 10-14 hours after the previous day's dosing with twice-daily medication. After two weeks of treatment, the dosage of study medication was doubled if adequate response to treatment (supine diastolic blood pressure ≤ 90 mm Hg and/or decreased from the baseline value by at least 10 mm Hg) was not achieved. Baseline vital signs were the mean values at the final placebo baseline period visit, just prior to the first dosing with active study medication. The primary index of efficacy was the reduction of mean supine diastolic blood pressure to 90 mm Hg or less and/or by at least 10 mm Hg from baseline. Secondary efficacy parameters were mean blood pressure and heart rate values, mean change in these parameters from baseline and achievement of a normalized blood pressure (mean supine diastolic blood pressure ≤ 90 mm Hg). Safety was evaluated by monitoring for adverse events and by comparing clinical laboratory test results obtained at baseline with those obtained during the treatment period.

Demography: A total of 217 patients (101 males and 116 females; 211 Caucasian and 6 other) received coded medication. The average age of the patients in the study was 53 years (range: 22 to 76 years) and the average body weight was 72.3 kg (range: 43 to 130

2.2 Study Design

The study was conducted in two phases (See Figure 1). There was a single-blind Placebo Baseline Period of two to five weeks, for patients not previously treated for hypertension, or of four to seven weeks, for patients who received pre-trial antihypertensive medication. The double-blind Treatment Phase then followed, during which patients were randomized to receive either carvedilol or acebutolol for a period of eight weeks. Visits were scheduled after two, four and eight weeks of active treatment.

Figure 1: Study Design



*The first baseline visit was scheduled after 3 weeks in patients previously treated with antihypertensive medication, for a total baseline period of 4 to 7 weeks duration, or after 1 week in patients who were not previously treated, for a total baseline period of 2 to 5 weeks duration.

^One or two additional baseline visits could have been scheduled if the blood pressure criteria for entering the active treatment phase were not satisfied at the second or third baseline visit.

Of the patients whose dosage of study medication was increased, the percentage whose MSDBP was normalized at endpoint.

Mean change and mean percent change (from baseline) in vital signs at endpoint.

Subgroup Analyses

While not specifically addressed in the protocol, subgroups of patients in the per-protocol and intent-to-treat sample were compared, both within a given treatment and between the two treatments, with regard to the percentage of patients achieving the primary index of response and the percentage of patients achieving a normalized (≤ 90 mm Hg) MSDBP at endpoint. The subgroupings were based on the following categories: gender, age (≤ 64 , ≥ 65 years old), severity of hypertension (baseline MSDBP 95 to 105 mm Hg, baseline MSDBP 106 to 115 mm Hg), duration of hypertensive condition (≤ 24 months, > 24 months), and prior use of antihypertensive pharmacotherapy (yes, no).

2.8.2 Planned Safety Evaluation

For all patients receiving at least one dose of active treatment, the two treatment groups were compared with regard to the following parameters:

The percentage of patients experiencing one or more adverse event(s) during active treatment, regardless of the investigator-determined relationship to study medication.

The percentage of patients experiencing specific adverse events of clinical interest (events which occurred during active treatment in $\geq 1\%$ of the patients in either treatment group).

The percentage of patients discontinued from the study because of one or more adverse event(s) considered possibly or probably related to active study medication.

Mean change from baseline in select laboratory parameters: liver function tests (ALAT, ASAT, alkaline phosphatase, total bilirubin), renal function tests (creatinine, urea, BUN), uric acid, fasting serum glucose and fasting serum lipids.

Within each treatment group, descriptive statistics for laboratory parameters assessed at baseline, at treatment phase Week 2, at treatment phase Week 8 and at endpoint (if not Week 8) were calculated.

Table 3
Summary of Baseline Characteristics

Number (%) of Patient or Mean Values and Range	Intent-to-Treat Sample		Per-Protocol Sample	
	Carvedilol (n=105)	Acetazolol (n=112)	Carvedilol (n=71)	Acetazolol (n=77)
Age (years):				
18-40	12 (11%)	15 (13%)	6 (8%)	12 (16%)
41-64	80 (76%)	79 (71%)	58 (77%)	51 (66%)
≥ 65	13 (12%)	18 (16%)	10 (14%)	14 (18%)
mean	53	54	54	54
Gender:				
Female	58 (53%)	60 (54%)	44 (62%)	41 (53%)
Male	49 (47%)	52 (46%)	27 (38%)	36 (47%)
Race:				
Caucasian	103 (98%)	108 (96%)	70 (98%)	75 (97%)
Other	2 (2%)	4 (4%)	1 (1%)	2 (3%)
MOSBP^a (mm Hg):				
< 95	0 (0%)	1 (1%)	0 (0%)	1 (1%)
95 - 105	76 (72%)	81 (72%)	53 (75%)	57 (74%)
106 - 115	29 (28%)	30 (27%)	18 (25%)	19 (25%)
mean [range]	102 [90-113]	102 [94-114]	102 [95-113]	102 [94-114]
MSSBP^a (mm Hg):				
mean [range]	167 [129-195]	168 [127-202]	168 [141-195]	168 [127-202]
Mean Duration of Hyper- tension (months):				
	34	47	31	46
Prior Antihypertensive Treatment:				
Yes	49 (47%)	50 (45%)	29 (39%)	33 (43%)
No	56 (53%)	62 (55%)	43 (61%)	44 (57%)
Smoking habits:				
Non-Smoker	79 (75%)	91 (81%)	52 (73%)	65 (84%)
Light Smoker	12 (11%)	14 (13%)	7 (10%)	10 (13%)
Heavy Smoker	14 (13%)	7 (6%)	12 (17%)	2 (3%)
Mean Weight (kg)	71.5	73.2	69.2	73.9

^aAt the final baseline period visit

Reference Documentation: Tables S.2 - S.5.2.

Table 6
Summary of Efficacy Analysis Results

	Intent-to-Treat Analysis		Per-Protocol Analysis	
	Control (n=104)	Active (n=111)	Control (n=71)	Active (n=77)
Mean Duration of Treatment (Days)	57	59	42	47
Mean Supine Systolic BP (mm Hg):				
Baseline	167	168	168	168
Endpoint	146	147	148	148
Change from Baseline	-20	-22	-19	-20
p-value	0.78	0.78	0.91	0.91
Mean Supine Diastolic BP (mm Hg):				
Baseline	102	102	102	102
Endpoint	88	87	90	88
Change from Baseline	-13	-15	-12	-14
p-value	0.18	0.18	0.18	0.18
Mean Supine Heart Rate (bpm):				
Baseline	79	79	79	78
Endpoint	67	67	68	67
Change from Baseline	-12	-11	-12	-11
p-value	0.83	0.83	0.87	0.87
Mean Standing Systolic BP (mm Hg):				
Baseline	167	168	168	168
Endpoint	146	146	147	147
Change from Baseline	-21	-22	-22	-21
p-value	0.80	0.77	0.80	0.80
Mean Standing Diastolic BP (mm Hg):				
Baseline	103	103	102	102
Endpoint	90	88	90	88
Change from Baseline	-13	-15	-12	-14
p-value	0.13	0.13	0.26	0.26
Mean Standing Heart Rate (bpm):				
Baseline	83	82	82	82
Endpoint	70	70	70	70
Change from Baseline	-13	-12	-12	-13
p-value	0.48	0.48	0.78	0.78
Endpoint Response Rates:				
MSDBP $\leq$ 90 mm Hg	87%	75%	84%	85%
MSDBP $\leq$ 90 and/or $\downarrow$ $\geq$ 10 mm Hg	78%	85%	88%	75%
p-value	0.23	0.39	0.18	0.48
Non-responders at Week 2 (thus requiring dose titration [†]):				
(n=87)	46%	(n=104)	34%	(n=87)
(n=76)	0.11	0.17	0.17	0.17
Response Rates After Titration [†] :				
MSDBP $\leq$ 90 mm Hg	(n=31)	(n=21)	(n=19)	(n=12)
MSDBP $\leq$ 90 and/or $\downarrow$ $\geq$ 10 mm Hg	32%	38%	23%	42%
p-value	0.77	1.00	1.00	1.00

Reference Documentation: Tables S.7, S.16.1, S.16.2, and S.18

[†]Between group comparisons.

[‡]Statistically significant reduction from baseline ($p < 0.01$)

[§]Regardless of whether titration was implemented.

[¶]Of the 35 patients in the control group and 23 patients in the escitalopram group whose dosage was doubled, 31 and 21 patients, respectively, completed a Week 8 visit at the dosage level and were included in the intent-to-treat analysis of response after titration. Only 13 and 12 of these patients, respectively, were available for inclusion in the per-protocol analysis at the Week 8 visit.

possibly related to study medication. All parameters returned to normal nine days after the last dose of study medication, which was given for a total of 20 days.

5.0 DISCUSSION AND CONCLUSIONS

The results of this study demonstrate that carvedilol (25 mg to 50 mg once daily) is as effective as acebutolol (200 to 400 mg twice daily) in the control of mild to moderate essential hypertension. Both drugs significantly lowered blood pressure at the endpoint of treatment as compared to baseline. There were no statistically or clinically significant differences between the treatment groups in blood pressure response, either at week 2 of treatment (before the titration step) or at endpoint.

For the primary efficacy parameter, data were included from 148 patients in the per-protocol and 215 in the intent to treat analyses. The primary index of efficacy or "response", defined as a reduction at endpoint in MSDBP to 90 mm Hg or less and/or a reduction in MSDBP from baseline of at least 10 mm Hg, was met in the per-protocol analysis by 66% and 73%, and in the intent-to-treat analysis by 78% and 83% of the carvedilol and acebutolol treatment groups, respectively. More than two-thirds of the responders at endpoint in each treatment group were treated with 25 mg carvedilol once daily or 200 mg acebutolol twice daily, respectively.

A MSDBP of 90 mm Hg or less was achieved at endpoint in 54% of the carvedilol patients in the per protocol analysis, as compared with 65% of patients in the acebutolol group. In the intent-to-treat analysis, the incidence of this "normalization" of diastolic blood pressure was 67% and 75% in the carvedilol and acebutolol groups, respectively. More than 85% of the patients in each treatment group who achieved a MSDBP of 90 mm Hg or less received the initial dosage level of 25 mg carvedilol once daily or 200 mg acebutolol twice daily, respectively.

In the per-protocol analysis, 31 of 67 patients (46%) in the carvedilol group and 27 of 76 patients (34%) in the acebutolol group were considered non-responders at the Week 2 treatment visit. Among these patients whose dosage of study medication was increased and who were included in the per-protocol analysis at the Week 8 visit, six of 13 patients (46%) in the carvedilol group and six of 12 patients (50%) in the acebutolol group were responders after six additional weeks of treatment at the higher dosage level. A normalized MSDBP was achieved by three patients (23%) treated with 50 mg carvedilol once daily and by five patients (42%) treated with 400 mg acebutolol twice daily.

Multiple subgroup analyses of response were made. No significant differences in response rates were observed within or between treatment groups for the various subgroups tested, including those within the categories of age, gender, baseline and severity of hypertension.

SB **SmithKline Beecham**
Pharmaceuticals

KREDEX (CARVEDILOL - SKF 105517)
NEW DRUG APPLICATION

Volume 1.343 of 1129

ITEM 8
CLINICAL DATA SECTION

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Protocol INT-CAR-10

In this multicenter trial in UK the primary endpoint was the proportion of patients who achieved a sitting DBP $\leq$ 90 mm Hg. Median values at baselines and the different scheduled visits are also presented. The study was blinded and randomized and had a placebo baseline observation but no concurrent placebo arm in the active treatment phase. The purpose of this study was to compare carvedilol 25 mg once daily with nifedipine 20 mg bid. After 2 weeks of double blind treatment, patients with an inadequate response could have their dose doubled.

Of 272 patients who entered the trial 171 made it to the end, and of these 138 were eligible by protocol standards. There was no significant difference between the treatments.

INT-CAR-10								
n	single blind	n	double blind	n	double blind	n	% response	Δ DBP mm Hg (median)
272	Placebo	103	Carvedilol 25 mg UID	-80	carvedilol 25 mg UID	86	64%	-16
				-20	carvedilol 50 mg UID			
		102	Nifedipine 20 mg BID	-80	Nifedipine 20 mg BID	85	82%	-16
				-20	Nifedipine 40 mg BID			
272	3-6 weeks	205	2 weeks	189	6 weeks	171		

RESULTS

1. Number of Patients

Two hundred and seventy two patients were recruited to take part in the study. Sixty seven patients were withdrawn before the start of active therapy. The 58 patients who received placebo medication were withdrawn by the investigators for the following reasons: adverse events (7), default (9), non-compliance (2), underlying condition (3) (myaesthemia gravis, carcinoma lung, elevated LFTs), diastolic blood pressure below level for inclusion (25), mean diastolic above 115 mmHg (5), patient taking prohibited medication 'Frumil' (1), domestic or administrative reason (2), withdrawal of consent (1), unknown (CRFs not received) (3).

A total of 32 investigators recruited patients to the study. (Table 1). This report presents data on 205 patients for whom records are available who were randomised to receive either carvedilol or nifedipine in the active treatment phase of the study. The safety section of the report will also consider data on placebo baseline phase patients who dropped out before receiving active medication.

Statistical analyses utilise data from all patients for whom results were available at a given point on an "intention to treat" basis; however "per protocol" analyses exclude data (individual visits or all data for a given patient, as appropriate) for reasons of protocol violation (Table 2).

The Mann Whitney U test was used to compare treatment group medians of efficacy parameters and laboratory values. Chi Squared tests were used to analyse parameters expressed as counts of patients (e.g. numbers of smokers, numbers of patients whose dose was increased, numbers fulfilling the primary efficacy criterion, etc). All changes or differences described as statistically significant in this report are significant at least at the 5 percent level.

Int-Car-10

Recruited - 272 Patients

67 **Withdrawn before active treatment**

205 Randomized

103 Carvedilol

102 Nifedipine

Week 2

84

85

**Total = 169
Intent-to-treat**

**19-Dose 2X (20%)
[3 T who responded]
[5 not T who should have been]**

**20-Dose 2X (20%)
[1 T who responded]
[5 not T who should have been]**

**Total = 168
per protocol**

Week 8 Intent-to-treat

86 68/86 = 79% response

85 77/85 = 91% response **Total = 171**

Per Protocol-

72 **A. 59/72=82% response
B. 49/72=68% response**

66 **A. 60/66=91% response
B. 54/66=82% response**

Total=138

**A. = ↓ BP to 90 or ↓ of 10
B. = ↓ BP to 90**

000010

000010

SUMMARY

Results are presented for 205 patients with mild to moderate essential hypertension who were randomised to receive either a once daily dose of carvedilol 25 mg or nifedipine 20 mg bd in a double blind study, following washout of existing antihypertensive medication and a 3-6 week placebo baseline period to confirm diagnosis. Duration of active treatment was 8 weeks and after 2 weeks the dose of either medication could be doubled according to response. The population comprised 63 males and 40 females, median age 59 years, range 30-82 years in the carvedilol group and 55 males and 47 females, median age 59 years, range 26-79 years in the nifedipine group. Losses occurred due to patient withdrawal, and, for "per-protocol" analyses, due to protocol violations, which are discussed in this report. There were no significant differences between the two groups with respect to demographic factors at entry or baseline efficacy assessments with the exception of end of baseline postural change in systolic blood pressure. Baseline sitting blood pressures were 168/102 mmHg for carvedilol and 167.5/102 mmHg for nifedipine and immediate standing blood pressures were 164/102 mmHg and 170/102 mmHg respectively, among 198 patients eligible per protocol analyses. (Korotkoff phase V readings).

There were no statistically significant differences between groups in changes in vital signs during the 2 hours following the first dose of active medication, except for immediate standing heart rate where the median decrease was greater in the carvedilol group. Confidence intervals revealed that this difference (max 3 b/min) was unlikely to be clinically important, however. Effects in the sub-population who were 65 years of age or under showed statistically significant differences between treatments for immediate standing and sitting diastolic blood pressure, with greater falls in the nifedipine group. Again, confidence intervals revealed maximum likely differences of only 5 mmHg. The over 65 years subgroup showed effects during the first 2 hours similar to those observed in the population as a whole. However, a greater median systolic blood pressure postural change occurred in the nifedipine group. The difference between treatments was statistically significant.

000007

At treatment week 2 there were statistically significant differences between groups for sitting and standing heart rate, together with the respective changes from baseline (the latter were no more than 5 b/min different between groups as indicated by confidence intervals with greater changes occurring with carvedilol) and change from baseline in systolic postural drop (maximum 4 mmHg as indicated by confidence intervals with greater changes occurring for nifedipine). Similar statistically significant differences between treatments occurred at treatment week 8. Additionally, although not achieving statistical significance changes from baseline in standing systolic blood pressure at week 8 were greater in the nifedipine group (confidence intervals: 0.10%). Median decreases of blood pressure from baseline were, at week 2, -14/-13 mmHg sitting for each group, -12.5/-12 mmHg standing for carvedilol and -17/-12 mmHg standing for nifedipine. At week 8 median decreases were -20/-16 mmHg sitting and standing for carvedilol, -21/-16 mmHg sitting and -24/-16 mmHg standing for nifedipine. Median heart rate decreases were -3 b/min sitting and standing for carvedilol, -1 b/min sitting and standing for nifedipine at week 2, while at week 8 decreases were -4 b/min sitting, -6 b/min standing for carvedilol and -1 b/min sitting, -2 b/min standing for nifedipine. At treatment week 2 approximately 20% patients in each treatment group had their dose doubled because of insufficient therapeutic response.

Seventy nine percent of carvedilol patients and 91% of nifedipine patients in the intention to treat analysis had a reduction of sitting diastolic pressure to 90 mmHg or below or a reduction of 10 mmHg or more after 8 weeks' treatment, a result which was statistically significant. The per-protocol analysis did not achieve statistical significance (82% carvedilol, 91% nifedipine) although a possible difference favouring nifedipine was indicated by the confidence intervals (-20%, 2%). Sixty four percent of carvedilol patients and 82% of nifedipine patients in the intention to treat analysis and 68% and 82%, respectively, in the per protocol analysis had diastolic pressures of 90 mmHg or below at week 8.

Both provided evidence of a difference favouring nifedipine ($p=0.01$ and 0.06 , respectively).

There were differences in the safety profiles of the two drugs, with 55 events reported by 31 patients taking carvedilol, 11 of whom were withdrawn and 60 events reported by 35 patients taking nifedipine, 18 of whom were withdrawn. Dizziness, tiredness and headaches were reported with both drugs, the incidence of dizziness being slightly greater with carvedilol. However, flushing occurred in 9 patients on nifedipine and ankle or peripheral oedema in 8 patients on this drug, with no reports of these symptoms in carvedilol patients. Most commonly contributing to patient withdrawal were dizziness and tiredness in carvedilol patients and flushing and oedema in nifedipine patients. One carvedilol patient experienced syncope after 6 weeks in the study but recovered fully within 24 hours of hospital admission. Seven patients were withdrawn from the placebo baseline period because of adverse events. Laboratory studies revealed no consistent trends or differences between treatments with the exception of a tendency of nifedipine patients to show increases in platelet counts and serum alkaline phosphatase with higher week 8 values and a tendency for carvedilol patients to show increases in uric acid while nifedipine patients showed decreases in uric acid. There were several isolated abnormalities in most parameters for individual patients, the more noteworthy of which are detailed in this report.

DISCUSSION

The results of the present study indicate that both carvedilol (25mg to 50mg od) and nifedipine (20mg bd to 40 mg bd) are effective in lowering blood pressure in mild to moderate hypertensive patients over an eight week treatment period from receipt of the first dose of active medication. With the exception of systolic blood pressure in the nifedipine group neither drug produced a noteworthy postural fall in blood pressure. Both drugs also reduced heart rate, but, as would be expected with a β -blocking drug, these were more marked with carvedilol. Figures 1 and 2 illustrate the falls in median values of blood pressure in each group over time, while Figure 3 illustrates the changes in heart rate over time.

The patient numbers used in this study were sufficient to detect statistical significance for very small differences between treatments and, in most analyses, any true differences of clinical importance would also have attained statistical significance.

The purpose of aiming for a population of 200 patients was so that a 15 percent difference between groups for response according to the primary efficacy parameter could be detected at 5% significance and 80% power. A 15% difference between treatments was judged to be clinically important where the response rate for one of the groups was between 80-90%. The primary efficacy parameter is based upon proportions of patients with a given response and is in essence a summary of clinical efficacy parameters. Because of this there is a reduction in sensitivity when compared to analyses of values of efficacy parameters. The primary efficacy parameter utilises data from 138 patients in the per-protocol analysis and 171 in the intention to treat analyses. The primary efficacy parameter shows response rates of 82% and 79% for carvedilol, respectively for the two analyses and 91% for nifedipine for each analysis. This response rate is

marginally lower than has been shown for carvedilol previously (84% in INT CARO7 (UK), 86% in INTCAR11) and somewhat higher than would have been expected for nifedipine. However, it is notable that there was no statistically significant difference between treatments in change from baseline for diastolic blood pressure (Table 17); nor was there a significant difference between treatments for baseline or week 8 blood pressures (Tables 8 and 16).

As with previous studies in which high proportions of patients fulfilled primary efficacy criteria, an alternative criterion (reduction of sitting diastolic pressure to 90mmHg or below, i.e. normotensive levels) was also considered. As expected the proportions of patients fulfilling this criterion were reduced in both treatment groups. Sixty eight percent of carvedilol patients and 82% of nifedipine patients in the per protocol analysis and 64% of carvedilol patients and 82% of nifedipine patients in the intention-to-treat analysis were thereby judged to be responders. These represent differences in response of 14% and 18% respectively (confidence intervals: -28%, 0% per protocol; -31%, -5% intention-to-treat).

Approximately 20% patients in each dosage group required a dosage increase after 2 weeks treatment. For the carvedilol group these proportions did not change when patients were subgrouped by age at entry. In the nifedipine group a smaller proportion of patients over the age of 65 years (16%) required titration compared with 20% in the group overall; however patient numbers in this subgroup were small, such that one additional patient requiring titration would have eliminated this difference.

During the 2 hours following the first dose of active medication the only statistically significant difference between treatments was in change in standing heart rates, with carvedilol, as expected, having more marked, but probably

clinically irrelevant effects. When results were examined by age-subgroup some differences between treatments for blood pressure were observed. Greater falls in sitting and standing diastolic blood pressure occurred in the nifedipine group, although confidence intervals indicate that the magnitude of these differences do not constitute a clinically relevant effect.

In the older age subgroup a statistically significant difference in pre-to-post changes in systolic blood pressure postural drop was found between treatments, greater changes being observed in nifedipine patients, although again confidence intervals indicate that this difference was within 5 percent of pre-dose levels. Median sitting systolic blood pressure was lower on carvedilol than on nifedipine in this sub-group. Median reductions over the two hours were -7/-4 mmHg sitting -10/-4 mmHg standing for carvedilol and -8/-6 mmHg sitting, -10/-8 mmHg standing for nifedipine in the younger age group, compared with -8/-4 mmHg sitting, -4.5/-3.5 mmHg standing for carvedilol and -2.5/-2.0 mmHg sitting, -3.5/-2.0 mmHg standing for nifedipine in the more elderly population. Thus in this study the more elderly population appeared no more susceptible to marked blood pressure reduction following the first dose compared to their younger counterparts. The carvedilol patient who was withdrawn mid-study following syncope was 58 years of age, although 5 other patients aged 56, 67, 69, 76 and 82 years experienced a sensation of faintness or dizziness between 2 days and 4 weeks after the start of active medication which contributed to eventual withdrawal. Five patients on nifedipine complained of giddiness/dizziness or light-headedness which contributed to withdrawal. In two cases (patients aged 61 and 37 years) this was associated with the first dose of active medication and in the other 3 (aged 59, 67 and 69 years) onset of symptoms was between 1 day and 2 weeks after starting active medication.

There were some noteworthy differences in the adverse event profiles of the two drugs, which were typical of their respective drug class. There was a slightly higher incidence of adverse events in patients on nifedipine overall. Flushing and oedema occurred only in this group and contributed to patient withdrawal in a number of cases. However dizziness and tiredness were the events most frequently associated with patient withdrawal in the carvedilol group. Both treatments were associated with reports of headaches, tiredness and dizziness, although the latter was reported with a slightly higher frequency in the carvedilol group. There were a number of reports in each treatment group of symptoms which might be associated with reduced general physical performance (e.g. 2 reports of lethargy, 1 of somnolence, 1 of fatigue and 4 of tiredness in the carvedilol group, and 2 reports of drowsiness, 1 of fatigue and 4 of tiredness in the nifedipine group.) Overall there were higher incidences of adverse events and withdrawals during active treatment with either drug and during placebo baseline therapy than would have been expected from experience with previous studies.

There were many individual patients' laboratory parameters outside normal range but there did not appear to be any significant trends for either treatment other than a tendency of nifedipine patients to show increases in platelet counts and serum alkaline phosphatase with higher 8 week values. These findings are of dubious clinical relevance. However, there was also a tendency for carvedilol patients to show increases in uric acid while nifedipine patients tended to show decreases in this parameter. This contrasts with findings in a previous study (INTCARII) in which decreases of uric acid in carvedilol patients were observed.

In this study population, both carvedilol and nifedipine were highly effective antihypertensive agents. The per protocol analysis did not show statistically significant differences between treatments in response rate or in changes in blood pressure from baseline, although the intention-to-treat analysis showed a significant difference in response rate favouring nifedipine after 8 weeks' treatment. The number of withdrawals for adverse events indicates that carvedilol at the doses employed may be better tolerated than nifedipine.

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All investigators listed in Table 1 of this report for
co-operation and recruitment of patients to the study.

Table 3

DEMOGRAPHIC DATA AT PRELIMINARY EXAMINATION

All randomised patients (N=205)

VARIABLE		CARVEDILOL	NIFEDIPINE	OVERALL	MEDIAN DIFFERENCE	95% C.I.		P-VALUE
						LOWER	UPPER	
DIASTOLIC IMMEDIATE	MEDIAN	104.0	105.0	104.0	-1.0	-2.0	0.0	0.13
	MAX							
	MIN							
	N	102.0	101.0	203.0				
SYSTOLIC IMMEDIATE	MEDIAN	170.0	170.0	170.0	-2.0	-6.0	2.0	0.40
	MAX							
	MIN							
	N	102.0	101.0	203.0				
DIASTOLIC SITTING	MEDIAN	102.0	103.0	102.0	0.0	-1.0	1.0	0.50
	MAX							
	MIN							
	N	103.0	102.0	205.0				
SYSTOLIC SITTING	MEDIAN	170.0	170.0	170.0	-1.0	-6.0	3.0	0.51
	MAX							
	MIN							
	N	103.0	102.0	205.0				
DIASTOLIC POSTURAL	MEDIAN	0.0	1.0	0.0	-1.0	-2.0	0.0	0.10
	MAX							
	MIN							
	N	102.0	101.0	203.0				
SYSTOLIC POSTURAL	MEDIAN	0.0	1.0	0.0	-1.0	-2.0	1.0	0.45
	MAX							
	MIN							
	N	102.0	101.0	203.0				
PULSE IMMEDIATE	MEDIAN	76.0	76.0	76.0	0.0	-2.0	2.0	0.88
	MAX							
	MIN							
	N	90.0	93.0	191.0				
PULSE SITTING	MEDIAN	76.0	76.0	76.0	1.0	-1.0	2.0	0.23
	MAX							
	MIN							
	N	103.0	102.0	205.0				

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Table 17

WEEK 8 ELIGIBLE PATIENTS (N=138)
ANALYSIS OF CHANGES WEEK 8 - WEEK 0

VARIABLE		CARVEDILOL	NIFEDIPINE	OVERALL	MEDIAN DIFFERENCE	95% C.I.		P-VALUE
						LOWER	UPPER	
DIASTOLIC IMMEDIATE	MEDIAN	-16.0	-16.0	-16.0	2.0	-2.0	5.0	0.27
	MAX							
	MIN							
	N	71.0	66.0	137.0				
SYSTOLIC IMMEDIATE	MEDIAN	-20.0	-24.0	-20.0	3.0	0.0	10.0	0.06
	MAX							
	MIN							
	N	71.0	66.0	137.0				
DIASTOLIC SITTING	MEDIAN	-16.0	-16.0	-16.0	1.0	-2.0	4.0	0.55
	MAX							
	MIN							
	N	72.0	66.0	138.0				
SYSTOLIC SITTING	MEDIAN	-20.0	-21.0	-20.0	1.0	-3.0	7.0	0.56
	MAX							
	MIN							
	N	72.0	66.0	138.0				
DIASTOLIC POSTURAL	MEDIAN	0.0	0.0	0.0	0.0	-1.0	2.0	0.57
	MAX							
	MIN							
	N	71.0	66.0	137.0				
SYSTOLIC POSTURAL	MEDIAN	0.0	-2.0	-1.0	3.0	1.0	5.0	0.00
	MAX							
	MIN							
	N	71.0	66.0	137.0				
PULSE IMMEDIATE	MEDIAN	-4.0	-2.0	-4.0	-4.0	-6.0	-2.0	0.00
	MAX							
	MIN							
	N	70.0	65.0	135.0				
PULSE SITTING	MEDIAN	-4.0	-1.0	-3.0	-4.0	-6.0	-2.0	0.00
	MAX							
	MIN							
	N	72.0	66.0	138.0				
WEIGHT	MEDIAN	0.0	0.0	0.0	0.0	0.0	1.0	0.04
	MAX							
	MIN							
	N	68.0	66.0	134.0				

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Protocol INT-CAR-11

This multicenter study in UK compared carvedilol 25 or 50 mg/day with HCTZ 25 or 50 mg/day. Titration to the higher dose after 4 weeks was result driven.

The study was randomized, double blinded in the active treatment phase, and while it had a single blinded placebo baseline observation, there was no concurrent placebo arm in the active treatment phase. Of 235 patients recruited, 200 continued to the double blind phase; 190 were included in the intent to treat analysis, 179 met all protocol criteria. The study could not find any difference between the two drugs. The data are presented as a median response with confidence limits. The actual analysis was based on a comparison of the proportion of 'responders' in each group.

INT-CAR-11								
n	single blind	n	double blind	n	double blind	n	% response	Δ DBP mm Hg (median)
235	Placebo	100	Carvedilol 25 mg UID	62	carvedilol 25 mg UID	93	85%	- 18
				32	carvedilol 50 mg UID			
		100	HCTZ 25 mg UID	67	HCTZ 25 mg UID	97	88%	
				30	HCTZ 50 mg UID			
235	3-6 weeks	200	4 weeks	191	4 weeks	190		

SUMMARY

Results are presented for 200 patients with mild to moderate essential hypertension who were randomised to receive either carvedilol 25 mg or hydrochlorothiazide 25 mg in a double blind study, following washout of existing antihypertensive medication and a 3-6 week placebo baseline period to confirm diagnosis. Duration of active treatment was 8 weeks and after 4 weeks the dose of either medication could be doubled according to response. The population comprised 49 males and 51 females, median age 59 years, range 34-88 years in the carvedilol group and 50 males and 44 females, median age 59 years, range 27-83 years in the hydrochlorothiazide group. Losses occurred due to patient withdrawal, and for "per-protocol" analyses, due to protocol violations which are discussed in this report. There were no significant differences between the two groups with respect to demographic factors at entry or baseline efficacy assessments. Baseline sitting blood pressures were 169/105 for carvedilol and 168.5/103 for hydrochlorothiazide (HCTZ) and immediate standing blood pressures were 166/102 in both groups. (Korotkoff phase V readings).

There were statistically significant falls in blood pressure and heart rate measurements in both treatment groups during the 2 hours following the first dose of active medication, which were greater in the carvedilol group and statistically significantly different from HCTZ at the 5% level or less. Effects in the sub-population who were over 65 years of age appeared to contribute substantially to the differences between carvedilol and HCTZ, but resulted in quite small median differences between treatments of changes over time in the population as a whole (0-5 mm Hg systolic, 0-2 mm Hg diastolic, 0-2 b/min heart rate, from 95% confidence intervals) and there was no evidence for significantly different changes in postural blood pressure drop.

There were no significant differences ($p > 0.05$) between treatments with respect to median blood pressures (sitting or immediate standing) at weeks 4 and 8 of treatment but there were greater

Patient Withdrawals

Thirty four of the 235 recruited to the study were withdrawn during the placebo baseline period. Eleven of the patients who received active medication were withdrawn prior to the end of the study. Five were withdrawn due to adverse events, four in the carvedilol group and one in the hydrochlorothiazide group.

Demography

No significant differences between the groups in respect of age, height, weight, sex, initial blood pressures, previous hypertensive treatment, or drinking habits. This was true for both statistical analyses.

Effect on Sitting Diastolic Blood Pressure

Good response was defined as a sitting diastolic blood pressure to below 90 mmHg or a decrease of at least 10 mmHg.

PERCENTAGE RESPONDERS

	<u>CARVEDILOL GROUP</u>	<u>HYDROCHLOROTHIAZIDE GROUP</u>
WEEK 4	*67.8	*69.6
WEEK 8	*85	*88

* No statistically significant difference between treatments.

Statistically significant falls in blood pressure (both diastolic and systolic) occurred in both groups, in both sitting and standing positions over the eight week period of treatment. Median changes for each group are shown below:

Antinuclear Antibodies

No trends occurred in the positivity rates of either group.

DISCUSSION

The results of this study show that carvedilol 25 mg and 50 mg once daily is as effective as hydrochlorothiazide 25 mg and 50 mg in the control of mild to moderate essential hypertension.

The response rate as determined by the primary efficacy parameter was 85% in the carvedilol group and 87.6% in the hydrochlorothiazide group at week 8, a non-significant difference at the 5% level.

This surprisingly high response rate led to a second statistical analysis utilizing a revised efficacy parameter. This new definition of efficacy was a diastolic blood pressure of less than 90 mmHg at week 8.

The response rates using this parameter were 69% for the carvedilol group and 74.1% for the hydrochlorothiazide group, again a non-significant difference at the 5% level.

Approximately one third of patients required an increase in dose after four weeks treatment, this was true of both treatment groups and was not affected by age of patient. 25% of each group was over 65 years and this did not appear to affect dosage requirements.

This study shows that over the 2 hours following the first dose of either preparation there were significant falls in blood pressure and heart rate measurements, sitting and standing. These changes were statistically significantly different between the groups, with greater changes for the carvedilol group than for the hydrochlorothiazide group as would be expected with a drug with vasodilatory properties. However, these reflect quite small differences between the treatment groups overall.

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Table 3

All Randomised Patients
Demographic data at Preliminary Examination

	Treatment Group		Level of Significance
	Carvedilol	ACEZ	
# of patients	100	100	
Sex			
Female	51(51%)	44(44%)	0.37
Male	49(49%)	56(56%)	
Recent Hypertensive Treatment			
No	55(55%)	46(46%)	0.20
Yes	45(45%)	54(54%)	
Drinking Habit			
No	46(46%)	42(42%)	0.57
Yes	54(54%)	58(58%)	
Smoking Habit			
High	10(10%)	17(17%)	0.09
Low	10(10%)	9(9%)	
None	72(72%)	74(74%)	

Comparison of Treatment Groups

	Treatment Group		Median Difference	95% C.I. for Difference		Level of Significance
	Carvedilol	ACEZ		Lower	Upper	
Age at Entry (yrs)						
Median	59	59	0	-3	4	0.80
Min						
Max						
N	100	100				
Height (cms)						
Median	168	168	-1	-3	1	0.40
Min						
Max						
N	100	100				
Weight (kgs)						
Median	71	71	1	-2	4	0.62
Min						
Max						
N	100	100				

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Table 4

Patients used for Intention to Treat Analyses
Demographic data at Preliminary Examination

# of patients	Treatment Group		Level of Significance
	Carvedilol	HCTZ	
	100	100	
Sex			
Female	48(52%)	43(44%)	0.32
Male	45(48%)	54(56%)	
Recent Hypertensive Treatment			
No	50(54%)	43(44%)	0.19
Yes	43(46%)	54(56%)	
Drinking Habit			
No	41(44%)	41(42%)	0.80
Yes	52(56%)	56(58%)	
Smoking Habit			
High	10(11%)	17(18%)	0.08
Low	18(19%)	9(9%)	
None	65(70%)	71(73%)	

Comparison of Treatment Groups

	Treatment Group		Median Difference	95% C.I. For Difference		Level of Significance
	Carvedilol	HCTZ		Lower	Upper	
Age at Entry (yrs)						
Median	59	59	0	-3	3	0.99
Max						
Min						
N	93	97				
Height (cms)						
Median	168	168	-1	-3	1	0.40
Max						
Min						
N	93	97				
Weight (kgs)						
Median	71	71	1	-2	5	0.47
Max						
Min						
N	93	97				

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Table 6

ALL PATIENTS RANDOMISED TO ACTIVE THERAPY (N=200)
 CLINICAL EFFICACY DATA
 FINAL PLACEBO BASELINE PERIOD VISIT

VARIABLE		CARVEDILOL	INCTZ	OVERALL	MEDIAN DIFFERENCE	95% LOWER	C.I. UPPER	P-VALUE
SYSTOLIC SITTING	MEDIAN	169.0	168.5	169.0	1.0	-3.0	5.0	0.47
	MAX							
	MIN							
	N	100.0	100.0	200.0				
DIASTOLIC SITTING	MEDIAN	105.0	103.0	104.0	1.0	0.0	2.0	0.22
	MAX							
	MIN							
	N	100.0	100.0	200.0				
SYSTOLIC IMMEDIATE	MEDIAN	166.0	166.0	166.0	2.0	-2.0	6.0	0.28
	MAX							
	MIN							
	N	100.0	100.0	200.0				
DIASTOLIC IMMEDIATE	MEDIAN	102.0	102.0	102.0	0.0	0.0	2.0	0.45
	MAX							
	MIN							
	N	100.0	100.0	200.0				
SYSTOLIC POSTURAL	MEDIAN	-2.0	-3.0	-3.0	1.0	0.0	2.0	0.13
	MAX							
	MIN							
	N	100.0	100.0	200.0				
DIASTOLIC POSTURAL	MEDIAN	-1.0	-1.0	-1.0	0.0	-1.0	0.0	0.57
	MAX							
	MIN							
	N	100.0	100.0	200.0				
PULSE SITTING	MEDIAN	77.0	77.0	77.0	0.0	-2.0	2.0	0.97
	MAX							
	MIN							
	N	100.0	100.0	200.0				
PULSE IMMEDIATE	MEDIAN	77.0	78.0	78.0	0.0	-2.0	2.0	0.87
	MAX							
	MIN							
	N	100.0	99.0	199.0				
WEIGHT	MEDIAN	71.0	71.0	71.0	0.0	-3.0	4.0	0.76
	MAX							
	MIN							
	N	100.0	98.0	198.0				

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Table 17

PATIENTS ELIGIBLE FOR ANALYSIS AT WEEK 8 OF THE TREATMENT PHASE (N=179)
 CLINICAL EFFICACY DATA
 WEEK 8 VALUES

VARIABLE		CARVEDILOL	MCT2	OVERALL	MEDIAN DIFFERENCE	95% C.I. LOWER	95% C.I. UPPER	P-VALUE
SYSTOLIC SITTING	MEDIAN	149.0	148.0	149.0	1.0	-3.0	6.0	0.59
	MAX							
	MIN							
	N	87.0	92.0	179.0				
DIASTOLIC SITTING	MEDIAN	87.0	87.0	87.0	0.0	-2.0	2.0	0.80
	MAX							
	MIN							
	N	87.0	92.0	179.0				
SYSTOLIC IMMEDIATE	MEDIAN	148.0	144.0	146.0	2.0	-2.0	0.0	0.30
	MAX							
	MIN							
	N	87.0	92.0	179.0				
DIASTOLIC IMMEDIATE	MEDIAN	86.0	86.0	86.0	0.0	-2.0	2.0	0.86
	MAX							
	MIN							
	N	87.0	92.0	179.0				
SYSTOLIC POSTURAL	MEDIAN	-2.0	-2.0	-2.0	0.0	-1.0	2.0	0.60
	MAX							
	MIN							
	N	87.0	92.0	179.0				
DIASTOLIC POSTURAL	MEDIAN	-1.0	-1.0	-1.0	0.0	-1.0	0.0	0.42
	MAX							
	MIN							
	N	87.0	92.0	179.0				
PULSE SITTING	MEDIAN	71.0	74.0	72.0	-2.0	-4.0	-1.0	0.00
	MAX							
	MIN							
	N	87.0	92.0	179.0				
PULSE IMMEDIATE	MEDIAN	72.0	74.0	74.0	-2.0	-4.0	0.0	0.01
	MAX							
	MIN							
	N	87.0	91.0	178.0				
WEIGHT	MEDIAN	71.0	70.5	71.0	2.0	-2.0	5.0	0.33
	MAX							
	MIN							
	N	87.0	92.0	179.0				

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**KREDEX (CARVEDILOL - SKF 105517)
NEW DRUG APPLICATION**

Volume 1344 of 1129

**ITEM 8
CLINICAL DATA SECTION**

Volume Table of Contents

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Volume 1 of 6

Protocol: INT-CAR-12	Report: MP/0019/SKF-105517	000002
Comparison of carvedilol with captopril in the treatment of mild to moderate essential hypertension		

000001

Protocol INT-CAR-12

In this multicenter, multinational (Belgium, France, Holland, Italy, Portugal, Spain and West Germany) study the assignment to medication was random and blinded but the up titration was result driven and obvious to both investigator and patient.

The study leaves the impression of being a marketing tool, or a safety evaluation, rather than an efficacy investigation.

The primary endpoint was 'response' rate but values for mean differences from baseline are also given. The two treatment appeared identical in efficacy.

INT-CAR-12						
- n	single blind	n	double blind	n	double blind	Δ DBP mm Hg
298 ?	Placebo	147	Carvedilol 25 mg UID	141	carvedilol 25 mg UID	- 16
					carvedilol 50 mg UID	
		151	Captopril 25 mg BID	142	Captopril 25 mg BID	-13
					Captopril 50 mg BID	
	3 weeks	298	2 weeks	283	6 weeks	

CLINICAL REPORT SUMMARY

PROTOCOL INT-CAR-12: COMPARISON OF CARVEDILOL TO CAPTOPRIL IN THE TREATMENT OF MILD TO MODERATE BENIGN HYPERTENSION

Investigators: This study was conducted by a total of 30 investigators in seven countries: Belgium, France, Germany, Italy, The Netherlands, Portugal, and Spain.

Objective: This study was designed to compare the safety and antihypertensive efficacy of carvedilol 25 to 50 mg once daily with captopril 25 to 50 mg twice daily in patients with mild to moderate essential hypertension over a period of eight weeks.

Study Design: Patients, at least 18 years of age, with a diagnosis of mild to moderate essential hypertension, defined as a mean sitting diastolic blood pressure of 95-115 mm Hg (disappearance of Korotkoff sound-Phase V) entered a single-blind placebo run-in phase to confirm diagnosis and establish baseline blood pressure. At each visit, blood pressure and heart rate were measured three times, at approximately one minute intervals, in the sitting position. Patients qualified to enter the Treatment Phase when the three measurements of sitting diastolic blood pressure at each of 3 consecutive weekly visits satisfied the following conditions: 1) the mean of all 9 measurements was 95-115 mm Hg, 2) the range of the individual measurements was not more than 30 mm Hg, and 3) there was an absence of a placebo response, defined as a continuous fall at each visit, with the decline over the last two visits being more than 4 mm Hg. Patients were then randomized in the treatment phase in a double-blind fashion to receive either 25 mg carvedilol once daily or 25 mg captopril twice daily. Carvedilol therapy was initiated with 12.5 mg once daily for two days. Visits were scheduled after 2, 4 and 8 weeks of treatment, at the time of day corresponding to 22-26 hours after the previous day's dosing with once-daily study medication 10-14 hours after the last dosing with twice-daily study medication. After two weeks of treatment, the dosage of study medication was doubled if adequate response to treatment (mean sitting diastolic blood pressure $\leq$ 90 mm Hg or decreased from the baseline value by at least 10 mm Hg) was not achieved. Baseline vital sign values were the means at the final placebo baseline period visit, just prior to the first dosing with active study medication.

The primary index of efficacy was the reduction of mean sitting diastolic blood pressure to 90 mm Hg or less and/or by at least 10 mm Hg from baseline. Secondary efficacy parameters were mean change in blood pressure and heart rate from baseline and achievement of a normalized blood pressure (mean sitting diastolic blood pressure $\leq$ 90 mm Hg). Safety was evaluated by monitoring for adverse events and by comparing clinical laboratory test results obtained at baseline with those obtained during the treatment period.

Demography: A total of 298 patients (140 males and 158 females; 295 Caucasian and 3 other) received coded medication. The average age of the patients in the study was 52.6 years (range:

weight, and race distributions of the patients assigned to the carvedilol (147 patients) and captopril (151 patients) treatment groups revealed no important differences in demographic characteristics.

Prior and Concomitant Medications: All antihypertensive medications were discontinued at least two weeks prior to the start of the placebo run-in phase and were not permitted for the remainder of the study. The use of any other investigational drug was not permitted during the study.

Withdrawals from Study: Of 298 patients who received coded medication, 96% (141 of 147) of the patients who received carvedilol and 94% (142 of 151) of the patients who received captopril completed the eight-week study. Two patients (1%) who received carvedilol and four patients (3%) who received captopril were withdrawn because of clinical events. Of the remaining discontinuations from the carvedilol group, one patient was discontinued for insufficient therapeutic effect, two requested withdrawal and one failed to return. In the captopril group, the discontinuations which were not due to adverse events were three cases of patients who failed to return, and two cases of failing to meet eligibility criteria.

Efficacy Results: Response was defined as achieving at endpoint a normalized mean sitting diastolic blood pressure (≤ 90 mm Hg) and/or demonstrating a reduction from baseline in mean sitting diastolic blood pressure by at least 10 mm Hg. Response rates in the carvedilol and captopril treatment groups were 72% and 65%, respectively, in the per-protocol analysis of efficacy at endpoint. The intent-to-treat analysis of efficacy demonstrated similar response at endpoint, with rates of 79% in the carvedilol group and 70% in the captopril group. The difference in achieving response between the two regimens was not statistically significant. Subgroup analyses, however, indicated a greater proportion of responders with carvedilol, as compared to captopril, in elderly patients (age ≥ 65 years) and in patients with mild hypertension (baseline diastolic pressure of 95-125 mm Hg).

A normalized mean sitting diastolic blood pressure was achieved at endpoint in 56% of the carvedilol patients in the per-protocol analysis, as compared with 50% of the patients in the captopril group. In the intent-to-treat analysis, the incidence of achieving a normalized sitting diastolic blood pressure was 66% in the carvedilol group and 60% in the captopril group. The difference in achieving a normalized pressure between the two regimens was not statistically significant.

Two-thirds or more of the responders to treatment at endpoint, as well as of the patients who achieved a normalized pressure at endpoint, received either 25 mg carvedilol once daily or 25 mg captopril twice daily.

In the per-protocol analysis, 52 of 120 patients (43%) in the carvedilol group and 59 of 129 patients (46%) in the captopril group were considered non-responders at the Week 2 treatment visit. Among these patients whose dosage of study medication was increased, and who were

included in the per-protocol analysis at the Week 8 visit, 23 of 39 patients (59%) in the carvedilol group and 22 of 40 patients (55%) in the captopril group were responders after six additional weeks of treatment at the higher dosage level. A normalized sitting diastolic blood pressure was achieved by 18 of the 39 patients (46%) treated with 50 mg carvedilol once daily and by 17 of the 40 patients (43%) treated with 50 mg captopril twice daily. Differences between regimens with regard to responder rate or incidence of achieving a normalized pressure after upward titration were not statistically significant.

In the per-protocol analysis, mean sitting blood pressure was significantly reduced ($p < 0.05$) in the carvedilol group from 164/104 mm Hg at baseline to 150/90 mm Hg at endpoint; mean change from baseline was -15/-14 mm Hg. In the captopril group, mean sitting blood pressure was significantly reduced ($p < 0.05$) from 165/103 mm Hg to 149/92 mm Hg; mean change from baseline was -15/-11 mm Hg. Mean change at endpoint in sitting heart rate was -7 beats/minute in the carvedilol group, representing a significant ($p < 0.05$) reduction from baseline, and -1 beat/minute in the captopril group. Intent-to-treat results for all parameters were similar to those in the per-protocol analysis. The analysis of mean change in blood pressure indicated no statistically significant difference between treatments in the per-protocol sample. There was, however, a statistically significant ($p < 0.01$) greater mean decrease in heart rate with carvedilol as compared with captopril.

SAFETY: No deaths occurred during or within 30 days after completion of the study. Eight patients in the study were reported as having an adverse event which met the definition of serious (two in the carvedilol group, five in the captopril group, and one never receiving active study medication). One of the serious events in the carvedilol group and two in the captopril group were considered at least possibly related to treatment. Twenty-four percent (36 of 147) of patients who received carvedilol reported clinical events compared to 26% (39 of 151) of patients who received captopril. The most commonly reported adverse events (i.e., those occurring in greater than 2% of the patients in either treatment group) which were considered by the investigator to be related to study medication were headache, dizziness/vertigo and gastrointestinal events in the carvedilol group and headache and dizziness/vertigo in the captopril group. There was no statistically significant difference between treatments with regard to the overall incidence of adverse events. Laboratory studies were unremarkable in each treatment group. This study supports the safe use of oral carvedilol in patients with mild to moderate hypertension.

CONCLUSIONS: In patients with mild to moderate hypertension, both carvedilol and captopril significantly lowered mean sitting diastolic blood pressure after eight weeks of treatment in this study. At endpoint, there was no statistically significant difference between the two treatment groups with regard to the degree of reduction in blood pressure or the percentage of patients achieving a reduction in mean sitting diastolic blood pressure to 90 mm Hg or less and/or by at least 10 mm Hg. Subgroup analyses, however, suggested some trends toward an increased response with carvedilol. Both carvedilol and captopril were well-tolerated in this study.

Table 3
Summary of Baseline Characteristics

	Intent-to-Treat Sample		Per-Protocol Sample	
	Carvedilol (n=147)	Captopril (n=151)	Carvedilol (n=120)	Captopril (n=129)
Number (%) of Patients				
Age (years):				
18-40	20 (14%)	27 (18%)	17 (14%)	23 (18%)
41-64	109 (74%)	102 (67%)	87 (73%)	91 (70%)
≥ 65	18 (12%)	22 (15%)	16 (13%)	15 (12%)
Gender:				
Female	78 (53%)	80 (53%)	65 (54%)	70 (54%)
Male	69 (47%)	71 (47%)	55 (46%)	59 (46%)
Race:				
Caucasian	144 (98%)	151 (100%)	118 (98%)	129 (100%)
Other	3 (2%)	0 (0%)	2 (2%)	0 (0%)
MSDBP^a (mm Hg):				
< 95	0 (0%)	2 (1%)	0 (0%)	0 (0%)
95 - 105	98 (66%)	107 (71%)	81 (68%)	94 (73%)
106 - 115	47 (32%)	42 (28%)	39 (32%)	35 (27%)
>115	4 (3%)	0 (0%)	0 (0%)	0 (0%)
Prior Antihypertensive Treatment:				
Yes	91 (62%)	88 (57%)	78 (65%)	73 (57%)
No	56 (38%)	63 (43%)	42 (35%)	56 (43%)
Mean Value				
Age (years)	53	52	52	51
Weight (kg)	78	77	77	77
MSDBP ^a (mm Hg)	103	103	103	103
Duration of Hypertension (months)	71	82	78	66

^aAt the first baseline period visit

^bAt the preliminary examination visit

Reference Documentation: Tables S.2 - S.5.2.

The distribution of patients according to type of pre-trial antihypertensive medication(s) used by 177 of the 298 patients in the intent-to-treat sample are detailed in Table 4. With the exception of

Table 6
Summary of Efficacy Analysis Results

	Intent-to-Treat Analysis			Per-Protocol Analysis		
	Carvedilol (n=148)	Captopril (n=150)	p-value*	Carvedilol (n=120)	Captopril (n=129)	p-value*
Mean Duration of Treatment (Days)	57	56		50	48	
Mean Sitting Systolic BP (mm Hg):						
Baseline	188	188	0.81	184	185	0.87
Endpoint	149	149		150	149	
Change from Baseline	-17 .	-17 .	0.99	-15 .	-15 .	0.40
Mean Sitting Diastolic BP (mm Hg):						
Baseline	105	103	0.05	104	103	0.87
Endpoint	89	90		90	92	
Change from Baseline	-18 .	-13 .	0.09	-14 .	-11 .	0.31
Mean Sitting Heart Rate (bpm):						
Baseline	77	78	0.24	77	78	0.40
Endpoint	70	78		70	77	
Change from Baseline	-7 .	-1	<0.001	-7 .	-1	<0.01
Endpoint Response Rates:						
MSDBP $\leq$ 90 mm Hg	68%	60%	0.34	68%	60%	0.37
MSDBP $\leq$ 90 or $\downarrow$ $\geq$ 10 mm Hg	79%	70%	0.11	72%	65%	0.28
Non-responders at Week 2 (thus requiring dose titration)	40%	44%	0.55	43%	46%	0.39
Response Rates After Titration:	(n=58)	(n=56)		(n=38)	(n=40)	
MSDBP $\leq$ 90 mm Hg	55%	45%	0.35	48%	43%	0.82
MSDBP $\leq$ 90 or $\downarrow$ $\geq$ 10 mm Hg	71%	67%	0.17	68%	65%	0.82

Reference Documentation: Tables S.7, S.16.1, S.16.2, and S.19

*Between group comparisons.

*Statistically significant reduction from baseline ($p < 0.05$).

Primary Efficacy Parameter

Response was defined as achieving a normalized MSDBP ($\leq$ 90 mm Hg) and/or demonstrating a reduction from baseline in MSDBP by at least 10 mm Hg. Response rates in the carvedilol and captopril treatment groups were 72% and 65%, respectively, in the per-protocol analysis of efficacy at endpoint. The difference in response between the two regimens (compared at a power of 0.80 to detect a difference of 15%) was not statistically significant. In the per-protocol analysis at endpoint 63% of the responders in each of the carvedilol and captopril treatment

5.0 DISCUSSION AND CONCLUSIONS

The results of this study demonstrate that carvedilol 25 mg to 50 mg once daily is as effective as captopril 25 to 50 twice daily in the control of mild to moderate essential hypertension. Both drugs significantly lowered blood pressure at the endpoint of treatment as compared to baseline. There were no statistically or clinically significant differences between the treatment groups in blood pressure response, either at week 2 of treatment (before the titration step) or at endpoint.

For the primary efficacy parameter, data were included from 249 patients in the per-protocol and 298 in the intent-to-treat analyses. The primary efficacy index (or "response"), defined as a reduction in MSDBP to 90 mm Hg or less, and/or a reduction from baseline of at least 10 mm Hg, was met in the per-protocol analysis by 72% and 65%, and in the intent-to-treat analysis by 79% and 70% of the carvedilol and captopril treatment groups, respectively. Two-thirds of the responders at endpoint in each treatment group were treated with 25 mg carvedilol once daily or 25 mg captopril twice daily.

A MSDBP of 90 mm Hg or less was achieved at endpoint in 56% of the carvedilol patients in the per-protocol analysis, as compared with 50% of patients in the captopril group. Of these patients achieving at endpoint a "normalized" MSDBP, 70% in each of the carvedilol and captopril groups achieved this level of blood pressure control while receiving the initial dosage level of 25 mg carvedilol once daily or 25 mg captopril twice daily, respectively.

Among the patients included in the per-protocol analysis, 43% in the carvedilol group and 46% in the captopril group were considered non-responders to treatment at the Week 2 visit and had their doses doubled. Of these, 59% of those who received carvedilol and 55% of those who received captopril were classified as responders after six additional weeks of treatment at the higher dosage level. A sitting diastolic blood pressure of 90 mm Hg or less was achieved by 46% of the patients titrated to 50 mg carvedilol once daily, and 43% of the patients titrated to 50 mg captopril twice daily.

Multiple subgroup analyses of response were made which suggested some indication of regimen by response association within specific subgroups. While many of these associations are weak, some trends are noteworthy. In the intent-to-treat sample, a greater proportion of elderly patients were responders to treatment ($p=0.08$) with carvedilol (69%) as compared with captopril (64%). Similarly, the incidence of response in mild hypertensives (MSDBP of 95 to 105) was greater with carvedilol (69%) as compared with captopril (69%, $p=0.08$).

The effect of carvedilol and captopril on heart rate was also assessed. Both the per-protocol and intent-to-treat analyses showed a statistically significant ($p < 0.01$) greater mean decrease in heart rate of 6 beats/minute with carvedilol as compared to captopril. The decrease in heart rate observed in patients treated with carvedilol is reflective of carvedilol beta-blocking activity.

No deaths occurred during or within 30 days after completion of the study. Eight patients in the study were reported as having an adverse event which met the definition of serious (two in the carvedilol group, five in the captopril group, and one never receiving medication). One of the events in the carvedilol group and two in the captopril group were considered at least possibly related to treatment. Twenty-five percent of patients in each group were reported as having clinical events, regardless of attribution to study drug. One and three patients in the carvedilol and captopril groups, respectively, were withdrawn from the study because of adverse events considered by the investigator to be related to treatment. The adverse event profiles were similar in the two treatment groups. With regard to severity of events and their relationship to treatment, there were no notable differences in the patterns between the two groups. Related adverse events reported most commonly (i.e., in at least 2% of the patients receiving either treatment) were headache, dizziness/vertigo and gastrointestinal events in the carvedilol group and headache and dizziness/vertigo in the captopril group.

Adverse events typical of those which also were observed during active therapy were reported during the placebo run in phase in approximately 10% of patients, so that the incidences occurring on carvedilol and captopril treatment should be viewed in the context of this relatively high background incidence. Many individual patients had laboratory parameters outside normal ranges, but there did not appear to be any significant trends in either group. The differences in the adverse event profiles of the two drugs used in this study are likely related to their individual pharmacological actions. The results suggest that the most commonly reported clinical events for carvedilol are associated with vasodilation, one of its two primary pharmacologic effects.

In conclusion, carvedilol once daily demonstrated in this study similar reductions in blood pressure as captopril twice daily, with some trends toward improved efficacy with carvedilol in certain populations. These results strongly support the antihypertensive efficacy of carvedilol administered in a once daily regimen. Furthermore, of the patients who responded to treatment, the majority achieved this response while receiving the initial dosage of 25 mg carvedilol once daily or 25 mg captopril twice daily. In addition, although the safety profiles of carvedilol and captopril were generally comparable, the observed trend toward improvement in patient tolerability with carvedilol, as evidenced by the lower discontinuation rates, indicates that carvedilol should be an important addition to the list of preferred antihypertensive treatments.

SMITHKLINE BEECHAM PHARMACEUTICALS

**SK&F 105517
Protocol MF3460**

**A MULTICENTER DOUBLE-BLIND, CONTROLLED, RANDOMIZED STUDY
COMPARING THE ANTIHYPERTENSIVE EFFICACY AND LONG-TERM SAFETY
OF CARVEDILOL WITH THAT OF PINDOLOL IN AMBULATORY PATIENTS
WITH MILD TO MODERATE ESSENTIAL UNCOMPLICATED HYPERTENSION**

By

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**SK&F Report No.:Mc/0090/105517
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Protocol MF3460

This trial involved 44 centers in Germany, Austria, Belgium and Holland. The data from 6 centers were discarded for efficacy purposes due to sloppy practices at the centers. The protocol is rather involved but has considerable value from a safety point of view in that the trial lasted a whole year. There was a single blind placebo baseline period but no placebo arm during the blinded portions of the trial. After 4 weeks the dose could be doubled; after 8 weeks the investigator might during the year add or withhold HCTZ to the regimen as they saw fit. The different permutations are presented in the analysis.

The changes from baseline in sitting diastolic Blood Pressure are larger than those seen in most other studies. The results after 8 weeks were all but identical to those after 1 year, although a large fraction received added HCTZ. It should be noted that both the up-titration after 4 weeks and the HCTZ addition were not random but result driven. One would expect, then, that those with the poorest response were pushed to maximum therapy.

Protocol MF3460										
n	Single blind (phase A)	n	Double blind (phase B)	n	Double blind (phase C)	Double blind (phase C)	n (completed)	n (endpoint)	ΔDBP mmHg	
?	502	?	264	Carvedilol 25 mg BID	135	Carvedilol 25 mg BID	Carvedilol 25 mg BID	92	104	-16
						Carvedilol + HCTZ	29	31	-8	
					110	Carvedilol 50 mg BID	Carvedilol 50 mg BID	28	39	-16
							Carvedilol + HCTZ	63	71	-10
			132	Pindolol 7.5 mg BID	69	Pindolol 7.5 mg BID	Pindolol 7.5 mg BID	45	56	-16
							Pindolol + HCTZ	11	13	-8
					59	Pindolol 15 mg BID	Pindolol 15 mg BID	15	18	-12
							Pindolol + HCTZ	31	41	-11
	2- 4 weeks	396	4 weeks	373	4 weeks	44 weeks	314	373		

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**Table 10: Effect of Titration on Peak MSDBP Among
Patients Continuing to Phase C
According to Medication Regimen and Dose:
Per Protocol and Basic Intent-to-Treat Analyses
(Appendix 8.2.20.1)**

	<u>PER PROTOCOL</u>		<u>BASIC INTENT-TO-TREAT</u>			
	<u>CARVEDILOL</u>	<u>PINDOLOL</u>	<u>CARVEDILOL</u>	<u>PINDOLOL</u>	<u>CARVEDILOL</u>	<u>PINDOLOL</u>
ACCORDING TO TREATMENT GROUP						
Baseline MSDBP — Visit 5 Predose (mm Hg)						
n	139	75	245		128	
Mean (SE)	101 (0.3)	102 (0.6)	102 (0.3)		102 (0.4)	
Peak Observations Visit 5: Change from Baseline (mm Hg)						
n	137	75	242		128	
Mean change (SE)	-10 (0.6)	-12 (0.8)	-10 (0.5)		-10 (0.6)	
ACCORDING TO DOSE						
Baseline Observations: Visit 5 Predose (mm Hg)						
— Not titrated at Visit 7						
n	70	39	135		69	
Mean (SE)	100 (0.3)	100 (0.6)	100 (0.4)		101 (0.5)	
— Titrated at Visit 7						
n	69	36	110		59	
Mean (SE)	103 (0.5)	104 (0.9)	104 (0.4)		103 (0.7)	
Visit 5 Peak Observations: Change from Baseline (mm Hg)						
— Not titrated at Visit 7						
n	69	39	133		69	
Mean change (SE)	-12 (0.8)	-13 (1.3)	-12 (0.6)		-11 (1.0)	
— Titrated at Visit 7						
n	68	36	109		59	
Mean change (SE)	-8 (0.8)	-10 (0.9)	-9 (0.7)		-10 (0.7)	
Visit 7 Predose Observations: Change from Baseline (mm Hg)						
— Not titrated at Visit 7						
n	66	37	135		69	
Mean change (SE)	-16 (0.6)	-17 (0.9)	-15 (0.5)		-15 (0.7)	
— Titrated at Visit 7						
n	68	36	110		59	
Mean change (SE)	-5 (0.6)	-6 (1.1)	-5 (0.6)		-4 (1.0)	
Visit 7 Peak Observations: Change from Baseline (mm Hg)						
— Not titrated at Visit 7						
n	56	29	122		51	
Mean change (SE)	-19 (0.7)	-20 (1.2)	-19 (0.6)		-19 (0.9)	
— Titrated at Visit 7						
n	68	36	110		59	
Mean change (SE)	-13 (1.0)	-13 (1.1)	-13 (0.8)		-11 (1.0)	

* Patients who were not titrated received either carvedilol 25 mg twice daily or pindolol 7.5 mg twice daily, and patients who were titrated received either carvedilol 50 mg twice daily or pindolol 15 mg twice daily.

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Protocol MFC460

Table 12: Change from Baseline MSDBP According to Maintenance Regimen for Patients Continuing into Phase C at Phase B Endpoint, Visit 8, One-Year and Phase C Endpoint: Per Protocol and Basic Intent-to-Treat Analyses (Table S-4; Appendixes 8.2.33, 8.2.34, 8.2.34.1)

	PER PROTOCOL						BASIC INTENT-TO-TREAT					
	CARVEDILOL			PINDOLOL			CARVEDILOL			PINDOLOL		
Baseline MSDBP (mm Hg)	n	Mean	(SE)	n	Mean	(SE)	n	Mean	(SE)	n	Mean	(SE)
Not titrated,												
monotherapy	59	99	(0.3)	35	100	(0.6)	104	100	(0.3)	56	100	(0.5)
+ HCTZ	11	100	(1.2)	4	103	(1.4)	31	102	(1.1)	13	102	(1.1)
Titrated,												
monotherapy	19	103	(1.2)	8	103	(2.4)	39	103	(0.8)	18	102	(1.3)
+ HCTZ	50	103	(0.5)	28	105	(1.0)	71	104	(0.5)	41	104	(0.9)
<u>Reduction in MSDBP: Change from Baseline (mm Hg)</u>												
Phase B endpoint*												
Not titrated,												
monotherapy	59	-16	(0.7)	35	-16	(0.9)	104	-16	(0.5)	56	-15	(0.7)
+ HCTZ	11	-16	(1.6)	4	-20	(1.4)	31	-14	(1.3)	13	-15	(2.7)
Titrated,												
monotherapy	19	-7	(1.1)	8	-12	(3.3)	39	-7	(0.9)	18	-6	(2.4)
+ HCTZ	50	-4	(0.7)	28	-5	(0.9)	71	-4	(0.7)	41	-3	(0.9)
Visit 8 Pre-dose (mm Hg)^b												
Not titrated,												
monotherapy	55	-17	(0.7)	32	-17	(1.1)	99	-17	(0.5)	54	-17	(0.9)
+ HCTZ	10	-11	(2.3)	1	-8	(...)	31	-11	(1.2)	13	-7	(1.5)
Titrated,												
monotherapy	14	-16	(1.6)	6	-20	(4.3)	38	-16	(1.2)	18	-12	(2.6)
+ HCTZ	40	-8	(1.1)	25	-9	(1.3)	71	-8	(0.9)	41	-7	(1.0)
One-Year (Visit 16)												
Not titrated,												
monotherapy	30	-20	(1.2)	17	-19	(1.9)	92	-16	(0.8)	45	-16	(1.1)
+ HCTZ	3	-18	(1.8)	1	-16	(...)	29	-8	(2.0)	11	-8	(1.6)
Titrated,												
monotherapy	3	-18	(2.7)	1	-8	(...)	28	-16	(1.3)	15	-12	(1.7)
+ HCTZ	30	-12	(1.2)	14	-12	(1.4)	63	-10	(1.2)	31	-11	(1.2)
Phase C endpoint												
Not titrated,												
monotherapy	59	-17	(0.9)	35	-17	(1.1)	104	-16	(0.7)	56	-16	(1.0)
+ HCTZ	11	-13	(2.4)	4	-16	(0.9)	31	-8	(1.9)	13	-8	(2.1)
Titrated,												
monotherapy	19	-17	(1.6)	8	-20	(3.3)	39	-15	(1.3)	18	-11	(2.3)
+ HCTZ	50	-11	(1.0)	28	-11	(1.3)	71	-9	(1.4)	41	-9	(1.2)

* Maintenance regimens were the following: Not titrated, monotherapy: carvedilol 25 mg or pindolol 7.5 mg twice daily; or, Not titrated + HCTZ: carvedilol 25 mg twice daily with HCTZ 25 mg once daily or pindolol 7.5 mg twice daily with HCTZ 25 mg once daily; Titrated, monotherapy: carvedilol 50 mg or pindolol 15 mg twice daily; Titrated + HCTZ: carvedilol 50 mg twice daily with HCTZ 25 mg once daily or pindolol 15 mg twice daily with HCTZ 25 mg once daily.

^a Patients were titrated at the end of Phase B (Visit 7).

^b HCTZ could be added at Visit 8 or any later visit.

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(31081), for whom the first finding was observed on Day 26, had experienced an adverse experience of precordial pressure on Day 14. The precordial pressure was considered by the investigator to be mild and possibly related to study medication; it cleared after 7 days with no treatment and no change in study medication. The patient continued on carvedilol therapy and completed the study after a total of 371 days with no other reports of precordial pressure or other related adverse experiences.

5.0 DISCUSSION AND CONCLUSIONS

Totals of 337 and 165 patients with mild to moderate hypertension were randomized to carvedilol and pindolol, respectively, at 44 centers in West Germany, Austria, Belgium, and Holland. Of these, data from 70 patients randomized to carvedilol and 33 patients randomized to pindolol at six centers were completely excluded from the *per protocol* analysis of efficacy and were analyzed separately in a *limited intent-to-treat* analysis (carvedilol, 65 patients; pindolol, 31 patients) because of questions regarding the conduct of study at the six centers. Efficacy results were comparable between the *basic intent-to-treat* and *per protocol* analyses.

The results of this study are consistent with those reported in an earlier open study in which carvedilol 25 mg twice daily was administered for one year.³⁵ In that study, 55.8% (86/154) of the patients completed the one-year treatment period. In the present study, 63.2% (213/337) of patients randomized to carvedilol and 61.8% (102/165) of patients randomized to pindolol completed the one-year treatment period (*full sample*).

In the same one-year open study of carvedilol 25 mg twice daily, the median sitting BP was decreased from 170/105 mm Hg to 145/90 mm Hg. At baseline in the present study, mean sitting BP was 160/102 mm Hg for 264 patients randomized to carvedilol and 159/102 mm Hg for 132 patients randomized to pindolol. After four weeks (Phase B endpoint), mean sitting BP (trough values) was reduced to 147/91 mm Hg for 263 patients who had received carvedilol 25 mg twice daily and to 146/92 mm Hg for 132 patients who had received pindolol 7.5 mg twice daily (*basic intent-to-treat* analysis).

In the present study, blood pressure response at the end of the four-week treatment phase (Phase B) was comparable between carvedilol and pindolol according to both the *per protocol* and *basic intent-to-treat* analyses of efficacy; mean changes from baseline for carvedilol 25 mg twice daily and pindolol

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adverse experiences that occurred while the patient was taking active study medication.

Dizziness was the most common on-therapy adverse experience reported for both treatment groups: 6.8% (23/337) of carvedilol patients and 10.3% (17/165) of pindolol patients. Bronchitis was reported for 6.8% (23/337) of carvedilol patients and for 5.5% (9/165) of pindolol patients. Hyperuricemia was reported for a similar percentage of both treatment groups, 5.3% (18/337) of carvedilol patients and 5.5% (9/165) of pindolol patients.

Differences between treatment groups were observed for the following adverse experiences reported for more than 5% of patients in one or both groups (*Fisher's exact test*):

- *back pain* 5.9% (20/337) of carvedilol patients (vs. 1.2%, 2/165, of pindolol patients; $p=0.018$)
- *increased sweating* 6.1% (10/165) of pindolol patients (vs. 0.9, 3/337, of carvedilol patients; $p=0.0018$).

Laboratory data were examined by comparing the number and percentage of patients with values of sponsor-defined concern at baseline to those on- and 1-day post-therapy. Results showed no consistent increase in the numbers or percentages of patients with values of concern relative to time on drug and there was no consistent difference between monotherapy versus combination therapy or between patients titrated versus patients not titrated.

In the earlier one-year open study of carvedilol,³⁵ lipid data were evaluated for 86 patients, and no effect was observed for serum triglycerides, total cholesterol, LDL cholesterol, or HDL cholesterol. In this study, the data suggest that both carvedilol and pindolol cause similar increases in serum triglycerides, with median percent change from baseline of 10.1% at endpoint. After one year, the median percent increases were also similar between groups: 11.7% for carvedilol and 13.9% for pindolol ($p=0.8051$, *Wilcoxon rank sum*, between groups).

Such changes are not believed to represent a clinically significant effect on coronary heart disease (CHD) risk, since similar changes were reported after one year of treatment with cholestyramine and mean percent increases of approximately 20% were observed after seven years of treatment with cholestyramine in the Lipid Research Clinics Primary Prevention Trial.^{36,37} In that same trial, mean percent increases in serum triglycerides of



**KREDEX (CARVEDILOL - SKF 105517)
NEW DRUG APPLICATION**

Volume 1.410 of 1129

**ITEM 8
CLINICAL DATA SECTION**

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Volume 1 of 2

Protocol: MF 3461

Report: MC 009 BS

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**A multicenter, double-blind, randomized, controlled study comparing
the efficacy and safety of carvedilol and pindolol in ambulatory patients
with mild to moderate essential uncomplicated hypertension (O21)**

000001

Protocol MF 3461

This multicenter study in Germany and Belgium compared once a day doses of Carvedilol up to 100 mg/day with pindolol 15 mg/day in patients with mild/moderate essential hypertension. The study was blinded and randomized but did not involve placebo control.

n	baseline (single blind)	n	Double blind	n	results, supine DBP Δ mmHg from baseline
	Placebo		25 mg carvedilol UID	39	-15.1 $\pm$ 1.24
			50 mg carvedilol UID	40	-16.7 $\pm$ 1.23
			100 mg carvedilol UID	38	-17.8 $\pm$ 1.25
			15 mg Pindolol UID	35	-16.3 $\pm$ 1.30
235	up to 4 weeks	205	13 weeks	152	

Of 235 patients who entered the study, 170 completed. Because of sloppy practices at 4 centers, only 152 patients were included in the analysis. On the face of it, the results seem better than those obtained in the US studies. The lack of placebo control precludes any further conclusions. It appears, however, that in the doses employed here carvedilol and pindolol were equivalent in their effect on blood pressure.

A selection of unedited pages from the report is appended.

OBJECTIVE

To compare the blood pressure lowering effect and the safety and tolerability of three different dosages of carvedilol with that of one dosage of pindolol, both administered once daily, and to characterize the dose-response relationship of carvedilol with respect to blood pressure reduction in patients with mild to moderate essential uncomplicated hypertension.

STUDY DRUG

Carvedilol was provided as 25 mg (batch number, 819156Ec); 50 mg (batch number, 819161Fc); and 100 mg (batch numbers, 819152Aa and 819703Aa) capsules. Placebo (batch numbers, 816349Ab and 819166Cb) and pindolol 15 mg (batch number 819187Eb) were provided as capsules identical in appearance to those containing carvedilol. Study medications were supplied by BOEHLINGER MANNHEIM GmbH, D-6800 Mannheim 31, Federal Republic of Germany.

MATERIALS AND METHODS

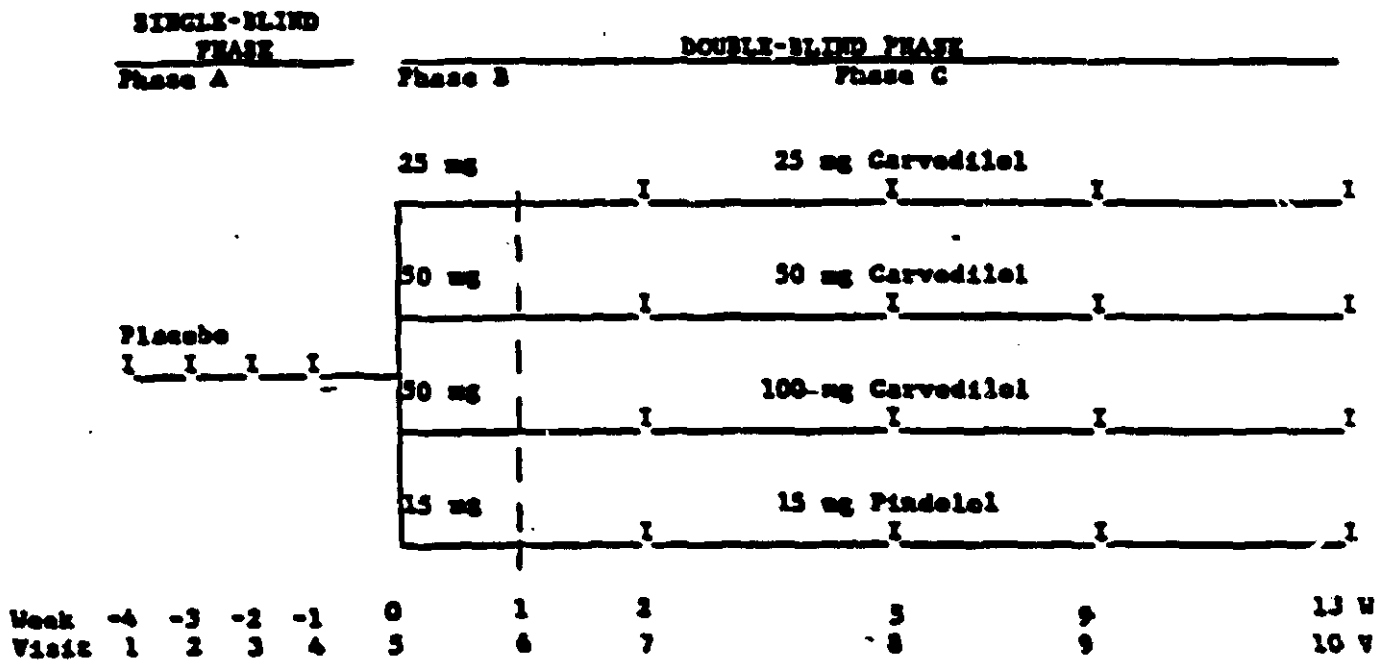
OVERALL DESIGN AND PLAN

This was a randomized double-blind, multicenter study in which patients with mild to moderate uncomplicated essential hypertension (defined as an untreated supine diastolic blood pressure (SDBP) ranging from 95 to 115 mmHg, inclusive) were randomly assigned to receive either 25 mg, 50 mg or 100 mg of carvedilol or 15 mg of pindolol once daily for 13 weeks. In order to avoid an acute marked reduction in blood pressure, patients assigned to the 100 mg carvedilol group received 50 mg carvedilol once daily for the first week of double-blind treatment and 100 mg carvedilol from the second week. Each patient received a single daily oral dose of placebo medication during a single-blind placebo baseline period which

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extended from a minimum of two weeks (for patients who had never previously received antihypertensive medication) to a maximum of four weeks (for previously-treated patients). Patients were eligible for admission into the double-blind phase of the study when their supine diastolic blood pressure on two consecutive visits ranged between 95 and 115 mmHg inclusive and varied not more than 10 mmHg.

The study design is graphically presented below:



Phase A: Placebo Weeks -4 to 0 (or -4 to -2, see Visit 5)
 Phase B: Double-Blind Adaptation Phase (first week of active treatment)
 Phase C: Double-Blind Continuation Phase, Weeks 2 to 13
 Visit 5: (or Visits 3 or 4) Admission to the double-blind phase if the SDP was within the range of ≥ 95 - ≤ 115 mmHg and did not vary by >10 mmHg on two consecutive visits.

STUDY DESIGN: CHOICE OF CARVEDILOL DOSES

The doses of carvedilol were selected on the basis of experience with the drug prior to initiation of this study. Multiple dose levels of carvedilol were used in order to investigate a dose-response relationship in patients with mild to moderate essential hypertension. The reference drug (pindolol) served as the positive control in order to compare the effect of carvedilol with changes in blood pressure associated with another nonselective beta-adrenergic receptor blocking agent known to reduce blood pressure.

STUDY POPULATION

A total of 205 patients, 102 male and 103 female, who ranged in age from 23 to 70 years, qualified for participation in the study. All patients had uncomplicated essential hypertension with untreated supine diastolic blood pressure values during placebo screening that ranged between 95 and 115 mmHg inclusive on two consecutive occasions and varied by no more than 10 mmHg. Patients were excluded from the study if their medical history revealed a tendency to hypotension, hypotensive collapse or shock or if they had any of the following: mitral valve stenosis, decompensated congestive heart failure, bradycardia (<55 bpm), sinoatrial block, AV block grades II and III, complete bundle branch block, bifascicular block, sick-sinus syndrome, unstable angina pectoris, any degree of cor pulmonale, metabolic acidosis or obstructive lung disease. In addition, patients were excluded from the study if they had renal insufficiency (creatinine >1.5 mg/dl); hepatic insufficiency (GPT >40 U/l); insulin-dependent diabetes mellitus; body weight greater than 20% above normal as defined by the Broca Index (height in cm. - 100). Female patients were excluded if pregnant, lactating or without satisfactory contraception. Concomitant use of oral contraceptives, cimetidine, thyrostatics, antiarrhythmics, psychotherapeutics, antihypertensive agents,

NDA 20297

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MF7018 (NB, PC, NR, parallel)

Venous plethysmography in patients revealed conflicting results.

E31 (11 elderly Japanese patients with essential hypertension)

After multiple doses (carvedilol 10-20 mg po q day for 8 weeks), patients in an uncontrolled study had increases in forearm and calf blood flow and venous outflow.

MF2740 (16 patients with coronary artery disease)

Single oral doses of carvedilol 50 mg failed to show changes in leg blood flow.

Venous plethysmography in healthy men did not reveal convincing effects of carvedilol.

CAR-UK-106 (7 healthy men)

Compared to placebo, carvedilol 50 mg po single dose (not 12.5 mg or 25 mg) caused significant decrease in corrected flow time during the 5-24 hours of observation after the dose. There was no consistent effect on forearm blood flow caused by single oral doses of carvedilol 12.5 mg, 25 mg, or 50 mg.

MF7017 (12 healthy men)

Active control (metipranolol suspension) was not active in this study. Single oral doses of carvedilol 50 mg and 75 mg suspensions did NOT show convincing changes in arm arterial flow, peripheral resistance, venous capacity, venous efflux, venous tone, venous pressure-volume curve.

MF7018 (46 healthy men)

Single intravenous doses of carvedilol from 0.313 mg up to 26.27 mg did NOT cause convincing increases in systolic baseline amplitude of the pulse curve during finger plethysmography.

Artery studies using pulsed doppler sonography in patients did not reveal convincing effects of carvedilol.

E31 (11 elderly Japanese patients with essential hypertension)

In an uncontrolled study, bilateral common carotid artery doppler flow increased only during the measurement at the 8th week of carvedilol 10-20 mg po q day.

Artery studies using pulsed doppler sonography in healthy volunteers did not reveal convincing effects of carvedilol.

MF3710 (9 healthy men)

Single oral doses of carvedilol 50 mg (not 25 mg) decreased brachial artery wall tension. Single oral doses of carvedilol 25 mg and 50 mg failed to change brachial artery diameter, blood flow velocity, arterial flow rate, peripheral resistance, arterial compliance, or pulse wave velocity.

Effect on *in vitro* platelet function

B1101 (DB, PC, NR, crossover)

CAR-UK-110 (see below)

Platelet aggregation was increased in healthy volunteers taking carvedilol 12.5 - 25 mg po per day.

B1101 (12 healthy men)

Multiple oral doses of carvedilol 12.5 - 25 mg po q day for 3 days produced decreases in the threshold for ADP-induced and epinephrine-induced platelet aggregation. Carvedilol concentrations were not measured in this study.

CAR-UK-110

Carvedilol acts like propranolol and inhibits platelet aggregation in platelets from healthy donors. The lowest IC₅₀ (in vitro) for inhibition by carvedilol in CAR-UK-110 was 54 μ M. The upper end of the range for C_{max} (in vivo) after carvedilol 25 mg po is 0.5 μ M (208 ng/mL).

Pharmacodynamic interaction with loop diuretic

MF3698 (NB, NC, NR)

After a single oral dose of carvedilol 25 mg with torasemide 2.5 mg, 4 of 5 hypertensive patients experienced decreases in systolic blood pressure of 20 - 70 mm Hg and decreases of diastolic blood pressure of 20 - 30 mm Hg. Three of 5 patients complained of orthostatic symptoms.

PART II: CLINICAL PHARMACOKINETICS**Studies of bioequivalence**

020 (NB, no placebo, R SEQ, crossover)
A0001 (NB, no placebo, R SEQ, crossover)
A0008 (NB, no placebo, R SEQ, crossover)
A9902 (NB, no placebo, R SEQ, crossover)
A9908 (NB, no placebo, R SEQ, crossover)
A9910 (NB, no placebo, R SEQ, crossover)
A9912 (NB, no placebo, R SEQ, crossover)
F39 (NB, no placebo, NR, crossover)
F40 (NB, no placebo, NR, crossover)
MF7008 (NB, no placebo, R SEQ, crossover)
MF7019 (NB, no placebo, R SEQ, crossover with formulation containing Myrj-52)
MF7022 (NB, no placebo, R SEQ, crossover with various capsule formulations)
MF7023 (NB, no placebo, R SEQ, crossover with suspension and slow release tablet)
MF7025 (NB, no placebo, R SEQ, crossover with 3 enteric-coated tablet formulations)

Comments regarding bioequivalence may be found in the Biopharmaceutics review and in the appendices A, B, and C of the Clinical Pharmacology review.

Studies of PK parameters in normal healthy volunteers

A9901 (NB, NC, NR, crossover), see studies of enantiomers, page 19
A9902 (NB, no placebo, R SEQ, crossover), bioequivalence study, page C14
A9907 (NB, NC, R SEQ, crossover), see effect of food, page 16
A9908 (NB, no placebo, R SEQ, crossover), bioequivalence study, page C28
CARV0001 (SB, PC, AC, parallel), see beta effect in healthy volunteers, page 6
CARV0002 (NB, NC, NR study of intravenous formulation)
CARV0012 (NB, NC, R SEQ, crossover of intravenous, oral solution, and capsule formulations)
MF2971 (DB, PC, R SEQ, crossover), see dose proportionality, page 16
MF3413 (DB, PC, AC, NR, crossover), see young and elderly subjects, page 18
MF3950 (NB, NC, NR, parallel), see multiple doses and younger and elderly, page 18
MF7008 (NB, no placebo, R SEQ, crossover), bioequivalence study, C157

MF7016.0539 (NB, NC, NR, dose escalation), see alpha effect in healthy volunteers, page 7
MF7016.0540 and 0541 (DB, AC, NR, crossover), see alpha effect in healthy volunteers, page 7
MF7018 (NB, PC, NR, parallel), see appendix, page A7, B35
MF7020 (NB, NC, R SEQ, crossover with intravenous and capsule formulations)
MF7029 (NB, NC, NR, metabolism study), see studies of metabolites, page 14
MF7034 (NB, NC, R SEQ, crossover), see PK of enantiomers, page 19
MF7038 (NB, NC, NR, crossover), see appendix, page C177
MF7097 (NB, NC, NR), see PK interaction with cimetidine, page 20

A9901 (12 healthy men)

After single oral doses of carvedilol 25 mg, the C_{max} (mean 55 ng/mL) varies over a 10-fold concentration range (12 - 112 ng/mL). AUC (mean 215 ng*hr/mL) varies over a 10-fold range (42 - 434 ng*hr/mL). T_{max} (mean 1.2 hours) varies between 0.5 and 4 hours. Elimination half-life (mean 9.71 hours) varies between 6.7 hours and 15 hours.

MF7018 (46 healthy men)

Single intravenous doses of carvedilol 0.313 mg up to 26.37 mg produced increasing AUC until the dose of 16.88 mg. There was no further increase in AUC for doses on 21.09 mg or 26.37 mg. The fractional excretion (0 - 8 hours after the dose) of unchanged carvedilol in the urine was less than 1% for all intravenous doses.

Additional comments regarding PK may be found in the Biopharmaceutics review and in the appendices of the Clinical Pharmacology review.

Studies of metabolites in humans

MF7029 (NB, NC, NR, metabolism study)

MF7029 (3 healthy men over 50 years old)

After single oral doses of radio-labelled carvedilol 50 mg, most of the radioactivity (56% - 64% of ingested radioactivity) was excreted in the feces. Due to a dosing error, the proportion of metabolites excreted in the feces is uncertain. Less than 19% of fecal radioactivity represented parent carvedilol. Between 15% - 17% of ingested radioactivity was excreted in the urine. Most of the urinary radioactivity came from various glucuronide conjugates of carvedilol and its metabolites. Less than 2% of urinary radioactivity represented parent carvedilol. The median elimination half-life for total radioactivity was 39 hours (range 20 - 50 hours).

Studies measuring metabolite, M2, desmethylcarvedilol

A0001 (NB, NC, R SEQ, crossover), bioequivalence study, page C4

A0008 (NB, NC, R SEQ, crossover), bioequivalence study, page C6

A9901 (NB, NC, NR, crossover), see studies of enantiomers, page 19

CAR8902 (NB, NC, NR, crossover), see interaction with cimetidine, rifampin, page 20

F34 (NB, NC, NR), see appendix, page A3, B10

MF3413 (DB, PC, AC, NR, crossover), see young and elderly subjects, page 18

MF3459 (NB, NC, NR), see PK in renal failure, page 17

MF3476 (NB, NC, NR, crossover), see PK in liver insufficiency, page 17

MF3702 (SB, NC, NR, dose escalation), see young and elderly subjects, page 18

MF3950 (NB, NC, NR, parallel), see young and elderly subjects, page 18

MF7029 (NB, NC, NR, metabolism study)

MF7097 (NB, NC, NR), see PK interaction with cimetidine, page 20

MF7108 (NB, NC, NR, crossover), see digitoxin interaction, page 21

A0001 (12 healthy men)

This is a study of bioequivalence using single oral doses of carvedilol 25 mg capsules. C_{max} desmethylcarvedilol is approximately 10% of C_{max} carvedilol. AUC desmethylcarvedilol is approximately 5% of AUC carvedilol. Six of 12 healthy men had symptomatic orthostatic hypotension in this study.

MF7029 (3 healthy men over 50 years old)

After volunteers ingested an uncertain amount of radiolabelled carvedilol, the sponsor reported that desmethylcarvedilol accounted for 1% - 6% of plasma radioactivity, 0.3% - 0.6% of urine radioactivity, and 8% - 10% of fecal radioactivity. There were no studies in humans measuring the pharmacodynamic effects of administration of desmethylcarvedilol.

Studies measuring metabolite, M4, 4'-hydroxyphenyl-carvedilol

F34 (NB, NC, NR), see appendix, page A3, B10

MF3459 (NB, NC, NR), see PK in renal failure, page 17

MF7097 (NB, NC, NR), see PK interaction with cimetidine, page 20

There were no studies in humans measuring the pharmacodynamic effects of administration of 4'-hydroxyphenyl-carvedilol.

Studies measuring metabolite, M5, 5'-hydroxyphenyl-carvedilol

F34 (NB, NC, NR), see appendix, page A3, B10

MF3459 (NB, NC, NR), see PK in renal failure, page 17

MF7029 (NB, NC, NR, metabolism study)

MF7097 (NB, NC, NR), see PK interaction with cimetidine, page 20

MF7029 (3 healthy men over 50 years old)

After volunteers ingested an uncertain amount of radiolabelled carvedilol, the sponsor reported that 5'-hydroxyphenyl-carvedilol accounted for 15% of fecal radioactivity. There were no studies in humans measuring the pharmacodynamic effects of administration of 5'-hydroxyphenyl-carvedilol.

Studies with PK data after multiple doses

F31 (NB, NC, NR, crossover)

MF3950 (NB, NC, NR, parallel)

MF7097 (NB, NC, NR), see PK interaction with cimetidine, page 20

F31 (25 healthy Japanese men)

There was no evidence for accumulation while subjects took carvedilol 20 mg po per day for 14 days.

MF3950 (10 healthy men aged 20 - 26 years and 11 healthy elderly men and women aged 66 - 77 years) Based on C_{max} and AUC values, carvedilol did not appear to accumulate after 13 days of treatment (carvedilol 25 mg po per day) in 10 healthy young men. Since 4 elderly subjects with elevated C_{max} and AUC withdrew, this study should not be used to claim the presence or absence of accumulation in the elderly.

Studies comparing single dose PK with multiple dose PK

F31 (NB, NC, NR, crossover), see dose proportionality, page 16

MF3702 (SB, NC, NR, dose escalation in non-responders), see PK in young and elderly, page 18

Studies of dose proportionality

A9903 (NB, NC, R SEQ, crossover)

F31 (NB, NC, NR, crossover)

MF2971 (DB, PC, R SEQ, crossover with extension SB, NC, NR, dose escalation)

MF3413 (DB, PC, AC, NR, crossover), see young and elderly subjects, page 18

MF3702 (SB, NC, NR, dose escalation in non-responders)

Two of three studies suggest proportional increases in C_{max} and AUC after single oral doses of carvedilol between 6.25 mg and 200 mg.

A9903 (12 healthy men)

After single oral doses of carvedilol 6.25 mg, 12.5 mg, 25 mg, and 37.5 mg, mean AUC and C_{max} for R(+)-carvedilol and S(-)-carvedilol showed increases that were approximately dose-proportional.

MF2971 (6 healthy men)

After single oral doses of carvedilol 50 mg, 100 mg, and 200 mg, there were proportional increases in C_{max} and AUC.

F31 (5 healthy Japanese men)

After single oral doses of carvedilol 5, 10, 20, 40, 60 mg, there was a lack of dose proportional increases in C_{max} and AUC. There was a plateau of C_{max} and AUC at doses above 20 mg.

MF3702 (8 young and 21 elderly hypertensive patients)

Multiple dose therapy with carvedilol 12.5 mg, 25 mg, or 50 mg per day for 4 - 8 weeks did not reveal convincing PK results for the 12.5 mg and 25 mg doses because of missing data or small sample size. See studies of PK in young and elderly subjects (page 18).

Studies of the effect of food on absorption

A9907 (NB, NC, R SEQ, crossover)

F31 (NB, NC, NR, crossover)

MF3413 (DB, PC, AC, NR, crossover), see young and elderly subjects, page 18

MF7021 (NB, NC, R SEQ, crossover)

Reference is made to the Biopharmaceutics review.

A9907 (12 healthy men and women)

The fat content of the meal was 40%. After single oral doses of carvedilol 25 mg, carvedilol absorption was significantly delayed by the presence of food. Median T_{max} was approximately one hour later in fed subjects. Carvedilol C_{max}, AUC, and elimination half-life were not significantly different between the fed and fasted conditions. There was a tendency for food to attenuate the effect of carvedilol on decreasing systolic blood pressure. In contrast, food tended to magnify the effect of carvedilol on decreasing diastolic blood pressure. The magnitude of the blood pressure differences resulting from food is difficult to interpret since there was no placebo.

F31 (25 healthy Japanese men)

The fat content of the meal used in this study was probably too low.

MF3413

The fat content of the meal used in this study was probably too low.

MF7021 (20 healthy men)

Assuming the fat content of the meal is appropriate, then single oral doses of carvedilol 25 mg do not affect C_{max}, AUC, or elimination half life. Food effects were limited to increases in absorption lag time and T_{max}.

Studies of PK in chronic renal failure and insufficiency

G20 (NB, NC, NR)

MF3459 (NB, NC, NR)

There are no convincing studies assessing the PK of carvedilol after chronic therapy. See comments below (MF3459) regarding PK after single doses.

G20 (6 hypertensive Japanese patients on hemodialysis)

Only 3 patients had measurements of carvedilol concentrations to assess accumulation after carvedilol 10 mg po per day for 4 weeks. Unexplained missing data hinder interpretation of the presence or absence of accumulation in patients on dialysis. One of 6 patients required dose reduction of carvedilol to 5 mg per day because she developed unspecified decreases in blood pressure.

MF3459 (24 hypertensive patients stratified into 3 groups based on creatinine clearance)

After single oral doses of carvedilol 50 mg, there was significantly less renal clearance of carvedilol and metabolites (M2, M4, M5) in patients with severe renal failure versus moderate renal failure. However, the amount of carvedilol, M2, M4, and M5 excreted in the urine is a small percentage of the total dose for all groups of creatinine clearance. In this study, the decrease in renal clearance of carvedilol and metabolites in patients with renal failure is not clinically meaningful. The concentration-versus-time curves show an interesting delayed peak that is compatible with entero-hepatic circulation of carvedilol, M2, M4, and M5. Two patients with the lowest AUCs were taking concomitant vitamin D3. There may be a pharmacokinetic drug interaction between carvedilol and vitamin D3. There is a non-significant trend toward more decrease in systolic and diastolic blood pressure in patients with the lowest creatinine clearance. In contrast, there is an opposite non-significant trend showing less decrease in heart rate in patients with the lowest creatinine clearance.

Studies of dialysis clearance

G20 (NB, NC, NR)

G20 (6 hypertensive Japanese patients on hemodialysis)

Only 2 patients had measurements of carvedilol concentrations to determine dialyzer clearance. Unexplained missing data hinder interpretation of dialyzer clearance.

Studies of PK in chronic liver failure and insufficiency

MF3476 (NB, NC, NR, crossover)

MF3837 (NB, NC, R SEQ, crossover)

There is increased bioavailability and decreased total clearance in patients with liver insufficiency. Severe side effects were reported in this patient population.

MF3476 (10 healthy volunteers and 21 patients with mild - severe liver insufficiency)

In vitro protein binding studies using plasma samples from 8 subjects with severe chronic liver insufficiency was 98.2% ± 0.4%. Some of the subjects had huge concentrations of carvedilol that were attributed to dosing error. The results of this study are not reliable.

MF3837 (6 patients with cirrhosis)

Single oral doses of carvedilol 25 mg were compared with single intravenous infusions of carvedilol 12.5 mg. When cirrhotic patients are compared to healthy historical controls, patients with cirrhosis have higher carvedilol bioavailability (mean F 99.7% versus. mean F 22.4%), higher volume of distribution (mean Vd 311.1 L versus. mean Vd 137.6 L), and lower plasma clearance (mean CL 449 mL/min versus. 624 mL/min). One patient had much higher plasma carvedilol concentrations (2 - 3 times higher than the mean of all six subjects) after a single intravenous dose of carvedilol 12.5 mg. This same patient developed hypotension, nausea, and oliguria.

Studies of PK in young and elderly subjects

MF3413 (DB, PC, AC, NR, crossover)

MF3950 (NB, NC, NR, parallel)

MF3702 (SB, NC, NR, dose escalation in non-responders)

Elderly healthy volunteers and hypertensive patients appear to have increased C_{max} and AUC when compared to younger control subjects. The magnitude of the effect on decreasing blood pressure appears to be greater in healthy older subjects. One study in patients (MF3702) does not provide enough information to confirm or refute the magnitude of the effect on blood pressure in elderly hypertensive patients.

MF3413 (10 healthy men between 20 and 40 years old, 10 healthy men and women between 57 and 66 years old)

Single oral doses of carvedilol 25 mg and 50 mg showed median bioavailability in older subjects is 1.6 times the bioavailability in younger subjects. Median total clearance in the older subjects is 0.6 times the clearance in younger adults. Median volume of distribution in the older subjects is 1.5 times the volume in the younger subjects. Median AUC for the older subjects is 1.7 times the AUC of the younger subjects. There were no convincing differences between C_{max}, T_{max}, and half-life between the two age groups. The proportion of subjects unable to stand for blood pressure determination after carvedilol was similar in the younger and older groups. There was no dose-dependent difference in the proportion of subjects unable to stand for blood pressure. The maximum fall in supine or standing blood pressure in the older subjects was 2 times greater than in the younger subjects. The time to maximal fall in blood pressure was 2 - 4 hours after the dose. Older subjects showed a non-significant trend toward later times to E_{max}. There was no significant difference between age groups with regard to decreases in heart rate.

MF3950 (10 healthy men aged 20 - 26 years and 11 healthy elderly men and women aged 66 - 77 years)

After multiple oral doses of carvedilol 25 mg per day for 2 weeks, four of 11 elderly subjects could not tolerate carvedilol because of symptomatic orthostatic hypotension. The C_{max} and AUC for elderly subjects withdrawn for adverse events were 2 - 3 times greater than the corresponding values for elderly subjects completing the trial.

MF3702 (8 young and 21 elderly hypertensive patients)

Multiple dose therapy with carvedilol 12.5 mg, 25 mg, or 50 mg per day for 4 - 8 weeks did not reveal convincing PK results for the 12.5 mg and 25 mg doses because of missing data or small sample size. After the 50 mg dose, mean C_{max} carvedilol was significantly greater in elderly patients versus young patients, 220 ng/mL versus 117 ng/mL. Time to C_{max} was between 0.5 and 2 hours. AUC was 49% higher for elderly patients. There was no dose-response correlation for diastolic blood pressure or systolic blood pressure.

Studies of PK of enantiomers

A9901 (NB, NC, NR, crossover)

A9903 (NB, NC, R SEQ, crossover)

CAR-SA-01 (NB, AC, NR)

F30 (NB, NC, NR)

MF7034 (NB, NC, R SEQ, crossover)

MF7097 (NB, NC, NR), see PK interaction with cimetidine, page 20

There are no studies in which only enantiomers of carvedilol were administered to humans. All studies administered racemic carvedilol. There is no information about the interconversion between enantiomers. There are no clinical trials testing the difference in hemodynamic effects between the enantiomers of carvedilol. Reference is made to the Biopharmaceutics review for further comments about the PK of enantiomers.

A9901 (12 healthy men)

Mean C_{max} and AUC values for R(+)-carvedilol are two to four times greater than values for S(-) carvedilol. Since half-life for R(+)-carvedilol and S(-)-carvedilol are almost the same, there may be stereoselective absorption favoring R(+)-carvedilol or stereoselective first-pass hepatic metabolism. Plasma concentrations of desmethylcarvedilol are 5% - 10% of plasma concentrations of carvedilol. C_{max} for desmethylcarvedilol is the same as R(+)-desmethyl-carvedilol. C_{max} of S(-) desmethylcarvedilol was quantifiable, i.e., greater than 1.25 ng/mL, in only 3 of 12 men.

A9903 (12 healthy men)

After single oral doses of racemic carvedilol 6.25 mg, 12.5 mg, 25 mg, and 37.5 mg, geometric mean AUC and C_{max} were approximately 3 times greater for R(+)-carvedilol than for S(-) carvedilol.

CAR-SA-01 (10 patients with hypertension and mild left ventricular dysfunction)

After a single oral dose of racemic carvedilol 25 mg, mean C_{max} values for R(+)-carvedilol and S(-) carvedilol in these patients were 2 - 3 times lower than C_{max} values achieved in healthy volunteers. Mean T_{max} values for R(+)-carvedilol and S(-) carvedilol were 1.8 times longer than T_{max} values recorded in healthy volunteers. Plasma concentrations of R(+)-carvedilol and S(-) carvedilol did not correlate with hemodynamic parameters measured during right heart catheter study.

F30 (5 healthy men)

After single oral doses of racemic carvedilol 20 mg, mean AUC and C_{max} were approximately 2 - 3 times greater for R(+)-carvedilol than for S(-)-carvedilol. The elimination half-life for each enantiomer was approximately equal.

MF7034 (10 healthy men)

After single oral doses of racemic carvedilol 50 mg, the ratio of R(+) carvedilol to S(-) carvedilol was 2.6 for C_{max} and 2.7 for AUC. This is the only study showing a difference in half-life after oral carvedilol with a ratio R(+)/S(-) of 0.4. After intravenous infusion of racemic carvedilol 12.5 mg, the ratio of R(+) carvedilol to S(-) carvedilol was 1.2 for C_{max} and 1.3 for AUC. These results are consistent with stereoselective first-pass metabolism.

Studies of PK in people with slow and normal metabolism (CYP450IID6, etc)

A9911 Ongoing study (no report)

Studies of PK: drug interaction with cimetidine, rifampin
CAR8902 (NB, NC, NR, crossover)
MF7097 (NB, NC, NR)

There are PK interactions between carvedilol and cimetidine and between carvedilol and rifampin. The pharmacodynamic consequences of these interactions in patients are unknown.

MF7097 (10 healthy men)

After multiple oral doses of carvedilol 25 mg per day for 4 - 7 days, carvedilol PK values were compared before and after therapy with oral cimetidine 1000 mg per day for 48 hours. Cimetidine caused a 30% increase in racemic carvedilol AUC and 27% increase in the amount of racemic carvedilol excreted in urine. Cimetidine caused a 25% increase in R(+) carvedilol AUC and 39% increase in the amount of R(+) carvedilol AUC excreted in the urine. Cimetidine caused a 15% increase in S(-) carvedilol AUC and 20% decrease in C_{max} for S(-) carvedilol. The differences in amount excreted in the urine (Ae%) and CL_{renal} between R(+) carvedilol and S(-) carvedilol might result from stereoselective renal elimination of carvedilol. Only oral racemic carvedilol was administered in this study. Therefore, no information is available from this study to answer questions about the interconversion of enantiomers of carvedilol. The enantiomers of the metabolites were not assayed in this study. The AUCs for M2, M4, and M5 are all less than 4% of the AUC of racemic carvedilol. The renal clearance of the M2, M4, and M5 is approximately 5 times greater than the renal clearance of racemic carvedilol.

The mechanism for cimetidine's effect on carvedilol kinetics is unknown. Cimetidine may cause an increase in carvedilol oral bioavailability perhaps through a change in gastric pH. The more likely explanation is cimetidine inhibits first-pass hepatic clearance by CYP450. Cimetidine does not appear to decrease the tubular secretion of carvedilol, carvedilol enantiomers, or carvedilol metabolites.

There was no placebo group with which to compare pharmacodynamic responses. In this small group of healthy men, the pharmacokinetic interaction between cimetidine and carvedilol did not cause clinically significant changes in blood pressure, pulse, or electrocardiographic intervals.

CAR8902 (8 healthy men)

Single oral doses of carvedilol 25 mg were used in this study. After therapy with rifampin 600 mg po per day for 11 days, mean carvedilol C_{max} was 33% of the mean carvedilol C_{max} prior to induction. Mean carvedilol AUC_∞ after rifampin was 31% of mean carvedilol AUC_∞ prior to induction. Standing systolic blood pressure fell more than 20 mm Hg in 7 of 8 men receiving carvedilol alone and in 4 of 8 men receiving carvedilol plus rifampin. After therapy with cimetidine 400 mg po every 12 hours for 72 hours, mean carvedilol AUC_∞ was 118% of the mean carvedilol AUC_∞ prior to cimetidine. Standing systolic blood pressure fell more than 20 mm Hg in 3 of 8 men receiving carvedilol plus cimetidine. The PK parameters of desmethylcarvedilol were not changed by rifampin or cimetidine.

Studies of PK interaction with warfarin

There were only *in vitro* tests of the interaction between carvedilol and warfarin. Reference is made to the Biopharmaceutics review for comments.

Studies of PK, drug interaction with diuretic
MF3877 (DB, AC, R SEQ, crossover)
MF7024 (NB, NC, R SEQ, crossover)

Concomitant administration of carvedilol and hydrochlorothiazide did not result in adverse PK or pharmacodynamic interaction. In contrast, concomitant administration of carvedilol and torasemide caused intolerable orthostatic side effects in 3 of 5 hypertensive patients.

MF3877 (12 men and women with diastolic BP > 110 mm Hg and systolic BP > 160 mm Hg)
After a single oral dose of carvedilol 25 mg with a single oral dose of hydrochlorothiazide 25 mg, there were no significant differences in PK values for either drug caused by combination therapy. Combination therapy did not cause significant changes in blood pressure or pulse when compared to either drug alone.

MF7024 (12 healthy men)

Multiple oral doses of carvedilol 25 mg per day for 5 days alone or in combination with torasemide 5 mg po per day for 5 days did not change PK parameters for carvedilol, torasemide, or torasemide M5 metabolite. There was no accumulation of carvedilol, torasemide, or torasemide M5 metabolite after 5 days of combination therapy. The absence of adverse events in this young population (mean age 24.6 years) in MF7024 contrasts with the intolerable orthostatic side effects in 3 of 5 hypertensive patients (age range 31 - 73 years) in MF3698 who received single oral doses of carvedilol 25 mg and torasemide 2.5 mg.

Studies of PK, drug interaction with digoxin or digitoxin

A9904 (DB, PC, R SEQ, crossover)

A9905 (DB, PC, R SEQ, crossover)

MF7108 (NB, NC, NR, crossover)

There is a pharmacokinetic interaction between carvedilol and digoxin resulting in increased C_{max} and AUC for digoxin. The pharmacodynamic consequences of this interaction in patients is unknown. There were no PK nor pharmacodynamic interactions between carvedilol and digitoxin in healthy volunteers.

A9904 (8 healthy men) and A9905 (8 healthy men)

After single oral dose of carvedilol 25 mg with single oral dose of digoxin 0.5 mg, there were significant increases in digoxin C_{max} and AUC. The differences in digoxin PK are probably caused by an increase in digoxin bioavailability as a result of concomitant carvedilol. When digoxin was administered intravenously, there was no difference in digoxin PK caused by concomitant carvedilol (see study A9905). Carvedilol was not assayed in either study. There were no significant differences in supine blood pressure or pulse as a result of the concomitant administration of carvedilol and digoxin.

A9905 (8 healthy men)

This study used a single oral dose of carvedilol 25 mg with a single intravenous dose of digoxin 0.5 mg. Other comments are included with study A9904.

MF7108 (12 healthy men and women)

After single oral doses of digitoxin 0.56 mg, carvedilol and desmethylcarvedilol PK parameters are not affected after multiple oral doses of carvedilol 25 mg per day for 7 days. There were no significant changes in systolic blood pressure, diastolic blood pressure, or heart rate caused by concomitant digitoxin and carvedilol.

Studies of PK in hypertensive patients

CARV0003 reviewed by Dr. Knudsen

CARV0021 reviewed by Dr. Knudsen

MF3877 (DB, AC, R SEQ, crossover), see drug interaction with diuretic, page 20

MF3702 (SB, NC, NR, dose escalation) see young and elderly subjects, page 18

CAR-SA-01 (NB, AC, NR), see PK in enantiomers, page 18

Studies of PK in patients with congestive heart failure

CAR-SA-01 (NB, AC, NR), see PK in enantiomers, page 18

Studies of PK in circadian variation

CARV0021 reviewed by Dr. Knudsen

Studies raising safety concerns

MF2971 (DB, PC, R SEQ, crossover with extension SB, NC, NR, dose escalation)

MF3132-I (DB, PC, AC, R SEQ, crossover)

MF3132-II (DB, PC, R SEQ, crossover)

MF3950 (NB, NC, NR, parallel)

Dose limiting side effects (orthostatic hypotension) occurred in the majority of healthy young volunteers taking oral doses of carvedilol 100 mg.

MF3132-I and MF3132-II (12 healthy men)

Single oral doses of carvedilol 100 mg caused statistically significant changes in standing mean systolic blood pressure (20-22 mm Hg decreases) and standing mean diastolic blood pressure (13-18 mm Hg decreases). Four of 6 healthy men in MF3132-II had symptomatic orthostatic faintness that prevented them from exercising.

MF2971 (6 healthy men)

Orthostatic hypotension was the dose-limiting side effect that prevented 4 of 6 healthy men from tolerating single oral doses of carvedilol greater than 200 mg. One subject (#5) tolerated single doses of carvedilol as high as 800 mg. When compared to other subjects, subject #5 had the lowest AUCs for the 50 mg, 100 mg, and 200 mg doses. Subject #5 was also the only subject to prolong his QTc from 0.41 to 0.46 seconds. The QTc prolongation was associated with ingestion of carvedilol 800 mg.

MF3950 (10 healthy men aged 20 - 26 years and 11 healthy elderly men and women aged 66 - 77 years)

After multiple oral doses of carvedilol 25 mg per day for 2 weeks, four of 11 elderly subjects could not tolerate carvedilol because of symptomatic orthostatic hypotension.

The following table shows noteworthy side effects of carvedilol. Please see appendices A, B, and C for details.

Adverse event	Study
urticaria in one subject	A0003
paresis in one subject	G10
asthma exacerbation in one hypertensive patient	G15
hypotension, oliguria in one cirrhotic patient	MF3837
syncope with seizure in one healthy subject	MF7019
elevated AST, ALT	MF7019
syncope, seizure, sinus arrest, hypotension	CARV0002
elevated serum phosphorus in 10 healthy men	MF3950
symptomatic hypotension in elderly man with carcinoma and anemia	MF3476



James F. Graumlich, MD

Appendix A
Appendix B
Appendix C

Distribution: Orig NDA
HFD-110 file
HFD-110 CSO
HFD-110 C. Ganley

Appendix A (NDA 20-297) Abbreviations: R= randomized, NR= not randomized, SEQ= sequence, Xover= crossover

PROTOCOL	VOL	Objective	Design	Subject	Treatment	single vs multi dose	n completed (enrolled)	Results
A0003	1.108	PD, renal inulin	DB, PC, R SEQ	healthy men	po carv 12.5 mg (n=4), 25 mg (n=6)	single	6(6), age 22 - 33 yrs. 1 dropout 2nd	results not believable. For inulin clearance, only n=3 placebo, n=2 carv 12.5 mg, n=3 carv 25 mg 2nd to fructose contamination in inulin. no change inulin clear but results doubtful 2nd small n. PAH clearance increased 2nd to placebo (n=5)
A0003, cont	1.108	urine chemistry	3-Xover		50 mg (n=2)		to urticaria	PAH clear no change 2nd carv 25 mg (n=6). unreliable PAH results 2nd small n for carv 12.5 mg (n=4), carv 50 mg (n=2). Creatinine clear, FeNa, FeK, FeCl, FeUricAc, FeCalcium, FePhos, clear osm, clear free water no change.
A0006	1.108	DI, HCTZ	SB, R SEQ, no placebo 2-Xover	healthy men age 22 - 32 yrs	carv 6.25 mg (n=3) or 12.5 mg (n=3) one po/day x 4 day+HCTZ 25 mg on day 4	multi x 4 days	6(n=24 in protocol). no dropouts. unknown reason for stopping at	hard to draw conclusions. only 3 subjects per treatment group. largest fall in standing SBP (approx 15 mm Hg) occurred after HCTZ x 4 days + carv (6.25 or 12.5 mg) on day 4 at 45 - 60 minutes after the dose.
A0006, cont	1.108				HCTZ 25 mg po/day x 4 day; carv 6.25 mg (n=3) or 12.5 mg (n=3) on day 4 only		n=6. Per protocol, only 2 subjects should get carv 6.25 mg	
B1101	1.109	PD, platelet	DB, PC, NR	healthy men	po carv 12.5 mg, 25 mg	multi x 3 doses only	12(12), 2 of 1st 3 subjects had bradycardia	25 mg dose deleted for last 9 subjects. carv(dose?) increased plasma norepi level (over placebo) at 1 hr post dose supine and stand 78-152 pg/mL. ADP induced platelet aggregation threshold borderline decreased by carv(dose?) pre exercise only
B1101, cont	1.109		2-Xover				or orthostat low BP on carv 25 mg	epinephrine induced platelet aggregation threshold decreased by carv (dose unknown) 1 hr post dose (supine) (n=11) and pre exercise. no change in euglobulin clot lysis time. plasma epinephrine level no change. no carv concentration measured
CAR.UK.109	1.84	PD, EEG, psychometric	DB, 4-Xover, R, PC, AC	healthy, sex?	carv 12.5 mg/d po, atenolol 5 mg/d po, enalapril 5-10 mg/d po	multi x 8 days	12(15), age 19-40 yr. 3 withdrew for "personal reasons"	no protocol, no full report, no tables, no figures; ? clin meaning of changes in EEG, auditory vertex potential, memory, mood. ? equipotent doses of active controls

Appendix A (NDA 20-297) Abbreviations: R= randomized, NR= not randomized, SEQ= sequence, Xover= crossover

PROTOCOL	VOL	Objective	Design	Subject	Treatment	single vs multi dose	n completed (enrolled)	Results
CAR8902, see appendix B1, B2	1.73	PK, metabolism, CYP induction	NB, NC, NR, 3-way-Xover	healthy men, avg 29 yrs	carv 25 mg po capsule, cimetidine 400 mg po q 12 hr days	single, carv on day 1, 5, 30	8(8)	Standing BP not recorded at Tmax for 4 subjects (reasons not reported). Standing SBP fell >20 mm Hg in 7/8 men on carv alone, 3/8 on carv+cimet, 4/8 on carv+rifamp. Time to lowest stand SBP 1.1-1.5 hrs post dose, unchanged by treatment. One symptomatic
CAR8902, cont	1.73	inhibition			2-5, rifam-picin 600 mg po/day on day 19-30			orthostat hypotension in each treatment group. mean carv Cmax after rifamp was 33% of Cmax carv alone. mean carv AUC _∞ after rifamp was 31% of AUC _∞ carv alone. mean carv AUC _∞ after cimet was 118% of AUC _∞ carv alone. desmethylcarv not changed in any group
CARV0012, see appendix P3-B6	1.78	PK, bioavailability	NB, NC, R SEQ, Xover	healthy men, no coffee, non-smoker	carv 50 mg po capsule, carv 50 mg po soln, carv IV	single	12(12), mean age 25.7 yr, mean weight	BP, pulse, orthostat BP, ECG intervals not tabulated. symptomatic orthostat SBP fall >20 mm Hg in 3/12 men. PK parameters in tables 3-6, pp 27-30. mean IV half-life less than half po half-life. F = 29-33% (geometric mean). less than 1% of dose excreted in
CARV0012, cont	1.78			smoker	0.084 mg/kg		81.5 kg	urine as unchanged carv. no oliguria.
E31	1.143	PD vein flow, RBCs	NB, NC, NR	elder Japanese (62-69 yr)	carv 10 or carv 20 po/d x 8 weeks	multi	11(11)	no protocol, ADR unknown, response measurement time after dose unknown; response 10-20 mg together; All responses compared to pretreatment baseline; SBP, DBP, HR decreased at 4, 8 weeks (clin significance?); cardiac output no change (method of measure?)
E31, cont	1.143	viscosity, platelets		ESS HTN	criteria for dose escalation not reported		power to detect difference unknown	bilat common carotid doppler flow increased, 8 wk only; venous occlusion plethysmography: bilat forearm and calf blood flow and venous outflow increased (clin significance?); plasma viscosity and RBC aggregation decreased; Plt aggregation no change
F32	1.143	PD GFR renal plasma	NB, NC, NR	Japanese, mid-mod ESS HTN	carv 5, 10, 20 mg po/d; criteria for dose escal-	multi > 12 wk, mean 17.3 wk	10(10)	no protocol; ADR unknown; response measurement time after dose or after enroll unknown; response 5-20 mg together; all responses compared to pretreatment baseline; SBP, DBP decreased; method renal function measure unknown: GFR, eff renal plas flow, filt
E32, cont	1.143	flow		41-71 yr	ation not reported			fraction, renal vasc resist, BUN, plas creatinine, plas uric acid showed no change; power to detect difference unknown

Appendix A (NDA 20-297) Abbreviations: R= randomized, NR= not randomized, SEQ= sequence, Xover= crossover

PROTOCOL	VOL	Objective	Design	Subject	Treatment	single vs multi dose	n completed (enrolled)	Results
F31, see appendix B7-B9	1.81	PK	NB, NC, NR, Xover	Japanese healthy men	carv (single) 5,10,20,40,60 mg po	multi 20 mg or 40 mg po/d x 2d; 10 or 20 mg po bid x 2d	25(26); 1 dropout reason unknown	no protocol; ? 2-compartment model with absorp lag; single-dose studies (n=5/study) non-dose-proportional C _{max} , AUC not consistent with model; fecal elimination 20% of 20 mg dose, 1 dose tested (?carv + conjugates), food study non-defined "light meal"
F31 cont	1.81					20 mg po/d x 14d		no dose accumulation on 20 mg/d x 14 d; 48-hr urine excretion mean (% of dose) 0.09, 0.24% after single dose 5-60 mg; see table 1, fig 2,3 pg 22,26,27
F34, see appendix B10	1.81	metab	NB, NC, NR	Japanese healthy men	carv 20 mg po	single	5(5)	no protocol; parent carvedilol, metabolite M2, M4, and M5 detected in stool. No quantification. M8, M9, M12 not detected in stool. chemical structure fig 1, pg 53
F39	1.81	bioequiv	NB, NC, NR, Xover	Japanese healthy men	carv 5,10,20 mg po	single	?(22)	abstract only, no protocol, no tables, no data, no figures. cannot corroborate claims in abstract
F40	1.81	bioequiv	NB, NC, NR, Xover	Japanese healthy men	carv 5,10,20 mg po	single	?(22)	abstract only, no protocol, no tables, no data, no figures. cannot corroborate claims in abstract
G2, see appendix B11-B12	1.143	PD, beta, LV eject fraction, cardiac index	NR, NB, NC	healthy Japanese men	carv 20(n=5) or 40(n=5) mg po q day pc x 2 d, carv 10 (n=4) or 20 (n=5) mg po	multi	15(16)	protocol Japanese. cover sheet English. projected n=24. no explanation for lower n enrolled no change in resting pulse with any treat. Both 20 and 40 mg po q day blocked exercise induced tachycardia day 1 (magnitude, onset, duration?) ?training effect
G2, cont	1.143	circadian			bid pc x 2d, carv 20 mg po q day x 14 d (n=5)			Fig 8 pg 70, 2 hours after dose (20 mg/day), cardiac index or EF decreased on days 1, 3, 5. Resting SBP decreased 12.4% on 40 mg. Resting DBP decreased 18%. SBP, DBP T _{Emax} =3 hr. Fig 7 pg 69 Circadian BP, pulse. Missing results=standing BP, PR, QRS, CXR
G3	1.143	PD	NR, DB, placebo washout	hypertension	carv 10 mg po a day x 5-7 d, nonresponders	multi	12(12), 6 took 10 mg/d and 6	protocol Japanese. cover sheet English. projected n=12. carv concentration results for only 4 patients. Responders and nonresponders not defined a priori. Pretreat vs end of treat (mean±SD) SBP 170.4±2.3 vs 149±2.3, DBP 99.6±1.7 vs 83.4±1.5, HR 69.8±3 vs
G3, cont	1.143		no concurrent control		increased to carv 20 mg po q day x 5-7 d		took 20 mg/d	HR 69.8±3 vs 64.2±2.3. No circadian variation in response. Onset of effect = 1 hr. Duration of effect = 24 hrs. All results for 10 and 20 mg lumped together. No orthostat (seat to stand) change in SBP or DBP. Time after dose of orthostat measure unknown.

Appendix A (NDA 20-297) Abbreviations: R= randomized, NR= not randomized, SEQ= sequence, Xover= crossover

PROTOCOL	VOL	Objective	Design	Subject	Treatment	single vs multi dose	n completed (enrolled)	Results
G10, important AE, see appendix B13	1.143	PD, echocardiography	NB, NC, NR, 6 centers	Japanese mild - mod ESS HTN, 61-82 yr	carv 10 mg po/d (n=6), carv 10 mg then 20 mg po/d (n=5)	multi x 8 weeks	9(11), 2 withdrawn: 1=rash, 1=paresis	no protocol; response measurement time after dose unknown; response 10-20 mg lumped together; results in table 5, pg 251; no significant hemodynamic changes measured with echo
G15, important asthma data	1.144	PD, oral gluc tol test	NB, NC, NR	Japanese ESS HTN	carv 10-30 mg po/day, mean 19 +/- 2.5	multi x 8-12 wks	17(20), 1 exclu for taking	no protocol. 75 g OGTT pre therapy then at end of 8-12 wks. criteria for dose escalation not defined. 1 asthma patient had asthma exacerbation while on carv improved with dechallenge. HTN+DM insulin grp n=4, HTN+DM diet+/-sulfonyl urea n=8 (missing data)
G15, cont, see appendix B14-B15	1.144			+/- DM	mg/day po		nifedipine, 2 exclu 2nd to no OGTT	HTN no DM group n=5 (missing data). no difference in OGTT not believable 2nd to small n and dropouts and missing data. See fig 3, pp 78-79. reason for excluding nifedipine subject not given.
G20, see appendix B16-B17	1.81	PD	NB, NC, NR	Japanese HTN, hemo-	carv 10 mg po/d	multi x 4 weeks	6(6), 1 female	no protocol; all results compared with pretreatment baseline; 1 female (wt ?) required dose reduction to 5 mg for decreased BP (amount ?). Only 2 patients had CL _{urea} (dialyzer) measured. Sponsor says no CL _{urea} (dialyzer). Data insufficient on CL _{urea} (dialyzer)
G20, cont	1.81			dialysis				AUC not reported. C _{max} not changed by dialysis in 5-6 patients (missing data not explained). claim no accumulation after multi dose not justified, only 3 patients measured. mean BP on fig 3,4,5 pg 120-121 (see appendix B16-B17)
G28, see appendix B18-B21	1.145	PD, LV function	NB, NC, NR	Japanese + MI	carv 20 mg po	single	10(10), mean age 67.6 yrs	no protocol. Swan-Ganz cath. radionuclide angiography. response (rest, max exercise, post exercise) measured pre and 1 hr post drug. carv failed to block exercise-induced increases in heart rate or SBP. (SBP baseline decreased).
G28, cont	1.145							no change in eject fract ? believable 2nd to 2 missing subjects data. no change central venous press or syst vasc resist. ? alpha-beta blockade claim. see fig table pp 17-20. No post exercise results reported. No change in HR reported at rest
G29, see appendix B22-B24	1.145	PD, LV function	NB, NC, NR	Japanese ASCHD on cor	carv 10 mg po/d	multi x 1 week	11(11), mean age 52 yrs	no protocol. Swan-Ganz cath. radionuclide angiography. response (rest and max exercise) measured prestudy then after carv x 1 wk (2-3 hrs after dose). max exercise is angina (n=8), ST depress (n=1), fatigue (n=2). results see fig 2,3,7, pp 52,53,57
G29, cont	1.145			angio				carv failed to block exercise induced increases in SBP, heart rate. No change card output, stroke vol, tot periph resist, rate press product, LV eject %, LV end diast vol, central venous press. carv increased pulm vasc resist with exercise (? significance)

Appendix A (NDA 20-297) Abbreviations: R= randomized, NR= not randomized, SEQ= sequence, Xover= crossover

PROTOCOL	VOL	Objective	Design	Subject	Treatment	single vs multi dose	n completed (enrolled)	Results
MF2684	1.84	PD, echocardiography	DB, R SEQ, AC, Xover	healthy, sex?	carv 50 mg po, propranolol 40 mg po	single	10(10)	no protocol, no full report, response (echo) measured ? time after dose; carv caused more decrease in cardiac index, preload, periph resist than propranolol; equipotent doses ?
MF2740, see appendix B25-B31	1.116	PD, beta no block, invasive hemo-	DB, no placebo, AC, parallel	ASCHD on angio, post	carv 50 mg po, propranolol 40 mg po	single	16(16), age 37-61 yr	? dose choice. ? equipotent doses. rest-exercise Swan-Ganz cath pre-90 min post dose. leg plethysmography. baseline different in rest syst BP. mixed exercise stoppoint=angina or exhaust in carv grp; endpt=angina, exhaust, VES, dyspnea in propran grp
MF2740, cont	1.116	dynamics, vein flow		PTC A, men only				See appendix B25-B31. carv showed no beta blockade of exercise-induced increases in heart rate or syst BP. carv (? propran) showed no change pulm art press, PCWP, CI, stroke vol, syst art resist, pulm art resist, leg blood flow.
MF3070	1.124	PD, FEV1, peak flow, FVC	DB, PC, R, 2-Xover	healthy men and women	carv 25 mg po, placebo	single	8(8)	Measures pre, 2 hr post dose at rest, exercise. carv blocked exercise induced increase in heart rate (-10 bpm at 200 watts) and SBP (-20 mm Hg at 150-200 watts)(delta rest, delta pbo). No change in resting FEV1, FVC, FEV1/FVC. peak flow not reported
MF3364	1.129	PD, lung	DB, FC, R SEQ, 2-Xover	healthy men and women	carv 25 mg po, placebo	single	10(11), 8 in protocol, 1 dropout reason ?	Measures pre, 2 hr post dose, pre and post histamine provocation. 2/10 decreased FEV1 more than 20% after carv + histamine. body plethysmography TLC, RV not analyzed in report. possible decreased mean peak expir flow 3 min post carv
MF3697	1.84	PD, PK	SB, NR, plac control ?	young 12, elder 9, ? healthy	carv 12.5 mg bid po x 7d, carv 25 mg bid po x 7d	multi	1 withdrew in placebo phase, ? young or elder	no protocol, no full report, no tables, no results, no figures
MF3698, important AE.	1.135	PD, drug interaction loop diuretic	NB, NC, NR	hypertension diast BP 100-115	carv 25 mg capsule po with torasemide 2.5	single	5(5), n=15 intended per protocol	Seated BP only hourly 1-4 hrs, then 6,8,12,24 hours post dose. 1/5 patients with diast BP 97 failed inclusion criteria. Syst BP fell 20-70 mmHg and diast BP fell 20-30 mmHg in 4/5 patients. Mean SBP, DBP, pulse showed decreasing trend over 24 hrs.
MF3698, continued	1.135			mmHg, 31-73 yrs old	mg tablet po			3/5 patients complained of orthostat symptoms. Lab results not reported. No standing BP reported. Trial enrollment cancelled due to adverse events in first 5 patients.

Appendix A (NDA 20-297) Abbreviations: R= randomized, NR= not randomized, SEQ= sequence, Xover= crossover

PROTOCOL	VOL	Objective	Design	Subject	Treatment	single vs multi dose	n completed (enrolled)	Results
MF3706	1.106	PD, invasive hemodynamic	DB, AC, R SEQ, parallel group	men, ASCHD on cor angio	carv 5 mg IV, propranolol 6 mg IV	single	17(19), 2 propran subject excluded	No placebo arm. Equipotent doses carv and propran not known in this population. Question appropriate dose for comparison carv vs propranolol. Compared to predose, carv decreased heart rate, aort syst and diast BP
MF3706, cont	1.106						2nd to total cor occlusion	compared to predose, carv decreased cor flow, rate press product and cor resist x RPP. carv increased cor resistance. inconsistent statistical alpha error used (0.01-0.10, 1 and 2-side alpha)
MF3710	1.135	PD, forearm vasodilation	DB, PC, R SEQ, Xover	healthy men	carv 25, 50 mg po, placebo po	single	9(10), 1 dropout for "personal reasons"	brachial artery pulsed doppler pre, 3,6,9 hrs post dose. SBP, MAP decreased by carv. carv 25 mg(not 50 mg) non-significant increased art diameter (vasodilate). No change blood flow velocity, art flow rate, periph resist, pulse wave velocity (missing data).
MF3710,cont	1.135							no change arterial compliance. Wall tension decreased for carv 50 mg (not 25 mg)
MF3817	1.106	PD, echocardiography	DB, PC, R SEQ, Xover	patients, ASCHD on cor angio	carv 5 mg IV, placebo	single	17(21), withdrawals: 1 arrhythmia, 1 calcified aortic valve, 2 problem echo equip	No change in LV parameters on echo. No positive control. No power analysis. Heart rate, DBP, SBP not affected by carv. Question appropriate choice of dose. ? appropriate withdrawals
MF3837, important AF, see appendix B32-B34	1.61	PK, liver impairment	NB, NC, R SEQ, Xover	cirrhosis cholinesterase <1800,	carv 25 mg capsule po, carv 12.5 mg IV over 1 hr	single	6(6), mean age 52.5 yrs, mean weight 76.9	After IV dose, 2 men sampled at wrong times but were included in calculation of PK parameters. Patient #6 with high carv concentration after IV excluded from all PK analyses. #6 (possible slow metabolizer) developed hypotension, nausea, oliguria requiring
MF3837, cont	1.61			Quick <70%			kg, 20 historical healthy controls	med treatment (no details). #6 carv conc 0.25-1 hr post po dose= 2-3 x above mean (n=6). F=>82.6% (much higher than healthy men). Carv dose excreted in urine after IV or po <1%. Compared to healthy, liver disease increase V, decrease CL. see appendix B32
MF3897	1.139	PD, skin temperature	DB, AC, R SEQ, 2-Xover	healthy men, women, non smoke	carv 25 mg po, propranolol 80 mg po, equipotent ?	single	14(14), 20 in protocol	hand thermography pre, 2 hr post dose showed no change for either drug. no conclusions can be drawn from this study. active control was not active. there was no placebo comparison.

Appendix A (NDA 20-297) Abbreviations: R= randomized, NR= not randomized, SEQ= sequence, Xover= crossover

PROTOCOL	VOL	Objective	Design	Subject	Treatment	single vs multi dose	n completed (enrolled)	Results
MF3898, important study	1.140	PD, beta, alpha block, blood	R, DB, PC, AC, Xover	healthy men	carve 25 mg/d, carve 50 mg/d, labetalol 400 mg/d,	multi for 1 week	4(4)	Measures 1.3 and 3 h 50 min after dose. Supine and tilt SBP fell 10-20 mm Hg. All active drugs blocked exercise-induced tachycardia and rise in SBP. Carv 50 blocked phenylephrine, noradrenaline. (angiotensin effect equivocal) Day 1 and 7 changes similar
MF3898, cont		flow, hemodynamics			placebo/d			Per protocol, 12 subjects were to be enrolled. No explanation for failure to enroll 8. No difference in supine DBP, tilt DBP, supine pulse, tilt pulse, calf blood flow, PR and QT intervals, card impedance stroke vol, card output
MF3924	1.107	PD angio hemodynamic	NB, NC, NR	patients, ASCHD on cor	carv 5 mg IV	single	10(10), all men, age 44 - 68 yrs	? dose choice. did not correlate carv concentration with effect. rt heart press no change except possible decreased pulm art diast press. no change cardiac output. poss decrease total systemic resist. LV segmental wall motion no change.
MF3924, cont	1.107	LV, RV function		angio				no change LV eject fraction, LV end diast press, LV stroke vol index. carv decreased LV systolic press, aort syst press, aort diast press, mean aort press, LV pos DP/dt max (contractility). PCWP not measured.
MF7017	1.141	PD alpha vaso-dilation	DB, AC, R SEQ, X-over, NR	healthy men, avg age	carv 50, 75 mg suspension po metipranolol	single	12(12). no dropouts reported	no protocol. Hourly venous plethysmography (arm) to 6 hrs post dose. Changes 2nd to meal confound after 3rd hour. Arterial flow non-significant increase from baseline with carv 50, 75 but not metipran. Periph resistance non-significant decrease from
MF7017, cont	1.141	vein flow	SB placebo	24.3 yrs	7 mg susp po		ECG results not reported	baseline with carv 50, 75 but not metipran. No convincing change with any active treatment on venous capacity, venous efflux, venous tone, venous pressure-volume curve. No placebo results reported. Alpha blockade questionable.
MF7018, see appendix B35	1.64	PD, dose finding, PK	NB, NR, PC, parallel	healthy men	carv mg IV: 0.313, 0.625, 1.25, 2.5, 5.0, 6.1, 7.5, 9.2	single	46(46), n=24 carv (2 men per dose level)	no protocol. doses changed from coversheet (reason ?). PK included only 5 samples in 2 hrs post infusion. orthostat BP measured only 2 (? 3) and 7 hrs post infusion. at doses above 17 mg, AUC falls. question saturation of hepatic reabsorption.
MF7018, cont	1.64				carv mg IV: 11.25, 16.88, 21.09, 26.37		n=22 placebo subjects	fractional excretion (0-8 hrs after dose) of carv in urine < 1% for all IV doses. orthostat SBP fell > 20 mm Hg (with no increase in pulse > 20 bpm) for 1 of 2 subjects on carv 0.625, 9.2, 21.09, and 26.37 mg at 3 hrs post infusion.
MF7018, cont	1.64							n-octanol/phosphate buffer partition coefficient = 817 (at pH 7.0) and 1993 (at pH 7.4). when dose increases, there is no convincing increase in systolic baseline amplitude of the pulse curve during finger plethysmography

Appendix A (NDA 20-297) Abbreviations: R= randomized, NR= not randomized, SEQ= sequence, Xover= crossover

PROTOCOL	VOL	Objective	Design	Subject	Treatment	single vs multi dose	n completed (enrolled)	Results
MF7019, important AE	1.65	PK, bioavailability	NB, NC, R SEQ, Xover	healthy men	carv 50 mg po capsule with Myrj-52, carv 50 mg po capsule no Myrj-52, carv 50 mg po tablet with	single	20(20), 1 withdrawal syncope + seizure while seated 20 min post dose with full recovery	no protocol. elevated AST, ALT (up to 10x up limit normal) with no elevated GGT in 1 subject withdrawn from one period in Xover. MYRJ-52 increases C _{max} (doubles), increases AUC (x 1.4). 6 - 10 fold inter-individual variability on both parameters
MF7019, cont	1.65				Myrj-52		after 5 hrs post dose	MYRJ-52 shortens half-life (trend yes, significant no), No change in T _{max} . No BP, pulse reported. These formulations not planned for market.
MF7020	1.66	PK, bioavailability	NB, NC, R SEQ, Xover	healthy men	carv 12.5 mg IV infuse over 1 hr, carv 50 mg po suspension, carv	single	20(20)	no protocol. F: susp 22%(10-73), 50 cap 24%(12-46), 25 cap 22%(10-49). total CL _(iv) 589 mL/min(375-848). V _{d(iv)} 132 L(92-255)= 1.68 L/kg(1.1-2.9 L/kg). C _{max} IV=173 ng/mL(109-234), susp 128 ng/mL(55-237), 50 cap=66 ng/mL(34-130), 25 cap=21.4 ng/mL(4.7-99)
MF7020, cont	1.66				50 mg po capsule, carv 25 mg po capsule			elim t _{1/2} : IV=2.38 hr(1.95-4.17), 50 mg susp=4.3 hr(1.9-8.7), 50 mg cap=6.35 hr(4.1-14.6), 25 mg cap=7.06 hr(2-20.9). no significant increase in serum K. urine chloride (24 hr) twice urine Na (24 hr). reason unknown. serum chloride had no change.
MF7021, see appendix B36	1.67	PK, bioavailability, food effect	NB, NC, R SEQ, Xover	healthy men, avg age 27.8 yr	carv 25 mg po	single	20(20), no dropouts reported	no protocol. breakfast= 40% bread, 29% ham, 17% cheese, 14% jam. breakfast before dose increased absorp lag time and T _{max} but did not affect elim half life, C _{max} , AUC, MRT. data from 2 subjects deleted. reason unknown. see appendix B36
MF7022, important AE	1.67	PK, bioavailability, capsule effect	NB, NC, R SEQ, Xover	healthy men, avg age 31.6 yr	carv 50 mg po caps (size 0), carv 25 mg po caps (size 0)	single	18(20), 1 dropout due to influenza	no protocol. no BP pulse reported. 1 dropout (2nd period) circ ⁿ story collapse, syncope, vomit, urine void 1.75 hr post dose. only 9/19 had samples at 14 hrs post dose. 3-4 men excluded from analysis for ? reasons included men with lowest AUC.
MF7022, note cont, see appendix B37	1.67				carv 50 mg po caps (size 3)		had highest C _{max}	lowest C _{max} , or highest C _{max} . PK unremarkable in syncope subject. PK parameters in table (see appendix B37)

Appendix A (NDA 20-297) Abbreviations: R= randomized, NR= not randomized, SEQ= sequence, Xover= crossover

PROTOCOL	VOL	Objective	Design	Subject	Treatment	single vs multi dose	n completed (enrolled)	Results
MF7023, see appendix B38	1.68	PK, bio-availability, resistant tab	NB, NC, R SEQ, Xover	healthy men, avg age 32.1 yr	carv 34 mg po suspension, carv 16.67 mg 2 tabs po	single	10(10)	no protocol. creatinine clearance no change. coated tablet resistant to gastric acid had delayed Tmax, lower Cmax, and lower AUC compared to suspension. PK parameters in table (see appendix B38). results do not represent commercial formulation.
MF7024, see appendix B39-B40	1.68	PK, interaction torasemide	NB, NC, R SEQ, Xover	healthy men, avg age 24.6 yr	carv 25 mg po capsule, torasemide 5 mg po tab, combo	multi, 1 dose/day x 5 days	12(13), 1 excluded had no measurable drug	body weight stable for all subjects throughout study. predose carv concentration on days 3-5 were borderline detectable(1-2 ng/mL) in 8/12 men and < 1 ng/mL in 4/12 men, ie showing no accumulation. No subject had detectable torasemide > 40 ng/mL or toras-
MF7024, cont	1.68	see tables pp 157, 162			carv 25 + torasemide 5 po		level, which drug, not reported	emide M5 metabolite > 20 ng/mL. predose on days 3-5 on combo carv + torasemide, ie, no accumulation. PK parameters for toras, toras M5, and carv unchanged by combo therapy. no change in mean heart rate, FVC, FEV1, FEV1/FVC, FEF25-75, SPEP by any treatment
MF7025	1.70	PK, bioavailability, enteric coated	NB, NC, R SEQ, Xover	healthy men, age 21-46 yrs	carv 25 mg, 2 tabs po, 3 enteric coated forms with different pH-resistances	single	9(9)	no withdrawals for adverse events. the formulations were not bioequivalent with large changes in Cmax and AUC. none of these forms is commercial form. no BP pulse recorded.
MF7027	1.84	PD, alpha B, hand vein	SB, 4-Xover, NR, PC	healthy men	carv 50 mg po	single	8(8) age 23-30 yr	no protocol, no full report, no tables, no figures; measured response= dorsal hand vein diameter pre and post carv. carv blocked response to norepinephrine and PGF2alpha at 1, 3.5 hrs post dose; placebo response not reported. ? alpha blockade
MF7108, see appendix B41-B43	1.72	PK, carv-digitoxin interaction	NB, NC, NR, Xover	healthy men and women, avg age 27.4 yrs	digitoxin 0.07 mg/tab, 8 tabs po/day, carv 25 mg tab, 1 po/day	multi carv x 7 days (days 31-37)	12(12), no dropouts	pp 209-231, including most of protocol, missing. PK measured on day 1 (dig alone), day 35 (carv alone at steady state), day 36 (carv + dig). one woman collapsed at work 2 hrs after 7th carv dose. Dig PK not affected by carv. Carv and desmethylcarv PK not
MF7108, cont	1.72					digitoxin single dose days 1, 36		affected by dig. see fig 1-3, table 2 in appendix B41-B43. Digitoxin did not change carv or desmethylcarv excreted in urine. no significant change in SBP, DBP, heart rate. ECG data not reported.
P15	1.142	safety, urine chemistry	NR, NB, NC	healthy men	carv 10 mg po x 1 day, 25 mg x 2 days, 25 mg q 12 h x 4 days	multi	6(6)	no protocol submitted. No ECG intervals reported. normal urine Na, Ur K, Ur creatinine, Ur volume, Ur pH. Supine and standing pulse and BP were not compared. Pulse and BP changes between doses not compared

AT B1

PHARMACOKINETIC DATA - COMPARISON BY SUBJECT

PROTOCOL ID.	: RD134/16996	SAMPLE TYPE	: PLASMA
FIRST SAMPLE TIME	: 01 00:00	COMPONENT	: CARVEDILOL
LAST SAMPLE TIME	: 01 12:00	TARGET DOSE	: 25 mg.
FORMULATION	: CARVEDILOL	DOSE TIME	: 01 00:00

ADMINISTRATION 01

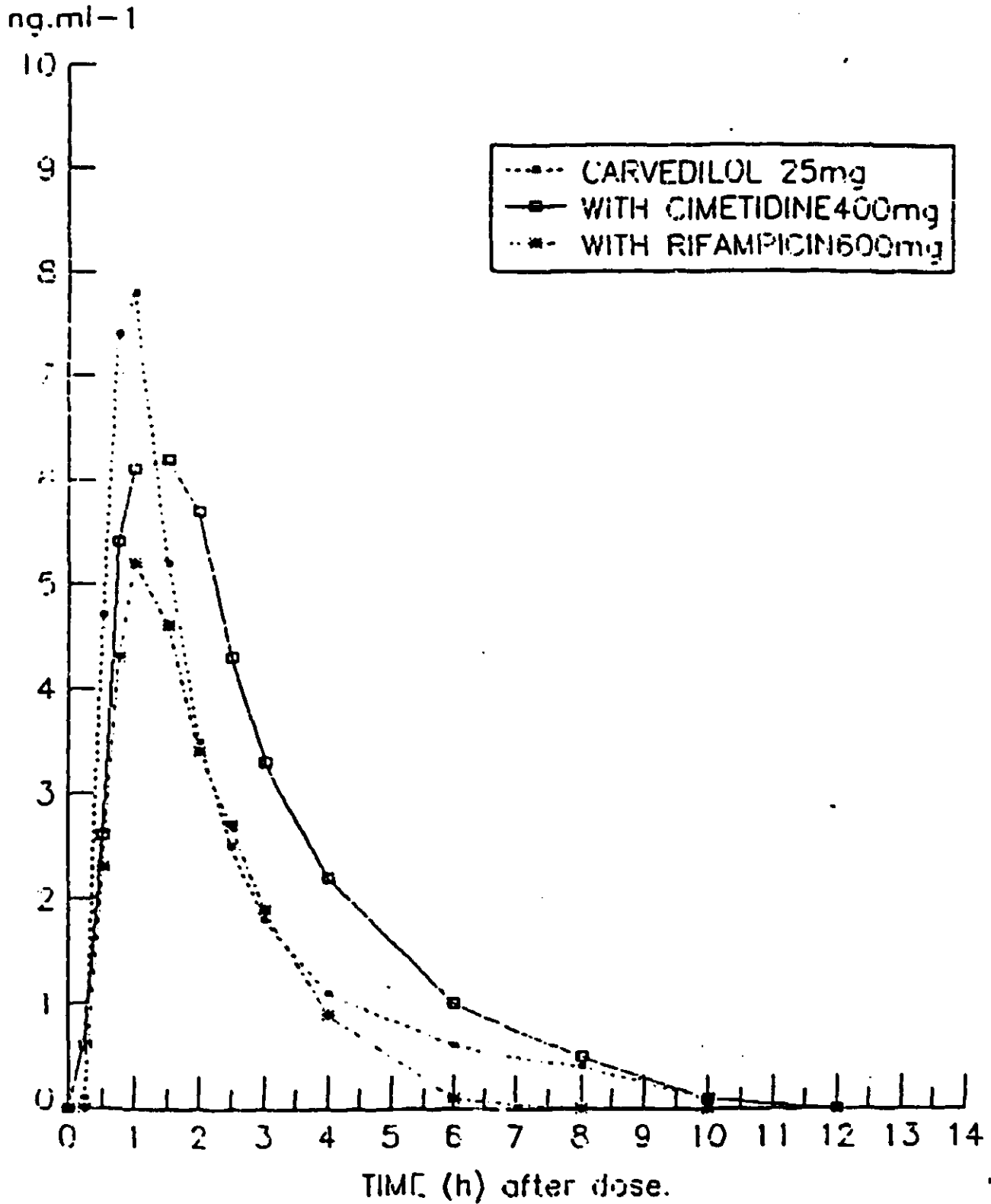
VSN INITIALS	C _{max} (ng.ml ⁻¹)	T _{max} (hr)	AUC(T) (ng.ml ⁻¹ .h)	AUC(I) (ng.ml ⁻¹ .h)	K _{elim} (hr ⁻¹)	T 1/2 (hr)	Cl (l/hr)
01							
02							
03							
04							
05							
06							
07							
08							
MEAN	86.5	MEDIAN 0.75	202.830	214.392	0.2915	2.43	0.135
S.D.	35.4	RANGE 0.75- 2.00	86.908	95.748	0.0484	0.36	0.055

CAR 8902
VOL 1.73

000073

FIGURE 5

MEAN PLASMA DESMETHYL CARVEDILOL LEVELS AFTER THREE SEPARATE CARVEDILOL DOSES.



CAR 8902
VOL 1.73
000092

BHP STUDY: CARV 0012
 INVESTIGATOR: KISICKI

TABLE 3
 INDIVIDUAL PHARMACOKINETIC PARAMETERS

INTRAVENOUS SOLUTION 0.084 MG/KG

SUBJECT	AUC 0-T MG HR/ML	AUC 0-INF MG HR/ML	C MAX MG/ML	KEL /HOUR	T HALF HOURS	MRT HOURS	CL SYSTEMIC L/HR	V _{SS} L/HR
01								
02								
03								
04								
05								
06								
07								
08								
09								
10								
11								
12								
MEAN	214.5	227.7	203.3	0.258	3.22	3.84	32.8	114.0
S.D.	73.3	78.6	54.1	0.105	1.73	1.60	9.2	30.4
MIN								
MAX								

SOURCE: BOEHR: [BIS.CARV.CARV0012]LIST.SAS RUN 8/4/87 BY CMH. TE: TE BY GTS 2/27/89

25

B 3

CARV 0012

VOL 1.78

000027

BMP STUDY: CARV 0012
 INVESTIGATOR: KISICKI

TABLE 4
 INDIVIDUAL PHARMACOKINETIC PARAMETERS
 CAPSULE 50 MG

SUBJECT	AUC 0-T NG HR/ML	AUC 0-INF NG HR/ML	C MAX NG/ML	T MAX	KEL /HOUR	T HALF HOURS	MRT HOURS	CL SYSTEMIC L/HR
01								
02								
03								
04								
05								
06								
07								
08								
09								
10								
11								
12								
MEAN	555.9	626.9	128.0	1.35	0.101	7.53	8.61	110.5
S.D.	341.4	410.1	87.1	0.89	0.031	2.62	2.65	59.5
MIN								
MAX								

SOURCE: BOHR: (BIS.CARV.CARV0012)LIST.SAS RUN 8/4/87 BY ERH, TE

000028
 VDL 1.78
 CARV 0012

B4

25

BMP STUDY: CARV 0012
 INVESTIGATOR: KISICKI

TABLE 5
 INDIVIDUAL PHARMACOKINETIC PARAMETERS
 ORAL SOLUTION

SUBJECT	AUC 0-T NG HR/ML	AUC 0-TNF NG HR/ML	C MAX NG/ML	T MAX	KEL /HOUR	T HALF HOURS	MRT HOURS	CL SYSTEMIC L/HR
01								
02								
03								
04								
05								
06								
07								
08								
09								
10								
11								
12								
MEAN	445.3	518.9	120.7	0.85	0.099	9.06	9.55	119.5
S.D.	207.3	270.3	57.9	0.70	0.060	4.37	3.66	52.4
MIN								
MAX								

SOURCE: BOEHR:(BIS.CARV.CARV0012)LIST.SAS RUN 8/4/87 BY ERH, TE

000029
 CARV 0012
 VOL 1.23

27
 165

66

BMP STUDY: CARV 0012
INVESTIGATOR: KISICKI

TABLE 6
INDIVIDUAL DOSE ABSORPTION FRACTIONS

SUBJECT NUMBER	AUC CAPSULE	AUC SOLUTION	AUC ^a IV	F CAP/SOL	F CAP/IV	F SOL/IV
01						
02						
03						
04						
05						
06						
07						
08						
09						
10						
11						
12						
GEOMETRIC MEAN				1.14	0.33	0.29

^a ADJUSTED FOR DOSE

SOURCE: BOEHR: [BIS.CARV.CARV0012]ANOVA.SAS RAN 8/4/87 BY ERH, TE

CARV 0012
VOL 1.78
000030

Table 1 Pharmacokinetic parameters of carvedilol in healthy male subjects

Parameter	Dose (mg/man)			
	10	20	40	80
Lag time (hr)	0.00±0.00	0.14±0.09	0.17±0.11	0.25±0.12
T _{max} (hr)	0.9±0.3	0.9±0.1	1.3±0.4	1.8±0.2
C _{max} (ng/ml)	22.0±4.7	53.1±14.7	78.7±20.4	70.0±20.0
t _{1/2β} (hr)	4.28±1.43	8.03±1.92	8.29±1.84	13.87±2.78
AUC(0-∞) (ng·hr/ml)	59.9±12.7	232.5±88.1	285.2±89.6	389.5±94.0
V _d (l)	247±33	347±88	425±128	618±212
K _a (hr ⁻¹)	7.268±3.293	3.052±0.815	3.765±1.443	1.688±0.544
K _e (hr ⁻¹)	0.815±0.128	0.368±0.044	0.527±0.171	0.414±0.124
K ₁₂ (hr ⁻¹)	0.819±0.229	0.204±0.031	0.511±0.385	0.211±0.042
K ₂₁ (hr ⁻¹)	0.452±0.128	0.225±0.088	0.307±0.219	0.134±0.059

Results are expressed as mean values±S.E. for five subjects.

000022

F 31
VOL 1.81

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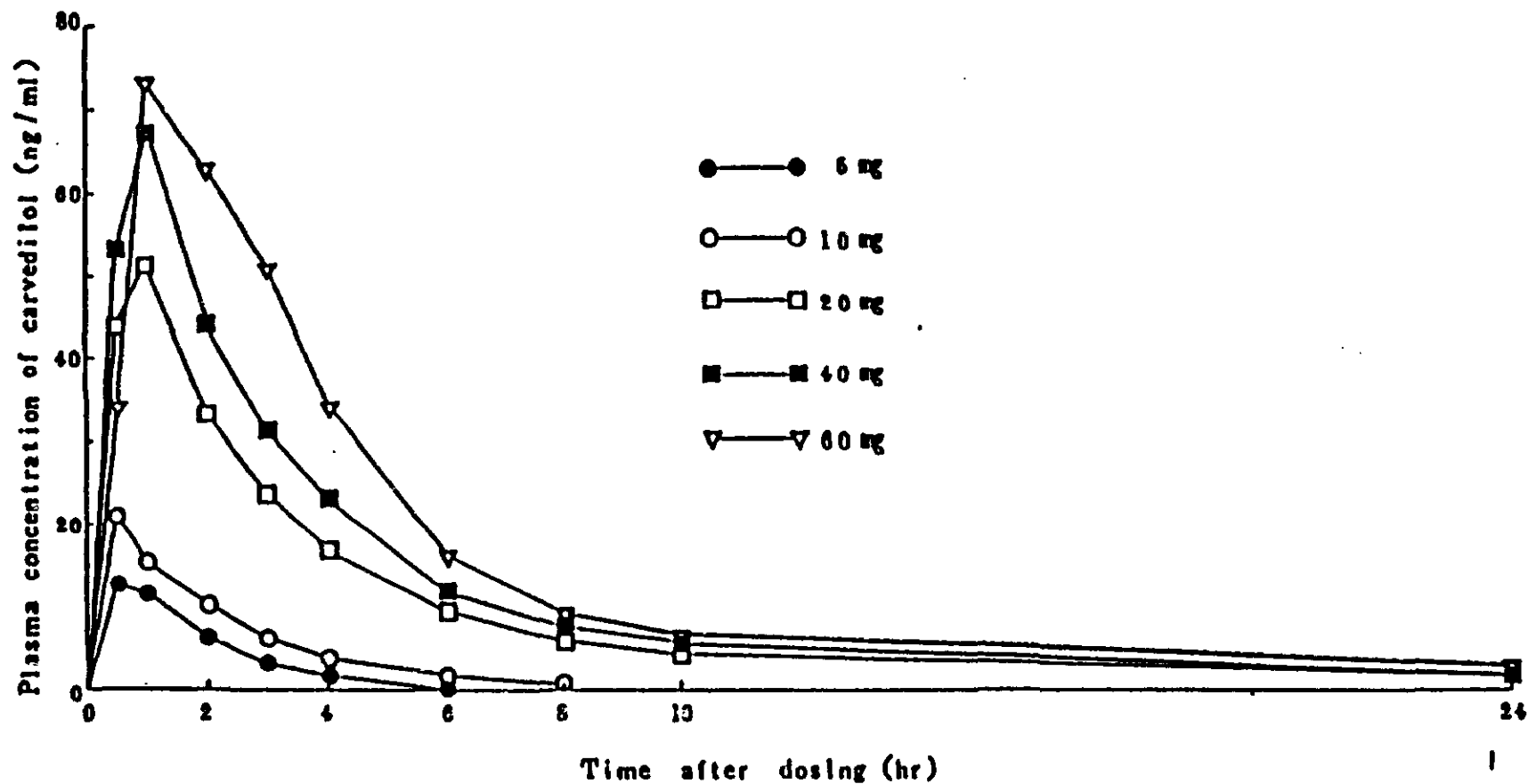


Fig. 2 Mean plasma concentrations of unchanged carvedilol following a single oral administration of carvedilol at various doses to healthy male subjects (n=5).

000026

F31
VOL 1.81

68

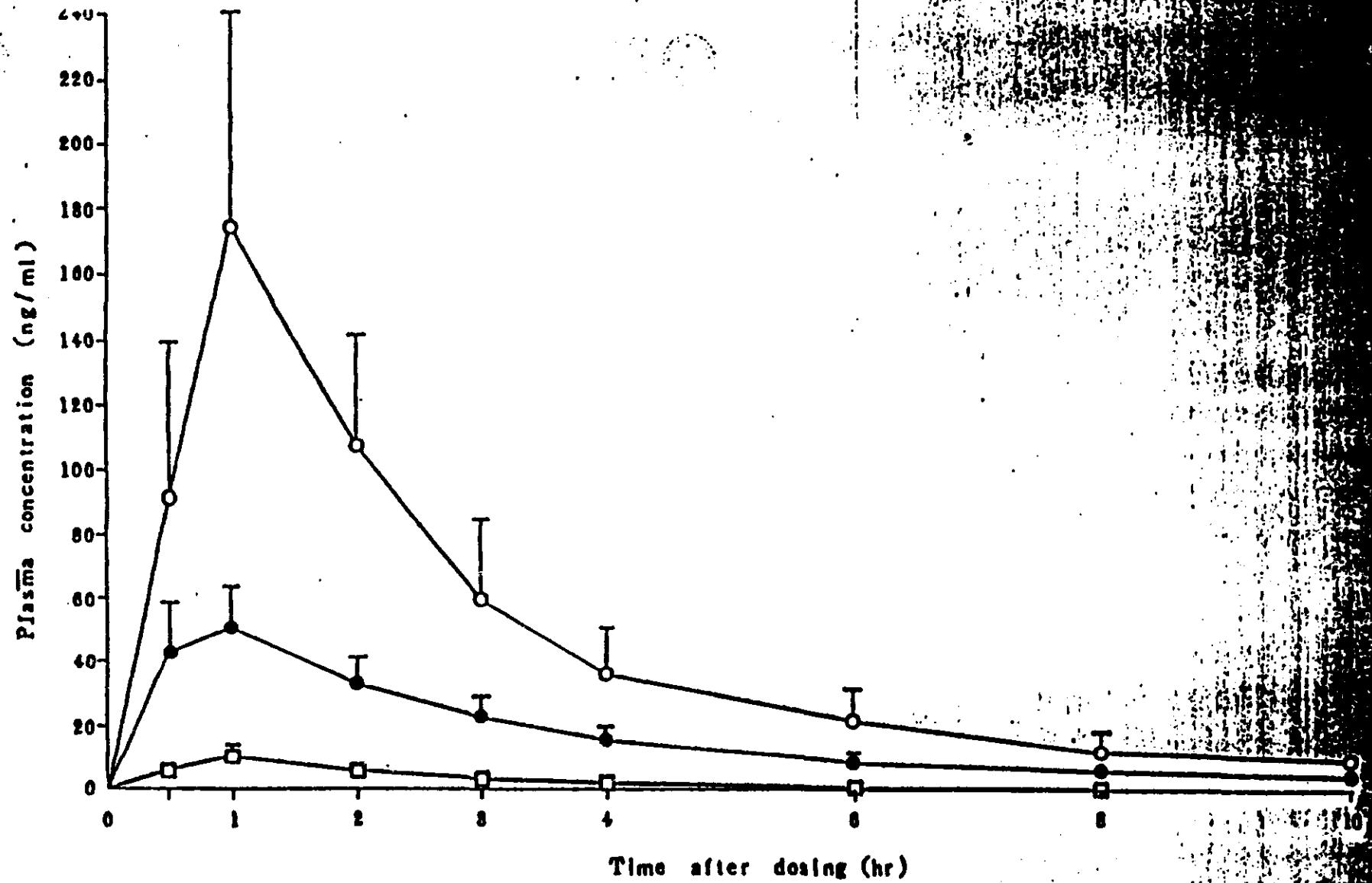


Fig. 3 Mean plasma levels of carvedilol glucuronide (O), desmethyl carvedilol (□) and carvedilol (●) in healthy subjects following a single oral dose of 20mg carvedilol (n=5). Plots are mean values $\pm$ S.E. from five subjects.

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VOL 1.81
000027

STATISTIK W/DO-27667(8-31)

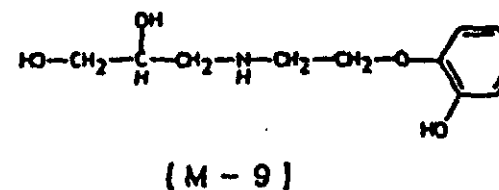
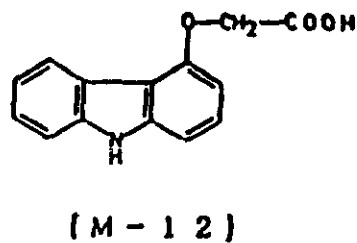
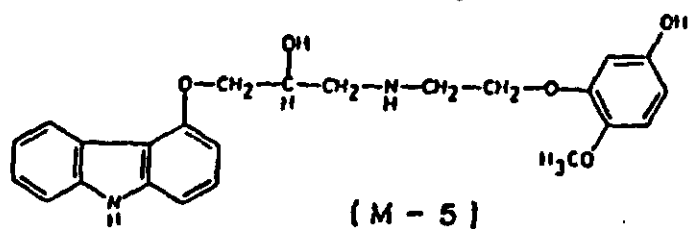
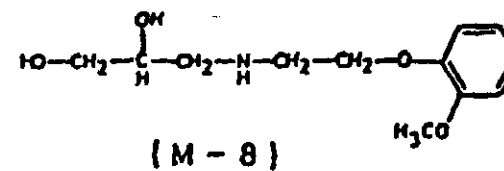
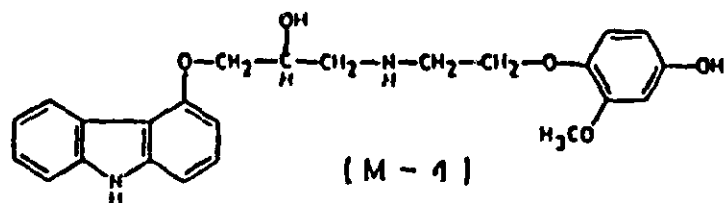
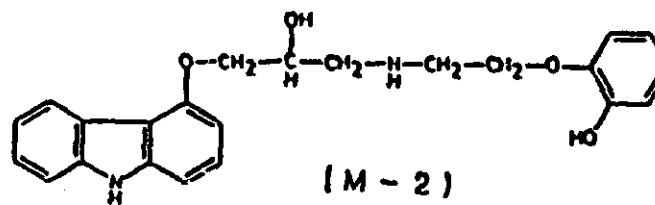
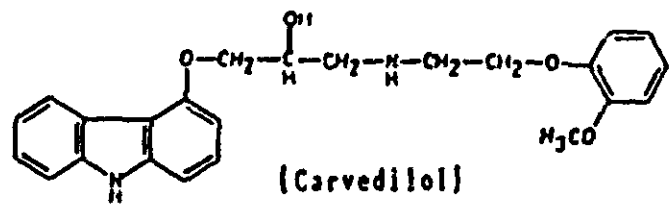


Figure 1. Chemical structures of DU-2468(carvedilol) and its metabolites.

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000053
F 34
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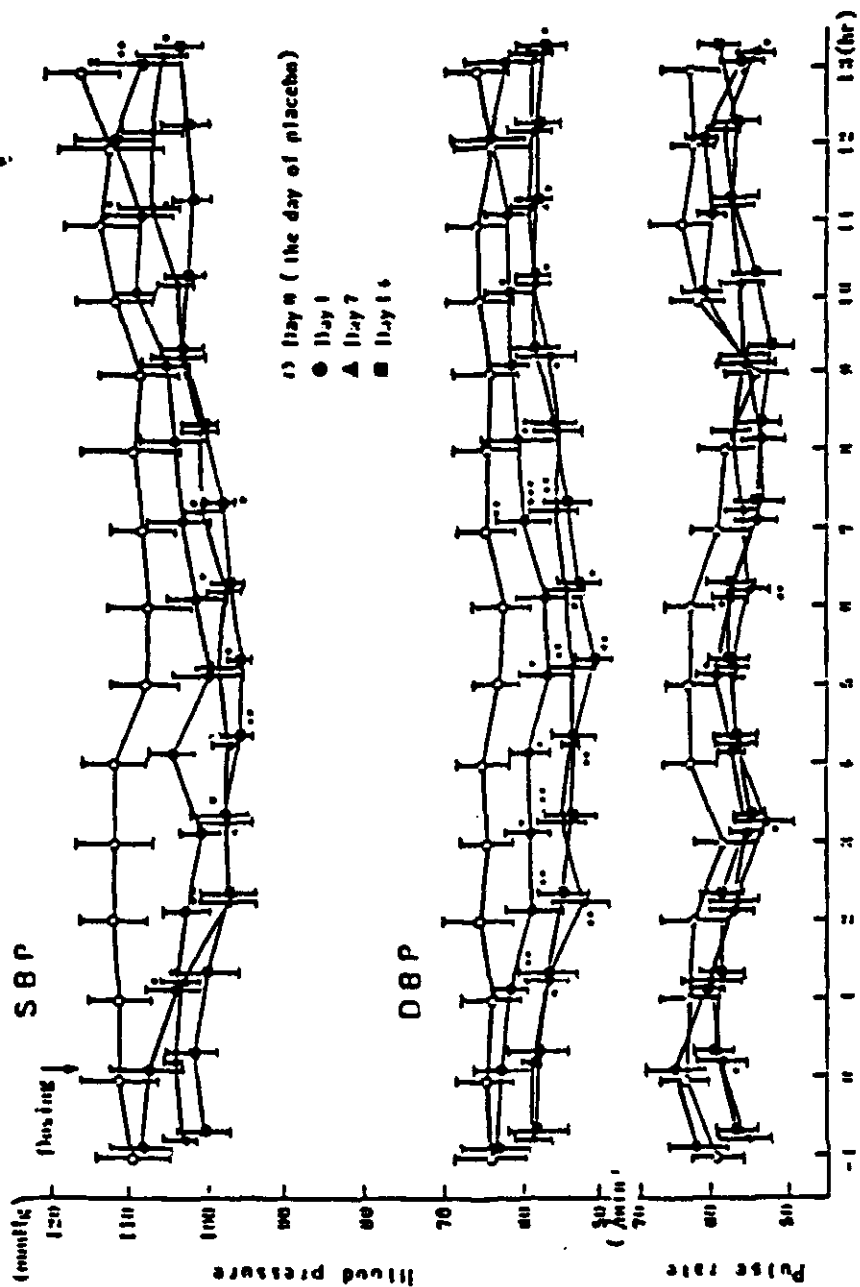


Fig. 7 Circadian variation of blood pressure and pulse rate at rest in sitting position in 14 days multiple dosing, 20mg once daily regimen

SBP: Systolic blood pressure, DBP: Diastolic blood pressure
o: p < 0.05, Δ : p < 0.01, $\square$: p < 0.001
* compared with Day 14 (the day of placebo dosing)

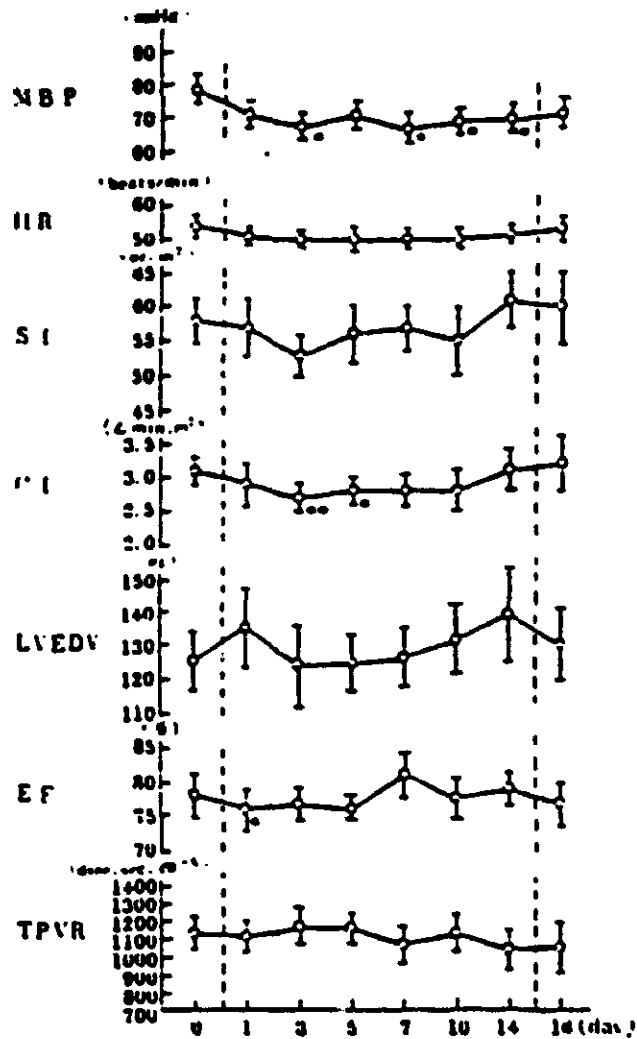


Fig. 8 Changes in hemodynamic parameters at rest in supine position in 14 days multiple dosing of carvedilol, 20mg once daily regimen (measurement 2 hrs after daily dosing)

MBP : Mean blood pressure, HR : Heart rate, SI : Stroke index, CI : Cardiac index
 LVEDV : Left ventricular end diastolic volume, EF : Ejection fraction.
 TPVR : Total peripheral vascular resistance
 (Mean ± S.E.)
 * : P < 0.05, ** : P < 0.01, *** : P < 0.001 (compared to before dosing)

B13

Table 5. Changes in hemodynamic parameters

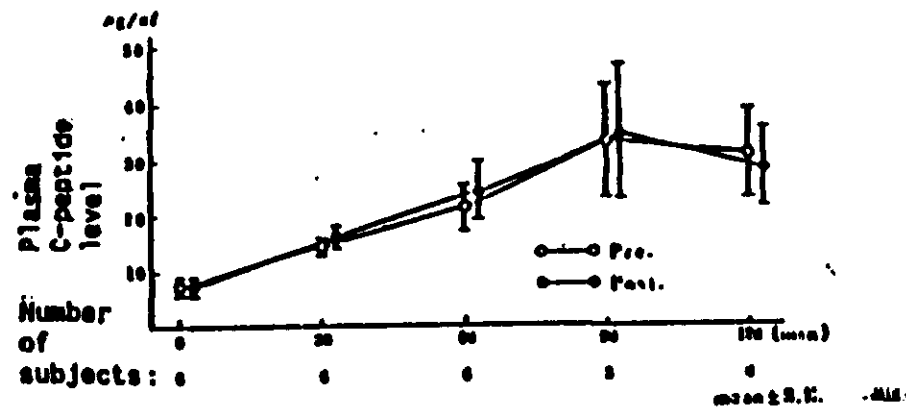
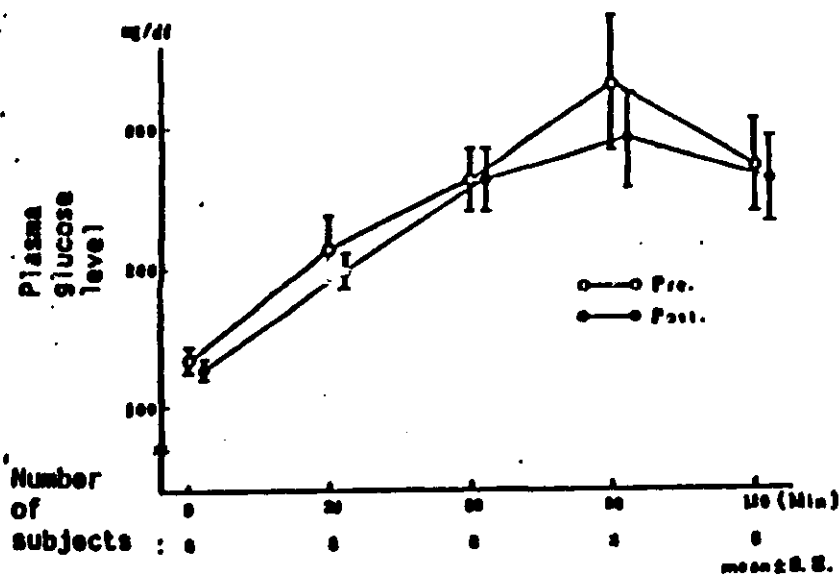
Item	Number of subjects	Observation period	End of treatment period	Test
S B P (mmHg)	9	166.9 ± 2.8	154.2 ± 6.6	n.s.
M B P (mmHg)	9	117.3 ± 2.9	106.7 ± 2.8	p < 0.01
D B P (mmHg)	9	92.7 ± 4.3	83.1 ± 3.4	p < 0.001
Heart rate (beats/min)	9	65.8 ± 2.4	60.8 ± 2.3	p < 0.05
P R P (×10 ²)	9	109.9 ± 4.3	93.6 ± 4.4	p < 0.05
L V D d (mm)	9	45.6 ± 1.8	45.1 ± 2.1	n.s.
L V D s (mm)	9	24.8 ± 1.7	26.4 ± 1.9	n.s.
E T (msec)	9	318.6 ± 13.7	332.3 ± 13.7	n.s.
L V E D V (ml)	9	98.2 ± 11.2	96.8 ± 13.2	n.s.
L V E S V (ml)	9	16.9 ± 3.4	20.7 ± 3.9	n.s.
S V (ml)	9	81.2 ± 8.4	76.1 ± 11.1	n.s.
S I (ml/m ²)	9	54.1 ± 4.5	51.0 ± 7.2	n.s.
C O (l/min)	9	5.4 ± 0.6	4.6 ± 0.7	n.s.
C I (l/min · m ²)	9	3.6 ± 0.3	3.1 ± 0.4	n.s.
E F (%)	9	83.7 ± 1.7	78.2 ± 4.1	n.s.
m V c r (msec ⁻¹)	9	1.5 ± 0.1	1.3 ± 0.1	n.s.
T P V R (dyne · sec · cm ⁻³)	9	1942.2 ± 216.4	2317.2 ± 347.9	n.s.

Mean ± S.E.

G-10
 VOL 1.143
 000251

In the dietary/SU-therapy group

SULFONYL UREA



In the insulin-therapy group

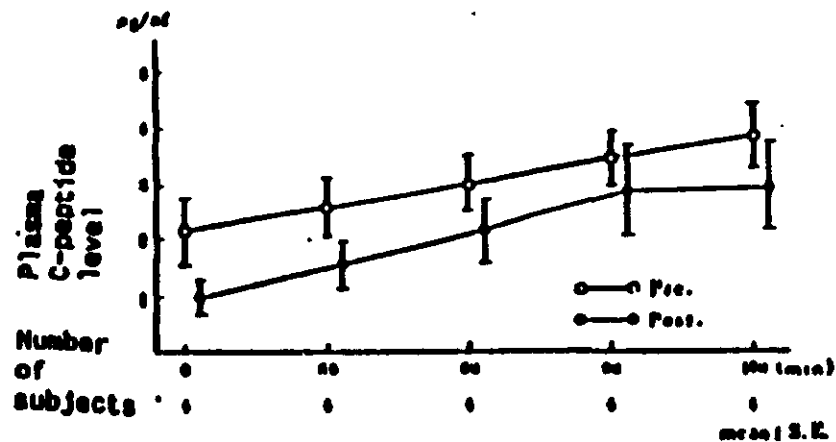
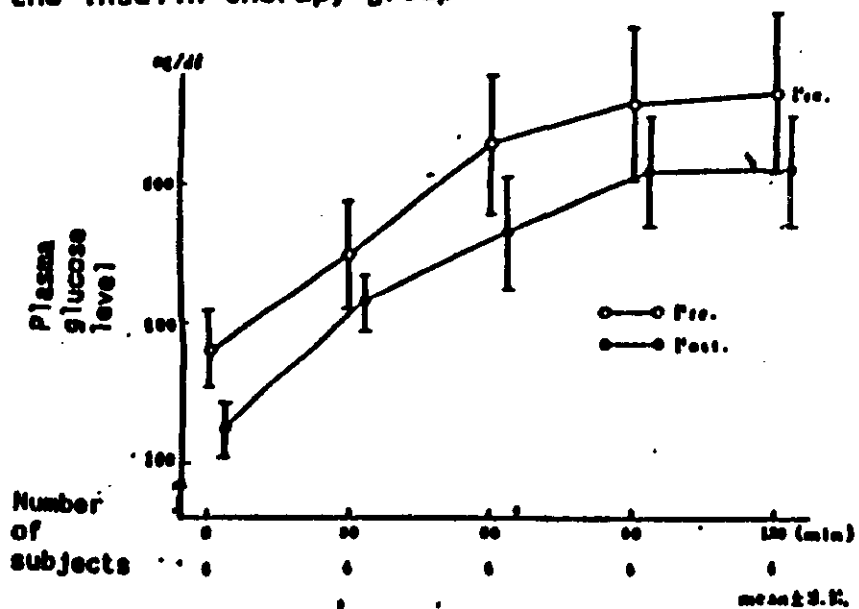


Figure 3. Effect of carvedilol on glucose tolerance

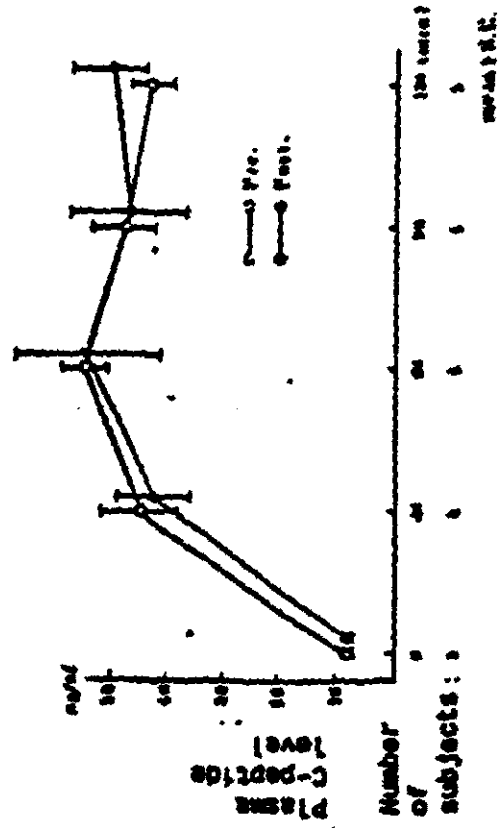
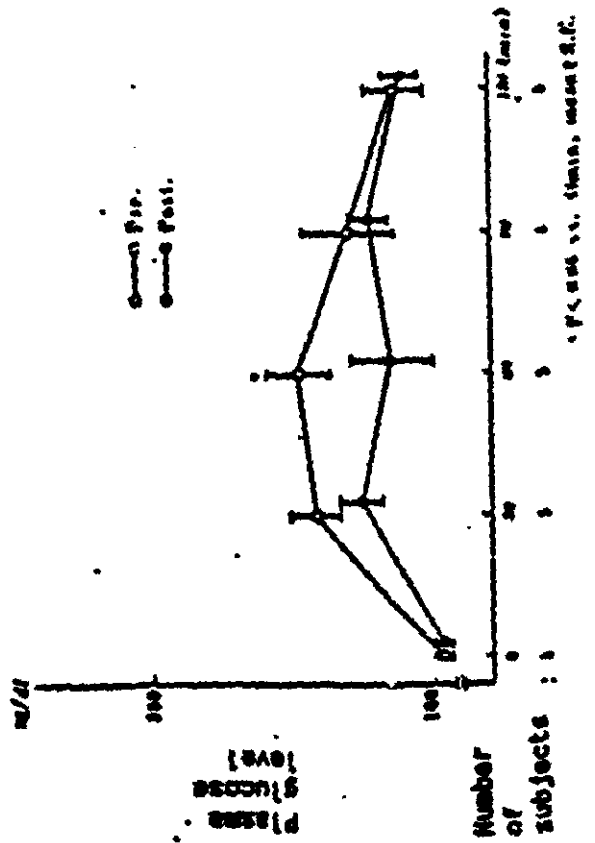
000078
VOL 1.144
G15

[Figure 3 continued next page]

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B15

[Figure 3, continued]
In the nondiabetic group:



[Translation by Josephine Howe (215) 348-7884, May 30, 1991]

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VOL 1.144
000079

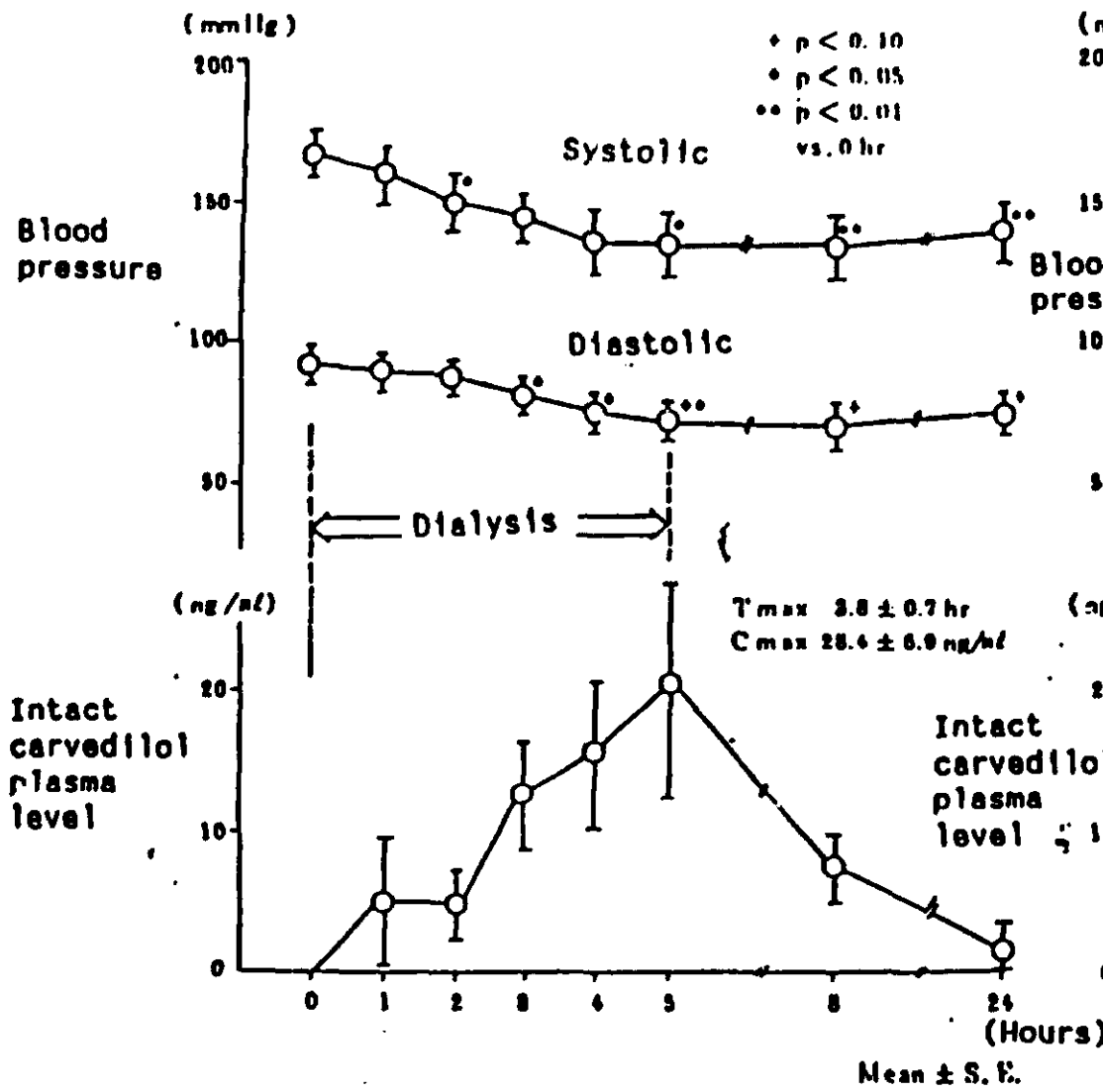


Figure 3 Changes in the blood pressure and intact carvedilol plasma level when a single dose of carvedilol was administered on a day the subjects underwent dialysis (n = 5-6)

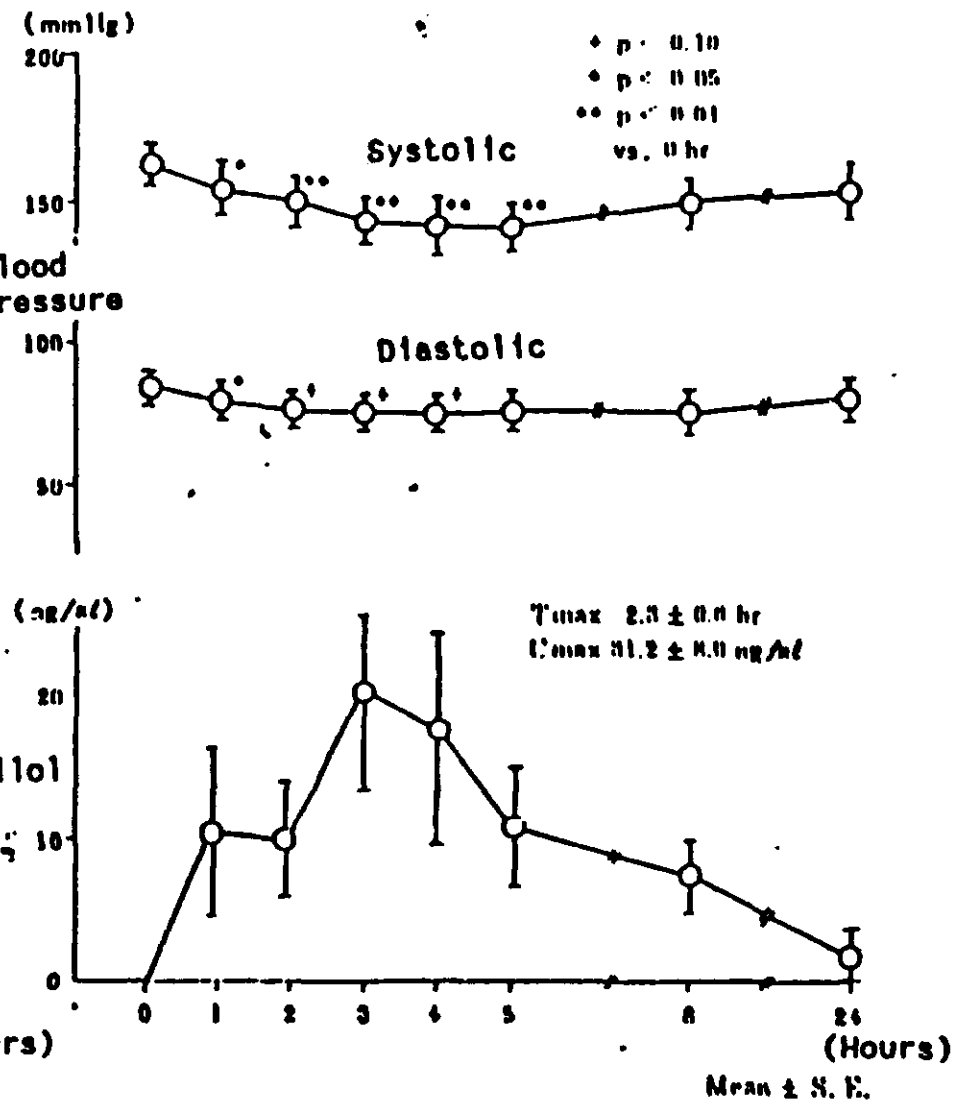


Figure 4 Changes in the blood pressure and intact carvedilol plasma level when a single dose of carvedilol was administered on a day the subjects did not undergo dialysis (n = 5-6)

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G 20

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B17

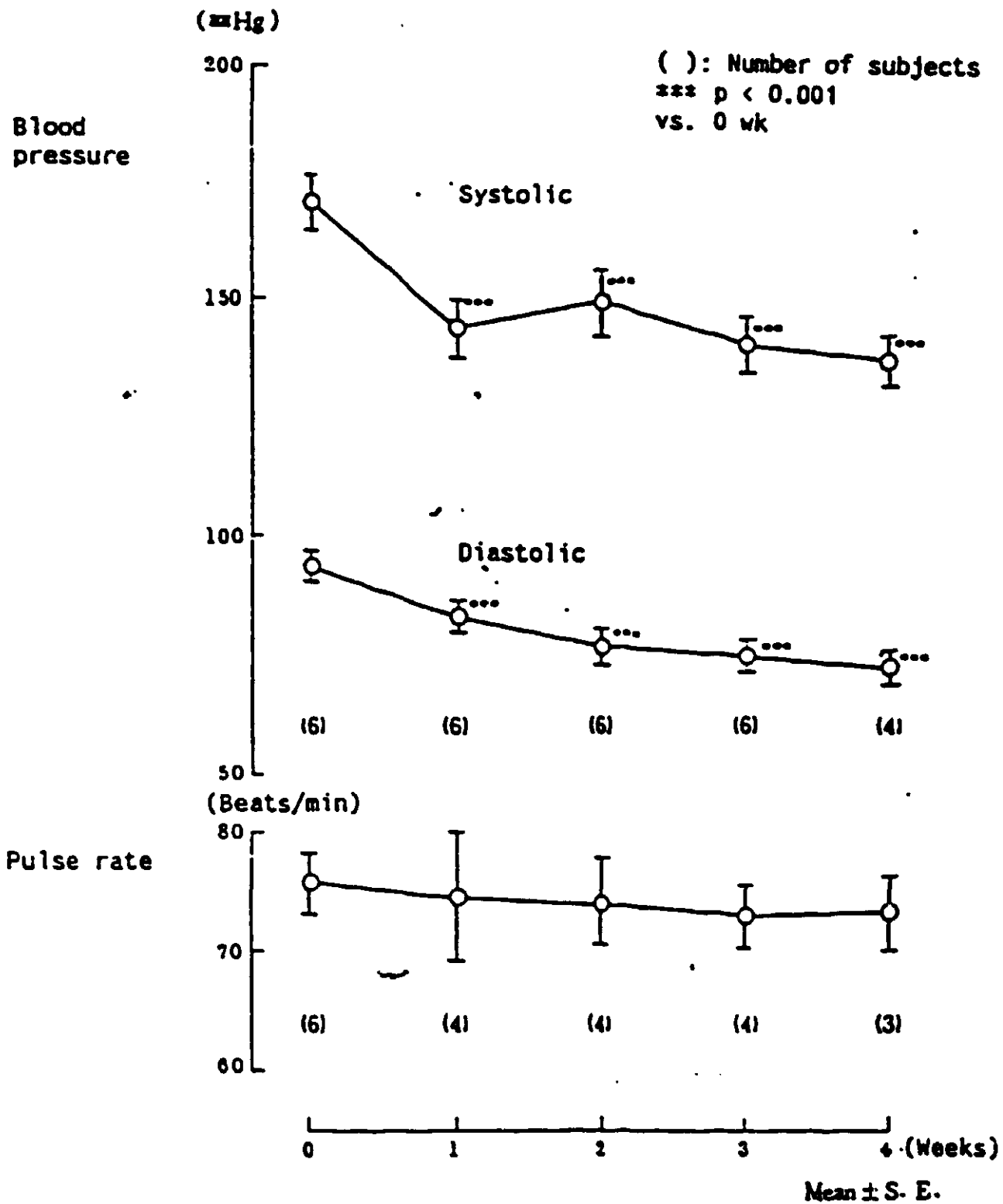


Figure 5. Changes in the blood pressure and pulse rate during long-term continuous administration of carvedilol

G20
 VOL 1.81

000121

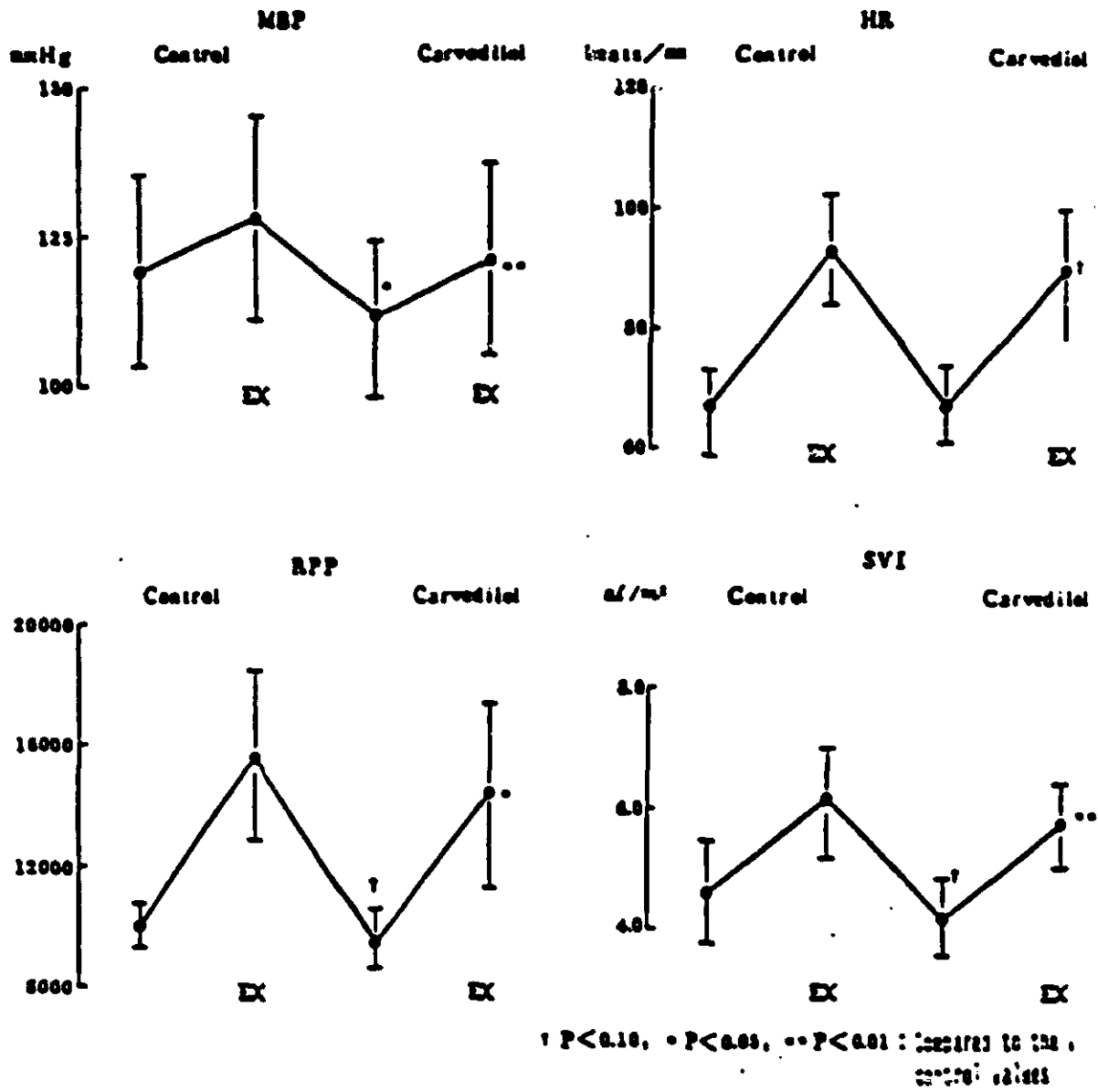


Figure 1-1. Effect of carvedilol on various hemodynamic values

ERROR BARS UNKNOWN STD DEV VS SEM

G 28

VOL 1.145

000017

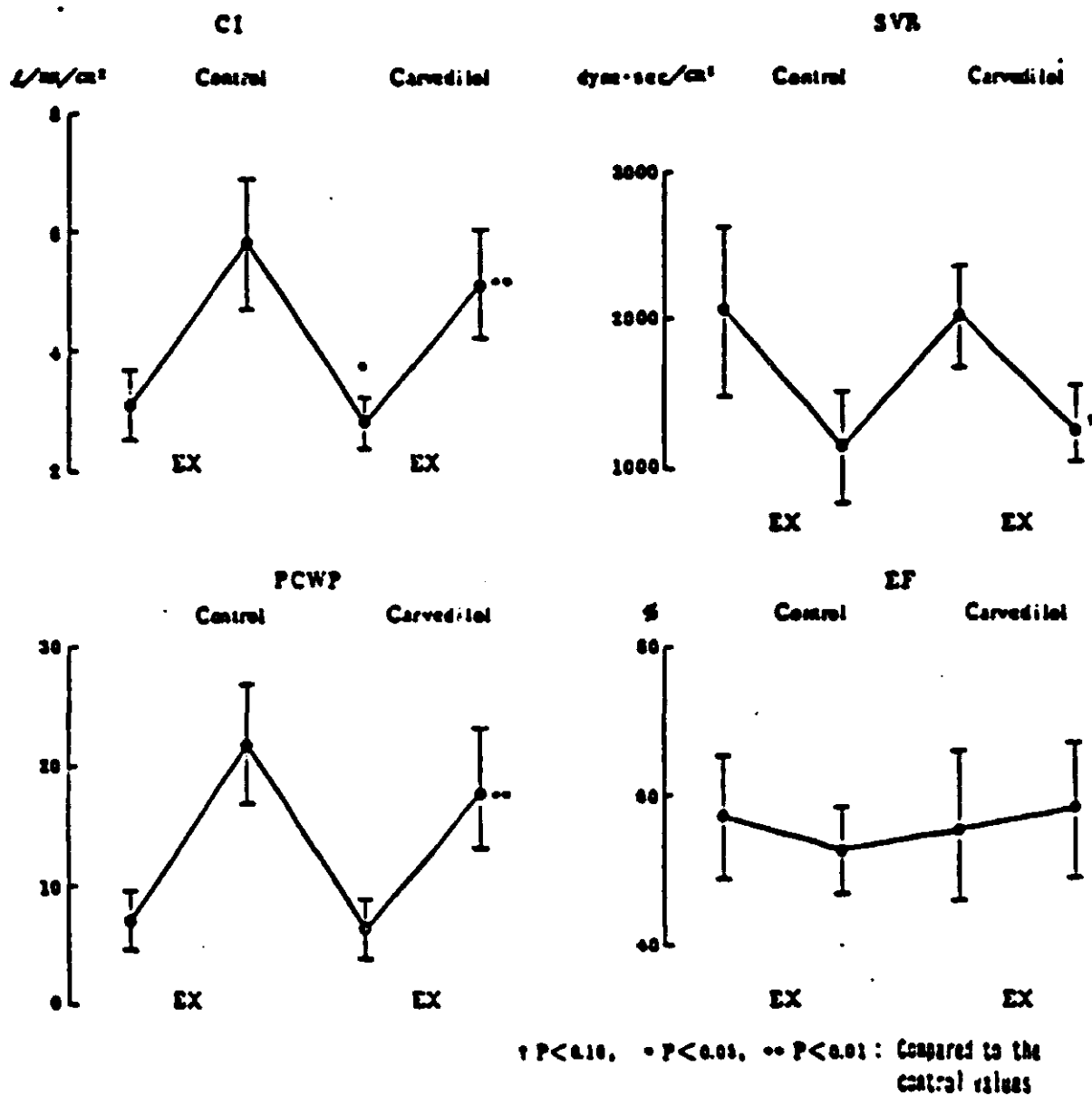


Figure 1-2. Effect of carvedilol on various hemodynamic values

ERROR BARS: UNKNOWN STD DEV VS SEM

G28.

VOL 1.145

000018

B20

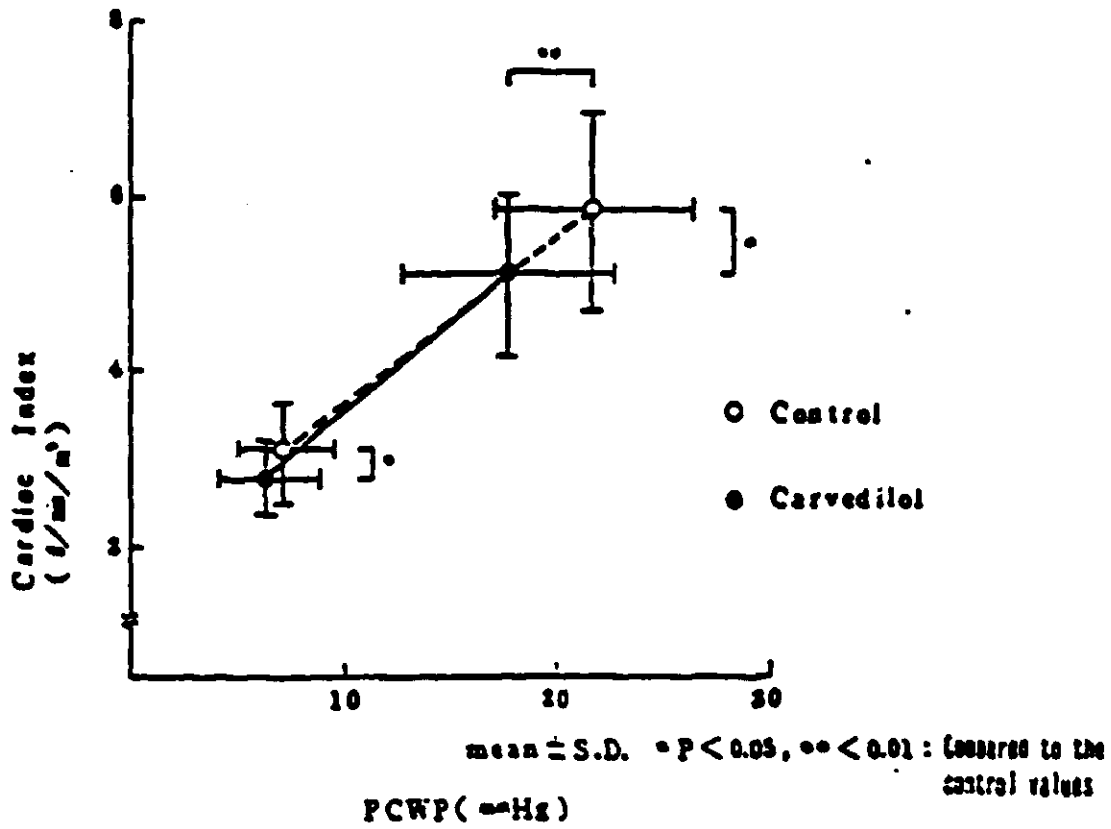


Figure 2. Effect of carvedilol on cardiac pump function during exercise loading

ERROR BARS : UNKNOWN STD DEV VS SEM

G 28

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000019

B21

Table 1. Various hemodynamic values

Item	No. of subjects	Before administration		One hour after administration		Test (Comparing values before and after administration of carvedilol)	
		While resting	During exercise loading	While resting	During exercise loading	While resting	During exercise loading
SBP (mmHg)	10	154±26.5	170±27.5 [*]	144±22.4	161±25.0 ^{**}	P<0.01	P<0.05
DBP (mmHg)	10	102±13.8	107±13.4	95.6±11.0	102±12.8 [*]	P<0.1	P<0.05
MBP (mmHg)	10	119±16.1	128±17.5 ⁺	112±13.5	121±16.1 ^{**}	P<0.05	P<0.01
HR (拍/分)	10	65.9±7.3	93.1±9.3 ^{***}	67.1±6.4	89.7±12.0 ^{***}	N. S.	P<0.1
RPP (×10 ³)	10	102±15.4	158±25.1 ^{***}	96.0±10.8	144±20.9 ^{***}	P<0.1	P<0.05
CI (L/m ² ·m)	10	3.1±0.6	5.8±1.1 ^{***}	2.8±0.4	5.1±0.9 ^{***}	P<0.05	P<0.01
SVI (ml/m ²)	10	4.6±0.9	6.2±1.0 ^{***}	4.2±0.7	5.7±0.7 ^{***}	P<0.1	P<0.01
SVR (dyne·sec·cm ⁻⁵)	10	2035±576	1154±348 ^{***}	2012±378	1246±289 ^{***}	N. S.	P<0.1
EF (%)	8	57.1±8.2	53.1±6.3 ⁺	55.8±10.1	58.0±9.0	N. S.	N. S.
SWI (g·s/m ²)	10	6.8±0.6	9.8±0.8 [*]	6.0±0.4	8.4±0.7 ^{**}	P<0.001	P<0.01
PCWP (mmHg)	10	7.2±2.4	21.8±5.0	6.5±2.4	17.6±5.0	N. S.	P<0.01
CVP (mmHg)	9	5.3±2.8	8.3±3.5 ^{***}	4.6±3.5	8.3±4.5 ^{**}	N. S.	N. S.

+P<0.10 *P<0.05 **P<0.01 ***P<0.001: In comparison to the resting values

UNKNOWN STA DEV VS SEM

B22

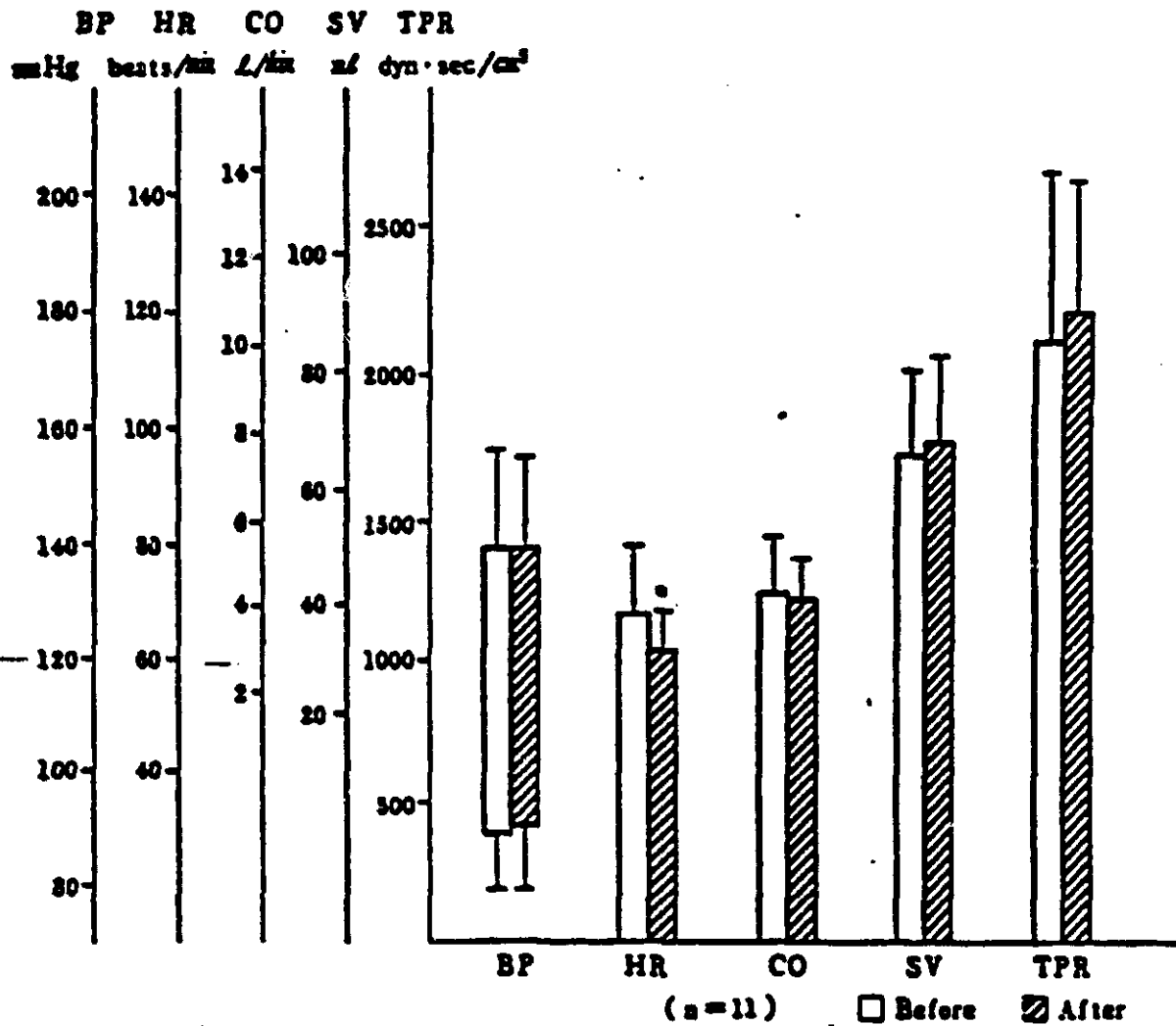


Figure 2. Resting hemodynamics before and after carvedilol treatment

BP: Blood pressure HR: Heart rate
 CO: Cardiac output SV: Stroke volume
 TPR: Total peripheral resistance

(Each bar graph shows the mean ± S.E., and the BP bar graph shows the SBP and the DBP.)

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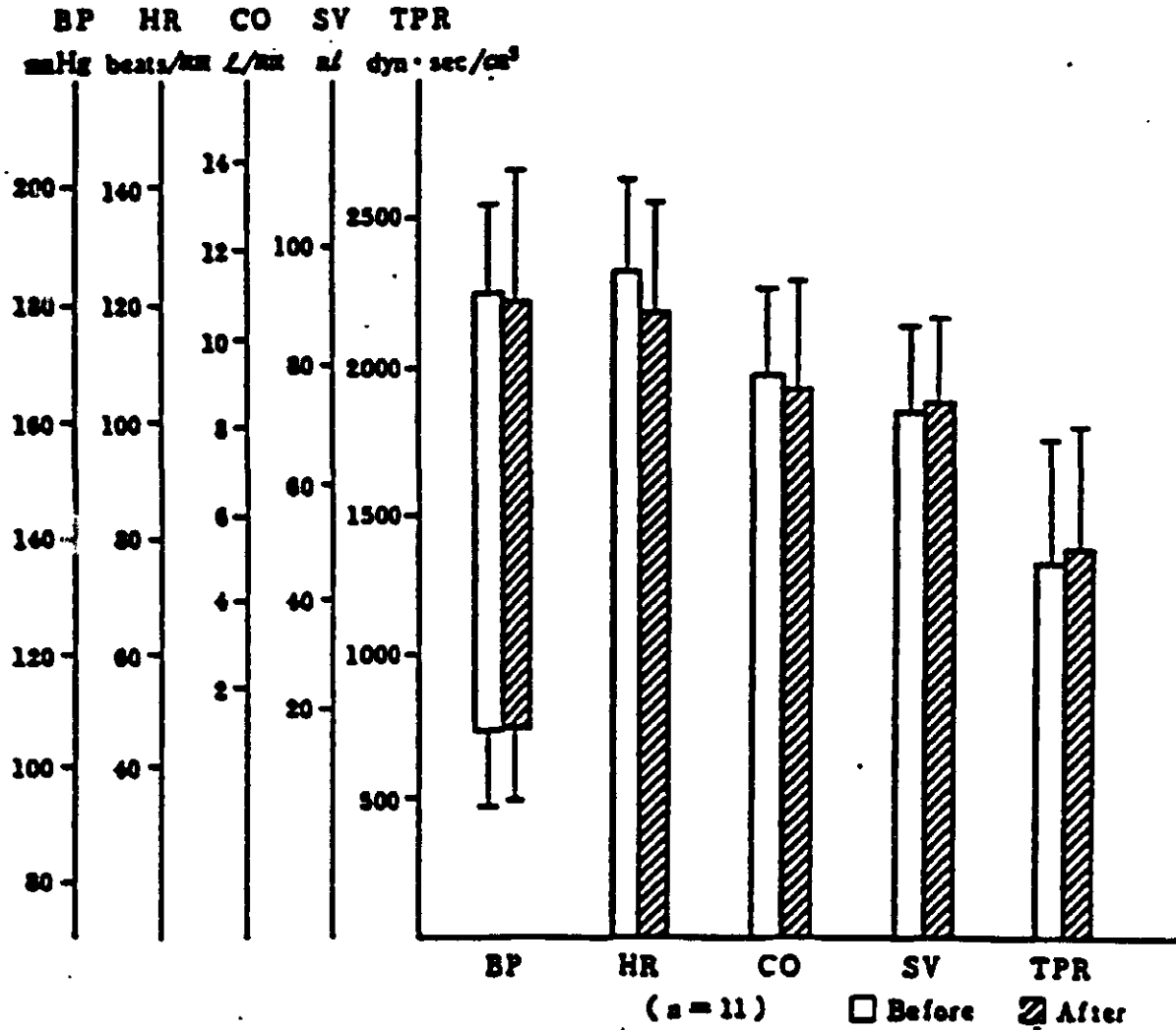


Figure 3. Hemodynamics during exercise loading before and after carvedilol treatment

BP: Blood pressure HR: Heart rate
 CO: Cardiac output SV: Stroke volume
 TPR: Total peripheral resistance

(Each bar graph shows the mean ± S.E., and the BP bar graph shows the SBP and the DBP.)

G 29
 VOL 1.145
 000053

624

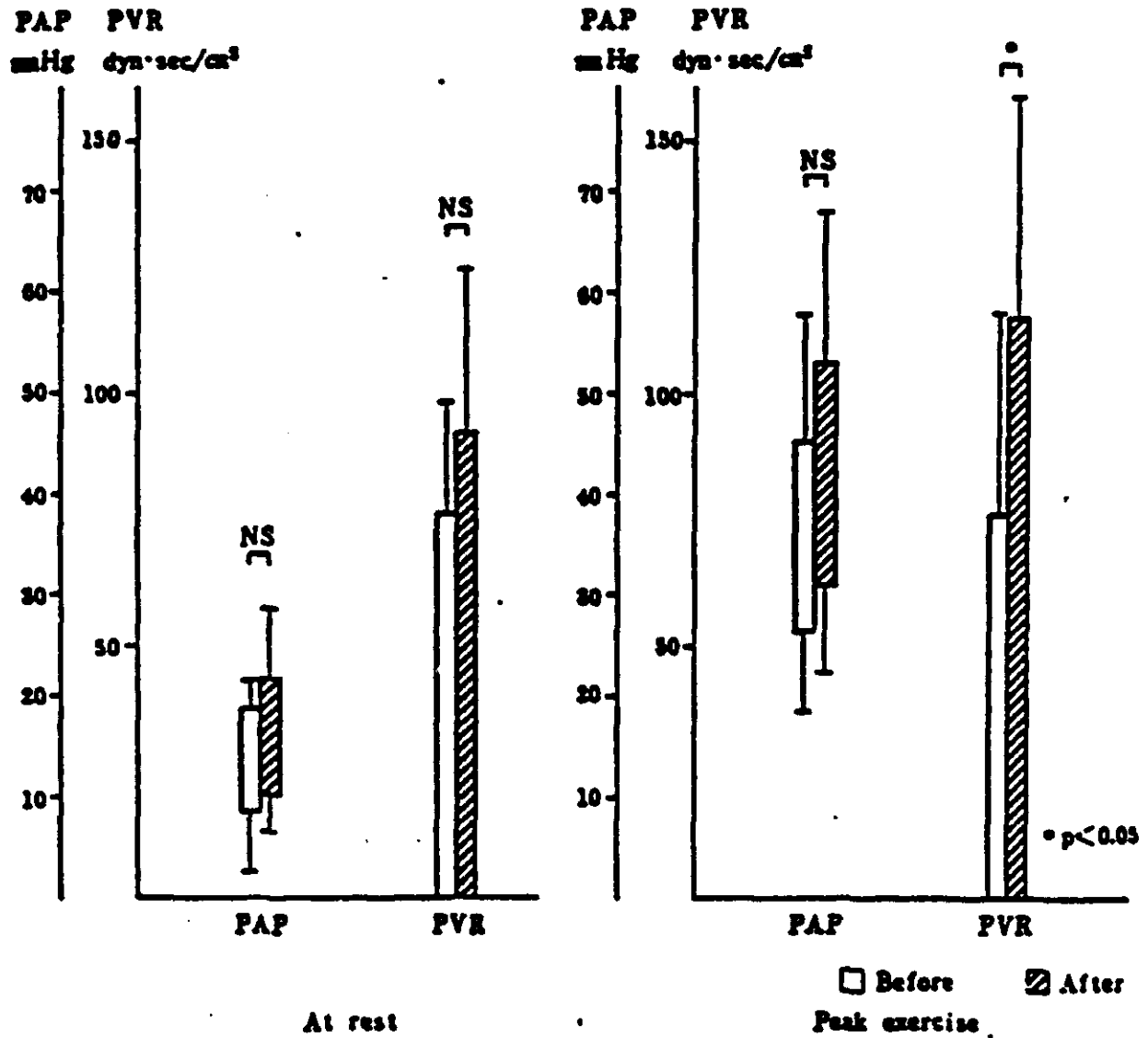


Figure 7. Changes in the pulmonary arterial pressure and pulmonary vascular resistance at rest and during exercise loading before and after carvedilol treatment

(n = 11, mean ± S.E.)

G 29,
VOL 1, 145
000057

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ABB. 1
HERZFREQENZ
HERZLAG

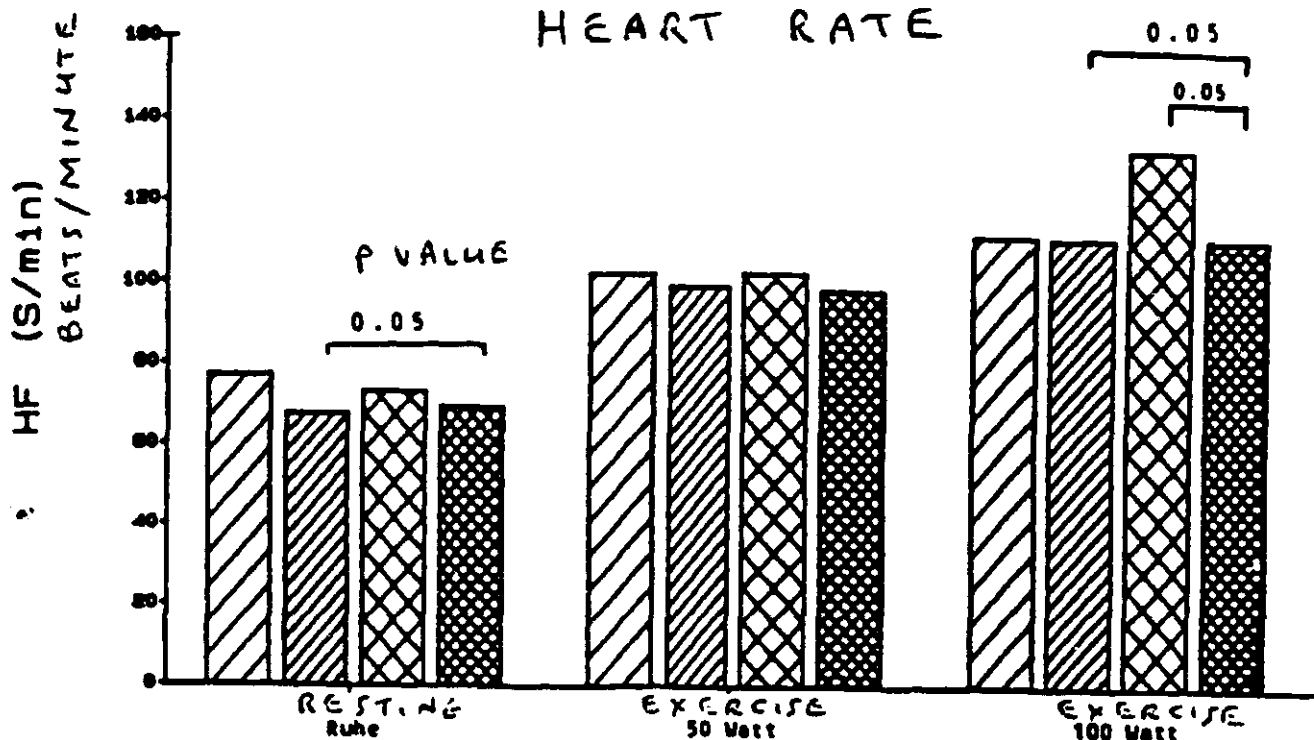
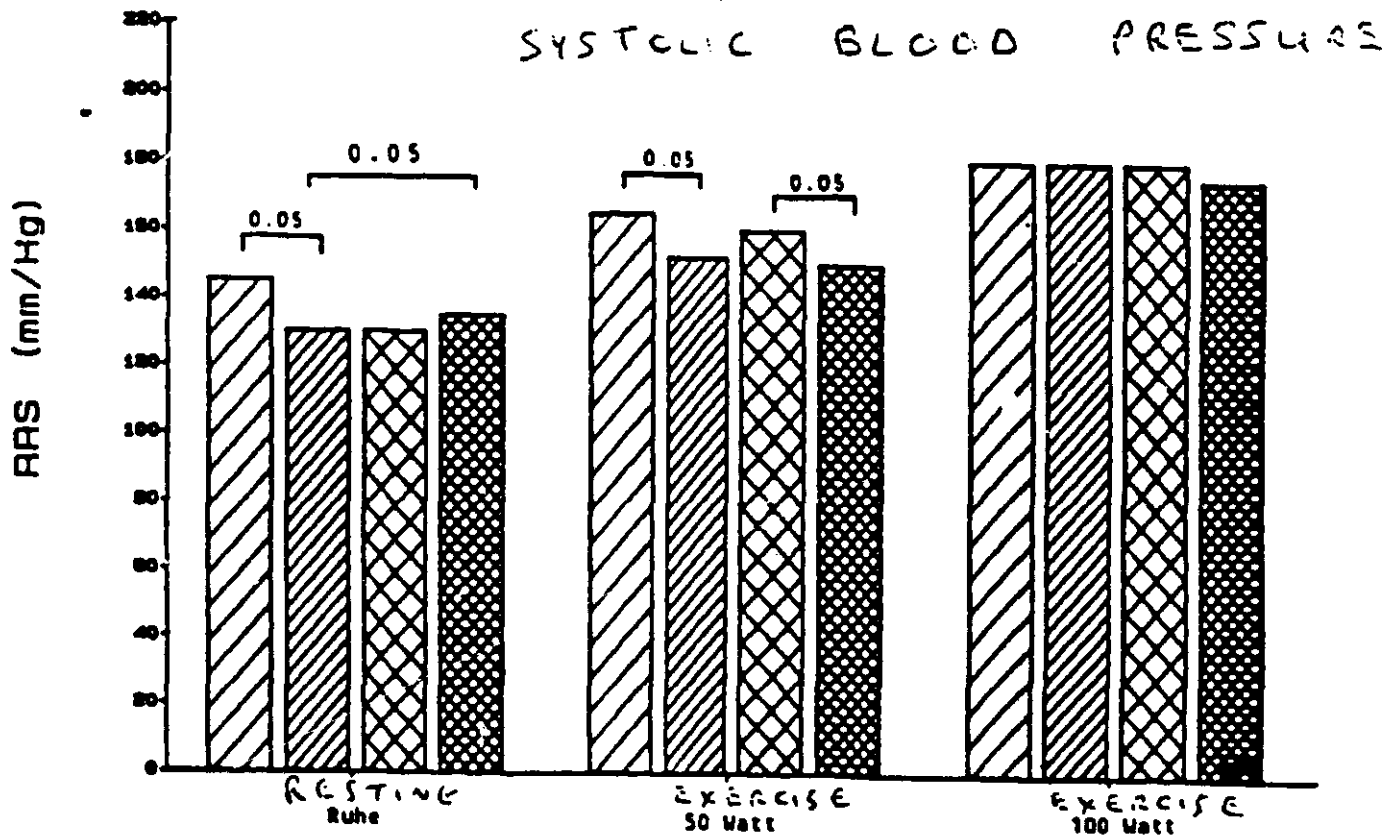


ABB. 2
SYSTOLISCHER BLUTDRUCK
BLUTLAG



vor Carvedilol. nach Carvedilol. vor Propranolol. nach Propranolol.

 BEFORE AFTER BEFORE AFTER
 ——— = statistisch signifikant

MF 2740

JULI 1966

000227

ABB. 3
DIASTOLISCHER BLUTDRUCK

DIASTOLIC BLOOD PRESSURE

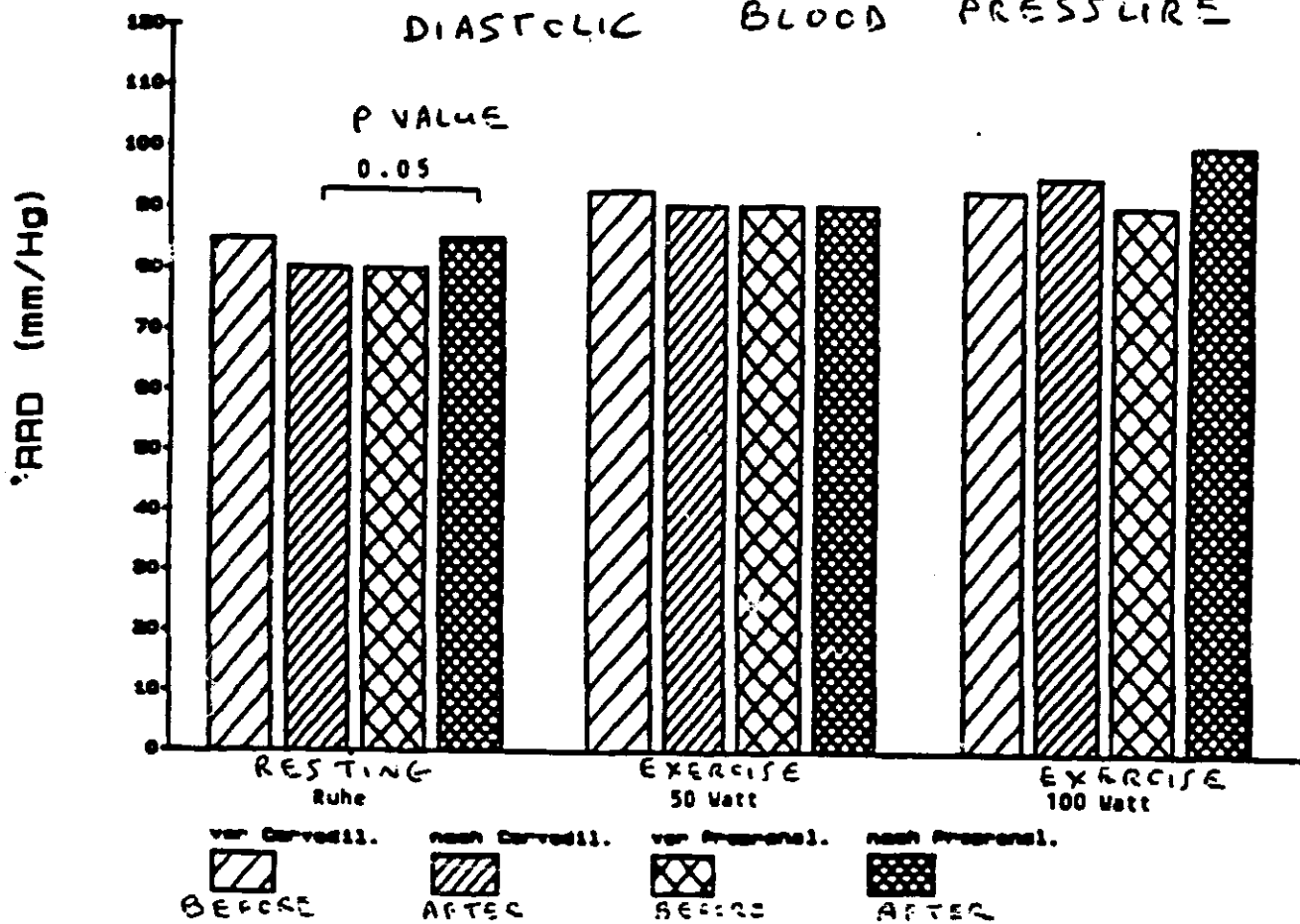
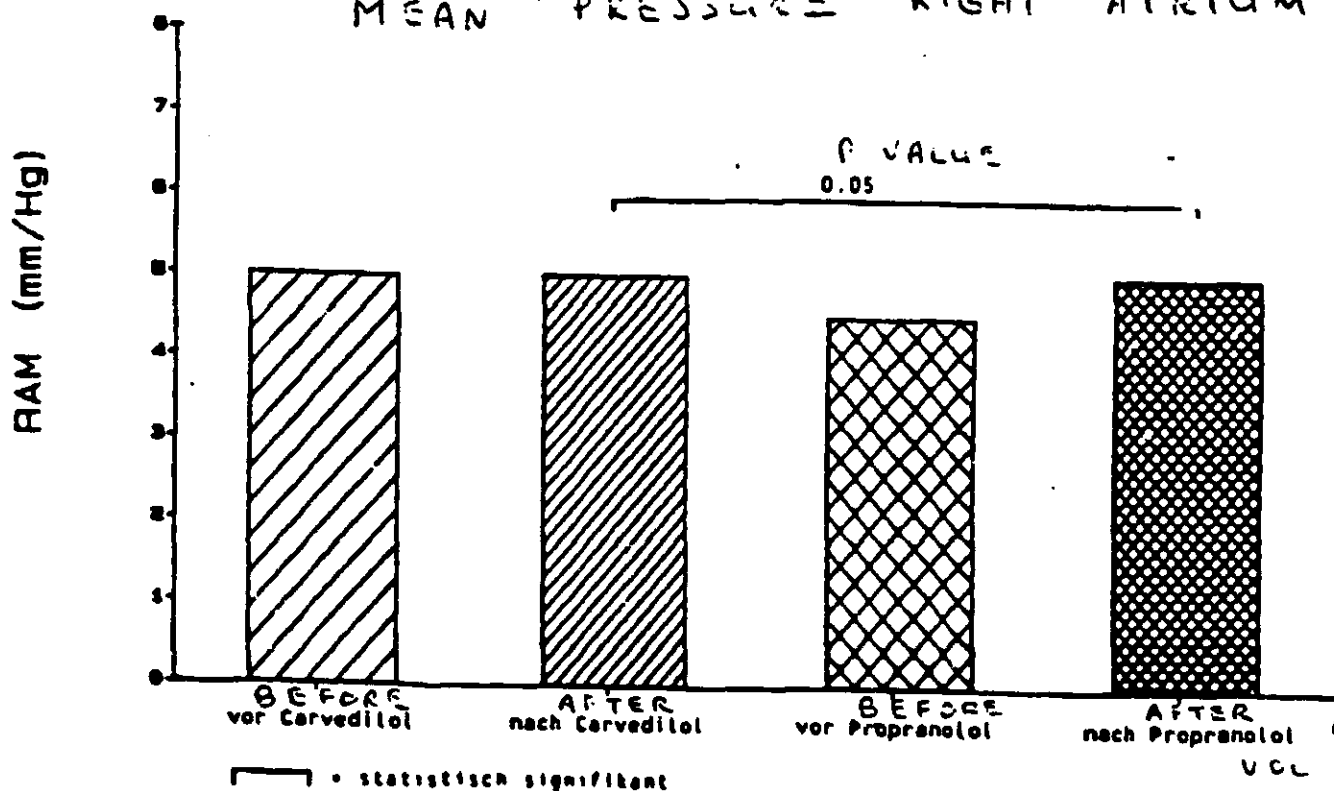


ABB. 4
MITTELDRUCK RECHTER VORHOF

MEAN PRESSURE RIGHT ATRIUM



920413

MF 2740

UCL 1.1.16

000228



ABB. 5
SYSTOLISCHER PULMONALARTERIENDRUCK

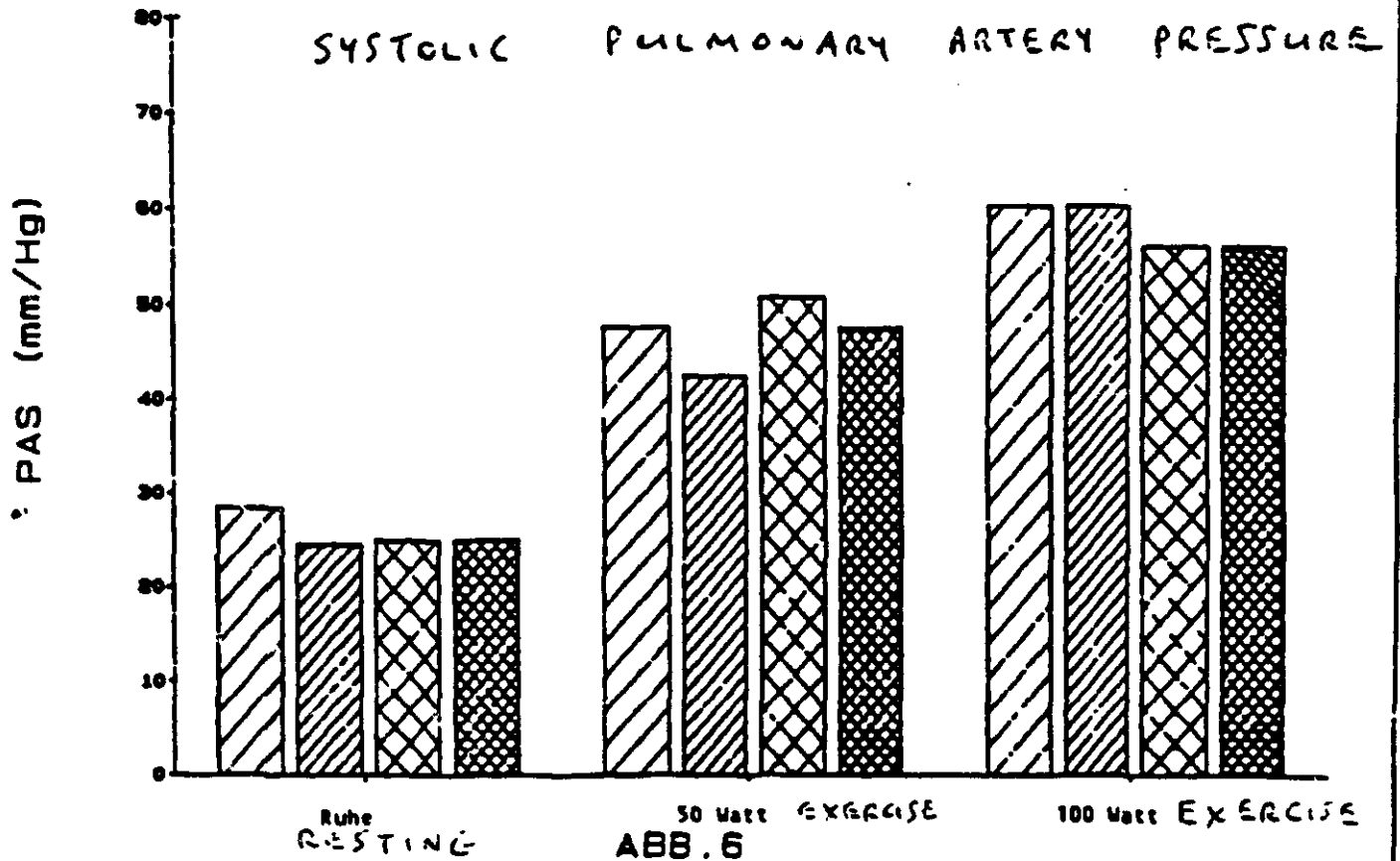
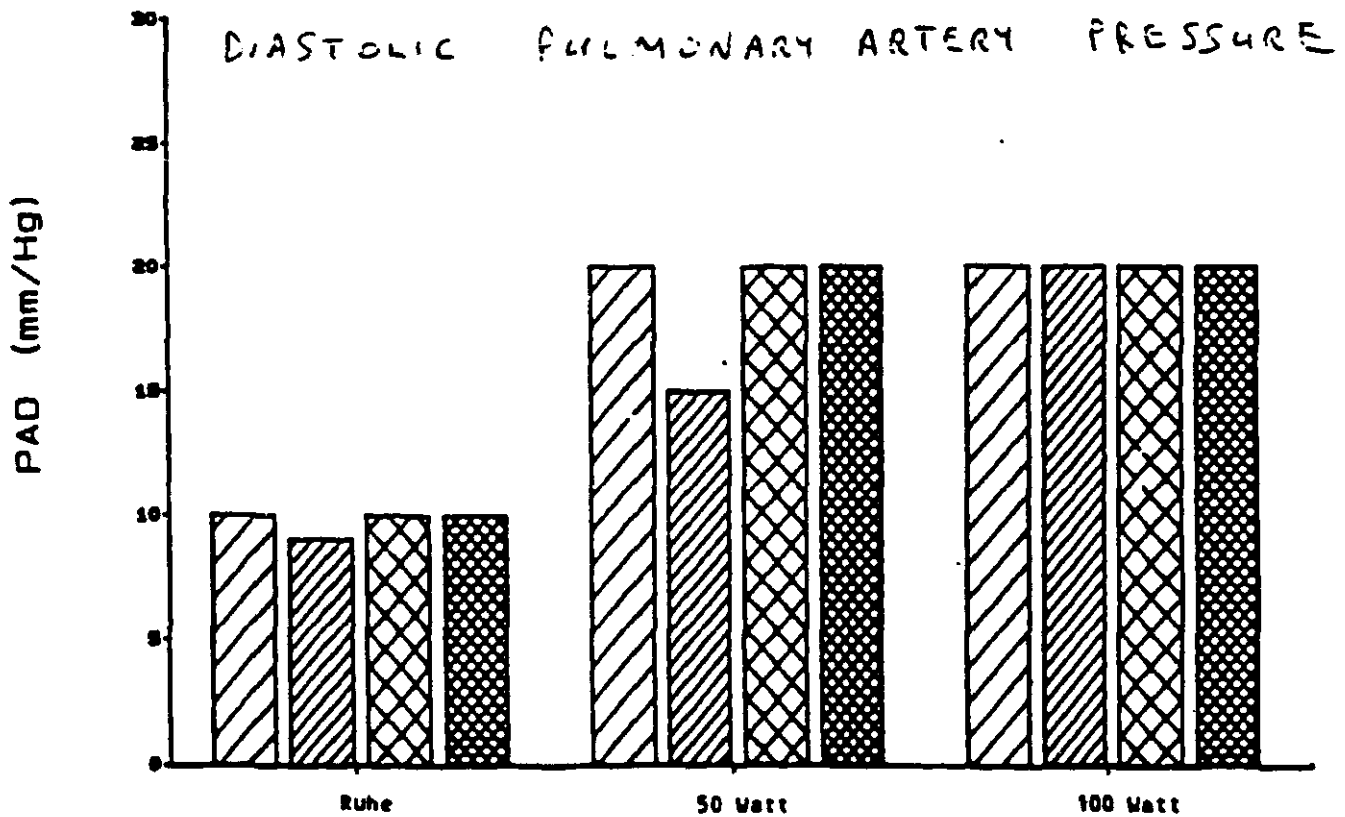


ABB. 6
DIASTOLISCHER PULMONALARTERIENDRUCK



vor Carvedilol GEFÜHRT nach Carvedilol AUFTEIL vor Propranolol GEFÜHRT nach Propranolol AUFTEIL

— = statistisch signifikant

MF 27 40

VOL 1.116

000229

ABB. 7
PULMONALKAPILLARER MITTELDRUCK

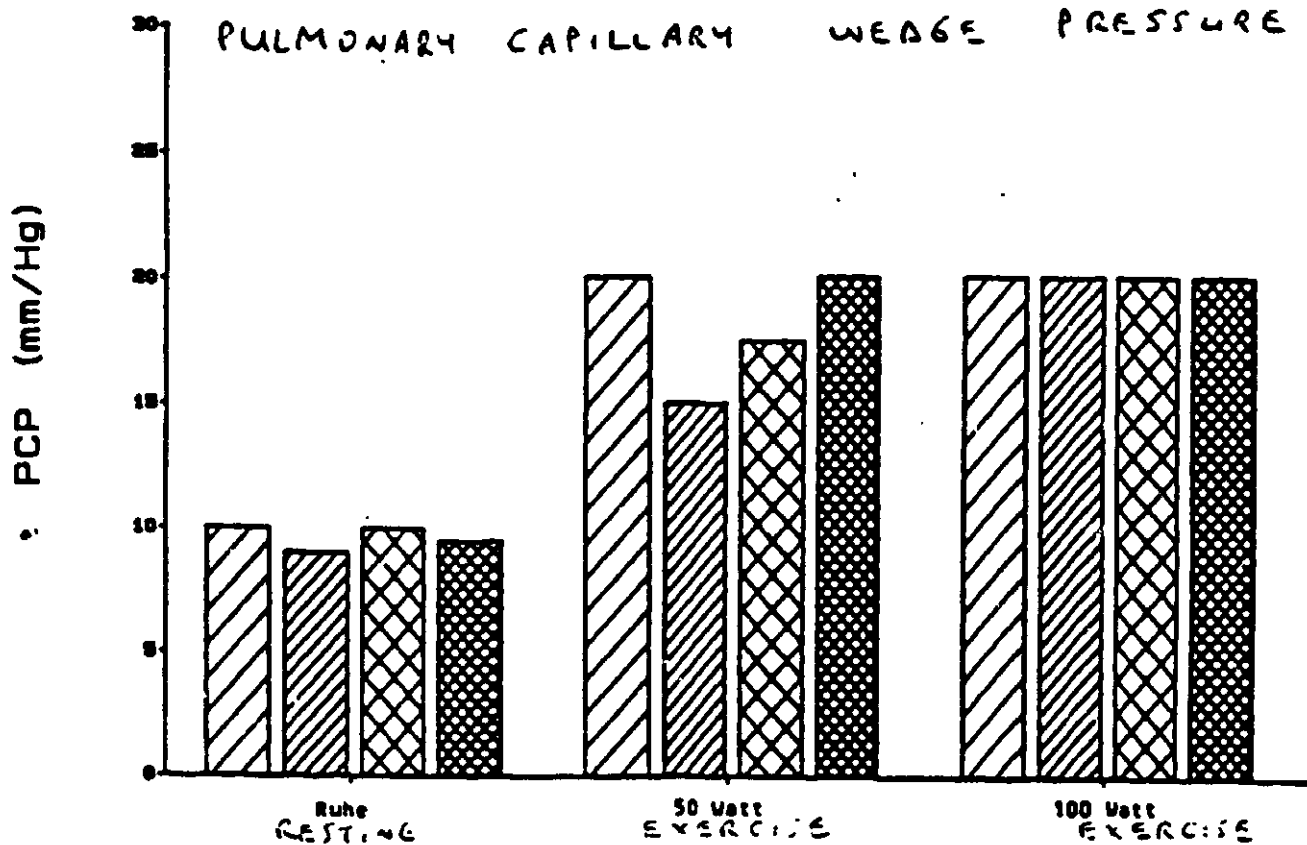
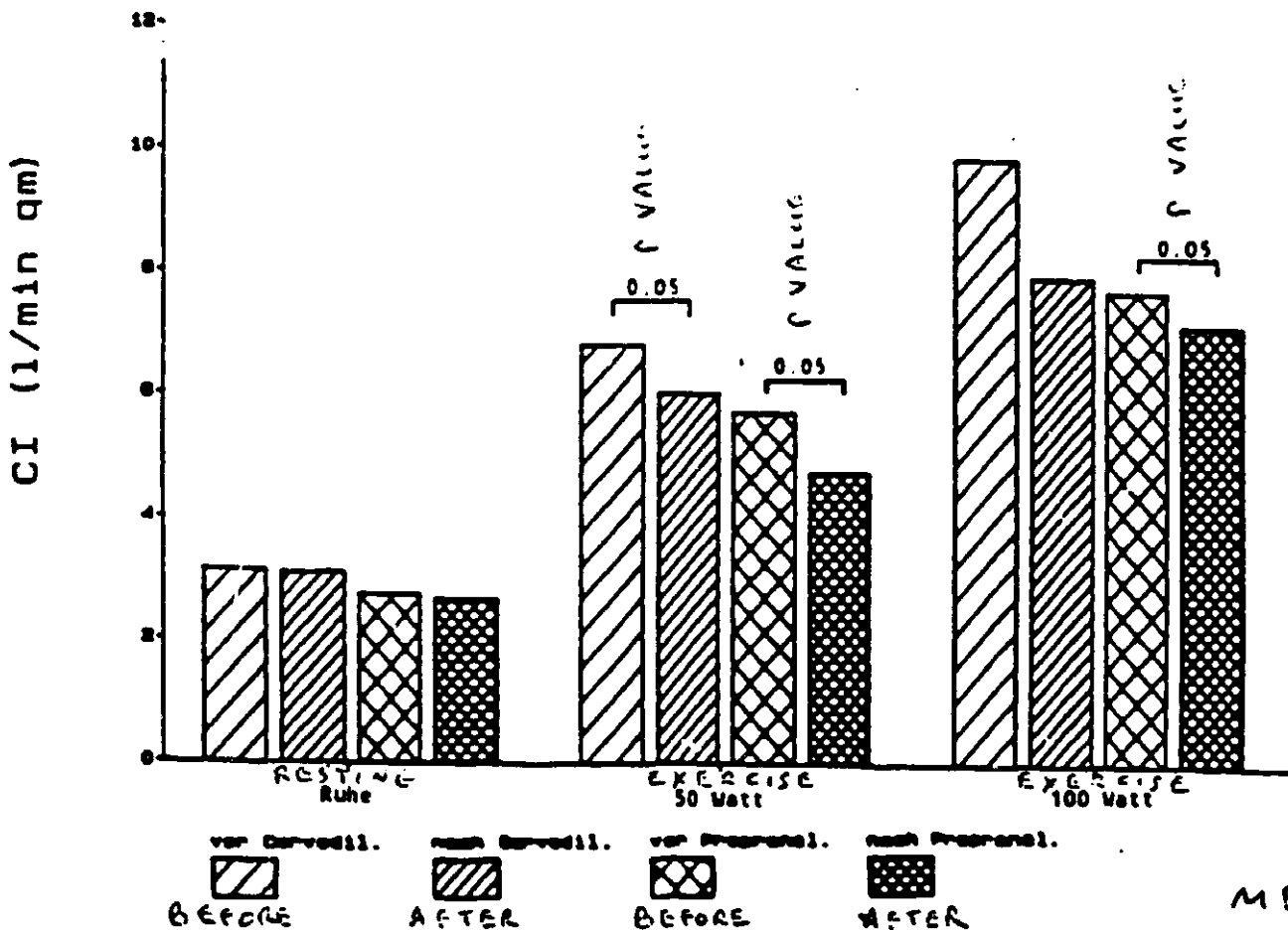


ABB. 8
CARDIAC - INDEX



vor Carvedilol. nach Carvedilol. vor Propranolol. nach Propranolol.
 BEFORE AFTER BEFORE AFTER

— = statistisch signifikant

MF 2740

VOL 1.116

000230

920613

B29

ABB. 9
SCHLAGVOLUMEN
MEDIANE

STROKE VOLUME

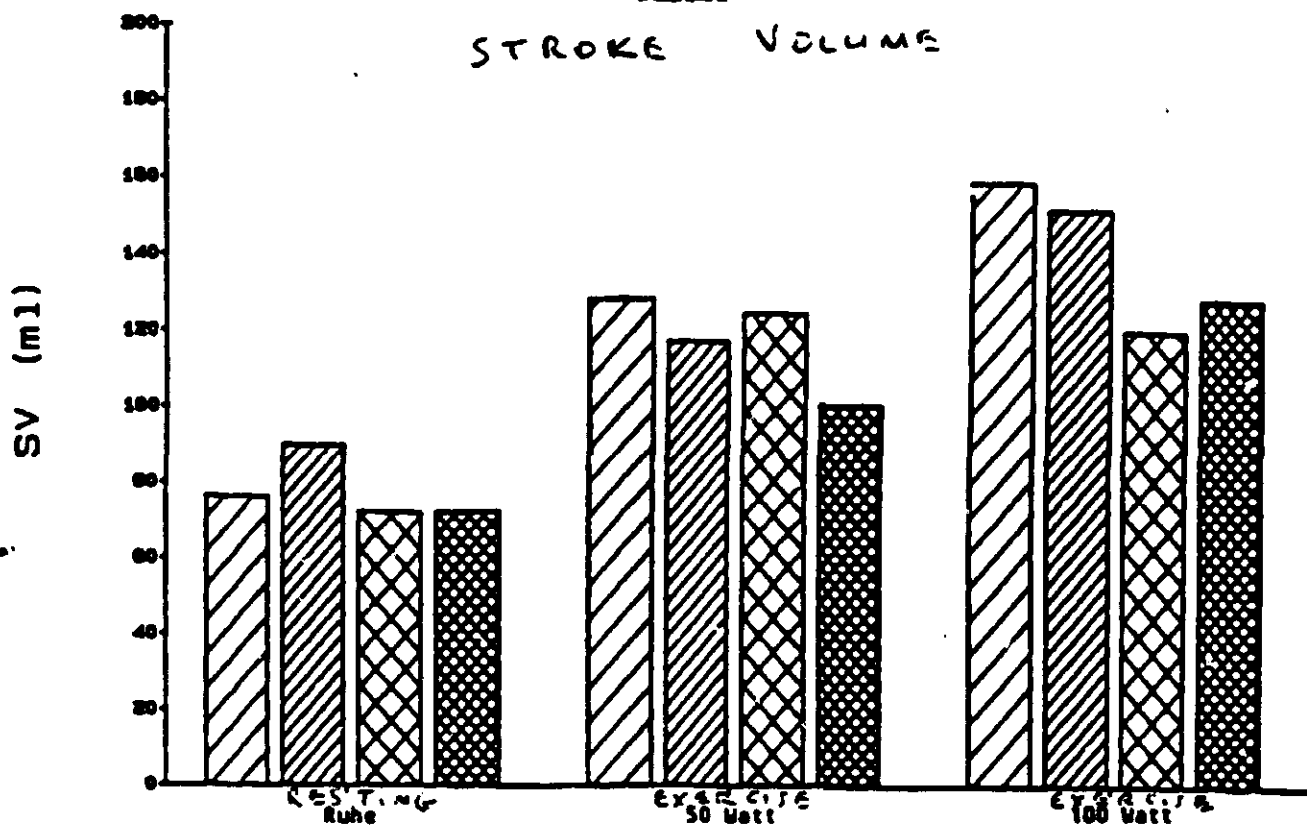
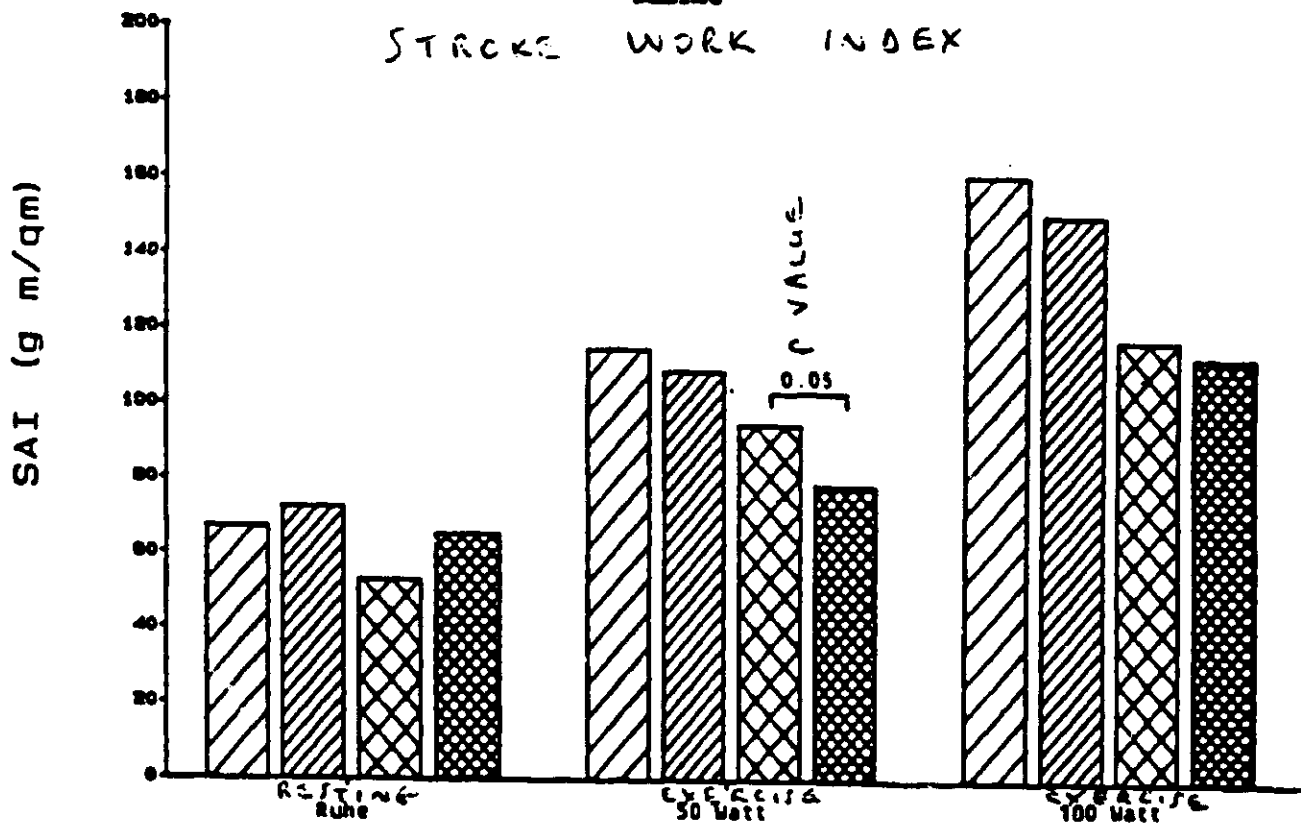


ABB. 10
SCHLAGARBEITSINDEX
MEDIANE

STROKE WORK INDEX



vor Carvedilol. nach Carvedilol. vor Propranolol. nach Propranolol.

 BEFORE AFTER BEFORE AFTER

—] = statistisch signifikant

MF 2740
VOL 1.116
000231



ABB. 11 SYSTEMISCHER ARTERIELLER WIDERSTAND SYSTEMIC ARTERIAL RESISTANCE

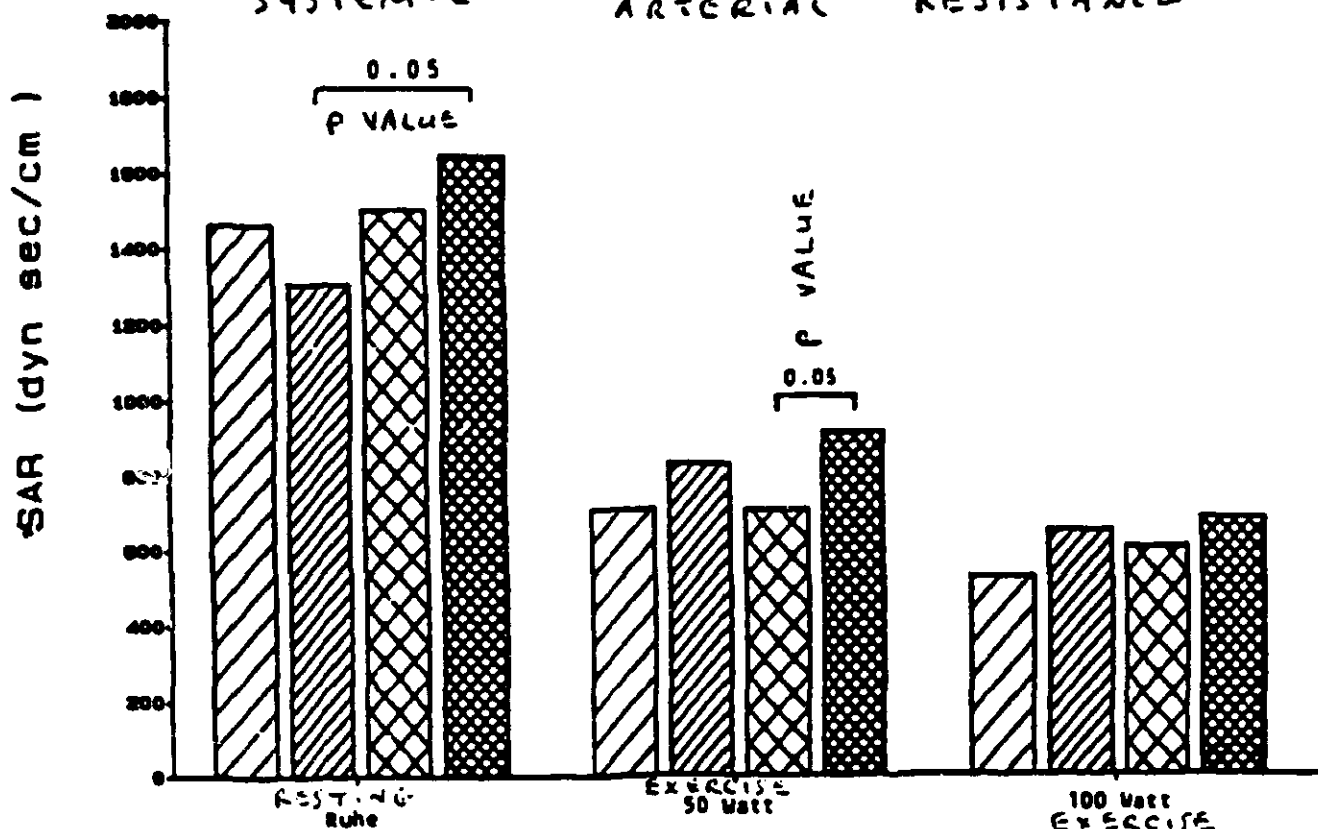
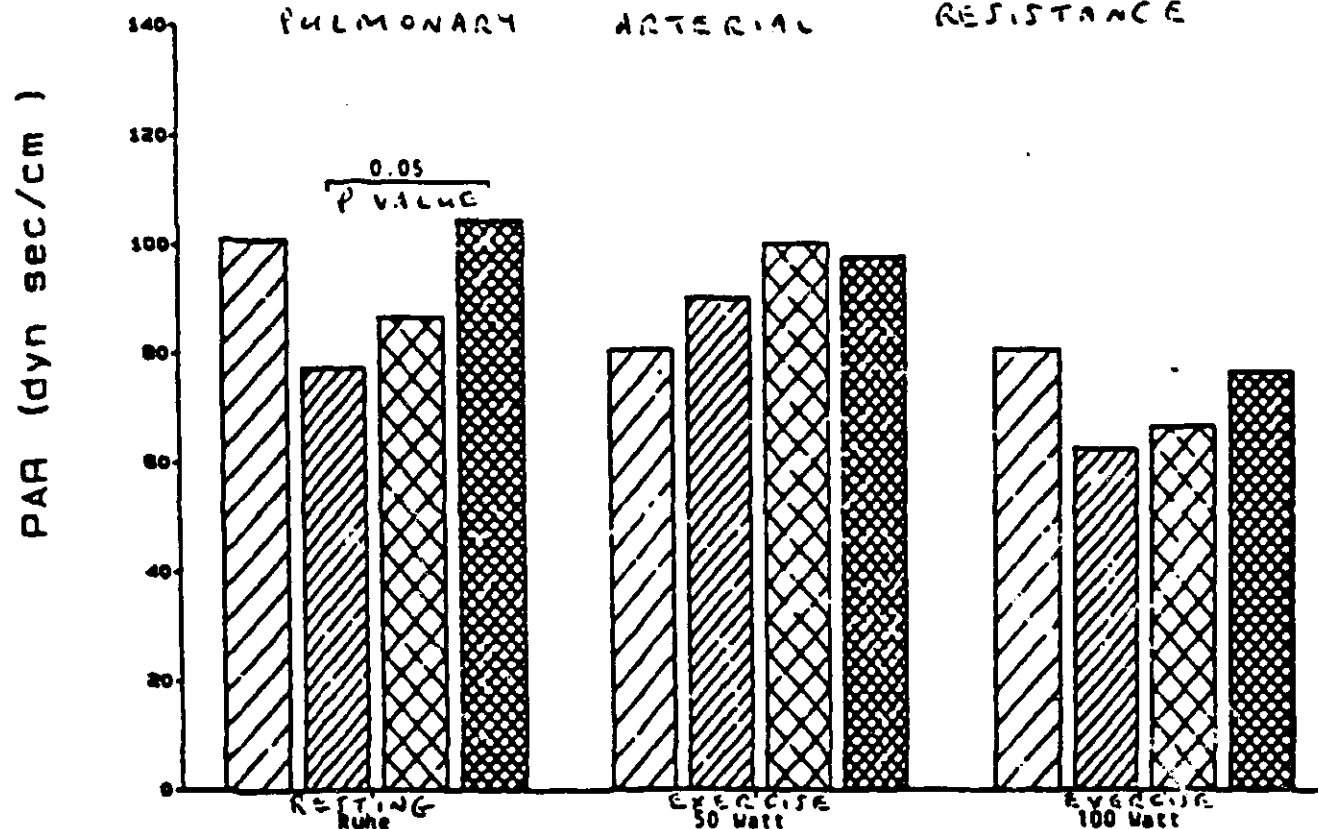


ABB. 12 PULMONALER ARTERIOLENWIDERSTAND PULMONARY ARTERIAL RESISTANCE



vor Carvedilol. nach Carvedilol. vor Propranolol. nach Propranolol.
 BEFORE AFTER BEFORE AFTER

— • statistisch signifikant

920413

MF 2740

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000232

ABB. 13
DRUCKFREQUENZPRODUKT

MEDIANE
PRESSURE - RATE - PRODUCT

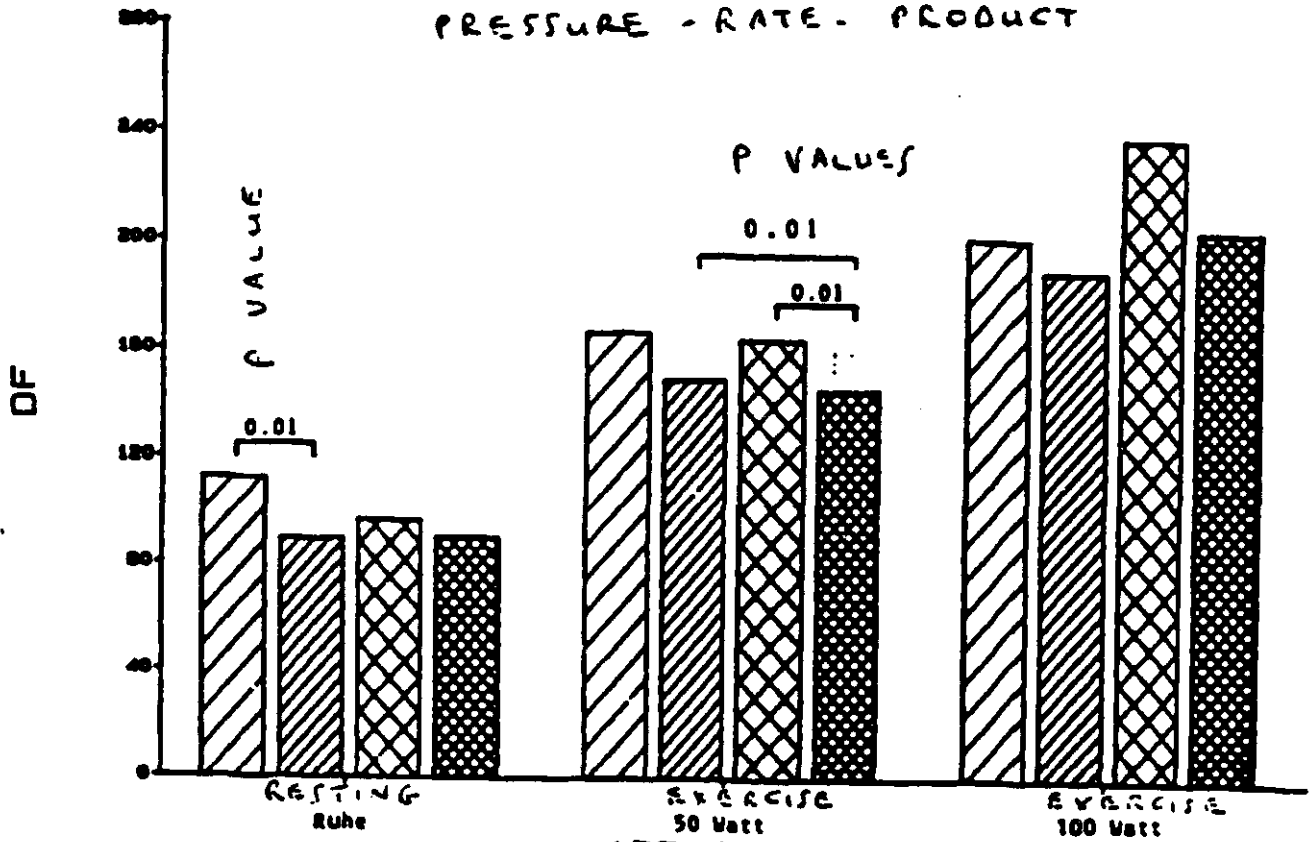
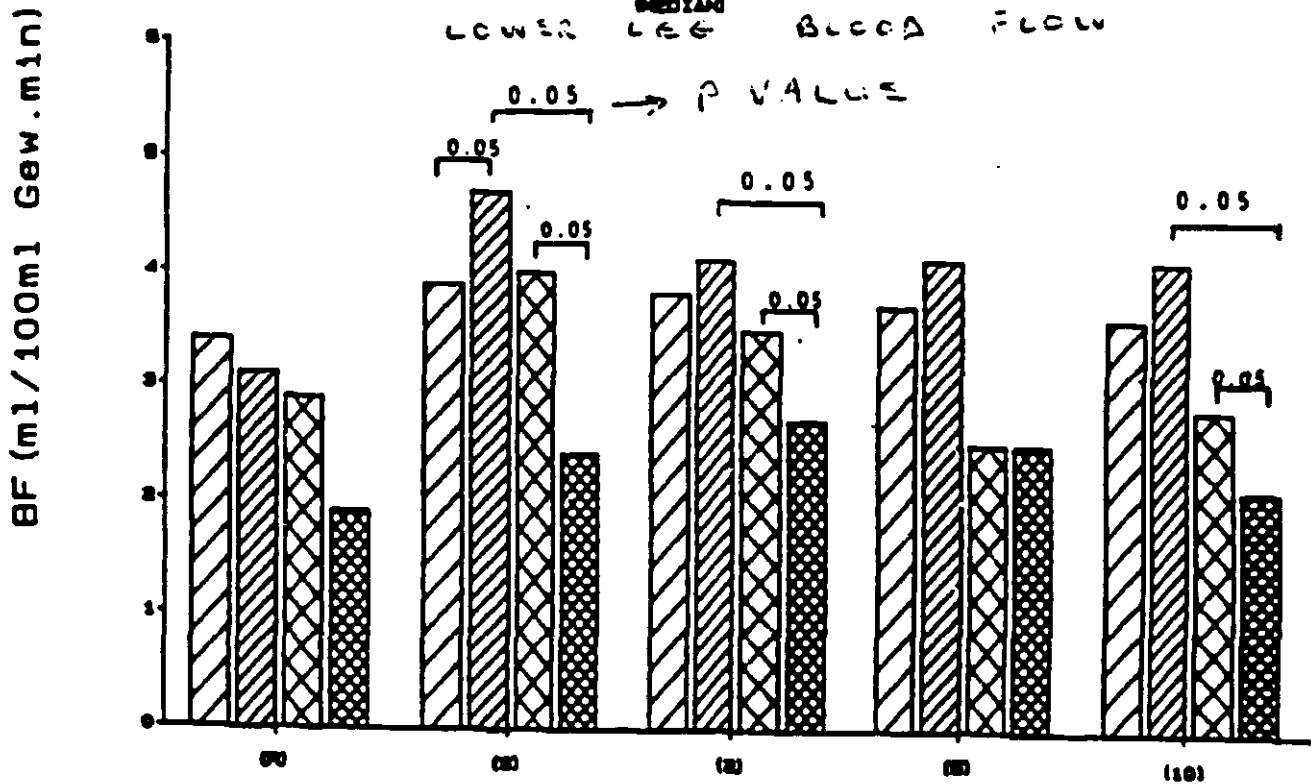


ABB. 14
UNTERSCHENKELBLUTFLUSS

MEDIANE
LOWER LEG BLOOD FLOW



(R) = in Ruhe RESTING
(S) = sofort nach Belastung IMMEDIATELY AFTER EXERCISE
(2), (5), (10) = 2, 5, 10 min nach Belastung 2, 5, 10 MINUTES AFTER EXERCISE

vor Carvedil. nach Carvedil. vor Propranol. nach Propranol.
BEFORE AFTER BEFORE AFTER

— • statistisch signifikant

MF 2740
VOL 1.116
000233

BOEHLINGER MANNHEIM GMBH
 KLINISCHE PHARMKOLOGIE - KINETIK
 PROGRAM: KNO
 DATE OF COMPUTATION: 29-JAN-68

Tab 1

632

GROUP A : PROJECT : MF 3837 ; BN 14.190 - PHARMACOKINETICS IN PATIENTS
 WITH LIVER INSUFFICIENCY (DR. GABOR, BERGISCHE GLADBACH) MF 3837
 DOSE : 12.5 MG BN 14.190 OVER 1 H I.V. INFUSION ; LOT : 819 673 99 D
 SIGASSAY : BN 14.190 IN PLASMA ; METHOD : HPLC

N: 2 - 1 :

GROUP B : PROJECT : BN 14.190 (AMPOULES) ; SERIAL NO. OF STUDY: 0 6 4 6
 LOT : 816 000 A
 DOSE : 12.5 MG ; ADM.: IV. INFUSION OVER 1 HOUR
 SIGASSAY: BN 14.190 IN SERUM. DETERMINATION: HPLC-FLUOROM.

GROUP C : PROJECT : MF 3837 ; BN 14.190 - PHARMACOKINETICS IN PATIENTS
 WITH LIVER INSUFFICIENCY (DR. GABOR, BERGISCHE GLADBACH) MF 3837
 DOSE : 25 MG BN 14.190 PERORAL ; LOT : 819 834 48 67
 SIGASSAY : BN 14.190 IN PLASMA ; METHOD : HPLC

GROUP D : PROJECT : BN 14.190 ; SERIAL NO. OF STUDY: 0 6 4 7
 LOT : 816 034 88
 DOSE : 25 MG = 1 CAPSULE NO. 3, WITHOUT HPLC ; ADM.: PERORAL
 SIGASSAY: BN 14.190 IN SERUM. DETERMINATION: HPLC-FLUOROM.

PARAMETER (RAW - DATA)	UNIT		"A"	"B"	"C"	"D"
AUC	per 1 mg	N	5.	20.	5.	19.
		MEAN	46.072	32.474	45.060	6.407
		C.V. (%)	48.00	82.48	67.60	53.83
		MEDIAN	42.836	27.388	35.374	5.934
		MINIM. MAXIM.				
C max	per 1 mg	N	5.	20.	5.	20.
		MEAN	11.242	13.093	3.932	1.370
		C.V. (%)	72.25	42.30	21.62	67.35
		MEDIAN	8.884	14.100	4.300	0.946
		MINIM. MAXIM.				
t max	[h]	N	5.	20.	5.	20.
		MEAN	1.000	1.250	0.700	1.300
		C.V. (%)	30.62	90.13	39.12	41.18
		MEDIAN	1.000	1.000	0.300	1.300
		MINIM. MAXIM.				
t 1/2	[h]	N	5.	20.	5.	19.
		MEAN	9.319	2.301	12.303	7.002
		C.V. (%)	61.30	20.22	98.17	48.89
		MEDIAN	7.109	2.460	9.015	7.110
		MINIM. MAXIM.				
Cl or Cl / f	[ml/min]	N	5.	20.	5.	19.
		MEAN	449.00	623.99	496.06	3417.05
		C.V. (%)	94.42	27.80	53.01	95.31
		MEDIAN	389.00	608.34	471.15	2808.88
		MINIM. MAXIM.				
V d	[l]	N	5.	20.		
		MEAN	311.3	137.6		
		C.V. (%)	41.16	33.90		
		MEDIAN	321.1	125.0		
		MINIM. MAXIM.				
V dd	[l]	N	5.	20.		
		MEAN	236.78	80.99		
		C.V. (%)	53.98	30.40		
		MEDIAN	294.00	77.33		
		MINIM. MAXIM.				
A o	[%]	N	5.		6.	
		MEAN	0.90		0.31	
		C.V. (%)	62.43		46.31	
		MEDIAN	1.02		0.41	
		MINIM. MAXIM.				
Cl R	[ml/min]	N	5.		6.	
		MEAN	3.75		2.49	
		C.V. (%)	26.82		39.07	
		MEDIAN	3.34		2.62	
		MINIM. MAXIM.				
f	[%]	N			5.	19.
		MEAN			99.63	22.42
		C.V. (%)			43.90	53.17
		MEDIAN			62.58	18.64
		MINIM. MAXIM.				

p < 0.001

MF 3837

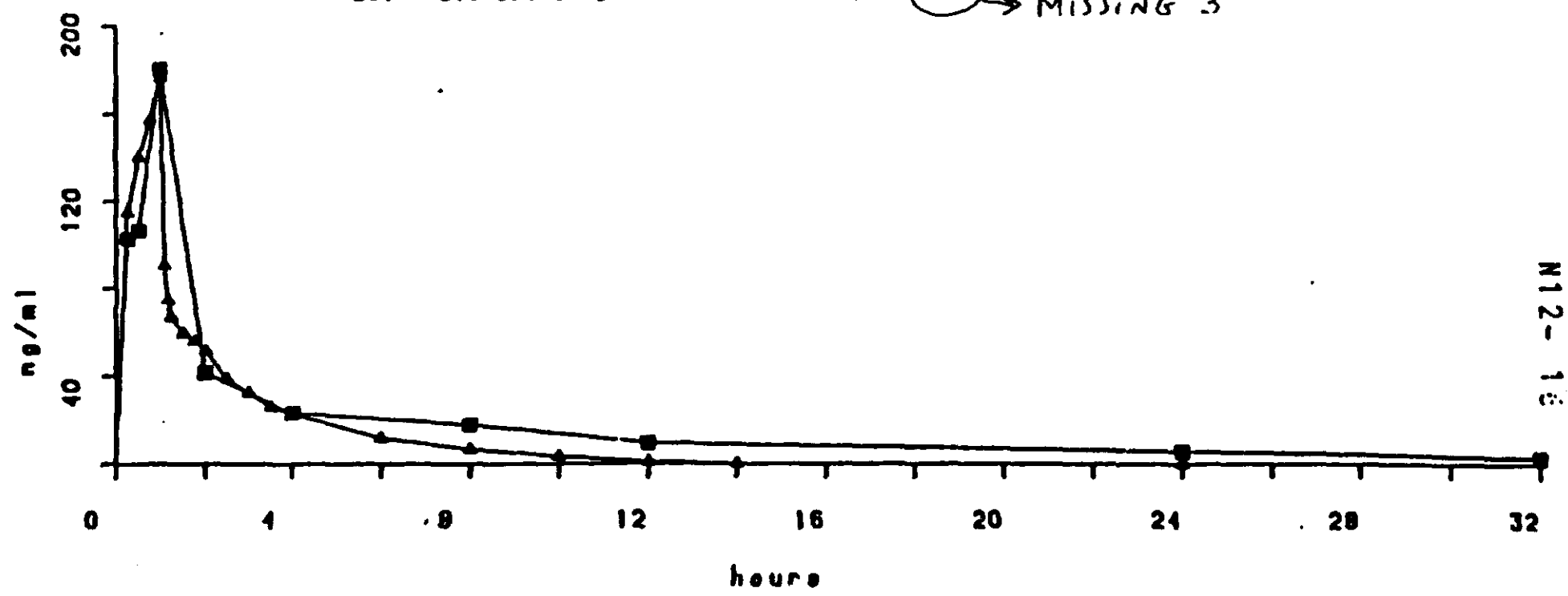
VOL 1.61

000280

Fig 1

PROJECT : BM 14.190
DOSE : 12.5 MG ; ADM. : IV. INFUSION OVER 1 HOUR
BIOASSAY : BM 14.190 IN SERUM. DETERMINATION : HPLC-FLUOROM.
MEDIAN - VALUES
DATE : 09-FEB-88
▲ - SERIAL NO. OF STUDY : 0 6 4 6 N = 20
 LOT : 816 000 A
■ - MF 3337 - PHARMACOKINETICS IN PATIENTS WITH LIVER INSUFF.
 LOT : 819 873 59 D N = 3 → MISSING 3

MF 3837



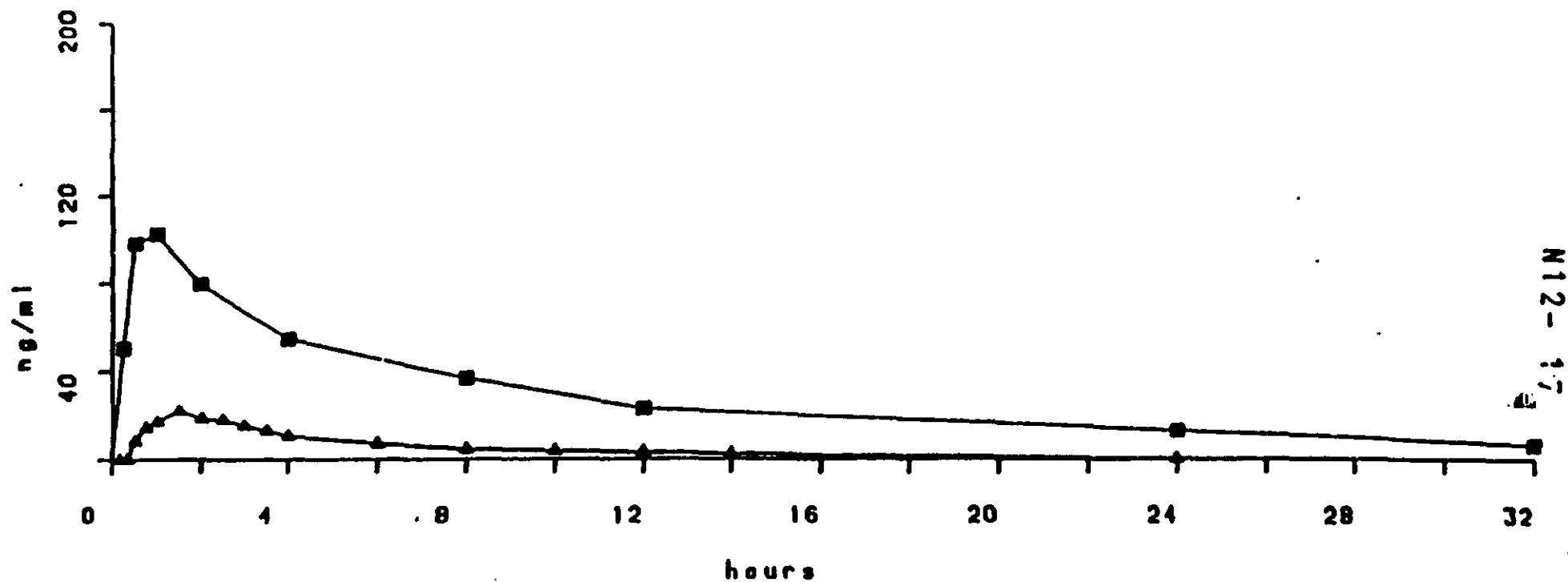
N12-18

B33

MF. 3837
Vol 1.61
000281

Fig 2

PROJECT : BM 14.190
DOSE : 25 MG PERORAL
BIOASSAY : BM 14.190 IN SERUM. DETERMINATION : HPLC-FLUOROM.
MEDIAN - VALUES
DATE : 09-FEB-88
▲ - SERIAL NO. OF STUDY : 0 6 4 7 N = 20
 LOT : 816 034 BB
■ - MF 3837 - PHARMACOKINETICS IN PATIENTS WITH LIVER INSUFF. MF 3837
 LOT : 819 854 40 CF N = 6



N12-173

MF 3837
Vol 1.61
000282

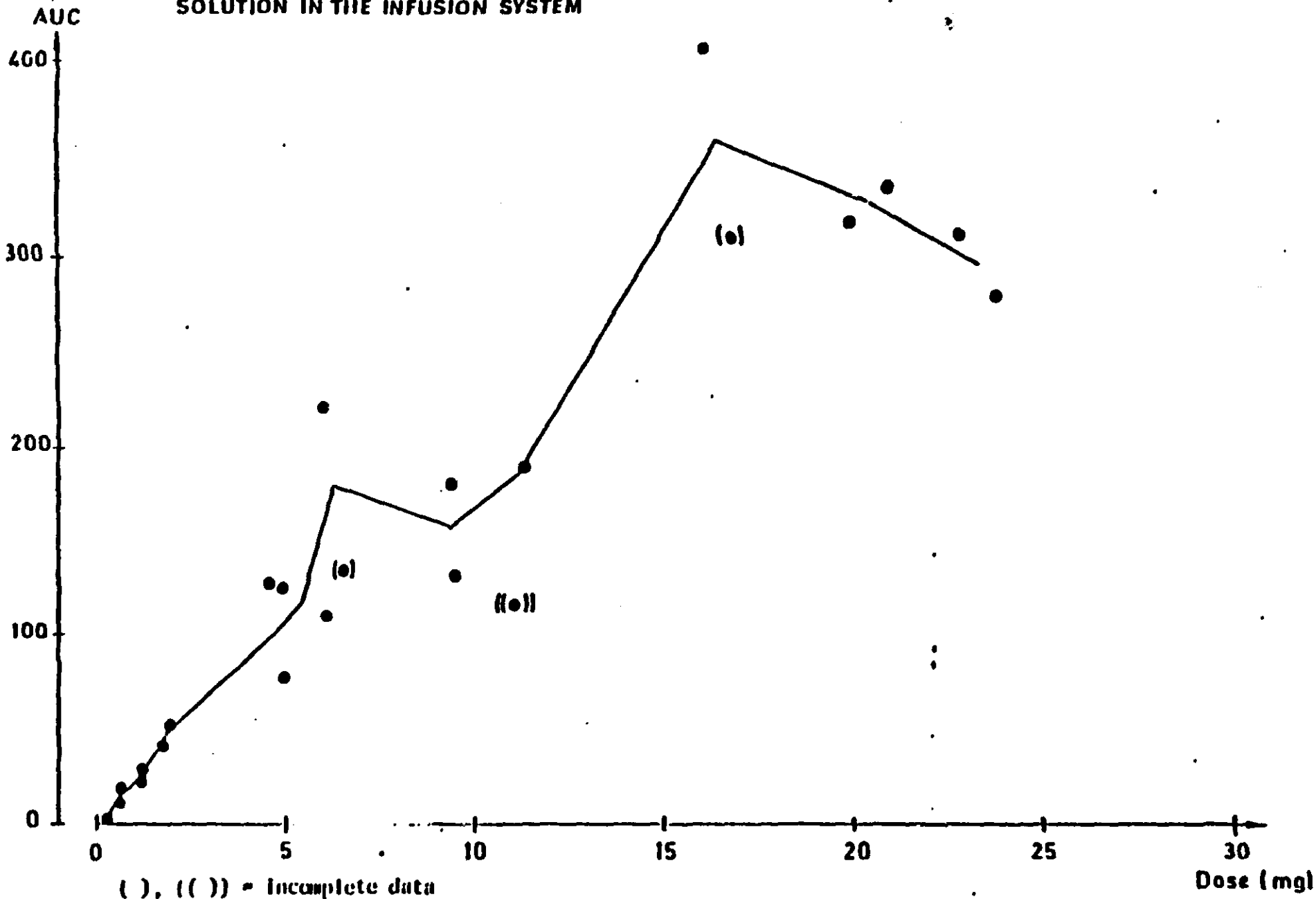
834

Concentration-time-areas (3hrs) after increasing i.v. doses of BM 14.190

Fig. 4

(ng/ml x h)

DOSES CALCULATED FROM THE MEASURED CONCENTRATIONS OF THE SOLUTION IN THE INFUSION SYSTEM



(), (()) = Incomplete data

M 3-19

B35

MF-1018
 vol 1.64
 000343



Results

The results are summarized in the tables and figures in the Appendix and in the following survey table.

Pharmacokinetic parameter	Breakfast	
	0.5 h before substance administration (human study no. 0636/A)	2 h after administration (human study no. 0636/B)
lag time (h)	0,752 0,822 (0,233-1,532)	0,451 0,426 (0,183-0,969)
initial increase (mcg/l/h)	104,92 41,57 (7,82-1157,82)	227,88 103,33 (10,16-1536,99)
$t_{1/2}$ (h)	3,731 3,478 (2,038-7,107)	4,052 4,480 (1,602-7,520)
C_{max} (mcg/l)	49,21 47,39 (18,22-97,35)	55,40 46,00 (15,23-143,85)
t_{max} (h)	2,732 2,514 (0,556-4,759)	1,466 1,249 (0,584-2,915)
AUC (mcg x h/l)	246,24 196,87 (80,38-637,28)	234,68 173,14 (82,12-675,62)
MRT (h)	5,384 5,225 (3,380-8,138)	5,009 4,933 (2,584-9,371)

(AUC: area under the curve, MRT: mean residence time)

Survey table of pharmacokinetic characteristic data from the substance concentrations in serum after oral administration of 25 mg Carvedilol (BM 14.190) with (human study no. 0636/A) and without breakfast (human study no. 0636/B). Stated are the mean values, below these the medians and in brackets the minima and maxima. The parameters were calculated from the compensation curves which were obtained by means of adapted regression functions for compensation of the measured data (2).

MF 7021
VOL 1.67

000013

Tat :
0966 V

Kinetic data, BM 14.190 oral
 $\bar{x}$, x, (minimum, maximum)

	(50 mg Caps. 0) n = 15	Result Wilcoxon-Test ↔	(25 mg Caps. 0) n = 16	Result Wilcoxon-Test ↔	(50 mg Caps. 3) n = 19	Result Wilcoxon-Test ↔	(50 mg Caps. 0) n = 15
init.increase conc. ($\mu\text{g}/\text{l}/\text{h}$)	201.8 55.15	n.s.*	123.9 90.3	n.s.	351.3 198.25	p = 0.008	
lag time (h)	0.42 0.38		0.46 0.44		0.34 0.31		
C _{max} ($\mu\text{g}/\text{l}$)	59.4 60.5	n.s.	42.1 47.8	n.s.	94.8 89.0	p = 0.001	see first column
t _{max} (h)	1.78 1.64	n.s.	1.51 1.55	n.s.	1.20 0.95	p = 0.035	
AUC ₀₋₂₄ ($\mu\text{g}\cdot\text{h}/\text{l}$)	316.57 317.08		195.48 183.52		368.91 379.61		
AUC _{0-∞} ($\mu\text{g}\cdot\text{h}/\text{l}$)	376.42 372.05	n.s.	217.26 194.45	n.s.	389.10 387.10	n.s.	
t _{1/2} (h)	8.40 6.24	n.s.	6.06 5.61	n.s.	4.73 4.24	p = 0.048	
mean residence time (h)	10.53 7.42	n.s.	7.29 6.19	n.s.	5.37 4.72	p = 0.007	

* Statistical differences calculated with the Wilcoxon test for paired differences; the n-numbers were in some cases smaller than stated in the table heading; n.s. = not significant

MF 7022

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037

B38

Table 1:

Pharmacokinetic data of SM 14.190 after administration of a gastric juice-resistant tablet in comparison with a suspension

Parameter		Tablet (2x16.67 mg) Human Exp. No. 0642	Suspension (34 mg) Human Exp. No. 0643
AUC 0 - 24 ($\mu\text{g} \times \text{h/l}$)	$\bar{x}$	171	382
	$\tilde{x}$ (min-max)	158	310
C_{max} ($\mu\text{g/l}$)	$\bar{x}$	13.7	107.5
	$\tilde{x}$ (min-max)	13.5	98.9
t_{max} (h)	$\bar{x}$	9.0	0.64
	$\tilde{x}$ (min-max)	9.0	0.62
$t_{1/2}$ (h)	$\bar{x}$	not determinable	7.3
	$\tilde{x}$ (min-max)		7.2

$\bar{x}$: mean
 $\tilde{x}$: median

MF7023
 VOL 1.68
 000015

TREATMENT TYPE

Parameter	Torasemide	Torasemide Combination
Coefficient of correlation (fitted to mathematical model [r])	0.985	0.973
AUD* ₀₋₂₄ [ng*h/ml]	2032 ± 571	1998 ± 656
c _{max} [ng/ml]	592.73 ± 174.99	539.54 ± 181.81
t _{max} [h]	1.24 ± 0.46	1.49 ± 0.57
Absorption half-life [h]	0.28 ± 0.16	0.31 ± 0.13
Elimination half-life [h]	5.25 ± 3.72	4.71 ± 2.41
Mean time [h]	5.86 ± 2.94	5.52 ± 2.49

*AUD = Area Under Data

(calculated using the linear trapezoidal rule)

Table 3: Means and standard deviations of the pharmacokinetic parameters (after fitting to the mathematical model) for torasemide in overview after administration of torasemide as a single entity and after administration of torasemide in combination.

MF 7024

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000157

B 40

TREATMENT TYPE N11-49

Parameter	Carvedilol	Carvedilol Combination
Coefficient of correlation (fitted to mathematical model [r])	0.993	0.993
AUD [*] ₀₋₂₄ [ng*h/ml]	168 ± 58	192 ± 39
c _{max} [ng/ml]	43.60 ± 16.85	45.56 ± 12.24
t _{max} [h]	1.30 ± 0.56	1.73 ± 0.43
Absorption half-life [h]	0.23 ± 0.15	0.27 ± 0.08
Elimination half-life [h]	6.17 ± 1.85	6.38 ± 3.23
Mean time [h]	5.91 ± 1.45	5.86 ± 2.15

*AUD = Area Under Data
(calculated using the linear trapezoidal rule)

Table 5: Means and standard deviations of the pharmacokinetic parameters (after fitting to the mathematical model) for carvedilol in overview after administration of carvedilol as a single entity and after administration of carvedilol in combination.

MF.7024
VOL.68
000162

B41

5. Results

5.1 Digitoxin in Plasma

The individual values of the plasma digitoxin concentration and the individual plasma concentration-time curves (for the sake of clarity shown only up to 24 hours) are presented in the appendix (Appendix III, Tables 1 and 2; Appendix VI, Figures 1 to 12). An examination of the individual curves reveals no marked difference between the two study phases. The mean value curves of the two study phases (Figure 1) are almost identical.

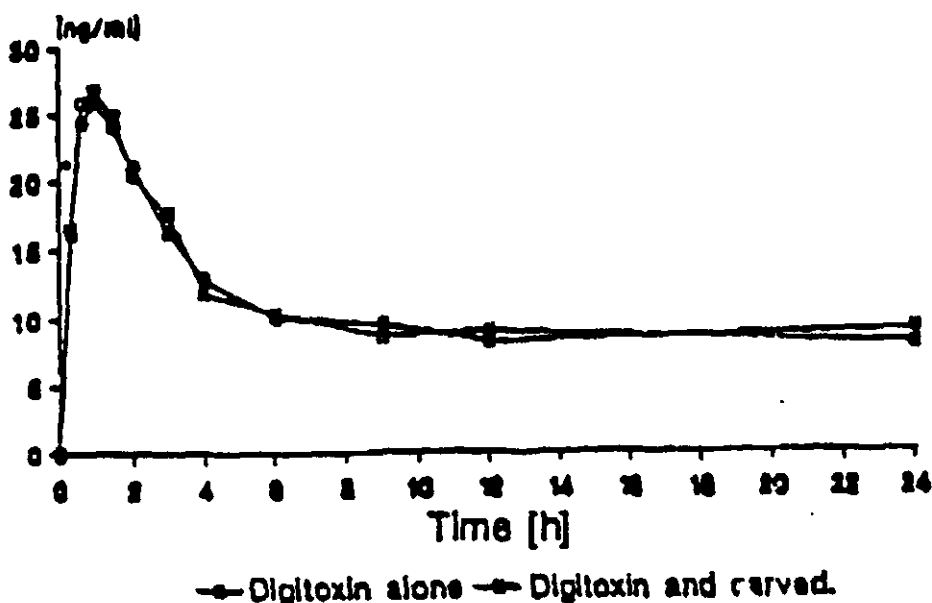


Figure 1: Mean plasma concentration-time curves of digitoxin after oral dosing of 0.56 mg digitoxin alone and in combination with 25 mg carvedilol under steady state conditions (n = 12)

As the Wilk-Shapiro test showed that the hypothesis of normal distribution could not be rejected at the 5 % level, parametric statistical methods were used. The intra-individual paired comparisons using Student's t-test did not show any significant differences for any of the parameters.

MF 7108

VOL 172

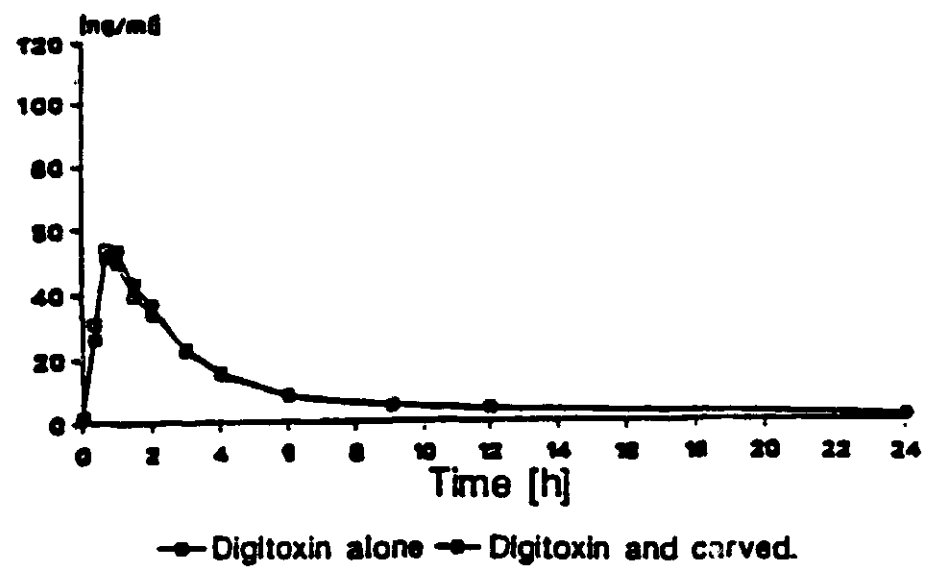


Figure 2: Mean plasma concentration-time curves of carvedilol under steady state conditions after oral administration of 25 mg carvedilol (n = 12).

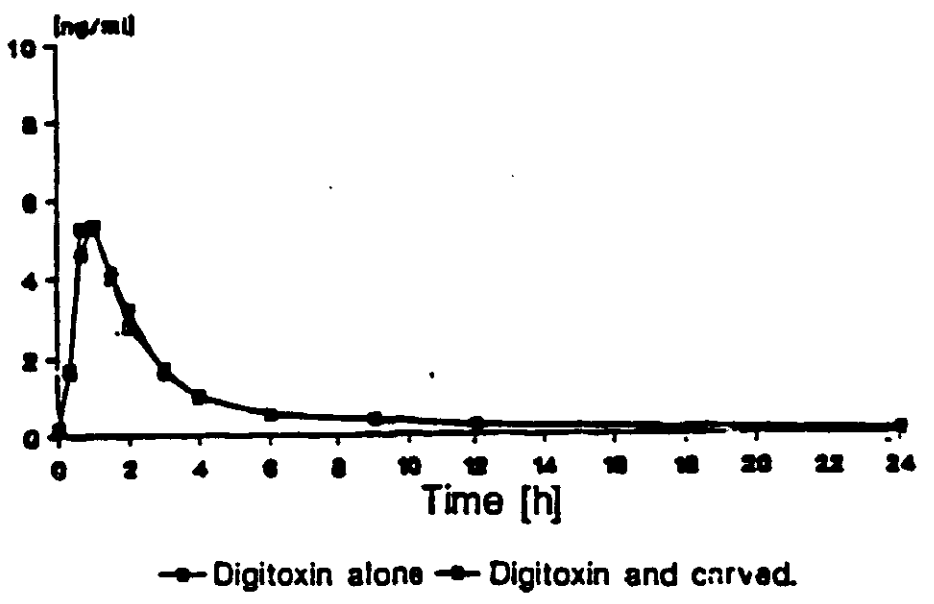


Figure 3: Mean plasma concentration time curves of demethylcarvedilol after oral administration of 25 mg carvedilol under steady state conditions (n = 12).

MF 7108



somewhat greater but also non-significant difference was found for the mean AUC_{0-24h} of demethylcarvedilol (study phase (II) 14.62 ± 5.22 ng/ml*h; study phase (III) 16.01 ± 6.24 ng/ml*h) (Appendix IV, Tables 5, 6 and 7; Appendix VII, Figures 13 and 16).

The AUC ratio as the relation of AUC (carvedilol) to AUC (demethylcarvedilol) was not significantly changed between study phase (II) with 12.89 ± 3.42 and study phase (III) with 12.20 ± 3.00 (Appendix IV, Table 7).

Table 2: Means of pharmacokinetic parameters of carvedilol and demethylcarvedilol

	Carvedilol alone (II)	Carvedilol + digitoxin (III)
Carvedilol		
Cmax (ng/ml)	60.37 ± 19.87	60.47 ± 21.39
tmax (h)	0.90 ± 0.45	0.82 ± 0.33
AUC (ng*h/ml)	200.84 ± 127.10	199.22 ± 105.62
Demethylcarvedilol		
Cmax (ng/ml)	5.83 ± 1.60	5.55 ± 1.30
tmax (h)	0.91 ± 0.38	0.93 ± 0.24
AUC (ng*h/ml)	14.62 ± 5.22	16.01 ± 6.24
AUC ratio (Carvedilol/demethylcarvedilol)	12.89 ± 3.42	12.20 ± 3.00

MF 7108

Protocol	Vol	Objective	Design	Subjects	Treatment	single vs multi dose	n completed (enrolled)	page
A0001	1.50	PK, bioequiv	NB, NC, R SEQ, Xover	healthy men	carv 25 mg capsule po	single	12(12)	C4
A0008	1.50	PK, bioequiv	NB, NC, R SEQ, Xover	healthy men	carv 25 mg capsule and tab po	single	12(13)	C6
A9901	1.51	PK, stereochem	NB, NC, NR, Xover	healthy men	carv 25 mg po	single	12(12)	C11
A9902	1.51	PK, bioequiv	NB, NC, R SEQ, Xover	healthy men	carv 25 mg capsule po, carv 25 mg tab po	single	12(13)	C14
A9903	1.51	PK, stereochem	NB, NC, R SEQ, Xover	healthy men	carv 6.25 mg po, carv 12.5 mg po, carv 25 mg po	single	12(12)	C16
A9904	1.52	PK, digoxin	DB, PC, R SEQ, Xover	healthy men	carv 25 mg po with digoxin 0.5 mg po, placebo with digoxin 0.5 mg po	single	8(8)	C19
A9905	1.52	PK, digoxin	DB, PC, R SEQ, Xover	healthy men	carv 25 mg po with digoxin 0.5 mg IV, placebo with digoxin 0.5 mg IV	single	8(8)	C21
A9907	1.52	PK, food effect	NB, NC, R SEQ, Xover	healthy men, women	carv 25 mg po	single	12(12)	C25
A9908	1.52	PK, bioequiv	NB, NC, R SEQ, Xover	healthy men, women	carv 25 mg po capsule	single	12(12)	C28
A9910	1.53	PK, bioequiv	NB, NC, R SEQ, Xover	healthy men	carv 25 mg po capsule and tab	single	16(17)	C30
A9912	1.53	PK, bioequiv	NB, NC, R SEQ, Xover	healthy men	carv 25 mg po capsule and tab	single	20(20)	C33
CAR.SA-01	1.54	PD, invasive hemodynamic, PK, stereochem	NB, AC, NR	patients, HTN, LV fail	carv 25 mg po, nitroprusside IV	single	10(10)	C36
CAR.UK-106	1.114	PD, non invasive hemodynamic	DB, PC, R SEQ (placebo only), dose escalation	healthy men	carv 12.5 mg, 25 mg, 50 mg, placebo po	single	7(8)	C40
CAR.UK-110	1.114	PD, platelet	in vitro	healthy donor	NA	NA	NA	C51
CARV.0001	1.114	PD, alpha beta	SB, PC, AC, parallel	healthy men	carv 15 mg IV, labetalol 80 mg IV, placebo IV	single	24(25)	C55
CARV.0002	1.75	PK	NB, NC, NR	healthy men	carv 0.042 mg/kg IV, carv 0.084 mg/kg IV	single	6(11)	C61

Protocol	Vol	Objective	Design	Subjects	Treatment	single vs multi dose	n completed (enrolled)	page
CARV.0011	1.115	PD, beta, LV function	DB, PC, R SEQ, Xover	patients ASCHD	carv 25 mg po	single	12(20)	C64
F30	1.44	PK, stereochem	NB, NC, NR	healthy men	carv 20 mg po	single	5(5)	C66
INT-CAR-22SCA	1.53	PD, beta	NB, NC, NR, parallel, dose escalation	healthy men	carv 12.5 mg/day for 1 week, carv 25 mg/day for 2 weeks po	multiple for 3 weeks	10(10)	C69
INT.CAR.30A		PD, beta	DB, R SEQ placebo only, ascending dose SEQ, Xover	healthy men	carv 6.25 mg, 12.5 mg, 25 mg, 50 mg po	single	5	C74
INT.CAR-30B	1.113	PD, alpha	DB, PC, partially R SEQ, Xover	healthy men	placebo; labetalol 400 mg po; carv 6.25 mg, 12.5 mg, 25 mg po	single	10(10)	C82
MF2971	1.56	PD, beta	DB, PC, R seq, Xover, with SB, NC, NR extension	healthy men	po carv 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 600 mg, 800 mg	single	6(6)	C88
MF3132 I	1.125	PD, beta	DB, PC, AC, R SEQ, Xover	healthy men	carv 100 mg, labetalol 200 mg, propranolol 160 mg, pindolol 10 mg, placebo po	single	6(7)	C93
MF3132 II	1.125	PD, beta	DB, PC, R SEQ, Xover	healthy men	carv 100 mg, placebo po	single	6(6)	C103
MF3223 I and II	1.125	PD, beta	DB, PC, AC, R SEQ, Xover	healthy men	carv 12.5 mg, 25 mg, 50 mg, 100 mg, 200 mg; labetalol 50 mg, 100 mg, 200 mg, 400 mg; propranolol 40 mg, 80 mg, 160 mg, 320 mg; pindolol 2.5 mg, 5 mg, 10 mg, 20 mg; placebo po	single	6(6)	C105
MF3270	1.125	PD, beta, exercise tolerance	SB, PC, NR, Xover	patients stable angina pectoris	carv 25 mg bid, 50 mg bid, placebo bid po	multiple doses for 2 weeks	15(20)	C109
MF3413	1.57	PK, PD, young, old	DB, PC, AC, NR, Xover	healthy men and women	carv 12.5 mg, 25 mg, 50 mg po, labetalol 200 mg po, carv 5 mg IV, placebo	single	8(20)	C122

Protocol	Vol	Objective	Design	Subjects	Treatment	single vs multi dose	n completed (enrolled)	page
MF3459	1.58	PK, renal fail	NB, NC, NR	patients with HTN and renal insufficiency	carv 50 mg po	single	24(25)	C133
MF3476	1.60	PK, liver fail	NB, NC, NR, Xover	patients with liver insufficiency	carv 25 mg po, carv 12.5 mg IV	single	28(31)	C140
MF3548	1.134	PD, alpha, beta	DB, PC, AC, R SEQ, Xover	healthy men	carv 50 mg, 100 mg; propranolol 160 mg; propranolol 80 + hydralazine 50 mg; labetalol 400 mg; placebo po	single	8(8)	C142
MF3702	1.61	PK, young, old	SB, NC, NR, dose escalation in non responders	patients HTN	carv 12.5 mg/day, 25 mg/day, 50 mg/day po	multiple for 12 weeks	29(32)	C144
MF3877	1.62	PK, interaction HCTZ, diuretic	DB, AC, R SEQ, Xover	patients HTN	carv 25 mg, HCTZ 25 mg, placebo po	single	12(12)	C145
MF3950	1.63	PK, young, old	NB, NC, NR, parallel	healthy men and women	carv 25 mg/day po	multiple for 2 weeks	17(21)	C153
MF7008	1.64	PK, bioequiv	NB, NC, R SEQ, Xover	healthy men	carv 25 mg tab po, carv 25 mg capsule po	single	20(20)	C157
MF7016-0539	1.64	PD, alpha	NB, NC, NR, dose escalation	healthy men	carv 2.5, 5, 10, 15, 22.5, 30, 34, 51, 76.5 mg suspension po	single	15(23)	C160
MF7016-0541	1.64	PD, beta	DB, AC, NR, Xover	healthy men	carv 50 mg; metipranolol 5 mg and 10 mg suspension po	single	6(7)	C163
MF7029	1.71	PK, metabolism	NB, NC, NR	healthy men	carv 50 mg po	single	6(6)	C169
MF7034	1.71	PK, stereochem	NB, NC, R SEQ, Xover	healthy men	carv 50 mg po, carv 12.5 mg IV	single	10(10)	C175
MF7038	1.71	PK	NB, NC, NR, Xover	one healthy man	carv 25 mg po, carv 10 mg IV	single	1(1)	C177
MF7097	1.71	PK, cimetidine	NB, NC, NR	healthy men	carv 25 mg/day, cimetidine 1000 mg/day po	multiple for 9 days	10(10)	C179
protocol-020	1.49	PK, bioequiv	NB, NC, R SEQ, Xover	healthy subjects	carv 25 mg capsule, 25 mg Tiltab® po	single	32(34)	C187

NDA 20-297 CARVEDILOL, Protocol A0001, Vol 1.50
BIOEQUIVALENCE
Reviewer: James F. Graumlich

Design: open label, randomized, period balanced, 4 way crossover with all four formulations in 12 - 24 healthy male subjects. Study periods were separated by one week.

Response variable: AUC, Cmax, Tmax, half-life, BP, and heart rate

Blood sampling times: baseline then 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 14, 20, and 24 hours after dose administration. Supine BP and heart rate were measured after the dose administration every 10 minutes x 4 hours then every 15 minutes x 4 hours.

Materials	Treatment	Studies
carvedilol 25 mg capsule, lot number Ch 819 854 40 Gf	A	Clinical supplies in 1987
carvedilol 25 mg capsule, lot number Ch 819 291 40 Df	B	Used in efficacy studies
carvedilol 25 mg capsule, lot number Ch 819 861 40 Df	C	Used in safety studies
carvedilol 25 mg capsule, lot number Ch 819 177 40 Fe	D	Used in dose ranging studies

Assay: plasma carvedilol concentration and plasma O-desmethyl-carvedilol concentration. HPLC reference is Varin. J Pharm Sci 1986; 75:1195-1197. Lower limit of quantification = 0.3 ng/mL.

Results: Standing BP and heart rate were not measured 1, 2, 4, 6 and 8 hours after dose administration because of symptomatic orthostatic "faintness," hypotension, and bradycardia in 6 of 12 subjects, i.e., subjects 4, 8, 6, 5, 7, 12.

formulation A, n = 12 [carvedilol]

Parameter	mean±SD	min	max		
AUC(0-24)	136.05±53.63			ng*hr/mL	
Cmax	45.19±22.86			ng/mL	
Tmax	1.02±0.27			hr	
half-life	4.96±1.43			hr	n = 11

formulation B, n = 12 unless noted otherwise [carvedilol]

Parameter	mean±SD	min	max		
AUC(0-24)	95.06±32.85			ng*hr/mL	
Cmax	26.8±15.03			ng/mL	
Tmax	1.27±0.87			hr	
half-life	6.8±4.92			hr	n = 7

formulation C, n = 12 unless noted otherwise [carvedilol]

Parameter	mean±SD	min	max		
AUC(0-24)	136.77±60.78			ng*hr/mL	
Cmax	43.17±22.86			ng/mL	
Tmax	1.02±0.34			hr	
half-life	5.33±2.0			hr	n = 12

formulation D, n = 12 unless noted otherwise [carvedilol]

Parameter	mean±SD	min	max		
AUC(0-24)	119.51±37.12			ng*hr/mL	
Cmax	37.21±17.12			ng/mL	
Tmax	1.15±0.58			hr	
half-life	9.53±11.99			hr	n = 12

formulation A, n = 12 unless noted otherwise			[0-desmethyicarvedilol]	
Parameter	mean±SD	min	max	
AUC(0-t)	7.82±3.18			ng*hr/mL
Cmax	4.14±1.79			ng/mL
Tmax	1.19±0.34			hr
half-life	1.63±1.15			hr
				n = 10

formulation B, n = 12 unless noted otherwise			[0-desmethyicarvedilol]	
Parameter	mean±SD	min	max	
AUC(0-t)	5.77±3.11			ng*hr/mL
Cmax	2.78±1.15			ng/mL
Tmax	1.40±0.62			hr
half-life	0.98±0.28			hr
				n = 10

formulation C, n = 12 unless noted otherwise			[0-desmethyicarvedilol]	
Parameter	mean±SD	min	max	
AUC(0-t)	7.64±2.2			ng*hr/mL
Cmax	3.66±0.65			ng/mL
Tmax	1.23±0.34			hr
half-life	1.36±0.46			hr
				n = 9

formulation D, n = 12 unless noted otherwise			[0-desmethyicarvedilol]	
Parameter	mean±SD	min	max	
AUC(0-t)	6.25±2.96			ng*hr/mL
Cmax	3.25±1.20			ng/mL
Tmax	1.38±0.53			hr
half-life	2.31±2.34			hr
				n = 9

Adverse events: See above regarding orthostatic hypotension.

Other lab abnormalities associated with drug treatment were elevated LDH, elevated CK and CK-MB, decreased hemoglobin, decreased platelets, decreased total protein

Conclusions:

None of the formulations were bioequivalent.

what about A+E

There was a range of Cmax [carvedilol] within the four formulations from 26.8 to 45.19 ng/mL.

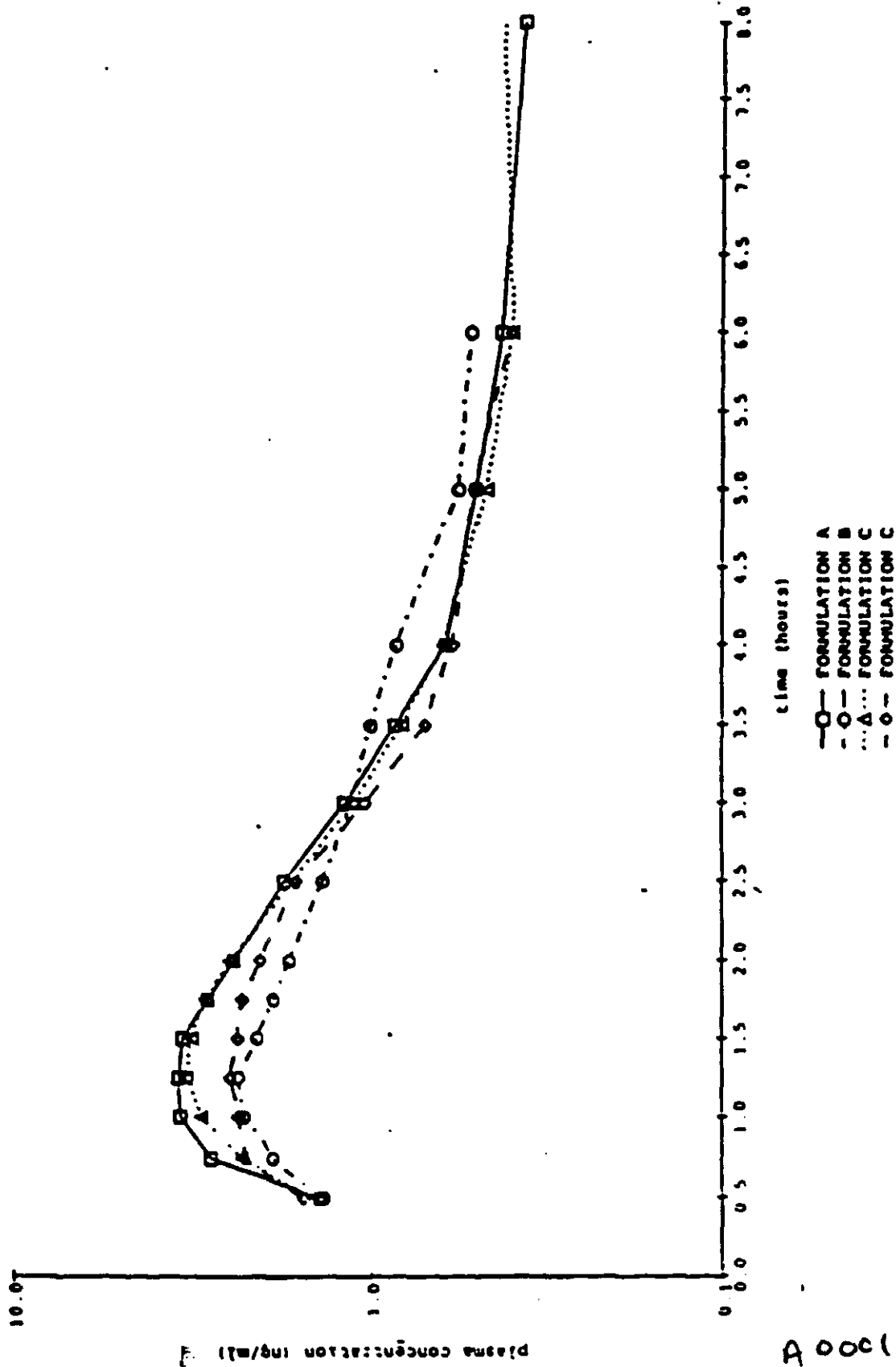
Tmax [carvedilol] was consistent at around 1 hour.

Cmax [0-desmethyicarvedilol] is about 10% of Cmax [carvedilol].

Orthostatic hypotension occurred in 6 of 12 healthy volunteers. There was no placebo comparison.

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A SmithKline Beecham Company

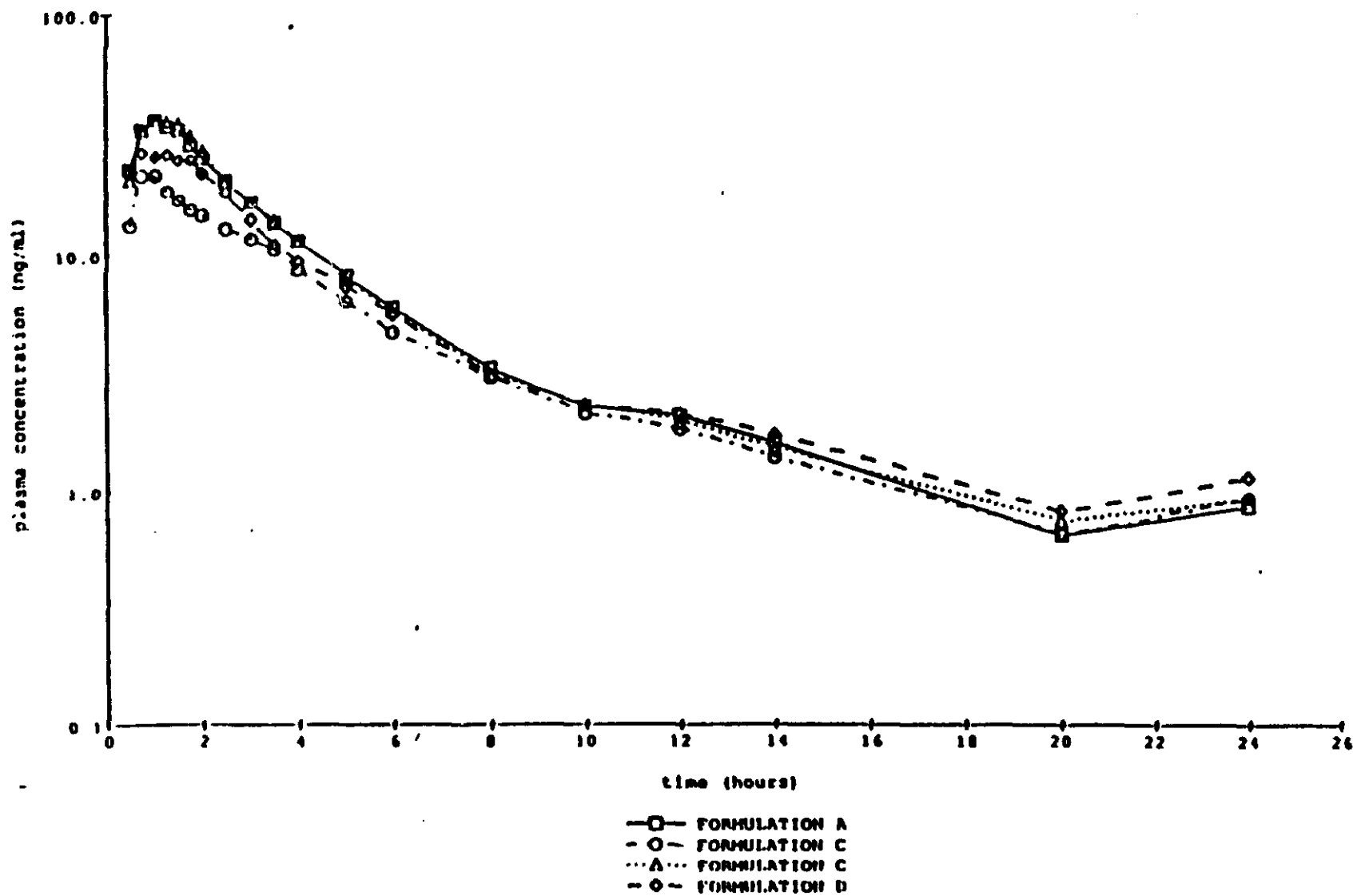
FIGURE 26
MEAN PLASMA O-DESMETHYLCARVEDILOL CONCENTRATION VERSUS TIME
IN NORMAL SUBJECTS (n=12) FOLLOWING ADMINISTRATION
OF 25 mg CAPSULES



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A SmithKline Beckman Company

FIGURE 13
MEAN PLASMA CARVEDILOL CONCENTRATION VERSUS TIME
IN SUBJECTS (n=12) FOLLOWING ADMINISTRATION
OF 25 mg CAPSULES



A0001
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NDA 20-297 CARVEDILOL, Protocol A0008, Vol 1.50
BIOEQUIVALENCE
 Reviewer: James F. Graulich

Objectives: Describe and compare the pharmacokinetics of single doses of carvedilol 25 mg given in 4 different formulations to determine bioequivalence.

Study design: Open label, randomized, period balanced, 4 way crossover with all four formulations in 12 healthy male subjects. Study periods were separated by one week.

Response variables: AUC, Cmax, Tmax, half-life, BP, and heart rate

Blood sampling times: baseline then 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2.0, 2.5, 3, 4, 6, 8, 10, 12, 14, and 24 hours after dose administration. Supine BP and heart rate were measured after the dose administration every 10 minutes x 4 hours then every 15 minutes x 4 hours. Standing BP and heart rate were measured 2 and 8 hours after dose administration.

Materials:

A=carvedilol 25 mg capsule, lot number Ch 819 854 40 Gf = A in A0001
 B=carvedilol 25 mg capsule, lot number Ch 819 291 40 Df = B in A0001
 C=carvedilol 25 mg capsule, lot number Ch 820 176 40 Lh = reference
 D=carvedilol 25 mg tablet, lot number Ch 819 896 20 B

C was used by SK Beecham for US clinical trials for hypertension.

Assay: plasma carvedilol concentration and plasma O-desmethyl-carvedilol concentration. HPLC reference is Varin. J Pharm Sci 1986; 75:1195-1197. Lower limit of quantification = 0.3 ng/mL.

Results: 13 subjects were recruited. Subject 13 was withdrawn due to adverse event. 12 subjects completed the study. See tables for carvedilol for AUC, Cmax, and Tmax means (pages 204, 205 volume 1.50).

AUC O-desmethyl-carvedilol (ng*hr/mL)

formulation	A	B	C	D
mean±SD	9.35±4.86	7.62±4.35	9.2±3.88	8.64±4.66
min				
max				

Cmax O-desmethyl-carvedilol (ng/mL)

formulation	A	B	C	D
mean±SD	3.44±1.57	2.7±1.02	4.15±1.89	3.26±1.65
min				
max				

Tmax O-desmethyl-carvedilol (hours)

formulation	A	B	C	D
mean±SD	1.59±0.72	1.17±0.29	1.35±0.62	1.33±0.66
min				
max				

The means for supine DBP, SBP, and pulse are shown vs time in Figure 25 from volume 1.50. There were minimal drug effects during the first 8 hours after the dose.

Adverse events:

Subject 13 had a wide complex tachycardia before dosing on the second study day. He received treatment A on the first study day. Since the arrhythmia occurred one week after a single dose of carvedilol, I do not associate the adverse event with the drug.

Subjects 1, 2, 3, 4, 5, 7, 9, 10 and 13 developed one or more symptoms with standing.

Conclusions:

None of the formulations were bioequivalent to formulation C for AUC and C_{max}.

Formulation B had less bioavailability than formulation C.

O-desmethyl-carvedilol concentrations were less than 5% carvedilol concentrations.

Subjects developed orthostatic symptoms.

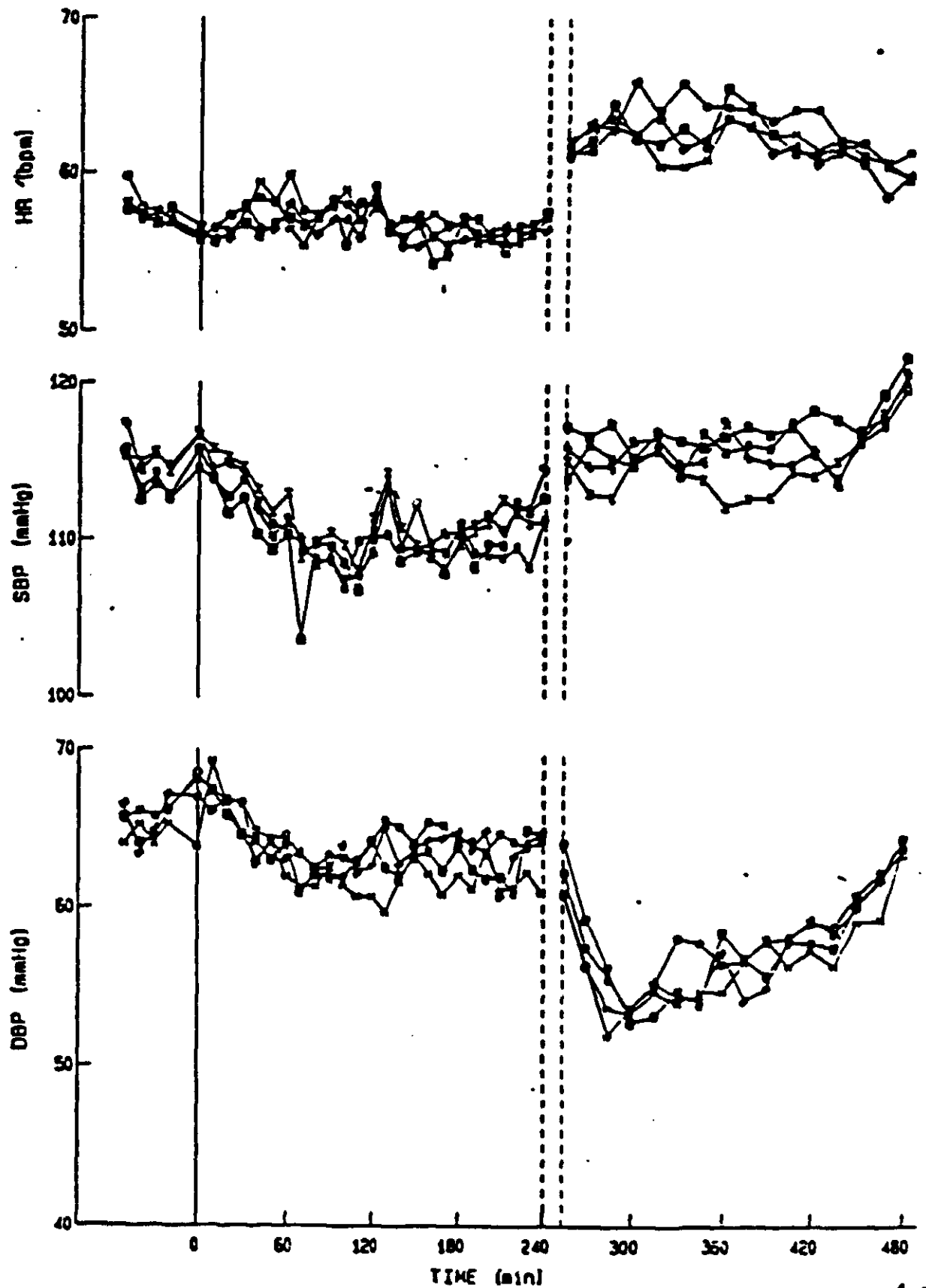
There was no definite effect of the drug on supine SBP, DBP, or pulse in these healthy men. There was no placebo comparison.

The conclusions of the sponsor appear valid.

Figure 25

CARVEDILOL/A08 : MEAN SUPINE VALUES

○: A / □: B / △: C / ●: D (25 mg)



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Time course of Treatment Means (n=12) of HR, SBP and DBP
Dotted lines equals lunch time.

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The means, medians, and ranges of CMAX data for each formulation were:

<u>Formulation</u>	<u>CMAX</u> <u>(ng/ml)</u>		
	<u>Mean</u>	<u>Median</u>	<u>Range</u>
C	62.99	70.90	
A	61.36	55.58	
B	47.96	40.37	
D	49.52	44.10	

The ratio of the mean CMAX for Formulations A, B, and D expressed as a percentage of the mean CMAX of Formulation C (reference) and the corresponding 90% confidence intervals for the true ratio of means (arithmetic scale analysis) were as follows:

	<u>Ratio %</u>	<u>90% Confidence Interval</u>
A/C	97.4	73.3 - 121.6
B/C	76.1	52.0 - 100.3
D/C	78.6	54.5 - 102.8

The means, medians, and ranges of TMAX data for each formulation were:

<u>Formulation</u>	<u>TMAX</u> <u>(hr)</u>		
	<u>Mean</u>	<u>Median</u>	<u>Range</u>
C	1.13	1.00	
A	1.52	1.13	
B	1.06	1.00	
D	1.38	1.00	

2. Pharmacokinetics of O-desmethylocarvedilol

Graphical and tabular representation of the plasma O-desmethylocarvedilol concentrations at all sampling times for each subject are provided in Figures 13 to 24 and Appendix III.

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000105

1. Comparative Pharmacokinetics1. Pharmacokinetics of Carvedilol

The plasma concentrations of carvedilol at all sampling times for each subject are reported in Appendix I. The plasma concentration-time profiles for each subject are shown in Figures 1-12. The individual and mean values for area under the concentration-time curves (AUC), peak plasma concentration (C_{MAX}), and time until peak plasma concentration (T_{MAX}) are reported in Tables 4-6.

The means, medians, and ranges of AUC data for each formulation were:

<u>Formulation</u>	<u>AUC</u> <u>(ng*hr/ml)</u>		
	<u>Mean</u>	<u>Median</u>	<u>Range</u>
C	221.89	201.24	
A	234.72	181.31	
B	198.61	165.90	
D	206.08	172.12	

The ratio of the geometric mean AUC for Formulations A, B, and D expressed as a percentage of the geometric mean AUC of Formulation C (reference) and the corresponding 90% confidence intervals for the true ratio of means (logarithmic scale analysis) were as follows:

	<u>Ratio %</u>	<u>90% Confidence Interval</u>
A/C	100.9	85.8 - 118.6
B/C	85.8	73.0 - 100.9
D/C	91.5	77.8 - 107.5

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NDA 20-297 CARVEDILOL STEREOSELECTIVE PK, Protocol A9901, Vol 1.51

Reviewer: James F. Graumlich

Name of study: A pharmacokinetic study of carvedilol, 25 mg orally, (SK&F 105517) to study the intra-subject variability and stereoselectivity of the pharmacokinetics in healthy subjects.

Objectives: To estimate the intra-subject variability for AUC, C_{max}, and T_{max} after a single dose of one capsule formulation.

Study design: Open label, non-randomized, 3 period study with single doses in 12 healthy male subjects. There was no placebo group. Study periods were separated by one week.

Response variables: AUC, C_{max}, T_{max}, half-life, BP, pulse

Blood sampling times: baseline then 10, 20, 30, 45 minutes then 1.0, 1.25, 1.5, 2.0, 2.5, 3, 4, 6, 8, 10, 12, 14, and 24 hours after dose administration. Supine BP and heart rate were measured 15, 30, 45 minutes then 1.0, 1.25, 1.5, 2.0, 2.5, 3, 4, 6, 8, 10, 12, 14, and 16 hours after dose administration.

Materials: carvedilol 25 mg capsule, lot number BM 820-176-40 Lh

Assay: Assay involved solid phase extraction and HPLC with fluorescence detection of plasma carvedilol concentration and plasma O-desmethyl-carvedilol concentration. Limit of quantification = 0.3 ng/mL. Plasma R (+) carvedilol and S (-) carvedilol concentration and plasma R (+) O-desmethyl-carvedilol and S (-) O-desmethyl-carvedilol concentrations were measured with chiral assay. Limit of quantification = 1.25 ng/mL.

Results: Twelve healthy male subjects between 22 and 33 years of age and weighing between 70.0 and 86.1 kg completed the study.

Pharmacokinetic parameters for carvedilol

	Period 1 mean±SD min, max	Period 2 mean±SD min, max	Period 3 mean±SD min, max	All periods mean
AUC(0-t)	222.64±147.4	205.67±111.79	217.73±115.74	215.35
AUC(0-∞)	278.45±158.17	229.19±128.67	235.97±125.74	
C _{max}	59.61±31.48	46.54±21.98	59.46±32.49	55.20
T _{max}	0.93±0.28	1.6±0.94	1.1±0.7	1.21
Half-life	9.71±1.72	10.03±2.44	8.96±1.65	

AUC in ng*hr/mL, C_{max} in ng/mL, T_{max} in hours, half-life in hours
t = time of last measured concentration

Pharmacokinetic parameters for R (+) carvedilol and S (-) carvedilol Enantiomers were measured only on samples from period 3.

	R (+) carvedilol mean±SD min, max	S (-) carvedilol mean±SD min, max	R/S ratio geometric mean min, max
AUC(0-t)	156.74±99.31	43.93±27.43	3.57
AUC(0-∞)	169.29±106.34	51.21±29.20	not tabulated
C _{max}	44.27±25.21	16.68±9.99	2.62
T _{max}	1.1±0.72	1.02±0.69	
Half-life lambda ₂	2.84±0.98	2.7±0.73	
Half-life lambda ₃	8.25±2.79*	missing data	

AUC in ng*hr/mL, C_{max} in ng/mL, T_{max} in hours, half-life in hours

*Represents only 3 subjects

t = time of last measured concentration

Pharmacokinetic parameters for O-desmethyl-carvedilol

	Period 1 mean±SD min, max	Period 2 mean±SD min, max	Period 3 mean±SD min, max	R (+) O-desmethyl-carvedilol mean±SD min, max
AUC(0-t)	12.5±9.03	15.33±7.67	13.89±7.52	7.18±5.07
C _{max}	3.68±1.28	3.17±1.12	4.62±1.81	4.17±1.61
T _{max}	0.99±0.23	1.44±0.97	1.13±0.25	1.29±0.52

Half-life not tabulated

AUC in ng*hr/mL, C_{max} in ng/mL, T_{max} in hours

t is the last measurable time point.

O-desmethyl-carvedilol not quantifiable (< 0.3 ng/mL) in 6 of 12 subjects at 12 hours after dose administration.

O-desmethyl-carvedilol not quantifiable (< 0.3 ng/mL) in 10 of 12 subjects at 24 hours after dose administration.

Enantiomers were measured only on samples from period 3.

S (-) O-desmethyl-carvedilol was quantifiable (≥ 1.25 ng/mL) in 3 of 12 subjects. C_{max} ranged from 1.37 to 2.48 ng/mL. T_{max} ranged from 0.75 to 1.5 hours after administration of the dose.

Supine systolic blood pressure SBP (mean $\pm$ SEM mm Hg), supine diastolic blood pressure DBP (mean $\pm$ SEM mm Hg), and pulse (mean $\pm$ SEM beats per minute) in 12 subjects. Time (T) to Emax is in hours.

Parameter	Period 1	Period 2	Period 3
SBP baseline	118 $\pm$ 2	116 $\pm$ 2	113 $\pm$ 2
SBP Emax	103 $\pm$ 2	103 $\pm$ 2	100 $\pm$ 2
SBP, T,Emax	0.75	1.5	1.5
SBP, 16 hours	111 $\pm$ 3	111 $\pm$ 2	109 $\pm$ 2
DBP baseline	73 $\pm$ 3	67 $\pm$ 2	71 $\pm$ 2
DBP Emax	54 $\pm$ 3	61 $\pm$ 3	59 $\pm$ 3
DBP, T-Emax	8	6	8
DBP, 16 hours	63 $\pm$ 2	72 $\pm$ 2	68 $\pm$ 2
Pulse baseline	63 $\pm$ 2	63 $\pm$ 2	64 $\pm$ 2
Pulse Emax	60 $\pm$ 2	57 $\pm$ 1	55 $\pm$ 2
Pulse, T-Emax	2	3	4
Pulse, 16 hours	66 $\pm$ 2	69 $\pm$ 2	63 $\pm$ 2

Adverse events:

headache
orthostatic lightheadedness
nausea
elevated AST
elevated ALT
elevated total bilirubin
elevated uric acid

Conclusions:

There is inter-subject and intra-subject variability in PK parameters.

Mean Cmax and AUC(0-t) values for R (+) carvedilol are two to four times greater than values for S (-) carvedilol

Plasma concentrations of O-desmethyl-carvedilol are 5 - 10% of plasma concentrations of carvedilol.

There is no placebo group with which to compare pharmacodynamic effects.

NDA 20-297 CARVEDILOL BIOEQUIVALENCE

Protocol A9902, Vol 1.51

Reviewer: James F. Graumlich

Name of study: A pharmacokinetic study of carvedilol (SK&F 105517), 25 mg orally, tablet vs capsule, in healthy subjects.

Objectives: To determine if 25 mg carvedilol "Tiltab" tablets and 25 mg carvedilol capsules are bioequivalent.

Study design: Open label, randomized, 2 period crossover study with single doses in 13 healthy male subjects. There was no placebo group. Study periods were separated by one week.

Response variables: Primary outcome: AUC (trapezoidal method)
Secondary outcome: Cmax, Tmax, half-life, BP, pulse

Blood sampling times: baseline then 10, 20, 30, 45 minutes then 1.0, 1.25, 1.5, 2.0, 2.5, 3, 4, 6, 8, 10, 12, 14, and 24 hours after dose administration.

Supine BP and heart rate were measured at baseline and 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2.0, 2.5, 3, 4, 5, 6, 8, 10, 12, and 14 hours after dose administration.

Materials: carvedilol 25 mg capsule, lot number IPO #87148
carvedilol 25 mg tablet, lot number IPO #88144 Tiltab

Assay: Assay involved solid phase extraction and HPLC with fluorescence detection of plasma carvedilol concentration. Limit of quantification = not stated

Results:

Thirteen healthy male subjects between 22 and 35 years of age and weighing between 63.0 and 87.8 kg enrolled in the study. One subject withdrew because of a headache.

Pharmacokinetic parameters for carvedilol

	Capsule mean±SD min, max	Tablet mean±SD min, max	90% Confidence Interval for ratio of means
AUC(0-t)	242.38±82.12	269.95±103.17	100.5, 118.6
Cmax	62.16±19.67	72.8±23.94	99.5, 134.8
Tmax	1.55±1.02	1.05±0.62	50.0, 86.6

Half-life not calculated

Log transformed AUC used to calculate confidence interval.

AUC in ng*hr/mL, Cmax in ng/mL, Tmax in hours, half-life in hours

t = time of last measured concentration

Supine systolic blood pressure SBP (mean $\pm$ SEM mm Hg), supine diastolic blood pressure DBP (mean $\pm$ SEM mm Hg), and pulse (mean $\pm$ SEM beats per minute) in 12 subjects. Time (T) to Emax is in hours.

Parameter	Tablet	Capsule
SBP baseline	112 $\pm$ 2	110 $\pm$ 2
SBP Emax	98 $\pm$ 1	100 $\pm$ 2
SBP, T,Emax	2	4
SBP, 14 hours	104 $\pm$ 4	108 $\pm$ 3
DBP baseline	71 $\pm$ 2	67 $\pm$ 2
DBP Emax	61 $\pm$ 2	61 $\pm$ 2
DBP, T-Emax	6	14
DBP, 14 hours	58 $\pm$ 2	61 $\pm$ 2
Pulse baseline	64 $\pm$ 2	65 $\pm$ 3
Pulse Emax	57 $\pm$ 2	57 $\pm$ 2
Pulse, T-Emax	3	4
Pulse, 14 hours	70 $\pm$ 2	67 $\pm$ 2

Adverse events:

headache
 orthostatic lightheadedness
 nasal stuffiness
 elevated alkaline phosphatase
 elevated AST
 elevated total bilirubin
 elevated glucose
 decreased CO₂
 decreased potassium
 decreased WBC

Conclusions:

The two formulations were bioequivalent based on log transformed AUC.

The two formulation were not bioequivalent based on Cmax (not transformed).

There is no placebo group with which to compare pharmacodynamic effects.

CARVEDILOL NDA 20-297

PROTOCOL A9903

DOSE PROPORTIONALITY AND STEREOSELECTIVE PK

Protocol A9903, Vol 1.51

Reviewer: James F. Graumlich

Name of study: A dose proportionality study of carvedilol enantiomers following doses of racemic carvedilol (SK&F 105517 capsules) of 6.25, 12.5, 25.0 and 37.5 mg orally in healthy subjects.

Objectives: To assess the dose proportionality of plasma concentrations of carvedilol enantiomers following single oral doses of racemic carvedilol.

Study design: Open label, randomized, 4 period crossover study with single doses in 12 healthy male subjects. There was no placebo group. Study periods were separated by one week.

Response variables: Primary outcome: AUC (trapezoidal method)
Secondary outcome: Cmax, Tmax, half-life, BP, pulse

Blood sampling times: baseline then 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2.0, 2.5, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours after dose administration. Supine BP and heart rate were measured at baseline then 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2.0, 2.5, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours after dose administration.

Materials: carvedilol 6.25 mg capsule, lot number IPO #87144
carvedilol 12.5 mg capsule, lot number IPO #88081
carvedilol 25.0 mg capsule, lot number IPO #88083

One carvedilol 12.5 mg capsule plus one carvedilol 25.0 mg capsule were given for the 37.5 mg dose.

Assay: Assay involved solid phase extraction, derivitization with GITC, and HPLC with fluorescence detection of plasma R (+) carvedilol and plasma S (-) carvedilol concentration. Limit of quantification for each enantiomer was 0.3 ng/mL.

Results: Twelve healthy male subjects between 23 and 35 years of age and weighing between 66.6 and 91.1 kg completed the study.

PK parameter values for different doses for carvedilol, mean±SD, n=12
AUC(0-t) in ng*hr/mL, Cmax in ng/mL t = time of last quantified concentration.

Table with 5 columns: Parameter, 6.25 mg, 12.5 mg, 25.0 mg, 25 + 12.5 mg. Rows include Cmax R (+), Cmax S (-), AUC(0-t) R (+), and AUC(0-t) S (-) with sub-rows for minimum and maximum values.

PK parameter values for different doses for carvedilol, mean±SD, n=12 with exceptions noted in table. The sponsor

CARVEDILOL NDA 20-297

PROTOCOL A9903

did not attempt to calculate half-life for subjects with less than three quantified plasma concentrations from 10 to 24 hours after dose administration. As a result of lost samples and samples with concentrations below the lower limit of quantification (<0.3 ng/mL), there were few subjects contributing data to half-life calculations as indicated below.

	6.25 mg	12.5 mg	25.0 mg	25 + 12.5 mg
Parameter				
Tmax R (+)	1.38±1.06	1.29±0.7	1.29±0.96	0.96±0.28
minimum				
maximum				
Tmax S (-)	1.17±0.96	1.06±0.66	1.13±0.96	0.79±0.23
min				
max				
Half-life R (+)	5.01±1.1 (n=3)	6.29±2.2 (n=7)	8.13±2.6 (n=9)	9.2±3.9 (n=11)
min				
max				
Half-life S (-)	10.5±6.97 (n=2)	10.51±4.57 (n=5)	10.21±3.85 (n=6)	7.39±2.56 (n=7)
min				
max				
AUC ratio (R/S)*	3.46	3.01	2.64	2.53
min				
max				
Cmax ratio (R/S)*	2.8	2.63	2.57	2.3
min				
max				

AUC(0-t) in ng*hr/mL, Cmax in ng/mL, Tmax in hours, half-life in hours

t = time of last quantified concentration. * = geometric mean

Pharmacodynamic response:

Supine systolic blood pressure SBP (mean±SEM mm Hg), supine diastolic blood pressure DBP (mean±SEM mm Hg), and pulse (mean±SEM beats per minute) in 12 subjects. Time (T) to Emax is in hours. Also shown are responses 12 and 24 hours after the dose administration.

Parameter	6.25 mg	12.5 mg	25.0 mg	25 + 12.5 mg
SBP baseline	116±3	115±2	113±4	114±2
SBP Emax	104±4	103±2	101±3	100±2
SBP T-Emax	4	3	3	2
SBP 12 hour	110±3	117±3	111±2	113±2
SBP 24 hour	114±2	115±2	112±3	115±2
DBP baseline	71±3	69±2	71±2	73±2
DBP Emax	60±2	60±2	60±2	61±2
DBP T-Emax	6	6	6	6
DBP 12 hour	66±2	63±2	63±2	65±2
DBP 24 hour	71±2	72±2	74±2	74±2
Parameter	6.25 mg	12.5 mg	25.0 mg	25 + 12.5 mg
Pulse baseline	66±3	67±5	69±3	68±3

CARVEDILOL NDA 20-297

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Pulse Emax	64±3	62±4	62±2	62±2
Pulse T-Emax	2.5	0.75	2.5	2.5
Pulse 12 hour	71±3	71±5	70±2	70±2
Pulse 24 hour	66±2	67±5	63±3	66±2

Adverse events:

headache in 6 of 12 subjects

orthostatic lightheadedness in 3/12: 1/12 with BP86/60, 1/12 with BP 78/52

elevated AST (normal 11-29): 1/12 = peaked at 32 and improved during follow-up

1/12 = peaked at 48 and improved during follow-up

elevated ALT (normal 2-27): 1/12 = peaked at 32 and improved during follow-up

1/12 = peaked at 48 and improved during follow-up

Conclusions:

The report does not provide 90% confidence intervals for the dose corrected AUC and Cmax for R(+) carvedilol and for S(-) carvedilol.

Claims of dose proportionality appear to be justified between the doses of 12.5 and 25.0 mg for Cmax and AUC for R(+) carvedilol and for S(-) carvedilol concentrations.

With respect to dose proportionality between doses of 6.25 and 12.5 mg and between doses of 25.0 and 37.5 mg, I would request the guidance of the biopharmaceutics reviewer before I would support a claim for dose proportionality based on this study. Claims in the label regarding dose proportionality will require documentation of bioequivalence of 12.5 and 25.0 mg capsules used in this study and 12.5 and 25.0 mg tablets proposed for the marketplace. The sponsor does not intend to market a 6.25 mg tablet according to the proposed draft label.

The calculations of half-life for R(+) carvedilol and for S(-) carvedilol are not reliable from this study since many subjects were excluded from analysis. When I apply the sponsor's criteria for exclusion from analysis of half-life, I exclude fewer subjects than the sponsor excluded.

Geometric mean AUC(0-t) and Cmax were 2 - 3 times greater for R(+) carvedilol than for S(-) carvedilol.

There is no placebo group with which to compare pharmacodynamic effects. No dose-response relationship was evident for supine SBP, DBP, or pulse.

Other trials addressing stereoselective metabolism include A9901, CAR-SA-01, MF7034, MF7097, F-30. A9911 is ongoing.

C19
DUPLICATE
1

CARVEDILOL NDA 20-297

CARVEDILOL EFFECT ON DIGOXIN PK

Protocol A9904, Vol 1.52

Reviewer: James F. Graumlich

Name of study: A study to assess the effects of the co-administration of a single oral dose of 25 mg carvedilol (SK&F 105517) on the plasma and urinary pharmacokinetics of digoxin after administration of a single oral dose of 0.5 mg digoxin in normal man.

Objectives: To assess the effects of a single oral dose of 25 mg carvedilol on the plasma and urinary pharmacokinetics of a single oral dose of 0.5 mg digoxin.

Study design: Double blind, randomized, placebo controlled, period balanced, 2 period crossover study with single doses in 8 healthy male subjects. Study periods were separated by one week.

Intervention: 1 tablet carvedilol (25 mg) plus 2 tablets of digoxin (0.25 mg)
1 placebo tablet identical to carvedilol plus 2 tablets of digoxin (0.25 mg)
The protocol was modified to decrease digoxin tablets from 3 to 2 tablets.

Response variables:

Primary outcome: digoxin AUC (0-t) calculated with trapezoidal rule

Secondary outcome: digoxin Cmax, Tmax, Ke, AUC (0-∞), AUMC (0-t), AUMC (0-∞), MRT, fractional and total urinary digoxin excretion, BP, pulse

Blood sampling times were at baseline then 0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 6, 8, 12, 24, 36 and 48 hours after dose administration. Urine collection were at baseline then 0-8, 8-24, 24-36, and 36-48 hours after dose administration.

Supine BP and pulse were measured at baseline then every 10 minutes for 4 hours then every 15 minutes for 4 hours. One-lead ECG was monitored for 8 hours. Twelve-lead ECGs were performed at baseline then 4 and 8 hours after dose administration.

Materials: digoxin 0.25 mg (Lenoxin®, Wellcome)
carvedilol 25.0 mg tablet, formulation 1/25, batch 6
placebo matched to carvedilol

Assay: Plasma digoxin assay was a radioimmunoassay. Limit of quantification for plasma digoxin was 0.07 ng/mL. Urine digoxin assay involved HPLC with ultraviolet detection. Limit of quantification for urine digoxin was 10 ng/mL. The report claims no interaction between the assay and carvedilol or carvedilol metabolites.

Results: Eight healthy male subjects between 23 and 27 years of age and weighing between 65 and 87 kg completed the study.

The table below is from A9904, vol 1.52, page 6: Digoxin PK parameters

Fig 1 from A9904, vol 1.52 page 45 shows the plasma digoxin concentration vs time for the two treatment groups.

Digoxin PK parameters

? Figure 1

Pharmacodynamic response: Treatment means were compared between digoxin + placebo vs digoxin + carvedilol.

- (1) Supine systolic blood pressure: Mean changes from baseline were significantly different and more than 3 mm Hg lower with carvedilol at 1-2, 2-3, and 3-4 hours after the dose (range -5.1 to -5.6 mm Hg difference between the mean change from baseline for placebo and the mean change from baseline for carvedilol).
- (2) Supine diastolic blood pressure: No significant differences.
- (3) Heart rate: No significant differences.

Adverse events: No symptoms were reported. No significant abnormalities of liver function tests (AST, ALT, gamma GT, total bilirubin).

Conclusions:

Concomitant administration of a single oral dose of carvedilol and a single oral dose of digoxin significantly increases the C_{max} and AUC of digoxin. The most likely explanation for the difference is an increase in the systemic bioavailability of digoxin.

No effects on supine diastolic blood pressure or supine heart rate were seen in this trial. Effect on supine systolic blood pressure was small and transient.

I agree with the conclusions of the sponsor with the following exceptions:

- (1) The sponsor speculates that the difference in C_{max} and AUC may result from "either an increase in digoxin's bioavailability and/or a decrease in its clearance." Review of the individual plasma-concentration-vs-time curves does not suggest a change in clearance (see Fig 1, A9904, vol 1.52, page 45). Differences in the elimination rate constant and U₄₈ (the renal excretion in 48 hours) do not appear to be clinically relevant.
- (2) The sponsor states the differences between the treatment groups are not related to assay interference. The sponsor does not provide assay validation data to support this assertion.

CARVEDILOL NDA 20-297**CARVEDILOL EFFECT ON DIGOXIN PK**

Protocol A9904, Vol 1.52

Reviewer: James F. Graumlich

Name of study: A study to assess the effects of the co-administration of a single oral dose of 25 mg carvedilol (SK&F 105517) on the plasma and urinary pharmacokinetics of digoxin after administration of a single oral dose of 0.5 mg digoxin in normal man.

Objectives: To assess the effects of a single oral dose of 25 mg carvedilol on the plasma and urinary pharmacokinetics of a single oral dose of 0.5 mg digoxin.

Study design: Double blind, randomized, placebo controlled, period balanced, 2 period crossover study with single doses in 8 healthy male subjects. Study periods were separated by one week.

Intervention: 1 tablet carvedilol (25 mg) plus 2 tablets of digoxin (0.25 mg)
1 placebo tablet identical to carvedilol plus 2 tablets of digoxin (0.25 mg)

The protocol was modified to decrease digoxin tablets from 3 to 2 tablets.

Response variables:

Primary outcome: digoxin AUC (0-t) calculated with trapezoidal rule

Secondary outcome: digoxin C_{max}, T_{max}, K_e, AUC (0-∞), AUMC (0-t), AUMC (0-∞), MRT, fractional and total urinary digoxin excretion, BP, pulse

Blood sampling times were at baseline then 0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 6, 8, 12, 24, 36 and 48 hours after dose administration. Urine collection were at baseline then 0-8, 8-24, 24-36, and 36-48 hours after dose administration.

Supine BP and pulse were measured at baseline then every 10 minutes for 4 hours then every 15 minutes for 4 hours. One-lead ECG was monitored for 8 hours. Twelve-lead ECGs were performed at baseline then 4 and 8 hours after dose administration.

Materials: digoxin 0.25 mg (Lenoxin®, Wellcome)
carvedilol 25.0 mg tablet, formulation 1/25, batch 6
placebo matched to carvedilol

Assay: Plasma digoxin assay was a radioimmunoassay. Limit of quantification for plasma digoxin was 0.07 ng/mL. Urine digoxin assay involved HPLC with ultraviolet detection. Limit of quantification for urine digoxin was 10 ng/mL.

Results: Eight healthy male subjects between 23 and 27 years of age and weighing between 65 and 87 kg completed the study.

The table below is from A9904, vol 1.52, page 6: Digoxin PK parameters

Fig 1 from A9904, vol 1.52 page 45 shows the plasma digoxin concentration vs time for the two treatment groups.

CARVEDILOL NDA 20-297

Digoxin PK parameters

The treatment means (R: [digoxin + placebo], T: [digoxin + carvedilol]), their contrast and related 2-sided 95% confidence interval are detailed here below :

	R	T	T-R	T/R	95% CI
C _{max}	1.62	2.59	0.97		0.20 to 1.73
C(24)	0.23	0.28		1.19	1.10 to 1.27
AUC(0-T)	15.0	17.9		1.19	1.10 to 1.30
AUC(0-i)	25.6	30.7		1.19	0.97 to 1.46
k	.0166	.0170		1.00	0.76 to 1.31
U48	216	188	-28		-115 to 57

Pharmacodynamic response: Treatment means were compared between digoxin + placebo vs digoxin + carvedilol.

- (1) Supine systolic blood pressure: Mean changes from baseline were significantly different and more than 3 mm Hg lower with carvedilol at 1-2, 2-3, and 3-4 hours after the dose (range -5.1 to -5.6 mm Hg difference between the mean change from baseline for placebo and the mean change from baseline for carvedilol).
- (2) Supine diastolic blood pressure: No significant differences.
- (3) Heart rate: No significant differences.

Adverse events: No symptoms were reported. No significant abnormalities of liver function tests (AST, ALT, gamma GT, total bilirubin).

Conclusions:

Concomitant administration of a single oral dose of carvedilol and a single oral dose of digoxin significantly increases the C_{max} and AUC of digoxin. The most likely explanation for the difference is an increase in the systemic bioavailability of digoxin.

No effects on supine diastolic blood pressure or supine heart rate were seen in this trial. Effect on supine systolic blood pressure was small and transient.

I agree with the conclusions of the sponsor with the following exceptions:

- (1) The sponsor speculates that the difference in C_{max} and AUC may result from "either an increase in digoxin's bioavailability and/or a decrease in its clearance." Review of the individual plasma-concentration-vs-time curves does not suggest a change in clearance (see Fig 1, A9904, vol 1.52, page 45). Differences in the elimination rate constant and U48 (the renal excretion in 48 hours) do not appear to be clinically relevant.
- (2) The sponsor states the differences between the treatment groups are not related to assay interference. The sponsor does not provide assay validation data to support this assertion.

105517/A9904-GER : MEDIAN VALUES

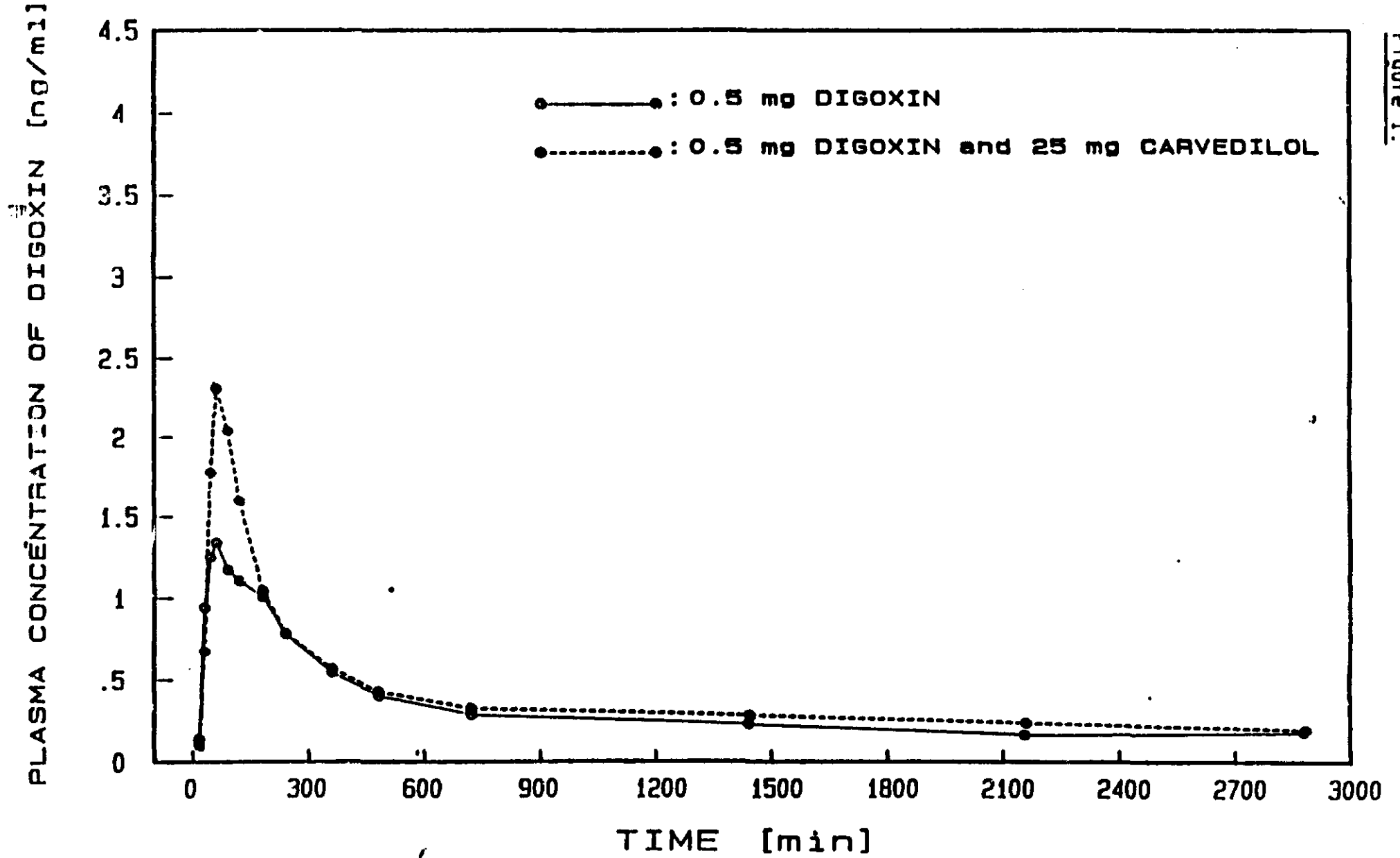


Figure 1:

A9904
Vol 1.5
000045

CARVEDILOL NDA 20-297**CARVEDILOL EFFECT ON DIGOXIN PK**

Protocol A9905, Vol 1.52

Reviewer: James F. Graumlich

Name of study: A study to assess the acute effects of the co-administration of a single oral dose of 25 mg carvedilol (SK&F 105517) on the plasma and urinary pharmacokinetics of digoxin after administration of a single intravenous dose of 0.5 mg digoxin in normal man.

Objectives: To assess the effects of a single oral dose of 25 mg carvedilol on the plasma and urinary pharmacokinetics of a single IV dose of 0.5 mg digoxin.

Study design: Double blind, randomized, placebo controlled, period balanced, 2 period crossover study with single doses in 8 healthy male subjects. Study periods were separated by two weeks.

Intervention: 1 tablet carvedilol (25 mg) plus digoxin (0.5 mg IV)
1 placebo tablet identical to carvedilol plus digoxin (0.5 mg IV)

Response variables:

Primary outcome: digoxin AUC (0-t) calculated with trapezoidal rule

Secondary outcome: digoxin C_{max}, T_{max}, K_e, AUC (0-∞), AUMC (0-t), AUMC (0-∞), MRT, CL (total), V_{dss} (calculated), fractional and total urinary digoxin excretion, BP, pulse

Blood sampling times were at baseline then 2, 5, 10, 15, 20, 30, 45 minutes then 1.0, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48 and 72 hours after dose administration. Urine collection were at baseline then 0-8, 8-24, 24-36, and 36-48 hours after dose administration.

Supine BP and pulse were measured at baseline then every 10 minutes for 4 hours then every 15 minutes for 4 hours. One-lead ECG was monitored for 8 hours. Twelve-lead ECGs were performed at baseline then 4 and 8 hours after dose administration.

Materials: Digoxin 0.25 mg (Lenoxin®, Wellcome)
carvedilol 25.0 mg tablet, formulation D, batch AAA
placebo matched to carvedilol

Assay: Plasma digoxin assay was a radioimmunoassay. Limit of quantification for plasma digoxin was 0.07 ng/mL. Urine digoxin assay involved HPLC with ultraviolet detection. Limit of quantification for urine digoxin was 10 ng/mL. The report claims no interaction between the assay and carvedilol or carvedilol metabolites.

Results: Eight healthy male subjects between 22 and 31 years of age and weighing between 63 and 92 kg completed the study.

The table below is from A9905, vol 1.52, page 78: Digoxin PK parameters
Figures 1 and 2 from A9905, vol 1.52 pages 125-126 show the plasma digoxin concentration vs time for the two treatment groups.

During the elimination phase, Subject 1 had one unexplained increase in plasma digoxin concentration 30 minutes after treatment with carvedilol. The single value was thought to be spurious and was not included in the analysis.

CARVEDILOL NDA 20-297

Digoxin PK parameters

The treatment means (R: [digoxin + placebo], T: [digoxin + carvedilol]) and their contrast are detailed here below. Point (PE) and 95% confidence interval (CI) estimates are provided for the true difference of the treatment means (T-R) as based on untransformed data, or the true ratio of the treatment means (T/R) as backtransformed from log-transformed data.

	R	T	Treatment Contrast PE	CI
C _{max}	16.7	17.0	T/R: 1.06	0.95 to 1.20
C(24)	0.29	0.27	T-R: -0.02	-0.054 to 0.002
AUC(0-7)	27.9	26.7	T-R: -1.20	-2.71 to 0.31
AUC(0-24)	15.3	17.3	T-R: 0.50	-1.19 to 0.20
k	.0169	.0152	T/R: 0.89	0.75 to 1.10
U48	256	246	T/R: 0.95	0.83 to 1.05

Pharmacodynamic response: Treatment means were compared between digoxin + placebo vs digoxin + carvedilol.

- (1) Supine systolic blood pressure: Mean changes from baseline were significantly different and more than 3 mm Hg lower with carvedilol at 2-3, and 4-7 hours after the dose (range -4.1 to -7 mm Hg difference between the mean change from baseline for placebo and the mean change from baseline for carvedilol).
- (2) Supine diastolic blood pressure: No significant differences.
- (3) Heart rate: No significant differences.

Adverse events: No symptoms were reported. No significant abnormalities of liver function tests (AST, ALT, gamma GT, total bilirubin).

Conclusions:

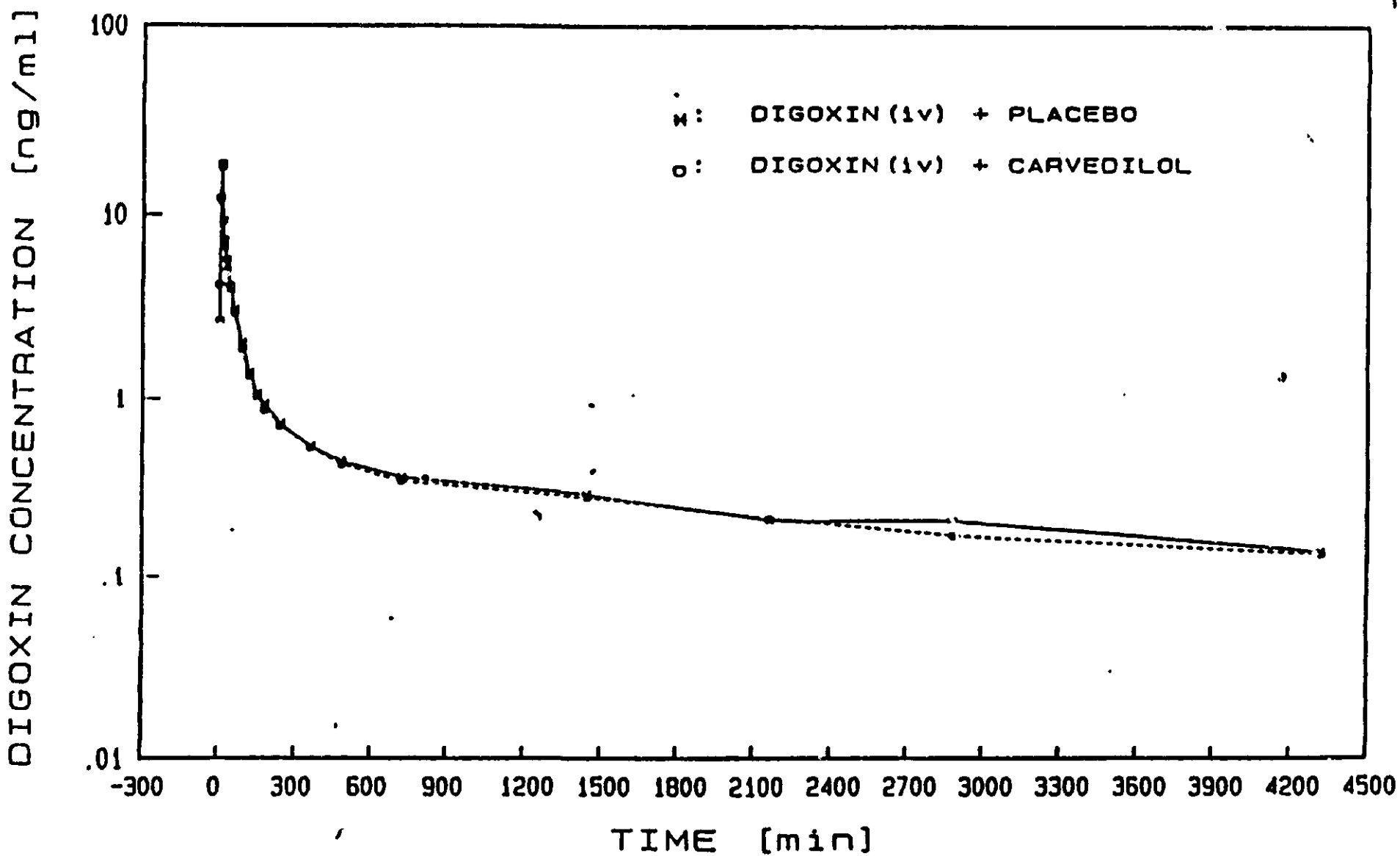
Concomitant administration of a single oral dose of carvedilol and a single IV dose of digoxin did not significantly change digoxin's C_{max}, AUC, k_e, or U48 (renal excretion of digoxin in 48 hours).

Study A9904 showed a significant increase in digoxin's C_{max} and AUC after concomitant single oral doses of digoxin and carvedilol. The most likely explanation for the difference is an increase in the systemic bioavailability of digoxin.

No effects on supine diastolic blood pressure or supine heart rate were seen in this trial. Effect on supine systolic blood pressure was small and transient.

I agree with the conclusions of the sponsor.

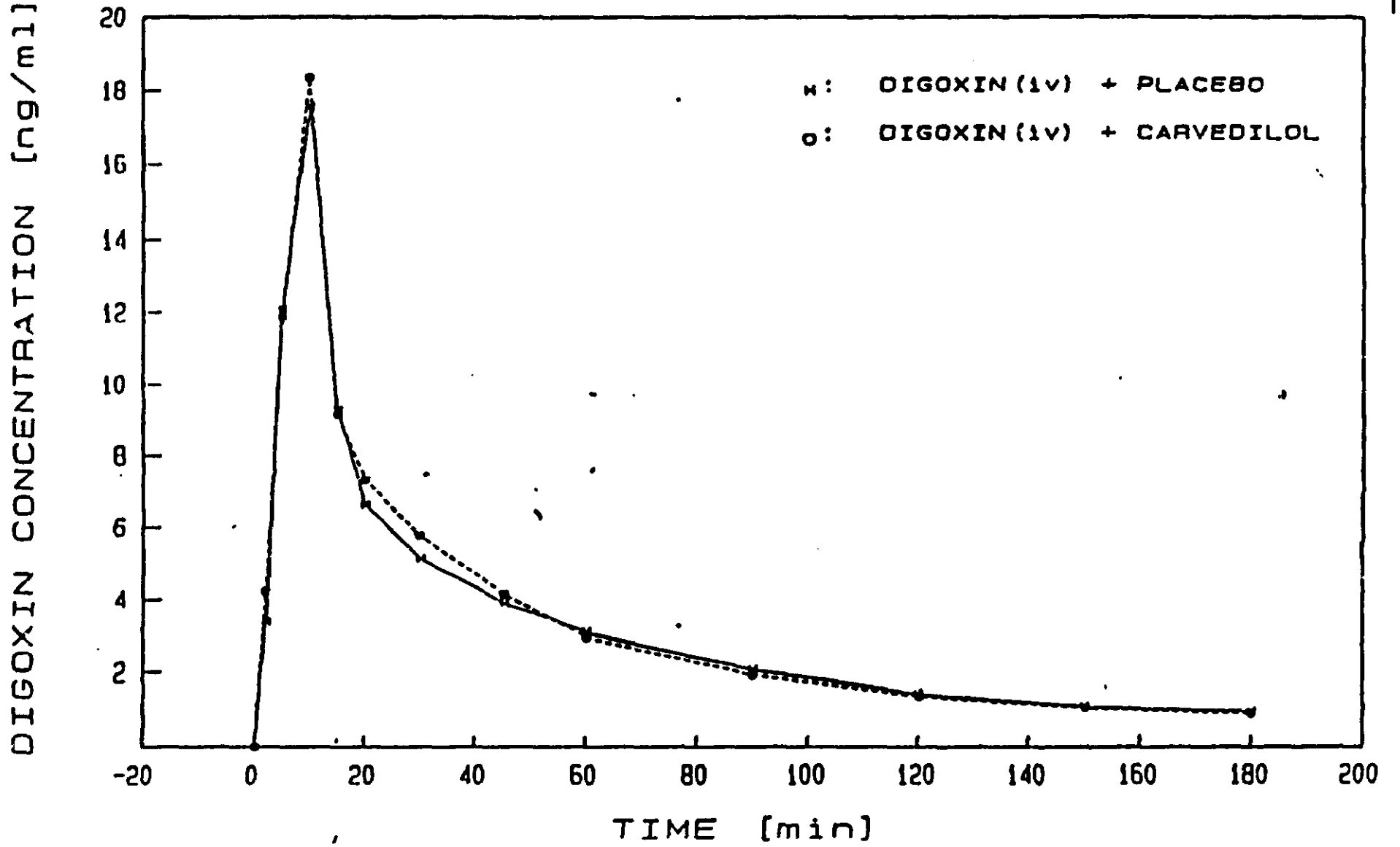
105517/A9905-GER : MEDIAN VALUES



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105517/A9905-GER : MEDIAN VALUES

Figure 2:



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CARVEDILOL NDA 20-297

5

FOOD EFFECT ON CARVEDILOL PK

Protocol A9907, Vol 1.52

Reviewer: James F. Graulich

Name of study: A study to assess the acute effects of a standard meal dose on the pharmacokinetics of carvedilol after administration of a single oral dose of 25 mg carvedilol in normal man.

Objectives: To describe and compare the plasma pharmacokinetics of carvedilol after a single oral dose of 25 mg carvedilol either in fasting condition or at the end of a standard meal.

Study design: Open label, randomized sequence, period balanced, 2 period crossover study with single doses in 12 healthy subjects. Study periods were separated by 7-14 days. There was no placebo control. Contraceptive medications were permitted.

Intervention: 1 tablet carvedilol (25 mg) with water (controlled for volume) after overnight fast since 10:00 PM
1 tablet carvedilol (25 mg) 5 min after the end of a standard meal that followed an overnight fast since 10:00 PM

Response variables:

Primary outcome: carvedilol AUC (0-t) calculated with trapezoidal rule

Secondary outcome: carvedilol C_{max}, T_{max}, K_e, AUC (0-∞), AUMC (0-t), AUMC (0-∞), MRT, half-life, BP, pulse

Blood sampling times were at baseline then 15, 30, 45 minutes then 1.0, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, and 24 hours after dose administration. There was no urine collection.

Supine BP and pulse were measured at baseline then every 10 minutes for 4 hours then every 15 minutes for 4 hours. One-lead ECG was monitored for 8 hours. No twelve-lead ECGs were performed.

Materials: standard meal (17% protein, 40% fat, 43% carbohydrate)
carvedilol 25.0 mg tablet, Tiltab® formulation IPO#88144, Lot #15444-195

Assay: Plasma carvedilol assay involved solid phase extraction, HPLC with fluorescence detection. The lower limit of quantification for plasma carvedilol was 0.3 ng/mL.

Results: Six male and 6 female healthy subjects between 23 and 32 years of age and weighing between 54 and 82 kg completed the study.

Carvedilol PK parameters are in the attached table.

Pharmacodynamic response: Treatment means were compared between carvedilol + fasting vs carvedilol + fed. There was no placebo group.

(1) Supine systolic blood pressure: Mean changes from baseline were significantly different from baseline during 0 - 2 hours after dose administration. Fed subjects had significantly less fall in SBP than fasted patients. Change from baseline was in the range of +3.5 to +5.2 mm Hg more in fed subjects than in fasted subjects. The difference in effect was at maximum 1 - 2 hours after dose administration.

(2) Supine diastolic blood pressure: Mean changes from baseline were significantly different from baseline during 0 - 1 and 2 - 4 hours after dose administration. Fed subjects had significantly less fall in DBP than fasted patients. Change from baseline was in the range of -3.6 to -4.7 mm Hg more in fed subjects than in fasted subjects. The difference in effect was at maximum 0 - 1 hours after dose administration.

CARVEDILOL NDA 20-297

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(3) Heart rate: Mean changes from baseline were significantly different from baseline during the first 5 hours after dose administration. Fed subjects had a higher pulse than fasted patients. Change from baseline was in the range of 2.9 to 8 beats per minute greater in fed subjects than in fasted subjects. The difference in effect was at maximum 1 - 2 hours after dose administration.

Adverse events: headache 2/12 subjects
 nausea 2/12 subjects
 elevated ALT = 24 (normal 0-22) in 1/12 subjects
 elevated ALT = 27 (normal 0-17) in 1/12 subjects

Conclusions:

The presence of food delays the absorption of carvedilol. There is a significant increase in carvedilol T_{max} associated with ingestion of food.

Carvedilol C_{max} and systemic bioavailability were minimally different between fasting and fed conditions. The study lacked statistical power to claim bioequivalence in the presence or absence of food.

Half-life was not significantly different in the presence of food.

The extrapolated AUMC(t_∞) had a wide range from 13% to 56% of the AUMC(0-t). The sponsor did not consider MRT for statistical analysis because of this variability.

Food tended to attenuate the systolic blood pressure lowering effect of carvedilol. Food tended to increase the diastolic blood pressure lowering effect of carvedilol. The magnitude of the difference is difficult to assess since the effect of placebo is unknown in this sample of subjects.

The increase in pulse in the fed group was small and not clinically meaningful.

T. J. J.

Carvedilol treatment means, point estimates, and 90% confidence intervals are detailed below

	FASTING		FED		POINT ESTIMATE	90% CI
mean		SD		SD		
C _{max} (ng/mL)	53.56 ±	27.82	48.35 ±	28.31	E/F (note 1)= 0.9	62% to 129%
	min		max			
T _{max} (hours)	1.15 ±	0.60	2.75 ±	2.22	E-F (note 2)= 0.9	0.25 to 2.5
	min		max			
AUC(0-t) (ng*hr/mL)	166.3 ±	100.37	171.7 ±	81.98	E/F (note 3)= 1.07	89% to 130%
	min		max			
AUC(0-∞) (ng*hr/mL)	174.9 ±	105.12	180.7 ±	87.82	E/F (note 3)= 1.07	90% to 128%
	min		max			
half-life (hours)	7.1 ±	1.97	5.9 ±	1.17	E-F (note 1)= -67.3	-2.3 to 0.04
	min		max			
MRT (hours)	6.3 ±	1.57	7.0 ±	2.75		
	min		max			

note 1: parametric analysis of untransformed data

note 2: non-parametric analysis of medians, not means

note 3: parametric analysis of log-transformed data

CARVEDILOL NDA 20-297

PROTOCOL A9908 VOL 1.52

BIOEQUIVALENCE

Reviewer: James F. Graumlich

Name of study: A study in healthy volunteers to assess the in vivo bioequivalence of two granulation processes for 25 µg carvedilol tablets.

Objectives: To describe and compare the pharmacokinetics of plasma carvedilol after administration of an investigational 25 mg formulation relative to the administration of the same dose by the standard product.

Study design: Open label, randomized sequence, 4 period crossover study with two administrations of each formulation given as single doses in 12 healthy male and female subjects. There was no placebo group. Study periods were separated by one week.

Response variables: Primary outcome: AUC (trapezoidal method)
Secondary outcome: Cmax, Tmax, ke, half-life, BP, pulse

Blood sampling times: baseline then 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3, 3.5, 4, 6, 9, 12 and 24 hours after dose administration. Supine BP and heart rate were measured at baseline then every 10 minutes for 4 hours then every 15 minutes for the next 4 hours.

Materials: reference: carvedilol 25 mg capsule, 1/25 batch 8, BPBR 1450
test: carvedilol 25 mg capsule, 1/25 batch 4, BPBR 1449

Assay: Carvedilol assay involved HPLC with fluorescence detection. The lower limit of quantification for carvedilol was 0.3 ng/mL.

Results: Six male and 6 female healthy subjects between 21 and 31 years of age and weighing between 46 and 85 kg completed the study. Three of 6 women were taking oral contraceptives.

PK parameter values for 2 formulations of carvedilol (n=12) from pages 327-328, vol 1.52

Parameter	Reference	Test	Ratio	90% CI	90% CI
			T/R	lower	upper
AUC (ng*hr/mL)			100.7	89.4	112
mean	218.60	220.12			
min					
max					
Cmax (ng/mL)			101.4	86.4	116.4
mean	57.67	58.49			
min					
max					
Tmax (hr)					
mean	1.5	1.7			
min					
max					

Pharmacodynamic response:

The mean of responses in one hour were reported. The sponsor did not calculate the difference between the mean baseline response and the mean response at specific times after dose administration. There was no placebo response to compare in this study. Lunch was consumed 4 hours after dose administration.

Supine heart rate: The mean of responses for each of the first eight hours after dose administration did not show meaningful changes from baseline. During 8 hours of observation after dose administration, the lowest heart rate mean was 51 and the highest mean was 81 beats per minute. Heart rate increased after the subjects ate lunch.

Supine diastolic blood pressure: The difference between the mean at baseline and the mean of the maximum decrease from baseline was 10 mm Hg. The maximum decrease occurred 5-6 hours after dose administration. During 8 hours of observation after dose administration, the lowest mean was 38 mm Hg. The highest mean was 80 mm Hg. Since Emax occurred after the subjects ate lunch, the effect of the drug is questionable.

Supine systolic blood pressure: The difference between the mean at baseline and the mean of the maximum decrease from baseline was 7 mm Hg. The maximum decrease occurred 1-3 hours after dose administration. During 8 hours of observation after dose administration, the lowest mean was 84 mm Hg. The highest mean was 133 mm Hg. SBP had an upward trend after the subjects ate lunch.

Adverse events:

headache 1/12 subjects
vomit 1/12
malaise 1/12
orthostatic lightheadedness in 1/12 with BP 90/62

decreased WBC in 2 of 12 subjects: 4.31 in 1/12, 3.51 in 1/12 (normal 4.6-6.2)
decreased hemoglobin in 4 of 12 subjects: 13.5 in 1/12, 10.6 in 1/12, 11.7 in 1/12, 12.4 in 1/12 (normal 14-18)
elevated potassium in 3 of 12 subjects who had no concomitant elevation of LDH: 7.1 in 1/12, 7.3 in 1/12, 11.2 in 1/12 (normal 3.5-5.5)
No AST, ALT, gamma GT abnormalities

Conclusions:

The report does not provide calculations for half-life or k_e .

The two formulations were bioequivalent.

Side effects were noted above.

There is no placebo group with which to compare pharmacodynamic effects.

NDA 20297

BIOEQUIVALENCE

Reviewer: James F. Graumlich

Name of study: A study in healthy volunteers to assess the in vivo bioequivalence of two 25 mg carvedilol formulations (SK&F 105517).

Objectives: To demonstrate the bioequivalence of a 25 mg carvedilol tablet formulation relative to a 25 mg carvedilol capsule formulation in healthy subjects.

Study design: Open label, randomized sequence, 4 period crossover study, single dose per period, two periods with same formulation, in 16 healthy male subjects. There was no placebo group. Study periods were separated by one week.

Response variables: Primary outcome: AUC (trapezoidal method)
Secondary outcome: Cmax, Tmax, ke, half-life, BP, pulse

Blood sampling times: baseline then 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3, 4, 6, 8, 10, 12 and 24 hours after dose administration. Supine BP and heart rate were measured at baseline then 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3, 4, 6, 8, 10, and 12 hours after dose administration.

Materials: reference: carvedilol 25 mg capsule, IPO#88083, LOT 82046940 Lh
test: carvedilol 25 mg tablet, IPO#90022 1/25 batch 4, process BPBR 1449

Assay: Carvedilol assay involved liquid/liquid extraction from plasma then HPLC with fluorescence detection. The lower limit of quantification for carvedilol was 0.3 ng/mL.

Results: Seventeen male healthy subjects between 23 and 39 years of age and weighing between 67 and 89.2 kg enrolled in the study. One subject withdrew after study day 2 because of a schedule conflict. The plasma concentrations of the subject who withdrew resembled the other subjects. Half-life calculations were not done by the sponsor.

PK parameter values for 2 formulations of carvedilol (n=16) from A9910, vol 1.53, page 16.

The mean AUC and Cmax values and median Tmax values along with the range of individual values are presented below:

	AUC (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)
<u>Capsule</u>			
First Administration	246.1	60.1	1.1
Repeat Administration	266.3	73.1	1.0
<u>Tablet</u>			
First Administration	213.9	48.9	1.6
Repeat Administration	213.8	41.9	1.3

Point estimates of ratios and differences and 90% confidence intervals from A9910, vol 1.53, page 17.

The point estimates and the 90% confidence intervals for the estimate of the true ratio (tablet/capsule) of AUC, Cmax and the difference (tablet/capsule) of Tmax medians were:

AUC (log-transformed)	
Mean Ratio:	82.0%
90% confidence Interval:	76.1% to 88.4%
Cmax (log-transformed)	
Mean Ratio:	63.7%
90% confidence Interval:	53.4% to 76.1%
Tmax (non-parametric)	
Median of Differences:	0.44
90% Confidence Interval:	0.25 to 0.88

Pharmacodynamic response:

The sponsor did NOT calculate the difference between the mean baseline response and the mean response at specific times after dose administration. There was no placebo response to compare in this study. Meals were consumed 4 and 9 hours after dose administration.

All values in the table are supine values. All blood pressure is in mm Hg. Pulse is in beats per minute. SBP = systolic blood pressure. DBP = diastolic blood pressure. Emax = maximum effect. T-Emax = time in hours after dose administration when maximum effect occurred. 24 hr = response 24 hours after dose administration.

	25 mg Capsule	25 mg Tablet
SBP, baseline	114±12	114±11
SBP, Emax	101±10	103±11
SBP, T-Emax	1.75	1.25
SBP, 24 hr	109±10	108±9
DBP, baseline	71±10	71±8
DBP, Emax	62±9	63±7
DBP, T-Emax	6	6
DBP, 24 hr	70±7	69±8
Pulse, baseline	64±9	66±7
Pulse, Emax	58±8	59±7
Pulse, T-Emax	4	2.5
Pulse, 24 hr	66±10	62±8

CARVEDILOL NDA 20-297

PROTOCOL A9910 VOL 1.53

Adverse events:

headache 3/17 subjects

nausea 1/17

dizzy 1/17

orthostatic lightheadedness in 2/17: no orthostatic vital signs recorded

lowest supine BP 82/52 with pulse 42 in one symptomatic subject

lowest supine BP 102/66 with pulse 64 in other symptomatic subject

diarrhea 2/17

dry skin 1/17

elevated AST (normal 11-29): peak 45 then returned to normal

Conclusions:

The report does not provide calculations for half-life or k_e .

The two formulations were NOT bioequivalent.

Side effects were noted above.

There is no placebo group with which to compare pharmacodynamic effects.

CARVEDILOL NDA 20-297

PROTOCOL A9912 VOL 1.53

BIOEQUIVALENCE

Reviewer: James F. Graumlich

Name of study: A study in healthy male volunteers to assess the in vivo bioequivalence of two 25 mg carvedilol formulations (SK&F 105517).

Objectives: To demonstrate the bioequivalence of a 25 mg carvedilol tablet Tiltab® formulation relative to a 25 mg carvedilol capsule formulation in healthy subjects.

Study design: Open label, randomized sequence, 4 period crossover study, single dose per period, two periods with same formulation, in 20 healthy male subjects. There was no placebo group. Study periods were separated by one week.

Response variables: Primary outcome: AUC (trapezoidal method)
Secondary outcome: Cmax, Tmax, ke, half-life, BP, pulse

Blood sampling times: baseline then 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3, 4, 6, 8, 10, 12 and 24 hours after dose administration. Supine BP and heart rate were measured at baseline then 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3, 4, 6, 8, 10, and 12 hours after dose administration.

Materials: reference: carvedilol 25 mg capsule, IPO#88083, LOT not specified
test: carvedilol 25 mg tablet Tiltab®, IPO#90122 Lot not specified

Assay: Carvedilol assay involved extraction (not specified) from plasma then reverse-phase HPLC with fluorescence detection. The lower limit of quantification for carvedilol was 0.3125 ng/mL.

Results: Twenty male healthy subjects between 22 and 44 years of age and weighing between 57.7 and 91.0 kg completed the study. Half-life calculations were not done by the sponsor.

PK parameter values for 2 formulations of carvedilol (n=20) are in Table 1 on next page. The difference between the medians for Tmax was 0.0 hours (90% confidence interval -0.3, 0.25).

Pharmacodynamic response:

The sponsor did NOT calculate the difference between the mean baseline response and the mean response at specific times after dose administration. There was no placebo response to compare in this study. Meals were consumed 4 and 9 hours after dose administration. See responses in Table 2 on next page.

Table 1

Parameter	Reference	Test	Ratio	90% CI	
	25 mg capsule	25 mg Tiltab®	T/R	lower	upper
AUC (ng*hr/mL)			99.1	92.28	106.44
mean	254.30	257.10			
SD	123.8	147.7			
min					
max					
Cmax (ng/mL)			103.46	91.75	116.65
mean	62.51	67.30			
SD	28.7	37.3			
min					
max					
Tmax (hr)					
mean	1.4	1.4			
SD	0.8	1.0			
min					
max					

Table 2

All values in the table are supine values. All blood pressure is in mm Hg. Pulse is in beats per minute. SBP = systolic blood pressure. DBP = diastolic blood pressure. Emax = maximum effect. T-Emax = time in hours after dose administration when maximum effect occurred. 12 hr = response 24 hours after dose administration.

	25 mg Capsule 1st, 2nd administration	25 mg Tiltab® 1st, 2nd administration
SBP, baseline	119±7, 116±9	117±11, 117±9
SBP, Emax	105±13, 102±7	103±9, 104±9
SBP, T-Emax	1.25, 2.5	2.5, 2
SBP, 12 hr	116±11, 112±11	112±8, 109±10
DBP, baseline	72±7, 69±7	69±8, 70±8
DBP, Emax	59±8, 60±12	60±9, 60±8
DBP, T-Emax	3, 3	4, 8
DBP, 12 hr	67±9, 64±7	65±8, 62±7
Pulse, baseline	67±12, 66±12	62±11, 66±10
Pulse, Emax	56±9, 56±8	57±9, 57±7
Pulse, T-Emax	3, 2.5	3, 2.5
Pulse, 12 hr	65±10, 64±9	64±11, 67±9

CARVEDILOL NDA 20-297

PROTOCOL A9912 VOL 1.53

Adverse events:

no orthostatic vital signs recorded

headache 10/20 subjects

subject J-161-90 became lightheaded, diaphoretic, and pale with BP 75/42. He was treated with saline infusion. His AUC was the fourth highest.

chest tightness (no ECG mentioned): 1/20

excess bleeding when IV removed: 1/20

constipation: 1/20

The following table comes from A9912, vol 1.53, page 142.

The number of clinically significant changes in blood pressure and heart rate are summarized as follows (n = 20 for each regimen):

<u>Parameter</u>	<u>First Capsule</u>	<u>Second Capsule</u>	<u>First 'Tiltab'</u>	<u>Second 'Tiltab'</u>
Systolic > -30 (mmHg)	5	0	4	0
Diastolic > -20 (mmHg)	10	6	5	5
HR < 35 or > 120 (bpm)	0	0	0	0

decreased HGB (normal 13.5-17.2): dropped to 12.3

decreased HGB (normal 13.5-17.2): dropped to 12.1

elevated AST (normal 11-29): peak at 41 then returned to baseline

elevated AST (normal 11-29): peak at 85 then returned to normal

elevated ALT (normal 2-27): peak at 46 then returned to normal

elevated ALT (normal 2-27): peak at 77 then returned to normal

elevated ALT (normal 2-27): peak at 60 then returned to baseline

Conclusions:The report does not provide calculations for half-life or k_e .

The two formulations were bioequivalent.

Side effects were noted above.

There is no placebo group with which to compare pharmacodynamic effects.

This study contrasts with A9902 which failed to demonstrate bioequivalence. The sponsor claims a switch from _____ contributed to the difference in the study outcomes. This hypothesis is unproven.

CARVEDILOL NDA 20-297

PROTOCOL CAR-SA-01 VOL 1.54

PD and STEREOSELECTIVE PK

Reviewer: James F. Graumlich

Name of study: Carvedilol: effects on left ventricular contractility and myocardial oxygen consumption in hypertensive patients with systolic dysfunction

Objectives: Measure the effect of carvedilol on left ventricular contractility, myocardial oxygen consumption

Study design: Open label, uncontrolled, single dose study in 10 patients (all black South Africans) with hypertension and mild left ventricular dysfunction determined by right heart catheterization. Prior to therapy with carvedilol, incremental doses of nitroprusside (starting at 0.125 µg/kg/min) were given until systolic blood pressure fell to 120 mm Hg, or mean aortic pressure fell to 80 mm Hg, or systolic or mean blood pressure fell by 40 mm Hg, or heart rate increased by $\geq$ 10 beats per minute. After recording hemodynamic results with nitroprusside, the nitroprusside was discontinued. After hemodynamic variables returned to baseline, patients received carvedilol. Other antihypertensive medications were prohibited.

Intervention: carvedilol 25 mg tablet po single dose (racemic carvedilol)

Response variables: Primary outcome: heart rate, cardiac index

Secondary outcome: R(+) and S(-) carvedilol concentrations in plasma, C_{max}, T_{max}, pulmonary capillary wedge pressure, mean aortic pressure, mean pulmonary artery pressure, systemic vascular resistance, circumferential stress, stroke volume, velocity of shortening, myocardial oxygen consumption, lab safety tests

Hemodynamic responses were measured with a right pulmonary artery catheter, coronary sinus catheter, and femoral artery catheter. Hemodynamic sampling times were at baseline then 0.5, 1, 1.5, 2, 2.5, and 3 hours after carvedilol administration. Plasma samples for carvedilol concentration were obtained at the same times as hemodynamic samples.

Materials: 25 mg carvedilol tablet (racemic carvedilol)

Assay: Plasma assay of R(+) and S(-) carvedilol involved liquid/liquid extraction, GITC derivatization, HPLC with fluorometric detection. The lower limit of quantification was 1 ng/mL for S(-) carvedilol and 2 ng/mL for R(+) carvedilol.

Results: 10 patients (7 men and 3 women) between 27 and 64 years of age completed the study. There were no dropouts. Weights of subjects were between 48.5 and 81 kg.

9 of 10 patients took furosemide during the study. There were protocol violations by investigators during the infusion of nitroprusside.

Pharmacodynamic response:

The nitroprusside hemodynamic data were used in a linear regression of wall stress versus rate-corrected velocity of fiber shortening. Carvedilol-induced deviations from this regression represented changes independent of heart rate or afterload. Means for all subjects were compared to baseline.

At baseline immediately before carvedilol, the patients had elevated mean aortic pressure, pulmonary capillary wedge pressure, mean pulmonary artery pressure, systemic vascular resistance.

At baseline immediately before carvedilol, the patients had normal heart rate, right atrial pressure, cardiac index.

The following variables changed more than 10% from baseline during 3 hours of observation after carvedilol therapy.

CARVEDILOL NDA 20-297

PROTOCOL CAR-SA-01 VOL 1.54

Mean aortic pressure (see table, page C39): The mean time to maximum change was 99 ± 53 minutes

Mean pulmonary capillary wedge pressure (see table, page C39): The mean time to maximum change was 63 minutes

Mean right atrial pressure (see table, page C39): The mean time to maximum change was 90 ± 62 minutes

Mean cardiac output and cardiac index (see table, page C39): The mean time to maximum change was 114 ± 64 minutes

Mean myocardial oxygen consumption (see table, page C39): The mean time to maximum change was 99 ± 38 minutes

The following variables changed less than or equal to 10% from baseline during 3 hours of observation after carvedilol therapy.

mean ejection time	mean heart rate
mean pulmonary artery pressure	mean systemic vascular resistance (SVR)
mean stroke volume	mean velocity of shortening
mean percent shortening	mean circumferential wall stress
mean meridional wall stress	

There was a large amount of variability of response to carvedilol.

Following carvedilol therapy, 5 patients had increased SVR and 5 patients had decreased SVR.

Plasma concentrations of R(+) carvedilol and S(-) carvedilol did not correlate with hemodynamic variables. Subjects 8 and 10 had no quantifiable R(+) carvedilol or S(-) carvedilol in their plasma.

PK parameters for carvedilol are presented below

Parameter	R(+) carvedilol n = 8	S(-) carvedilol n = 8
Cmax (ng/mL)		
mean	23.99	10.06
SD	21.18	9.92
minimum		
maximum		
Tmax (minutes)		
mean	140	140
SD	43	43
minimum		
maximum		

Adverse events: There were no deaths nor withdrawals. Due to the design of the study, delayed adverse events from nitroprusside are indistinguishable from events caused by carvedilol. Treatment emergent symptoms and signs were

1/10 ventricular trigeminy	2/10 nausea	1/10 vomiting
1/10 dizziness	1/10 diarrhea	4/10 decreased hemoglobin

Conclusions:

Nitroprusside served as a positive control in this study. All subjects had a decrease in aortic systolic and diastolic blood pressure (minimum change defined in study design) as a response to nitroprusside.

Carvedilol decreased mean aortic pressure, decreased pulmonary capillary wedge pressure, decreased cardiac output, decreased myocardial oxygen consumption, and increased right atrial pressure.

Carvedilol did not demonstrate a consistent effect on systemic vascular resistance.

Mean C_{max} values of R(+) carvedilol and S(-) carvedilol in these patients were 2 - 3 fold lower than C_{max} values achieved in healthy volunteers.

Mean T_{max} for R(+) carvedilol and S(-) carvedilol in these patients was 1.8 times longer than mean T_{max} in healthy volunteers.

Orthostatic hypotension was not assessed with this protocol.

Plasma concentrations of R(+) carvedilol and S(-) carvedilol did not correlate with hemodynamic variables.

There was no placebo group with which to compare pharmacodynamic responses.

The results of this study must be interpreted in the context of a single dose, open label study.

Table 2

**EFFECT OF CARVEDILOL ON HEMODYNAMIC VARIABLES IN HYPERTENSIVE
PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION (N=10)**
Baseline Values, Maximum Change, % Maximum Change
Mean (SD)
(Appendixes 10 and 12)

<u>VARIABLE</u>	<u>BASELINE</u>	<u>MAXIMUM CHANGE</u>	<u>MAXIMUM % CHANGE</u>
Ejection time (sec)	0.257 (0.027)	-0.012 (0.019)	-4 (7)
Heart Rate (bpm)	79 (14)	-4 (14)	-3 (19)
Mean Aortic Pressure (mmHg)	125 (9)	-14 (14)	-11 (11)
*Pulmonary Capillary Wedge Pressure (mmHg)	12.3 (5.2)	-1.3 (4.8)	-12 (43)
Right Atrial Artery Pressure (mmHg)	7.3 (5.9)	1 (5)	40 (78)
Mean Pulmonary Artery Pressure (mmHg)	31 (12)	0 (11)	4 (35)
Systemic Vascular Resistance (dyne/sec/cm ⁻⁵)	2110 (402)	110 (521)	4 (24)
Cardiac Output (L/min)	4.53 (0.56)	-1 (1)	-12 (16)
Cardiac Index (L/min/m ²)	2.66 (0.42)	-0.29 (0.42)	-12 (16)
Stroke Volume (ml)	59.3 (12.4)	-3.2 (10.9)	-6 (19)
Myocardial Oxygen Consumption (ml/min)	9.92 (2.86)	-1.3 (2.15)	-13 (18)
Velocity of Shortening (circ/secX100)	52.2 (10.1)	-0.8 (8.7)	0 (19)
Percent Shortening (%)	15.2 (3.1)	-0.7 (2.6)	-3 (19)
Circumferential Wall Stress (gm/cm ²)	283 (51)	-26 (60)	-10 (22)
Meridional Wall Stress (gm/cm ²)	123 (29)	-10 (30)	-10 (25)

Reviewer: James F. Graumlich

CAR-UK-106 is a dose escalation design with double-blind, random-sequence placebo. Treatments were single doses of carvedilol 12.5 mg, 25 mg, 50 mg and placebo. Treatments were separated by one week. Efficacy measurements made for 24 hours after each treatment were pulse, BP, aortic doppler stroke distance (proportional to stroke volume), aortic doppler peak velocity, aortic doppler flow time, aortic doppler acceleration, forearm blood flow (venous occlusion plethysmography). Significant differences in these parameters were not defined a priori. The objective was to assess the relative contribution of vasodilation produced by carvedilol and its effect on myocardial contractility. Subjects were 8 healthy men. One subject experienced nausea and palpitations after 25 mg carvedilol and withdrew from the study. Other treatment-emergent symptoms were postural hypotension (BP changes not specified) after 25 mg carvedilol in 2 subjects. Other symptoms were headache and nausea. In one subject, T. bili (normal 0-20) rose from 17 (pre-study) to 38 on carvedilol 50 mg.

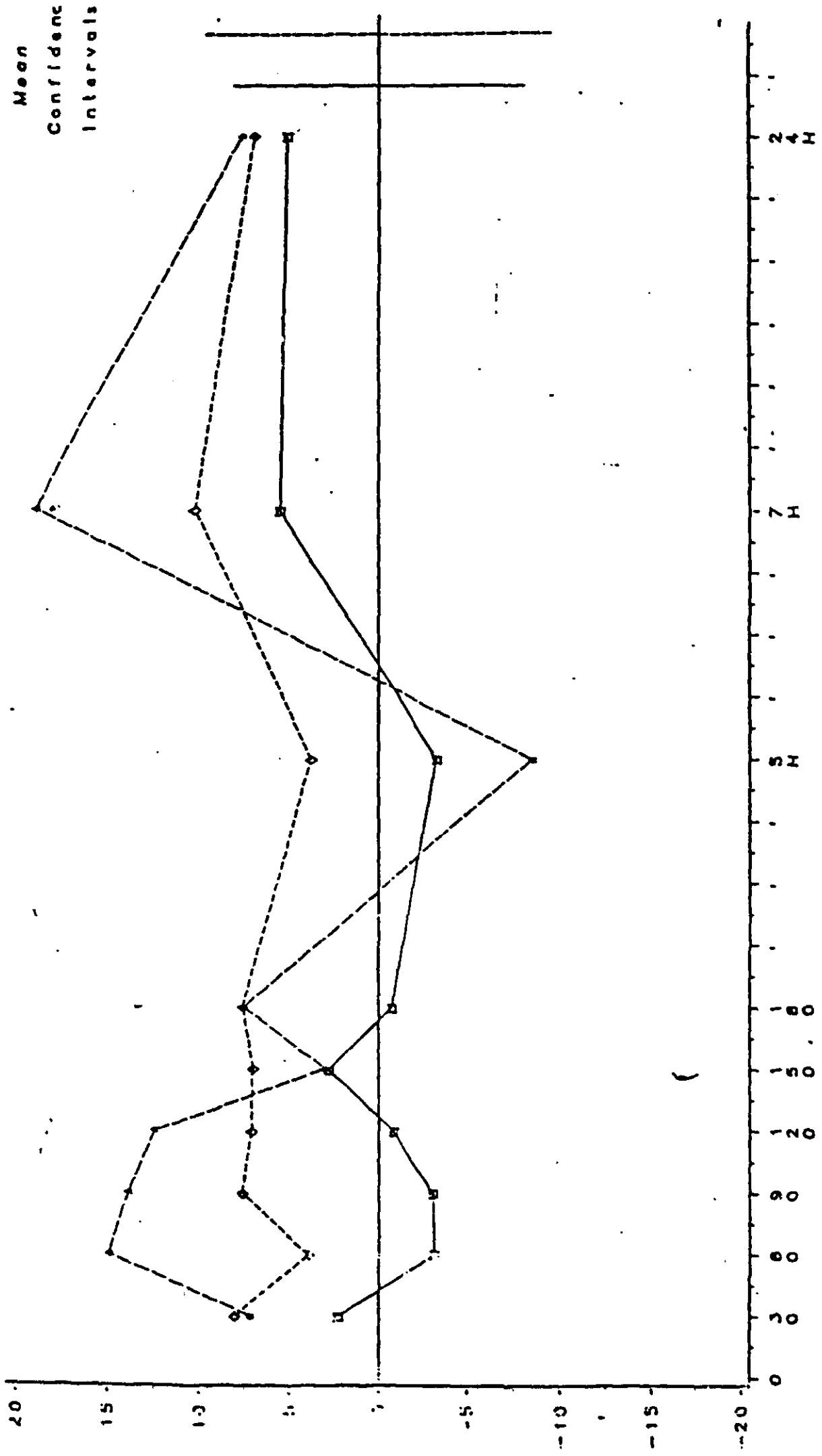
The report does not contain efficacy data for individual subjects.

Figure 4, page 98, volume 1.114, shows systolic blood pressure changes from baseline. The effect of carvedilol on SBP was inconsistent over 24 hours. Figure 5, page 99, volume 1.114, shows diastolic blood pressure effects were not clinically meaningful. Heart rate (Figure 6, page 100, volume 1.114) was significantly decreased between 5 and 7 hours after carvedilol 50 mg. Stroke distance (Figure 7, page 101, volume 1.114) was significantly decreased between 0.5 and 24 hours after carvedilol 50 mg. Other doses did not significantly change stroke distance. Minute distance (Figure 8, page 102, volume 1.114) was significantly decreased between 2 and 24 hours after carvedilol 50 mg. Peak velocity (Figure 9, page 103, volume 1.114) was significantly decreased between 0.5 and 24 hours after carvedilol 50 mg. Changes of mean acceleration (Figure 10, page 104, volume 1.114) were inconsistent among the doses of carvedilol. Corrected flow time (Figure 12, page 106, volume 1.114) was significantly decreased between 5 and 24 hours after carvedilol 50 mg. The index of systemic vascular resistance (Figure 13, page 107, volume 1.114) was significantly increased between 5 and 24 hours after carvedilol 50 mg.

Conclusions: In these healthy men, non-invasive tests showed carvedilol 50 mg decreased heart rate, decreased stroke volume (stroke distance), decreased peak velocity, and increased systemic vascular resistance. These changes are not consistent with carvedilol's putative role as an alpha blocker. It is difficult to predict if these changes are clinically meaningful.

SYSTOLIC B.L. D.PRESSURE (MMHG)
 (Changes from Baseline)

FIGURE 4



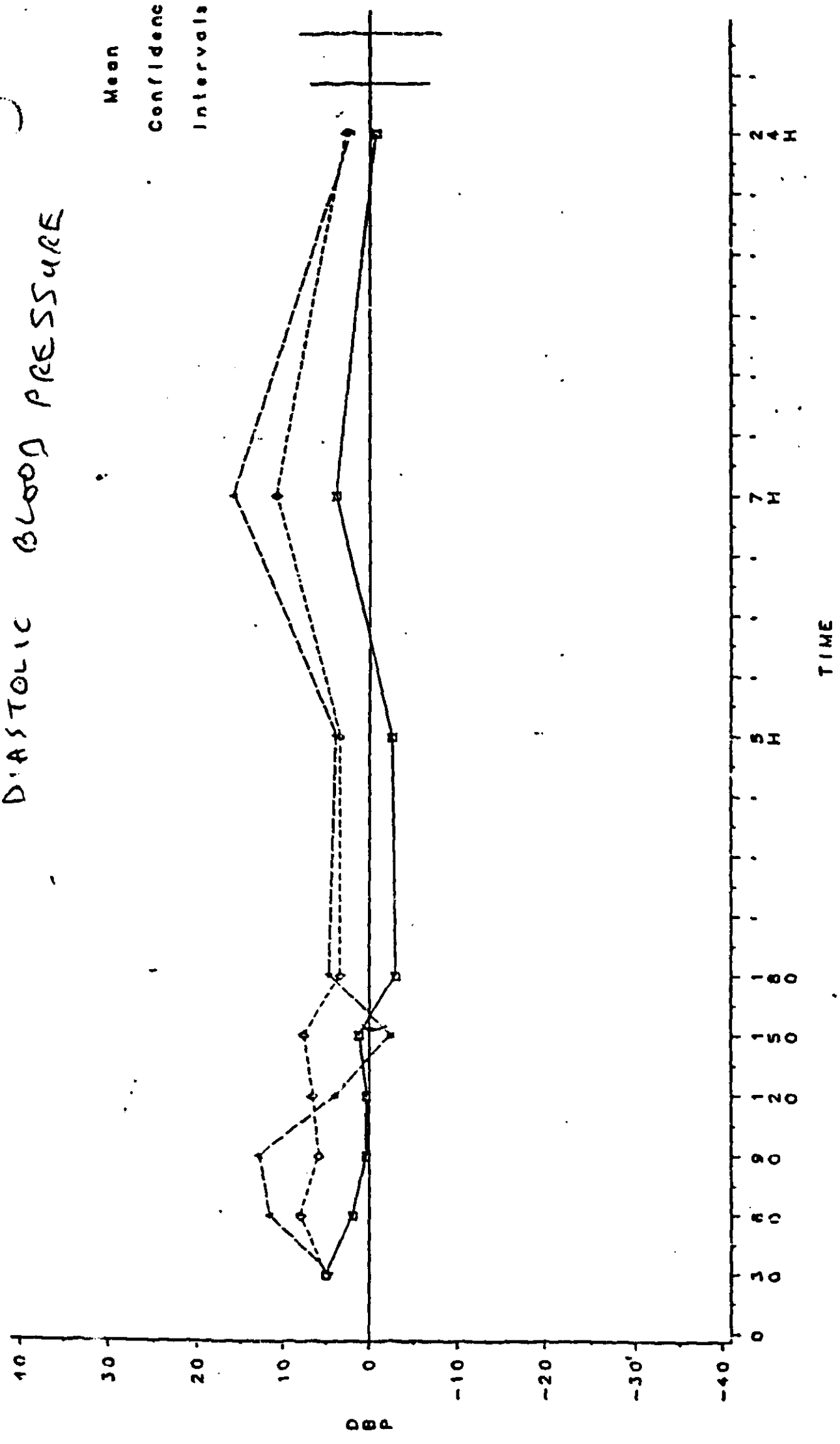
--□-- 12.5MG CARVEDILOL - PLACEBO
 --○-- 25MG CARVEDILOL - PLACEBO
 --△-- 50MG CARVEDILOL - PLACEBO

000098

C41

Change from Baseline

DIASTOLIC BLOOD PRESSURE



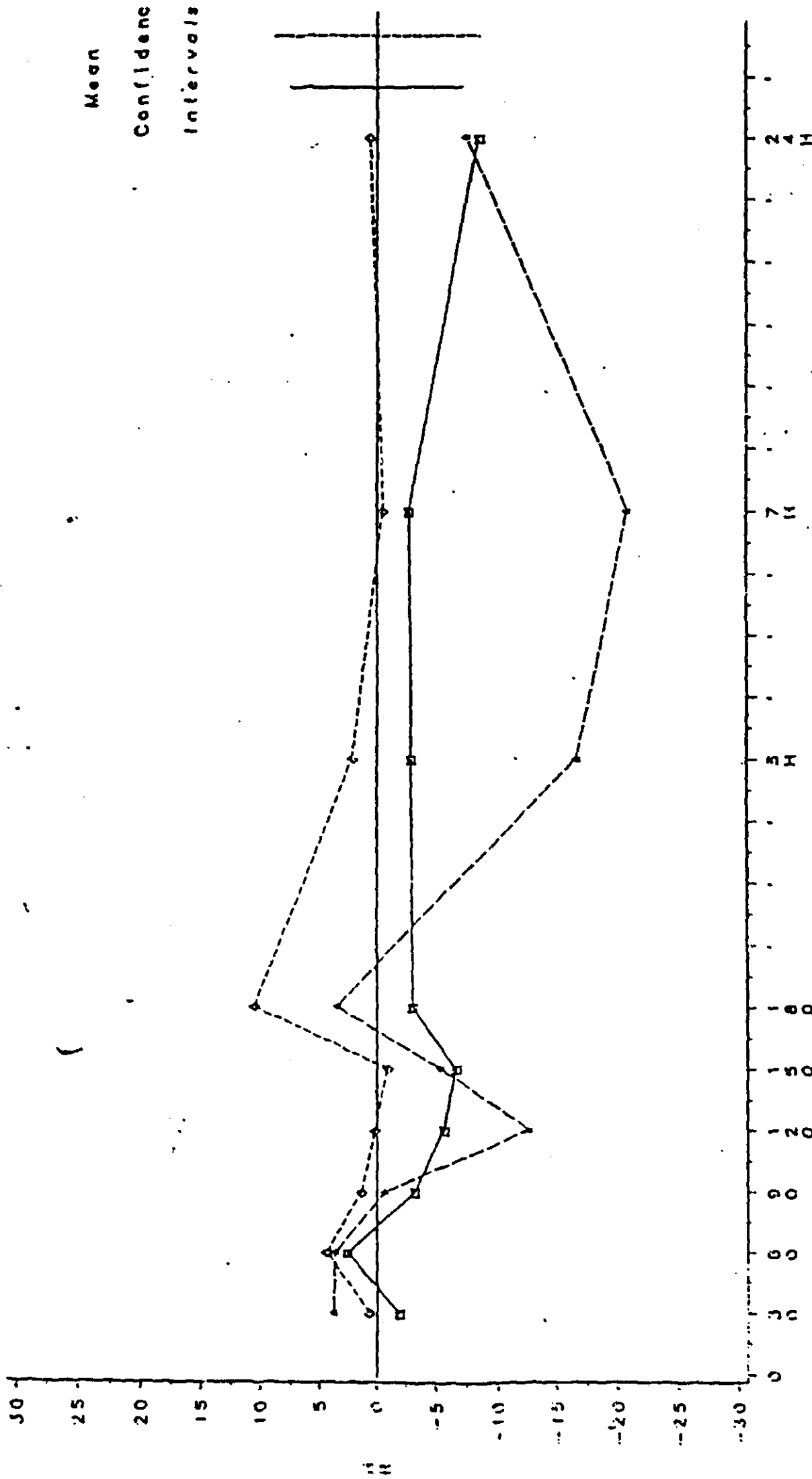
-□- 12.5MG CARVEDILOL - PLACEBO
 -○- 25MG CARVEDILOL - PLACEBO
 -△- 50MG CARVEDILOL - PLACEBO

TIME

000099

FIGURE 6

HEART RATE (BEATS/MIN) (Change from Baseline)



TIME

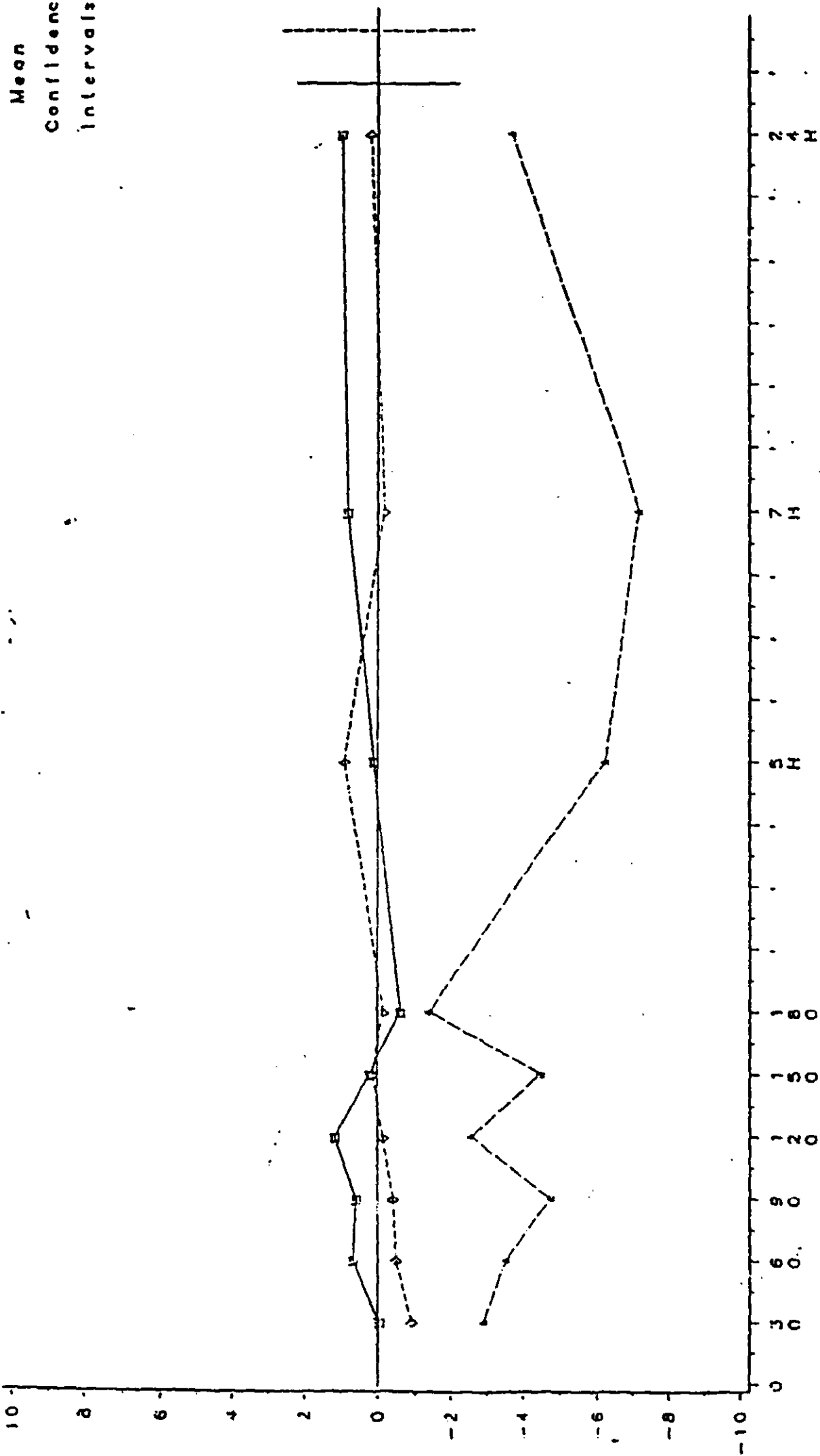
- 12.5MG CARVEDILOL - PLACEBO
- 25MG CARVEDILOL - PLACEBO
- ▲- 50MG CARVEDILOL - PLACEBO

000100

C43

FIGURE 7

STROK DISTANCE (CM)
(Change from Baseline)



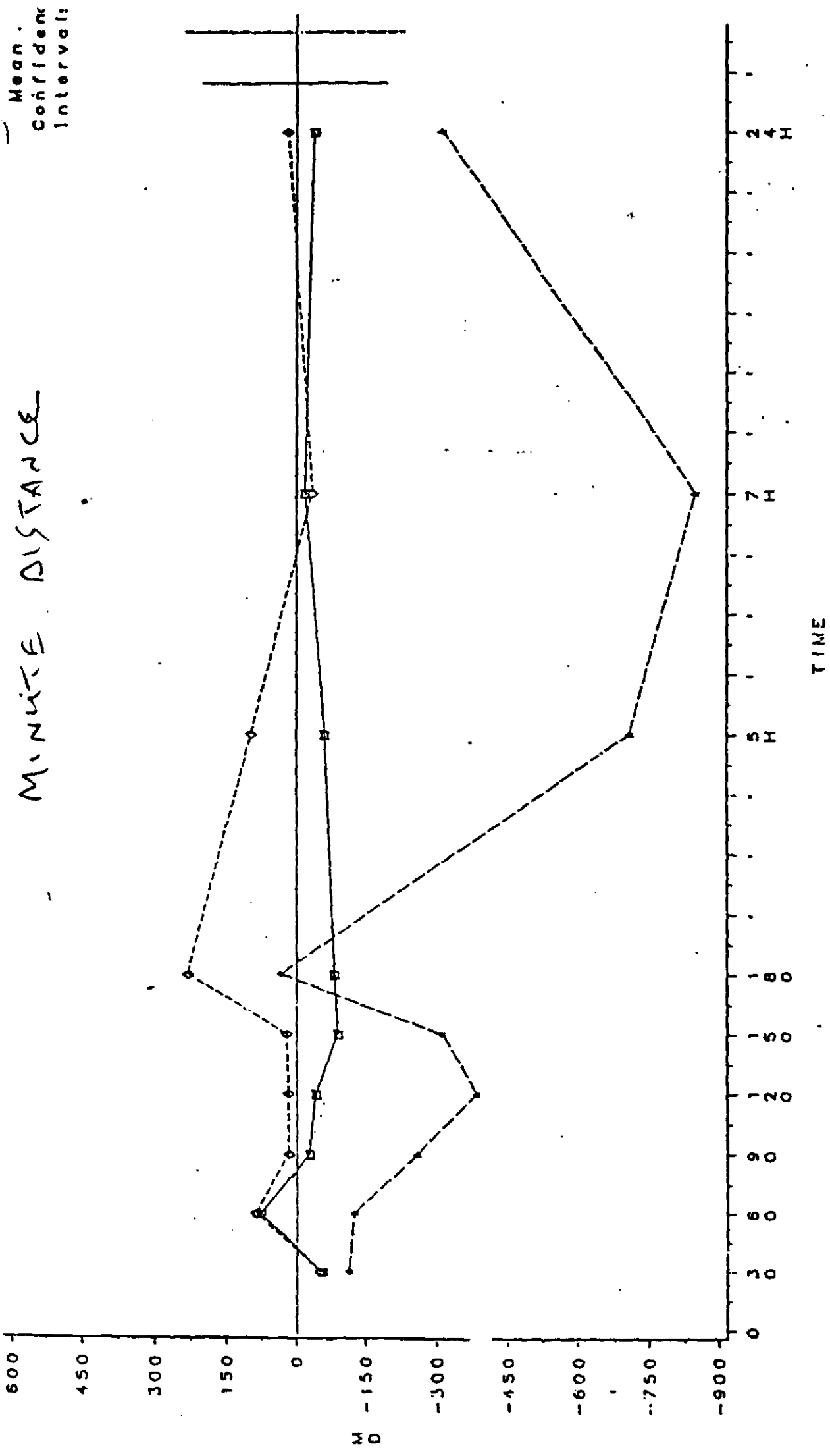
000101

C44

FIGURE 8

MINUTE (Chang) ~~MINUTE (Chang)~~
(from Baseline)

MINUTE DISTANCE

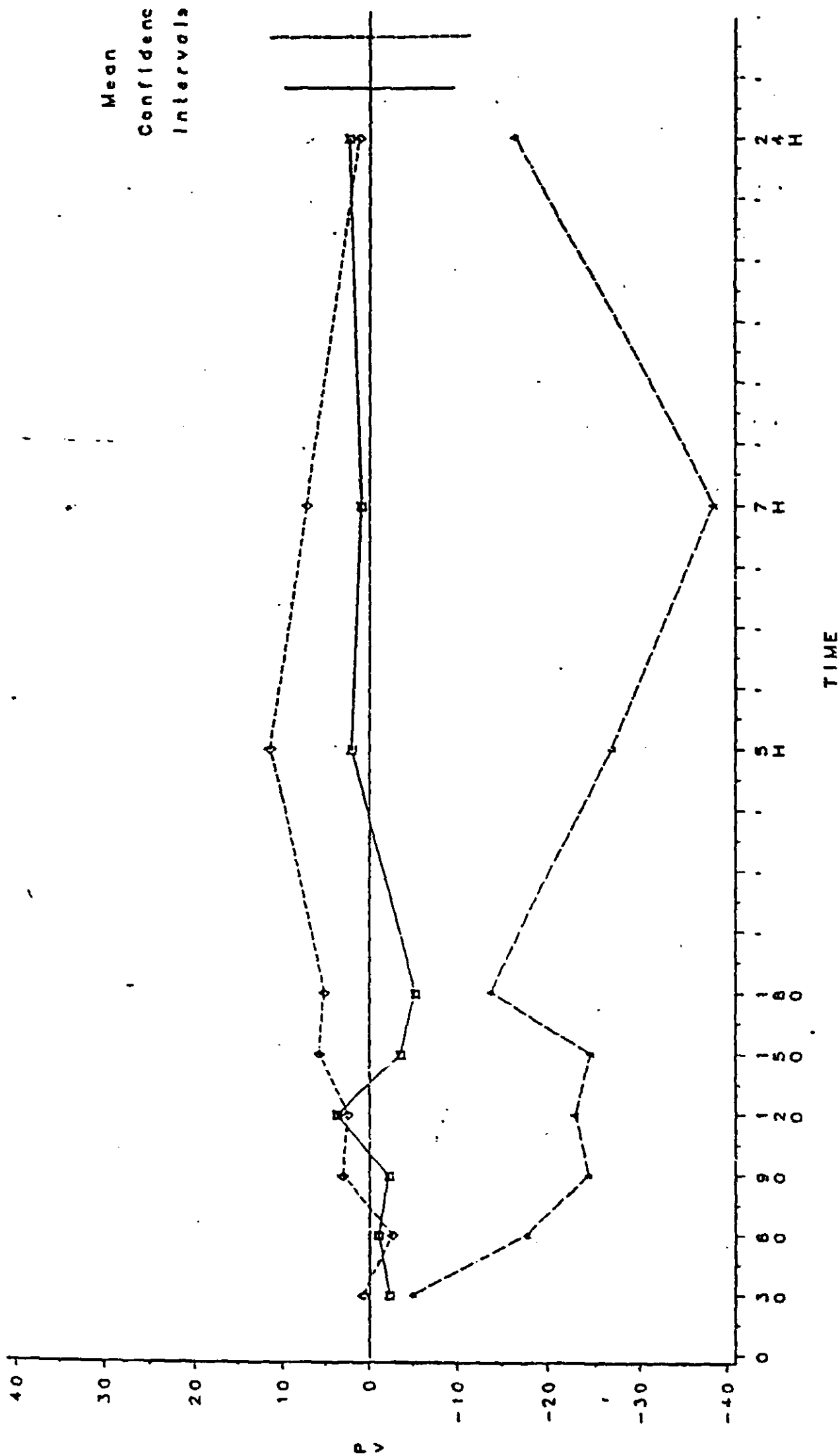


-□- 12.5MG CARVEDILOL - PLACEBO
 -○- 25MG CARVEDILOL - PLACEBO
 -▲- 50MG CARVEDILOL - PLACEBO

000102

FIGURE 9

PEAK VI
(Chang)
VELOCITY (CM/SEC)
(from Baseline)



-□- 12.5MG CARVEDILOL - PLACEBO
-○- 25MG CARVEDILOL - PLACEBO
-△- 50MG CARVEDILOL - PLACEBO

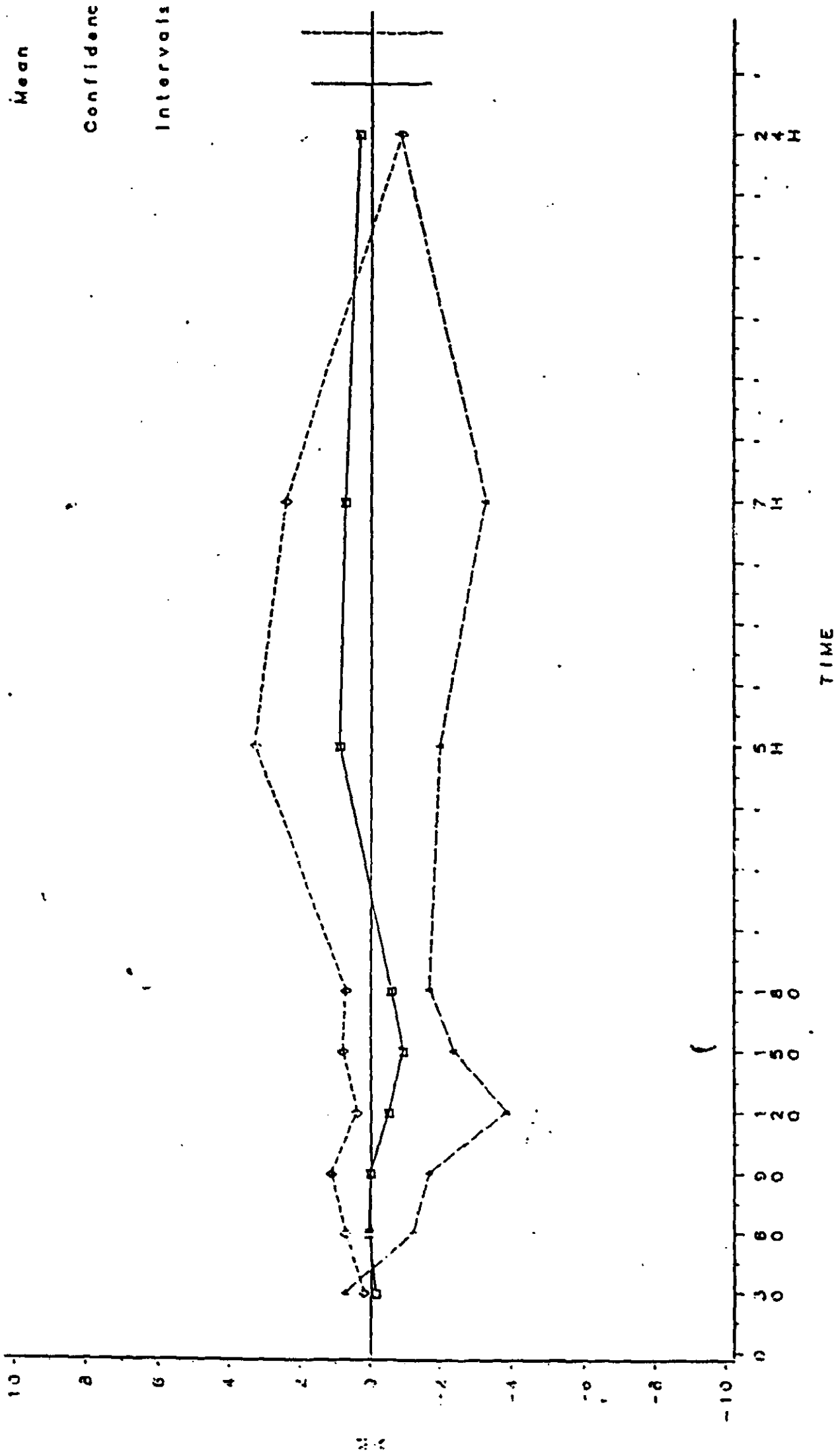
TIME

000103

C46

FIGURE 10

MEAN ACCF RATION (CM/S/ST)
(Change from Baseline)

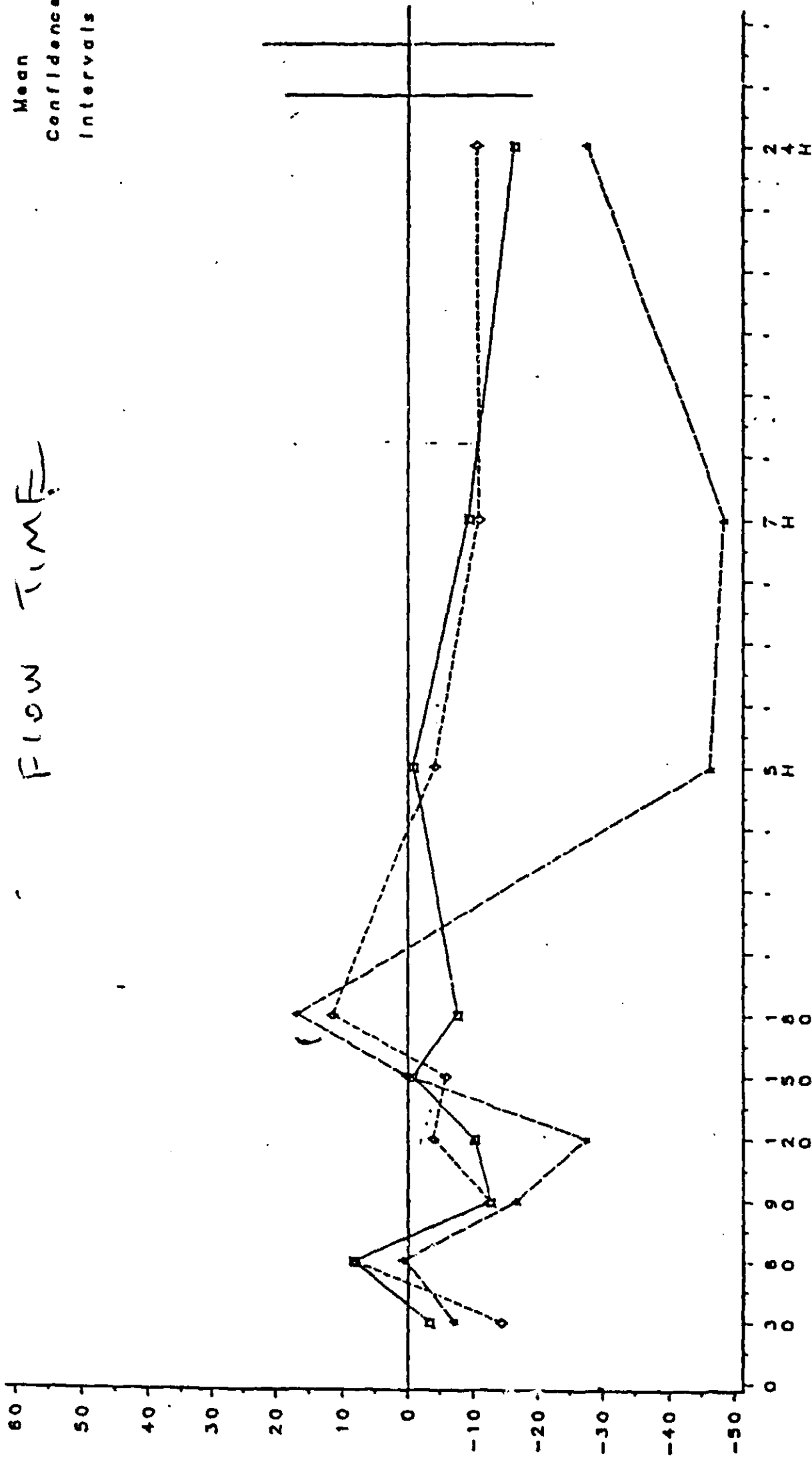


000104

FLOW TIME CORRECTED
(Changes from Baseline)

FLOW TIME

Mean
Confidence
Intervals

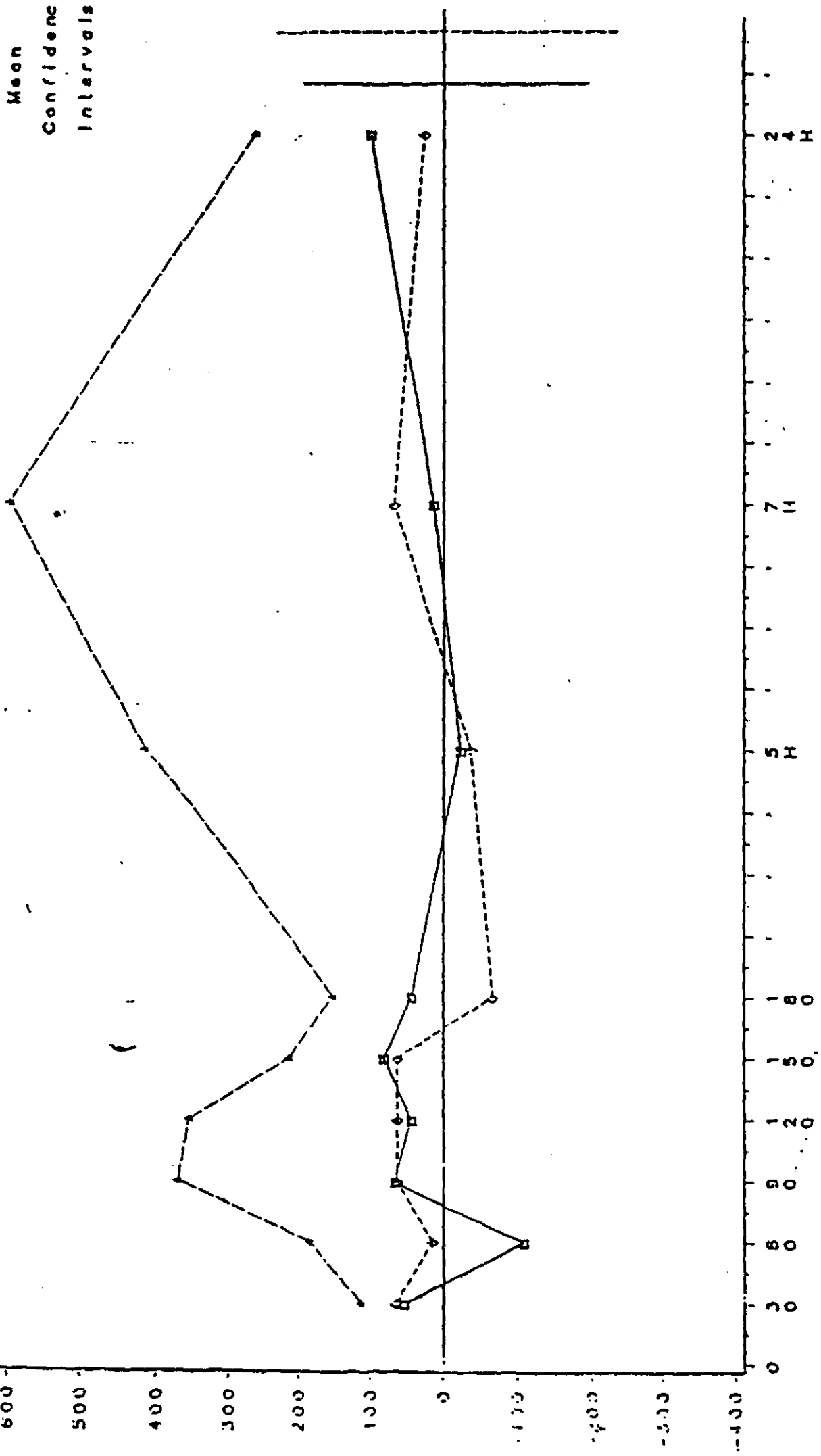


-□- 12.5MG CARVEDILOL - PLACEBO
 -◇- 25MG CARVEDILOL - PLACEBO
 -*- 50MG CARVEDILOL - PLACEBO

TIME

FIGURE 12

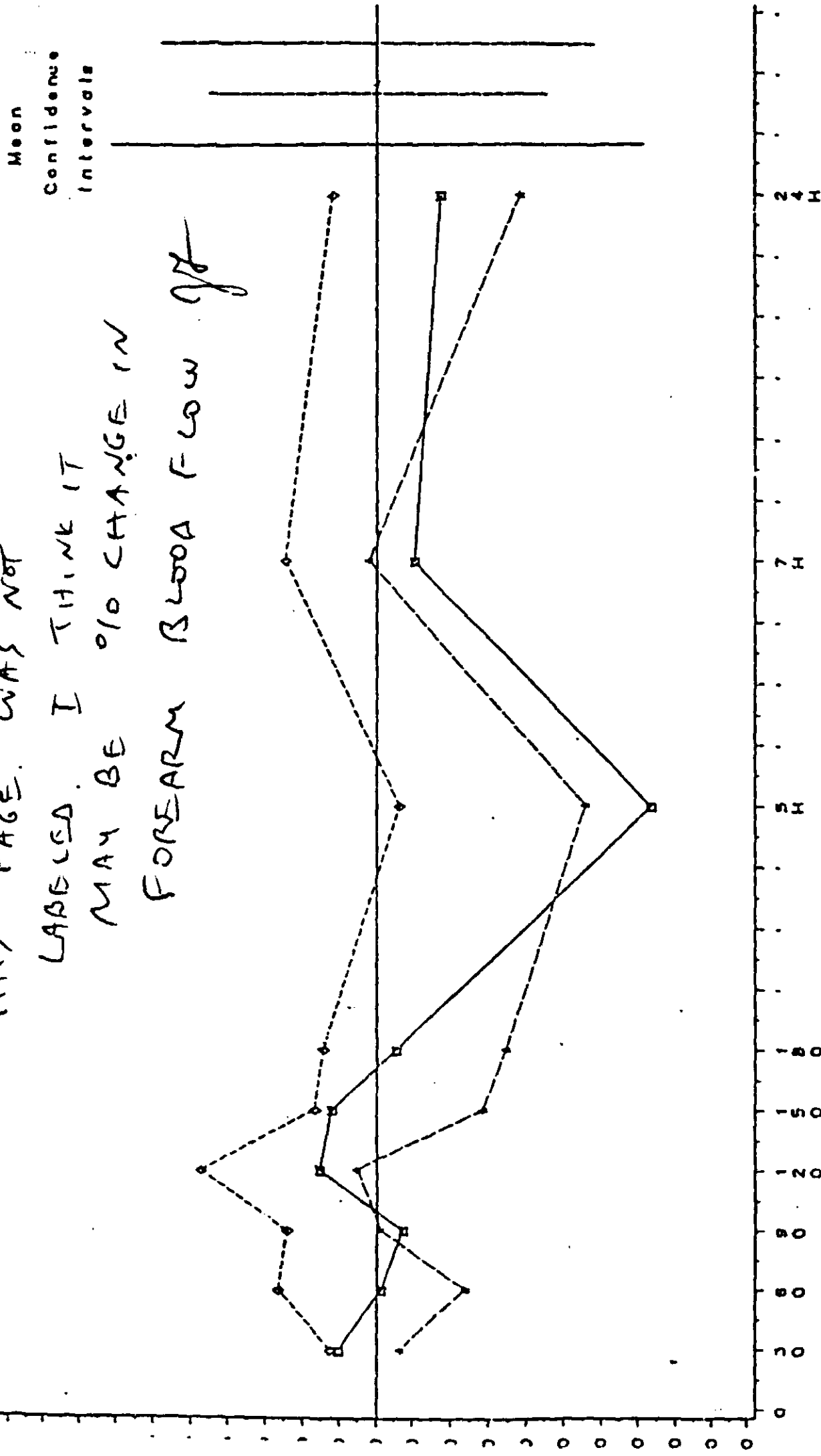
INDEX OF SYSTEMIC VASCULAR RESISTANCE (Changes from Baseline)



-□- 12.5MG CARVEDILOL - PLACEBO
 -○- 25MG CARVEDILOL - PLACEBO
 -▲- 50MG CARVEDILOL - PLACEBO

000107

THIS PAGE WAS NOT
 LABELED. I THINK IT
 MAY BE % CHANGE IN
 FOREARM BLOOD FLOW *off*



—○— 12.5MG CARVEDILOL - PLACEBO
 -□- 25MG CARVEDILOL - PLACEBO
 -△- 50MG CARVEDILOL - PLACEBO

Reviewer: James F. Graumlich

CAR-UK-110 is an in vitro study using venous blood from 8 healthy volunteers. The volunteers had normal coagulation tests and they were prohibited from using other drugs that might influence platelet function. Test drugs were propranolol, carvedilol, and verapamil. Platelet aggregation was induced by ADP, adrenaline and collagen. Figures 1-3 on pages 138-140, volume 1.114, show inhibition of platelet aggregation by the test drugs.

In most humans receiving carvedilol 25 mg po, carvedilol plasma concentrations range up to 208 ng/mL = 0.5 μM (molecular weight of carvedilol = 406.5). The lowest concentration of carvedilol used in this in vitro study was 1.0 μM. The lowest IC50 for carvedilol determined in this study was 54 μM = 21951 ng/mL.

Background information: Alpha 2 receptors on platelets mediate platelet aggregation. Beta 2 receptors mediate inhibition of platelet activation. However, beta blockers do not block the inhibition of platelet activation. Beta blockers inhibit platelet aggregation by stabilizing platelet membranes.

Conclusions: Carvedilol acts like propranolol and inhibits platelet aggregation. The IC50 for inhibition by carvedilol occurs at concentrations higher than plasma levels usually achieved in humans.

INHIBITION OF ADP-INDUCED AGGREGATION

Inhibition (%)

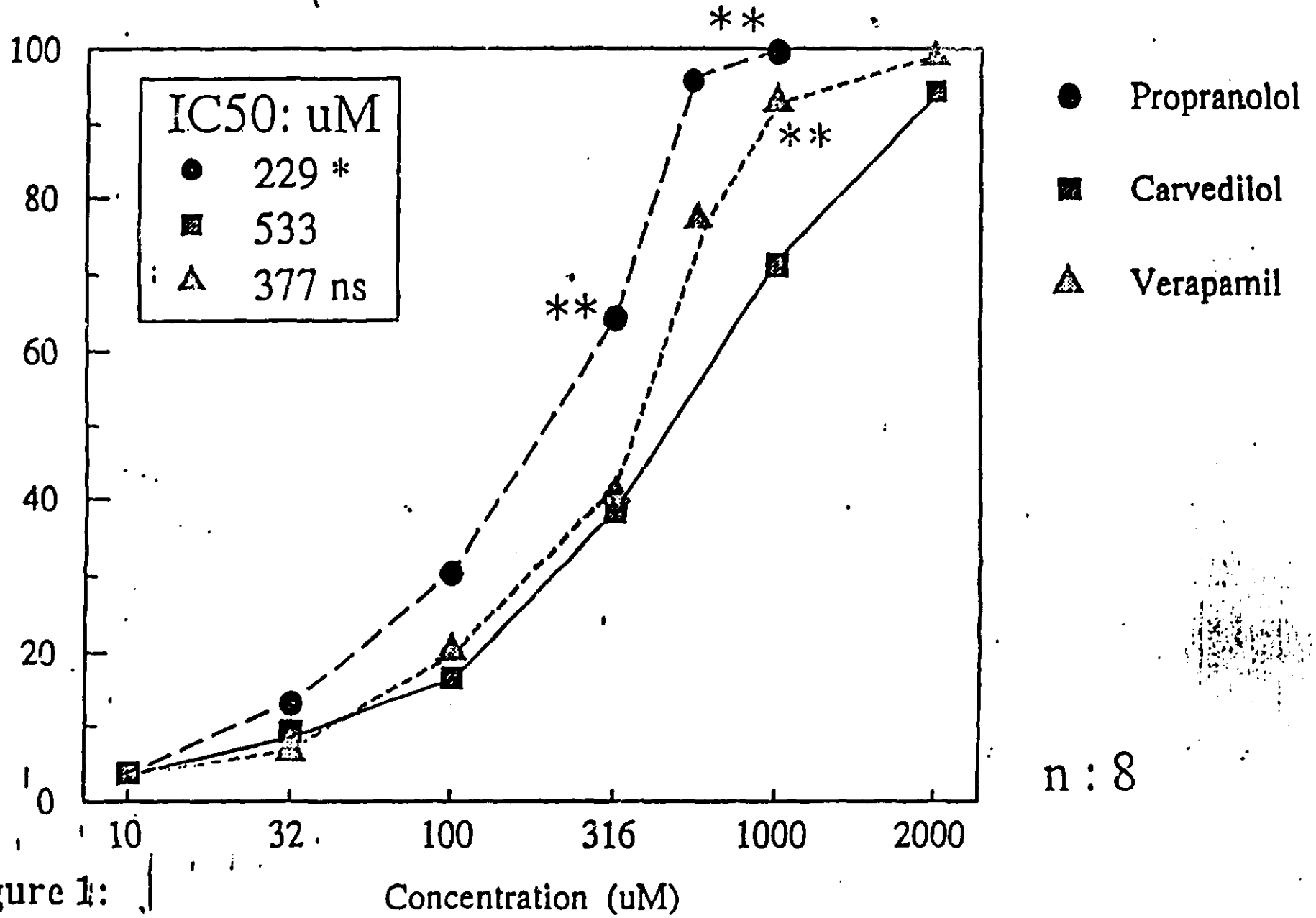


Figure 1:

Concentration (uM)

000138

INHIBITION OF ADRENALINE 10 μ M INDUCED PLATELET AGGREGATION

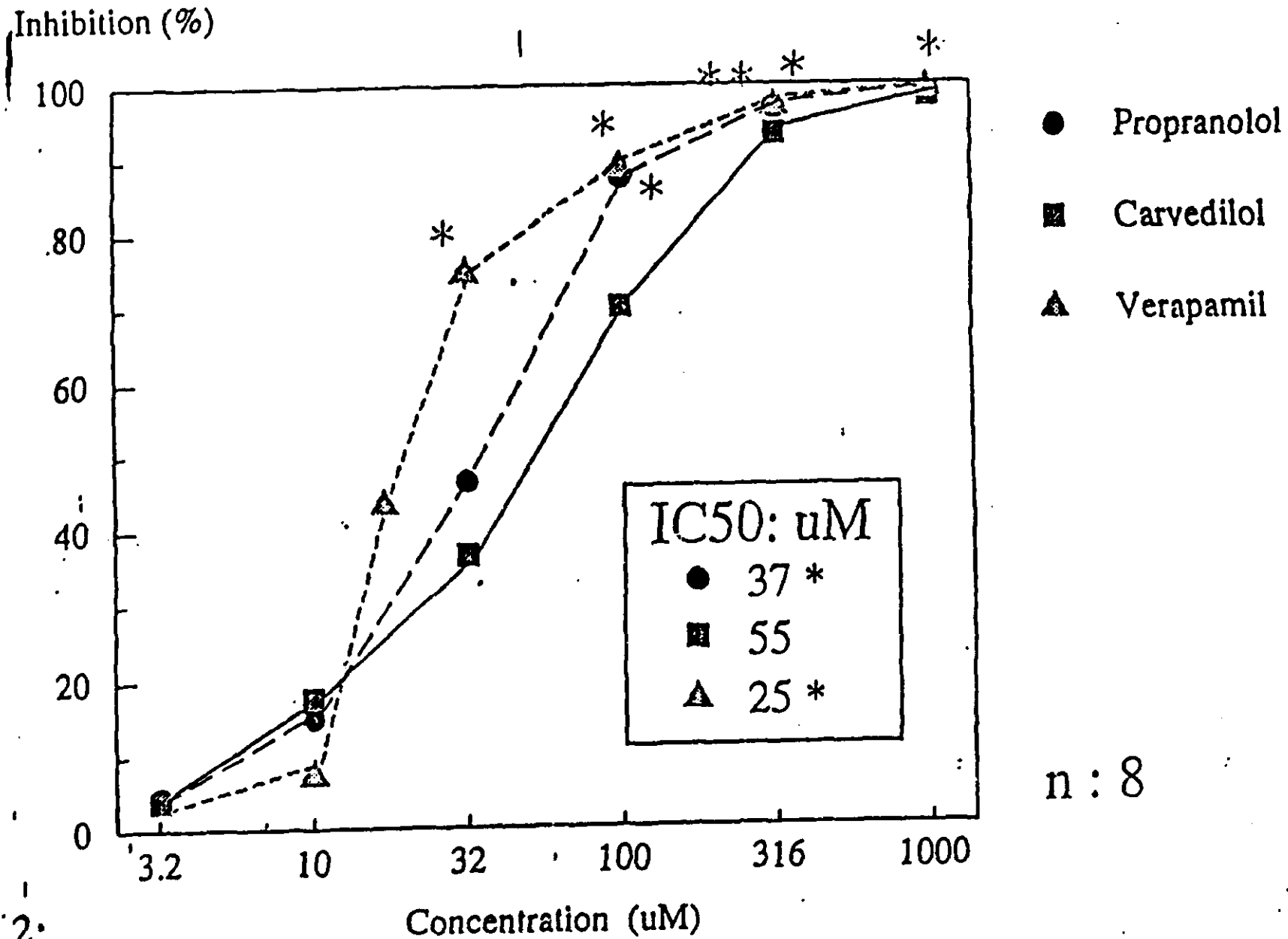


Figure 2:

000139

CS3

000000

INHIBITION OF COLLAGEN 1ug/ml INDUCED PLATELET AGGREGATION

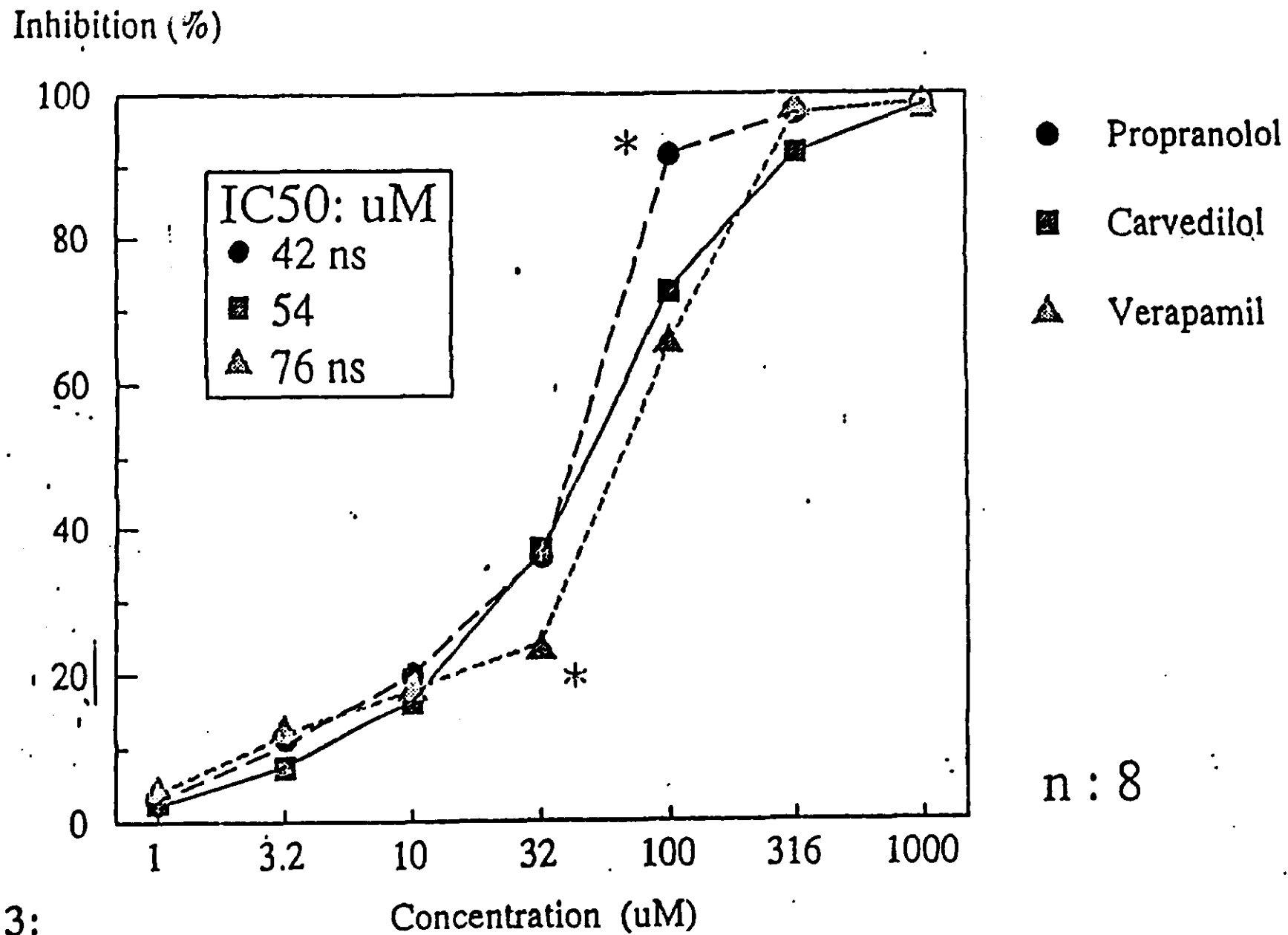


Figure 3:

000140

CSF

NDA 20-297 CARVEDILOL, Protocol CARV0001, Vol 1.74 and 1.82

Reviewer: James F. Graulich

Publication: Cubeddu et al. Clinical pharmacology of carvedilol in normal volunteers. Clin Pharmacol Ther 1987; 41:31-44. Vol 1.82 page 12.

Design: single-blind, placebo-controlled, parallel group design in healthy men. There was random assignment to carvedilol, labetalol, or placebo.

Treatments were infusions of antagonists over 15 minutes:

IV carvedilol 1 mg/min, total 15 mg (n=8), lot number 818651A (Boehringer Mannheim)

IV labetalol HCl 1.33 mg/min, total 20 mg (n=1)

IV labetalol HCl 2.67 mg/min, total 40 mg (n=4)

IV labetalol HCl 5.3 mg/min, total 80 mg (n=3)

placebo 1 mL/min (n=9)

Before receiving treatments, each subject had infusions of agonists (angiotensin II, isoproterenol and phenylephrine) at various doses to produce a dose-response curve. Doses of agonists producing defined responses (changes in pulse and blood pressure) were extrapolated from the dose-response curve and were used to measure baseline responses pre-antagonist. After antagonist treatment, response to agonists was recorded at 5 minutes and 1, 2, 3, 4, 6, 8 hours. Response variables were heart rate, diastolic blood pressure, and carvedilol concentration in plasma.

Results: Subjects were healthy men (age range 21 to 37 years, mean weight of 170 lbs was similar in the placebo, carvedilol and labetalol groups). Only one subject (# 18) withdrew due to an adverse event. He developed unifocal ventricular ectopy 6 hours after carvedilol infusion. At the time of the ectopy, the plasma carvedilol concentration, 11.09 ng/mL, was decreased from Cmax of 74 ng/mL at Tmax 15 minutes after the end of the infusion. During the ectopy, all of the following were normal: symptoms, blood pressure, heart rate, electrolytes, calcium, magnesium. Six days after discharge from the study, a holter monitor was normal except for 4 premature atrial beats.

The first labetalol subject had no blood pressure or pulse response to 20 mg so the next 4 subjects received labetalol 40 mg. The blood pressure response to labetalol 40 mg was thought to be inadequate so the last 3 subjects received labetalol 80 mg.

At baseline before antagonist therapy, there were differences in the placebo and carvedilol groups in the responses to angiotensin II and phenylephrine. Adjustments for baseline differences were made in the analysis of endpoints measured after antagonist therapy.

Antagonist response (mean ± SD)

Antagonist	Measurement	n	pre-infusion	end of infusion
carvedilol 15 mg	dias BP	8	61.2 ± 6.5	50.2 ± 5.3
	syst BP	8	137.4 ± 17.1	105.5 ± 6.6
	heart rate	8	57.2 ± 12.4	59.0 ± 10.0
labetalol 80 mg	dias BP	3	67.7 ± 7.1	58.0 ± 4.0
	syst BP	3	138.0 ± 7.2	120.3 ± 9.0
	heart rate	3	61.3 ± 16.0	66.7 ± 12.1
placebo	dias BP	9	56.2 ± 6.7	56.4 ± 6.6
	syst BP	9	128.2 ± 13.2	129.8 ± 12.2
	heart rate	9	57.0 ± 12.8	57.8 ± 11.3

Beta effect: See Figures 6 and 7 (pages C57, C58). When compared with placebo, intravenous carvedilol blocked isoproterenol-induced increases in pulse for up to 8 hours after carvedilol infusion. Intravenous carvedilol blocked

isoproterenol-induced (1.4 μ g) decreases in supine DBP. The extent of blockade of isoproterenol-induced effects remained unchanged during the 8-hour experiment. Consequently, the carvedilol concentration-response relationship was flat.

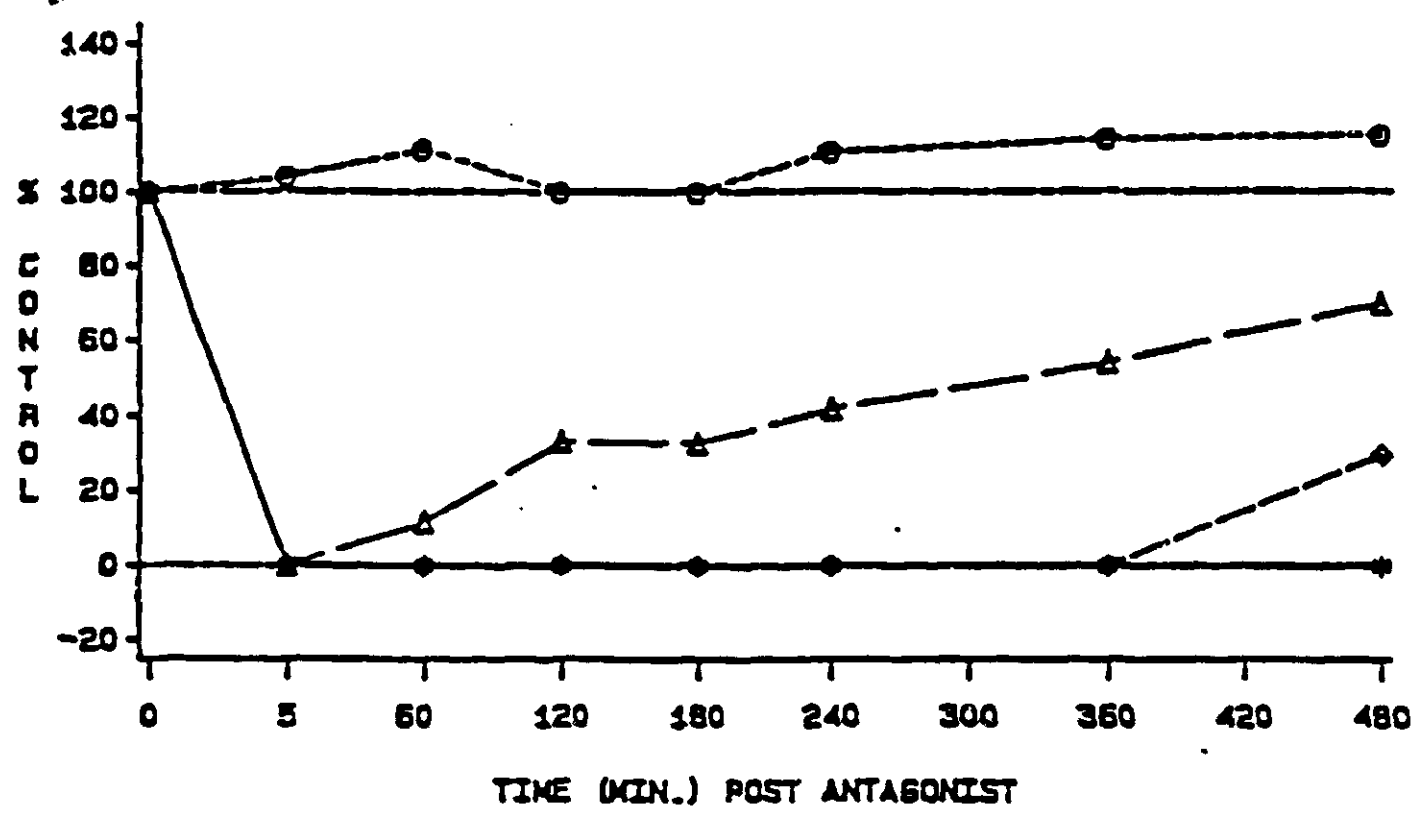
Alpha effect: See Figure 8 (page C59). Phenylephrine (mean dose 0.58 mg in a 2-minute infusion) produced an approximate 25 mm Hg increase in SBP and DBP and an average 18 BPM decrease in heart rate. Intravenous carvedilol blocked phenylephrine-induced increases in SBP and DBP for up to 4 hours. Carvedilol serum concentrations correlated with percent inhibition of phenylephrine effects. The smallest detectable difference between placebo and carvedilol blockade of phenylephrine-induced effects occurred at 4 hours after the end of the carvedilol infusion when the carvedilol serum concentration was approximately 28 ng/mL.

Intravenous carvedilol did not block the pressor effects of intravenous angiotensin II (mean 2.96 μ g). See Figure 9 (page C60). Serum concentrations as high as 150 ng/mL failed to block angiotensin II-induced effects.

Adverse events: Ventricular ectopy is described above. There were no clinically significant changes in mean laboratory values or ECG intervals.

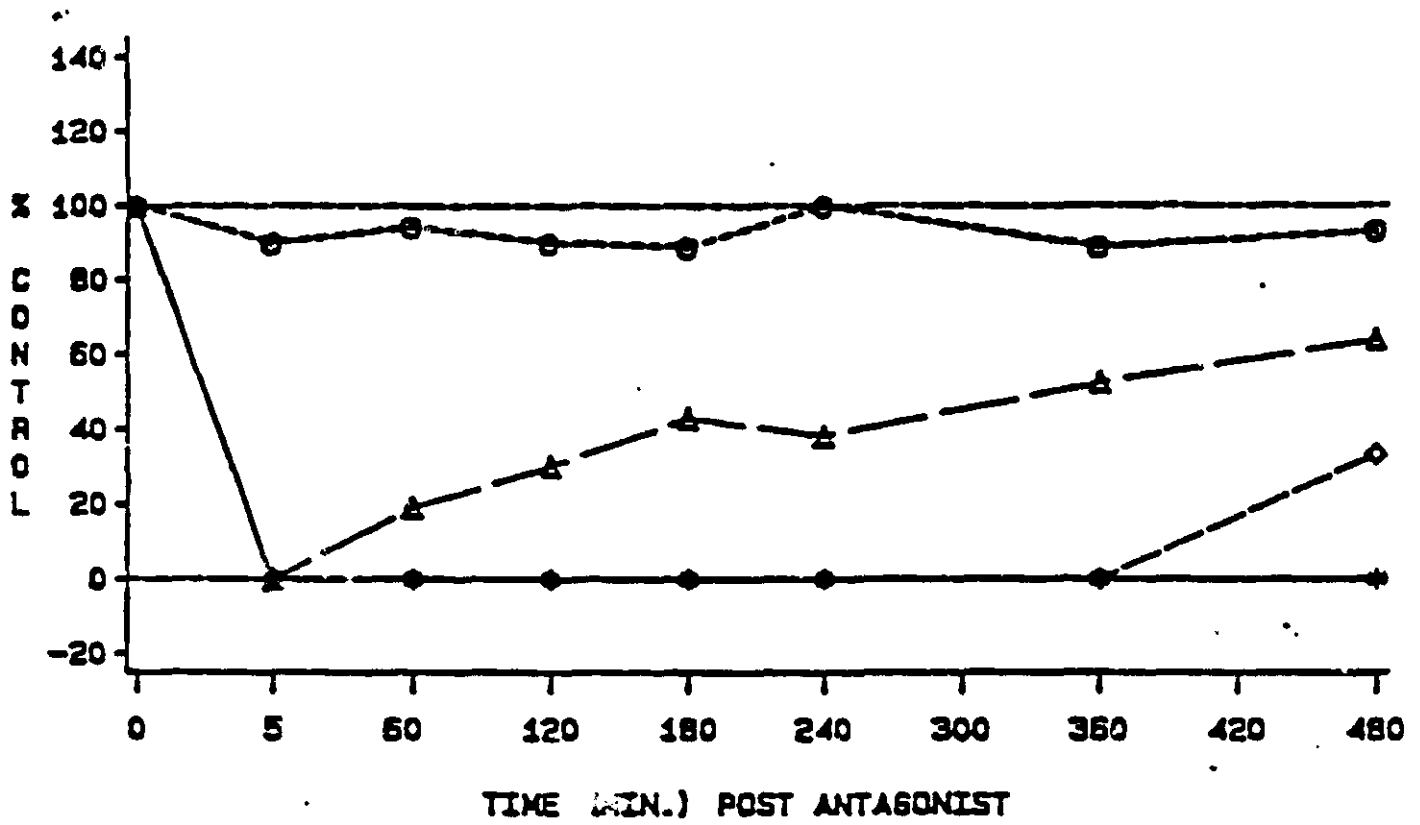
Conclusion: This study demonstrates the non-selective beta and alpha blockade by intravenous carvedilol in healthy men.

FIGURE 8
MEDIAN CHANGE IN HEART RATE (PERCENT OF CONTROL)
ISOPROTERENOL



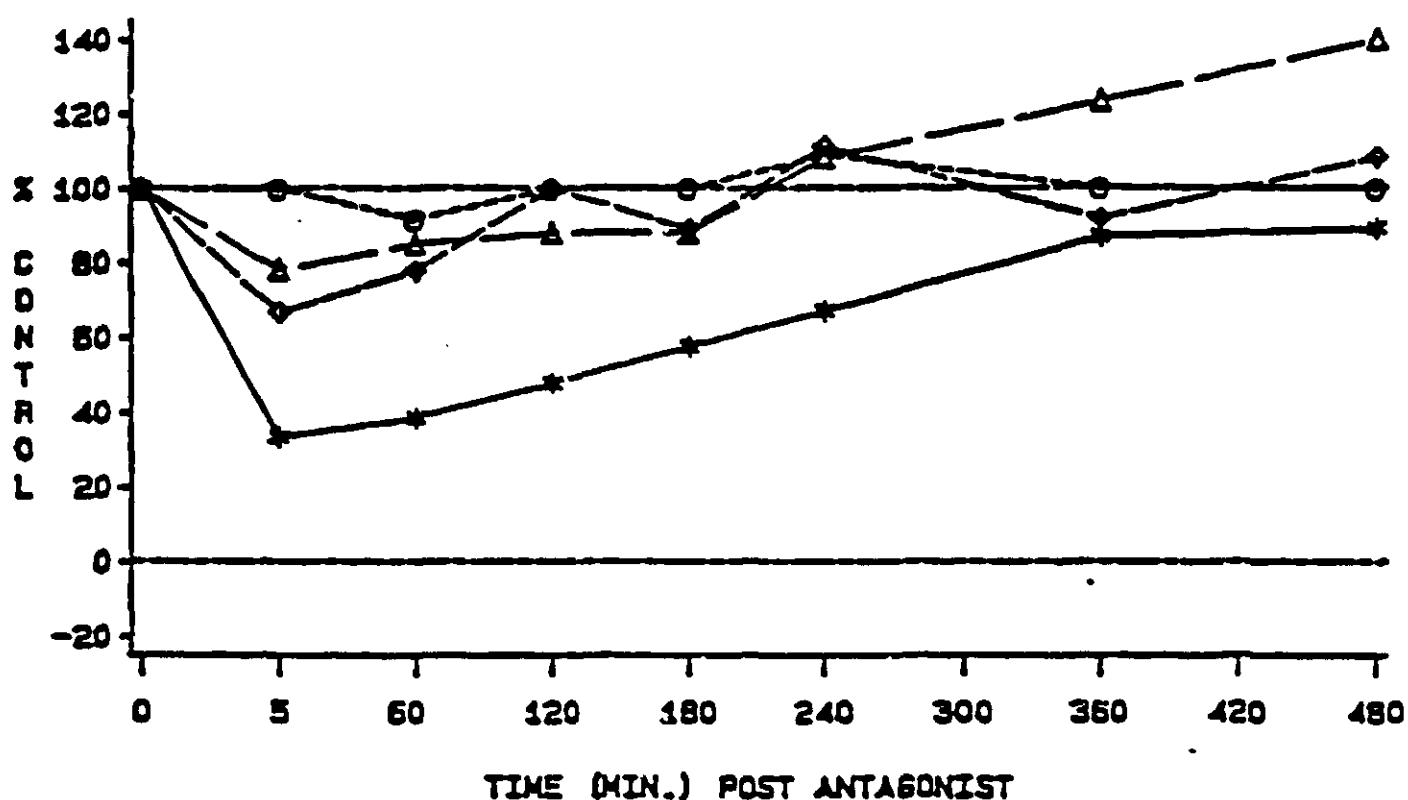
SYMBOL ●-●-● CARVEDILOL ○-○-○ PLACEBO
 ▲-▲-▲ LABETALOL-40 ◆-◆-◆ LABETALOL-80

FIGURE 7
MEDIAN CHANGE IN DIASTOLIC BLOOD PRESSURE (PERCENT OF CONTROL)
ISOPROTERENOL



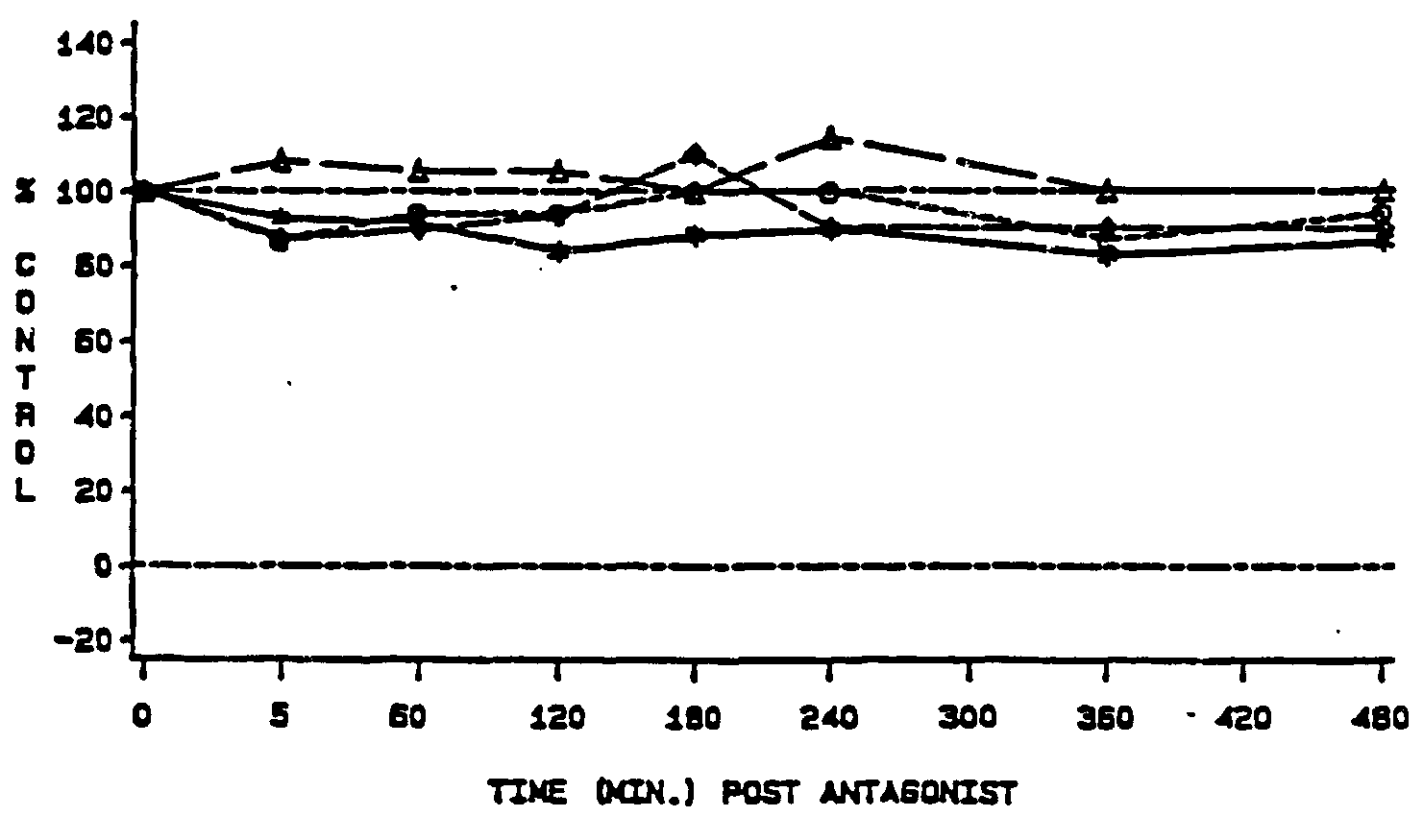
SYMBOL ●-●-● CARVEDILOL ○-○-○ PLACEBO
 ▲-▲-▲ LABETALOL-40 ◆-◆-◆ LABETALOL-90

FIGURE 8
 MEDIAN CHANGE IN DIASTOLIC BLOOD PRESSURE (PERCENT OF CONTROL)
 PHENYLEPHRINE



SYMBOL *-*-* CARVEDILOL ○-○-○ PLACEBO
 △-△-△ LABETALOL-40 ◆-◆-◆ LABETALOL-80

FIGURE .9
MEDIAN CHANGE IN DIASTOLIC BLOOD PRESSURE (PERCENT OF CONTROL)
ANGIOTENSIN II



SYMBOL ◆◆◆ CARVEDILOL ○○○ PLACEBO
 ▲▲▲ LABETALOL-40 ◆◆◆ LABETALOL-80

CARVEDILOL NDA 20-297

PROTOCOL CARV0002 VOL 1.75

Reviewer: James F. Graumlich
PK, metabolites

CARV0002 was an open-label, uncontrolled, non-randomized, study of IV carvedilol 0.042 mg/kg and 0.084 mg/kg in 6 healthy men. Endpoints were plasma carvedilol concentration, urine carvedilol, desmethylcarvedilol, and carvedilol conjugates; blood pressure; pulse. PK sampling occurred for 32 hours after the infusion.

Results: 11 healthy men enrolled (age range 22 - 33 years, weight range 140 - 193 lbs). 6 completed. Subject 5 received carvedilol 10 mg IV and had a sinus arrest, junctional escape rhythm, hypotension (BP not reported), syncope, seizure, carvedilol plasma concentration $C_{max} = 308.3$ ng/mL. The C_{max} in Subject 5 was lower than C_{max} recorded in other subjects. Subject 5 had the lowest body weight (140 lbs). The subject recovered after treatment with atropine 1.0 mg. There were no reported residual deficits. Calculated PK parameters for subjects 1-5 were not reported. Blood pressure and pulse were not reported for subjects 1-5. Calculated PK parameters for subjects 6-11 are in Table 2 from page 36 volume 1.75. Urinary elimination of carvedilol and desmethylcarvedilol are listed in Table 3 from page 37 volume 1.75. Mean systolic and diastolic BP fell 8 - 10 mm Hg. The significance of this change in BP is unknown since there is no placebo comparison. Heart rate did not decrease or increase during 12 hours of observation after the dose. Orthostatic vital signs were not reported. There were no clinically significant laboratory safety abnormalities as a result of treatment in subjects 1-11.

Conclusion: Intravenous carvedilol 10 mg caused a serious adverse event in one healthy man. Carvedilol did not decrease heart rate in this study. The small number of subjects and the lack of placebo comparison prevent interpretation of the clinical significance of BP changes.



Table 2
 Pharmacokinetic Data Analysis of
 Subjects 6-11

Subject	AUC _{0-∞} (hr x ng/ml)	CL _t (ml/hr/kg)	CL _r (ml/hr/kg)	V _{ss} (L/kg)	t _{1/2β} (hr)	C _{max} (ng/ml)
0.042 mg/kg						
6						
7						
8						
9						
10						
11						
Mean	113.9	394	5.9	1.41	6.0	125
S.D.	31.4	113	1.9	0.50	4.0	28
0.084 mg/kg						
6						
7						
8						
9						
10						
11						
Mean	232.2	368	6.1	1.46	6.0	253
S.D.	32.7	50	2.5	0.36	2.0	40

Carvedilol was infused intravenously over 15 minutes. Each subject received 0.042 mg/kg as the first treatment followed one week later by 0.084 mg/kg.

Statistical analyses were not applied to the pharmacokinetic data. The data were summarized as means and standard deviations.



Table 3

Elimination of Carvedilol and Desmethylcarvedilol in the Urine

Subject	Carvedilol				Desmethylcarvedilol			
	Unconjugated		Conjugated		Unconjugated		Conjugated	
	μg	% Dose	μg	% Dose	μg	% Dose	μg	% Dose
0.042 mg/kg								
6								
7								
8								
9*								
10								
11								
Mean		1.5		7.7		0.10		2.2
S.D.		0.7		3.6		0.06		0.6

0.084 mg/kg								
6								
7								
8								
9*								
10								
11								
Mean		1.7		8.2		0.09		2.2
S.D.		0.7		4.0		0.08		0.5

* Urine collection was incomplete for Subject 9 at both doses.

Reviewer: James F. Graumlich

CARV0011 is a double-blind, placebo-controlled, randomized-sequence, two-period crossover study of a single oral dose of carvedilol 25 mg in patients with coronary artery disease. Patients were included if they had "suspected or established diagnosis of coronary artery disease" and if they could exercise on a bicycle ergometer. The endpoints, measured by MUGA, were left ventricular ejection fraction at rest, LV EF during exercise. Concomitant beta blocker and calcium channel blocker therapies were prohibited for specified times prior to the first MUGA.

Baseline screening MUGA was not done at the request of the FDA. Rest and exercise MUGA were not done at the same time relative to the dose. The design did not account for potential bias due to training effect.

20 patients were screened. 5 did not qualify for randomization for the following reasons: 1 had a low ejection fraction, 1 had pain with exercise, and 3 had family conflicts or inconveniences. Of the 15 randomized patients (aged 41 to 74 years), 2 were withdrawn for the following reasons: one had a low ejection fraction after placebo treatment, one had total knee arthroplasty that prevented exercise. Of the 13 remaining randomized patients, one was excluded from analysis of efficacy because the treatment sequence was uncertain.

Results are shown in Table 2 from page 40, volume 1.115. Carvedilol did not affect ejection fraction at rest or with exercise. Carvedilol blocked exercise-induced tachycardia and exercise-induced increases in systolic blood pressure. Exercise duration was significantly shorter after carvedilol. The report does not contain information on baseline differences in the efficacy parameters between carvedilol and placebo. The statistical analysis reported "the observed sequence effects were very small, with only one F-statistic greater than 1.0." I assume any baseline effects would be manifest as a sequence effect in this 2 x 2 design.

Treatment-emergent symptoms dizziness (4 carvedilol and 3 placebo), back pain (1 carvedilol and 0 placebo), hypotension (1 carvedilol and 0 placebo), nausea (1 carvedilol and 0 placebo). One patient had a decrease in WBC from 5900 to 3400.

Conclusion: In this group of patients with a history of coronary artery disease, carvedilol did not affect cardiac ejection fraction at rest or with exercise. Carvedilol acted as a beta blocker by blocking exercise-induced increases in heart rate and systolic blood pressure. Exercise time was significantly shorter by 0.9 minutes after carvedilol.

TABLE 2
 MUGA RESULTS

MEASUREMENT	PLACEBO	CARVEDILOL	DIFFERENCE ¹	P-VALUE
EJECTION FRACTION AT REST (%):				
MEAN	49.2	49.7	1.0	.61
S.D. ²	5.0	6.8	1.8	
N	12	12		
EJECTION FRACTION ON EXERCISE (%):				
MEAN	57.3	57.5	0.7	.67
S.D. ²	7.0	6.5	1.6	
N	12	12		
EJECTION FRACTION EXERCISE-REST (%):				
MEAN	8.2	7.8	-0.3	.84
S.D. ²	2.6	4.1	1.2	
N	12	12		
DIASTOLIC BP AT MAX. EXERCISE (MM.HG.):				
MEAN	93.6	87.6	-6.3	.01**
S.D. ²	8.4	7.6	2.0	
N	12	12		
SYSTOLIC BP AT MAX. EXERCISE (MM.HG.):				
MEAN	172.3	148.5	-23.0	<.001***
S.D. ²	21.3	18.0	4.6	
N	12	12		
HEART RATE AT MAX. EXERCISE (BPM):				
MEAN	107.0	88.4	-18.6	<.001***
S.D. ²	11.5	8.9	3.3	
N	12	12		
RATE PRESSURE PRODUCT AT MAX (BPM X MMHG):				
MEAN	18489.1	13098.7	-5311.0	<.001***
S.D. ²	3407.2	1729.0	861.6	
N	12	12		
EXERCISE DURATION (MINUTES):				
MEAN	10.6	9.9	-0.9	.03*
S.D. ²	3.3	3.0	0.4	
N	12	12		
WORKLOAD AT MAXIMUM EXERCISE (KPM/MIN):				
MEAN	575.0	537.5	-45.0	.10
S.D. ²	167.2	149.4	24.8	
N	12	12		

* : p < .05
 ** : p < .01
 *** : p < .001

1: Estimated from Analysis of Variance

2: Standard Error is given for estimated mean difference

CARVEDILOL NDA 20-297

PROTOCOL F-30 VOL 1.44

STEREOSELECTIVE PK

Reviewer: James F. Graumlich

Objectives: To examine the pharmacokinetic parameters of R(+) and S(-)carvedilol after single oral doses of carvedilol to humans.

Study design: Open label, uncontrolled, prospective study in 5 healthy men. All subjects are presumed to be Japanese. Subjects received breakfast 30 minutes after the dose. Subjects again received food 4 hours after the dose.

Intervention: Humans received 20 mg carvedilol tablet po as a single dose after an overnight fast.

Response variables: Primary outcome: AUC (trapezoidal)
Secondary outcome: Cmax, Tmax, half-life, F, Vd, CLtot

Blood sampling times were at baseline then 0.5, 1, 2, 3, 4, 6, 8, 10, 24 hours after dose administration.

Materials: racemic carvedilol 20 mg tablet, formulation not specified, batch not specified

Assay: R(+) and S(-)carvedilol assay involved liquid-liquid extraction from plasma, chiral derivatization with GITC, then HPLC with fluorescence detection. The lower limit of quantification for R(+) and S(-)carvedilol was not specified.

Results: 5 male healthy subjects between 32 and 42 years of age completed the study. Weights of subjects were between 67 and 80 kg.

The attached figure 3 from protocol F-30 (page C68) shows the mean plasma concentration vs time for R(+) and S(-)carvedilol. N = 5 subjects. The table on the next page has the pharmacokinetic parameters for the two enantiomers.

Pharmacodynamic response: None recorded

Adverse events: None recorded

Conclusions: The study used a single dose of carvedilol in healthy Japanese men. Potential distribution differences in hepatic oxidative metabolism between Japanese and American populations limit the generalization of the results.

The distribution of the data was not analyzed. Therefore, statistical comparisons in the report are not reliable due to the small sample size.

The PK analysis assumes absorption of carvedilol from the GI tract is complete. This assumption remains to be proven. Since there was no intravenous dose given, F was calculated using assumptions regarding hepatic blood flow. Since these assumptions are not proven in this sample, the validity of the F calculation is questioned. The Vd and CLtot were calculated using the calculated value of F. Therefore, Vd and CLtot may not be reliable estimates.

The results suggest stereoselective, hepatic first-pass metabolism. S(-) carvedilol is metabolized to a greater extent than R(+) carvedilol.

CARVEDILOL NDA 20-297

PROTOCOL F-30 VOL 1.44

Pharmacokinetic parameters in 5 healthy Japanese men after oral dose

Parameter		R(+) carvedilol	S (-) carvedilol
C _{max} (ng/mL)	mean	25.3	9.8
	SD	15.6	6.8
	min		
	max		
T _{max} (hours)	mean	0.9	0.7
	SD	0.2	0.3
	min		
	max		
AUC _∞ (ng*hr/mL)	mean	105.01	37.95
	SD	58.7	19.59
	min		
	max		
half-life (hours)	mean	5.33	5.05
	SD	1.91	1.8
	min		
	max		
F	mean	0.45	0.24
	SD	0.17	0.1
	min		
	max		
V _d (L)	mean	362	498
	SD	101	188
	min		
	max		
CL _{tot} (L/hr)	mean	49.58	68.48
	SD	15.15	10.29
	min		
	max		

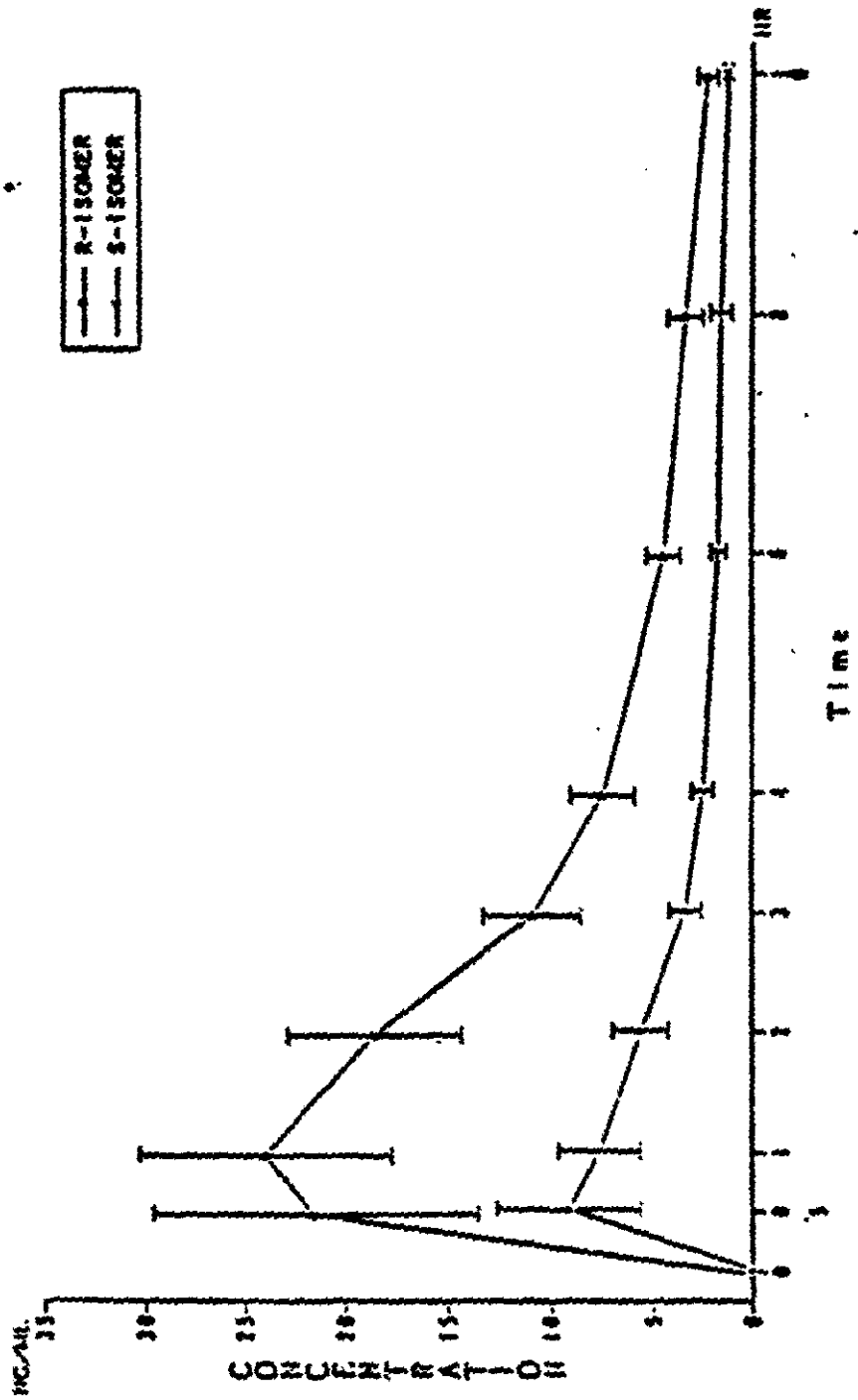


Fig. 3 Mean plasma concentrations of (R)- and (S)-enantiomer after oral administration of racemic DQ-2466 at a dose of 20 mg to healthy volunteers.

F30
000276
VOL 1.44

PHARMACODYNAMIC EFFECT

Reviewer: James F. Graumlich

Name of study: Effect of carvedilol on haemodynamic and performance parameters at rest, during and post exercise testing in healthy volunteers: an open uncontrolled pilot study

Objectives: To investigate the tolerance to and influence of carvedilol at peak and trough concentrations, on central and peripheral hemodynamics as well as on performance parameters in healthy subjects at rest and during exercise testing.

Study design: Open label, uncontrolled, prospective, 3 week study in 10 well-trained, healthy male subjects. There was forced dose escalation: 12.5 mg po q day for 7 days then 25 mg po q day for 14 days. Analgesic use by subjects was permitted. The definition of well-trained athlete was not provided. Exercise tolerance was measured on a bicycle ergometer. Workload was increased continuously by 30 watts/minute from 50 watts to 320 watts. Exercise duration was 10 minutes or until the subject achieved 17 on the Borg scale.

Intervention: All subjects exercised (bicycle ergometry) at baseline on day 0.
4 subjects exercised 2 hours after the dose on day 21
6 subjects exercised 8 hours after the dose on day 21

Response variables: Primary outcome: change in heart rate before and after exercise
Secondary outcome: change in respiratory rate, change in blood pressure, workload (watts), oxygen consumption, carbon dioxide production, minute exercise ventilation, respiratory quotient, orthostatic vital signs, trough plasma carvedilol concentration on day 21

Materials: carvedilol 12.5 mg tablet, formulation 2, batch 2
carvedilol 25 mg tablet formulation 1/25, batch 6

Assay: R(+) and S(-)carvedilol assay involved liquid-liquid extraction from plasma then HPLC with fluorescence detection. The lower limit of quantification for R(+) and S(-)carvedilol was 0.3 ng/mL.

Results: 12 evaluated, 10 enrolled male healthy subjects between 27 and 53 years of age completed the study. Weights of subjects are not reported. One subject ran a marathon race during the study.

subject 7 acetaminophen, oxymetazoline (adrenergic vasoconstrictor)
subject 9 acetaminophen + caffeine
subject 10 aspirin + caffeine

Pharmacodynamic response:

There was no placebo response to compare in this study.

Figures 4 and 5 (vol 1.53 pages 293-294) show trends suggesting blockade of exercise-induced increases in heart rate and systolic blood pressure. In the figures, responses are recorded at rest, 1/2 AT (anaerobic threshold), AT, and WLmax (maximum workload).

The sponsor claims there was no difference between baseline and end-of-study with regard to

exercise-induced changes in diastolic blood pressure, respiratory rate, workload (watts/kg), oxygen consumption VO₂ (mL/min/kg)

Orthostatic changes in vital signs during the course of carvedilol maintenance therapy are summarized in Table 1.

Table 1

Number of subjects with orthostatic changes on carvedilol therapy (N=10)

Parameter measured supine to standing	Number with fall > 10 mm Hg			
	Pretreatment baseline	12.5 mg/d x 1 week	25 mg/d x 1 week	25 mg/d x 2 weeks
DBP	0	0	0	0
SBP	0	1	0	3
	Number with increase > 20 beats per minute			
Pulse	3	0	3	2

SBP = systolic blood pressure. DBP = diastolic blood pressure.

Adverse events:

tiredness 6/10 subjects
 common cold 4/10
 headache 1/10
 dizzy 1/10
 nocturia 1/10
 weight gain 1/10
 increased sleep 1/10
 swollen feeling 1/10

decreased platelets (normal 150-400): 1/10 fell to 130, 1/10 fell to 106

Conclusions:

The protocol claims to measure exercise tolerance at "peak (2 hours post-dose) or trough (8 hours post-dose)." Neither the protocol nor the study report indicate (1) if peak refers to peak plasma carvedilol concentration or to E_{max}, (2) if trough refers to trough plasma carvedilol concentration or time of least effect. Other studies suggest T_{max} is 1.5 hours. Time to E_{max} varies depending on the parameter being measured. Since 8 hours represents about one-half life of carvedilol, the trough plasma carvedilol concentration cannot occur at 8 hours. Since time to E_{max} is up to 6 hours for some parameters, e.g., diastolic blood pressure, the time of least effect is unlikely at 8 hours after dose administration. The study report indicates overlap of responses measured 2 and 8 hours after the dose on day 21.

No statistical comparisons were attempted in this study due to small sample size. There is an

unexplained problem with missing data from subjects exercised 2 hours after dose administration at the end of the study.

When results are combined for subjects exercised 2 and 8 hours after dose administration on the last study day, there appears to be a trend suggesting carvedilol's effect on reduction of exercise-induced increases in heart rate and systolic blood pressure.

I do not feel this study can support the following claims:

(1) that there is no difference between baseline and treatment effects for any of the other response variables.

(2) that there is no difference between peak and trough effects for any of the other response variables.

There was no method for assessment of compliance.

The study reported carvedilol concentrations obtained after 2 weeks of dosing. Assessment of concentration effect relationships is difficult because there is no placebo-corrected effect to correlate with concentration.

There is no report of R(+) and S(-)carvedilol concentrations.

Although the report and the protocol claim the subjects exercised either 2 or 8 hours after dose administration on the last day of the study, the tables in Appendices 1.1, 1.2, 1.3, 1.4, 1.5, and 1.6 claim subjects were exercised either 2 or 6 hours after dose administration.

Side effects are listed above.

The time of analgesic use with relation to exercise is unknown. The confounding effect of analgesic use on exercise performance is unknown.

There is no placebo group with which to compare pharmacodynamic effects. Therefore, I do not feel this study can support a claim that there is a significant difference between baseline and treatment for any of the response variables.

Figure 4 Effects of Carvedilol on Blood Pressure

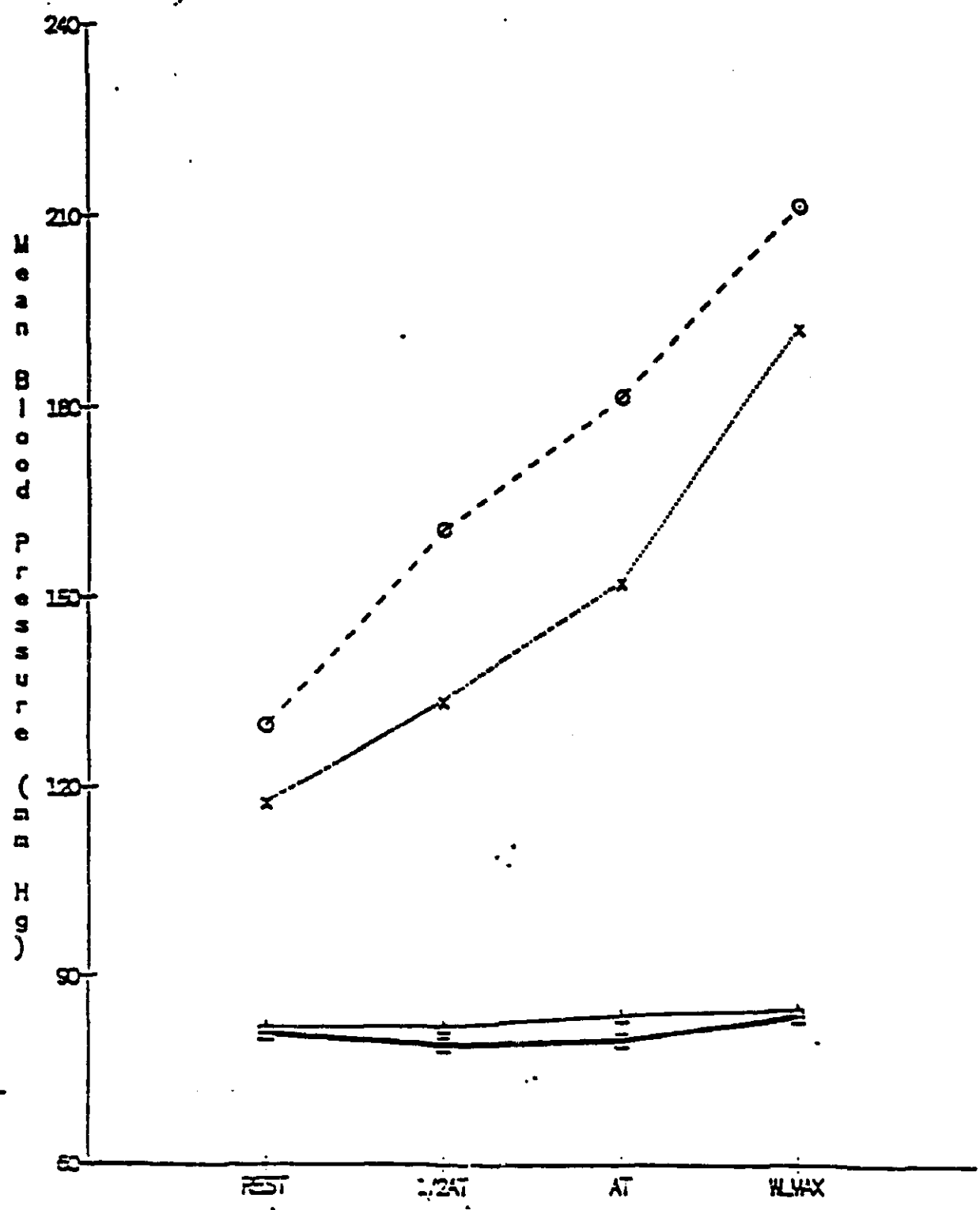


Figure 4. Mean systolic blood pressure immediately before exercise and at 1/2 anaerobic threshold, anaerobic threshold, and maximal workload (X; n=10, 10, 10, 9, respectively) and after three weeks of carvedilol treatment (CIRCLE; n=10, 10, 10, 10, respectively).

Mean diastolic blood pressure immediately before exercise and at 1/2 anaerobic threshold, anaerobic threshold, and maximal workload prior to first dose (TRIANGLE; n=10, 10, 10, 10, respectively) and after three weeks of carvedilol treatment (SQUARE; n=10, 9, 9, 8, respectively).

Figure 5

Effect of Carvedilol on Heart Rate

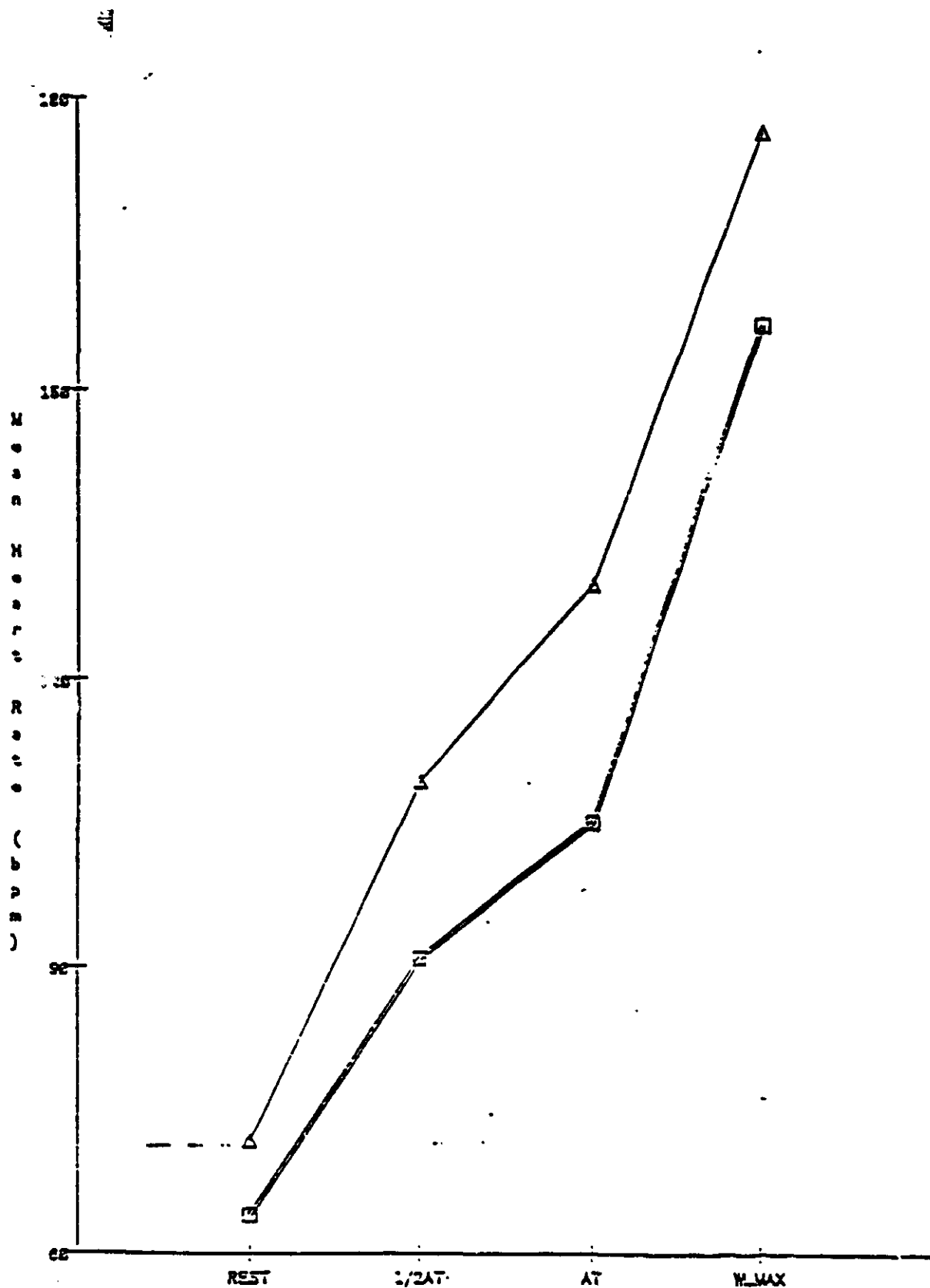


Figure 5. Mean heart rate (bpm) immediately before and during exercise (at 1/2 anaerobic threshold, anaerobic threshold, and maximal workload) prior to first dose (TRIANGLE) and after three weeks of carvedilol treatment (SQUARE); n = 10.

VOL 1.53
INT-CAR-225CA
PAGE 000294

Reviewer: James F. Graumlich

INT-CAR-30A is a double-blind placebo-controlled, 4-period crossover study of single doses of carvedilol 6.25 mg, 12.5 mg, 25 mg, and 50 mg in 7 healthy men. The sequence for carvedilol treatments was ascending in dose strength. Placebo sequence was random. Treatment periods were separated by one week. The objective was to measure beta-blockade by carvedilol using the exercise step test. An additional objective was to determine the lowest dose causing an acute decrease in systolic blood pressure. The subjects (aged 21 - 31 years) had a mean weight of 77.6 kg. There were no clinically significant lab abnormalities related to treatment. There were 2 drop-outs. One subject had symptomatic orthostatic hypotension (supine BP 112/68, standing BP 68/58) 2 hours after carvedilol 25 mg po. Another subject was withdrawn because he had asthma during childhood and because he was drunk on one of the treatment days. Another subject, who completed the study, had symptomatic orthostatic hypotension (supine BP 108/72, standing BP 42/0) one hour after carvedilol 25 mg po. Other symptoms associated with carvedilol were lightheadedness in 6 of 7, headache in 3 of 7, nausea in 2 of 7, sweating in 1 of 7, and chest tightness in 1 of 7. Most of these symptoms occurred in subjects receiving carvedilol 50 mg. There were no symptoms reported in subjects receiving placebo. Beta blockade was determined based on carvedilol's blockade of exercise-induced increases in heart rate (see Figure 2 from page 147, volume 1.113). The maximum reduction in exercise-induced increases in heart rate occurred 2 hours after the dose. The following table shows the effect on exercise heart rate at 2 hours after the dose (from page 144, volume 1.113). Volume 1.113 contains no information on minimum or maximum values for individuals.

Dose	Exercise heart rate beats/min (mean $\pm$ SD)	reduction compared to baseline %
placebo	164.5 $\pm$ 15.8	+ 1.2
6.25 mg	153.2 $\pm$ 10.3	- 5.9
12.5 mg	150.8 $\pm$ 4.7	- 8.7
25 mg	141.2 $\pm$ 5.4	- 14
50 mg	136.0 $\pm$ 13.7	- 14.9

The sponsor does not offer statistical comparisons between the means for the dose groups. It appears the 95% confidence intervals for the various means overlap. Therefore, the various carvedilol group means are not statistically, significantly different from the placebo group mean. There is a trend suggesting a dose-response relationship for carvedilol doses and reductions in exercise-induced tachycardia.

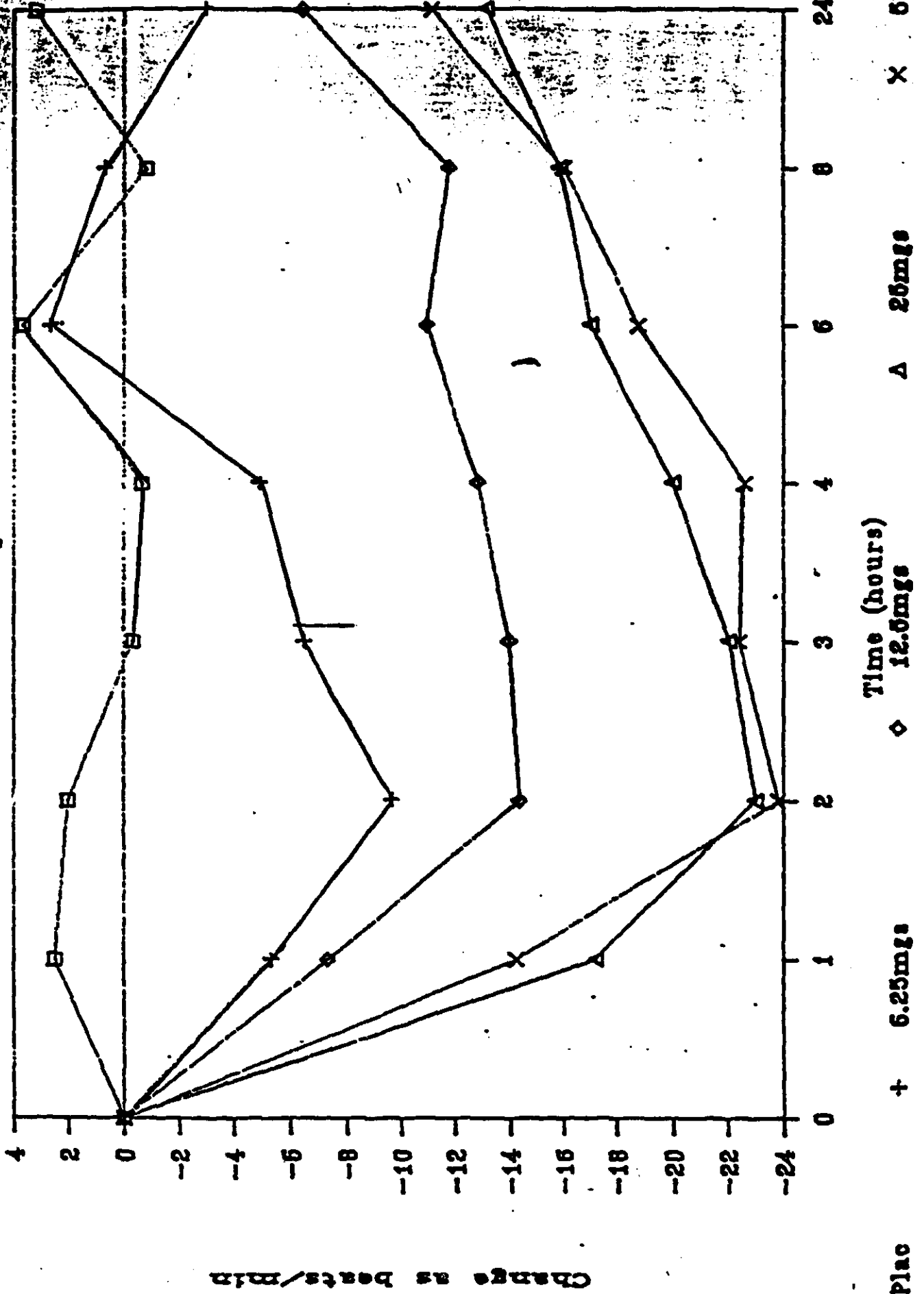
Carvedilol did not cause significant changes in supine heart rate during the 24 hours of observation after the dose (see Figure 8, page 153, volume 1.113). It is unknown if the sample size was adequate to detect a difference. Carvedilol did not cause significant changes in standing heart rate (see Figure 7, page 152, volume 1.113). It is unknown if the sample size was adequate to detect a difference. The effect of carvedilol on supine and standing systolic and diastolic blood pressure are shown in Figures 4 (page 149), Figure 6 (page 151), Figure 10 (page 155), and Figure 12 (page 157). Means for carvedilol groups were not significantly different from the mean for placebo for each response.

Conclusions: This cross-over study was not randomized with respect to the sequence of carvedilol treatments. The sample size was small. The study may not have had adequate power to detect differences if present. The study did not demonstrate significant beta-blocker effect when compared to placebo although there were trends suggesting treatment effect. Vasodilation (as measured by changes from baseline in mean standing diastolic blood pressure) was not statistically, significantly different in any of the treatment groups when compared to placebo.

FIGURE 2

INTCAR30

Exercise H.R.-Mean Change from Baseline



C 75

□ Place

+

6.25mg

◇

12.5mg

△

25mg

X

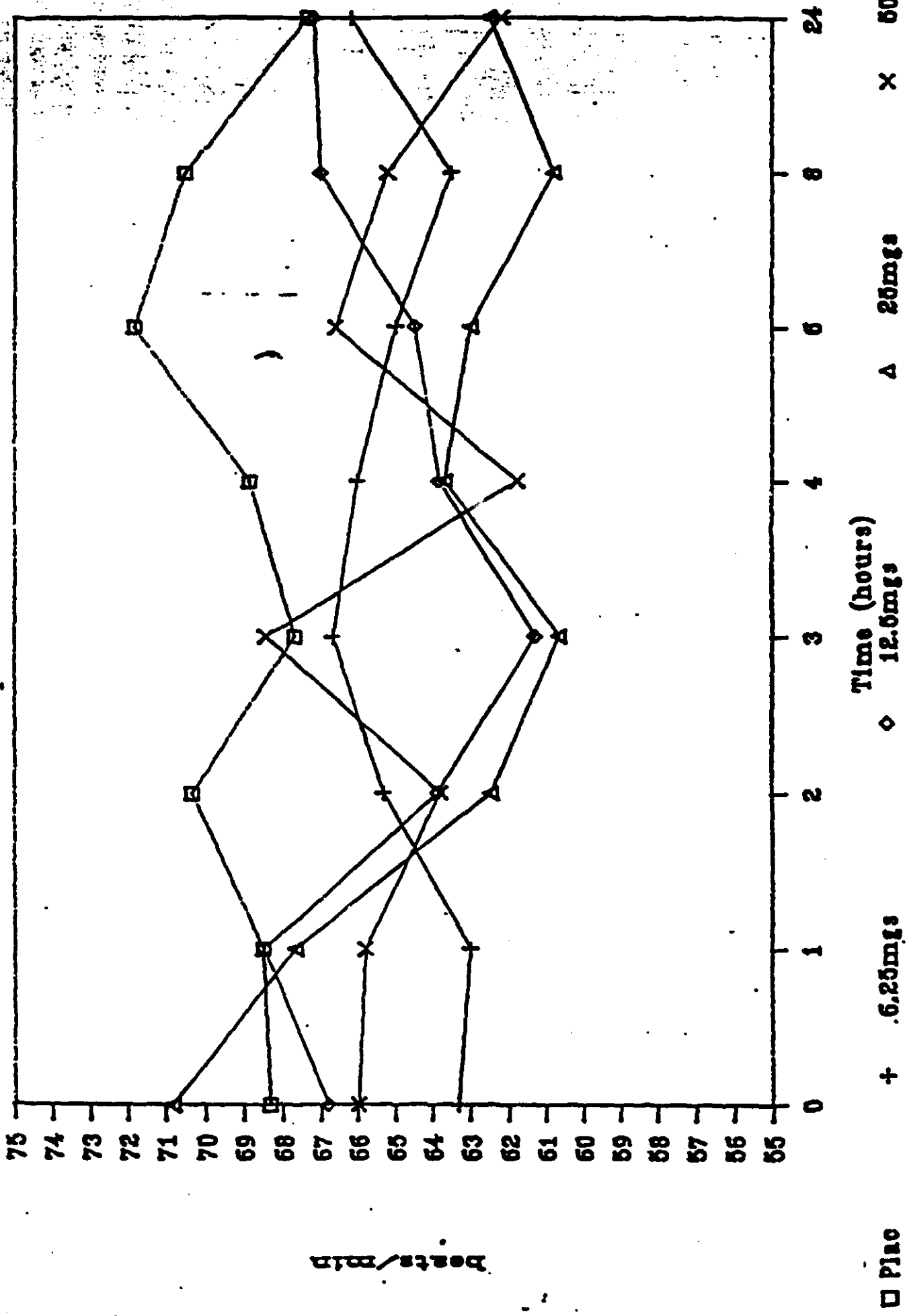
60mg

000147

INTCAR30

Supine Heart Rate

FIGURE 8



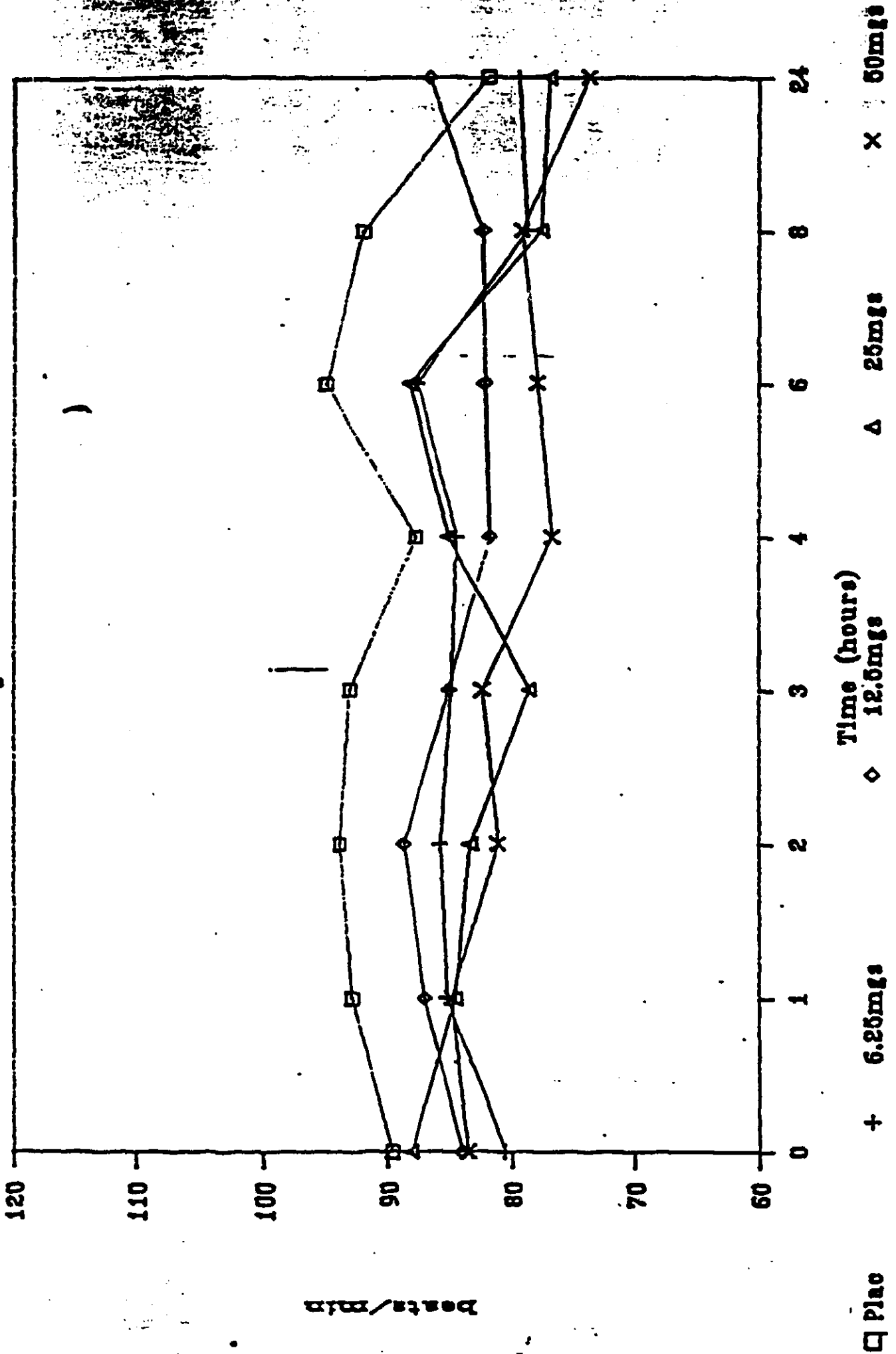
C76

FIGURE 7

: 30 :

INTCAR30

Standing Heart Rate



000152

: 27 :

INTCAR30

Standing DBP -- Change from Baseline

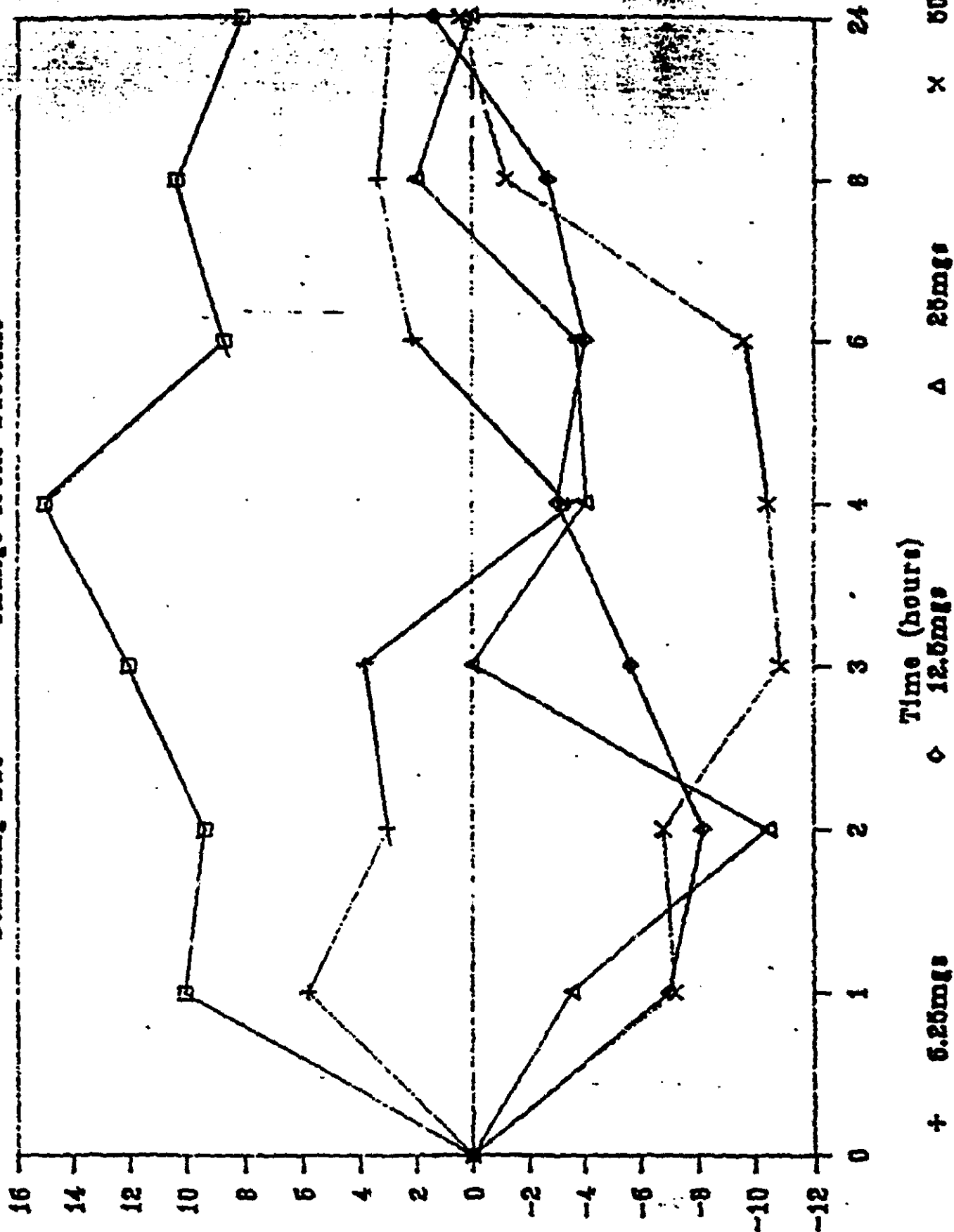


FIGURE 4

Change in DBP mm Hg

□ Place

+ 6.25mg

◇ 12.5mg

Δ 25mg

x 50mg

000149

: 29 :

INTCAR30

Standing SBP - - - Change from Baseline

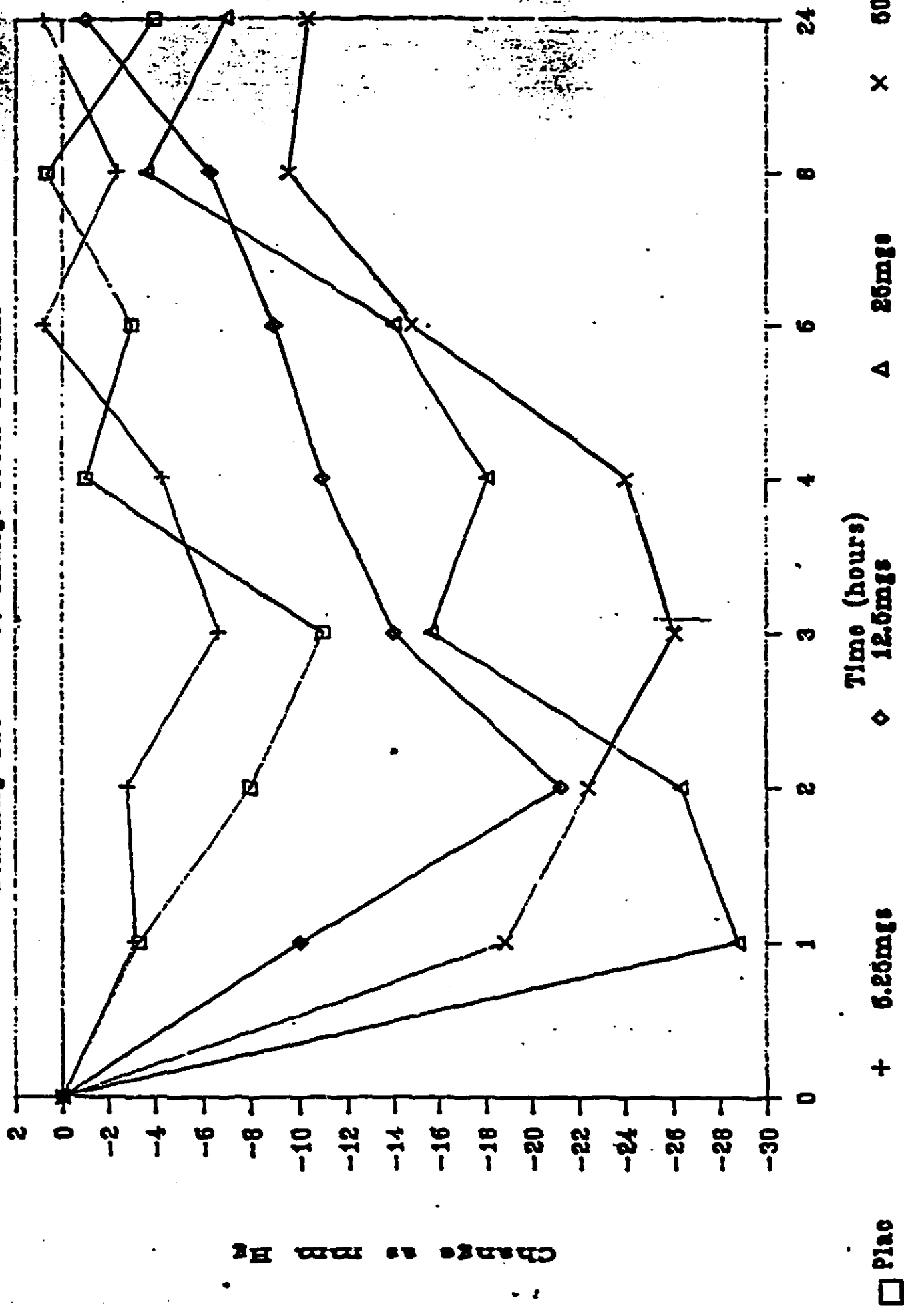


FIGURE 6

INTCAR30

Supine SBP - - - Change from Baseline

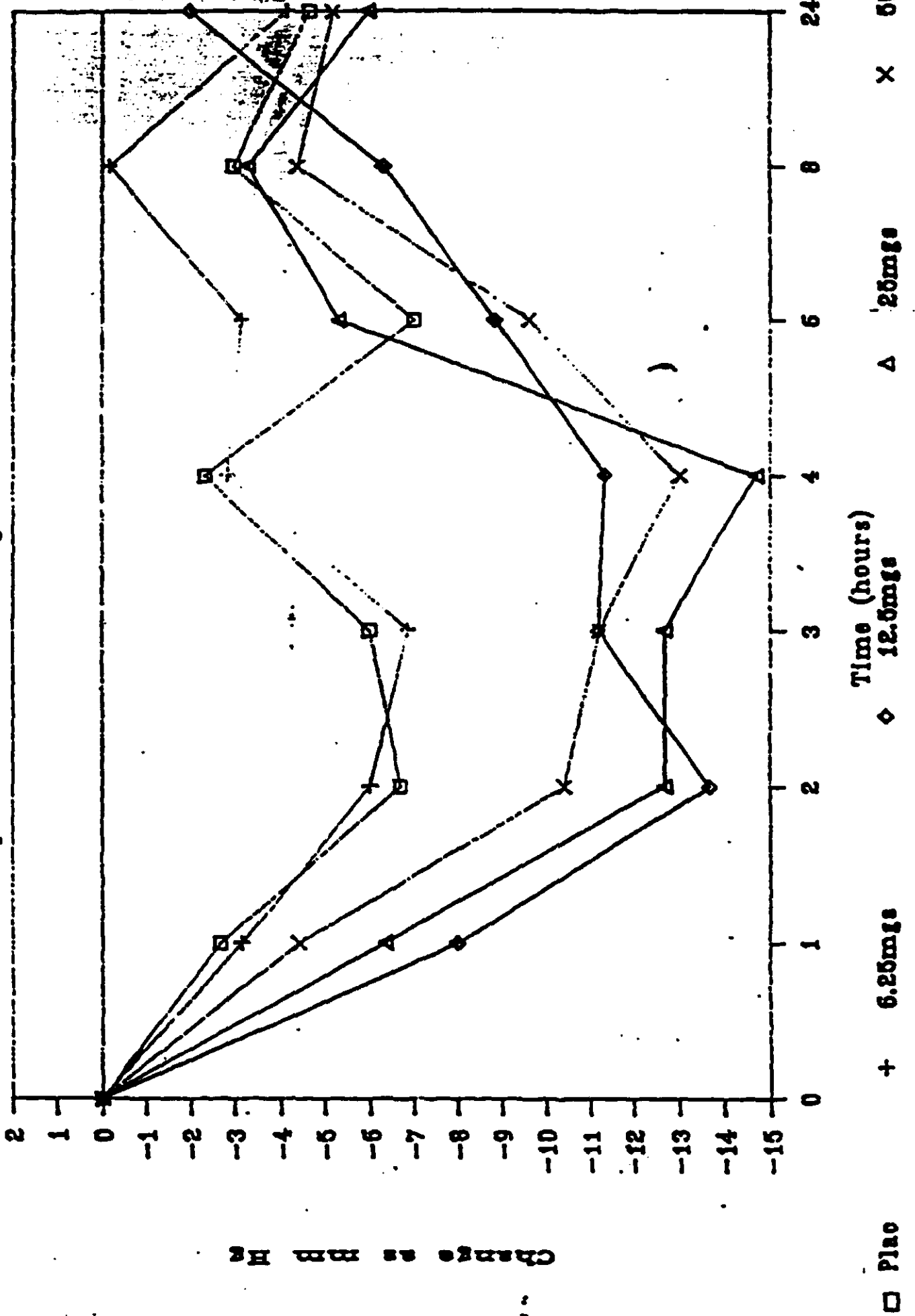


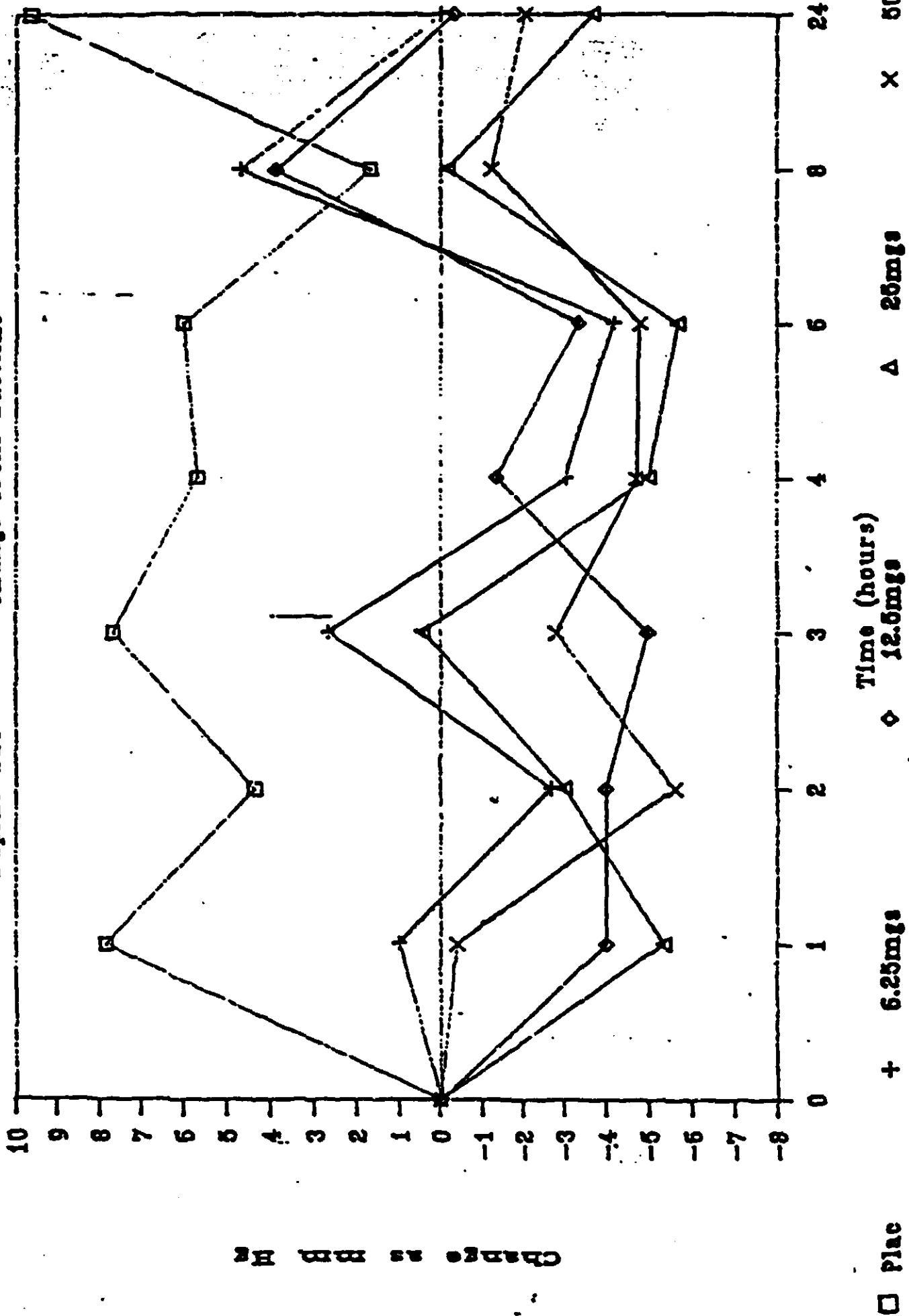
FIGURE 10

: 35 :

FIGURE 12

INTCAR30

Supine DBP - Change from Baseline



Time (hours)

□ Plac

+ 6.25mg

◇ 12.5mg

△ 25mg

× 50mg

PROTOCOL INT.CAR.30B VOL 1.113

Reviewer: James F. Graumlich, Carvedilol NDA 20-297

INT-CAR-30B is a double-blind, placebo-controlled, partially-randomized, 5-period crossover study comparing single doses of study medication: placebo, labetalol 400 mg, and carvedilol 6.25 mg, 12.5 mg, 25 mg. The study was partially-randomized because carvedilol 6.25 mg, labetalol and placebo were presented in random sequence while, for safety reasons, carvedilol 25 mg was always preceded by carvedilol 12.5 mg. Treatments were separated by a week. Subjects were 10 healthy men, aged 19 - 32 years, median weight 73 kg. The objective was to determine the threshold oral dose of carvedilol for alpha blockade as assessed by the effect of carvedilol on phenylephrine (alpha 1 receptor stimulant) -induced elevations in blood pressure, to determine the threshold oral dose of carvedilol for beta blockade as assessed by the effect of carvedilol on isoproterenol (isoproterenol, non-selective beta receptor stimulant) -induced changes in heart rate and blood pressure, and to compare the effects on the above parameters caused by various doses of carvedilol, labetalol and placebo. On each study day, measurements were made before and 2 hours after the dose of study drug for the following response variables: phenylephrine-induced elevations in blood pressure, isoproterenol-induced changes in heart rate, exercise-induced (step test) changes in heart rate. The step test was 30 minutes after the last infusion of phenylephrine or isoproterenol. However, the timing of the step test was not standardized with respect to the time of the dose of study medication. The endpoint for statistical analysis was not prospectively defined. Post hoc, ED50 was defined for SBP as the dose of infusion producing an increase of 15 mm Hg in SBP. Post hoc, ED 50 for heart rate was defined as the dose of infusion producing an increase of 25 beats/min in heart rate. Dose-response curves were drawn for phenylephrine and isoproterenol pre- and post-dose of study medication. ED50 was extrapolated from the dose-response curves.

There were no drop-outs. Other than the usual symptoms of lightheadedness, headache, and nausea, no other clinically significant adverse events were reported.

Hypoglycemia occurred in 4 of 10 subjects (normal glucose 3.5 - 7.0): glucose 1.4 after carvedilol 6.25, glucose 1.6 after carvedilol 6.25, glucose 3.2 after carvedilol 25 mg, and glucose 3.2 after labetalol 400 mg. See Conclusions (page C83) for a potential explanation of the hypoglycemia.

One of 10 subjects had serum sodium 153 (normal 135 - 145) after carvedilol 25 mg. No data were reported from the phenylephrine, isoproterenol, and step-test studies done before the dose of study medication.

The mean % response in SBP versus log-dose of phenylephrine is displayed on the top graph, Figure 1a, page C86. At the ED50, SBP responses to phenylephrine were not statistically different for carvedilol 6.25 mg vs placebo and carvedilol 25 mg vs placebo. Although carvedilol 12.5 mg was statistically different from placebo at the ED50 (ratio of ED50 = 1.33, 95% confidence interval 1.07 to 1.65, $p = 0.013$), the clinical significance of this difference is questionable. Labetalol was a positive control and was significantly different from placebo at the ED50 (ratio of ED50 = 2.05, 95% confidence interval 1.66 to 2.54, $p < 0.001$). When reviewing the ED50 for individual subjects, only 2 of 10 had ascending ED50 values correlating with ascending doses of carvedilol. The data do not suggest carvedilol behaves as an alpha blocker.

The mean % response in SBP versus log-dose of isoproterenol is displayed on the bottom graph, Figure 1b, page C86. Subject 10 was able to increase SBP by 15 mm Hg after carvedilol 12.5 mg and labetalol. However, Subject 10 was excluded from analysis because he did not increase SBP by 15 mm Hg while on placebo, carvedilol 6.25 mg or carvedilol 25 mg. The report does not state if Subject 10 increased SBP by 15 mm Hg when tested pre-dose. In the other 9 subjects at the ED50, carvedilol 12.5, carvedilol 25 mg, and labetalol caused significant reduction in SBP changes induced by isoproterenol.

The mean % response in heart rate versus log-dose of isoproterenol is displayed on the bottom graph, Figure 2b, page C87. Subjects 5, 7, and 9 did not achieve 50% increases in heart rate while on some doses of carvedilol or labetalol. ED50 values for subjects 5, 7, and 9 were extrapolated from the fitted curve of heart rate versus log-dose of isoproterenol. ANOVA revealed a significant interaction due to order of infusion of isoproterenol and phenylephrine.

CARVEDILOL NDA 20-297**PROTOCOL INT.CAR.30B VOL 1.113**

At the ED50, each of the doses of carvedilol, as well as labetalol, was different from placebo. Although there are problems with the post hoc analysis, carvedilol did appear to have an effect as a beta-blocker with respect to suppression of tachycardia induced by isoproterenol.

The pulse rate post exercise is shown (C84, C85). All doses of carvedilol and labetalol, when compared to placebo, produced statistically significant decreases in post exercise heart rate.

Conclusions: The results of the phenylephrine and isoproterenol portions of the study may be biased by the post hoc analysis and the exclusion (post hoc) of a non-responder. In this study of healthy men, carvedilol has an effect as a beta blocker because it blocks exercise-induced increases in heart rate. Hypoglycemia was more common in this sample than in other studies I have reviewed. Alpha 2 stimulation of pancreatic beta cells results in decreased insulin secretion. Beta 2 stimulation causes increased insulin secretion. Non-specific alpha blockade with phentolamine with concomitant beta stimulation with isoproterenol increases insulin secretion (Exp-Pathol 1991; 43 (1-2):57-61). In theory, alpha blockade by carvedilol and beta stimulation by isoproterenol could produce hypoglycemia. Neither phenylephrine nor isoproterenol, when given alone, are associated with hypoglycemia.

CARVEDILOL NDA 20-297

PROTOCOL INT.CAR.30B VOL 1.113

and phenylephrine. At the ED50, each of the doses of carvedilol, as well as labetalol, was different from placebo. Although there are problems with the post hoc analysis, carvedilol did appear to have an effect as a beta-blocker with respect to suppression of tachycardia induced by isoproterenol.

The pulse rate post exercise is shown in Appendix 8 (page 238, volume 1.113) and Table 8 (page 211, volume 1.113). All doses of carvedilol and labetalol, when compared to placebo, produced statistically significant decreases in post exercise heart rate.

Conclusions: The results of the phenylephrine and isoproterenol portions of the study may be biased by the post hoc analysis and the exclusion (post hoc) of a non-responder. In this study of healthy men, carvedilol has an effect as a beta blocker because it blocks exercise-induced increases in heart rate. Hypoglycemia was more common in this sample than in other studies I have reviewed. Alpha 2 stimulation of pancreatic beta cells results in decreased insulin secretion. Beta 2 stimulation causes increased insulin secretion. Non-specific alpha blockade with phentolamine with concomitant beta stimulation with isoproterenol increases insulin secretion (Exp-Pathol 1991; 43 (1-2):57-61). In theory, alpha blockade by carvedilol and beta stimulation by isoproterenol could produce hypoglycemia. Neither phenylephrine nor isoproterenol, when given alone, are associated with hypoglycemia.

α_2 stim $\rightarrow$ $\downarrow$ insulin

β_2 stim $\rightarrow$ $\uparrow$ insulin secretion

isoproterenol $\rightarrow$ $\uparrow$ insulin secretion

TABLE 8

PROTOCOL INT-CAR 300
PULSE RATE (bts/min) POST EXERCISE

(a) ANOVA on Pulse Rate

SOURCE	df	SS	F-Value	Sign.
SUBJECT	9	4728.400		
DAY	4	121.000		
TREAT	4	1983.486	10.77	<0.001
ERROR	32	1473.114		
TOTAL	49	8306.000		

(b) Estimated Treatment Differences

Contrast	Diff.	95% Conf. Interval		Sign.
		Lower	Upper	
6.25mg - Plac.	-8.9	-15.1	-2.7	0.006
12.5mg - Plac.	-10.7	-17.1	-4.4	0.002
25.0mg - Plac.	-17.4	-23.7	-11.0	<0.001
Labet. - Plac.	-17.0	-23.2	-10.8	<0.001
6.25mg - Labet.	8.1	1.9	14.3	0.012
12.5mg - Labet.	6.3	-0.1	12.6	0.052
25.0mg - Labet.	-0.4	-6.7	6.0	0.906

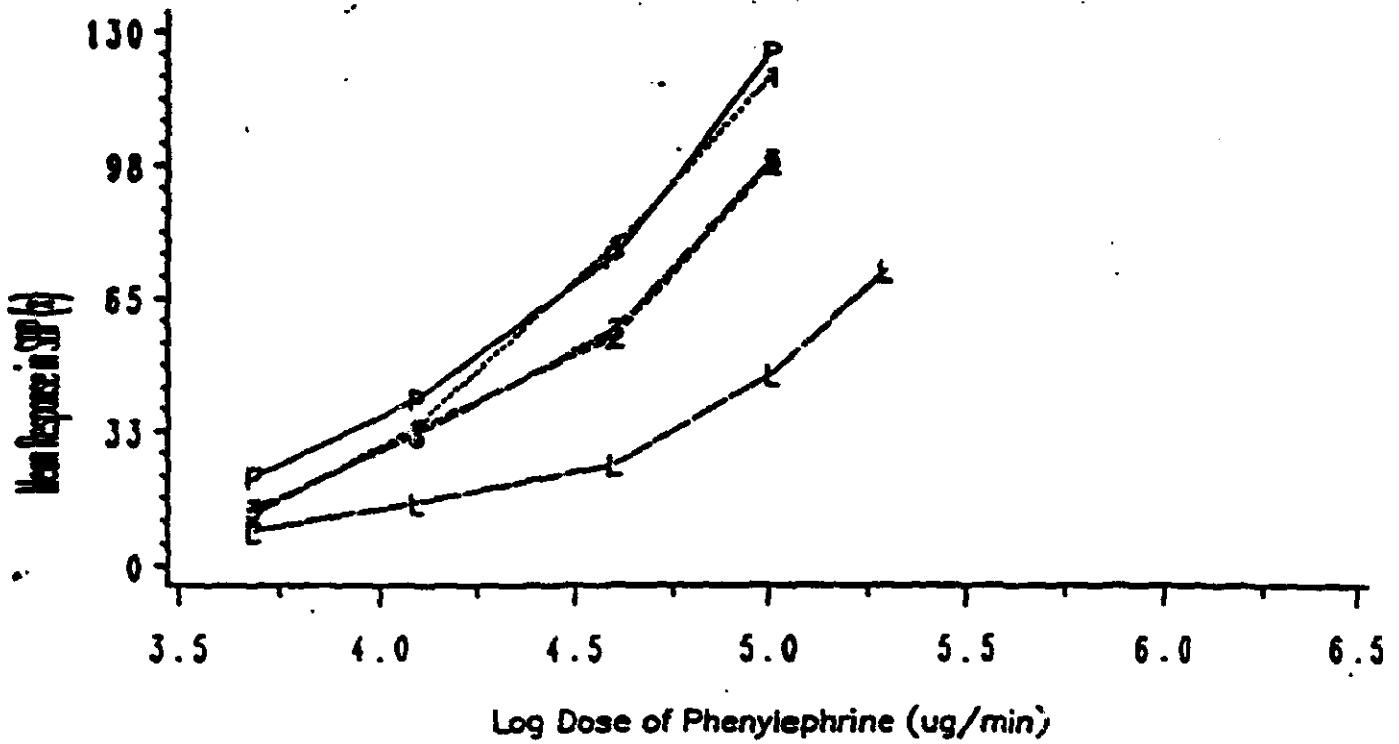
APPENDIX 8

PROTOCOL INT-CAR 308
PULSE RATE (bts/min) POST EXERCISE

Subject	Carvedilol			Labetalol	Placebo
	6.25mg	12.5mg	25.0mg		
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
No.	10	10	10	10	10
Mean	153	151	144	145	162
SD	13	9	10	11	14

Fig. 1a

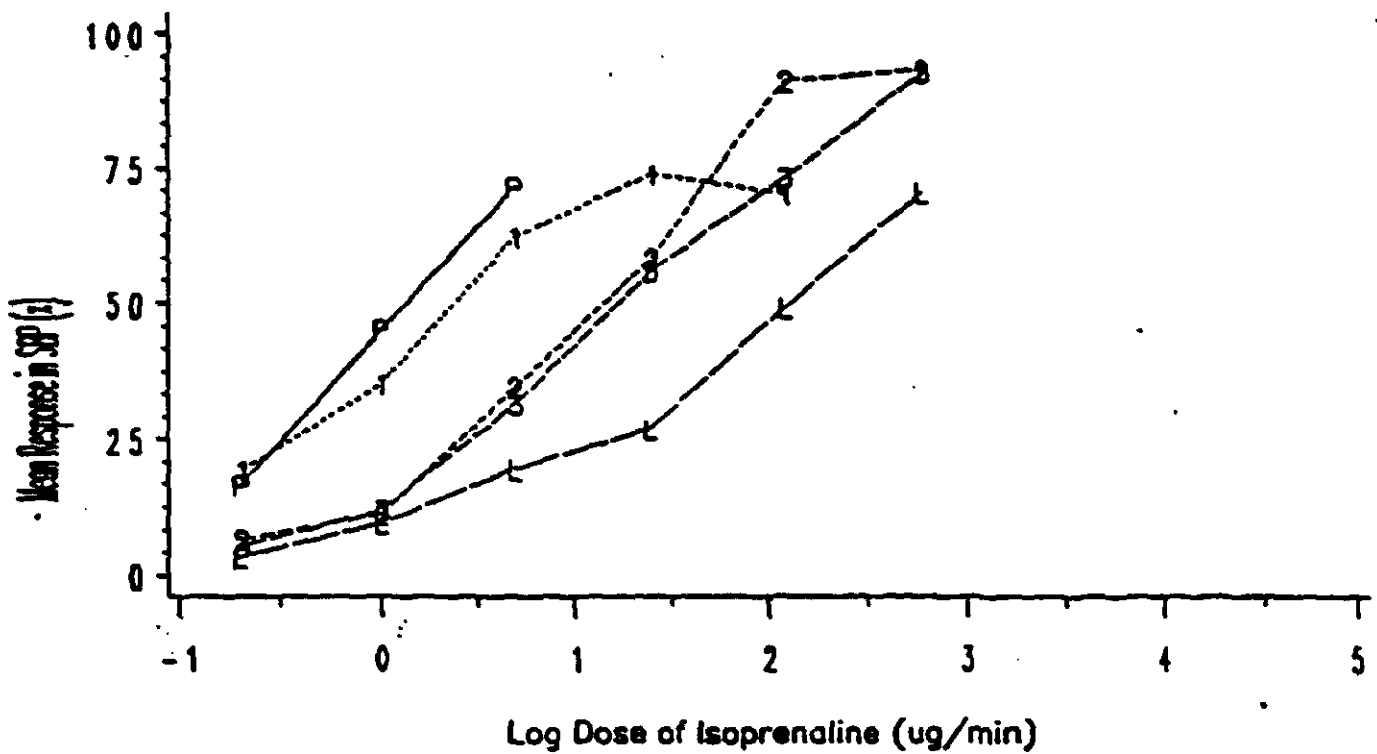
MEAN RESPONSE IN SBP VERSUS LOG-DOSE OF PHENYLEPHRINE



Treatment ~~+~~-~~+~~-~~+~~ 6.25mg ~~2~~-~~2~~-~~2~~ 12.5mg ~~3~~-~~3~~-~~3~~ 25.0mg
 ~~t~~-~~t~~-~~t~~ Labetalol ~~P~~-~~P~~-~~P~~ Placebo

Fig. 1b

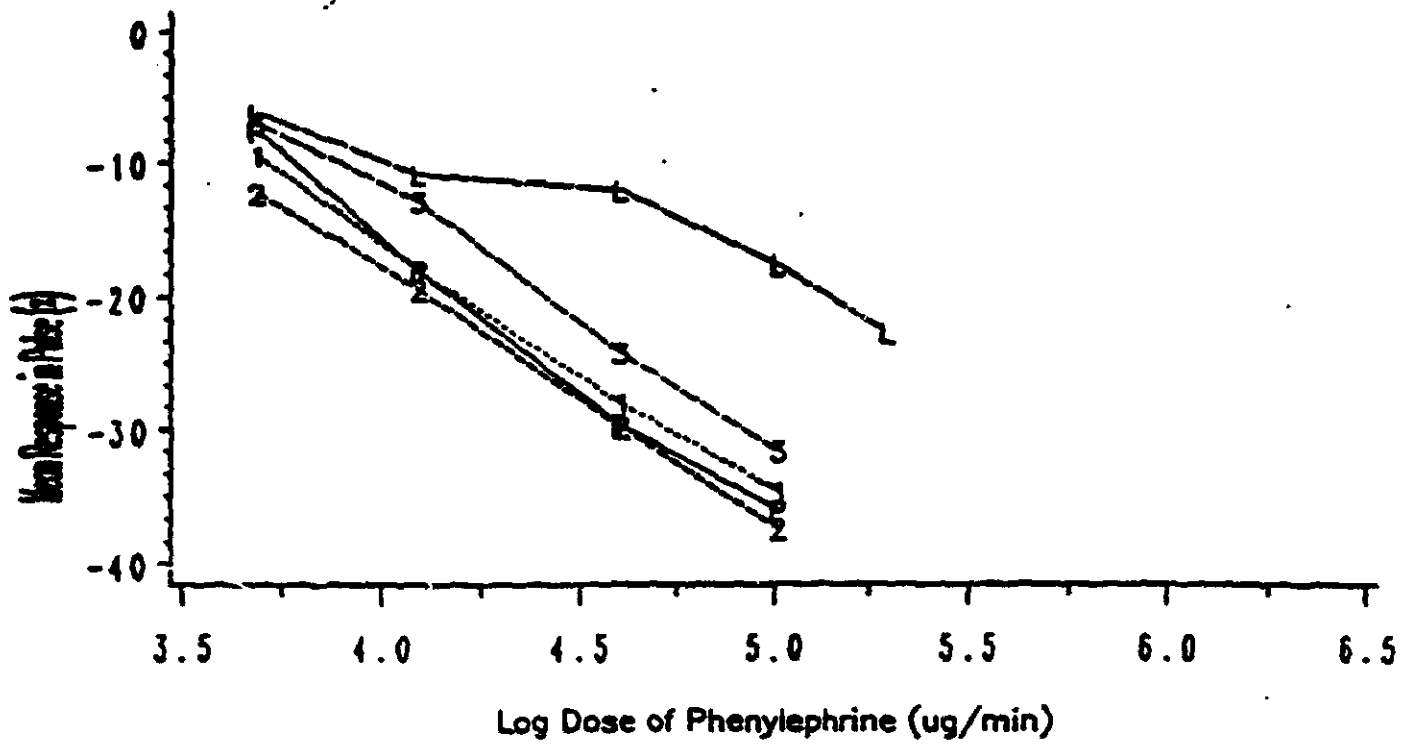
MEAN RESPONSE IN SBP VERSUS LOG-DOSE OF ISOPRENALINE



Treatment ~~+~~-~~+~~-~~+~~ 6.25mg ~~2~~-~~2~~-~~2~~ 12.5mg ~~3~~-~~3~~-~~3~~ 25.0mg
 ~~t~~-~~t~~-~~t~~ Labetalol ~~P~~-~~P~~-~~P~~ Placebo

Fig. 2a

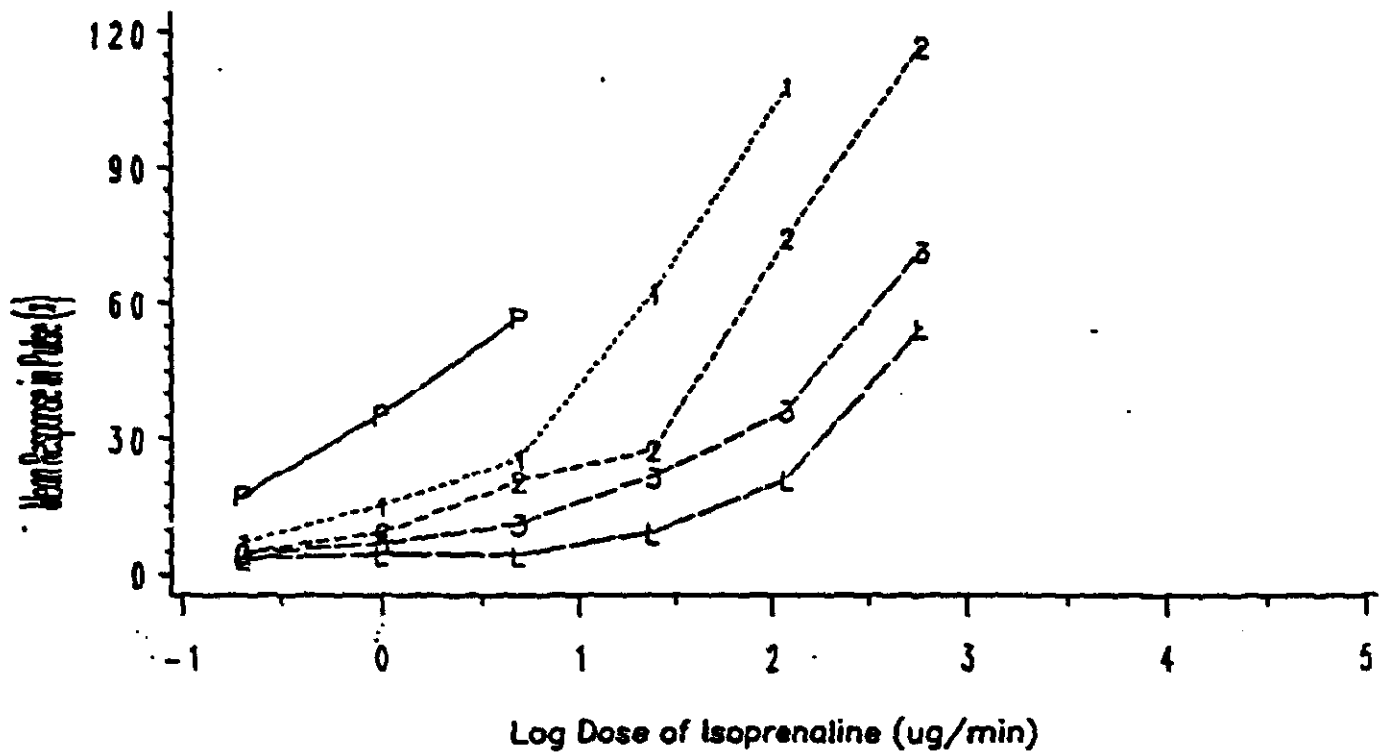
MEAN RESPONSE IN PULSE VERSUS LOG-DOSE OF PHENYLEPHRINE



Treatment ~~1-1-1~~ 6.25mg ~~2-2-2~~ 12.5mg ~~3-3-3~~ 25.0mg
~~L-L-L~~ Labelalol ~~P-P-P~~ Placebo

Fig. 2b

MEAN RESPONSE IN PULSE VERSUS LOG-DOSE OF ISOPRENALINE



Treatment ~~1-1-1~~ 6.25mg ~~2-2-2~~ 12.5mg ~~3-3-3~~ 25.0mg
~~L-L-L~~ Labelalol ~~P-P-P~~ Placebo

CARVEDILOL NDA 20-297

PROTOCOL MF2971 VOL 1.56

PD

Reviewer: James F. Graulich

Name of study: The efficacy, safety and tolerance of carvedilol in incrementing doses with observations on haemodynamic parameters in healthy volunteers

Objectives: To study the tolerance and safety of carvedilol following single oral doses and to determine the effects of these doses on heart rate and blood pressure at rest and under dynamic exercise

Study design: 2 phase study. Phase 1 was double-blind, randomized sequence, placebo controlled, 3 period crossover phase in 6 healthy men using single oral doses of placebo, carvedilol 50 mg, and carvedilol 100 mg. Phase 2 was single-blind, uncontrolled dose escalation phase using single oral doses of 200, 300, 400, 600, and 800 mg of carvedilol per period. Periods were separated by at least 5 days.

Intervention: placebo and various doses of racemic carvedilol

Response variables: Primary outcome: heart rate and blood pressure before, during, and after exercise, supine and standing

Secondary outcome: carvedilol concentrations in plasma, C_{max}, T_{max}, AUC, lab safety tests

Bicycle ergometry to standardized workload was used during this study. Hemodynamic responses were measured and plasma samples were collected at baseline then 0.5, 1, 2, 4, 6, 8, and 24 hours after carvedilol administration.

Materials: carvedilol capsules (50, 100, 200, 300, 400, 600, and 800 mg) lot number 814966 Ab

Assay: Plasma assay of carvedilol involved liquid/liquid extraction, HPLC with fluorometric detection. Propranolol was the internal standard. The lower limit of quantification was 1 ng/mL.

Results: 6 healthy men between 23 and 42 years of age completed the phase 1 of the study. There were no dropouts. Weights of subjects were between 70.6 and 93.7 kg. 5 subjects took 200 mg. Orthostatic hypotension was the dose-limiting side effect that prevented 4 of 6 subjects from tolerating more than 200 mg of carvedilol.

Maximum tolerated dose (mg) based on orthostatic symptoms	Number of subjects
100	1
200	3
400	1
800	1

Pharmacodynamic response: n = 6 unless otherwise specified.

Supine systolic blood pressure after 50 mg: When comparing the means, there was no significant decrease compared to placebo during 24 hours of observation.

Supine systolic blood pressure after 100 mg: onset of effect was at 2 hours, E_{max} was at 4 hours (-12 mm Hg compared to placebo). After 8 hours, there was no effect when compared to placebo.

Supine systolic blood pressure after 200 mg (n = 5): onset of effect was at 2 hours, Emax was at 2 hours (-13 mm Hg compared to placebo). After 8 hours, there was no effect when compared to baseline.

Supine diastolic blood pressure after 50 mg: there was no significant decrease compared to placebo during 24 hours.

Supine diastolic blood pressure after 100 mg: onset of effect was at 4 hours, Emax was at 4 hours (-10 mm Hg compared to placebo). After 4 hours, there was no effect when compared to placebo.

Supine diastolic blood pressure after 200 mg (n = 5): onset of effect was at 2 hours, Emax was at 2 hours (-9 mm Hg compared to placebo). After 2 hours, there was no effect when compared to baseline.

Supine heart rate after 50 mg: there was a statistically significant increase (+4 beats per minute) 30 minutes after the dose. The clinical significance of this difference is questionable. There was no significant change in heart rate at the corresponding time after the 100 mg dose.

Supine heart rate after 100 mg: onset of effect was at 4 hours, Emax was at 4 hours (-4 beats per minute compared to placebo). After 8 hours, there was no effect when compared to placebo.

Supine heart rate after 200 mg (n = 5): onset of effect was at 6 hours, Emax was at 8 hours (-10 beats per minute compared to placebo). After 8 hours, there was no effect when compared to baseline.

Standing systolic blood pressure after 50 mg: onset of effect was at 2 hours, Emax was at 2 hours (-10 mm Hg compared to placebo). After 8 hours, there was no effect when compared to placebo.

Standing systolic blood pressure after 100 mg: onset of effect was at 1 hour, Emax was at 2 hours (-21 mm Hg compared to placebo). After 8 hours, there was no effect when compared to placebo.

Standing systolic blood pressure after 200 mg (n = 5): onset of effect was at 1 hour, Emax was at 2 hours (-32 mm Hg compared to placebo). After 8 hours, there was no effect when compared to baseline.

Standing diastolic blood pressure after 50 mg: there was no significant difference when compared to placebo.

Standing diastolic blood pressure after 100 mg: onset of effect was at 4 hours, Emax was at 4 hours (-17 mm Hg compared to placebo). After 6 hours, there was no effect when compared to placebo.

Standing diastolic blood pressure after 200 mg (n = 5): onset of effect was at 2 hours, Emax was at 2 hours (-25 mm Hg compared to placebo). Blood pressure was decreased from baseline at 24 hours after the dose.

Standing heart rate after 50 mg was complex: 1 hour after the dose, mean heart rate increased significantly (+14 beats per minute compared to placebo). There was no significant difference from placebo until 24 hours after the dose when mean heart rate decreased (-7 beats per minute). No other significant differences from placebo were noted.

Standing heart rate after 100 mg was complex, too. 30 minutes after the dose, mean heart rate increased (+11 beats per minute compared to placebo). At 6 and 24 hours after the dose (but not at 8 hours after the dose), there were significant decreases. Emax was at 6 hours (-10 beats per minute compared to placebo).

Standing heart rate after 200 mg (n = 5): onset of effect was at 4 hours, Emax was at 6 hours (-15 beats per minute compared to placebo). When compared to baseline, decreased heart rate continued to 24 hours.

Effects on exercise parameters: end exercise hemodynamics - pre exercise hemodynamics were compared to placebo.

Exercise-induced increases in systolic blood pressure were blunted by 50 mg (-24 mm Hg compared to placebo). Onset of effect was at 2 hours. Emax was at 4 hours. After 4 hours, there was no effect when compared to placebo.

Exercise-induced increases in systolic blood pressure were blunted by 100 mg (-33 mm Hg compared to placebo). Onset of effect was at 1 hour. Emax was at 2 hours. After 8 hours, there was no effect when compared to placebo.

In 5 subjects, exercise-induced increases in systolic blood pressure were blunted by 200 mg. Onset of effect was at 1 hour. Emax was at 2 hours. After 8 hours, there was no effect when compared to baseline.

Exercise-induced decreases in diastolic blood pressure after 50 mg were not statistically different from placebo responses.

Exercise-induced decreases in diastolic blood pressure were blunted by 100 mg (+21 mm Hg compared to placebo). Effect was significant only at 6 hours after the dose.

Exercise-induced increases in heart rate were blunted by 50 mg: Onset of effect was at 1 hour. Emax was at 2 hours (-20 beats per minute compared to placebo). After 8 hours, there was no effect when compared to placebo.

Exercise-induced increases in heart rate were blunted by 100 mg: Onset of effect was at 1 hour. Emax was at 2 hours (-29 beats per minute compared to placebo). When compared to placebo, decreases in heart rate were present 24 hours after the dose.

Exercise-induced increases in heart rate were blunted by 200 mg: Onset of effect was at 1 hour. Emax was at 2 hours (-40 beats per minute compared to placebo). When compared to baseline, decreases in heart rate were present 24 hours after the dose.

There are no tables or figures demonstrating an attempt to correlate plasma concentrations of carvedilol with hemodynamic variables.

PK parameters for carvedilol are in table 18 (attached).

Subject 5 tolerated doses of carvedilol up to 800 mg. When compared to the other subjects, subject 5 had the lowest AUCs for the 50, 100, and 200 mg doses.

Adverse events: There were no deaths nor withdrawals.

Treatment emergent symptoms and signs were

headache 5/6

nausea 3/6

vomit 1/6

orthostatic faintness 6/6

Only one subject, subject 5, had prolongation of QTc. His QTc change was from 0.41 on placebo to 0.46 sec on 800 mg.

Conclusions:

In healthy men, single oral doses of carvedilol cause beta blockade by blocking exercise-induced tachycardia.

Carvedilol 50 mg did not significantly effect supine blood pressure. However, carvedilol 50 mg significantly decreased standing and exercising blood pressure. The duration of effect was less than 8 hours.

There appears to be dose-proportionality of AUC for single doses between 50 and 200 mg of oral carvedilol.

Orthostatic hypotension was the dose-limiting side effect that prevented 1 of 6 subjects from tolerating more than 100 mg of carvedilol.

Orthostatic hypotension was the dose-limiting side effect that prevented 4 of 6 subjects from tolerating more than 200 mg of carvedilol.

Concentration-effect relationships were not analyzed.

There was no placebo group with which to compare pharmacodynamic responses for carvedilol doses greater than 100 mg.

Doses of carvedilol less than 100 mg did not have an effect on supine systolic or diastolic blood pressure in this study.

The results of this study must be interpreted in the context of a single dose study in healthy men.

Table 18

Pharmacokinetic parameters.

$$\text{Conc} = -A e^{-bt} + C e^{-dt} + F e^{-gt}$$

	50 mg	100 mg	200 mg.	
A	126.67	255.20	2232.44	
b	3.465	2.524	0.770	
C	104.65	232.07	2154.65	
d	0.361	0.343	0.599	
F	21.92	23.21	47.02	
g	0.067	0.040	0.045	
$t_{1/2}$				
(b)	0.20	0.27	0.88	hours
(d)	1.92	2.02	1.20	hours.
(g)	7.96	14.40	15.40	hours.
Delay	0.331	0.132	0.319	hours.
r_2	0.9597	0.9970	0.9523	
A.U.C.	503.00	1050.09	2060.35	ng/ml . h
Peak Conc.	91.5	146.5	282.3	ng/ml
Time to peak	1.10	1.00	1.07	hours.

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MF 2971
VOL 1.56
000126

Reviewer: James F. Graumlich

MF3132I is a double-blind, placebo-controlled, randomized-sequence, 5-period crossover study in 6 healthy men. The objective was to determine the tolerance, time course and peak effect of single doses of carvedilol 100 mg, labetalol 200 mg, propranolol 160 mg, pindolol 10 mg and placebo. The randomized crossover phase was preceded by measurement of exercise load then exercise training to achieve maximum load in a reproducible manner. During the randomized treatment phase, treatments were separated by at least 5 days. Response endpoints were systolic and diastolic blood pressure in supine and standing positions at rest and during exercise, heart rate PR interval, QT interval, ventricular extra-systoles/min, norepinephrine concentrations, and lab safety tests. Serial observations occurred up to 4 hours after the dose.

Subjects were 6 healthy men (aged 25 - 43 years) who weighed 62.8 - 93.7 kg. Subject #3 withdrew due to a scheduling conflict and another subject replaced Subject #3.

There were four observations of effect at 1, 2, 3, and 4 hours after the dose. The pre-dose baseline measurements appear to be comparable between treatments for the following endpoints: supine and standing SBP, supine and standing DBP, supine and standing pulse, exercise SBP, exercise DBP, exercise pulse, plasma norepinephrine concentration. The time course of the effect is shown in Figures 1 - 4, pages C94-C97. The maximum effect of carvedilol 100 mg occurs at 1 - 2 hours for the following endpoints: supine and standing BP, resting and exercising BP. Propranolol, pindolol, and labetalol served as positive controls. Figure 4 shows little change in pulse over 4 hours of observation for all 5 treatments. Neither the maximum effect of carvedilol 100 mg on pulse nor the time to maximum effect on pulse can be determined from this study.

Figures 7 - 8 (C98, C99) show blood pressure and heart rate 2 hours after the dose and the comparisons to the pre-dose baseline. Carvedilol 100 mg acted like the other beta blockers to block exercise-induced increases in systolic blood pressure and pulse. Carvedilol 100 mg also caused significant decrease in supine SBP but no significant change in supine DBP. The difference of the placebo mean minus the carvedilol mean is 16.6 mm Hg. Carvedilol 100 mg caused significant decrease in orthostatic SBP and DBP. Supine and orthostatic pulse were not affected by carvedilol in this study. As noted in the paragraph above, the observation time may not have been long enough to detect a maximum effect on pulse.

Changes in norepinephrine concentration are shown in Figures 5, 6, and 9 (pages C100-C102). When compared to pre-dose baseline concentrations, carvedilol 100 mg increased norepinephrine concentrations in supine, standing, and exercising subjects. However, when compared to placebo, the increases in norepinephrine concentrations were not significant.

PR and QTc results were not subjected to statistical analysis. There was no trend suggesting treatment-emergent clinically-relevant, prolongation of PR or QTc. There are no tables in the report showing ventricular extra-systoles.

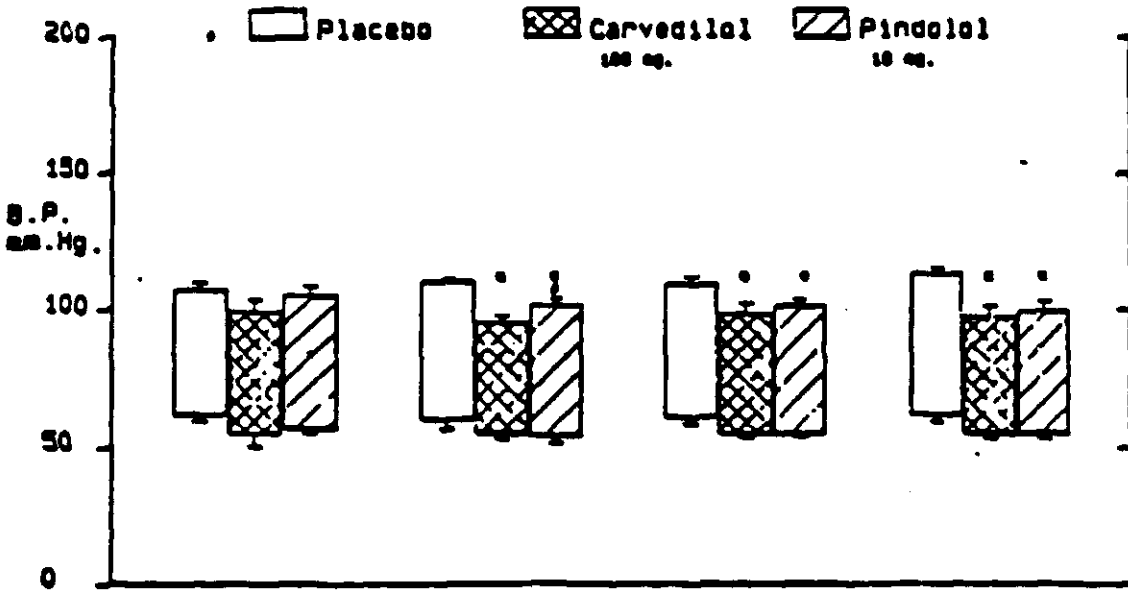
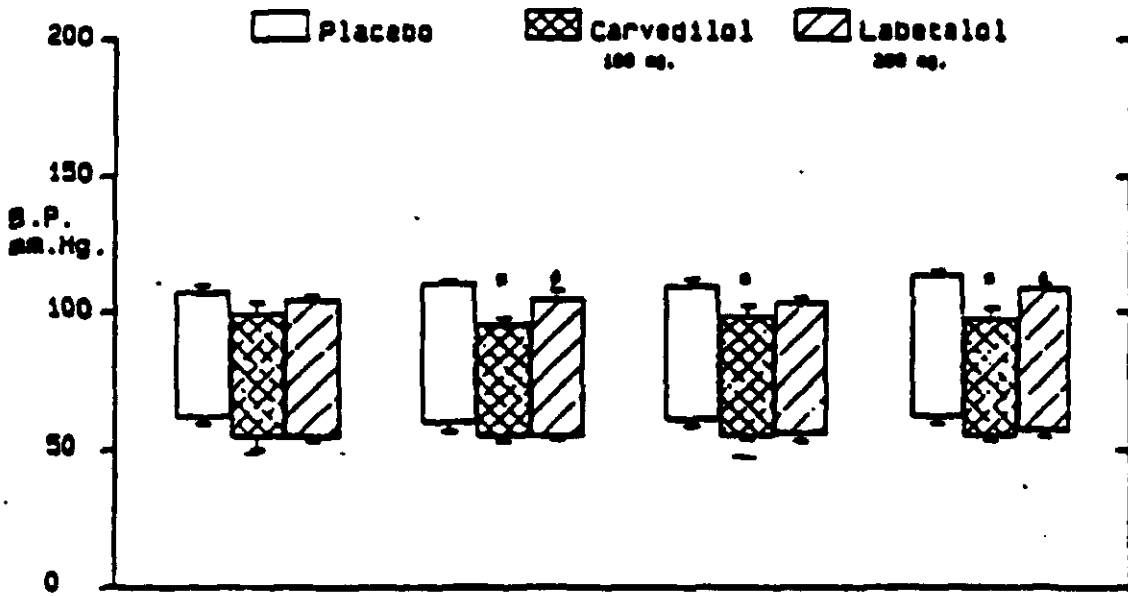
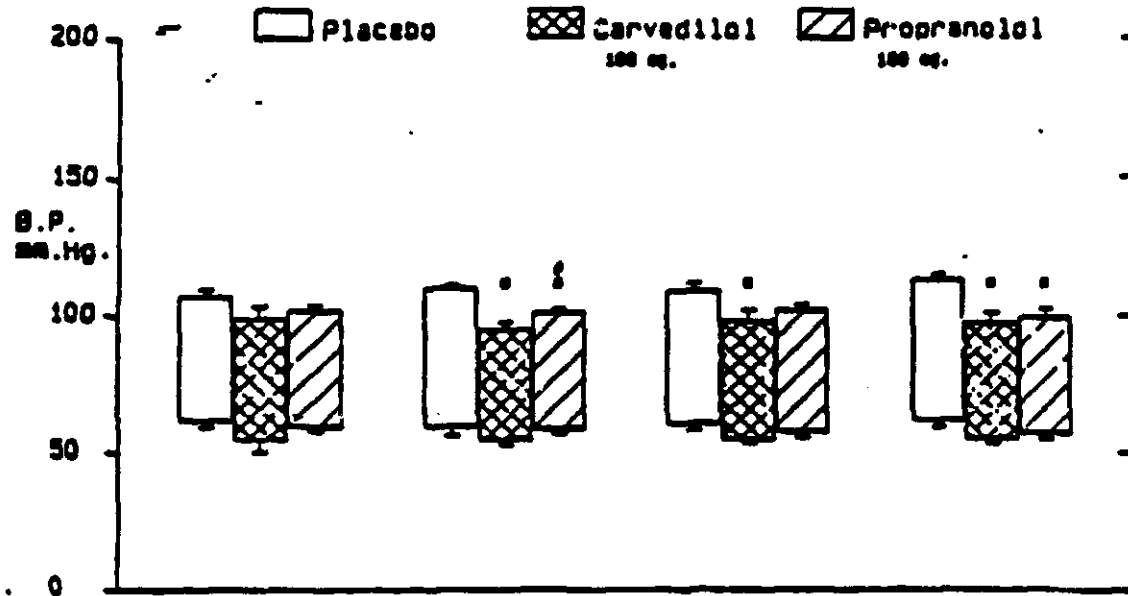
Adverse events: headaches, tiredness, dyspnea on exertion, dreams, faintness on exertion, orthostatic faintness.

Conclusions: The maximum effect of carvedilol 100 mg on SBP and DBP occurs at 1 - 2 hours after the dose. Carvedilol 100 mg acted like the other beta blockers to block exercise-induced increases in systolic blood pressure and pulse. Carvedilol 100 mg also caused significant decrease in supine SBP but no significant change in supine DBP. Carvedilol 100 mg caused significant decrease in orthostatic SBP and DBP. Supine and orthostatic pulse were not affected by carvedilol in this study.

When compared to placebo, increases in norepinephrine concentrations were not significant.

Supine Blood Pressure with Carvedilol compared to Placebo, Propranolol, Labetalol and Pindolol (n=6). M9 - 45

C94

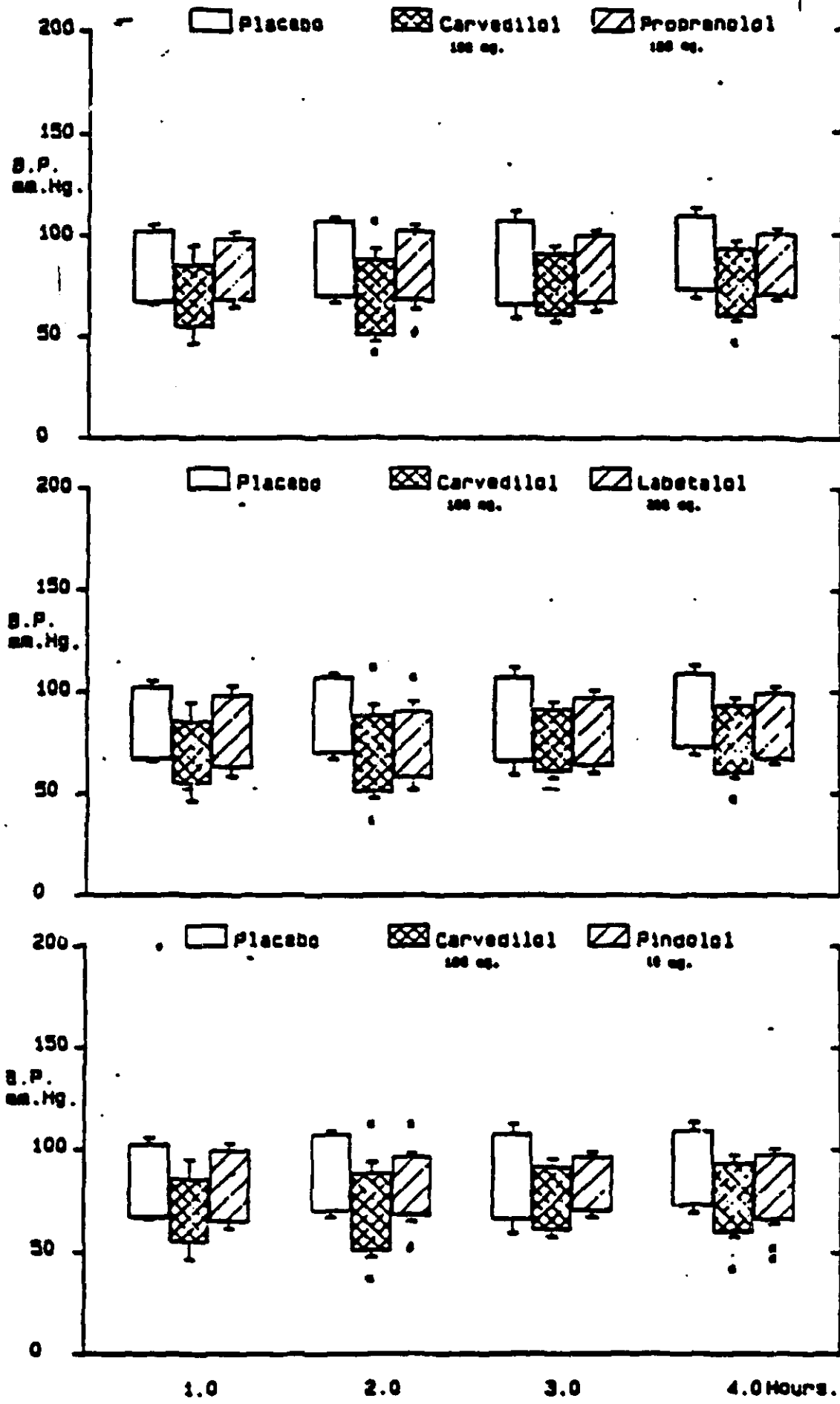


* p < 0.05 compared with Placebo.
 • p < 0.05 compared with Carvedilol.

Figure 2

20
M9 - 45
C95

Erect Blood Pressure with Carvedilol compared to
Placebo, Propranolol, Labetalol and Pindolol (n=6).
except for Car. at 2h. (n=4)



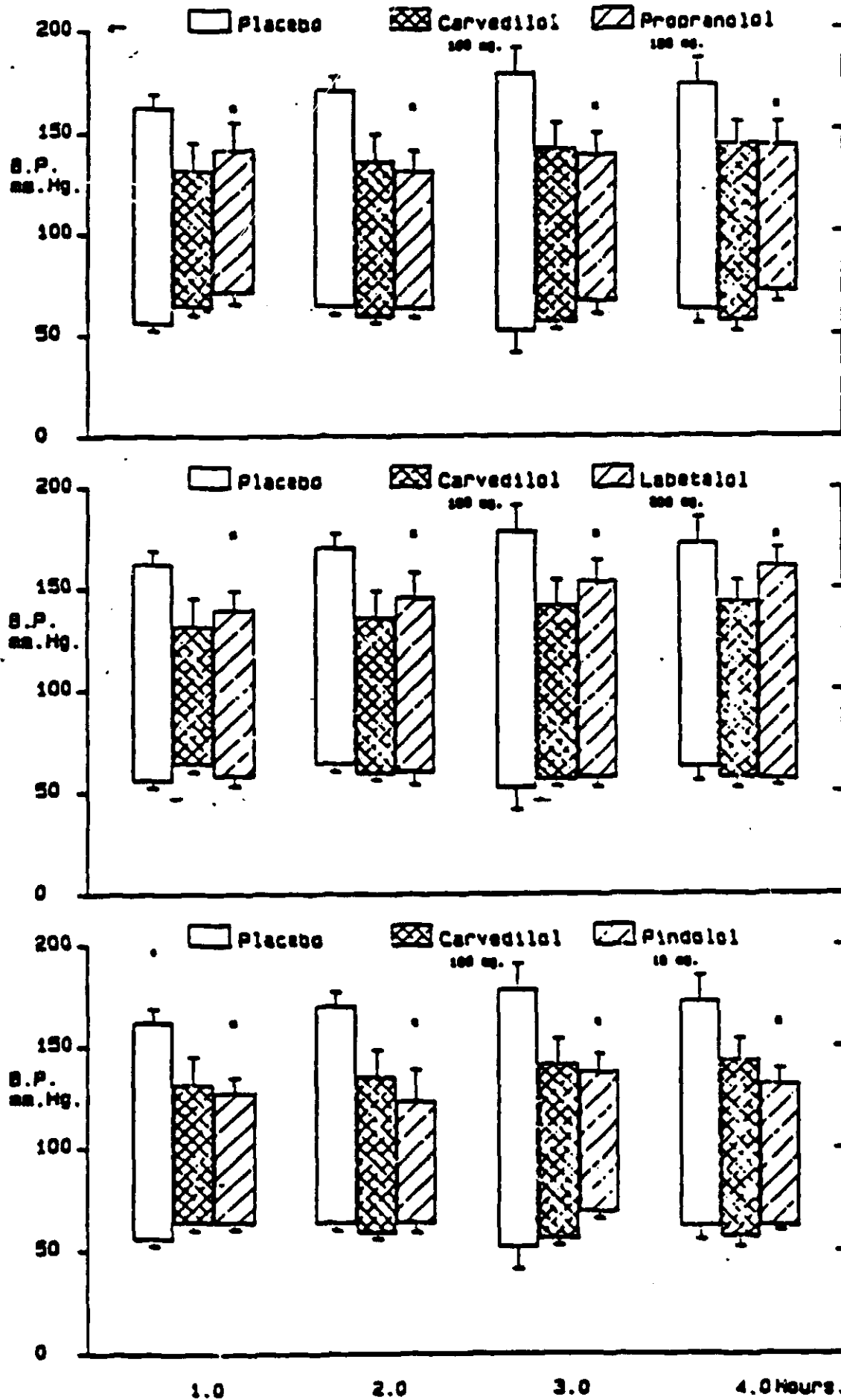
- p < 0.05 compared with Placebo.
- p < 0.05 compared with Carvedilol.

Figure 3

Exercise Blood Pressure with Carvedilol compared to Placebo, Propranolol, Labetalol and Pindolol (n=6).

M9 - 47

C96



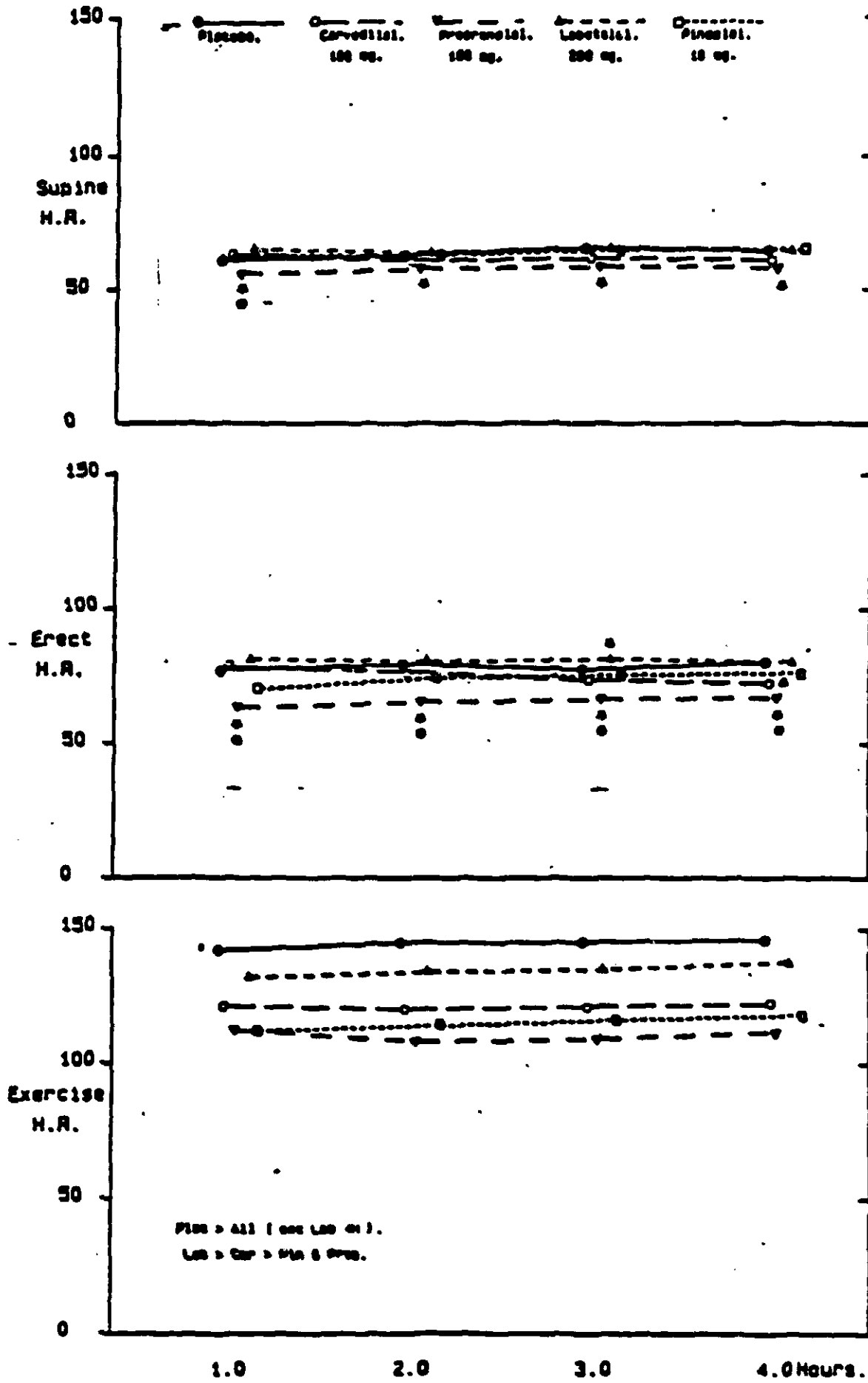
* p < 0.05 compared with Placebo.
 * p < 0.05 compared with Carvedilol.

000050

Figure 1
Heart Rates with Carvedilol compared to Placebo,
Propranolol, Labetalol and Pindolol (n=6).

M9 - 48

C97



Placebo > All (one Labetalol only).
Labetalol > Carvedilol > Pindolol > Propranolol.

○ p < 0.05 compared with Placebo.
● p < 0.05 compared with Carvedilol.

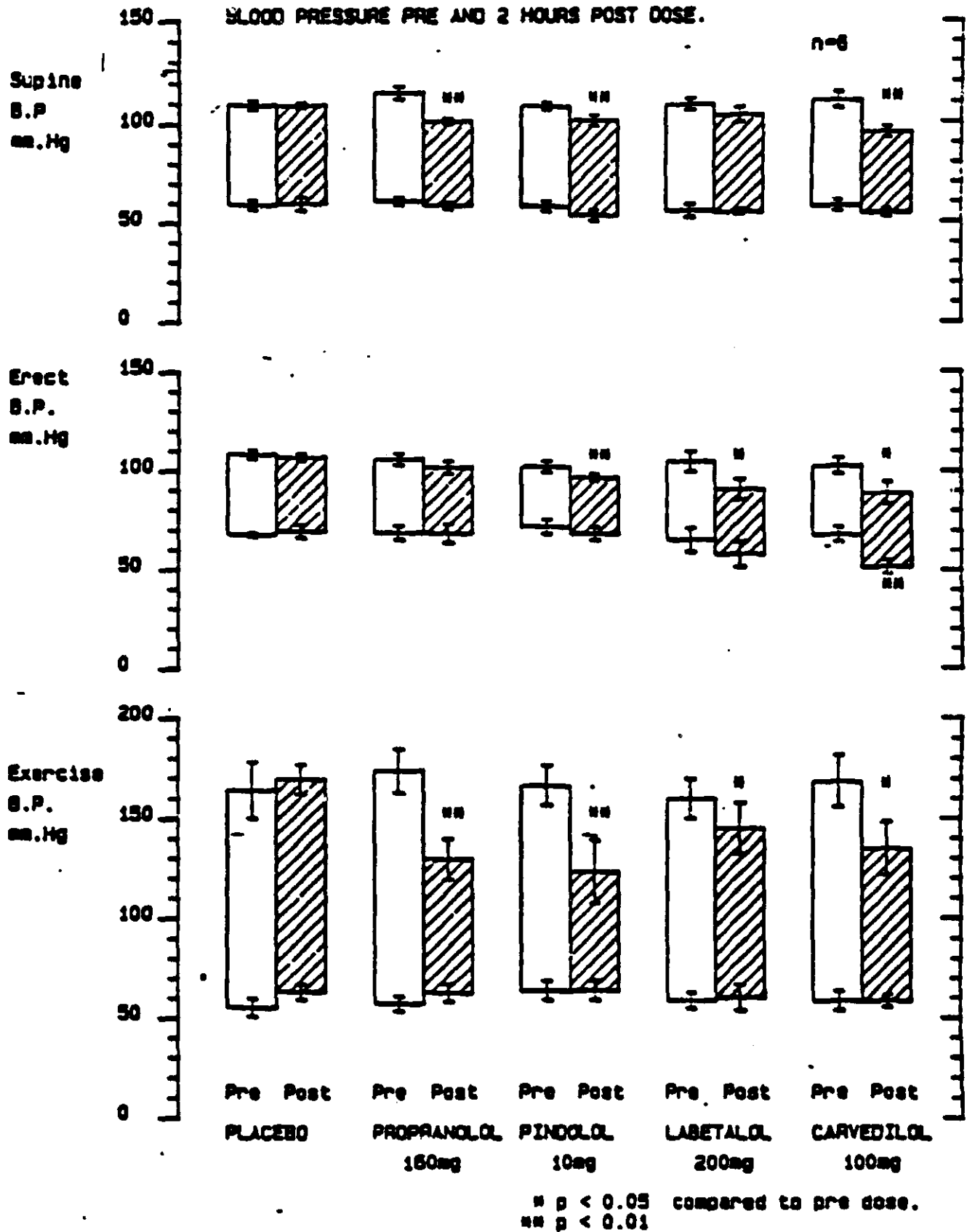
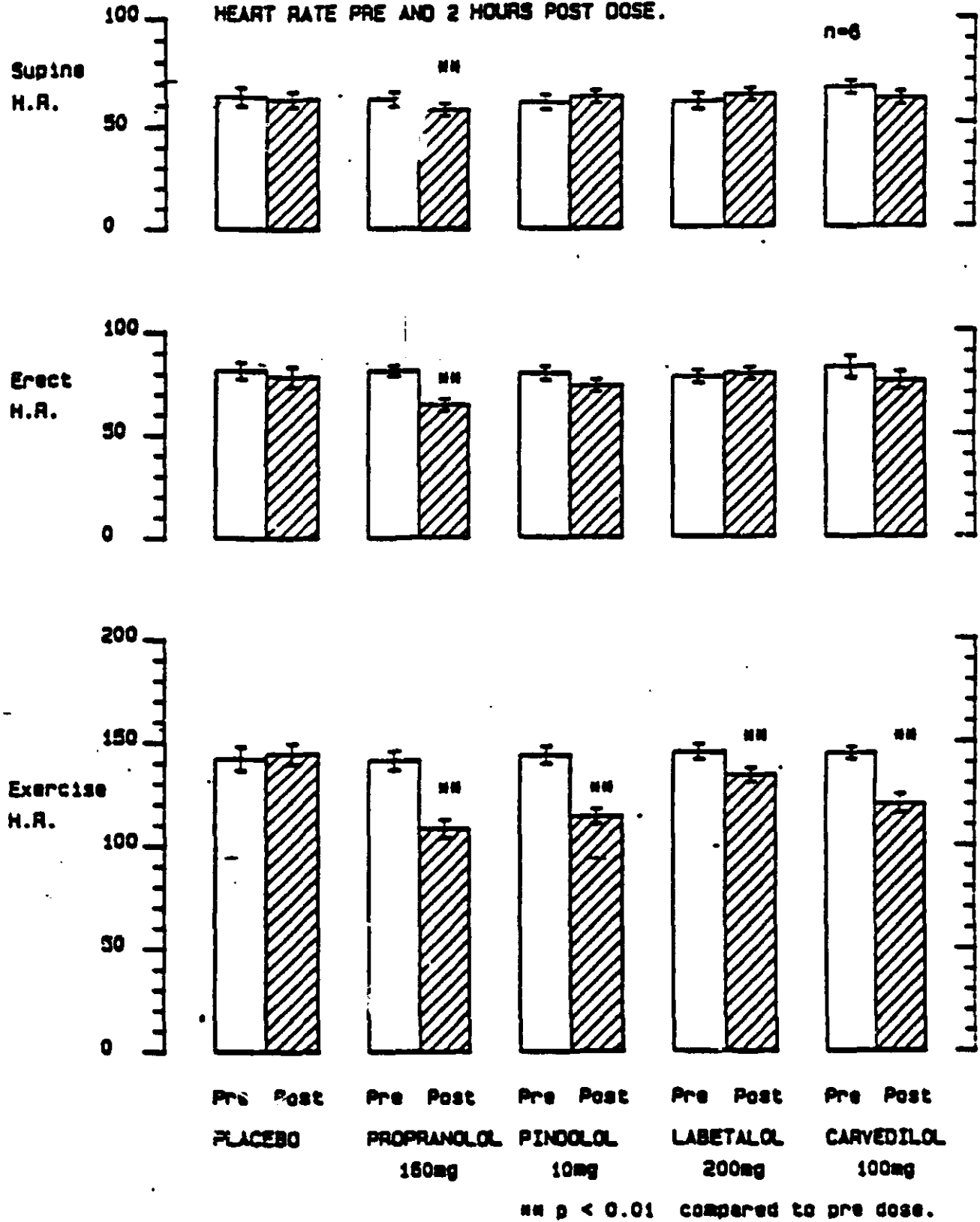


Figure 3

HEART RATE PRE AND 2 HOURS POST DOSE.

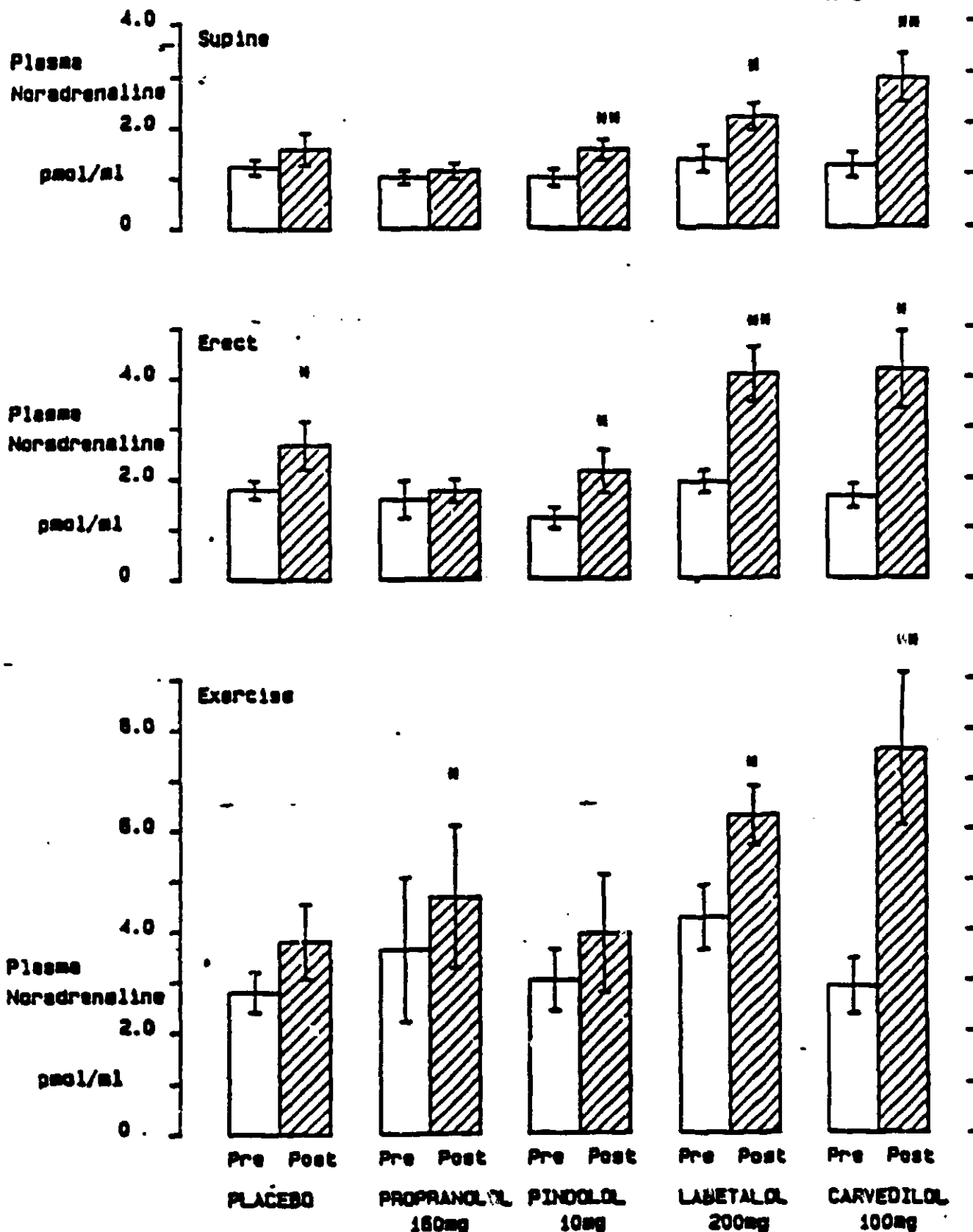
n=6

C99



C100

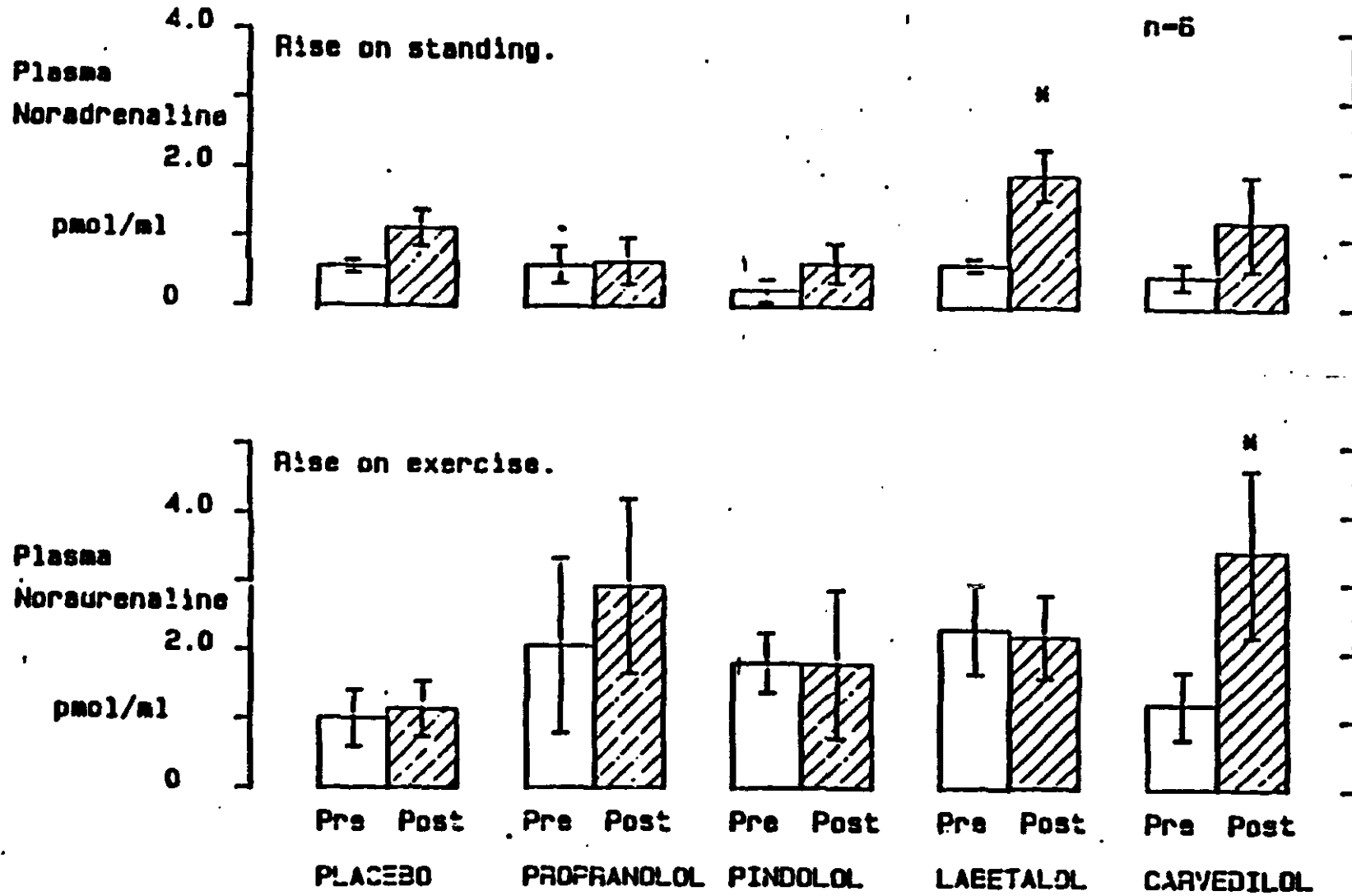
PLASMA NORADRENALINE LEVELS PRE AND 2 HOURS POST DOSE. n=8



* p < 0.05 compared to pre dose.
 ** p < 0.01

Figure 6

CHANGE IN NORADRENALINE LEVELS WITH STANDING AND EXERCISE.



* p < 0.05 compared to pre dose.

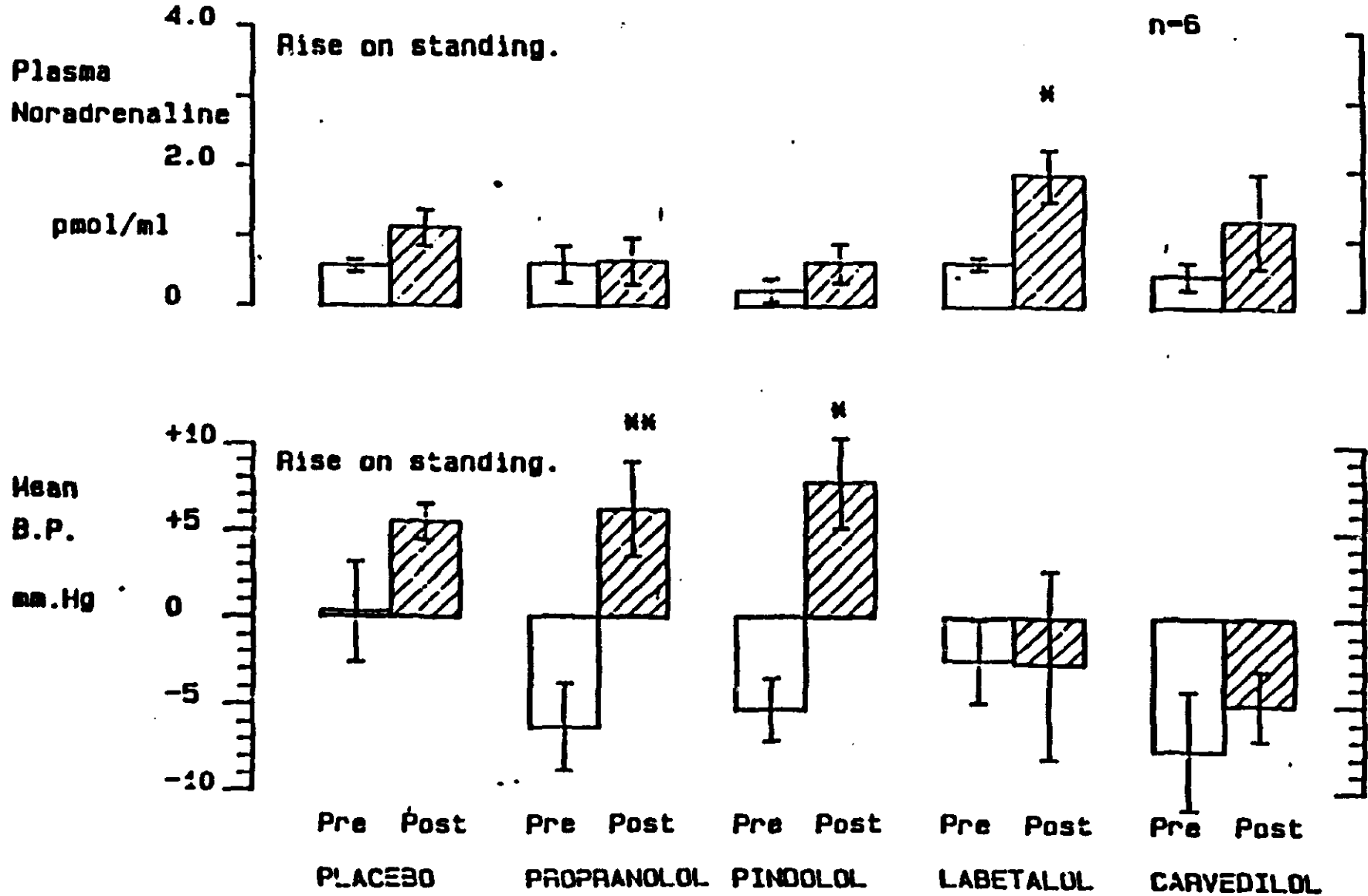
000053

M9 - 53

C101

Figure 9

CHANGE IN NORADRENALINE AND MEAN BLOOD PRESSURE LEVELS WITH STANDING.



* p < 0.05 compared to pre dose.
 ** p < 0.01

000056

M9 - 53

C102

CARVEDILOL NDA 20-297

PROTOCOL MF3132II VOL. 1.125

Reviewer: James F. Graumlich

MF3132II is a double-blind, placebo-controlled, randomized-sequence, 2-treatment crossover study of carvedilol 100 mg single dose po and placebo single dose po. This study has the same design and endpoints as MF3132I with the following exceptions: there were only 2 treatments, subjects were a different set of 6 healthy men (aged 20 - 42 years with weights 69.6 - 82.4 kg).

The report displays results for the six subjects in MF3132II by themselves. The report also displays the results of the six subjects in MF3132II combined with the 6 subjects in MF3132I who received carvedilol 100 mg and placebo. Table 9.C from page 35, volume 1.125 shows the results of the 12 subjects from the combined trials. I believe combining the trials is appropriate because I do not perceive systematic biases with regard to the conduct of the two trials.

During the 4 hours of observation, the maximum effect of carvedilol occurred 1 - 2 hours after dose administration. When compared to pre-dose baseline and when compared to placebo, carvedilol 100 mg caused the following clinically relevant changes:

decreased	increased	no significant change
sup SBP		sup DBP
sup HR		
stand SBP		
stand DBP		
stand HR		
ex SBP		ex DBP
ex HR		

Abbreviations: sup = supine, ex = exercise, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate.

PR and QTc results were not subjected to statistical analysis. There was no trend suggesting treatment-emergent, clinically-relevant, prolongation of PR or QTc. There are no tables in the report showing ventricular extra-systoles.

Adverse events: 4 of 6 had orthostatic faintness that prevented completion of exercise at one or more time points. Other complaints included dreams, nausea, dyspnea on exertion, headaches, lack of energy, difficulty concentrating, dry mouth, visual disturbance, myalgia, palpitation. There were no clinically relevant laboratory safety abnormalities.

Conclusions: In healthy men, carvedilol 100 mg po acted as a beta blocker to block exercise-induced increases in systolic blood pressure and heart rate.

TABLE 9.C
HAEMODYNAMICS NH4.190 100mg v PLACEBO
ALL SUBJECTS (n=12)

SUBJECTS 1-6,11-16.

	Time	SYSTOLIC PRESSURE						DIASTOLIC PRESSURE						HEART RATE					
		PLACEBO			NH4.190 100mg			PLACEBO		NH4.190 100mg		PLACEBO		NH4.190 100mg		PLACEBO		NH4.190 100mg	
		Mean	sd	p	Mean	sd	p	Mean	sd	p	Mean	sd	p	Mean	sd	p	Mean	sd	p
SUPINE	-45m	111.3	2.4		109.7	2.0		59.6	2.0		57.2	2.3		60.8	2.3		63.7	2.1	
	-15m	106.7	1.9		108.4	2.0		58.3	2.4		57.6	1.9		58.0	3.1		61.8	2.3	
	+ 1h	107.4	1.9		98.8	2.3**		62.3	1.8		55.0	2.5		59.2	1.9		60.8	1.8	
	+ 2h	110.1	2.0		93.3	2.0**		60.8	2.4		55.4	1.2		60.7	2.1		57.3	2.0**	
	+ 3h	108.4	2.3		94.2	2.5**		61.7	1.7		54.2	1.3		62.3	2.6		58.2	2.2**	
	+ 4h	111.2	1.8		94.9	2.3**		62.8	1.9		53.9	1.6		61.3	1.9		57.0	2.1**	
ANOVA/LSD(83)		p<.0001/8.4						p<.02/8.8						p<.01/8.7					
ERECT +1	-45m	108.3	2.0		106.6	3.1		68.2	1.8		71.3	2.3		78.3	3.0		78.3	3.2	
	-15m	102.1	2.7		104.8	3.9		63.1	2.6		69.1	2.6		80.5	2.7		81.0	2.7	
	+ 1h	108.4	2.6		89.8	3.7*		72.3	3.7		57.6	3.8**		74.4	2.6		76.0	3.0	
	+ 2h	114.2	1.5*		87.3	4.0**		70.7	2.9		59.2	2.6**		73.0	3.0		74.3	3.9	
	+ 3h	106.1	3.0		91.4	2.7**		69.0	3.1		57.0	2.3**		75.8	2.4		69.3	3.3*	
	+ 4h	110.6	2.2		95.2	2.5**		75.2	2.4**		61.5	2.6**		76.8	2.9		70.3	2.8*	
ANOVA/LSD(83)		p<.0001/8.7						p<.0001/8.8						p<.02/8.1					
ERECT +2	-45m	108.3	1.7		109.4	3.9		70.6	1.8		72.7	2.2		77.5	3.4		77.3	3.1	
	-15m	107.3	2.0		104.2	2.6		69.1	2.4		70.8	2.9		79.3	2.3		80.7	3.6	
	+ 1h	107.0	2.9		90.7	3.8*		72.6	2.9		59.6	5.0*		76.3	2.7		75.1	3.2	
	+ 2h	109.2	2.4		88.1	4.2**		71.8	2.6		59.0	2.8**		77.3	2.8		71.1	3.7	
	+ 3h	109.0	2.8		87.0	4.4**		70.9	3.8		58.0	3.1*		76.8	1.9		68.4	3.8*	
	+ 4h	109.8	2.2		93.3	2.9**		75.2	2.4		61.9	2.0**		77.4	2.4		69.7	2.7*	
ANOVA/LSD(83)		p<.0001/11.1						p<.0001/8.6						p<.02/7.3					
PRE EX	-45m	108.9	2.2		110.1	3.1		68.1	1.8		68.7	2.6		73.3	2.6		73.8	2.6	
	-15m	107.9	2.5		104.7	2.4		71.8	2.4		68.9	2.6		76.0	2.6		78.0	2.9	
	+ 1h	107.1	2.3		94.3	3.6*		69.3	2.6		59.4	3.5**		71.3	2.3		74.5	2.4	
	+ 2h	112.1	2.6		85.4	3.8**		71.3	2.3		55.3	3.3**		74.6	2.2		71.9	3.2	
	+ 3h	109.9	3.8		89.3	3.8**		67.3	4.6		57.6	3.5*		73.1	2.2		69.7	2.4	
	+ 4h	111.0	3.5		95.9	2.7**		69.8	3.0		61.7	2.4*		74.2	2.8		69.0	2.6	
ANOVA/LSD(83)		p<.0001/8.4						p<.02/8.0						p<.02/8.0					
EX LOAD 1	-45m	141.6	4.8		140.8	7.7		56.1	3.6		57.8	4.6		118.2	3.5		116.8	2.8	
	-15m	141.9	6.3		138.3	6.7		61.2	4.2		60.9	4.3		118.4	4.0		119.7	2.6	
	+ 1h	139.2	4.6		103.3	7.9**		56.3	6.8		57.1	4.4		116.7	3.4		101.7	3.4**	
	+ 2h	144.8	4.7		103.7	6.3**		58.3	6.3		54.6	4.2		117.8	3.4		104.4	2.9**	
	+ 3h	146.6	7.9		108.2	7.0**		54.1	6.9		54.1	4.0		120.8	3.4		100.9	2.8**	
	+ 4h	148.8	6.5		117.3	5.4**		56.3	6.4		56.1	4.4		120.2	3.4		103.1	2.3**	
ANOVA/LSD(83)		p<.0001/18.1						p=.33/18						p<.0001/8.8					
EX LOAD 2	-45m	165.7	5.2		171.7	6.5		55.6	8.0		59.0	5.9		139.4	3.8		139.9	3.0	
	-15m	163.3	7.3		166.0	6.9		57.4	7.3		58.6	5.9		139.7	3.9		141.3	2.9	
	+ 1h	166.2	6.1		131.7	8.4**		54.9	7.2		64.3	4.6		138.2	3.7		118.3	3.2**	
	+ 2h	170.1	4.8		133.6	8.4**		58.8	6.8		61.9	4.1		140.6	3.3		117.7	2.9**	
	+ 3h	170.1	8.6		136.7	8.3**		51.0	8.8		61.3	5.4		140.9	3.5		117.1	2.9**	
	+ 4h	172.6	7.1		137.3	7.4**		60.9	7.6		57.3	3.7		142.0	3.6		118.2	2.9**	
ANOVA/LSD(83)		p<.0001/11.8						p=.28/18						p<.0001/4.7					
POST EX	-45m	141.3	5.2		144.0	5.5		51.7	2.8		59.0	3.5		103.6	5.9		104.4	4.2	
	-15m	142.6	5.1		139.3	5.8		52.3	3.2		54.7	3.1		103.6	6.5		104.2	5.8	
	+ 1h	141.3	5.3		112.9	7.6**		53.9	3.9		53.4	3.7		97.8	6.8		93.9	3.9*	
	+ 2h	145.3	4.3		110.1	7.0**		59.8	1.9**		51.4	3.3		99.3	6.2		88.2	4.0**	
	+ 3h	147.8	7.4		117.9	6.0**		55.8	4.0		50.0	2.8		100.2	6.3		87.5	4.1**	
	+ 4h	144.4	6.8		120.3	6.6**		56.3	3.2		50.2	4.6		101.3	5.6		86.3	3.8**	
ANOVA/LSD(83)		p<.0001/13.3						p<.02/8.9						p<.0001/7.8					

* n=9 - n=10 - n=11
Significant changes v. both pre values.
v. placebo.

p<.05 CO.01
* **

CARVEDILOL NDA 20-297

PROTOCOL MF3223.I and MF3223.II VOL 1.125

Reviewer: James F. Graumlich

MF3223.I is a double-blind, placebo-controlled, randomized-sequence, 18-period crossover study of healthy men. The treatments were carvedilol 12.5 mg, 25 mg, 50 mg, 100 mg, 200 mg; labetalol 50 mg, 100 mg, 200 mg, 400 mg; propranolol 40 mg, 80 mg, 160 mg, 320 mg; pindolol 2.5 mg, 5 mg, 10 mg, 20 mg; placebo. Treatments were separated by at least 5 days. Using a bicycle ergometer, subjects were exercised and trained to a standardized workload. Blood samples for PK were collected but not reported. Other endpoints were blood pressure and pulse at rest, during exercise, and after exercise. Endpoints were measured pre-dose then 1 and 2 hours after the dose. The same six healthy men studied in MF3132.I participated in MF3223.I (ages 25 - 43, weights 62.8 - 93.7). Subject #3 had an elevation of alkaline phosphatase up to 494 noted at treatment 7 (placebo) after receiving pindolol (various doses), carvedilol 100 mg, and labetalol (various doses) during treatments 1 - 6. In Subject #3, ALT rose from 46 to 113, ALT rose from 35 to 212, gamma GT rose from 17 to 28. The crossover design makes it difficult to determine which one of 5 drugs was associated with the LFT abnormalities.

MF3223.II is a double-blind, placebo-controlled, randomized-sequence, 6-period crossover study in 6 healthy men. The design was similar to MF3223.I with the following exception: the treatments were carvedilol 12.5 mg, 25 mg, 50 mg, 100 mg, 200 mg and placebo. The six healthy men in MF3223.II are the same subjects who participated in MF3132.II (ages 20 - 42 and weights 69.6 - 82.4 kg).

Results: Tables 10.1 and 10.2 (pages C106-C107) show results for MF3223.I only. Propranolol, pindolol, and labetalol served as positive controls by blocking exercise-induced increases in pulse and systolic blood pressure.

It appears to be reasonable to combine the results of MF3223.I and MF3223.II when looking at the effects of carvedilol 12.5 mg, 25 mg, 50 mg, 100 mg, 200 mg and placebo (see Table 9.0, page C108). All doses of carvedilol caused significant reduction in exercise-induced increases in systolic blood pressure and pulse. There are trends showing a dose-response relationship for systolic blood pressure and pulse.

Adverse events were discussed in the reports for MF3132.I and MF3132.II.

Conclusions: In these healthy men, carvedilol doses from 12.5 mg to 200 mg showed beta blocker effects on exercise-induced changes in systolic blood pressure and pulse.

TABLE 10.1

	% Reduction in Exercise Heart Rate				Mean Exercise Tachycardia				% Inhibition of Exercise Tachycardia			
	+1H		+2H		+1H		+2H		+1H		+2H	
PLACEBO					67.3	3.9	69.5	3.9				
CAR12.5	-0.6	1.7	5.4	-1.6	64.7	5.2	56.0	3.4	4.3	3.6	19.2	2.8
25	0.5	1.3	6.3	2.8	64.5	4.0	58.8	5.7	4.1	4.5	15.6	5.6
50	2.2	2.7	7.3	2.1	64.3	5.5	59.2	5.7	4.9	4.5	15.6	3.8
100	7.1	2.9	13.9	2.3	55.7	6.9	51.7	7.0	18.6	6.5	26.9	6.0
200	5.3	3.7	14.4	2.1	55.5	5.8	45.7	3.8	17.5	7.7	33.3	7.0
PROP 40	11.5	2.2	15.0	1.9	56.7	2.8	55.7	2.4	15.0	5.7	19.4	2.5
80	15.7	1.0	18.7	1.0	52.0	3.7	48.7	2.6	22.3	4.9	29.1	4.9
160	17.7	2.2	19.3	3.1	51.0	4.3	50.8	3.6	23.3	7.3	25.5	7.7
320*	20.7	4.2	26.0	1.5	47.2	3.2	38.6	0.5	26.9	3.9	41.4	3.6
PIN 2.5	10.4	3.4	17.2	1.5	56.3	5.1	46.0	2.3	16.8	4.5	33.3	3.4
5	18.4	0.8	18.4	1.4	52.2	3.0	50.2	2.8	22.2	2.6	27.4	3.4
10	18.5	1.1	19.3	1.5	47.7	2.1	48.3	3.1	28.9	1.2	30.5	1.7
20	20.8	1.4	20.4	1.5	45.3	2.8	45.3	3.0	32.7	1.5	34.8	1.4
LAB 50	5.1	4.6	-1.8	1.9	59.7	5.5	67.5	3.6	10.0	8.7	2.5	3.8
100	1.6	1.9	3.5	1.1	63.0	5.1	60.3	2.9	6.9	4.0	12.7	3.4
200	7.9	3.3	5.7	1.4	54.7	4.4	56.7	2.8	18.2	6.1	17.8	4.4
400	10.0	1.2	12.5	1.2	55.5	4.1	49.8	1.5	17.3	5.3	27.6	3.1
Anova F	<0.0001		<0.0001		<0.0001		<0.0001		<0.0001		<0.0001	
L.S.D (5%)	7.5		5.2		9.6		8.1		14.4		11.9	
n=5												

000044

M9 - 41

C106

TABLE 10.2

	Mean Rise in EXERCISE Systolic Blood Pressure				% Reduction in Exercise Systolic B.P.				% Reduction in Exercise Double Product.			
	+1H		+2H		+1H		+2H		+1H		+2H	
PLACEBO	70.0	5.2	65.7	6.2								
CAR12.5	59.8	9.4	56.7	11.0	8.5	2.0	8.2	4.8	7.9	2.8	12.9	5.3
25	54.3	8.7	54.8	9.6	10.6	5.8	11.4	4.2	10.8	6.6	16.7	5.7
50	51.2	6.8	48.3	8.3	12.4	1.8	14.5	3.2	14.2	3.5	20.6	3.9
100	47.8	9.9	45.2	7.8	20.6	3.0	25.1	3.2	26.1	3.8	35.3	4.0
200	53.7	10.9	47.0	7.1	12.3	3.9	20.5	3.4	16.5	6.1	31.8	4.0
PROP 40	48.2	9.0	42.3	6.4	14.0	3.1	17.3	2.6	23.5	4.7	29.6	3.1
80	39.7	6.5	44.0	7.2	18.6	2.3	16.2	3.7	31.3	2.3	31.9	3.3
160	39.7	7.7	31.8	6.5	16.8	2.0	21.9	2.6	31.4	3.4	36.7	4.3
320*	31.6	8.0	17.2	13.2	24.4	2.1	32.1	6.5	39.8	4.6	49.7	4.9
PIN 2.5	48.3	5.1	41.5	7.7	12.7	0.8	17.8	3.3	21.7	3.4	32.1	2.4
5	34.2	5.5	44.7	10.5	22.1	3.3	18.9	4.6	36.5	2.8	33.9	3.4
10	38.3	6.0	40.2	4.3	20.5	1.0	18.6	1.1	35.2	1.5	34.3	1.0
20	38.8	7.3	42.8	6.9	21.2	1.7	19.9	2.4	37.7	1.4	36.4	1.9
LAD 50	53.8	9.0	64.8	10.2	10.8	4.1	2.2	3.7	15.3	5.9	0.4	4.2
100	58.3	7.9	50.5	9.8	7.6	1.8	12.9	4.5	9.1	2.8	15.9	4.5
200	49.5	10.5	54.5	10.2	11.0	3.6	11.8	5.9	17.6	5.9	16.6	6.2
400	39.7	10.7	44.5	10.4	17.4	4.0	16.9	4.5	25.4	4.4	27.1	4.6
Anova F	<0.0001		<0.0001		<0.0001		<0.0001		<0.0001		<0.0001	
L.S.D. (5%)	14.3		12.5		8.4		7.0		12.1		9.3	
n=5												

000045

M9 - 42

C107

TABLE 9.0
 HAEMODYNAMICS - COSE RESPONSE AT 1 & 2h.
 ALL SUBJECTS (n=12)

SUBJECTS 1-6.11-10

		SYSTOLIC PRESSURE						DIASTOLIC PRESSURE						HEART RATE					
		MOON		SO		D		MOON		SO		D		MOON		SO		D	
		MOON	SO	MOON	SO	D	MOON	SO	D	MOON	SO	D	MOON	SO	D	MOON	SO	D	
SUPINE																			
	PLACEBO	109.3	3.4	111.7	2.8	A	58.0	3.1	58.4	2.1	A	58.4	2.1	58.8	1.8	40			
	BM 12.5	109.3	2.1	105.8	3.7	AB	56.6	3.6	54.8	2.7	BC	58.3	2.2	59.8	2.1	40			
	25	108.3	3.3	104.3	3.3	B	57.2	3.4	58.8	2.3	AB	60.3	2.1	58.8	1.8	A			
	50	103.7	2.8	101.9	2.4	BC	53.3	3.3	53.1	1.9	ABC	58.1	1.3	57.3	1.4	A			
	100	99.1	2.8	97.0	3.8	C	53.9	2.2	53.7	2.8	BC	58.3	1.6	58.4	1.8	A			
	200	104.2	3.9	96.9	3.3	C	54.3	2.3	51.8	2.5	C	58.3	1.4	61.3	1.8	B			
	ANOVA/LSD	0.003/3.1			0.0001/4.7			0.37/MS			0.02/4.3			0.31/MS			0.11/MS		
ERECT +1																			
	PLACEBO	118.9	4.0	112.7	3.8	A	72.3	2.3	78.4	1.6	A	78.2	2.2	72.3	2.3	A			
	BM 12.5	104.8	2.6	109.8	3.8	B	72.4	3.3	68.8	3.5	AB	78.6	3.4	73.7	2.8	AB			
	25	108.8	3.2	108.4	2.7	B	72.4	2.3	68.3	3.8	AB	79.2	2.5	77.4	2.4	B			
	50	102.7	3.3	97.6	2.1	BC	68.7	8.4	67.7	1.7	AB	73.2	2.8	72.4	2.5	A			
	100	94.9	3.5	94.8	3.4	C	62.7	2.8	64.3	1.9	BC	72.9	2.4	73.8	2.3	AB			
	200	98.1	4.1	98.3	5.2	C	104.3	3.0	99.8	3.3	C	77.6	2.8	73.3	2.3	AB			
	ANOVA/LSD	0.0001/8.2			0.0001/7.6			0.0001/4.8			0.01/3.8			0.02/3.8			0.14/MS		
ERECT +2																			
	PLACEBO	109.4	3.7	109.7	2.4	A	72.3	2.2	71.8	2.3	A	73.7	1.9	73.7	2.7	A			
	BM 12.5	103.0	2.9	103.8	4.3	B	72.9	3.8	78.3	3.1	A	77.3	3.4	74.3	3.8	A			
	25	104.2	3.1	103.7	2.7	B	73.5	2.3	79.3	2.4	A	88.4	2.3	78.2	2.7	A			
	50	104.4	2.1	99.3	2.9	B	66.3	6.3	68.8	1.9	A	77.9	2.8	73.3	2.5	A			
	100	79.3	3.8	91.3	2.8	C	64.8	1.8	61.8	1.9	B	76.9	2.3	71.8	2.1	A			
	200	106.8	8.2	92.2	3.7	C	101.1	6.8	99.6	2.9	B	173.4	2.7	173.3	3.1	A			
	ANOVA/LSD	0.003/8.1			0.0001/6.3			0.003/3.3			0.0001/3.6			0.88/MS			0.33/MS		
ERE EX																			
	PLACEBO	112.8	3.2	113.8	3.1	A	78.4	3.3	71.9	2.8	A	68.8	1.9	68.4	1.7	A			
	BM 12.5	108.9	3.3	106.1	4.8	B	72.1	2.8	67.8	3.8	AB	71.4	2.9	71.1	2.3	A			
	25	108.2	3.1	104.3	2.7	B	68.3	3.2	68.3	2.3	AB	72.1	2.2	69.3	2.4	A			
	50	106.3	3.8	102.8	2.9	B	69.7	6.3	63.6	3.8	BC	78.3	2.2	67.8	2.1	A			
	100	107.7	3.3	99.4	2.9	C	102.1	2.9	98.8	2.2	CD	69.7	2.8	66.8	2.8	A			
	200	97.3	4.4	107.7	4.2	C	62.7	4.6	98.3	2.8	B	78.9	2.8	78.1	2.2	A			
	ANOVA/LSD	0.001/7.6			0.0001/7.4			0.18/MS			0.0001/6.7			0.78/MS			0.38/MS		
EX LOAO 1																			
	PLACEBO	148.8	3.7	149.3	3.1	A	83.8	4.8	88.8	4.8	AB	119.3	3.1	113.7	2.6	A			
	BM 12.5	138.7	3.7	133.7	6.1	B	62.9	3.8	68.4	4.2	AB	112.8	2.3	109.8	2.3	B			
	25	134.8	2.8	134.1	8.8	B	62.7	3.8	63.8	3.8	A	122.1	2.8	118.3	3.1	B			
	50	133.7	4.7	123.8	5.1	C	59.7	3.2	67.8	3.3	A	113.6	2.7	108.4	3.8	B			
	100	118.8	6.8	113.4	3.3	B	61.8	3.7	58.7	3.2	AB	101.8	3.3	102.7	3.8	C			
	200	119.8	8.8	104.8	8.8	B	61.8	3.2	58.8	3.8	B	106.4	3.3	101.9	3.1	C			
	ANOVA/LSD	0.0001/18.7			0.0001/9.1			0.87/MS			0.22/MS			0.003/3.8			0.0001/4.4		
EX LOAO 2																			
	PLACEBO	177.8	8.7	179.3	8.3	A	68.7	8.3	62.3	3.8	A	134.7	2.9	137.3	3.8	A			
	BM 12.5	161.8	8.8	138.9	7.8	B	67.9	3.3	63.8	4.3	A	134.7	2.7	127.8	3.2	B			
	25	158.8	7.8	136.3	7.7	BC	63.4	3.3	66.7	4.4	A	133.8	2.9	126.8	3.8	B			
	50	159.4	3.8	147.3	3.7	C	62.3	3.4	61.3	4.2	A	132.8	3.2	123.3	3.8	C			
	100	1138.7	7.2	131.8	3.3	B	104.3	4.7	63.8	4.9	A	123.4	6.2	117.2	3.4	B			
	200	142.3	18.8	133.8	8.8	B	64.1	3.7	66.8	3.2	A	121.8	6.9	115.1	3.1	B			
	ANOVA/LSD	0.0001/11.8			0.0001/9.8			0.37/MS			0.68/MS			0.0001/3.3			0.0001/4.4		
POST EX																			
	PLACEBO	132.8	7.1	133.8	8.3	A	31.4	4.8	33.3	4.8	A	99.8	4.3	98.8	4.9	A			
	BM 12.5	148.8	7.8	137.8	3.8	B	68.9	3.8	34.9	4.8	A	99.8	6.3	98.8	6.8	B			
	25	137.2	7.4	138.9	3.8	C	56.8	3.1	38.2	3.8	A	100.3	4.7	91.2	6.2	B			
	50	133.3	3.2	138.8	3.8	C	48.1	3.9	39.3	2.4	A	108.7	3.8	98.8	3.2	B			
	100	117.3	3.1	115.8	6.9	B	53.3	3.1	32.8	4.4	A	104.9	4.8	92.8	4.3	A			
	200	121.3	8.3	113.3	3.8	B	37.2	3.8	35.9	2.3	A	93.4	3.8	98.3	3.8	B			
	ANOVA/LSD	0.0001/18.8			0.0001/8.1			0.88/MS			0.37/MS			0.24/MS			0.82/6.8		

* p < 0.05

^ p < 0.01

Results in 2h columns with same letter (A-B) are not significantly different (p < 0.05) on paired t-tests of post vs pre.

CARVEDILOL NDA 20-297

PROTOCOL MF3270 VOL 1.125

Reviewer: James F. Graumlich

MF3270 is a single-blind, placebo-controlled, non-randomized, 4-period crossover study of patients with chronic, stable angina pectoris. Angina was reproducible on a treadmill exercise test. Patients with hypertension were not excluded. Wash-out (10 days) preceded the first treatment period. Treatments were placebo bid for 2 weeks, carvedilol 25 mg po bid for 2 weeks, carvedilol 50 mg po bid for 2 weeks, and placebo bid for 2 weeks. At the end of each treatment period, the following endpoints were measured: 24-hour ambulatory ST-segment monitoring, maximal symptom-limited graded treadmill exercise test 2 hours after the dose (ETT), resting and exercising radionuclide MUGA ventriculography.

Results: 20 patients entered the study (15 men and 5 women, mean age 62 years, age range 52 - 72 years, 4 of 20 with previous MI, radionuclide ejection fraction 35 - 67%, 9 of 20 with coronary artery disease documented by angiography). Weights were not reported.

3 patients withdrew during the placebo phase for unstable angina and 2 patients withdrew during the carvedilol 25 mg po bid phase for adverse events (unstable angina, lightheadedness). Details about the withdrawn patients are not in the report. Results are depicted in the attached figures: pages 206 - 212 and 228 - 232 from volume 1.125.

Conclusions:

The study was not adequately blinded so bias may influence results.

None of the tables and figures in the report indicate the sample size used to calculate means.

The maximum total daily dose, 100 mg per day, used in this study is twice the maximum total daily dose recommended in the proposed label.

Carvedilol 25 mg po bid and 50 mg po bid decreased resting heart rate when compared to placebo.

There was no difference between carvedilol 25 mg po bid and 50 mg po bid in maximum, minimum, and mean heart rate measured hourly with holter monitor.

Carvedilol 25 mg po bid and 50 mg po bid blocked exercise-induced increases in heart rate at peak exercise.

Carvedilol 50 mg po bid but not carvedilol 25 mg po bid decreased systolic blood pressure at rest. Carvedilol 50 mg po bid but not carvedilol 25 mg po bid blocked exercise-induced increases in systolic blood pressure at peak exercise.

Carvedilol 25 mg po bid and 50 mg po bid appeared to prolong exercise time and prolong time to 1 mm ST segment depression during ETT.

The maximum number of millimeters of ST depression at each stage of exercise was not significantly influenced by carvedilol.

Carvedilol 25 mg po bid and 50 mg po bid appeared to decrease the rate-pressure product.

Carvedilol 25 mg po bid and 50 mg po bid did not cause significant decreases in exercise EF. There was a trend toward decrease in exercise EF. The power of the study to detect a difference is unknown.

Although carvedilol concentrations were measured, no concentration results were reported.

015- 19

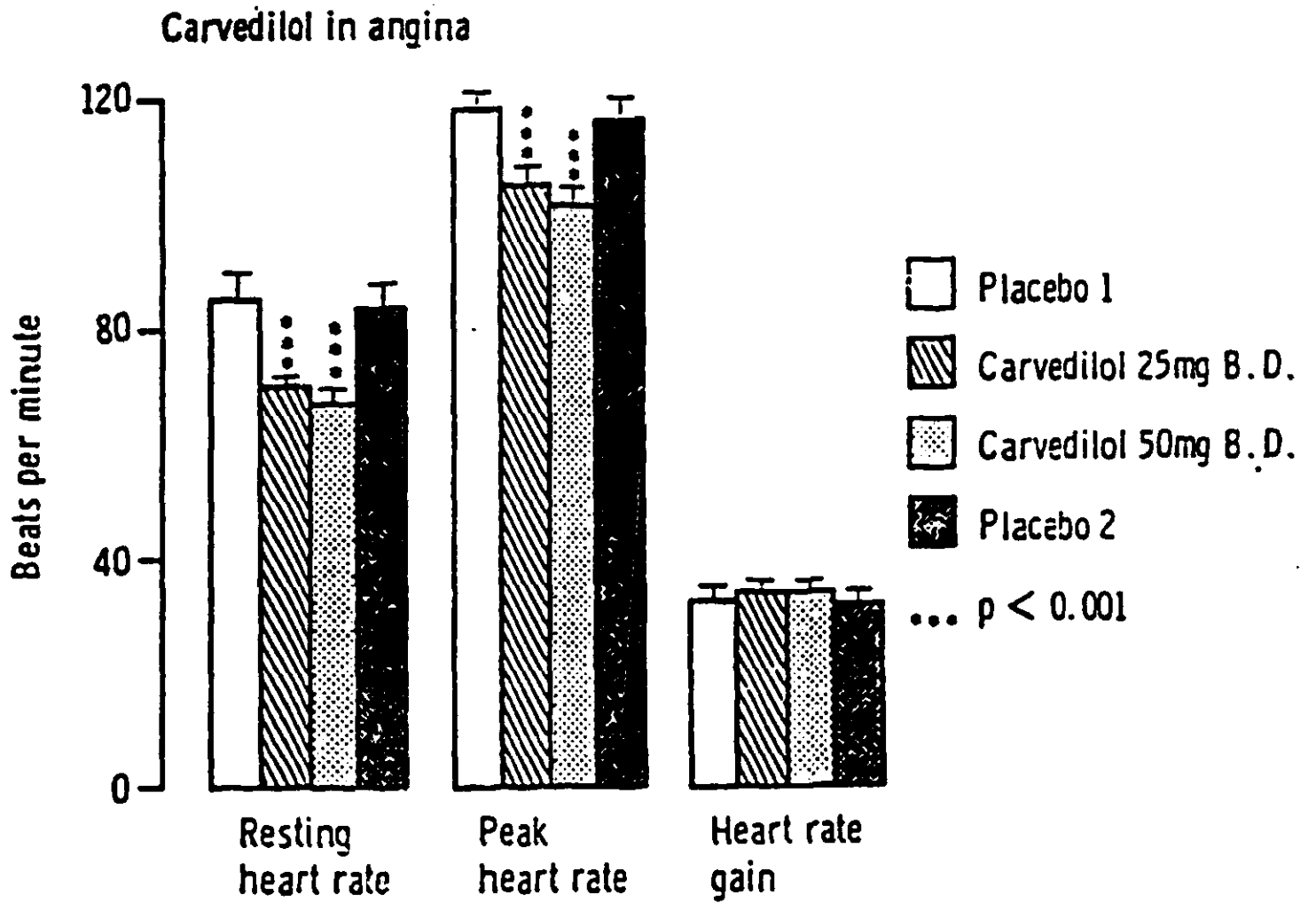


Figure 1 Rest and peak exercise heart rate and exercise heart rate gain on placebo and on Carvedilol.

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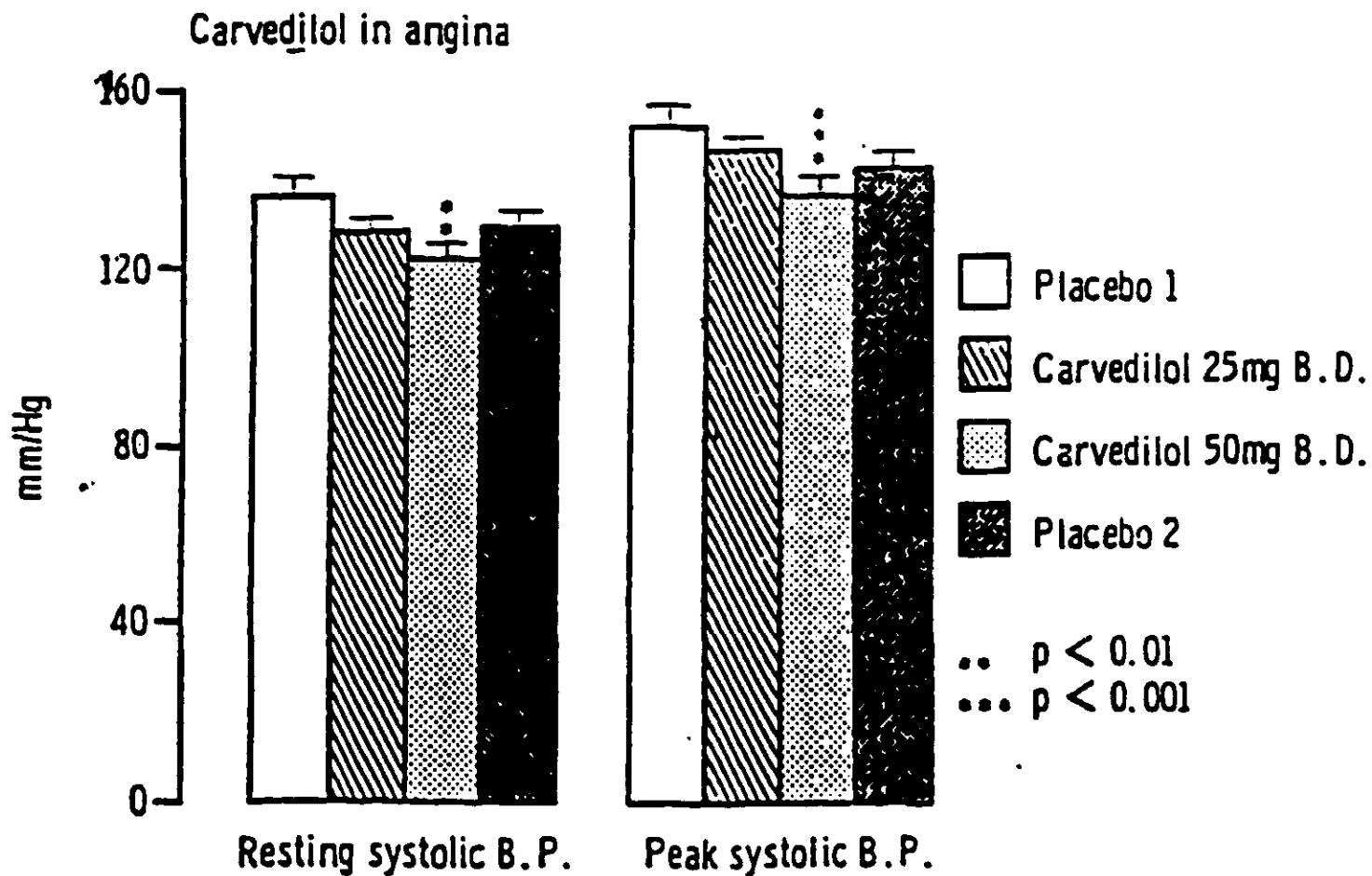


Figure 2 Rest and peak exercise systolic blood pressure on placebo and on Carvedilol.

015- 21

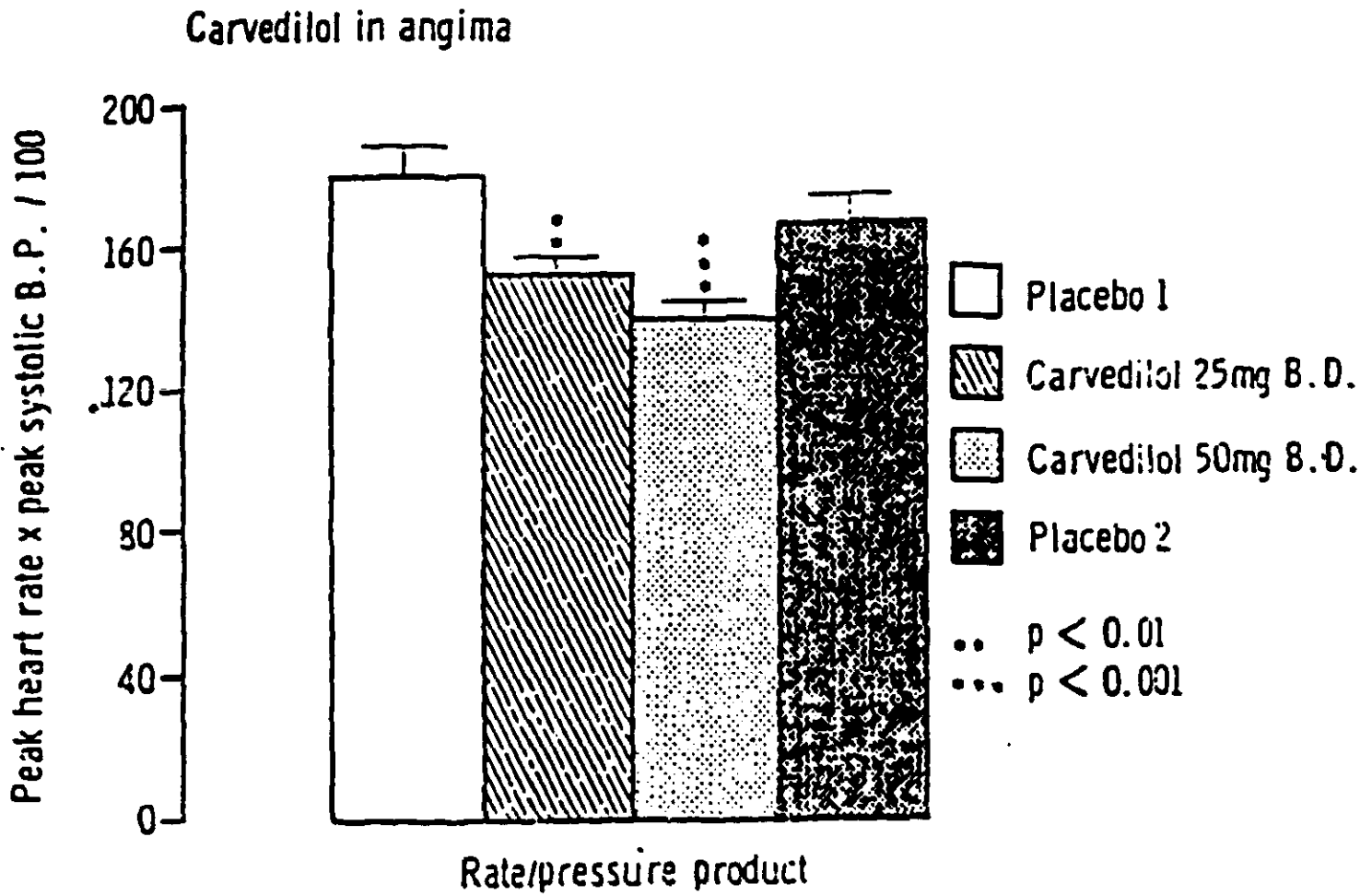


Figure 3 Rate-pressure product on exercise with placebo and Carvedilol.

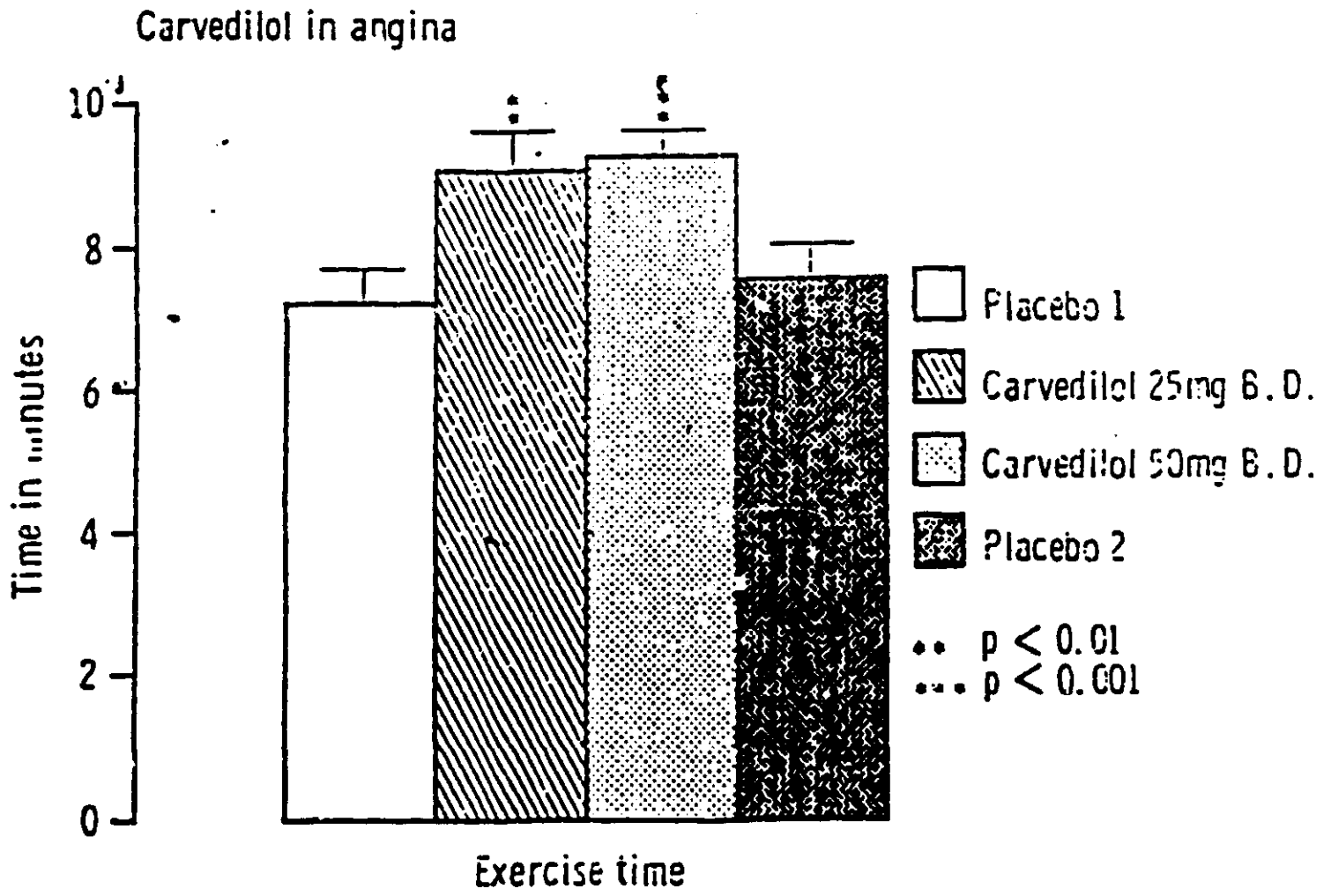


Figure 4 Exercise time on placebo and on Carvedilol.

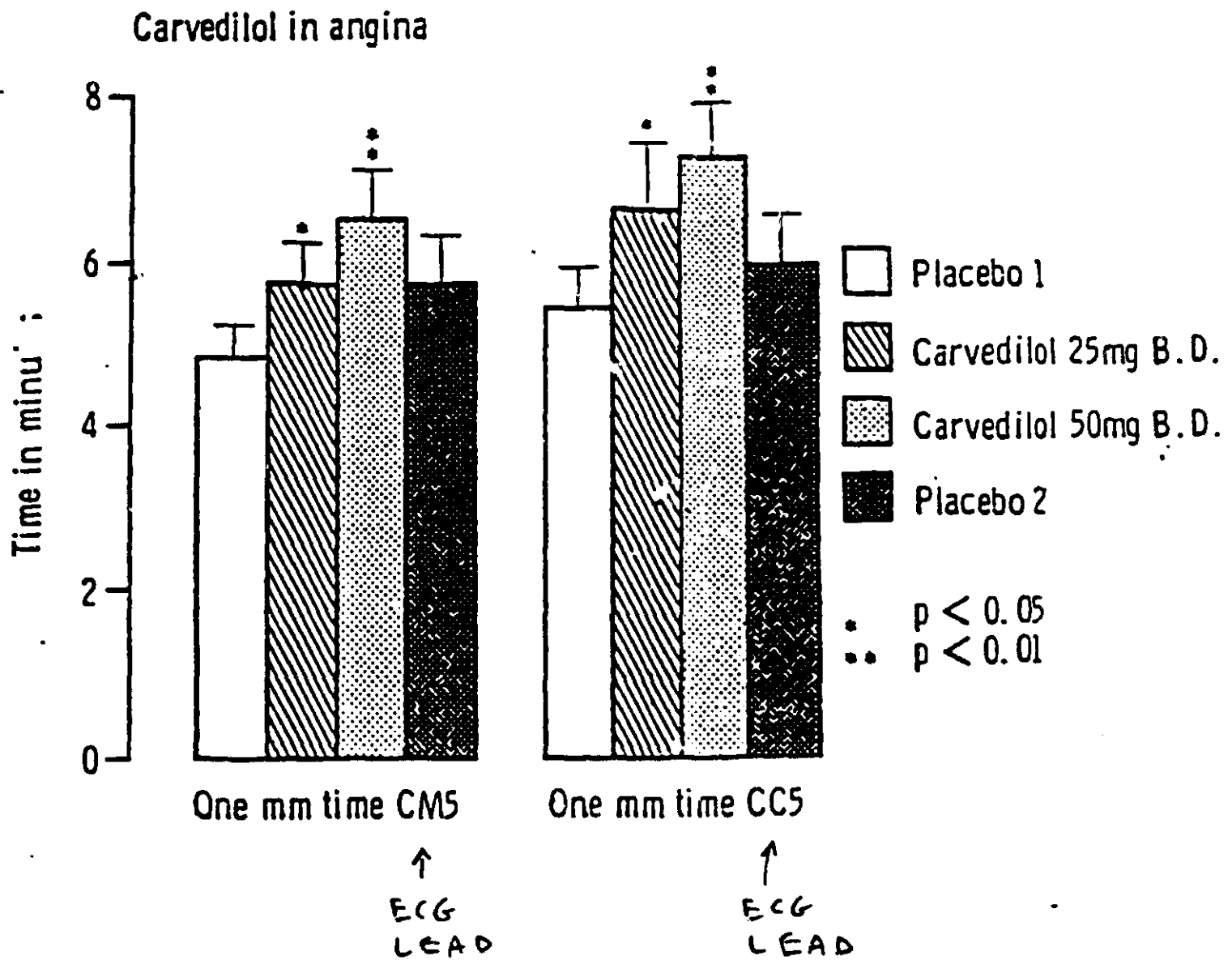


Figure 5 Time to 1 mm ST-depression on placebo and on Carvedilol.

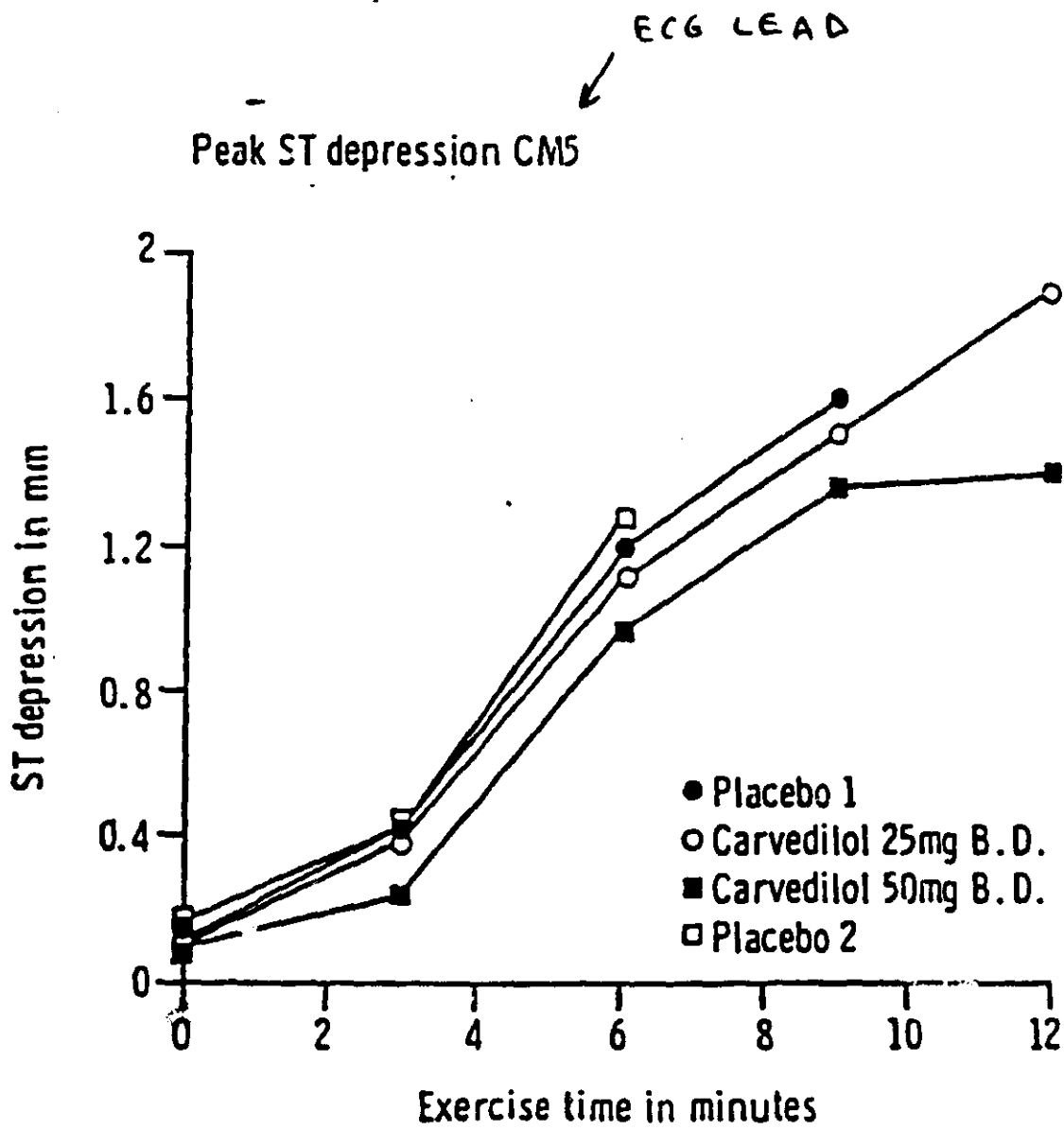


Figure 6 Peak ST-depression at each stage of exercise on placebo and on Carvedilol.

015- 25

Carvedilol in Angina

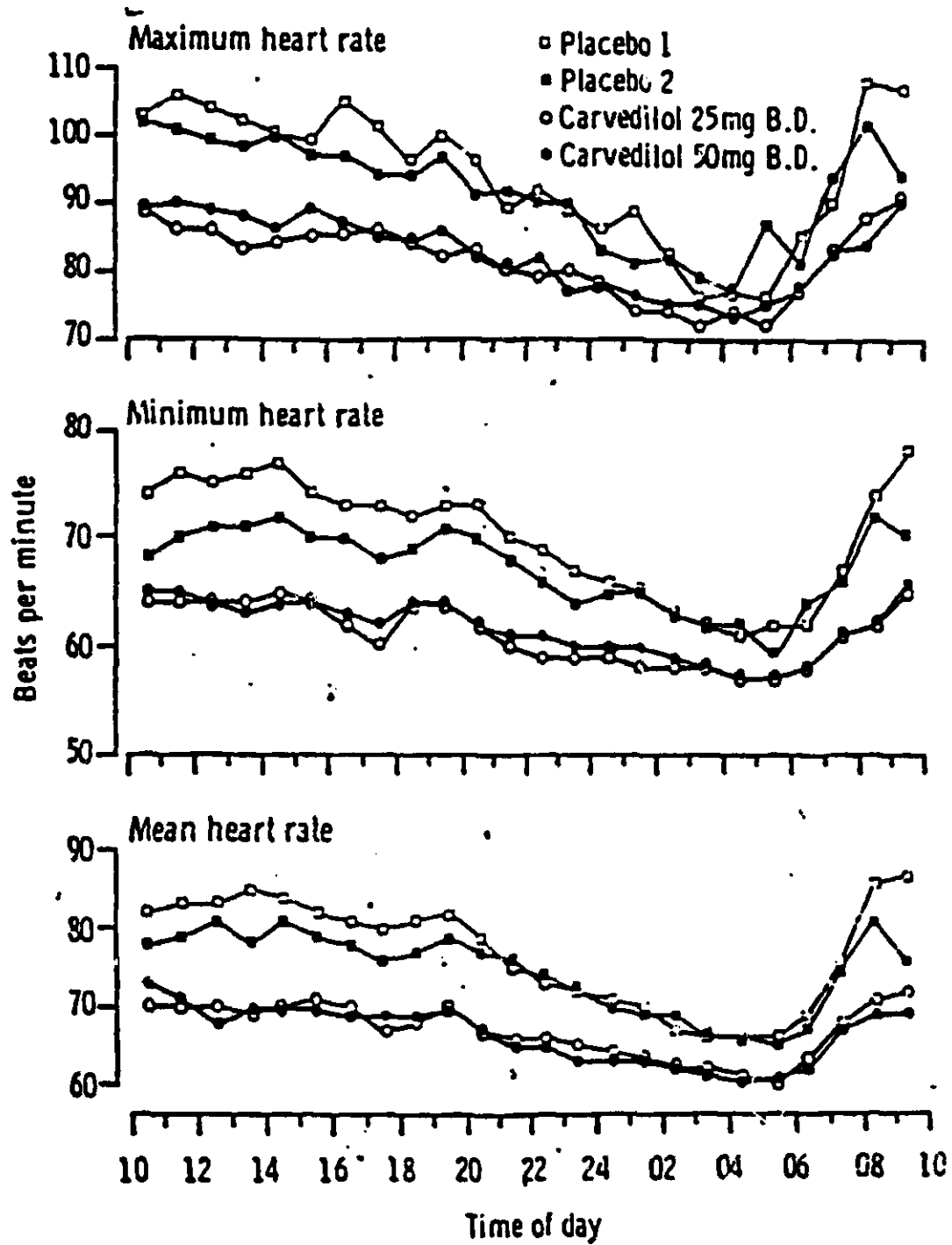


Figure 7 Minimum, maximum and mean hourly heart rates recorded by Holter monitoring on placebo and on Carvedilol.

heart rate and ST change

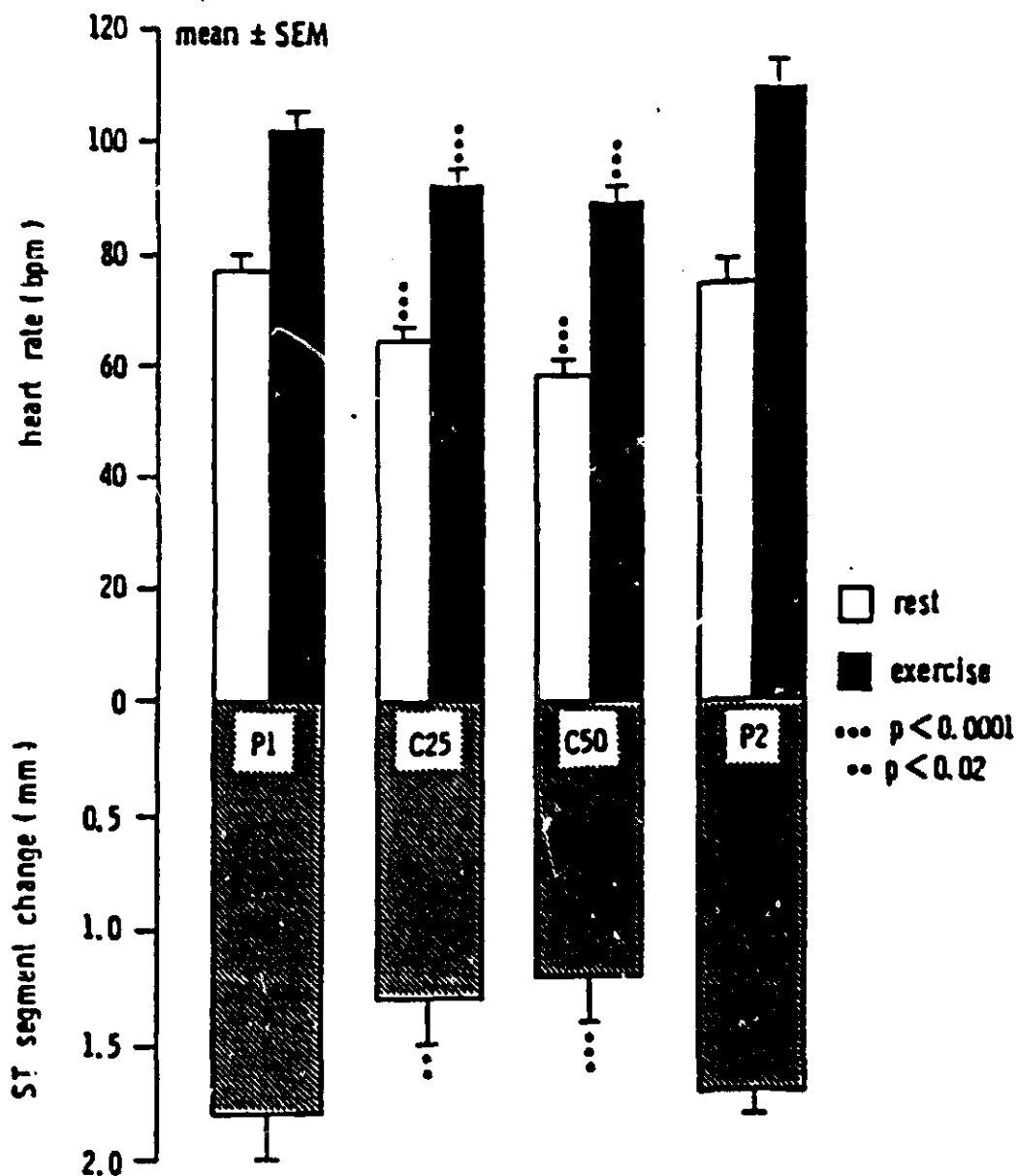


Figure 1

Change in heart rate and ST-segment depression on placebo and on the two doses of carvedilol are shown to highlight the effect of reducing myocardial oxygen demand on ST changes. P1 and P2 = placebo 1 and 2; C25 and C50 = Carvedilol 25 mg and 50 mg twice daily.

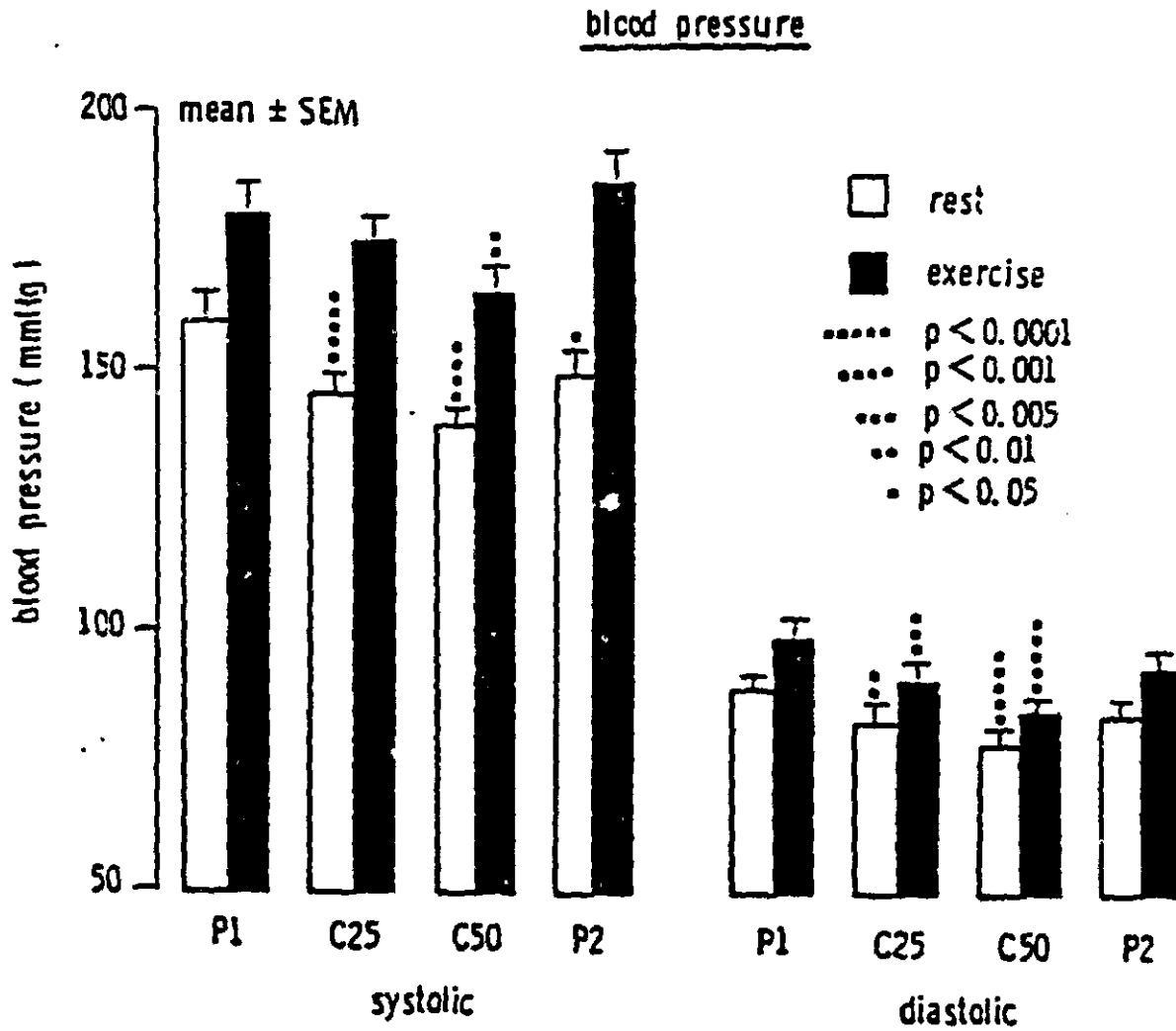


Figure 2

Rest and exercise blood pressure changes on placebo and on carvedilol. BP = blood pressure; C25 and C 50 = carvedilol 25mg and 50 mg twice daily; P1 and P2 = placebo 1 and 2.

~~C118~~
C119

015- 43 a

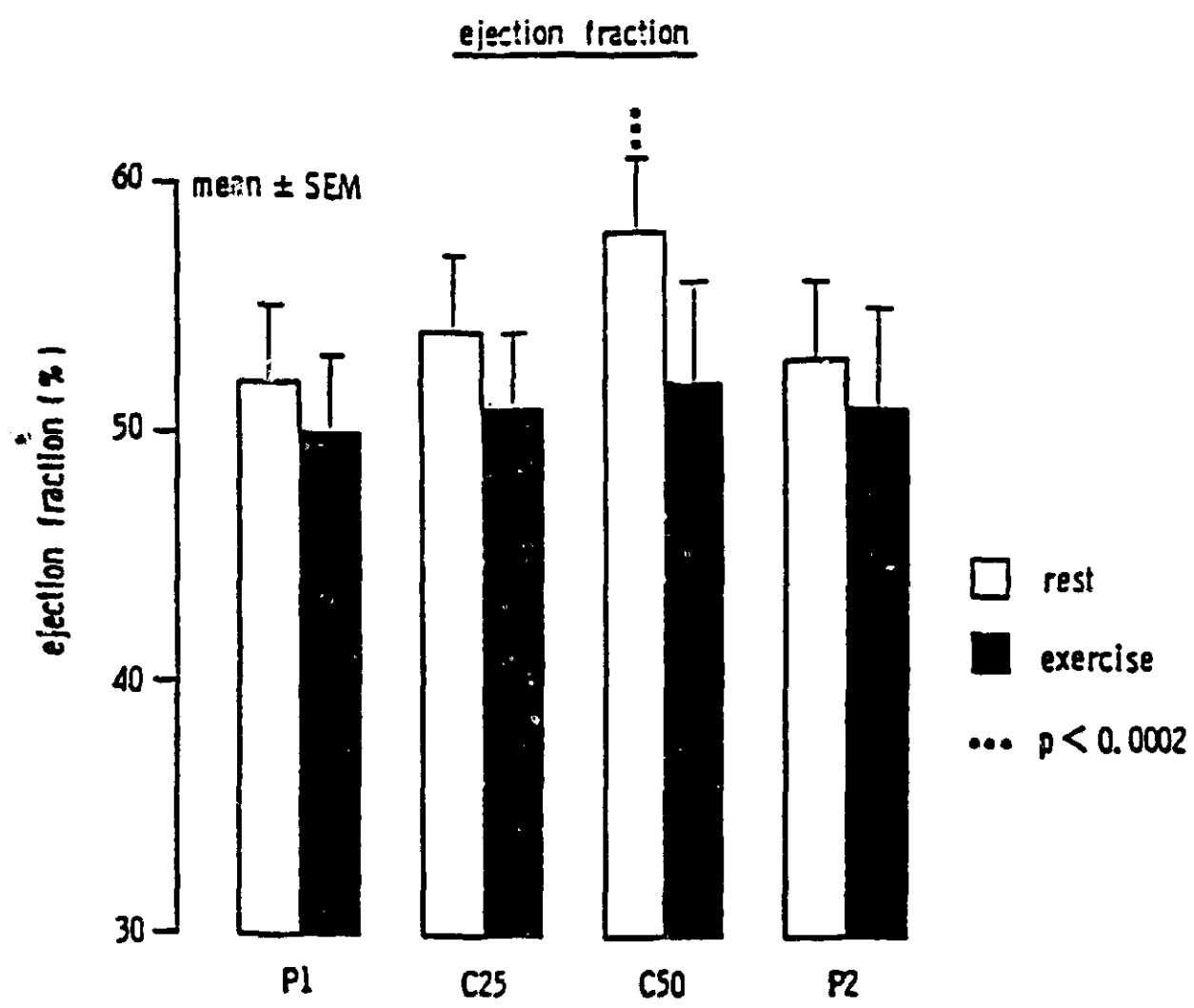


Figure 3

Resting and exercise ejection fraction values on placebo and on carvedilol.

P1 and P2 = placebo 1 and 2; C25 and C50 = carvedilol 25 and 50 mg twice daily.

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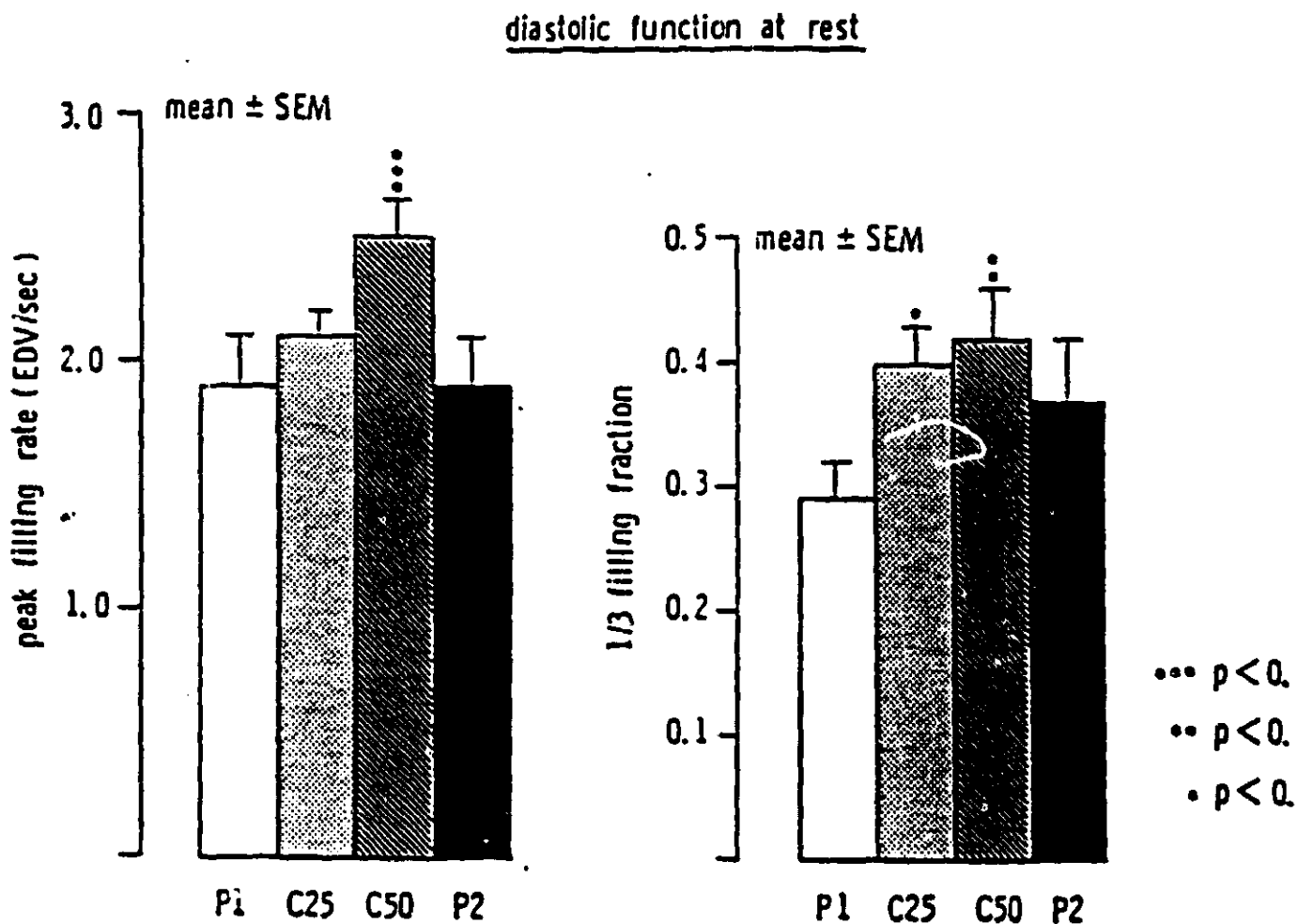


Figure 4

Peak filling rate and first one-third filling fraction values on placebo and on carvedilol at rest. 1/3 filling fraction = first one-third filling fraction; P1 and P2 = placebo 1 and 2; C25 and 50 = carvedilol 25 mg and 50 mg twice daily.

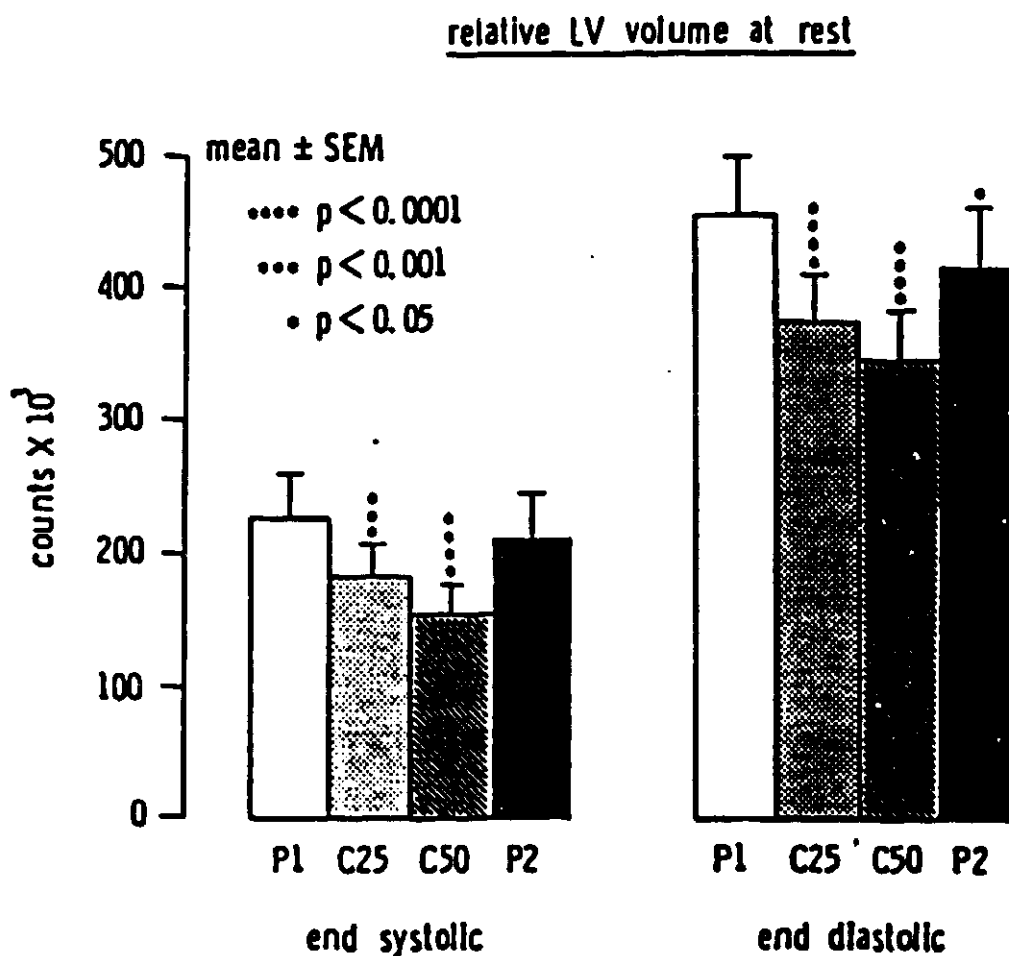


Figure 5

Relative LV volumes are represented by end-systolic and end-diastolic counts. C25 and C50 = Carvedilol 25 mg and 50 mg twice daily; P1 and P2 = placebo 1 and 2.

CARVEDILOL NDA 20-297

PROTOCOL MF3413 VOL 1.57

PK and PD in ELDERLY

Reviewer: James F. Graumlich

Name of study: Single dose pharmacokinetic and pharmacodynamic study of BM 14.190 in young and old healthy volunteers

Objectives: To determine the pharmacokinetics and haemodynamic effects of 5 mg intravenous and 25 mg and 50 mg oral doses of carvedilol, to compare the hypotensive effects of these single oral doses of carvedilol with a single oral dose of labetalol 200 mg, to determine whether the PK of carvedilol is influenced by food ingestion, to examine the conversion of carvedilol to its active desmethyl metabolite in 10 healthy young men and 9 older healthy men and 1 older healthy woman.

Study design: Study in 3 phases. Phase 1 was double-blind, non-randomized sequence, placebo-controlled, 5 period crossover phase in 10 healthy young men and 10 healthy older subjects using single oral doses of placebo, carvedilol 25 mg, carvedilol 50 mg, labetalol 200 mg, and carvedilol 50 mg + food. Periods were separated by at least 14 days. Phase 2 was open, uncontrolled phase using single intravenous doses of 5 mg of carvedilol. Phase 3 was open, uncontrolled phase using single oral doses of 12.5 mg carvedilol.

Intervention: placebo
carvedilol 12.5 mg, 25 mg, 50 mg
carvedilol 50 mg + food (toast, orange juice, 1-2 eggs)
labetalol 200 mg
carvedilol 5 mg intravenous infusion over 5 minutes

Response variables: Primary outcome: carvedilol concentrations in plasma, C_{max}, T_{max}, AUC
Secondary outcome: heart rate and blood pressure before, during, and after exercise, supine and standing; other PK parameters; lab safety tests

Bicycle ergometry to standardized workload was used during this study. BP, pulse, plasma concentration were measured at baseline then 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, 30, and 48 hours after carvedilol administration. BP and pulse after exercise were measured at 13 of the times listed above. Urine was collected for 48 hours. Additional early blood samples were obtained after the IV dose of carvedilol. Symptoms were elicited by questionnaire.

Materials: not specified

Assay: Plasma assay of carvedilol involved liquid/liquid extraction, HPLC with fluorometric detection. Propranolol was the internal standard. The lower limit of quantification was not specified.

Results: 10 healthy young men between 20 and 40 years of age completed phase 1 of the study. Weights of young subjects were between 59 and 87 kg (mean ± SE = 78 ± 3). 9 healthy older men between 57 and 66 years of age and one woman aged 63 years completed phase 1 of the study. Weights of older subjects were between 74 and 89 kg (mean ± SE = 79 ± 2). One elderly subject (#19) experienced hypotension after carvedilol 50 mg po (supine BP 105/72, standing BP 74/70 with documented absence of orthostatic hypotension prior to dose) and was withdrawn from the study and replaced by subject 21. 7 of 20 subjects (5 young and 2 old) were lost to followup and did not complete phase 2 (carvedilol 5 mg IV). 5 of 20 subjects (1 young and 4 old) were lost to followup and did not complete phase 3 (carvedilol 12.5 mg po).

Protocol violations included subject 2 who took penicillin while taking labetalol.
5 of 14 subjects had fewer blood samples collected during the distribution phase after the IV dose.

Carvedilol Pharmacokinetics

A two-compartment open model with a lag time of approximately 0.3 hours described the kinetics in most subjects.

C_{max} was not affected by age or food (see table A, page C126). There appeared to be dose-proportionality of C_{max} in the range of 12.5 to 50 mg (single dose). Dose-proportionality was not addressed statistically in this study. There was a four-fold range of minimum to maximum concentrations.

AUC was increased about 50% in elderly subjects after the 25 and 50 mg doses (page C127). Food caused a small increase in AUC for young and elderly although the differences were not statistically significant. The AUCs were roughly dose-proportional in the range of 12.5 to 50 mg. Dose-proportionality was not addressed statistically in this study.

Bioavailability was increased in older subjects (see table 10, page C128).

Total clearance and renal clearance were decreased in older subjects (see table 10 and 12, pages C128-C129).

Volume of distribution was increased in older subjects (see table 10, page C128).

T_{max} was not affected by age. Food prolonged T_{max} in young and old subjects.

Half-life was longer in younger subjects. The longer half-life may be partially explained by the wider range of variability in younger subjects. Food decreased half-life in young subjects.

Metabolite BM14,242 was not detectable in some subjects. In subjects with detectable BM14,242, C_{max} was approximately 10% of parent carvedilol, T_{max} was 1.2 ± 0.1 hours, n=12.

Pharmacodynamic response:

Maximum fall in resting blood pressure is summarized in table 15 (area under the blood pressure versus time curve, page C130). After carvedilol 12.5 mg, significant decreases in blood pressure occurred only for supine resting blood pressure. After carvedilol 25 and 50 mg, there were significant decreases in supine and standing blood pressure for young and old subjects. The older subjects had twice the effect seen in younger subjects after carvedilol 25 and 50 mg. Labetalol served as a positive control.

The time to maximal fall in resting blood pressure is summarized in table 16 (page C131). The range is 2-4 hours. Older subjects show a trend toward later times to E_{max}.

There were trends suggesting an increased effect on resting blood pressure associated with food (see table 15, page C130).

Duration of effect was not tabulated for fall in resting blood pressure.

The correlation between plasma concentration and PD is summarized in table iii (page C132). The only significant correlation coefficients occurred with standing blood pressure.

Reduction in exercise-induced tachycardia is biased by subjects who failed to exercise secondary to orthostatic blood pressure deterioration.

Carvedilol 12.5 mg did not produce an effect in young subjects. In older subjects, carvedilol 12.5 caused a decrease of 10 beats per minute in exercise-induced tachycardia. Onset of effect was 1 hour. Duration of effect was from 1 to 2

hours.

Carvedilol 25 mg caused a decrease of approximately 12 BPM. Onset of effect was 1-2 hours. Duration of effect was from 2 to 3 hours after the dose in young and old subjects. There were no significant differences between young and old subjects

Carvedilol 50 mg caused a decrease of approximately 30 BPM. Onset of effect was at 1 hour after the dose. Emax was at 3 hours after the dose. Duration of effect was from 1 to 12 hours after the dose. There was no difference in response between young and old subjects except a trend toward a longer duration of effect in older subjects.

Carvedilol 50 mg with food caused a decrease of approximately 20 BPM. Onset of effect was at 1 hour after the dose. Duration of effect was from 1 to 12 hours after the dose. There was no difference in response between young and old subjects except a trend toward a longer duration of effect in older subjects.

Noradrenaline concentrations in plasma showed inconsistent results and large variability. I could not perceive meaningful trends in the data when comparing dose, age, or time after dose.

Adverse events: There were no deaths.

Number of subjects unable to stand for blood pressure determination after doses of carvedilol

	12.5 mg	25 mg	50 mg	50 mg + food
young	0/9	3/10	4/10	3/10
older	1/6	3/10	3/10	5/10

Treatment emergent symptoms and signs were
 headache 4/10 young, 4/10 older
 nausea 5/10 young, 5/10 older
 dizzy/faint 20/20
 felt sleepy 8/10 young, 8/10 older

Other events that occurred more often after carvedilol than after placebo

short of breath	palpitations	indigestion	
cold extremities	stuffy nose	dry mouth	
heart burn	confusion	depression	pressure/pain behind eyes

Lab safety changes from pre-study normal values
 1/10 decreased potassium
 3/10 young, 6/10 older decreased hematocrit
 1/10 young, 1/10 older prolonged QT to 0.44 sec

Conclusions:

In phase 1, most subjects received treatments in chronological sequence and not in random sequence. The analysis did not consider sequence effects on results. The importance of sequence effects to the results of this study is unknown.

The statistical rationale for the sample size was not discussed. It is unknown if the sample size was sufficient to detect a difference if present.

Single doses of carvedilol from 12.5 to 50 mg cause dose-dependent increases in beta blockade of exercise-induced tachycardia in healthy volunteers.

CARVEDILOL NDA 20-297**PROTOCOL MF3413 VOL 1.57**

There is a problem with orthostatic hypotension after carvedilol 25 and 50 mg.

Emax occurs about 1-2 hours after Cmax.

There were trends suggesting an increased effect on resting blood pressure associated with food. Food was also associated with PK effects.

There were significant PK and PK changes associated with age.

The duration of effect in this study would not support a regimen of once-per-day doses.

The results of this study must be interpreted in the context of a single dose study in a small number of healthy subjects.

NDA 20297

7 OF 11

2. To Test for Alpha-adrenergic Receptor Blockade.

a) α_1 -Adrenoceptor Blockade

Carvedilol is a competitive antagonist of α_1 -adrenoceptors *in vivo* and *in vitro*. In isolated rabbit aorta, the α_1 -adrenoceptor mediated vasoconstrictor effects of norepinephrine are antagonized in a competitive manner with a pA₂ value of 7.97 ± 0.11 , which corresponds to an apparent K_B of 11 nM at α_1 -adrenoceptors. These results indicate that carvedilol is about 10-fold less potent as an α_1 -adrenoceptor antagonist than as a β_1 - or β_2 -adrenoceptor antagonist (Fig. 33).

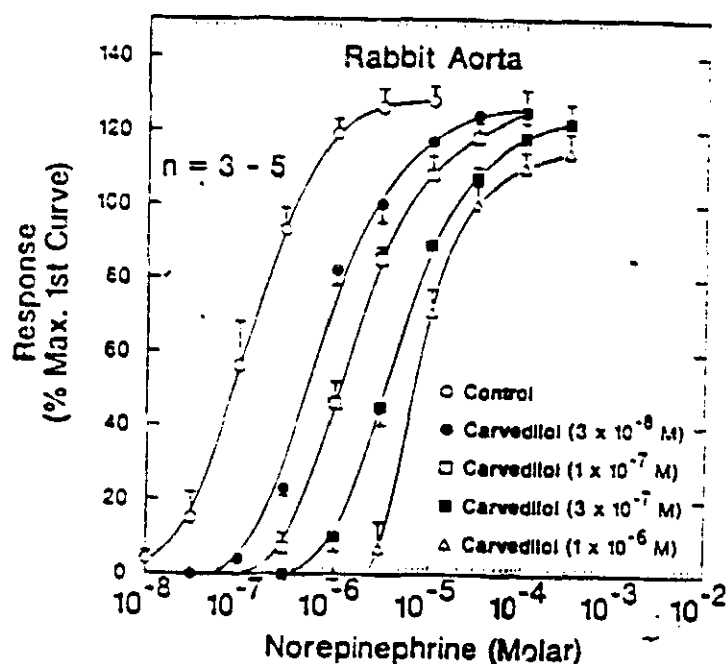


Figure 33 The α_1 -adrenoceptor antagonist activity of carvedilol in rabbit aorta.

b) α_2 -Adrenoceptor Blockade

Carvedilol (1 μ M) inhibits the α_2 -adrenoceptor mediated vasoconstrictor response of B-HT 920 (an α_2 -adrenoceptor agonist) in the isolated canine saphenous vein. However, this inhibition is noncompetitive, suggesting that carvedilol may inhibit some other component of the α_2 -adrenoceptor effector system (Fig. 34 below).

Electrically stimulated isolated vas deferens of the rat showed that carvedilol had almost no α_2 -adrenoceptor blocking properties.

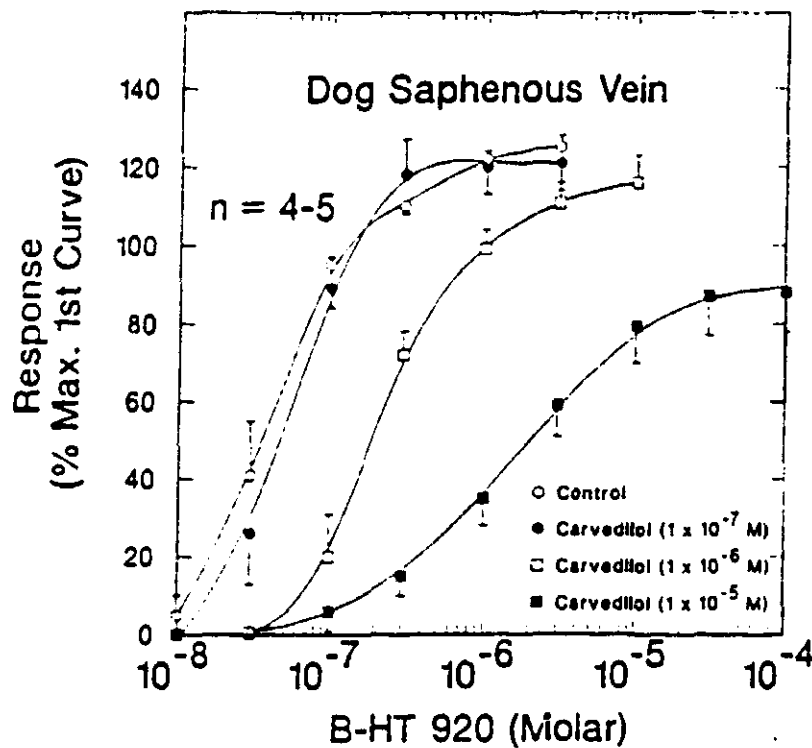


Figure 34. The effect of carvedilol on the contractile response to B-HT 920 in the canine saphenous vein.

3. Test for Calcium Channel Blocking Activity

Sponsor asserts that α_2 -adrenoceptor mediated vasoconstriction in the dog saphenous vein is dependent upon the translocation of extracellular calcium. Since no compelling evidence exists to suggest that carvedilol interacts competitively with α_2 -adrenoceptors, sponsor hypothesized that carvedilol may have calcium channel blocker activity.

A series of experiments were performed to elucidate whether or not there is a calcium channel antagonist effect of the drug. Depolarization of the rat uterus by KCl (70 μ M) produces a nifedipine-sensitive contractile response which results from opening of calcium channels. In this KCl precontracted rat uterus, carvedilol produced a concentration-dependent relaxation with an ED_{50} of $7.65 \pm 0.62 \mu$ M, consistent with the notion of that of calcium channel blockade (Fig. 35a).

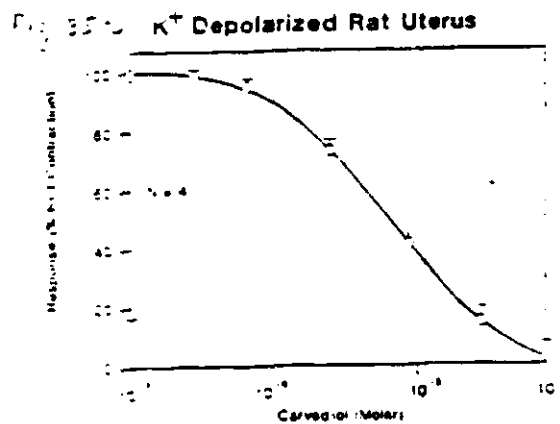


Fig. 35a Concentration-response curve for the relaxant effect of carvedilol on the rat uterus precontracted by 70 μ M depolarizing KCl.

Support for the above results were obtained with the potassium-depolarized rabbit aorta. In rabbit aorta incubated with calcium-free buffer, and subsequently depolarized with KCl (70 mM), a response to exogenously administered calcium can be observed that is sensitive to inhibition by calcium channel blockers. Carvedilol, at concentrations from about 1 μ M, and above, significantly inhibits (parallel shift to the right), the concentration-response curve of calcium-induced contractile response in this tissue (Fig. 35b).

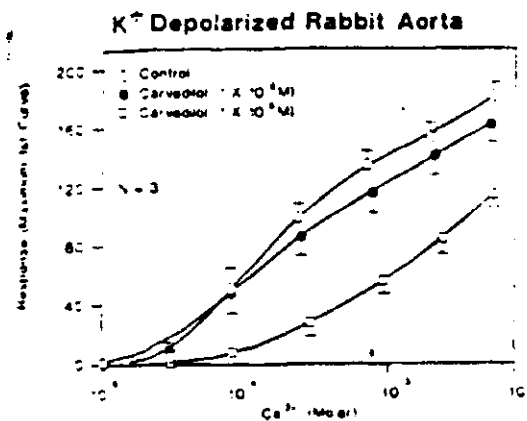


Fig. 35b Effect of carvedilol on the concentration-response curve for calcium-induced contractile response in the rabbit aorta.

The apparent calcium channel blocking activity of carvedilol was also seen *in vivo*. In the pithed rat, the direct calcium channel activator, Bay K-8644, produces a dose-dependent vasoconstrictor response that is inhibited by calcium channel antagonists. Carvedilol, at a dose of 1 mg/kg, i.v., which represents the higher portion of the antihypertensive dose-response curve, significantly inhibits the vasoconstrictor response of Bay K-8644, thereby suggesting that *in vivo* carvedilol has some calcium channel antagonist activity (Fig. 36).

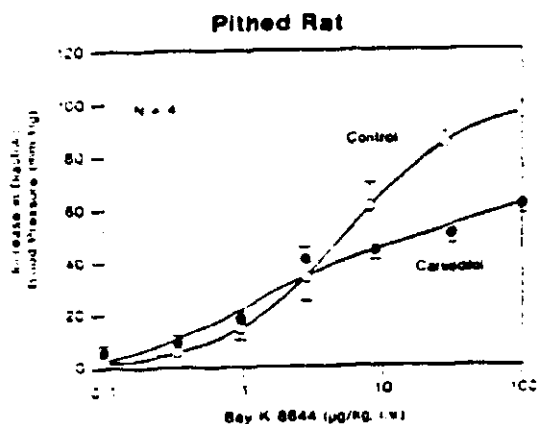


Figure 36 The effect of carvedilol (1 mg/kg, i.v.) on the vasoconstrictor response to Bay K-8644 in the pithed rat.

Sponsor considers that studies do not demonstrate a prominent role for this calcium channel antagonistic activity in the overall antihypertensive response of the carvedilol. This is observed in SHR pretreated with propranolol and prazosin to block β - and α_1 -adrenoceptors, respectively, carvedilol does not produce an additional reduction in blood pressure, whereas the potent calcium channel antagonist, nifedipine, still does. The calcium channel blocking activity of carvedilol may be of importance in increasing blood flow in specific regional vascular beds that are highly sensitive to calcium channel antagonists, such as the cutaneous circulation. Sponsor states that the effectiveness of calcium channel blockers in the treatment of peripheral vascular disease suggests the involvement of extracellular calcium in the regulation of cutaneous blood flow.

To determine whether the calcium channel blocking activity of carvedilol, or some other unidentified activity, is relevant to pharmacologic action of the drug, carvedilol was compared to labetalol (a drug with combined β - and α_1 -adrenoceptor antagonist properties), on cutaneous circulation.

At doses of carvedilol and labetalol that produce equivalent reductions in mean arterial BP and HR, labetalol significantly reduced cutaneous blood flow by over 20% with no change in cutaneous vascular resistance being observed. In contrast, carvedilol increased cutaneous blood flow by over 60%, and this effect resulted from a reduction in cutaneous vascular resistance. Because the cutaneous circulation is highly sensitive to calcium channel

antagonists, sponsor speculated that the decrease in cutaneous vascular resistance produced by carvedilol (but not labetalol), results from calcium channel blockade.

The table below was prepared by sponsor summarizing the an overall adrenergic receptor activity profile of carvedilol.

ADRENERGIC RECEPTOR SELECTIVITY OF CARVEDILOL

RECEPTOR	TISSUE	K _B or K _i (nM)
β	Guinea Pig Ventricle ([³ H]DHA)	1.5
β_1	Guinea Pig Atrium	0.8
		5.8
		0.9
		1.0
	Right	1.8
	Left	2.2
		0.4*
		45+
	Rat Atrium	0.3
	Right	0.9
Left	2.0	
β_2	Guinea Pig Trachea	1.3
		37
		1.2
α_1	Rabbit Aorta	10
		6.3
		56
		16*
		14+
	Rat Aorta	0.6
	Guinea Pig Aorta	10
	Rat Vas Deferens	20
	Rat Cortex ([³ H]-Prazosin)	9.4
	α_2	Canine Saphenous Vein
Rat Vas Deferens		10,000

* Data obtained with S(-)Carvedilol

+ Data obtained with R(+)-Carvedilol

BRIEF OVERVIEW OF NONCLINICAL RENAL EFFECTS

In conscious SHR, intragastric (i.g.) administration of carvedilol (10 mg/kg) is associated with dose-dependent antihypertensive activity. The hypotension is rapid in onset, lasting 4-8 hrs depending on the dose: the maximal decreases in BP exceeded 35 mm Hg (Fig 37a). Repeated administration of the drug over 3 days is not associated with tachyphylaxis. No synergistic effect was noted with low (hydrochlorothiazide 50 mg/kg i.g.) or high ceiling (furosemide) diuretics (Fig. 38b).

In these rats, administration of carvedilol or labetalol was associated with reductions in urine volume and urinary electrolyte, urea and creatinine excretion rates when given alone or in association with diuretics. Sponsor considers these effects are due to reductions in renal perfusion pressure associated with the antihypertensive activities of these agents and combinations.

FIGURE 37a CARVEDILOL DOSE RESPONSE CURVE

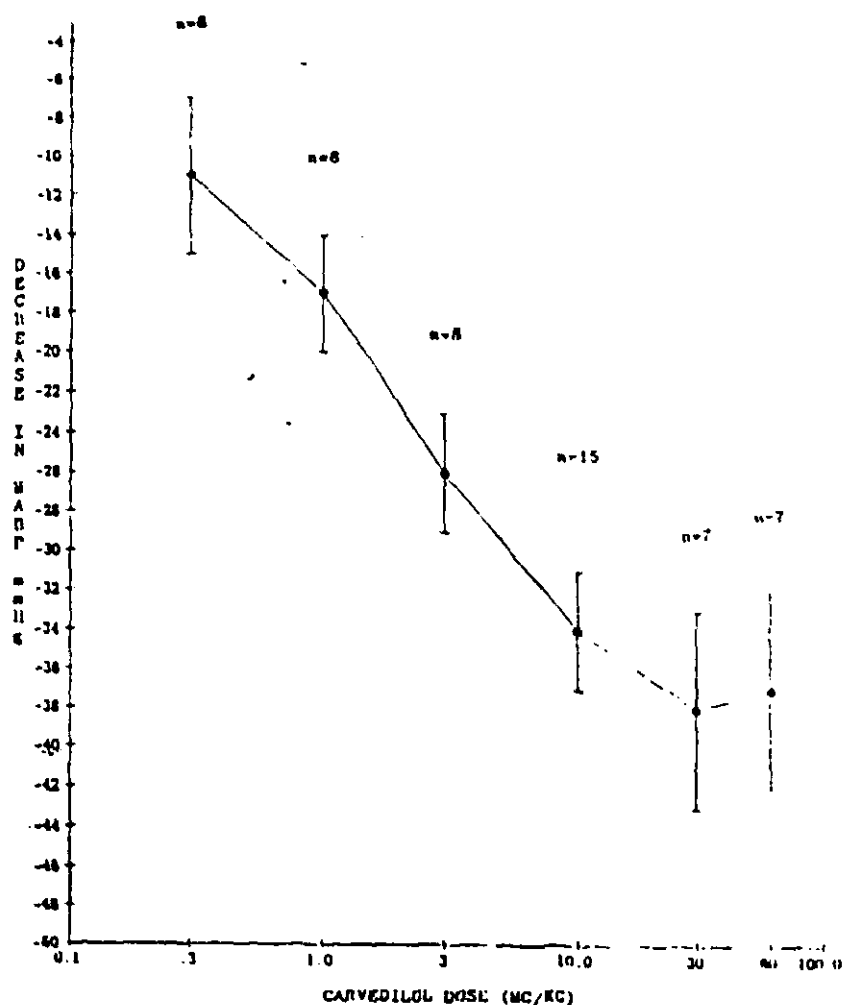
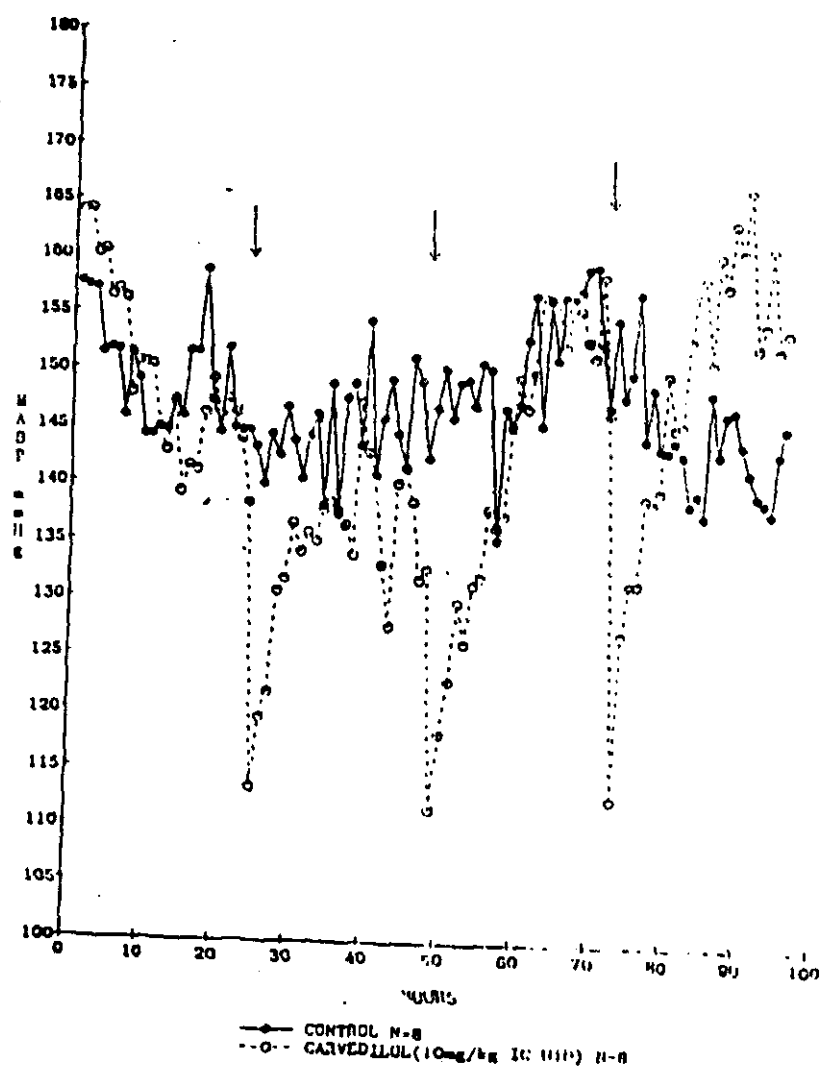


FIGURE 37b EFFECT OF CARVEDILOL ON MEAN ARTERIAL BLOOD PRESSURE IN SHR



In SHR and normotensive WKY rats, the effects of carvedilol on renal hemodynamics and excretory functions were compared to those of labetalol. In conscious SHR, dose-dependent decreases of BP were recorded when carvedilol was given as i.v. bolus, sustained i.v. infusion (10 $\mu\text{g}/\text{kg}$ min for 80 min). Cardiac performance remained unchanged, thus the hypotensive effect was considered due to a decrease of systemic vascular resistance (VR) (Fig. 38b). In SHR, regardless of the route of administration, carvedilol and labetalol were equipotent in lowering the BP of SHR (Fig. 38a).

Renal VR (calculated as MAP/ERBF^*) was also decreased by carvedilol in both strains of rats and with labetalol in the SHR (only group studied.) A 14% decrease in GFR was observed with carvedilol in WKY and with labetalol in SHR. In the SHR, autoregulation of GFR and renal blood flow was maintained during carvedilol infusion (Fig. 38c). Fall in BP was associated with a decrease in urine excretion, electrolytes and urea, with the exception NA^+ excretion which was unchanged in the SHR receiving carvedilol. Inasmuch as carvedilol reduces BP while maintaining renal blood flow, GFR and sodium excretion in SHR, sponsor suggests that carvedilol possesses renal sparing effect (Table 9 below).

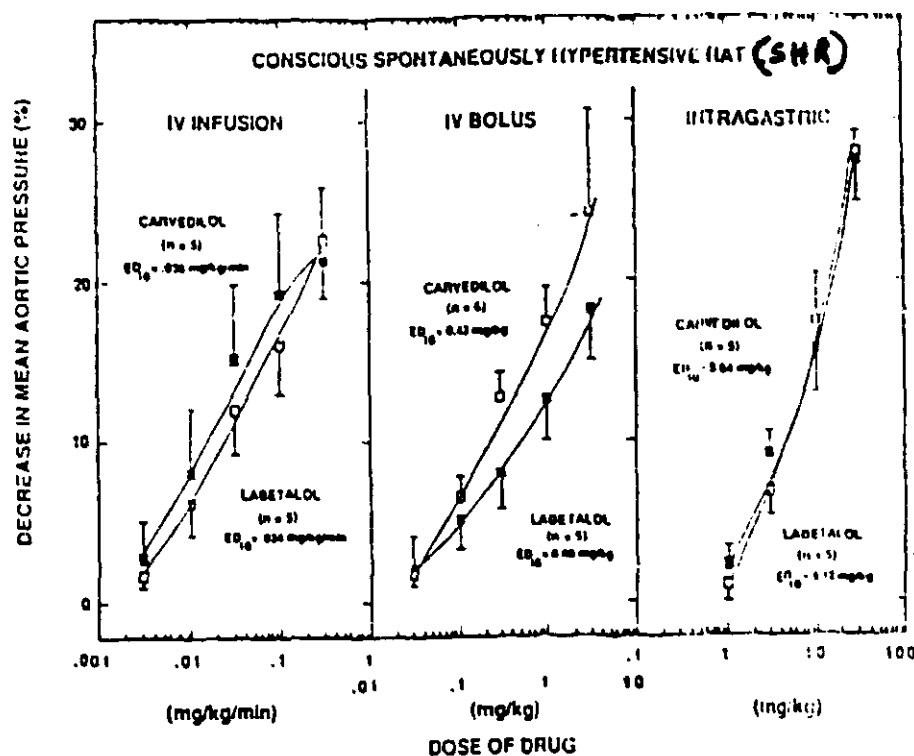


Figure 39a. Dose-response curves for the depressor effects of carvedilol (open squares) and labetalol (solid squares) in conscious spontaneously hypertensive rats. ED₅₀ denotes 50% decrease in blood pressure.

*Effective Renal Blood Flow

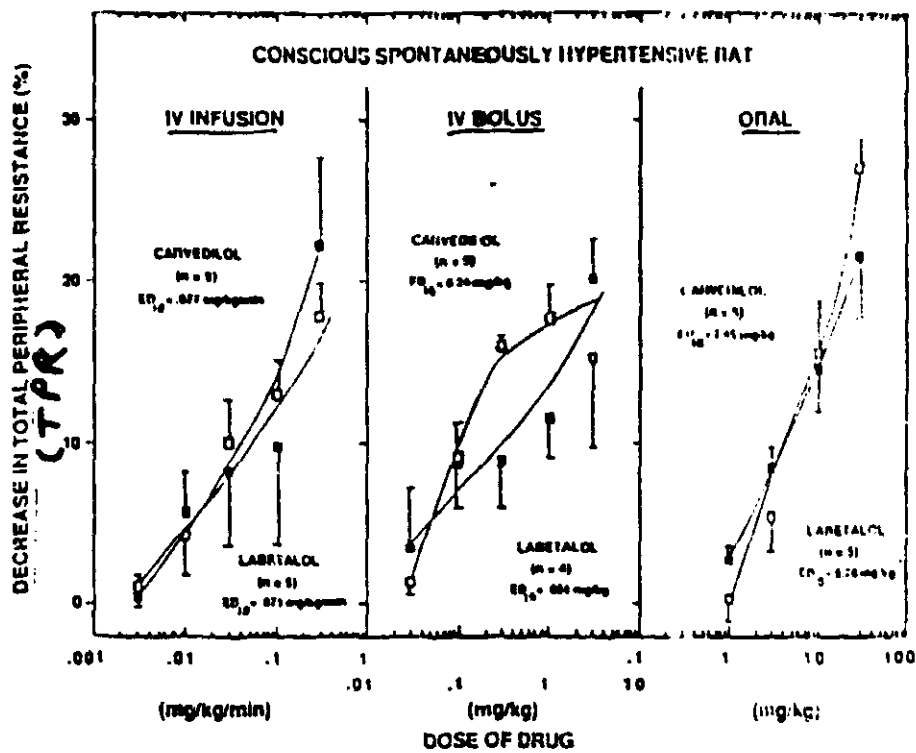


Figure 3B. Effects of carvedilol (open squares) and labetalol (solid squares) on systemic peripheral resistance in conscious spontaneously hypertensive rats.

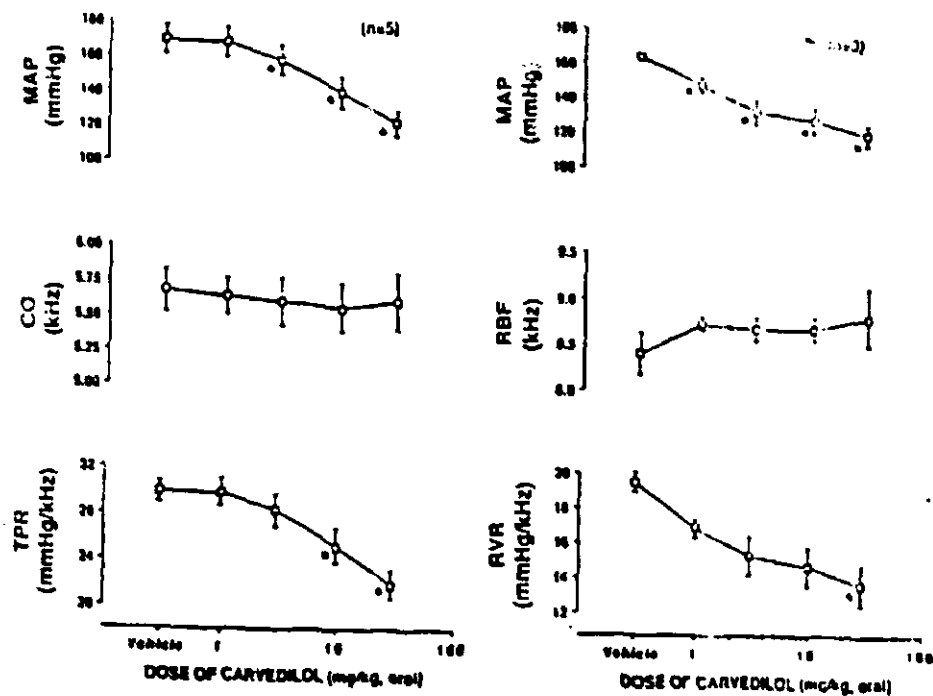


Figure 3C. Comparison of systemic and renal hemodynamic effects of orally administered carvedilol in conscious spontaneously hypertensive rats. Symbols and bars represent means $\pm$ SEM of maximum changes following drug administration. *Significantly different from vehicle-induced changes.

TABLE 4
Summary of Renal Effects of Carvedilol and Labetalol

	<u>CARVEDILOL</u>				<u>LABETALOL</u>	
	<u>HKY (n=5)</u>		<u>SHR (n=6)</u>		<u>SHR (n=6)</u>	
	<u>Control</u>	<u>Exptl.</u>	<u>Control</u>	<u>Exptl.</u>	<u>Control</u>	<u>Exptl.</u>
A. Renal Hemodynamics						
MAP (mm Hg)	113 ± 2.4	98 ± 2.8*	176 ± 5.3	160 ± 4.7*	176 ± 3.9	157 ± 3.0*
GFR (ml/min·100g)	731 ± 58	628 ± 39*	647 ± 90	636 ± 93	772 ± 32	673 ± 28*
ERBF (μl/min·100g)	5366 ± 488	5490 ± 437	4211 ± 404	4372 ± 387	4817 ± 223	4765 ± 219
RVR (MAP/ERBF)	21.0 ± 2.4	17.3 ± 1.4*	42.3 ± 3.6	36.5 ± 2.7*	36.1 ± 1.9	32.4 ± 1.4*
FF (%)	23.9 ± 2.2	19.9 ± 2.2*	28.5 ± 3.9	26.6 ± 4.8	28.1 ± 1.1	24.8 ± 1.2*
B. Handling of Electrolytes and Urea						
Urine flow (μl/min·100g)	33.3 ± 7.6	20.8 ± 3.6*	9.5 ± 1.8	5.5 ± 0.9*	11.8 ± 1.2	5.04 ± 0.7*
V·U _{Na} (μEq/min·100g)	0.45 ± 0.11	0.19 ± 0.06*	0.92 ± 0.18	0.95 ± 0.25	.98 ± 0.14	0.54 ± 0.12*
C _{Na} /C _{in} (%)	0.46 ± 0.12	0.22 ± 0.07*	1.01 ± 0.16	1.24 ± 0.36	0.88 ± 0.18	0.55 ± 0.12*
V·U _K (μEq/min·100g)	1.16 ± 0.22	0.73 ± 0.09*	0.98 ± 0.08	0.72 ± 0.05	1.09 ± 0.1	0.55 ± 0.02*
C _K /C _{in} (%)	40.3 ± 6.7	31.5 ± 4.76*	41.7 ± 7.19	34.3 ± 5.6*	37.18 ± 3.5	27.33 ± 254*
V·U _{urea} (μmoles/min·100g)	3.44 ± 0.32	2.09 ± 0.11*	3.16 ± 0.19	2.39 ± 0.21*	3.72 ± 0.16	2.34 ± 0.12*

Values listed under "control" are the means ± SEM of two control clearance periods; those under "Exptl." are the means ± SE of two 30 min measurements during infusion of carvedilol. MAP, mean aortic pressure; GFR, glomerular filtration rate; ERBF, effective renal blood flow; FF, filtration fraction; U_{osm}, urine osmolality; V·U_X, excretion of X; C_X/C_{in}, fractional excretion of X. *significantly different from control (p<0.05).

In female beagles, carvedilol administered as an oral suspension at doses of 1, 3, 10 and 30 mg/kg caused a decrease only on the volume of urine excreted up to 2 hrs after drug administration. Electrolyte excretion was not affected. The oral "no -effect" dose in these dogs was 1 mg/kg. In this study, carvedilol 3 mg/kg, p.o. and above, the dogs showed a dose-dependent relaxation of the nictitating membrane demonstrating postganglionic α_1 -adrenergic blockade and not ganglionic blockade. The absence of ganglionic blocking effect was also demonstrated in anesthetized cats in which carvedilol reduced the contraction of the nictitating membrane brought on by pre- and postganglionic stimulation of the cervical sympathetic ganglia.

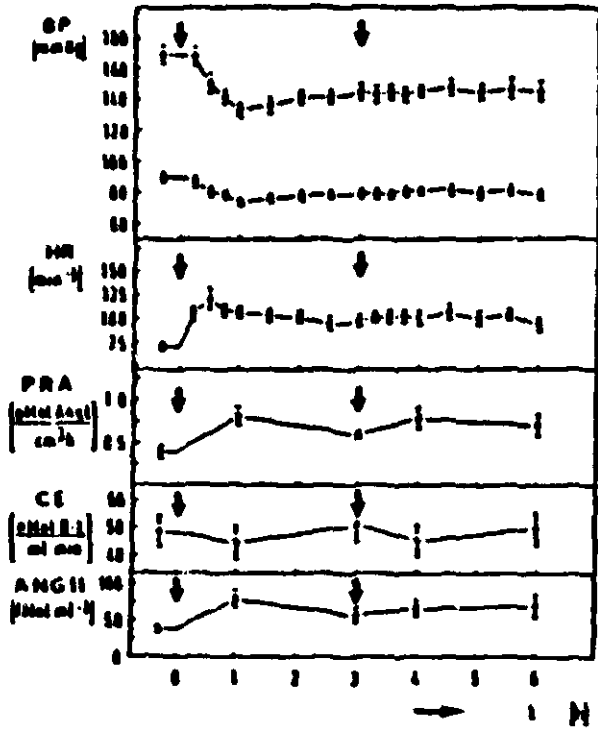
In beagles, carvedilol (6 mg/kg, p.o.) given as a suspension for 5 days, was associated with an increase in HR, slight increase in plasma-renin activity and plasma-angiotensin II concentration on the first day only. By the 5th day, BP was clearly lowered and increase in HR was only slightly detectable. These findings suggest that counter-regulatory mechanisms (increased HR, stimulation of renin-angiotensin system) were only activated during the acute phase of the study and that the ACE-inhibition is not involved in the antihypertensive effect of the drug (Fig. 39, next page.)

Studies reported in the dog show that in spite of reductions in mean arterial BP with carvedilol, the drug increased renal blood flow indicating renal vasodilatation while glomerular filtration rate urine flow, Na⁺ and K⁺ urinary excretion and venous plasma-renin activity were unaffected.

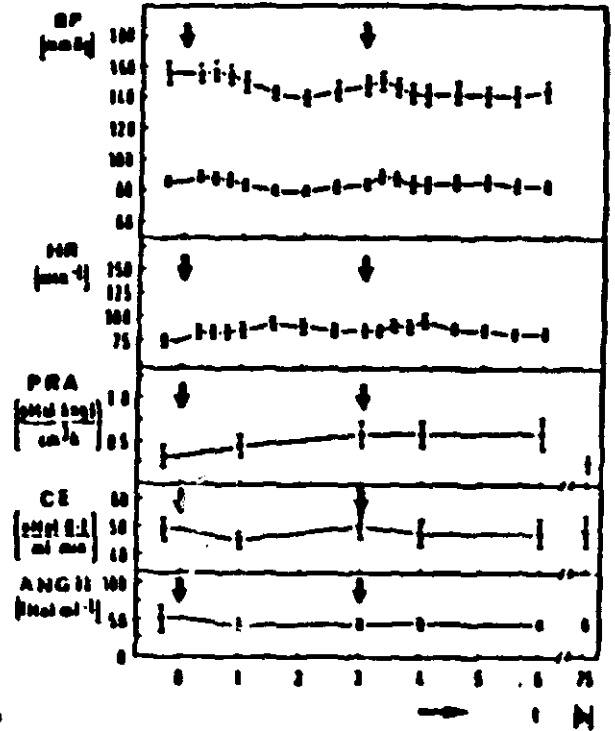
Beagles

Fig. 39 Responses of arterial blood pressure (BP), heart rate (HR), and renin-angiotensin system to oral administration of different vasodilating drugs. The arrows indicate the drug administration. PRA = plasma renin activity; ANG II = plasma angiotensin II concentration; CE = converting-enzyme-activity

carvedilol: 6 mg/kg



1st day



5th day

SOME STUDIES TO TEST FOR POTENTIAL ORGAN PROTECTIVE EFFECTS

Cardioprotection in Experimental Models of Myocardial Infarction

Sponsor states that many marketed β -blockers (except those with intrinsic sympathomimetic activity) possess cardioprotective properties. Sponsor indicates that it is commonly accepted that cardioprotection provided by β -blockers may result of improvement in the balance between myocardial oxygen supply/demand by reducing myocardial work (secondary to reductions in HR and myocardial contractility.)

The literature reports that HR reduction is required for infarct size limitation. (Kjekshus JK: Am J Cardiology 57: 43F, 1986.) Since the hypotensive activity of carvedilol occurs without reflex tachycardia (due to β -blockade), sponsor investigated the potential cardioprotective action of the drug in several different models of myocardial infarction. Four experimental models of acute myocardial infarction in 3 animals species (rat, dog and minipig) were described in the NDA.

Briefly, in anesthetized rat, the left main coronary artery was ligated for 30 min and then reperfused for 24 hours. Carvedilol (0.3 or 1 mg/kg i.v.) or vehicle was administered 15 min before acute ischemia and again 4 hours after the onset of reperfusion (post-ischemia) period. Twenty-four hours after reperfusion, the rats were killed, hearts removed, sliced, fixed and stained. The infarct size was then evaluated.

Compared to the vehicle treated rats, carvedilol (at 1 mg/kg) reduced the infarct size from $14.2 \pm 1.0\%$ to $7.5 \pm 1.0\%$ ($p < 0.01$) of the left ventricle mass. This protective effect of carvedilol was calculated by sponsor to represent 47% reduction of the infarct zone (Table II). Although actual data was not submitted in this report, sponsor stated that in this rat model, propranolol showed no cardioprotective effect (Smith EF II, et al, "Effect of Propranolol on Ischemic Myocardial Damage and Left Ventricular Hypertrophy following Permanent Coronary Artery Occlusion or Occlusion Followed by Reperfusion" in Pharmacol 38: 298-309, 1989.)

Briefly, the left anterior descending (LAD) coronary artery of Yucatan minipigs were isolated. After a period of stabilization, bolus injections of carvedilol (0.3 and 1 mg/kg, i.v.), propranolol (1 mg/kg, i.v.) or vehicle were given to the animals. After 15 min the LAD was occluded with a microaneurysm clip for 45 min. When the clip was removed, reperfusion was maintained for 4 hrs. Following the reperfusion period, the hearts were removed, treated with buffer solutions, dyed, rinsed, sliced, photographed, weighed, infarcted areas identified and quantified. Pretreatment with carvedilol, produced a dose-dependent reduction in infarct size in the pig model of coronary artery occlusion. Compared to the vehicle treated control pigs, the two doses of carvedilol tested reduced dose-dependently the infarct size (46% and 89%, $p < 0.01$). The reduction in infarct size produced by carvedilol was greater than the reduction produced by propranolol at an equivalent β -adrenoceptor blocking dose (Table 1).

In anesthetized mongrel dogs subjected to 1 hr of transient myocardial ischemia by left circumflex coronary artery followed by 24 hr reperfusion, carvedilol (1 mg/kg i.v.) reduced the infarct size by 78% ($p < 0.05$), compared to a 64% reduction produced by propranolol. In a canine model of permanent LAD coronary artery occlusion (6 Hr), pretreatment with carvedilol (0.3 or 1 mg/kg i.v.) produced dose-dependent reductions in infarct size of 45% and 63%, respectively, compared to propranolol which did not reduce infarct size in this model (Table 11).

The following is a summary table of findings prepared by sponsor for the above studies.

Table. 11

Cardioprotection by Carvedilol (1 mg/kg, i.v.) and Propranolol (1 mg/kg, i.v.) in Experimental Models of Acute Myocardial Infarction in Several Species

Species	Treatment with Carvedilol or Propranolol	Duration of Occlusion	Period of Reperfusion	Percent Reduction in Infarct Size ^a		Reference
				Propranolol	Carvedilol	
Rat	Pre-occlusion (15 min) and post-occlusion (4 hr)	30 min	24 hr	NE ^b	47 ± 12% ^c	68
Pig	Pre-occlusion (15 min)	45 min	4 hr	49 ± 17% ^c	90 ± 6% ^{c,d}	68
Dog	Pre-occlusion (15 min)	60 min	24 hr	64 ± 10% ^c	78 ± 8% ^c	68
Dog	Post-occlusion (15 min)	360 min	None	20 ± 10%	63 ± 9% ^{c,d}	68

^aCompared to vehicle control

NE: Not Estimated.

^bPropranolol has been shown to have no effect on infarct size in the rat model of acute myocardial infarction (Ref. 68)

^c $p < 0.05$ vs vehicle

^d $p < 0.05$ vs propranolol

Sponsor reports that abnormal cell growth and proliferation of vascular smooth muscle play a fundamental role in advancing lesions of atherosclerosis in hypertensive patients and experimental animals*.

Studies submitted show that carvedilol produced anti-mitogenic effects against a diverse group of vascular smooth muscle mitogens (e.g., endothelin-1, epidermal growth factor, platelet-derived growth factor A/B, etc.)

Carvedilol (at 10^{-7} to 10^{-5} M) inhibited dose-dependently both basal (control) and endothelin-1-stimulated [^{3} H]thymidine incorporation (measure of DNA synthesis) in rat aortic vascular smooth muscle cultured cells. The IC_{50} for inhibition of [^{3} H]thymidine incorporation by carvedilol was about 1 μ M (Figs. 40a, 40b, and 40c). This inhibitory effect is not considered by sponsor to be due to a cytotoxic effect of carvedilol.

Carvedilol (1-10 μ M) also produced significant concentration-dependent inhibition of the mitogenic response mediated by endothelin-1, angiotensin II, EGF, PDGF_{A/B}, TGF α and thrombin. Although PDGF_{A/B}-induced rat aortic vascular smooth muscle cell mitogenesis, this was not significantly reduced by 1 μ M carvedilol, however, mitogenesis was inhibited by higher doses of the drug (10 μ M) (Fig. 40d).

This anti-mitogenic effect of carvedilol on rat aortic vascular smooth muscle was not shared by other β -adrenoceptor antagonists. At equimolar concentrations only carvedilol and propranol (non-selective β -adrenoceptor antagonist) inhibited both basal (Fig. 40e) and endothelin-1-stimulated (Fig. 40f) mitogenesis. Labetalol (α -1, β 1-, β 2- adrenoceptor antagonist) and sotalol (non-selective β -adrenoceptor antagonist) did not affect either basal or endothelin-1 stimulated mitogenesis in this preparation.

Nifedipine did not significantly affect basal [^{3} H]thymidine incorporation in rat vascular smooth muscle cells (Fig. 7a). Nifedipine (1 μ M) did inhibit endothelin-1-mediated muscle cell mitogenesis by about 36% and at a higher concentration (10 μ M) nifedipine inhibited both basal and endothelin-1-stimulated mitogenesis about 58% and 72%, respectively (Figs. 40g and 40h).

Since carvedilol produced an antimitogenic effect against a diverse group of vascular smooth muscle mitogens, the mechanism of this action is not clear. This relatively high-concentration effect does not appear to be mediated simply through α - or β -adrenoceptor antagonism or calcium channel blockade.

*Ross, R. and Glomset JA, "The Pathogenesis of Atherosclerosis" in NEJM 295: 369, 1976

Ross, R. "The Pathogenesis of Atherosclerosis- An Update" in NEJM 314: 488, 1986.

CARVEDILOL AND VASCULAR PROLIFERATION INDUCED BY MITOGENS

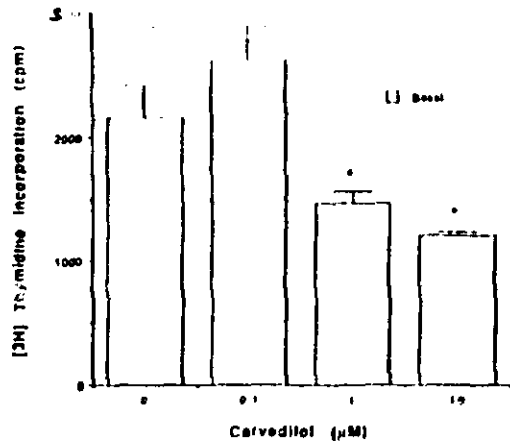


Figure 2

Figure 2 Effect of carvedilol on unstimulated (basal) rat aortic vascular smooth muscle cell proliferation. A typical experiment with triplicate determination. The basal [3H]thymidine incorporation was 2159 ± 344 cpm.

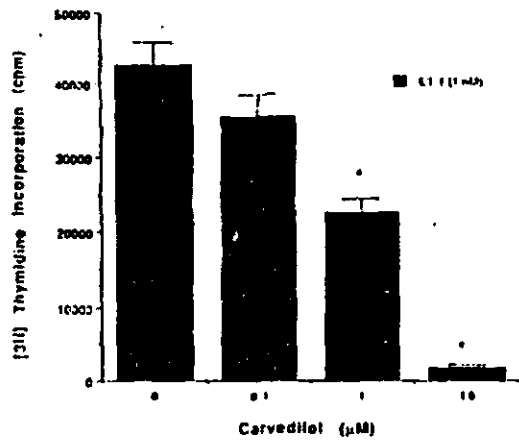


Figure 3 Effect of carvedilol on endothelin-1-stimulated rat aortic vascular smooth muscle cell proliferation. A typical experiment with triplicate determination. ET-1-stimulated [3H]thymidine incorporation was 42652 ± 3307 cpm.

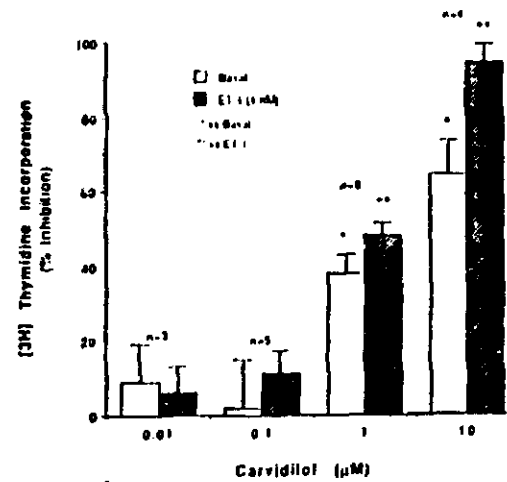


Figure 4 The percent inhibition of basal and endothelin-1-stimulated vascular smooth muscle cell proliferation. Data are from 3-8 experiments with triplicate determinations in each experiment.

CARVEDILOL AND VASCULAR PROLIFERATION INDUCED BY MITOGEN (Cont'd.)

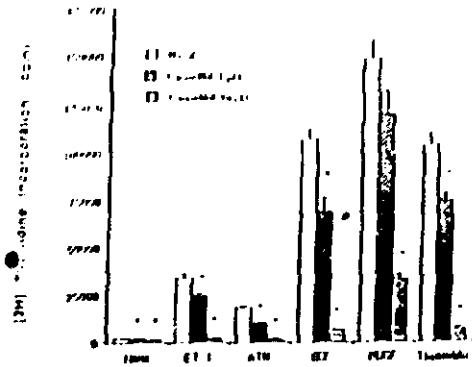


Figure 40d

Effect of carvedilol on different mitogen-stimulated rat aortic vascular smooth muscle cell proliferation. Quiescent rat aortic vascular smooth muscle cells were treated with and without mitogen in the absence and presence of 1-10 μM carvedilol for 24 hr. The concentrations of mitogen used was predetermined to give maximal mitogenic effect on rat aortic vascular smooth muscle cells: endothelin-1 (1 nM), PDGF A/B (1 nM), EGF (1 nM), TGFα (2 nM), All (5 nM); Ilronbin (0.5 U/ml). The results were from three experiments with triplicate determinations in each experiment.

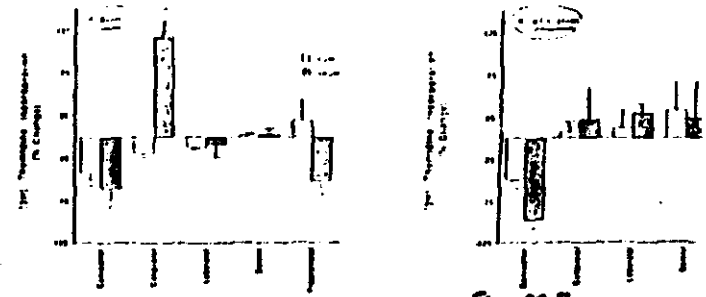


Fig. 40f

Effects of various β-adrenoceptor antagonists on the mitogenesis of endothelin-stimulated rat aortic vascular smooth muscle cells. Quiescent rat aortic vascular smooth muscle cells were pretreated with β-blocker for 10 min followed by the addition of A medium (basal), or B endothelin-1 (1 nM) for additional 24 hr incubation. ³H-thymidine incorporation into TCA insoluble fraction was determined as described in the Method. Data was expressed as % change ± SEM from corresponding controls

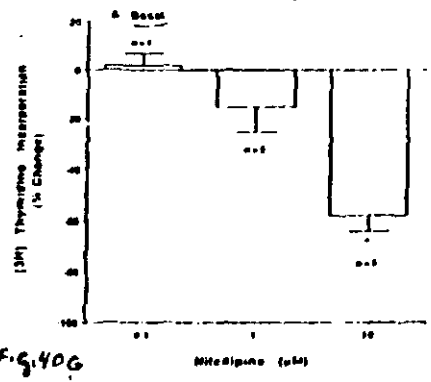


Fig. 40g

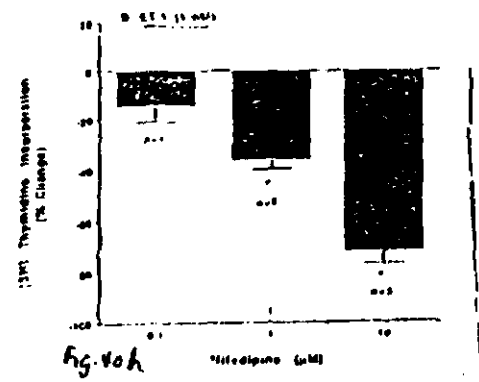


Fig. 40h

Effect of nifedipine on basal and endothelin-1-stimulated mitogenesis of vascular smooth muscle cells. Quiescent rat aortic vascular smooth muscle cells were pretreated with nifedipine for 10 min followed by the addition of A medium (basal), or B endothelin-1 (1 nM) for additional 24 hr incubation. Data was expressed as % change ± SEM from corresponding control in 3-5 experiments with triplicate determinations in each experiment.

Experimental Stroke Studies

Stroke-prone (SP) strain of SHR are inbred to develop/exhibit severe hypertension and very high (80%) incidence of strokes. Sponsor reports that the strokes are considered to be similar to human strokes. SHR-SP were fed a high salt (8%) diet containing carvedilol for 94 days. The drug concentrations administered in diet were 300 ppm for 50 days and raised to 600 ppm for the remaining last 44 days of study. The mean daily intake of carvedilol was reported as 19.5 mg/kg/day at the lower dose (300 ppm) and 46.2 mg/kg/day at the high (600 ppm) in diet.

All carvedilol treated SHR-SP survived the study while 20.8% (5) of the controls died. Compared to controls, the carvedilol treated rats did not differ in their systolic blood pressure, food intake, body weight or motor/neurologic status except for a decreased heart rate. Blood analyses indicated that compared to the controls, the carvedilol treated rats had a significantly higher plasma levels of potassium and alkaline-phosphatase and potassium. Significantly lower mean blood cell volume, glucose, gamma glutamyl transferase, total bilirubin and triglycerides were also reported in drug treated animals.

In a separate group of SHR-SP fed same carvedilol diets, the blood levels of the drug were about 133.9 ng/ml and about 1507 ng/ml for the 300 ppm and 600 ppm carvedilol treatment.

The Table 12 below, prepared by sponsor, summarizes significant changes associated with the treatment of carvedilol.

Table 12

Summary of Significant Differences Observed in Blood Studies Between Carvedilol Treated Rats and Control Rats

Major Changes

- Blood Lipids
 - Triglycerides significantly lower in carvedilol fed rats as compared to the controls

Minor Changes

- Blood Chemistry
 - Potassium significantly higher in carvedilol fed rats as compared to the controls
 - Alkaline Phosphatase significantly higher than controls
 - MCV significantly lower than controls
 - Glucose significantly lower than controls
 - Gamma Glutamyl transferase significantly lower than controls
- Liver Function
 - Total bilirubin significantly lower than controls
 - Direct bilirubin significantly lower than controls

Neuroprotective Properties of Carvedilol

Sponsor states that brain ischemia is known to be accompanied by lipid peroxidation following oxygen free radical formation.* Further, that free radical formation may mediate part of the ischemic neuronal damage caused by the excitatory amino acid glutamate.

Sponsor cites investigations (unpublished reports) that claim that carvedilol is an inhibitor of lipid peroxidation in swine heart** and rat*** brain homogenate exposed to different free-radical generating systems. Thus, the neuroprotective potential of carvedilol (oxygen free radical scavenging) was also tested in an *in vitro* model of cultured rat cerebral neurons (exposed to glutamate or an oxygen free radical generating system) and, in an *in vivo* model of global forebrain ischemic stroke in Mongolian gerbils induced by a 6 min bilateral carotid artery occlusion and 7 days reperfusion. These methodologies are fully reported in the NDA. Neuroprotective mechanism or prevention of lipid peroxidation was determined by measuring the formation of thiobarbituric acid-reactive substances (TBARS).

Briefly, results reported suggested that carvedilol ($IC_{50} = 1.1 \mu M$) protected rat cerebral granule cells against glutamate-mediated neuronal death (Fig. 41 below). To determine if the apparent neuroprotection was due to an oxygen free radical scavenging property by carvedilol, neurons were exposed for 60 min to an hydroxyl radical generating system- DHF- Fe^{3+} /ADP. Cell mortality (in this study >95%) was assessed by staining with fluorescein diacetate dye. In this study, the time required for 50% cell killing time (ET_{50}) with this hydroxyl radical generating system was reported to be 25.3 min. By incubating the neurons with $10 \mu M$ carvedilol 15 min prior to the addition of DHF- Fe^{3+} /ADP system, there was evidence of protection with an increased ET_{50} to 42.7 min. Despite the 17 min protection time, this neuroprotection by carvedilol was not total because when the exposure time to DHF- Fe^{3+} /ADP was reduced from 60 min to 20 min in the presence of glucose (considered the primary substrate in brain), cells were also resistant to damage from free radicals for at least 4 hrs (Fig. 42). Cell mortality was nearly complete at 50 min after replacement of the free radical generating system with the glucose-free buffer. However, carvedilol ($IC_{50} = 5 \mu M$) still protected dose-dependently against the 20 min oxidative challenge. Growing rat cerebral cells in the presence of the lipophilic carvedilol augmented the neuroprotection of the 20 min challenge with free radicals generating system by reducing the IC_{50} from $5 \mu M$ to $1.3 \mu M$ (Fig. 43).

* Braugher JM, Hall ED et al in "Central nervous system trauma and stroke. I Biochemical considerations for oxygen radical formation and lipid peroxidation." and, Part II. "...Physiological and pharmacological evidence for involvement of oxygen radicals and lipid peroxidation" in *Biol Med* 6:289-301, 1989 and 6:303-313, 1989, respectively.

** Yue T-L et al in "Carvedilol, a new vasodilator and Beta-adrenoceptor antagonist, inhibits oxygen-radical-mediated lipid peroxidation in swine" (in press)

*** Yue T-L et al in "Carvedilol, a new vasodilator and beta adrenoceptor antagonist, is an antioxidant and free radical scavenger." *JPET* (in press)

The potential of carvedilol for preventing lipid peroxidation, induced by the free radical generating system DHF-Fe³⁺/ADP, was also tested on rat cultured neurons by measuring the amount of TBARS produced 50 min after washout of the free radical generating system. In this assay, pretreatment with carvedilol (10 μM) for 15 min resulted in 50% reduction of the levels of TBARS produced by a 20 min challenge of DHF-Fe³⁺/ADP (Fig. 44).

Even when using a different free radical generating system (Fe²⁺/vitamin C), carvedilol was still neuroprotective against continuous exposure to this system. Pretreatment with carvedilol (10 μM) for 15 min prior to addition of this radical generating system provided a 73% reduction in TBARS production (Fig. 45).

In vivo hippocampal neurons in gerbils exposed to 6 min bilateral carotid artery occlusion were reported as protected 7 days after ischemic insult (Fig 46).

Sponsor considers that these findings suggest a free-radical scavenging mechanism for carvedilol.

Although no data was submitted, sponsor reported that when each of the carvedilol enantiomers were tested separately, and no difference in neuroprotective ability was noted. Thus, sponsor considered that protection from lipid peroxidation was not enantiomer selective.

POTENTIAL NEUROPROTECTIVE PROPERTIES OF CARVEDILOL (In vivo and in vitro studies)

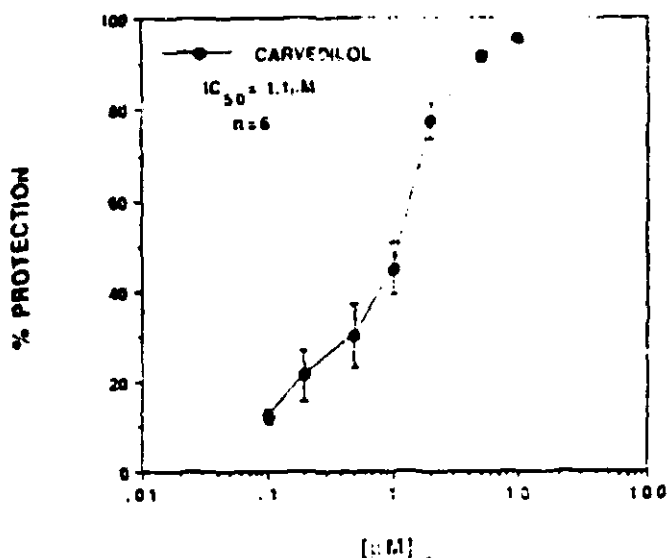


FIGURE LEGENDS

FIGURE 4 Carvedilol protects against glutamate-mediated neuronal death. Cerebellar granule cells grown in 35mm dishes were incubated in the absence of glucose for 40 minutes prior to the addition of 20μM glutamate. Carvedilol was incubated with the cells for 15 minutes prior to the addition of glutamate, and toxicity was assessed 30 minutes later by staining with fluorescein diacetate. Protection of neurons was determined by counting cells and expressing the percent viability.

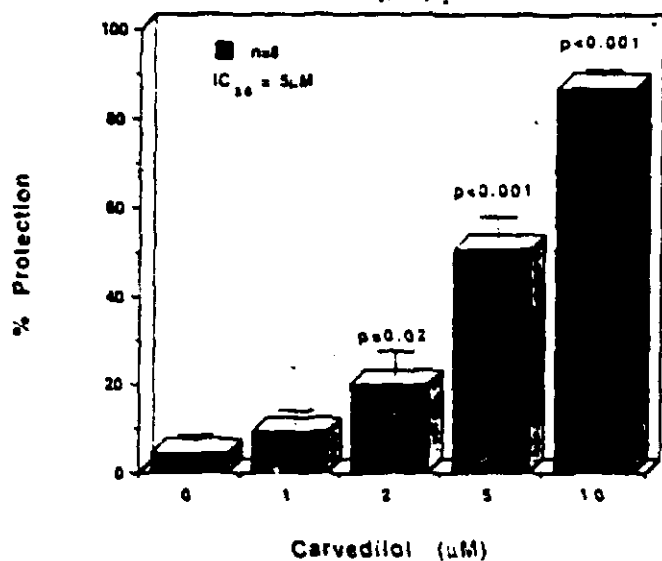


FIGURE 5 Carvedilol protects against hydroxyl radical-mediated neuronal death. Cerebellar granule cells grown in 35mm dishes were incubated in the absence of glucose for 40 minutes prior to the addition of the DHF-Fe³⁺/ADP free radical generating system. Carvedilol was incubated with the cells for 15 minutes prior to a 20 min exposure to DHF-Fe³⁺/ADP. Contents of the dishes were then removed, replaced with buffer, and toxicity was assessed 50 minutes later by staining with fluorescein diacetate. Protection of neurons was determined by counting cells and expressing the percent viability. Significance was determined with Student's unpaired t-test.

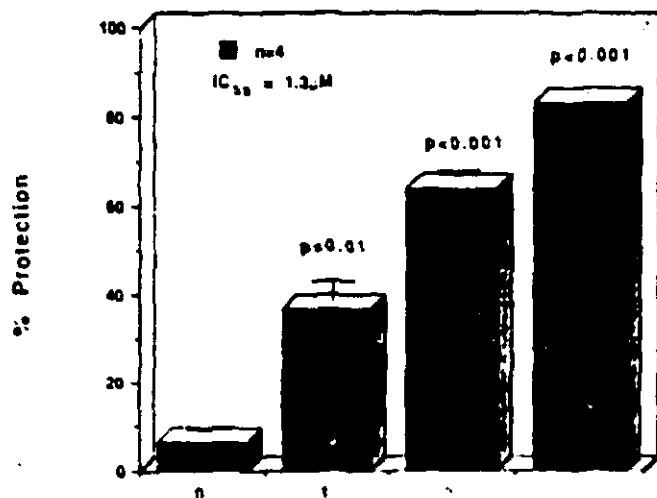


FIGURE 6 Carvedilol protection is augmented by growing cells in the presence of the drug for 24 hours. Cerebellar granule cells were grown with the indicated concentration of carvedilol for 24 hours prior to removal of the growth medium and duplication of the experiments shown in Figure 2. Significance was determined with Student's unpaired t-test.

POTENTIAL NEUROPROTECTIVE PROPERTIES OF CARVEDILOL (Cont'd)

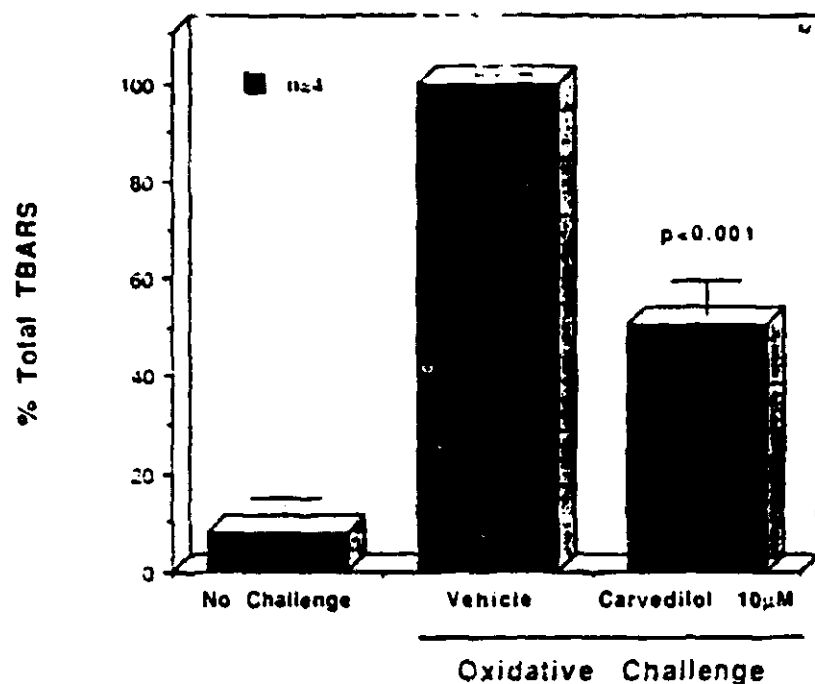


FIGURE 4. Carvedilol inhibits $\text{OH}\cdot\text{Fe}^{3+}/\text{ADP}$ -catalyzed lipid peroxidation.

Cerebellar granule cells grown in 60 mm dishes were incubated in the absence of glucose for 40 minutes prior to the addition of the $\text{OH}\cdot\text{Fe}^{3+}/\text{ADP}$ free radical generating system. Carvedilol was incubated with the cells in a total volume of 3 ml for 15 minutes prior to a 20 minute exposure to $\text{OH}\cdot\text{Fe}^{3+}/\text{ADP}$. Contents of the dishes were then removed, replaced with 3 ml buffer, and after 50 minutes, the reaction was stopped by adding 0.3 ml of 0.2% butylated hydroxytoluene. Samples were then assayed for TBARS as described in Methods. Significance was determined with Student's unpaired t-test.

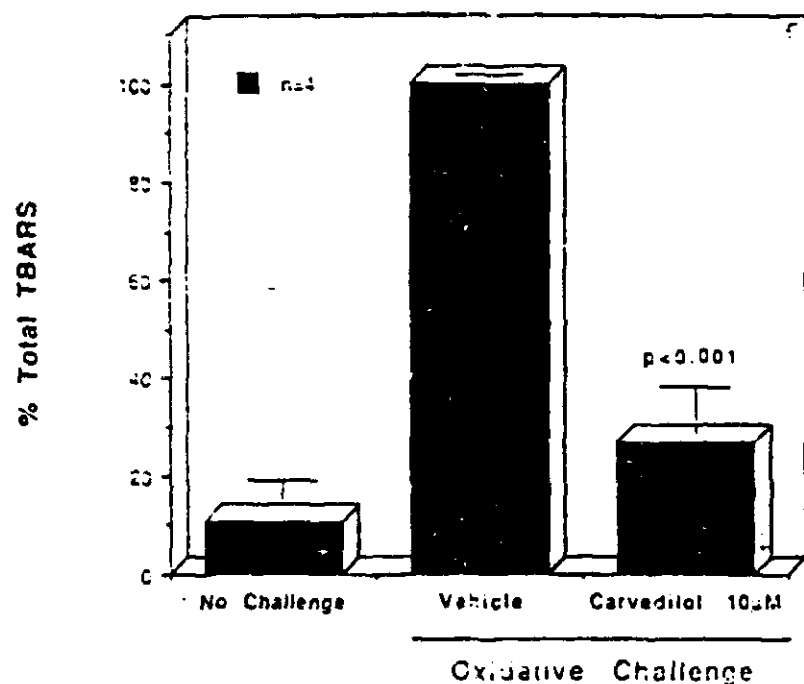


FIGURE 5. Carvedilol inhibits $\text{Fe}^{2+}/\text{vitamin C}$ -catalyzed lipid peroxidation.

Cerebellar granule cells grown in 60 mm dishes were incubated in the absence of glucose for 40 minutes prior to the addition of the $\text{Fe}^{2+}/\text{vitamin C}$ free radical generating system. Carvedilol was incubated with the cells in a total volume of 3 ml for 15 minutes prior to a 120 minute exposure to $\text{Fe}^{2+}/\text{vitamin C}$. The reaction was stopped by adding 0.3 ml of 0.2% butylated hydroxytoluene, and samples were then assayed for TBARS as described in Methods. Significance was determined with Student's unpaired t-test.

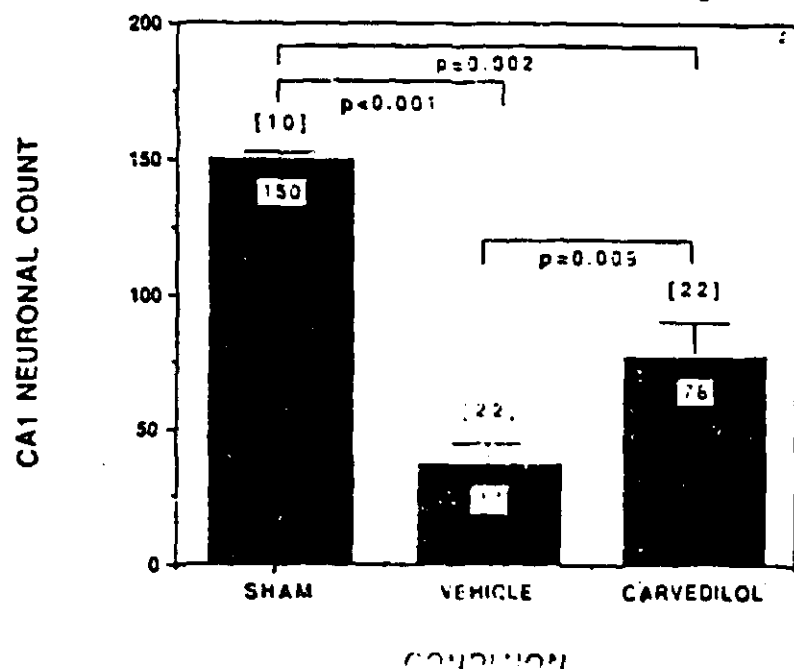


FIGURE 6. In vivo protective effects of carvedilol 7 days after 6-minute ischemia. Carvedilol was given as pretreatment with a bolus of 3 mg/kg s.c. BID for 4 days prior to ischemia and as posttreatment with the same dosing regimen for 3 days thereafter. The number of animals used is indicated over each bar. Data were analyzed by the Kruskal-Wallis procedure, and p values are given for each set of animals. Protection by carvedilol was highly significant as compared to vehicle-treated gerbils ($p = 0.005$).

Vascular Protection

The antiproliferative effects of carvedilol was tested in cultured vascular smooth muscle cells exposed to various mitogens. Carvedilol ($IC_{50} = 1 \mu M$) produced a dose-dependent decrease in basal or endothelin-stimulated ^3H -thymidine incorporation in rat aortic vascular smooth muscle cells. To test the potential of the drug in blocking neointimal growth in response to angioplasty, rats were treated for 3 days with carvedilol (1 mg/kg i.p., BID) and then subjected to left carotid artery balloon angioplasty. Sponsor reported that balloon angioplasty of the left common carotid artery was shown to produce profound intimal thickening in the vehicle-treated rats resulting in a significant (20-fold) increase in the intima:media ratio. The rats were then followed for 14 days with/without treatment with carvedilol, and then sacrificed. Quantitative image analysis of stained cross sections of the carotid vessels revealed profound neointimal growth in the injured vessels of vehicle treated rats; carvedilol treatment caused 80% decrease in the intimal cross-sectional area and intima:media ratio.

These studies suggested to sponsor that *in vivo* the carvedilol treatment afforded protection from the myointimal proliferation that usually results from vascular wall injury following balloon angioplasty. Further, sponsor considered that an antihypertensive regimen with carvedilol might protect against vascular re-stenosis in the clinic following balloon angioplasty injury.

Antioxidant Activity in Heart.

In addition to apparent high-concentration neuroprotective properties of carvedilol (e.g., inhibition of lipid peroxidation inhibition in rat brain homogenates exposed to oxygen free radical generating systems), sponsor reported that lipid peroxidation was also prevented in swine ventricular membranes and rat cardiac microsome preparations (pre-incubated with carvedilol or several β -blocking agents for comparison, and exposed to 2 oxygen free radical generating systems- Fe^{2+} -Vit. C and/or DHF/ Fe^{3+} -ADF). As in the nervous tissues/cell preparations, the rate of swine heart membranes lipid peroxidation was measured by the formation of thiobarbituric acid reactive substances (TBARS). Carvedilol inhibited TBARS formation dose-dependently (Fig. 47 and Table 13 below).

The antioxidant activity of carvedilol was calculated by sponsor as percent (%) inhibition of the lipid peroxidation elevation obtained in the absence of the inhibitor; this is assumed to be 100%. A 50% inhibition of lipid peroxidation was expressed as IC_{50} value.

The EC_{50} values for carvedilol and other β -blockers and a reported inhibitor of lipid peroxidation U74500A are seen below in Table 13 prepared by sponsor. The S(-) and R(+)-enantiomers were equally effective inhibiting lipid peroxidase formation in this preparation (Fig 48 below).

Sponsor considers that the antioxidant activity exhibited by carvedilol is likely through some free radical scavenging mechanism.

ANTIOXIDANT ACTIVITY OF CARVEDILOL IN HEART

Fig. 47

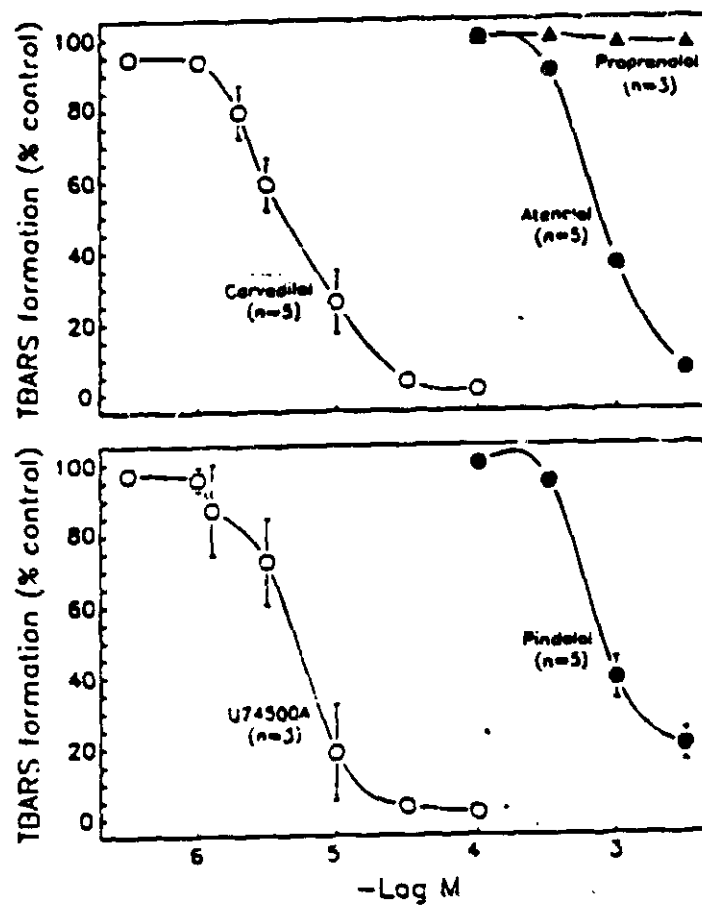


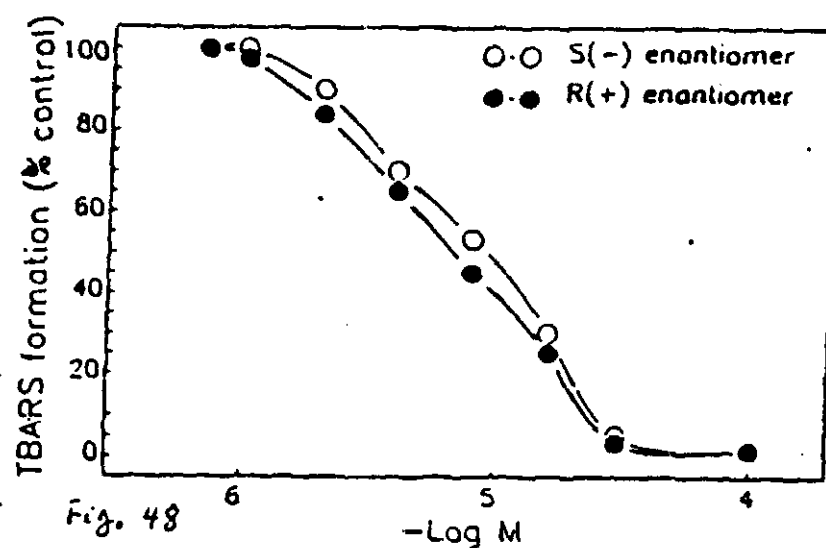
Table 13

IC₅₀ VALUES FOR INHIBITION OF LIPID PEROXIDATION INITIATED BY Fe³⁺-VIT C or DHT/Fe³⁺-ADP IN SWINE VENTRICULAR MEMBRANES

Agent	Fe ³⁺ -vit c		DHT/Fe ³⁺ -ADP	
	IC ₅₀ (M)	Potency	IC ₅₀ (M)	Potency
Carvedilol	5.1 ± 0.9 × 10 ⁻⁶	100	1.4 ± 0.1 × 10 ⁻³	100
Pindolol	1.3 ± 0.1 × 10 ⁻³	0.4	4.1 ± 0.8 × 10 ⁻³	0.3
Atenolol	9.4 ± 0.1 × 10 ⁻⁴	0.5	2.2 ± 0.2 × 10 ⁻³	0.6
Propranolol	>3.2 × 10 ⁻³		3.8 ± 1.3 × 10 ⁻³	0.4
Celiprolol	>1.0 × 10 ⁻³		ND	
Labetolol	>1.0 × 10 ⁻³		ND	
U74500A	4.6 ± 1.8 × 10 ⁻⁶	111	3.5 ± 0.5 × 10 ⁻⁶	400

Values are the mean ± S.E. (n=4-5). ND: not determined

ANTIOXIDANT PROPERTIES OF THE S(-) AND R(+) ENANTIOMERS OF CARVEDILOL



The following table was provided by sponsor summarizing findings of all studies reported in the NDA examining the antioxidant properties of carvedilol.

Table 14

SUMMARY OF ANTIOXIDANT PROPERTIES OF CARVEDILOL

SYSTEM FOR STUDY OF LIPID PEROXIDATION	CARVEDILOL	IC ₅₀ PROPRANOLOL
Swine ventricular membranes Fe ²⁺ -Vit. C-induced	5.1 μM	> 3 mM
DHF/Fe ³⁺ -ADP-induced	14 μM	> 3 mM
Rat Cardiac Microsomes	3.9 μM	170 μM
Rat Brain Homogenates	8.1 μM	> 3 mM
Human LDL Oxidation Macrophage-induced	4 μM	> 100 μM
Cu ²⁺ -induced	17 μM	> 300 μM
Rat Cerebellar Neurons Fe ²⁺ -Vit. C-induced	<10 μM	Not Determined
DHF/Fe ³⁺ -ADP-induced	10 μM	Not Determined
Human Neutrophils	28 μM	> 100 μM
EPR	25 μM	No effect >(0.5 mM)
DHF Autooxidation (NBT Test)	41 μM	No effect >(0.3 mM)

BRIEF OVERVIEW OF NONCLINICAL NEUROPHARMACOLOGIC EFFECTS

In mice, carvedilol (30 - 300 mg/kg p.o) had no effect on the tonic hindlimb extension induced by maximal electroshock. Propranolol (10 to 100 mg/kg p.o) blocked the convulsion completely. Carvedilol (30-300 mg/kg p.o.) failed to show anticonvulsant effect.

In mice, carvedilol, p.o., one hour prior to i.p. injection with phenyl-p-benzoquinone to induce abdominal constriction, the drug dose-dependently produced an analgesic effect (ED-50 14 mg/kg). The analgesia was time dependent. Analgesic activity of carvedilol could not be detected after 8 hours of treatment.

In mice, doses ranging from 1 up to 10 mg/kg p.o. had little or no analgesic effect against acetic acid writhing; at higher doses (30 to 300 mg/kg p.o. the number of writhing significantly decreased. Propranolol (10 mg/kg p.o.) did not influence writhing.

In a journal article submitted by sponsor, compared to propranolol, carvedilol (30 mg/kg p.o) had little or no effect on the spontaneous motor activity of mice. A slight dose-dependent decrease in the activity was observed after dosing with higher doses of carvedilol (100-300 mg/kg). Propranolol also showed similar but stronger decrease in the same doses.

Carvedilol (3 mg/kg p.o.) was without effect on sleeping time induced by hexobarbital. The drug dose-dependently increased in the sleeping time at higher doses. Propranolol (10-100 mg/kg) also tended to potentiate the anesthesia.

In cats, the drug (0.06 mg/kg i.v.) had little effect on spontaneous EEG activity. At higher doses the drug produced a slight arousal patterns in all cats tested; the EEG pattern returned to normal within 60 min in most of the cats. Propranolol (0.04- 0.4 mg/kg) produced similar but stronger changes in the EEG.

In rabbits, carvedilol (30-300 mg/kg p.o.) had inconsistent effects on body temperature.

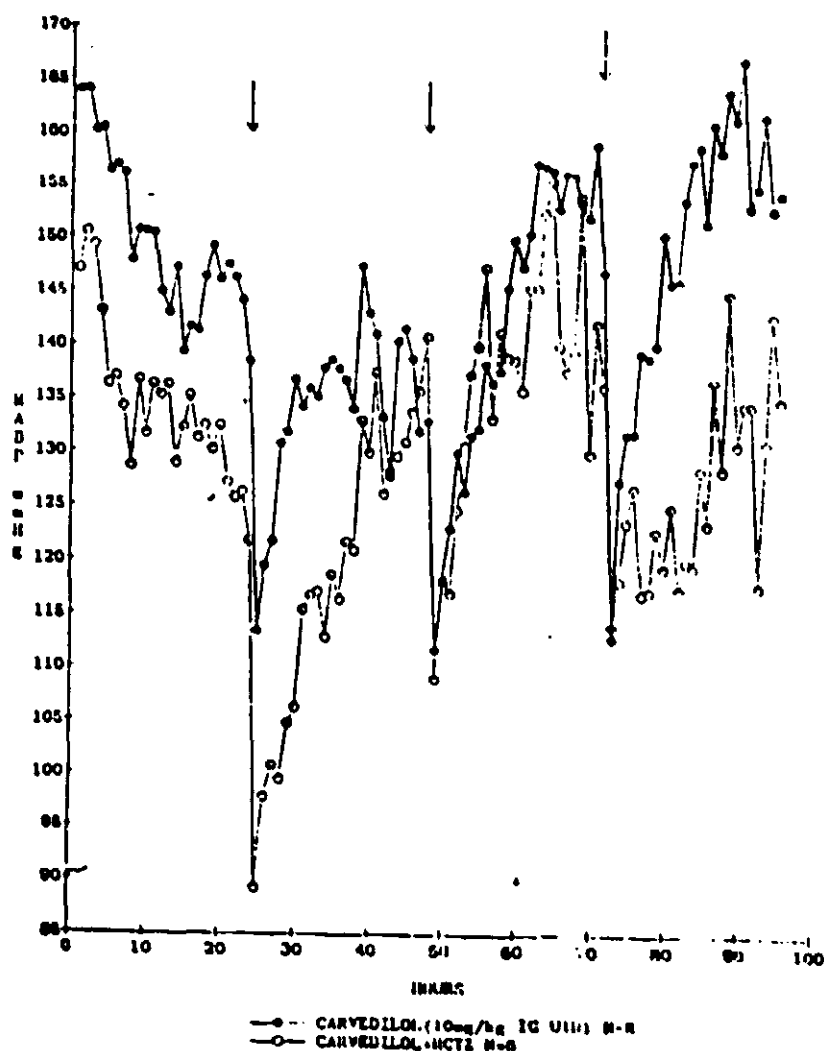
SOME DRUG INTERACTIONS STUDIES

Although not statistically significant, in the rabbit the combination of carvedilol (5 mg/kg i.v. infusion) and the diuretic tor[a]semide (0.5 mg/kg i.v. injection) produced a fall in rectal temperature (up to 1.8°C at this high dose) and increase blood glucose concentrations; the fall in body temperature was completed in about 90 min after treatment and remained at this level. At a lower dose of 1.25 carvedilol and 0.125 mg/kg tor[a]semide, blood sugar decreases occurred within one hour after administration of the combination of drugs. BP effects were not reported.

In conscious SHR, carvedilol, i.g., was associated with rapid dose-dependent decreases in arterial BP (lasting 4-8 hr dependent on the dose). There was no evidence of tachyphylaxis or drug accumulation when the drug was given repeatedly for 3 days. When the drug was given in combination with 50 mg/kg i.g. of each diuretic hydrochlorothiazide (Fig. 49) or furosemide, there was no clear evidence of synergistic antihypertensive response over 3 days of dosing.

Combinations of carvedilol and labetalol with hydrochlorothiazide were associated with acute hemodynamic responses not substantially different than those associated with carvedilol or labetalol alone (no synergistic effect was noted). However, in SHR, carvedilol when given in combination with low or high ceiling diuretics was associated with reductions in urine volume.

FIGURE 49. EFFECT OF CARVEDILOL AND CARVEDILOL-HCTZ ON MEAN ARTERIAL BLOOD PRESSURE IN SHR RATS



SOME GASTROINTESTINAL STUDIES

In anesthetized rats, the action of carvedilol on gastric secretion was investigated in comparison with cimetidine, carbachol and propranolol. In these animals, carvedilol (5 or 0.8 mg/kg i.v. infusion) had no effect on gastric secretion. At the higher dose, there was a clear reduction of gastric acid secretion to about the same level as the cimetidine. Propranolol (5 mg/kg i.v.) also showed a reduction of gastric acid production. In this preparation, carbachol (9 μ /kg i.v.) caused as expected a promotion of gastric acid (reduction of the pH) and the H₂-antagonists cimetidine (8 mg/kg i.v.) caused a reduction of the gastric acid production.

Sponsor asserts that the reduction in gastric acid produced by carvedilol in the rat does not arise via H₂-antagonistic activity. Sponsor bases this assertion on the results from studies using the isolated guinea pig atria. In this preparation, histamine (concentration of 0.13 μ g/ml in bath) produces a moderate rise in atrial rate; the effects of histamine were not affected by carvedilol up to the highest tolerated dose of 1×10^{-5} M (the β -blocking concentration lie in the range of 10^{-9} - 10^{-8} M.), while H₂-cimetidine dose-dependently inhibited the histamine-induced rate increase in guinea pig atria.

In a journal article supplied by sponsor, it was reported that carvedilol (4×10^{-4} to 7 g/ml and propranolol 8×10^{-4} to 7) had little or no effect on tonus of isolated rat stomach. At higher concentrations, propranolol increased the tonus of the stomach in the preparation.

Carvedilol (30-300 mg/kg p.o.) and propranolol (10 to 100 mg/kg p.o.) showed little or no effect on the gastrointestinal transit in mice.

In rats, carvedilol (10 mg/kg i.g.) had little or no effect on gastric pH and acidity of gastric juice or acid and pepsin output. A rise in pH of gastric juice was reported for a dose of 300 mg/kg carvedilol. Propranolol (10 mg/kg i.g.) was without any effect.

In rats, carvedilol (3 - 10 mg/kg p.o.) did not induce gastric mucosal lesions (length of lesions were measured and lesion index reported). At higher doses (30 to 300 mg/kg, gastric lesion of the mucosa by carvedilol was dose-dependent. Propranolol (10 to 300 mg/kg p.o.) caused a slight lesion of gastric mucosa in the rat.

In rabbits, carvedilol (0.6 - 2 mg/kg i.v.) produced no appreciable change in gastric motility. Propranolol increased the gastric motility and tonus in some rabbits at 1.2 mg/kg and in all at 4 mg/kg.

SUMMARY TABLE 15
(Provided by the sponsor)

**EFFECT OF CARVEDILOL ON ARTERIAL BLOOD PRESSURE IN
SPONTANEOUSLY HYPERTENSIVE RATS**

<u>Preparation (Reference)</u>	<u>Route</u>	<u>n</u>	<u>Dose</u>	<u>Maximum % Change</u>	
				<u>MAP</u>	<u>HR</u>
Conscious SHR SK&F Report #PC002BS	p.o.	8-14	1-25 mg/kg	-35%	-11%
Conscious SHR SK&F Report #PC036BS	p.o.	3-6	1-10 mg/kg	-25%	
Conscious SHR, chronic dosing SK&F Report #PP1001BS	p.o.	22	20 mg/kg/d	-9%	-13%
Conscious SHR SK&F Report #PP003DS	i.g.	7-15	0.3-60 mg/kg	-27%	
Conscious SHR SK&F Report #PP004BS	i.g.	5	1-30 mg/kg	-28%	
Conscious SHR SK&F Report #PP004BS	i.v.	5	0.03-3 mg/kg	-25%	-22%
Conscious SHR SK&F Report #PP004BS	i.v.	5	0.003-0.3 mg/kg/min (30 min)	-22%	-11%
Conscious SHR SK&F Report #PC002BS	i.v.	12	0.03-1 mg/kg	-35%	-15%
Conscious SHR SK&F Report #PC055BS	i.v.	12	0.03-1 mg/kg	-22%	
Conscious SHR SK&F Report #PC036BS	i.v.	3-6	0.03-1 mg/kg	-25%	
Anesthetized SHR SK&F Report #PP009BS	i.v.	4	0.03-1 mg/kg	-34%	-13%
Anesthetized SHR SK&F Report #PP016BS	i.v.	1	0.001-3 mg/kg	-29%	-25%

TOXICOLOGY:**ACUTE (SINGLE DOSE) TOXICITY STUDIES**

The acute toxicity of carvedilol, its enantiomer and four metabolites were studied in 3 animal species. The results of these studies were described in detail in summary tables prepared by sponsor. Although sponsor has submitted in depth summary tables of acute toxicity in mouse, rat and dog given carvedilol by the oral, i.v., and i.p. routes, this reviewer has extracted only oral and i.v. data to prepare the summary tables presented below.

The approximate LD-50 values for the difference species and routes of administration appear below.

Species	Duration (days)	Doses (mg/kg)	Report No.	Approximate LD-50 Values and Drug-Related Observations
			Location in NDA IND Submission	
Mouse	14	8000 oral	TC004BS (Boehringer Mannheim report F1) Ref. 1 Location: Vol. 1.15 Page 000003 Submitted to IND on 2/15/85	Oral LD ₅₀ >8000 mg/kg in males and females. Apart from hair loss, no other clinical signs were observed. Two animals died and showed macroscopically, lung edema and hemorrhage.
Mouse	14	4000, 8000 oral	TC0031/SKF-105517 (Daiichi report D-1-1) Ref. 2 Location: Vol. 1.15 Page 000044	Oral LD ₅₀ >8000 mg/kg in males and females. Clinical signs consisted of decreased body weight or body weight gain during the first 2 to 4 days, blepharoptosis, decreased motor activity, depressed respiration, soiling of the fur and wasting. Animals that died showed congestion of various organs and microhemorrhages in the brain. Animals that were killed at the end of the study showed splenic congestion and increased extramedullary hematopoiesis. Absolute and relative spleen weights were increased.
Rat	14	500, 1000, 2000, 3200, 4000, 8000 oral	TC004BS (Boehringer Mannheim report F2) Ref. 1 Location: Vol. 1.15 Page 000003 Submitted to IND on 2/15/85	Oral LD ₅₀ >8000 mg/kg in males and females after 1-14 days. Slight hair loss was the only clinical sign observed.
Rat	14	4000, 8000 oral	TC0031/SKF-105517 (Daiichi report D-1-1) Ref. 2 Location: Vol. 1.15 Page 000044	Oral LD ₅₀ >8000 mg/kg in males and females. Clinical signs consisted of decreased body weight or body weight gain during the first 2 to 4 days, blepharoptosis, decreased motor activity, suppressed respiration, soiling of the fur and wasting. Animals that died showed congestion of various organs and microhemorrhages in the brain. Animals that were killed at the end of the study showed splenic congestion and increased extramedullary hematopoiesis. Relative spleen weights were increased.

**ACUTE (SINGLE DOSE) TOXICITY STUDIES OF CARYEDILOL'S⁽¹⁾
METABOLITES**

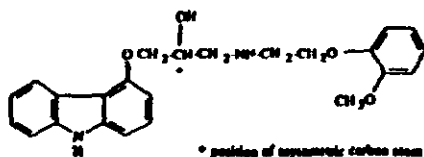
Species	Duration (days)	Doses (mg/kg)	Report No. Ref. No. Location in NDA IND Submission	Drug-Related Observations
Rat	14	30, 50 ⁽²⁾ i.v.	TC0024/SKF-105517 (Boehringer Mannheim report F0011) Location: Vol. 1.15 Page 00168	I.V. LD ₅₀ of metabolite M2 >50 mg/kg. At 30 mg/kg, apathy (0-45') and ptosis (5-60'). At 50 mg/kg, severe apathy (2-60') and clonic spasms (2-10'). <i>No animals died.</i>
Rat	14	30, 40, 50 ⁽³⁾ i.v.	TC0025/SKF-105517 (Boehringer Mannheim report F0012) Location: Vol. 1.15 Page 00185	Approximate I.V. LD ₅₀ >40 mg/kg. At 30 mg/kg, slight apathy (2-60'); at 40 mg/kg, clonic spasm (0-5'), moderate apathy and staggering (up to 120' or death), ptosis in survivors (20-120') and at 50 mg/kg, clonic spasms (0-1'), severe apathy (1-2') and death within 2 minutes (<i>2/2 F tested</i>). Macroscopic findings at 40 and 50 mg/kg: red marbled and slightly swollen liver. <i>Survivors at LD and MD showed no liver pathology.</i>
Rat	14	30, 50 ⁽⁴⁾ i.v.	TC0026/SKF-105517 (Boehringer Mannheim report F0013) Location: Vol. 1.15 Page 00203	Approximate I.V. LD ₅₀ >50 mg/kg. At 30 mg/kg, trembling (5') and slight apathy (15-25'). At 50 mg/kg, apathy (60-90'), clonic spasm (5') and bristling of the fur (30'). One female at 50 mg/kg died 3 minutes after dosing. <i>Postmortem examination showed no pathology.</i>

Chemical structure of Caryediol (SKF 105517, BM 14 198, DQ 3446)

② M2 metabolite (BM 14.242)

③ M4 metabolite (BM 14.0686)

④ M5 metabolite (BM 14.0830) ⑤



Structure	24 Metabolite Number	26 Metabolite Number	Species
	M2	22	Mus [70]
	M4	26	Mus [70]
	M5	32	Mus

BEST POSSIBLE COPY

Acute Toxicity (Cont'd.)

ACUTE (SINGLE DOSE) TOXICITY STUDIES OF CARVEDILOL (SLO-27 10002)

Report No.

Location in FDA
IND Submission

Summary of Observations

M (dog)
(Boehr)

14

500, 1000, 2000
oralTC0028/SKF-105517
(Daichi report D-1-3)

Location: Vol. 1.15 Page 000262

Oral LD₅₀ ≥ 1000 mg/kg. One of the 2 dogs at 1000 mg/kg and 2 of 2 at 2000 mg/kg vomited. Other clinical signs consisted of blepharospasm, reduced locomotor activity and unsteady gait. Transient changes in clinico-pathology parameters were observed. No macroscopic or microscopic changes were found.

Intravenous Route

Mouse

14

32, 40, 50
i.v.TC004BS
(Boehringer Mannheim report F7)Location: Vol. 1.15 Page 000003
Submitted to IND on 2/15/85

I.V. LD₅₀: 41.1 (35.9-47.9) mg/kg after 1-14 days. Clinical signs: apathy and convulsions. No macroscopic findings.

Mouse

14

males: 10, 20, 30, 40, 50, 100
females: 10, 20, 30, 35, 40, 50, 100
i.v.

TC004BS
(Boehringer Mannheim report F5)Location: Vol. 1.15 Page 000003
Submitted to IND on 2/15/85

I.V. LD₅₀: females: 36 (31-40) mg/kg after 1-14 days; males: 31 (26-36) mg/kg after 1 day and 27 (21-33) mg/kg after 7-14 days. Apathy only clinical sign observed. Macroscopic findings: lung edema (20, 50, 100 mg/kg), discolored liver (40, 50, 100 mg/kg), light red spleen (30, 40 mg/kg) and watery gastrointestinal contents (30, 40 mg/kg).

Rat

14

males: 22, 25, 27, 30
females: 15, 20, 22, 23, 25, 30
i.v.

TC004BS
(Boehringer Mannheim report F6)Location: Vol. 1.15 Page 000003
Submitted to IND on 2/15/85

I.V. LD₅₀: females: 25 (24-26) mg/kg after 1-14 days; males: 27 (26-28) mg/kg after 1-14 days. Clinical signs: ptosis and apathy. No dose free of signs. Macroscopic findings: lung edema and hemorrhage.

SYNOPSIS OF ACUTE TOXICITY STUDIES WITH CARVEDILOL

The drug sponsor reported estimated median lethal doses for carvedilol and related compounds in mouse, rat and dog. The calculated median lethal oral doses in both rodent species was above 8000 mg/kg and for dog above 1000 mg/kg. In the rodents, toxic signs reported after receiving a range of large oral doses of the drug included- hair loss, decreased motor activity, blepharoptosis, depressed respiration and microhemorrhages in the brain (mouse) and, in dog- decreased motor activity and, unsteady gait.

The estimated median lethal dose for carvedilol by the i.v. route, was not significantly different among the rodents tested. Estimated values in 2 mouse i.v. studies were 36 mg/kg in females and, 27 mg/kg i.v. in males. Remarkable toxic signs in these mice treated with carvedilol i.v. included apathy, convulsions and, macroscopic signs in the second mouse study included lung edema and discolored liver. In male rats the estimated median lethal dose for carvedilol was 27 mg/kg i.v. The median i.v. lethal dose in the dog was not calculated.

Limited studies were conducted to characterize the toxic profile of S(-) and R(+)- enantiomers of carvedilol. Acute toxic signs reported for both enantiomers given by i.v. to mouse were apathy and convulsions; macroscopic findings reported consisted in pulmonary edema. In these mice, the mean lethal doses were estimated as 43.4 mg/kg for S(-)-enantiomer and 30.8 mg/kg i.v., for R(-)-enantiomer. In mouse the overt toxic signs for the enantiomers were no different that for the racemic mixture given i.v.

Acute i.v. toxicity in rat of 3 of the major (and pharmacologic active*) metabolites of carvedilol in mouse and rat was calculated. The metabolites tested were the hydroxy-metabolites M2 (BM 14.242), M4 (BM 14.0686) and M5 (BM 14.0830). In mouse, the median acute dose for M2 was 38 mg/kg i.v. In rat, the estimated value for M2 was above 50 mg/kg (at 30 mg/kg i.v. apathy occurred and, at 50 mg/kg severe apathy and clonic spasms), but no rats died. The mean lethal i.v. dose for M4 and M5 is estimated to be about 40 mg/kg and 50 mg/kg i.v., and greater, respectively. Toxic signs were similar to that of the M2 metabolite and included in common- apathy and clonic spasms. Rat given the M4 metabolite, macroscopic examination in one rat study showed red marbled and slightly swollen liver at 40 and 50 mg/kg i.v. Other postmortem observations, including survivors, were unremarkable.

Data submitted indicate that the estimated mean lethal oral doses of the drug for rodents and dogs of 8000 and 1000 mg/kg, respectively, represent about 8000 and 1000 times the maximum recommended human oral dose of 1 mg/kg carvedilol, assuming a 50 Kg patient.

In dog, limiting toxicities studies with carvedilol (15 mg/kg i.v.), were convulsions and alterations in the ECG (prolongation of P wave, PR and QRS intervals).

* In separate studies the metabolites M2, M4 and M5 showed some β -blocking activity.

SUMMARY OF MULTIDOSE TOXICITY STUDIES

The following tables are the extracted portions of tables submitted by drug sponsor. Footnotes have been added to these new tables where added information was considered needed.

Species	Duration (weeks)	Doses (mg/kg)	Report No. Location in NDA (NDA Submission)	Drug-Related Observations
* 1- Mouse	13	20, 60, 200, 600, 800 diet	TPXXX/SKI-105517 (Boehringer Mannheim report J6) Location: Vol. 1.15 Page 000289	Body weight was lower (-11 and -17%) in males of the 2 highest dose groups. Hemoglobin was significantly increased in drug-treated males without a dose response being evident. Increases (<2x control) in alkaline phosphatase values were present in males of the 2 highest dose groups. sGPT was increased (max. 2x control) in all drug-treated males and females with exception of high-dose females. Serum total protein was decreased (~10%) in males of the 2 highest dose groups. Liver weights were increased in females at dosages ≥200 mg/kg (up to 30%) and only relative liver weight was increased in high-dose males (20%). Histopathology was not performed. <i>The no-observed effect dose is considered 60 mg/kg/day in this mouse study.</i>
* 2- Rat	13	30, 100, 300 oral	TC007BS (Boehringer Mannheim report 112) Location: Vol. 1.16 Page 00002 Submitted to INF on 2/15/85	Hair loss was observed in 8/10 high-dose animals and blepharophimosis in the majority of mid- and high-dose animals. sGPT was increased (<2.5x control) in high-dose females with value returning to normal in off-dose period. Relative liver weight was increased in drug-treated animals (up to 25% in high-dose males and up to 50% in high-dose females). Light microscopic examination revealed exacerbation of spontaneous cardiomyopathy in mid- and high-dose animals. Regenerative hepatocellular hyperplasia was observed in 1 high-dose male, nodular hepatocellular hyperplasia in 1 high-dose male and 2 high-dose female and minimal pericholangitis in 3 high-dose males and 3 high-dose females. Furthermore, high-dose animals showed splenic congestion.

* 1.- Sixteen (16) mice (NMRI)/sex/group were used; animals were housed individually. Although alkaline phosphatase was increased in drug treated males, only HD females (800 mg carvedilol/kg/day in diet) a slight increase in this enzyme levels. Toxicokinetic studies revealed that carvedilol was detected in the serum of all drug treated mice with the exception of a few treated with 20 mg/kg/day in diet. Based on the findings in this 13-week study, sponsor considered that the MTD (see toxic signs above) for the mice was 200 mg/kg/day, thus the doses selected for the mouse carcinogenicity study were 20, 65 and 200 mg/kg/day.

* 2.- Twelve (12) rats (Sprague-Dawley, Caw-Ico-Wiga)/sex/group were used. In this study, the NOAEL for carvedilol was estimated as 30 mg/kg/day. Blepharophimosis appeared within 2 hours after treatment with the MD and HD. Although reversible, early in the study elevations of hemoglobin, hematocrit and sGPT were seen at MD and HD. Remarkable histopathologic changes reported included cell infiltrates in the myocardium and inflammatory changes in peripheral biliary tract.

REDACTIONS MADE BY APPLICANT

Multidose rat (Cont'd)

Species	Duration (weeks)	Doses (mg/kg)	Report No. Ref. No. Location in NDA IND Submission	Drug-Related Observations
3) Rat	13	30, 100, 300 oral	TCX0029/SKF-105517 (Daiichi report D-4-1) Location: Vol. 1.17 Page 000002	Salivation, lacrimation and blepharoptosis were observed in mid- and high-dose animals. Three high-dose females died as a result of respiratory/cardiac failure. Less body weight gain associated with less food intake were noted in mid- and high-dose males and high-dose females. Blood pressure was increased in high-dose animals (~13%) and heart rate was decreased in drug-treated animals. Slight increases in serum alkaline phosphatase, leucine aminopeptidase, bilirubin, cholesterol, uric acid, CPK, potassium, phosphorous and calcium concentrations were observed in mid- and/or high-dose animals. Decreases were observed for cholinesterase, creatinine, triglycerides, total protein, albumin and chlorine concentrations. Various organ weight increases (adrenal, liver, spleen) and decreases (uterus, thymus, pituitary) were observed in mid- and/or high-dose animals. Dark spleen and dilation of the common bile duct were macroscopic observations in high-dose animals whereas bile duct hyperplasia, biliary ductular dilation, centrilobular hepatocellular hypertrophy, adrenal cortical hypertrophy, uterine atrophy and exacerbation of spontaneous cardiomyopathy were observed microscopically in mid- and/or high-dose animals. Most changes appeared to be reversible after a 5-week drug-free period.
4) Rat	15	(200 ppm) - 11(M), 13(F); (400 ppm) - 33(M), 42(F); (2000 ppm) - 100(M), 126(F); (6000 ppm) - 385(M), 413(F); (2000 ppm) - 532(M), 486(F) diet	TP-0004/SKF-105517 (Boehringer Mannheim report 15) Location: Vol. 1.16 Page 000333	Rough pelt was observed in animals of the highest dose groups. Animals of the 2 highest dose groups consumed less food (down to 17% in males and 30% in females). Body weight was decreased accordingly in these animals. Erythrocyte parameters (Hgb, PCV, MCV) were slightly decreased in animals of the 2 highest dose groups. Significant increase in leukocyte count was observed in high-dose animals (29% and 94% in males and females, respectively). Alkaline phosphatase values did not decrease with age in animals of the 2 highest dose groups. There was no consistent pattern in organ weight changes compared to controls in both sexes. Drug-related macroscopic findings were dilated bile ducts and concretion formation. Histopathology was not performed. <i>The "no-adverse-effect" dose may be considered 200 ppm (1-13 mg/kg/day)</i>

* 4.- Twelve (Sprague Dawley, Caw-Ico-Wiga) rats/sex/group used. Carvedilol was fed in the diet at concentrations ranging from 200 up to 6000 ppm (see above the calculated drug intake by end of study). Remarkable findings reported, not included above summary, included dose-related increases in liver weight (absolute/relative; significant at the 3 highest doses tested); testicular atrophy and edema in some males at the 2 highest doses, and in both sexes some rats had dilated ductus choledochus/punctate stone formation. Present reviewer's calculations of final body weights showed a decrement of more than 10% at the 2 highest doses compared to controls. Sponsor estimated from this study the MTD and selected a "... dose of 4000 ppm based on effects on body weight development, absolute and relative organ weights, haematological and biochemical parameters." Sponsor also stated that "Based on body weight, food consumption and clinical pathology dosages of ≥ 6000 ppm exceeded the maximally tolerated dose in a carcinogenicity study." Toxicokinetic data for this 15-week rat study showed animals were exposed to the drug; compared to week 1, serum concentrations of carvedilol were higher at the end of the study suggesting a decrease in clearance after repeated administration (Table 30 under Overview of ADME Studies)

Multidose rat (Cont'd)

Species	Duration (weeks)	Doses (mg/kg)	Report No. Ref. No. Location in NDA IND Submission
Rat	52	(100 ppm) - 33(M), 38(F); (2000 ppm) 106(M), 128(F); (6000 ppm) 333(M), 354(F) ² diet	TC008BS (Boehringer Mannheim report 114) Location: Vol. 1.18 Page 000002 Submitted to IND on 2/14/86
Rat	78 (19 mo)	31, 89, 261 ¹ diet (600, 1700 and 5000 ppm)	TC0003/SKF-105517 (Boehringer Mannheim report 116) Location: Vol. 1.19 Page 000002

Drug-Related Observations

The mid- and high-dose animals showed narrowing of the eyelids, slightly encrusted snout, apathy and rough pelt. Food intake was decreased in high-dose females and varied between -24 and -59%. Drug-treated females gained less body weight in a dose-related fashion (-3 to -27%). High-dose males also gained less weight (-14%). A control male and female, 3 mid- and 2 high-dose males and 1 high-dose female died during the study. Death of the control female and 1 mid-dose male was considered accidental. Alkaline phosphatase values were higher in high-dose animals (<3.5x control value). Liver weights were increased in females in a dose-related fashion. Mid- and high-dose animals showed exacerbation of spontaneous cardiomyopathy. Biliary hyperplasia occurred in a higher incidence in drug-treated animals, particularly in high-dose animals. The latter also showed a higher incidence of proliferative liver lesions (altered foci) compared to other groups.
The No. adverse effects could not be determined.

Only during the first 4 weeks, high-dose animals showed sticky eyes, unkempt fur and apathy. Food intake was less in mid- and high-dose animals (down to -6 and -26%, respectively). Drug-treated animals showed a dose-related decrease in body weight (-23% and -43% in high-dose males and females, respectively). Mortality was lower in the mid- and high-dose animals than in the control and low-dose animals. A slight increase in cholesterol and triglyceride serum values was seen in high-dose females. A minimal chronic inflammatory cell infiltrate and fatty infiltration were observed in the hearts of drug-treated animals. A dose-dependent increase in incidence of biliary hyperplasia with all high-dose animals affected was observed. The hyperplastic change was associated with a mixed inflammatory cell infiltrate. Liver cell hyperplasia (altered foci) was also increased dose-dependently. Two high-dose males and 3 high-dose females had developed a hepatocellular adenoma.

¹ Mean daily drug intake over study period
² Actual drug intake at end of study period

Multidose rat (Cont'd)

Species	Duration (weeks)	Doses (mg/kg)	Report No. Ref. No. Location in NDA IND Submission	Drug-Related Observations
Rat	78	10 <i>in diet</i>	TC/0003/SKF-105517 (Boehringer Mannheim report H6) (supplement) Location: Vol. 1.19 Page 000002	No differences between control and drug-treated animals were observed.
Rat	4	2.5, 5, 10 i.v.	TP/0003/SKF-105517 (Boehringer Mannheim report G3) Location: Vol. 1.23 Page 000002	Blepharospasm and apathy were observed in mid- and high-dose animals. Tail vein changes precluded further dosing of high-dose animals after 16 days. High-dose females showed decreased food consumption at end of study (~10%). High-dose animals showed decreased body weight from 3 weeks onward (down to -8%). Grossly, tails of the high-dose animals showed subcutaneous hemorrhage, brownish discoloration of the liver in mid- and high-dose males and females and enlargement of the spleen in some high-dose animals. Mid-dose females showed an increase in heart and spleen weights (up to 14 and 28%, respectively). Perivascular inflammation was evident at the injection site. Severity was dose-related. Fatty infiltration of the liver was observed in mid- and high-dose females. Intravenous no effect dose was 2.5 mg/kg.

Multidose dog (beagle)

Species	Duration (weeks)	Doses (mg/kg)	Report No. Ref. No. Location in NDA (IND) Submission	Drug-Related Observations
* 1) - Dog	13	15, 50, 150 oral	TC009BS (Boehringer Mannheim report III) Location: Vol. 1.24 Page 00002 Submitted to IND on 2/15/85	An episode of vomiting was seen in high-dose females during the 9th week of treatment. ECG recordings demonstrated a decrease in heart rate and a prolonged PQ interval in drug-treated dogs (due to B-blocking activity of carvedilol). A transient decrease in hemoglobin value was observed in the first week of the study. Relative liver weights were increased in mid- and high-dose male dogs. A dose-dependent increase in relative spleen weight was noted in female dogs; mid-dose male dogs also showed an increase. One low- and one mid-dose male showed fatty infiltration of the heart muscle. Fatty infiltration of the liver was seen in a mid-dose male and female. Iron negative pigmentation was seen in the spleen of one low-dose male and one mid-dose female.
* 2) Dog	13	10, 50, 250 oral	TC0032/SKF-105517 (Daiichi report D-5-1) Location: Vol. 1.24 Page 000325	High-dose animals showed vomiting, blepharoptosis, protrusion of the membrane nictitans, decreased motor activity and less weight gain. One high-dose female died and showed drug-related pulmonary congestion, hemorrhage and edema. Blepharoptosis was also observed in mid-dose animals. The liver function test showed a significant increase in low-dose females only. A prolonged mean PQ-interval was noted in mid-dose males. Serum potassium (K ⁺) concentrations ($\leq 21\%$) were increased in mid- and high-dose animals. Liver weights were increased in high-dose animals ($\leq 41\%$), adrenal weights in low- and high-dose males ($\leq 40\%$), thyroid weights in high-dose females (25%) and pituitary weights in high-dose females (29%). However, thyroid weights were decreased in low-dose females (down to 38%). Splenic congestion was common in high-dose animals. The no effect dose was considered to be 10 mg/kg/day.

* 1- Three beagles/sex/group were used; 3 dogs of the same sex/dose were housed together. Drug doses used in this 13-week study were based on multiples of the effective pharmacologic dose of 3 mg carvedilol/kg p.o. for inhibition of isoprenaline tachycardia in dogs. In these dogs, carvedilol (15, 50 and 150 mg/kg p.o.) was given in capsules.

* 2- In this 2nd dog study, the doses of carvedilol tested were based determined because all carvedilol- 30 up to 300 mg/kg p.o., dogs included consisted in decreased in spontaneous activity at HD. The treatment with carvedilol (0.2, 1.0 and 5.0 mg/kg for 4 weeks), resulted in no

a previous study. (See that study below as #3 in which a "no-effect" dose could not be determined due to bile duct proliferation.) In the present study (# 2 above), a remarkable effect not observed in the low dose was 10 carvedilol/kg. In a separate subchronic study with beagles, i.v. treatment with carvedilol (0.2, 1.0 and 5.0 mg/kg for 4 weeks), resulted in no biological arrhythmias or extrasystoles, and no dose-dependent changes in QRS-complex.

Multidose beagle (Cont'd)

Species	Duration (weeks)	Doses (mg/kg)	Report No. Ref. No. Location in NDA IND Submission	Drug-Related Observations
*3) - Dog	26	30, 100, 300 oral	TC1010BS (Boehringer Mannheim report 113) Location: Vol. 1.25 Page 000002 Submitted to IND on 3/17/90	Transient clinical signs in high-dose animals were lacrimation, swollen eyes, ptosis, slight apathy and respiratory problems. Most of these signs were also seen in one mid-dose male in week 21 of the study. One mid- and one high-dose male died during the study. The mid-dose male showed the clinical signs mentioned above before he died. The other had not shown any signs before death. ECG recordings showed prolongation of the PQ-interval in low- and mid-dose animals but not in high-dose animals. White blood cell counts were up 1.3x in high-dose females but not in high-dose males. Serum alkaline phosphatase values were higher in high-dose animals (up to 1.7x) than in controls. sGPT was increased up to 1.5x in high-dose males during the last 6 weeks of the study. Congestion of various organs was the only drug-related macroscopic finding. Relative liver (up to 1.5x) and spleen (up to 4x) weights were increased in high-dose males. Mid- and high-dose females also showed an increase in relative spleen weight (up to 1.7x). Bronchopneumonia was observed in control and drug-treated animals but was more common in the latter ones. Minimal biliary hyperplasia ¹ was only observed in drug-treated animals.

*3.- In this study, 5 beagles/sex/group were used. Carvedilol was administered in capsules. Although this study was designed to last for more than 26 weeks, the duration was reduced to according to drug sponsor to be in "line with European Economic European regulations." NB- To date the FDA has not agreed comply with these EEC guidelines.

In addition to listed toxic signs in the sponsor's summary table above, transient reduction in food intake at HD and, decrease in Hbg in some drug-treated dogs were seen (reversible only in females). Sponsor concludes that the minimal biliary duct hyperplasia in drug-treated animals is of "limited toxicologic importance." (NB- This effect was also reported in a second species treated with carvedilol; in long-term studies hyperplasia of bile duct was also reported.)

A table entitled was provided ("Table 150 "Determination of drug level" in vol 25, p. 250) with no explanation as to what these "drug levels" refer to. Protocol was or sponsor's summary of study was helpful in clarifying the significance of this table.

Multidose beagle (Cont'd.)

Species	Duration (weeks)	Doses (mg/kg)	Report No. Ref. No. Location in NDA IND Submission	Drug-Related Observations
4- ² Dog	52	10 oral	TC011BS (Boehringer Mannheim report 115) Location: Vol. 1.26 Page 000002 Submitted to IND IND on 6/3/87	Infrequent vomiting and diarrhea and a slight increase in the number of erythrocytes were the only observations made.
1- ² Dog	52	30, 100, 300 oral	TC011BS (Boehringer Mannheim report 115) Location: Vol. 1.26 Page 000002 Submitted to IND on 6/3/87	Apathy, slight ataxia and blepharostenosis were observed in high-dose animals in the first week of the study. From week 5 onward, vomiting and diarrhea were common observations in mid- and high-dose animals and were seen infrequently in low-dose animals. Heart rate was decreased in high-dose females only. ECG recordings showed prolonged PQ-intervals in the drug-treated animals, particularly in the low-dose group. A dose-related increase in relative liver weight was observed in both sexes (up to 18% in males and 43% in females). Biliary hyperplasia occurred more frequently in mid- and high-dose animals and was graded as more severe than in the controls. <i>CL: "no-adverse effect" CL could not be determined.</i>

4 - In the 52-week dog study, 5 beagles/sex/group were used. Study was divided in 2 sections (listed as 8a and 8b above), each with its own control group. Doses of carvedilol were given in 2 daily oral portions for the 52 weeks and then, 1 dog/sex/group were placed on a drug free schedule for 17 weeks for observation.

-a) In the 10 mg/kg/day group, no remarkable histopathologic changes were reported.

-b) Although controls beagles (1M, 1F) and at LD (1M and 1F) exhibited minimal bile duct hyperplasia, this pathologic change (severity minimal to moderate) was mainly observed in drug-treated beagles at MD (2F and 4M) and HD (4M and 5 F). Sponsor explains the bile duct epithelial hyperplasia as "an expression of regeneration of a drug-induced minimal damage and the balance between local damage and its repair remain stationary over 12 months." No remarkable finding were reported in beagles from drug-free portion of the study. Use in was noted at the beginning of the study in some dogs at 10 mg/kg/day considered due to excitement from manipulation.

ORGAN TOXICITY REPORTED IN VARIOUS STUDIES WITH CARVEDILOL

The primary targets of organ toxicity were liver and heart in mouse, rat and dog treated with repeated doses of carvedilol by oral route. In these 3 species, repeated doses of the drug were associated with liver changes (increase liver weights and unremarkable increases in liver enzymes); rats and dogs also showed biliary hyperplasia. In the heart histopathologic changes were reported as "exacerbated spontaneous cardiomyopathy" or "minimal chronic inflammatory cell infiltrate and fatty infiltration" for rat, and fatty infiltration in dog.

In the 12-month study in rats with carvedilol (LD-600, MD- 2000 and HD- 6000 ppm with with an average daily intake of LD-35.5, MD-117 and HD- 343.5 mg/k), compared to controls there was a higher incidence of bile duct hyperplasia in all carvedilol treated groups. In these rats, the combined (males and females) bile duct hyperplastic findings were reported as C-0, LD- 30, MD- 28 and HD- 59 by one pathologist vs C-5, LD- 9, MD- 43 and HD- 56 by a second pathologist. (Slides were reported as read blindly. No statistical analyses were found for the biliary duct hyperplasia findings.) Also reported in these rats were focal liver hyperplasia, and increase in myocardium interstitial infiltrates and occasionally swelling of the myocardial fibers (See Table 16a below) In this rat study, the apparent "no-effect" level for carvedilol was at the LD (35.5 mg/kg daily p.o.) In the 18-month rat study with carvedilol (LD- 200, MD- 600, HD-1 1700 and HD-2 5000 ppm), liver hyperplasia was reported by sponsor to be an expression of metabolic overload of the liver; hepatomas also were reported in 5 animals at HD (261 mg/kg daily intake at the end of the study). Since some of these rats were allowed to be drug-free for 3 months, and scar formation and telangiectases were later observed, sponsor interpreted these findings as signs of regressive changes. Although in these rats biliary hyperplasia was dose-dependent compared to control, no dose-dependent changes were found in the heart histopathologic changes.

Biliary hyperplasia in the rat was reported as resembling the "type of biliary epithelial hyperplasia seen spontaneously in the rat" and that seen in the dog as being minimal to mild and mostly within the range of untreated controls.

In the dog, heart histopathologic changes consisted of fatty infiltration of the heart muscle; but since these changes were also noted in the control dogs, sponsor did not consider them drug related.

Heart and liver histopathologic changes are summarized by sponsor in Tables 16a, b, c and d.

Table 16 Incidence of Cardiomyopathy in the Rat as Observed in Various Toxicity Studies of Carvedilol

16a)

Doses (ppm)	Males			Females		
	12-Month	18-Month	18-Month	12-Month	18-Month	18-Month
0	0/30	3/30	23/30	0/30	0/30	10/30
200			7/30			7/30
600	3/30	18/30		1/30	6/30	
1700		10/30				
2000	10/30			13/30	10/30	
3000		21/30				
6000	27/30			23/30	8/30	

Organ Toxicity (Cont'd)

Table 16 (Cont'd)

Incidence of Hepatocellular Adenomas in the Rat as Observed
in 18-Month Toxicity and 24-Month Carcinogenicity Studies of Carvedilol

16b)

Dose (ppm)	Males		Females	
	18-Month	24-Month	18-Month	24-Month
0	0/30	1/100	0/30	1/100
200	1/30	2/30	0/30	0/30
400		1/30		0/30
600	0/30		0/30	
800		3/30		0/30
1600		2/30		1/30
3200	0/30		0/30	
5000	2/30		3/30	

Incidence of Fatty Change in Heart Muscle of Dogs as Observed in Various
Toxicity Studies of Carvedilol

16c)

Dose (mg/kg)	Duration of Study			
	3-Month	6-Month	12-Month	12-Month
0	0/6	1/10	5/10	3/10
10				1/10
15	1/6			
30		0/10	3/10	
50	1/6			
100		5/10	2/10	
150	0/6			
300		0/10	6/10	

Incidence of Biliary Hyperplasia in the Dog as Observed
in 6- and 12-Month Toxicity Studies of Carvedilol

16d)

Dose (mg/kg)	Males		Females	
	6-Month	12-Month	6-Month	12-Month
0	0/5	1/10	0/5	1/10
10		0/5		0/5
30	3/5	1/5	1/5	1/5
100	4/5	4/5	3/5	3/5
300	4/5	4/5	3/5	5/5

CARCINOGENICITY STUDIES

The carcinogenicity studies were previously submitted in IND reviewed by consultant pharmacologist M. Winbury, Ph.D. (Final reviews are in Division files dated April 1993.) Previous reviews have undergone a secondary review by supervisory pharmacologist Charles Resnick, Ph.D.

The following is the summary table prepared by the drug sponsor. This table is followed by present reviewer's brief overview of the mouse carcinogenicity study.

MOUSE (SPF-NMRI-HAN-WIGA)

SUMMARY

CARCINOGENICITY STUDIES OF CARVEDILOL (SK&F 105517)

Species	Duration (weeks)	Doses (mg/kg)	Report No. Ref. No. ⁶⁸ Location in NDA IND Submission	Drug-Related Observations
*D Mouse	97 (females) 114 (males)	20, 65, 200 diet	TC002BS (Boehringer Mannheim report J4) Location: Vol. 1.29 Page 000002 Submitted to INI n 8/11/89	Drug-related clinical signs were apathy, cold skin and ptosis. Mean cumulative food consumption was significantly decreased in mid- and high-dose males and high-dose females. A significant decrease in median body weight gain was seen in high-dose males (-13%). High-dose females showed a non-significant decrease (-6%). The mortality for control, low-, mid- and high-dose males at 114 weeks was 58%, 38%, 56% and 56%, respectively. The respective values for females at week 97 were 73%, 80%, 78% and 80%. Urea nitrogen values were higher in the high-dose males and mid- and high-dose females. sGPT values were significantly higher in low- and high-dose males. Single cell hepatocellular necrosis occurred with a slightly higher incidence in high-dose females than in controls (22% vs 14%). Overall tumor incidence and per cent of tumor bearing animals decreased with dose.

*1.- In the mouse (NMRI) study, 100 animals/sex were used in the controls and 50/animals/sex in drug treated groups. No interim sacrifice was performed. No remarkable changes were reported for macroscopic examinations. Microscopic findings reported was a decrease in the number of HD males with tumors (controls 83% vs HD males 68%) and female tumor carriers at HD (controls 62% vs HD 26%). Study was terminated in males in September 1986 because of sudden death of animals with no previous signs of sickness. Sudden deaths reported: controls- 2M, 7F; LD- 3F; MD- 3M, 2F; HD- 4M, 3F; the total number of drug treated mice dying in the study were 15 animals. Study revealed no carcinogenic effect associated with the doses of carvedilol tested.

Brief overview mouse study.

Oral Carcinogenicity Study: Life-time Application to Mice [TC002BS (Boehringer Mannheim report J4; Vol. 29. Dosing dates: 17-07-84 up to 21-05-86 (for females- week 97), and, up to 16-Sep-86 (for males- week 114).]

Dose selection for the mouse carcinogenicity study was based on the results of a mouse 13-week dose-ranging study (J6 above) at doses from 20 to 800 mg/kg carvedilol. Based on body weight, food consumption and clinical pathology of the mice in this study, sponsor considered that carvedilol at 200 mg/kg/day is the MTD.

Animals: Two hundred and fifty (250) NMRI mice, 5-week old, from Charles River Wiga, Sulzfeld, Germany were used in this study. Animals were randomized to obtain 3 treatment groups of 50 animals per sex and a control group of 100 per sex. Animals were housed individually in type II macrolon cages in an environmentally controlled room ($\approx 23^{\circ}\text{C}$ and 55% relative humidity with a 12-hour light/dark cycle). Tap water was provided in bottles and the animals were fed *ad libitum* standard double-ground SSNIFF R meal with 1% soy bean oil added.

Methods: Groups of 50 males and 50 females each received carvedilol* in the diet for their life-time and a group of 100 mice per sex received the diet only and served as controls.

Daily drug intake for the respective groups was 0, LD-20, MD-65 and HD-200 mg/kg for 97 and 114 weeks for females and males, respectively. Drug concentration in the diet was adjusted according to body weight weekly for the first 2 mo. and at 4 week intervals thereafter. Food consumption was recorded weekly for the first 2 months and monthly thereafter. Body weight was determined weekly. Animals were checked twice daily for clinical status and mortality. Although drug exposure could only be determined (detection limit 20 ng/ml) in serum of LD mice at 1, 6 and 13 weeks, sponsor reported carvedilol exposure in other mice treated for 13 weeks at doses ranging from 60 up 800 mg/kg/day.

At 1-year on study, mice were examined monthly for palpable masses. Blood was collected from 10 males and 10 females of each group at the end of the study. A blood smear was prepared from all animals killed during the study.

Statistical analysis (Kruskall-Wallis Anova and/or Mann-Whitney tests) of food consumption, body weight, clinical pathology and tumor data was performed.

Results:

Except were noted, tables below were extracted from IND review prepared by previous pharmacologist and incorporated in the present NDA review.

*Drug in micronized form ($< \mu 20$ particle size) from Batch No. 814396A

Clinical Signs: Most remarkable signs considered to be drug-related signs were apathy, cold skin and ptosis. Cold skin and ptosis were seen in control and drug-treated animals but more frequently in the treated animals. Apathy was seen in HD males and in a few females of all groups.

Food Consumption: Food consumption was significantly decreased in drug treated mice at certain time intervals; HD mice consumed less feed compared to controls. Mean cumulative food consumption was significantly decreased in MD and HD males (3% and 7%, respectively) and high-dose females (5%) (See table below labeled FOOD CONSUMPTION.)

FOOD CONSUMPTION

Dose (mg/kg/day)		0	20	65	200
START	Male	√/5.00/144.7√	5.00/141.8	5.00/141.4	4.80/146.0
	Female	4.50/179.3	4.40/173.7	4.50/173.4	4.30/173.3
END	Male	4.50/101.2	4.50/100.1	4.50/100.0	4.50/107.1
	Female	4.50/121.2	4.50/125.0	4.30/121.7	4.30/118.9

√/ gm/day - Median Values

√/ gm/day/kg body weight

Source: Vol. 1, 000064, 000065, 000165, 000166

Drug Intake: This parameter was calculated on the basis of the animals's body weight and re-adjusted food consumption during the study at 1 to 4 weeks intervals. (See table below labeled DRUG INTAKE.)

DRUG INTAKE (mg/kg/day)

Dose (mg/kg/day)		20	65	200
START	Male	19.4√/	64.2	202.1
	Female	19.0	65.0	201.3
END	Male	17.9	61.3	189.7
	Female	17.8	57.1	175.3

√/ Median Values

Source: Vol. 1, 000113, 000069

Levels of carvedilol in serum (mean values reported for several mice after 1, 6 and 13 weeks of treatment) could only be determined in mice treated at 20 mg/kg/day using an HPLC fluorometric method which gave variable results (Vol. 29, p.278).

Body Weight: A significant decrease in median body weight gain was seen in HD males (-13% at end of study). HD females also showed a lower median body weight gain (-6%) than controls but that difference was not statistically significant. (See table below labeled **BODY WEIGHT**.)

BODY WEIGHT (G)

Dose (mg/kg/day)		0	20	65	200
START	Male	14.0 [∇]	15.0	15.5	13.5
	Female	6.5	6.0	6.5	6.5
END	Male	27.0	25.0	26.0	23.5
	Female	17.0	16.5	17.0	16.0

[∇] Median Values

Source: Vol. 1, 000062, 000063, 000163, 000164

Pathology and Clinical Chemistry: These parameter were examined in 10 mice/sex/group. The differential blood count did not reveal differences between control and treated animals. Urea nitrogen values were higher in the HD males and MD and HD females. sGPT values were higher in all male treatment groups but were only significantly higher in the LD and HD groups. (See table labeled **BIOCHEMICAL CHANGES**.)

BIOCHEMICAL CHANGES

Dose (mg/kg/day)		0	20	65	200
Blood Urea Nitrogen mML	M	6.3 [∇]	7.7	8.6	9.5
	F	5.4	7.1	8.5	9.5
GPT μML	M	24.5	52.6	33.4	41.2
	F	28.0	29.5	39.0	38.5

[∇] Median Values

Source: Vol. 1, 000070, 000071

Mortality: Sponsor reports that in the month that the study was to end (undetermined days), there were some sudden deaths with no previous signs of illness in controls (2M, 7F) and drug treated mice, LD (3F), MD (3M, 2F) and HD (4M, 3F). Overall mortality rates were not significantly affected by carvedilol. The mortality for control, LD, MD and HD males at the end of the study (week 114) was 58%, 38%, 56% and 56%, respectively; the respective values for females (study termination was week 97) were 73%, 80%, 78% and 80%. Overall a higher mortality was noted in all groups of females in this study. With the exception of LD males, mortality rate in control and treatment groups was comparable. (See MORTALITY tables below.)

OVERALL MORTALITY - ALL CAUSES

Dose (mg/kg/day)		0	20	65	200
MALE	Animals per Group	100	50	50	50
	Total Dead	58 (58) ^{1/}	19 (38)	28 (56)	28 (56)
	Tumor Present	46 (79) ^{2/}	13 (68)	21 (75)	17 (61)
	No Tumor	12 (21)	6 (32)	7 (25)	11 (39)
FEMALE	Animals per Group	100	50	50	50
	Total Dead	73 (73) ^{1/}	40 (80)	39 (78)	40 (80)
	Tumor Present	39 (53) ^{2/}	23 (58)	19 (49)	19 (48)
	No Tumor	34 (47)	17 (42)	20 (51)	21 (52)

^{1/} No. Dead (%)

^{2/} No. Event (% of No. Dead)

Source: Vol. 1, 000026-27, 000095-112

MORTALITY RATE (%) AT 18 MONTHS

Dose (mg/kg/day)		0	20	65	200
MALE	Fatal Tumor	3	0	2	2
	Except Fatal Tumor	3	8	10	16
FEMALE	Fatal Tumor	12	12	14	6
	Except Fatal Tumor	31	32	38	36

Source: Vol. 3, 000373-377

ADJUSTED MORTALITY - FREQUENCY OF ANIMALS WITH FATAL TUMORS^{1/}

Dose (mg/kg/day)		0	20	65	200
MALE	Animals per Group	100	50	50	50
	Total	58 (58) ^{2/}	19 (38)	28 (56)	28 (56)
	Fatal Tumor ^{1/}	28 (28)	8 (16)	16 (32)	9 (18)
	Without Fatal Tumor	30 (30)	11 (22)	12 (24)	19 (38)
FEMALE	Animals per Group	100	50	50	50
	Total	73 (73)	40 (80)	39 (78)	40 (80)
	Fatal Tumor ^{1/}	36 (36)	13 (26)	15 (30)	13 (26)
	Without Fatal Tumor	37 (37)	27 (54)	24 (48)	27 (54)

^{1/} Includes fatal tumors according to context 3 and 4 of Para.

^{2/} No. and (%)

Source: Vol. 1, 000026-27, 000143-146

Gross Pathology: Sponsor stated that no drug-related effects were identified because most observations were considered related to poor body condition.

Histopathology: Non-neoplastic changes reported consisted of single cell hepatocellular necrosis occurring a slightly higher incidence in high-dose females than in controls (14% versus 22%). All other histopathologic changes noted were regarded by sponsor as spontaneous, incidental or infectious in nature.

Compared to controls, the total number of tumor carriers decreased as the dose of carvedilol increased for either sex. The number of animals with tumors with the highest frequencies are presented in table below provided by investigators in the study report.

Carcinogenicity Study with Carvedilol in mice								J 4 - 67
Table 7: Number of animals with tumors of the organs with the highest frequencies (100 mice per control and 50 mice/dose/sex)								
male mice								
Organs								
Dosage Group	Lungs	Adrenal cortex	Harder. gland	Liver	lymphat. system	Pituitary	Testes	
Control	46	26	25	16	9	6	0	
20 mg/kg	22	4	13	9	10	2	1	
65 mg/kg	17	6	14	7	7	1	3	
200 mg/kg	18	11	11	2	6	2	1	
female mice								
Organs								
Dosage Group	Pituitary	lymphat. system	Lungs	Ovary	Uterus	Harder. gland	Mamma. gland	
Control	25	25	16	15	10	9	4	
20 mg/kg	7	14	6	3	5	3	2	
65 mg/kg	11	15	4	0	3	4	1	
200 mg/kg	5	13	3	1	2	8	0	

NB. The following table was extracted from previous reviews which shows a breakdown of lung tumors and repeats some of the data from the above table.

ORGANS WITH GREATEST TUMOR FREQUENCY

Dose (mg/kg/day)		0	20	65	200
No. Per Group		100	50	50	50
Lung [∇]	M	46 (27+19) [∇]	22 (16+6)	17 (11+6)	18 (14+4)
	F	16 (13+3)	4 (4+0)	6 (4+2)	3 (3+0)
Pituitary [∇]	F	25	7	11	5
Lymphatic Tissue [∇]	F	25	14	15	13

[∇] Broncho-alveolar cell tumor

[∇] Adenoma

[∇] Leucosis

[∇] n (n benign + n malignant)

Source: Vol. 1, 000038-43, 000073

Tables were extracted from previous reviews to show the absence of dose-dependency in the decrease in frequency of with malignant tumors, and the analysis of tumor severity.

FREQUENCY OF ANIMALS WITH TUMORS

Dose (mg/kg/day)	0	20	65	200
No. Per Group	100	50	50	50
MALE	√/46+37 (83)√/	13+25 (76)	21+19 (80)	17+17 (68)
FEMALE	39+23 (62)	23+6 (58)	19+9 (56)	19+7 (52)

√/ n unscheduled killed or died with tumor + n scheduled killed with tumor

√/ % tumor

Source: Vol. 1, 000026-27

FREQUENCY OF ANIMALS WITH MALIGNANT TUMORS

Dose (mg/kg/day)		0	20	65	200
MALE	Animals Per Group	100	50	50	50
	No. with tumor	83	38	40	34
	No. with malignant tumor	40	17	23	16
	No. with metastasizing tumor	1	1	1	2
FEMALE	Animals Per Group	100	50	50	50
	No. with tumor	62	29	28	26
	No. with malignant tumor	37	20	18	16
	No. with metastasizing tumor	5	1	0	2

Source: Vol. 1, 000044-45, 000072

ANALYSIS OF TUMOR SEVERITY - ACCORDING TO PETO

Dose (mg/kg/day)		0	20	65	200
MALE	Animals per Group	100	50	50	50
	Total	83	38	40	34
	Fatal Tumor (3,4)√/	28 (34)√/	8 (21)	16 (40)	9 (26)
	Incidental Tumor (1,2)√/	55 (66)	30 (79)	24 (60)	25 (74)
FEMALE	Animals per Group	100	50	50	50
	Total	62	29	28	26
	Fatal Tumor (3,4)	36 (58)	13 (45)	15 (54)	13 (50)
	Incidental Tumor (1,2)	26 (42)	16 (55)	13 (46)	13 (50)

√/ No. and (% of Total)

√/ Context of Peto

Source: Vol. 1, 000143-46

These neoplastic lesions occurring with an incidence of 5% or greater in any dose group are listed in table below prepared by sponsor.

Table 18

Neoplastic Lesions in Mouse Carcinogenicity Study of Carvedilol
Occurring with an Incidence $\geq 5\%$ in any Dose Group

Lesion	Sex	Control	20 mg/kg	65 mg/kg	200 mg/kg
Liver cell adenoma	M	12/100	6/50	5/50	1/50
	F	1/100	0/50	0/50	0/50
Liver cell carcinoma	M	4/100	3/50	2/50	1/50
	F	0/100	0/50	0/50	0/50
Adrenal cortical adenoma	M	18/100	4/50	6/50	10/50
	F	1/100	1/50	0/50	0/50
Adrenal cortical carcinoma	M	8/100	0/50	1/50	1/50
	F	1/100	1/50	0/50	0/50
Bronchoalveolar adenoma	M	27/100	16/50	11/50	14/50
	F	13/100	4/50	4/50	3/50
Bronchoalveolar carcinoma	M	19/100	6/50	6/50	4/50
	F	3/100	0/50	2/50	0/50
Testicular interstitial cell tumor	M	0/100	1/50	3/50	~~1/50~~
Uterine stromal polyp	F	5/100	2/50	0/50	0/50
Ovarian granulosa cell tumor	F	10/100	1/50	0/50	1/50
Malignant lymphoma	M	9/100	10/50	7/50	6/50
	F	25/100	14/50	15/50	13/50
Pituitary adenoma	M	6/100	2/50	1/50	2/50
	F	25/100	7/50	11/50	5/50
Lacrimal gland adenoma	M	27/100	13/50	15/50	11/50
	F	10/100	3/50	4/50	6/50
Lacrimal gland carcinoma	M	0/100	0/50	2/50	1/50
	F	0/100	0/50	0/50	2/50
Mammary gland carcinoma	F	6/100	2/50	1/50	0/50

Sponsor asserts that the number of tumor carriers, counting all tumors and the number of carriers with malignant tumors did not show any increase with dose for either sex.

Table 19									
BM 14.190									
SURVEY OF TUMOR FREQUENCY IN MALE MICE									
Dose	n	unscheduled killed or died	with tumors	without tumors	scheduled killed	with tumors	without tumors	total with tumors	total without tumors
Control	100	50-50	46-79,5%	12-20,7%	42-42	37-88,1%	5-11,9%	83-83%	17-17%
20 mg/kg	50	19-38	13-68,4%	6-31,6%	31-62	25-80,6%	6-19,4%	38-76%	12-24%
65 mg/kg	50	28-56	21-75%	7-25%	22-44	19-86,4%	3-13,6%	40-80%	10-20%
200 mg/kg	50	28-56	17-60,7%	11-39,3%	22-44	17-77,3%	5-22,7%	34-68%	16-32%

Table 2									
BM 14.190									
SURVEY OF TUMOR FREQUENCY IN FEMALE MICE									
Dose	n	unscheduled killed or died	with tumors	without tumors	scheduled killed	with tumors	without tumors	total with tumors	total without tumors
Control	100	73-73%	39-53,4%	34-46,6%	27-27%	23-85,2%	4-14,8%	62-62%	38-38%
20 mg/kg	50	40-80%	23-57,5%	17-42,5%	10-20%	6-60%	4-40%	29-58%	21-42%
65 mg/kg	50	39-78%	19-48,7%	20-51,3%	11-22%	9-81,8%	2-18,2%	28-56%	22-44%
200 mg/kg	50	40-80%	19-47,5%	21-52,5%	10-20%	7-70%	3-30%	26-52%	24-48%



BM 14.190
Page 1

Carcinogenicity study with BM 14.190



BM 14.190
Page 2

Carcinogenicity study with BM 14.190 in mice

J 4 - 22

Division of Biometrics evaluation reports that in female mice there was a marginally significant positive linear trend in harderian gland carcinoma ($p= 0.052$) and harderian gland carcinoma and adenoma combined ($p= 0.06$); no trend was found in males. (N.B. The total number of harderian gland tumors reported by sponsor for both sexes does not agree with the numbers reported by Biometrics. However, both reports shows the incidence of these tumors was not dose-related.) (See Table 19 above prepared by investigators.)

In addition, the Biometrics' report expresses concern about the number of surviving female mice and their body weight data. Even when Biometrics recognizes that at HD the MTD had been reached in the mouse carcinogenicity study, the reports stated- "It seems that there were not sufficient female mice in the control and treated groups living long enough to get an adequate exposure to the chemical....." Biometrics considers that because the survival rates in mice the study in the control, LD, MD and HD groups was 42%, 62%, 44% and 44%, respectively for males, and 27%, 20%, 22%, and 20%, respectively for females, there "were not sufficient females mice" in these groups living long enough to get an adequate exposure to carvedilol and to be at risk of forming late-developing tumors. This concern by Biometrics is based on a personal communication between JK Haseman and KK Lin at FDA.

This reviewer considers the low survival and the lack of remarkable effect on body weight uninterpretable in the absence of toxicokinetic data collected during this carcinogenicity study in mice. However, limited pharmacokinetic data with ^{14}C -carvedilol (100 mg/kg p.o. single dose) given the NMRI mice showed no significant different metabolic profile of the drug among the two sexes (about 25 were identified in urine and feces). Unchanged carvedilol was a minor component in urine while being the most abundant component in plasma in both male and female mice determined up to 6 hrs post dosing. Although qualitatively the plasma metabolic profile carvedilol was similar in both sexes, there quantitative differences. The most remarkable pharmacokinetic finding reported was that plasma from female mice contained higher concentrations of carvedilol metabolites, relative to unchanged carvedilol, than found in the plasma from male mice. The unchanged carvedilol concentrations in male mice plasma were 3-4 fold higher than in female mice.

This reviewer concludes that the data submitted show that long-term administration of carvedilol in feed to mouse showed no clear evidence of carcinogenic activity when males received median oral doses ranging from 202 to 189 mg/kg/day for 114 weeks and, females 201 to 175 mg/kg/day for 97 weeks. An interesting finding was that although not dose-related, carvedilol-treated mice showed testicular tumors (C-0, LD-1; MD-3, HD-1) drug-treated male showed a few testicular tumors.(See Table 19 above.)

CARCINOGENICITY STUDIES (Cont'd)

The following is the sponsor's summary tables of an aborted and a definitive carcinogenicity studies, followed by a brief overview of these studies.

RAT (SPRAGUE-DAWLEY, CAW-ICO-WIGA)

Species	Duration (weeks)	Doses (mg/kg)	Report No. Ref. No. Location in NDA IND Submission
1) Rat	28 (early termination) (600 ppm) (2000 ppm) (4000 ppm)	30(M), 35(F); 98(M), 124(F); 199(M), 250(F) diet	TPA006/SKF-105517 (Boehringer Mannheim report J7) Location: Vol. 1.33 Page 000002

Drug-Related Observations

Mortality was observed around the occurrence of a steep decrease in body weight. One female died in the low-dose group, 1 male and 1 female in the mid-dose group and 11 females of the high-dose group died between days 81 and 115. Animals that died during the study showed weight loss, slow movement, cool skin, apathy, blepharostenosis and marked emaciation. Although these symptoms were considered to be excessive pharmacological actions, it is more likely that they resulted from a combination of drug treatment and water deprivation. High-dose males and females showed a lower body weight gain from the start of the study. A steep decrease in body weight was observed around day 112 in high-dose males and in mid- and high-dose females. At this time point, the automatic drinking water system was replaced by glass bottles. This resulted in a return to the original body weights as present before the steep decrease. At day 182 of the study, high-dose males and females showed a lower body weight than the controls, 11 and 14%, respectively. A dose-related decrease in hemoglobin was observed in both sexes (approx. 10% in high-dose). All drug-treated males showed an increase in lymphocyte count; the increase was significant in the low- and mid-dose males but not in high-dose males. BUN was significantly increased in high-dose females and serum creatinine and glucose values were significantly decreased in mid-dose females. A variety of macroscopic observations were made in the animals that died and was related to poor condition (fat and lymphoid atrophy, empty GI tract). Main lesions observed light microscopically in these animals were slight biliary hyperplasia (treatment-related) and atrophy of lymphoid tissues. Based on body weight depression prior to and after a technical failure of the automatic drinking water system and the occurrence of deaths due to the technical failure, the study was terminated on day 199.

1. Doses of carvedilol (600, 2000 and 4000 ppm in diet) were selected on the basis of a 13-weeks study (J5 above). In present study, 50 rats/sex/groups were used. Drug intake diminished up to the end of the study; doses reported above represent the drug intake by the end of the study, when the study was stopped (10-06-93) after 6 months of treatment (28-07-83.)

Rat carcinogenicity (Cont'd.)

Species	Duration (weeks)	Doses (mg/kg)	Report No. Ref. No. Location in NDA (N1) Submission	Drug-Related Observations
Rat	104	(200 ppm) 8(M), 10(F); (400 ppm) 11(M), 19(F); (800 ppm) 31(M), 38(F); (1600 ppm) 62(M), 75(F) diet	TC001BS (Boehringer Mannheim report J2) Location: Vol. 1.34 Page 000002 Submitted to INF 8/26/88	Swollen eyelids, cold to touch and a distended abdomen were observed in drug-treated females. Light and touch sensitivity and chromodacryorrhea were more common in drug-treated females than in controls. Food intake was less in high-dose animals (up to 5% in males and 11% in females). At various intervals, median body weight in mid- and high-dose males was approx. 5% higher than controls. Mid- and high-dose females showed a lower median body weight of approximately 8%. A statistically significant increase in unscheduled deaths without a fatal tumor occurred in high-dose animals. This was not associated with any statistically significant changes in the mean life span. Macroscopically, there were less masses observed in the drug-treated animals than in the controls. Drug-treated males showed a higher incidence of lung edema and hemorrhage than the controls. A rounded apex of the heart and ventricular dilation were more common in drug-treated animals than in controls. Liver enlargement, discoloration and congestion and splenic enlargement were observed more frequently in high-dose males than in controls. Adrenal and splenic enlargement were more common in high-dose females than in controls and discoloration of the pituitary was seen more frequently in mid- and high-dose females than in controls. A slightly higher incidence of thyroid adenoma/carcinoma was observed in drug-treated females (4 to 12%) than in controls (2%). Since there was no dose response relationship, the highest incidence being within the expected range for SD rats and the absence of a positive response in males, the thyroid tumor response was not considered to be treatment-related. The number of benign and malignant mammary tumors were greater in females at 200 and 400 ppm than in the controls but the number in females at 800 and 1600 ppm was lower than in the controls. Therefore, the increased number in the low, and mid-low dose groups were considered to be normal variations, particularly since the number of malignant tumors were the greatest in controls. No other significant effect on tumor formation was observed other than the total number of tumor bearing males and females with malignant tumors decreased with increasing dose.

Brief overview of rat studies.

Oral Carcinogenicity Study of Carvedilol in Rats (stopped after 6 months).

[TP/0006/SKF-105517 (Boehringer Mannheim report J7) Vol. 33; This study started on 18-Jan-83 and was aborted by 28-July-83].

Dose selection was based on the results of a rat (Sprague-Dawley, Caw-Ico-Wiga) 3-month dose-ranging study from 200 ppm up to 8,000 ppm carvedilol (TP-0004/SKF-105517 summarized above by sponsor, Boehringer Mannheim report J5). In that rat study the MTD was determined to be 4000 ppm.

Same strain of rats were used. Methods used in the conduct of the study were reported in the NDA and essentially similar to those used in the actual rat carcinogenicity study described below. Carvedilol (batch no. 814936A) was incorporated in the diet at concentrations of 600, 2000 and 4000 ppm and 2 controls groups of 50 animals per sex received the diet only.

At the start of the study, drug intake in the various male groups was reported as approximately 83, 281, and 579 mg/kg and 76, 276 and 545 mg/kg for females. At termination of the study (day 199), drug intake in males was 30, 98 and 199 mg/kg and 35, 124 and 250 mg/kg in females.

Necropsy was performed and the following organs from 10 animals per group were weighed: heart, liver, spleen, kidneys, adrenals, thyroid, testes or ovaries, pituitary and brain. Only tissues from animals that died during the study were examined light microscopically.

Results

Clinical signs: Animals that died during the study showed weight loss, slow movement, cool skin, apathy, blepharostenosis and marked emaciation. Although these symptoms were considered to be excessive pharmacological actions, it is more likely that they were the results of a combination of drug treatment and water deprivation.

Mortality was observed around the occurrence of the steep decrease in body weight. One female died in the LD group, 1 male and 1 female in the MD group and 11 females of the HD group died between days 81 and 115.

Body weights of HD group showed a lower body weight gain from the start of the study. A steep decrease in body weight was reported for day 112 in HD males and, in MD and HD females; this observation was completely reversed when the automatic drinking water system was replaced by glass bottles. However, at day 182 of study, HD rats showed about 13% lower body weight than the controls.

A dose-related decrease in hemoglobin was observed in both sexes, decrease in HD animals was approximately 10%. Both, MD and HD rats showed lower hematocrit values. All drug-treated males showed an increase in lymphocyte count; the increase was statistically significant ($p < 0.05$)* in the LD and MD males but not in the HD group. Blood urea nitrogen was significantly increased ($p < 0.05$) in HD females and serum creatinine and glucose values were significantly decreased ($p < 0.05$) in MD females.

Necropsy was performed. Most animals that died showed poor condition (i.e., atrophy of various tissues, such as fat and lymphoid and an empty gastro-intestinal tract). Absolute spleen weight was increased in MD and HD males, absolute adrenal and liver weights were decreased in HD males and absolute adrenal, ovary, liver, kidney, and brain weights were decreased in HD females. When compared to body weight, relative spleen weight was increased in HD males and MD and HD females, relative liver weight decreased in HD males and relative heart weight increased in all drug-treated females. When compared to brain weight, relative spleen weight was increased in MD and HD males, relative pituitary and liver weights were decreased in HD males and relative pituitary, liver and kidney weights were decreased in HD females.

The LD female that died during the study was diagnosed with a malignant lymphoma, lesion was considered to be spontaneous. Although the rest of the deaths were attributed to drug treatment, the data suggest that water deprivation was at least a contributing factor. The main lesions found in these animals were slight biliary hyperplasia (treatment-related) and atrophy of lymphoid tissues.

Sponsor concludes that the marked body weight depression resulted from too high dosages used. Thus, the study was terminated at day 199.

*Kruskal-Wallis Anova and/or Mann-Whitney tests. $p < 0.05$.

Definitive Oral Carcinogenicity Test of Carvedilol. 2-Year Rat Study (Sprague-Dawley, Caw-Ico-Wiga). (TC001BS; Boehringer Mannheim report J2 in Vol. 34. Dosing dates: 01-06-83 and 10-06-85)

Dose Selection: Although the previous attempt to perform a carcinogenicity study was based on a 3-month dose-range, doses used were found to be too high based because of the marked body weight depression that resulted. The study had to be aborted after 6 months of animal dosing (see above), and this second rat carcinogenicity study was started using lower doses of carvedilol- 200, 400, 800 and 1600 ppm in diet.

Animals: In this study, 250 rats (5 week old)/sex were used. Rats were randomly assigned to 4 treatment groups of 50 animals per sex and 1 control group of 50 per sex. A second control group was taken from a parallel running carcinogenicity study. Rats were housed in pairs in wire cages H3 (V2A-4301) in an environmentally controlled room (~23°C and 55% relative humidity with a 12 hours light/dark cycle). Initially, rats received distilled water via an automatic drinking tap water system. This system was replaced by glass bottles after 6 to 7 months in the study. The animals were fed *ad libitum* standard double milled meal with 1% soy bean oil added.

Methods: Groups of 50 males and 50 females each received carvedilol* in the diet at concentrations of 200, 400, 800 and 1600 ppm and 1 group of 50 rats/sex received the diet only and served as controls.

Drug concentrations in the diet were kept constant during the course of the study and were calculated in mg/kg/day from food consumption. Animals were checked twice daily for clinical status and mortality. Food consumption over a 2-day period was recorded biweekly and expressed as mean per day up to 14 months and monthly thereafter. Body weights were recorded once a week.

After one-year on study, animals were examined monthly for palpable masses. At the termination of the study, clinical pathology parameters were determined in 10 males and 10 females from each group. Necropsy was performed on all animals. Tissues from all animals were examined light microscopically.

Results

Except were noted, tables below were extracted from IND review prepared by previous pharmacologist and incorporated in the present NDA review.

Clinical Signs: HD rats appeared leaner than controls. Swollen eyelids, cold to touch and a distended abdomen were only observed in drug-treated females. Light and touch sensitivity and chromadacryorrhea were more commonly observed in drug-treated females than in controls. All these signs were neither severe nor life-threatening.

*Batch nos. 814 396A and 814 723A

Food Consumption: Food intake in HD males was between 0 and 5% less than the controls during the study. The percentage range for HD females was 3 to 11%. (See Table labeled FOOD CONSUMPTION.)

FOOD CONSUMPTION

ppm		0	200	400	800	1600
START	Male	26.8/107 ^W	26.0/107	25.3/102	27.5/107	26.0/106
	Female	18.8/107	18.5/109	18.3/108	19.3/108	18.0/103
END	Male	26.1/39.6	25.8/38.5	25.8/40.5	26.5/39.2	25.3/38.8
	Female	19.6/48.3	20.5/47.7	20.1/46.9	18.8/47.6	18.8/46.7

^W gm/day - Median Values

^W gm/day/kg body weight

Source: Vol 1, 000107, 108, 109, 110

Drug Intake: This parameter varied during the study. At the start of the study, drug intake in the various male groups was approximately 21, 41, 86 and 169 mg/kg and 22, 43, 87 and 165 mg/kg in females. At the end of the study, drug intake had decreased in males to 8, 16, 31 and 62 mg/kg and in females to 10, 19, 38 and 75 mg/kg. (See DRUG INTAKE table.)

DRUG INTAKE (mg/kg/day)

ppm		200	400	800	1600
START	Male	21.3 ^W	40.8	85.5	169.3
	Female	21.7	43.0	86.7	165.3
END	Male	7.7	16.2	31.4	62.1
	Female	9.5	18.8	38.1	74.7

^W Median Values

Source: Vol. 1, 000022; Table 5, 000112

Body Weight: At various intervals, median body weight in MD and HD males was 4 to 6% higher than controls. Remarkable body weight increases in males were seen particularly at the beginning of the study from day 84 to 181. Overall the body weight of the males was reported as not affected by the treatment with carvedilol. (See BODY WEIGHT table below). Females showed a dose-related reduction in body weight gain; the difference in medians between the HD and control was about 8% between days 427 and 727 of study.

BODY WEIGHT (g)

ppm		0	200	400	800	1600
START	Male	171 ^W	175	175	176	170
	Female	110	113	109	118	114
END	Male	568	598	593	596	577
	Female	344	349	353	318	318

^W Median Values

Source: Vol. 1, 000105, 106

Based on body weight findings, Division of Biometrics evaluation considered that it was important to check the toxic signs of the HD rats to determine the adequacy of this for males in this carcinogenicity study. This reviewer considers that since at the 2 highest doses of carvedilol, the males had a higher death rate compared to the other groups as well as lower glucose values (not seen in other studies) at the 3 highest doses, the HD intake (about 169 mg/kg/day at the start of the study later reduced to about 62 mg/kg/day by the end of the study) may be considered adequate for the males. Further, in the previous attempt by sponsor to conduct an oral carcinogenicity study in rat at the determined MTD of 4000 ppm animals that died showed weight loss and marked emaciation.

Hematology and Clinical Chemistry: Data were collected from selected survivors as a single determination at the end of the study. The data showed marked variation and a correlation with drug treatment was not apparent.

Mortality: The overall mortality appears in a table below. Male mortality was dose dependent; higher percentage of males died compared to females.

OVERALL MORTALITY - ALL CAUSES

ppm		0	200	400	800	1600
Male	Total	32 (64) ^W	35 (70)	35 (70)	39 (78)	42 (84)
	Tumor Present	25 (78) ^W	24 (69)	16 (46)	24 (62)	14 (33)
	No Tumor	7 (22) ^W	11 (31)	19 (54)	15 (38)	28 (67)
Female	Total	27 (54)	27 (54)	28 (56)	26 (52)	21 (42)
	Tumor Present	27 (100)	26 (96)	28 (100)	23 (89)	20 (95)
	No Tumor	0 (0)	1 (4)	0 (0)	3 (11)	1 (5)

^W No. Dead (%);

^W No. Event (% of No. Dead)

Source: Vol 1, 000032-33, 000132-150

A statistically significant increase (Kaplan-Meier and Mantel-Cox or Breslow tests, $p < 0.05$) in unscheduled deaths without a fatal tumor occurred in animals receiving the highest dose of carvedilol. The unscheduled deaths without a fatal tumor were not associated with any statistically significant changes in mean life span (Table 20 extracted from previous review.)

Table 20

Total Unscheduled Deaths and Unscheduled Deaths without Fatal Tumor
in Male Rats from the Carcinogenicity Study of Carvedilol

Dose (ppm)	Total Unscheduled Deaths	Unscheduled Deaths without Fatal Tumor	Mean Life span
0	32 (64%)	12	608 ± 33
200	35 (70%)	21	587 ± 30
400	35 (70%)	22	543 ± 32
800	39 (78%)	22	555 ± 28
1600	42 (84%)	30	569 ± 22

Gross Pathology: The liver was the target organ of toxicity. Liver enlargement, discoloration and congestion and splenic enlargement were observed more frequently in high-dose males than in controls.

There were less masses observed in the drug-treated animals than in the controls. Drug-treated males showed a higher incidence of lung edema and hemorrhage than the controls. A rounded apex of the heart and ventricular dilation were more common in drug-treated animals than in controls. Adrenal and splenic enlargement were more common in HD females than in controls and discoloration of the pituitary was seen more frequently in mid- and high-dose females than in controls.

Histopathology: Males showed dose-related focal hyperplasia in liver. Occasional benign hepatoma were found in all drug treated males. In female rats, there was marginally statistically significant linear trend in thyroid adenoma ($p = 0.054$). In females, pairwise comparison of HD vs. controls showed that the increase in thyroid adenomas was statistically significant ($p = 0.0457$). When thyroid adenomas/carcinomas were combined, there was no dose-related trend found in either sex, although females did show a higher incidence of the combined tumors over controls. Also in females, although when compared to controls the number of mammary adenomas in groups treated with 200 ppm, 400 ppm and 1600 ppm were increased, the incidence of these tumors was not dose related.

Of the non-neoplastic lesions, liver cell hyperplasia with/without angiectasis, chronic nephropathy and an inflammatory cell infiltrate in the heart were more common in HD males than in controls whereas the opposite was the case in females. Splenic congestion occurred more frequently in drug-treated animals than in controls. Lung edema was more common in drug-treated males than in controls and angiectasis of the adrenal cortex was observed more frequently in HD males and MD and HD females than in controls.

The frequency of tumor bearing rats declined with drug treatment appeared in tables below extracted from previous pharmacologist's review.

FREQUENCY OF ANIMALS WITH TUMORS

ppm	0	200	400	800	1600
Male	1/25 + 16 (82) 1/2	24 + 9 (66)	16 + 8 (48)	24 + 8 (64)	14 + 5 (38)
Female	27 + 21 (96)	26 + 22 (96)	28 + 21 (98)	23 + 22 (90)	20 + 26 (92)

1/ n unscheduled killed or died with tumor + n scheduled killed with tumors.

1/2 % tumors

Source: Vol 1, Table 1.2, 000032-33, 000167-170

FREQUENCY OF ANIMALS WITH MALIGNANT TUMORS

ppm	0	200	400	800	1600	
M 50	No. With Tumor	41	33	24	32	19
	No. With Malignant Tumor	14	8	8	11	5
	No. with Metastasizing Tumor	12	0	12	6	12
F 50	No. With Tumor	48	48	49	45	46
	No. With Malignant Tumor	17	14	9	7	11
	No. with Metastasizing Tumor	6	12	12	12	6

Source: Vol. 1, STAT, Table 7, 000117, Table 18, 000049-50, Vol. 1, 000151-170

When deaths caused by tumors were excluded data showed that the mortality in males was higher than females and controls. Based on these finding Division of Biometrics asserted in its evaluation that "There were not sufficient males in the control and treated groups living long enough to get an adequate exposure to the chemical and to be at risk of forming late-developing tumors based on Haseman's proposition," personally communicated to Dr. Karl K. Lin at FDA.

ADJUSTED MORTALITY - FREQUENCY OF ANIMALS WITH FATAL TUMORS 1/

ppm	0	200	400	800	1600
Male Total	33 (66) 1/2	36 (72)	35 (70)	39 (78)	42 (84)
Fatal Tumor 1/	21 (42)	15 (30)	13 (26)	17 (34)	12 (24)
Without Fatal Tumor	12 (24)	21 (42)	22 (44)	22 (44)	30 (60)
Female Total	34 (68)	31 (62)	28 (56)	27 (54)	21 (42)
Fatal Tumor 1/	34 (68)	29 (58)	28 (56)	22 (44)	20 (40)
Without Fatal Tumor	0 (0)	2 (4)	0 (0)	5 (10)	1 (2)

1/ Includes fatal tumors according to context 3 and 4 of Peto

1/2 No. and (%)

Source: Vol 1, 0000132-150, 000151-166, 000167-170, 000171-187; Vol. 4, 000282-283.

The following Table 21 was prepared by sponsor.

NEOPLASTIC LESIONS OCCURRING IN RAT CARCINOGENICITY STUDY OF CARVEDILOL WITH AN INCIDENCE $\geq 5\%$ IN ANY DOSE GROUP.

Lesion	Sex	Control	200 ppm	400 ppm	800 ppm	1600 ppm
Liver cell adenoma	M	0/50	2/50	1/50	3/50	2/50
	F	0/50	0/50	0/50	0/50	1/50
Skin, fibroma	M	3/50	3/50	2/50	4/50	1/50
	F	1/50	0/50	0/50	0/50	0/50
Skin, (neuro-) fibrosarcoma	M	1/50	0/50	2/50	2/50	1/50
	F	0/50	0/50	0/50	0/50	0/50
Pituitary adenoma	M	17/50	15/50	7/50	14/50	~~10~~ 1/50
	F	~~7~~ 0/50	31/50	29/50	34/50	30/50
Thyroid adenoma	M	4/50	2/50	4/50	2/50	0/50
	F	0/50	6/50	2/50	~~4~~ 5/50	5/50
Thyroid carcinoma	M	4/50	0/50	1/50	0/50	0/50
	F	1/50	0/50	0/50	0/50	0/50
Mammary adenoma	M	1/50	0/50	0/50	1/50	0/50
	F	37/50	53/50	65/50	37/50	45/50
Mammary carcinoma	M	0/50	0/50	0/50	0/50	0/50
	F	16/50	13/50	6/50	6/50	5/50

NE: - The following table, on 2 specific tumors, was extracted from data submitted in NDA Amendment From the response to FDA request for historical control tumor data for the strain of rats used in the carcinogenicity study with carvedilol, the following table on 2 specific tumors was prepared with data extracted from sponsor's response in NDA Amendment dated 03-29-94.

Historical Control Tumor Data from
Sprague-Dawley rats (Caw-leo-Wiga) during the period 1983-1985.

Number of tumors occurring in 100 animals are provided in the table below:

Organ System/ Lesion	Males	Females
Thyroid gland		
Follicular cell adenoma	5/100	3/100
Follicular cell carcinoma	1/100	
C cell tumor	2/100	5/100
Liver		
Liver cell adenoma	1/100	3/100

The following Table 22, submitted by sponsor, shows a survey of tumor frequency in rats for the oral carcinogenicity study.

Table 22

SURVEY OF TUMOR FREQUENCY IN MALE RATS

Dose	n	unscheduled killed or died	with tumors	without tumors	scheduled killed (SURVIVAL)	with tumors	without tumors	total with tumors	total without tumors
Control I	50	32-648	25-788	7-21,88	18-368	16-88,98	2-11,18	41-828	9-188
Control II	50	26-528	21-80,88	5-19,28	24-488	16-66,78	8-33,38	37-748	13-268
100 ppm	50	35-708	24-68,68	11-31,48	15-308	9-608	6-408	33-668	17-348
400 ppm	50	35-708	16-45,78	19-54,38	15-308	8-53,38	7-46,68	24-488	26-528
800 ppm	50	39-788	24-61,58	15-38,58	11-228	8-72,78	3-27,35	32-648	18-368
1600 ppm	50	42-848	14-33,38	28-66,65	8-168	5-62,58	3-37,58	19-388	31-628

SURVEY OF TUMOR FREQUENCY IN FEMALE RATS

Dose	n	unscheduled killed or died	with tumors	without tumors	scheduled killed (SURVIVAL)	with tumors	without tumors	total with tumors	total without tumors
Control I	50	27-548	27-1008	-	23-468	21-93,38	2- 8,78	48-968	2- 48
Control II	50	23-468	23-1008	-	27-548	26-96,38	1- 3,78	49-988	1- 28
200 ppm	50	27-548	26-93,38	1- 3,78	23-468	22-95,68	1- 4,38	48-968	2- 48
400 ppm	50	28-568	28-1008	-	22-448	21-95,48	1- 4,58	49-988	1- 28
800 ppm	50	26-528	23-88,58	3-11,58	24-488	22-91,68	2- 8,38	45-908	5-108
1600 ppm	50	21-428	20-95,28	1- 4,88	29-588	26-89,68	3-10,38	46-928	4- 88

From the data submitted, it may be concluded that in the 2-year feed study, there was no evidence of carcinogenic activity with carvedilol in rats receiving median doses ranging in the male from 169 down to 62 mg/kg/day and, in females 165 down to 75 mg/kg/day. Although not dose-related, when compared to control carvedilol intake was associated with slightly higher incidence of thyroid tumors in all drug-treated females and, mammary tumors in LD and MD females (Table 23). Division of Biometrics analysis of the tumor data reported that there was a significant positive linear trend in stomach papilloma ($p=0.049$) and, marginally significant trend in liver hepatocellular adenoma ($p=0.057$) in male rats.

Carcinogenicity Study with Carvedilol in Rats		J2 -113					
Table 23: Number of animals with tumors of the organs with the highest frequencies							
male rats							
Organs							
Dosage Group	Pituitary	Urinary bladder	Pancreas	Skin + Subcutis	Thyroid		
Control 1	17	8	8	11	6		
Control 2s	17	9	10	11	4		
200 ppm	15	8	5	8	2		
400 ppm	7	3	5	7	5		
800 ppm	14	2	3	11	2		
1600 ppm	10	0	2	7	0		
female rats							
Organs							
Dosage Group	Pituitary	Urinary bladder	Pancreas	Skin + Subcutis	Thyroid	Mamma. gland	Uterus
Control 1	41	0	3	3	1	35	7
Control 2s	36	3	3	2	2	41	6
200 ppm	31	0	2	2	6	37	5
400 ppm	29	0	0	2	2	36	5
800 ppm	35	0	0	0	4	30	5
1600 ppm	30	0	1	0	5	36	5
At begin of study there were 50 animals per dosage and sex.							
s = Control 2 were the controls of a parallel study with another substance. Their results were not used for statistical comparisons in this study.							

SPECIAL TOXICITY STUDIES

Special toxicity studies were performed to detecting the potential of carvedilol to produce adverse reactions on an immunological basis, and limiting toxicity studies.

Immunologic effects associated with the exposure to drugs may result in increased susceptibility to pathologic conditions or diseases. All of the immunotoxicologic tests reported by sponsor were *in vivo* models. The following summary tables were prepared by the sponsor. Brief overview of the studies follows the tables.

SUMMARY

SPECIAL TOXICITY STUDIES OF CARVEDILOL (SK&F 105517)

<u>Species</u>	<u>Dose</u>	<u>Type of Study</u>	<u>Report No. Ref. No.⁷⁵ Location in NDA IND Submission</u>	<u>Methods and Results</u>
Mouse	10, 100 mg/animal i.p.	Antigenicity	TC-0021/SKF-105517 (Daiichi report D-14) Location: Vol. 1.38 Page 000002	Carvedilol mixed with alum gel was given to male BALB/c mice twice intraperitoneally. Six days later, blood was collected and serum separated. Sera was injected i.c. on the dorsum of rats to passively sensitize them. Twenty-four hours later, the rats were challenged intravenously with carvedilol (3 mg/kg) to evoke a passive cutaneous anaphylaxis reaction. No reaction was observed and no IgE antibodies were found.
Guinea Pig	0.2, 2 mg/animal s.c.	Antigenicity	TC-0021/SKF-105517 (Daiichi report D-14) Location: Vol. 1.38 Page 000002	Carvedilol plus Freund's complete adjuvant was given thrice subcutaneously to guinea pigs. Eleven days later, blood was collected and serum separated. Serum was given i.c. to naive guinea pigs. Four hours or 8 days later, these sensitized animals were challenged intravenously with 3 mg/kg carvedilol. One animal (0.2 mg/animal) challenged after 4 hours showed a positive reaction. All other animals, also those challenged after 8 days, showed a negative reaction. In addition, no systemic anaphylaxis could be evoked in all animals tested. Carvedilol-specific antibodies were determined in sera by RIA employing Protein-A-Sepharose-CL-4B. Serum that had given a positive PCA reaction showed a reading about twice as that of normal serum. All other serum samples were comparable with readings of normal serum.
Guinea Pig	0.2, 2 mg/animal oral & s.c.	Antigenicity	TC-0021/SKF-105517 (Daiichi report D-15) Location: Vol. 1.38 Page 000 Submitted to IND	Guinea pigs were given carvedilol orally 3/week for 3 weeks. Other groups were given carvedilol with Freund's complete adjuvant with and without ovalbumin. Twelve days later, blood was collected and serum separated. Serum was given i.c. to guinea pigs and animals were challenged with carvedilol (3 mg/kg) or ovalbumin intravenously 4 hours later. Except for the positive controls, no passive cutaneous anaphylaxis reaction was evoked.

Special Toxicity Studies (Cont'd.)

Species	Dose	Type of Study	Report No. Ref. No. ⁷⁶ Location in NDA IND Submission	Methods and Results
Guinea Pig	0.5, 5 s.c.	Delayed Hypersensi- tivity	TC/0018/SKF-105517 (Daiichi report D-R-11) Location: Vol. 1.38 Page 000231	Guinea pigs were twice sensitized by subcutaneous injection with carvedilol plus Freund's complete adjuvant. Seven days later, the animals were challenged with 30 mg carvedilol/site. Twenty-four and 48 hours later, skin sites were examined. There was no evidence of a delayed type hypersensitivity reaction.
Rabbit	1, 2, 10 mg/animal oral & s.c.	Antigenicity	TC-0020/SKF-105517 (Daiichi report D-15) Location: Vol. 1.38 Page 000131	Male NZ White rabbits were given carvedilol orally 3/week for 3 weeks. Other groups were given carvedilol with Freund's complete adjuvant with and without ovalbumin. Eleven days later, blood was collected and serum separated. Serum was given i.c. to guinea pigs and animals were challenged intravenously with carvedilol (3 mg/kg) 4 hours later. Except for the positive controls, no positive passive cutaneous anaphylaxis reaction was observed. Carvedilol-specific antibodies were determined in sera by RIA employing Protein-A-Sepharose-CL-4B. Except positive controls, all other serum samples were comparable with readings of normal serum.
Dog	12.6, 54 mg/kg i.v. infusion & 7.5, 15, 30 mg/kg i.v. bolus	Limiting toxicity	T1002BS Location: Vol. 1.38 Page 000246 Submitted to IND on 8/18/88	In the conscious dog, limiting toxicity was produced by 15 mg/kg (i.v. bolus) and consisted of convulsions and alterations of the ECG, including prolongation of the P-wave, PR and QRS intervals. In the anesthetized dog, the limiting toxic dosage was 30 mg/kg (i.v. bolus) which produced death of the animals within 5 minutes. Widening of the P-wave and the QRS and QT intervals were typical events. Blood pressure reduction, possibly resulting from a cardiac depressant action of the compound, was the cause of death. Carvedilol may produce alterations in blood pressure and heart rate by exerting a direct depressant effect on cardiac tissue. The cardiac depressant effect is most likely due to the membrane-stabilizing activity of carvedilol.

Brief overview of the special toxicity studies with carvedilol.

1.-Antigenicity and Delayed Hypersensitivity to Carvedilol

The potential for carvedilol to affect the immune system was examined in male species- (BALB/c), guinea pig (Hartley) and rabbit (NZ White). Various antigenicity studies were performed which included determinations of the possibility of the development of passive cutaneous anaphylaxis reaction (PCA), delayed type hypersensitivity reaction, anti-carvedilol antibodies, or carvedilol-induced anti-erythrocyte antibodies.

All studies were conducted in Japan and translations submitted in the NDA. Sponsor prepared detailed summary tables of these studies (see above.) The following overview of the findings is extracted from English translations of the Japanese studies and from the sponsor's summary.

The rationale for doses of carvedilol used is unclear. Reports included results of determination of PCA reaction using the mouse-rat, guinea pig-guinea pig, and rabbit-guinea pig models. The active systemic anaphylaxis reaction (instantaneous type allergy) was measured in guinea pig. Measurement of carvedilol-specific antibody formation was performed in guinea pig and rabbit sera by means of radio-immunoassay (RIA). Delayed type hypersensitivity reaction was determined in guinea pigs sensitized with subcutaneous injections of carvedilol with/or without Freund's complete adjuvant (FCA) and ovalbumin.

Briefly, male mice (BALB/c) were treated with carvedilol (10 or 100 mg/animal i.p. twice). Days after the second sensitization, blood was collected and serum separated. Rats were then passively sensitized with this serum by intracutaneous injection. Twenty four hours later, the rats were challenged with carvedilol (3 mg/kg i.v.) to examine the potential of evoking PCA. No PCA reactions was observed and no IgE antibodies were found.

Guinea pigs were treated 3 times at 2 weeks intervals with carvedilol (0.2 or 2 mg emulsified with FCA.) Days after the last injection, blood was collected, serum separated and injected in intracutaneously to naive guinea pigs. Hours or days later, these passively sensitized guinea pigs were challenged with carvedilol (3 mg/kg i.v.) to examine the potential of evoking PCA. Only one animal treated with the LD carvedilol showed PCA; all other guinea pigs were PCA negative. Serum from the one positive guinea pig showed a higher binding rate as normal serum in a RIA suggesting the presence of IgE antibodies. When all animals were rechallenged with i.v. carvedilol, no systemic anaphylaxis was observed even in the guinea pig that had shown PCA positive.

In a rabbit-guinea pig model, carvedilol was first given to rabbits (1 or 10 mg/animal p.o. 3 times a week for 3 weeks). Different rabbits were injected with carvedilol (1 or 10 mg/animal) plus FCA, or 2 mg/animal carvedilol plus FCA and ovalbumin, or 2 mg/animal FCA. Days after the final sensitization, blood was collected, serum separated and guinea pigs were passively sensitized with i.c. injection of the rabbit's sera. Four hrs later the guinea pigs

were challenged with carvedilol (3 mg/kg or 1 mg/kg ovalbumin.) All guinea pigs treated with carvedilol were PCA negative except for the positive controls.

Similar procedures as the above were used in a guinea pig-guinea pig model with the exception that the animals were treated with lower doses of carvedilol (0.2 or 2 mg/animal.) Again all guinea pigs tested were PCA negative.

Systemic anaphylaxis was determined in guinea pigs previously sensitized in the manner described above. The animals were later challenged with i.v. doses of carvedilol to determine the potential for evoking system anaphylaxis. None of the guinea pigs tested exhibited symptoms of active systemic anaphylaxis.

Guinea pigs were twice sensitized by subcutaneous injection of carvedilol (0.5 or 5 mg/kg) and FCA. Days after the second sensitization, guinea pigs were challenged with 30 mg carvedilol/site, to evoke a skin reaction. Twenty four to 48 hours later, skin sites were examined, and there was no evidence of a delayed type hypersensitivity reaction.

In a direct Coomb's test, no agglutination occurred with carvedilol at concentrations of 0.63 and lower.

The sera of animals used in these studies was tested to determine antibody formation. Using a RIA, no difference in binding rate was found compared to normal rabbit and guinea pig demonstrating that no antibody was formed against carvedilol.

2. Limiting Toxicity Studies.

Studies were conducted to determine the i.v. dose of carvedilol that would produce "limiting toxicity" in conscious and anesthetized dog. In conscious dog, limiting toxicity for carvedilol, produced by 15 mg/kg i.v. (bolus), was intermittent convulsions prior to the end of the dosing and alterations of the ECG (prolongation of the P-wave, PR and QRS intervals.) In anesthetized dogs, the limiting toxic dose of the drug was 30 mg/kg i.v. (bolus) which produced widening of P-wave and increases QRS and QT intervals occurring simultaneously with the fall in BP and HR; this effect was considered to be a direct cardiodepressant action giving rise to an apparent cardiogenic hypotension.

Most dogs receiving i.v. infusions of 225 ug carvedilol/kg/min for 4 hr or 450 ug/kg/min for 28 min showed very little change in the ECG. An initial fall in systolic BP was seen within 15 min of treatment of dogs. Intermittent convulsions began just minutes prior to the end of 4 hr infusion. Some other remarkable observations included rapid onset of action in conscious dogs on ECG, BP and HR changes; these observations were followed by the convulsions with no recovery of BP (no convulsions were seen at 7.5 mg/kg and only slight/transient changes in ECG.) Investigators pointed out that β -blocking agents at clinical doses would also show P wave widening; at higher doses some drugs (e.g. propranolol) produce prolongation of the PR and QRS intervals produced by a direct depression of A-V

transmission. Investigators considered that this depression may be the result of membrane stabilizing activity (MSA) because β -blockers that do not possess MSA have been reported as not producing this change. It was concluded that carvedilol "may produce alterations in BP and HR by exerting a depressant effect directly on cardiac tissue.....The cardiac depressant effect of carvedilol likely is due to its MSA."

REPRODUCTION STUDIES

Oral reproduction studies with carvedilol were performed following the FDA guidelines in 2 animal species (rats and rabbits). Only the teratology studies (FDA Seg.II) were reviewed in IND by previous pharmacologist N. Winbury, Ph.D. These reviews are reproduced/included below in the appropriate section of this document because N. Winbury's summaries had undergone secondary review by his supervisor C.Resnick, Ph.D., and the evaluations were found adequate.

Detailed summary tables of the reproduction studies (preliminary and definitive) conducted with carvedilol were prepared by sponsor are reproduced below with minor editorial changes. These summary tables are followed by FDA evaluations of all 3 segments of the reproduction studies.

SPONSOR'S SUMMARY TABLE OF REPRODUCTION TOXICITY STUDIES WITH CARVEDILOL

Species	Type of Study	Doses (mg/kg)	Report No. Ref. No. Location in NDA IND Submission	Drug-Related Observations
Rat	Dose Range Segment I/A	300, 400 pre-mating oral	TC015BS (Boehringer Mannheim report K4) Location: Vol. 1.39 Page 000043 Submitted to IND on 6/3/87	Both dosages were associated with less or no body weight gain during the first 4 to 5 days of drug administration. Sedation, red-stained nose and hair loss occurred during the first 2 weeks of the 64-day drug administration period.
Rat	Dose Range Segment I/B	200, 300 oral	TC015BS (Boehringer Mannheim report K4) Location: Vol. 1.39 Page 000043 Submitted to IND on 6/3/87	Sedation and hair loss were seen at 300 mg/kg. Most females at 200 mg/kg showed hair loss. During the first 5 days of drug administration, the high-dose females showed a marked decrease in body weight (approx. 20 g) followed by less weight gain during the 15-day drug administration period. Females at 200 mg/kg showed less weight gain during the first 8 days.
Rat	Segment I/A-I/B	12, 60, 300 oral	TC015BS (Boehringer Mannheim report K4) Location: Vol. 1.39 Page 000043 Submitted to IND on 6/3/87	Sedation, hair loss and less body weight gain were noted in high-dose animals. Forty-three % of high-dose females did not become pregnant versus 0 in controls. Days taken for successful mating were significantly increased in high-dose females. Median uterine weight of full-term high-dose females was lower than controls (70 vs 108 g). The median number of corpora lutea and implants were lower than controls. Developmental delays (stunted or missing 13th ribs) were observed more frequently in fetuses from mid- and high-dose females than from controls. Pup mortality was also increased in offspring of high-dose females. Underdevelopment of offspring of the high-dose group was observed (less weight, delay in placenta detachment, hair coat development, incisor eruption, eyelid separation and grip strength and decreased performance in the swimming maze). Lowest observable effect levels were 300 mg/kg for paternal toxicity and impairment of fertility and 60 mg/kg for developmental effects, and the no observable effect level was 12 mg/kg.
Rat	Food Intake and Pregnancy/Lactation	12, 60, 200 oral	TC-0019/SKF105517 (Daiichi report D-13)	Food intake of the high-dose females was significantly less on gestation days 0-7 and 7-14. Less body weight gain was observed in high-dose females during gestation and lactation.

Sponsor's Summary Table of Reproduction Toxicity with Carvedilol (Cont'd.)

Species	Type of Study	Doses (mg/kg)	Report No. Ref. No. Location in NDA IND Submission	Drug-Related Observations
Rat	Dose Range Segment II	Non-pregnant: 100, 200, 300, 400, 500, 1000, 1500 Pregnant: 50, 100, 200, 400 oral	TC012BS (Boehringer Mannheim report K1) Location: Vol. 1.39 Page 000176 Submitted to IND on 2/15/85	First study in non-pregnant animals consisted of a dose of 1000 mg/kg. Two of 4 animals showed marked weight loss at days 3 and 4. The animals were weak, the eyelids and nose had a bloody appearance and the urogenital area was brown-stained. Dosages of 500, 1000 and 1500 mg/kg were used in the 2nd study. The high-dose was only administered once due to the development of severe toxic signs, such as apathy, ataxia and low cutaneous temperature. High-dose also showed a steep fall in body weight. One of 2 animals in the mid-dose group showed a decrease in body weight. Animals also exhibited signs as observed in the first study. The low-dose animals behaved as the controls. In the 3rd study, the 100 and 200 mg/kg dose groups gained more weight than the controls in the 1st week, the 300 mg/kg group was not different from controls and the 400 and 500 mg/kg groups lost weight. In the 2nd week, the weight loss was abolished in the 400 and 500 mg/kg dose groups. Food intake was increased at 100 mg/kg in the 1st week and was decreased at 200 mg/kg and greater. In the 2nd week, no difference in food intake was observed. The 400 and 500 mg/kg animals showed signs of toxicity. In pregnant animals, less weight gain or a decrease in body weight was observed at 200 mg/kg and above. Food intake was less at 400 mg/kg. A dosage of 100 mg/kg or above was associated with impairment of general well being, including sedation.
Rat	Segment II	12, 60, 300 oral	TC012BS (Boehringer Mannheim report K1) Location: Vol. 1.39 Page 000176 Submitted to IND on 2/15/85	One high-dose animal died. Sedation, hair loss and red stained eyelids were observed in mid- and high-dose animals. High-dose animals showed less and mid-dose animals more body weight gain than controls. Median full-term uterine weight was lower and post-implantation losses higher in high-dose animals. The latter also implied that there were less live fetuses in the high-dose group. Fetal and placental weights were lower in the high-dose group. Developmental delays were seen in the high-dose group. The lowest observable effect levels were 60 mg/kg for maternal effects and 300 mg/kg for developmental toxicity, and the no observed effect levels were 12 and 60 mg/kg, respectively.

Sponsor's Summary Table of Reproduction Toxicity with Carvedilol (Cont'd.)

Species	Type of Study	Doses (mg/kg)	Report No. Ref. No. Location in NDA IND Submission	
Rabbit	Dose Range Segment II	Non-pregnant: 100, 200 Pregnant: 150 oral	TC013BS (Boehringer Mannheim report K2) Location: Vol. 1.39 Page 000225 Submitted to IND on 2/15/85	At 200 mg/kg, non-pregnant animals showed a decrease in body weight compared to controls during a 12-day period (approx. 100 to 250 g). No other signs were noted. Pregnant animals at 150 mg/kg showed less food intake and marked body weight loss (approx. 250 g) during the period of drug administration (days 7-19 of gestation). There was an increase in post-implantation loss.
Rabbit	Segment II	3, 15, 75 oral	TC013BS (Boehringer Mannheim report K2) Location: Vol. 1.39 Page 000225 Submitted to IND on 2/15/85	A slight increase in median post-implantation loss and consequently less live fetuses were seen in the high-dose group. Fetal and placental weights were higher in treated groups than in controls. The lowest observable effect level was 75 mg/kg for developmental toxicity, and the no observed effect levels were 75 mg/kg for maternal effects and 15 mg/kg for developmental toxicity.
Rat	Segment III	12, 60, 200 oral	TC014BS (Boehringer Mannheim report K3) Location: Vol. 1.39 Page 000270 Submitted to IND on 10/3/89	<u>Drug-Related Observations</u> Hair loss was seen at all doses. Sedation occurred in high-dose animals. In the last week of gestation, high-dose females gained less weight. However, the mid- and high-dose females showed more weight gain than the controls during lactation. Pups from mid- and high-dose females showed a higher mortality rate during the first 2 days postpartum. Reduced body weight of pups from the mid- and high-dose groups remained detectable into adulthood. Pups of these dose groups also showed delayed pinna detachment and it took them longer to fulfill the criteria for the grip strength test. The lowest observable effect levels were 60 mg/kg for maternal effects and for developmental toxicity, and the no observed effect level was 12 mg/kg.

Summary of Fertility and General Reproductive Performance in Rat (Seg. I)
(SK&F Report No. TC015BS. Boehringer Mannheim GMH, Germany.
Study Dates: 08-08-84 until 03-22-85. Report date: November 1986)

No./Dose/Level/Strain: 24 M, 24 F, Sprague-Dawley (CrI:CD(SD)BR)

Route: Orally by gavage

Dose Levels: 0 (vehicle - 1% methylcellulose), 12, 60 or 300 mg carvedilol suspension as 10 ml/kg/day. Doses were based on preliminary studies.

Treatment Schedule and Synopsis of Procedures:

Males (F_0) were treated daily at least 62 days before mating, dosing continued up until successful mating. Body weight was recorded daily for the first 80 days of study, then once weekly until day 129 of study. Females (F_0) were treated daily for 15 days prior to mating and treatment continued through and up to day 21 of lactation. Body weights were determined daily. All rats were observed daily for clinical signs.

Caesarian Group: Groups of dams were killed and laparotomized on 22 p.c. The uteri were removed and weighed before and after the removal of the fetuses, placenta, dead implants and fetal membranes. The fetuses were counted in situ, removed, examined for signs of life and their position in the uterine horns recorded. Observations included: counting of the resorption sites, early resorptions, and corpora lutea, as well as weighing of the placenta, fetuses, inspection of each fetus for externally visible malformations, and sex determination.

Malformations of the skeleton were sought in at least 50% of each litter of caesarian-delivered fetuses. The detection of the skeleton malformations was by means of alizarin staining. Examination for internal organ malformations and determination of sex was carried out in situ after fixation in Bouin's solution.

Examination of F_1 Generation: The litter size of F_1 generation was determined daily until weaning took place; their body weights were recorded once a week. In selected F_1 pups, physical parameters were recorded (pinna detachment, down, full coat of hair, incisor eruption, eye opening, grip strength). At protocol specified times, tests were carried to check the neuromuscular coordination and reflexes (cliff avoidance, air righting, corneal, pupillary and auditory startle reflexes). After that, selected F_1 pups (3 M and 3 F) per litter were subjected to a combined learning and behavior test. All other F_1 pups were sacrificed.

Weaning Groups (rats allowed to litter): Dams that were allowed to litter, their litters (F_1 generation) underwent similar examinations as described above for the "caesarian group."

Selected F₁ males and females from treatment group were allowed to mate. All dams were allowed to deliver spontaneously. F₂ generation pups were observed for physical development, neuromuscular coordination, reflexes and behavior as done for the F₁ generation.

F₁ and F₂ generation were examined for visceral and skeletal abnormalities.

Results:

Parenteral (F₀ generation) Observations:

Remarkable effects were reported at MD and HD. At HD, caesarian group rats showed loss of hair and sedation for both male and female rats; sedation was not long lasting. Body weight gain was also reduced at HD. Compared to control, at MD and HD showed significantly less corpora lutea. Fewer uterine implants were noted at HD compared to controls. On the fetuses, no notable effects of carvedilol were reported on pre- and post-implantation losses, live/dead fetuses, sex ratio or placental weights. The findings in the fetal weight were variable. Compared to controls, fetal weight at LD and HD showed slight dose-related increases and, at HD a slight decrease.

In F₀ generation allowed to litter, loss of hair and delayed body weight gain was also seen at HD; body weight was significantly lower than controls. Compared to controls, drug related effects at HD included decreased uterine implants and live pups.

Litter Observations (F₁ generation):

More malformations in caesarian delivered fetuses were found in the MD and HD dams. Malformations consisted of slight increase in the number of short 13th ribs; however, this malformation was also observed in controls.

F₁ pups from HD group allowed to litter were always lighter in weight than those from other treated groups.

The physical development of F₁ generation was slightly, but persistently retarded. Fertility in this generation exposed in utero to HD could not be reliably evaluated because of the apparently small number of HD offspring that could be reared to sexual maturity.

No adverse effects on development, behavior or fertility was reported for the F₁ generation or development/behavior effects on their F₂ generation.

OVERVIEW OF ADME STUDIES

The drug sponsor has submitted 52 nonclinical ADME and toxicokinetics reports on carvedilol (labelled and unlabelled) administered to whole animals by various routes and miscellaneous types of studies. Breakdown of studies according to species is as follows: mouse- 2, rat- 25 (11 conducted in Japan), rabbit- 1, dog-10, monkey- 3 conducted in Japan, the remaining 12 (3 conducted in Japan) studies included in vitro studies. Numerous of these studies were conducted in Japan. The following overview is essentially that submitted by the sponsor with editorial changes.

In rat and dog, oral doses of carvedilol are rapidly and extensively absorbed. The absolute bioavailability of the drug in these species is low, 20-25% for rat and 10-30% for dog considered the result of first-pass metabolism and only minor sex differences were noted. In rat, following single dose oral administration of pharmacological active dose of ^{14}C -carvedilol, within 1 hour peak levels of carvedilol were detected in serum samples (138 ng/ml in males and 200 ng/ml in females, Table 28). By 24 hr serum concentrations of the drug were below the limit of quantitation (2 ng/ml). The median AUC_{0-8} values for carvedilol were 587 and 608 ng.hr/ml in male and female rats, respectively. Also, following oral administration of ^{14}C -labeled carvedilol, serum concentrations of radioactivity at all sampling times were significantly higher than those observed for non-labeled carvedilol. In rat and dog, slow terminal elimination $T_{1/2}$ for radioactivity in serum were observed (about 60 hours) and $T_{1/2}$ of carvedilol was about 5 and 7 hours, respectively.

Male beagles, treated with 150 mg/kg ^{14}C -carvedilol showed peak serum concentration of the parent compound (2.8 ug/ml) and radioactivity (11.9 ug equiv. hr/ml) at 1.75 hrs indicating a median rate of absorption at this dose. The median AUC_{0-144} for carvedilol was 40.7.hr/ml compared to 213 ug-equiv.-hr/ml for radioactivity (Table 28). The median terminal elimination $T_{1/2}$ for radioactivity in serum was 75 hrs.

In rat and dog, following i.v. administration of carvedilol, concentrations of the drug declined rapidly with a terminal elimination $T_{1/2}$ of about 1 hour for both species. Plasma clearance of carvedilol (determined on serum) was 45-60 ml/min/kg in rat and 22 ml/min/kg in dog. The volume of distribution (V_d) in the dog was 1.7 L/kg showing that there is substantial distribution into extravascular tissues.

In rat (Sprague-Dawley) and monkey, carvedilol exhibited stereoselective pharmacokinetics when single doses of carvedilol were tested (2 mg/kg i.v. or 10 mg/kg p.o.). The lower limit of quantitation for both enantiomers was 1.55 ng/ml in plasma. In rat, following oral administration, plasma levels of R(+)-carvedilol were higher than the S(-)-carvedilol up to 6 hrs postdose. The R/S enantiomeric ratios for C_{max} and AUC were 2.5 and 2.2, respectively. The absolute bioavailability for R(+)-carvedilol (5.9%) was 40% greater than that of the S(-)-carvedilol (4.2%) (Table 29)

In the cynomolgus monkey, following 10 mg/kg carvedilol p.o., plasma concentration of the R(+)-carvedilol were higher than those of the S(-)-carvedilol up to 6 hrs after dosing. The T_{max} was about 2.5 hrs post dose for both enantiomers. The C_{max} for R(+)-carvedilol was

38.3 ng/ml and for the S(-)-carvedilol 25.1 ng/ml. The R/S enantiomeric ratios for C_{max} and AUC were 2.5 and 1.2, respectively. (Table 29) Following i.v. administration of racemic carvedilol in the rat, mean plasma clearance of R(+)-carvedilol was 20 ml/min/kg vs 33 ml/min/kg for S(-)-carvedilol. The mean volume of distribution (V_d) for R(+)-carvedilol was 1.9 L/kg compared to 3.9 L/kg for S(-)-carvedilol. In both rat and monkey, terminal elimination T_{1/2} for R(+)-carvedilol was slightly faster than that observed for the S(-)-enantiomer.

Table 28
Pharmacokinetic parameters for parent and radioactivity following single doses of ¹⁴C-carvedilol in animals.*

Species	Dose (mg/kg)	Dose Route	No./Sex of animals	Parent Compound			Radioactivity in Urine		
				T _{max} (hr)	C _{max} (ng/ml)	AUC _{0-t} [†] (ng·hr/ml)	T _{max} (hr)	C _{max} [‡] (ng/ml)	AUC _{0-t} ^{†‡} (ng·hr/ml)
Rat	10	p.o.	4M	1.0 [§] (1.0-1.0)	~ 138 (68-173)	587 [†] (397-726) (0-8 hr)	1.0 [§] (1.0-1.0)	420 (190-447)	6341 [†] (4227-8722) (0-48 hr)
	10	p.o.	4F	1.0 [§] (1.0-1.0)	~ 200 (128-254)	680 (538-884) (0-8 hr)	1.0 [§] (1.0-1.0)	427 (321-502)	4848 (3899-5275) (0-48 hr)
Dog	0.25	i.v.	4M	0.681 [§]	492 (125-1339)	198 (107-336) (0-8 hr)	3.241 [§]	616 (172-1863)	1592 (1145-1910) (0-48 hr)
	5	p.o.	4M	0.5 (0.25-1.0)	123 (75-1563)	324 (157-2244) (0-24 hr)	0.5 (0.5-1.5)	578 (305-1721)	8552 (7979-10888) (0-144 hr)
	150	p.o.	3M/3F	1.75 (1.0-2.0)	~ 2.82 [†] (1.03-4.97)	~ 42.7 [†] (12.9-139.6) (0-144 hr)	~ 1.75 (1.0-3.0)	~ 11.9 [†] (7.3-45.8)	~ 213 [†] (153-451) (0-144 hr)

* Data presented as median and range.

[†] sampling interval noted in brackets.

[‡] expressed in ng equivalents of carvedilol.

[§] time of first sample.

[†] n=3; data from one male rat excluded due to incomplete sampling.

[‡] units are ug/ml for C_{max} and ug·hr/ml for AUC_{0-t}.

Pharmacokinetics Parameters of Enantiomers

Table 29 Pharmacokinetic parameters for carvedilol enantiomers following single dose administration of racemic carvedilol in the rat and mon

Species	Dose (mg/kg)	Dose Route	No. /Sex of animals	Pharmacokinetic Parameters (mean ± SD)				
				Enantiomer	T _{max} (hr)	C _{max} (ng/ml)	AUC _{0-∞} (ng·hr/ml)	T _{1/2} (hr)
Rat	2	i.v.	3M	• R(+)	0.083 ^a	814 ± 36	848 ± 184	1.09 ± 0.03
				• S(-)	0.083 ^a	446 ± 16	544 ± 158	1.46 ± 0.50
	10	p.o.	4M	• R(+)	0.5 ^f	110 ^f	251 ^f	4.3 ^f
				• S(-)	0.5 ^f	44 ^f	116 ^f	5.6 ^f
Monkey	10	p.o.	3F	• R(+)	2.7 ± 0.6	38.3 ± 13.7	160 ± 49	2.8 ± 0.8
				• S(-)	2.3 ± 1.2	25.1 ± 8.4	129 ± 41	3.9 ± 0.9

^atime of first sample.

^fpharmacokinetic analysis performed on mean plasma concentration-time data.

Toxicokinetics.

In a 3-mo dose-range study in mice (NMRI) given carvedilol (20, 60, 200, 600 or 800 mg/kg in diet), a single point measurement (at the end of study for the LD alone) showed serum ranges of the drug from 22 up to 685 ng/ml. Sponsor asserts, but no data were provided, that qualitatively concentrations of the drug increased with the dose showing that the mice were exposed to carvedilol. Sponsor again asserts, without providing data, that systemic exposure to the drug increased with increasing doses when determined for single-point measurements of serum at the end of the 2-year mouse carcinogenicity study.

In a 3-mo rat toxicokinetic study, rats treated with carvedilol (90 and 300 mg/kg/day), C_{max} and AUC_{0-24} values for carvedilol increased about 2 to 3 fold after dosing 1-week suggesting a decrease in the metabolic clearance of the drug with chronic dosing. At the end of the study serum concentrations of the drug in the 90 mg/kg/day more than 10 to 20-fold greater than those reported in hypertensive patients receiving 50 mg once a day (the maximum recommended daily therapeutic dose assuming a 50 kg patient.)

In the 3-month dose-ranging study in rat, carvedilol was administered in the diet at concentrations of 200, 600, 2000, 6000 and 8000 ppm. Drug intake was determined after 1, 6 and 15 weeks of drug treatment. Compared to week 1 of treatment the median intake of the drug was decreased (Table 30) Serum concentrations of the drug were determined at the same time intervals; however, despite the decrease of drug intake between weeks 1 and 15 of study, serum concentrations of drug were higher at week 15 suggesting a decrease in the clearance of carvedilol after repeated administration.

Table 30 SUBSTANCE INTAKE IN THE 3-MONTH DOSE-RANGING STUDY IN RATS FOR THE CARCINOGENICITY STUDY WITH BM 14,190

Dose	Substance intake median (mg/kg)				Blood levels mean value (ng/ml)					
	after 1 week	6 weeks	15 weeks	n	after 1 week	n=4	6 weeks	n=2	15 weeks	n=6
MALE										
200 ppm	27.27	15.85	11.19	6	17		22		26.8	
600 ppm	85.7	46.64	32.52	6	40		44.5		55.3	
2000 ppm	293.19	152.32	100.42	6	605.25		457.5		324.3	
6000 ppm	862.86	498.66	384.88	6	1814		2878		3890.3	
8000 ppm	1268.96	789.36	531.63	6	2929		5925		6409.3	
FEMALE										
200 ppm	27.25	14.94	11.13	6	16.5		33.5		18.6	
600 ppm	79.61	48.40	42.25	6	55.5		141		75.6	
2000 ppm	316.1	155.48	126.08	6	539.75		1071		865.16	
6000 ppm	971.4	508.03	412.79	6	2091.75		4684		6328.8	
8000 ppm	1062.1	654.24	486.24	6	2424.25		8260.5		6282.5	

In a separate study, serum concentrations of carvedilol were determined in rats receiving carvedilol 400 and 1600 ppm in the diet for 28 weeks. At 6 months the mean daily drug intake in the LD group was about 14 mg/kg (equivalent to about the "no-effect" dose in a 18-month study) (Table 31) Sponsor states that mean C_{max} values for carvedilol in this dose group (about 14 mg/kg/day) was close to that seen in hypertensive patients receiving carvedilol 50 mg once daily but this was the result of limited sampling in rat. Mean AUC₀₋₂₄ values for carvedilol in rats receiving the LD were roughly 2-fold higher than that observed in patients administered carvedilol 50 mg once daily.

In the 2-year carcinogenicity study in the rat, 4 doses of carvedilol were administered in the diet (summary above shows that mean daily intake ranged from 8 up to 75 mg/kg at the end of the study.) Serum concentrations of the drug determined at one time point in all dose groups showed mean plasma concentrations of carvedilol in males of 21, 31, 94 and 215 ng/ml and, in females 18, 39, 94 and 354 ng/ml. These results show that the rats used in the carcinogenicity study were exposed to carvedilol and that systemic exposure increase with dose.*

In the 12-month chronic toxicity study in the dog, carvedilol was administered orally at doses of 10, 30, 100, and 300 mg/kg/day. The "no effect" dose in this study was considered to be around 30 mg/kg/day. Based on mean C_{max} and AUC data, serum concentrations of carvedilol were approximately 6-fold higher in these dogs (30 mg/kg/day) compared to that observed in hypertensive patients receiving 50 mg once daily. (Tables 31a and 31b)

With the exception of metabolite M5 (barely quantifiable in rat and dog), plasma levels of the active metabolites in the rat and dog were comparable to those observed in man. In conscious rabbits, the M2 (desmethyl), M4 (4¹-hydroxyphenyl), and M5 (5¹-hydrophenyl) metabolites exhibited β-adrenoceptor blocking activity. Compared to carvedilol, metabolites M2, M4 and M5 possess only weak vasodilating activity. In both healthy volunteers and in patients with renal dysfunction, plasma concentrations of these metabolites are less than 10% of those observed for carvedilol and follow a similar time course with parent.

* These data were not submitted in the Original NDA. Data were requested and were submitted by sponsor in NDA Amendment dated 03-29-94.

PHARMACOKINETIC PARAMETERS FOR CARVEDILOL FOLLOWING CHRONIC ORAL DOSING IN RAT AND HYPERTENSIVE (HTN) PATIENTS

<u>431a</u>				Pharmacokinetic Parameters (mean ± standard deviation)			
Species	Dose (mg/kg/day)	Study Day	No./Sex of animals	T _{max} (hr)	C _{max} (ng/ml)	AUC ₀₋₂₄ (ng·hr/ml)	CL/F (ml/min/kg)
Rat (average)	90	8	15M	4.9 ± 2.3	1182 ± 301	14771 ± 6018 ^a	115 ± 40 ^a
			15F	4.9 ± 3.0	1256 ± 373	15412 ± 4195	109 ± 48
	300	88	14M	6.9 ± 2.0	1919 ± 685	26108 ± 9203	64 ± 24
			14F	5.5 ± 3.4	2578 ± 565	41340 ± 11898	39 ± 12
	300	8	15M	6.4 ± 2.4	2146 ± 516	33734 ± 10923	160 ± 42
			15F	6.9 ± 2.5	2560 ± 607	40645 ± 14358	135 ± 41
	300	88	14M	7.6 ± 1.3	4417 ± 1087	71994 ± 15283 ^b	72 ± 13 ^b
			15F	7.3 ± 1.9	7393 ± 2014	139631 ± 42398	40 ± 16
Rat (individual)	<u>30 ppm</u>						
	28	8	12M	12.0	219 ± 37	2756 ± 472	176 ± 39
	30	10	12F	16.0 ± 3.0	249 ± 69	3603 ± 856	143 ± 36
	12	192	12M	15.0 ± 5.4	167 ± 54	1981 ± 384	101 ± 23
	14	193	12F	14.5 ± 7.0	170 ± 109	2062 ± 809	128 ± 68
	<u>1600 ppm</u>						
	109	8	12M	15.5 ± 3.1	1152 ± 278	18476 ± 3586	102 ± 27
	87	10	12F	17.5 ± 1.7	1278 ± 185	19680 ± 3634	76 ± 17
	45	192	12M	18.5 ± 1.7	794 ± 187	10092 ± 1644	77 ± 27
	87	193	12F	15.5 ± 7.9	1280 ± 335	17259 ± 5019	79 ± 35

n=6.
n=13.

<u>431b</u>				Pharmacokinetic Parameters (mean ± standard deviation)			
Species	Dose (mg/kg/day)	Study Day	No./Sex of animals	T _{max} (hr)	C _{max} (ng/ml)	AUC ₀₋₂₄ (ng·hr/ml)	CL/F (ml/min/kg)
Dog	30 ^b	343	5M/5F	2.4 ± 0.8	977 ± 654	7340 ± 4406 ^b	96 ± 57
HTN Patients	12.5 mg/day (0.15) ^b	28	7M/2F	1.6 ± 1.1	32 ± 18	184 ± 142	ND
	25 mg/day (0.31) ^b	28	8M/2F	1.0	73 ± 34	343 ± 226	ND
	50 mg/day (0.53) ^b	28	8M/1F	2.7 ± 1.6	167 ± 108	1136 ± 810	ND

administered in two equally divided doses (15 mg/kg every 12 hours).

AUC₀₋₂₄ calculated as 2 times the observed AUC₀₋₁₂.

^b approximate mg/kg/day.

Protein Binding/RBC Partitioning.

Carvedilol is bound (about 98-99%) to plasma proteins; similar to values observed. Over the range of 50 to 1000 ng/ml, protein binding of carvedilol in human serum has been shown to be independent of concentration. Since carvedilol is lipophilic, it would be expected to readily cross the red blood cell membrane. However, because the drug is extensively bound to plasma protein, partitioning into the red blood cell is limited. At blood concentrations of about 500 ng/ml, the blood to plasma concentration ratios for carvedilol were 0.92, 0.89, 0.83 and 0.69 and 0.83 in mouse, rat, human and guinea pig, respectively.

Tissue Distribution.

In the rat, following oral administration of labelled carvedilol the radioactivity was relatively well distributed in all tissues considered due to the high lipophilicity of the drug. In the rat, following a single oral dose, concentrations of radioactivity were highest in the gastrointestinal tissues, liver, kidneys, Harderian gland, lungs, hypophysis, submaxillary gland and pancreas. In the rat, carvedilol-related material exhibits high affinity for the erythrocyte resulting in a prolonged elimination $T_{1/2}$ (> 200 hours) for radioactivity in blood. As a consequence of the long elimination $T_{1/2}$ in rats, blood concentrations of radioactivity increased about 14-fold after consecutive daily doses of radiolabeled carvedilol p.o. for 21 days.

Radioactivity did not markedly accumulate in plasma upon repeated oral doses of labeled carvedilol. In the rat, following repeated oral doses of the drug, concentrations of radioactivity were highest in the erythrocyte, liver, and Harderian gland but other tissues also showed concentrations of radioactivity (e.g., cecum, kidneys, ileum, and brown fat.)

In rat, placenta transfer of carvedilol and/or its metabolites was low. In pregnant rat, single oral dose of radiolabeled carvedilol showed a $\leq 0.01\%$ of the administered dose distribution of radioactivity on days 12 and 19 of gestation. Studies in lactating rats demonstrate carvedilol and/or its metabolites were excreted into breast milk. After a single oral dose of ^{14}C -carvedilol, concentration radioactivity in breast milk exceeded those observed in plasma at all sampling times; by 24 hrs after dosing the milk to plasma concentration ratio was decreased.

In rabbit, a single oral dose of radiolabeled carvedilol resulted in the highest concentrations of radioactivity in the liver and kidney at 48 hours post-dose.

In the monkey, whole body autoradiography experiments demonstrated that the highest levels of radioactivity were present in the gall bladder 1 hour after both i.v. and oral administration of ^{14}C -carvedilol suggesting that biliary excretion is a major route of elimination in this species. Concentrations of radioactivity following oral administration were considerably lower compared to i.v. administration indicating substantial first-pass clearance in the monkey. By 24 hours after the oral dose, concentrations of radioactivity had declined from all tissues. Carvedilol and its metabolites exhibit affinity for melanin containing tissues (e.g. uvea and hair follicles.)

Enzyme Inhibition/Induction.

In rat, multiple oral dosing of carvedilol had a minimal effect on hepatic P450-dependent enzyme activities. *In vitro* and *in vivo* studies indicate that the drug at high concentrations is an inhibitor of hepatic cytochrome P450-mediated activities. However, at plasma concentrations approximately 2- to 5-fold higher than those observed in hypertensive patients, carvedilol did not inhibit cytochrome P450-dependent clearance of antipyrine in the rat.

In rat, no major differences were found in the pattern of metabolites in the liver after single and multiple dosing with carvedilol suggesting that the drug does not have an inhibitory effect on its own metabolism and that its metabolic pattern does not change during chronic dosing in this species.

Metabolism.

Carvedilol undergoes extensive metabolism via oxidation and conjugations pathways. The biotransformation of carvedilol was characterized and major metabolic pathways fully described for mouse, rat and dog.

In mouse, given ¹⁴C-carvedilol (100 mg/kg p.o. in a suspension), circulating plasma displayed a complex mixture of products, however, unchanged drug was the most abundant plasma component at 2 and 6 hrs postdosing with the females showing higher concentration of carvedilol metabolites relative to unchanged drug. In this study, the drug was excreted primarily in the feces and a small amount in the urine. The profile of urine and fecal radioactive metabolites was complex, not sex difference was reported in the more than 25 metabolites. (Fig. 50 below) Most of these products identified were minor, accounting for <5% of the administered dose. In the mouse and rat, the primary route of metabolism of carvedilol is hydroxylation of the carbazoyl ring with subsequent phenolic glucuronidation. In dog, carbazoyl ring hydroxylation with subsequent glucuronidation and direct glucuronidation of carvedilol were the major metabolic pathways. In species studied, oxidative dealkylation and sulfation were relatively minor metabolic pathways for carvedilol. In each of the animal species and in humans, unchanged carvedilol was identified as a major drug-related component circulating in plasma (Table 32). Sponsor asserts that essentially all the other circulating metabolites identified in plasma were conjugates of carvedilol or hydroxylated carvedilol which were also identified in excreta.

In humans, carvedilol was also metabolized extensively; drug-related products were excreted primarily in feces. Metabolites identified in urine were considered formed primarily via direct glucuronidation, carbazoyl and phenyl ring hydroxylation with subsequent glucuronidation (as in rat, mouse and dog) or sulfation (a minor pathway in animals), and O-demethylation with subsequent glucuronidation or sulfation. Unchanged carvedilol was a major product circulating in plasma; metabolites in plasma were qualitatively similar to those in urine. Fecal analysis showed unchanged carvedilol, O-desmethyl carvedilol and carbazoyl and phenyl ring hydroxylation products. Based on the metabolites identified in urine, sponsor considers that the majority of the metabolites identified in feces were probably excreted into bile as glucuronide and sulfate conjugates which were subsequently hydrolyzed in the gut.

Some Metabolic Parameters (Cont'd.)

STRUCTURES OF CARVEDILOL AND 3 PRINCIPAL METABOLITES

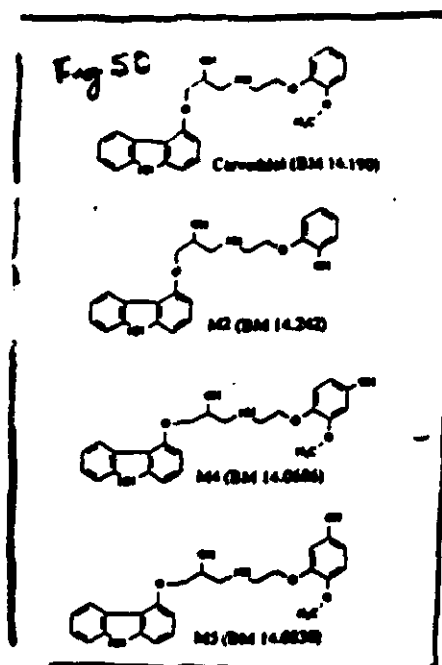


Table 32 Maximum observed plasma concentrations of carvedilol and metabolites M2, M4, and M5 following oral administration of carvedilol in rat, dog, and man.

Species (#/sex)	Dose	Component			
		Carvedilol	Desmethyl (M2)	4'-hydroxy phenyl (M4)	5'-hydroxy phenyl (M5)
Rat (3M/3F)	30 mg/kg ^a	1778 [†] (595-3265) (3M/3F)	7.2 (3.6-12.5) (1M/3F)	5.1 (2.0-6.7) (1M/2F)	2.6, 2.9 (1M/1F)
Dog (2M/2F)	10 mg/kg ^a	826 [†] (634-1721) (2M/2F)	1.9 (1.0-3.3) (1M/2F)	5.3 (4.1-12.0) (2M/2F)	1.01 (1F)
Man (10M)	25 mg [§] (0.3 mg/kg)	49 (20-84)	3.9 (3.1-6.6)	4.1 (2.4-5.1)	3.3 (2.0-5.8)

^a single dose.

[†] data presented as median and range (units in ng/ml); brackets indicate number and sex of animals with measurable (≥ 1 ng/ml) concentrations.

[§] multiple dose (1st dose 12.5 mg, then 25 mg once daily for 6 days).

In conscious rabbits, studies show that the desmethyl (M2), 4'-hydroxyphenyl (M4) and 5'-hydroxyphenyl (M5) metabolites of carvedilol possess β -adrenoceptor blocking activity. Based on dose, the M4 metabolite of carvedilol is about 13 times more potent than carvedilol with respect to β -adrenoceptor blocking activity. The M2 metabolite is about 2.5 fold more potent than carvedilol. The M5 metabolite exhibits the weakest β -adrenoceptor blocking activity, approximately 60% of that observed for carvedilol. In rat and dog, single oral doses of 30 mg/kg or 10 mg/kg of carvedilol, respectively, showed plasma concentrations of metabolites M2 and M4 which were more than 100-fold lower than those observed for parent compound; plasma concentrations of M5 were barely quantifiable in both species. Urinary concentrations of the active metabolites mirrored the plasma concentration. Following enzymatic hydrolysis of the urine of both rat and dog, minor amounts of all three metabolites (M2, M4 and M5) were observed. Results of these studies indicate that both the rat and dog metabolize carvedilol via demethylation and hydroxylation of the phenyl ring. However, these metabolites are primarily present in the rat and dog as conjugates.

Excretion.

Excretion of carvedilol was studied after oral administration of radiolabeled carvedilol in mouse, rat, rabbit, dog, and monkey. Similarly to man, the majority of the radioactivity was excreted in the feces with only a small fraction of the dose excreted in the urine. In bile-duct cannulated rats and dogs, most of the radiolabeled dose was excreted in the bile following both oral and i.v. administration indicating good oral absorption and significant biliary elimination. In both rat and dog, renal elimination of unchanged carvedilol accounts for less than 0.2% of the dose. In the rat, enterohepatic recirculation of carvedilol-related material has been demonstrated; sponsor considered that this finding may explain the slow elimination of radioactivity from the body. (Tables 33a and 33b)

Excretion Parameters (Cont'd.)

Table 33a

Excretion of radioactivity following single doses of ^{14}C -carvedilol in animals and man.

Species	Dose (mg/kg)	Dose Route	No./Sex of animals	Time Period (hr)	Percent of dose recovered (mean $\pm$ SD)			
					Urine	Feces	Bile	Total
Mouse	100	p.o.	10M	0-24	1.7 $\pm$ 0.7	66.1 $\pm$ 22.7	ND	68.1 $\pm$ 23.3 ^a
				0-96	3.2 $\pm$ 0.5	92.9 $\pm$ 5.8	ND	97.1 $\pm$ 5.6 ^b
	100	p.o.	10F	0-24	8.1 $\pm$ 3.3	61.2 $\pm$ 8.8	ND	69.9 $\pm$ 7.1 ^a
				0-96	10.3 $\pm$ 3.5	79.6 $\pm$ 2.3	ND	91.5 $\pm$ 1.9 ^b
Rat	10	p.o.	5M ^b	0-24	2.5 $\pm$ 0.6	69.2 $\pm$ 12.3	ND	71.7 $\pm$ 12.1
				0-48	2.8 $\pm$ 0.7	87.0 $\pm$ 23.2	ND	89.8 $\pm$ 23.2
	10	p.o.	6F	0-24	1.9 $\pm$ 0.5	48.4 $\pm$ 9.0	ND	50.3 $\pm$ 9.0
				0-48	2.2 $\pm$ 0.5	53.2 $\pm$ 7.6	ND	55.4 $\pm$ 7.7
	10	p.o.	3M	0-24	4.4 $\pm$ 0.9	83.0 $\pm$ 3.3	ND	87.4 $\pm$ 4.2
				0-72	4.5 $\pm$ 0.9	90.8 $\pm$ 0.5	ND	95.4 $\pm$ 1.4
	2.5	i.v.	5M	0-48	12.0 $\pm$ 11.8	1.0 $\pm$ 0.4	81.1 $\pm$ 11.4	90.2 $\pm$ 2.2 ^b
				30	3.5 $\pm$ 2.9	26.2 $\pm$ 5.6	67.9 $\pm$ 6.1	90.2 $\pm$ 2.6 ^b
	2.5	i.v.	6F	0-48	5.8 $\pm$ 4.3	1.4 $\pm$ 0.5	32.9 $\pm$ 7.6	102.0 $\pm$ 3.7 ^b
				30	1.6 $\pm$ 1.2	20.9 $\pm$ 4.5	73.4 $\pm$ 8.9	96.3 $\pm$ 6.6 ^b
	1.26	i.v.	6M	0-48	8.1 $\pm$ 7.3	2.2 $\pm$ 0.7	89.9 $\pm$ 6.6	100.5 $\pm$ 3.7 ^b
				10	2.9 $\pm$ 0.5	14.1 $\pm$ 8.3	84.9 $\pm$ 8.6	102.5 $\pm$ 2.2 ^b
Rabbit	5	p.o.	3M	0-24	3.8 $\pm$ 3.2	24.8 $\pm$ 28.7	ND	28.6 $\pm$ 30.3
				0-48	6.1 $\pm$ 3.6	33.6 $\pm$ 34.6	ND	39.7 $\pm$ 36.3
	5	p.o.	3F	0-24	6.0 $\pm$ 5.5	44.2 $\pm$ 34.9	ND	50.2 $\pm$ 39.9
				0-48	9.2 $\pm$ 2.3	56.1 $\pm$ 31.2	ND	65.3 $\pm$ 32.2

Excretion Parameters (Cont'd.)

Excretion of radioactivity following single doses of ¹⁴C-carvedilol in animals and man.

Table 33b

Species	Dose (mg/kg)	Dose Route	No./Sex of animals	Time Period (hr)	Percent of dose recovered (mean ± SD)				
					Urine	Feces	Bile	Total	
Dog	0.25	i.v.	3F	0-96	14.6 ± 2.0	64.9 ± 3.5	ND	80.2 ± 1.7 ^o	
	5	p.o.	3F	0-96	11.9 ± 3.2	66.2 ± 7.1	ND	79.0 ± 6.6 ^o	
	0.25	i.v.	4M	0-144	16.2 ± 2.5	53.5 ± 9.8	ND	69.7 ± 11.5	
	5	p.o.	4M	0-144	9.2 ± 9.6	48.4 ± 36.1	ND	57.7 ± 36.7	
	<u>150</u>	p.o.	3M/3F	0-144	4.6 ± 2.3	41.8 ± 16.5 ^o	ND	46.1 ± 18.3 ^o	
	10	p.o.	2F	0-96	8.4, 8.6 ^o	73.7, 74.2	ND	82.0, 82.8 ^o	
	10	p.o.	2F	0-96	6.6, 9.0 ^o	21.0, 44.2	35.4, 60.2	87.8, 88.5 ^o	
	Monkey	10	p.o.	3F	0-240	15.7 ^v	64.5 ^v	ND	80.2 ^v
	Man	50 mg	p.o.	3M	0-192 ^{**}	15.9 ± 1.0	59.6 ± 2.9	ND	75.5 ± 3.5

^o includes cage debris.

¹ includes cage debris and carcass.

⁵ mean data recalculated from data included in report - 1 male rat excluded due to incomplete urine and feces collection.

[†] includes carcass.

[‡] includes gastrointestinal contents.

[^] data from one dog excluded due to lack of defaecation on last study day.

^v mean data only presented in report.

^{**} urine collection period from 0-168 hours.

ND: not determined.

LABELING:

The following minor changes in language are recommended with respect to the sponsor's proposed text.

■ Under the section heading **CLINICAL PHARMACOLOGY**, subsection **Pharmacodynamics** is interpreted by this reviewer as promotional. Thus, if this subsection is allowed in the label the following wording is suggested:

- 4th paragraph, please state- "In animal models of acute myocardial infarction, carvedilol doses up to 1 mg/kg i.v. reduced myocardial infarct size by 47% in rats, 78% in dogs and 89% in minipigs."

-5th paragraph, "In a gerbil model of brain ischemia, subcutaneous doses of carvedilol of 3 mg/kg improved the survival of neurons compared to vehicle treated gerbils. In studies with stroke-prone spontaneously hypertensive rats, repeated oral doses of carvedilol demonstrated a protective effect against lethal strokes compared to controls."

-6th paragraph, " In rat smooth muscle cultured cell preparations, carvedilol exhibited an antiproliferative effect against various smooth muscle mitogens such as angiotensin II, and, a variety of growth factors."

■ Under the section heading **OVERDOSAGE**:

-1st paragraph, "Single oral doses of 8000 mg/kg and higher were lethal to mice and rats. Toxic signs in these species consisted of blepharoptosis, decreased motor activity and depressed respiration."

-2nd paragraph should clearly state that the toxic signs reported to "overdosage" with carvedilol refer to humans, if so.

■ Under the section heading **PRECAUTIONS**, subsection "**CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY**":

-1st paragraph, "In 2-year mouse study in which carvedilol was administered in the feed at concentrations providing up to approximately 200 mg/kg/day, i.e., up to 18 times the maximum recommended dose (MRHD) as mg/M² of body surface area for a 50 kg patient, marginally significant harderian gland carcinomas occurred in females treated at the two highest doses of the drug. In a 2-year rat study in which carvedilol was administered in feed at concentrations providing doses up to approximately 75 mg/kg/day (up to 13 times the MRHD as mg/M²), carvedilol showed no statistically significant tumorigenic effect."

-2nd paragraph, "Carvedilol was not mutagenic when tested for genotoxicity in a variety of assays including *in vitro* bacterial (Ames test) and mammalian (Chinese hamster ovary/hypoxanthine-guanine phosphoribosyl transferase, sister chromatic exchange, human lymphocytes) cell systems or, *in vivo* mammalian system (Chinese hamster bone marrow, mouse host-mediated, mouse micronucleus, DNA synthesis inhibition, and DNA repair by unscheduled DNA synthesis in mouse testicular cells).

-3rd paragraph, "A general reproduction and fertility study in rats was conducted with carvedilol administered at oral doses of 12, 60 and 300 mg/kg/day (up to 52 times the MRHD as mg/M² of body surface area for a 50 kg patient). The high-dose was associated with loss of hair, delayed body weight gain, delayed mating, and reduced fertility when compared to controls. In this study, the no-observed adverse effect level on fertility was estimated to be about 60 mg/kg/day (up to 10 times the MRHD as mg/M²).

■ Under the subsection **Pregnancy: Teratogenic Effects, Pregnancy Category C:**

"Teratology studies were conducted with rats and rabbits given oral doses of carvedilol of 12, 60 and 300 mg/kg/day and, 3, 15 and 75 mg/kg/day, respectively. In rats, carvedilol at 300 mg/kg/day (up to 52 times the MRHD as mg/M²), was associated with maternal sedation, hair loss, decreased body weight gain, and increased post-implantation loss, and significantly fewer fetuses, lower fetal weight, and retarded skeletal development but no increase in skeletal malformations. In these rats, the no-observed adverse effect was estimated as 12 mg/kg/day (2 times the MRHD as mg/M²). In rabbits, carvedilol at 75 mg/kg/day (27 times the MRHD as mg/M²), was associated with increased post-implantation loss, and reduced number of fetuses; however, no malformations were observed. In these rabbits, the no-observed adverse effect was estimated to be below 3 mg/kg/day (about equal to the MRHD as mg/M²). There are no adequate and well controlled studies in pregnant women. Since animal reproductive studies are not always predictive of human response, carvedilol should be used in pregnancy only if the potential benefit justifies the risk to the fetus."

■ We suggest you consider additional information under the subsection **Nursing Mothers.** Such information would appear under the heading "Non-Teratogenic effects" and would read "A study was conducted in pregnant rats orally dosed with carvedilol at 6, 60 and 200 mg/kg/day during day 16 of pregnancy through day 22 of lactation. The offspring of dams treated with carvedilol at 60 mg/kg/day (10 times the MRHD as mg/M²) and above showed reduced body weight, increased number of deaths during the first of week post-partum, and reduced early physical development. However, mating ability of offspring did not appear to be significantly affected by parental treatment with carvedilol."

EVALUATION

Carvedilol is a chiral compound with one asymmetric carbon atom which gives rise to 2 enantiomers. The drug sponsor proposes to market carvedilol as a racemic mixture of the R(+) and S(-)- enantiomers to treat hypertension.

The sponsor asserts that carvedilol was "designed" to produce 2 complimentary pharmacologic actions- vasodilation that leads to lower BP and a non-selective β -adrenergic receptor blockade without intrinsic sympathomimetic activity. Sufficient nonclinical studies were submitted to characterize the principal pharmacologic effects of a racemic mixture carvedilol, and for each of the 2 enantiomers.

Studies conducted with reliable animal models (conscious or anesthetized) show that carvedilol given as single or repeated doses, by i.v. or oral routes, lowers blood pressure (BP). Animal models used in these studies included spontaneously hypertensive rat (SHR), normotensive or pithed rat, rabbit, cat and dog. In conscious SHR, the effective oral hypotensive dose of carvedilol is in the range of 1-10 mg/kg. In numerous studies, the hypotensive effect of the drug was compared to several clinically effective antihypertensive drugs such as prazosin, labetalol, hydralazine, nitroprusside and propranolol, used as standards. The mechanism for the hypotensive action of carvedilol was studied by using numerous in vitro and in vivo assays. Although the mechanism of action is not completely elucidated, the drug displays non-selective β -adrenoceptor and, at approximately 10x higher concentrations, α_1 -adrenoceptor blocking activities.

The following is a brief overview of some remarkable findings in nonclinical pharmacology, toxicology and pharmacokinetics:

A. PHARMACOLOGY

In anesthetized rats, carvedilol (0.3 mg/kg i.v.) reduced arterial BP. In SHR, repeated administration of carvedilol (1 mg/kg i.v. for 8 days), was not associated with tachyphylaxis. In whole animal preparations, decreases in BP activate baroreflexes producing an increase in sympathetic activity which leads to an increased force and rate of heart contraction, rise in total peripheral resistance (TPR) and retention of Na^+ . However, during the hypotensive action of carvedilol in whole animals, cardiac output (CO) and heart rate (HR) are unchanged and TPR declines in parallel with BP. Since the decrease in BP produced by carvedilol is not associated with reflex tachycardia, the action of carvedilol appears to differ from that of pure vasodilators without sympatholytic activity. The hemodynamic profile of carvedilol is distinct from that of β -adrenoceptor blockers which decrease both HR and CO, and increase TPR.

In conscious dogs, i.v. infusion of carvedilol (0.01 - 5.1 mg/kg) or propranolol caused a dose-related fall in HR attributed to β -blockade, with a simultaneous fall in left ventricle maximum speed of pressure rise (dP/dt_{max}); lowering of BP took place via reduction of both CO and HR.

Diuretics are often used with antihypertensive drugs to prevent fluid retention and potentiate their hypotensive effect. In conscious SHR, i.g. carvedilol (10 mg/kg), the fall in BP was associated with reductions in glomerular filtration rate (GFR) and, in urea and urine volume; levels of electrolytes (Na^+ , K^+ and Cl^-) were unaffected. The combination of carvedilol and diuretics (hydrochlorothiazide or furosemide) showed no synergistic hypotensive effect. Compared to carvedilol alone, the combinations of carvedilol with each of the diuretics, caused higher urine volumes and electrolytes excretion. However, when the effects of each of the diuretics alone were compared to the drug combinations, there were dose-related decreases in urine volumes, electrolytes and urea excretion. In separate studies using normotensive WKY and SH rats, again dose-related decreases in BP were reported with carvedilol alone regardless of the routes of administration (i.v. or oral.) In both strains of rats, i.v. infusion of carvedilol reduced renal vascular resistance and GFR without affecting effective renal blood flow suggesting that renal autoregulation was unaffected by carvedilol. In both strains of rats, urine flow decreased significantly ($p < 0.05$) during the infusion of carvedilol; this finding was accompanied with decreases in the excretion of electrolytes and urea in WKY rats. However, in the SHR rats the infusion of carvedilol was associated with a decrease in K^+ and urea excretion while Na^+ excretion was unaffected. These findings in SHR suggest a "renal sparing" effect for carvedilol since antinatriuretic activity might have been expected.

In female beagles, carvedilol (1, 3, 10 and 30 mg/kg in oral suspension) caused only reduction in urine volume during the first 2 hrs of study. Electrolyte excretion was not affected, again indicating renal sparing. In these dogs the "no-effect" dose was 1 mg/kg p.o.

In beagles, repeated oral doses of carvedilol (6 mg/kg for 5 days), was associated with an increase in HR, and slight increase in plasma-renin activity and plasma-angiotensin II concentration on the first day only; by 5th day BP was clearly lowered and increase in HR was only slightly detectable.

In anesthetized rabbits, carvedilol (0.01- 3.0 mg/kg i.v.) dose-dependently reduced BP from 101 mmHg down to approximately 54 mmHg at the highest dose tested. In conscious rabbits, oral doses of the drug (1, 3 and 10 mg/kg), dose-dependently antagonized isoprenaline induced tachycardia.

The vasodilatory action of carvedilol appears to result from its blocking action on the postjunctional α_1 -adrenoceptor blockade because in isolated aortic rings of the rabbit, the α_1 -adrenoceptor-mediated vasoconstrictor effect of norepinephrine (NE) is competitively antagonized by carvedilol with a K_B of 11 nM. Studies show that the drug is about 10-fold less potent as an α_1 -adrenoceptor antagonist than as a β_1 or β_2 -adrenoceptor antagonist.

In dog isolated saphenous vein, carvedilol produced non-competitive blockade of α_2 -adrenoceptor mediated vasoconstrictor response to B-HT 920 suggesting some activity at these receptors sites. Electrophysiologic studies suggest only very weak interaction of carvedilol with presynaptic α_2 -adrenoceptors. Because α_2 -adrenoceptor mediated vasoconstriction in this tissue is dependent upon the translocation of extracellular calcium, and since there was a lack of clear evidence that carvedilol interacts directly with α_2 -adrenoceptors, studies were conducted to determine if carvedilol was acting as a calcium

channel blocker. The literature reports that some Ca^{2+} channel blockers are effective in the treatment of peripheral vascular diseases because extracellular calcium is involved in the regulation of cutaneous blood flow. To investigate whether or not carvedilol may have a Ca^{2+} channel blocking action on the voltage-dependent Ca^{2+} channels, studies were conducted using rat uterus depolarized by potassium (which produces a nifedipine-sensitive contractile response resulting from opening of Ca^{2+} channels). In this preparation, carvedilol (at ED_{50} of about $7.65 \mu\text{M}$) produced a concentration-dependent relaxation of the potassium-depolarized tissue consistent with Ca^{2+} channel blockade. In potassium-depolarized rabbit aorta, similar results were noted. Further, also in rabbit aorta incubated with calcium-free buffer, and subsequently depolarized with potassium, a contractile response to administration of calcium was seen; this effect is sensitive to inhibition by Ca^{2+} channel blockers and in the case of carvedilol ($1 \mu\text{M}$), this drug inhibited the calcium-induced contractile response. In *in vivo* preparation using the pithed rat, the direct Ca^{2+} channel activator Bay-K-8644 produced a dose-dependent vasoconstrictor response that is inhibited by Ca^{2+} channel antagonists. In this preparation, carvedilol (at a high dose of 1 mg/kg i.v.), significantly inhibited the vasoconstrictor effect induced by Bay-K-8644 further suggesting that carvedilol exhibits some Ca^{2+} channel antagonism, but at several orders of magnitude higher concentrations than those for sympatholytic activity.

In pithed rat, effects of carvedilol on cutaneous circulation were compared, not to Ca^{2+} channel blockers but to labetalol- the 1st drug marketed known to exhibit combined β and α_1 -adrenoceptor antagonism. In this model, the drug and labetalol (both at 1 mg/kg i.v.) caused equivalent reduction in mean arterial BP and HR, carvedilol increased cutaneous blood flow (CBF) by over 60% and reduced cutaneous vascular resistance (CVR). Labetalol reduced CBF by only 20% with no change in CVR. Although in some studies there is suggestion of Ca^{2+} channel antagonism with carvedilol, this activity appears not to be prominent in animals. That is, in SHR pretreated with propranolol and prazosin to block the β - and α_1 -adrenoceptors, respectively, carvedilol did not cause additional reduction in BP unlike nifedipine, evidence of indirect sympatholytic vasodilating activity.

In guinea pig heart, carvedilol showed competitive β_1 -adrenoceptor antagonism to the positive chronotropic effect of isoproterenol (ISO). Sponsor's analysis of the data indicated that the blockade of β_1 -adrenoceptors by carvedilol binding with an apparent equilibrium dissociation constant (K_B) of 0.9 nM at this receptor.

In pithed normotensive rat, the hypotensive dose of carvedilol (0.3 mg/kg i.v.) competitively inhibits the β_1 -adrenoceptor mediated positive chronotropic response to ISO. This dose of carvedilol inhibited the chronotropic response of ISO by 100-fold, indicating β_1 -adrenoceptor blockade *in vivo* at antihypertensive doses.

In the guinea pig trachea, carvedilol dose-dependently inhibited the β_2 -adrenoceptor mediated relaxation induced by ISO; the inhibition was competitive with a K_B of 0.9 nM at the β_2 -adrenoceptors. This K_B value is the same as that calculated for the β_1 -adrenoceptors indicating that the drug is a nonselective β -adrenoceptor antagonist.

In pithed rat, the hypotensive dose of carvedilol (0.3 mg/kg i.v.) inhibited the β_2 -adrenoceptor mediated vasodilator response of the selective β_2 -agonist salbutamol demonstrating the β_2 -blocking effect of carvedilol in vivo. The degree of inhibition was reported to be similar to that observed for β_1 -adrenoceptors in this preparation indicating a non-selective blockade for β_1 - and β_2 -adrenoceptors in vivo.

Each enantiomer of carvedilol was also evaluated in in vitro and in vivo preparations to determine the stereoselectivity for α_1 -adrenoceptor and β_1 -antagonism. Studies show that the β -adrenoceptor blocking effect of the drug is attributed alone to the levo isomer S(-)-carvedilol; this is considered a non-selective β -adrenoceptor blocking activity.

Both the R(+)- and S(-)-enantiomers possess hypotensive activity in vivo, and vasorelaxant activity in in vitro. While the R(+)-enantiomer is an hypotensive agent without β -adrenoceptor blockade, the hypotensive effect of S(-)-carvedilol may be mainly attributed to β -adrenoceptor blockade which inhibits counter-regulatory mechanism provoked by vasodilatation.

In the guinea pig atrium, the S(-)-enantiomer demonstrates β_1 -adrenoceptor antagonism with a K_B of 0.4 nM (about 2-fold more potent than the racemic mixture.) R(+)-enantiomer is about 100-fold weaker than the S(-)-enantiomer as a β_1 -adrenoceptor blocker with a K_B of 45nM.

In anesthetized SHR, the S(-)-enantiomer was 6-fold more potent as an antihypertensive than the R(+)-enantiomer. Studies show that the vasodilator and acute antihypertensive effect of carvedilol is considered to result from α_1 -adrenoceptor blockade produced by both enantiomers, the concomitant β_1 -adrenoceptor blockade produced by the S(-)-enantiomer (preventing reflex tachycardia) apparently enhancing the antihypertensive potency of carvedilol. The drug sponsor speculates that the clinical use of the S(-)-enantiomer alone could lead to relatively strong β -blockade with weak vasodilating effect while the use of the R(+)-enantiomer alone would result in hypotensive effects without β -blockade.

In the pithed rat, S(-)-enantiomer (0.1 mg/kg, i.v.) produced a 25-fold rightward shift in the positive chronotropic dose-response curve of ISO. In this model, R(+)-enantiomer, even at a 10-fold higher i.v. dose showed had no antagonistic activity on the positive chronotropic effect.

In conscious rabbits, the ED-50 for inhibition of ISO tachycardia was 0.025 mg/kg/i.v. for the S(-)-enantiomer, and 4 mg/kg i.v. for the R(+)-enantiomer; the S(-)-enantiomer being over 100 times more potent the R(+)-enantiomer. These findings indicate that the β_1 -adrenoceptor blocking activity of carvedilol (the racemic mixture) results predominantly from the S(-)-enantiomer. Further, that the greater hypotensive activity of S(-)-enantiomer may be attributed to β -adrenoceptor blockade, which inhibits the counter-regulatory mechanisms (tachycardia) provoked by vasodilation.

In isolated rabbit aorta, as stated above, carvedilol showed competitive antagonism at α_1 -adrenoceptors (K_B value of 10 nM); the K_B values for the S(-)- and R(+)-enantiomers at α_1 are equipotent with values of 16 and 14 nM, respectively.

The α - and β -blocking activities of carvedilol, compared to other drugs, on vasculature of the hind limb were investigated. In rabbit and mongrel dog, maximum fall in perfusion pressure of hind limb induced with a drug was taken as a measure of vasodilation.

In rabbit hind limb, carvedilol (at the highest- 2.5 ug i.v.), was reported to cause a -32 mmHg fall in perfusion pressure, while the vasodilator adenosine (at 10 ug) caused a -51 mm Hg fall (the highest fall with that dose.) Sponsor's calculations of the dosages in the study, indicated that the vasodilatory activity of carvedilol could be considered to be approximately twice as great as that of adenosine. And, in mongrel dog, carvedilol (1-30 ug i.a.) and standard vasodilator drugs (i.e., papaverine, ISO), produced a dose-dependent increase in femoral artery blood flow. In this model, the vasoconstrictor effect of norepinephrine (NE) and the vasodilator effect of isoproterenol were tested before and after i.v. doses of carvedilol; after carvedilol, the vasoconstriction by NE was inhibited in a dose-related fashion while the vasodilation of ISO was completely inhibited.

In conscious SHR, intragastric doses of carvedilol (10 mg/kg) were associated with dose-dependent antihypertensive activity which was rapid in onset and long lasting (4-8 hrs). Repeated administration of the drug in this model was not associated with tachyphylaxis. No synergism for the hypotensive effect was noted with diuretics (HCTZ or furosemide).

Other general cardiovascular effects and their duration were reported for carvedilol. In reserpinized rats, no intrinsic sympathomimetic activity was noted with carvedilol. In rats there was no tolerance or tachyphylaxis to the hypotension and lack of reflex tachycardia with repeated i.v. doses of the drug (1 mg/kg). Carvedilol potentiated the BP fall in response to an orthostatic (tilt) stimulus, reflecting α -blockade. In dogs, i.v. doses of carvedilol (0.03 -1.0 mg/kg) produced hypotension but did not change QTc, PR or QRS intervals; oral doses did not affect coronary blood flow in dogs. Also in dogs, BP reduction after repeated oral doses of carvedilol (6 mg/kg/5 days) were not associated with remarkable increases in HR, or plasma-renin (PRA) activity or angiotensin II concentrations by the end of the study, however some increases in PRA and AII were seen with the first dose of the drug. In anesthetized rabbits, when compared to control values, doses of carvedilol (1 - 3 mg/kg i.v.) were associated with slight decreases in HR and slight increases in PQ and QRS intervals.

The drug sponsor notes that some patients surviving an acute myocardial infarction are at risk for reinfarction and/or sudden cardiac death. In some of these patients, the cardioprotective effect provided by β -antagonists is generally believed to result from an improvement in the balance between myocardial oxygen demand by reduced myocardial work which occurs secondary to reductions in heart rate and contractility. Thus, the potential cardioprotective effect of carvedilol was investigated in several animal models of acute myocardial infarction. In dogs subjected to 1 hr. of left ventricular cardiac ischemia followed by 24 hr reperfusion, carvedilol (1 mg/kg i.v.) significantly ($p < 0.05$) reduced the left ventricular the infarct size by 78% when compared to control; propranolol (1 mg/kg i.v.) reduced the infarcted size by 64%. In dogs subjected to occlusion of the left anterior descending coronary artery for 6 hrs (permanent), compared to controls, carvedilol (0.3 and 1.0 mg/kg i.v.) significantly ($p < 0.05$) reduced the infarcted area size by 46% and 63% and propranolol reduced the infarct size only

by 20%. Cardioprotective effects of carvedilol were also reported in other experimental models of acute myocardial infarction in the rat and pig.

Based on findings in models of orthostatic stress using anesthetized rat and rabbit, in which i.v. doses of carvedilol impaired the compensatory recovery of BP to pretilt level (similar to labetalol and prazosin), investigators considered that in the clinics typical α and β -blocker side effects might be expected from carvedilol. The sponsor further considered that as with propranolol, reduced blood supply of the extremities (Raynaud syndrome) could also occur as a side effect of carvedilol.

Cytoprotective actions reported for the drug included increasing the survival of stroke prone rats; reducing lipid peroxidation (measured by the formation of thiobarbituric acid reactive substances) in rat brain mainly by scavenging free radicals. The reported free radicals scavenging activity and anti-mitogenic effect (against a group of vascular smooth muscle mitogens) of carvedilol were considered to be potential cardiovascular protective effect.

Briefly, neuropharmacologic effects reported with carvedilol included: in mice, reduced spontaneous motor activity, ptosis, some analgesic effect against chemically induced pupal constriction, but no prolongation on hexobarbital sleeping time or antagonism against electroshock convulsion; in rabbit, inconsistent effects on body temperature (in combination with a diuretic a fall in body temperature was reported as well as increase in blood sugar); in cat little effect on EEC activity.

In rat, except for decrease in gastric acid with carvedilol (5 mg/kg i.v.), gastrointestinal effects of the drug were unremarkable in mice and rat.

It may be concluded from the studies described above, that carvedilol produces vasodilation by α_1 -adrenoceptor blockade and antagonizes reflex tachycardia through B_1 -adrenoceptor antagonism. Mechanism of action studies show that cGMP is not associated with the vasorelaxation induced by the drug. At doses higher than those needed for α_1 and β blocking activity, carvedilol shows some evidence of Ca^{2+} channel blockade, however; this action is not predominant. There was no evidence of inhibition of angiotensin converting enzyme activity with carvedilol.

B. TOXICOLOGY

Toxicity studies were performed with carvedilol administered by i.v., i.p. and oral routes. Mutagenicity studies were conducted in vitro and in vivo. Except for mutagenicity studies, this evaluation mainly discusses oral dosing studies because this is the proposed route of administration of carvedilol. Drug sponsor reports that toxicity studies were conducted in accordance with GLP practices.

1. Single Dose

Single oral dose toxicity studies (acute toxicity) with carvedilol were conducted in mouse, rat and male beagles. For both the mouse and rat, the median lethal doses were estimated to be 8000 mg/kg p.o. and above and, for dog above 1000 mg/kg p.o (although no beagles died when treated with 2000 mg/kg p.o., the dogs vomited and vomitus contained a substance believed to be carvedilol). Remarkable acute toxic signs in both rodent species included hair loss, blepharoptosis, reduced spontaneous activity and, depressed respiration. Necropsy of mouse and rat that died showed congestion of various internal organs and, in addition rats killed showed micro-hemorrhages in the brain. Remarkable acute toxic signs in the dog included decreased locomotor activity, unsteady gait, blepharoptosis, and transient pathologic changes but no histopathologic changes. A remarkable toxic sign in beagles was a slight increase in blood glucose, 1 day after the drug treatment. However, blood glucose level changes were not noted in a rabbit study in which carvedilol was given 3 mg/kg, i.v. to examine its effect on this parameter.

Except for an acute i.v. study in mouse, the toxicity profile of each enantiomer was not studied to a great extent. In mouse, remarkable signs of toxicity to i.v. doses of the enantiomers were within the range of the racemic mixture (41.1 mg/kg i.v.). Other acute i.v. toxicity in rat included administration of several major and pharmacologically active metabolites of carvedilol (M2, M4 and M5, See Fig. 27 and Table 33). Remarkable toxic signs reported included clonic spasms with all 3 metabolites lasting 2-10 min, apathy lasting up to 45 min and deaths with M4 and M5 metabolites. The calculated median lethal doses were about 50 mg/kg i.v.

In the acute toxicity studies with carvedilol, the calculated median lethal dose for rodents and non-rodents are above 8000 and 1000 mg/kg, respectively. These values represent about 8,000 and 1,000 times, respectively, the maximum recommended therapeutic dose of carvedilol assuming a 50 Kg patient.

In one special study in dog to determine limiting toxicity of i.v. doses of carvedilol. Data show that the drug at 15 to 30 mg/kg i.v., provoked intermittent convulsions and ECG changes (prolongation of P-wave, increases in PR and QRS intervals). However, no convulsions and only slight ECG changes were reported at 7.5 mg carvedilol/kg i.v. From these dog studies with i.v. doses of the drug, investigators considered that the cardiac depression seen is due to a membrane stabilizing activity of carvedilol drug because some β -blockers at high doses produce direct depression of A-V transmission of the drug. The literature reports that such activity is not relevant to clinical practice, but in overdose, this property is potentially dangerous.

2. Multidose

In a 4-week rat i.v. study of carvedilol at 2.5, 5 and 10 mg/kg day, ECG tracings revealed no anomalies. Blepharospasm and apathy as well fatty infiltration of liver in females were reported at the 2 highest doses. The NOAEL for the drug was estimated as 2.5 mg/kg, i.v.

Since it is expected that carvedilol will be taken chronically by hypertensive patients, sponsor has conducted several multidose oral toxicity studies with the drug in rodent and non-rodent species. Briefly, in subchronic studies the drug was administered daily to mice (NMRI) up to 13 weeks in the diet, to rats (Sprague-Dawley) up to 15 weeks given by gavage or in diet, and to beagles up to 26 months in capsules. In chronic and 2-year carcinogenicity studies, carvedilol was administered in diet to mouse and rat for up to 78 weeks, and in capsules to beagles for up to 52 weeks.

In a 13-week study, mice treated with carvedilol (20 up to 800 mg/kg in diet) showed at the 2 highest doses (600 and 800 mg/kg/day) increases in alkaline phosphatase in males and sGPT values in both sexes and decreases in total serum proteins. Body weights in males were reduced > 10% at 600 and 800 mg/kg/day; in females the body weight reduction was >10% only at 20 mg/kg/day dose, and remained fairly constant at the higher doses of carvedilol. Although a NOAEL was not determined, the dose of 200 mg/kg/day was selected by sponsor as the MTD based on the elevation of the relative liver weights of the females which was 9% (at the two highest doses the increases were >20%, respectively, $p < 0.05$) when compared to controls. Although males at 200 mg/kg/day, the elevation in relative liver weight over control was about 4%, the increase was 12 and 20% at the two highest doses, respectively. No histopathology was done. In toxicokinetic studies, serum samples obtained at 1, 6 and 13 weeks of the study from the LD (20 mg/kg/day) showed that levels of carvedilol ranged from 22 to 96 ng/ml. Quantification of carvedilol in serum at the higher dose levels was not possible due to technical difficulties. However, qualitatively determinations reported that carvedilol was detected in all samples and concentrations of the drug increased with dose.

In one 13-week rat study with carvedilol at 30, 100 and 300 mg/kg/day p.o., remarkable toxic signs (reversible after 5 week drug-free period), included blepharoptosis, decreased food intake, increases in BP at HD, bile duct hyperplasia, myocardium cell infiltrates and inflammatory changes in biliary tract. Lethal respiratory/cardiac failure occurred in 3 HD rats. Other remarkable toxic signs in rat and mouse were decreases in total serum protein and (rat only) albumin. In a separate 13-week rat study, in which rats were treated with similar oral doses of carvedilol (up to 300 mg/kg), HD rats had mild hepatic changes described as pericholangitis and single small hyperplastic nodules. The NOAEL for the drug was estimated to be 30 mg/kg/day and below (or 30 X the maximum recommended therapeutic human dose in a 50 kg patient.)

From the 13-week oral dose studies, the accepted MTDs for carvedilol in mouse was 200 mg/kg/day and in rat- 4,000 ppm in diet (actual intake 486-532 mg/kg/day.) These MTDs were based on dose-related increases in liver weights in mouse (no histopathology performed) and, multiple biologic changes in rat which included reduced body weight, reduced erythrocyte parameters, increased leukocyte counts and dilated bile ducts (no histopathology was performed). Based on these studies, drug doses selected for the oral carcinogenicity studies were for the mouse 20, 65 and 200 mg/kg/day and, for the rat 600, 2,000 and 4,000 ppm (in diet). These MTDs range from about 200 to 500 times, respectively, the maximum recommended human therapeutic dose of carvedilol.

In the rat chronic toxicity study (3 doses of carvedilol in diet for up to 52 weeks), remarkable toxic signs in drug-treated rats included decreased food intake (at HD of about 343 mg/kg/day), dose-related decrease of body weight gain, increase alkaline phosphatase for HD rats, exacerbation of spontaneous cardiomyopathy (at MD of about 117 mg/kg/day and at HD), biliary hyperplasia and, increased incidence of proliferative liver lesions.

In a separate rat study (3 doses of carvedilol in diet for up to 78 weeks), remarkable toxic signs were similar to those reported in the 52-week rat study. Other toxic signs reported included a slight increase in cholesterol/triglycerides serum values in females (at HD-5000 ppm in diet with an actual intake determined at the end of the study of 261 mg/kg p.o.). Changes in lipid values were not present at the end of the study in HD females who had an off-drug phase following carvedilol administration. Minimal chronic inflammatory cell infiltrate and fatty infiltration in hearts and dose-dependent liver cell hyperplasia (5 HD rat had developed a hepatocellular adenoma) were noted. Hepatocellular effects were considered to reflect the consequence of excretion of carvedilol and a functional adaptation to hepatic metabolism.

Two 13-week dog studies were conducted with 3 doses of carvedilol ranging from 15 up to 250 mg/kg/day (drug sponsor's labs.) and, from 10 up to 250 mg/kg/day p.o. (conducted in Japan). Remarkable toxic signs noted in some drug-treated dogs in both studies included vomiting and blepharoptosis. Some LD and MD dogs showed fatty infiltration of liver and heart. Serum K^+ was increased at MD and at 250 mg/kg/day. Although not dose-related, absolute weight in some organs (liver, adrenals and thyroid) were increased at 250 mg/kg/day. ECG tracings showed decrease heart rate and prolonged PQ interval in dogs treated with carvedilol doses of 15, 50 and 150 mg/kg/day p.o.

In a 52-week study, beagles were treated with carvedilol (0, 10, 30, 100 and 300 mg/kg/day p.o.) in capsules given in 2 divided doses. Drug effects were compared to controls and, signs noted after a 17-week drug free period. After weeks of dosing with the drug, at the 2 highest doses vomiting and diarrhea occurred. ECG tracings in drug-treated dogs showed prolonged PQ-intervals. Compared to controls, dose-related increases were reported for relative liver weight. Minimal to moderate bile duct hyperplasia was reported at the 3 highest doses, but also in controls; none were reported for dogs treated with carvedilol at 10 mg/kg/day group. NOAEL is estimated to be around 10 mg carvedilol/kg/day p.o. and below (equivalent to about 10 times the maximum recommended therapeutic dose assuming a 50 kg patient). At the beginning of study, toxic signs included ataxia, apathy and blepharostenosis. Treated dogs were unremarkable during the drug-free period. Toxicokinetic reports show that in these beagles, at about week 49 of study, the MD dogs (15 mg/kg/day in 2 divided doses), peak serum concentration of carvedilol were reached at about 2 hrs post-dose. Values for median serum C_{max} were 277 ng/ml for males and 153 ng/ml for females, suggesting sex difference in this study. At 11 months (343 days) of treatment with carvedilol (30 mg/kg/p.o. 2 divided doses), the C_{max} (at about 2 hrs) and AUC_{0-24} values for the drug were about 6 X higher than that reported in hypertensive patients treated for once a day for 28 days with 50 mg/kg/day p.o. carvedilol.

In a 2nd repeat oral dose study with beagles, doses of 30, 100 and 300 mg/kg/day p.o., at 21 weeks of treatment 2 males died (1MD, 1HD). Signs before death included swollen eyes, ptosis, apathy and respiratory problems. During the study, ECG recordings showed prolongation of the PQ-intervals at LD and MD only. At HD, clinical chemistry showed increased levels of serum alkaline phosphatase and, sGPT during the last months of the study. Study was terminated at 26 weeks because investigators wanted "to be in line with EEC regulations." Histopathologic examination for both dog studies showed mild biliary hyperplasia, as seen in previous 52-wk dog study, which drug sponsor considers to be of "limited toxicologic importance" since there is "no known correlation to any human disease.....and this lesion has been reported in animals exposed to marketed beta-adrenergic blocking agent, metoprolol.*" Reviewer notes that hyperplasia of bile duct also reported in rat after long term treatment with carvedilol.

Beagles treated with carvedilol (0.2, 1.0 and 5.0 mg/kg for 4 weeks), no evidence of adverse effects on heart as reported as determined by ECG.

3. Carcinogenicity

Dietary carcinogenicity studies were conducted with 2 rodent species- NMRI mouse (3 drug doses and 1 control) and Sprague-Dawley, CAW-Ico-Wiga rat (4 drug doses and 1 concurrent control and 1 control from another study). The HDs selected for the carcinogenicity studies were based on MTDs (200mg/kg/day p.o. for mouse and 4000 ppm in diet for rat) determined in 13-week studies in the same species/strains.

In this mouse carcinogenicity study, the 3 groups of animals were administered the following daily doses of carvedilol in diet- LD-20, MD-65 and HD-200 mg/kg; the females were dosed for 97 weeks and males for 114 weeks. By the end of the mouse carcinogenicity study, the average drug intake at the HD (182.5 mg/kg/day) represents about 182 X the maximum recommended daily human therapeutic dose for carvedilol. At the end of the study, the survival rates of control, LD, MD and HD mice were 42%, 62%, 44% and, 44% for males, respectively, and 27%, 20%, 22%, and, 20%, respectively, for females. The only clinical chemistry disturbances reported were significantly higher urea nitrogen and, SGOT at the highest doses tested. No remarkable drug-related macroscopic changes were noted. Histopathologic examination of HD mice revealed a higher incidence of single cell hepatocellular necrosis (females) and, an overall lower tumor incidence as well as lower percentage of tumor bearing mice. Accordingly, no evidence of carcinogenicity with carvedilol was noted after dietary administration for 97 to 114 weeks.

Division of Biometrics concluded from the evaluation of data provided by sponsor for the mouse carcinogenicity study with carvedilol, that in both sexes there was no statistically significant difference ($p=0.05$) in the survival distribution, intercurrent mortality rate or linear trend in tumor incidence rates. However, Biometrics asserts that although the survival rates of the HD mice at 1-year satisfied a criterion applied**, it seems that there were not

* INT Annual Report received at CDER on December 12, 1993 (page 142).

** "Factors in the evaluation of 200 NCI carcinogen bioassays." Chu, et al. J Tox and Environ Health 8:251-80, '81

sufficient female mice in the control and treated groups living long enough to get adequate exposure to carvedilol and to be at risk for forming late-developing tumors as FK Haseman* proposes.

For the rat carcinogenicity study, sponsor attempted to conduct a study using the selected MTD of 4000 ppm carvedilol in diet as the HD. The study was stopped after 6 months for various reasons which included steep decrease in body weight of treated rats (considered by sponsor to be due to too high doses of carvedilol), water deprivation (failure of automatic drinking water system) and, increased mortality. A remarkable histopathologic lesion observed in the rats that died was slight biliary hyperplasia. Biliary hyperplasia associated with long term administration of carvedilol was reported in 2 species (1 rodent and 1 non-rodent.)

A second rat carcinogenicity study was started. This was the definitive carcinogenicity study conducted with 4 doses of carvedilol in diet at LD-200 ppm, MDs- 400 and 800 ppm and HD-1600 ppm. The actual drug intake varied but by the end of study the mean daily drug intake values were for males 8, 16, 31 and 62 mg/kg and, for females 10, 19, 38 and 75 mg/kg for 2-years. By the end of the study, the average drug intake at HD (68.4 mg/kg/day) represents about 68 X the maximum recommended daily human therapeutic dose for

carvedilol. Serum concentrations of carvedilol were determined at one time point (sampled at about 9:00 AM) in all 4 dose groups at the end of the study. The mean concentrations of the drug reported were for male rats- 21, 31, 94 and 215 ng/ml, respectively, and in females- 18, 39, 94 and 354 ng/ml, respectively, for the LD, 2- MDs and HD carvedilol.** Male mortality was dose-dependent and unscheduled deaths without fatal tumors occurred in rats at HD. Although some remarkable histopathologic non-neoplastic findings were also noted in controls, these included liver hyperplasia, chronic nephropathy, cell infiltrates in the heart (in males), splenic congestion and lung edema.

No clear evidence of tumorigenicity was noted in rats treated with daily doses of carvedilol up to MTD given in diet for 104 weeks. Although not-dose related, neoplastic lesions included thyroid adenomas/carcinomas, mammary adenomas/carcinomas, and liver cell adenomas. In female rats at HD-1600 (calculated intake of 75 mg carvedilol/kg/day), there were thyroid and liver cell adenomas; neither of which were reported in controls.

Regarding thyroid adenomas, this reviewer notes that C. Gopinath reports that "... Certain pharmaceutical drugs are known to affect thyroid gland through adrenergic mechanisms.....some....cardiovascular drugs of adrenergic class influence thyroid follicular growth and function, increase TSH secretion and modify iodine organification....The mechanism underlying thyroid lesions are complex****

* Biometrics evaluation states that JK Haseman personally communicated to Dr.KLin, FDA that a 50% survival rate of the initial animals in HD group between weeks 80-90 will be considered a sufficient number animals and an adequate exposure. But, the percentage can be lower or higher if the number of animals used in each treatment/sex is larger or smaller than 50 as long as there are between 20 to 30 animals still alive during these weeks.

** These data were requested and later submitted as " Best Copy Available" by sponsor in NDA Amendment dated 03-29-94.

*** "Causes and interpretation of thyroid tumors in rodent Bioassays" by C. Gopinath,

Chapter 3, p. 19, in Current Issues in Drug Development, Huntington Research Center Limited, UK 1991

NDA 20297

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4. Special Studies

Immunologic effects may be associated with the exposure to drugs. Drug sponsor has submitted numerous studies performed in Japan in which guinea pigs showed no evidence of a delayed type hypersensitivity or passive cutaneous anaphylaxis reaction to carvedilol.

5. Reproductive Toxicology

Reproductive toxicity studies included the customary Segments I, II and III in 2 animals species (1 rodent and 1 nonrodent) given orally carvedilol suspended in 1% methylcellulose. In rats, fertility and general reproductive performance studies (Seg.I) included dose-ranging studies with carvedilol (200 up to 400 mg/kg/day in rats prior to mating), and the definitive study where 12, 60 and 300 mg/kg/day p.o. was administered daily prior to mating to males and females for 62 and 15 days, respectively, but continued through day 21 of lactation in the females. Impaired fertility was reported at 300 mg/kg/day and developmental effects in offspring (F1 generation) of HD parents. Overall the NOAEL on reproductive performance and fertility in both sexes was considered to be 12 mg/kg/day p.o. In a separate rat study (performed in Japan) designed to evaluate the effect of carvedilol (12 up 300 mg/kg/day on days 0 up 21 days postpartum) on food intake/body weight on dams, these two parameters were significantly decreased at the HD.

Teratology studies (Seg.II), conducted in 2 species (rat and Himalaya rabbit), consisted of preliminary studies in pregnant and non-pregnant rats at doses ranging from 50 up to 400 mg/kg/day and 100 up to 1500 mg/kg/day, respectively. The definitive study, using pregnant rats treated at 3 dose levels 12, 60 and 300 mg/kg/day during the period of organogenesis (days 7-16 postconception), showed sedation, hair loss, and reduced body weight gain at 60 and 300 mg/kg/day. Compared to control, dams from the 300 mg/kg/day groups showed increase in post-implantation losses and decrease in number of live fetuses. Offspring from the 300 mg/kg groups showed developmental delays (missing of stunted 13th rib) but, no malformations were reported. In this study, the NOAEL for dams was considered to be 12 mg/kg/day, and for F₁ developmental toxicity to be 60 mg/kg/day carvedilol.

The rabbit Seg. II studies consisted also of dose-range studies in pregnant and non-pregnant rabbits. For the definitive study in pregnant rabbits the 3 doses tested were 3, 15 and 75 mg/kg/day given during the period of organogenesis (days 7-19 postconception). At 75 mg/kg/day, compared to controls there was an increase in post-implantation losses and decrease in live fetuses. The weights of the live fetuses and the placentas from drug treated animals were heavier than those from the controls. No drug-related malformations were reported in offspring of treated rabbits. The NOAEL for maternal toxicity may be considered to be below 3 mg/kg/day.

In rats, peri- and postnatal toxicity studies (Seg. III) were conducted with carvedilol (12, 60 and 200 mg/kg/day p.o. (on days 16 of gestation to day 22 end of lactation). Remarkable effects noted in dams (F₀ generation) included decreased body weight gain and mild sedation in some dams at HD and hair-loss in drug-treated. At the HD, dams showed increased intrauterine embryo losses and, reduced rearing activity. Carvedilol did not significantly affect

the gestation duration and, the number of uterine implants and number of live pups (F₁ generation). Offspring (F₁ generation) from MD and HD F₀ dams showed a slight decrease in body weight and early deaths (2 days post-partum) as well as retarded development of pinna detachment and grip strength. There were no significant effects of carvedilol on the mating behavior of the F₁ generation or on the parturition and development of the F₂ generation. From this study, the oral NOAEL of carvedilol on dams (F₀ generation) and offspring (F₁ generation) may be considered to be 12 mg/kg/day.

6. Mutagenicity and Clastogenicity

Numerous genotoxicity assays (*in vitro* and *in vivo*) were reported examining the potential for carvedilol, its metabolites and an intermediate to adversely affect bacterial, yeast and mammalian cell genes.

Prokaryotic cells systems used included 5 strains of *Salmonella typhimurium*, *Escherichia Coli*, *Serratia marcescens* and *Saccharomyces cerevisiae*. Based of the results in the Ames test, compared to appropriate controls, carvedilol (5 to 5000 ug/plate) produced no significant increase in revertant frequencies in any of the 5 appropriate tester strains of *S. typhimurium* and either in the presence or absence of microsomal activation (S9 fraction from rat liver induced with Aroclor or other enzyme inducing chemicals.) An intermediate compound in the synthesis of carvedilol (n-benzyl carvedilol) was assayed in the same 5 strains of *S. typhimurium*. Except for one strain (TA1535), all test strains gave equivocal results with n-benzyl carvedilol. Since this assay showed a limited increase in revertant frequency in microsomal activated TA 1535 strain, the finding was not considered to be significant to human safety. The potential of carvedilol to induce reverse mutation in *E. coli* was studied. Results submitted indicate that in this bacterial assay, with/without S9 activation, carvedilol had no mutation inducing activity. Carvedilol was tested in the mouse host-mediated assay (mouse dosed with 200 or 2000 mg/kg carvedilol, p.o. and injected i.p. with *S. typhimurium* G 46 or *S. marcescens*) to determine the drug's potential for inducing revertants strains of these microorganisms. Results reported from this assay did not indicate that carvedilol at the HD had antibacterial activity and LD was not mutagenic. Results from the assay to detect potential of carvedilol for inducing yeast genetic toxicity were inconclusive.

Mammalian test systems used to examine genotoxicity potential of carvedilol included Chinese hamster ovary (CHO), hamster and mice and bone marrow cells, human lymphocytes lymphocyte cultures, and mouse testicular cells. In a gene mutation test using somatic mammalian cells, carvedilol at concentrations up to 33 ug/ml (with and without S9 liver fraction) showed no evidence of mutagenic activity in the HGPRT locus of the CHO cells when compared to positive controls.

When studies were conducted to examine the potential of carvedilol, with and without microsomal activation, to cause chromosomal aberration *in vitro* and *in vivo* preparations, carvedilol (8 to 80 ug/ml) caused no chromosomal damage in cultured human lymphocytes. However, in separate studies carvedilol concentrations of 70 ug/ml, there was a 25% reduction in mitotic index and, at 200 ug/ml and above the drug was highly toxic to cultured human lymphocytes compared to positive controls. At lower doses tested carvedilol was not

clastogenic in this *in vitro* test. In an *in vivo* chromosome aberration test in bone marrow using Chinese hamster, the animal was dose with the maximally tolerated dose of carvedilol (2000 mg/kg, p.o.), and prior to sacrifice the animal was treated with demecolcine to arrest the cells in metaphase. When bone marrow cells were removed from their femurs, stained and scored, there was no evidence of chromosomal damage: carvedilol was not clastogenic. *In vivo*, using the Chinese hamster micronucleus tests, animals were dosed orally with carvedilol (1500 mg/kg for 2 days). Mean number of micronuclei in bone marrow samples (formed from chromosome or chromosome fractions left behind during anaphase) from carvedilol-treated animals were not significantly different from vehicle treated controls.

Additional tests were also conducted to assess interaction of carvedilol with DNA. They included determination of primary DNA damage by using a sister chromatic exchange (SCE) assay in the Chinese hamster, determination of DNA covalent binding by applying a DNA synthesis inhibition test, and measurement of DNA repair by unscheduled DNA synthesis in mouse testicular cells. Results of all these tests were considered negative for carvedilol when compared to controls because the drug (at 1000 mg/kg p.o.) did not increase the mean numbers of SCE in hamsters and, at doses ranging from 50 up to 100 mg/kg, had no effect on DNA replication in mice or unscheduled DNA synthesis in their testicular cells. Carvedilol doses of 50, 100 and 200 mg/kg produced a significant reduction in body temperature.

C. PHARMACOKINETICS

Carvedilol is extensively metabolized via both oxidation/conjugation pathways. Following oral administration of the drug more than 20 major and minor metabolites have been identified among the 5 species studied. The metabolite profiles for male and female animals appeared qualitatively similar. Usual pharmacokinetics parameters examined showed that oral doses of the drug are rapidly absorbed, undergo first-pass metabolism in the liver, resulting in an estimated low bioavailability for carvedilol (below 30% in rat and dog). The drug binds to blood albumin, peak levels are seen within 1 hr post dosing and elimination T_{1/2} is about 5 hrs (rat). Stereoselective pharmacokinetics was reported in rat and monkey after single oral doses of carvedilol; R/S enantiomeric ratios for C_{max} and AUC were 2.5 and 2.2, respectively, in rat and, in monkey C_{max} and AUC were 1.5 and 1.5, respectively. The oral administration of 10 mg/kg to rat of R(+)- and S(-)-enantiomers led to the excretion of M1 and M2 metabolites, respectively, in bile.

In conclusion, drug sponsor has submitted nonclinical pharmacologic and safety data on carvedilol (a racemic mixture of 2 enantiomers). Nonclinical pharmacology studies show that carvedilol reduces mean arterial blood pressure and peripheral vascular resistance. Absence of reflex tachycardia is considered to be due to inhibition of β_1 -adrenoceptors. Carvedilol showed no intrinsic sympathomimetic activity in the models tested. Studies to elucidate the mechanism of action of carvedilol in *in vivo* and *in vitro* models show that the drug is a competitive antagonist at β_1 , β_2 and, α_1 -adrenoceptors. Studies show that the S(-)-enantiomer is the most active as a β_1 -adrenoceptor and both S(-)- and R(+) contribute to the vasodilating

effects of the drug through α_1 -adrenoceptor blockade. Electrophysiologic studies suggest only a weak interaction with α_2 -adrenoceptors. Studies suggest that at high doses carvedilol may have some Ca^{2+} channel blocking activity. In appropriate animal models of orthostatic stress, carvedilol interfered with the orthostatic response to tilt suggesting that the drug might exhibit this activity in humans. In contrast with other vasodilators, carvedilol did not diminish kidney function; glomerular filtration and Na^+ excretion are maintained at vasodepressor dosages. Other potential activities of carvedilol suggested from nonclinical studies included cardioprotection based on reductions in infarct size in models of acute myocardial infarction, protection against mortality in stroke-prone SHR, antiproliferative effect in cultured vascular smooth muscle cells exposed to various mitogens, antioxidant activity by inhibition of lipid peroxidation in swine cardiac membranes, inhibition of superoxide release from phorbol ester-activated human neutrophils exposed to oxygen radical generating system, and protection against glutamate-induced neurotoxicity of cultured rat cerebral granule cells.

Safety studies with the drug appear to have been conducted in appropriate animal models. Although most toxicity data reported are said to have been obtained in accordance with GLP regulations, some studies predate these regulations and were poorly organized and not properly edited before submitting to FDA. Nonclinical toxicity studies reviewed/evaluated include short-term, long-term toxicity and special toxicity studies in up to 5 animal species. In 2 animal species (both sexes of rats and dogs), the target organs for chronic toxicity were liver and heart. In rat, after 1 year administration of carvedilol (LD- 600, MD- 2000 and HD- 6000 ppm in diet corresponding to a mean daily intake of 35.4, 117 and 343.5 mg/kg, respectively), the apparent "no-adverse effect" dose for heart histopathologic findings was 35.4 mg/kg (or 209 mg/M² in rat which is equivalent to 5.6X the maximum recommended dose for carvedilol of 37 mg/M² in human); however, this dose in rats was associated with increases in bile duct hyperplasia when compared to controls.

In the dog, after 1 year administration of carvedilol (LD- 10, MD- 30, HD-1 100 and HD-2 300 mg/kg/po), the apparent "no-adverse effect" dose may be considered 10 mg/kg/po for both liver and heart histopathologic findings; this "no-adverse effect" dose represents 200 mg/M² kg for the dog and 5.4X the maximum recommended dose for carvedilol of 37mg/M² in humans.

Results of nonclinical studies submitted in this NDA appear acceptable to support the safe use of carvedilol for the intended therapeutic indication as an oral antihypertensive drug. Although extrapolation of findings with carvedilol across species could be unreliable, adverse effects reported for marketed nonselective β -adrenoceptor antagonists and vasodilator drugs might be expected in humans treated with carvedilol such as bronchospasm, cold extremities, hyperlipidemia, and fatigue particularly in severely ill patients. Remarkable findings in the toxicity studies which are associated with or caused by the administration of carvedilol to mice and rats in the carcinogenicity, to rat and rabbit in the reproduction studies and, in the genotoxicity assays are recommended for inclusion in the appropriate sections and subsections of the sponsor's proposed label for this drug. (See LABELING in the present report for language).

RECOMMENDATIONS:

1. NDA 20,297 is approvable from the standpoint of PHARMACOLOGY.
2. Suggested language changes for subsections in proposed label appear above under LABELING.

Barry 4-21-94
Estela Gonzalez Barry, M.S.
Pharmacologist
02-02-94//04-04-94

cc:
HFD-502/ATaylor
HFD-345/GJames
HFD-110
HFD-110/CSO
HFD-110/EBarry
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ABF
4/24/94

**MINUTES OF THE EXECUTIVE CARCINOGENICITY ASSESSMENT COMMITTEE
(ECAC) MEETING ON CARVEDILOL (3-22-94)**

TO: ALAN TAYLOR

**CC: JOSEPH CONTRERA
CC: CHARLES RESNICK
CC: ALBERT F. DEFELICE**

**SUBJECT: RODENT DOSE-RANGE AND CARCINOGENICITY STUDIES WITH
CARVEDILOL IN DIET. (NDA 20-297)**

FROM: ESTELA BARRY 

PREVIOUS TO THE MEETING, MEMBERS OF THE ECAC REVIEWED A BRIEF OVERVIEW OF FINDINGS FROM THE DOSE-RANGING AND CARCINOGENICITY STUDIES WITH CARVEDILOL FED TO MICE AND RATS. THE STATISTICAL ANALYSES OF THE CARCINOGENICITY DATA ESTIMATED THAT THERE WERE NO STATISTICALLY SIGNIFICANT (AT 0.05 LEVEL) TREND IN THE TUMOR INCIDENCE RATES OF THE TUMOR TYPES TESTED. ALTHOUGH THERE WERE MARGINALLY SIGNIFICANT POSITIVE LINEAR TRENDS REPORTED FOR A SMALL NUMBER OF TUMORS IN BOTH RODENT STUDIES, ONLY THE THYROID GLAND ADENOMAS IN DRUG TREATED FEMALE RATS WERE OF CONCERN BECAUSE OF THE $P = 0.0504$ VALUES APPROACHED SIGNIFICANCE. NO HISTORICAL CONTROL DATA HAD BEEN PROVIDED BY THE SPONSOR IN THE NDA 20-297 TO HELP WITH THE OVERALL ASSESSMENT OF THESE THYROID TUMOR FINDINGS.

ALTHOUGH ECAC AGREED THAT THE STUDIES WERE ADEQUATE, IT RECOMMENDED THAT A PAIRWISE COMPARISON ON THE THYROID GLAND ADENOMAS WOULD BE AN APPROPRIATE STATISTICAL ANALYSES TO BE CONDUCTED.

THE PAIRWISE COMPNARISON (AGE-ADJUSTED METHOD USED) WAS PERFORMED BY DIV. OF BIOMETRICS WITH THE FOLLOWING RESULTS:

**"Thyroid Gland Adenoma in Female Rats:
Control vs. High-1: $p = 0.0535$
Control vs. High-2: $p = 0.0457$"**

CONSIDERING THIS TUMOR FINDING IS STATITICALLY SIGNIFICANT AT THE HIGHEST DOSE OF CARVEDILOL TESTED AND IN THE ABSENCE OF HISTORICAL CONTROLS, ALL THOSE PRESENT AT THE MEETING HAD PREVIOUSLY AGREED THAT IN SUCH A CASE ONLY THIS TUMOR FINDING WOULD BE LISTED ON THE LABEL OF CARVEDILOL.

* Carvedilol intake (mg/kg/day) at end of study: Females: LD- 9.5, MD- 18.8, HD-1 38.1, HD-2 74.7. Males: LD- 7.7, MD- 16.2, HD-1 31.4, HD-2 62.1 RD: EBARRY B:\WP51\FILES\CAC-MEET. MIN. ADsF:s/off-3-25-94

DATE: 04-13-95

FROM: Estela A. Gonzalez Barry, M.S., Pharmacologist. *EB 4-17-95*

SUBJECT: NDA 20-297, Carvedilol Tablets, SmithKline Beecham Pharmaceuticals.

TO: File through Albert DeFelice, Ph.D., Supervisor. *ADSF 4/21/95*

Carvedilol is proposed by sponsor as an antihypertensive agent.

Oral carcinogenicity studies with carvedilol were conducted using mice and rats, and the data submitted revealed no clear evidence of carcinogenicity.

Briefly, labeling recommendations that appeared in the Pharmacology review (04-22-94) of this NDA, suggested the inclusion of some tumor data under the subsection "Carcinogenesis, Mutagenesis, Impairment of Fertility".

The carcinogenicity data had been previously presented to the Executive Carcinogenicity Assessment Committee (ECAC) on 03-22-94. At the meeting, ECAC recommended some additional (pairwise) analyses of the data.

MICE

Prior to ECAC meeting and reanalyses of the data, Pharmacology had recommended including the harderian tumor findings in mice on the label because the drug sponsoring firm was unable to provide FDA with historical control data on the strain of mice used. Tumor findings reported in the harderian glands of treated mice in the carcinogenicity study, underwent several additional statistical analyses by the Division of Biometrics as recommended by ECAC. At this time, Pharmacology concluded that since the combination of harderian gland adenomas and carcinomas (the tumors of Pharmacology concern) did not show a significant positive linear trend, thus these tumors might not need to be listed in the label. At the time of the original presentation to ECAC, the Committee did not appear to be unduly concerned about harderian tumors in mice.

RAT

As for thyroid tumors (tumors of concern by Pharmacology and ECAC) reported in treated rats in the carcinogenicity study, although reanalyses found that there was a marginally statistically significant ($p=0.0504$) linear trend in thyroid gland adenomas in female rats, when the number of thyroid adenomas and carcinomas was combined (as is customarily done), there was no significant positive trend ($p=0.199$) noted.

The above results of the statistical reanalyses were discussed/reviewed, and the final version of the minutes of the ECAC meeting, which included the results of the Division of Biometrics reanalyses recommended by ECAC, were finally issued on 05-05-94.

Subsequent to the Pharmacology final review of NDA 20-297 (04-22-94) with labeling recommendations and the release of the Minutes of the ECAC meeting (05-05-94), a labeling markup version was issued (= March '95). In this labeling version, the subsection under "Carcinogenesis..." did not include references to the above mentioned tumors. This decision was based on further consideration of the Biometrics additional analyses of the carcinogenicity data.

Attachment: Minutes of the ECAC meeting of 03-22-94

cc: Z. McDonald, CSO
Orig. NDA

HFD-110

HFD-110/ADeFelice

HFD-110/EBarry

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Mr. Donald

MAY - 5 1994

**Minutes of the Executive Carcinogenicity Assessment Committee
(ECAC) Meeting on Carvedilol (3-22-94)**

To: Alan Taylor

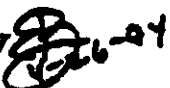
Through: A.F. DeFelice



CC: Joseph Contrera

CC: Charles Resnick

**Subject: Rodent Dose-Range and Carcinogenicity Studies with
Carvedilol in Diet (NDA 20-297)**

From: Estela González Barry 

Prior to the meeting, members of the ECAC reviewed a brief overview of findings from the dose-range and carcinogenicity studies with carvedilol fed to mice and rats.

1. MICE STUDIES

The dosage level for carvedilol selected for the 2-year carcinogenicity study (20, 65 and 200 mg/kg/day) were based on the results of the 13-week mouse study (at 20 up to 800 mg/kg/day.)

At the meeting, discussions on the adequacy of dose-selection for the 2-year study included particular concerns about the doses tested because of the unremarkable effect reported on the bodyweights of female mice.

The data provided showed that at the end of the dose-range study, male mice at the 2 highest doses (600 and 800 mg/kg/day) showed >10% decrement in bodyweight relative to controls, however; the bodyweights of drug treated females had been minimally affected. Remarkable clinical chemistry findings reported consisted of statistically significant increases in both serum alkaline phosphatase values in males at the 2 highest doses, and increased sGPT values (not significant) in all drug treated mice except for HD females. Absolute liver weights

changes were unremarkable in males but elevated in females [dose-related at 60 mg/kg/day and above and, statistically significant ($p < 0.05$) at the 2 highest doses of carvedilol.] Although relative liver weights in treated mice showed dose-related increases (at 60 mg/kg/day and above), the increases were statistically significant only at 800 mg/kg/day for males, and at 200 mg/kg/day and above for females. Based on these findings, drug sponsor selected the 200 mg/kg/day dose as the MTD for purposes of the 2-year carcinogenicity study.

ECAC considered that although these data appear to support the choice of 200 mg/kg/day as MTD for male mice, there were concerns about whether or not this dose approached the MTD in females in light of the unremarkable effect on bodyweight of the females relative to the controls during the dose-range study and, also during the carcinogenicity study.

Although no histopathology was conducted on tissues from mice in dose-range study, data showed that histopathology of livers for the 2-year mouse study revealed a higher incidence of single cell hepatocellular necrosis in these HD females compared to controls. This histopathologic finding suggests that the 200 mg/kg/day dose was close to the MTD in females. Thus, majority of members of **ECAC** agreed that the 3 doses selected/used in the mouse carcinogenicity study were considered acceptable.

Division of Biometrics analysis of the 2-year mice carcinogenicity reported "no statistically significant (at 0.05 level) linear trend in the tumor incidence rates of tumor types tested in both sexes. However, there was a marginally significant positive linear trend in harder's gland carcinoma ($p = 0.0523$) and harder's gland carcinoma and adenoma combined ($p = 0.0663$) in female mice." Pursuant to repeated requests from FDA for historical controls tumor data on this strain of mice, drug sponsor finally confirmed that these data are not unavailable for the SPF-NMRI-HAN-WIGA mice. (NDA Amendment dated 3-30-94.

2. RAT STUDIES

Based on the results of the 15-week dose-range study (at 200 ppm up to 8,000 ppm carvedilol); levels of 600 ppm up to 4,000 ppm in diet were selected for a 2-year rat carcinogenicity study. The 2-year study was started and the HD proved to be toxic, and the study was stopped after 6 months.

Based on the same 15-week study, 4 levels of carvedilol (LD-200, MD-400, HD-1 1,800 and HD-2 1,600 ppm) were tested in a second 2-year carcinogenicity*. The HD in the definitive study was 2.5 X lower than HD used in the aborted 2-year rat study. ECAC considered the 15-week dose-ranging study and the selected MTD as adequate.

Division of Biometrics analyses of the tumor data 2-year rat carcinogenicity study showed "that there was a significant (at 0.05 level) positive linear trend in stomach papilloma ($p = 0.0494$) and skin subcutis sebaceous adenoma ($p = 0.0414$) in male rats. There were marginally statistically significant linear trends in thyroid gland adenoma ($p = 0.0504$)...in female rats * and in liver hepatocellular adenoma ($p = 0.0579$) in male rats." Although the thyroid adenomas in female rats were not dose-related, ECAC was concerned because the linear trend analysis approached statistical significance.

***Carvedilol intake (mg/kg/day) at end of rat carcinogenicity study: Females: LD- 9.5, MD- 18.8, HD-1 38.1 and, HD-2 74.7. Males: LD- 7.7, MD- 16.2, HD-1 31.4 and, HD-2 62.1**

+Thyroid adenoma plus adenocarcinoma combined in carvedilol treated rats (50/sex/group): Females- C- 1, LD- 6, MD- 2, HD-1 4, HD- 5. Males- C- 6, LD- 2, MD- 6, HD-1 2 and HD-2 0.

Since at the time of the ECAC meeting, no historical control tumor data had been submitted for the strain of rats used in the 2-year carcinogenicity study (even after repeated requests by FDA), ECAC recommended that a pairwise analysis be conducted and if the results of the analysis were statistically significant, the thyroid adenoma findings would be included on the label with the proviso that the findings were marginally significant, if that were the case. In another comment, ECAC pointed out that statistical analysis of thyroid adenomas are usually performed on the combination of adenomas and thyroid carcinomas. Although stomach papilloma and skin subcutis sebaceous adenomas were only found in some drug-treated male rats (stomach papilloma, HD-1 1/50 and HD-2 1/50, at the 2 highest doses of the drug and, skin subcutis sebaceous adenomas, HD-2 2/50, only at the highest dose), ECAC recommended that concerns over statistically significant increases in these 2 tumors should be noted in the minutes.

About the thyroid tumors, as suggested by ECAC, Biometrics performed all of the suggested analysis (age-adjusted pairwise comparisons, and trend test on the combined thyroid adenomas and carcinomas). The following results were extracted from a brief report from Biometrics.

● "... Thyroid Gland Adenoma In Female Rats:

Control vs. High-1: P = 0.0535

Control vs. High-2: P = 0.0457...

● ...[T]rend test on thyroid gland adenoma and adenocarcinoma combined.

Male rats: C, L, M, H1, H2

6 2 5 2 0 P= 0.0173 (sign. negative)

Female rats: C, L, M, H1, H2

1, 6, 2, 4, 5 P= 0.199... "

Regarding the increases in stomach papilloma and subcutis sebaceous adenoma in male rats, the following was extracted from the Biometrics' report:

- "...pairwise comparison on stomach papilloma in male rats...

C, H-1: P = 0.3793

C, H-2: P = 0.3077...

- ...pairwise comparison on skin subcutis sebaceous adenoma in male rats,

C, H-2: P = 0.2347..."

N.B. Pharmacology considers that the biological significance to humans of the tumors described above is uncertain. However, in the absence of historical control tumor data for mice, Pharmacology recommends the inclusion on the label of carvedilol the harderian gland tumors reported for females treated with the 2 highest doses of carvedilol in the 2-year mouse carcinogenicity study.

As for tumors reported for the rat 2-year carcinogenicity study, Pharmacology considers that since the statistical analysis of the data did not show a trend or clear evidence of tumorigenicity induced by carvedilol, the tumors reported might not be included in the label of carvedilol. As for the thyroid tumors in rat, C. Gopinath reports in "**Causes and Interpretation of Thyroid Tumors in Rodent Bioassay**" Chapter 3, p. 19 in Current Issues in Drug Development, Huntingdon Research Center Limited, UK, 1991 that "...Certain pharmaceutical drugs are known to affect thyroid gland through adrenergic mechanisms....cardiovascular drugs of adrenergic class influence thyroid follicular growth and function.....The mechanism underlying thyroid lesions are complex"

R/D EBarry: 3-25-94/4-25-94 B:\ECAC-MTG.MIN

112

AUG 15 1995

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-297

CHEM.REVIEW #: 5

REVIEW DATE: 8 Aug 95

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	31 Mar 93		
AMENDMENT BC	20 Jul 95	20 Jul 95	24 Jul 95

NAME & ADDRESS OF APPLICANT:

SmithKline Beecham Pharmaceuticals
Four Falls Corporate Center
Route 23 & Woodmont Avenue
King of Prussia, PA 19406

DRUG PRODUCT NAME:

Proprietary:	Coreg, Covrim or Proreg
Nonproprietary/USAN:	Carvedilol
Code Name/#:	SK&F 105517, BM 14.190
Chem.Type/Ther.Class:	1 S

PATENT STATUS:

US 4,503,067, expires 5 March 02

PHARMACOL.CATEGORY/INDICATION: Antihypertensive

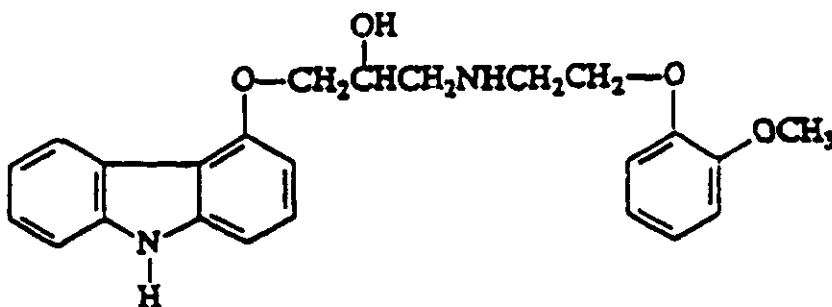
DOSAGE FORM: TCM

STRENGTHS: 6.25, 12.5 and 25 mg

ROUTE OF ADMINISTRATION: Oral

DISPENSED: Rx OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:



(R,S)-1-(Carbazol-4-yloxy)-3-[[2-(o-methoxyphenoxy)ethyl]amino]-2-propanol

C₂₄H₂₆N₂O₄

406.5

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS (if applicable): None

CONSULTS: None

REMARKS/COMMENTS:

The applicant has requested that the Agency consider Proreg as a possible tradename for the drug product in case the Patents and Trademark Office does not find Coreg or Covrim acceptable. A Request for Trademark Review, dated 15 May 95, was sent to the Labeling and Nomenclature Committee requesting review of the proposed tradename. Response, dated 20 Jul 95, was received on 4 Aug 95. The committee found the name acceptable, but with reservations. Some members of the committee thought that the name could be considered to be fanciful. There was also concern that the name could be confused with Prorex, but, since the latter product is for injection, the feeling was that there would be no danger of confusion as long as the product in question was not made available in injection form.

The amendment of 20 Jul 95 provides for the manufacture of a 6.25 mg tablet. This tablet is manufactured from the same granulation as is used for the other strengths, but a proportionally smaller amount of material is used for the new tablet. I noted a number of discrepancies and ambiguities during my review of this amendment. These matters were discussed and satisfactorily resolved, as noted below, with Mr. Peter Kitz by telephone on 8 Aug 95.

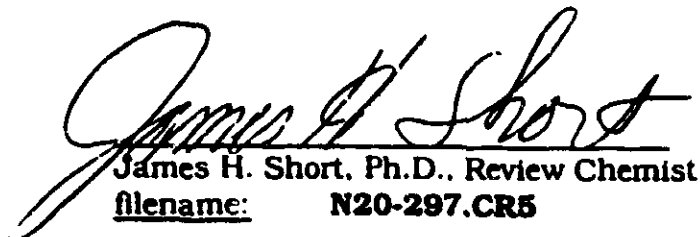
CONCLUSIONS & RECOMMENDATIONS:

The information provided for the manufacture of a 6.25 mg tablet is satisfactory.

APPROVABLE in regard to the chemistry, manufacturing and controls portion of the application at the present time. Trademark, MV, EER (29 Mar 95) and EA are acceptable.

FUR, dated 31 Jul 95, was sent to HFD-320.

cc:
Orig. NDA
HFD-110/Division File
HFD-110/Short '7/20/95
HFD-110/CSO
District
R/D Init by: RWolters/8/11/95


James H. Short, Ph.D., Review Chemist
filename: N20-297.CR5

STATISTICAL REVIEW AND EVALUATION

NDA #: 20-297 Drug Class: 1S
Applicant: SmithKline Beecham Pharmaceuticals
Drug Name: Kredex (Carvedilol)
Indication: Hypertension
Document Reviewed:

Vols. 1.1, 1.2, 1.504, 1.505, 1.506, 1.521, 1.549, 1.581,
1.594, 1.606, 1.630

Diskettes for datasets

This review was completed after discussion with Dr. Knudson, medical reviewer for the efficacy.

1. INTRODUCTION

The NDA contains numerous volumes. This review pertains to six main Phase III clinical studies for efficacy and dose-effect relationship submitted for supporting the proposed indication that carvedilol is an antihypertensive agent.

2. STUDY OVERVIEW AND REVIEWER'S EVALUATION

In some studies the sponsor attempted to adjust p-value for multiple comparisons in analysis of weekly visit data. In my view such practice is unnecessary since weekly visit analysis is secondary and exploratory.

In the sponsor's subgroup analysis, p value was constantly used to determine whether drug effect is significant in subpopulation. In this review the subgroup p-value will not be reported since it is often misleading in assessing statistical significance.

A few errors were found in some of the key tables in the NDA documents. This review will not report these errors; instead, it will present correct numbers, based on the SAS database provided by the sponsor.

Study B100

This 33-center US study was conducted to assess the antihypertensive effect of carvedilol (CARVDL) 6.25 mg, 12.5 mg, 25 mg administered twice daily as compared to placebo, in patients with mild to moderate hypertension (baseline sitting DBP of 95 to 115 mm Hg inclusive) treated for eight weeks.

After a single-blind placebo baseline phase of up to eight weeks, a total of 480 patients were randomly allocated to receive placebo, CARVDL 6.25 mg, CARVDL 12.5 mg, or CARVDL 25 mg for eight weeks. There were 36% protocol violators that were

believed to affect the evaluability of data; thus, 306 of the 480 patients were included in the per-protocol analysis and were evenly distributed to the four treatment groups. The four treatment groups were comparable at baseline characteristics and vital signs in both intent-to-treat and per-protocol patients, except a possible difference in standing DBP between CARVDL 25 mg and placebo in per-protocol cohort. Of the 480 patients, 419 completed eight-week treatment phase. The percentage of withdrawals due to adverse experience seemed to increase as the CARVDL dosage increases (CARVDL 6.25 mg - 3.4%, CARVDL 12.5 mg - 4.0%, CARVDL 25 mg - 6.0%, placebo - 8.4%), whereas the percentage of withdrawals due to insufficient therapeutic response seemed to decrease in dosage of CARVDL (CARVDL 6.25 mg - 5.9%, CARVDL 12.5 mg - 5.6%, CARVDL 25 mg - 3.4%, placebo - 7.6%).

As seen in Table S, a 4 mm Hg greater reduction in sitting DBP at endpoint was observed in the 12.5 mg group and a 5.2 mm Hg greater reduction in the 25 mg group, as compared to placebo; the differences were statistically significant. A similar trend was observed on other blood pressures (Table 1). CARVDL 6.25 mg seemed to yield a 2.1 mm Hg greater reduction in sitting DBP than placebo; the difference was marginally significant (after adjustment based on Dunnett's procedure). The effect of this dose on DBP in supine or standing position seemed minimal; the effect on SBP was significant (Table 1).

There was a strong trend of positive dose-response ($p < 0.0001$ for slope); no evidence of a leveling-off with dose-response curve was found.

The CARVDL 12.5 mg and 25 mg groups had a 16%-23% higher rate in normalized sitting DBP and a 21%-28% higher rate of responders (those whose sitting DBP ≤ 90 mm Hg and/or decreased by at least 10 mm Hg) than the placebo group ($p < 0.005$). Mean decreases in heart rate of 3 to 8 bpm from baseline greater than placebo were observed with each of carvedilol doses (almost all $p < 0.05$, Table 2).

Trough/peak ratio ($[(\text{mean decrease of active} - \text{mean decrease of placebo at trough}) / (\text{mean decrease of active} - \text{mean decrease of placebo at peak})]$) for sitting DBP/SBP was 47%/85% for CARVDL 6.25 mg, 66%/63% for CARVDL 12.5 mg, and 55%/67% for CARVDL 25 mg. For standing DBP/SBP, they were 94%/127%, 10%/63%, and 55%/58%, for CARVDL 6.25 mg, 12.5 mg and 25 mg, respectively.

On average black patients did not seem to respond to any one of the study doses of carvedilol (Table 3).

Reviewer's Evaluation

Carvedilol 12.5 mg and 25 mg administered twice daily significantly decreased blood pressure, as compared to placebo. The effect of the 6.25 mg dose on DBP appeared only marginal.

This study does not provide sufficient information to tell how far one may increase the dosage of carvedilol before the effect levels off. The percentage of withdrawals due to adverse experience tends to increase as the carvedilol dosage increases.

Study B101

This 47-center US+CANADA placebo-controlled trial was carried out to evaluate the antihypertensive effect of CARVDL 6.25, 12.5, 25, or 50 mg administered once daily compared to placebo, in patients with mild to moderate hypertension (sitting DBP between 95 and 115 mm Hg inclusive) treated for eight weeks.

Following the initiation of the study, the protocol was amended to eliminate the 50 mg group due to the concern regarding the potential incidence of postural hypotension. After a placebo washout period of up to eight weeks, 520 patients were randomized into one of the five treatment groups for eight weeks. The 50 mg group had 6% of the total randomized population. There were 46% protocol violators; thus, 281 of the 520 patients were included in the per-protocol analysis. The five treatment groups appeared comparable in baseline characteristics and vital signs in both intent-to-treat and per-protocol patients. Of the 520 patients, 384 completed eight-week treatment phase. The percentage of withdrawals due to adverse experience seemed to increase as the CARVDL dosage increases (CARVDL 6.25 mg - 3.3%, CARVDL 12.5 mg - 3.9%, CARVDL 25 mg - 8.7%, CARVDL 50 mg - 13.8%, placebo - 6.0%), whereas the percentage of withdrawals due to insufficient therapeutic response seemed to decrease in dosage of CARVDL (CARVDL 6.25 mg - 14.0%, CARVDL 12.5 mg - 13%, CARVDL 25 mg - 13%, CARVDL 50 mg - 0%, placebo - 16%).

When compared to placebo, a 2.5 mm Hg greater reduction in sitting DBP at endpoint was observed in the 12.5 mg group and a 2.1 mm Hg greater reduction in the 25 mg group; these differences were statistically significant (Table S). Similar observations were made on supine and standing DBP (Table 4), but their performance on SBP was not clear (Table 4). The effect of CARVDL 6.25 mg was found little. CARVDL 50 mg seemed to have a greater effect on all blood pressures than other doses; statistical significance was inconclusive because of the small number of patients.

There was a significant trend of positive dose-response ($p < 0.05$).

The carvedilol 12.5-50 mg doses had a 10%-17% higher rate of responders than placebo. Mean decreases in heart rate of about 1 to 3.5 bpm greater than placebo were observed with each of carvedilol doses (Table 5).

The ratio of the mean change in trough sitting DBP to mean change in peak sitting DBP was 45% for CARVDL 6.25 mg, 49% for CARVDL

12.5 mg, 41% for CARVDL 25 mg, and 59% for placebo. Trough/peak ratio (as defined in Study B100) for sitting DBP was 53% for CARVDL 6.25 mg, 33% for CARVDL 12.5 mg, and 15% for CARVDL 25 mg. The mean of the individual trough/peak ratio for those patients whose response led to a determinate ratio between 0 and 100% was 56% for CARVDL 6.25 mg, 52% for CARVDL 12.5 mg, 44% for CARVDL 25 mg, and 57% for placebo.

Females seemed to respond less well than males. Patients with moderate hypertension seemed to respond better than patients with mild hypertension. No pattern was observed to suggest that blacks respond less well than nonblacks.

Reviewer's Evaluation

Carvedilol 12.5 mg and 25 mg given once daily are significantly different from placebo, but the magnitude of their effects (about 2.1-2.9 mm Hg greater reduction in sitting and supine DBP than placebo) is not impressive. Clinical significance needs to be determined. The 6.25 mg dose qd had little effect. With or without placebo being included, dose-response analysis performed by this reviewer suggests that the positive slope for the decrease in sitting/standing DBP and SBP versus dosage is at borderline significance ($p = 0.02$ to 0.07 for slopes). Thus the positive trend suggests that the 50 mg dose have a significant effect, though it is not quite significant according to Table S and Table 4 due to small sample size. The data is not able to tell how far one may increase dosage to see the effect level off.

With or without placebo being included, logistic analysis done by this reviewer suggests that the percentage of withdrawals due to adverse experience increases as the carvedilol dosage increases (p -value for slope is between 0.01 and 0.05).

Study C1106

This 13-center US study was carried out to compare the antihypertensive effect of titrated doses of carvedilol administered once daily to carvedilol administered twice daily (total daily doses of 6.25-50 mg for either regimen) and to placebo. The BP criteria for entry to treatment phase were: mean sitting DBP and standing DBP were 95-115 mm Hg with the highest to the lowest mean not varying by more than 10 mm Hg, the mean sitting DBP did not vary by more than 5 mm Hg at the last two placebo baseline visits, and the mean standing DBP did not vary by more than 5 mm Hg at the the last two placebo baseline visits.

After a five- to six-week placebo baseline period, 280 patients were randomized to one of three treatment groups: carvedilol once daily with placebo once daily, carvedilol twice-daily, or placebo twice-daily for a 2 to 12 week up-titrated treatment period, followed by a four week fixed-dose maintenance period. Initial doses were CARVDL 6.25 mg and placebo one capsule once daily,

carvedilol 3.125 mg twice daily, and placebo one capsule twice daily. The dose of study medication was increased until the mean sitting DBP was less than 90 mm Hg at two consecutive weekly visits or until the highest allowable dose level (equivalent to a total daily dose of carvedilol 50 mg) had been prescribed for two consecutive weeks.

There were 279 patients in the intent-to-treat sample. About 14% of the patients in each treatment group had protocol violations for which data were completely excluded from the per-protocol analysis; the most common reason for complete exclusion was failure to meet baseline BP data (about 7%). The intent-to-treat sample and the per-protocol sample were similar in baseline characteristics; the three treatment groups were also comparable.

Of the 280 patients randomized, 55% completed the study (25% for placebo, 64% for carvedilol qd; 77% for carvedilol bid); insufficient therapeutic effect was the most common reason for early withdrawal (69% for placebo, 28% for carvedilol qd, 15% for carvedilol bid). A higher percentage of black patients were withdrawn for insufficient therapeutic effect than nonblack patients (77% vs. 64% for placebo, 35% vs. 23% for carvedilol qd, 19% vs. 12% for carvedilol bid). About 3% of the withdrawals were due to adverse experiences.

As said in the study report, evidence of possible deviations in the treatment effects across centers was found. One source of deviation comes from data of the investigator (Dr. Gray), which showed the large decrease in BP in both carvedilol regimens as compared to placebo. Some directional interaction was observed. Three of the 13 investigators observed a smaller decrease in sitting DBP for carvedilol qd than for placebo; only one investigator observed a smaller decrease for carvedilol bid than for placebo. In eleven centers carvedilol bid regimen had a numerically larger decrease in sitting DBP than qd regimen. Thus the rank of performance seemed to indicate that the bid regimen work better, on average, than the qd regimen.

A number of analyses were performed to see the potential impact of possible directional treatment by center interactions. It was explained in the sponsor's report that treatment by center interactions were attributed to Dr. Gray's data and a few possible directional interactions. By pooling all centers, the analysis including the treatment-by-center term in the ANOVA model indicated that both carvedilol regimens yielded a significantly greater reduction in sitting and standing DBP and heart rate ($p < 0.001$) than placebo. The bid regimen also yielded a significantly greater decrease in sitting and standing SBP ($p < 0.001$) than placebo, whereas the qd regimen resulted in a marginally significantly greater decrease. The bid regimen group had a significantly greater reduction in sitting and standing DBP than the qd regimen group ($p < 0.02$). Summary statistics of the study endpoint analysis are displayed in Table S and Table 7. The results of titration phase endpoint analysis and the results

of study endpoint analysis were very similar; so were the results of intent-to-treat analysis and per-protocol analysis. There was a significantly ($p < 0.001$) larger normalized (sitting DBP < 90 mm Hg) rate in both carvedilol groups than in the placebo group (55% for CARVDL bid, 43% for CARVDL qd, 18% for placebo). Response (sitting DBP normalized or decreased by ≥ 10 mm Hg) rates in both carvedilol groups were also significantly ($p < 0.001$) greater (66% for CARVDL bid, 51% for CARVDL qd, 19% for placebo); the difference between qd and bid was statistically significant ($p = 0.024$).

The criterion for entering fixed-dose maintenance period was that the patient had either achieved a mean sitting DBP < 90 mm Hg for two consecutive weeks or had received the highest dose for two weeks during the up-titration period. Only 57% (158/279) had maintenance period data and the number or percentage of patients with maintenance period data differed among the treatment groups: 64% (58/90) for carvedilol qd, 80% (77/96) for carvedilol bid, and 25% (23/93) for placebo. Among these patients, mean decrease in sitting/standing DBP from baseline at titration endpoint was 11.5/12.2 mm Hg for placebo, 13.4/13.0 mm Hg for carvedilol qd, and 13.9/13.8 mm Hg for carvedilol bid. At maintenance endpoint, mean sitting/standing DBP increased from titration endpoint for all three treatment groups: 1.3/3.8 mm Hg for placebo, 1.8/1.4 mm Hg for carvedilol qd, and 1.1/1.9 mm Hg for carvedilol bid.

At study endpoint, the placebo adjusted trough/peak ratio was 47% for the qd regimen and 66% for the bid regimen.

Both carvedilol regimens appeared to be effective in all subgroups by sex, age, race or severity of hypertension (Table 8).

Reviewer's Evaluation

Treatment by center interactions are investigated further. There are 15 centers in total, based on the SAS database provided by the sponsor. In Center 016 only two patients were randomized (one in qd, one in placebo, none in bid). In Center 028 only three patients were randomized (one per treatment group). In 13 of the 15 centers carvedilol bid was numerically superior (i.e., greater decrease in sitting DBP) to placebo, whereas carvedilol qd was numerically superior to placebo in 11 centers. Carvedilol bid was numerically superior to carvedilol qd in 10 centers. The sponsor thought that treatment by center interactions were partly attributed to the data of Dr. Gray (Center 010). Excluding Dr. Gray, analysis still shows a significant treatment by center interaction ($p < 0.02$). Pooling the remaining centers, analysis shows that carvedilol bid yields a 6.5 mm Hg greater decrease in sitting DBP and the qd regimen yields a 2.8 mm Hg greater decrease, than placebo; these differences are statistically significant ($p < 0.03$). Further analysis with Center 016 and Center 028 being also excluded produces very similar results. Based on overall evidence presented by this study, it is clear that the bid regimen is

superior to the qd regimen.

Data suggests that the effect of carvedilol given either once-daily or twice-daily may be maintained for four weeks in patients who had their blood pressure controlled via dose titration.

Study C1109

This 13-center US study was carried out to compare the efficacy of carvedilol (12.5 mg, 25 mg and 50 mg) and atenolol (50 mg, 100 mg) with placebo, administered once daily, for the treatment of patients with mild to moderate essential hypertension. The BP entry criteria were: mean sitting and standing DBP was 95 to 115 mm Hg at each of the last three placebo baseline period visits, the highest to the lowest mean sitting DBP and the highest to the lowest mean standing DBP of the last three placebo baseline visits did not vary by more than 10 mm Hg, and the mean sitting DBP and the mean standing DBP did not vary by more than 5 mm Hg between the last two placebo baseline visits.

After a 5-6 weeks placebo baseline period, a total of 258 patients were randomized to receive once daily regimens of either carvedilol 12.5 mg, atenolol 50 mg, or placebo. After one week, coded medication was titrated upward if mean sitting DBP was ≥ 90 mm Hg (unless mean standing SBP was ≤ 120 mm Hg or mean standing DBP was ≤ 80 mm Hg). At this titration step, eligible patients in the atenolol group remained on an actual dose of 50 mg. In further weekly visits, patients could be titrated to carvedilol 50 mg, atenolol 100 mg, or placebo. The dose was maintained and fixed-dose maintenance period was begun if the mean sitting DBP was < 90 mm Hg for two consecutive weekly visits, or if the patient had received the highest dose level for two consecutive visits. There were a total of 231 patients in the per protocol sample (about 88%-92% of the randomized patients in each treatment group were included in the per protocol sample). The three treatment groups were comparable in baseline characteristics and vital signs in both the intent-to-treat and the per protocol samples.

Among the 258 patients entering treatment phase, completion rates were 86% (87/101) for the atenolol treatment group, 62% (65/105) for the carvedilol group, and 35% (18/52) for the placebo group. Thirty (60%) placebo patients, 31 (30%) carvedilol patients, and 9 (9%) atenolol patients were discontinued for insufficient therapeutic effect (p-value for every pairwise difference < 0.001).

Statistically significant treatment by center interaction terms were detected for sitting and standing blood pressures only at titration endpoint. The sponsor found virtually no difference in the results of analyses using either the model with interaction terms or the model without interaction terms; thus, they considered that the interactions had no effect on the conclusions

of the study. As shown in Tables 8 and 9, at study endpoint, both carvedilol and atenolol regimens reduced sitting and standing diastolic blood pressures and sitting SBP significantly greater than placebo ($p < 0.005$). Atenolol decreased systolic blood pressures significantly greater than placebo ($p < 0.05$), whereas carvedilol seemed to have little effect. Atenolol decreased blood pressures significantly greater than carvedilol ($p < 0.05$). Both atenolol and carvedilol slowed heart beat. Analysis of percent of patients normalized and responders showed similar results.

Change from titration endpoint to maintenance endpoint was calculated for the subset of patients who had maintenance endpoint data: 19 patients receiving placebo, 91 patients receiving atenolol, and 69 patients receiving carvedilol. At maintenance endpoint, mean sitting/standing DBP increased slightly from titration endpoint for all three regimens: 2.8/2.5 mm Hg for placebo, 1.9/1.9 mm Hg for atenolol, 2.3/2.2 mm Hg for carvedilol.

Placebo adjusted trough/peak ratio at study endpoint was 68% for atenolol and 32% for carvedilol. Unadjusted ratio was 87% for atenolol and 53% for carvedilol.

Both carvedilol regimens appeared to be effective in all subgroups by sex, age, race or severity of hypertension (Table 10).

Reviewer's Evaluation

Atenolol yields a significantly greater reduction in blood pressure than carvedilol; both are effective. Atenolol seems to maintain its effect slightly better than carvedilol.

Study C1107

This 12-center US study was conducted to assess the effect of carvedilol 6.25 to 25 mg once daily when added to the treatment regimen of patients whose sitting and standing DBP was uncontrolled (≥ 90 mm Hg) by treatment with hydrochlorothiazide (HCTZ) 25 mg once daily. The BP criteria for entry to treatment phase were: mean sitting and standing DBP were 90-115 mm Hg, and the mean sitting DBP and mean standing DBP did not vary by more than 5 mm Hg between the last two baseline visits.

After a four-week baseline phase during which they took HCTZ 25 mg once daily, a total of 266 patients were randomized to receive once daily regimens: placebo, CARVDL 6.25 mg, CARVDL 12.5 mg, or CARVDL 12.5 mg for one week with possible increase to 25 mg later (the criteria to increase dose were the same as those used in Study C1109). Of them, 243 (91%) completed the four-week treatment phase. Eleven of the 23 dropouts withdrew due to an adverse experience; the percentage of adverse event related dropouts seemed to increase as CARVDL dosage increases (CARVDL

6.25 mg - 1.5%, CARVDL 12.5 mg - 3.8%, CARVDL 25 mg - 6.1%, placebo - 4.5%). There were 239 patients in the per protocol sample. The four treatment groups were comparable in baseline characteristics and vital signs.

The same titration was used for all patients in each treatment group to maintain the blind, but actual dose increase occurred only in the carvedilol 12.5/25 mg group. The carvedilol 12.5/25 mg group showed a statistically significantly greater decrease in sitting DBP than the placebo group; the difference was 3.0 mm Hg (Table S). The following table summarized the mean decrease in sitting DBP at study endpoint for those who underwent the titration step and for those who did not (intent-to-treat patients).

Patients who underwent titration step:

	Baseline		Decrease from baseline	
	n	Mean	n	Mean (s.e.)
PLacebo	40	100.7	40	3.0 (1.0)
CARVDL-6.25	39	99.8	39	3.2 (1.2)
CARVDL-12.5	38	98.0	38	3.4 (1.0)
CARVDL-25	32	99.8	32	6.6 (1.1)

Patients who did not undergo titration step:

	Baseline		Decrease from baseline	
	n	Mean	n	Mean (s.e.)
PLacebo	26	94.2	26	3.7 (1.3)
CARVDL-6.25	28	94.5	28	6.7 (1.6)
CARVDL-12.5	29	96.0	27	7.0 (1.8)
CARVDL-12.5	34	96.9	34	6.1 (1.3)

As shown in the above table, 32 (48%) patients in the carvedilol 12.5/25 mg group were titrated to 25 mg dose; the mean decrease in sitting DBP was 6.6 mm Hg. The mean decrease of the remaining 34 patients staying on 12.5 mg was 6.1 mm Hg. The mean decrease of the 65 patients originally randomized to carvedilol 12.5 mg dose was 4.9 mm Hg at study endpoint. For the combined 12.5 mg set, the mean decrease was 5.3 mm Hg. With or without including those who remained on the 12.5 mg dose in the carvedilol 12.5/25 mg group, the sponsor's dose response analysis found a statistically significant linear relationship between actual dosing level and mean sitting DBP decrease ($p < 0.01$) and no indication of leveling-off. The per protocol analysis showed a similar numerical trend. The linear trend was marginally significant ($p = 0.076$) and there was no evidence of a quadratic

trend.

Ordering of treatment groups by magnitude of decrease in standing DBP, sitting and standing S3P was consistent with that seen in sitting DBP; the numerical difference between each carvedilol group and placebo was not statistically significant. The three carvedilol groups showed a significantly greater decrease in heart rate than the placebo group. Summary statistics are provided in Table 11.

The three carvedilol groups had a similar rate (30%) of responders and rate (26-30%) of patient normalized; numerically, they were about 10-12% greater than the rates of the placebo group.

Black patients seemed to need high dose of carvedilol. Patients with moderate hypertension also seemed to need high dose of carvedilol (Table 12).

Reviewer's Evaluation

The percentage of adverse event related dropouts tend to increase as carvedilol dosage increases. Data clearly suggests that when their blood pressures are not properly controlled with HCTZ 25 mg, patients with relatively high blood pressure need a higher dose (e.g. only the 25 mg dose of carvedilol appears effective, see the tables on page 9) whereas those with relatively low blood pressure may start with the 6.25 mg dose. There is no evidence of leveling-off in this dose range, 6.25-25 mg/day.

Study B104

This 23-center US study was conducted to study the antihypertensive effects of carvedilol 6.25 to 25 mg twice daily and labetalol 100 to 400 mg twice daily, as compared to placebo, in black patients with mild to moderate hypertension (baseline mean sitting DBP of 95-115 mm Hg inclusive) treated for eight weeks.

After a 2-8 weeks placebo baseline period, a total of 246 patients were randomized to receive either carvedilol 6.25 mg twice daily, labetalol 100 mg twice daily, or placebo twice daily. Patients were seen at the end of Weeks 2, 4, 6, and 8 from randomization. The dose of double-blind medication was increased until the mean sitting DBP was $\leq$ 90 mm Hg. The patient was maintained at that dose as long as the mean sitting DBP $<$ 95 mm Hg at subsequent visits. If the mean sitting DBP was $\geq$ 95 mm Hg at subsequent visits, the dose was increased. The increases in study medication dose were made incrementally during regularly scheduled visits. If the patient's medication had been titrated to the highest dose level, that dose was maintained until the end of the treatment phase or until any criterion for discontinuing treatment was met. Patients were then seen at a follow-up visit

scheduled 7-10 days after the last treatment period visit. Study medication was gradually down-titrated during the follow-up period.

There were a total of 210 patients in the per protocol sample (about 83%-90% of the randomized patients in each treatment group). The three treatment groups were comparable in baseline characteristics and vital signs in both the intent-to-treat and the per protocol samples. Distribution of intent-to-treat patients according to type of pre-trial antihypertensive medication also appeared comparable. A total of 56 patients withdrew from the study after randomization; the placebo group had a largest percentage of dropouts (29%), followed by the carvedilol group (21%) and then by the labetalol group (18%). The percentage of dropouts due to adverse events was similar in the three treatment groups. Sixteen percents of the placebo patients, 8% of the carvedilol patients and 4% of the labetalol patients withdrew due to insufficient therapeutic effect.

For endpoint analysis, six (two per treatment group) of the 246 patients in the intent-to-treat sample did not have vital sign measurements. A Bonferroni adjustment made by the sponsor's analysis showed that only the difference between labetalol and placebo in mean change of sitting DBP was significant. The per-protocol analysis also supported this conclusion. The difference between carvedilol and placebo was marginally significant. Analysis of secondary blood pressures showed that carvedilol had a significant effect in reducing blood pressure. Numerically, labetalol seemed to have a larger effect than carvedilol, though the difference was only at best marginally significant; see Table S and Table 13. Both carvedilol and labetalol decrease heart rate in black patients.

Labetalol appeared more effective than carvedilol. Both seemed to be more effective in elderly black patients (Table 14).

Reviewer's Evaluation

Both carvedilol 6.25-25 mg and labetalol 100-400 mg given twice daily significantly decrease blood pressure, as compared to placebo. The mean effect of carvedilol is about 2-3 mm Hg in DBP in black patients, whereas the effect of labetalol is 4.5 to 5.6 mm Hg; the latter is marginally significantly greater than the former.

3. SUMMARY OF REVIEWER'S EVALUATION

Carvedilol given once-daily is studied in four (B101, C1106, C1109 and C1107) of the six studies reviewed. Carvedilol bid administration is studied in B100 and C1106, and B104 specifically in black population. The dose range under study is 6.25 to 50 mg/day.

Once-daily administration

The 6.25 mg dose has little effect. Both the 12.5 and 25 mg

doses show a significantly greater decrease in DBP than placebo; the effect is not impressive (2.1-2.9 mm Hg greater in sitting/standing DBP); see Tables S and 4. Two titration studies (C1106 and C1109) show that carvedilol 6.25-50 mg could yield a 4-6 mm Hg greater reduction in sitting/standing DBP than placebo (Tables S, 7 and 9).

Based on C1107, when their blood pressures are not properly controlled with HCTZ 25 mg, patients with relatively high blood pressure at baseline need a higher dose (only the 25 mg dose appears effective, see the tables on page 9) whereas those with relatively low blood pressure may start with the 6.25 mg dose.

Twice-daily administration

The effect of the 6.25 mg dose (i.e., 12.5 mg/day) on DBP appears only marginal (Tables S and 1). The 12.5 mg and 25 mg doses yield a significant greater reduction in blood pressures than placebo. The effect of the 12.5 dose is 4.0 mm Hg in sitting DBP and about 2.5 mm Hg in supine/standing DBP; the effect of the 25 mg dose is about 5 mm Hg in DBP; see Tables S and 1. The titration study, C1106, shows that the bid administration of carvedilol 6.25-50 mg/day could have an effect of 7.6 mm Hg in sitting/standing DBP.

Dose response

There was a positive trend indicating an increase in BP reduction effect as carvedilol dosage increases in the dose range of 6.25 to 50 mg per day, based on the data of two parallel-group trials (B100 and B101) and one titration study (C1107). None of these studies are able to tell how far one may increase dosage to see the effect level off.

QD vs. BID

Based on C1106, carvedilol 6.25-50 mg/day when given twice daily shows a significantly greater decrease in DBP than carvedilol given once-daily. Data also suggests that the effect of carvedilol may be maintained for four weeks in patients who had blood pressure controlled via dose titration in this dose range.

Atenolol vs. Carvedilol

Atenolol 50-100 mg/day qd yields a significantly greater reduction in blood pressure than carvedilol 12.5-50 mg/day qd. Atenolol seems to maintain its effect slightly better than carvedilol.

Effect on black population

Based on B104, carvedilol 12.5-50 mg/day bid yields a significantly greater decrease in DBP than placebo in black patients; the mean effect is not impressive (about 2 mm Hg in

sitting/supine DBP and 3 mm Hg in supine DBP). Labetalol 200-800 mg/day bid shows a significantly greater reduction in DBP than carvedilol.

Sex and Age

There is no evidence that carvedilol is not effective in a subgroup by sex or age.

Adverse event related withdrawals

B100, B101 and C1107 suggest that the percentage of withdrawals due to adverse experience increases as carvedilol dosage increases.

4. CONCLUSION (MAY BE CONVEYED TO THE SPONSOR)

Main statistics are presented in Table S and summary of my evaluation is given in last section. When given once daily, the 6.25 mg dose of carvedilol has little effect. Both the 12.5 and 25 mg doses show a significantly greater decrease in DBP than placebo; the size of their effects is not impressive. Carvedilol 6.25-50 mg given in the upward-titration-to-effect fashion could, on average, yield a 4-6 mm Hg greater reduction in sitting/standing DBP than placebo. When their blood pressures are not properly controlled with HCTZ 25 mg, patients with relatively high blood pressure at baseline need a higher dose whereas those with relatively low blood pressure may start with the 6.25 mg dose.

When given twice daily, the effect of the 6.25 mg (i.e. 12.5 mg/day) dose on DBP appears only marginal. The 12.5 mg and 25 mg doses yield a significant greater reduction in blood pressures than placebo. The bid administration of carvedilol 6.25-50 mg/day given in the upward-titration-to-effect fashion could have an effect of 7.6 mm Hg in sitting/standing DBP.

There is a positive trend indicating an increase in BP reduction effect as carvedilol dosage increases in the dose range of 6.25 to 50 mg per day. There is no information in these studies reviewed to tell how far one may increase dosage to see the effect level off.

Carvedilol 6.25-50 mg/day when given twice daily shows a significantly greater decrease in DBP than carvedilol given once-daily. Data also suggests that the effect of carvedilol may be maintained in patients who had blood pressure controlled via dose titration in this dose range.

Atenolol 50-100 mg/day qd yields a significantly greater reduction in blood pressure than carvedilol 12.5-50 mg/day qd. Atenolol seems to maintain its effect slightly better than carvedilol.

Carvedilol 12.5-50 mg/day bid yields a significantly greater decrease in DBP than placebo in black patients; the effect is not impressive. Labetalol 200-800 mg/day bid shows a significantly greater reduction in DBP than carvedilol in black patients.

There is no evidence that carvedilol is not effective in a subgroup by sex or age.

The percentage of withdrawals due to adverse experience increases as carvedilol dosage increases.


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Mathematical Statistician

This review consists of 14 pages of text and 15 tables.

Concur:

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10/26/93

Dr. Dubey *DT-1-93*

cc:

Orig. NDA

HFD-110

HFD-110/Dr. Lipicky

HFD-110/Dr. Knudsen

HFD-110/Ms. Morgenstern

HFD-344/Dr. Lisook

HFD-713/Dr. Dubey [File: DRU 1.3.2 NDA]

HFD-713/Dr. Chi

HFD-713/Dr. Hung

JHung/443-4594/SERB/KREDEX.*/08-25-93

Table S. Mean decrease from baseline in sitting DBP (mm Hg) - intent-to-treat study endpoint analysis

Treatment Group	N	Mean Decrease (S.E.)	Treatment minus Placebo	95% C.I.	p-value*
STUDY B100 (BID regimen)					
CARVDL-6.25	117	5.4 (0.7)	2.1	(-0.1, 4.2) [#]	0.027
CARVDL-12.5	125	7.3 (0.8)	4.0	(1.9, 6.1) [#]	0.0001
CARVDL-25	114	8.5 (0.8)	5.2	(3.1, 7.4) [#]	0.0001
Placebo	117	3.3 (0.8)			
STUDY B101 (QD regimen)					
CARVDL-6.25	121	4.4 (0.7)	0.7	(-1.3, 2.7) [#]	0.39
CARVDL-12.5	126	6.3 (0.7)	2.6	(0.5, 4.5) [#]	0.004
CARVDL-25	126	5.8 (0.7)	2.1	(0.1, 4.1) [#]	0.016
CARVDL-50	28	8.0 (1.3)	4.3	(1.0, 7.5) [#]	0.083
Placebo	115	3.7 (0.7)			
STUDY C1106 (QD VS. BID, 6.25-50 mg/day)\$\$\$					
CARVDL BID	96	10.9 (0.8)	7.6 [@]	(5.4, 9.8)	0.0001
CARVDL QD	90	7.9 (0.8)	4.6	(2.4, 6.8)	0.0009
Placebo	93	3.3 (0.8)			
STUDY C1109 (CARVDL 12.5-50 mg QD VS. ATENOLOL 50-100 mg QD)					
CARVDL	105	7.5 (0.8)	4.0	(1.5, 6.3)	0.002
ATENOLOL	100	11.3 (0.6)	7.8 ⁺⁺	(5.3, 10.1)	<0.001
Placebo	52	3.5 (0.9)			
STUDY C1107 (QD, HCTZ ADDED)					
CARVDL-6.25	67	4.7 (1.0)	1.4	(-1.2, 4.0) [#]	NS
CARVDL-12.5	65	4.9 (1.0)	1.6	(-1.0, 4.2) [#]	NS
CARVDL-12.5/25	66	6.3 (0.9)	3.0	(0.5, 5.7) [#]	< 0.02
PLACEBO	66	3.3 (0.8)			
STUDY B104 (mg/day BID, BLACK PATIENTS only)					
CARVDL 12.5-50	83	6.3 (0.9)	2.2	(0.1, 4.9)	0.040
LABTLOL 200-800	77	8.6 (0.8)	4.5 ⁺	(2.2, 7.1)	0.0002
PLACEBO	80	4.1 (1.0)			

[#] adjusted based on Dunnett's one-sided procedure

* two-sided p-value not yet adjusted for multiple comparisons

[@] p < 0.01 between BID and QD

⁺ p = 0.080 between carvedilol and labetalol

⁺⁺ p < 0.001 between carvedilol and atenolol

^{\$\$\$} unadjusted means are reported (see Reviewer's Evaluation of Study C1106)

Table 1. Mean decrease from baseline at study endpoint in Secondary blood pressure (mm Hg) - intent-to-treat Study B100

Treatment Group	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	95% C.I. [#]	unadjusted p-value*
Supine DBP					
CARVDL-6.25	117	4.2 (0.8)	1.5	(-1.0, 4.0)	0.15
CARVDL-12.5	125	5.1 (1.0)	2.4	(-0.1, 4.9)	0.0020
CARVDL-25	114	8.1 (0.9)	5.4	(2.9, 7.8)	0.0001
Placebo	116	2.7 (0.9)			
Standing DBP (3 min)					
CARVDL-6.25	117	4.3 (0.8)	1.0	(-1.5, 3.5)	0.24
CARVDL-12.5	125	5.8 (0.8)	2.5	(0.0, 5.0)	0.021
CARVDL-25	114	8.1 (1.0)	4.8	(2.3, 7.3)	0.0001
Placebo	116	3.3 (0.9)			
Sitting SBP					
CARVDL-6.25	117	6.0 (1.2)	4.9	(0.9, 8.8)	0.0044
CARVDL-12.5	125	7.8 (1.3)	6.7	(2.8, 10.6)	0.0001
CARVDL-25	114	8.4 (1.6)	7.3	(3.3, 11.2)	0.0001
Placebo	117	1.1 (1.4)			
Supine SBP					
CARVDL-6.25	117	4.6 (1.3)	3.9	(-0.4, 8.2)	0.053
CARVDL-12.5	125	6.8 (1.5)	6.1	(1.9, 10.4)	0.0020
CARVDL-25	114	6.5 (1.7)	5.8	(1.5, 10.2)	0.0033
Placebo	117	0.7 (1.5)			
Standing SBP (3 min)					
CARVDL-6.25	117	4.2 (1.5)	3.8	(1.0, 8.6)	0.055
CARVDL-12.5	125	7.5 (1.7)	7.1	(2.4, 11.9)	0.0009
CARVDL-25	114	7.5 (1.8)	7.1	(2.3, 12.0)	0.0010
Placebo	117	0.4 (1.6)			

[#] adjusted confidence interval based on Dunnett's one-sided multiple comparison procedure

* two-sided p-value not yet adjusted for multiple comparisons

Table 2. Mean decrease from baseline at study endpoint in Heart rate (bpm) - intent-to-treat Study B100

Treatment Group	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	95% C.I. #	unadjusted p-value*
Sitting HR					
CARVDL-6.25	117	3.4 (0.7)	2.6	(0.4, 4.7)	0.029
CARVDL-12.5	125	6.6 (0.7)	5.8	(3.6, 7.9)	0.0001
CARVDL-25	114	8.2 (0.9)	7.4	(5.2, 9.6)	0.0001
Placebo	117	0.8 (0.7)			
Supine HR					
CARVDL-6.25	117	2.9 (0.8)	2.0	(-0.3, 4.3)	0.11
CARVDL-12.5	125	5.6 (0.7)	4.7	(2.4, 6.9)	0.0001
CARVDL-25	114	7.1 (0.9)	6.2	(3.9, 8.5)	0.0001
Placebo	116	0.9 (0.8)			
Standing HR					
CARVDL-6.25	117	3.4 (0.9)	3.6	(1.2, 6.1)	0.0047
CARVDL-12.5	125	6.8 (0.8)	7.0	(4.5, 9.3)	0.0001
CARVDL-25	114	8.8 (0.7)	9.0	(6.5, 11.4)	0.0001
Placebo	116	-0.2 (0.9)			
Standing HR (3 min)					
CARVDL-6.25	117	3.6 (0.7)	3.7	(1.2, 6.1)	0.0035
CARVDL-12.5	125	6.9 (0.8)	7.0	(4.6, 9.4)	0.0001
CARVDL-25	114	8.8 (0.9)	8.9	(6.4, 11.3)	0.0001
Placebo	117	-0.1 (0.9)			

adjusted confidence interval based on Dunnett's one-sided multiple comparison procedure

* two-sided p-value not yet adjusted for multiple comparisons

Table 3. Mean decrease from baseline in sitting DBP (mm Hg) at study endpoint by subgroup - intent-to-treat
~~Study 8100~~

Treatment Group	Males			Females		
	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO
CARVDL-6.25	84	5.9 (0.8)	2.8	33	4.0 (1.3)	0.4
CARVDL-12.5	79	6.5 (0.9)	3.4	46	8.6 (1.3)	5.0
CARVDL-25	75	8.5 (1.0)	5.4	39	8.6 (1.3)	5.0
Placebo	69	3.1 (1.0)		48	3.6 (1.2)	

Treatment Group	Age ≤ 64 years			Age > 64 years		
	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO
CARVDL-6.25	89	5.5 (0.8)	2.1	28	5.1 (1.3)	2.5
CARVDL-12.5	92	7.8 (0.9)	4.4	33	5.8 (1.5)	3.2
CARVDL-25	84	8.3 (0.9)	4.9	30	9.1 (1.4)	6.5
Placebo	100	3.4 (0.8)		17	2.6 (2.3)	

Treatment Group	Blacks			Non-blacks		
	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO
CARVDL-6.25	19	2.6 (1.9)	-5.2	98	5.9 (0.7)	3.2
CARVDL-12.5	23	8.7 (2.3)	0.9	102	6.9 (0.8)	4.2
CARVDL-25	13	8.3 (2.6)	0.5	101	8.6 (0.8)	5.9
Placebo	15	7.8 (2.1)		102	2.7 (0.8)	

Treatment Group	Mild hypertension [#]			Moderate hypertension [#]		
	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO
CARVDL-6.25	85	4.2 (0.8)	0.8	26	9.7 (0.7)	5.1
CARVDL-12.5	90	6.5 (0.9)	3.1	32	9.9 (0.8)	5.3
CARVDL-25	82	7.7 (0.8)	4.3	29	10.5 (2.1)	5.9
Placebo	84	3.4 (0.9)		27	4.6 (0.9)	

[#] Mild hypertension: baseline sitting DBP 95-105 mm Hg
 Moderate hypertension: baseline sitting DBP 106-115 mm Hg

Table 4. Mean decrease from baseline at endpoint in Secondary blood pressure (mm Hg) - intent-to-treat Study 2101

Treatment Group	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	95% C.I. [#]	unadjusted p-value*
Supine DBP					
CARVDL-6.25	121	3.3 (0.8)	1.0	(-1.4, 3.4)	0.26
CARVDL-12.5	126	4.9 (0.9)	2.6	(0.2, 5.0)	0.011
CARVDL-25	125	5.2 (0.8)	2.9	(0.5, 5.3)	0.005
CARVDL-50	28	5.9 (1.4)	3.6	(-0.4, 7.5)	0.19
Placebo	115	2.3 (0.8)			
Standing DBP					
CARVDL-6.25	121	3.0 (0.9)	0.7	(-1.8, 3.2)	0.46
CARVDL-12.5	126	5.1 (0.9)	2.8	(0.3, 5.2)	0.006
CARVDL-25	126	6.0 (0.8)	3.7	(1.2, 6.2)	0.001
CARVDL-50	28	7.5 (1.8)	5.2	(1.1, 9.2)	0.019
Placebo	115	2.3 (0.8)			
Sitting SBP					
CARVDL-6.25	121	4.8 (1.3)	1.9	(-1.9, 5.7)	0.24
CARVDL-12.5	126	7.1 (1.2)	4.2	(0.4, 8.0)	0.012
CARVDL-25	126	4.7 (1.2)	1.8	(-2.0, 5.6)	0.23
CARVDL-50	28	7.9 (5.0)	5.0	(-1.2, 11.2)	0.16
Placebo	115	2.9 (1.2)			
Supine SBP					
CARVDL-6.25	121	3.6 (1.5)	2.4	(-1.9, 6.6)	0.25
CARVDL-12.5	126	4.9 (1.3)	3.7	(-0.5, 7.9)	0.053
CARVDL-25	126	5.7 (1.4)	4.5	(0.3, 8.7)	0.021
CARVDL-50	28	7.3 (2.5)	6.1	(-0.8, 12.9)	0.32
Placebo	115	1.2 (1.5)			
Standing SBP					
CARVDL-6.25	121	3.6 (1.6)	0.9	(-3.6, 5.3)	0.62
CARVDL-12.5	126	4.8 (1.4)	2.1	(-2.4, 6.4)	0.25
CARVDL-25	125	5.7 (1.4)	3.0	(-1.5, 7.3)	0.14
CARVDL-50	28	6.8 (2.5)	4.1	(-3.1, 11.3)	0.40
Placebo	115	2.7 (1.5)			

[#] adjusted confidence interval based on Dunnett's one-sided multiple comparison procedure

* two-sided p-value not yet adjusted for multiple comparisons

**Table 5. Mean decrease from baseline at endpoint in
Heart rate (bpm) - intent-to-treat
Study B101**

Treatment Group	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	95% C.I.[#]	unadjusted p-value*
Sitting HR					
CARVDL-6.25	121	2.7 (0.7)	0.4	(-2.0, 2.9)	0.77
CARVDL-12.5	126	3.5 (0.8)	1.2	(-1.2, 3.6)	0.26
CARVDL-25	126	5.6 (0.8)	3.3	(1.0, 5.8)	0.002
CARVDL-50	28	4.6 (1.6)	2.3	(-1.6, 6.3)	0.31
Placebo	115	2.3 (0.9)			
Supine HR					
CARVDL-6.25	120	2.1 (0.7)	0.7	(-1.5, 2.9)	0.61
CARVDL-12.5	126	2.6 (0.7)	1.2	(-1.0, 3.4)	0.23
CARVDL-25	126	4.5 (0.7)	3.1	(0.9, 5.3)	0.002
CARVDL-50	28	4.6 (1.6)	3.2	(-0.4, 6.8)	0.079
Placebo	115	1.4 (0.8)			
Standing HR					
CARVDL-6.25	120	3.0 (0.9)	1.4	(-1.2, 4.1)	0.30
CARVDL-12.5	126	2.8 (0.8)	1.2	(-1.4, 3.8)	0.34
CARVDL-25	125	5.3 (0.7)	3.7	(1.1, 6.3)	0.002
CARVDL-50	28	4.9 (1.9)	3.3	(-1.0, 7.6)	0.12
Placebo	115	1.6 (0.9)			

[#] adjusted confidence interval based on Dunnett's one-sided multiple comparison procedure

* two-sided p-value not yet adjusted for multiple comparisons

Table 6. Mean decrease from baseline in sitting DBP (mm Hg) at study endpoint by subgroup - intent-to-treat Study B101

Treatment Group	Males			Females		
	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO
CARVDL-6.25	76	2.9 (0.9)	0.3	45	6.9 (1.2)	1.3
CARVDL-12.5	77	5.6 (1.0)	3.0	47	7.4 (1.0)	1.8
CARVDL-25	81	5.5 (0.8)	2.9	45	6.3 (1.1)	0.7
CARVDL-50	19	8.2 (1.6)	5.6	9	7.6 (2.8)	2.0
Placebo	73	2.6 (0.8)		42	5.6 (1.1)	

Treatment Group	Age ≤ 64 years			Age > 64 years		
	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO
CARVDL-6.25	100	4.4 (0.8)	1.0	21	4.5 (1.7)	-0.3
CARVDL-12.5	100	6.3 (0.8)	2.9	26	6.3 (1.7)	1.5
CARVDL-25	98	6.4 (0.7)	3.0	28	3.8 (1.6)	-1.0
CARVDL-50	24	7.1 (1.4)	3.7	4	13.0 (3.5)	8.2
Placebo	91	3.4 (0.7)		24	4.8 (1.3)	

Treatment Group	Blacks			Non-blacks		
	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO
CARVDL-6.25	19	4.9 (1.9)	3.2	102	4.3 (0.7)	0.2
CARVDL-12.5	17	9.1 (2.3)	7.4	109	5.8 (0.7)	1.7
CARVDL-25	20	3.6 (1.8)	1.9	106	6.2 (0.7)	2.1
CARVDL-50	5	7.4 (2.8)	5.7	23	8.1 (1.5)	4.0
Placebo	18	1.7 (1.7)		97	4.1 (0.7)	

Treatment Group	Mild hypertension [#]			Moderate hypertension [#]		
	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO
CARVDL-6.25	86	4.6 (0.8)	0.9	33	4.0 (1.4)	0.2
CARVDL-12.5	89	5.6 (0.7)	1.9	37	8.0 (1.6)	4.2
CARVDL-25	92	5.2 (0.8)	1.5	32	7.8 (1.2)	4.0
CARVDL-50	20	6.6 (1.4)	2.9	8	11.4 (2.9)	7.6
Placebo	80	3.7 (0.7)		33	3.8 (1.4)	

[#] Mild hypertension: baseline sitting DBP 95-105 mm Hg

Moderate hypertension: baseline sitting DBP 106-115 mm Hg

Table 7. Mean decrease from baseline at endpoint in Secondary blood pressure (mmHg) and Heart rate (bpm) Study C1106 (Intent-to-treat analysis)

Treatment Group	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	95% C.I.	unadjusted p-value
Standing DBP					
CARVDL BID	96	9.9 (0.8)	7.6 ^e	(5.0, 9.2)	0.0001
CARVDL QD	90	7.6 (0.9)	5.3	(2.4, 6.7)	0.0001
Placebo	93	2.3 (0.8)			
Sitting SBP					
CARVDL BID	96	10.9 (1.3)	6.8	(2.4, 9.9)	0.0013
CARVDL QD	90	7.2 (1.3)	3.1	(-0.5, 7.2)	0.084
Placebo	93	4.1 (1.2)			
Standing SBP					
CARVDL BID	96	11.3 (1.3)	8.1 ^e	(3.9, 11.5)	0.0001
CARVDL QD	90	6.5 (1.4)	3.3	(-0.5, 7.3)	0.086
Placebo	93	3.2 (1.3)			
Sitting HR					
CARVDL BID	96	8.1 (0.8)	7.7	(4.6, 10.0)	0.0001
CARVDL QD	90	5.4 (0.9)	5.0	(3.2, 8.7)	0.0001
Placebo	93	0.4 (1.0)			
Standing HR					
CARVDL BID	96	9.0 (0.9)	8.8	(6.2, 12.0)	0.0001
CARVDL QD	90	5.8 (1.0)	5.6	(3.9, 9.9)	0.0001
Placebo	93	0.2 (1.0)			

^e p < 0.03 between QD and BID

Table 8. Mean decrease from baseline in sitting DBP (mm Hg) at study endpoint by subgroup - intent-to-treat Study C1106

Treatment Group	Males			Females		
	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO
CARVDL BID	53	10.3 (1.2)	8.3	43	11.5 (1.1)	6.1
CARVDL QD	58	6.5 (1.0)	4.5	32	10.5 (1.5)	5.1
Placebo	57	2.0 (0.9)		36	5.4 (1.5)	

Treatment Group	Age ≤ 64 years			Age > 64 years		
	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO
CARVDL BID	82	10.8 (0.8)	7.0	14	11.4 (2.6)	11.0
CARVDL QD	76	7.7 (0.9)	3.9	14	9.4 (2.2)	9.0
Placebo	80	3.8 (0.8)		13	0.4 (2.2)	

Treatment Group	Blacks			Non-blacks		
	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO
CARVDL BID	36	11.3 (1.3)	9.0	60	10.6 (1.0)	6.7
CARVDL QD	33	6.5 (1.7)	4.2	57	8.8 (0.8)	4.9
Placebo	35	2.3 (1.2)		58	3.9 (1.0)	

Treatment Group	Mild hypertension [#]			Moderate hypertension [#]		
	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO
CARVDL BID	81	9.9 (0.9)	6.7	15	16.3 (1.7)	12.8
CARVDL QD	75	7.8 (0.9)	4.6	15	8.8 (2.1)	5.3
Placebo	72	3.2 (0.8)		21	3.5 (2.2)	

[#] Mild hypertension: baseline sitting DBP 95-105 mm Hg
 Moderate hypertension: baseline sitting DBP 106-115 mm Hg

Table 9. Mean decrease from baseline at study endpoint in Secondary blood pressure (mmHg) and Heart rate (bpm) Study C1109 (Intent-to-treat analysis)

Treatment Group	N	Mean Decrease (S.E.)	Treatment minus PLACEBO	95% C.I.	unadjusted p-value
Standing DBP					
CARVDL	105	6.4 (0.9)	4.1	(1.5, 6.7)	0.002
ATENOLOL	100	9.9 (0.7)	7.6 ⁺	(5.0, 10.2)	<0.001
Placebo	52	2.3 (1.0)			
Sitting SBP					
CARVDL	105	6.1 (1.3)	1.4	(-2.7, 5.7)	0.47
ATENOLOL	100	11.4 (1.2)	6.7 ⁺	(2.5, 10.9)	<0.001
Placebo	52	4.7 (1.7)			
Standing SBP					
CARVDL	105	7.3 (1.4)	2.7	(-1.7, 7.1)	0.23
ATENOLOL	100	9.6 (1.3)	5.0	(0.7, 9.6)	0.023
Placebo	52	4.6 (1.6)			
Sitting HR					
CARVDL	105	8.4 (0.8)	7.5	(4.9, 10.0)	<0.001
ATENOLOL	100	9.8 (0.7)	8.9	(6.3, 11.5)	<0.001
Placebo	52	0.9 (1.2)			
Standing HR					
CARVDL	105	8.4 (0.8)	7.8	(4.9, 10.4)	<0.001
ATENOLOL	100	10.7 (0.8)	10.1 ⁺	(7.3, 12.8)	<0.001
Placebo	52	0.6 (1.2)			

⁺ p < 0.05 between carvedilol and atenolol, based on modified Bonferroni procedure

Table 10. Mean decrease from baseline in sitting DBP (mm Hg) at study endpoint by subgroup - intent-to-treat Study C1109

Treatment Group	Males			Females		
	N	Mean Decrease (S.E.)	Trtment minus PLACEBO	N	Mean Decrease (S.E.)	Trtment minus PLACEBO
CARVDL	78	7.4 (0.9)	3.9	27	7.6 (1.4)	3.9
ATENOLOL	66	11.2 (0.9)	7.7	34	11.5 (0.9)	7.8
Placebo	36	3.5 (1.0)		16	3.7 (1.8)	

Treatment Group	Blacks			Non-blacks		
	N	Mean Decrease (S.E.)	Trtment minus PLACEBO	N	Mean Decrease (S.E.)	Trtment minus PLACEBO
CARVDL	80	8.1 (0.7)	4.5	25	5.5 (1.9)	2.1
ATENOLOL	76	11.8 (0.7)	8.2	24	9.8 (1.3)	6.4
Placebo	40	3.6 (1.0)		12	3.4 (1.8)	

Treatment Group	Age ≤ 64 years			Age > 64 years		
	N	Mean Decrease (S.E.)	Trtment minus PLACEBO	N	Mean Decrease (S.E.)	Trtment minus PLACEBO
CARVDL	81	7.1 (0.9)	3.7	24	8.8 (1.4)	4.8
ATENOLOL	82	11.3 (0.7)	7.9	18	11.6 (1.8)	7.6
Placebo	41	3.4 (1.1)		11	4.0 (1.5)	

Treatment Group	Mild hypertension [#]			Moderate hypertension [#]		
	N	Mean Decrease (S.E.)	Trtment minus PLACEBO	N	Mean Decrease (S.E.)	Trtment minus PLACEBO
CARVDL	87	6.9 (0.9)	3.5	18	10.1 (1.8)	5.3
ATENOLOL	87	11.3 (0.6)	7.9	13	11.6 (2.5)	6.8
Placebo	48	3.4 (0.9)		4	4.8 (3.3)	

[#] Mild hypertension: baseline sitting DBP 95-105 mm Hg
 Moderate hypertension: baseline sitting DBP 106-115 mm Hg

... mean decrease from baseline at study endpoint 1:
Secondary blood pressure (mmHg) and Heart rate (l
Study C1107 (Intent-to-treat analysis)

Treatment Group	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	95% C.I. [†]	unadjusted p-value
Standing DBP					
CARVDL 6.25	66	4.1 (0.9)	0.9	(-1.7, 3.6)	NS
CARVDL 12.5	65	4.7 (0.9)	1.5	(-1.1, 4.2)	NS
CARVDL 12.5/25	66	5.6 (0.9)	2.4	(-0.2, 5.1)	0.074
Placebo	66	3.2 (1.0)			
Sitting SBP					
CARVDL 6.25	67	3.5 (1.5)	1.5	(-2.9, 5.7)	NS
CARVDL 12.5	65	4.4 (1.6)	2.4	(-2.0, 6.7)	NS
CARVDL 12.5/25	66	4.5 (1.4)	2.5	(-1.9, 6.7)	NS
Placebo	66	2.0 (1.4)			
Standing SBP					
CARVDL 6.25	66	2.4 (1.4)	-0.2	(-4.5, 4.1)	NS
CARVDL 12.5	65	3.4 (1.5)	0.8	(-3.6, 5.0)	NS
CARVDL 12.5/25	66	4.0 (1.5)	1.4	(-2.9, 5.7)	NS
Placebo	66	2.6 (1.5)			
Sitting HR					
CARVDL 6.25	67	4.7 (1.1)	5.0	(2.2, 7.8)	<0.001
CARVDL 12.5	65	3.3 (1.0)	3.6	(0.8, 6.3)	<0.02
CARVDL 12.5/25	66	6.3 (1.1)	6.6	(3.8, 9.3)	<0.001
Placebo	66	-0.3 (0.9)			
Standing HR					
CARVDL 6.25	66	3.8 (1.1)	3.0	(-0.0, 5.9)	0.024
CARVDL 12.5	65	3.4 (1.1)	2.6	(-0.4, 5.6)	0.048
CARVDL 12.5/25	66	7.0 (1.1)	6.2	(3.3, 9.2)	<0.0001
Placebo	66	0.8 (0.7)			

[†] adjusted based on Dunnett's one-sided procedure

Table 12. Mean decrease from baseline in sitting DBP (mm Hg) at study endpoint by subgroup - intent-to-treat Study C1107

Treatment Group	Males			Females		
	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO
CARVDL-6.25	43	4.3 (1.2)	2.1	24	5.4 (1.6)	0.3
CARVDL-12.5	42	3.8 (1.2)	1.6	23	6.7 (1.6)	1.6
CARV-12.5/25	44	5.3 (1.0)	3.1	22	8.5 (1.5)	3.4
Placebo	42	2.2 (1.0)		24	5.1 (1.2)	

Treatment Group	Age ≤ 64 years			Age > 64 years		
	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO
CARVDL-6.25	58	4.2 (1.0)	0.7	9	7.7 (2.4)	5.0
CARVDL-12.5	50	4.8 (1.1)	1.3	15	5.2 (1.9)	2.5
CARV-12.5/25	58	6.1 (0.9)	2.6	8	8.3 (2.0)	5.6
Placebo	51	3.5 (0.9)		15	2.7 (1.7)	

Treatment Group	Blacks			Non-blacks		
	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO
CARVDL-6.25	22	3.8 (2.1)	0.2	45	5.1 (1.0)	2.0
CARVDL-12.5	25	4.1 (1.8)	0.5	40	5.3 (1.2)	2.2
CARV-12.5/25	21	6.1 (1.8)	2.5	45	6.4 (0.9)	3.3
Placebo	21	3.6 (1.5)		45	3.1 (1.0)	

Treatment Group	Mild hypertension [#]			Moderate hypertension [#]		
	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO	N	Mean Decrease (S.E.)	CARVDL minus PLACEBO
CARVDL-6.25	59	4.6 (1.1)	1.7	8	5.3 (2.4)	-1.0
CARVDL-12.5	62	4.7 (1.0)	1.8	3	8.0 (1.5)	1.7
CARV-12.5/25	58	6.1 (0.9)	3.2	8	8.5 (2.8)	2.2
Placebo	58	2.9 (0.9)		8	6.3 (1.6)	

[#] Mild hypertension: baseline sitting DBP 95-105 mm Hg
 Moderate hypertension: baseline sitting DBP 106-115 mm Hg

Duplicate

Z.M.C.L.N.A

Statistical Review and Evaluation

NDA #: 20-297

Date:

Applicant: SmithKline Beecham Pharmaceuticals

Name of Drug: Kredex (Carvedilol - SKF 105517)

Documents Reviewed:

1. NDA Submission, Volumes 1.34 - 1.37, "Chronic Oral Carcinogenicity Test of BM 14.190 2-Year Experiment in Rats" SK&F Report No. TC001BS, BM Report No. J2, May 1986.
2. NDA Submission, Volumes 1.29 - 1.32, "Chronic Oral Carcinogenicity Study of BM 14.190 Life-Time Application To Mice", SK&F Report No. TC002BS, BM Report No. J4, June 1987.
3. NDA special submission, Data Diskettes and Hardcopy of the Animal Data, Date of Document, April 30, 1993, and May 24, 1993.

I. Background

Two animal carcinogenicity studies (one in rats and one in mice) were included in this NDA submission. The purpose of these two-year studies was to examine whether the oral application of BM 14.190, a vasodilating beta-blocker, to rats and mice has a tumorigenic or carcinogenic effect. Ms. Estela Barry, HFD-110, who is the reviewing pharmacologist of this NDA has requested the Division of Biometrics to perform the statistical review and evaluation of these two studies. The data submitted on computer floppy diskettes were used in the reviewer's independent analyses.

II. The Rat Study

II. a. Design

In this study, 250 male and 250 female white Sprague-Dawley rats of the Cav-Ico-Wiga strain were randomly and equally distributed to four treated and one control groups. A second control group was taken from a parallel study of another drug (BM 41.332) that ran at the same time as this experiment. Carvedilol was administered to rats at the following feed concentrations: 200, 400, 800, and 1600 ppm for two years. Since relative food consumption declined with age and with weight increase, drug dosage declined during the experimental period. The decline in dosage in males was greater than that in females. The group median drug intakes were listed in Table 1. The drug was administered in the period from June 1, 1983 to June 10, 1985 inclusively. Final killings began in May 1985. Initially food consumption was measured for 2 consecutive days at 2 week intervals but from August 2, 1984 on, it was determined once a month. Body

weight was measured weekly. All rats were observed twice daily for mortality and moribundity. At the end of the study, 10 males and 10 females in good health were killed and the blood was submitted to hematological and clinical chemical investigations. After one year the animals were examined at 4-weekly intervals for palpable and suspected tumors. Living animals were anesthetized with pentobarbital and then bled. Animals that died spontaneously were autopsied immediately after they were found. The animals and organs were studied macroscopically as well as microscopically.

II. b. Sponsor's Analyses

Survival data were analyzed by the National Cancer Institute life table analysis (Thomas, Breslow and Gart, "Trend and Homogeneity Analyses of Proportions and Life Table Data", Computers and Biomedical Research, 10, 373-381, 1977) and CARTEST ("A Program for Simple, Sensitive Significance Tests for Carcinogenic Effects in Long-term Animal Experiments", International Agency for Research on Cancer, Lyon, 1981). These packages used the following three methods: Kaplan-Meier product limit estimates of survival data, Cox-Tarone logistic tests and Gehan-Breslow generalized Kruskal-Wallis tests on life table data. Results of the statistical analyses showed that there was a significant negative linear trend in survival time in male rats ($p = 0.01$ for non-time-adjusted evaluation and $p = 0.003$ for time-adjusted evaluation). The female rats in all dose groups lived equally long. For the heterogeneity test, no significant difference in survival distribution was detected in males ($p = 0.18$ for non-time-adjusted and $p = 0.07$ for time-adjusted evaluation). No trend with dose can be seen in the females. The Kaplan-Meier estimates of survival data are presented in Figures 1 and 2 for males and females, respectively. When deaths caused by tumors are excluded, the results show that the males have a higher mortality with increase in dose. This trend is very marked with $p = 0.0006$. For the females no trend with dose is detectable.

The methods described in Peto et al. ("Guidelines for Simple, Sensitive Significance Tests for Carcinogenic Effects in Long-Term Animal Experiments", In Long-Term and Short-Term Screening Assays for Carcinogens: A Critical Appraisal, International Agency for Research on Cancer Monographs, Annex to Supplement 2, World Health Organization, 311-426, 1980) were used to test the linear trend in the tumor data. For small tumor incidence cases, the number of tumor-bearers in the highest dose group was compared with tumor-bearers in the control group by means of the Fisher-Exact test for chance occurrence. The sponsor summarized tumor frequencies in Tables 2 and 3 for males and females, respectively. Based on the results in Tables 2 and 3, the sponsor indicated that "on the basis of the ratio of observed tumor events/expected tumor events, one can see that there is a negative trend with dose for the male animals. For females the groups do not show any trend behavior with dosage." Table 4 lists the total numbers of all tumor-bearers and those with malignant tumors. Table 5 lists numbers of animals with tumors on

the organs with the highest frequencies. No statistical analyses were performed on these tumor data.

Based on the above summaries, the sponsor concluded that "the administration of BM 14.190 at feed concentrations of 200 ppm, 400 ppm, 800 ppm and 1600 ppm over a period of 2 year to growing Sprague-Dawley rats did not provide any indication of tumorigenic or carcinogenic action of the substance."

II.c. Reviewer's Analyses and Comments

The sponsor indicated that there are 50 animals/sex/group in the study, however, the sponsor's submitted diskettes has 51 animals recorded in female low dose group. The reviewer found a mis-coding in animal number 1318, it should be coded as animal number 318. The following analyses are based on 50 animals/sex/group. In addition, the sponsor indicated that a second control group was taken from a parallel study of another drug (BM 41.332) that ran at the same time as this experiment. However, these data were not included in sponsor's submitted diskettes and hence were not included in the following analyses.

The Cox test and the generalized Wilcoxon test described in the paper of Thomas, Breslow, and Gart (1977) were used to test for heterogeneity in survival distribution. The p-values of the Cox test were 0.1095 and 0.8928 for males and females, respectively. Hence, No significant difference in the survival distribution was detected in both sexes. A similar conclusion was obtained in the generalized Wilcoxon test. The p-values of the test were 0.1044 and 0.7704 for males and females, respectively.

The intercurrent mortality rates for both male and female rats (see Table 6) were tested for linear trend according to the death rate method described in the paper of Peto et al. (1980) using the time intervals 0-50, 51-80, and 81-105 weeks. The actual dose levels 0, 200, 400, 800, and 1600 ppm were the scores assigned to the control, low, medium, high-1, and high-2 dose groups, respectively. The results of the analyses showed that there was no significant (at 0.05 level) linear trend in the intercurrent mortality rate in female rats ($p = 0.1625$). However, there was a significant (at 0.05 level) linear trend in the intercurrent mortality rate in male rats ($p = 0.0017$).

The methods described in Peto et al. (1980) and the methods of age-adjusted exact permutation trend test were used to test the linear trend in the tumor data. The results of the above analyses showed that there were significant (at 0.05 level) positive linear trends in stomach papilloma ($p = 0.0494$) and skin subcutis sebaceous adenoma ($p = 0.0414$) in male rats. There were marginally statistically significant linear trends in thyroid gland adenoma ($p = 0.0504$) and brain oligodendroglioma ($p = 0.0852$) in female rats and in liver hepatocellular adenoma ($p = 0.0579$) in male rats. The incidence

rates of stomach papilloma, skin subcutis sebaceous adenoma, and liver hepatocellular adenoma in male rats and thyroid gland adenoma and brain oligodendroglioma in female rats are given in Tables 7 to 11.

Ms. Barry raised the question "Were the doses of Carvedilol proposed in the study protocol significantly affected by food intake, age, or weight of the animals?" Since the concentration of the drug in the feed was kept constant throughout the entire study period, there is a reduction in dose concentration ppm/kg/day as the age of the animals increases. Tables 12 to 13 show the median body weights of male and female rats, respectively, grouped by time intervals. Tables 14 to 15 listed the food consumptions of male and female rats, respectively. Apparently, food consumption did not increase with the increase in body weight. There was a decline in relative food consumption over the course of the study. As a result, there is a decline in drug intake over the course of the study. This is consistent with the findings of the reviewing pharmacologist, Dr. Martin Winbury, a FDA consultant on this NDA.

The reviewer also evaluated the validity of the experiment. The following two issues are important in determining the validity of an experiment: (1) The numbers of animals alive over the course of the study to get an adequate exposure to the chemical and to be at risk of forming late-developing tumors. (2) If the doses are high enough to present a reasonable tumor challenge to the animals.

With regard to the first issue, the following criteria or rules of thumb have been proposed by some experts in the field:

(A) Haseman proposes (through personal communication with Dr. Karl Lin) that a 50% survival rate of the 50 initial animals in the high dose group between weeks 80-90 will be considered as a sufficient number and an adequate exposure. However, the percentage can be lower or higher if the number of animals used in each treatment/sex is larger or smaller than 50 as long as there will be between 20 to 30 animals still alive during these weeks.

(B) Chu, Ceuto, and Ward ("Factors in the Evaluation of 200 National Cancer Institute Carcinogen Bioassays", Journal of Toxicology and Environmental Health, 8, 1981, pp. 251-280) propose that an experiment that has not shown a chemical to be carcinogenic should have (high dose) groups of animals with greater than 50% survival at one year (52 weeks).

In this study, the survival rates of the 1600 ppm dose group at one-year were 96% and 100% for males and females, respectively. These one-year survival rates satisfied the criterion of Chu et al. (1981). The survival rates of the control, 200, 400, 800, and 1600 ppm dose groups at the terminal sacrifice were 36%, 30%, 34%, 22%, and 16%, respectively, for males, and 46%, 46%, 44%, 48%, and 58%, respectively, for females. There were not sufficient male rats in

the control and treated groups living long enough to get an adequate exposure to the chemical and to be at risk of forming late-developing tumors based on Haseman's proposition.

With regard to the second issue, in the paper of Chu, Ceuto and Ward (1981), the following criteria for dose adequacy are mentioned.

(A) "A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls."

(B) "The administered dose is also considered an MTD (Maximum Tolerated Dose) if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."

(C) "In addition, doses are considered adequate if the dosed animals show a slightly increased mortality compared to the controls."

Figures 3-6 are the median body weight curves of control and treated groups of male and female rats. In Tables 12-13, median body weights of the male and female rats grouped by time intervals are given. All male treated rats gained more body weight than their counterparts in the control groups. Different from the male rats, the female high dose groups gained less body weight than the female control group did. The weight gains in the female low and median dose groups are greater than that of the female control group. The high dose is close to MTD for female rats but not for male rats using the above mentioned criteria. However, it is important to check the clinical and toxic signs of the animals in the male high dose group in the final determination of the adequacy of the high dose for male rats.

III. The Mouse Study

III. a. Design

In this study, 250 male and 250 female Charles River (SPF-NMRI-HAN-WIGA strain) mice were randomly assigned into three treated groups and one control groups. The control group was made up of 100 animals of each sex and the dosed groups were made up of 50 animals of each sex. Carvedilol (BM 14.190) was administered in food with concentration adjusted at 1-4 week intervals to maintain constant doses of 20, 65, and 200 mg/kg/day. The substance was applied in the period from July 17, 1984 to May 21, 1986 (97th week) for the female animals and to September 16, 1986 (114th week) for the male animals. Feed consumption was determined on 2 consecutive days at weekly intervals and the average value for 1 day was recorded. Starting on September 11, 1984, food intake was ascertained at 4-week intervals. Body weight was determined once a week. All animals were checked twice daily for morbidity and mortality. After a running time of 1 year, the animals were examined at 4-week intervals for palpable and presumed tumors. At the end of the study during the terminal sacrifice, 10 males and 10 females in good health were killed and

blood submitted to hematological and clinical chemical investigations. Living animals were anesthetized with pentobarbital and then bled. Animals that died spontaneously were autopsied immediately after they were found. The animals and organs were studied macroscopically as well as microscopically.

III. b. Sponsor's Analyses

Survival data were analyzed by the National Cancer Institute life table analysis (Thomas, Breslow and Gart, 1977) and CARTEST (1981). The results showed there was no difference in overall mortality among the groups for both sexes. The probabilities of survival for animals which died of tumors were approximately constant with dose for both sexes. The Kaplan-Meier estimates of survival data are presented in Figures 7 and 8 for males and females, respectively.

The procedure of Peto et al. was used to test any dose-dependent trend in the number of tumor carriers. The sponsor summarized tumor frequencies for each group/sex and listed them in Tables 16 and 17 for males and females, respectively. The total numbers of animals with tumors and malignant tumors are listed in Table 18. The sponsor indicated that "the total number of tumors remained approximately the same with dose in the two sexes. Nor did adjusted analysis show any differences in the rate of occurrence of tumors as a function of dosage." Table 19 listed the organs which have higher tumor incidence rates. However, no statistical analyses were performed on these tumor data.

Based on the above analyses, the sponsor stated that "life-long application of BM 14.190 to NMRI mice in the doses of 20, 65, and 200 mg/kg/day revealed no tumorigenic or carcinogenic effect."

III.c. Reviewer's analyses and Comments

The Cox test and the generalized Wilcoxon test described in the paper of Thomas et al. (1977) were used to test for heterogeneity in survival distribution. The p-values of the Cox test were 0.2841 and 0.6980 for males and females, respectively. Hence, no statistically significant difference (at 0.05 level) in the survival distribution was detected in both sexes. A similar conclusion was obtained in the generalized Wilcoxon test. The p-values were 0.4450 and 0.5736 for males and females, respectively.

The intercurrent mortality rates for both male and female mice (see Table 20) were tested for linear trend according to the death rate method described in the paper of Peto et al. (1980) using the time intervals 0-50, 51-80, and 81-97 weeks for female mice and 0-50, 51-80, and 81-113 weeks for male mice. The actual dose levels 0, 20, 65, and 200 mg/kg/day were the scores assigned to the control, low, medium, and high dose groups, respectively. The results of the analyses showed that there was no significant (at 0.05 level) linear trend in the intercurrent mortality rate in male ($p = 0.1819$) and

female mice ($p = 0.3866$).

The methods described in Peto et al. (1980) and the methods of age-adjusted exact permutation trend test were used to test the linear trend in the tumor data. The results of the above analyses showed that there was no statistically significant (at 0.05 level) linear trend in the tumor incidence rates of the tumor types tested in both sexes. However, there was a marginally significant positive linear trend in harder's gland carcinoma ($p = 0.0523$) and harder's gland carcinoma and adenoma combined ($p = 0.0663$) in female mice. The incidence rates of harder's gland carcinoma in female mice are 0/100, 0/50, 0/50, and 2/50. The incidence rates of harder's gland carcinoma and adenoma combined in female mice are 9/100, 3/50, 4/50, and 8/50. Although there was no significant linear trend in harder's gland carcinoma ($p = 0.1072$) in male mice, the incidence rates of harder's gland carcinoma in male mice are higher in the treated groups than in the control group (0/100, 0/50, 2/50, and 1/50).

Similar to the rat study, the validity of this mouse experiment has been evaluated. In this study, the survival rates of the high dose mice at one-year were 98% and 92% for males and females, respectively. These one-year survival rates satisfied the criterion of Chu et al. (1981). The survival rates of the control, low, medium, and high dose mice at the terminal sacrifice were 42%, 62%, 44%, and 44%, respectively, for males, and 27%, 20%, 22%, and 20%, respectively, for females. There were not sufficient female mice in the control and treated groups living long enough to get an adequate exposure to the chemical and to be at risk of forming late-developing tumors basing on Haseman's proposition.

Figures 9-10 contain the median body weight curves of control and treated groups of male and female mice, respectively. In Tables 21-22, the median body weights of the male and female mice grouped by time intervals are given. All treated male mice gained less body weight than their counterparts in the control group. Different from the male mice, the female low and medium dose groups had the same body weight gains as the female control group. The female high dose group gained less body weight than the female control group did. The body weight gain data suggest that the high dose is over MTD for both male and female mice using the above mentioned criteria. However, it is important to check the clinical and toxic signs of the animals in the female high dose group in the final determination of the adequacy of the high dose for female mice.

IV. Summary

IV. a. The Rat Study

The oncogenic potential of carvedilol was evaluated in this rat study when administered to rats at the following feed concentrations: 0, 200, 400, 800, and 1600 ppm for two years. A second control group was taken from a parallel study of another drug (BM 41.332) that ran

at the same time as this experiment.

The Cox and the generalized Wilcoxon methods were used to test the heterogeneity in survival distribution. The test results revealed that there was no significant difference in the survival distribution in both sexes.

The statistical methods given in the paper of Peto et al. (1980) and an exact permutation trend test were used to test the positive linear trend in intercurrent mortality and incidental tumor rates. The results of the analyses showed that there was no significant (at 0.05 level) linear trend in the intercurrent mortality rate in female rats ($p = 0.1625$). However, there was a significant (at 0.05 level) linear trend in the intercurrent mortality rate in male rats ($p = 0.0017$). Results of tumor data analyses showed that there was a significant (at 0.05 level) positive linear trend in stomach papilloma ($p = 0.0494$) and skin subcutis sebaceous adenoma ($p = 0.0414$) in male rats. There were marginally statistically significant linear trends in thyroid gland adenoma ($p = 0.0504$) and brain oligodendroglioma ($p = 0.0852$) in female rats and in liver hepatocellular adenoma ($p = 0.0579$) in male rats.

With regard to the questions raised by Ms. Barry: "if the doses of Carvedilol proposed in the study protocol were significantly affected by food intake, age, or weight of the animals?" Since the concentration of the drug in the feed was kept constant throughout the entire study period, there is a reduction in dose concentration as the age of the animals increases. This is consistent with the findings of the reviewing pharmacologist, Dr. Martin Winbury, a FDA consultant on this NDA.

The validity of the experiment has been evaluated. As mentioned previously, the numbers of animals alive over the course of the study and the adequacy of dose levels are the two important factors considered in the evaluation.

In this study, the survival rates of the 1600 ppm dose group at one-year were 96% and 100% for males and females, respectively. These one-year survival rates satisfied the criterion of Chu et al. (1981). The survival rates of the control, 200, 400, 800, and 1600 ppm dose groups at the terminal sacrifice were 36%, 30%, 34%, 22%, and 16%, respectively, for males, and 46%, 46%, 44%, 48%, and 58%, respectively, for females. There were not sufficient male rats in the control and treated groups living long enough to get an adequate exposure to the chemical and to be at risk of forming late-developing tumors based on Haseman's proposition.

The weight gain data show that the high dose is close to MTD for female rats but not for male rats. However, it is important to check the clinical and toxic signs of the animals in the male high dose group in the final determination of the adequacy of the high dose for male rats.

IV. b. The Mouse study

The oncogenic potential of carvedilol was evaluated in this mouse study when administered in food with concentration adjusted at 1-4 week intervals to maintain a constant dose of 20, 65, and 200 mg/kg/day for 97 weeks for the females and 114 weeks for the males. One control group was made up of 100 animals of each sex and the dosed groups were made up of 50 animals of each sex.

The Cox and the generalized Wilcoxon methods were used to test the heterogeneity in survival distribution. No statistically significant difference (at 0.05 level) in the survival distribution was detected in both sexes in both tests.

The statistical methods given in the paper of Peto et al. (1980) and an exact permutation trend test were used to test the positive linear trend in intercurrent mortality and incidental tumor rates. Applying the above methods to the data on sponsor's computer diskettes, the results of the analyses showed that there was no significant (at 0.05 level) linear trend in the intercurrent mortality rate in male ($p = 0.1819$) and female mice ($p = 0.3866$).

Results of tumor data analyses showed that there was no statistically significant (at 0.05 level) linear trend in the tumor incidence rates of tumor types tested in both sexes. However, there was a marginally significant positive linear trend in harder's gland carcinoma ($p = 0.0523$) and harder's gland carcinoma and adenoma combined ($p = 0.0663$) in female mice. The incidence rates of harder's gland carcinoma in female mice are 0/100, 0/50, 0/50, and 2/50. The incidence rates of harder's gland carcinoma and adenoma combined in female mice are 9/100, 3/50, 4/50, and 8/50. Although there was no significant linear trend in harder's gland carcinoma ($p = 0.1072$) in male mice, the incidence rates of harder's gland carcinoma in male mice are higher in the treated groups than in the control group (0/100, 0/50, 2/50, and 1/50).

However, before drawing the final conclusion that the chemical is not carcinogenic, the validity of the experiment has been evaluated. The survival rates of the high dose mice at one-year were 98% and 92% for males and females, respectively. These one-year survival rates satisfied the criterion of Chu et al. (1981). The survival rates of the control, low, medium, and high dose mice at the terminal sacrifice were 42%, 62%, 44%, and 44%, respectively, for males, and 27%, 20%, 22%, and 20%, respectively, for females. It seems that there were not sufficient female mice in the control and treated groups living long enough to get an adequate exposure to the chemical and to be at risk of forming late-developing tumors basing on Haseman's proposition.

The weight gain data show that the high dose is over MTD for both male and female mice. However, it is important to check the clinical and toxic signs of the animals in the female high dose group in

the final determination of the adequacy of the high dose for female mice.

Daphne Lin

Daphne Lin, Ph.D.
Mathematical Statistician

Concur:

Karl K. Lin 6/30/93
Karl K. Lin, Ph.D., Group Leader, SARB

cc: Original NDA 20-297
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HFD-715/Dr. Karl Lin
HFD-715/Dr. Daphne Lin
HFD-715/Chron (SARB)
HFD-502/Assistant Director (Pharmacology)
HFD-715/DRU 2.1.1, Carvedilol, SmithKline Beecham

Figure 1

Fig. 7a. PROPORTION SURVIVING - MALE
(Kaplan Meier)

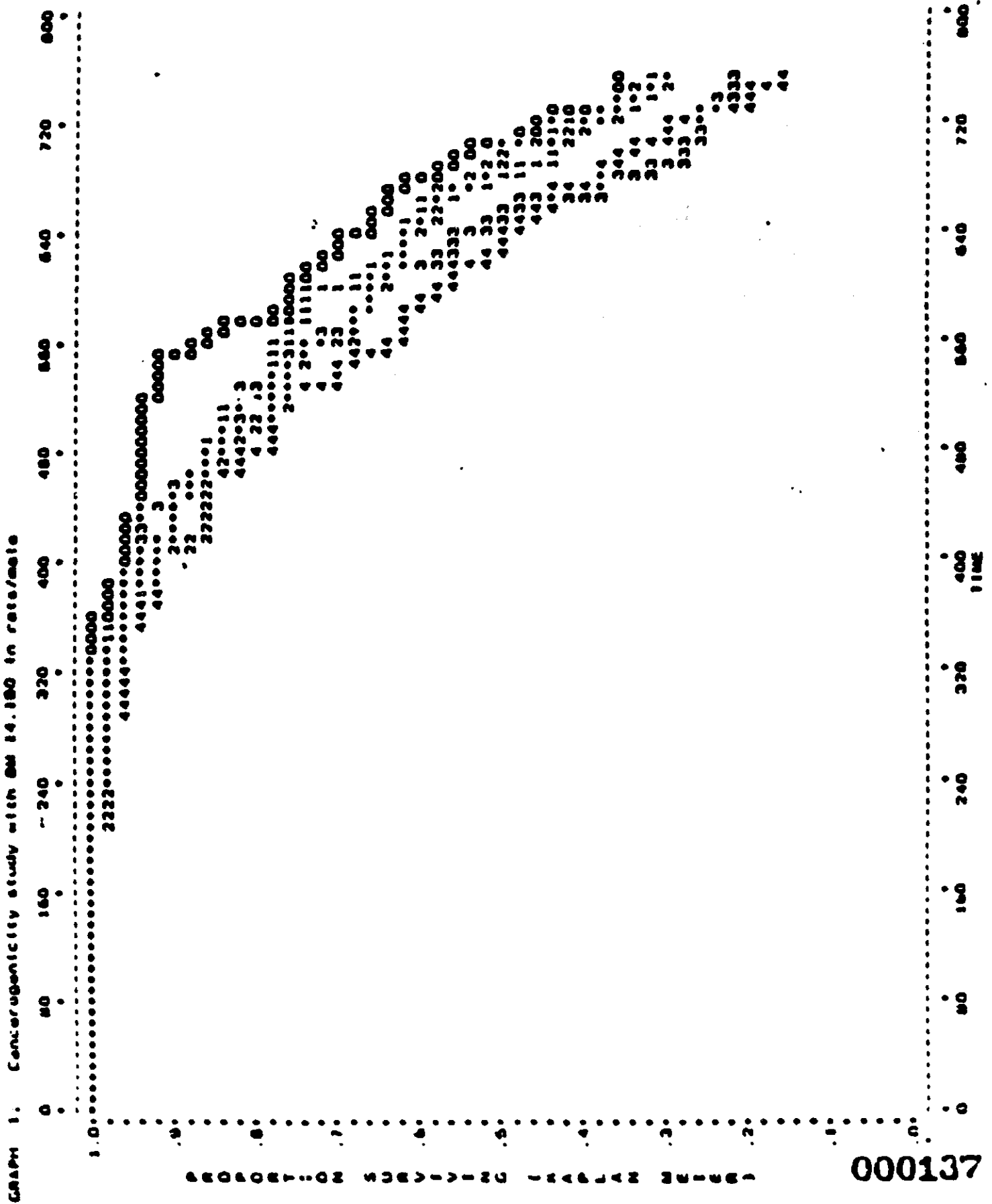


Figure 2

Fig. 8a. PROPORTION SURVIVING - FEMALE (Kaplan Meier)

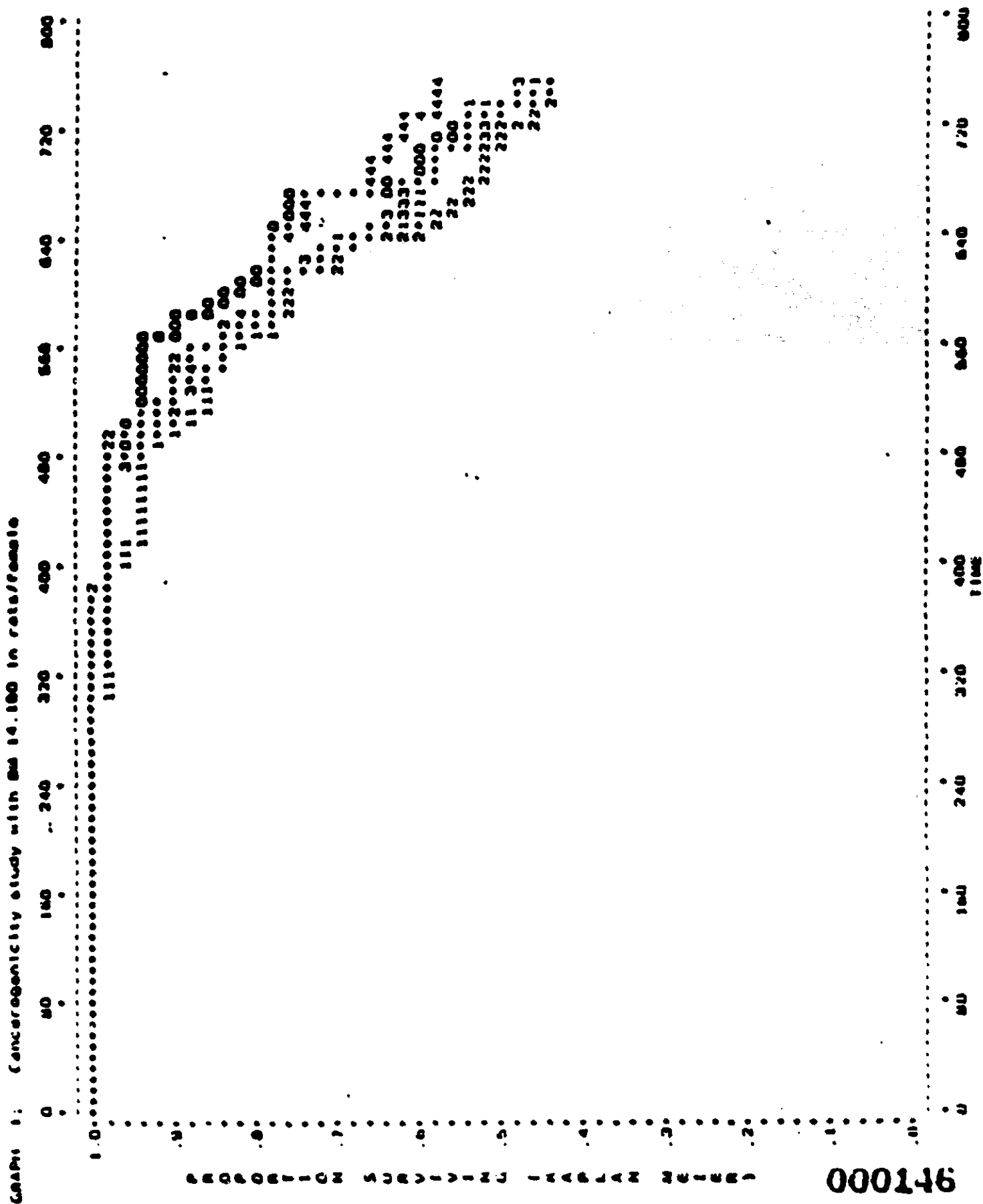


Figure 3



Fig. 1a CARCINOGENICITY STUDY WITH BM 14.190 IN RATS
Body weight of male rats (median) for low
dose groups

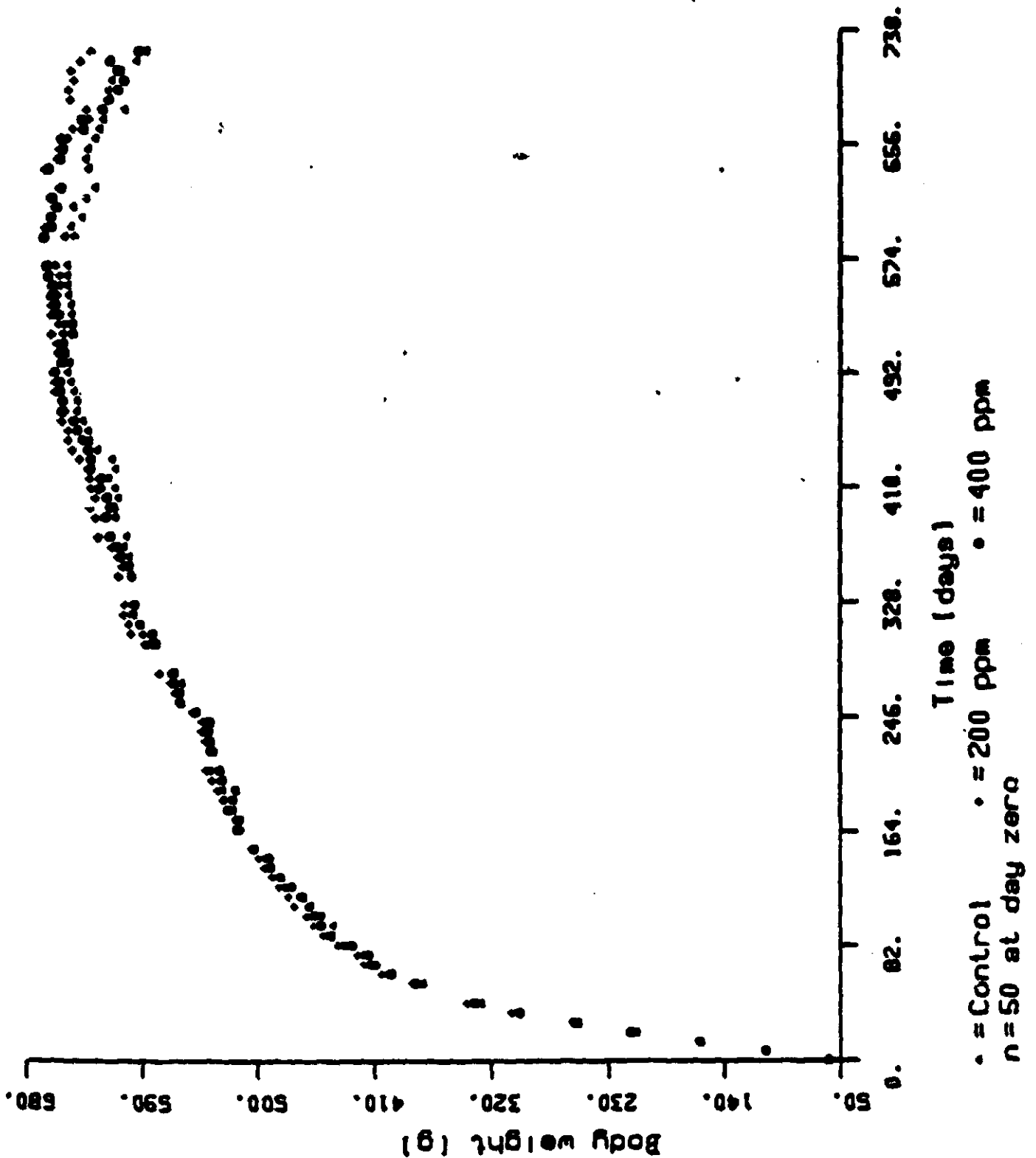
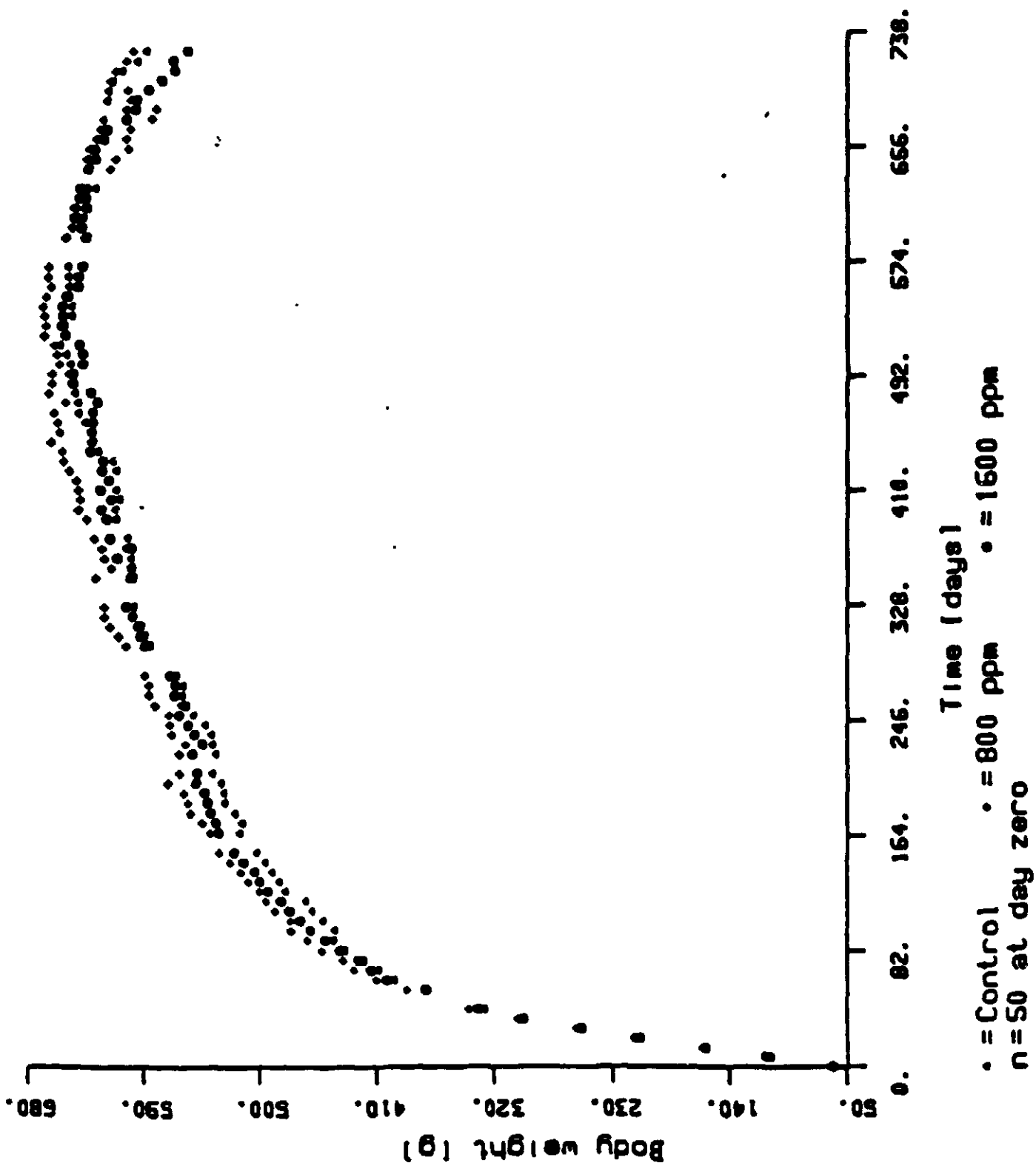




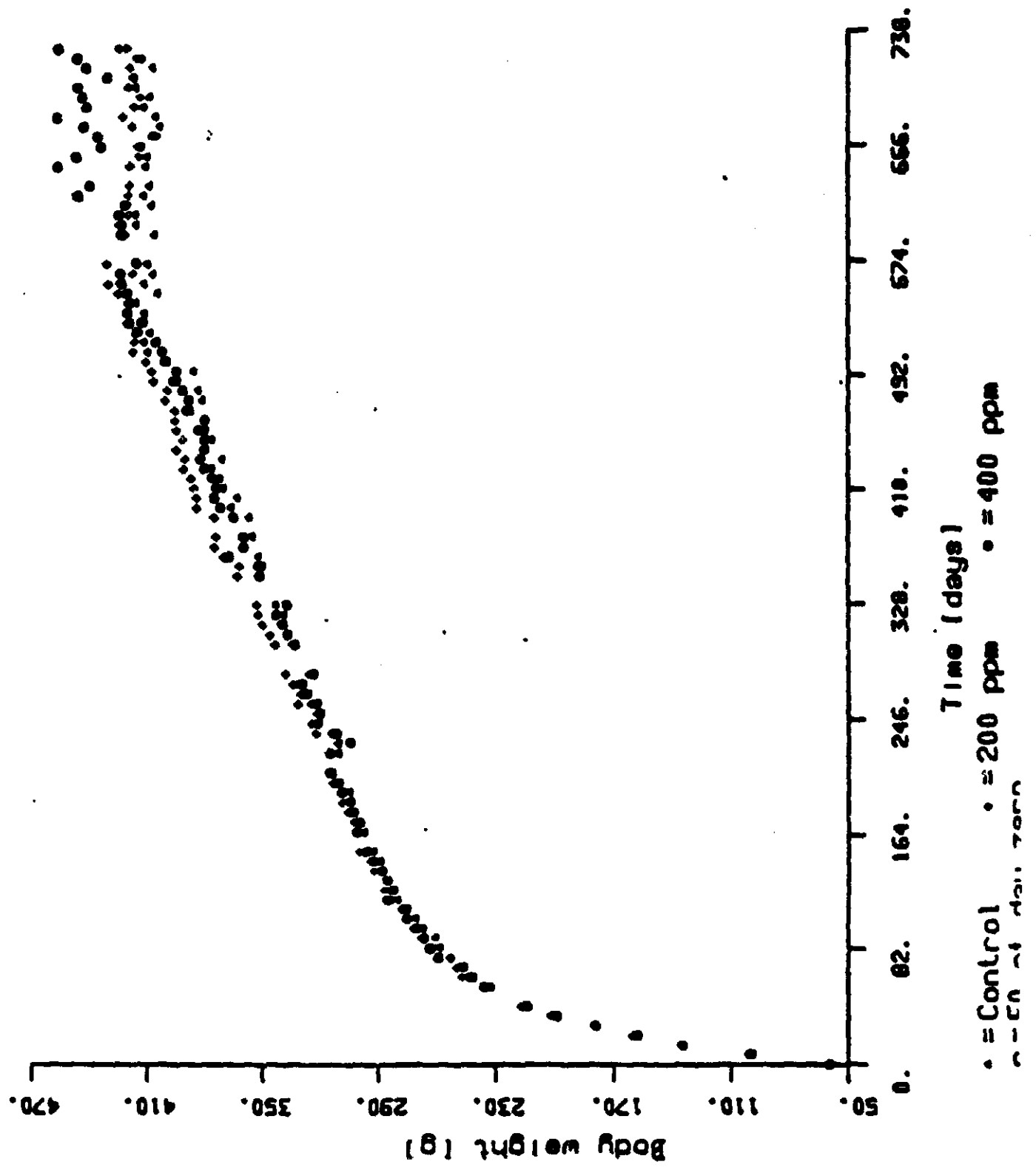
Fig.1b CARCINOGENICITY STUDY WITH BM 14.190 IN RATS
Body weight of male rats (median) for high
dose groups



100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400 420 440 460 480 500 520 540 560 580 600 620 640 660 680 700 720 740 760 780 800 820 840 860 880 900 920 940 960 980 1000

000119

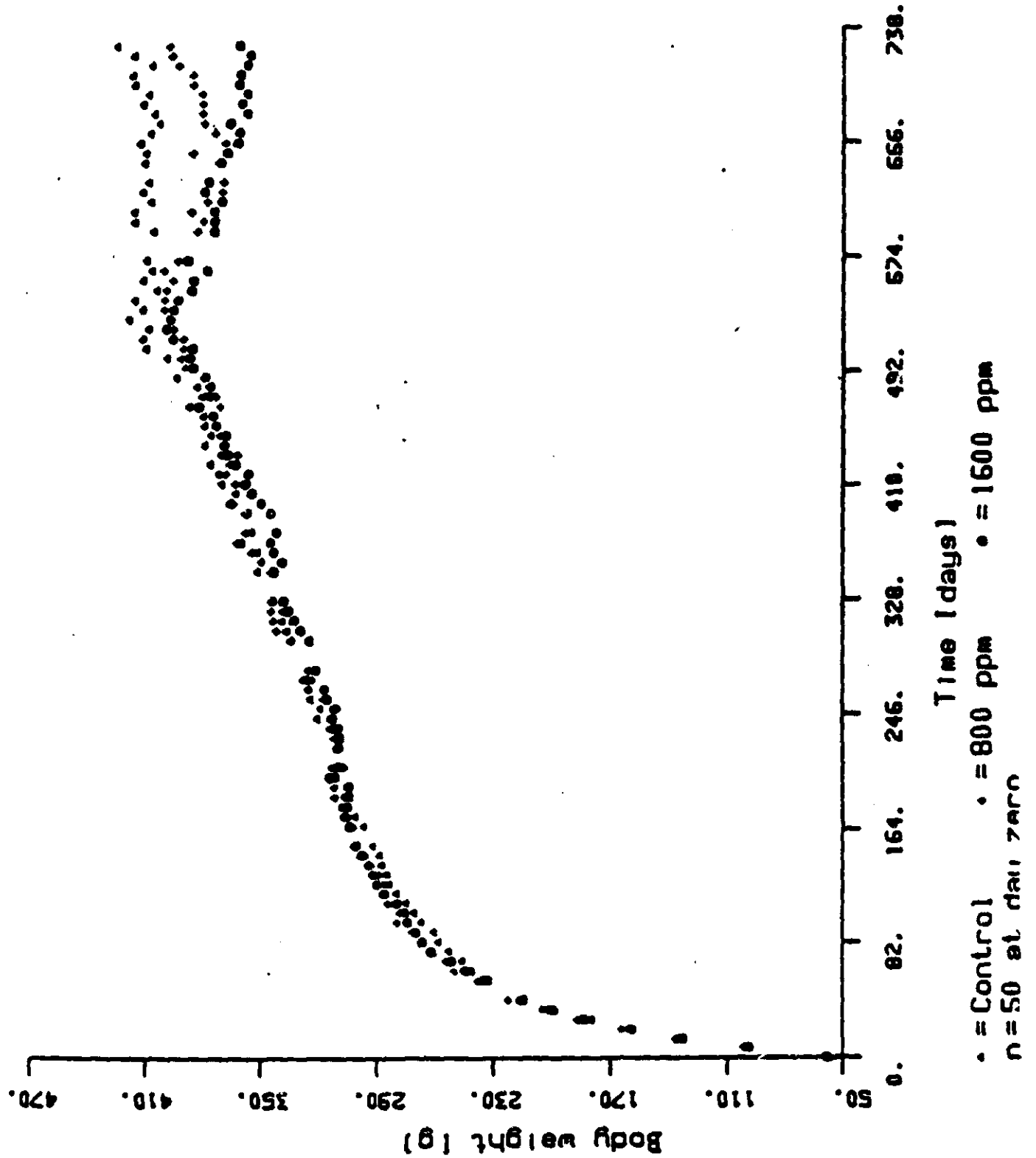
Fig.2a CARCINOGENICITY STUDY WITH BM 14.190 IN RATS
Body weight of female rats (median) for low
dose groups



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000120

Fig. 2b CARCINOGENICITY STUDY WITH BM 14.190 IN RATS
Body weight of female rats (median) for high dose groups



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Fig. 4a. PROPORTION SURVIVING - MALE (Kaplan Meier)

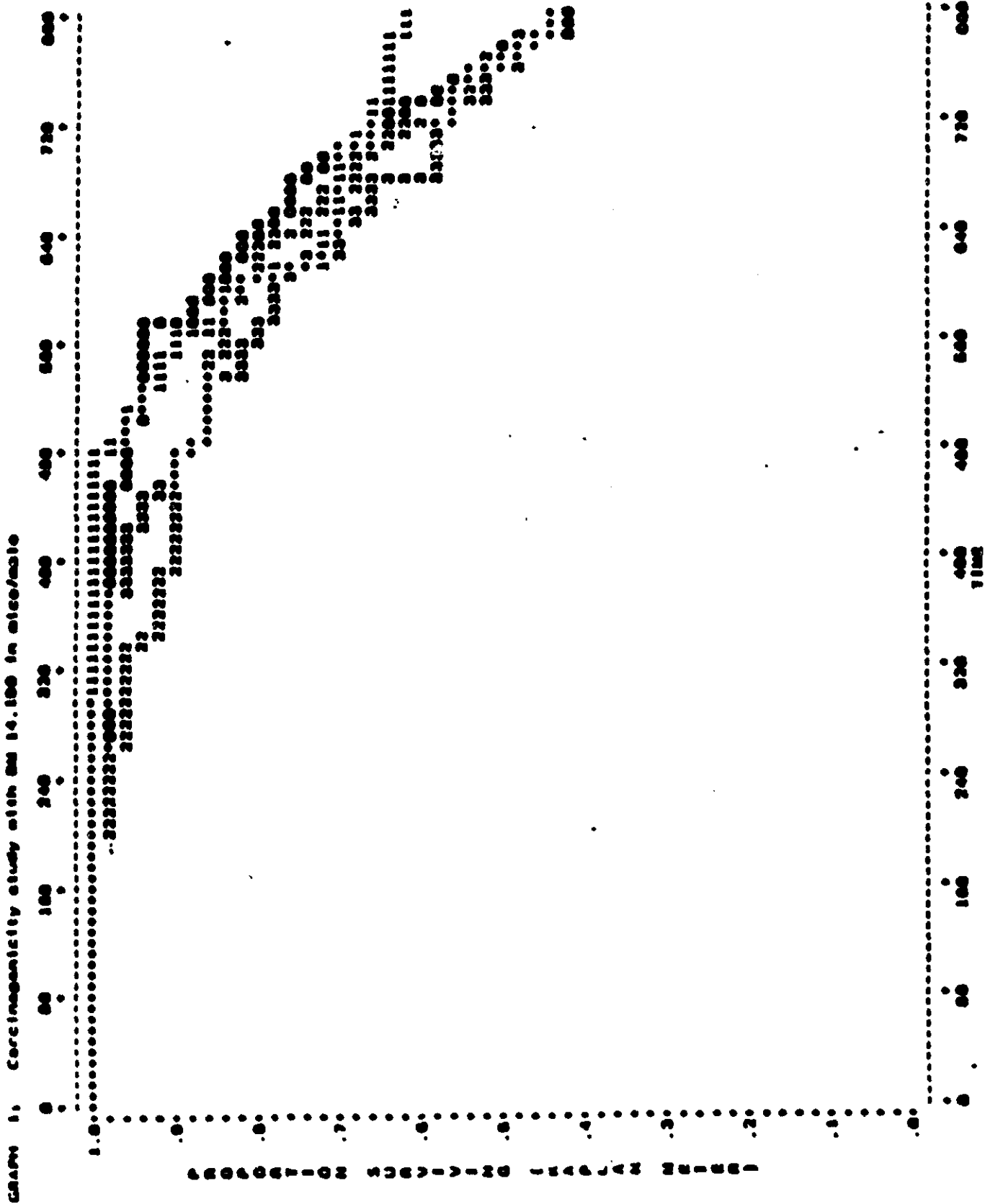


Fig. 5a. PROPORTION SURVIVING - FEMALE (Kaplan Meier)

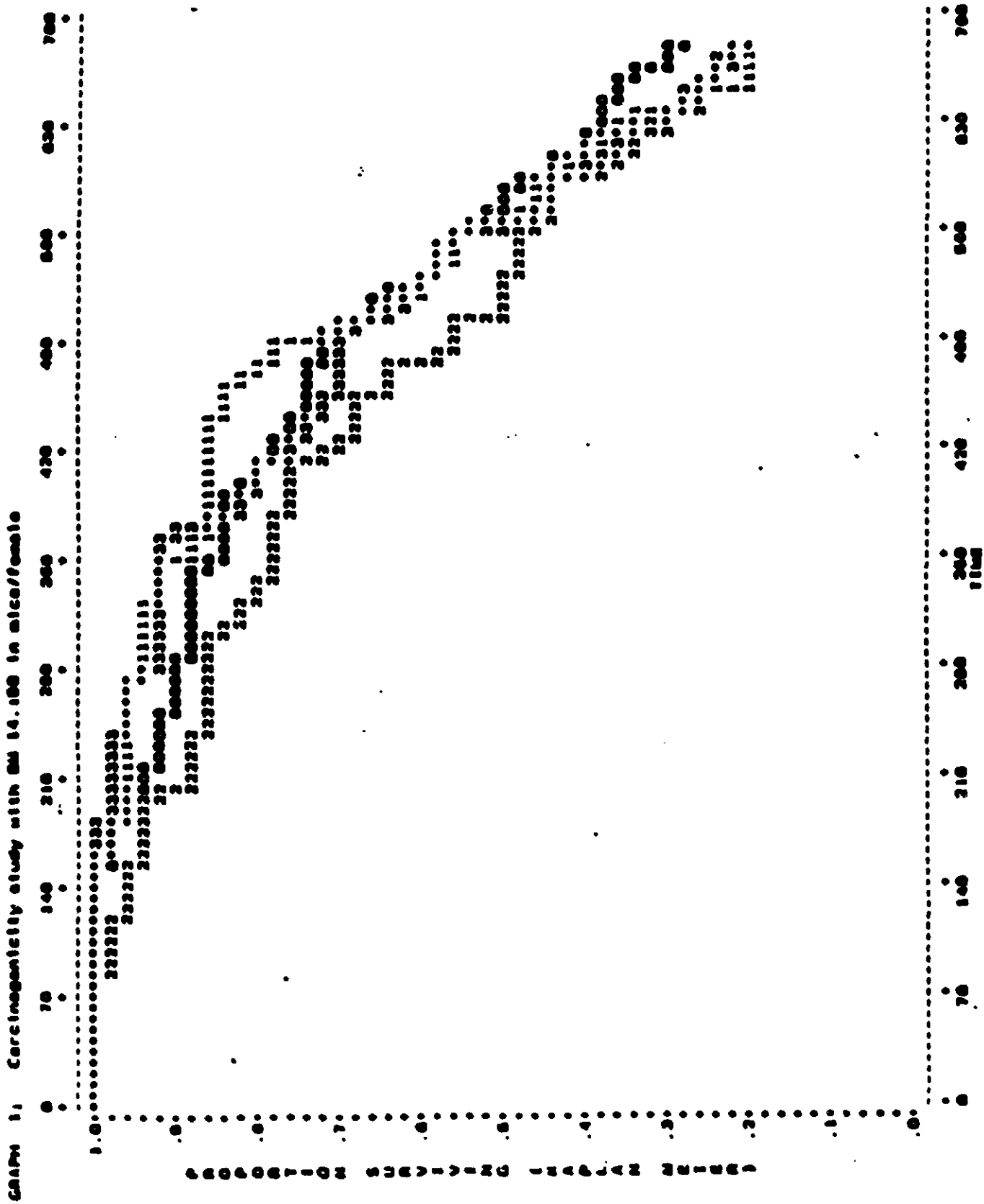
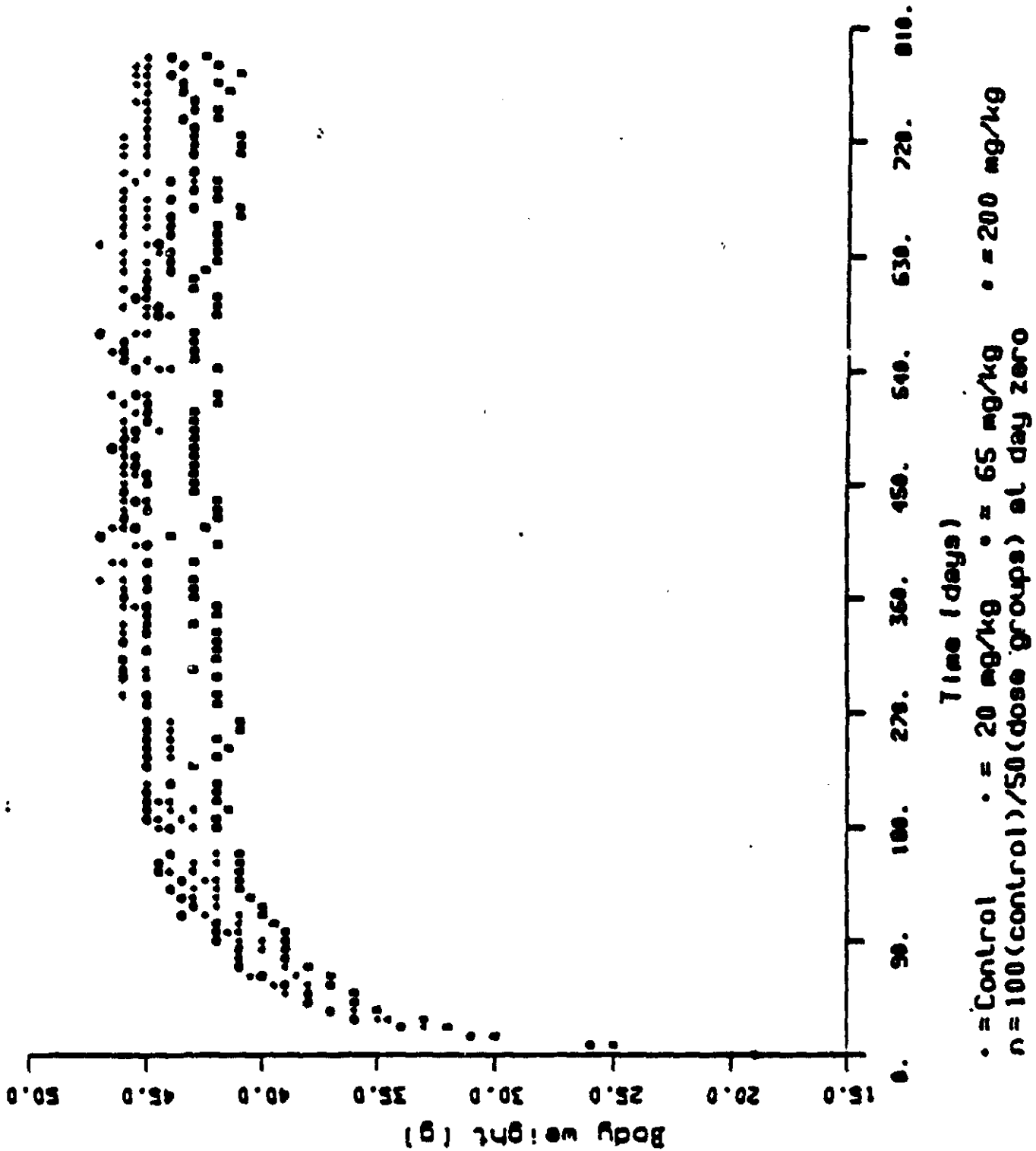


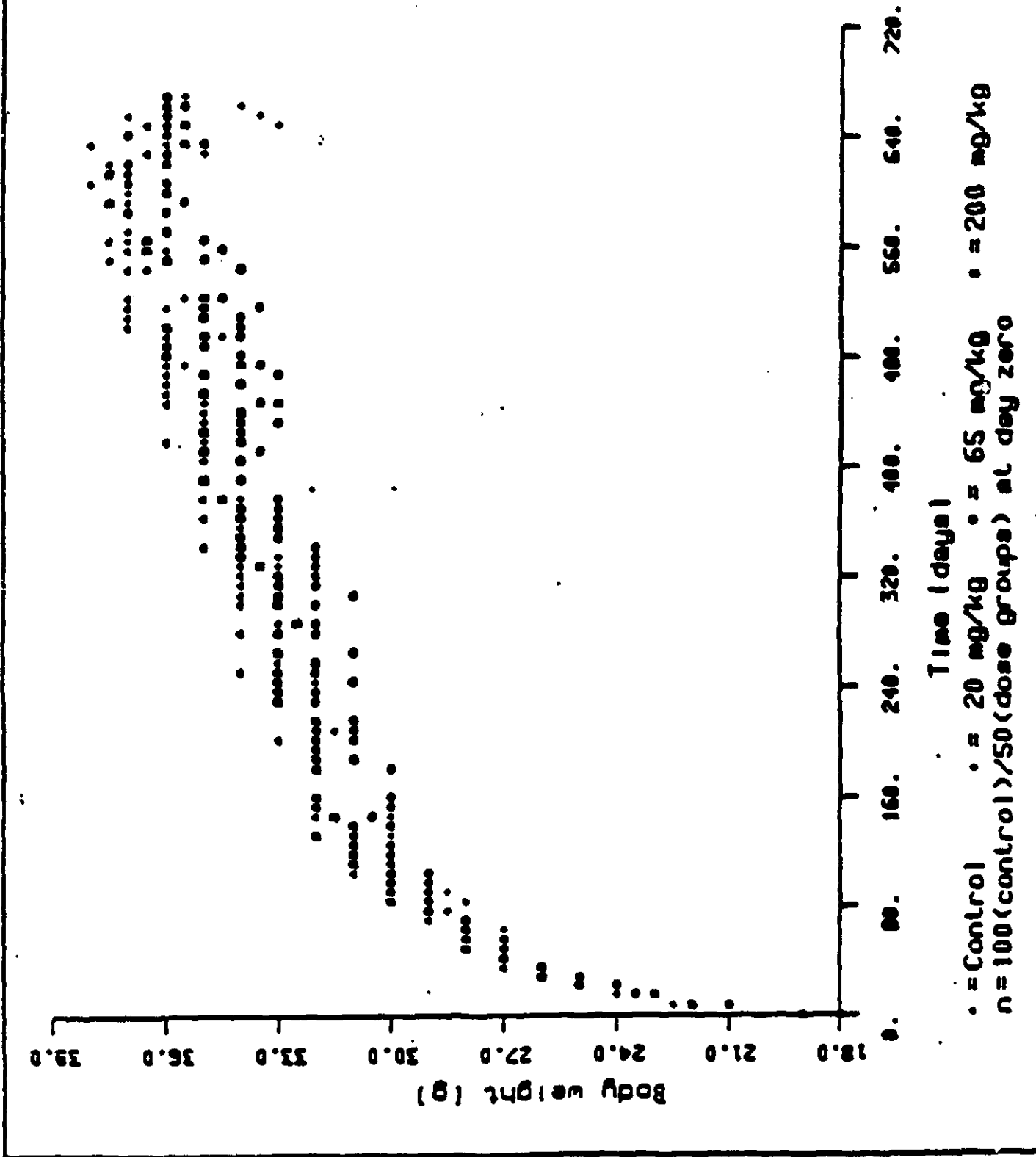
Figure 9

Fig. 1a. CARCINOGENICITY STUDY WITH CARVEDILOL IN MICE
Body weight of male mice (median)



000163

Fig. 1b. CARCINOGENICITY STUDY WITH CARVEDILOL IN MICE
Body weight of female mice (median)



000164

Short title and project name		Page 18 Carcinogenicity Study with Carvedilol in Rats			J2 -107
Table 5: Drug intake per day of male and female rats in mg/kg body weight, grouped by time intervals. Median; n = sample size. (1st quartile; 3rd quartile)					
first day - last day	Group 2 200 ppm	Group 3 400 ppm	Group 4 800 ppm	Group 5 1600 ppm	
0 - 41 male	21.30;n=50 (20.05; 21.85)	40.80;n=50 (38.38; 42.33)	85.50;n=50 (83.40; 90.65)	169.30;n=50 (162.95;175.22)	
female	21.70;n=50 (20.13; 22.60)	43.00;n=50 (40.35; 45.63)	86.70;n=50 (81.48; 94.48)	165.30;n=50 (153.52;174.75)	
42 - 83 male	12.40;n=50 (11.95; 12.75)	24.90;n=50 (24.20; 25.88)	50.10;n=50 (48.38; 51.78)	98.40;n=50 (96.40;102.13)	
female	12.80;n=50 (14.00; 15.73)	30.50;n=50 (29.08; 32.18)	61.00;n=50 (57.78; 64.35)	121.00;n=50 (110.05;127.52)	
84 - 118 male	10.70;n=50 (10.45; 10.90)	21.60;n=50 (20.55; 22.05)	42.70;n=50 (41.38; 43.73)	85.60;n=50 (83.50; 88.25)	
female	13.40;n=50 (12.85; 14.00)	27.50;n=50 (26.43; 29.53)	51.10;n=50 (49.60; 54.65)	102.80;n=50 (96.18;113.00)	
119 - 181 male	10.10;n=50 (9.90; 10.33)	20.10;n=50 (19.38; 20.80)	39.10;n=50 (37.08; 40.10)	77.20;n=50 (75.30; 80.98)	
female	12.30;n=50 (11.68; 12.98)	24.60;n=50 (23.48; 25.38)	48.20;n=50 (46.65; 50.03)	93.40;n=50 (90.45; 96.80)	
182 - 279 male	9.60;n=50 (9.20; 9.83)	19.20;n=49 (18.20; 20.60)	37.60;n=49 (37.00; 39.00)	73.30;n=50 (68.68; 75.90)	
female	11.60;n=50 (11.40; 12.15)	23.50;n=50 (22.50; 24.30)	43.30;n=50 (41.53; 45.35)	84.30;n=50 (81.28; 89.38)	
280 - 426 male	8.30;n=47 (8.10; 8.60)	16.65;n=48 (16.13; 17.80)	31.80;n=46 (31.18; 33.80)	64.60;n=47 (60.30; 67.70)	
female	11.30;n=49 (10.80; 11.70)	21.70;n=50 (20.75; 22.85)	44.00;n=49 (41.20; 46.25)	90.70;n=50 (85.33; 92.33)	
427 - 727 male	7.70;n=37 (7.40; 8.35)	16.20;n=39 (15.00; 17.30)	31.40;n=39 (29.60; 34.00)	62.10;n=35 (59.00; 67.30)	
female	9.50;n=43 (8.90; 10.50)	18.80;n=45 (17.70; 19.95)	38.10;n=44 (35.20; 41.28)	74.70;n=43 (70.60; 81.40)	

Table 1
BM 14.190

SURVEY OF TUMOR FREQUENCY IN MALE RATS

Dose	n	unscheduled killed or died	with tumors	without tumors	scheduled killed	with tumors	without tumors	total with tumors	total without tumors
Control I	50	32-64%	25-78%	7-21,8%	18-36%	16-88,9%	2-11,1%	41-82%	9-18%
Control II	50	26-52%	21-80,8%	5-19,2%	24-48%	16-65,7%	8-33,3%	37-74%	13-26%
200 ppm	50	35-70%	24-68,6%	11-31,4%	15-30%	9-60%	6-40%	33-66%	17-34%
400 ppm	50	35-70%	16-45,7%	19-54,3%	15-30%	8-53,3%	7-46,6%	24-48%	26-52%
800 ppm	50	39-78%	24-61,5%	15-38,5%	11-22%	8-72,7%	3-27,3%	32-64%	18-36%
1600 ppm	50	42-84%	14-33,3%	28-66,6%	8-16%	5-62,5%	3-37,5%	19-38%	31-62%

Table 2

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Table 2
BM 14.190

SURVEY OF TUMOR FREQUENCY IN FEMALE RATS

Dose	n	unscheduled killed or died	with tumors	without tumors	scheduled killed	with tumors	without tumors	total with tumors	total without tumors
Control I	50	27=54%	27=100%	-	23=46%	21=93,3%	2= 8,7%	48=96%	2= 4%
Control II	50	23=46%	23=100%	-	27=54%	26=96,3%	1= 3,7%	49=98%	1= 2%
200 ppm	50	27=54%	26=93,3%	1= 3,7%	23=46%	22=95,6%	1= 4,3%	48=96%	2= 4%
400 ppm	50	28=56%	28=100%	-	22=44%	21=95,4%	1= 4,5%	49=98%	1= 2%
800 ppm	50	26=52%	23=88,5%	3=11,5%	24=48%	22=91,6%	2= 8,3%	45=90%	5=10%
1600 ppm	50	21=42%	20=95,2%	1= 4,8%	29=58%	26=89,6%	3=10,3%	46=92%	4= 8%

BM 14.190 (Table 2) (C)

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TABLE 2

Table 4

Short title and project name		Page 23 Carcinogenicity Study with Carvedilol in Rats					J2 -112
Table 7: Frequencies of animals with tumors respective malignant tumors							
male rats							
Dosage	Group 1 Control 1	Control 2s	Group 2 200 ppm	Group 3 400 ppm	Group 4 800 ppm	Group 5 1600 ppm	
Number of animals with a tumor	41	37	33	24	32	19	
Number of animals with a malignant tumor	14	10	8	8	11	5	
female rats							
Dosage	Group 1 Control 1	Control 2s	Group 2 200 ppm	Group 3 400 ppm	Group 4 800 ppm	Group 5 1600 ppm	
Number of animals with a tumor	48	49	48	49	45	46	
Number of animals with a malignant tumor	17	22	14	9	7	11	
At begin of study there were 50 animals per dosage and sex.							
s. = Control 2 were the controls of a parallel study with another substance. Their results were not used for statistical comparisons in this study.							

Table 5

Table 8: Number of animals with tumors of the organs with the highest frequencies

male rats

Dosage Group	Organs				
	Pituitary	Urinary bladder	Pancreas	Skin + Subcutis	Thyroid
Control 1	17	8	8	11	6
Control 2s	17	9	10	11	4
200 ppm	15	8	5	8	2
400 ppm	7	3	5	7	5
800 ppm	14	2	3	11	2
1600 ppm	10	0	2	7	0

female rats

Dosage Group	Organs						
	Pituitary	Urinary bladder	Pancreas	Skin + Subcutis	Thyroid	Mamma. gland	Uteru
Control 1	41	0	3	3	1	35	7
Control 2s	36	3	3	2	2	41	6
200 ppm	31	0	2	2	6	37	5
400 ppm	29	0	0	2	2	36	5
800 ppm	35	0	0	0	4	30	5
1600 ppm	30	0	1	0	5	36	5

At begin of study there were 50 animals per dosage and sex.

s = Control 2 were the controls of a parallel study with another substance. Their results were not used for statistical comparisons in this study.

Table 6
Intercurrent Mortality Rates
Male Rats

Weeks	Control			Low			Medium			High-1			High-2		
	S	D	%	S	D	%	S	D	%	S	D	%	S	D	%
0-50	50	0	0	50	1	2	50	2	4	50	3	6	50	2	4
51-80	50	7	14	49	10	20.4	48	14	29.1	47	10	21.3	48	16	33.3
81-105	43	25	58.1	39	24	61.5	34	17	50.0	37	26	70.3	32	24	75
Term.	18			15			17			11			8		

Female Rats

Weeks	Control			Low			Medium			High-1			High-2		
	S	D	%	S	D	%	S	D	%	S	D	%	S	D	%
0-50	50	1	2	50	1	2	50	0	0	50	1	2	50	0	0
51-80	49	2	4.1	49	7	14.3	50	7	14	49	7	14.3	50	8	16
81-105	47	24	51.1	42	19	45.2	43	21	48.8	42	18	42.8	42	13	30.9
Term.	23			23			22			24			29		

Notes: S: Number of animals starting during the period
D: Deaths
%: Percent of death during the period

Table 7
Tumor Incidence Rates
Male Rats, Stomach Papilloma

Weeks	Control		Low		Medium		High-1		High-2	
	T	N	T	N	T	N	T	N	T	N
0-50	0	0	0	1	0	2	0	3	0	2
51-80	0	7	0	10	0	14	0	10	0	16
81-105	0	25	0	24	0	17	0	26	0	24
terminal	0	18	0	15	0	17	1	11	1	8
Total	0	50	0	50	0	50	1	50	1	50

Table 8
Tumor Incidence Rates
Male Rats, Skin Subcutis Sebaceous Adenoma

Weeks	Control		Low		Medium		High-1		High-2	
	T	N	T	N	T	N	T	N	T	N
0-50	0	0	0	1	0	2	0	3	0	2
51-80	0	7	0	10	0	14	0	10	0	16
81-105	0	25	0	24	0	17	0	26	2	24
terminal	0	18	0	15	0	17	0	11	0	8
Total	0	50	0	50	0	50	0	50	2	50

Notes: T: Number of necropsies with the above tumor.
N: Number of necropsies.

Table 9
Tumor Incidence Rates
Male Rats, Liver Hepatocellular Adenoma

Weeks	Control		Low		Medium		High-1		High-2	
	T	N	T	N	T	N	T	N	T	N
0-50	0	0	0	1	0	2	0	3	0	2
51-80	0	7	0	10	0	14	0	10	0	16
81-105	0	25	0	24	0	17	2	26	0	24
terminal	0	18	2	15	1	17	1	11	2	8
Total	0	50	2	50	1	50	3	50	2	50

Notes: T: Number of necropsies with the above tumor.
N: Number of necropsies.

Table 10
Tumor Incidence Rates
Female Rats, Thyroid Gland Adenoma

Weeks	Control		Low		Medium		High-1		High-2	
	T	N	T	N	T	N	T	N	T	N
0-50	0	1	0	1	0	0	0	1	0	0
51-80	0	2	0	7	0	7	0	7	0	8
81-105	0	24	3	19	0	21	1	18	0	13
terminal	0	23	3	23	2	22	3	24	5	29
Total	0	50	6	50	2	50	4	50	5	50

Table 11
Tumor Incidence Rates
Female Rats, Brain Oligodendroglioma

Weeks	Control		Low		Medium		High-1		High-2	
	T	N	T	N	T	N	T	N	T	N
0-50	0	1	0	1	0	0	0	1	0	0
51-80	0	2	0	7	0	7	0	7	2	8
81-105	0	24	0	19	0	21	0	18	0	13
terminal	0	23	0	23	0	22	0	24	0	29
Total	0	50	0	50	0	50	0	50	2	50

Notes: T: Number of necropsies with the above tumor.
N: Number of necropsies.

Table 12

Short title and project name		Page 11 Carcinogenicity Study with Carvedilol in Rats					J2 -10
Table 1a: Difference of body weights of male rats in grams, grouped by time intervals.							
median 1st quartile; 3rd quartile n = sample size							
first day - last day	Group 1 Control 1	Control 2 ⁸	Group 2 200 ppm	Group 3 400 ppm	Group 4 800 ppm	Group 5 1600 ppm	
0 - 41	171.25 162.0;181.6 n = 50	190.00 182.9;196.6 n = 50	174.50 169.9;184.6 n = 50	175.25 166.8;184.6 n = 50	175.50 167.0;181.5 n = 50	170.25 159.0;183.1 n = 50	
42 - 83	350.50 320.5;375.5 n = 50	348.75 333.3;368.9 n = 50	358.50 339.5;370.8 n = 50	351.50 331.8;376.3 n = 50	366.50 345.3;393.5 n = 50	356.50 331.0;379.5 n = 50	
84 - 118	393.50 358.5;422.0 n = 50	401.50 383.0;442.0 n = 50	401.50 381.0;417.8 n = 50	398.00 373.0;418.0 n = 50	414.50 [*] 387.0;444.3 n = 50	410.00 [*] 376.5;444.0 n = 50	
119 - 181	440.50 396.5;474.4 n = 50	444.50 421.4;490.4 n = 50	441.80 421.8;471.1 n = 50	437.30 404.5;471.9 n = 50	445.00 [*] 427.5;499.9 n = 50	457.30 417.8;494.1 n = 50	
182 - 279	481.50 438.3;522.8 n = 50	481.00 456.0;531.5 n = 49	484.50 467.5;516.5 n = 50	476.00 450.5;528.0 n = 49	510.00 473.5;547.0 n = 49	494.00 451.5;542.0 n = 50	
280 - 426	546.50 505.3;586.0 n = 49	553.00 515.7;602.0 n = 47	553.00 517.5;577.9 n = 48	540.50 507.0;612.8 n = 48	563.50 521.5;619.0 n = 47	551.50 505.0;609.6 n = 48	
427 - 727	568.00 538.0;612.0 n = 37	584.50 552.0;633.0 n = 40	598.00 546.8;626.8 n = 33	592.50 555.4;645.4 n = 32	595.50 547.3;632.8 n = 32	576.50 538.0;633.1 n = 28	
1 = Kruskal-Wallis-Test: no significance, alpha = 0.05 1+ = Kruskal-Wallis-Test: significance, alpha = 0.05 * = Mann-Whitney-Test: significantly different from group 1, alpha = 0.05 8 = Control 2 were the controls of a parallel study with another substance. Their results were not used for statistical comparisons in this study.							

Table 13

	Short title and project name Page 12 Carcinogenicity Study with Carvedilol in Rats	J2 -10

Table 1b: Difference of body weights of female rats in grams, grouped by time intervals.

median
 1st quartile; 3rd quartile
 n = sample size

first day - last day	Group 1 Control 1	Control 2 [§]	Group 2 200 ppm	Group 3 400 ppm	Group 4 800 ppm	Group 5 1600 ppm
0 - 41	110.25 102.0;123.5 n = 50	110.50 102.6;114.3 n = 50	113.25 106.9;119.0 n = 50	108.75 103.9;117.8 n = 50	118.00 107.9;123.8 n = 50	114.25 106.3;119.5 n = 50
42 - 83	187.50 177.8;206.3 n = 50	190.00 179.9;202.6 n = 50	190.50 178.0;209.5 n = 50	188.50 175.8;205.0 n = 50	196.00 181.8;214.5 n = 50	195.50 184.8;207.3 n = 50
84 - 118	211.00 196.8;235.0 n = 50	218.00 204.8;232.3 n = 50	216.00 202.0;236.8 n = 50	215.00 198.0;231.3 n = 50	219.50 203.0;241.0 n = 50	218.00 207.0;232.5 n = 50
119 - 181	231.25 216.3;257.0 n = 50	237.00 226.8;252.9 n = 50	236.50 219.4;261.3 n = 50	229.50 214.0;254.8 n = 50	237.25 221.6;258.1 n = 50	240.50 228.9;254.1 n = 50
182 - 279	254.50 233.8;287.8 n = 50	258.50 245.8;278.0 n = 50	258.50 240.5;287.3 n = 50	251.50 236.0;281.5 n = 50	255.50 233.8;271.3 n = 50	253.00 ~~230.2;287.5~~ n = 50
280 - 426	293.50 266.5;338.0 n = 49	314.00 277.6;337.8 n = 50	311.00 273.5;347.3 n = 49	293.75 270.8;351.4 n = 50	292.50 262.5;318.8 n = 49	286.25 270.9;305.9 n = 50
427 - 727	344.00 298.4;385.1 n = 40	362.00 319.5;396.0 n = 43	348.50 326.0;413.0 n = 39	352.75 307.8;425.9 n = 38	318.00 289.0;379.0 n = 39	318.00 293.5;349.5 n = 39

1 = Kruskal-Wallis-Test: no significance, alpha = 0.05

1+ = Kruskal-Wallis-Test: significance, alpha = 0.05

§ = Control 2 were the controls of a parallel study with another substance. Their results were not used for statistical comparisons in this study.

Table 14

E		Short title and project name					J2 - 10
Page 13		Carcinogenicity Study with Carvedilol in Rats					
Table 2a: Food consumption of male rats in grams per day, grouped by time interval							
Median 1st quartile; 3rd quartile n = sample size							
first day - last day	Group 1 Control 1	Control 2 ³	Group 2 200 ppm	Group 3 400 ppm	Group 4 800 ppm	Group 5 1600 ppm	
0 - 41	26.80 26.3; 28.5 n = 50	26.00 25.3; 26.6 n = 50	26.00 ¹ 25.2; 27.5 n = 50	25.30 ¹ 24.5; 27.5 n = 50	27.50 25.3; 29.1 n = 50	26.00 ¹ 24.7; 27.0 n = 50	
42 - 83	26.50 25.0; 28.3 n = 50	26.30 24.5; 28.0 n = 50	26.00 24.5; 27.6 n = 50	25.80 25.2; 27.5 n = 50	27.00 25.0; 29.0 n = 50	26.50 25.5; 27.0 n = 50	
84 - 118	25.10 23.3; 26.6 n = 50	26.10 24.5; 26.8 n = 50	26.40 23.5; 26.3 n = 50	24.30 23.3; 25.7 n = 50	25.50 23.8; 26.9 n = 50	25.10 24.1; 26.5 n = 50	
119 - 181	25.50 23.7; 27.2 n = 50	25.10 23.8; 26.7 n = 50	26.90 24.1; 25.7 n = 50	24.30 24.0; 25.9 n = 50	24.90 23.7; 26.9 n = 50	25.00 24.2; 26.3 n = 50	
182 - 279	26.60 25.0; 27.8 n = 50	25.30 24.3; 26.7 n = 49	25.90 25.2; 27.0 n = 50	26.00 25.2; 28.0 n = 49	27.30 25.0; 28.9 n = 49	25.40 ¹ 24.8; 26.7 n = 50	
280 - 426	26.40 24.5; 27.5 n = 48	25.50 24.8; 27.8 n = 47	26.00 25.3; 27.0 n = 47	25.80 24.8; 26.8 n = 48	26.00 24.9; 28.0 n = 46	25.30 24.0; 26.0 n = 47	
427 - 727	26.10 23.4; 27.3 n = 45	24.90 23.3; 25.9 n = 45	25.80 25.0; 26.8 n = 37	25.80 25.0; 27.8 n = 39	26.50 25.3; 27.8 n = 39	25.30 24.0; 27.2 n = 35	
1 = Kruskal-Wallis-Test: no significance, alpha = 0.05 1* = Kruskal-Wallis-Test: significance, alpha = 0.05 * = Mann-Whitney-Test: significantly different from group 1, alpha = 0.05 3 = Control 2 were the controls of a parallel study with another substance. Their results were not used for statistical comparisons in this study.							

Table 15

Short title and protocol name		Page 14 Carcinogenicity Study with Carvedilol in Rats					J2 -1
Table 2b: Food consumption of female rats in grams per day, grouped by time interval							
median 1st quartile; 3rd quartile n = sample size							
first day - last day	Group 1 Control 1	Control 2 ³	Group 2 200 ppm	Group 3 400 ppm	Group 4 800 ppm	Group 5 1600 ppm	
0 - 41	18.80 18.0; 20.3 n = 50	20.00 18.7; 20.4 n = 50	18.50 17.7; 19.6 n = 50	18.30 17.7; 19.5 n = 50	19.30 18.8; 20.4 n = 50	18.00 ¹ 17.5; 19. n = 50	
42 - 83	19.80 18.5; 21.5 n = 50	19.00 18.5; 21.1 n = 50	19.30 18.2; 20.1 n = 50	19.30 18.0; 20.4 n = 50	19.30 19.0; 19.9 n = 50	18.80 ¹ 17.8; 19. n = 50	
84 - 118	19.50 18.3; 20.6 n = 50	19.10 18.3; 20.4 n = 50	18.90 ² 18.0; 19.3 n = 50	19.10 18.3; 19.8 n = 50	18.50 ² 17.9; 19.4 n = 50	18.10 ² 17.2; 19. n = 50	
119 - 181	19.00 18.0; 20.3 n = 50	19.80 18.6; 20.5 n = 50	18.00 ² 17.0; 19.2 n = 50	18.30 ² 17.0; 18.8 n = 50	18.30 ² 17.3; 18.9 n = 50	17.80 ² 17.1; 18. n = 50	
182 - 279	18.90 18.1; 20.6 n = 50	18.80 18.0; 19.9 n = 50	19.10 18.1; 19.8 n = 50	18.40 ² 17.5; 19.5 n = 50	17.00 ² 16.5; 17.4 n = 50	16.80 ² 16.2; 17. n = 50	
280 - 426	19.80 18.8; 21.5 n = 49	19.00 18.5; 20.5 n = 50	20.50 ² 19.8; 21.3 n = 49	20.00 19.0; 21.8 n = 50	19.00 ² 18.3; 20.3 n = 49	19.30 18.5; 20. n = 50	
427 - 727	19.60 18.6; 20.6 n = 47	20.00 19.0; 21.1 n = 46	20.50 ² 19.1; 21.5 n = 43	20.10 18.4; 21.3 n = 45	18.75 ² 17.6; 19.5 n = 44	18.80 ² 17.3; 20. n = 43	
1 = Kruskal-Wallis-Test: no significance, alpha = 0.05 1+ = Kruskal-Wallis-Test: significance, alpha = 0.05 * = Mann-Whitney-Test: significantly different from group 1, alpha = 0.05 3 = Control 2 were the controls of a parallel study with another substance. Their results were not used for statistical comparisons in this study.							

The following summary tables were submitted by sponsor. Table 24 shows that in fetuses from dams sacrificed on day 22 of pregnancy (caesarean group), variations occurred in all groups; these variations were not dose-dependent. As for skeletal abnormalities, these were also found in all treated groups, except for malformations of the 13th rib which occurred at the MD and HD. Sponsor considered that 13th-rib malformations as spontaneous malformations "which also occurred with varying frequency in the control group." Sponsor does not consider that these findings are teratogenic because in the rat teratology study (see below review by previous pharmacologist N. Winbury, Ph.D.), there was no indication of an increase in these anomalies, even the same doses tested in the fertility and general reproduction study.

Table 24

VISCERAL AND SKELETAL ABNORMALITIES
IN CAESAREAN FETUSES/DAM

F0-generation, caesarean group -

Median (1st and 3rd quartiles in case of
statistical evaluation)

	Group 1 Control	Group 2 12 mg/kg	Group 3 60 mg/kg	Group 4 300 mg/kg	STAT. TEST
VISCERAL ABNORMALITIES	n=9	n=9	n=11	n=8	-
Retardations x 100 no. fetuses examined	0.0	0.0	0.0	0.0	-
Variations x 100 no. fetuses examined	11.1 0.0;33.0	12.2 0.0;66.6	0.0 0.0;14.3	0.0 0.0;12.5	2
Malformations x 100 no. fetuses examined	0.0	0.0	0.0	0.0	-
SKELETAL ABNORMALITIES	n=9	n=9	n=11	n=8	
Retardations x 100 no. fetuses examined	79.0 69.2;88.7	28.6 20.0;78.6	62.3 40.0;85.7	83.3 39.7;100.0	2
Variations x 100 no. fetuses examined	18.7 0.0;33.0	25.0 0.0;62.9	14.3 0.0;23.0	18.3 0.0;32.9	2
Malformations x 100 no. fetuses examined	0.0 0.0;0.0	0.0 0.0;0.0	0.0 0.0;28.6	38.0 12.2;64.7	2-

2 = Jonckheere-Test: no significance (alpha = 0.05)

2- = Jonckheere-Test: significance (alpha = 0.05)

- = Wilcoxon-U-Test: significantly different from group 1 (alpha = 0.05)

- = no statistical test was performed

Sponsor provided the following tables (25a and b below) showing the frequency of visceral and skeletal abnormalities found in the fetuses of the F₀ dams on day 22 of pregnancy.

Table 25a- FREQUENCIES OF VISCERAL ABNORMALITIES IN CAESAREAN FETUSES

	Group 1 Control	Group 2 12 mg/kg	Group 3 60 mg/kg	Group 4 300 mg/kg
No. fetuses examined	66	62	76	33
Viscerations (V)				
RPU syndrome	0	14	11	1
Thymus enlarged	1	1	0	0
Thyroid enlarged	4	0	0	1
Thymus and thyroid enlarged	1	0	0	0
RPU-syndrome and thyroid enl.	1	0	0	0

Ameslab. Study (Fertility)
On 12.158. Rec. D.O.

Table 25b

FREQUENCIES OF SKELETAL ABNORMALITIES IN CAESAREAN FETUSES

	Group 1 Control	Group 2 12 mg/kg	Group 3 60 mg/kg	Group 4 300 mg/kg
No. fetuses examined	66	62	73	33
Malformations (M)				
sternum	2	3	3	0
ribs	3	4	0	2
vertebrae	4	4	11	2
thoracic vertebral centers	4	2	2	0
cervical vertebral centers	1	0	0	0
center of hyoid bone	1	0	0	0
more than one bone retarded	18	4	15	9
Viscerations (V)				
sternum	2	3	1	1
ribs	2	3	1	0
vertebrae	0	2	1	0
Malformations (M)				
ribs	0	0	3	1
Combinations:				
R + V	0	4	4	4
R + M	1	1	0	0
R + V + M	0	0	3	1
V + M	0	2	1	2
D + R	0	0	1	0

NB- RPU (Dilated renal pelvis and/or ureter.)

For further clarification of type of skeletal anomalies reported above as found in the fetuses of the F₀ dams, the following table submitted by the sponsor is provided below.

SKELETAL ANOMALIES ("COMBINATIONS") IN CAESAREAN FETUSES			
Group 1 Control	Group 2 12 pups	Group 3 65 pups	Group 4 285 pups
Sk phalange (fingers) partly ossified; thumb discal phalanx os- sified (bilat.); sternura VI asym- etric Sk IV 1 ossified (bilat.); cervical ribs (bilat.); sternura IV asymmetric; sternura V ossified Sk IV 1 ossified (bilat.); 11th thorac- al vertebral center missing; rudimentary rib (right) Sk bilat.; 12th thorac- al vertebral center missing; sternura VI asymmetric Sk IV 1 ossified (bilat.); sternura IV and V asymmetric; sternura VI asym- metric; scapula asymmetric (bilat.) Sk IV 1 ossified (right); thumb distal phalanx ossified (bilat.); scapula asym- metric (left); center of scapula base os- sified; intercarpal bone partly ossified	Sk IV 1 ossified (right); scapula asymmetric (bilat.) Sk IV 1 ossified (right); scapula asymmetric (bilat.) Sk thumb distal phalanx ossified (left); sternura VI asym- etric Sk IV 1 ossified (bilat.); sternura VI asymmetric Sk IV 1 ossified (bilat.); sternura IV and VI asymmetric; scapula asymmetric (left) Sk scapula asymmetric (right); 12th thorac- al vertebral center missing Sk Sternura IV and VI asymmetric; 12th rib short (right)	Sk IV 1 ossified (bilat.); thumb distal phalanx ossified (bilat.); sternura VI asymmetric Sk IV 1 ossified (bilat.); thumb distal phalanx ossified (bilat.); sternura VI asymmetric; center of scapula base, inter- carpal bone and carpal bones partly ossified Sk IV 1 ossified (bilat.); thumb distal phalanx ossified (right); rudimentary rib (bilat.) Sk IV 1 ossified (bilat.); thumb distal phalanx ossified (left); sternura VI asym- Sk IV 1 ossified (bilat.); 11th thoracal vertebral center missing; 12th rib short (bilat.); sternura IV asymmetric Sk IV 1 ossified (right); 12th rib short (bilat.) Sk IV 1 ossified (bilat.); 12th thoracal vertebral center missing; 12th rib short (bilat.); sternura IV asymmetric Sk IV 1 ossified (right); 12th rib short (bilat.) Sk IV 1 ossified (bilat.); 12th thoracal vertebral center missing Sk 12th rib missing (left); sternura V ossified	Sk scapula asymmetric (bilat.); sternura IV and VI asymmetric Sk IV 1 ossified (bilat.) sternura VI asymmetric Sk IV 1 ossified (bilat.); sternura asymmetric Sk IV 1 ossified (bilat.); sternura asymmetric Sk 12th rib short (right); sternura V ossified Sk IV 1 ossified (bilat.); thumb distal phalanx ossified (bilat.); 11th thoracal vertebral center missing; 12th rib short (bilat.) Sk IV 1 ossified (bilat.); 12th rib missing (left) Sk 12th rib short (left), missing right; fetus with 3 lumbar vertebrae; sternura V ossified Sk Cervical ribs (bilat.); 12th rib short (bilat.); fetus with 3 lumbar vertebrae; sternura V ossified

SKELETAL ANOMALIES ("COMBINATIONS") IN CAESAREAN FETUSES (CONCL.)			
Group 1 Control	Group 2 12 pups	Group 3 65 pups	Group 4 285 pups
Sk IV 1 ossified (bilat.); phalange (fingers) partly ossified; thumb discal phalanx ossified (bilat.); 11th thoracal vertebral center missing; sternura IV asym- metric; cervical bone depressed (left); intercarpal bone partly ossified Sk phalange (fingers) partly ossified; thumb discal phalanx ossif. (bilat.); 12th thoracal vertebral ctr. missing; sternura VI asym- metric; phalange (hand) partly ossified Sk thumb distal phalanx ossified (bilat.); 12th rib short (bilat.); inter- carpal bone and carpal bones partly ossified	Sk IV 1 ossified (right); thumb distal phalanx ossified (bilat.); 12th rib short (right); sternura VI asymmetric Sk IV 1 ossified (bilat.); thumb distal phalanx ossif. (bilat.); 12th rib short (bilat.); fetus with 3 lumbar vertebrae; sternura V ossified; VI asym- Sk IV 1 ossified (bilat.); 12th rib short (bilat.); sternura VI asymmetric; center of scapula base partly ossified Sk IV 1 ossified (right); 12th rib short (bilat.); sternura VI asymmetric Sk Phalange (fingers) partly ossified; thumb discal phalanx ossif. (bilat.); 12th rib short (bilat.); sternura V ossified, VI asym. Sk 12th rib short (right); sternura VI asymmetric Sk Phalange (hand) partly ossified; thumb distal phalanx ossified (bilat.); ray ribs (right); intercarpal bone partly ossified	Sk IV 1 ossified (bilat.); thumb distal phalanx ossified (bilat.); phalange (fingers) partly ossified; 11th thoracal vertebral center missing; 12th rib short (right) Sk IV 1 ossif. (bilat.); thumb distal phalanx ossif. (bilat.); 12th rib short (bilat.); fetus with 3 lumbar vertebrae; sternura V ossified, VI asym- Sk center of scapula base partly ossified Sk IV 1 ossified (bilat.); 12th rib short (bilat.); sternura VI asymmetric; center of scapula base partly ossified Sk IV 1 ossified (right); 12th rib short (bilat.); sternura VI asymmetric Sk Phalange (fingers) partly ossified; thumb discal phalanx ossif. (bilat.); 12th rib short (bilat.); sternura V ossified, VI asym. Sk 12th rib short (right); sternura VI asymmetric Sk Phalange (hand) partly ossified; thumb distal phalanx ossified (bilat.); ray ribs (right); intercarpal bone partly ossified	Sk 12th rib short (bilat.); sternura V asymmetric Sk 12th rib short (left); sternura VI asymmetric

When F₀ dams were allowed to litter, although there were no external malformations reported, there were a small number of visceral variations and skeletal retardations and malformations reported (Tables 26a and b below). However, none of these histopathologic findings in F₁ animals were dose-related.

Table 26a. FREQUENCIES OF VISCERAL ABNORMALITIES IN RAISED F₁-INDUALS

	Group 1 Control	Group 2 12 mg/kg	Group 3 60 mg/kg	Group 4 300 mg/kg
No. fetuses examined	148	99	142	28
Variations (V)				
Thymus enlarged	15	3	11	1
Thymus bronchopulmonary. short or missing	2	2	3	0
HPV syndrome	1	3	3	0
HPV syndrome; Thymus bronchopulmonary short	0	0	1	0
Malformations (M)				
retarded testis descent; additional liver lobe	1	0	0	0
additional liver lobe	1	0	0	0
spleen inverted	0	2	0	0
hypoplasia of left kidney with hypoplasia of right kidney	0	1	0	0

Table 26b. SKELETAL ABNORMALITIES IN PRENATURALLY DIED PUPS OF F₁-GENERATION

	Group 1 Control	Group 2 12 mg/kg	Group 3 60 mg/kg	Group 4 300 mg/kg
No. fetuses examined (F₁)	3	3	4	13
Retardations (R)				
NT I unossified more than one bone with retarded ossification	1	0	0	0
thoracic vertebral centers retarded	0	1	0	1
lumbal vertebral centers retarded	0	0	0	2
Variations (V)				
scapula asymmetric	1	0	0	1
sternum asymmetric	0	1	0	2
Combinations				
R + V	0	1	0	1
R + M	0	0	0	2

Explanation of Combinations:

Group 2, 11A/11 asymmetric scapula + retarded thoracic vertebral centers + asymmetric sternal center

Group 4, 30B/10 asymmetric scapula + sternal center No. V unossified

323/ 2 13th rib short (unilateral) + only 3 lumbar vertebrae + sternal center No. IV asymmetric

323/ 3 13th rib short (bilateral) + sternal center No. V unossified

NT = metatarsal bone

The offspring of F₁ generation (that is F₂ generation), showed a small number of abnormalities. Tables 27a and 27b below were provided by sponsor and show the actual number of visceral and skeletal changes in the animals examined. No dose-relation was found in small number of changes reported, but there were only 8 HD pups available.

INSTRUMENT, SCOPY (PNEUMOSCOPY) ON 10.190, Act. p.e.		R4 -113			
Table 27a FREQUENCIES OF VISCERAL ABNORMALITIES IN F ₂ -PUPS					
	Group 1 Control n = 133	Group 2 12 mg/kg n = 106	Group 3 60 mg/kg n = 103	Group 4 300 mg/kg n = 8	
SPH-epidymus	1	0	9	0	
thymus enlarged	3	0	3	0	
hydrothorax	0	1	6	0	
trachea bronchodysplasia short	0	0	1	0	
malposition of right A. subclavia	0	1	0	0	

FREQUENCIES OF SKELETAL ABNORMALITIES IN FRONTALLY GUIDED F ₂ -PUPS					
	Group 1 Control	Group 2 12 mg/kg	Group 3 60 mg/kg	Group 4 300 mg/kg	
no. fetuses examined	18	13	13	8	
Ribcage (R)					
thoracic vertebral centers ostea	0	1	1	0	
sternum ossified more than one bone retained	0	1	0	0	
	0	3	1	0	
Incisions (V)					
sternum asymmetric	1	0	1	0	
Chimerisms (W)					
thoracic vertebral fragmented centers	1	0	0	0	
ribs chimeric	0	1	0	0	
multiple chimerisms	1	0	0	0	
Combinations					
R + O	0	1	0	0	
V + R	0	1	0	0	
R + V	0	0	1	0	

Examination of Combinations:

Group 2, 117/11	ossified epiphysis (phalanges, metacarpal and metatarsal base, cervical vertebral centers, sternal centers) hypid bone and clavicle poorly ossified, scapulae bilateral
119/ 6	9th and 11th thoracic vertebral centers fragmented; sternum VI ossified
Group 3, 201/12	Sternum VI asymmetric; parietal bone poorly ossified

Data provided indicate that the HD (300 mg/kg/day oral carvedilol) reduced fertility in the parental generation, caused high post-natal mortality in the F₁-generation and some delay in some parameters of the physical/mental development of surviving offspring. A remarkable finding was hair loss in some HD rats.

Teratology Studies in Rats and Rabbits:

The following 2 reviews/evaluations of rat oral teratology studies (Seg. II) with carvedilol were prepared by previous pharmacologist M. Winbury, Ph.D. when submitted to the IND, and have received a secondary review by C. Resnick, Ph.D.

Report No. K 1. Reproduction Toxicology Study (Teratogenicity) with BM 14,190 in Rats. Drug Administration per os. (Boehringer

Mannheim, Germany; Report dated Nov. 8, 1982, vol. 1.7, p. 06 001454; Study Director's statement of compliance with GLP dated Nov. 8, 1982, p. 06 001502; Quality Assurance Unit Statement of Compliance dated Jan. 24, 1983, p. 06 001501)

Report No. K 2. Reproductive Toxicology Study (Teratogenicity) with BM 14,190 in Rabbits. Drug Administration per os. (Boehringer Mannheim, Germany; Report dated Nov. 29, 1982, vol. 1.7, p 05 001503; Study Director's statement of compliance with GLP dated Nov. 29, 1982, p. 06 001547; Quality Assurance Unit Statement of Compliance dated Jan. 24, 1983, p. 06 001546)

Report No. K 1: Oral Teratology Study - Rat:

Species/Strain: Rat/Sprague-Dawley.

Study Dates: July 1 to July 29, 1980.

Test Substance: Micronized Carvedilol, batch No. 812755 A, suspended in 1% methylcellulose; prepared fresh daily. A suspension of 200 mg in 10 ml MC was stable for 4 hrs.

Route/Schedule of Administration: Oral by gavage on days 7 through 15 of pregnancy. Day sperm detected in vaginal smear = day 1.

Doses: 0 (methylcellulose), 12, 60 and 300 mg/kg/day. Each dose was administered in a volume of 10 ml/kg.

Rationale For Doses: Based on results of 3 experiments in non-pregnant female rats and 1 experiment in pregnant rats 300 mg/kg was expected to cause adverse but tolerated maternal effects. The 12 mg/kg dose was selected as a low multiple of a pharmacodynamically active dose (in SH rats 3.5 mg/kg, p.o., reduced blood pressure 30 mmHg). The mid-dose was selected as a high multiple of the pharmacodynamic dose but probably a non-toxic dose.

Number of Animals: 112 mated females divided into 28/dose group. In the control, low-, mid-, and high-dose groups, 2, 4, 3 and 5 rats, respectively, were not pregnant and 1 high-dose rat died. Therefore, 26 control, 24 low-dose, 25 mid-dose and 22 high-dose rats reached study termination.

Caesarean Section: Day 22.

(Cont'd. Rat Teratology-MWinbury's review)

Results: Maternal Effects: Mortalities: 1 high-dose Day 17. Body weight (Days 1, 6, 17 & 22): High-dose dams not only failed to gain weight during drug administration they in fact lost weight; from day 16 to 22 (i.e. after drug administration) they gained significantly less weight (about 1/2) than controls. During drug administration the low- and mid-dose groups tended to gain more weight than controls; this was statistically significant for only the mid-dose group. Clinical Signs of Toxicity: There was a dose-related increase in the incidence of hair loss (1/26 control, 4/24 low-dose, 9/25 mid-dose, and 15/22 high-dose), sedation (14/22 mid-dose, 22/22 high-dose) and blood covered eye (1 mid-dose), nose (6 high-dose) and/or vulva (1 high-dose). Implantation Sites: There was no differences between groups in the median number of

implantation sites/dam. Resorptions: The median number of resorptions as a % of implantation sites was significantly higher in the 300 mg/kg group than controls. In fact, there was 100% resorptions in 9 out of 22 dams; all were early resorptions in 7 dams, late in 1 dam, and both early and late in 1 dam. Thus, certain observations refer to 13, not 22, animals. Uterine Weight both full and empty was reduced in the high-dose group. Fetal Effects. Dead Fetuses: There were no dead fetuses in any of the treatment groups. Relative to the control group the following differences were seen in the 300 mg/kg group: decreased median number of live fetuses (as a % of implantation sites), median Fetal weight/Dam, and median Placental Weight/Dam; increased median number of Skeletal Retardations/Dam (due to retardations in the paws). The low- and mid-doses had no apparent effect on these parameters and none of the doses of carvedilol affected the Sex Ratio of fetuses, caused Visceral Abnormalities (variations or malformations) or Skeletal Variations and/or Malformations.

Conclusion: Carvedilol, 12, 60 or 300 mg/kg/day (suspended in 1% methylcellulose), was administered orally to pregnant Sprague-Dawley rats on days 7 through 16 of pregnancy. None of the doses were teratogenic and the 12 and 60 mg/kg/day doses were also not embryotoxic or fetotoxic. While 12 mg/kg/day had no clear maternal effects it is about 4 times the dose shown to lower blood pressure in hypertensive rats. The 60 mg/kg/day dose caused sedation in the dams and the 300 mg/kg/day dose was clearly toxic to the dams (causing death of one animal and weight loss in the others) and was also embryotoxic, fetotoxic and retarded skeletal growth of the paws. The fetal effects of the high-dose could be related to maternal effects.

The following is the review by previous pharmacologist of rabbit Seg. II study which has been also reviewed by C. Resnick and found adequate.

Report No. K 2: Oral Teratology Study - Rabbit:

Species/Strain: Himalaya rabbits/Chbb:W1

Study Dates: Sept. 23, 1980 to Oct. 29, 1980

Test Substance: Micronized carvedilol, batch No. 812 755A, suspended in 1% methylcellulose. Prepared fresh daily. A suspension of 200 mg in 10 ml MC was stable for 4 hours.

Route/Schedule of Administration: Oral by gavage on day 7 to day 19 of pregnancy. Day 1 was the day of artificial insemination.

Doses: 0 (1% methylcellulose), 3, 15 and 75 mg/kg/day. Doses were administered in a volume of 5 ml/kg.

Rationale For Doses: Preliminary studies in non-pregnant rabbits indicated 1) a dose of 200 mg/kg, but not 100 mg/kg, administered daily for 10 days reduced body weights, and 2) that beta-receptor antagonism occurred at an oral dose of 1 mg/kg and increased dose-dependently at 3 and 10 mg/kg. A preliminary study in pregnant rabbits indicated that 150 mg/kg/day on days 7 to 19 of pregnancy caused a marked reduction of body weight and increased post implantation losses. Therefore, the high dose of 75 mg/kg/day

was selected for the present study since this dose was considered to be at the lower limit for maternal toxicity. The low dose of 3 mg/kg was selected because it was above the beta-blocking dose in the rabbit.

Number of Animals: 17/dose group. At study termination there were 15 control animals, 17 low-dose animals, and 16 mid- and high-dose animals (1 animal each in the control, mid- and high-dose groups was non-pregnant; 1 control animal aborted).

Caesarean Section: Day 30 of pregnancy (15 controls, 17 low-dose, 16 mid-dose and 15 high-dose).

Results: Maternal Effects: Mortalities: None. Clinical Signs: None.

Body Weight: No significant differences between groups either overall or during the period of drug administration. Food

Consumption: Unremarkable except for a reduction in controls on day 14 to 17. There were no significant differences between groups in

the median Uterine Weight (full or empty) or median number of Implantation Sites. Fetal Effects: There was a tendency for

increased resorptions in the high-dose group (expressed as a % of implantation sites, total # of resorptions, # dams with

resorptions, or average # resorptions/dam) but this was not statistically significant. There was 100 % resorptions in 1

low-dose, 2 mid-dose and 1 high-dose dams. Therefore, fetuses were obtained from 15 control, 16 low-dose, 14 mid-dose and 15 high-dose

rabbits. Dead Fetuses: There were none in any group. Live Fetuses:

The number of live fetuses as a % of implantation sites tended to be lower in the high-dose group but this was not statistically

significant. Sex Ratio: The median number of males at the low-dose was significantly lower than controls. This was not seen with the

other doses. The median Placental Weight/dam was higher in all drug groups than in controls but was statistically significant for the low- and high-dose groups.

(Cont'd. Rabbit teratology- MWinbury's review)

fetal Weight: The median fetal weight/dam was significantly higher in the low-dose group than in controls. Visceral and Skeletal Abnormalities: There were no significant differences between drug and vehicle treated groups in terms of visceral malformations or skeletal retardations, variations or malformations.

Conclusions: Carvedilol, 3, 15 or 75 mg/kg/day (suspended in 1% methylcellulose), was administered orally to Himalayan rabbits on days 7 to 19 of pregnancy. The doses used in this study were all higher than the oral dose shown to have significant but sub-maximal beta blocking activity (1 mg/kg) in the rabbit. None of the doses were teratogenic. The 75 mg/kg dose was slightly embryotoxic/fetotoxic but this effect was not statistically significant. A preliminary study in pregnant rabbits indicated that twice this dose (150 mg/kg/day) was embryotoxic/fetotoxic (increased number of resorptions) and toxic to the dams (marked decreases in body weight). In the present study, there was no indication of maternal toxicity at the 75 mg/kg/day dose. The increased placental weights in all dose groups, the increased fetal

weight in in the low-dose group, and the tendency for increased resorptions in the high-dose group were considered by the Sponsor as being secondary to the pharmacodynamic (beta-blockade/vasodilation) effects of the compound.

Perinatal and Postnatal Studies in Rats.

(SK&F Report No. TCO14BS Boehringer Mannheim GmbH, Germany. Study dates: March 25-26, 1985 to September 16, 1985. Report date: November 1986)

No./Dose Level and Strain: About 23 pregnant rats [Sprague-Dawley, Cri:CD(SD)BR].

Route: Orally, by gavage.

Dose Levels and Treatment Schedule: 0 (vehicle - 1% methylcellulose), LD-12, MD-60 and HD-200 mg carvedilol in a 10 ml suspension/body weight on day 16 of gestation and continued up to the end (day 22) of lactation phase.

Synopsis of Procedures: Observations of F₀ females included mortality, body weight, appearance/behavior, pregnancy rate, duration of gestation, number of uterine implants/dam, number of live neonates/dam, fetotoxic effects and sex distribution of the F₁ pups. Observations in F₁ generation included body weights of individuals, and per litter, physical development and behavior. Numerous tests were listed in the NDA that were conducted on selected F₁ pups to determine the development of physical characteristics of F₁ generation. F₁ animals were mated (no sibling pairing), observed/weighed and allowed to litter and rear F₂ pups. F₁ dams and their pups who died prematurely were necropsied. F₂ pups were observed through developmental stages, reflexes tested and sacrificed/necropsied at the end of lactation.

Results:

Maternal (F₀ generation) Observations:

Remarkable toxic signs seen during treatment period were reported mainly for HD; these consisted of narrowing of palpebral fissures suggesting sedation. Hair loss was noted in all treated groups including controls. At sacrifice time, gross findings in treated rats were similar to those seen in controls. A significant resorption of 5 litters was noted at HD compared to controls. Compared to controls, treated dams were reported as showing no significant changes in implantation sites, onset/course of parturition, live pups/dam or reproductive indices per litter (birth index or viability indices) and no significant differences in sex ratio of pups.

Litter Observations:

F₁ Generation: Body weight of F₁ pups was determined about once a week starting on day 1 after birth up to day 43 of study. Except for a significantly lower median body weight in F₁ pup from the HD F₀ dams, no remarkable toxic effects were reported for the F₁ pups. The body weight of neonates was dose-dependently depressed and body weights continued this way until the end of study (day 43 after birth). Starting in the 1st week post partum, at MD and HD groups, more pups were found dead or cannibalized by the dams than in the controls. This effect was also dose-dependent but is regarded as a drug effect deriving both from

unspecific retardation of the fetuses and deficient rearing activity by the dams treated with a toxic dose of carvedilol. Except for pinna detachment and grip strength, all other parameter of physical development (e.g., testicular descent into scrotum, vaginal opening, incisor eruption) as well as reflexes test (e.g., auditory startle, corneal and pupillary), and behavior (e.g., learning and memory) were unaffected. The necropsy findings of the F₀ and F₁ animals revealed no drug-related effects.

F₂ Generation: Although there were some differences in the median weight of groups in this F₂ generation the number of F₂ pups born alive (derived from HD F₀ dams), there were no remarkable observations in these animals regarding the number of pups born alive or their physical development of reflexes or learning and memorizing capacity. These did not differ from the control group. The necropsy findings at the end of the study did not reveal any possible drug effects in the F₂ pups.

Sponsor concluded that 200 mg carvedilol/kg p.o. caused increased intrauterine embryo losses in the F₀ dams, reduced their rearing activity, and retarded physical development of the F₁ generation. This dosage also had a slight influence on the number of F₂ pups born live, the development of some reflexes and behavioral parameters.

60 mg/kg) had only a marginal effect on the rearing activity of the F₀ generation and on the physical development of the F₁ generation.

Sponsor provided necropsy of findings of F₁ pups dying prematurely, F₁ dams and F₂ pups; findings reported did not reveal any drug effects.

Overall, the data presented above indicate that in the definitive Segment I rat study the "no-observed-effect level" (NOEL) for overt toxicity and impairment of fertility may be considered 60 mg/kg/p.o., and that for developmental retardation of offspring was 12 mg/kg/p.o. Further, for the rat and rabbit Segment II studies, for the rat the NOEL for maternal toxicity is considered 12 mg/kg/p.o. and 60 mg/kg/p.o. for developmental toxicity; in the rabbit the NOEL for maternal toxicity, 75 mg/kg/day and 15 mg/kg/day for developmental toxicity. In the rat Segment III studies, the NOEL is considered to be 12 mg/kg/day.

GENOTOXICITY STUDIES

Carvedilol was tested for genotoxic potential using various non-mammalian and mammalian cell systems. Except where indicated for new studies below (Aii, -iv, Bi, -ii, -vii), results of assays were previously reported and submitted to the injectable carvedilol application (IND). These reports were reviewed/evaluated by previous pharmacologist M. Winbury, Ph.D.; portion of the reviews are reproduced below. The reviews/evaluations were secondarily reviewed by supervisory pharmacologist C. Resnick, Ph.D. and were found acceptable. In the present NDA, sponsor has submitted numerous summary tables of the assays. Pertinent portions of these summaries have been extracted, edited and presented below, followed by a brief overview of new studies not previously evaluated. Some studies were conducted prior to implementation of GLP regulations.

MUTAGENICITY STUDIES OF CARVEDILOL (SK&F 105517) AND ITS INTERMEDIATE (SK&F 105569)

Study	Concentrations Tested	Report No. Ref. No. Location in NDA IND Submission	Drug-Related Observations
A - IN VITRO NON-MAMMALIAN SYSTEMS			
i) Ames test (Salmonella) ** (Detect gene reuse mutation)	1, 10, 50, 100, 500, and 1000 µg/plate w/w S9 (1st test) 10, 50, 100, 500 µg/plate w/w S9 (2nd test)	TC016BS (Boehringer Mannheim report J1) Location: Vol. 1.40 Page 000004 Submitted to IND on 2/15/85	First test: Not assessed since concentrations above 100 µg/test plate were bactericidal. Second test: No increase in revertant frequencies in any strain tested.
ii) Ames test (Salmonella) **	50, 150, 500, 1500, and 5000 µg/plate w/w S9 (initial experiment); 5, 15, 50, 150, and 500 µg/plate (repeat experiment) Positive controls without S9: 2-nitro-fluorene and 1-ethyl-2-nitro-3-nitrosoguanidine Positive control with S9: 2-amino-anthracene.	TC017BS (Boehringer Mannheim report J3) Location: Vol. 1.40 Page 000090 Submitted to IND on 2/15/85 (Report states that studies were conducted in 1996)	Initial experiment: Concentrations of 1500 µg/plate and greater resulted in precipitation of carvedilol. A mild precipitation was also seen at 500 µg/plate. Repeat experiment: No statistically significant increases in revertant frequencies over the negative controls were observed in 2 independent experiments.
iii) Ames test (Salmonella)	n-Benzyl Carvedilol (intermediate) 50, 167, 500, 1670, 3330, and 5000 µg/plate w/w S9	TP001BS Location: Vol. 1.40 Page 000269 Submitted to IND on 10/3/89	The intermediate was minimally positive (2-fold elevation) in strain TA1535 without S9 mix and an equivocal response was observed in strain TA1537 with S9 mix. All other 4 test strains (w/w S9) were negative. The observed difference was considered of limited biological significance and of no significance relative to safety. (Complies with GLP)
* n-Benzyl carvedilol is less than 0.02% of the drug. 1) w/w = with/without S9 from rat liver induced with phenobarbital+ methylcholanthrene. ** S. typhimurium strains TA 100, TA 1535, TA 1537 and TA 1538.			

Genotoxicity (Cont'd)

A- IN VITRO NON-MAMMALIAN CELL SYSTEMS (Cont'd.)

Study	Concentrations Tested	Report No. Ref. No. Location in NDA IND Submission	Drug-Related Observations
iV) <i>E. coli</i> WP2 <i>uvrA</i> (Reverse Mutation Assay)	5, 15, 50, 150, 500, 1500 and 5000 µg/plate w/w S9 ⁺ DMSO used as negative control and 2AA and EBV as positive controls.*	TC0030/SK17-105517 (Daiichi report D-17) Location: Vol. 1.40 Page 000298	Toxic effects and precipitation were noted at dosages ≥500 mg/plate w/w activation. Dosages below 500 mg/plate were negative. Carvedilol was considered negative in this assay. Positive controls showed increases in mutation colonies.
v) Mouse liver mediated assay (Reverse Mutation Assay)	200, and 2000 mg/kg p.o. Saline appears to have been used as control.	TC016BS (Boehringer Mannheim report J1) Location: Vol. 1.40 Page 000004 Submitted to IND on 2/15/85	At 2000 mg/kg, bactericidal effects were seen in both <i>S. typhimurium</i> and <i>S. marcescens</i> but were absent at 200 mg/kg. There were no compound- related relevant significant increases in gene mutation in any of these tests.
vi) <i>Saccharomyces cerevisiae</i> MP-1 (Detects gene forward mutation and other genetic changes)	0.01, 0.1, 1, 10, and 50 mg/ml w/w S9 ⁺ Solvent was used as the control.	TC016BS (Boehringer Mannheim report J1) (supplement) Location: Vol. 1.40 Page 000004 Submitted to IND on 2/15/85	No yeast growth at concentrations of 0.1 mg/kg or greater. Therefore, the results of this assay were not taken into account.

* S9 mix prepared from liver fraction of phenobarbital and 5,6-benzoflavone induced male Sprague Dawley rats.
** 2-aminoanthracene and n-ethyl-N-nitrosoguanidine.

Genotoxicity (Cont'd)

Study	Concentrations Tested	Report No. Ref. No. Location in NDA IND Submission	Drug-Related Observations
β- IN VITRO MAMMALIAN CELL SYSTEMS			
i) Chinese Hamster Ovary Cell Mutation Assay (Detects forward mutation at the hypoxanth locus)	8, 9, 12, 15, 16, 18, 20, 2, and 24 µg/ml without S9 mutation assay 15, 20, 21, 24, 28, 30, 37 and 33 µg/ml with S9 <i>Positive for ethyl methyl sulfonate and 3-methylcholanthrene.</i>	TC017BS (Boehringer Mannheim report J3) Location: Vol. 1.40 Page 000090 Submitted to IND on 2/15/85 (Report prepared in 1986, data study was conducted not directly related.)	In the absence of S9 mix, small increases in mutation frequency over vehicle control values were obtained in the cultures treated only with 15 µg/ml of carvedilol. This isolated incidence was not regarded as significant. In the presence of S9 mix, no evidence of mutagenic activity was obtained in carvedilol-treated cultures. This mutagenicity assay was considered to be negative. (Under GHP conditions)
ii) Chromosome aberration test with human lymphocytes	8, 40, and 80 µg/l w/o S9 ^{**} <i>Positive for ethylmethyl sulfonate, methylcholanthrene, and methylcellulose.</i>	TC017BS (Boehringer Mannheim report J3) Location: Vol. 1.40 Page 000090 Submitted to IND on 2/15/85 (Report states that findings conducted in 1986)	There was no significant increase either in damage to chromosome structure or in numerical changes at dosages tested. Thus, carvedilol did not cause significant chromosomal damage in this test. (Under GHP conditions)
iii) DNA synthesis inhibition test (Detects damage to normal testicular DNA replication)	<i>Mouse origin</i> 50, 100, and 200 mg/kg p.o.	TC016BS (Boehringer Mannheim report J1) Location: Vol. 1.40 Page 000004 Submitted to IND on 2/15/85	Lowering of the body temperature by 10 ⁰ C occurred by using the 200 mg/kg solution (2 of 3 experiments). One of 2 experiments showing a lower body temperature demonstrated a decrease in thymidine incorporation. This effect was related to the body temperature change and not considered a primary DNA damaging effect. It was concluded that carvedilol did not affect DNA replication. (Not under GHP conditions)

*S9 mix obtained from liver fraction of Aroclor induced male Fisher 144 rats.

** S9 mix obtained from liver fraction of phenobarbital and 3-methylcholanthrene induced male Sprague Dawley rats.

Genotoxicity (Cont'd)

B- IN VITRO MAMMALIAN CELL SYSTEM (cont'd.)

Study	Concentrations Tested	Report No. Ref. No. Location in NDA IND Submission	Drug-Related Observations
i) <i>✓</i> Unscheduled DNA synthesis test (<i>Detects repair of DNA damage.</i>)	<i>Mouse sperm</i> 2100 mg/kg p.o.	TC016BS (Boehringer Mannheim report J1) Location: Vol. 1.40 Page 000004 Submitted to IND on 2/15/85	There was no difference in % UDS between control and drug-treated animals. Thus, carvedilol did not induce unscheduled DNA synthesis in mouse testicular cells in this system.
j) <i>✓</i> Micronucleus test in Chinese hamster (<i>Detects chromosomal aberrations.</i>)	1500 mg/kg p.o.	TC016BS (Boehringer Mannheim report J1) Location: Vol. 1.40 Page 000004 Submitted to IND on 2/15/85	The mean number of micronuclei in control and drug-treated animals was 13.90 and 20.67, respectively. Since these numbers represented less than a doubling in the micronucleus rate, the test was considered negative.
k) <i>✓</i> Sister Chromatid exchanges in Chinese hamster (<i>Detects chromosome breakage (clastogenic) & chemical.</i>)	1000 mg/kg p.o.	TC016BS (Boehringer Mannheim report J1) Location: Vol. 1.40 Page 000004 Submitted to IND on 2/15/85	The mean number of sister chromatid exchanges in cells of control and drug-treated animals was 85.16 and 70.83, respectively. Carvedilol did not enhance sister chromatid exchange <i>in vivo</i> .
l) <i>✓</i> Chromosome aberration test in <u>bone marrow</u> of Chinese hamster	2000 mg/kg p.o.	TC016BS (Boehringer Mannheim report J1) Location: Vol. 1.40 Page 000004 Submitted to IND on 2/15/85 TC017BS (<i>Not under GMP conditions</i>) (Boehringer Mannheim report J3) Location: Vol. 1.40 Page 000090 Submitted to IND on 2/15/85 <i>(Report states that studies were conducted in 1982)</i>	* <u>First study</u> : Three gaps and one fracture were observed in 3200 metaphase nuclei of drug-treated animals. These numbers corresponded to past observations in nuclei of control animals. Therefore, the control animals were not examined and the test was considered to be negative. <u>Second study</u> : Not any drug-related increase in either structural or numerical changes compared to the negative control. Thus, carvedilol has no effect on chromosomal aberrations <i>in vivo</i> . (<i>Correlates with GMP</i>)

Genotoxicity Studies (Cont'd)

OVERVIEW OF GENOTOXICITY STUDIES NOT PREVIOUSLY REVIEWED

(Identification symbols refer to studies listed above in Table submitted by drug sponsor and edited by present reviewer.) All studies submitted in Vol. 40 of this NDA.

A.iii) Mutagenicity Evaluation of n-Benzyl Carvedilol (Intermediate [SK&F 105569]) in the Ames Salmonella/Microsome Plate Test [TP001BS]. Submitted to IND on 10/3/89; Study Dates: 15-Apr-87 and 5-May-87).

n-Benzyl carvedilol is an intermediate in the synthesis of carvedilol and is not found in the finished drug substance.

n-Benzyl carvedilol was tested for its ability to cause gene mutation (reverse mutation at selected histidine loci) in *S. typhimurium* tester strains TA98, TA100, TA1535, TA1537 and TA1538, both in the absence and presence of microsomal activation system (S9). The tests were performed at 6 concentrations of n-benzyl carvedilol: 50, 167, 500, 1670, 3330 and 5000 µg/plate (lot no. AC10368). n-Benzyl carvedilol precipitated out at the highest concentration tested.

Statistically significant, dose-dependent increases in revertant frequencies were seen with n-benzyl carvedilol (2-fold elevation) in strain TA1535 without S9 mix, and an equivocal response was observed at 500 µg/plate in strain TA1537 with S9 mix. All other strains were negative. Although n-benzyl carvedilol was considered to have produced a positive response in strain TA1535 with S9 and equivocal response in strain TA1537 with S9, these were considered by sponsor to be of "uncertain biological significance" and of no significance relative to safety.

The negative and positive and negative control values were reported as within historical limits and all positive controls produced positive responses under the plating conditions.

A.iv) Study of Mutagenicity of Carvedilol (DQ-2466): Reverse Mutation Assay using Escherichia Coli [TC/0030/SKF-105517 (Daiichi report D-17). Test Dates: 11-Apr-88 - 26-May-88). Carvedilol Lot no. 437265 was tested

Carvedilol was tested for its ability to cause gene mutation in *E. coli* WP2uvrA, a strain sensitive to a wide range of mutagens. Carvedilol was tested both with and without microsomal activation in *E. coli* WP2uvrA at 7 concentrations: 5, 15, 50, 150, 500, 1500 and 5000 µg/plate. DMSO was used as negative control and 2-aminoanthracene and n-ethyl-n-nitrosoguanidine as positive controls.

Toxic effects and precipitation were noted at concentrations of 500 µg/plate and above with and without metabolic activation. Levels below 500 µg/plate did not show an increase in revertant frequency with and without S. Thus, sponsor considered that the drug did not demonstrate gene mutation activity in this test.

B.i) Carvedilol (BM14.190): Chinese Hamster Ovary Cell (CHO) Mutation Assay [TC017BS (Boehringer Mannheim report J3)] Submitted to IND on 2/15/85; Study Dates: Apr-86 and Oct-86. Carvedilol batch no. 815164A was tested.

Carvedilol was tested to determine its potential to induce mutation in cultured CHO cells at the sex-linked hypoxanthine-guanine-phosphoribosyl transferase (hgprt) locus, from hgprt+ to hgprt^y. This forward mutation results in colony growth in agar containing 6-thioguanine which is cytotoxic to cells possessing hgprt and less toxic to the mutants.

In preliminary toxicity tests CHO cell cultures exposed to the drug at concentrations ranging from 0.03 up to 300 µg/ml; at 30 µg/ml in the presence of S9 there was reduced cell growth to 7% of vehicle control value, and in the absence of S9 total cell death.

After preliminary tests to determine adequate concentrations of carvedilol to be tested for mutagenic potential, the final concentrations selected were 8-9, 12, 15-16, 18-20 and 21-24 µg/ml in the absence of S9 mix, and 16-21, 20-24, 27-28 and 30-32 or 33 µg/ml in the presence of S9 mix; assays were repeated 4 times. Concurrent positive controls were ethyl methanesulphonate (EMS) and 3-methylcholanthrene (3-MC) and vehicle used DMSO.

In this assay, sponsor reported that mutant fractions obtained with the positive control and vehicle controls were within the normal ranges of the testing laboratory.

In the absence of S9 mix, a small increase in mutation frequency over vehicle control values was obtained only in the cultures treated with 15 µg/ml of carvedilol. This isolated incidence was not regarded as significant by sponsor. In the presence of S9 mix, no evidence of mutagenic activity was obtained in carvedilol-treated cultures.

Data suggest that carvedilol is not mutagenic in Chinese hamster ovary cells, in the presence or absence of S9 mix, when tested in DMSO at close to toxic concentrations.

B.ii) Chromosome Aberration Test with Human Lymphocytes *in vitro* [TC017BS (BM/J3)] Submitted to IND on 2/15/85; Study Dates: 17-Mar-86 and 17-Apr-86). Carvedilol batch no. 815164A was tested.

Carvedilol was tested to determine its potential to cause chromosomal damage in human lymphocytes cell cultures. The drug was tested, both with and without microsomal activation, by metaphase analysis of the cultured human lymphocytes.

In a preliminary assay, carvedilol was highly toxic to the lymphocytes at concentrations of 200 µg/ml and above; 25% reduction in mitotic index was obtained at 70 µg/ml. The definitive assays were performed with carvedilol at concentrations of 8, 40 and 80 µg/ml in the absence/presence of S9. The positive controls were bleomycin 10 µg/ml and cyclophosphamide 100 µg/ml. All treatments were in duplicate cultures.

No significant damage in chromosome structure or numerical changes were reported for this assay with carvedilol.

B.iv) DNA-Synthesis Inhibition Test [TC]16 BS (BM/J1) submitted to IND on 2/15/85; Study Dates: 13-Jan-82 and 11-Feb-82)

Carvedilol was tested for its ability to detect covalent binding to testicular DNA which interferes with normal DNA replication synthesis. This effect is measured as a reduction in uptake of radio-labeled thymidine.

ICR mice were administered carvedilol (batch no. 811012A), orally by gavage, at dosages of 50, 100 and 200 mg/kg dissolved in 10% DMSO/90% PEG 400.

Lowering of the animal's body temperature by 10°C using this solution was found in 2 of 3 experiments at a dosage of 200 mg/kg. At this dose, one of the two experiments showed a decrease in thymidine incorporation. This finding was related to the extreme decrease in body temperature and was not considered to be due to damage to DNA. Thus, it may be concluded that carvedilol had no effect on DNA replication in this *in vivo* DNA test.

The following are the summaries/evaluations of mutagenicity studies (J series) are reproduction of previously submitted to FDA and that have undergone a secondary review by supervisory pharmacologist Charles Resnick, Ph.D. Thus, since they were found to be adequate, these are incorporated in this document unedited.

Report No. J1. Mutagenicity of BM 14,190. (Boehringer Mannheim, Germany; Dated March 26, 1979. vol. 1.7, p 06 001371): Quality Assurance Unit statement for this report dated Nov. 18, 1983, concerns only the report and not the study conduct. Statement of Compliance with GLP dated Dec. 10, 1984 (p. 06 0014248) indicates that studies in Part 1 of Report J1 were performed prior to GLP regulations. Deviations from GLP are stated. Studies described in Part 2, i.e., "Supplement to the Report of March 26, 1979" were conducted according to GLP except: 1) "The protocol did not meet all formal requirements of the GLP regulation", and 2) "The conduct of the tests was not inspected by the quality assurance unit. The final report however, was completely audited by the quality assurance unit."

- Host-Mediated Assay in the Mouse with Salmonella typhimurium G 46 and Serratia marcescens a 21. (A test for substance-induced revertants). Doses: 200 and 2000 mg/kg, p.o. With Salmonella typhimurium G 46, Carvedilol at 2000 mg/kg was too antibacterial to determine mutagenicity; at 200 mg/kg the compound was neither antibacterial or mutagenic. With Serratia marcescens a 21 carvedilol at 2000 mg/kg (but not 200 mg/kg) was both antibacterial and mutagenic. No positive control.

Mutagenicity studies (Cont'd.)

- In vitro test with Multiple Purpose Strain *Saccaromyces cerevisiae* NP-1 with and without Liver Homogenate. (A test for substance-induced gene conversion, forward mutation and recombinations). Concentrations: 0.01 to 50 mg/ml with and without liver homogenate (S9 mix from rat liver induced with phenobarbital and methylcholanthrene). Carvedilol was toxic to the organism at 0.1 mg/ml and above without the liver homogenate and at concentrations of 1 mg/ml and above with the liver homogenate. There was no indication that 0.01 mg/ml with or without the S9 mix or 0.1 mg/ml with the S9 mix was mutagenic. Conclusions with this test are, therefore, limited since only low concentrations were not lethal to the yeast. No positive control.
- Micronucleus Test in the Chinese Hamster (A test for chromosome breaking). Dose: 1500 mg/kg. Bone marrow obtained at 24 hrs. The increase of micronuclei per 10,000 RBCs from 13.5 ± 6.1 in controls to 20.7 ± 4.6 in treated hamsters was less than the doubling considered by the Sponsor to be necessary for the test to be positive. No positive control.
- Test for Sister Chromatid Exchange (SCE) in the SCE-test in Chinese Hamster. Dose: 1000 mg/kg p.o. Carvedilol did not induce sister chromatid exchange. No positive control.
- Ames Test with and without Liver Homogenate using the Test Strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 (A test for substance-induced revertants). Concentration: 1 to 5000 mcg/plate with or without liver homogenate (S9 fraction of homogenized liver from Sprague Dawley rats treated with phenobarbital and methylcholanthrene). This study was done twice. Carvedilol was markedly antibacterial at concentrations above 100 mcg/plate, therefore, only the mutagenic potential of carvedilol at low concentrations (100 mcg/plate or less) could be assessed. Carvedilol was not mutagenic based on the criteria of a concentration-response relationship and/or at least a 2 fold increase in the number of revertants. There were, however, statistically significant increases in the number of revertants in some strains. The statistics applied consisted of an overall one-way analysis of variance (ANOVA) and a multiple comparison of each concentration with vehicle. Consistency between studies occurred only with strain TA 1535 in which, without metabolic activation, a statistically significant increase in revertants was seen by ANOVA and at 100 mcg/plate. Occasional significant (by ANOVA or at 100 mcg/plate) increases in the number of revertants were seen with strains TA 98, TA 100, TA 1537 and TA 1538. In conclusion, the results of the Ames test were inconclusive since, although not clearly mutagenic, carvedilol tended to be mutagenic at 100 mcg/plate. Higher concentrations could not be tested because of the marked antibacterial activity of the compound. No positive controls.

Mutagenicity studies (Cont'd.)

- Bone Marrow Test in the Chinese Hamster (*Cricetus griseus*) (A test for substance-induced chromosome aberrations). Dose: 2000 mg/kg, p.o., single dose. Sponsor refers to data presented in Table 29 but no such table found. Sponsor's description of results: "the three gaps (holes in the staining) and one fracture found in the 3200 metaphase nuclei examined correspond to our control values. We therefore omitted the further examination of the control group that was also included in the test." No positive control.

Summary and Conclusions: Failure to use positive controls in any of these studies lessens their value.

Carvedilol at oral doses of from 1000 to 2000 mg/kg did not show any effects in mammalian tests in which chromosome-breaking activity was tested directly (bone marrow test, micronucleus test) or indirectly (SCE).

In non-mammalian tests for substance-induced gene mutation (Ames test, *Saccharomyces cerevisiae* MP-I test, and host-mediated assay with *Salmonella typhimurium* G and *Serratia marcescens*). Carvedilol was mutagenic in the host-mediated assay with *Serratia marcescens* at 2000 mg/kg (this dose was also antibacterial). The results of all the other tests are inconclusive since the marked antibacterial activity of carvedilol prevented testing high doses and/or concentrations. Although not satisfying strict criteria for positivity, carvedilol did tend to be mutagenic in the Ames test at 100 mcg/plate. The highest concentrations of carvedilol that could be tested in the *Saccharomyces cerevisiae* MP-I test (10 mcg/ml without the S9 mix and 100 mcg/ml with the S9 mix) were negative.

BM 14,190 - Mutagenicity. Supplement to Report of March 26, 1979 (report dated August 10, 1983, vol 1.7, p. 06 001418.) This supplement was included in Report J1 but not summarized. Three studies are presented:

1. DNA-Synthesis Inhibition (DSI) Test (mouse)
2. Unscheduled DNA-Synthesis (UDS) Test
3. Ames Test

The first two tests were performed in Dr. Seiler's laboratory at the Wädenswil Federal Research Institute, Switzerland while the last test was carried out by Boehringer Mannheim, Germany.

- DNA-Synthesis Inhibition (DSI) Test. Mouse testes. Doses: 50, 100 and 200 mg/kg, p.o. given as single doses. Rationale for doses not presented. Dr. Seiler's general methods indicate the high dose is usually the established LD50. This is clearly not the case for carvedilol (oral LD50 in mouse is in excess of 8000 mg/kg). Test drug is administered to mice preabled with 14C-thymidine; Three

Mutagenicity studies (Cont'd.)

hours post-test drug, ³H-thymidine is administered and 45 minutes later the incorporation of ³H-thymidine into the testes is determined. The test was repeated twice at 50 and 100 mg/kg and in both tests carvedilol failed to inhibit DNA synthesis. The 100 mg/kg dose reduced rectal temperature 2-3 degrees C. Three tests were performed at 200 mg/kg and in one of these tests DNA synthesis was inhibited by 54% and rectal temperature fell by 12 degrees C. DNA synthesis was not significantly inhibited (-12 and -18%) in the other two tests and rectal temperature was not reduced (-40 and -100, respectively) less markedly.

● Unscheduled DNA Synthesis (UDS) Test. Mouse. Dose: 200 mg/kg three hours prior to removal of testes to measure, in vitro, DNA synthesis and repair. This test was in fact performed by Dr Seiler as a part of the above report. The experiment was performed twice and in neither test was there a significant change in unscheduled DNA synthesis. In the absence of statements to the contrary, it is assumed that these UDS studies used testicular preparations from different mice than used for DSI test at 200 mg/kg. It is also not known what effect the compound had on rectal temperature or on DNA synthesis in these animals. The table presented in Dr. Seiler's report combines the data and suggests that the UDS data were from testicular preparations from the two studies in which carvedilol did not inhibit DNA synthesis.

Conclusion: Dr. Seiler concluded that the reduced DNA synthesis associated with carvedilol in 1 out of 3 studies at 200 mg/kg, p.o., was secondary to the drug-induced fall in body temperature and not due to a direct effect of the compound on DNA synthesis. This dose of carvedilol did not affect unscheduled DNA synthesis.

● Ames Test: Test strains: TA 98, TA 100, TA 1535, TA 1537 and TA 1538. Concentrations: 10 to 500 mcg/plate with and without liver homogenate (S-9 mix from Sprague Dawley rats induced with phenobarbital and methycolanthrene). Carvedilol at up to 500 mcg/plate was not mutagenic in any of the test strains. The significantly (statistically) higher number of revertants seen with the S-9 mix in TA 98 at 10 & 100 mcg/plate (but not at 50 or 500 mcg/plate) and in TA 100 at 50 & 100 mcg/plate (but not at 10 or 500 mcg/plate) was less than twice the number of revertants seen with vehicle.

		Carcinogenicity study with BN 14,190 in mice						J 4 - 21	
		unscheduled killed or died	with tumors	without tumors	scheduled killed	with tumors	without tumors	total with tumors	total without tumors
Table 1									
BN 14,190									
	Dose	n	with tumors	without tumors	scheduled killed	with tumors	without tumors	total with tumors	total without tumors
	Control	100	46-79,31	12-20,71	42-421	37-88,11	5-11,91	83-831	17-171
	20 mg/kg	50	13-88,41	6-31,61	31-621	25-80,61	6-19,41	30-761	12-241
	65 mg/kg	50	21-751	7-251	22-441	19-86,41	3-13,61	40-801	10-201
	200 mg/kg	50	17-60,71	11-39,31	22-441	17-77,31	5-22,71	34-681	16-321

		Carcinogenicity study with DM 14.190 in mice					J 4 - 22			
		with tumors	without tumors	scheduled killed	with tumors	without tumors	total with tumors	total without tumors		
Table 2 DM 14.190	Dose	n	unscheduled killed or died	with tumors	without tumors	scheduled killed	with tumors	without tumors		
	Control	100	73-735	39-53, 41	34-46, 61	27-270	23-05, 20	4-14, 01	62-629	38-381
	20 mg/kg	50	40-801	23-57, 51	17-42, 51	10-201	6-601	4-401	29-501	21-421
	65 mg/kg	50	39-701	19-40, 71	20-51, 31	11-221	9-01, 01	2-10, 21	28-561	22-441
200 mg/kg	50	40-801	19-47, 51	21-52, 51	10-201	7-701	3-301	26-521	24-481	

000025

Table 18



Table 7: Frequencies of animals with tumors
respective malignant tumors

male mice

Dosage	Group 1 Control	Group 2 20 mg/kg	Group 3 65 mg/kg	Group 4 200 mg/kg
Number of animals with a tumor	63	38	40	36
Number of animals with a malignant ¹⁾ tumor	40	17	23	16

female mice

Dosage	Group 1 Control	Group 2 20 mg/kg	Group 3 65 mg/kg	Group 4 200 mg/kg
Number of animals with a tumor	62	29	28	26
Number of animals with a malignant ¹⁾ tumor	37	20	18	16

At begin of study there were 100 animals per Control and 50 animals per dosage and sex.

¹⁾ = malignant is not the same as fatal

NDA 20297

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AUC(0-24) and AUC(0-∞) were log-transformed, and data for t1/2 and Cmax were untransformed. These parameters were analyzed using ANOVA model with linear effects for group, sequence, period, and treatment.

Results: Mean (range) pharmacokinetic parameters, point estimates, and 90% CI for carvedilol are shown in Table 1. Individual subject data and statistical analysis for parameters are listed in Appendix II.

Table 1
Mean (Range) Pharmacokinetic Parameters, Point Estimates,
and 90% Confidence Intervals for Carvedilol
(Protocol 105517/A9907-GER).

	Fasted State	Fed State	Point Estimate	90% CI
Cmax (ng/ml)	53.6	48.4	E/F [*] : 0.90	0.62 - 1.29
Tmax (min)	60 [†]	135 [‡]	E-F [†] : 90 min	15 - 150 min
AUC _{0-t} (ng·min/ml)	9976	10301	E/F [§] : 1.07	0.89 - 1.30
AUC _{0-∞} (ng·min/ml)	10492	10843	E/F [§] : 1.07	0.90 - 1.28
T1/2 (min)	423	355	E-F [*] : -67 min	-137 - +3 min

- * parametric analysis of untransformed data
- † non-parametric analysis
- § parametric analysis of log-transformed data
- ‡ medians

When administered in the fed state, there was a significant increase in median Tmax (135 mins vs. 60 mins in the fasted state). Also there was overall increase in its variability in the presence of food. In contrast to the change in Tmax, the extent of bioavailability of carvedilol did not appear to be altered in the presence of food. Compared to the fasted state, only small differences (7-10%) in mean Cmax and AUC values for carvedilol were observed in the fed state. Although, their 90% CI fell outside the 80% to 120% range normally accepted for bioequivalence because of the large variability, these parameters were not significantly different between two treatments.

Conclusions and Comments: Following an oral dose of 25 mg carvedilol tablet in the presence of food, there was a significant increase in T_{max} as well as increase in variability. Although there was little change in terms of mean C_{max} , $AUC(0-24)$, $AUC(0-\infty)$, and $t_{1/2}$ values, these were not statistically significantly different.

Single-dose PK in Young & Elderly Healthy Volunteers

Study No.: MF 3413

Volume: 1.57

Pages: 2-263

Investigators and Site:

Objectives: To determine the pharmacokinetics of carvedilol in young versus elderly healthy volunteers.

Formulations: • Carvedilol 5 mg ampoules, batch # 818 651 59 A

- Carvedilol 12.5 mg capsules, batch # 819 155 Fc
- Carvedilol 25 mg capsules, batch # 818 902 Db, 819 561 Ec
- Carvedilol 50 mg capsules, batch # 818 173 Cd, 819 292 Ed
- Placebo capsules, batch # 817 944 40 Ac
- Labetalol 200 mg tablets, batch # 195068, 195177

Study Design: Ten young male subjects (age: 20-40 yrs; weight: 59-87 kg) and 10 elderly subjects (9 M, 1 F; age: 57-66 yrs; weight: 74-89 kg) with a supine DBP between 70 and 100 mm Hg were recruited. Twenty subjects received first 5 treatments (cross-over) in a randomized order (double blinded) after an overnight fast:

1. single oral dose of 25 mg carvedilol
2. single oral dose of 50 mg carvedilol
3. single oral dose of 200 mg labetalol
4. single oral dose of placebo capsule
5. single oral dose of 50 mg carvedilol plus a standard breakfast (2 pieces of toast, 1 drink of orange juice and 1-2 eggs)
6. 5 mg carvedilol iv infusion over 5 mins.
7. single oral dose of 12.5 mg carvedilol

Only 5 young and 8 elderly subjects received carvedilol intravenously. Only 6 elderly and 9 young subjects completed the 7th study. Each treatment was separated by at least 2 weeks.

Specimens: Plasma samples were collected before and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, 30, and 48 hours following oral administration of carvedilol. During i.v. study, additional samples were taken at 4, 10, 20, 30, 40, 50, and 75 mins after cessation of the infusion. In some subjects, additional plasma samples were collected immediately after the infusion ceased and at 2, 6, and 8 mins. Urine was collected over the 0-12, 12-24, and 24-48 hr time periods after oral and intravenous administration.

Assay:

Plasma and urine samples were analyzed for carvedilol and desmethylcarvedilol by HPLC with fluorescence detection.

Linearity: not reported

Precision: not reported

Sensitivity: LLQ for carvedilol: 2-5 ng/ml, for desmethylcarvedilol: 5 ng/ml

Specificity: not reported

Data Analysis: Pharmacokinetic parameters were determined by noncompartmental methods. The data sets relating to the oral doses of carvedilol were analyzed by repeated measures analysis of variance with age as a between subjects factor and dose as a within subjects factor.

Parameters derived from i.v. and 12.5 mg oral doses were compared between young and old groups using a non-paired t-test.

Results: The mean pharmacokinetic parameters for carvedilol derived from the data after oral and intravenous dosing are shown in Tables 1 and 2. Mean plasma profiles for carvedilol are shown in Fig. 1 to 6.

Table 1
Pharmacokinetic Parameters for Carvedilol*
(Protocol MF 3413)

		12.5 mg	25 mg	50 mg	50 mg (+ food)	5 mg (iv)
C _{max} (ng/ml)	Y	24 (N = 9)	54	119	96	
	E	27 (N = 6)	68	122	134	
T _{max} (hr)	Y	1.4 (N = 9)	1.1	1.4	1.8	
	E	1.4 (N = 6)	1.0	1.2	1.4	
AUC _{0-∞} (ng·hr/ml)	Y	156 (N = 9)	226 [†]	496 [†]	585 [†]	144 (N = 5)
	E	166 (N = 6)	385	717	810	233 (N = 8)
t _{1/2} [§] (hr)	Y	18.5 (N = 9)	14.0	14.7	8.2	4.3 (N = 5)
	E	9.2 (N = 6)	13.3	9.8	9.3	9.8 (N = 8)

* Data are presented as mean and range; Y = young; E = elderly; Number of subjects (N) equals 10 unless otherwise indicated.

[†] p = 0.02 between young and elderly subjects.

[§] Estimates obtained using the modeling program AUTOAN2.

2.
Table Pharmacokinetic parameters calculated using 5 mg iv MCl₄.190

	% Bioavailability	Clearance (ml/min)	Volume of distribution (l)
Young	34 ± 7	718 ± 129	189 ± 32
Old	44 ± 7	503 ± 108	317 ± 98

Results are means ± SE

Following oral administration plasma concentrations in the majority of subjects were best described by 2 compartment model. Carvedilol was rapidly absorbed after oral doses. Tmax generally occurred within 2 hours after drug administration. The Cmax and AUC in both groups increased linearly over the dose range 12.5-50 mg in the fasted state (Fig. 7). Mean Tmax and Cmax were similar between two age groups. In the older group, AUC(0-∞) was about 1.5 times larger than that of the young group (p=0.02) after 25 mg and 50 mg carvedilol (both fasting and fed) administration. The AUC(0-∞) was not significantly different between two groups after 12.5 mg dose. Because of the wide variability in elimination half-life there was no significant difference in t1/2 between two groups.

Following i.v. administration, mean t1/2 was approximately 10 hrs in the elderly. In the young group, mean t1/2 was about 4 hrs. Because of the variability in the data and the smaller number of subject, t1/2 was not significantly different between two groups. Mean AUC(0-∞) was 1.6 times larger in the elderly, but was not statistically different between two groups.

Conclusions: Mean Tmax and Cmax values were similar between young and elderly groups. The Cmax and AUC in both groups increased linearly over the dose range 12.5-50 mg in the fasted state. However, at the 25 mg and 50 mg doses AUC(0-∞) was significantly higher in the elderly (approximately 1.5 times higher in the elderly).

The elimination half-life was highly variable and was not different between the young and elderly after oral and intravenous administration and no difference over dose.

There is a trend in increase in bioavailability, decrease in clearance, and increase in volume of distribution after intravenous administration of carvedilol in elderly subjects.

The administration of food with carvedilol did not significantly alter the disposition of the drug.

Comments: The quality control data were not provided.

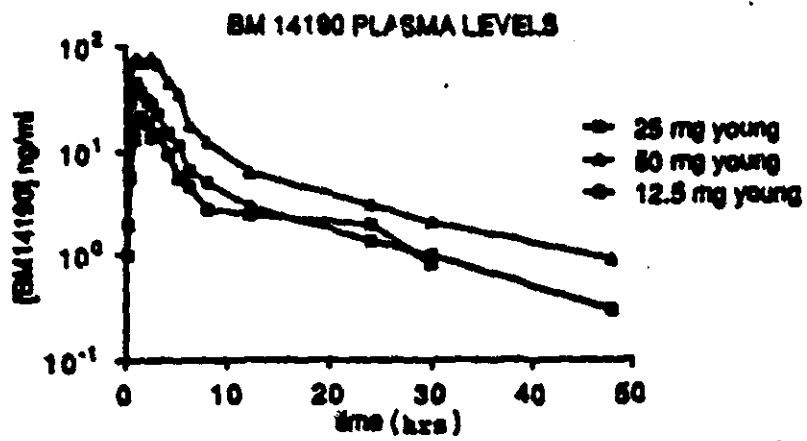


Fig. 1

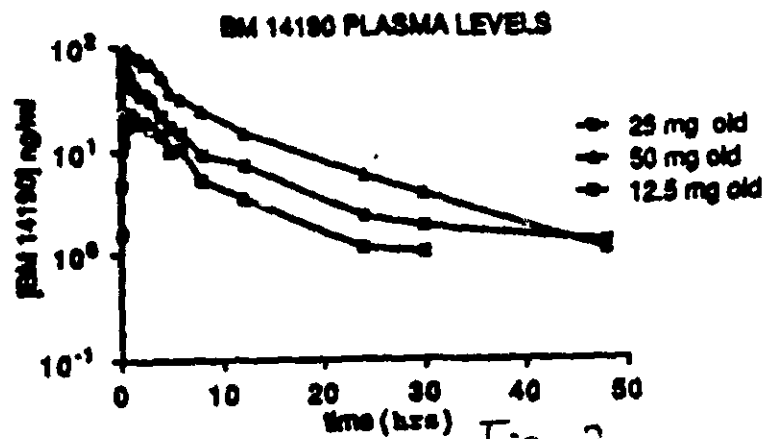


Fig. 2

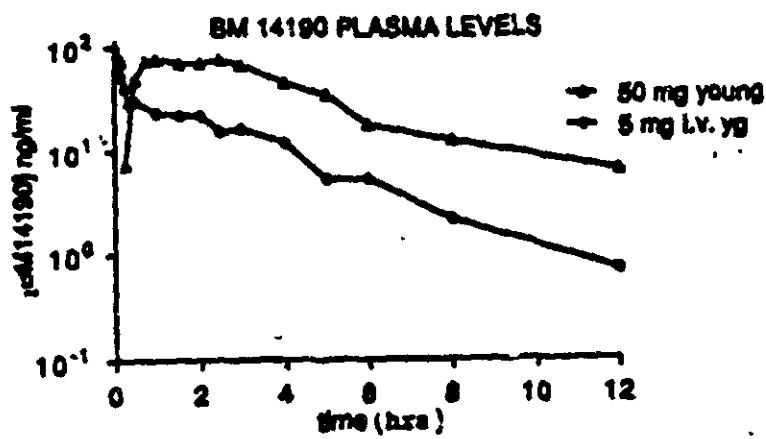


Fig. 3

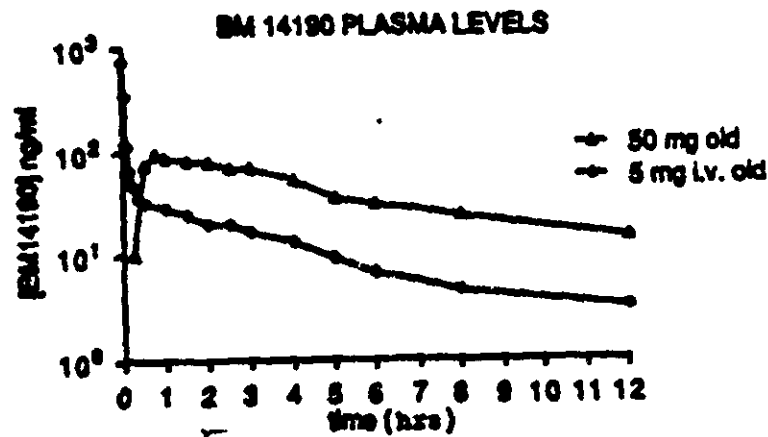


Fig. 4

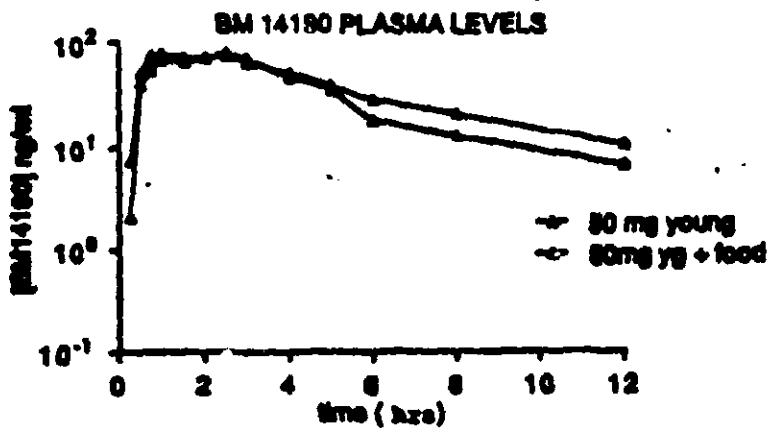


Fig. 5

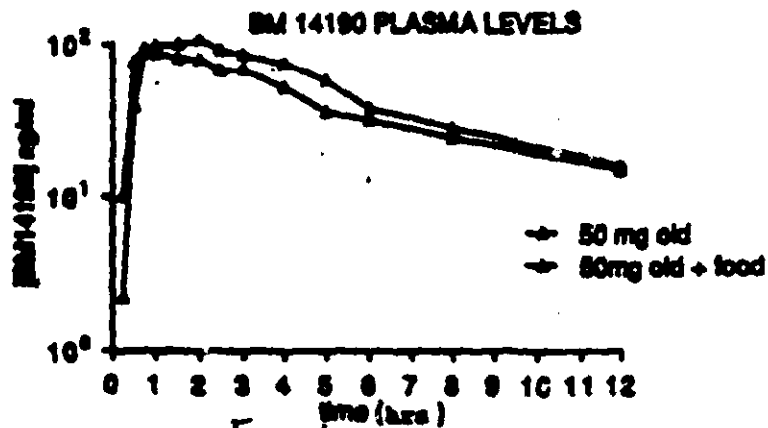
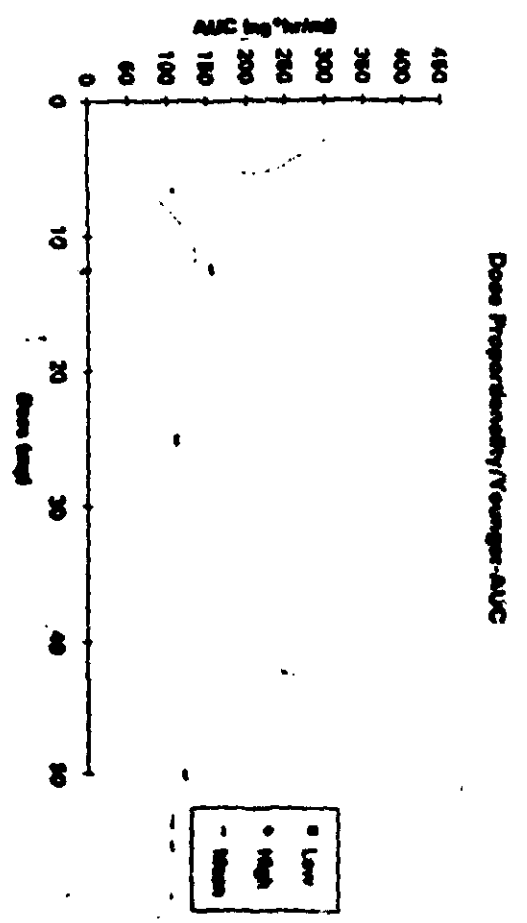
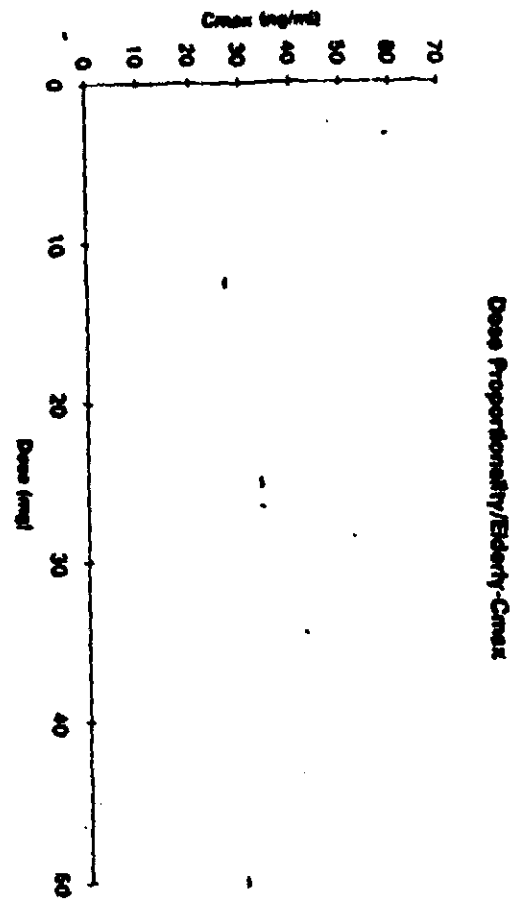
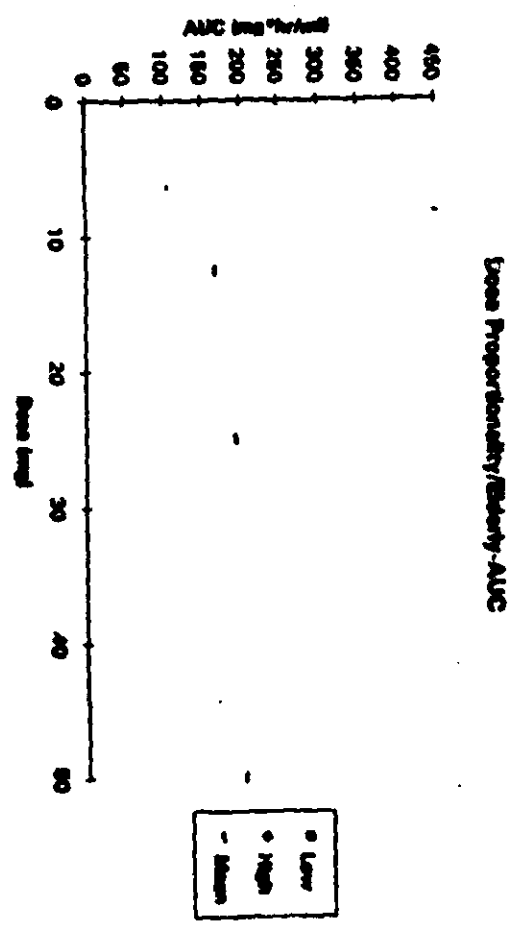
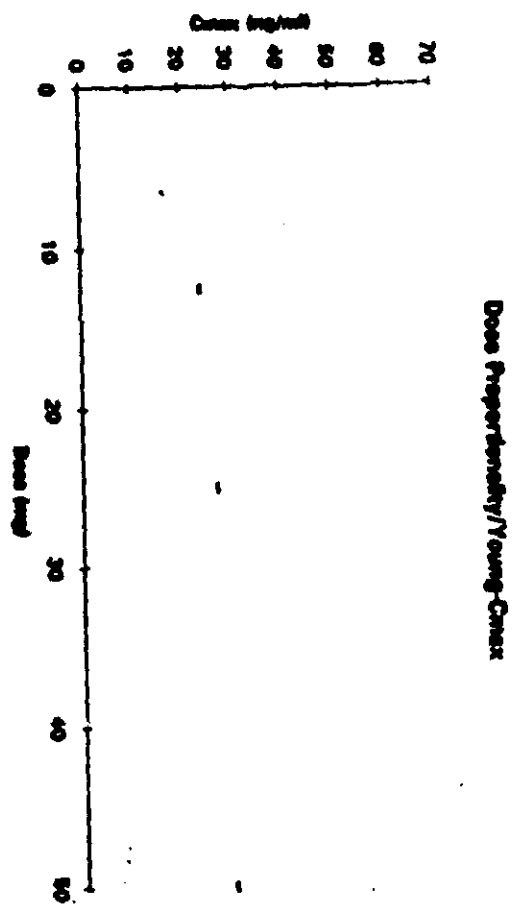


Fig. 6

Fig. 7.



* AUC A (mean) ave. normalized w/rt 12.5mg dose

Single and Multiple-dose PK in Young & Elderly Healthy Volunteers

Study No.: MF 3950

Volume: 1.63

Pages: 2-253

Investigator and Sites:

Center 1:

Center 2:

Objectives: To determine the pharmacokinetics of carvedilol in young and elderly population after single and multiple oral doses.

Formulations: • Carvedilol 25 mg capsules, batch # 819 156 40 Ec

Study Design: Two-center, open, uncontrolled multiple dose study. Ten young male subjects (age: 20-26 yrs; weight: 59-85 kg) were studied at one center and a parallel study was conducted in 11 elderly male and female subjects (age: 66-71 yrs; weight: 59-85 kg) at a separate geriatric facility. They received 25 mg carvedilol capsules once daily for 2 weeks.

The first evaluation on day 1 could be performed in all 21 subjects. Four of the elderly subjects were withdrawn from the study due to postural hypotension, so only 17 subjects could be included into the second evaluation on day 14.

On days 1 and 14 the drug was administered after overnight fast and no food was given until 4 hours post dose. On the other days subjects were dosed 1 hr prior to a standard breakfast comprising cereal, toast, butter, marmalade, fruit juice, and tea or coffee.

Specimens: Plasma samples, at pre dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours post-dose in the single dose study. Additional samples were obtained at 36 and 48 hours post-dose in the multiple dose study. All urine was collected over 0-24 hour time period on days 1, 14, and 15.

Assay:

Plasma and urine samples were analyzed for carvedilol and desmethylcarvedilol by HPLC with fluorescence detection. Samples were analyzed at

Linearity: satisfactory, calibration curves from 5.0 ng/ml to 200 ng/ml for carvedilol, calibration curves from 5.0 ng/ml to 100 ng/ml for desmethylcarvedilol.

Sensitivity: LLQ in plasma for carvedilol: 1 ng/ml, for desmethylcarvedilol: 0.5 ng/ml

LLQ in urine for carvedilol and desmethylcarvedilol : 1.0 ng/ml

Precision: Interday CV for carvedilol ranged from 6.4% at 10 ng/ml to 4.5% for 150 ng/ml.

Interday CV for desmethylcarvedilol ranged from 7.8% at 5.0 ng/ml to 6.4% at 50 ng/ml.

Specificity: satisfactory

Data Analysis: Pharmacokinetic parameters were determined by noncompartmental methods. The two-sample t-test was also used to compare the pharmacokinetic parameters for carvedilol and desmethylcarvedilol between the young and elderly. When the residual is not normally distributed, Mann-Whitney and Wilcoxon matched pair tests was used instead of t-test.

Results: The pharmacokinetic parameters for carvedilol in young and elderly subjects are shown in Tables 1 and 2. Figures 1 and 2 show the mean plasma-time profile for carvedilol for both the young and elderly subjects on day 1 and 14.

0.014

Table 1
Pharmacokinetic Parameters for Carvedilol*
(Protocol MF 3950)

	SINGLE DOSE		MULTIPLE DOSE	
	Young (n=10)	Elderly (n=11)	Young (n=10)	Elderly (n=7)
AUC ₀₋₂₄ (ng*hr/ml)	382	397 ²⁶⁹	423	342
AUC _{0-∞} (ng*hr/ml)	401	462	505	396
C _{max} (ng/ml)	92.9	78.7	96.6	52.8
t _{1/2} (hr)	7.0	7.8 9.3	13.1	10.1
T _{max} (hr)	1.2	1.3	1.1	1.9

* Data are presented as mean and range

Table 2
Comparison of Single and Multiple Dose Pharmacokinetics
(Protocol MF 3950)

	Single Dose*	Multiple Dose*	Ratio†
<u>Young (n = 10)</u>			
AUC ₀₋₂₄ (ng*hr/ml)	382 (220)	423 (256)	1.11
C _{max} (ng/ml)	92.9 (38.0)	96.6 (41.0)	1.04
<u>Elderly (n = 7)</u>			
AUC ₀₋₂₄ (ng*hr/ml)	267 (70)	342 (110)	1.28
C _{max} (ng/ml)	48.1 (18.9)	59.8 (33.3)	1.24

* Data are presented as mean (SD)

† Ratio calculated as mean AUC₀₋₂₄ or C_{max} after multiple dosing divided by mean AUC₀₋₂₄ or C_{max} after a single dose

There were no statistically significant differences in the pharmacokinetics of carvedilol between young and elderly subjects after both single and multiple administration of carvedilol. Carvedilol was handled in a similar manner by the two groups after a single oral dose of 25 mg. C_{max} were achieved after about 1 hour, and half-lives were about 7 hours and 9 hours in young and elderly groups, respectively. C_{max} and AUC were significantly greater for the elderly subjects who withdrew than for those elderly subjects who completed the study. However, the PK parameters of the 4 elderly subjects were not different from those of the young subjects.

The comparison of PK parameters obtained on day 1 (young n=10, elderly n=11) and day 14 (young n=10, elderly n=7) showed no significant differences between the young and elderly, except for a slightly longer T_{max} in the elderly.

Conclusions: Compared to young healthy volunteers, the pharmacokinetics of carvedilol appeared to be similar in the elderly, although carvedilol plasma level is lower in the elderly. After 14 days dosing, there was only modest increase in carvedilol plasma levels in elderly group. On average, plasma levels of desmethylcarvedilol was less than 5% of those observed for carvedilol.

MEAN VALUES YOUNG SUBJECTS (n=10): PLASMA CARVEDILOL/TIME CURVE
COMPARISON OF DAY 1 & DAY 14

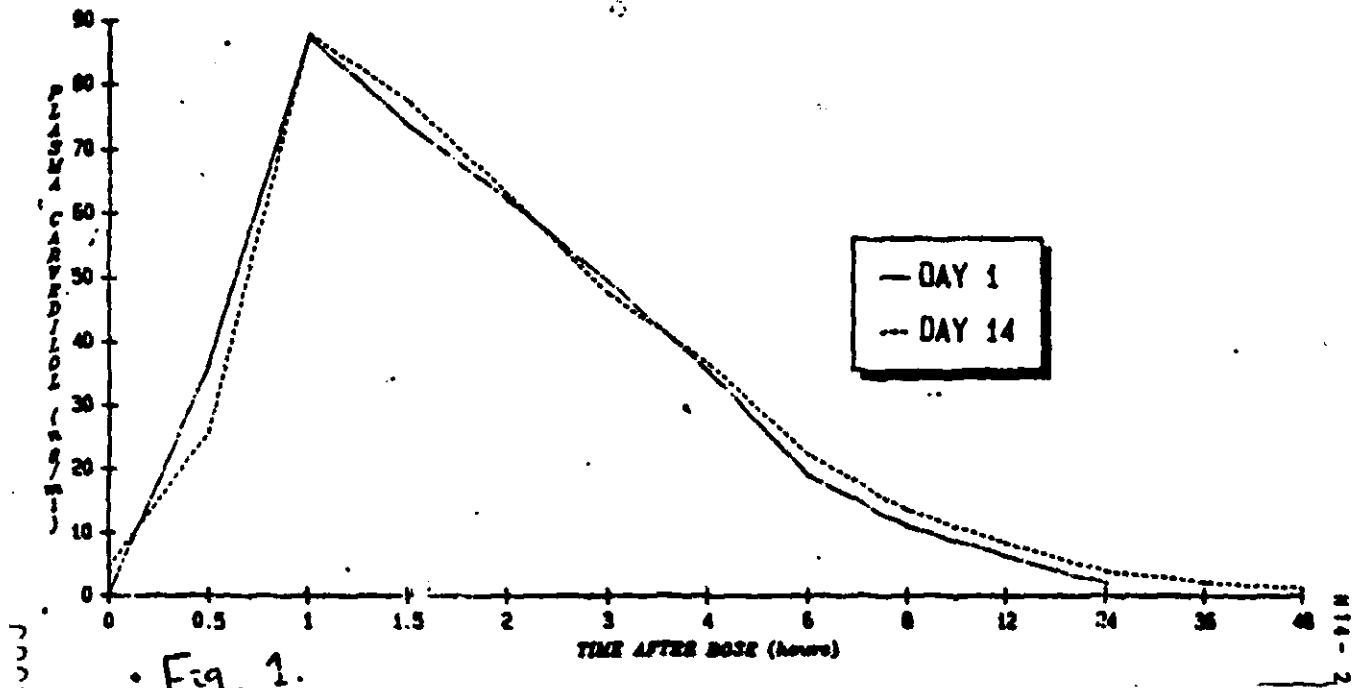


Fig. 1.

MEAN VALUES ELDERLY SUBJECTS (n=7): PLASMA CARVEDILOL/TIME CURVE
COMPARISON OF DAY 1 & DAY 14

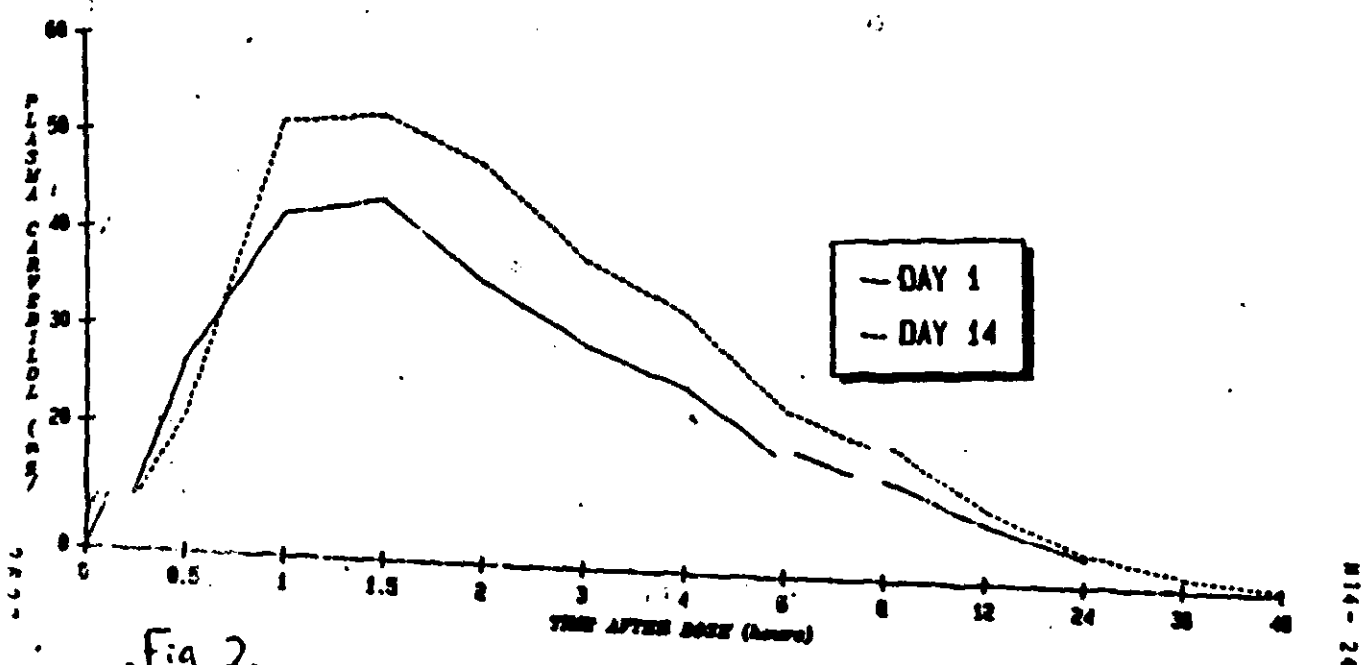


Fig. 2.

Single and Multiple-dose PK in Young & Elderly Hypertensive Patients

Study No.: MF 3702

Volume: 1.61

Pages: 2-263

Investigator and Site:

Objectives: To compare the steady-state pharmacokinetics of carvedilol between young and elderly hypertensive patients.

Formulations: • Carvedilol 12.5 mg capsules, batch # 820 020 40 Jd

• Carvedilol 25 mg capsules, batch # 819 789 40 Hb

• Carvedilol 50 mg capsules, batch # 819 787 40 Ld

• Placebo capsules, batch # 817 944 40 Ac

Study Design: Open, subchronic sequential clinical monocenter trial in two groups of young and elderly hypertensive patients over 12 weeks. Thirty-two patients with essential hypertension entered into a four-week placebo run-in period. Twenty-one older patients (17 M, 4 F: 63-79 yrs) and 8 younger male patients (age 39-47 yrs) with a supine DBP of 95-115 mm Hg qualified for the active drug study. They were initially given 12.5 mg of carvedilol daily as a test dose. The dose of carvedilol was titrated to 25 mg or 50 mg daily according to the patient's blood pressure response. Plasma levels of carvedilol was measured in 5 younger and 17 older patients after single dose of 12.5 mg dose. Plasma levels of carvedilol were measured after patients received 25 mg (3 younger and 9 older patients) or 50 mg (8 younger and 17 older patients) of carvedilol once a day for 14 days. The patients were instructed to take the drug before breakfast.

Specimens: Plasma samples, at pre dose and at 0.5, 1, 1.5, 2, 8, 4, 5, 6, 7 and 24 hours post-dose.

Assay:

Plasma samples were analyzed for carvedilol and desmethylcarvedilol by HPLC with fluorescence detection. Samples were analyzed at the investigational site.

Plasma

Linearity: linear from 0 to 4000 ng/ml

Precision: Inter CV (%) for carvedilol was 6.86% at 50.0 ng/ml.

Intra CV (%) for carvedilol was 10.04% at 50.0 ng/ml.

Sensitivity: LOD, 0.1 ng/ml

Specificity: satisfactory

Data Analysis: Pharmacokinetic parameters were determined by noncompartmental methods. The Wilcoxon test were applied for paired data. Comparisons between the groups were

performed with the Mann-Whitney U-test, $p=0.05$.

Results: Mean pharmacokinetic parameters for carvedilol are shown in Table 1. Figures 1 to 3 show the mean plasma levels of carvedilol in young and elderly patients after administration of 12.5 mg, 25 mg, and 50 mg doses of carvedilol.

Table 1.
Pharmacokinetic Parameters for Carvedilol*
(Protocol MF 3702)

	Younger 12.5 mg [†] (n=5)	Older 12.5 mg [†] (n=17)	Younger 25 mg [‡] (n=1)	Older 25 mg [‡] (n=2)	Younger 50 mg [‡] (n=8)	Older 50 mg [‡] (n=17)
C _{max} (ng/ml)	58 (25)	69 (41)	105 (21)	151 (63)	189 (48)	252 (136)
T _{max} (min)	80 (49)	58 (49)	80 (35)	60 (21)	105 (59)	79 (45)
AUC ₀₋₂₄ (ng·hr/ml)	225 (103)	208 (148)	572 (294)	947 (450)	1073 (571)	1595 (1336)
t _{1/2} (min)	138 (67)	114 (74)	257 (61)	280 (165)	300 (204)	318 (173)

* Data are presented as mean (standard deviation)

[†] Single dose

[‡] Multiple dose

After single dose of 12.5 mg carvedilol, no differences in C_{max}, T_{max}, AUC(0-24), and t_{1/2} were observed between two groups. In contrast, steady-state C_{max} and AUC(0-24) after 25 and 50 mg carvedilol daily for 14 days were higher in the elderly group [C_{max} by 44 % and 33 %, AUC(0-24) by 66% and 49%, respectively] ($p=0.1$). However, these differences were not statistically significant due to large variability and the small number of young patients studied. Half-life values at steady-state were similar between two groups.

A lag-time existed between C_{max} for carvedilol and maximum effect on supine DBP resulting in a hysteresis of mean concentration-effect curve (Figure 4).

After chronic dosing, there was no apparent relationship between individual trough concentration of carvedilol and reduction in supine diastolic blood pressure (Figure 5).

Conclusions: The pharmacokinetics of carvedilol were similar for both groups after single administration of 12.5 mg carvedilol.

After multiple administration of 25 and 50 mg carvedilol daily for 14 days, there was a tendency for C_{max} and AUC(0-24) to be increased (approximately 50%) in the elderly hypertensive patients.

Comments: Plasma concentrations of carvedilol were about 2-3 times higher in both group of patients as compared to those observed in previous study. In the current study, mean C_{max} of 189 ng/ml (younger patients) or 252 ng/ml (older patients) was measured after multiple oral dose of 50 mg carvedilol.

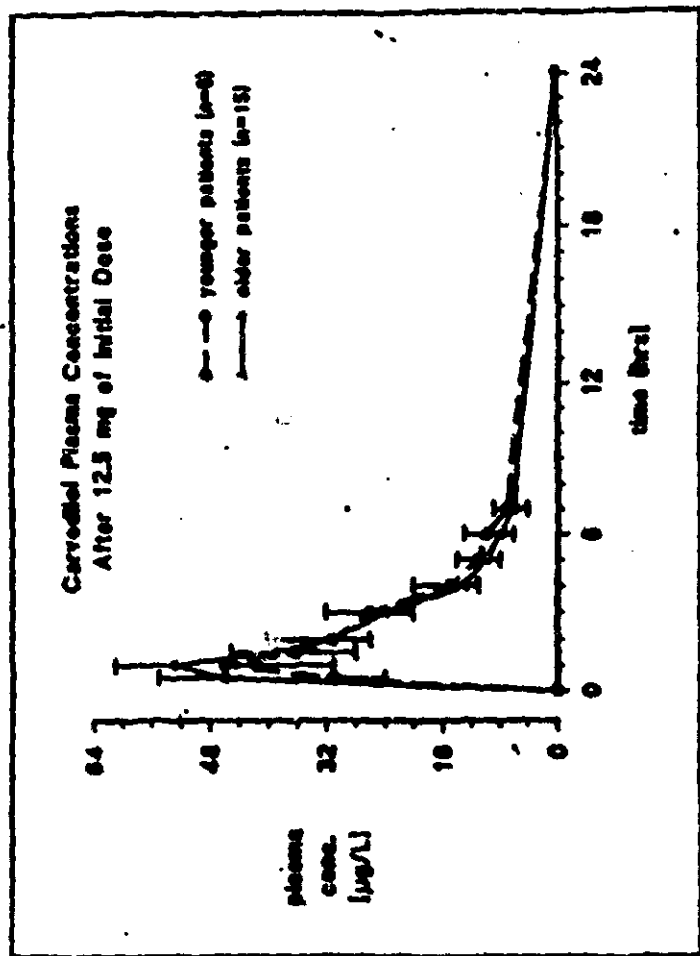


Figure 1: Plasma concentrations obtained with the first dose of 12.5 mg in younger and older patients. (mean ± SEM) See Tab. 27 for values

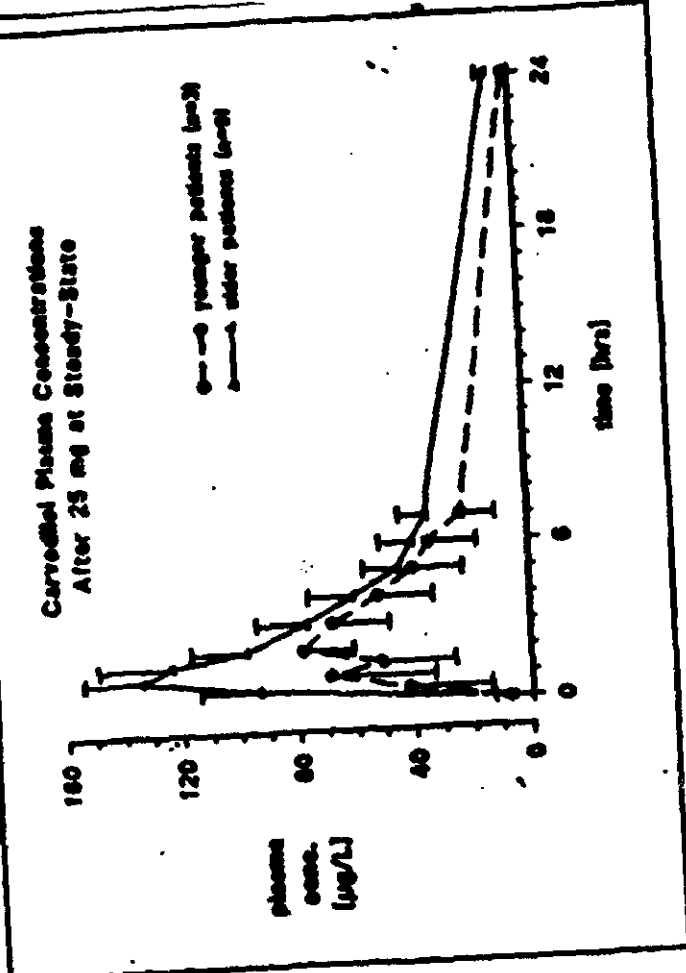


Figure 2: Plasma concentrations obtained in a dose-interval with 25 mg at steady-state. (mean ± SEM) See Tab. 28 for values

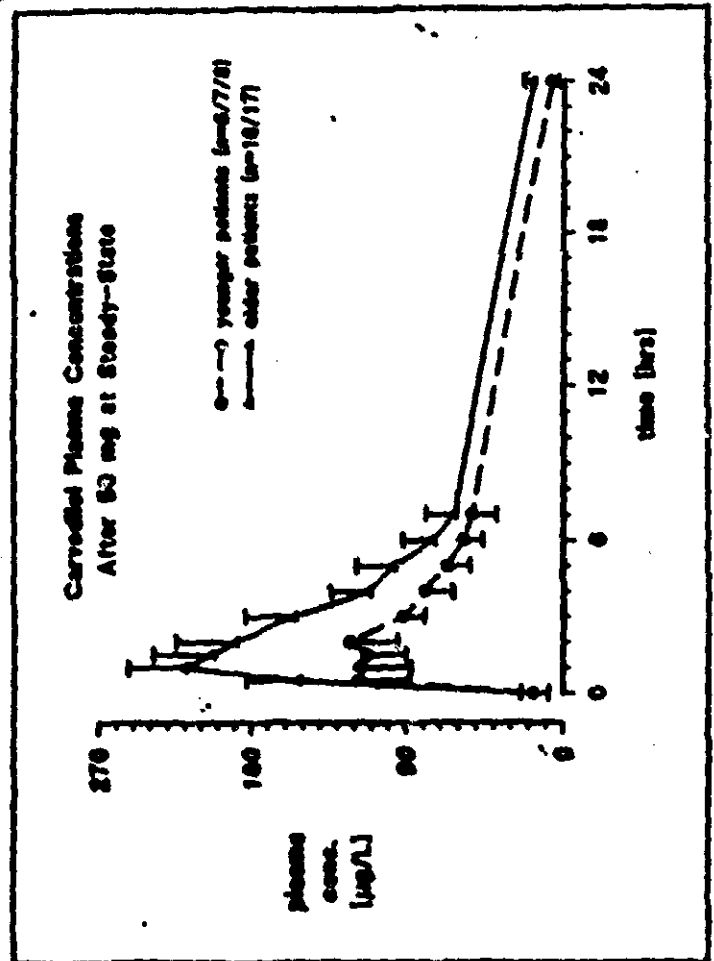


Figure 3: Plasma concentrations obtained in a dose-interval with 50 mg at steady-state. (mean ± SEM) See Tab. 29 for values

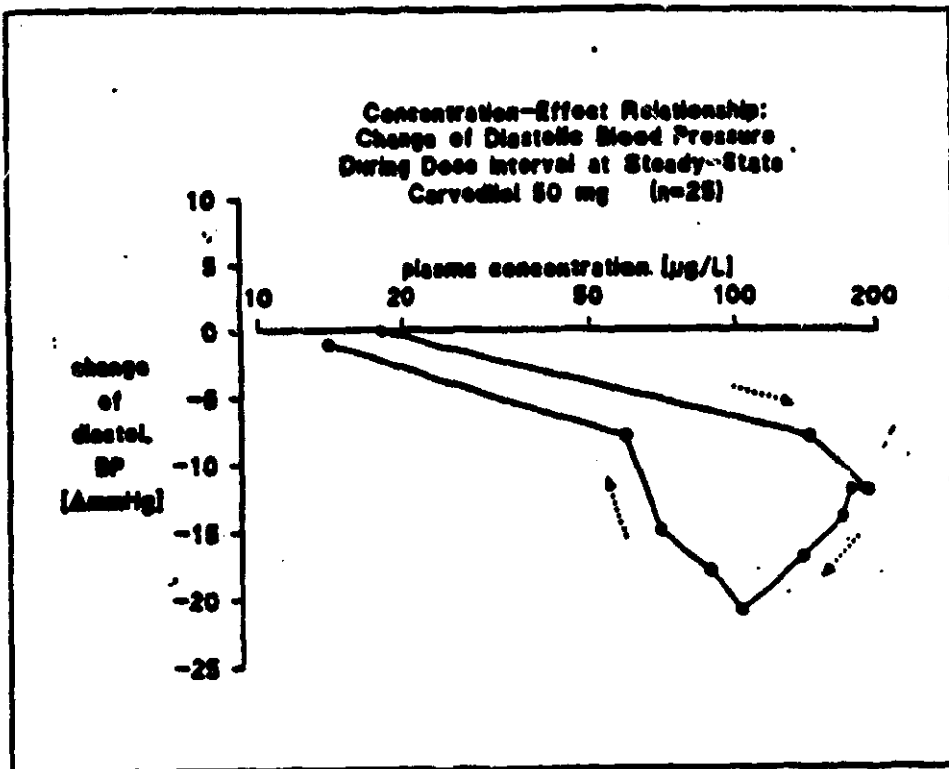


Figure 4: Effect of plasma concentrations (log scale) on BP_{diastol} with 50 mg. See Table 6 for values.

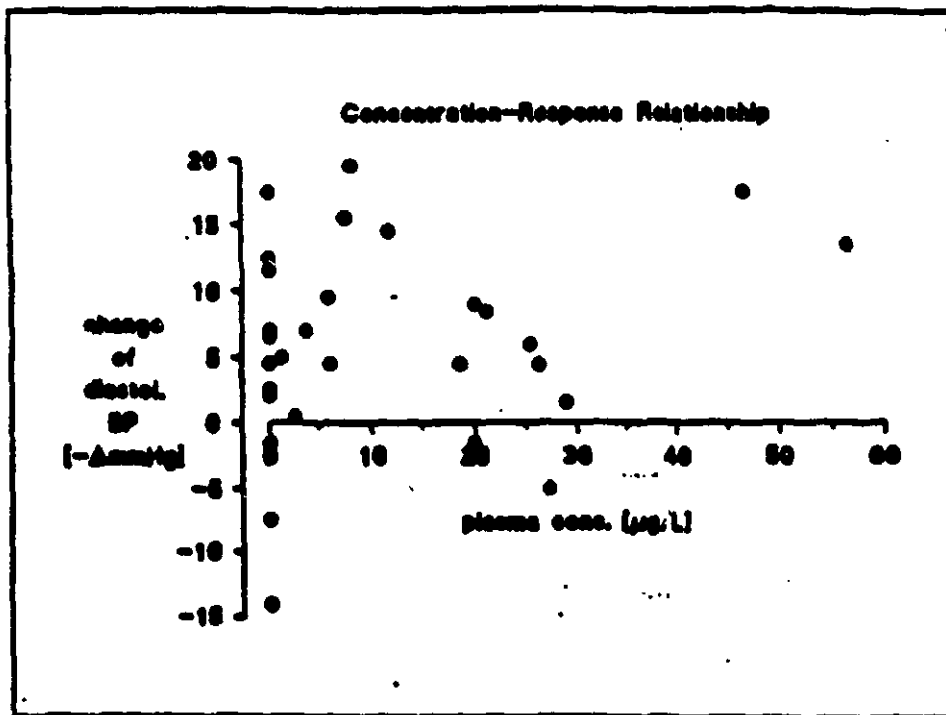


Figure 5: Relationship between plasma concentration and reduction of systolic BP_{diastol} at trough levels of diastolic change. Each point = one patient. Concentrations of 0 means below limit of quantitation. For values see Tab.

PK in Hypertensive Patients with Chronic Renal Failure

Study No.: MF 3459

Volume: 1.58

Investigators and Sites: Multicentre Trial

Centre 1

Centre

Centre

Centre

Objectives: To determine if the pharmacokinetics of carvedilol and its metabolites (M2, M4, and M5) are altered in hypertensive patients with chronic renal failure after single oral administration of 50 mg carvedilol.

Formulations: • Carvedilol 50 mg capsules, batch # 819 789 40 Ld

Study Design: Open, uncontrolled, single-dose multicentre trial. Twenty-five male and female hypertensive patients with chronic renal failure (age: 20-69 y., weight: 47-100 kg) were stratified into three groups according to their grade of renal impairment as measured by creatinine clearance (Cl_{cr}):

Group I Cl_{cr} 51-90 ml/min (n=3)

Group II Cl_{cr} 26-50 ml/min (n=9)

Group III Cl_{cr} 4-25 ml/min (n=13)

Each patients received a single dose of 50 mg of carvedilol capsule orally after an overnight fast. Since this dose is not recommended as the starting dose for the treatment of hypertension. The patients were asked to stay in the supine position for the first 6 hours.

Specimens: Blood, at pre dose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 48, and 72 hours post dose. Urine was collected before, and at 0-4, 4-8, 8-12, 12-24, and 24-48 hours post dose.

Assay:

Plasma and urine samples were analyzed for carvedilol and its active metabolites M2, M4, and M5 by HPLC with fluorescence detection. Samples were analyzed at the Dept. of Biochemical Analysis, Boehringer Mannheim GmbH.

Carvedilol (plasma)

Linearity: linear

Precision: Inter CV ranged from 3.0 to 11.8%. Intra CV ranged from 4.4 to 10.9%.

Accuracy: range 96.9-101%

Specificity: satisfactory

Sensitivity: LLQ=0.078 ng/ml

Desmethylcarvedilol (plasma)

Linearity: linear

Precision: Inter CV ranged from 3.0 to 12.1%. Intra CV ranged from 1.2 to 19.3%.

Accuracy: range 105-119%

Specificity: satisfactory

Sensitivity: LLQ=0.078 ng/ml

Data Analysis: Pharmacokinetic parameters were determined by noncompartmental methods. Statistical evaluation was done by means of the Mann-Whitney U-test between Group II and III only, because the limited number of patients (n=3) did not permit statistical analysis.

Results: The pharmacokinetic parameters for carvedilol and the active metabolites M2, M4, and M5 are shown in Tables 1, 2, 3, and 4, respectively.

Table 1
Pharmacokinetic Parameters for Carvedilol*
(Protocol MF 3459)

	Group I (n=3)	Group II (n=8)	Group III (n=12)
C _{max} (ng/ml)	318.3	178.8	173.6
T _{max} (hr)	0.5	1.0	1.25
AUC _{0-∞} (ng*hr/ml)	1324	1110†	1064§
t _{1/2} (hr)	21.9	22.8†	23.4§
Ae ₀₋₄₈ (%)	0.66	0.20	0.10
Cl _r (ml/min)	4.9	1.9	0.8

Table 2
Pharmacokinetic Parameters for Carvedilol Metabolite M2*
(Protocol MF 3459)

	Group I (n=3)	Group II (n=8)	Group III (n=12)
C _{max} (ng/ml)	18.3	23.2	10.7
T _{max} (hr)	1.5	1.5	1.5
AUC _{0-∞} (ng*hr/ml)	77	37	62
Ae ₀₋₄₈ (%)	0.07	0.01†	0.001
Cl _r (ml/min)	7.7	1.8	0.1

* Data are presented as median and range.

† Group I Cl_r > 30 ml/min, Group II Cl_r 26 - 30 ml/min, and Group III Cl_r < 25 ml/min
‡ n=9

* Data are presented as median and range.

† Group I Cl_r > 30 ml/min, Group II Cl_r 26 - 30 ml/min, and Group III Cl_r < 25 ml/min

‡ n=8

§ n=11

Table 3
Pharmacokinetic Parameters for Carvedilol Metabolite M4*
 (Protocol M2 3499)

	Group I (n = 11)	Group II (n = 8)	Group III (n = 12)
C _{max} (ng/ml)	15.3	11.8	13.6
T _{max} (hr)	1.0	1.25	1.25
AUC _{0-t} (ng*hr/ml)	64	62	54
Ae ₀₋₄₈ (%)	0.13	0.03 [†]	0.01 [§]
Cl _r (ml/min)	17.0	3.5	1.3 [§]

* Data are presented as median and range.

Group I Cl_{cr} > 50 ml/min, Group II Cl_{cr} 26 - 50 ml/min, and Group III Cl_{cr} < 25 ml/min

[†] n = 9

[§] n = 10

Table 4
Pharmacokinetic Parameters for Carvedilol Metabolite M5*
 (Protocol M2 3499)

	Group I (n = 11)	Group II (n = 8)	Group III (n = 12)
C _{max} (ng/ml)	14.2	9.6	10.3
T _{max} (hr)	1.0	1.25	1.25
AUC _{0-t} (ng*hr/ml)	53	30	32
Ae ₀₋₄₈ (%)	0.10	0.02 [†]	0.003 [§]
Cl _r (ml/min)	15.6	6.3	0.9 [§]

* Data are presented as median and range.

Group I Cl_{cr} > 50 ml/min, Group II Cl_{cr} 26 - 50 ml/min, and Group III Cl_{cr} < 25 ml/min

[†] n = 9

[§] n = 11

An unexplained finding in this investigation are the approximately 2 to 3 fold higher concentrations of carvedilol in all three patients groups compared to previous pharmacokinetic studies. The AUC, t_{1/2}, C_{max}, and T_{max} were not significantly different between two groups, whereas the amount of unchanged drug or metabolite excreted in urine (Ae) and the renal clearance of carvedilol and its metabolites (M2, M4 and M5) were significantly decreased in Group III.

Plasma levels of M2, M4, and M5 were approximately ten-fold lower than those observed for carvedilol.

Conclusions: Renal impairment in hypertensive subjects led to a proportional decrease in the renal clearance of carvedilol and its metabolites but not to a corresponding increase in plasma C_{max} and AUC values.

Comments: An unexplained finding in this investigation are the approximately 2 to 3 fold higher concentrations of carvedilol when compared to previous studies. The median C_{max} for carvedilol in Group I was 318.3 ng/ml after single oral dose of 50 mg carvedilol.

Because the dose administered was relatively high, the patients were asked to stay in the supine position for the first 6 hours to prevent the first-dose syncope effect.

PK in Patients with Liver Cirrhosis

Study No.: MF 3837
Investigator and Site:

Volume: 1.61

Pages: 264-403

Objectives: To investigate changes of pharmacokinetics of carvedilol (e.g. systemic clearance, half-life, distribution volume, and first pass effect) due to impaired liver function. Historical comparison was made with a similar study in healthy volunteers.

Formulations:

- Carvedilol 5 mg ampules, batch # 819 673 59 D. The infusion solution was prepared by diluting 3 ampoules of 5 ml each with sterile saline solution to 36 ml (15 mg in 36 ml). 30 ml of this solution (12.5 mg) was infused intravenously over 1 hour.
- Carvedilol 25 mg capsules, batch # 819 854 40 Gf

Study Design: Open, non-controlled, randomized two-way cross-over study. Six patients (5 males and 1 female) with liver cirrhosis were included in the study (age: 40-76 yrs; weight: 66-96 kg). Liver cirrhosis was diagnosed according to clinical signs, biopsy, laparoscopy or ultrasonography. Only patients with impaired liver function measured by a diminished serum cholinesterase of less than 1800 U/I and a Quick test of less than 70% were entered the study. They received either 12.5 mg carvedilol infused intravenously within one hour or 25 mg orally after overnight fast which were separated at least 6 to 7 days. Data following i.v. dosing in one patient were excluded from the PK analysis due to erratic plasma level profile. A group of 20 healthy subjects (age: 19-45 yrs; weight: 60-92 kg), who had been studied previously under similar conditions served as historical controls.

Specimens: Plasma samples, at pre dose and at 0.25, 0.5, 1, 2, 4, 8, 12, 24, and 32 hours post dose. During i.v. medication, the plasma samples were collected from the contralateral arm. Urine was collected before drug administration, and at 0-12, 12-24, and 24-32 hours post dose. The plasma samples were collected for 24 hrs after i.v. and oral dosing for healthy controls.

Historical Controls: A group of 20 healthy volunteers who were previously investigated served as a historical control (Study MF 7020). The PK profile of carvedilol was determined in random order following i.v. (12.5 mg infused over one hour) and oral 50 mg suspension (various lots), 50 mg capsule (batch # 815120 40 Ba), and 25 mg capsule (batch # 816034 40 Bb) doses of carvedilol.

Assay (carvedilol):

Plasma and urine samples were analyzed for carvedilol and desmethylcarvedilol by HPLC with fluorescence detection. Samples were analyzed at the Dept. of Biochemical Analysis, Boehringer Mannheim GmbH.

Plasma

Linearity: linear from 0 to 100 ng/ml

Precision: Inter CV (%) for carvedilol and desmethylcarvedilol were 5.6% and 5.35% at 40.0 ng/ml, respectively. Intra CV (%) for carvedilol and desmethylcarvedilol were 6.76% and 6.00% at 50.0 ng/ml, respectively.

Sensitivity: LLQ:1 ng/ml

LODs for carvedilol and desmethylcarvedilol were 0.38 and 0.46 ng/ml

Specificity: satisfactory

Urine

Linearity: linear from 0 to 100 ng/ml

Precision: Inter CV (%) for carvedilol and desmethylcarvedilol were 3.64% and 4.67% at 50.0 ng/ml, respectively. Intra CV (%) for carvedilol and desmethylcarvedilol were 6.59% and 9.06% at 50.0 ng/ml, respectively.

Sensitivity: LLQ: 1 ng/ml

LODs for carvedilol and desmethylcarvedilol were 0.82 and 1.07 ng/ml

Specificity: satisfactory

Data Analysis: Pharmacokinetic parameters were determined by noncompartmental methods. Non-parametric tests were used for statistical comparisons. The Wilcoxon test were applied for paired data. Comparison between the groups were performed with the Mann-Whitney U-test, $p = 0.05$.

Results: The following table summarizes the pharmacokinetic variables in healthy controls and patients with liver cirrhosis. Median time courses of carvedilol levels after i.v. and oral administrations in liver patients and healthy controls are shown in Fig. 1 and 2, respectively.

Table I
Pharmacokinetic Parameters for Carvedilol
in Patients with Liver Cirrhosis and in Healthy Subject
(Protocol MF 3837)^a

	12.5 mg IV (Cirrhosis) (n = 5)	12.5 mg IV (Healthy) ^b (n = 20)	25 mg oral (Cirrhosis) (n = 6)	25 mg oral (Healthy) ^b (n = 20)
C _{max} (ng/ml)	101.1	176.4	104.3	23.7
T _{max} (hr)	1.00	1.00	0.50	1.5
AUC _{0-τ} [†] (ng·hr/ml)	490	340	355	114
AUC _{0-∞} (ng·hr/ml)	535	342	1040	148 (n = 19)
t _{1/2} (hr)	7.1	2.5	9.0	7.1 (n = 19)
CL [‡] (ml/min)	389	609	410	2809 (n = 19)
V _{dβ} (L)	321	125		
V _{d∞} (L)	294	77		
P(0)			83 (n = 5)	19

^a Data are presented as median and range

[†] AUC₀₋₃₂ in patients with liver cirrhosis; AUC₀₋₂₄ in healthy subjects

[‡] CL_T after oral administration

^b Data from Protocol MF 7020

Compared to historical data in healthy subjects, clearance was reduced by 36% ($p > 0.05$) in the patients with hepatic disease while V_d at steady-state was significantly larger 280% ($p < 0.008$). Elimination half-life was about 3-fold longer in patients after i.v. doses of carvedilol ($p < 0.001$).

After 25 mg carvedilol oral doses, C_{max} was increased by over 4-fold in patients with liver disease. Terminal half-life did not differ between two groups. Oral clearance was decreased by 85% in patients ($p < 0.001$). Mean absolute bioavailability increased from 19% to 83% in patients with liver cirrhosis ($p < 0.01$).

Half-life of carvedilol was dependent on the route of administration in healthy subjects, this difference was absent in the liver patients. This findings were mainly explained by an absorption dependence of half-life after oral doses. Since i.v. half-life increases in liver patients in part to due to reduced clearance, and mainly due to the increase in distribution volume.

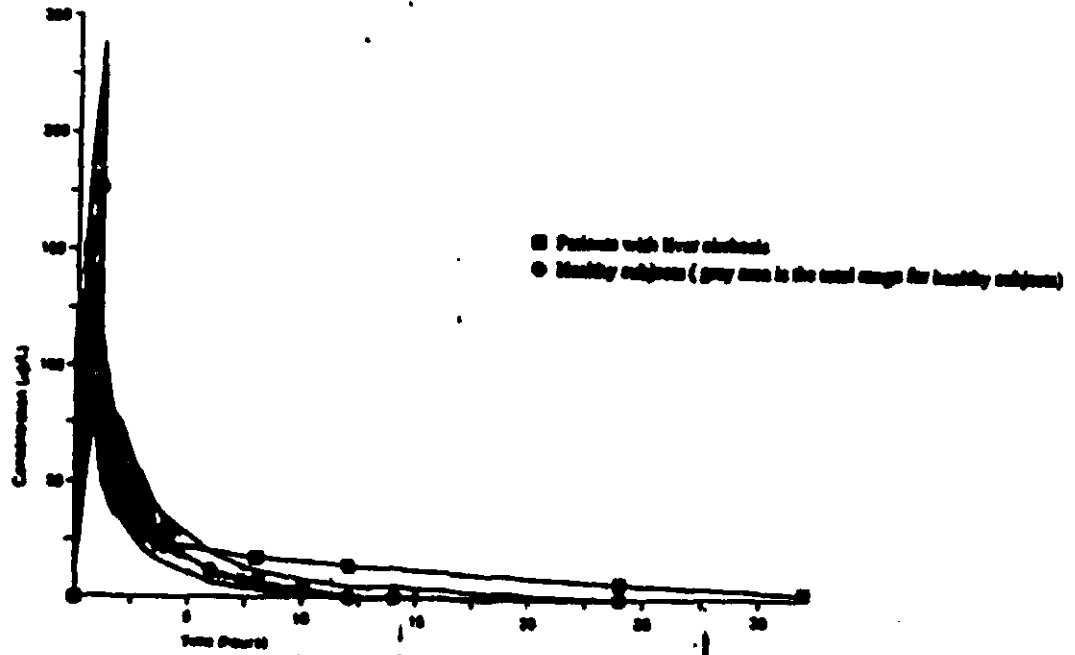
Plasma levels of desmethylcarvedilol were below the detection limit (1 ng/ml) in the majority of subjects after i.v. and oral doses.

Conclusions: After intravenous administration, patients with liver disease exhibited decreased clearance and increased volume of distribution at steady-state compared to healthy volunteers. Following oral administration of 25 mg carvedilol, significant increases in C_{max} (from 31.75 ± 21.38 to 134.64 ± 93.31 ng/ml), $AUC(0-\infty)$ (from 160.17 ± 84.93 to 575.90 ± 276.43 ng*hr/ml), and bioavailability were observed in liver cirrhotic patients.

Comments: The formulations of 25 mg carvedilol used in historical controls and used in patients with liver cirrhosis are not identical. C_{max} and AUC values of the historical controls is relatively small compared to those observed for other 25 mg carvedilol formulations.

Protocol MS-3257 Figure 1

Mean plasma concentration-time profiles for carvedilol following a single intravenous dose of 12.5 mg carvedilol infused over 1 hour in healthy subjects (shaded control from Protocol MS-3252) and in patients with liver cirrhosis.

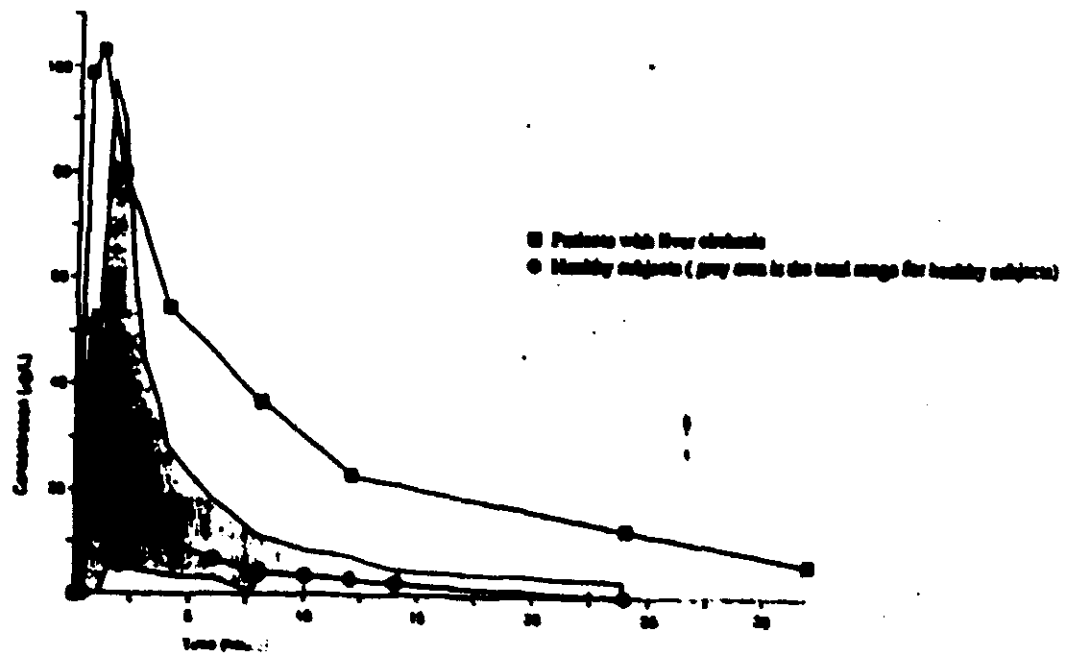


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Figure obtained from: Neuhäuser G, Gahr M, Reiff K. Pharmacokinetics and bioavailability of carvedilol in patients with liver cirrhosis. *Drugs* 1988;36(Suppl. 6):148-154.

Protocol MS-3257 Figure 2

Mean plasma concentration-time profiles for carvedilol following a single oral dose of 20 mg carvedilol in healthy subjects (shaded control from Protocol MS-3252) and in patients with liver cirrhosis.



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Figure obtained from: Neuhäuser G, Gahr M, Reiff K. Pharmacokinetics and bioavailability of carvedilol in patients with liver cirrhosis. *Drugs* 1988;36(Suppl. 6):148-154.

PK in Patients with Chronic Liver Insufficiency

Study No: MF 3476
Investigator and Site:

Volume: 1.60

Pages: 2-228

Objectives: To investigate the pharmacokinetics and absolute bioavailability of carvedilol in patients with chronic liver insufficiency in comparison with healthy volunteers.

Formulations: • Carvedilol 5 mg ampules, batch # 818 651 59 A.

The infusion solution was prepared by diluting 3 ampoules of 5 ml each with sterile saline solution to 36 ml (15 mg in 36 ml). 30 ml of this solution (12.5 mg) was infused intravenously over 1 hour.

• Carvedilol 25 mg capsules, batch # 818 902 40 Db

Study Design: Open, randomized, two-way cross-over study. Three groups of patients were enrolled:

Group I: Patients with slight impaired liver function (serum cholinesterase 900-1500 U/I, Quick test $\geq$ 50%, n=13, 5 F/8 M).

Group II: Patients with severe liver impairment (serum cholinesterase < 900 U/I, Quick test < 50%, n=8 all male).

Group III: Healthy subjects (n= 10, 4 F/6 M).

These patients were given carvedilol in randomized sequence at intervals of about 1 week in one of the following modes of administration: 12.5 mg carvedilol i.v. as a 1 hour infusion or 25 mg carvedilol orally. The drug was given at about 8:00 a.m.

Specimens: Plasma samples, at pre dose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 32, and 48 hours post dose. Urine was collected before drug administration, and at 0-12, 12-24, and 24-48 hours post dose.

Assay: Plasma samples were analyzed for carvedilol and desmethylcarvedilol by HPLC with fluorescence detection.

Plasma

Linearity: linear from 0 to 100 ng/ml

Precision: Inter CV (%) for carvedilol and desmethylcarvedilol were 5.6% at 57.78 ng/ml and 5.35% at 48.60 ng/ml, respectively. Intra CV (%) for carvedilol and desmethylcarvedilol were 6.76% at 53.36 ng/ml and 6.00% at 46.53 ng/ml, respectively.

Sensitivity: LLQ:1 ng/ml

LODs for carvedilol and desmethylcarvedilol were 0.38 and 0.46 ng/ml

Specificity: satisfactory

Urine

Linearity: linear from 0 to 100 ng/ml

Precision: Inter CV (%) for carvedilol and desmethylcarvedilol were 3.64% and 4.67% at 50.0 ng/ml, respectively. Intra CV (%) for carvedilol and desmethylcarvedilol were 6.59% and 9.06% at 50.0 ng/ml, respectively.

Sensitivity: LLQ: 1 ng/ml

LODs for carvedilol and desmethylcarvedilol were 0.82 and 1.07 ng/ml

Specificity: satisfactory

Data Analysis: Pharmacokinetic parameters were determined by noncompartmental methods.

Results: The pharmacokinetic parameters for carvedilol after 25 mg oral dose are shown in Table 1.

Table 1
Pharmacokinetic Parameters Following Oral Administration of Carvedilol*
(Protocol MF 3476)

	Group I 25 mg oral	Group II 25 mg oral	Group III† 25 mg oral
C_{max} (ng/ml)	81	92	91
n	13	3	7
T_{max} (hr)	3.9	4.0	1.6
n	13	3	7
AUC₀₋₄₈ (ng•hr/ml)	720	777	388
n	11	3	7

* Data are presented as mean and range. Group I - slight impaired liver dysfunction; Group II - severe liver impairment; Group III - normal liver function

† Two patients excluded from statistics due to aberrant or incomplete plasma concentration-time profiles.

Observed C_{max} appeared to be similar between groups. In contrast, AUC(0-48) in both groups of patients with liver disease were higher (about 2-fold) compared to healthy subjects. Based on C_{max} and AUC data, plasma desmethylcarvedilol levels were less than 10% of those observed for carvedilol in all groups.

Some patients in all groups showed unaccountably high plasma levels of carvedilol following i.v. dosing. The intravenous data was not evaluated because of inappropriate blood sampling. The in vitro binding of carvedilol in patients with severe liver dysfunction (Group II) was examined. At a total concentration of 200 ng/ml, carvedilol was approximately 98.2% bound to plasma proteins. This value is similar to that in healthy volunteers, suggesting that protein binding is not altered in patients with liver disease.

Conclusions: Following oral administration of 25 mg carvedilol, observed C_{max} appeared to be similar between groups. AUC(0-48) in both patients with liver disease were approximately 2 times higher than that in healthy subjects. Plasma levels of desmethylcarvedilol were less than 10-fold than those observed for carvedilol in all study groups.

Comments: Two patients with severe liver impairment (Group II) received 12.5 mg single oral dose instead of 25 mg carvedilol. The PK data from these patients were not included in Table 1. The dose was reduced due to preceding severe hypotensive patients.

Evaluation of Drug Interaction of Carvedilol with Hydrochlorothiazide (HCTZ) in Hypertensive Patients

Study No: MF 3877

Volume: 1.62

Pages: 2-382

Investigator and Site:

Objectives: To determine the pharmacokinetic interactions between carvedilol and HCTZ after single oral administration of each drug and in combination.

Formulations:

- Carvedilol 25 mg capsules, batch # 819 776 40 Hc, batch size:
- HCTZ 25 mg capsules, batch # 819 974 40 Aa, batch size: . . . (in-house)
- Placebo capsules, batch # 819 560 Cb, batch size:

Study Design: This was a controlled, randomized, double-blind, three way cross-over study in which 12 patients with mild to moderate hypertension (6 M, 6 F; age 30 - 69 yrs; weight 74 - 109 kg) received single oral doses of each of the following treatments separated by at least 96 hrs:

1. carvedilol 25 mg capsule and placebo capsule
2. HCTZ 25 mg capsule and placebo capsule
3. carvedilol 25 mg capsule and HCTZ 25 mg capsule

Administration was performed in the morning between 8:00 a.m. and 9:00 a.m. together with a standard breakfast comprising one bread roll, 20 g butter, 50 g cottage cheese and 150 ml mineral water.

Specimens: Blood samples were collected before and at 15, 30, 45 min and 1, 1.5, 2, 3, 4, 5, 6, 8, 16, and 24 hrs after dosing.

Assay:

Carvedilol

Plasma samples were analyzed for carvedilol at the Dept. of Biochemical Analysis, Boehringer Mannheim GmbH by means of HPLC with fluorescence detection using in-house standardized methods.

Plasma

Linearity: linear up to 4 ug/ml

Precision: Inter CV (%) was 8.9% at 2 ng/ml.

Sensitivity: LLQ = 1 ng/ml

HCTZ

Plasma samples were analyzed for HCTZ at the

Linearity: linear, from 10 to 60 ng/ml, and from 60 to 400 ng/ml

Precision: Inter CV ranged from 2.6% at 100 ng/ml to 8.3% at 25 ng/ml. Intra CV ranged from 2.8% at 100 ng/ml to 4.5% at 25 ng/ml.

Sensitivity: LOQ was 7 ng/ml (CV 10%)

Accuracy: not reported

Specificity: not reported

Data Analysis: Pharmacokinetic parameters were determined by noncompartmental methods. The parameters were tested for significant differences using ANOVA.

Results: Table 1 shows mean pharmacokinetic parameters for carvedilol when administered alone and in combination with HCTZ. Table 2 shows the mean pharmacokinetic parameters for HCTZ. Table 3 summarized the ANOVA for possible pharmacokinetic interaction between carvedilol and HCTZ. The mean plasma concentration-time profiles for carvedilol and HCTZ, when administered alone and in combination, are shown in Fig. 1 and 2, respectively. Individual data for carvedilol and HCTZ are listed in Appendix II.

Table 1. Mean ($\pm$ SD) pharmacokinetic parameters for carvedilol

Treatment	C _{max} (ng/ml)	T _{max} (hr)	AUC(0- ∞)	t _{1/2} (hr)
carvedilol	82.3 $\pm$ 73.5	1.9 $\pm$ 1.0	420 $\pm$ 397	5.5 $\pm$ 2.8
carvedilol with HCTZ	77.1 $\pm$ 51.9	1.7 $\pm$ 0.8	427 $\pm$ 343	5.9 $\pm$ 2.0

AUC: ng*hr/ml

Table 2. Mean ($\pm$ SD) pharmacokinetic parameters for HCTZ

Treatment	C _{max} (ng/ml)	T _{max} (hr)	AUC(0- ∞)	t _{1/2} (hr)
HCTZ	187.9 $\pm$ 60.8	3.0 $\pm$ 1.5	1564 $\pm$ 480	7.7 $\pm$ 2.4
HCTZ with carvedilol	211.5 $\pm$ 92.5	2.5 $\pm$ 0.9	1653 $\pm$ 521	8.2 $\pm$ 1.3

AUC: ng*hr/ml

Table 3. P values for the unifactorial ANOVA (single vs. combined administration)

Drug	Variable	p-Value
carvedilol	AUC	0.749
	Cmax	0.580
	Tmax	0.605
HCTZ	AUC	0.401
	Cmax	0.244
	Tmax	0.301

Conclusions: Single-dose oral administration of 25 mg carvedilol with 25 mg HCTZ in hypertensive patients did not result in any differences in their pharmacokinetics in comparison with administration of drugs as single entities.

Comments: The firm did not submit the quality control data for carvedilol.

015- 52

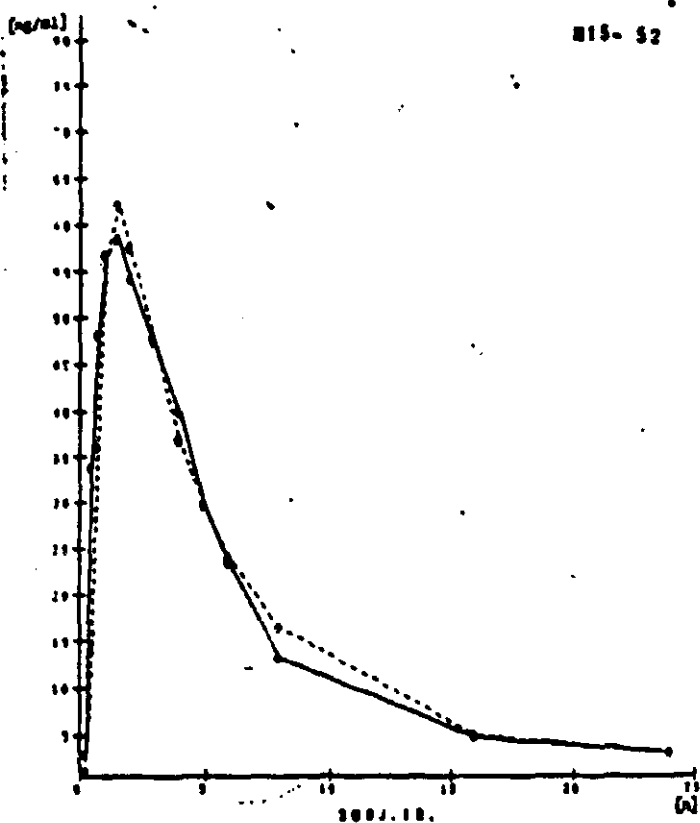


Fig. 1: Synthesis plot of the mean concentration/time curves for carvedilol after single entity administration and combined administration with hydrochlorothiazide (d 1 = carvedilol, d 2 = carvedilol + HCT)

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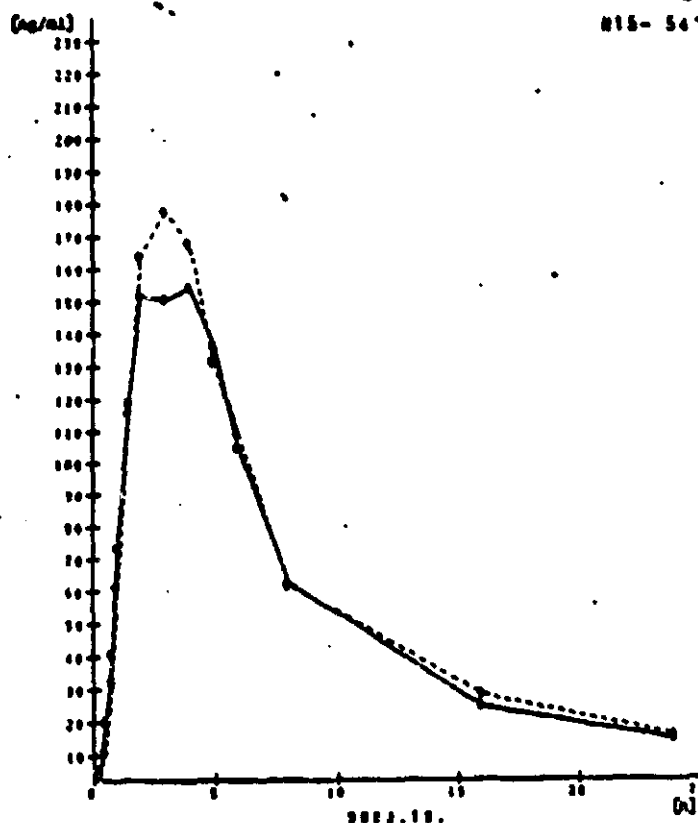


Fig. 2: Synthesis plot of the mean concentration/time curves for hydrochlorothiazide after single entity administration and combined administration with carvedilol (d 1 = HCT, d 2 = HCT + carvedilol)

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Evaluation of Steady-state Pharmacokinetic Interaction of Carvedilol with Torsemide

Study No: MF 7024
Investigator and Site:

Volume: 1.68

Pages: 113 - 424

Objectives: To determine the possible drug interaction between carvedilol and torsemide and to determine the steady-state pharmacokinetic profile following oral administration of single entities and their combination after 5 days of administration.

Formulations:

- Torsemide 5 mg tablets, batch # 819 018 C (in-house)
- Carvedilol 25 mg capsules, batch # 819 406 40 Df

Study Design: Open, randomized three-way cross-over study in 3 sections each comprising 5 medication days. The washout period between medications was at least 1 week. The pharmacokinetic profiles of carvedilol, torsemide, and torsemide M5 (metabolite) were determined in 12 healthy male volunteers (age: 19-34 yrs; weight: 61-87 kg). The volunteers were hospitalized 36 hrs before the first administration, at which time they were all put on the same diet. The volunteers drank 1.5 l water daily. Each volunteer received following 3 treatments in randomized order:

1. carvedilol 25 mg once daily for 5 days
2. torsemide 5 mg once daily for 5 days
3. carvedilol 25 mg plus torsemide 5 mg once daily for 5 days.

Administration took place in the morning between 8.00 and 9.00 a.m. together with a standard breakfast comprising one bread roll, 20 g butter, 50 g cottage cheese and 150 mg water.

Specimens: Blood, at pre dose and at 10, 30, 40 mins and 1, 1.5, 2, 2.5, 3, 6, 8, 10, 12, 14, and 24 hrs after dosing on study day 5 of each regimen. All urine was collected from 0-24 hrs after dosing.

Assay:

Plasma and urine samples were analyzed for carvedilol, torsemide, and torsemide M5 at the Dept. of Biochemical Analysis, Boehringer Mannheim GmbH by means of HPLC with fluorescence detection.

Carvedilol (Plasma)

Linearity: satisfactory, linear from 0.3 to 160 ng/ml

Precision: Inter-day CV (%) ranged from 3.8 to 9.5% and intra-day CV (%) ranged from 6.2 to 12.1%.

Accuracy: Mean accuracy ranged from 97 to 108%

Sensitivity: LLQ=0.32 ng/ml

Specificity: satisfactory

Torsemide and Torsemide M5

Analytical methods for torsemide and the M5 metabolite were not described in the report.

Data Analysis: Pharmacokinetic parameters were determined by noncompartmental methods. ANOVA was used to test for statistically significant differences of the pharmacokinetic parameters.

Results: Table 1 shows mean pharmacokinetic parameters for carvedilol when administered alone and in combination with torsemide. Tables 2 and 3 show the mean pharmacokinetic parameters for torsemide and torsemide M5, respectively. Individual data for carvedilol in each subject are listed in Appendix II.

Table 1. Mean ($\pm$ SD) steady-state pharmacokinetic parameters for carvedilol

Treatment	C _{max} (ng/ml)	T _{max} (hr)	AUC(0-24)	t _{1/2} (hr)	Ae (%)
carvedilol	43.6 $\pm$ 16.9	1.3 $\pm$ 0.6	168 $\pm$ 58	6.2 $\pm$ 1.9	0.25
carvedilol with torsemide	45.6 $\pm$ 12.2	1.7 $\pm$ 0.4	192 $\pm$ 39	6.4 $\pm$ 3.2	0.29

AUC: ng*hr/ml

Ae (%) : amount of carvedilol excreted in urine as a percentage of the dose

Table 2. Mean ($\pm$ SD) steady-state pharmacokinetic parameters for torsemide

Treatment	C _{max} (ng/ml)	T _{max} (hr)	AUC(0-24)	t _{1/2} (hr)	Ae (%)
torsemide	592.7 $\pm$ 175.0	1.2 $\pm$ 0.5	2132 $\pm$ 571	5.3 $\pm$ 3.7	22.8
torsemide with carvedilol	539.5 $\pm$ 181.8	1.5 $\pm$ 0.6	1998 $\pm$ 656	4.7 $\pm$ 2.4	22.2

AUC: ng*hr/ml

Table 3. Mean ($\pm$ SD) steady-state pharmacokinetic parameters for torsemide M5

Treatment	C_{max} (ng/ml)	T_{max} (hr)	AUC(0-24)	t_{1/2} (hr)	Ae (%)
torsemide	83.1 $\pm$ 24.7	2.4 $\pm$ 0.6	412 $\pm$ 153	3.3 $\pm$ 0.9	80.4
torsemide with carvedilol	80.5 $\pm$ 26.6	2.7 $\pm$ 0.	429 $\pm$ 184	3.4 $\pm$ 0.9	82.7

AUC: ng*hr/ml

The pharmacokinetics of carvedilol were not affected by torsemide. The pharmacokinetic parameters for torsemide and torsemide M5 were not changed when torsemide was administered in combination with carvedilol.

Less than 1% of dose of carvedilol was excreted in the urine as unchanged carvedilol. Renal excretion of unchanged torsemide in the 24 h urine is approximately 23% of the dose administered.

Conclusions: The combination of carvedilol and torsemide did not result in any differences in their pharmacokinetics in comparison with administration of the drugs as single entities.

Comments: Volunteer no. 3 did not have any measurable plasma or urine levels and it was suspected that medication was not taken. He was excluded from the evaluations on the PK. He was replaced by volunteer no. 13.

Evaluation of Drug Interaction of Carvedilol with Cimetidine and Rifampin

Study No: CAR 8902
Investigator and Site:

Volume: 1.73

Pages: 2 - 200

Objectives: To investigate the influence of inhibition (cimetidine) and induction (rifampin) of hepatic mixed function oxidase activity on the pharmacokinetics of a single oral dose of 25 mg carvedilol in healthy volunteers.

Formulations:

- Cimetidine (Tagamet®) 400 mg tablets, batch # HL 0059
- Carvedilol 25 mg capsules, batch # 820156 40 Kc
- Rifampin (Rifadin®) 300 mg capsules, batch # 7003

Study Design: Open, non-randomized, three-way cross-over study in 8 healthy male volunteers (age: 19-45 yrs; weight: 57-88 kg). All the volunteers completed following three phases:

Phase I: single oral dose of 25 mg carvedilol.

Phase 2: cimetidine 400 mg orally every 12 hours for 7 doses. The last dose of cimetidine was co-administered with 25 mg carvedilol.

Phase 3: rifampin 600 mg orally once daily for 12 days. The last dose of rifampin was co-administered with 25 mg carvedilol.

The second phase started 24 hrs after carvedilol dosing in phase 1. There was a wash-out period of 13 days between phase 2 and phase 3.

Subjects were required to fast for at least 10 hours prior to each carvedilol dosing and were not allowed any food until 4 hours after the dose. Each dose was taken orally with 240 ml of water.

Specimens: Blood samples were collected before and at 15, 30, 45 mins and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 hrs after each carvedilol dosing.

Assay (carvedilol and desmethylcarvedilol):

Plasma samples were analyzed for carvedilol and desmethylcarvedilol at the _____ by means of HPLC with fluorescence detection.

Data Analysis: Data were analyzed using model-independent methods. C_{max} , AUC_T , AUC_I , and $T_{1/2}$ for the three doses of carvedilol were analyzed by an ANOVA. T_{max} was analyzed using Wilcoxon matched signed rank test. The Westlake 95% CI and two 1-sided t-test 90% CI were calculated for C_{max} and AUC_I between Dose 1 and 2 and 1 and 3.

Results: The pharmacokinetic parameters for carvedilol and desmethylcarvedilol when carvedilol was administered alone and in combination with cimetidine and rifampin are shown in Tables 1 and 2. P values are also shown in Tables 1 and 2. The mean plasma levels for carvedilol and desmethylcarvedilol after three separate 25 mg oral administrations are shown Figs. 1 and 2. Individual data are listed in Appendix II.

Carvedilol PK parameters (C_{max} , $t_{1/2}$, T_{max} , and AUC_1) were not statistically significantly altered following multiple oral administration of cimetidine.

Multiple oral administration of rifampin statistically reduced both carvedilol C_{max} ($p=0.0003$) and AUC_1 ($p=0.0002$) but not T_{max} , compared with the values determined when carvedilol was administered alone.

There was a significant difference in metabolic ratio between carvedilol and carvedilol with rifampin ($p=0.0003$) but not between carvedilol and carvedilol with cimetidine ($p=0.4516$)

Based on mean C_{max} and AUC data, plasma concentration of desmethylcarvedilol were around 10% of those of carvedilol when carvedilol were administered alone or in combination with cimetidine.

Conclusions: Carvedilol (25 mg) administered after multiple oral doses of cimetidine (400 mg, BID for 3 days) expressed a slightly lower C_{max} and later T_{max} although those are not significantly different. The extent of absorption was apparently unchanged. There was a statistically significant reduction in C_{max} and extrapolated AUC_1 (approximately 70%) but not T_{max} when carvedilol was co-administered with the enzyme inducer, rifampin.

Comments: The plasma samples were collected up to 12 hours, the mean elimination half-life (2.46 ± 0.36 hrs) for carvedilol was shorter compared to other studies. Quality control data were not submitted.

From the mean profiles of carvedilol in Fig. 5, the lower C_{max} with cimetidine may be due to the lower solubility of this drug in intestinal fluid.

Table: 1

SUMMARY OF PLASMA CARVEDILOL PHARMACOKINETIC DATA

DOSE 01 : CARVEDILOL 25 mg.

	C _{max} (ng.ml-1)	T _{max} (h) MEDIAN RANGE	AUC(T) (ng.ml-1.h)	AUC(I) (ng.ml-1.h)	K _{elim} (h-1)	T 1/2 (h)	Cl (l/hr)
MEAN	86.5	0.75	202.830	214.392	0.2915	2.43	0.135
S.D.	35.4		86.908	95.748	0.0484	0.36	0.055

DOSE 02 : CARVEDILOL 25mg and Cimetidine 400 mg.

	C _{max} (ng.ml-1)	T _{max} (h) MEDIAN RANGE	AUC(T) (ng.ml-1.h)	AUC(I) (ng.ml-1.h)	K _{elim} (h-1)	T 1/2 (h)	Cl (l/hr)
MEAN	71.7	1.50	238.212	252.309	0.2854	2.59	0.111
S.D.	39.1		85.392	85.254	0.0671	0.82	0.044

DOSE 03 : CARVEDILOL 25 mg AND RIFAMPICIN 400 mg.

	C _{max} (ng.ml-1)	T _{max} (h) MEDIAN RANGE	AUC(T) (ng.ml-1.h)	AUC(I) (ng.ml-1.h)	K _{elim} (h-1)	T 1/2 (h)	Cl (l/hr)
MEAN	28.4	0.88	62.947	66.904	0.3503	2.02	0.394
S.D.	14.4		16.905	16.399	0.0532	0.32	0.098

Dose 1 and Dose 2:

	p value	Two one sided t-test		Westlake limits
		lower limit	upper limit	
C _{max}	0.2486	90.4 %	143.8 %	+/- 45.01 %
AUC I	0.2220	53.7 %	109.0 %	+/- 45.80 %
T 1/2	0.5023			
T _{max} *	> 0.05			
R B (1.270)	0.1328			
Metabolic ratio	0.4516			

Dose 1 and Dose 3:

C _{max}	0.0003	140.3 %	193.9 %	+/- 94.65 %
AUC I	0.0002	139.2 %	197.9 %	+/- 98.31 %
T 1/2	0.1042			
T _{max} *	> 0.05			
R B (0.349)	0.0001			
Metabolic ratio	0.0003			

* - Wilcoxon matched signed test.
R B - Relative bioavailability.

SUMMARY OF PLASMA DESMETHYLCARVEDILOL PHARMACOKINETIC DATADOSE 01 : CARVEDILOL 25 mg.

	C_{max} (ng.ml-1)	T_{max} (h)	AUC(T) (ng.ml-1.h)	AUC(I) (ng.ml-1.h)	K_{elim} (h-1)	T 1/2 (h)	Cl (1/hr)
MEAN	8.1	MEDIAN 0.88	16.109	19.234	0.7665	1.62	1.702
S.D.	3.3	RANGE	9.617	11.623	0.6341	1.19	0.855

DOSE 02 : CARVEDILOL 25mg and CIMETIDINE 400 mg.

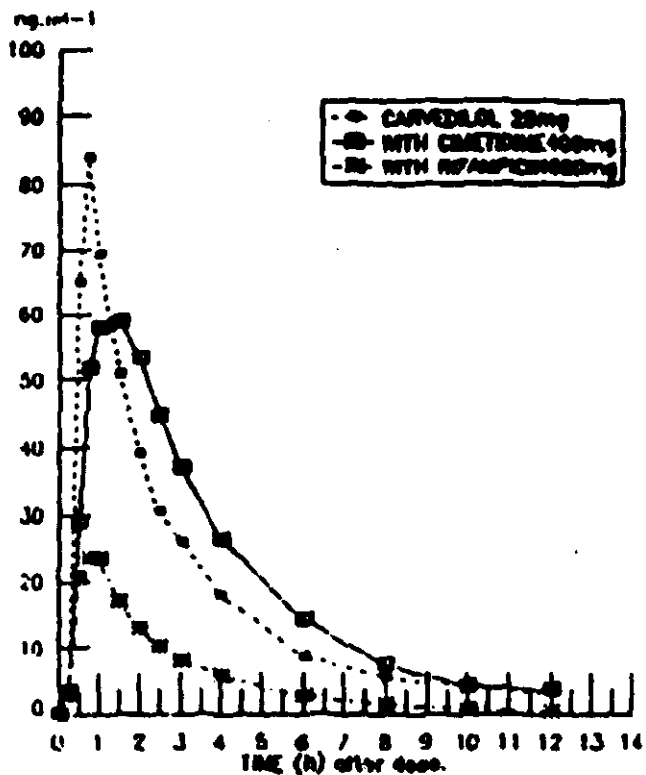
	C_{max} (ng.ml-1)	T_{max} (h)	AUC(T) (ng.ml-1.h)	AUC(I) (ng.ml-1.h)	K_{elim} (h-1)	T 1/2 (h)	Cl (1/hr)
MEAN	8.1	MEDIAN 1.50	21.093	24.917	0.4242	2.05	1.164
S.D.	3.6	RANGE	8.680	10.161	0.1789	1.30	0.466

DOSE 03 : CARVEDILOL 25 mg AND RIFAMPICIN 400 mg.

	C_{max} (ng.ml-1)	T_{max} (h)	AUC(T) (ng.ml-1.h)	AUC(I) (ng.ml-1.h)	K_{elim} (h-1)	T 1/2 (h)	Cl (1/hr)
MEAN	5.4	MEDIAN 1.00	11.750	14.256	0.5517	1.31	1.835
S.D.	1.2	RANGE	2.751	3.072	0.1183	0.29	0.447

FIGURE 1

MEAN PLASMA CARVEDILOL LEVELS AFTER THREE SEPARATE 25mg ORAL ADMINISTRATIONS



MEAN PLASMA CARVEDILOL LEVELS AFTER THREE SEPARATE 25mg ORAL ADMINISTRATION

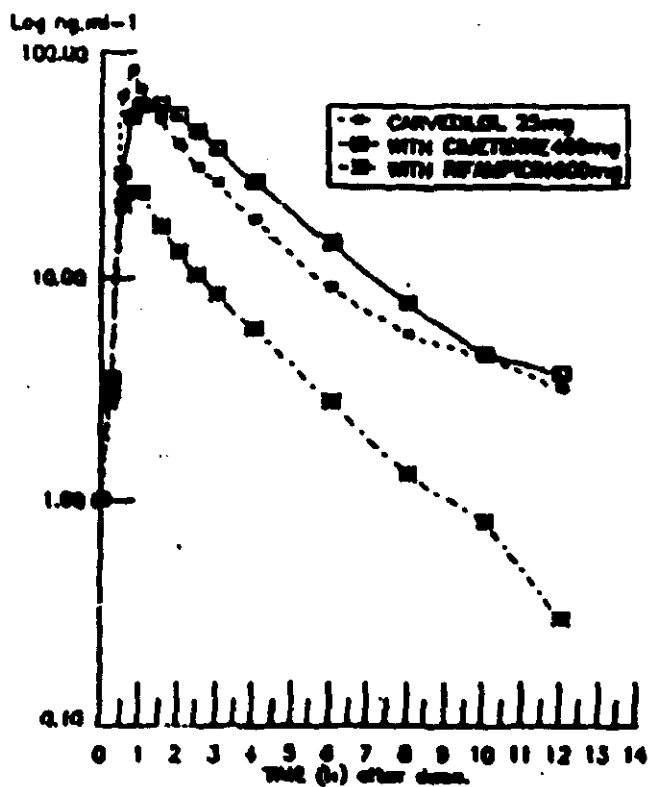
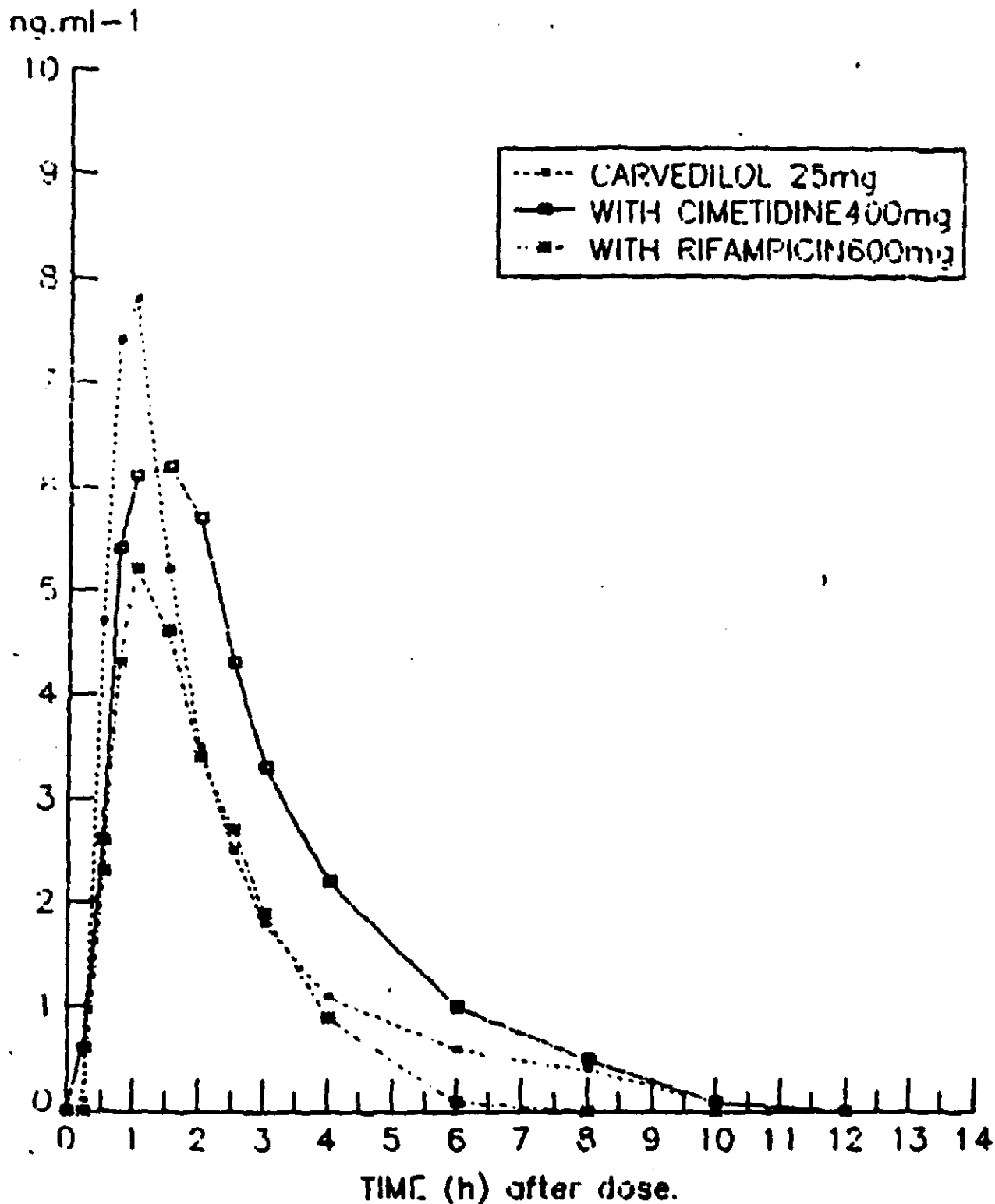


FIGURE 2.

MEAN PLASMA DESMETHYL CARVEDILOL LEVELS AFTER THREE SEPARATE CARVEDILOL DOSES.



Evaluation of Steady-state Kinetics of Carvedilol with Cimetidine

Study No: MF 7097

Volume: 1.71

Pages: 265-432

Investigator and Site: E. v. Möllendorff, M.D., Dept. of Clinical Pharmacology
Boehringer Mannheim GmbH, Sandhofer Str. 116, 6800 Mannheim 31, FRG

Objectives: To determine steady-state kinetics of carvedilol, carvedilol enantiomers, and the desmethyl (M2), 4-hydroxyphenyl (M4), and 5-hydroxyphenyl (M5) metabolites of carvedilol before and after concomitant cimetidine administration.

Formulations: • Carvedilol 25 mg tablets (Dilatrend[®], Boehringer Mannheim GmbH, Mannheim), batch # 746874-01
• Cimetidine 200 mg tablets (Tagamet[®], SmithKline Davelsberg GmbH, Goettingen) batch # 270790K19

Study Design: This was an open, single center study in which 10 healthy male volunteers (age: 24-33 yrs; weight: 74-94 kg) participated. Subjects were administered single oral doses of carvedilol, 12.5 mg on day 1 and then 25 mg on day 2 to day 6 after a standard breakfast. Subjects then continued to receive carvedilol (25 mg per day) along with cimetidine (200 mg at 0830, 1230, and 1630 and 400 mg at 2030) on day 7 to day 9.

Specimens: Blood samples were obtained before and at 0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 6, 8, 10 and 24 hrs after dosing on day 6 and day 9. Urine was collected over 24 hours.

Assay:

Carvedilol and M2 (HPLC with fluorescence detection)

Plasma

Linearity: linear from 0 to 100 ng/ml

Precision: Inter CV (%) for carvedilol and M2 were 5.6% and 5.35% at 50.0 ng/ml, respectively. Intra CV (%) for carvedilol and M2 were 6.76% and 6.00% at 50.0 ng/ml, respectively.

Sensitivity: LLQ for carvedilol and M2: 1.15 ng/ml

Specificity: satisfactory

Urine

Linearity: linear from 0 to 100 ng/ml

Precision: Inter CV (%) for carvedilol and M2 were 3.64% and 4.67% at 50.0 ng/ml, respectively. Intra CV (%) for carvedilol and M2 were 6.59% and 9.06% at 50.0 ng/ml, respectively.

Sensitivity: LLQs in urine for carvedilol and M2: 1.24 ng/ml

Specificity: satisfactory

M4 and M5 (HPLC with fluorescence detection)

Plasma

Linearity: satisfactory

Precision: Inter CV (%) for M4 ranged from 2.4% to 9.5% and intra CV (%) ranged from 5.7% to 9.8%. Inter CV (%) for M5 ranged from 2.2% to 15.9% and intra CV (%) ranged from 7.0% to 12.0%.

Sensitivity: LLQ=1.26 ng/ml

Specificity: satisfactory

Urine

Linearity: satisfactory

Precision: Inter CV (%) for M4 ranged from 1.44% to 5.64% and intra CV (%) ranged from 4.55% to 6.20%. Inter CV (%) for M5 ranged from 2.03% to 13.89% and intra CV (%) ranged from 8.18% to 11.65%.

Sensitivity: LLQ=1.22 ng/ml

Specificity: satisfactory

R(+)- and S(-)-carvedilol (Stereospecific HPLC method)

Linearity: satisfactory

Precision: not reported

Sensitivity: LLQ: 1.0 ng/ml for plasma, 0.5 ng/ml for urine.

Data Analysis: Pharmacokinetic parameters for carvedilol, carvedilol enantiomers, M2, M4, and M5 metabolites were determined using model-independent methods. The Wilcoxon test for paired data was used for statistical comparisons, with $\alpha=0.05$.

Results: The steady-state pharmacokinetic parameters for carvedilol, R(+)- and S(-)-carvedilol when administered alone and in combination with cimetidine are shown in Table 1. The pharmacokinetic parameters for M2, M4 and M5 after administration of racemic carvedilol alone and in combination with cimetidine are shown in Table 2. The mean plasma concentration-time profiles for carvedilol, R(+)- and S(-)-carvedilol, M2, M4, and M5 are shown in Figs. 1 to 6.

DEUTSCHER PLANKEIN GEM KLINISCHE PHARMKOLOGIE - KINETIK
 PROGRAM: 120 DATE OF COMPUTATION: 24-FEB-92

RAW DATA EVALUATION; LOG.-LIN. REGR. BEGINNING AT 5.9 DN

PROJECT: ON 14.100 CARVEDILOL ; RP 7007
 DOSE : DAY 1: 12.5 mg DAY 2-9: 25 mg CARVEDILOL(?); ONCE DAILY
 DAY 7-9: 1000 mg CONTOLOL (TARQUET(?)) PER DAY, ORAL

- * 1 * : ASSAY: ON 14.100 IN PLASMA AND URINE ; DET. BY HPLC --- DAY 6 ---
- * 2 * : ASSAY: ON 14.100 IN PLASMA AND URINE ; DET. BY HPLC --- DAY 9 ---
- * 3 * : ASSAY: R(+)- ON 14.100 IN PLASMA AND URINE ; DET. BY HPLC --- DAY 6 ---
- * 4 * : ASSAY: R(+)- ON 14.100 IN PLASMA AND URINE ; DET. BY HPLC --- DAY 9 ---
- * 5 * : ASSAY: S(-)- ON 14.100 IN PLASMA AND URINE ; DET. BY HPLC --- DAY 6 ---
- * 6 * : ASSAY: S(-)- ON 14.100 IN PLASMA AND URINE ; DET. BY HPLC --- DAY 9 ---

PARAMETER (RAW - DATA) UNIT

			"1"	"2"	"3"	"4"	"5"	"6"
AUC (0-24)	[ng ² /ml]	N	10.	10.	10.	10.	10.	10.
		MEAN	<u>221.18</u>	<u>209.40</u>	<u>166.21</u>	<u>201.24</u>	<u>62.99</u>	<u>66.10</u>
		C.V. (%)	<u>47.28</u>	<u>48.75</u>	<u>53.08</u>	<u>31.31</u>	<u>38.28</u>	<u>45.35</u>
		MEDIAN	211.08	276.92	138.08	194.34	67.63	70.16
		MINIM. MAXIM.						
C _{0H}	[ng/ml]	N	10.	10.	10.	10.	10.	10.
		MEAN	<u>50.36</u>	<u>47.76</u>	<u>38.30</u>	<u>34.98</u>	<u>32.82</u>	<u>11.06</u>
		C.V. (%)	<u>39.98</u>	<u>24.38</u>	<u>42.61</u>	<u>24.88</u>	<u>24.98</u>	<u>23.84</u>
		MEDIAN	48.68	48.44	33.94	34.22	13.69	10.91
		MINIM. MAXIM.						
t _{0H}	[h]	N	10.	10.	10.	10.	10.	10.
		MEAN	<u>1.280</u>	<u>1.455</u>	<u>1.328</u>	<u>1.680</u>	<u>1.175</u>	<u>1.500</u>
		C.V. (%)	<u>38.23</u>	<u>28.32</u>	<u>28.34</u>	<u>31.38</u>	<u>41.62</u>	<u>38.59</u>
		MEDIAN	1.250	1.750	1.250	2.000	1.000	1.500
		MINIM. MAXIM.						
t _{1/2}	[h]	N	10.	10.	10.	10.	9.	10.
		MEAN	<u>5.288</u>	<u>5.135</u>	<u>6.438</u>	<u>9.897</u>	<u>8.489</u>	<u>6.536</u>
		C.V. (%)	<u>35.67</u>	<u>48.79</u>	<u>38.32</u>	<u>42.64</u>	<u>52.98</u>	<u>37.39</u>
		MEDIAN	6.798	5.897	6.154	5.688	9.171	6.686
		MINIM. MAXIM.						
CL / f	[ml/min]	N	10.	10.	10.	10.	10.	10.
		MEAN	<u>2105.48</u>	<u>2021.64</u>	<u>1718.81</u>	<u>1688.77</u>	<u>2048.34</u>	<u>4234.73</u>
		C.V. (%)	<u>37.33</u>	<u>35.91</u>	<u>77.45</u>	<u>81.88</u>	<u>43.97</u>	<u>6.85</u>
		MEDIAN	2011.08	1585.98	1368.08	1875.27	3082.73	2665.48
		MINIM. MAXIM.						
V _{Z / f}	[l]	N	10.	10.	10.	10.	9.	10.
		MEAN	<u>1188.7</u>	<u>787.3</u>	<u>695.6</u>	<u>486.8</u>	<u>2312.2</u>	<u>1998.7</u>
		C.V. (%)	<u>69.98</u>	<u>38.29</u>	<u>78.89</u>	<u>25.64</u>	<u>75.34</u>	<u>33.53</u>
		MEDIAN	736.2	678.5	439.2	451.6	2843.3	2017.2
		MINIM. MAXIM.						
A ₀	[%]	N	10.	10.	10.	10.	10.	10.
		MEAN	<u>0.34</u>	<u>0.64</u>	<u>0.84</u>	<u>1.04</u>	<u>0.29</u>	<u>3.23</u>
		C.V. (%)	<u>33.49</u>	<u>47.31</u>	<u>37.73</u>	<u>47.77</u>	<u>42.54</u>	<u>37.89</u>
		MEDIAN	0.51	0.68	0.72	1.08	0.22	3.23
		MINIM. MAXIM.						
CL _R	[ml/min]	N	10.	10.	10.	10.	10.	10.
		MEAN	<u>18.48</u>	<u>18.91</u>	<u>11.14</u>	<u>11.98</u>	<u>6.77</u>	<u>7.33</u>
		C.V. (%)	<u>24.98</u>	<u>16.88</u>	<u>37.73</u>	<u>36.84</u>	<u>17.25</u>	<u>23.73</u>
		MEDIAN	18.45	11.44	10.91	11.57	6.86	7.59
		MINIM. MAXIM.						

Carvedilol (R(+)-) S(-) Carvedilol

DEPARTMENT OF PHARMACY AND CLINICAL PHARMACOLOGY - KINETIC
PROGRAM: MSD
DATE OF COMPUTATION: 24-FEB-68

RAW DATA EVALUATION

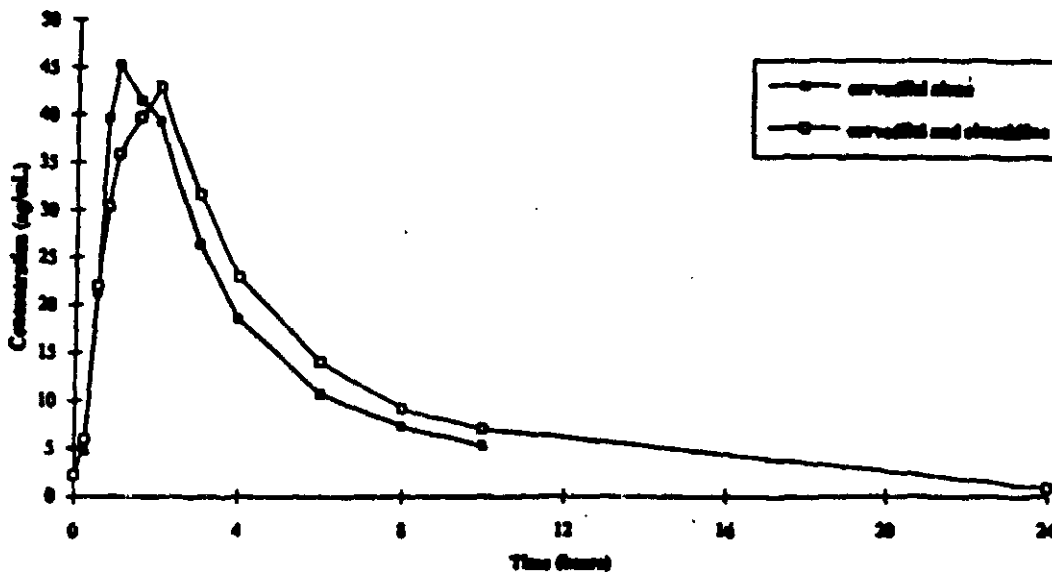
PROJECT: ON 14.700 BICUCILLIN ; NF 7097
DOSE : DAY 1: 12.5 mg DAY 2-9: 25 mg BILATRON(R) ; ONCE DAILY
DAY 7-9: 1000 mg CLOBETISIN (TACOMET(R)) PER DAY, ORAL

- * 1 * : ADOPT: ON 14.242 IN PLASMA AND URINE ; DET. BY HPLC *** DAY 6 ***
- * 2 * : ADOPT: ON 14.242 IN PLASMA AND URINE ; DET. BY HPLC *** DAY 9 ***
- * 3 * : ADOPT: ON 14.0000 IN PLASMA AND URINE ; DET. BY HPLC *** DAY 6 ***
- * 4 * : ADOPT: ON 14.0000 IN PLASMA AND URINE ; DET. BY HPLC *** DAY 9 ***
- * 5 * : ADOPT: ON 14.0000 IN PLASMA AND URINE ; DET. BY HPLC *** DAY 6 ***
- * 6 * : ADOPT: ON 14.0000 IN PLASMA AND URINE ; DET. BY HPLC *** DAY 9 ***

PARAMETER (RAW - DATA)	UNIT	"1"	"2"	"3"	"4"	"5"	"6"
AUC	(ng/ml)	10.	10.	10.	10.	10.	10.
	MEAN	8.80	9.33	7.47	7.23	5.11	4.33
	C.V. (%)	<u>54.18</u>	<u>28.98</u>	<u>31.38</u>	<u>54.67</u>	<u>24.77</u>	<u>50.74</u>
	MEDIAN	7.02	7.43	6.64	6.39	6.57	6.33
	MINIM. MAXIM.						
C _{max}	(ng/ml)	10.	10.	10.	10.	10.	10.
	MEAN	<u>4.28</u>	<u>3.78</u>	<u>3.98</u>	<u>3.34</u>	<u>3.34</u>	<u>2.78</u>
	C.V. (%)	<u>23.12</u>	<u>27.86</u>	<u>18.93</u>	<u>22.82</u>	<u>30.83</u>	<u>28.32</u>
	MEDIAN	3.04	3.44	4.10	3.13	3.30	2.74
	MINIM. MAXIM.						
t _{max}	(h)	10.	10.	10.	10.	10.	10.
	MEAN	<u>1.275</u>	<u>1.675</u>	<u>1.250</u>	<u>1.000</u>	<u>1.225</u>	<u>1.625</u>
	C.V. (%)	<u>33.14</u>	<u>28.19</u>	<u>37.71</u>	<u>28.72</u>	<u>38.37</u>	<u>37.82</u>
	MEDIAN	1.000	2.000	1.000	1.750	1.000	2.000
	MINIM. MAXIM.						
A _s	(%)	10.	10.	10.	10.	10.	10.
	MEAN	0.09	0.10	0.11	0.12	0.08	0.09
	C.V. (%)	31.08	23.08	28.57	21.57	35.14	40.57
	MEDIAN	0.09	0.11	0.11	0.13	0.08	0.08
	MINIM. MAXIM.						
CL _R	(ml/min)	10.	10.	10.	10.	10.	10.
	MEAN	49.89	35.48	44.84	68.87	67.44	121.04
	C.V. (%)	32.98	47.98	48.84	42.14	38.16	83.40
	MEDIAN	38.17	38.28	37.87	88.91	62.18	75.03
	MINIM. MAXIM.						

Protocol MF-707 / Figure 1

Mean plasma concentration-time profiles for carvedilol following multiple dose administration of carvedilol alone (25 mg once daily) and in combination with diltiazem (1800 mg/day) in ten healthy male volunteers.

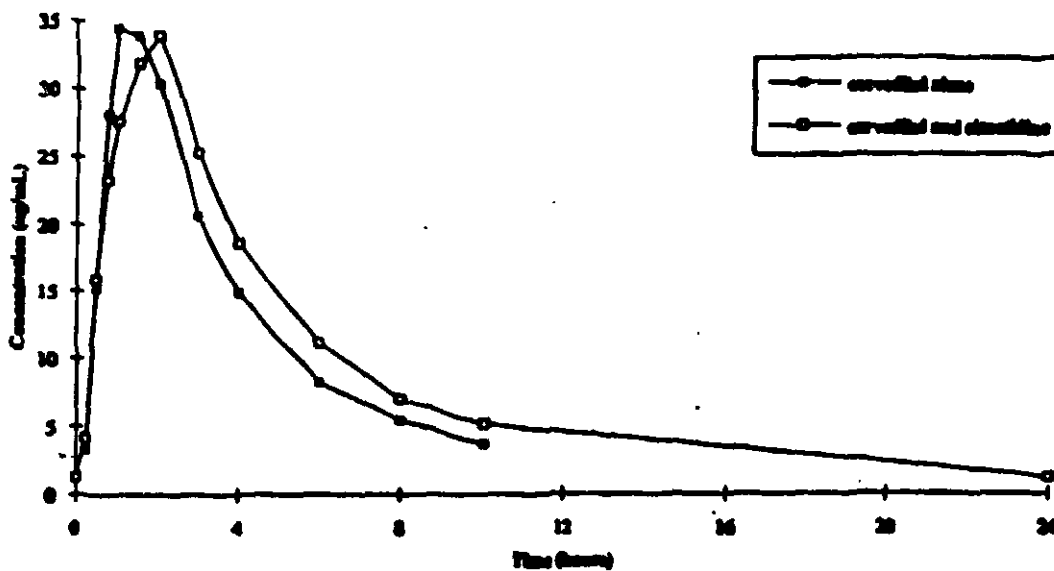


Note: As per report, non-quantifiable values were set equal to zero in the calculation of mean data; mean data are not presented if more than one-half of the subjects exhibited non-quantifiable values.

1300000

Protocol MF-707 / Figure 2

Mean plasma concentration-time profiles for R(+)-carvedilol following multiple dose administration of carvedilol alone (25 mg once daily) and in combination with diltiazem (1800 mg/day) in ten healthy male volunteers.

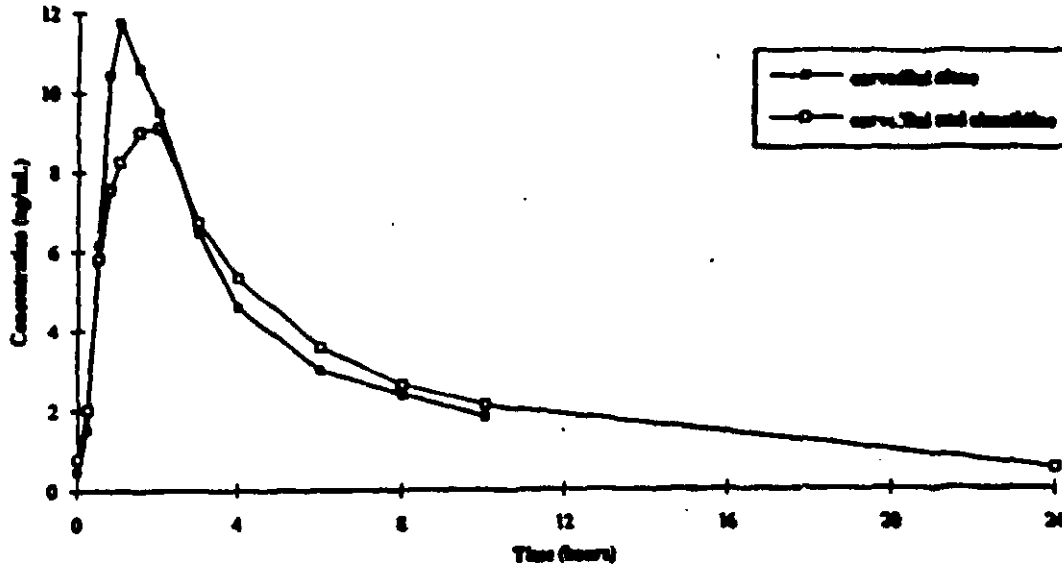


Note: As per report, non-quantifiable values were set equal to zero in the calculation of mean data; mean data are not presented if more than one-half of the subjects exhibited non-quantifiable values.

100000

Protocol MF-7097 / Figure 3

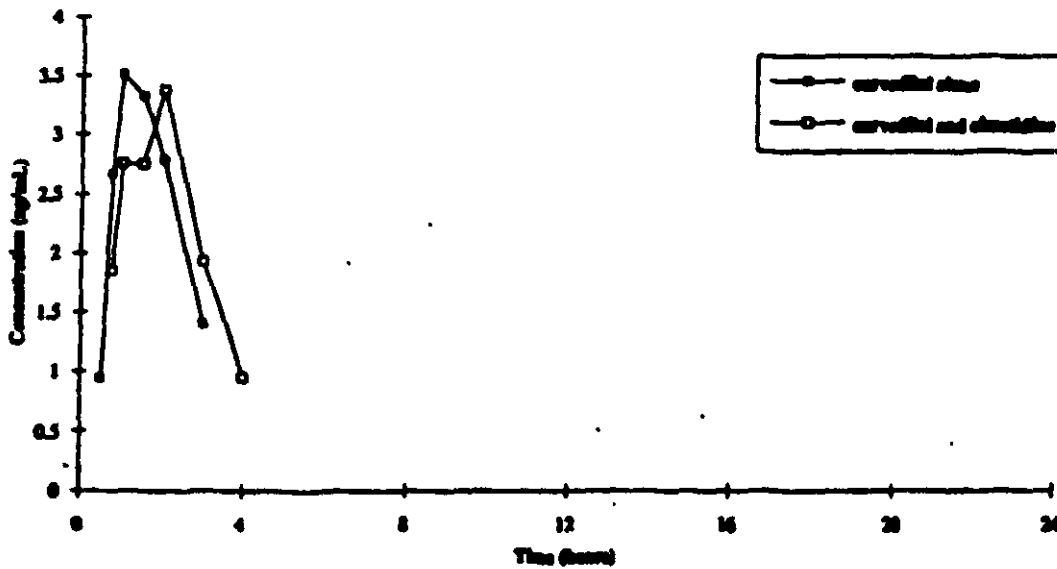
Mean plasma concentration-time profiles for (S)-carvedilol following multiple dose administration of carvedilol alone (25 mg once daily) and in combination with atenolol (1000 mg/day) in ten healthy male volunteers.



Note: As per report, non-quantifiable values were set equal to zero in the calculation of mean data; mean data are not presented if more than one-half of the subjects exhibited non-quantifiable values.

Protocol MF-7097 / Figure 4

Mean plasma concentration-time profiles for desmethyl-carvedilol (metabolite M2) following multiple dose administration of carvedilol alone (25 mg once daily) and in combination with atenolol (1000 mg/day) in ten healthy male volunteers.

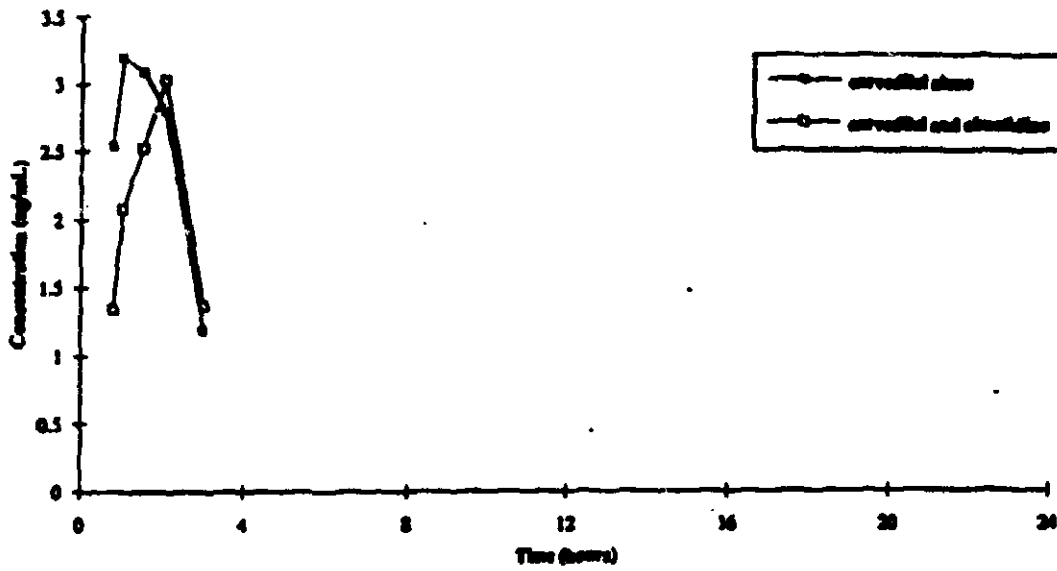


Note: As per report, non-quantifiable values were set equal to zero in the calculation of mean data; mean data are not presented if more than one-half of the subjects exhibited non-quantifiable values.

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Protocol MF-7007 / Figure 5

Mean plasma concentration-time profiles for 4'-hydroxyphenyl-carvedilol (metabolite M4) following multiple dose administration of carvedilol alone (25 mg once daily) and in combination with clonidine (1000 mg/day) in ten healthy male volunteers.

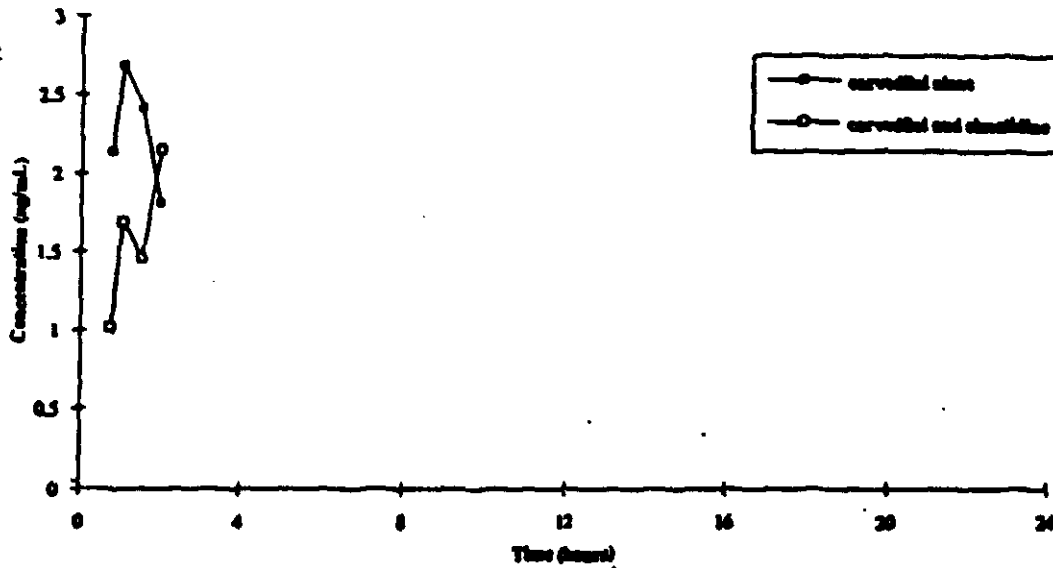


30000

Note: As per report, non-quantifiable values were not equal to zero in the calculation of mean data; mean data are not presented if more than one-half of the subjects exhibited non-quantifiable values.

Protocol MF-7007 / Figure 6

Mean plasma concentration-time profiles for 3'-hydroxyphenyl-carvedilol (metabolite M3) following multiple dose administration of carvedilol alone (25 mg once daily) and in combination with clonidine (1000 mg/day) in ten healthy male volunteers.



Note: As per report, non-quantifiable values were not equal to zero in the calculation of mean data; mean data are not presented if more than one-half of the subjects exhibited non-quantifiable values.

There were no statistical differences in C_{max} , T_{max} , $t_{1/2}$, or CL_r for carvedilol when carvedilol was co-administered with cimetidine. Mean AUC(0-24) increased approximately 17% ($p < 0.05$) and mean A_e (amount of carvedilol excreted in urine) increased approximately 22% ($p < 0.05$).

Based on mean C_{max} data, metabolites levels were less than 10% of those of carvedilol when carvedilol was administered alone or in combination.

Mean AUC(0-t) for R(+)-carvedilol was increased approximately 21% ($p < 0.05$) and mean A_e for R(+)-carvedilol increased about 24% ($p < 0.05$) when carvedilol was administered with cimetidine.

Mean C_{max} for S(-)-carvedilol was approximately 14% decreased ($p < 0.05$) when carvedilol was administered with cimetidine.

Conclusions and Comments: Administration of carvedilol with cimetidine caused a moderate increase in mean AUC(0-24) (17%) and mean A_e (22%) of carvedilol. This was reflected by a moderate increase in mean AUC(0-24) (21%) and mean A_e (24%) for R(+)-carvedilol in combined administration. For S(-)-carvedilol, there was a slight decrease in mean C_{max} (14%). There were no major changes in the kinetic parameters of the M2, M4, and M5 metabolites of carvedilol following with cimetidine.

Evaluation of Drug Interaction of Carvedilol with Digoxin (administered orally)

Study No.: A9904

Volume: 1.52

Pages: 2-72

Investigator and Site: Christian de May, M.D.

SK & F Institute for Applied Clinical Pharmacology, Göttingen, FRG

Objectives: To assess the acute effects of the co-administration of a single dose of 25 mg carvedilol on the plasma and urinary pharmacokinetics of digoxin. For the assessment of acute interaction on concomitant administration, relatively high dose of digoxin was administered in order to profile the plasma kinetics in sufficient detail, without however exposing the subjects to undue risk.

Formulations: • Carvedilol 25 mg tablets, batch #: 1/25/B/6

- Matched placebo, formulation: 1/25-P-S, batch #: 2, provided by Dept. of Pharmaceutical Development, SK & F Labs, Welwyn, UK.
- Digoxin 0.25 mg tablets (Lenoxin[®], Wellcome, Ch.B.: M5161A)

Study Design: In a double blind, period-balanced, within-subject cross-over design with randomly allocated sequences, 8 healthy male subjects (age 22 to 27 yrs; weight 65 to 87 kg) received the two study treatments separated by 1 week. On one occasion a single oral dose of 0.5 mg digoxin (two tablets of 0.25 mg digoxin) was administered concomitantly with 25 mg carvedilol, on the other occasion, a single oral dose of 0.5 mg digoxin was administered concomitantly with carvedilol matched placebo. The medications were administered with 150 ml water, then 200 ml of water was given every 2 hrs up to 8 hrs after dosing.

Specimens: Blood samples were collected before and at 15, 30, 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36 and 48 hours after dosing. Urine was collected in 5 fractions: pre-dosing blank, 0-8, 8-24, 24-36 and 36-48 hours after dosing.

Assay (digoxin):

Plasma digoxin levels were determined by radio-immuno assay (Amersham, UK).

Linearity: Calibration curve from 0.09 to 5.40 ng/ml

Precision: 0.7% at 1.0 ng/ml and 6.1% at 5.0 ng/ml

Sensitivity: LLQ=0.07 ng/ml

Specificity: Satisfactory

Digoxin levels in urine were assayed using HPLC with UV detection.

Linearity: Calibration curve from 10 to 400 ng/ml

Precision: 15.6% at 10 ng/ml and 3.0% at 3.0%

Sensitivity: LLQ=10 ng/ml

Specificity: Satisfactory

These assays were performed by the Bio-Analytical Unit of the SK & F Institute.

Data Analysis: C_{max}, C₂₄ (plasma concentration at 24 hrs after dosing), AUC₀₋₄ (up to the last measurable plasma concentration), AUC_{0-∞} (extrapolated to infinity), K (apparent elimination rate constant), and U₄₈ (48 hours urinary recovery) for digoxin were calculated.

C_{max} and the log-transformed AUC₀₋₄, C₂₄ and K were assessed for subject, treatment and period related variance, with a subplot to assess group and sequence effects. The resulting residual variance was used to calculate the 95% CI. Two-sided 95% confidence intervals were provided for the estimates of the true difference or ratio of the treatment means.

Results: The pharmacokinetic parameters, point estimates, and two-sided 95% CI for digoxin/placebo and digoxin/carvedilol are shown in Table 1. The median plasma concentration-time profiles are shown in Fig. 1.

Table 1. Pharmacokinetic parameters (mean ± SD) for digoxin with point estimates and 95% confidence intervals following administration with placebo and with carvedilol

Parameter	Digoxin and Placebo (R)	Digoxin and Carvedilol (T)	Point Estimate		95% CI
			T - R	T/R	
C _{max} (ng/ml)	1.62 ± 0.56	2.59 ± 1.00	0.97		0.20 - 1.73*
C ₂₄ (ng/ml)	0.23 ± 0.04	0.28 ± 0.05		1.19	1.10 - 1.27*
AUC ₀₋₄ (ng*hr/ml)	15.0 ± 2.7	17.9 ± 2.9		1.19	1.10 - 1.30*
AUC _{0-∞} (ng*hr/ml)	25.6 ± 7.1	30.7 ± 9.6		1.19	0.97 - 1.46
K (hr ⁻¹)	0.017 ± 0.004	0.017 ± 0.006		1.00	0.76 - 1.31
U ₄₈ (ng)	216 ± 116	188 ± 47	-28		-113 - 57

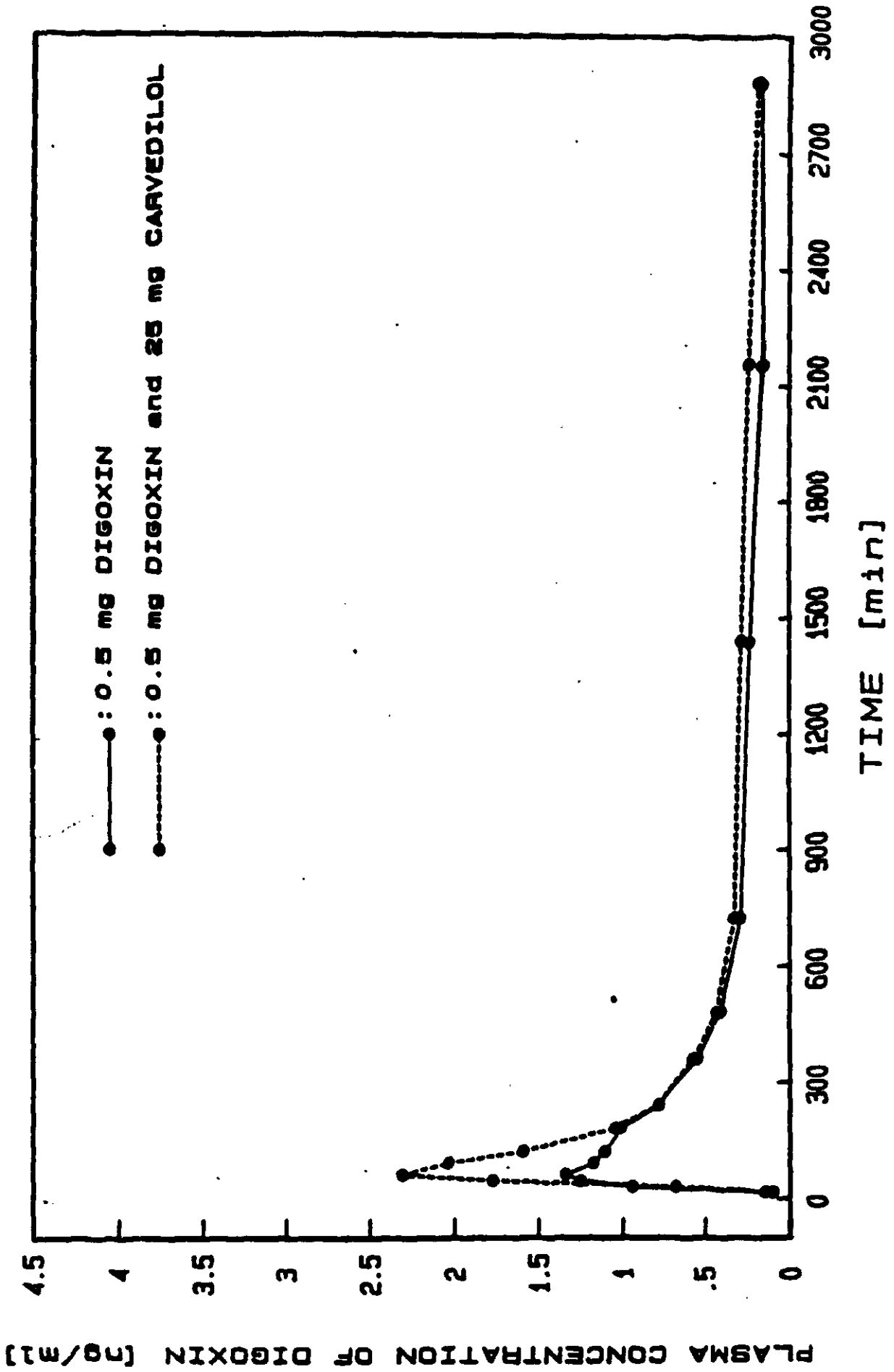
*p < 0.05

Mean C_{max} for digoxin increased from 1.62 to 2.59 ng/ml (60% increase) and mean AUC₀₋₄ increase from 15.0 to 17.9 ng*hr/ml (19% increase). Mean plasma concentration of digoxin at 24 hours was significantly increased from 0.23 to 0.28 ng/ml, for digoxin/placebo versus digoxin/carvedilol, respectively. In contrast, AUC_{0-∞}, K, U₄₈ were not significantly different between treatments.

Conclusions and Comments: Administration of a single oral dose of 25 mg carvedilol with an oral dose of 0.5 mg digoxin in healthy volunteers, caused a significant increase in C_{max} and AUC₀₋₄ of digoxin. The changes were almost entirely confined to the early course of the curves up to 4 hrs after dosing although the effects were evident after 24 hrs after dosing.

105517/A9904-GER : MEDIAN VALUES

Figure 1:



Evaluation of Drug Interaction of Carvedilol with Digoxin (administered intravenously)

Study No: A9905

Volume: 1.52

Pages: 73-164

Investigator and Site: Christian de Mey, M.D.

SK & F Institute for Applied Clinical Pharmacology, Göttingen, FRG

Objectives: To assess the acute effects of a single dose of 25 mg carvedilol on the plasma and urinary pharmacokinetics of a single dose of 0.5 mg digoxin administered via constant rate intravenous infusion over 10 minutes.

Formulations: • Carvedilol 25 mg tablets, batch #: 1/25/B/7

- Matched placebo, formulation: 1/25-P-5, batch #: 2, provided by Dept. of Pharmaceutical Development, SK & F Labs, Welwyn, UK.
- Commercially available digoxin solutions for parenteral administration (Lenoxin[®], Wellcome, FRG). Digoxin (0.5 mg) was diluted in isotonic saline and administered as a 10 ml/10 min infusion in sideline to a mainline of isotonic saline at 100 ml/min.

Study Design: In a double blind, period-balanced, within-subject cross-over design with randomly allocated sequences, 8 healthy male subjects (age 23 to 32 yrs; weight 63 to 92 kg) received the two study treatments separated by 2 weeks. On one occasion a single intravenous dose of 0.5 mg digoxin was administered via 10 min iv-infusion, immediately after the administration of a single oral dose of 25 mg carvedilol. On the other occasion digoxin was administered immediately after oral administration of carvedilol matched placebo. The medications were administered with 150 ml water, then 200 ml of water was given every 2 hrs up to 8 hrs after dosing. The subjects remained in bed up to 8 hrs after dosing.

Specimens: Blood samples were collected before and at 2, 5, 10, 15, 20, 30, 45 min and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48 and 72 hrs after dosing. Urine was collected in 5 fractions: pre-dosing blank, 0-8, 8-24, 24-36 and 36-48 hours after dosing.

Assay (digoxin):

Plasma digoxin levels were determined by radio-immuno assay (Amersham, UK).

Linearity: Calibration curve from 0.09 to 5.40 ng/ml

Precision: 0.7% at 1.0 ng/ml and 6.1% at 5.0 ng/ml

Sensitivity: LLQ=0.07 ng/ml

Specificity: Satisfactory

Digoxin levels in urine were assayed using HPLC with UV detection.

Linearity: Calibration curve from 10 to 400 ng/ml

Precision: 15.6% at 10 ng/ml and 3.0% at 3.0%

Sensitivity: LLQ=10 ng/ml

Specificity: Satisfactory

These assays were performed by the Bio-Analytical Unit of the SK & F Institute.

Data Analysis: C_{max} , C_{24} (plasma concentration at 24 hrs after dosing), AUC_{0-4} (up to the last measurable plasma concentration), AUC_{0-24} , K (apparent elimination rate constant), and U_{48} (48 hours urinary recovery) for digoxin were calculated.

C_{max} and the log-transformed AUC_{0-4} , C_{24} and K were assessed for subject, treatment and period related variance, with a subplot to assess group and sequence effects. The resulting residual variance was used to calculate the 95% CI. Two-sided 95% confidence intervals were provided for the estimates of the true difference or ratio of the treatment means.

Results: The pharmacokinetic parameters, point estimates, and two-sided 95% CI for digoxin/placebo and digoxin/carvedilol are shown in Table 1. The median plasma concentration-time profiles are shown in Fig. 1.

Table 1. Pharmacokinetic parameters (mean $\pm$ SD) for digoxin with point estimates and 95% confidence intervals following administration with placebo and with carvedilol

Parameter	Digoxin and Placebo (R)	Digoxin and Carvedilol (T)	Point Estimate		95% CI
			T - R	T/R	
C_{max} (ng/ml)	16.7 $\pm$ 4.3	17.6 $\pm$ 4.2		1.06	0.93 - 1.20
C_{24} (ng/ml)	0.29 $\pm$ 0.07	0.27 $\pm$ 0.06	-0.026		-0.054 - 0.002
AUC_{0-4} (ng $\cdot$ hr/ml)	27.9 $\pm$ 4.1	26.7 $\pm$ 3.9	-1.20		-2.71 - 0.31
AUC_{0-24} (ng $\cdot$ hr/ml)	18.3 $\pm$ 2.2	17.8 $\pm$ 2.2	-0.50		-1.19 - 0.20
K (hr $^{-1}$)	0.017 $\pm$ 0.004	0.015 $\pm$ 0.004		0.89	0.73 - 1.10
U_{48} (ng)	258 $\pm$ 18	246 $\pm$ 29		0.95	0.83 - 1.08

There was not a statistically significant difference in the PK parameters of digoxin (C_{max} , C_{24} , AUC_{0-4} , AUC_{0-24} , K , or U_{48}) when the administration of i.v. digoxin (and placebo) was compared with the administration of i.v. digoxin and carvedilol.

Conclusions: Administration of a single oral dose of 25 mg carvedilol with an intravenous dose of 0.5 mg digoxin in healthy volunteers, did not alter the digoxin's PK.

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-109-

105517/A9905-GER : MEDIAN VALUES

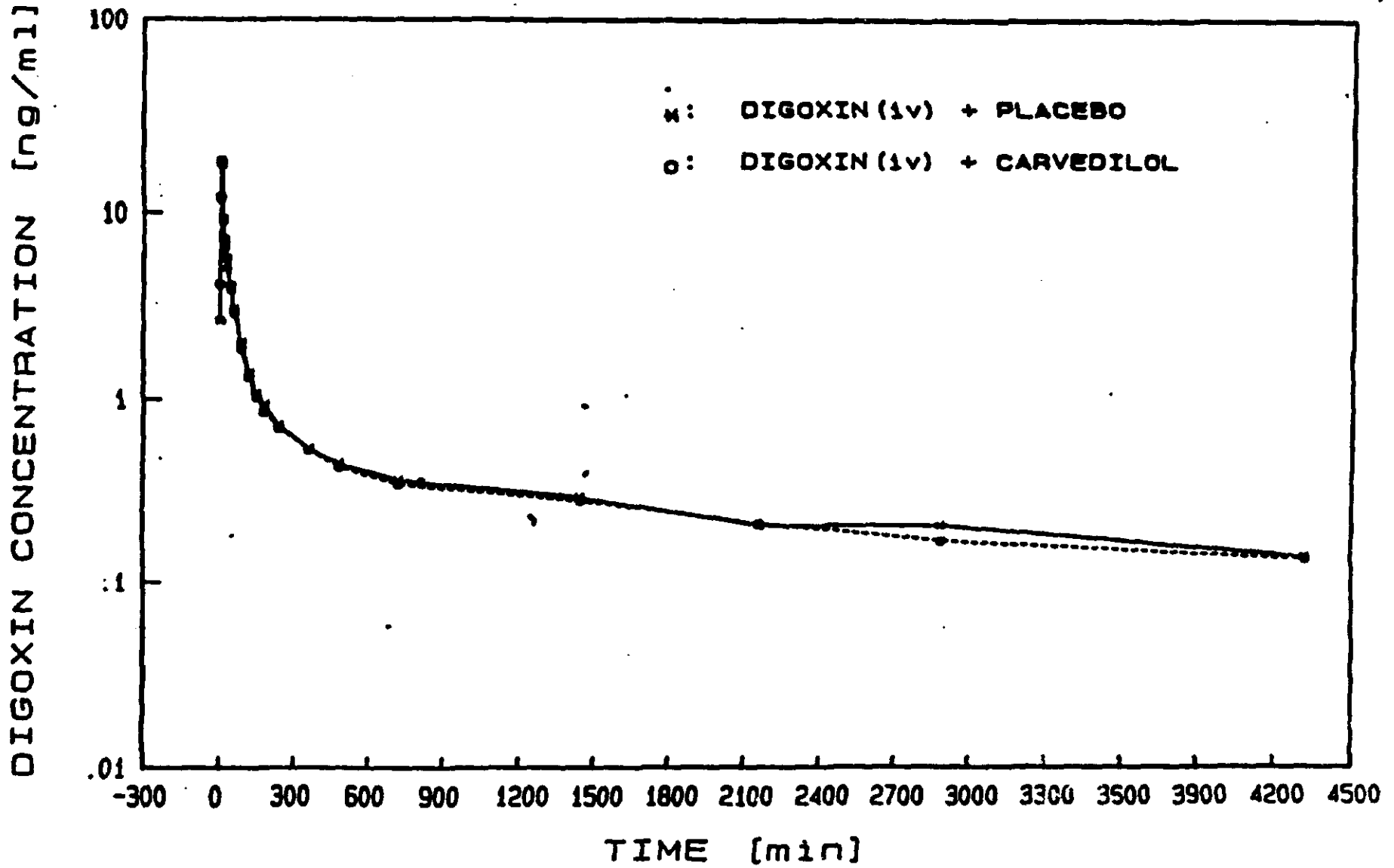


Figure 1:

Evaluation of Drug Interaction of Carvedilol with Warfarin (In-Vitro)

Study No: BP006BS

Volume: 1.55

Pages: 2-17

Investigator and Site: Brian R. Smith, Ph.D.

The Department of Drug Metabolism, SK & F Laboratories, Pennsylvania, USA

Objective: To assess the effect of carvedilol on the in-vitro plasma protein binding of warfarin

Study Design and Methods: Four carvedilol concentrations (300, 100, 17.4, and 3 ng/ml) and two warfarin concentrations (1.8 and 5.4 ug/ml) were studied. Bound and free fractions of warfarin were determined in triplicate from pooled plasma of healthy volunteers using equilibrium dialysis and ¹⁴C-warfarin. The warfarin concentrations correspond to the range required to produce a target prothrombin time ratio of 1.5 and 3.5 in human subjects, respectively. Dialysis cells were rotated to equilibrium (3 hrs) at 37°C. Samples were quantitated by determination of radiochemical content using liquid scintillation counting.

Results: The mean $\pm$ SD warfarin free fraction in the absence of carvedilol was $0.677 \pm 0.033\%$ (99.31% bound) and $0.794 \pm 0.148\%$ (99.21% bound) at 1.8 and 5.4 ug/ml, respectively (Table 1). ANOVA showed that the warfarin free fraction was not significantly changed ($p \geq 0.3$) at any of the 4 carvedilol concentrations studied.

Table 1. Effect of carvedilol on the free fraction of warfarin (mean $\pm$ SD, N=3)

Carvedilol (ng/ml)	% Free Fraction	
	1.8 ug/ml	5.4 ug/ml
0.0	0.688 ± 0.033	0.794 ± 0.148
3.0	0.698 ± 0.169	0.685 ± 0.089
17.4	0.554 ± 0.137	0.746 ± 0.093
100	0.698 ± 0.144	0.651 ± 0.025^b
300	0.801 ± 0.113	0.547 ± 0.06

^b N=2

Conclusions: At carvedilol concentrations which occur clinically, the free fraction of warfarin at therapeutic concentrations was not changed in-vitro in pooled plasma from healthy volunteers.

Protein Binding/Carvedilol

Study No: BC019BS

Volume: 1.73

Pages: 201-212

Investigator and Site: A. Haak and Dr. P. Neubert

Boehringer Mannheim GmbH, FRG

Objective: To describe the plasma protein binding of carvedilol in the presence of torsemide and the plasma protein binding of torsemide in the presence of carvedilol.

Study Design and Methods: The plasma protein binding for carvedilol and torsemide were determined in duplicate using equilibrium dialysis. Three radioactive working solutions were made to contain:

1. 200 ng/ml of ^{14}C -carvedilol
2. 1000 ng/ml ^3H -torsemide
3. 200 ng/ml ^{14}C -carvedilol and 1000 ng/ml ^3H -torsemide

Two ml of the working solutions were dialyzed against an equal volume of plasma for 6 hrs at 37°C. Samples were quantified by determination of radiochemical content using liquid scintillation counting.

Results:

Table 1. Percent protein binding of carvedilol in the presence of carvedilol in plasma of three subjects

Compound	Subject 1	Subject 2	Subject 3	Mean $\pm$ SD
Carvedilol	97.8	98.3	98.7	98.3 $\pm$ 0.3
	98.1	98.4	98.4	
Carvedilol with Torsemide	98.6	98.5	98.8	98.6 $\pm$ 0.3
	98.8	98.1	98.6	
Torsemide	94.0	94.2	92.7	93.9 $\pm$ 0.6
	94.2	94.1	93.9	
Torsemide with Carvedilol	94.3	94.2	94.1	94.1 $\pm$ 0.
	94.5	93.6	94.0	

Conclusions: It was demonstrated that plasma protein binding of carvedilol (98%) was unchanged in the presence of torsemide and the plasma protein binding of torsemide (94%) was unchanged in the presence of carvedilol.

Protein Binding/Carvedilol Enantiomers

Study No: 170

Volume: 1.55

Pages: 18-56

Investigator and Site: R.D. Eckardt, B.S., The Department of Drug Metabolism and Pharmacokinetics, SmithKline Beecham Pharmaceuticals, Upper Merion, Pennsylvania, USA

Background: Carvedilol undergoes stereospecific first-pass metabolism with plasma levels of R-carvedilol approximately 2 to 3 times higher than S-carvedilol following oral dose in healthy volunteers.

Objective: To describe the plasma protein binding of the two enantiomers over a therapeutic range

Methods: Plasma protein binding of ^3H -R- and ^3H -S-carvedilol over a concentration range of 0.3 to 300 ng/ml was carried out by equilibrium dialysis in semi-micro cells at 37°C for 6 hrs. Samples were quantified by determination of radiochemical content using liquid scintillation counting.

Results: The observed percent free fraction of ^3H -R-carvedilol remained constant with a mean value of 0.85% (± 0.13) over the concentration range used in this study. The observed percent free fraction of ^3H -S-carvedilol also remain constant with a mean value of 1.60% (± 0.27) (Fig. 1). After correction of overestimation due to radiochemical impurities, the actual mean free fraction of ^3H -R- and ^3H -S-carvedilol were approximately 0.5 - 0.6% and 1.2 - 1.3%, respectively.

Conclusions: It was demonstrated that plasma protein binding of both ^3H -R- and ^3H -S-carvedilol, was linear over the concentration range of 0.3 to 300 ng/ml. The mean free fraction of ^3H -S-carvedilol was 2-3 fold higher than ^3H -R-carvedilol. However, the correction of overestimation of free fraction due to radiochemical impurities is not well explained.

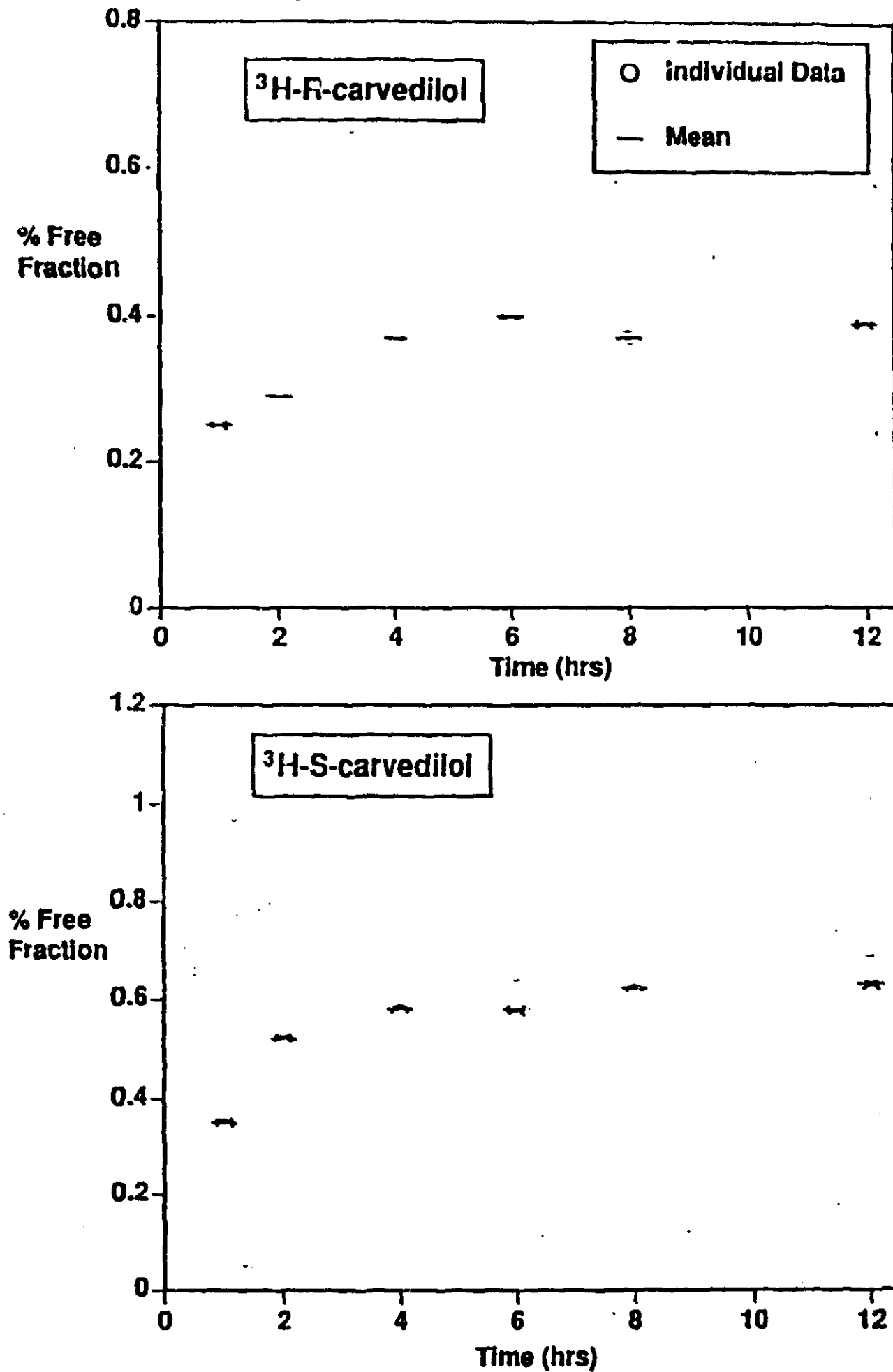


Figure 1. Effect of incubation time on the free (unbound) fraction of $^3\text{H-R}$ or $^3\text{H-S-carvedilol}$ in plasma.

Data points displayed are replicate analyses of pooled heparinized plasma from two subjects.

000037

Carvedilol Metabolites/Protein Binding

Study: BP-0018/SKF-105517

Volume: 1.55

Page: 57-81

Investigator and Site:

Lee Ann P. Yodis, B.S.

Smith Kline Beecham, Upper Merion

Background: O-desmethyl carvedilol (M2), 4'-hydroxyphenyl carvedilol (M4) and 5'-hydroxyphenyl carvedilol are pharmacologically active metabolites of carvedilol. In human volunteers, these metabolites are observed over a concentration range of 0.3 to 30 ng/ml.

Objectives: To describe the plasma protein binding of the carvedilol metabolites M2, M4 and M5.

Methods

Plasma protein binding of ^3H -M2, ^3H -M4 and ^3H -M5 over a concentration range of 0.3 - 30 ng/ml was carried out by equilibrium dialysis in semi-micro cells at 37°C for 4 hrs. Samples were quantitated by determination of radiochemical content using liquid scintillation counting.

Results

The observed percent free fraction of ^3H -M2 remained constant at a mean value of approximately 1.3% over the concentration range used in this study. Because radiochemical impurities could lead to an overestimation of the free fraction, the contribution of impurities to the estimated free fraction were evaluated by quantitation of the radiochemical species in the dialysate. For ^3H -M2 (approximately 10 ng/ml), impurities represented approximately 17% of the radioactivity in the plasma dialysate suggesting that the actual mean free fraction of ^3H -M2 is approximately 1.0-1.1%. The observed percent free fraction of ^3H -M4 and ^3H -M5 also remained constant over the concentration used in this study but were approximately 3 fold greater than ^3H -M2 at a mean value of 3.3 and 3.4%, respectively. For ^3H -M4 and ^3H -M5 (approximately 10 ng/ml), impurities represented less than 2% of the radioactivity in the plasma dialysate suggesting that the observed free fraction is an appropriate estimate of the actual mean free fraction of ^3H -M4 and ^3H -M5.

Conclusions and Comments: It was demonstrated that the plasma protein binding of the carvedilol metabolites, was linear over concentration range of 0.3 to 30 ng/ml. The mean free fraction of M4 and M5 were 2-3 fold higher than the actual free fraction of M2.

This study is acceptable. However, correction of overestimation of free fraction due to radio-labelled impurities (in case of M2) is not well explained.

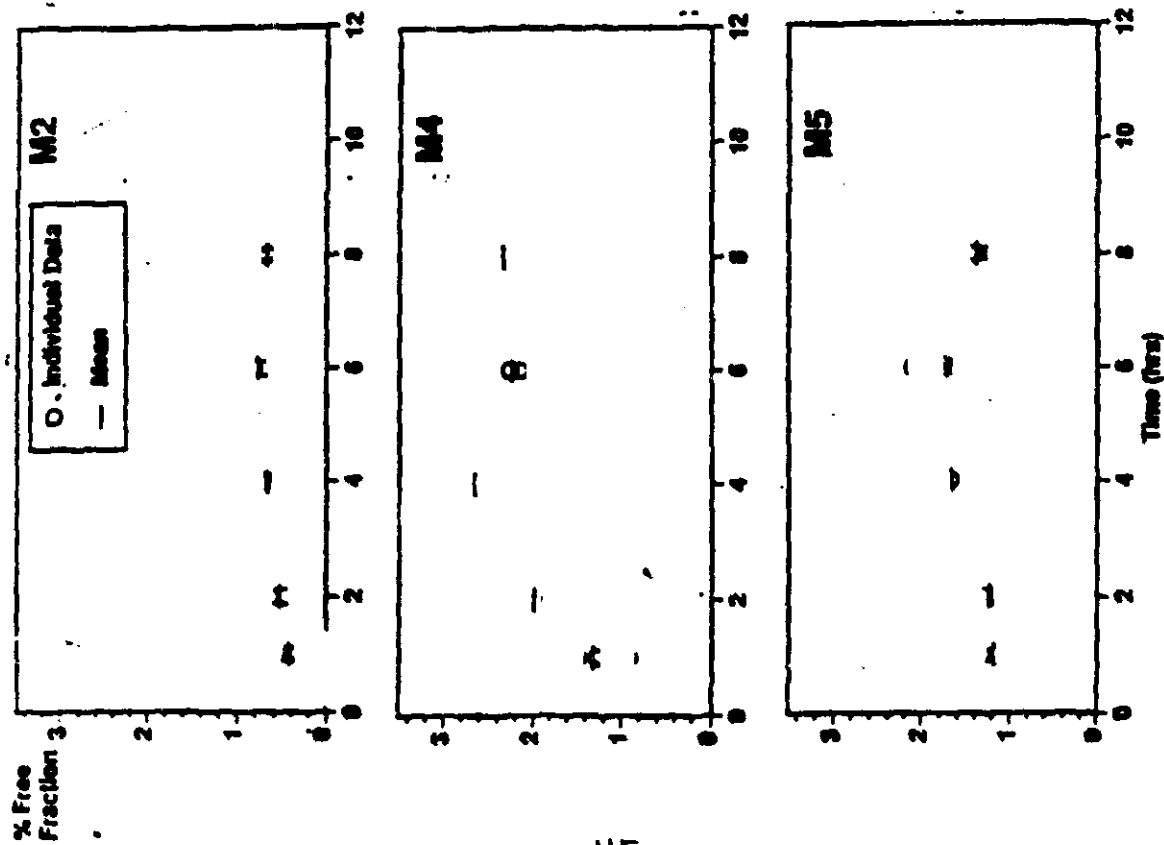


Figure 1. Effect of incubation time on free (unbound) fraction of H-125, 3H-M4 and 3H-B metabolites of SKF 105817. Data points displayed are replicate analyses of blood from pooled hepatized blood from human subjects. For actual data see Appendix Table I - III.

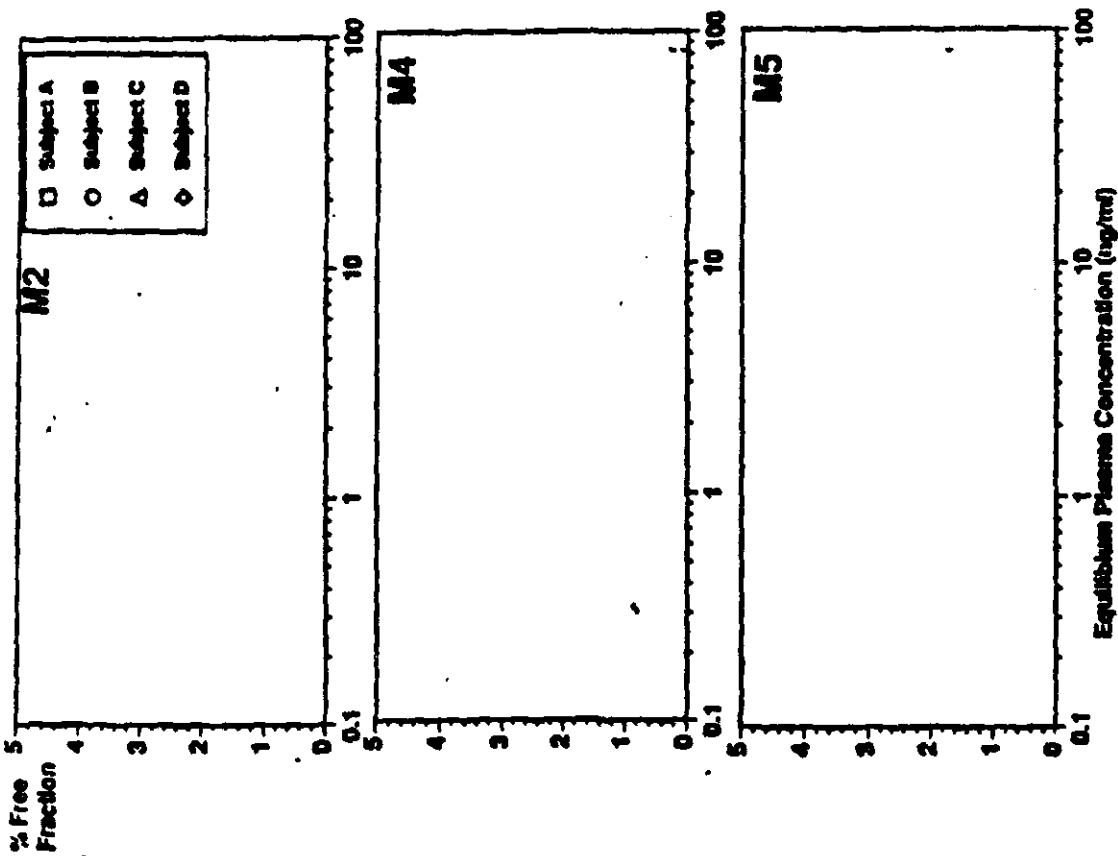


Figure 2. Concentration dependence of the plasma protein binding of H-125, 3H-M4 and 3H-B metabolites of SKF 105817. Data points displayed are analyses of individual blood samples from four normal male volunteers. For actual data see Appendix Table IV - VI.

In-Vitro Dissolution

The proposed dissolution method is listed below:

Medium: 900 ml simulated gastric fluid (USP XXII) at 37°C

Apparatus: USP Apparatus II (paddle), 50 rpm

Sampling times: 15, 30, 45, and 60 minutes or as requested

The dissolution samples were analyzed by HPLC using a C-18 column. The detection wavelength was 285 nm. The dissolution was rapid and almost complete at 15 minutes. In-vitro dissolution data for the tablets and capsules used in bio-study (Study 020) and pivotal clinical trials (Studies B100, B101, C1106, C1107 and C1109) are shown in Table 1.

Carvedilol Batches used in Pivotal Clinical Trials and in Bioequivalence Study 020

<u>Dosage Form</u>	<u>Formula</u>	<u>Strength</u>	<u>Batch Lot Number</u>	<u>Protocol Number</u>
Capsule	A	3.125 mg	820-168-40Aa	B101
Capsule	A	3.125 mg	820-354-40Aa	C1106
Capsule	B	6.25 mg	820-169-40Cc	B100, B101, C1106, C1107 -
Capsule	C	12.5mg	820-173-40Lg	B100, B101
Capsule	C	12.5mg	820-468-40Lg	C1106, C1107, C1109 -
Capsule	D	25 mg	820-176-40Lh	B100, B101
Capsule	D	25 mg	820-469-40Lh	C1106, C1107, C1109 -
Capsule	D	25 mg	821-522-40Lh	A9914/020
Tablet	A	25 mg	X205-1CV2	A9914/020

ATTACHMENT 2

Dissolution Profile Data for Biobatch Tablets

Tablet 25 mg						
SD Reference No.	704					
Method Reference No.	DI-105517-F	% Dissolved - (Avg.)				
Lot X205-1CV2	Interval - minutes	0	15	30	45	60
	initial	0	94	94	94	94
SD 704Chart5	12 mo 30°C	0	94	96	96	97

Table 1

Carvedilol Stability Dissolution Profile Data

Capsule 3.125 mg					
SD Reference No.	383				
Method Reference No.	DI-105517-B-0				
Lot 820-354-40Aa	Interval - minutes				
	initial	0	15	30	45
		0	94	97	97
SD383/chart1	36 mo 30°C	0	94	98	98
Capsule 6.25 mg					
SD Reference No.	355				
Method Reference No.	DI-105517-B				
Lot 820-169-40Cc	Interval - minutes				
	initial	0	15	30	45
		0	97	100	102
SD355Chart2	36 mo 30°C	0	94	97	98
Capsule 12.5 mg					
SD Reference No.	354				
Method Reference No.	DI-105517-A				
Lot 820-173-40Lg	Interval - minutes				
	initial	0	15	30	45
		0	96	102	103
SD354Chart3	48 mo 30°C	0	90	97	98
Capsule 12.5 mg					
SD Reference No.	419				
Method Reference No.	DI-105517-A				
820-468-40Lg	Interval - minutes				
	initial	0	15	30	45
		0	101	100	101
SD419chart6	48 mo 30°C	0	91	104	107
Capsule 25 mg					
SD Reference No.	353				
Method Reference No.	DI-105517-A				
Lot 820-176-40Lh	Interval - minutes				
	initial	0	15	30	45
		0	88	97	96
SD353Chart4	12 mo 30°C	0	88	100	102
Capsule 25 mg					
SD Reference No.	418				
Method Reference No.	DI-105517-A				
Lot 820-469-40Lh	Interval - minutes				
	initial	0	15	30	45
		0	82	91	93
SD418chart7	48 mo 30°C	0	79	93	99
Capsule 25 mg					
SD Reference No.	NP				
Method Reference No.	DI-105517-F				
Lot 821-522-40Lh	Interval- minutes				
		0	15	30	45
		0	96	102	102
chart8					

MAY 19 1995

ENVIRONMENTAL ASSESSMENT
AND
FINDING OF NO SIGNIFICANT IMPACT
FOR
KREDEX® TABLETS
(Carvedilol)
12.5 and 25 mg
NDA 20-297

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIO-RENAL DRUG PRODUCTS
(HFD-110)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-297

Kredex® Tablets

(Carvedilol)

The Food and Drug Administration (FDA) recognizes the National Environmental Policy Act of 1969 (NEPA) as the national charter for protection, restoration, and enhancement of the environment. NEPA establishes policy, sets goals (section 101), and provides procedures (section 102) for carrying out the policy.

Environmental information is to be available to the public and the decisionmaker before decisions are made about actions that may significantly affect the quality of the human environment; FDA actions are to be supported by accurate scientific analyses; and environmental documents are to concentrate on timely and significant issues, not to amass needless detail.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for **Kredex® Tablets**, **SmithKline Beecham Pharmaceuticals** has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Carvedilol is administered as an oral tablet in the treatment of essential hypertension. Drug substance intermediates are manufactured by Boehringer Mannheim GmbH, Mannheim, Germany. The drug substance will be manufactured at SmithKline Beecham (Manufacturing) Limited, County Cork, Ireland and the drug product will be manufactured and packaged at SmithKline Beecham Pharmaceuticals Co., Cidra, Puerto Rico. The finished drug product will be used in hospitals, clinics and by patients in their homes.

Chemical and physical test results and information indicate that carvedilol will most likely be restricted to the aquatic and terrestrial environments. A substantial amount of the drug will be removed from the aquatic environment as the compound will adsorb to sludge in waste water treatment plants. The compound degrades rapidly upon exposure to light although this will vary depending on the exposure conditions in the environment and it is also susceptible to aerobic biodegradation. As the compound is expected to persist in the environment for some time, acute toxicity studies were conducted using water fleas (*Daphnia pulex*) and bluegill sunfish (*Lepomis macrochirus*). The studies indicate that the drug would not be expected to exhibit acute toxicity effects to aquatic organisms at concentrations expected to be emitted into and exist in the environment. Carvedilol may enter the terrestrial environment from sludge that is applied to land and will remain tightly bound to soil. The material is not expected to persist in the soil compartment and toxicity to terrestrial organisms is expected to be less than that determined for aquatic organisms due to the decreased exposure pathways.

Microbial inhibition studies indicate that respiration in activated sludge is not inhibited at concentrations several orders of magnitude greater than the maximum expected environmental concentration (MEEC).

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, pharmaceutical processing waste, and user disposal of empty or partly used product and packaging. Waste drug product and pharmaceutical processing waste will be disposed of predominantly at licensed incineration facilities although small quantities may be emitted in effluent waste streams. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system while some unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. A certification has been provided by the German authorities stating that Boehringer Mannheim GmbH is operating in compliance with their environmental laws and regulations.

Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

5/19/95 *[Signature]*
DATE Prepared by
Felix D. Sager
Review Chemist
Center for Drug Evaluation and Research

5/19/95 *[Signature]*
DATE Approved
Phillip G. Vincent, Ph.D.
Principal Assessment Officer
Center for Drug Evaluation and Research

5/19/95 *[Signature]*
DATE Searched
Joseph L. Gerussi, Ph.D.
Associate Director for Chemistry
Center for Drug Evaluation and Research

Attachments:

- I: Environmental Assessment
- II: Compliance Statements
- III: Batch Summary Table
- IV: Material Safety Data Sheet

CC: Original NDA 20-297/ZMcDonald copy to NDA/HFD-110
FONSI File 20-297/HFD-004
P. Vincent/HFD-004
Docket File 20-387/HFD-004
FOI Copy/HFD-019

20297.FON
F/T by NBS 05/19/1995

ATTACHMENT I

ENVIRONMENTAL ASSESSMENT INFORMATION

Carvedilol

1. DATE: March 17, 1995
2. NAME OF APPLICANT: SmithKline Beecham Pharmaceuticals
3. ADDRESS: Four Falls Corporate Center
Route 23 and Woodmont Avenue
P.O. Box 1510
King of Prussia, PA 19406

4. DESCRIPTION OF THE PROPOSED ACTION:

4.1 Description of the Requested Approval

SmithKline Beecham Pharmaceuticals is requesting approval for use of carvedilol for the treatment of essential hypertension. β -blocking and vasodilator effects occur in the same dosage range; carvedilol thus offers two active mechanisms of value in the management of hypertension. Carvedilol may also be effective in the management of other cardiovascular disorders, such as angina pectoris and/or left ventricular dysfunction.

4.2 Need for the Proposed Action

Carvedilol is a non-selective β -receptor blocking agent with vasodilative properties. It reduces peripheral vascular resistance through vasodilation and suppresses the renin-angiotensin-aldosterone system through β -blockage. Through these effects, carvedilol significantly reduces blood pressure in hypertensive patients. Carvedilol has no intrinsic sympathomimetic activity. By balancing vasodilation and β -adrenoreceptor blockage, carvedilol maintains myocardial function without affecting left ventricular ejection fraction. It causes no significant decrease in heart rate. The multiple actions of carvedilol are responsible for the antihypertensive efficacy of the drug in animals and in humans, and may also provide effective therapy in angina and congestive heart failure.

This Environmental Assessment Information reflects effluent discharges based on estimated fifth year production of drug substance and product, as well as detailed information on the waste treatment and disposal processes at SmithKline Beecham Pharmaceuticals facilities at Cork, Ireland, (drug substance production), and Cidra, Puerto Rico (drug product production), as well as summary information on the production of key drug intermediates at the Boehringer Mannheim facility in Mannheim, Germany (drug intermediate production). Details on the Boehringer Mannheim facility are available in DMF 9502. This report also includes all of the fate and effects data and evaluations which are currently available for carvedilol drug substance.

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ENVIRONMENTAL ASSESSMENT INFORMATION

Carvedilol

The manufacture of carvedilol substance and product will employ the same environments and utilize existing plants that are also currently manufacturing other pharmaceutical products.

4.3 Location where Product will be Produced

Carvedilol drug intermediates, used to produce the product that is the subject of the proposed action, are manufactured at the following facility:

Boehringer Mannheim GmbH
Sandhofer Strasse 116
Postfach 310120
D-6800 Mannheim 31
Federal Republic of Germany

The Boehringer Mannheim facilities used to produce these intermediates are located in Mannheim, Germany.

Carvedilol, the drug substance in the product which is the subject of the proposed action, is manufactured (stages 4-8) at the following facility:

SmithKline Beecham (Manufacturing) Limited
Currabinny, Carrigaline
County Cork
Ireland

SmithKline Beecham (Manufacturing) Limited is located approximately twelve miles south of Cork City on the southern shores of Cork Harbor. There is a total land bank of 130 acres, but the facility occupies only 28 acres. The immediate area is rural, with some farms and dwellings within a half mile radius of the boundary fence. The site discharges an aqueous waste into Cork Harbor after on-site biological treatment.

Carvedilol drug product will be prepared at the following facility:

SmithKline Beecham Pharmaceuticals Co.
Road 172
KM9.1/Bo Certenejas
Cidra, Puerto Rico 00739

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ENVIRONMENTAL ASSESSMENT INFORMATION

Carvedilol

The Cidra facility for the drug product manufacture is a site of approximately 52 acres located in an agricultural/urban/industrial area on the central mountainous ridge of the island of Puerto Rico.

4.4 Locations where Product will be Used

Carvedilol drug product will be used in the United States of America (the subject of this NDA) and world-wide, with predominant use coinciding with areas of greatest population density.

4.5 Locations where Product will be Disposed of

Carvedilol drug product returned goods will be collected at the following site:

Division KENCO Group Inc.
1704 Mid Park Drive
Knoxville, Tennessee 37291

From this site, the materials will be shipped to one or more of the following licensed facility for destruction by high temperature incineration:

SmithKline Beecham Pharmaceuticals
Bristol Industrial Park
Weaver Pike
Bristol, Tennessee 37620

Ogden Martin Systems of Lake, Inc.
3830 Rogers Industrial Park Road
Okahumpka, Florida 34762

Documentation for these disposal facilities is provided in Appendix I.

5. DESCRIPTION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION:

5.1 Complete Nomenclature

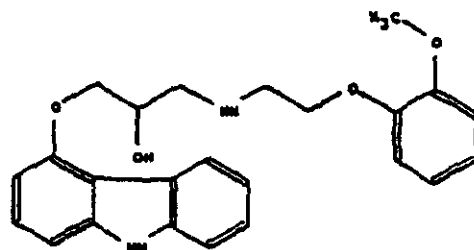
British Adopted Name (BAN):	Carvedilol
INN:	Carvedilol
United States Adopted Name (USAN):	Carvedilol

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ENVIRONMENTAL ASSESSMENT INFORMATION

Carvedilol

Trade Name:	
Chemical Name:	(±)-1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxy-phenoxy)-ethyl]amino]-2-propanol
5.2 <u>CAS Number:</u>	72956-09-3
5.3 <u>Laboratory Codes:</u>	SK&F 105517; BM 14.190
5.4 <u>Molecular Formula:</u>	C ₂₄ H ₂₆ N ₂ O ₄
5.5 <u>Molecular Weight:</u>	406.5
5.6 <u>Structural Formula:</u>	



5.7 <u>Description:</u>	A white to off-white powder
5.8 <u>Melting Range:</u>	SK&F 105517 typically melts over a 2-3°C range within 113-119°C
5.9 <u>Additives:</u>	Not applicable
5.10 <u>Impurities:</u>	

Organic impurities arising from the synthesis are determined by GC and HPLC. Solvent content is also measured by GC and the inorganic impurities, heavy metals, and sulfated ash are also monitored. Identification is included on the drug substance specification. The compound is stable, and no degradants are likely to arise under normal conditions.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

6.1 Introduction from Production

The production of carvedilol drug substance, intermediates and drug product will utilize the same facilities currently being used for the production of other pharmaceutical products. The following evaluation of the anticipated environmental impact of carvedilol production is based on estimated fifth year production and on existing waste treatment systems at the production facilities. Engineering estimates are used to predict anticipated discharge levels; however, the evaluations do not reflect changes in treatment process operations or technology which might be implemented before actual approval of the carvedilol application.

This Environmental Assessment contains non-confidential information on the control and disposition of gaseous, aqueous, and solid wastes at the production facilities.

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ENVIRONMENTAL ASSESSMENT INFORMATION

Carvedilol

6.1.1 Drug Intermediate Production at Boehringer

The Boehringer Mannheim facilities used to produce the intermediates (2) are located in Mannheim, Germany. One intermediate will be produced at Production Plant HC-B 21, and the second intermediate will be produced at Production Plants HC-B 4, HC-B 10 and HC-B/OB.

6.1.1.1 Introduction from Production of Drug Intermediate at HC-B 21

The following information was provided by Boehringer Mannheim GmbH regarding the introduction of substances into the environment from production of intermediate at Production Plant HC-B 21.

6.1.1.1.1 Emissions as Part of Waste Water

The substances described in the following table are expected to be emitted as part of the wastewater. This wastewater is discharged from the production plants, pretreated in the BM waste water purification plant and then discharged into the community wastewater system/sewage plant, where final treatment takes place.

Substance ^a	CAS Number
Sodium chloride	7647-14-5
Toluene	108-88-3
Organic By-products	NA

^a Substances expected to be emitted during each process step.

6.1.1.1.2 Solid/Liquid Wastes

No other solid or liquid wastes are produced during the production steps of the intermediate.

6.1.1.2 Emissions Requirements at the Boehringer Mannheim Plant

Boehringer Mannheim GmbH reached an agreement on pollution control with Mannheim in the state of Baden-Wurtemberg, where its plant is located. This agreement requires Boehringer Mannheim GmbH to comply with the regulations for environmental protection enacted by the German Federal Government.

6.1.1.2.1 Emission Requirements for Sewage into the Municipal Wastewater System

The following table summarizes the maximum wastewater permit levels established by the government.

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ENVIRONMENTAL ASSESSMENT INFORMATION

Carvedilol

Parameter	Value
pH	6.0 - 9.5
Temperature	max. 35°C
COD	700 mg/L
Ratio COD/BOD	< 2.5 :1
Settling substances (solvents)	1 mL/30 minutes
Sulfate (SO ₄)	400 mg/L
Sulfide (S)	10 mg/L
Sulfite (SO ₃)	50 mg/L
Fluoride	50 mg/L
Phenols	20 mg/L
Aromatic Hydrocarbons	30 mg/L
Ammonia as NH ₄	100 mg/L
AOX	0.5 mg/L
Organic solvents miscible with water	3000 mg/L
Organic solvents not miscible with water	According to solubility in water
Cu	1 mg/L
Fe	20 mg/L
Cr (III)	3 mg/L
Cr (VI)	0.1 mg/L
Zn	3 mg/L

6.1.1.2.2 Emission Requirements on Waste Gases

The following table summarizes the permit levels for waste gas emissions, according to the "Technical Directions for Maintaining Clean Air" (TA Luft).

Emission	Value
Ethylene oxide	≤ 5 mg/m ³
Toluene	0.15 g/Nm ³

If more than one substance in the waste gas is classified as carcinogenic III, the total concentration is not allowed to exceed 5 mg/m³ at a mass flow of 25 grams (or more) per hour. If there is more than one organic substance (vapor) in the waste gas, the total concentration is not allowed to exceed 0.15 g/Nm³ at a mass flow of 3 kg (or more) per hour.

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Carvedilol

Manufacture of the intermediate in the Boehringer Mannheim plant (HC-B 21) will not result in the discharge of any emissions in excess of the amounts allowed by the applicable laws. A citation of and statement of compliance with applicable emissions requirements is provided in Appendix II. In addition, a certification of compliance signed by the appropriate government authority (Regierungsprasidium Karlsruhe) is also included in Appendix II.

6.1.2 Drug Intermediate Production at Boehringer

6.1.2.1 Introduction from Production of Drug Intermediate at HC-B 4, HC-B 10, and HC-B/OB

The following information was provided by Boehringer Mannheim GmbH regarding the introduction of substances into the environment from production of intermediate at Production Plants HC-B 4, HC-B 10 and HC-B/OB.

6.1.2.1.1 Emissions as Part of Wastewater

The substances described in the following table are expected to be emitted as part of the wastewater. This wastewater is discharged from the production plants, pretreated in the BM wastewater purification plant and then discharged into the community wastewater system/sewage plant, where final treatment takes place.

Substance	CAS Number
Acetic acid	64-19-7
Methanol	67-56-1
Organic By-products	NA
Intermediates	NA
Phosphoric acid	7664-38-2
Ethanol	64-17-5
Potassium chloride	7447-40-7

6.1.2.1.2 Solid/Liquid Wastes

The substances listed in the following table are produced as liquid or solid wastes. Solid wastes are disposed of through incineration at a community plant, and liquid wastes are disposed of through incineration at an outside company licensed to dispose of industrial waste products.

ENVIRONMENTAL ASSESSMENT INFORMATION

Carvedilol

Substance	CAS Number
Resin by-products dissolved in solvent	NA
Activated carbon	7440-44-0
Filter aid	NA
Waste solvents	NA
Alumina	1344-28-1
Solvent/Oil mixture (residue of distillation)	NA

6.1.2.2 Emissions Requirements at the Boehringer Mannheim Plant

Boehringer Mannheim GmbH reached an agreement on pollution control with Mannheim in the state of Baden-Wurtemberg, where its plant is located. This agreement requires Boehringer Mannheim GmbH to comply with the regulations for environmental protection enacted by the German Federal Government.

6.1.2.2.1 Emission Requirements for Sewage into the Municipal Wastewater System

The following table summarizes the wastewater permit levels required by the government.

ENVIRONMENTAL ASSESSMENT INFORMATION

Carvedilol

Parameter	Value
pH	6.0 - 9.5
Temperature	max. 35°C
COD	700 mg/L
Ratio COD/BOD	< 2.5 :1
Settling substances (solvents)	1 mL/30 minutes
Sulfate (SO ₄)	400 mg/L
Sulfide (S)	10 mg/L
Sulfite (SO ₃)	50 mg/L
Fluoride	50 mg/L
Phenols	20 mg/L
Aromatic Hydrocarbons	30 mg/L
Ammonia as NH ₄	100 mg/L
AOX	0.5 mg/L
Organic solvents miscible with water	3000 mg/L
Organic solvents not miscible with water	According solubility in water
Cu	1 mg/L
Fe	20 mg/L
Cr (III)	3 mg/L
Cr (VI)	0.1 mg/L
Zn	3 mg/L

6.1.2.2.2 Emission Requirements on Waste Gases

The following table summarizes the permit levels for waste gas emissions, according to the "Technical Directions for Maintaining Clean Air" (TA Luft).

Emission	Value
Ethanol	0.15 mg/m ³
Diisopropylether	0.15 g/Nm ³

If more than one of the substances listed in the table above is found in the waste gas, the total concentration is not allowed to exceed 0.15 g/Nm³ at a mass flow of 3 kg (or more) per hour.

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Carvedilol

Manufacture of the intermediate in the Boehringer Mannheim plant (HC-B 4, HC-B 10 and HC-B/OB) will not result in the discharge of any pollutants in excess of the amounts allowed by the applicable laws. A citation of and statement of compliance with applicable emissions requirements is provided in Appendix III. In addition, a certification of compliance signed by the appropriate government authority (Regierungsprasidium Karlsruhe) is also included in Appendix III.

6.1.3 Drug Substance Production at Cork

Carvedilol (SK&F 105517) drug substance process stages 4-8 will be performed at SmithKline Beecham (Manufacturing) Limited, a SmithKline Beecham Pharmaceuticals' facility in Cork, Ireland. Environmental evaluations of the impacts from drug substance production at Cork follow.

SmithKline Beecham (Manufacturing) Limited, Cork, Ireland is expected to remain in compliance with applicable waste effluent permits throughout the production of carvedilol drug substance. The Cork facility is regulated under an Integrated Pollution Control (IPC) license (Reference Number in Register of Licenses: 4; Date of Notification: October 28, 1994), under authority of the Environmental Protection Agency and the Environmental Protection Agency Act, 1992. This license contains permit levels and monitoring procedures for all plant emissions (wastewater, air, incinerators, etc.), as well as guidelines for the establishment of an Environment Management Programme, to assess all operations for the use of cleaner technology and the minimization of waste.

6.1.3.1 Waste Stream Summary and Disposition

The types of waste streams generated at SmithKline Beecham (Manufacturing) Limited will be disposed of such that release into the environment (gaseous and aqueous waste) will not exceed SmithKline Beecham (Manufacturing) Limited' plant permit levels (Appendix III).

6.1.3.2 Material Balance

Material balance information for the chemical inputs, process intermediates and effluents was determined for stages 4-8, thus accounting for all materials and amounts used in or produced by these stages. Waste outputs include leftover material resulting from production, inspection operations, assay solutions sampled before and after filtration, and floor and equipment washings.

ENVIRONMENTAL ASSESSMENT INFORMATION

Carvedilol

6.1.3.3 Controls Exercised on Wastes

6.1.3.3.1 Air and Fugitive Emissions

Hydrogen, the only off-gas produced, is vented directly to the atmosphere through a flame arrestor. Fugitive emissions are monitored if there is reason to suspect a gaseous leak. Air from the buildings where chemical processes are performed is filtered through two chemical absorbers. Air is automatically monitored every half hour by gas chromatography for several compounds, depending on the processes being performed, as it is discharged to the atmosphere.

6.1.3.3.2 Incinerated Wastes

Most process waste streams produced during carvedilol production at SmithKline Beecham (Manufacturing) Limited are incinerated at 1000°C. Process effluents are stored prior to incineration, and approximately 200 L of waste per hour are burned in each of two incinerators. After incineration, the effluent gas is passed through an absorber for the scrubbing of acidic compounds before discharge to the environment through a stack. This scrubber unit consists of a caustic solution circulating through a packed bed. Scrubber liquors are sent to the on-site wastewater treatment facility.

At discharge, incinerator gases are continuously monitored for carbon monoxide, sulphur dioxide and total organic carbon (TOC). The amount of organic material remaining after incineration is calculated using a 99.99% incineration destruction efficiency, based upon the known removal efficiencies for mercaptan and methylethyl ketone (MEK). The Cork facility is regulated under an Integrated Pollution Control (IPC) license (Reference Number in Register of Licenses: 4; Date of Notification: October 28, 1994), under authority of the Environmental Protection Agency and the Environmental Protection Agency Act, 1992.

6.1.3.3.3 Biotreatment System

Several of the carvedilol process wastestreams are treated in the on-site wastewater biotreatment facility. Scrubber liquors from the incinerators are sent for aerobic biological treatment before being discharged.

The treatment facility incorporates a basin of activated sludge, which has a retention time of 10 days. The biotreated waste (including domestic effluents and mutrators, floor washes, incinerator quench streams, and scrubber and environmental spent liquors) is sent to a balancing tank prior to neutralization in a second tank. The wastes are then sent to a stripping tank, prior to passing to an aeration tank to reduce biological oxygen demand (BOD). After aeration, some of the waste is aerated a second time in another tank, while the remaining waste is sent to a clarifier. The twice-aerated effluent is passed to another

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Carvedilol

clarifier. Both clarifiers are dosed with polyelectrolytes, and effluent wastes are sent to the final holding tank prior to discharge.

Several parameters of the effluent are monitored on a daily basis at three stages of the treatment process. The flow rate, pH, COD, total dissolved solids and load (kg of COD per day) are monitored at the input stage, and the pH, dissolved oxygen, MLSS and F/M are monitored at the sludge plant. At the final holding tank, the pH, COD, suspended solids, ammonia and flow rate are also monitored. In addition to normal testing, effluent liquors are sampled if a problem (e.g., equipment malfunction) is discovered.

Treatment of effluents results in >80% reduction in BOD. Review of the measured (confidential) and calculated concentrations of affected aqueous effluent components and a comparison with their permit levels resulted in the determination that the SmithKline Beecham (Manufacturing) Limited facility is in compliance with their aqueous effluent permits.

6.1.3.3.4 Solid Waste

Solid wastes produced during Cork carvedilol substance production process are sent off-site for disposal.

All treatment plant sludge is mechanically dewatered to approximately 15% solids prior to off-site disposal, with the extracted liquid returned to the effluent treatment plant. The Cork facility is regulated under an Integrated Pollution Control (IPC) license (Reference Number in Register of Licenses: 4; Date of Notification: October 28, 1994), under authority of the Environmental Protection Agency and the Environmental Protection Agency Act, 1992. Wastes and leachate will be tested for the presence of heavy metals, organohalogenes and other micropollutants; solid waste regarded as non-hazardous will then be disposed of in a lined landfill designated for non-hazardous materials, with leachate monitoring. There are currently no limits as to the amount of solid wastes disposed of off-site.

6.1.3.4 Certification of Compliance

SmithKline Beecham Pharmaceuticals Co. (SmithKline Beecham (Manufacturing) Limited) is committed to environmental control and will operate within its permit during the production of carvedilol drug substance. A citation of and statement of compliance with applicable emissions requirements is provided in Appendix II.

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Carvedilol

6.1.4 Introduction from Production of Drug Product

Carvedilol (SK&F 105517) drug product will be produced in a continuous process, consisting of granulation, drying and blending, compression and coating, and printing and packaging at SmithKline Beecham Pharmaceuticals Co. in Cidra, Puerto Rico. The manufacture of carvedilol will employ the same environment and utilize the existing plants that are currently used to manufacture other pharmaceutical products. Carvedilol will be prepared as 12.5 and 25 mg tablets. Environmental evaluations of the impacts from drug product production follow.

6.1.4.1 Waste Stream Summary and Disposition

The waste streams generated at the Cidra facility will be disposed of using appropriate procedures, such that release into the environment (gaseous and aqueous waste) will not exceed Cidra permit levels (Appendix IV) and off-site disposal of solid wastes will not violate applicable regulations.

6.1.4.2 Material Balance

Material balance information for the chemical inputs, process intermediates and effluents was determined, thus accounting for all materials and amounts used in or produced during the drug product process. Waste outputs include leftover material resulting from production, inspection operations (rejects are discarded), assay solutions sampled before and after filtration, and floor and equipment washings.

For the purposes of this evaluation, the production campaign is assumed to use all of the drug substance, which is based on the projected fifth year of carvedilol production for the U.S. Market.

6.1.4.3 Controls Exercised on Wastes

6.1.4.3.1 Dryer Water Vapor

Two waste streams consist of water evaporated during drying processes. These streams are filtered before venting to the environment and should contain no hydrocarbons or particulates. The water collected is sent to the on-site wastewater treatment facility for biotreatment.

Air emissions from the process fall under the State Rules and Regulations for Air Pollution Control. The regulations are administered by the Environmental Quality Board of the Commonwealth of Puerto Rico. Currently, the facility is operating under Permit No. PFE-21-

ENVIRONMENTAL ASSESSMENT INFORMATION

Carvedilol

0590-0477-I-III-0 and PFE-21-1089-0929-I-II-III-0, and is not considered to be a major pollutant source; thus, a PSD review (under the EPA program) will not be necessary.

6.1.4.3.2 Solvent Vapor

The incinerator at the Cidra facility is expected to burn only four solvent vapors, none of which are produced during the carvedilol production process. The scrubber blowdown liquors from the incinerator are sent to the SmithKline Beecham Pharmaceuticals Co. facility in Guayama, Puerto Rico for treatment and disposal.

6.1.4.3.3 Aqueous Wastes Disposed Of Through Biotreatment

The aqueous waste streams (1-4) are sent to the wastewater treatment facility. The streams are first pumped through a series of sand filters and an activated carbon adsorption system. The waste streams are then discharged into an equalization holding tank for aeration. Sanitary waste bypasses sand and carbon columns and goes directly to the equalization basin. The pH of the influent stream is adjusted with sodium hydroxide or carbon dioxide prior to entering the activated sludge system. The residence time of effluent in the activated sludge basin is 24 hours, and the average volume maintained is 80,000 gallons. The treatment facility is designed for a 85,000 gallon per day flow, with a maximum capacity of 127,000 gallons per day. The biotreatment waste stream then enters a clarifier, where the sludge is allowed to settle and separate from the biotreated aqueous effluent as supernatant.

The pH of the aqueous effluent is adjusted to 11.0 with hydrated lime and sent to a second clarifier, where solids are precipitated out of solution and removed by flocculation. The clarifier's precipitated solids are sent to the aerobic digester for further processing. The wastewater effluent is recarbonated and neutralized with carbon dioxide prior to passing through a second series of sand and carbon filters. The filtered effluent is collected in a filter effluent sump. This filtered effluent then passes through a Reverse Osmosis (RO) module for total dissolved solids and organic removal. Reverse Osmosis (RO) Permeate is collected in a 100,000 gallon effluent storage tank and Reverse Osmosis (RO) reject is disposed off to PRASA (Permit Number GDG-94-505-032). A copy of the permit is attached in Appendix V. The effluent is then chlorinated, aerated and monitored for pH, temperature and dissolved oxygen before entering Quebrada Las Quebradillas (Las Quebradillas Creek). After aeration in the biotreatment facility, 55,000 gallons per day of final effluent is recycled to cooling and quench towers and 25,000 gallons per day of final effluent is discharged. Rainwater runoff from the grounds of the Cidra facility are also discharged to this creek, which empties into the Turabo River and flows into Carraizo Lake (the water source for the metropolitan area of San Juan).

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For the purpose of this environmental assessment, the total quantity of drug product components expected to be emitted into the site biotreatment facility is estimated at 3% of the total batch.

Final effluent levels from biotreatment were calculated using the following equation:

$$(A \times 10^6 \text{ mg/kg} / B/C)D = E$$

where: A = total quantity of component to waste per day (kg/day);
B = number of days over which discharge is made (1);
C = site effluent discharge rate (240,175 L/day);
D = removal efficiency;
E = concentration of component in effluent in mg/L.

For developing the discharge level data, it is assumed that no volatilization or bioadsorption of these materials occurs during treatment, and that biodegradation is the only operative removal mechanism for some of the effluent compounds. Review of the measured (confidential) and calculated concentrations of affected aqueous effluent components and a comparison with their permit levels resulted in the determination that the Cidra facility is in compliance with their aqueous effluent permits.

The contributions of the compounds used in the tablet formulation of carvedilol (SK&F 105517) to the total quantity of regulated components in the effluent will not cause total effluent concentrations to exceed the permit levels, assuming complete removal of carvedilol by the wastewater treatment facility. The quality of the effluent discharge meets Puerto Rico's water quality standards. The treatment facility operates under National Pollutant Discharge Elimination System (NPDES) Permit PR 0021997. In Puerto Rico, the NPDES Permit Program is administered by the Federal Environmental Protection Agency.

The facility is also regulated by the Puerto Rico Water Pollution Law, which is administered by the Assistant Secretary of Health for Environmental Health and Consumer Protection. Additional regulations are the Puerto Rico Harmful Spills Law, the Puerto Rico Public Policy Environmental Act, and the Puerto Rico Water Quality Standards, each administered by the Board of Environmental Quality. Permit limits for the wastewater discharge are stated in the NPDES permit. The discharge limits are presented in Appendix IV.

6.1.4.3.4 Solid Wastes

The activated carbon (granular Calgon AC, 8 X 30 mesh) from the biotreatment filters is replaced every three months. Settled sludge from the first clarifier in the biotreatment process is divided into two streams: sludge waste to an aerobic digester and sludge returned to the system. Within the digester the sludge waste is concentrated by settling and decanting the water. More water is then removed from the concentrated sludge slurry

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by means of a wedge filtration system and solar drying beds. The decanted water is recycled back to the feed of the wastewater treatment system. Sludge is maintained in the drying beds at a depth of two feet, and the waste volume is reduced by at least 92% during the drying period of two weeks. The dried sludge, and the spent carbon are disposed of as non-hazardous material at a municipal landfill, after testing using the Toxicity Characteristic Leaching Procedure (TCLP). Other solid wastes containing drug product (rejects, protective clothing, drums, filters, collected dust) are disposed of off-site to Orden Martin Systems of Lake, Inc., Okahumpka, Florida, US (see Appendix I). There are no limits or restrictions placed on the quantities of materials that may be sent to the licensed disposal facilities.

6.1.4.4 Environmental Legislation

The following partial list of federal legislation may affect operation of the wastewater treatment facility.

- Federal Water Pollution Control Act, as amended
- Clean Water Act, as amended
- Resource Conservation and Recovery Act
- Safe Drinking Water Act
- Toxic Substances Control Act
- National Environmental Policy Act

6.1.4.5 Safety

The Cidra facility has adopted personnel safety procedures in all areas of plant activity, including procedures and information on electrical hazards, tool use, fire hazards, chemical handling and first aid.

6.1.4.6 Certification of Compliance

SmithKline Beecham Pharmaceuticals Co., Cidra, Puerto Rico, will operate within its permits during the production of carvedilol drug product. A citation of and statement of compliance with applicable emissions requirements is provided in Appendix IV.

6.2 Introduction from Use of Drug Product

Estimates of the maximum expected emitted concentrations (MEEC) from use of carvedilol tablets were calculated in part using data from reference [1]. At concentrations expected to be emitted into and exist in the environment, carvedilol is expected to exhibit no toxicity to aquatic organisms.

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6.3 Introduction from Disposal of Drug Product

Carvedilol drug product returned goods will be collected at the following site:

[REDACTED]

From this site, the materials will be shipped to the following licensed facilities for disposal (e.g., destruction by high temperature incineration).

SmithKline Beecham Pharmaceuticals
Bristol Industrial Park
Weaver Pike
Bristol, Tennessee 37620

[REDACTED]

Documentation for these disposal facilities is provided in Appendix I. Based on the controlled and highly efficient thermal destruction of unused drug substance and product, no material should be introduced into the environment from disposal.

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

7.1 Metabolism

The biotransformation and excretion of carvedilol in normal male human volunteers following single oral administration of ¹⁴C-carvedilol was investigated [2]. Radiometabolites in both feces and urine were separated, quantified, and characterized structurally using a combination of HPLC and mass spectral techniques. The majority of the radiolabeled dose was found to be excreted in the feces (52%), with a lesser amount excreted in the urine (20%). The carvedilol-related products observed in the feces in this study included unchanged carvedilol and several oxidation products. Carvedilol-related products identified in feces represented 71% of the fecal radioactivity, with all of the products each accounting for more than 6.4% of the fecal radioactivity characterized.

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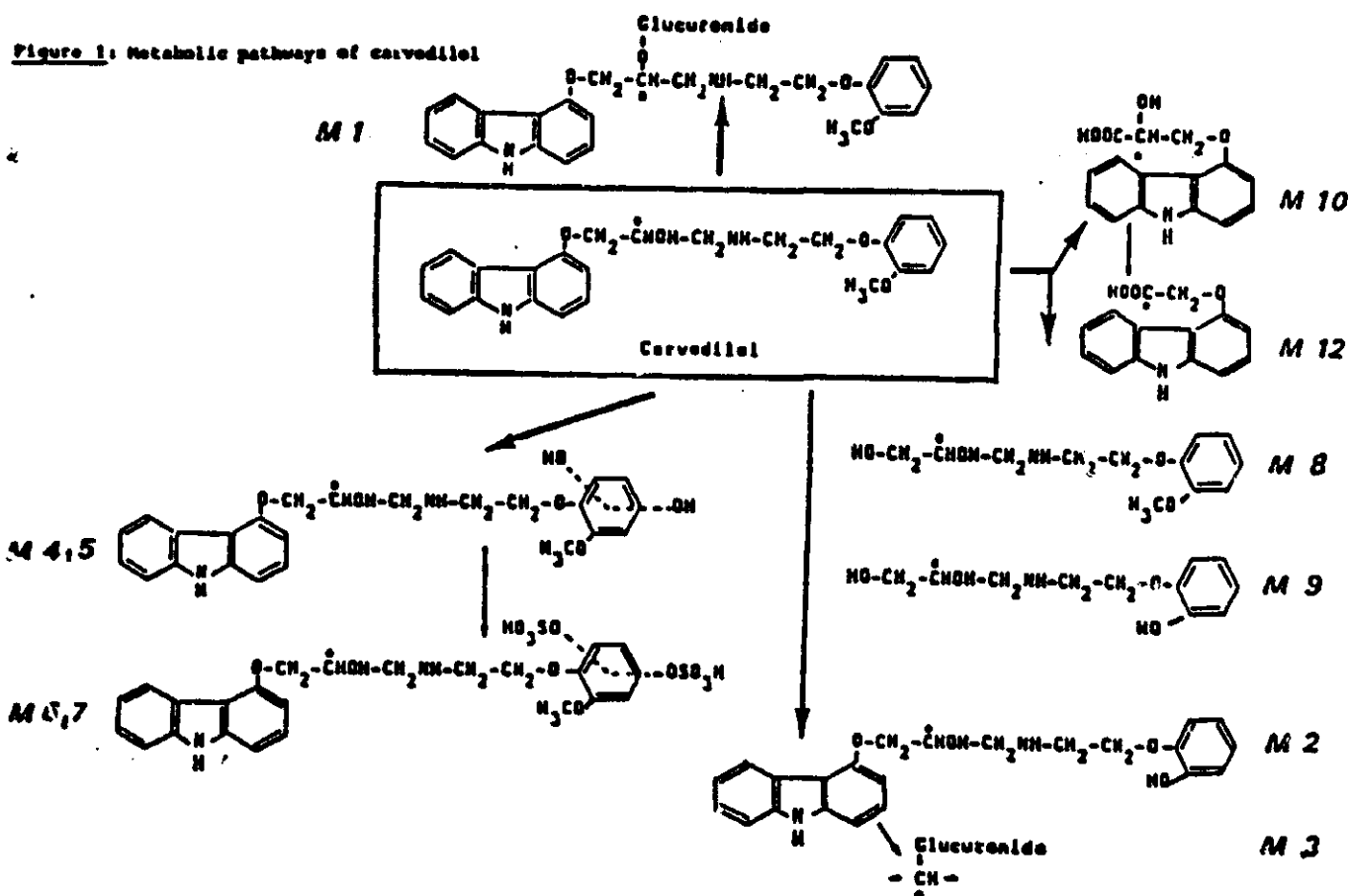
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The profile of urinary metabolites was much more complex, containing more than 26 compounds. The most abundant urinary metabolites were glucuronide derivatives of carvedilol. While the majority of the carvedilol metabolites excreted in feces were products of oxidation pathways, urinary metabolites included products of both oxidation and conjugation pathways. In general, all of the major metabolites structurally related to carvedilol are more polar analogs, and for the purposes of this environmental assessment, assessment of the fate and effects of carvedilol itself may be taken to represent a worst-case scenario.

The reported percent of an administered radioactive dose (range) recovered in the urine and feces is 15.29% - 20.00% and 52.12% - 61.40% respectively [31, 32]. The percent dose representing drug substance which was excreted unmetabolized was 0.21% - 0.28% for urine and 8.39% - 9.89% for feces [32].

A summary of the fecal, urinary and plasma metabolites of carvedilol in male human subjects is presented in Figure 1.

Figure 1



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7.2 Physical Properties

Physical properties were determined for carvedilol in-house, at the Environmental Research Laboratory. Several detailed reports are given in Appendix VI and summarized below.

7.2.1 Water Solubility

The water solubility of carvedilol as a function of pH was determined at 25°C. The results are given below and detailed in reference [3].

pH	Water Solubility (mg/L)			95% Confidence Range	
	mean	stdev	%RSD	low	high
5.04	434	46.3	10.7	416	452
7.09	30.8	3.66	11.9	29.4	32.2
9.04	1.61	0.356	22.1	1.46	1.76
8.43(DI H ₂ O)	5.46	1.88	34.3	4.72	6.20

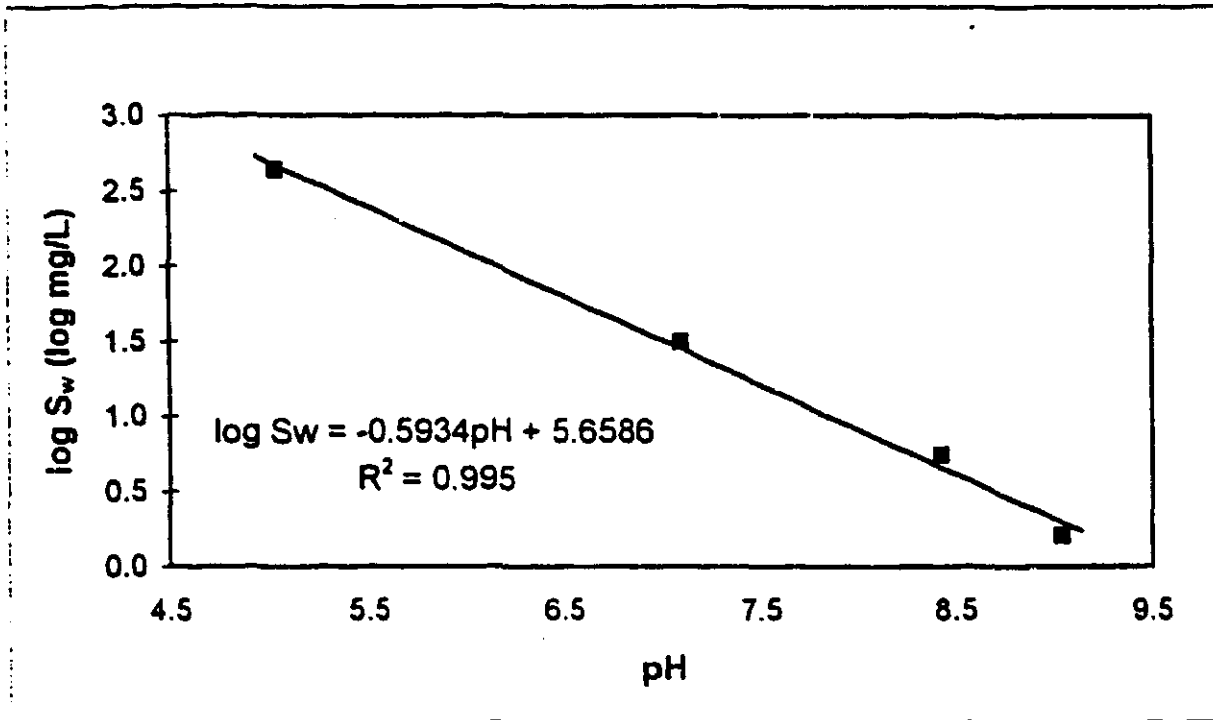
A log transformation of the solubility data plotted against pH shows a linear relationship, as illustrated in Figure 2 below.

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Figure 2

Aqueous Solubility of SK&F 105517.



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7.2.2 Dissociation Constant

Because of its low water solubility, the pK_a for carvedilol was determined by preparing methanol-water solutions of carvedilol containing 45, 50, 57, 66 and 71 v/v% methanol and then titrating these solutions with 0.1N HCl. The apparent pK_a was plotted versus concentration of methanol, resulting in a straight line whose intercept is the value of pK_a in water. A pK_a of 7.8 was obtained for the secondary amine group. The pK_a 's of the -NH- group in the carbazole ring, which is amphoteric, were not determined. According to published data, the pK_a 's of carbazole are 16.7 [4] (proton lost) and -5.7 [5] (proton gained). This suggests that the acidity or basicity of the carbazole in SK&F 105517 is extremely weak. The experiment is detailed in SB report code CSL-14467-250 which is included in Appendix VI; see reference [6].

7.2.3 Octanol/Water Distribution Coefficient

The octanol/water distribution coefficients (K_{ow}) for carvedilol were determined at two concentrations in triplicate test systems consisting of pH 5, 7 and 9 buffers and high-purity n-octanol. The results are reported in reference [7] and summarized below.

Solvent	26.3 mg/L		263 mg/L	
	K_{ow}	log K_{ow}	K_{ow}	log K_{ow}
Octanol/pH 5 buffer	106	2.02	85.7	1.93
Octanol/pH 7 buffer	528	2.72	549	2.74
Octanol/pH 9 buffer	1040	3.01	1260	3.10

7.2.4 Vapor Pressure, Volatilization, Henry's Law Constant

The vapor pressure of a substance is the property governing the tendency of a chemical substance to be transported into and in air and is thus an important parameter for predicting the distribution of chemicals into environmental compartments. For non-ionizable organic compounds, measurement of the vapor pressure is straightforward, and the value obtained is meaningful in environmental predictions. However, for compounds such as carvedilol, which will be ionized in solution at environmental pHs, the vapor pressure of the free base of the compound alone is less useful for predicting air-water partitioning. Vapor pressure may over-predict volatilization of chemicals which are partially ionized in aqueous solution. Since carvedilol has a basic pK_a of 7.8, approximately 86% of dissolved carvedilol species (ionized) will exist as the protonated base at pH 7. Therefore, only 14% (neutral) of dissolved species are available for volatilization.

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A more useful parameter for estimating the air-water partition coefficient for a chemical, and thus the likelihood of its entering into and being transported by the atmosphere, is Henry's law constant. The apparent Henry's law constant, H_L , represents the ratio of the equilibrium concentration of a chemical substance in air to its corresponding concentration in water in a closed system. It can be used to estimate the tendency of a chemical to volatilize from aqueous solution at a given pH. H_L is related to vapor pressure (VP) and aqueous solubility (S_w) as follows:

$$H_L = VP/S_w$$

Since carvedilol exists primarily as a protonated base at environmental pH levels, the Henry's law constant was measured directly experimentally. Values of $<2.66 \times 10^{-7} \text{ m}^3 \text{ atm/mol}$ at pH 6.7 and $3.93 \times 10^{-7} \text{ m}^3 \text{ atm/mol}$ at pH 6.55 were obtained. The results are detailed in reference [9].

Lyman et al. in reference [10] provides the following interpretation of H_L values:

H_L ($\text{m}^3 \cdot \text{atm/mol}$)	Aquatic Volatility
1E-5 to 1E-7	"volatilizes slowly"
1E-7 to 3E-7	"essentially non-volatile"
< 1E-7	"less volatile than water"

With an H_L of $3.93 \times 10^{-7} \text{ m}^3 \cdot \text{atm/mol}$, the aquatic volatility of carvedilol may be characterized as a very slow process. In the presence of any significant depletion mechanism, mass transfer to the atmospheric compartment over time would be negligible.

7.2.5 UV/Vis Spectrum

The UV/Vis spectra of aqueous solutions of carvedilol were determined at pH 5, 7 and 9. The detailed study report is given in reference [11]. The experimental results indicate that the UV/Vis absorption spectrum of carvedilol is not affected by solution pH. In addition, significant absorbance at wavelengths greater than 290 nm was found, which suggests that carvedilol is likely to be susceptible to direct photochemical degradation in the environment.

7.2.6 Soil Sorption/Desorption (K_{OC}) and K_D

Soil sorption/desorption isotherms are carried out in order to generate a water-soil partitioning coefficient (K_{OC}) for use in predicting the mobility of a chemical in the terrestrial

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environmental compartment. For human drugs, however, the majority of users will discharge into municipal wastewater treatment systems [1]. As a result, a more meaningful partitioning coefficient to predict initial sorption to biomass or sludge is K_p , a measure of the partitioning between the aqueous phase and the biosolids phase in a wastewater treatment plant (WWTP).

From preliminary experiments, a mean K_p was determined to be 5500 ($\log K_p = 3.74$). From definitive equilibrium Freundlich isotherm data with active sludge, the sludge adsorption isotherm constant K was determined to be 20,400 ($\log K = 4.31$). The difference between these results may be due to different sludge sources and treatments. Standardized methodology for sludge adsorption studies has not yet been established. Details of the studies are given in reference [12]. The use of this constant to predict environmental partitioning is shown in section 7.3 below.

A soil sorption/desorption isotherm study was also carried out to generate a K_{OC} value for carvedilol. The detailed study report is given in reference [13] and summarized below.

Soil	%TOC	Solvent	K_{OC}	$\log K_{OC}$
Kansas	2.06	H ₂ O	23500	4.37
California	1.59	H ₂ O	40900	4.61
Iowa	1.53	H ₂ O	<u>36900</u>	<u>4.57</u>
Average			33800	4.53
Kansas	0.8	CaCl ₂	143000	5.16
California	1.59	CaCl ₂	530000	5.72
Iowa	1.53	CaCl ₂	<u>227000</u>	<u>6.36</u>
Average			300,000	5.47

The average K_{OC} from studies in water was 33,800; from studies in CaCl₂, a value of 300,000 was determined. Usually, if a lower K_{OC} is determined in the CaCl₂ solvent system, this is taken as indicating a significant amount of ion-exchange character in the sorption process, since the calcium ions would compete with the carvedilol protonated free base ions for ion-exchange sites, resulting in less carvedilol partitioning into the soil organic carbon phase. However, for carvedilol, the CaCl₂ studies gave a higher value. This may be due to a "salting out" effect of the CaCl₂, decreasing the water solubility of the carvedilol and resulting in stronger hydrophobic interactions with the soil organic carbon. Thus the

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sorption appears to be a more complex function of the chemical nature of the carvedilol and of the soil organic carbon. The usual name given to this complex phenomenon is chemisorption. It is interesting to note that correction of the sludge partition coefficient, $\log K_p = 4.31$, for organic carbon content (assumed to be approximately 50% (reference [14]), yields a $\log K_{OC}$ for sludge of 4.61. This is essentially the same as the $\log K_{OC}$ obtained for soils using water as the solvent.

Carvedilol exhibited very little desorption from soil. The percent desorbed from the soil systems tested ranged from only 0.34-2.36%.

In summary, the sludge and soil adsorption studies indicate that carvedilol will adsorb strongly to particulate organic materials and that once adsorbed it will be relatively immobile in the environment.

7.3 Environmental Partitioning Estimates for Carvedilol

Since the majority of carvedilol used in the United States will be introduced into the environment through Wastewater Treatment Plants (WWTPs), the partitioning of carvedilol in that system must first be considered. Taking total production as unity, the maximum fraction of drug entering the aquatic and terrestrial compartments after discharge from the WWTPs can be calculated as follows:

CALCULATION OF MAXIMUM EXPECTED EMITTED CONCENTRATION

Carvedilol

Given the following assumptions:

Total annual market volume (5th year)(MV_{total})	=	1
Fraction of US population using WWTF($F_{sewered}$)	=	0.74 [1]
Fraction of Drug Substance not excreted(F_m)	=	0
Annual US Sewage Flow(SF_{annual})	=	3.7×10^{13} L/yr [1]
Annual Yield of Dry Sludge from WWTPs(DS_{annual})	=	5.9×10^9 kg/yr [1]
Dilution rate from Application of Sludge to Agricultural Land (DR_{annual})	=	0.025 [1]
K_p (carvedilol)	=	

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Then the maximum expected emitted concentration (MEEC) into the environment of carvedilol from use of the drug product is calculated as follows, assuming 100% excretion of carvedilol and its metabolites in one day:

$$\begin{aligned} \text{Fraction emitted into WWTPs} &= MV_{\text{total}} \times F_{\text{sewered}} \\ &= \\ &= \end{aligned}$$

Based on the distribution of carvedilol between sludge and water,

$$\begin{aligned} K_p &= \frac{\text{Concentration in sludge } (C_2)}{\text{Concentration in sewer effluent } (C_1)} \\ 2.04 \times 10^4 &= \frac{C_2}{C_1} \\ C_2 &= \text{(equation 1)} \end{aligned}$$

Since the fraction emitted (0.74) will be distributed between the sludge and the sewer effluent, the balance around the WWTP is

$$C_1 \times SF_{\text{annual}} + C_2 \times DS_{\text{annual}} = \text{(equation 2)}$$

Substitution of the equation for C_2 (equation 1) into equation 2 gives

$$\begin{aligned} (3.7E13C_1) + (5.9E09)(2.04E04C_1) &= \\ (3.7E13C_1) + (1.20E14C_1) &= \\ 1.57E14C_1 &= \\ C_1 &= \\ C_2 &= \\ C_2 &= \\ C_2 &= \end{aligned}$$

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Using the relationships of equation 2 gives:

$$\begin{aligned} (3.7E13C_1) &= \\ &= \\ (5.9E09)(C_2) &= \\ &= \end{aligned}$$

Thus, of the carvedilol emitted to wastewater treatment plants from use will distribute into the aqueous phase, with sorbing to the sludge and entering the terrestrial compartment. Given the high soil sorption and very low desorption of carvedilol, very little migration of carvedilol through the terrestrial compartment is likely to occur.

7.4 Transformation and Depletion Mechanisms of Carvedilol

7.4.1 Hydrolysis

The hydrolytic stability of carvedilol was determined in deionized water and in pH 5, 7 and 9 buffers. The results indicated that carvedilol is hydrolytically stable under the conditions tested, and has an estimated hydrolytic half-life ≥ 1 year [15]. The study is detailed in reference [16].

7.4.2 Aqueous Photolysis

Given carvedilol's significant absorption of light at wavelengths > 290 nm, the photolysis study on carvedilol was carried out at pH 7 in natural sunlight. The first-order direct aqueous photoreaction rate constant was determined to be 0.468 hr^{-1} , giving a half-life of 1.48 hours. The detailed study report is given in reference [17].

7.4.3 Aerobic Biodegradation

Aerobic biodegradability studies were carried out on carvedilol using a modification of standard methodology. The analytical method validation study is given in reference [18]. The definitive aerobic biodegradation study is detailed in references [19] and [33]. ERL study 92-021, reference [19], determined that biotransformation of carvedilol was detected after ~ 40 days with a first-order rate constant of 0.03 day^{-1} giving a half-life of 26.2 days. Another study, ERL Study 92-050, used methanol as a carrier to facilitate carvedilol bioavailability in the biodegradation test systems. For comparison it also contained treatments that added carvedilol to the test system without methanol carrier.

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The two treatment groups that used methanol had first-order rate constants of 0.1 and 0.05 day⁻¹ at 5 and 10 mg/L carvedilol concentration, respectively. This corresponds to respective half-lives of 6.9 and 13.9 days. The no methanol treatments had first-order rate constants of 0.02 and 0.01 day⁻¹ at 5 and 10 mg/L carvedilol concentration, respectively. This corresponds to respective half-lives of 34.6 and 69.3 days. The presence of a carrier solvent appears to significantly enhance the biodegradation kinetics in the test systems employed for the study probably as a direct consequence of increased bioavailability to the degrading microorganisms.

In addition to carvedilol itself, biodegradation/biotransformation studies were carried out on 4-hydroxycarbazole and carbazole, substructures of the carvedilol molecule likely to be the most recalcitrant to biotransformation. The half-lives for these two compounds were 21.8 days and 0.39 days, respectively. This may be taken as indicative of the eventual mineralization of the carvedilol molecule once the initial acclimation is accomplished. Interestingly, the two replicate experiments for the biodegradation studies showed different HPLC profiles, indicating that carvedilol in the different flasks was undergoing biotransformation by two different pathways. The details of these studies are given in references [20] and [21]. See also aquatic toxicity evaluations in Section 8.2.3.

It is clear from these data that carvedilol is indeed susceptible to biodegradation in aerobic compartments and should not persist in the environment. Given the high biomass concentrations in activated sludge systems, the likely presence of surface-active agents which may facilitate bioavailability, and higher levels of dissolved organics which would enhance the solubility of carvedilol, the degradation of carvedilol in unacclimated waste water treatment plant systems would be expected to be more rapid than the conservative kinetics presented in typical biodegradation test systems.

7.4.4 Fate Summary

From the data presented above, the following are predictions concerning the environmental fate of carvedilol from use:

1. Based on environmental partitioning estimates presented in section 7.3, approximately 77% of carvedilol introduced into WWTPs is expected to distribute into the sludge phase. Biotransformation may occur during the solids retention, which may reduce sludge concentrations considerably. Due to the high turbidity of activated sludge mixed liquor, little photolysis is expected to occur during aeration. During secondary settling, dissolved carvedilol may be more susceptible to photodegradation in the clarified secondary effluent.
2. Carvedilol discharged into the aquatic environmental compartment will not likely persist based on photolysis and slow biotransformation depletion mechanisms. An

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overall depletion rate may be estimated from the individual depletion rate constants. An estimation of half-life in the aquatic compartment may range from 1.5 hours to 40-50 d_{lys} based on the dominant active depletion mechanism.

3. Carvedilol entering the terrestrial compartment by land application of sludge would likely remain sorbed, immobile and undergo, under aerobic conditions, slow biotransformation. It would not be expected to persist in the soil compartment.
4. The very low Henry's constant suggests that transport of carvedilol to the atmosphere by volatilization from either the treatment plant or the terrestrial compartment will be insignificant.
5. Given that the log of the octanol/water distribution coefficient varies from 2 to 3 at environmental pH levels, little bioconcentration of carvedilol is likely to occur. This prediction is further supported by the metabolism studies, which indicate that carvedilol is biotransformed by a variety of mechanisms into more polar materials, which are excreted.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES:

8.1 Human and Mammalian Health Effects Summary [22]

8.1.1 Acute Toxicity Studies

8.1.1.1 Oral Toxicity

No lethality occurred in rats after administration of a single oral dose of 8000 mg/kg. The oral LD₅₀ in rats was greater than 8000 mg/kg.

8.1.1.2 Inhalation Toxicity

Inhalation toxicity was not determined. However, symptoms after exposure to dust might include slow pulse, dizziness, fainting, difficult or irregular breathing or bluish colored fingernails or palms.

8.1.1.3 Skin Irritation

Skin irritation potential was not determined. We can assume that direct contact can produce irritation or allergic skin reaction. Symptoms such as itching, redness or swelling might be immediate or delayed.

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8.1.1.4 Eye Irritation

Eye irritation potential was not determined. Assume that direct contact can produce irritation. Symptoms might include redness or swelling.

8.1.1.5 Sensitization

The sensitization potential of carvedilol has not been determined.

8.1.2 Chronic Toxicity Studies

8.1.2.1 Reproduction Toxicology

Carvedilol did not produce adverse effects on male or female reproduction in studies with rats.

8.1.2.2 Teratogenicity

Carvedilol did not produce teratogenic effects in studies with rats.

8.1.2.3 Genetic Toxicology

Carvedilol was not found to be mutagenic in bacteria (Ames test) or other genotoxicity tests. It is not listed as a carcinogen by IARC, NTP, or US OSHA. There was no evidence of a carcinogenic effect in chronic studies with rats or mice.

8.1.2.4 Other Effects

Carvedilol exhibits an effect on the cardiovascular system by lowering blood pressure.

8.2 Aquatic Toxicity Studies

8.2.1 Acute Aquatic Toxicities of Carvedilol

Acute aquatic toxicity studies were carried out on microorganisms (Microtox[®] and Microbial Respiration Inhibition), *Daphnia magna*, and bluegill sunfish (*Lepomis macrochirus*) using carvedilol. The detailed reports on the Microtox[®] studies for carvedilol, 4-hydroxycarbazole, and carbazole are given in references [23,24,25]. The reports of the contract study of the activated sludge respiration inhibition of carvedilol is given in reference [26]. Reports of the contract studies on the acute toxicities of carvedilol to *Daphnia pulex* and bluegill sunfish (*Lepomis macrochirus*) are given in references [27] and [28], respectively. The results are summarized below.

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Toxicity Test	Carvedilol (mg/L)
Microtox [®] - EC ₅₀	5.43 ± 0.25 6.71 ± 1.87 (4-OH carbazole) 0.26 ± 0.031 (carbazole)
Respiration Inhibition - EC ₅₀	98.4
<i>Daphnia pulex</i> - EC ₅₀ ^{el}	> 2.8
<i>Daphnia pulex</i> - NOEL ^{1.8/45}	< 0.37
Bluegill Sunfish - LC ₅₀	0.99 (95% CI=0.87-1.1)
Bluegill Sunfish - NOEL	< 0.43

8.2.2 Acute Aquatic Toxicity of Carvedilol Photolysis By-Products

Since carvedilol was found to degrade in the presence of sunlight, the relative toxicity of the photo-degradant(s) compared to carvedilol itself was determined using the Microtox[®] test carried out on samples of carvedilol solutions that had been exposed to sunlight. No EC₅₀ could be determined for the degraded solutions because of a lack of toxic effect. Based on these results, any compounds entering the environment from the photolysis of carvedilol would not be expected to exert toxic effects on aquatic organisms. Details of the study are given in reference [29].

*

8.2.3 Acute Aquatic Toxicity of Carvedilol Biodegradation By-Products

The relative acute aquatic toxicity of carvedilol biodegradation by-products was also determined by a Microtox[®] test carried out on samples of carvedilol solutions after laboratory biodegradation experiments. For one sample of biodegradants, no EC₅₀ could be determined for the degraded solutions because of a lack of toxic effect. For the "replicate" sample, an EC₅₀ of 15.4% was calculated. See reference [30] in Appendix VII. However, as noted in Section 7, the carvedilol in the two samples appeared to be biotransformed by two different pathways, and by consortia of apparently different microorganisms. However, even though minimal toxic effect was observed, the unknown biodegradants responsible were derived from carvedilol at a concentration far in excess of what could be emitted into the environment from use.

From the data above, carvedilol and its degradants would not be expected to exhibit acute toxic effects to aquatic organisms at concentrations expected to be emitted into and exist in the environment.

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9. USE OF RESOURCES AND ENERGY

9.1 Use of Resources and Energy at Boehringer

9.1.1 Use of Resources and Energy at Plant HC-B 21

The following tables summarize the known amounts of energy and resources utilized during intermediate production at the production plant HC-B 21.

**Percent of Energy and Resources Utilized at Boehringer Mannheim
for Production of Intermediate in 1990
HC-B 21 Plant**

Consumption	Electricity (kw-hour)	Steam / 2.5 bar (t)	Tap Water (m ³)	Cooling Water (m ³)	Demineralized Water (m ³)
Percent of Total Consumption at Boehringer Mannheim	0.02	0.005	0.006	0.06	0.05

9.1.2 Use of Resources and Energy at Plants HC-B 4, HC-B 10 and HC-B/OB

The following tables summarize the known amounts of energy and resources utilized during intermediate production at production plants HC-B 4, HC-B 10 and HC-B/OB.

**Percent of Energy and Resources Utilized at Boehringer Mannheim
for Production of Intermediate in 1990
HC-B 4, HC-B 10 & HC-B/OB Plants**

Process Step	Electricity (kw-hour)	Steam / 2.5 bar (t)	Tap Water (m ³)	Cooling Water (m ³)	Demineralized Water (m ³)
Percent of Total Consumption at Boehringer Mannheim	0.13	0.08	0.13	0.38	0.36

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9.1.3 Effect Upon Endangered Species And Historic Places

The production of carvedilol intermediates and the disposal of associated wastes at the Boehringer Mannheim production facilities should have no impact on threatened or endangered species. Property listed in or eligible for listing in the National Register of Historic Places will not be impacted by intermediate production or waste disposal activities since the production is taking place outside of the United States and the Boehringer-Mannheim facility is not a designated historic site.

9.2 Use of Resources And Energy At Cork

The effects on the use of resources and land for the production of carvedilol drug substance are minimal because of the low production volumes and associated wastes, and the existing treatments units that will be used.

The following table summarizes the percent of energy and resources utilized during carvedilol substance production stages at the SmithKline Beecham (Manufacturing) Limited facility, based on the projected 5th year of production and current use.

Consumption	Electricity (kw-hour)	Fuel Therms	Water (m ³)
Percent of Total Consumption	0.05	4.2	0.07

9.2.1 Effect Upon Endangered Species And Historic Places

The production of carvedilol substance and the disposal of associated wastes should have no impact on threatened or endangered species. Property listed in or eligible for listing in the National Register of Historic Places will not be impacted by carvedilol substance production or waste disposal activities since the production is taking place outside of the United States and the SmithKline Beecham (Manufacturing) Limited facility is not a designated historic site.

9.3 Use of Resources and Energy to Produce Drug Product at Cidra

The Cidra facility for carvedilol product manufacture is a 52 acre site located in an agricultural/urban/industrial area on the central mountainous ridge of the island of Puerto Rico. The effects on the use of resources and land for the production of carvedilol drug

ENVIRONMENTAL ASSESSMENT INFORMATION

Carvedilol

product are minimal because of the low production volumes and associated wastes, and the existing treatments units which will be used. Manufacture of this product uses only a small percentage of the resources and energy available at this site and of resources and energy required for transport.

The following table summarizes the total known amounts of energy and resources used at the Cidra plant.

Consumption	Electricity (kw-hour)	Fuel Oil (gallons)	Water (gallons)
Percent of Total Consumption	4%	4%	4%

To produce the carvedilol drug product at maximum yearly production levels at Cidra, it is estimated that 4% of total yearly Cidra plant usage of electricity, fuel and water will be used.

9.3.1 Effect Upon Endangered Species And Historic Places

The production of carvedilol product and the disposal of associated wastes should have no effect on threatened or endangered species. Property listed in or eligible for listing in the National Register of Historic Places will also not be impacted by carvedilol product production or waste disposal activities since the Cidra facility is not a designated historic site.

10. MITIGATION MEASURES

10.1 Mitigation Measures at Boehringer

Potential adverse environmental impacts associated with drug intermediate production at Boehringer Mannheim are minimized by the following:

No waste or exhaust streams are directly discharged, but are directed to major treatment units;

Treated effluent streams are checked before discharge, with ample capacity for emergency storage in the event that effluent criteria are not met;

Floor spills are swept and incinerated;

ENVIRONMENTAL ASSESSMENT INFORMATION

Carvedilol

Off-spec or rejected materials are returned to the supplier or are incinerated in an outside incineration plant for industrial wastes;

Accidental introductions of bulk product into the environment during storage is mitigated by controlled packaging and storage operations. Bulk drug product is packaged in new corrugated cardboard boxes lined with two polyethylene bags. These boxes are heat-sealed, sealed with plastic tape, properly labeled, and stored in a secured bulk storage area of the plant warehouse.

Storage facilities are designed to allow for the capture and treatment of any spills before any major environmental effects could result. Also, the adopted spills prevention, control and contingency plans have been demonstrated to be effective in the prevention of such emergencies.

The plant personnel are well-trained and follow written instructions when performing their work.

The site is audited regularly by the Boehringer Mannheim central Environment Department, to assist in the identification and implementation of any additional mitigation measures as circumstances warrant.

10.2 Mitigation Measures At Cork

Plans to minimize waste output were considered and implemented at the outset of carvedilol development, as well as during substance production. The Integrated Pollution Control (IPC) license contains guidelines for the establishment of an Environment Management Programme to assess all operations for the use of cleaner technology and the minimization of waste. Potential environmental impacts associated with production at Cork are also minimized by the following:

Most waste streams are incinerated, and the gases scrubbed before being discharged. Scrubber liquors are biotreated in the on-site wastewater treatment facility before discharge.

Biotreated effluent streams are checked before discharge, with ample capacity for emergency storage in the event that effluent criteria are not met.

Airstreams from the process buildings are filtered prior to venting to the atmosphere.

ENVIRONMENTAL ASSESSMENT INFORMATION

Carvedilol

10.3 Mitigation Measures at Cidra

Potential adverse environmental impacts associated with the proposed action are minimized at the Cidra facility by the following:

10.3.1 General

The proposed formulation process involves small production lots, which will generate very small quantities of waste;

No waste or exhaust streams are directly discharged. All streams are directed to major treatment units. Treated effluent streams are checked before discharge, with ample capacity for emergency storage in the event that effluent criteria are not met;

Airstreams from the process are small and directed to dust collectors, which minimize the effects of the emissions by at least 99.9%;

Storage facilities are designed to allow for the capture and treatment of any spills before any major environmental effects could result. Also, the adopted spills prevention, control and contingency plans have been demonstrated to be effective in the prevention of such emergencies.

10.3.2 Energy and Resources

A thermal oxidizer with a regenerative heat recovery system is used to incinerate gaseous waste streams produced during tablet coating operations. The heat recovery system is operated to recover at least 85% of the heat generated, for use in continual incineration of the gases. After aeration in the biotreatment facility, 55,000 gallons per day of final effluent is recycled to cooling and quench towers and 25,000 gallons per day of final effluent is discharged.

10.4 Mitigation from Use

The potential environmental risk from carvedilol centers on the aquatic and terrestrial compartments. Carvedilol will not be directly discharged into the environment from use, but instead most will be subjected to depletion mechanisms found in wastewater treatment plants (WWTP).

Two mechanisms at the plants will decrease environmental concentrations of carvedilol: sorption and biodegradation. Approximately 77% of carvedilol in WWTP influent will be sorbed onto plant biomass solids, thus dramatically decreasing carvedilol concentrations in WWTP effluent. Carvedilol in solution will likely be at least partially biotransformed based

ENVIRONMENTAL ASSESSMENT INFORMATION

Carvedilol

upon data described in ERL Report 9501. Any carvedilol that is released from the WWTP into surface waters will be subjected to aqueous photolysis. Since the carvedilol photolysis rate constant was determined to be approximately 0.47 hr^{-1} , photolysis will serve as a significant depletion mechanism in the aquatic compartment.

Carvedilol sorbed onto sludge biomass will be ultimately disposed of, in some cases, by incineration or placed into secure landfills. Those WWTPs that do dispose of sludge via landfarming or distribution and marketing could serve to release carvedilol into the terrestrial compartment. However, carvedilol in sludge-amended soil will be subjected to aerobic biodegradation, albeit at slower rates than those determined in aqueous matrices. Finally, carvedilol in sludge-amended soil will be tightly bound to organic matter and not bioavailable.

In conclusion, predicted environmental concentrations of carvedilol are well below predicted toxicity concentrations and carvedilol will not require any additional mitigation actions.

11. ALTERNATIVE TO THE PROPOSED ACTION

No potential adverse environmental impacts have been identified for the proposed action. The approval of carvedilol will provide an important benefit to patients requiring its administration with no adverse environmental risk. The only alternative to the proposed action is that of no action, thus depriving patients an important therapy.

12. LIST OF PREPARERS

12.1 List of Contributors:

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790 Main Street
Wareham, Massachusetts

Antonio Garcia
Plant Services &
Environmental Manager
SmithKline Beecham
Pharmaceuticals Co.
Cidra, Puerto Rico

ENVIRONMENTAL ASSESSMENT INFORMATION

Carvedilol

12.2 List of Preparers:

Virginia L. Cunningham, Ph.D. & ERL Staff
Director
Environmental Research Laboratory (ERL)
SmithKline Beecham
(See Appendix V for Curricula Vitae)

13. CERTIFICATION:

The undersigned official certifies that the information presented is true, accurate, and complete to the best knowledge of the Environmental Research Laboratory.

Date:

March 17, 1995

Signature:

James Hagan

James R. Hagan, P.E.
Vice President
Corporate Environment & Safety
SmithKline Beecham

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Carvedilol

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Carvedilol

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ATTACHMENT II

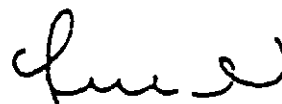
Note: The current name for Penn Chemicals (Cork, Ireland)
is SmithKline Beecham (Manufacturing) Limited

GENERAL COMPLIANCE STATEMENT

Boehringer Mannheim GmbH states that it is in compliance with all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of Guaiacol-O-ethyltosylate at its facilities in Mannheim, Federal Republic of Germany.

February 14, 1992

Date

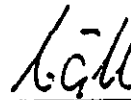


Dr. G. Lettenbauer

Senior Vice President
of
Chemical Production and
Development Department

February 14, 1992

Date



Dr. W. Wible

Vice President
of
Safety and Environmental Department

BOEHRINGER
MANNHEIM

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GENERAL COMPLIANCE STATEMENT

Boehringer Mannheim GmbH states that it is in compliance with all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of 4-Hydroxycarbazole at its facilities in Mannheim, Federal Republic of Germany.

February 14, 1992

Date



Dr. G. Lettenbauer

Senior Vice President
of
Chemical Production and
Development Department

February 14, 1992

Date



Dr. W. Wäble

Vice President
of
Safety and Environmental Department

BOEHRINGER
MANNHEIM

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Boehringer Mannheim GmbH
D-68298 Mannheim
Hausadresse:
Sandhofer Straße 116
D-68305 Mannheim

Boehringer Mannheim GmbH
Telez: 463193 bmg
Fax: (0621) 7592890

BOEHRINGER
MANNHEIM

February 3, 1994



TO WHOM IT MAY CONCERN
"ENVIRONMENTAL ASSESSMENT"

Boehringer Mannheim GmbH, as the manufacturer of various pharmaceutical active ingredients (drug substances) and finished medicinal products (drug products), having the official address

Boehringer Mannheim GmbH
Sandhofer Straße 116
D-68305 Mannheim
Federal Republic of Germany,

herewith certifies that the manufacture of active ingredients and finished products in the facilities of the above mentioned plant site is carried out according to the current laws and regulations of the Federal Republic of Germany for purposes of environmental protection.

The construction and the operation of plants for the manufacture of pharmaceutical products is principally subject to approval according to §4 of the Bundesimmissionsschutzgesetz (BImSchG) "Federal Law on Immissions". This requirement is based on the regulations concerning plants subject to approval (4th BImSchV = Regulations on the Federal Law on Immissions), which are given in the enclosures under subparagraph

4.1: Plants for the manufacture of products by chemical conversion ...

and under subparagraph

4.3: Plants for the manufacture of medicinal products or medicinal-product intermediates ...

Approval for these plants is to be obtained by submitting a detailed written application to the relevant authorizing body. Only after thorough inspection is a notice of approval conferred by the authorizing body (for Boehringer Mannheim GmbH, the Regierungspräsidium Karlsruhe = Directorate of the Administrative District, Karlsruhe). This notice may only be conferred if the relevant permit requirements have been satisfied according to §6 BImSchG (see enclosure).

It is therefore essential to guarantee the fulfillment of the obligations in §5 BImSchG which are incumbent on the operator of plants subject to approval. In addition, the construction and operation of the plants should not contravene further regulations under public law and the interest of industrial safety.

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Deutsche Bank AG, Mannheim
BLZ: 63070010 - Konto 01/02 832
 Dresdner Bank AG, Mannheim
BLZ: 670 80650 - Konto 6 608 231

Registernummer Mannheim HRB 1962
Gesellschaftsführung: Bernhard Kubitz (Abw.), Prof. Dr. rer. nat. Dr. med. Uwe Dicker (Chir.),
Dr. Ing. Fern. Metzger (Steuer), Gern. v. Mutschler, Klaus Schradt,
Vorsitzender des Aufsichtsrates: Curt Engstler

... 2

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In accordance with §5 BImSchG plants subject to approval are to be constructed and operated in such a manner that

1. harmful environmental effects and other hazards, considerable disturbance and considerable inconvenience to the community and vicinity cannot be evoked,
2. provisions are made against harmful environmental effects, in particular through the use of state-of-the-art measures for the limitation of emissions,
3. residues are avoided where possible, or are processed and rendered harmless according to regulations, or, where avoidance and processing is not technically feasible or is unreasonable, they are removed as waste without harm to the well-being of the community, and
4. any resulting heat is used in the operator's plant or transferred to a third party that has declared itself as willing to accept, provided that the process involved is technically possible and acceptable, and that it is compatible with the obligations according to subparagraphs 1 to 3.

However, where plants not subject to approval with respect to the BImSchG, approvals according to other laws may be binding (e.g. according to building regulations, according to industrial code and others). Moreover, §22 and §23 of the BImSchG lay down the obligations for the operator and also the requirements for the construction and the operation of such plants (see enclosure). Accordingly, such plants are to be constructed and operated so that

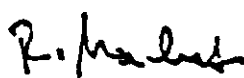
1. harmful environmental effects are prevented through the use of state-of-the-art technology,
2. unavoidable harmful effects on the environment are minimized through the use of state-of-the-art technology, and
3. waste arising from the operation of the plants can be removed according to regulations.

We are obliged to comply strictly with such legal regulations. This is being controlled by the responsible administration.

Additionally, we draw attention to the fact that we are subject to the constant supervision of the civil Industrial Inspection Board.

Yours faithfully,

DOEHRINGER MANNHEIM GMBH
ppa. i.V.



Dr. Machat



Dr. Ochmichen

7 Enclosures

Karlsruhe, 2-23-1994

Regierungspräsidium Karlsruhe
Agreed:



Hoffmann

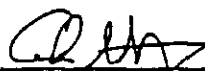
Oberregierungsrat



GENERAL COMPLIANCE STATEMENT

PENN CHEMICALS B.V. states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of Carvedilol at its facilities in Currabinny, Carrigaline, Co. Cork, Ireland as well as emission requirements set forth in applicable federal state, and local statutes and regulations applicable to the production of Carvedilol at its facilities in Currabinny, Carrigaline, Co. Cork


DECLAN RYAN
MANAGER ENGINEERING/ENVIRONMENTAL


COLM HARTY
DIRECTOR FINANCE & ADMINISTRATION

PENN CHEMICALS B.V., Currabinny, Carrigaline, Co. Cork, Ireland.

Tel. 021-371201, Fax 021-372383, Telex 75869 Int Dialing +353-21-371201



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SmithKline Beecham
Pharmaceuticals

GENERAL COMPLIANCE STATEMENT

SmithKline Beecham Pharmaceuticals Co. states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of CARVEDILOL (KREDEX) at its facilities in Cidra, Puerto Rico as well as emission requirements set forth in applicable federal, state, and local statutes and regulations applicable to the production of CARVEDILOL at its facilities in Cidra, Puerto Rico.

Jose L. Rosado 4-13-92

JOSE L. ROSADO DATE
PRESIDENT & GENERAL MANAGER

Antonio Garcia 4-13-92

ANTONIO GARCIA DATE
ENVIRONMENTAL & PLANT
SERVICES LEADER

ATTACHMENT III

**SMITHKLINE BEECHAM ENVIRONMENTAL RESEARCH LABORATORY
SUMMARY OF ENVIRONMENTAL FATE AND EFFECT STUDIES**

compound - SK&F 105517 (CARVEDILOL)

summary prepared by - Scott Ziegenfuss

revised as of 3/17/95

ENVIRONMENTAL FATE

		pH 5	pH 7	pH 9	O1 H2O (pH 8.4)	
Water Solubility	definitive data - mean	434	30.9	1.81	5.46 (mg/L)	
	stdev	46.3	3.66	0.356	1.88	
Octanol/Water Distribution Coefficient (K_{ow}) *				C1 (26.3 ug/L)	pH 5 pH 7 pH 9	
				C2 (263 ug/L)	106 528 1040	
Sludge Adsorption	preliminary experiment - mean K _p = 5500, log mean K _p = 3.74					
	factorial experiment - 19 hour equilibration Freundlich isotherm data					
	active sludge - log K = 2.76				poisoned sludge - log K = 3.64	
	1/n = 0.713				1/n = 0.999	
	R ² = 0.993				R ² = 0.964	
	log K _p = 3.37				log K _p = 3.65	
	definitive isotherm experiment - 19 hour equilibration					
	log K = 4.31		mean K _p = 10800			
	1/n = 1.1		log K _p = 4.03			
	R ² = 0.931		stdev = 2400			
Soil Adsorption			H2O	CaCl2		
	soil	TOC (%)	log K	log K _{oc}	log K	log K _{oc}
	Kansas	2.06	2.69	4.37	3.47	5.16
	Calif.	1.59	2.81	4.61	3.93	5.72
	Iowa	1.53	2.75	4.57	4.54	6.36
Henry's Constant	< 2.66E-7 m ³ *atm/mol @ pH 6.70, 3.93E-7 m ³ *atm/mol @ pH 6.55					
UV/vis Spectrum	in 10% water in methanol	lambda	E (M ⁻¹ .cm ⁻¹)			
		204	34200			
		224	36900			
		242	50200			
		286	14500			
		320	4610			
		332	6040			
Dissociation Constant (pKa)	7.8 (from SB Analytical Chemistry report #3077)					
Aerobic Biodegradation	carvedilol	k = 0.03 /day, t1/2 = 26.2 days				
	carbazole	k = 1.76 /day, t1/2 = 0.39 days				
	4-hydroxycarbazole	k = 0.03 /day, t1/2 = 21.8 days				
Photolysis	k = 0.4679 /hr, t1/2 = 1.5 hrs					

ENVIRONMENTAL EFFECTS

D. pulex 48-hr acute	EC50 -	> 2.8 mg/L	(95% c.i. - N/A)
	NOEC -	< 0.37 mg/L	
Bluegill 96-hr acute	LC 50	0.99 mg/L	(95% c.i. - 0.87 to 1.1)
	NOEC -	< 0.43 mg/L	
Microbes Microtox	carvedilol	EC50-15 = 5.43	mg/L (stdev = 0.25)
	carbazole	EC50-15 = 0.26	mg/L (stdev = 0.031)
	4-hydroxycarbazole	EC50-15 = 6.71	mg/L (stdev = 1.87)
	biologically-degraded solution - #1 - EC50 at 15.4%, #3 - non-toxic		
	photolytically-degraded solution - 0 and 5 hours exposure: non-toxic		
	1.5 hours exposure: EC50-5 = 41.0 +/- 11.9 % (SD)		
Activated Sludge Respiration Inhibition (OECD 209)	EC50 -	98.4 mg/L	

ATTACHMENT IV

MATERIAL SAFETY DATA SHEET

**1. IDENTIFICATION OF THE SUBSTANCE/PREPARATION
AND OF THE COMPANY/UNDERTAKING**

SUBSTANCE/PREPARATION:

CARVEDILOL

TRADENAMES/SYNONYMS:

1-(9H-CARBAZOL-4-YLOXY)-3-[[2-(2-METHOXYPHENOXY)ETHYL]AMINO]-2-PROPANO
L * SK&F 105517 * BM 14.190 * SKF 105517 * KREDEX * 105517 (SK&F) *
105517 (SKF)

CHEMICAL FAMILY:

Substituted carbazole.

MOLECULAR FORMULA:

C24-H26-N2-O4

MOLECULAR WEIGHT:

406.481

EINECS NUMBER:

Not Assigned

ELINCS NUMBER:

Not Assigned

COMPANY:

SMITHKLINE BEECHAM, CORPORATE ENVIRONMENT & SAFETY

U.S. OFFICE:

709 SWEDELAND ROAD
KING OF PRUSSIA, PA, 19406
U.S.A.

U.K. OFFICE:

NORFOLK HOUSE, DOWNSBROOK TRADING ESTATE
SOUTHDOWNVIEW WAY, WORTHING
WEST SUSSEX, BN14 8NQ, ENGLAND

PHONE NUMBERS:

++1-610-270-7807

++44-(0)903-822650

EMERGENCY AND AFTER HOURS CONTACT:

++1-800-228-5635 (EXTENSION 157)

2. COMPOSITION/INFORMATION ON INGREDIENTS

INGREDIENTS

CARVEDILOL

CAS REGISTRY NO

72956-09-3

PERCENT

MORE THAN 99%

CONTAMINANTS:

No significant hazardous contaminants.

3. HAZARDS IDENTIFICATION

PRIMARY ROUTES OF EXPOSURE:

Avoid breathing dust, eye contact, skin contact, ingestion.

SKIN CONTACT:

Allergic skin reaction can occur following direct contact with this material.
Symptoms such as itching, redness or swelling might be delayed.

EYE CONTACT:

Irritation can occur following direct contact with this material. Symptoms might
include redness or swelling.

INHALATION:

Symptoms after overexposure to dust might include slow pulse, dizziness,
fainting, difficult or irregular breathing, or bluish colored fingernails or
palms.

INGESTION:

Toxicity is not expected but ingestion should be avoided. Symptoms after
overexposure might include slow pulse, dizziness, fainting, difficult or

MATERIAL SAFETY DATA SHEET

irregular breathing, or bluish colored fingernails or palms.

CONDITIONS AGGRAVATED BY EXPOSURE:

Diabetics or individuals taking cardiovascular medications might be sensitive to the effects of this material. In cases of overexposure, seek medical assistance concerning possible drug interactions.

4. FIRST-AID MEASURES

SKIN CONTACT:

Remove contaminated clothing and flush exposed area with large amounts of water. Obtain medical assistance if skin reaction occurs, which may be delayed.

NOTE TO PHYSICIAN:

None.

EYE CONTACT:

Flush eyes continuously with water for at least 15 minutes. Do not use a chemical neutraliser. Obtain medical assistance if symptoms occur.

NOTE TO PHYSICIAN:

None.

INHALATION:

Move exposed subject to fresh air. Seek medical assistance in case of known or possible overexposure to this material or with symptoms including chest pain, difficulty breathing, loss of consciousness or other adverse effects which may be delayed. IF BREATHING HAS STOPPED, START BASIC LIFE SUPPORT AND SEEK IMMEDIATE MEDICAL ATTENTION.

NOTE TO PHYSICIAN:

For combustion products, refer to section number 5.

INGESTION:

In the event of swallowing this material, seek medical assistance. Do not induce vomiting.

NOTE TO PHYSICIAN:

Medical treatment in cases of overexposure should be treated as an overdose of beta-adrenergic blockers. Gastric lavage is recommended. Refer to current prescribing information or to local poison control information centers. This material is not a corrosive agent.

ANTIDOTES:

None known.

5. FIRE-FIGHTING MEASURES

FIRE CONTROL:

Use water, carbon dioxide, foam or dry chemical extinguishers. Toxic or corrosive gases are expected from fires involving this material.

SPECIAL FIREFIGHTING PROCEDURES:

Toxic or corrosive gases including oxides of carbon and nitrogen are expected in fires involving this material. Self contained breathing apparatus and full protective equipment are recommended for firefighters. Move containers from fire area if possible without increased personal risk. Dike area if possible to contain water for later disposal.

6. ACCIDENTAL RELEASE MEASURES

SPILLS:

Instruct all personnel not involved in clean up operations to keep at a designated, safe distance. Do not allow this material to enter surface drainage systems. Wear protective clothing and equipment consistent with

MATERIAL SAFETY DATA SHEET

the degree of hazard. Carefully scoop up the spillage, avoid dust generation and place in a suitable, properly labeled container for recovery or disposal. Wash down spillage area with copious amounts of water. This must only be undertaken if waste water can be directed to an on-site waste water treatment system.

DECONTAMINATION PROCEDURES:

Detergent solutions can be used for clean-up and decontamination operations. No specific detoxification procedures have been identified for this substance.

7. HANDLING AND STORAGE

HANDLING:

This material has not been tested for its dust explosion properties. However, like most organic dusts, it is expected to explode when ignited as a dust cloud. Care should be taken to avoid dispersion as a dust cloud. Ensure that all items of plant and equipment used for handling this material are bonded and earthed (grounded). The presence of isolated conductors should be avoided. Enclosure is recommended to routinely control airborne dust levels below published exposure limits.

STORAGE:

Avoid prolonged storage at elevated temperatures (greater than room temperature, approximately 20 degrees C). Keep in tightly closed containers or packages away from moisture and away from sources of ignition.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

EXPOSURE CONTROLS:

CARVEDILOL:

SmithKline Beecham(PEL):
0.03 MG/M3 (8 HR TWA)

INDUSTRIAL HYGIENE METHOD:
SB/1210 analytical method.

PERSONAL PROTECTION:

RESPIRATORS:

Respirators are normally not required when handling small quantities. If the airborne dust level is greater than allowable levels, a laboratory fume hood, local exhaust ventilation or an appropriate respirator should be used. The specific type used will be determined by air concentrations present. Follow local regulations for respirator use in the workplace.

GLOVES:

Wear neoprene or other impervious gloves for handling wet or dry powder.

EYE PROTECTION:

In laboratories, wear safety glasses with sideshields when handling this material. In production areas, wear full face respirator for dry powder, goggles for wet powder.

HYGIENE PRACTICES:

Wash hands and arms thoroughly after handling this material.
Clean up spills immediately.

OTHER PROTECTIVE EQUIPMENT:

In laboratories, wear lab coat or other protective clothing with long sleeves. In production areas, wear protective clothing that is laundered or discarded after each use. An eye wash station should be available.

9. PHYSICAL AND CHEMICAL PROPERTIES

MATERIAL SAFETY DATA SHEET

APPEARANCE:

White to off-white crystalline powder.

FLASH POINT:

Expected to be greater than 55 degrees C.

AUTOIGNITION TEMP:

Not determined.

LOWER EXPLOSIVE LIMIT:

Not applicable solids.

UPPER EXPLOSIVE LIMIT:

Not applicable solids.

MELTING POINT:

115 to 117 degrees C.

BOILING POINT:

Not determined.

VAPOUR DENSITY:

Expected to be negligible.

VAPOUR PRESSURE:

Expected to be negligible.

EVAPORATION RATE:

Expected to be negligible.

VOLATILE COMPONENTS (%):

None expected.

VISCOSITY:

Not applicable for solids.

PH OF AQUEOUS SOLUTIONS:

Not determined.

RELATIVE DENSITY:

Not determined.

CONDUCTIVITY:

Not applicable for solids.

OCTANOL/WATER DISTRIBUTION COEFFICIENT:

KOW (26.3 micrograms/l) = 106 (pH 5), 528 (pH 7), 1040 (pH 9)

KOW (263 micrograms/l) = 85.7 (pH 5), 549 (pH 7), 1260 (pH 9)

DISSOCIATION CONSTANT (pKA):

7.8

SOLUBILITY:

Soluble in many polar solvents.

Insoluble in water.

OXYGEN BALANCE:

This material is considered to be of low energy hazard potential based on oxygen balance calculated as minus 224.

TRAIN FIRE TEST:

Since this material has not been train fire tested, it should be assumed to support combustion in bulk quantities.

DUST EXPLOSIVITY:

Classification: Not determined.

Minimum explosive concentration (grams/cubic metre): Not determined.

Minimum ignition temperature - cloud (degrees C): Not determined.

Minimum ignition temperature - layer (degrees C): Not determined.

Minimum oxygen concentration (% v/v): Not determined.

Explosion characteristics:

Pmax (bar): Not determined.

dP/dT (bar/second): Not determined.

Kst (bar metre/second): Not determined.

St class: Not determined.

MATERIAL SAFETY DATA SHEET

DUST ELECTRICAL PROPERTIES:

Minimum ignition energy (mjoules): Not determined.
Resistivity at ambient humidity (ohm meter): Not determined.
Charge decay time at ambient humidity (seconds): Not determined.
Resistivity at low humidity (ohm metre): Not determined.
Charge decay time at low humidity (seconds): Not determined.

10. STABILITY AND REACTIVITY

CONDITIONS TO AVOID:

Avoid direct sunlight, conditions that might generate heat and dispersion as a dust cloud.

INCOMPATIBILITY:

None known.

STABILITY:

This material is expected to be stable.

THERMAL STABILITY:

Capillary tube test:

Thermal degradation can be expected at temperatures greater than 200 degrees C.

Differential scanning calorimetry:

Not determined.

Accelerating rate calorimeter:

Not determined.

HAZARDOUS POLYMERIZATION:

Not expected to occur.

HAZARDOUS DECOMPOSITION PRODUCTS:

Not identified.

FIRE AND EXPLOSION HAZARDS:

Not identified. As with many organic dusts, explosions might result when excessive dust concentrations are present.

11. TOXICOLOGICAL INFORMATION

ORAL TOXICITY:

The oral LD50 in rats was greater than 8000 mg/kg. No lethality occurred in rats after administration of a single oral dose of 8000 mg/kg.

INHALATION TOXICITY:

Not determined for this material.

SKIN IRRITATION:

This material was classified as a non irritant to rabbit skin. No signs of irritation occurred up to 3 days after direct application in rabbits for 4 hours.

EYE IRRITATION:

This mixture was classified as a minimal irritant in rabbit eyes. Conjunctival redness occurred up to 1 day after direct application in rabbits. Eyes appeared normal 2 days after treatment.

SENSITISATION:

This material was classified as a mild sensitiser to guinea pig skin. Adverse skin reactions or irritation occurred in 4 out of 20 guinea pigs used to test for allergic reaction or sensitisation (maximisation test).

MUTAGENICITY:

This material was not mutagenic in bacteria (Ames Test) or other genotoxicity tests.

CARCINOGENICITY:

This material is not listed as a carcinogen by SB, IARC, NTP or US OSHA.

MATERIAL SAFETY DATA SHEET

There was no evidence of a carcinogenic effect in chronic studies with rats or mice.

REPRODUCTIVE EFFECTS:

This material did not produce teratogenic effects (birth defects) or adverse effects on male or female reproduction in studies with rats.

OTHER EFFECTS:

This material exhibits an effect on the cardiovascular system by lowering blood pressure.

12. ECOLOGICAL INFORMATION

ACUTE AQUATIC EFFECTS:

48-hour Daphnia EC50 = greater than 2.8 mg/l.

48-hour Daphnia no-observed-effect-concentration less than 0.37 mg/l.

96-hour Bluegill EC50 = 0.99 mg/l.

96-hour Bluegill no-observed-effect-concentration less than 0.43 mg/l.

BIODEGRADATION:

Not determined.

ACTIVATED SLUDGE RESPIRATION INHIBITION (OECD 209 PROTOCOL):

EC50 = 98.4 mg/l (draft results).

SOIL ADSORPTION:

Not determined.

OTHER EFFECTS:

None.

13. DISPOSAL CONSIDERATIONS

Collect for recycling or recovery, if possible. Dispose of material on site in a licensed chemical incinerator, if allowed by the incinerator license or permit. If no on-site incinerator is available, dispose of material in a licensed commercial chemical incinerator.

14. TRANSPORT INFORMATION

FOR AIR TRANSPORT (IATA REQUIREMENTS):

Proper Shipping Name: NOT RESTRICTED

Technical Name (for n.o.s., not otherwise specified): Not applicable

UN/Identification Number: Not applicable

Class/Division: Not applicable

Sub Risk: Not applicable

Packing Group: Not applicable

RQ (Reportable Quantity): Not applicable

Emergency Response Guide Number: Not applicable

FOR MARITIME TRANSPORT (IMDG REQUIREMENTS):

Proper Shipping Name: NOT RESTRICTED

Technical Name (for n.o.s., not otherwise specified): Not applicable

UN/Identification Number: Not applicable

Class: Not applicable

Sub Risk: Not applicable

Packing group: Not applicable

IMDG page number: Not applicable

MFAG number: Not applicable

EMS number: Not applicable

Marine Pollutant: Not applicable

Emergency Response Guide Number: Not applicable

FOR UNITED STATES GROUND TRANSPORT (DOT REQUIREMENTS):

MATERIAL SAFETY DATA SHEET

Proper Shipping Name: NOT RESTRICTED

Technical Name (for n.o.s., not otherwise specified): Not applicable

UN/Identification Number: Not applicable

Class/Division: Not applicable

Sub Risk: Not applicable

Packing Group: Not applicable

RQ (Reportable Quantity): Not applicable

Emergency Response Guide Number: Not applicable

FOR EUROPEAN GROUND TRANSPORT (ADR/RID/ROAD/RAIL REQUIREMENTS):

Not determined. Hazards according to ADR/RID requirements not identified.

EMERGENCY INFORMATION:

HAZCHEM code: Not applicable.

TREMCARD number: Not applicable.

15. REGULATORY INFORMATION

EUROPEAN UNION CLASSIFICATION AND LABELLING REQUIREMENTS:

No European Union labelling requirements.

16. OTHER INFORMATION

HAZARD LABEL:

**** NOT CLASSIFIED AS A SIGNIFICANT FIRE HAZARD ****

**** NO FIRE HAZARD IDENTIFIED ****

**** NOT CLASSIFIED AS A SIGNIFICANT ENVIRONMENTAL HAZARD ****

** TARGET ORGAN- PHARMACEUTICAL AGENT- MAY REDUCE BLOOD PRESSURE.

** SYMBOL: NOT REQUIRED. (NN)

REFERENCES:

SB HAZARD DETERMINATION

OTHER INFORMATION:

IF HMIS RATINGS ARE USED AT YOUR SITE, USE THE FOLLOWING:

HEALTH = 2 FIRE = U REACTIVITY = U

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13E1

MAY 19 1995

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

KREDEX® TABLETS

(Carvedilol)

12.5 and 25 mg

NDA 20-297

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

(HFD-110)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-297

Kredex® Tablets

(Carvedilol)

The Food and Drug Administration (FDA) recognizes the National Environmental Policy Act of 1969 (NEPA) as the national charter for protection, restoration, and enhancement of the environment. NEPA establishes policy, sets goals (section 101), and provides procedures (section 102) for carrying out the policy.

Environmental information is to be available to the public and the decisionmaker before decisions are made about actions that may significantly affect the quality of the human environment; FDA actions are to be supported by accurate scientific analyses; and environmental documents are to concentrate on timely and significant issues, not to amass needless detail.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Kredex® Tablets, SmithKline Beecham Pharmaceuticals has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Carvedilol is administered as an oral tablet in the treatment of essential hypertension. Drug substance intermediates are manufactured by Boehringer Mannheim GmbH, Mannheim, Germany. The drug substance will be manufactured at SmithKline Beecham (Manufacturing) Limited, County Cork, Ireland and the drug product will be manufactured and packaged at SmithKline Beecham Pharmaceuticals Co., Cidra, Puerto Rico. The finished drug product will be used in hospitals, clinics and by patients in their homes.

Chemical and physical test results and information indicate that carvedilol will most likely be restricted to the aquatic and terrestrial environments. A substantial amount of the drug will be removed from the aquatic environment as the compound will adsorb to sludge in waste water treatment plants. The compound degrades rapidly upon exposure to light although this will vary depending on the exposure conditions in the environment and it is also susceptible to aerobic biodegradation. As the compound is expected to persist in the environment for some time, acute toxicity studies were conducted using water fleas (*Daphnia pulex*) and bluegill sunfish (*Lepomis macrochirus*). The studies indicate that the drug would not be expected to exhibit acute toxicity effects to aquatic organisms at concentrations expected to be emitted into and exist in the environment. Carvedilol may enter the terrestrial environment from sludge that is applied to land and will remain tightly bound to soil. The material is not expected to persist in the soil compartment and toxicity to terrestrial organisms is expected to be less than that determined for aquatic organisms due to the decreased exposure pathways.

Microbial inhibition studies indicate that respiration in activated sludge is not inhibited at concentrations several orders of magnitude greater than the maximum expected environmental concentration (MEEC).

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, pharmaceutical processing waste, and user disposal of empty or partly used product and packaging. Waste drug product and pharmaceutical processing waste will be disposed of predominantly at licensed incineration facilities although small quantities may be emitted in effluent waste streams. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system while some unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. A certification has been provided by the German authorities stating that Boehringer Mannheim GmbH is operating in compliance with their environmental laws and regulations.

Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

5/19/95 *[Signature]*
DATE Prepared by
Fancy D. Sager
Review Chemist
Center for Drug Evaluation and Research

5/19/95 *[Signature]*
DATE Approved
Phillip G. Vincent, Ph.D.
Environmental Assessment Officer
Center for Drug Evaluation and Research

5/19/95 *[Signature]*
DATE Concurred
Robert A. Janni, Ph.D.
Associate Director for Chemistry
Center for Drug Evaluation and Research

Attachments:

- I: Environmental Assessment
- II: Compliance Statements
- III: Toxicological Table
- IV: Material Safety Data Sheet

CC: Original NDA 20-297/ZMcDonald copy to NDA/HFD-110
FONSI File 20-297/HFD-004
P. Vincent/HFD-004
Docket File 20-387/HFD-004
FOI Copy/HFD-019

20297.FON
F/T by NBS 05/19/1995

ATTACHMENT I

ENVIRONMENTAL ASSESSMENT INFORMATION

Carvedilol

1. DATE: March 17, 1995
2. NAME OF APPLICANT: SmithKline Beecham Pharmaceuticals
3. ADDRESS: Four Falls Corporate Center
Route 23 and Woodmont Avenue
P.O. Box 1510
King of Prussia, PA 19406

4. DESCRIPTION OF THE PROPOSED ACTION:

4.1 Description of the Requested Approval

SmithKline Beecham Pharmaceuticals is requesting approval for use of carvedilol for the treatment of essential hypertension. β -blocking and vasodilator effects occur in the same dosage range; carvedilol thus offers two active mechanisms of value in the management of hypertension. Carvedilol may also be effective in the management of other cardiovascular disorders, such as angina pectoris and/or left ventricular dysfunction.

4.2 Need for the Proposed Action

Carvedilol is a non-selective β -receptor blocking agent with vasodilative properties. It reduces peripheral vascular resistance through vasodilation and suppresses the renin-angiotensin-aldosterone system through β -blockage. Through these effects, carvedilol significantly reduces blood pressure in hypertensive patients. Carvedilol has no intrinsic sympathomimetic activity. By balancing vasodilation and β -adrenoreceptor blockage, carvedilol maintains myocardial function without affecting left ventricular ejection fraction. It causes no significant decrease in heart rate. The multiple actions of carvedilol are responsible for the antihypertensive efficacy of the drug in animals and in humans, and may also provide effective therapy in angina and congestive heart failure.

This Environmental Assessment information reflects effluent discharges based on estimated fifth year production of drug substance and product, as well as detailed information on the waste treatment and disposal processes at SmithKline Beecham Pharmaceuticals facilities at Cork, Ireland, (drug substance production), and Cidra, Puerto Rico (drug product production), as well as summary information on the production of key drug intermediates at the Boehringer Mannheim facility in Mannheim, Germany (drug intermediate production). Details on the Boehringer Mannheim facility are available in DMF 9502. This report also includes all of the fate and effects data and evaluations which are currently available for carvedilol drug substance.

ENVIRONMENTAL ASSESSMENT INFORMATION

Carvedilol

The manufacture of carvedilol substance and product will employ the same environments and utilize existing plants that are also currently manufacturing other pharmaceutical products.

4.3 Location where Product will be Produced

Carvedilol drug intermediates, used to produce the product that is the subject of the proposed action, are manufactured at the following facility:

Boehringer Mannheim GmbH
Sandhofer Strasse 116
Postfach 310120
D-6800 Mannheim 31
Federal Republic of Germany

The Boehringer Mannheim facilities used to produce these intermediates are located in Mannheim, Germany.

Carvedilol, the drug substance in the product which is the subject of the proposed action, is manufactured (stages 4-8) at the following facility:

SmithKline Beecham (Manufacturing) Limited
Currabinny, Carrigaline
County Cork
Ireland

SmithKline Beecham (Manufacturing) Limited is located approximately twelve miles south of Cork City on the southern shores of Cork Harbor. There is a total land bank of 130 acres, but the facility occupies only 28 acres. The immediate area is rural, with some farms and dwellings within a half mile radius of the boundary fence. The site discharges an aqueous waste into Cork Harbor after on-site biological treatment.

Carvedilol drug product will be prepared at the following facility:

SmithKline Beecham Pharmaceuticals Co.
Road 172
KM9.1/Bo Certenejas
Cidra, Puerto Rico 00739

ENVIRONMENTAL ASSESSMENT INFORMATION

Carvedilol

The Cidra facility for the drug product manufacture is a site of approximately 52 acres located in an agricultural/urban/industrial area on the central mountainous ridge of the island of Puerto Rico.

4.4 Locations where Product will be Used

Carvedilol drug product will be used in the United States of America (the subject of this NDA) and world-wide, with predominant use coinciding with areas of greatest population density.

4.5 Locations where Product will be Disposed of

Carvedilol drug product returned goods will be collected at the following site:

Division KENCO Group Inc.
1704 Mid Park Drive
Knoxville, Tennessee 37291

From this site, the materials will be shipped to one or more of the following licensed facility for destruction by high temperature incineration:

SmithKline Beecham Pharmaceuticals
Bristol Industrial Park
Weaver Pike
Bristol, Tennessee 37620

Ogden Martin Systems of Lake, Inc.
3830 Rogers Industrial Park Road
Okahumpka, Florida 34762

Documentation for these disposal facilities is provided in Appendix I.

5. DESCRIPTION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION:

5.1 Complete Nomenclature

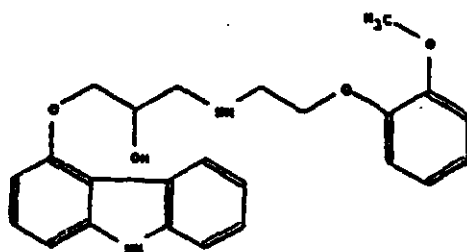
British Adopted Name (BAN):	Carvedilol
INN:	Carvedilol
United States Adopted Name (USAN):	Carvedilol

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ENVIRONMENTAL ASSESSMENT INFORMATION

Carvedilol

Trade Name:	
Chemical Name:	(±)-1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxy-phenoxy)-ethyl]amino]-2-propanol
5.2 <u>CAS Number:</u>	72956-09-3
5.3 <u>Laboratory Codes:</u>	SK&F 105517; BM 14.190
5.4 <u>Molecular Formula:</u>	C ₂₄ H ₂₆ N ₂ O ₄
5.5 <u>Molecular Weight:</u>	406.5
5.6 <u>Structural Formula:</u>	



5.7 <u>Description:</u>	A white to off-white powder
5.8 <u>Melting Range:</u>	SK&F 105517 typically melts over a 2-3°C range within 113-119°C
5.9 <u>Additives:</u>	Not applicable
5.10 <u>Impurities:</u>	

Organic impurities arising from the synthesis are determined by GC and HPLC. Solvent content is also measured by GC and the inorganic impurities, heavy metals, and sulfated ash are also monitored. Identification is included on the drug substance specification. The compound is stable, and no degradants are likely to arise under normal conditions.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

6.1 Introduction from Production

The production of carvedilol drug substance, intermediates and drug product will utilize the same facilities currently being used for the production of other pharmaceutical products. The following evaluation of the anticipated environmental impact of carvedilol production is based on estimated fifth year production and on existing waste treatment systems at the production facilities. Engineering estimates are used to predict anticipated discharge levels; however, the evaluations do not reflect changes in treatment process operations or technology which might be implemented before actual approval of the carvedilol application.

This Environmental Assessment contains non-confidential information on the control and disposition of gaseous, aqueous, and solid wastes at the production facilities.

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ENVIRONMENTAL ASSESSMENT INFORMATION

Carvedilol

6.1.1 Drug Intermediate Production at Boehringer

The Boehringer Mannheim facilities used to produce the intermediates (2) are located in Mannheim, Germany. One intermediate will be produced at Production Plant HC-B 21, and the second intermediate will be produced at Production Plants HC-B 4, HC-B 10 and HC-B/OB.

6.1.1.1 Introduction from Production of Drug Intermediate at HC-B 21

The following information was provided by Boehringer Mannheim GmbH regarding the introduction of substances into the environment from production of intermediate at Production Plant HC-B 21.

6.1.1.1.1 Emissions as Part of Waste Water

The substances described in the following table are expected to be emitted as part of the wastewater. This wastewater is discharged from the production plants, pretreated in the BM waste water purification plant and then discharged into the community wastewater system/sewage plant, where final treatment takes place.

Substance ^a	CAS Number
Sodium chloride	7647-14-5
Toluene	108-88-3
Organic By-products	NA

^a Substances expected to be emitted during each process step.

6.1.1.1.2 Solid/Liquid Wastes

No other solid or liquid wastes are produced during the production steps of the intermediate.

6.1.1.2 Emissions Requirements at the Boehringer Mannheim Plant

Boehringer Mannheim GmbH reached an agreement on pollution control with Mannheim in the state of Baden-Wurtemberg, where its plant is located. This agreement requires Boehringer Mannheim GmbH to comply with the regulations for environmental protection enacted by the German Federal Government.

6.1.1.2.1 Emission Requirements for Sewage into the Municipal Wastewater System

The following table summarizes the maximum wastewater permit levels established by the government.

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ENVIRONMENTAL ASSESSMENT INFORMATION

Carvedilol

Parameter	Value
pH	6.0 - 9.5
Temperature	max. 35°C
COD	700 mg/L
Ratio COD/BOD	< 2.5 :1
Settling substances (solvents)	1 mL/30 minutes
Sulfate (SO ₄)	400 mg/L
Sulfide (S)	10 mg/L
Sulfite (SO ₃)	50 mg/L
Fluoride	50 mg/L
Phenols	20 mg/L
Aromatic Hydrocarbons	30 mg/L
Ammonia as NH ₄	100 mg/L
AOX	0.5 mg/L
Organic solvents miscible with water	3000 mg/L
Organic solvents not miscible with water	According to solubility in water
Cu	1 mg/L
Fe	20 mg/L
Cr (III)	3 mg/L
Cr (VI)	0.1 mg/L
Zn	3 mg/L

6.1.1.2.2

Emission Requirements on Waste Gases

The following table summarizes the permit levels for waste gas emissions, according to the "Technical Directions for Maintaining Clean Air" (TA Luft).

Emission	Value
Ethylene oxide	≤ 5 mg/m ³
Toluene	0.15 g/Nm ³

If more than one substance in the waste gas is classified as carcinogenic III, the total concentration is not allowed to exceed 5 mg/m³ at a mass flow of 25 grams (or more) per hour. If there is more than one organic substance (vapor) in the waste gas, the total concentration is not allowed to exceed 0.15 g/Nm³ at a mass flow of 3 kg (or more) per hour.

ENVIRONMENTAL ASSESSMENT INFORMATION

Carvedilol

Manufacture of the intermediate in the Boehringer Mannheim plant (HC-B 21) will not result in the discharge of any emissions in excess of the amounts allowed by the applicable laws. A citation of and statement of compliance with applicable emissions requirements is provided in Appendix II. In addition, a certification of compliance signed by the appropriate government authority (Regierungsprasidium Karlsruhe) is also included in Appendix II.

6.1.2 Drug Intermediate Production at Boehringer

6.1.2.1 Introduction from Production of Drug Intermediate at HC-B 4, HC-B 10, and HC-B/OB

The following information was provided by Boehringer Mannheim GmbH regarding the introduction of substances into the environment from production of intermediate at Production Plants HC-B 4, HC-B 10 and HC-B/OB.

6.1.2.1.1 Emissions as Part of Wastewater

The substances described in the following table are expected to be emitted as part of the wastewater. This wastewater is discharged from the production plants, pretreated in the BM wastewater purification plant and then discharged into the community wastewater system/sewage plant, where final treatment takes place.

Substance	CAS Number
Acetic acid	64-19-7
Methanol	67-56-1
Organic By-products	NA
Intermediates	NA
Phosphoric acid	7664-38-2
Ethanol	64-17-5
Potassium chloride	7447-40-7

6.1.2.1.2 Solid/Liquid Wastes

The substances listed in the following table are produced as liquid or solid wastes. Solid wastes are disposed of through incineration at a community plant, and liquid wastes are disposed of through incineration at an outside company licensed to dispose of industrial waste products.

ENVIRONMENTAL ASSESSMENT INFORMATION

Carvedilol

Substance	CAS Number
Resin by products dissolved in solvent	NA
Activated carbon	7440-44-0
Filter aid	NA
Waste solvents	NA
Alumina	1344-28-1
Solvent/Oil mixture (residue of distillation)	NA

6.1.2.2 Emissions Requirements at the Boehringer Mannheim Plant

Boehringer Mannheim GmbH reached an agreement on pollution control with Mannheim in the state of Baden-Wurtemberg, where its plant is located. This agreement requires Boehringer Mannheim GmbH to comply with the regulations for environmental protection enacted by the German Federal Government.

6.1.2.2.1 Emission Requirements for Sewage into the Municipal Wastewater System

The following table summarizes the wastewater permit levels required by the government.

ENVIRONMENTAL ASSESSMENT INFORMATION

Carvedilol

Parameter	Value
pH	6.0 - 9.5
Temperature	max. 35°C
COD	700 mg/L
Ratio COD/BOD	< 2.5 :1
Settling substances (solvents)	1 mL/30 minutes
Sulfate (SO ₄)	400 mg/L
Sulfide (S)	10 mg/L
Sulfite (SO ₃)	50 mg/L
Fluoride	50 mg/L
Phenols	20 mg/L
Aromatic Hydrocarbons	30 mg/L
Ammonia as NH ₄	100 mg/L
AOX	0.5 mg/L
Organic solvents miscible with water	3000 mg/L
Organic solvents not miscible with water	According solubility in water
Cu	1 mg/L
Fe	20 mg/L
Cr (III)	3 mg/L
Cr (VI)	0.1 mg/L
Zn	3 mg/L

6.1.2.2.2 Emission Requirements on Waste Gases

The following table summarizes the permit levels for waste gas emissions, according to the "Technical Directions for Maintaining Clean Air" (TA Luft).

Emission	Value
Ethanol	0.15 mg/m ³
Diisopropylether	0.15 g/Nm ³

If more than one of the substances listed in the table above is found in the waste gas, the total concentration is not allowed to exceed 0.15 g/Nm³ at a mass flow of 3 kg (or more) per hour.

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Manufacture of the intermediate in the Boehringer Mannheim plant (HC-B 4, HC-B 10 and HC-B/OB) will not result in the discharge of any pollutants in excess of the amounts allowed by the applicable laws. A citation of and statement of compliance with applicable emissions requirements is provided in Appendix III. In addition, a certification of compliance signed by the appropriate government authority (Regierungsprasidium Karlsruhe) is also included in Appendix III.

6.1.3 Drug Substance Production at Cork

Carvedilol (SK&F 105517) drug substance process stages 4-8 will be performed at SmithKline Beecham (Manufacturing) Limited, a SmithKline Beecham Pharmaceuticals' facility in Cork, Ireland. Environmental evaluations of the impacts from drug substance production at Cork follow.

SmithKline Beecham (Manufacturing) Limited, Cork, Ireland is expected to remain in compliance with applicable waste effluent permits throughout the production of carvedilol drug substance. The Cork facility is regulated under an Integrated Pollution Control (IPC) license (Reference Number in Register of Licenses: 4; Date of Notification: October 28, 1994), under authority of the Environmental Protection Agency and the Environmental Protection Agency Act, 1992. This license contains permit levels and monitoring procedures for all plant emissions (wastewater, air, incinerators, etc.), as well as guidelines for the establishment of an Environment Management Programme, to assess all operations for the use of cleaner technology and the minimization of waste.

6.1.3.1 Waste Stream Summary and Disposition

The types of waste streams generated at SmithKline Beecham (Manufacturing) Limited will be disposed of such that release into the environment (gaseous and aqueous waste) will not exceed SmithKline Beecham (Manufacturing) Limited' plant permit levels (Appendix III).

6.1.3.2 Material Balance

Material balance information for the chemical inputs, process intermediates and effluents was determined for stages 4-8, thus accounting for all materials and amounts used in or produced by these stages. Waste outputs include leftover material resulting from production, inspection operations, assay solutions sampled before and after filtration, and floor and equipment washings.

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6.1.3.3 Controls Exercised on Wastes

6.1.3.3.1 Air and Fugitive Emissions

Hydrogen, the only off-gas produced, is vented directly to the atmosphere through a flame arrestor. Fugitive emissions are monitored if there is reason to suspect a gaseous leak. Air from the buildings where chemical processes are performed is filtered through two chemical absorbers. Air is automatically monitored every half hour by gas chromatography for several compounds, depending on the processes being performed, as it is discharged to the atmosphere.

6.1.3.3.2 Incinerated Wastes

Most process waste streams produced during carvedilol production at SmithKline Beecham (Manufacturing) Limited are incinerated at 1000°C. Process effluents are stored prior to incineration, and approximately 200 L of waste per hour are burned in each of two incinerators. After incineration, the effluent gas is passed through an absorber for the scrubbing of acidic compounds before discharge to the environment through a stack. This scrubber unit consists of a caustic solution circulating through a packed bed. Scrubber liquors are sent to the on-site wastewater treatment facility.

At discharge, incinerator gases are continuously monitored for carbon monoxide, sulphur dioxide and total organic carbon (TOC). The amount of organic material remaining after incineration is calculated using a 99.99% incineration destruction efficiency, based upon the known removal efficiencies for mercaptan and methylethyl ketone (MEK). The Cork facility is regulated under an Integrated Pollution Control (IPC) license (Reference Number in Register of Licenses: 4; Date of Notification: October 28, 1994), under authority of the Environmental Protection Agency and the Environmental Protection Agency Act, 1992.

6.1.3.3.3 Biotreatment System

Several of the carvedilol process wastestreams are treated in the on-site wastewater biotreatment facility. Scrubber liquors from the incinerators are sent for aerobic biological treatment before being discharged.

The treatment facility incorporates a basin of activated sludge, which has a retention time of 10 days. The biotreated waste (including domestic effluents and mutrators, floor washes, incinerator quench streams, and scrubber and environmental spent liquors) is sent to a balancing tank prior to neutralization in a second tank. The wastes are then sent to a stripping tank, prior to passing to an aeration tank to reduce biological oxygen demand (BOD). After aeration, some of the waste is aerated a second time in another tank, while the remaining waste is sent to a clarifier. The twice-aerated effluent is passed to another

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clarifier. Both clarifiers are dosed with polyelectrolytes, and effluent wastes are sent to the final holding tank prior to discharge.

Several parameters of the effluent are monitored on a daily basis at three stages of the treatment process. The flow rate, pH, COD, total dissolved solids and load (kg of COD per day) are monitored at the input stage, and the pH, dissolved oxygen, MLSS and F/M are monitored at the sludge plant. At the final holding tank, the pH, COD, suspended solids, ammonia and flow rate are also monitored. In addition to normal testing, effluent liquors are sampled if a problem (e.g., equipment malfunction) is discovered.

Treatment of effluents results in > 80% reduction in BOD. Review of the measured (confidential) and calculated concentrations of affected aqueous effluent components and a comparison with their permit levels resulted in the determination that the SmithKline Beecham (Manufacturing) Limited facility is in compliance with their aqueous effluent permits.

6.1.3.3.4 Solid Waste

Solid wastes produced during Cork carvedilol substance production process are sent off-site for disposal.

All treatment plant sludge is mechanically dewatered to approximately 15% solids prior to off-site disposal, with the extracted liquid returned to the effluent treatment plant. The Cork facility is regulated under an Integrated Pollution Control (IPC) license (Reference Number in Register of Licenses: 4; Date of Notification: October 28, 1994), under authority of the Environmental Protection Agency and the Environmental Protection Agency Act, 1992. Wastes and leachate will be tested for the presence of heavy metals, organohalogens and other micropollutants; solid waste regarded as non-hazardous will then be disposed of in a lined landfill designated for non-hazardous materials, with leachate monitoring. There are currently no limits as to the amount of solid wastes disposed of off-site.

6.1.3.4 Certification of Compliance

SmithKline Beecham Pharmaceuticals Co. (SmithKline Beecham (Manufacturing) Limited) is committed to environmental control and will operate within its permit during the production of carvedilol drug substance. A citation of and statement of compliance with applicable emissions requirements is provided in Appendix III.

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6.1.4 Introduction from Production of Drug Product

Carvedilol (SK&F 105517) drug product will be produced in a continuous process, consisting of granulation, drying and blending, compression and coating, and printing and packaging at SmithKline Beecham Pharmaceuticals Co. in Cidra, Puerto Rico. The manufacture of carvedilol will employ the same environment and utilize the existing plants that are currently used to manufacture other pharmaceutical products. Carvedilol will be prepared as 12.5 and 25 mg tablets. Environmental evaluations of the impacts from drug product production follow.

6.1.4.1 Waste Stream Summary and Disposition

The waste streams generated at the Cidra facility will be disposed of using appropriate procedures, such that release into the environment (gaseous and aqueous waste) will not exceed Cidra permit levels (Appendix IV) and off-site disposal of solid wastes will not violate applicable regulations.

6.1.4.2 Material Balance

Material balance information for the chemical inputs, process intermediates and effluents was determined, thus accounting for all materials and amounts used in or produced during the drug product process. Waste outputs include leftover material resulting from production, inspection operations (rejects are discarded), assay solutions sampled before and after filtration, and floor and equipment washings.

For the purposes of this evaluation, the production campaign is assumed to use all of the drug substance, which is based on the projected fifth year of carvedilol production for the U.S. Market.

6.1.4.3 Controls Exercised on Wastes

6.1.4.3.1 Dryer Water Vapor

Two waste streams consist of water evaporated during drying processes. These streams are filtered before venting to the environment and should contain no hydrocarbons or particulates. The water collected is sent to the on-site wastewater treatment facility for biotreatment.

Air emissions from the process fall under the State Rules and Regulations for Air Pollution Control. The regulations are administered by the Environmental Quality Board of the Commonwealth of Puerto Rico. Currently, the facility is operating under Permit No. PFE-21-

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0590-0477-I-III-0 and PFE-21-1089-0929-I-II-III-0, and is not considered to be a major pollutant source; thus, a PSD review (under the EPA program) will not be necessary.

6.1.4.3.2 Solvent Vapor

The incinerator at the Cidra facility is expected to burn only four solvent vapors, none of which are produced during the carvedilol production process. The scrubber blowdown liquors from the incinerator are sent to the SmithKline Beecham Pharmaceuticals Co. facility in Guayama, Puerto Rico for treatment and disposal.

6.1.4.3.3 Aqueous Wastes Disposed Of Through Biotreatment

The aqueous waste streams (1-4) are sent to the wastewater treatment facility. The streams are first pumped through a series of sand filters and an activated carbon adsorption system. The waste streams are then discharged into an equalization holding tank for aeration. Sanitary waste bypasses sand and carbon columns and goes directly to the equalization basin. The pH of the influent stream is adjusted with sodium hydroxide or carbon dioxide prior to entering the activated sludge system. The residence time of effluent in the activated sludge basin is 24 hours, and the average volume maintained is 80,000 gallons. The treatment facility is designed for a 85,000 gallon per day flow, with a maximum capacity of 127,000 gallons per day. The biotreatment waste stream then enters a clarifier, where the sludge is allowed to settle and separate from the biotreated aqueous effluent as supernatant.

The pH of the aqueous effluent is adjusted to 11.0 with hydrated lime and sent to a second clarifier, where solids are precipitated out of solution and removed by flocculation. The clarifier's precipitated solids are sent to the aerobic digester for further processing. The wastewater effluent is recarbonated and neutralized with carbon dioxide prior to passing through a second series of sand and carbon filters. Filtered effluent is collected in a filter effluent sump. This filtered effluent then passes through a Reverse Osmosis (RO) module for total dissolved solids and organic removal. Reverse Osmosis (RO) Permeate is collected in a 100,000 gallon effluent storage tank and Reverse Osmosis (RO) reject is disposed off to PRASA (Permit Number GDG-94-505-032). A copy of the permit is attached in Appendix V. The effluent is then chlorinated, aerated and monitored for pH, temperature and dissolved oxygen before entering Quebrada Las Quebradillas (Las Quebradillas Creek). After aeration in the biotreatment facility, 55,000 gallons per day of final effluent is recycled to cooling and quench towers and 25,000 gallons per day of final effluent is discharged. Rainwater runoff from the grounds of the Cidra facility are also discharged to this creek, which empties into the Turabo River and flows into Carraizo Lake (the water source for the metropolitan area of San Juan).

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For the purpose of this environmental assessment, the total quantity of drug product components expected to be emitted into the site biotreatment facility is estimated at 3% of the total batch.

Final effluent levels from biotreatment were calculated using the following equation:

$$(A \times 10^6 \text{ mg/kg} / B/C)D = E$$

where: A = total quantity of component to waste per day (kg/day);
B = number of days over which discharge is made (1);
C = site effluent discharge rate (240,175 L/day);
D = removal efficiency;
E = concentration of component in effluent in mg/L.

For developing the discharge level data, it is assumed that no volatilization or bioadsorption of these materials occurs during treatment, and that biodegradation is the only operative removal mechanism for some of the effluent compounds. Review of the measured (confidential) and calculated concentrations of affected aqueous effluent components and a comparison with their permit levels resulted in the determination that the Cidra facility is in compliance with their aqueous effluent permits.

The contributions of the compounds used in the tablet formulation of carvedilol (SK&F 105517) to the total quantity of regulated components in the effluent will not cause total effluent concentrations to exceed the permit levels, assuming complete removal of carvedilol by the wastewater treatment facility. The quality of the effluent discharge meets Puerto Rico's water quality standards. The treatment facility operates under National Pollutant Discharge Elimination System (NPDES) Permit PR 0021997. In Puerto Rico, the NPDES Permit Program is administered by the Federal Environmental Protection Agency.

The facility is also regulated by the Puerto Rico Water Pollution Law, which is administered by the Assistant Secretary of Health for Environmental Health and Consumer Protection. Additional regulations are the Puerto Rico Harmful Spills Law, the Puerto Rico Public Policy Environmental Act, and the Puerto Rico Water Quality Standards, each administered by the Board of Environmental Quality. Permit limits for the wastewater discharge are stated in the NPDES permit. The discharge limits are presented in Appendix IV.

6.1.4.3.4 Solid Wastes

The activated carbon (granular Calgon AC, 8 X 30 mesh) from the biotreatment filters is replaced every three months. Settled sludge from the first clarifier in the biotreatment process is divided into two streams: sludge waste to an aerobic digester and sludge returned to the system. Within the digester the sludge waste is concentrated by settling and decanting the water. More water is then removed from the concentrated sludge slurry

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by means of a wedge filtration system and solar drying beds. The decanted water is recycled back to the feed of the wastewater treatment system. Sludge is maintained in the drying beds at a depth of two feet, and the waste volume is reduced by at least 92% during the drying period of two weeks. The dried sludge, and the spent carbon are disposed of as non-hazardous material at a municipal landfill, after testing using the Toxicity Characteristic Leaching Procedure (TCLP). Other solid wastes containing drug product (rejects, protective clothing, drums, filters, collected dust) are disposed of off-site to Ogden Martin Systems of Lake, Inc., Okahumpka, Florida, US (see Appendix I). There are no limits or restrictions placed on the quantities of materials that may be sent to the licensed disposal facilities.

6.1.4.4 Environmental Legislation

The following partial list of federal legislation may affect operation of the wastewater treatment facility.

Federal Water Pollution Control Act, as amended
Clean Water Act, as amended
Resource Conservation and Recovery Act
Safe Drinking Water Act
Toxic Substances Control Act
National Environmental Policy Act

6.1.4.5 Safety

The Cidra facility has adopted personnel safety procedures in all areas of plant activity, including procedures and information on electrical hazards, tool use, fire hazards, chemical handling and first aid.

6.1.4.6 Certification of Compliance

SmithKline Beecham Pharmaceuticals Co., Cidra, Puerto Rico, will operate within its permits during the production of carvedilol drug product. A citation of and statement of compliance with applicable emissions requirements is provided in Appendix IV.

6.2 Introduction from Use of Drug Product

Estimates of the maximum expected emitted concentrations (MEEC) from use of carvedilol tablets were calculated in part using data from reference [1]. At concentrations expected to be emitted into and exist in the environment, carvedilol is expected to exhibit no toxicity to aquatic organisms.

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6.3 Introduction from Disposal of Drug Product

Carvedilol drug product returned goods will be collected at the following site:

[REDACTED]

From this site, the materials will be shipped to the following licensed facilities for disposal (e.g., destruction by high temperature incineration).

SmithKline Beecham Pharmaceuticals
Bristol Industrial Park
Weaver Pike
Bristol, Tennessee 37620

[REDACTED]

Documentation for these disposal facilities is provided in Appendix I. Based on the controlled and highly efficient thermal destruction of unused drug substance and product, no material should be introduced into the environment from disposal.

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

7.1 Metabolism

The biotransformation and excretion of carvedilol in normal male human volunteers following single oral administration of ^{14}C -carvedilol was investigated [2]. Radiometabolites in both feces and urine were separated, quantified, and characterized structurally using a combination of HPLC and mass spectral techniques. The majority of the radiolabeled dose was found to be excreted in the feces (52%), with a lesser amount excreted in the urine (20%). The carvedilol-related products observed in the feces in this study included unchanged carvedilol and several oxidation products. Carvedilol-related products identified in feces represented 71% of the fecal radioactivity, with all of the products each accounting for more than 6.4% of the fecal radioactivity characterized.

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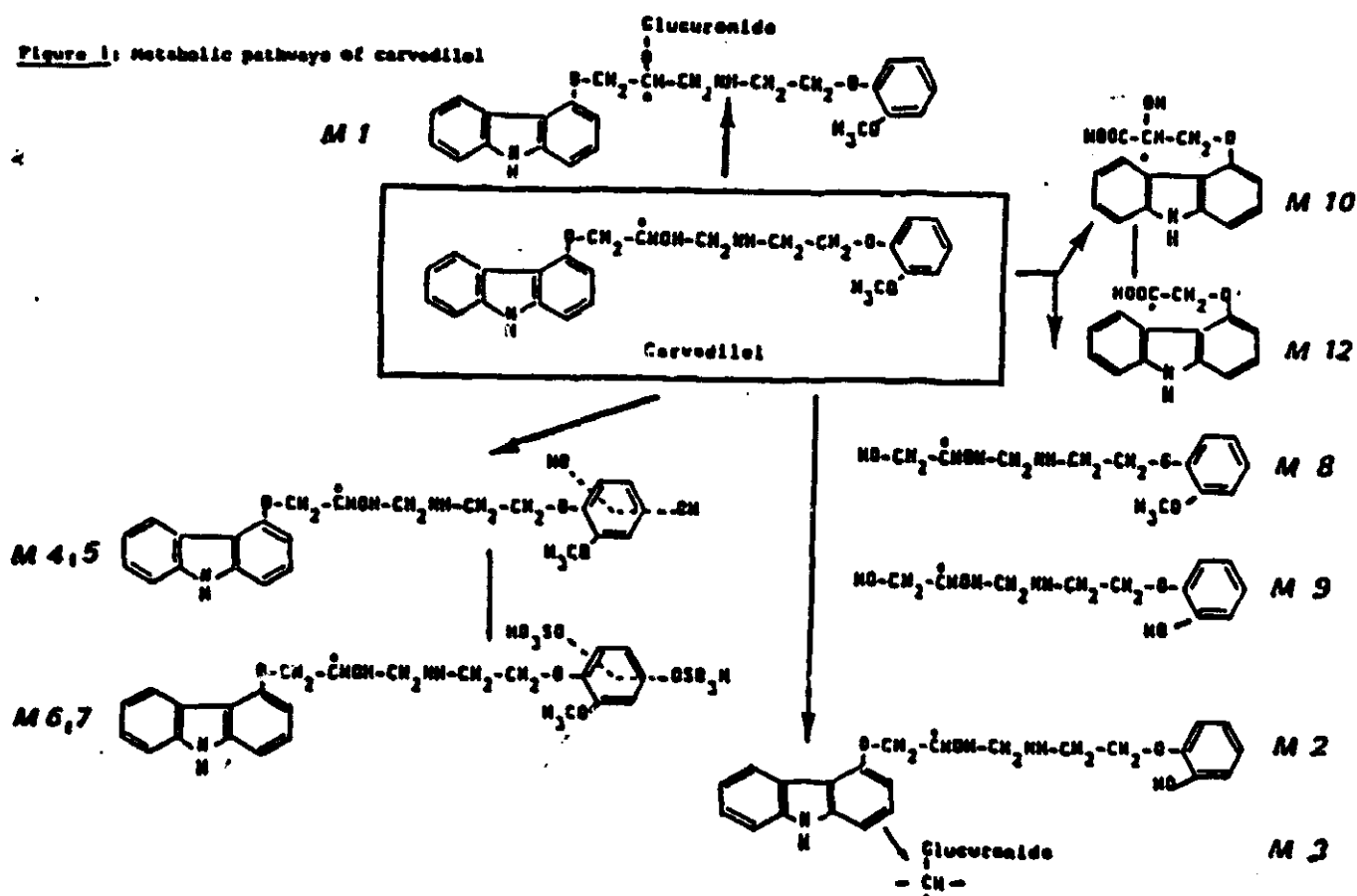
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The profile of urinary metabolites was much more complex, containing more than 26 compounds. The most abundant urinary metabolites were glucuronide derivatives of carvedilol. While the majority of the carvedilol metabolites excreted in feces were products of oxidation pathways, urinary metabolites included products of both oxidation and conjugation pathways. In general, all of the major metabolites structurally related to carvedilol are more polar analogs, and for the purposes of this environmental assessment, assessment of the fate and effects of carvedilol itself may be taken to represent a worst-case scenario.

The reported percent of an administered radioactive dose (range) recovered in the urine and feces is 15.29% - 20.00% and 52.12% - 61.40% respectively [31, 32]. The percent dose representing drug substance which was excreted unmetabolized was 0.21% - 0.28% for urine and 8.39% - 9.89% for feces [32].

A summary of the fecal, urinary and plasma metabolites of carvedilol in male human subjects is presented in Figure 1.

Figure 1



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7.2 Physical Properties

Physical properties were determined for carvedilol in-house, at the Environmental Research Laboratory. Several detailed reports are given in Appendix VI and summarized below.

7.2.1 Water Solubility

The water solubility of carvedilol as a function of pH was determined at 25°C. The results are given below and detailed in reference (3).

pH	Water Solubility (mg/L)			95% Confidence Range	
	mean	stdev	%RSD	low	high
5.04	434	46.3	10.7	416	452
7.09	30.8	3.66	11.9	29.4	32.2
9.04	1.61	0.356	22.1	1.46	1.76
8.43(DI H ₂ O)	5.46	1.88	34.3	4.72	6.20

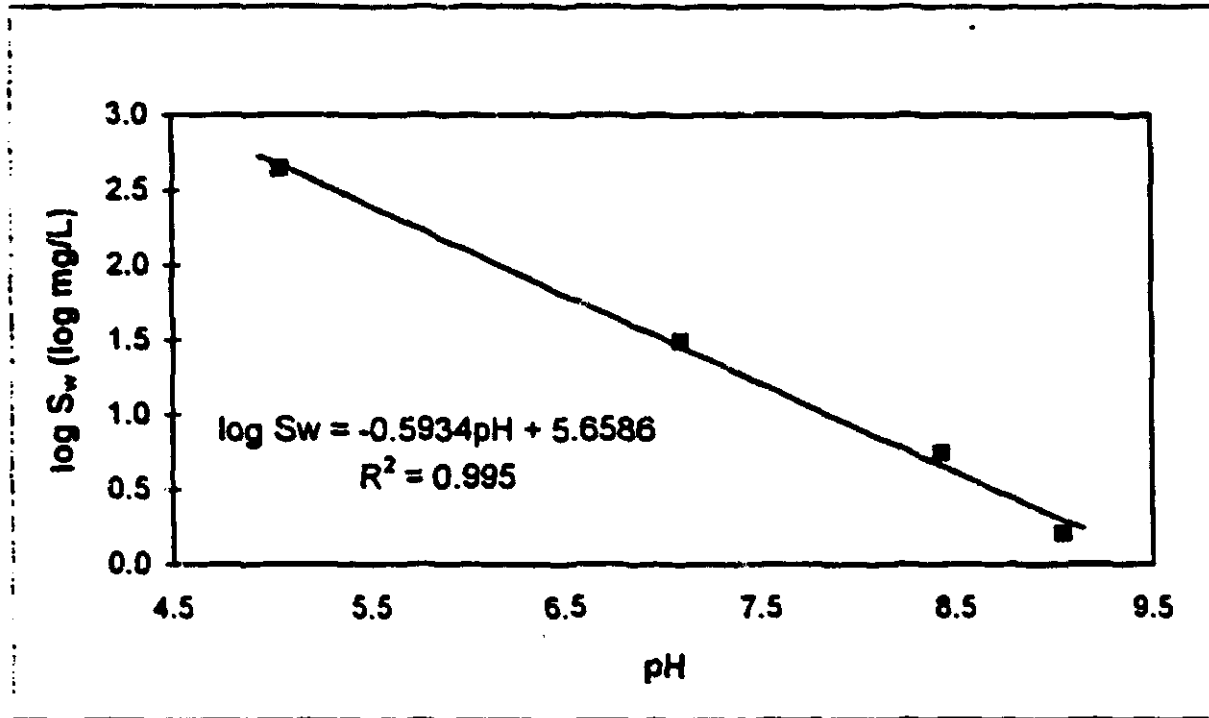
A log transformation of the solubility data plotted against pH shows a linear relationship, as illustrated in Figure 2 below.

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Figure 2

Aqueous Solubility of SK&F 105517.



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7.2.2 Dissociation Constant

Because of its low water solubility, the pK_a for carvedilol was determined by preparing methanol-water solutions of carvedilol containing 45, 50, 57, 66 and 71 v/v% methanol and then titrating these solutions with 0.1N HCl. The apparent pK_a was plotted versus concentration of methanol, resulting in a straight line whose intercept is the value of pK_a in water. A pK_a of 7.8 was obtained for the secondary amine group. The pK_a 's of the -NH- group in the carbazole ring, which is amphoteric, were not determined. According to published data, the pK_a 's of carbazole are 16.7 [4] (proton lost) and -5.7 [5] (proton gained). This suggests that the acidity or basicity of the carbazole in SK&F 105517 is extremely weak. The experiment is detailed in SB report code CSL-14467-250 which is included in Appendix VI; see reference [6].

7.2.3 Octanol/Water Distribution Coefficient

The octanol/water distribution coefficients (K_{ow}) for carvedilol were determined at two concentrations in triplicate test systems consisting of pH 5, 7 and 9 buffers and high-purity n-octanol. The results are reported in reference [7] and summarized below.

Solvent	26.3 mg/L		263 mg/L	
	K_{ow}	$\log K_{ow}$	K_{ow}	$\log K_{ow}$
Octanol/pH 5 buffer	106	2.02	85.7	1.93
Octanol/pH 7 buffer	528	2.72	549	2.74
Octanol/pH 9 buffer	1040	3.01	1260	3.10

7.2.4 Vapor Pressure, Volatilization, Henry's Law Constant

The vapor pressure of a substance is the property governing the tendency of a chemical substance to be transported into and in air and is thus an important parameter for predicting the distribution of chemicals into environmental compartments. For non-ionizable organic compounds, measurement of the vapor pressure is straightforward, and the value obtained is meaningful in environmental predictions. However, for compounds such as carvedilol, which will be ionized in solution at environmental pHs, the vapor pressure of the free base of the compound alone is less useful for predicting air-water partitioning. Vapor pressure may over-predict volatilization of chemicals which are partially ionized in aqueous solution. Since carvedilol has a basic pK_a of 7.8, approximately 86% of dissolved carvedilol species (ionized) will exist as the protonated base at pH 7. Therefore, only 14% (neutral) of dissolved species are available for volatilization.

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A more useful parameter for estimating the air-water partition coefficient for a chemical, and thus the likelihood of its entering into and being transported by the atmosphere, is Henry's law constant. The apparent Henry's law constant, H_L , represents the ratio of the equilibrium concentration of a chemical substance in air to its corresponding concentration in water in a closed system. It can be used to estimate the tendency of a chemical to volatilize from aqueous solution at a given pH. H_L is related to vapor pressure (VP) and aqueous solubility (Sw) as follows:

$$H_L = VP/S_w$$

Since carvedilol exists primarily as a protonated base at environmental pH levels, the Henry's law constant was measured directly experimentally. Values of $<2.66 \times 10^{-7} \text{ m}^3 \text{ atm/mol}$ at pH 6.7 and $3.93 \times 10^{-7} \text{ m}^3 \text{ atm/mol}$ at pH 6.55 were obtained. The results are detailed in reference [9].

Lyman et al. in reference [10] provides the following interpretation of H_L values:

H_L ($\text{m}^3 \cdot \text{atm/mol}$)	Aquatic Volatility
1E-5 to 1E-7	"volatilizes slowly"
1E-7 to 3E-7	"essentially non-volatile"
< 1E-7	"less volatile than water"

With an H_L of $3.93\text{E-}7 \text{ m}^3 \cdot \text{atm/mol}$, the aquatic volatility of carvedilol may be characterized as a very slow process. In the presence of any significant depletion mechanism, mass transfer to the atmospheric compartment over time would be negligible.

7.2.5 UV/Vis Spectrum

The UV/Vis spectra of aqueous solutions of carvedilol were determined at pH 5, 7 and 9. The detailed study report is given in reference [11]. The experimental results indicate that the UV/Vis absorption spectrum of carvedilol is not affected by solution pH. In addition, significant absorbance at wavelengths greater than 290 nm was found, which suggests that carvedilol is likely to be susceptible to direct photochemical degradation in the environment.

7.2.6 Soil Sorption/Desorption (K_{OC}) and K_D

Soil sorption/desorption isotherms are carried out in order to generate a water-soil partitioning coefficient (K_{OC}) for use in predicting the mobility of a chemical in the terrestrial

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environmental compartment. For human drugs, however, the majority of users will discharge into municipal wastewater treatment systems [1]. As a result, a more meaningful partitioning coefficient to predict initial sorption to biomass or sludge is K_p , a measure of the partitioning between the aqueous phase and the biosolids phase in a wastewater treatment plant (WWTP).

From preliminary experiments, a mean K_p was determined to be 5500 ($\log K_p = 3.74$). From definitive equilibrium Freundlich isotherm data with active sludge, the sludge adsorption isotherm constant K was determined to be 20,400 ($\log K = 4.31$). The difference between these results may be due to different sludge sources and treatments. Standardized methodology for sludge adsorption studies has not yet been established. Details of the studies are given in reference [12]. The use of this constant to predict environmental partitioning is shown in section 7.3 below.

A soil sorption/desorption isotherm study was also carried out to generate a K_{oc} value for carvedilol. The detailed study report is given in reference [13] and summarized below.

Soil	%TOC	Solvent	K_{oc}	$\log K_{oc}$
Kansas	2.06	H ₂ O	23500	4.37
California	1.59	H ₂ O	40900	4.61
Iowa	1.53	H ₂ O	<u>36900</u>	<u>4.57</u>
Average			33800	4.53
Kansas	0.8	CaCl ₂	143000	5.16
California	1.59	CaCl ₂	530000	5.72
Iowa	1.53	CaCl ₂	<u>227000</u>	<u>6.36</u>
Average			300,000	5.47

The average K_{oc} from studies in water was 33,800; from studies in CaCl₂, a value of 300,000 was determined. Usually, if a lower K_{oc} is determined in the CaCl₂ solvent system, this is taken as indicating a significant amount of ion-exchange character in the sorption process, since the calcium ions would compete with the carvedilol protonated free base ions for ion-exchange sites, resulting in less carvedilol partitioning into the soil organic carbon phase. However, for carvedilol, the CaCl₂ studies gave a higher value. This may be due to a "salting out" effect of the CaCl₂, decreasing the water solubility of the carvedilol and resulting in stronger hydrophobic interactions with the soil organic carbon. Thus the

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sorption appears to be a more complex function of the chemical nature of the carvedilol and of the soil organic carbon. The usual name given to this complex phenomenon is chemisorption. It is interesting to note that correction of the sludge partition coefficient, $\log K_p = 4.31$, for organic carbon content (assumed to be approximately 50% (reference [14]), yields a $\log K_{OC}$ for sludge of 4.61. This is essentially the same as the $\log K_{OC}$ obtained for soils using water as the solvent.

Carvedilol exhibited very little desorption from soil. The percent desorbed from the soil systems tested ranged from only 0.34-2.36%.

In summary, the sludge and soil adsorption studies indicate that carvedilol will adsorb strongly to particulate organic materials and that once adsorbed it will be relatively immobile in the environment.

7.3 Environmental Partitioning Estimates for Carvedilol

Since the majority of carvedilol used in the United States will be introduced into the environment through Wastewater Treatment Plants (WWTPs), the partitioning of carvedilol in that system must first be considered. Taking total production as unity, the maximum fraction of drug entering the aquatic and terrestrial compartments after discharge from the WWTPs can be calculated as follows:

CALCULATION OF MAXIMUM EXPECTED EMITTED CONCENTRATION

Carvedilol

Given the following assumptions:

Total annual market volume (5th year)(MV_{total})	=	1
Fraction of US population using WWTP($F_{sewered}$)	=	0.74 [1]
Fraction of Drug Substance not excreted(F_m)	=	0
Annual US Sewage Flow(SF_{annual})	=	3.7×10^{13} L/yr [1]
Annual Yield of Dry Sludge from WWTPs(DS_{annual})	=	5.9×10^9 kg/yr [1]
Dilution rate from Application of Sludge to Agricultural Land (DR_{annual})	=	0.025 [1]
K_p (carvedilol)	=	

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Then the maximum expected emitted concentration (MEEC) into the environment of carvedilol from use of the drug product is calculated as follows, assuming 100% excretion of carvedilol and its metabolites in one day:

$$\begin{aligned} \text{Fraction emitted into WWTPs} &= MV_{\text{total}} \times F_{\text{sewered}} \\ &= \\ &= \end{aligned}$$

Based on the distribution of carvedilol between sludge and water,

$$\begin{aligned} K_p &= \frac{\text{Concentration in sludge } (C_2)}{\text{Concentration in sewer effluent } (C_1)} \\ 2.04 \times 10^4 &= \frac{C_2}{C_1} \\ C_2 &= \text{ (equation 1) } \end{aligned}$$

Since the fraction emitted (0.74) will be distributed between the sludge and the sewer effluent, the balance around the WWTP is

$$C_1 \times SF_{\text{annual}} + C_2 \times DS_{\text{annual}} = \text{ (equation 2) }$$

Substitution of the equation for C_2 (equation 1) into equation 2 gives

$$\begin{aligned} (3.7E13C_1) + (5.9E09)(2.04E04C_1) &= \\ (3.7E13C_1) + (1.20E14C_1) &= \\ 1.57E14C_1 &= \\ C_1 &= \\ C_2 &= \\ C_2 &= \\ C_2 &= \end{aligned}$$

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Using the relationships of equation 2 gives:

$$(3.7E13C_1) =$$

=

$$(5.9E09)(C_2) =$$

=

Thus, $\frac{1}{3}$ of the carvedilol emitted to wastewater treatment plants from use will distribute into the aqueous phase, with $\frac{2}{3}$ sorbing to the sludge and entering the terrestrial compartment. Given the high soil sorption and very low desorption of carvedilol, very little migration of carvedilol through the terrestrial compartment is likely to occur.

7.4 Transformation and Depletion Mechanisms of Carvedilol

7.4.1 Hydrolysis

The hydrolytic stability of carvedilol was determined in deionized water and in pH 5, 7 and 9 buffers. The results indicated that carvedilol is hydrolytically stable under the conditions tested, and has an estimated hydrolytic half-life ≥ 1 year [15]. The study is detailed in reference [16].

7.4.2 Aqueous Photolysis

Given carvedilol's significant absorption of light at wavelengths > 290 nm, the photolysis study on carvedilol was carried out at pH 7 in natural sunlight. The first-order direct aqueous photoreaction rate constant was determined to be 0.468 hr^{-1} , giving a half-life of 1.48 hours. The detailed study report is given in reference [17].

7.4.3 Aerobic Biodegradation

Aerobic biodegradability studies were carried out on carvedilol using a modification of standard methodology. The analytical method validation study is given in reference [18]. The definitive aerobic biodegradation study is detailed in references [19] and [33]. ERL study 92-021, reference [19], determined that biotransformation of carvedilol was detected after ~ 40 days with a first-order rate constant of 0.03 day^{-1} giving a half-life of 26.2 days. Another study, ERL Study 92-050, used methanol as a carrier to facilitate carvedilol bioavailability in the biodegradation test systems. For comparison it also contained treatments that added carvedilol to the test system without methanol carrier.

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The two treatment groups that used methanol had first-order rate constants of 0.1 and 0.05 day⁻¹ at 5 and 10 mg/L carvedilol concentration, respectively. This corresponds to respective half-lives of 6.9 and 13.9 days. The no methanol treatments had first-order rate constants of 0.02 and 0.01 day⁻¹ at 5 and 10 mg/L carvedilol concentration, respectively. This corresponds to respective half-lives of 34.6 and 69.3 days. The presence of a carrier solvent appears to significantly enhance the biodegradation kinetics in the test systems employed for the study probably as a direct consequence of increased bioavailability to the degrading microorganisms.

In addition to carvedilol itself, biodegradation/biotransformation studies were carried out on 4-hydroxycarbazole and carbazole, substructures of the carvedilol molecule likely to be the most recalcitrant to biotransformation. The half-lives for these two compounds were 21.8 days and 0.39 days, respectively. This may be taken as indicative of the eventual mineralization of the carvedilol molecule once the initial acclimation is accomplished. Interestingly, the two replicate experiments for the biodegradation studies showed different HPLC profiles, indicating that carvedilol in the different flasks was undergoing biotransformation by two different pathways. The details of these studies are given in references [20] and [21]. See also aquatic toxicity evaluations in Section 8.2.3.

It is clear from these data that carvedilol is indeed susceptible to biodegradation in aerobic compartments and should not persist in the environment. Given the high biomass concentrations in activated sludge systems, the likely presence of surface-active agents which may facilitate bioavailability, and higher levels of dissolved organics which would enhance the solubility of carvedilol, the degradation of carvedilol in unacclimated waste water treatment plant systems would be expected to be more rapid than the conservative kinetics presented in typical biodegradation test systems.

7.4.4 Fate Summary

From the data presented above, the following are predictions concerning the environmental fate of carvedilol from use:

1. Based on environmental partitioning estimates presented in section 7.3, approximately 77% of carvedilol introduced into WWTPs is expected to distribute into the sludge phase. Biotransformation may occur during the solids retention, which may reduce sludge concentrations considerably. Due to the high turbidity of activated sludge mixed liquor, little photolysis is expected to occur during aeration. During secondary settling, dissolved carvedilol may be more susceptible to photodegradation in the clarified secondary effluent.
2. Carvedilol discharged into the aquatic environmental compartment will not likely persist based on photolysis and slow biotransformation depletion mechanisms. An

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overall depletion rate may be estimated from the individual depletion rate constants. An estimation of half-life in the aquatic compartment may range from 1.5 hours to 40-50 days based on the dominant active depletion mechanism.

3. Carvedilol entering the terrestrial compartment by land application of sludge would likely remain sorbed, immobile and undergo, under aerobic conditions, slow biotransformation. It would not be expected to persist in the soil compartment.
4. The very low Henry's constant suggests that transport of carvedilol to the atmosphere by volatilization from either the treatment plant or the terrestrial compartment will be insignificant.
5. Given that the log of the octanol/water distribution coefficient varies from 2 to 3 at environmental pH levels, little bioconcentration of carvedilol is likely to occur. This prediction is further supported by the metabolism studies, which indicate that carvedilol is biotransformed by a variety of mechanisms into more polar materials, which are excreted.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES:

8.1 Human and Mammalian Health Effects Summary [22]

8.1.1 Acute Toxicity Studies

8.1.1.1 Oral Toxicity

No lethality occurred in rats after administration of a single oral dose of 8000 mg/kg. The oral LD₅₀ in rats was greater than 8000 mg/kg.

8.1.1.2 Inhalation Toxicity

Inhalation toxicity was not determined. However, symptoms after exposure to dust might include slow pulse, dizziness, fainting, difficult or irregular breathing or bluish colored fingernails or palms.

8.1.1.3 Skin Irritation

Skin irritation potential was not determined. We can assume that direct contact can produce irritation or allergic skin reaction. Symptoms such as itching, redness or swelling might be immediate or delayed.

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8.1.1.4 Eye Irritation

Eye irritation potential was not determined. Assume that direct contact can produce irritation. Symptoms might include redness or swelling.

8.1.1.5 Sensitization

The sensitization potential of carvedilol has not been determined.

8.1.2 Chronic Toxicity Studies

8.1.2.1 Reproduction Toxicology

Carvedilol did not produce adverse effects on male or female reproduction in studies with rats.

8.1.2.2 Teratogenicity

Carvedilol did not produce teratogenic effects in studies with rats.

8.1.2.3 Genetic Toxicology

Carvedilol was not found to be mutagenic in bacteria (Ames test) or other genotoxicity tests. It is not listed as a carcinogen by IARC, NTP, or US OSHA. There was no evidence of a carcinogenic effect in chronic studies with rats or mice.

8.1.2.4 Other Effects

Carvedilol exhibits an effect on the cardiovascular system by lowering blood pressure.

8.2 Aquatic Toxicity Studies

8.2.1 Acute Aquatic Toxicities of Carvedilol

Acute aquatic toxicity studies were carried out on microorganisms (Microtox[®] and Microbial Respiration Inhibition), *Daphnia magna*, and bluegill sunfish (*Lepomis macrochirus*) using carvedilol. The detailed reports on the Microtox[®] studies for carvedilol, 4-hydroxycarbazole, and carbazole are given in references [23,24,25]. The reports of the contract study of the activated sludge respiration inhibition of carvedilol is given in reference [26]. Reports of the contract studies on the acute toxicities of carvedilol to *Daphnia pulex* and bluegill sunfish (*Lepomis macrochirus*) are given in references [27] and [28], respectively. The results are summarized below.

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Toxicity Test	Carvedilol (mg/L)
Microtox [®] - EC ₅₀	5.43 ± 0.25 6.71 ± 1.87 (4-OH carbazole) 0.26 ± 0.031 (carbazole)
Respiration Inhibition - EC ₅₀	98.4
<i>Daphnia pulex</i> - LC ₅₀ ^{1.1/95}	> 2.8
<i>Daphnia pulex</i> - NOEL	< 0.37
Bluegill Sunfish - LC ₅₀	0.99 (95% CI = 0.87-1.1)
Bluegill Sunfish - NOEL	< 0.43

8.2.2 Acute Aquatic Toxicity of Carvedilol Photolysis By-Products

Since carvedilol was found to degrade in the presence of sunlight, the relative toxicity of the photo-degradant(s) compared to carvedilol itself was determined using the Microtox[®] test carried out on samples of carvedilol solutions that had been exposed to sunlight. No EC₅₀ could be determined for the degraded solutions because of a lack of toxic effect. Based on these results, any compounds entering the environment from the photolysis of carvedilol would not be expected to exert toxic effects on aquatic organisms. Details of the study are given in reference [29].

8.2.3 Acute Aquatic Toxicity of Carvedilol Biodegradation By-Products

The relative acute aquatic toxicity of carvedilol biodegradation by-products was also determined by a Microtox[®] test carried out on samples of carvedilol solutions after laboratory biodegradation experiments. For one sample of biodegradants, no EC₅₀ could be determined for the degraded solutions because of a lack of toxic effect. For the "replicate" sample, an EC₅₀ of 15.4% was calculated. See reference [30] in Appendix VII. However, as noted in Section 7, the carvedilol in the two samples appeared to be biotransformed by two different pathways, and by consortia of apparently different microorganisms. However, even though minimal toxic effect was observed, the unknown biodegradants responsible were derived from carvedilol at a concentration far in excess of what could be emitted into the environment from use.

From the data above, carvedilol and its degradants would not be expected to exhibit acute toxic effects to aquatic organisms at concentrations expected to be emitted into and exist in the environment.

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9. USE OF RESOURCES AND ENERGY

9.1 Use of Resources and Energy at Boehringer

9.1.1 Use of Resources and Energy at Plant HC-B 21

The following tables summarize the known amounts of energy and resources utilized during intermediate production at the production plant HC-B 21.

Percent of Energy and Resources Utilized at Boehringer Mannheim for Production of Intermediate in 1990 HC-B 21 Plant					
Consumption	Electricity (kw-hour)	Steam / 2.5 bar (t)	Tap Water (m³)	Cooling Water (m³)	Demineralized Water (m³)
Percent of Total Consumption at Boehringer Mannheim	0.02	0.005	0.005	0.06	0.05

9.1.2 Use of Resources and Energy at Plants HC-B 4, HC-B 10 and HC-B/OB

The following tables summarize the known amounts of energy and resources utilized during intermediate production at production plants HC-B 4, HC-B 10 and HC-B/OB.

Percent of Energy and Resources Utilized at Boehringer Mannheim for Production of Intermediate in 1990 HC-B 4, HC-B 10 & HC-B/OB Plants					
Process Step	Electricity (kw-hour)	Steam / 2.5 bar (t)	Tap Water (m³)	Cooling Water (m³)	Demineralized Water (m³)
Percent of Total Consumption at Boehringer Mannheim	0.13	0.08	0.13	0.38	0.36

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9.1.3 Effect Upon Endangered Species And Historic Places

The production of carvedilol intermediates and the disposal of associated wastes at the Boehringer Mannheim production facilities should have no impact on threatened or endangered species. Property listed in or eligible for listing in the National Register of Historic Places will not be impacted by intermediate production or waste disposal activities since the production is taking place outside of the United States and the Boehringer-Mannheim facility is not a designated historic site.

9.2 Use of Resources And Energy At Cork

The effects on the use of resources and land for the production of carvedilol drug substance are minimal because of the low production volumes and associated wastes, and the existing treatments units that will be used.

The following table summarizes the percent of energy and resources utilized during carvedilol substance production stages at the SmithKline Beecham (Manufacturing) Limited facility, based on the projected 5th year of production and current use.

Consumption	Electricity (kw-hour)	Fuel Therms	Water (m ³)
Percent of Total Consumption	0.05	4.2	0.07

9.2.1 Effect Upon Endangered Species And Historic Places

The production of carvedilol substance and the disposal of associated wastes should have no impact on threatened or endangered species. Property listed in or eligible for listing in the National Register of Historic Places will not be impacted by carvedilol substance production or waste disposal activities since the production is taking place outside of the United States and the SmithKline Beecham (Manufacturing) Limited facility is not a designated historic site.

9.3 Use of Resources and Energy to Produce Drug Product at Cidra

The Cidra facility for carvedilol product manufacture is a 52 acre site located in an agricultural/urban/industrial area on the central mountainous ridge of the island of Puerto Rico. The effects on the use of resources and land for the production of carvedilol drug

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product are minimal because of the low production volumes and associated wastes, and the existing treatments units which will be used. Manufacture of this product uses only a small percentage of the resources and energy available at this site and of resources and energy required for transport.

The following table summarizes the total known amounts of energy and resources used at the Cidra plant.

Consumption	Electricity (kw-hour)	Fuel Oil (gallons)	Water (gallons)
Percent of Total Consumption	4%	4%	4%

To produce the carvedilol drug product at maximum yearly production levels at Cidra, it is estimated that 4% of total yearly Cidra plant usage of electricity, fuel and water will be used.

9.3.1 Effect Upon Endangered Species And Historic Places

The production of carvedilol product and the disposal of associated wastes should have no effect on threatened or endangered species. Property listed in or eligible for listing in the National Register of Historic Places will also not be impacted by carvedilol product production or waste disposal activities since the Cidra facility is not a designated historic site.

10. MITIGATION MEASURES

10.1 Mitigation Measures at Boehringer

Potential adverse environmental impacts associated with drug intermediate production at Boehringer Mannheim are minimized by the following:

No waste or exhaust streams are directly discharged, but are directed to major treatment units;

Treated effluent streams are checked before discharge, with ample capacity for emergency storage in the event that effluent criteria are not met;

Floor spills are swept and incinerated;

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Off-spec or rejected materials are returned to the supplier or are incinerated in an outside incineration plant for industrial wastes;

Accidental introductions of bulk product into the environment during storage is mitigated by controlled packaging and storage operations. Bulk drug product is packaged in new corrugated cardboard boxes lined with two polyethylene bags. These boxes are heat-sealed, sealed with plastic tape, properly labeled, and stored in a secured bulk storage area of the plant warehouse.

Storage facilities are designed to allow for the capture and treatment of any spills before any major environmental effects could result. Also, the adopted spills prevention, control and contingency plans have been demonstrated to be effective in the prevention of such emergencies.

The plant personnel are well-trained and follow written instructions when performing their work.

The site is audited regularly by the Boehringer Mannheim central Environment Department, to assist in the identification and implementation of any additional mitigation measures as circumstances warrant.

10.2 Mitigation Measures At Cork

Plans to minimize waste output were considered and implemented at the outset of carvedilol development, as well as during substance production. The Integrated Pollution Control (IPC) license contains guidelines for the establishment of an Environment Management Programme to assess all operations for the use of cleaner technology and the minimization of waste. Potential environmental impacts associated with production at Cork are also minimized by the following:

Most waste streams are incinerated, and the gases scrubbed before being discharged. Scrubber liquors are biotreated in the on-site wastewater treatment facility before discharge.

Biotreated effluent streams are checked before discharge, with ample capacity for emergency storage in the event that effluent criteria are not met.

Airstreams from the process buildings are filtered prior to venting to the atmosphere.

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10.3 Mitigation Measures at Cidra

Potential adverse environmental impacts associated with the proposed action are minimized at the Cidra facility by the following:

10.3.1 General

The proposed formulation process involves small production lots, which will generate very small quantities of waste;

No waste or exhaust streams are directly discharged. All streams are directed to major treatment units. Treated effluent streams are checked before discharge, with ample capacity for emergency storage in the event that effluent criteria are not met;

Airstreams from the process are small and directed to dust collectors, which minimize the effects of the emissions by at least 99.9%;

Storage facilities are designed to allow for the capture and treatment of any spills before any major environmental effects could result. Also, the adopted spills prevention, control and contingency plans have been demonstrated to be effective in the prevention of such emergencies.

10.3.2 Energy and Resources

A thermal oxidizer with a regenerative heat recovery system is used to incinerate gaseous waste streams produced during tablet coating operations. The heat recovery system is operated to recover at least 85% of the heat generated, for use in continual incineration of the gases. After aeration in the biotreatment facility, 55,000 gallons per day of final effluent is recycled to cooling and quench towers and 25,000 gallons per day of final effluent is discharged.

10.4 Mitigation from Use

The potential environmental risk from carvedilol centers on the aquatic and terrestrial compartments. Carvedilol will not be directly discharged into the environment from use, but instead most will be subjected to depletion mechanisms found in wastewater treatment plants (WWTP).

Two mechanisms at the plants will decrease environmental concentrations of carvedilol: sorption and biodegradation. Approximately 77% of carvedilol in WWTP influent will be sorbed onto plant biomass solids, thus dramatically decreasing carvedilol concentrations in WWTP effluent. Carvedilol in solution will likely be at least partially biotransformed based

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upon data described in ERL Report 9501. Any carvedilol that is released from the WWTP into surface waters will be subjected to aqueous photolysis. Since the carvedilol photolysis rate constant was determined to be approximately 0.47 hr^{-1} , photolysis will serve as a significant depletion mechanism in the aquatic compartment.

Carvedilol sorbed onto sludge biomass will be ultimately disposed of, in some cases, by incineration or placed into secure landfills. Those WWTPs that do dispose of sludge via landfarming or distribution and marketing could serve to release carvedilol into the terrestrial compartment. However, carvedilol in sludge-amended soil will be subjected to aerobic biodegradation, albeit at slower rates than those determined in aqueous matrices. Finally, carvedilol in sludge-amended soil will be tightly bound to organic matter and not bioavailable.

In conclusion, predicted environmental concentrations of carvedilol are well below predicted toxicity concentrations and carvedilol will not require any additional mitigation actions.

11. ALTERNATIVE TO THE PROPOSED ACTION

No potential adverse environmental impacts have been identified for the proposed action. The approval of carvedilol will provide an important benefit to patients requiring its administration with no adverse environmental risk. The only alternative to the proposed action is that of no action, thus depriving patients an important therapy.

12. LIST OF PREPARERS

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Carvedilol

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(See Appendix V for Curricula Vitae)

13. CERTIFICATION:

The undersigned official certifies that the information presented is true, accurate, and complete to the best knowledge of the Environmental Research Laboratory.

Date:

March 17, 1995

Signature:

James Hagan

James R. Hagan, P.E.
Vice President
Corporate Environment & Safety
SmithKline Beecham

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ATTACHMENT II

Note: The current name for Penn Chemicals (Cork, Ireland)
 is SmithKline Beecham (Manufacturing) Limited

GENERAL COMPLIANCE STATEMENT

Boehringer Mannheim GmbH states that it is in compliance with all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of Guaiacol-O-ethyltosylate at its facilities in Mannheim, Federal Republic of Germany.

February 14, 1992

Date

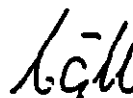


Dr. G. Lettenbauer

Senior Vice President
of
Chemical Production and
Development Department

February 14, 1992

Date



Dr. W. Wäble

Vice President
of
Safety and Environmental Department

BOEHRINGER
MANNHEIM

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GENERAL COMPLIANCE STATEMENT

Boehringer Mannheim GmbH states that it is in compliance with all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of 4-Hydroxycarbazole at its facilities in Mannheim, Federal Republic of Germany.

February 14, 1992

Date



Dr. G. Lettenbauer

Senior Vice President
of
Chemical Production and
Development Department

February 14, 1992

Date



Dr. W. Wible

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**BOEHRINGER
MANNHEIM**

February 3, 1994



TO WHOM IT MAY CONCERN

"ENVIRONMENTAL ASSESSMENT"

Boehringer Mannheim GmbH, as the manufacturer of various pharmaceutical active ingredients (drug substances) and finished medicinal products (drug products), having the official address

Boehringer Mannheim GmbH
Sandhofer Straße 116
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Federal Republic of Germany.

herewith certifies that the manufacture of active ingredients and finished products in the facilities of the above mentioned plant site is carried out according to the current laws and regulations of the Federal Republic of Germany for purposes of environmental protection.

The construction and the operation of plants for the manufacture of pharmaceutical products is principally subject to approval according to §4 of the Bundesimmissionschutzgesetz (BImSchG) "Federal Law on Immissions". This requirement is based on the regulations concerning plants subject to approval (4th BImSchV = Regulations on the Federal Law on Immissions), which are given in the enclosures under subparagraph

4.1: Plants for the manufacture of products by chemical conversion ...

and under subparagraph

4.3: Plants for the manufacture of medicinal products or medicinal-product intermediates ...

Approval for these plants is to be obtained by submitting a detailed written application to the relevant authorizing body. Only after thorough inspection is a notice of approval conferred by the authorizing body (for Boehringer Mannheim GmbH, the Regierungspräsidium Karlsruhe = Directorate of the Administrative District, Karlsruhe). This notice may only be conferred if the relevant permit requirements have been satisfied according to §9 BImSchG (see enclosure).

It is therefore essential to guarantee the fulfillment of the obligations in §5 BImSchG which are incumbent on the operator of plants subject to approval. In addition, the construction and operation of the plants should not contravene further regulations under public law and the interest of industrial safety.

... 2

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Dr. Ing. Fritz Heuniger (Stehl), Cornelia Metzner, Hans Schmidt,
Vizepräsident des Aufsichtsrates: Curt Engelhorn

To whom it may concern
"Environmental Assessment"

February 3, 1994
Page 2

In accordance with §5 BImSchG plants subject to approval are to be constructed and operated in such a manner that

1. harmful environmental effects and other hazards, considerable disturbance and considerable inconvenience to the community and vicinity cannot be evoked,
2. provisions are made against harmful environmental effects, in particular through the use of state-of-the-art measures for the limitation of emissions,
3. residues are avoided where possible, or are processed and rendered harmless according to regulations, or, where avoidance and processing is not technically feasible or is unreasonable, they are removed as waste without harm to the well-being of the community, and
4. any resulting heat is used in the operator's plant or transferred to a third party that has declared itself as willing to accept, provided that the process involved is technically possible and acceptable, and that it is compatible with the obligations according to subparagraphs 1 to 3.

However, where plants not subject to approval with respect to the BImSchG, approvals according to other laws may be binding (e.g. according to building regulations, according to industrial code and others). Moreover, §22 and §23 of the BImSchG lay down the obligations for the operator and also the requirements for the construction and the operation of such plants (see enclosure). Accordingly, such plants are to be constructed and operated so that

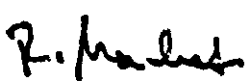
1. harmful environmental effects are prevented through the use of state-of-the-art technology,
2. unavoidable harmful effects on the environment are minimized through the use of state-of-the-art technology, and
3. waste arising from the operation of the plants can be removed according to regulations.

We are obliged to comply strictly with such legal regulations. This is being controlled by the responsible administration.

Additionally, we draw attention to the fact that we are subject to the constant supervision of the civil industrial inspection Board.

Yours faithfully,

DOEHRINGER MANNHEIM GMSH
ppa. LV.



Dr. Machal



Dr. Ochmichen

Karlsruhe, 2-23-1994

Regierungspräsidium Karlsruhe
Agreed:



Hoffmann

Oberregierungsrat

7 Enclosures

BOEHRINGER
MANNHEIM



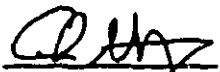
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GENERAL COMPLIANCE STATEMENT

PENN CHEMICALS B.V. states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of Carvedilol at its facilities in Currabinny, Carrigaline, Co. Cork, Ireland as well as emission requirements set forth in applicable federal state, and local statutes and regulations applicable to the production of Carvedilol at its facilities in Currabinny, Carrigaline, Co. Cork


DECLAN RYAN
MANAGER ENGINEERING/ENVIRONMENTAL


COLM HARTY
DIRECTOR FINANCE & ADMINISTRATION

PENN CHEMICALS B.V., Currabinny, Carrigaline, Co. Cork, Ireland.

Tel. 021-371201, Fax 021-372263, Telex 75668 and Dating -353-21-371201



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**SmithKline Beecham
Pharmaceuticals**

GENERAL COMPLIANCE STATEMENT

SmithKline Beecham Pharmaceuticals Co. states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of CARVEDILOL (KREDEX) at its facilities in Cidra, Puerto Rico as well as emission requirements set forth in applicable federal, state, and local statutes and regulations applicable to the production of CARVEDILOL at its facilities in Cidra, Puerto Rico.

Jose L. Rosado

JOSE L. ROSADO
PRESIDENT & GENERAL MANAGER

4-13-92
DATE

Antonio Garcia

ANTONIO GARCIA
ENVIRONMENTAL & PLANT
SERVICES LEADER

4-13-92
DATE

ATTACHMENT III

**SMITHKLINE BEECHAM ENVIRONMENTAL RESEARCH LABORATORY
SUMMARY OF ENVIRONMENTAL FATE AND EFFECT STUDIES**

compound - SK&F 108817 (CARVEDILOL)

summary prepared by - Scott Ziegenfuss

revised as of 3/17/95

ENVIRONMENTAL FATE

		pH 5	pH 7	pH 9	DI H2O (pH 8.4)	
Water Solubility	definitive data - mean	434	30.8	1.81	5.48	mg/L
	stdev	48.3	3.68	0.356	1.88	

Octanol/Water Distribution Coefficient (K _{ow}) *		C1 (28.3 ug/L)	pH 5	pH 7	pH 9
				108	529
		C2 (283 ug/L)	85.7	549	1280

Sludge Adsorption preliminary experiment - mean K_p = 5500, log mean K_p = 3.74
 (factorial experiment - 18 hour equilibration Freundlich isotherm data
 active sludge - log K = 2.78 1/n = 0.713 R² = 0.993 log K_p = 3.37
 poisoned sludge - log K = 3.84 1/n = 0.898 R² = 0.964 log K_p = 3.63
 definitive isotherm experiment - 18 hour equilibration
 log K = 4.31 1/n = 1.1 R² = 0.931
 mean K_p = 10800 log K_p = 4.03 stdev = 2400

Soil Adsorption

soil	TOC (%)	H2O		CaCl2	
		log K	log K _{oc}	log K	log K _{oc}
Kansas	2.06	2.69	4.37	3.47	5.18
Calif.	1.58	2.81	4.61	3.93	5.72
Iowa	1.53	2.75	4.57	4.54	6.38

Henry's Constant < 2.66E-7 m³·atm/mol @ pH 6.70, 3.93E-7 m³·atm/mol @ pH 6.55

UV/vis Spectrum	in 10% water in methanol	lambda	E (at 1 cm-1)
		204	34200
		224	38900
		242	50200
		288	14500
		320	4610
		332	6040

Disassociation Constant (pKa) 7.8 (from SB Analytical Chemistry report #3077)

Aerobic Biodegradation
 carvedilol k = 0.03 /day, t_{1/2} = 28.2 days
 carbazole k = 1.78 /day, t_{1/2} = 0.39 days
 4-hydroxycarbazole k = 0.03 /day, t_{1/2} = 21.8 days

Photolysis k = 0.4679 /hr, t_{1/2} = 1.5 hrs

ENVIRONMENTAL EFFECTS

D. pulex 48-hr acute	EC50 -	> 2.8 mg/L	(95% c.i. - N/A)
	NOEC -	< 0.37 mg/L	
Bluegill 96-hr acute	LC 50	0.99 mg/L	(95% c.i. - 0.87 to 1.1)
	NOEC -	< 0.43 mg/L	
Microbia Microtox	carvedilol	EC50-15 -	5.43 mg/L (stdev = 0.25)
	carbazole	EC50-15 -	0.28 mg/L (stdev = 0.031)
	4-hydroxycarbazole	EC50-15 -	6.71 mg/L (stdev = 1.87)
biologically-degraded solution - #1 - EC50 at 15.4%, #3 - non-toxic photochemically-degraded solution - 0 and 5 hours exposure: non-toxic 1.5 hours exposure: EC50-5 = 41.0 +/- 11.9 % (SD)			
Activated Sludge Respiration Inhibition (OECD 209)	EC50 -	98.4 mg/L	

ATTACHMENT IV

MATERIAL SAFETY DATA SHEET

**1. IDENTIFICATION OF THE SUBSTANCE/PREPARATION
AND OF THE COMPANY/UNDERTAKING**

SUBSTANCE\PREPARATION:

CARVEDIOL

TRADENAMES/SYNONYMS:

1-(9H-CARBAZOL-4-YLOXY)-3-[[2-(2-METHOXYPHENOXY)ETHYL]AMINO]-2-PROPANO
L * SK&F 105517 * BM 14.190 * SKF 105517 * KREDEX * 105517 (SK&F) *
105517 (SKF)

CHEMICAL FAMILY:

Substituted carbazole.

MOLECULAR FORMULA:C₂₄-H₂₆-.12-O₄**MOLECULAR WEIGHT:**

406.481

EINECS NUMBER:

Not Assigned

ELINCS NUMBER:

Not Assigned

COMPANY:

SMITHKLINE BEECHAM, CORPORATE ENVIRONMENT & SAFETY

U.S. OFFICE:

709 SWEDLAND ROAD
KING OF PRUSSIA, PA, 19406

U.S.A.

PHONE NUMBERS:

++1-610-270-7807

++44-(0)903-822650

EMERGENCY AND AFTER HOURS CONTACT:

++1-800-228-5635 (EXTENSION 157)

2. COMPOSITION/INFORMATION ON INGREDIENTS

INGREDIENTS

CARVEDIOL

CAS REGISTRY NO

72956-09-3

PERCENT

MORE THAN 99%

CONTAMINANTS:

No significant hazardous contaminants.

3. HAZARDS IDENTIFICATION

PRIMARY ROUTES OF EXPOSURE:

Avoid breathing dust, eye contact, skin contact, ingestion.

SKIN CONTACT:

Allergic skin reaction can occur following direct contact with this material.
Symptoms such as itching, redness or swelling might be delayed.

EYE CONTACT:

Irritation can occur following direct contact with this material. Symptoms might
include redness or swelling.

INHALATION:

Symptoms after overexposure to dust might include slow pulse, dizziness,
fainting, difficult or irregular breathing, or bluish colored fingernails or
palms.

INGESTION:

Toxicity is not expected but ingestion should be avoided. Symptoms after
overexposure might include slow pulse, dizziness, fainting, difficult or

MATERIAL SAFETY DATA SHEET

irregular breathing, or bluish colored fingernails or palms.

CONDITIONS AGGRAVATED BY EXPOSURE:

Diabetics or individuals taking cardiovascular medications might be sensitive to the effects of this material. In cases of overexposure, seek medical assistance concerning possible drug interactions.

4. FIRST-AID MEASURES

SKIN CONTACT:

Remove contaminated clothing and flush exposed area with large amounts of water. Obtain medical assistance if skin reaction occurs, which may be delayed.

NOTE TO PHYSICIAN:

None.

EYE CONTACT:

Flush eyes continuously with water for at least 15 minutes. Do not use a chemical neutraliser. Obtain medical assistance if symptoms occur.

NOTE TO PHYSICIAN:

None.

INHALATION:

Move exposed subject to fresh air. Seek medical assistance in case of known or possible overexposure to this material or with symptoms including chest pain, difficulty breathing, loss of consciousness or other adverse effects which may be delayed. IF BREATHING HAS STOPPED, START BASIC LIFE SUPPORT AND SEEK IMMEDIATE MEDICAL ATTENTION.

NOTE TO PHYSICIAN:

For combustion products, refer to section number 5.

INGESTION:

In the event of swallowing this material, seek medical assistance. Do not induce vomiting.

NOTE TO PHYSICIAN:

Medical treatment in cases of overexposure should be treated as an overdose of beta-adrenergic blockers. Gastric lavage is recommended. Refer to current prescribing information or to local poison control information centers. This material is not a corrosive agent.

ANTIDOTES:

None known.

5. FIRE-FIGHTING MEASURES

FIRE CONTROL:

Use water, carbon dioxide, foam or dry chemical extinguishers. Toxic or corrosive gases are expected from fires involving this material.

SPECIAL FIREFIGHTING PROCEDURES:

Toxic or corrosive gases including oxides of carbon and nitrogen are expected in fires involving this material. Self contained breathing apparatus and full protective equipment are recommended for firefighters. Move containers from fire area if possible without increased personal risk. Dike area if possible to contain water for later disposal.

6. ACCIDENTAL RELEASE MEASURES

SPILLS:

Instruct all personnel not involved in clean up operations to keep at a designated, safe distance. Do not allow this material to enter surface drainage systems. Wear protective clothing and equipment consistent with

MATERIAL SAFETY DATA SHEET

the degree of hazard. Carefully scoop up the spillage, avoid dust generation and place in a suitable, properly labeled container for recovery or disposal. Wash down spillage area with copious amounts of water. This must only be undertaken if waste water can be directed to an on-site waste water treatment system.

DECONTAMINATION PROCEDURES:

Detergent solutions can be used for clean-up and decontamination operations. No specific detoxification procedures have been identified for this substance.

7. HANDLING AND STORAGE

HANDLING:

This material has not been tested for its dust explosion properties. However, like most organic dusts, it is expected to explode when ignited as a dust cloud. Care should be taken to avoid dispersion as a dust cloud. Ensure that all items of plant and equipment used for handling this material are bonded and earthed (grounded). The presence of isolated conductors should be avoided. Enclosure is recommended to routinely control airborne dust levels below published exposure limits.

STORAGE:

Avoid prolonged storage at elevated temperatures (greater than room temperature, approximately 20 degrees C). Keep in tightly closed containers or packages away from moisture and away from sources of ignition.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

EXPOSURE CONTROLS:

CARVEDILOL:

SmithKline Beecham(PEL):

0.03 MG/M3 (8 HR TWA)

INDUSTRIAL HYGIENE METHOD:

SB/1210 analytical method.

PERSONAL PROTECTION:

RESPIRATORS:

Respirators are normally not required when handling small quantities. If the airborne dust level is greater than allowable levels, a laboratory fume hood, local exhaust ventilation or an appropriate respirator should be used. The specific type used will be determined by air concentrations present. Follow local regulations for respirator use in the workplace.

GLOVES:

Wear neoprene or other impervious gloves for handling wet or dry powder.

EYE PROTECTION:

In laboratories, wear safety glasses with sideshields when handling this material. In production areas, wear full face respirator for dry powder, goggles for wet powder.

HYGIENE PRACTICES:

Wash hands and arms thoroughly after handling this material.

Clean up spills immediately.

OTHER PROTECTIVE EQUIPMENT:

In laboratories, wear lab coat or other protective clothing with long sleeves. In production areas, wear protective clothing that is laundered or discarded after each use. An eye wash station should be available.

9. PHYSICAL AND CHEMICAL PROPERTIES

MATERIAL SAFETY DATA SHEET

APPEARANCE:

White to off-white crystalline powder.

FLASH POINT:

Expected to be greater than 55 degrees C.

AUTOIGNITION TEMP:

Not determined.

LOWER EXPLOSIVE LIMIT:

Not applicable solids.

UPPER EXPLOSIVE LIMIT:

Not applicable solids.

MELTING POINT:

115 to 117 degrees C.

BOILING POINT:

Not determined.

VAPOUR DENSITY:

Expected to be negligible.

VAPOUR PRESSURE:

Expected to be negligible.

EVAPORATION RATE:

Expected to be negligible.

VOLATILE COMPONENTS (%):

None expected.

VISCOSITY:

Not applicable for solids.

PH OF AQUEOUS SOLUTIONS:

Not determined.

RELATIVE DENSITY:

Not determined.

CONDUCTIVITY:

Not applicable for solids.

OCTANOL/WATER DISTRIBUTION COEFFICIENT:

KOW (26.3 micrograms/l) = 106 (pH 5), 528 (pH 7), 1040 (pH 9)

KOW (263 micrograms/l) = 85.7 (pH 5), 549 (pH 7), 1260 (pH 9)

DISSOCIATION CONSTANT (pKA):

7.8

SOLUBILITY:

Soluble in many polar solvents.

Insoluble in water.

OXYGEN BALANCE:

This material is considered to be of low energy hazard potential based on oxygen balance calculated as minus 224.

TRAIN FIRE TEST:

Since this material has not been train fire tested, it should be assumed to support combustion in bulk quantities.

DUST EXPLOSIVITY:

Classification: Not determined.

Minimum explosive concentration (grams/cubic metre): Not determined.

Minimum ignition temperature - cloud (degrees C): Not determined.

Minimum ignition temperature - layer (degrees C): Not determined.

Minimum oxygen concentration (% v/v): Not determined.

Explosion characteristics:

Pmax (bar): Not determined.

dP/dT (bar/second): Not determined.

Kst (bar metre/second): Not determined.

St class: Not determined.

MATERIAL SAFETY DATA SHEET

DUST ELECTRICAL PROPERTIES:

Minimum ignition energy (mjoules): Not determined.
Resistivity at ambient humidity (ohm metre): Not determined.
Charge decay time at ambient humidity (seconds): Not determined.
Resistivity at low humidity (ohm metre): Not determined.
Charge decay time at low humidity (seconds): Not determined.

10. STABILITY AND REACTIVITY

CONDITIONS TO AVOID:

Avoid direct sunlight, conditions that might generate heat and dispersion as a dust cloud.

INCOMPATIBILITY:

None known.

STABILITY:

This material is expected to be stable.

THERMAL STABILITY:

Capillary tube test:

Thermal degradation can be expected at temperatures greater than 200 degrees C.

Differential scanning calorimetry:

Not determined.

Accelerating rate calorimeter:

Not determined.

HAZARDOUS POLYMERIZATION:

Not expected to occur.

HAZARDOUS DECOMPOSITION PRODUCTS:

Not identified.

FIRE AND EXPLOSION HAZARDS:

Not identified. As with many organic dusts, explosions might result when excessive dust concentrations are present.

11. TOXICOLOGICAL INFORMATION

ORAL TOXICITY:

The oral LD50 in rats was greater than 8000 mg/kg. No lethality occurred in rats after administration of a single oral dose of 8000 mg/kg.

INHALATION TOXICITY:

Not determined for this material.

SKIN IRRITATION:

This material was classified as a non irritant to rabbit skin. No signs of irritation occurred up to 3 days after direct application in rabbits for 4 hours.

EYE IRRITATION:

This mixture was classified as a minimal irritant in rabbit eyes. Conjunctival redness occurred up to 1 day after direct application in rabbits. Eyes appeared normal 2 days after treatment.

SENSITISATION:

This material was classified as a mild sensitiser to guinea pig skin. Adverse skin reactions or irritation occurred in 4 out of 20 guinea pigs used to test for allergic reaction or sensitisation (maximisation test).

MUTAGENICITY:

This material was not mutagenic in bacteria (Ames Test) or other genotoxicity tests.

CARCINOGENICITY:

This material is not listed as a carcinogen by SB, IARC, NTP or US OSHA.

MATERIAL SAFETY DATA SHEET

There was no evidence of a carcinogenic effect in chronic studies with rats or mice.

REPRODUCTIVE EFFECTS:

This material did not produce teratogenic effects (birth defects) or adverse effects on male or female reproduction in studies with rats.

OTHER EFFECTS:

This material exhibits an effect on the cardiovascular system by lowering blood pressure.

12. ECOLOGICAL INFORMATION

ACUTE AQUATIC EFFECTS:

48-hour Daphnia EC50 = greater than 2.8 mg/l.

48-hour Daphnia no-observed-effect-concentration less than 0.37 mg/l.

96-hour Bluegill EC50 = 0.99 mg/l.

96-hour Bluegill no-observed-effect-concentration less than 0.43 mg/l.

BIODEGRADATION:

Not determined.

ACTIVATED SLUDGE RESPIRATION INHIBITION (OECD 209 PROTOCOL):

EC50 = 98.4 mg/l (draft results).

SOIL ADSORPTION:

Not determined.

OTHER EFFECTS:

None.

13. DISPOSAL CONSIDERATIONS

Collect for recycling or recovery, if possible. Dispose of material on site in a licensed chemical incinerator, if allowed by the incinerator license or permit. If no on-site incinerator is available, dispose of material in a licensed commercial chemical incinerator.

14. TRANSPORT INFORMATION

FOR AIR TRANSPORT (IATA REQUIREMENTS):

Proper Shipping Name: NOT RESTRICTED

Technical Name (for n.o.s., not otherwise specified): Not applicable

UN/Identification Number: Not applicable

Class/Division: Not applicable

Sub Risk: Not applicable

Packing Group: Not applicable

RQ (Reportable Quantity): Not applicable

Emergency Response Guide Number: Not applicable

FOR MARITIME TRANSPORT (IMDG REQUIREMENTS):

Proper Shipping Name: NOT RESTRICTED

Technical Name (for n.o.s., not otherwise specified): Not applicable

UN/Identification Number: Not applicable

Class: Not applicable

Sub Risk: Not applicable

Packing group: Not applicable

IMDG page number: Not applicable

MFAG number: Not applicable

EMS number: Not applicable

Marine Pollutant: Not applicable

Emergency Response Guide Number: Not applicable

FOR UNITED STATES GROUND TRANSPORT (DOT REQUIREMENTS):

MATERIAL SAFETY DATA SHEET

Proper Shipping Name: NOT RESTRICTED
Technical Name (for n.o.s., not otherwise specified): Not applicable
UN/Identification Number: Not applicable
Class/Division: Not applicable
Sub Risk: Not applicable
Packing Group: Not applicable
RQ (Reportable Quantity): Not applicable
Emergency Response Guide Number: Not applicable

FOR EUROPEAN GROUND TRANSPORT (ADR/RID/ROAD/RAIL REQUIREMENTS):
Not determined. Hazards according to ADR/RID requirements not identified.

EMERGENCY INFORMATION:
HAZCHEM code: Not applicable.
TREM CARD number: Not applicable.

15. REGULATORY INFORMATION

EUROPEAN UNION CLASSIFICATION AND LABELLING REQUIREMENTS:
No European Union labelling requirements.

16. OTHER INFORMATION

HAZARD LABEL:
**** NOT CLASSIFIED AS A SIGNIFICANT FIRE HAZARD ****
**** NO FIRE HAZARD IDENTIFIED ****
**** NOT CLASSIFIED AS A SIGNIFICANT ENVIRONMENTAL HAZARD ****
** TARGET ORGAN- PHARMACEUTICAL AGENT- MAY REDUCE BLOOD PRESSURE.
** SYMBOL: NOT REQUIRED. (NN)

REFERENCES:
SB HAZARD DETERMINATION

OTHER INFORMATION:
IF HMIS RATINGS ARE USED AT YOUR SITE, USE THE FOLLOWING:
HEALTH = 2 FIRE= 0 REACTIVITY = 0

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0003

SPECIFICATIONS AND ANALYTICAL METHODS FOR DRUG SUBSTANCE

b. Analytical Methods

(1) Description: A white to off-white powder.

(2) Identification:

- **Infrared:** The infra red spectrum of the sample run as a KBr disc corresponds to that of reference material (see the scan on the following page).

SPECIFICATIONS AND ANALYTICAL METHODS FOR DRUG SUBSTANCE

b. Analytical Methods

(2) Identification: Continued

- **TLC:** The R_f of the main spot for the sample corresponds to an equally concentrated spot of reference material, similarly measured utilizing the method listed below.

Standard and Sample Preparation:

Dissolve 25 mg of carvedilol reference standard or sample in 1.0 mL of acetone.

Procedure

Score a TLC plate (HPTLC silica gel 60 F₂₅₄) which has been dried overnight at 80°C, and cooled in a desiccator. Spot 1 μ L and 2 μ L of both standard and sample preparations (i.e. 25 μ g and 50 μ g).

Place the spotted plate in a chromatography chamber, lined with filter paper and containing the following solvent system.

Isopropanol	50.0 mL
Acetic acid-n-butylester	30.0 mL
Water	15.0 mL
Concentrated Acetic Acid	5.0 mL

Equilibrate with the solvent vapors for 10 minutes. Allow solvent to rise to the 10 cm line, remove plate from the chamber, and dry at 70°C until solvent is no longer detectable (30 minutes). Observe plate under short wave (254 nm) and long wave (365 nm) UV light, noting size and location of the spots. Allow the plate to cool to room temperature, and place in an iodine chamber containing a liberal sprinkling of iodine crystals. After maximum detection sensitivity is reached, (approximately 10 minutes), remove the plate from the chamber and photograph. The photograph should approximate the visual assessment of the plate.

SPECIFICATIONS AND ANALYTICAL METHODS FOR DRUG SUBSTANCE

b. Analytical Methods

(3) Assay (HPLC):

This method is equivalent to Analytical Method 3045B given on pages 000268-000279 but has been reformatted for routine use. The validation for this method is contained in Analytical Chemistry Report 3046B given on pages 000280-000300.

Mobile Phase:

Mix water, acetonitrile and trifluoroacetic acid (77:23:0.1). Filter and degas.

Standard and Sample Preparation:

Accurately weigh approximately 50 mg of standard and sample into separate 50 mL volumetric flasks. Dissolve and dilute to volume with mobile phase and mix. Dilute 10 mL of each solution to 50 mL with mobile phase. Dilute 5 mL of each solution to 50 mL with mobile phase (0.02 mg/mL).

System Suitability (USP Methods):

The following system suitability requirements must be met prior to reporting results:

- The relative standard deviation of the reference peak area for five replicate injections is not greater than 2.0%.
- The tailing factor of the reference standard peak at 5% of the peak height is not greater than 2.0.
- The number of theoretical plates is not less than 5000.

SPECIFICATIONS AND ANALYTICAL METHODS FOR DRUG SUBSTANCE

b. Analytical Methods

(3) Assay (HPLC): Continued

Chromatography:

Inject 20 microliters of each of the standard and sample preparations onto a liquid chromatograph under the following conditions:

Column: Supelco Suplex pKb-100, 5 microns, 15 cm x 4.6 mm
Flow Rate: 1.0 mL/min
Detection: UV, 240 nm
Temperature: Ambient

Approximate retention time: 20.0 min.

Alternate equipment and conditions which produce equivalent results can be used.

Calculation:

Standard Factor (SF) = $\frac{\text{wt. of ref. std. (mg)} \times P}{\text{peak area of ref. std}}$

% SK&F 105517 (w/w) = $\frac{\text{peak area of spl.} \times \text{SF} \times 100}{\text{wt. spl (mg)} \times [100 - (\text{KF (\%w/w)} + \text{resid. solv. (\%w/w)})]}$

P = % purity of the reference sample



SPECIFICATIONS AND ANALYTICAL METHODS FOR DRUG SUBSTANCE

b. Analytical Methods

(4) *Related Substances (HPLC):*

This method is equivalent to Analytical Method 3045B given on pages 000268-000279 but has been reformatted for routine use. The validation for this method is contained in Analytical Chemistry Report 3046B given on pages 000280-000300.

Mobile Phase

Solvent A: 100% acetonitrile, 0.1% trifluoroacetic acid (TFA)
Solvent B: 100% water, 0.1% trifluoroacetic acid
Solvent C: 23% acetonitrile, 77% water, 0.1% TFA

Sample Preparation

Accurately weigh approximately 50 mg of sample into a 50 mL volumetric flask. Dissolve and dilute to volume with solvent C and mix (1 mg/mL; concentrated impurity profile solution).

Dilute 2 mL of the impurity profile solution to 100 mL with solvent C and mix (0.02 mg/mL; dilute assay solution).

System Suitability Preparation:

- (i) Accurately weigh 3 mg of [REDACTED] into a 50 mL volumetric flask. Dissolve in and dilute to volume with solvent C. Mix well. Further dilute this solution 4.0 mL to 10 mL with solvent C and mix.
- (ii) Accurately weigh 3 mg of [REDACTED] into a 50 mL volumetric flask. Dissolve in and dilute to volume with solvent C. Mix well. Further dilute this solution 2.0 mL to 50 mL with solvent C and mix.

SPECIFICATIONS AND ANALYTICAL METHODS FOR DRUG SUBSTANCE

b. Analytical Methods

(4) Related Substances (HPLC): Continued

System Suitability Preparation: (Continued)

- (iii) Accurately weigh 50 mg of [REDACTED] reference standard into a 50 mL volumetric flask. Add about 30 mL of solvent C and sonicate to dissolve. Accurately pipette 4 mL of [REDACTED] solution (i) and 4 mL of [REDACTED] solution (ii) into this volumetric flask. Dilute to volume with solvent C and mix. The resulting system suitability solution represents a 1 mg/mL sample of [REDACTED] containing 0.2% w/w [REDACTED] and 0.2% w/w [REDACTED].

A solvent blank should also be injected.

System Suitability (USP Methods):

The following system suitability requirements must be met prior to reporting results:

- The resolution factor between [REDACTED]
- The retention time for the [REDACTED]
- The retention time for the [REDACTED]

SPECIFICATIONS AND ANALYTICAL METHODS FOR DRUG SUBSTANCE

b. Analytical Methods

(4) Related Substances (HPLC): Continued

Chromatography

Inject 20 microliters of both sample preparations onto a liquid chromatograph under the same conditions as described in the Assay (HPLC).

<u>Gradient</u>		
<u>Time (min)</u>	<u>% A</u>	<u>% B</u>
Initial	23	77
20	23	77
33	38	62
45	38	62
55	55	45
65	55	45
68	23	77

Note: the gradient must not begin before elution 

Approximate retention times:

Alternate equipment and conditions which produce equivalent results can be used.

SPECIFICATIONS AND ANALYTICAL METHODS FOR DRUG SUBSTANCE

b. Analytical Methods

(4) Related Substances (HPLC): Continued

Calculation

$$\% \text{ Area Individual Related Substance (RS)} = \frac{A_i \times 100}{A_t \times 50 (A_m)}$$

Limit:

Where:

A_i = The peak area of each individual RS in the impurity profile solution (1 mg/mL)

A_m = The area of the [REDACTED] peak in the dilute assay solution (0.02 mg/mL)

A_t = The sum of the peak areas for each individual RS in the concentrated impurity profile solution, excluding any peak areas due to the solvent front.

(5) Water Content (Karl Fischer):

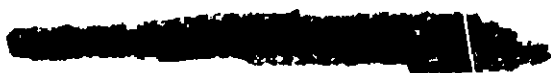
Add sufficient methanol to cover the electrodes of the titration vessel. Titrate with Karl Fischer reagent until all the water has been removed. Disregard this number. Accurately weigh 1 g of sample and transfer to the titration vessel, stirring continuously until the sample dissolves. Titrate the water in the sample with Karl Fischer reagent.

Calculation:

$$\% \text{ water content (w/w)} = \frac{X \text{ (mg/mL)} \times Y \text{ (mL)} \times 100}{\text{Sample wt (g)} \times 1000 \text{ (mg/g)}}$$

X = water equivalent in mg per mL of KF reagent

Y = mL of water in the sample



SPECIFICATIONS AND ANALYTICAL METHODS FOR DRUG SUBSTANCE

b. Analytical Methods

(6) *Residual Solvent (GC)*

This method is equivalent to Analytical Method 3054 given on pages 000301-000305. The validation for this method is contained in Analytical Chemistry Report 3052 given on pages 000306-000314.

Standard Preparation

Accurately weigh about 1 mL each of methanol, isopropanol and toluene into separate 100 mL volumetric flasks. Dilute to volume with DMSO and mix. Dilute 5 mL of each solution to 50 mL with DMSO. Further dilute this solution 5 mL to 50 mL with internal standard solution and mix.

Internal Standard Preparation

Accurately weigh about 1 mL of n-butanol into a 100 mL volumetric flask. Dilute to volume with DMSO and mix. Further dilute 10 mL of this solution to 1000 mL with DMSO and mix.

Sample Preparation

Accurately weigh about 500 mg of sample into a 10 mL volumetric flask. Dilute to volume with internal standard solution and mix.

Chromatography

Inject 2 microliters of the standard and sample preparations onto a gas chromatograph under the following conditions:

Column:	DB-624 (J&W), fused silica, 30 m x 0.32 mm
Carrier Gas:	Helium
Split Flow (waste):	50 mL/min
Injector Temperature:	160°C
Injector Port:	Glassliner with quartz wool to retain solids
Column Temperature Program:	40°C for 20 min, then 25°C/min to 180°C, hold at 180°C for 5 min.
Detector:	Flame Ionization
Detector Temperature:	260°C

SPECIFICATIONS AND ANALYTICAL METHODS FOR DRUG SUBSTANCE

b. Analytical Methods

(6) Residual Solvent (GC): Continued

Alternate equipment and conditions which produce equivalent results can be used.

Calculation

$$R = \frac{\text{Area of int. std.} \times \text{wt. of ref. std. (mg)} \times D_1}{\text{Area of ref. std.}}$$

$$D_1 = \text{Dilution factor of std. (1/100} \times \text{1/100)}$$

$$\% \text{ resid. solv. (w/w)} = \frac{\text{Solvent area in sample} \times R \times 100}{\text{Area of int. std.} \times \text{wt. of sample (mg)} \times D_2}$$

$$D_2 = \text{Dilution factor of sample (1/10).}$$

Calculation

Limit:

(7) Residue on Ignition (sulfated ash):

USP (281)

(8) Heavy Metals

USP (231); Method II

SPECIFICATIONS AND ANALYTICAL METHODS

a. Specifications

1. Product Specifications for Carvedilol 25 mg Tablets

TEST	SPECIFICATION
Description	
Identification	
- TLC	
- HPLC	
Assay (HPLC)	
Degradation Products (Total of all)	
Dissolution	
Content Uniformity	

000101

SPECIFICATIONS AND ANALYTICAL METHODS

a. Specifications

2. Product Specifications for Carvedilol 12.5 mg Tablets

TEST	SPECIFICATION
Description	
Identification	
- TLC	
- HPLC	
Assay (HPLC)	
Degradation Products (Total of all)	
Dissolution	
Content Uniformity	

SPECIFICATIONS AND ANALYTICAL METHODS

b. Analytical Methods

1. Description

[REDACTED]

SPECIFICATIONS AND ANALYTICAL METHODS

b. Analytical Methods

2. Identity Method by Thin Layer Chromatography

Summary

A Thin Layer Chromatography (TLC) procedure has been developed to determine the presence or absence of carvedilol in tablet formulations. The analysis is performed on a silica gel stationary phase using a mobile phase consisting of butanol, ethyl acetate, acetic acid and water. The method is specific for carvedilol with the drug substance being resolved from excipients, known degradation products and process impurities.

Validated Applications and Sample Requirements

This method has been validated for carvedilol 12.5 mg and 25 mg tablets. Ten tablets are required for each sample preparation.

Safety Precautions

Refer to the Material Safety Data Sheet for current information regarding the toxicity of carvedilol to humans. Acetic acid, butanol, ethyl acetate and methanol are toxic. Avoid skin contact and breathing vapors. Routine laboratory safety practices must be followed ensuring all mobile phase preparation and plate development is carried out in a vented fume hood.

Equipment (as stated below or equivalent)

Balance:	Mettler AE 163
Centrifuge:	IEC Model HN-SII Centrifuge, top speed of 2400 rpm
Centrifuge Tubes:	Becton Dickinson, Falcon 2059, Blue Max , 10 mL polypropylene graduated conical tube with cap, 17 mm X 100 mm.
Developing Chamber:	Camag, Twin Trough Chamber 12 cm X 12 cm fitted with a stainless steel lid.
Filter Paper:	Whatman N ^o 4. Qualitative Filter Paper.

Disposable Pipettes:	Microcaps, Drummond Scientific, 2 μ L
Thin Layer Chromatograph Plates:	EM Science, Merck precoated Silica Gel 60F ₂₅₄ , 250 micron, 5cm X 10cm.
Ultrasonic Bath:	Branson 52 Sonicator
Ultraviolet Light Source:	Ultraviolet Products, Inc.
Forced Air Dryer:	HeJet Model HI-700

Reagents (as stated below or equivalent)

Methanol:	HPLC Grade
Ethyl Acetate:	HPLC Grade
Butanol (n-butyl alcohol) :	AR Grade
Glacial Acetic Acid:	AR Grade
Water:	Milli-Q, HPLC Grade
Carvedilol:	Analytical Standard

Solutions

Mobile Phase: Add 40 mL of butanol and 40 mL ethyl acetate to a 100 mL capacity stoppered measuring cylinder. Pipette in 15.0 mL of glacial acetic acid followed by 5.0 mL of water. Replace the stopper and shake the solution to mix the components. Prepare fresh mobile phase each day.

Standard Preparation

Weigh approximately 25 mg of carvedilol analytical standard into a 10 mL volumetric flask. Add 1 mL of water to the sample, fill the flask to approximately half capacity with methanol and sonicate until the carvedilol is completely in solution. Mix well and make up to volume with methanol.

Sample Preparation

Weigh ten carvedilol tablets and calculate the average tablet weight. Crush the tablets in a suitable vessel. Weigh out the equivalent of the average tablet weight and place into a 10 mL centrifuge tube. Pipette in 1 mL of water and shake well for approximately 30 seconds. Pipette in 9.0 mL of methanol, stopper the tube and shake by hand for 30 seconds. Place the centrifuge tube into the centrifuge and balance by preparing a similar tube containing only methanol. Centrifuge at 2400 rpm for 10 minutes. Use the supernatant layer for the TLC determination.

Procedure

Prepare mobile phase as directed in the solutions section of the method and add to each trough of the development chamber, 0.5 cm depth of mobile phase. Use Whatman N^o 4 qualitative filter papers to line each side of the tank and ensure they become completely impregnated with mobile phase.

Approximately 1 cm from the bottom of the TLC plate apply a 2 µL aliquot each of the standard and sample solutions, separating the spots by approximately 1.5 cm. Allow the spots to air dry for at least 10 minutes, then dry the plate utilizing a hot forced air dryer for approximately 10-15 seconds before placing the TLC plate into the mobile phase. Cover the development chamber and allow the solvent to ascend to within 2 cm of the top of the plate. Remove the plate at this point (after approximately 30-40 minutes) and allow to air dry in the fume hood for at least one minute. A forced air dryer may again be employed to completely dry the plate prior to viewing under a 254 nm light source.

Visualize the spots under a 254 nm light source and heavily mark them by scratching away the silica with a pencil. Photocopy the plate with a dark background and label the spots.

Calculations

1. Chromatographic Retardation Factor, R_f :

$$R_f = \frac{\text{distance traveled by the spot from origin (cm)}}{\text{distance from origin to the solvent front (cm)}}$$

The following criterion must be met for the carvedilol spot on the thin layer chromatography plate (see Figure 6.1):

R_f must be between 0.40 - 0.60.

If the system suitability condition is not met, prepare fresh mobile phase and/or clean the developing chamber.

2. Chromatographic Identity Analysis:

The identity of an active tablet is confirmed when the spot present in the sample solution has an R_f corresponding to the R_f of the carvedilol standard spot.

Figure 6.1: Depiction of Thin Layer Chromatography Developments of Carvedilol Standard, Placebo, 25 mg Tablet and Known Degradation Products

The following figure is a depiction of the thin layer chromatography plates from a 25 mg tablet sample solution, a placebo solution to match the sample solution, a standard solution (2.5 mg/mL) and a degraded sample (lot #UB9036-T1A), thermally stressed at 80°C for three months, all prepared as specified in the method.

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SPECIFICATIONS AND ANALYTICAL METHODS

b. Analytical Methods

3. Identity Method by High Performance Liquid Chromatography

See Stability Indicating Assay Method described in Section 6.b.(4).

SPECIFICATIONS AND ANALYTICAL METHODS

b. Analytical Methods

4. Stability Indicating Assay by High Performance Liquid Chromatography

Summary

A stability indicating HPLC assay procedure has been developed for carvedilol in tablet formulations. This method is also used for identification of carvedilol in the 12.5 mg and 25 mg tablet formulations. The analysis is performed using a C-8 column at 40°C and UV detection wavelength set at 240 nm. Because slight changes in the acetonitrile percentage in the mobile phase make a critical difference in the retention time and peak shape of the carvedilol peak, an isocratic two pump system consisting of low (35%) and high (45%) percentage organic mobile phases on individual pumps is utilized. The flow rates of the two pumps are adjusted in order to maintain a k' for the carvedilol peak between 30 and 35 under the conditions specified in this method. As an alternative, a procedure using a single pump system with manual adjustment of mobile phase composition to meet system suitability criteria is presented.

Validated Applications and Sample Requirements

This method has been validated for carvedilol 12.5 mg and 25 mg tablets. Ten tablets are required for each composite sample preparation. One tablet is required for each single tablet assay preparation.

Safety Precautions

Refer to the Material Safety Data Sheet for current information regarding the toxicity of carvedilol to humans. Acetonitrile, hydrochloric acid, methanol, phosphoric acid and triethylamine are toxic. Avoid touching skin or breathing vapor. Routine laboratory safety practices must be followed.

Equipment (as stated below or equivalent)

Balance:	Mettler AE 163
Centrifuge:	IEC Model HN-SII Centrifuge, top speed of 2400 rpm
Centrifuge Tubes:	Becton Dickinson, Falcon 2070, Blue Max, 50 mL polypropylene graduated conical tube with cap (stock #2070)
Chromatograph:	Isocratic, two pump system with column oven, variable wavelength UV detector, and general purpose integrator
Column:	Type L7 as described in the USP XXII/NF XVII, 5 cm, page 1567. The following columns have been determined to be suitable: Keystone (10853V), Keystone (100477D), Beckman (002) and J&W Scientific (8081011)
Data Acquisition System:	A general purpose chromatography integrator
Filters:	Alltech 0.2 μm Nylon 66 membrane filter (stock #2034) Gelman Acrodisc-CR PTFE 25 mm, 0.45 μm filter (product #4219)
Mechanical Shaker:	Ederbach Benchtop Shaker
pH Meter:	Orion Research Model SA 520
Stir Plate:	Corning Stirrer/Hotplate Model PC-320
Ultrasonic Bath:	Bransonic 52 Sonicator

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Reagents (as stated below or equivalent)

Acetonitrile:	HPLC grade
1 M Hydrochloric Acid:	Reagent Grade, Dilut-it concentrate for 1.0 M solution or Reagent Grade, Concentrated Acid
Methanol:	HPLC Grade
85% Phosphoric Acid:	HPLC Grade
Potassium Phosphate, Monobasic (KH ₂ PO ₄):	Reagent grade
Water:	Milli-Q, HPLC grade
Carvedilol:	Analytical Standard
Sodium Dodecyl Sulfate (SDS):	Reagent Grade
Triethylamine (TEA):	HPLC grade

Solutions

0.01 M Potassium Phosphate and 0.14 M Triethylamine Solution: Weigh approximately 0.7 grams of potassium phosphate, monobasic and transfer to a 1-liter beaker. Add 500 mL of water using a graduated cylinder, cover with plastic wrap or a watch glass, and sonicate until dissolved. Add 10 mL of triethylamine using a graduated cylinder while stirring on a mechanical stir plate. Adjust the pH of the solution to 3.00 ± 0.10 by dropwise addition of 85% phosphoric acid while stirring (originally the pH of the solution is approximately 10.5). Approximately 5 mL of 85% phosphoric acid will be required to adjust the pH of this volume of solution.

Mobile Phase A: Weigh approximately 1.04 grams of sodium dodecyl sulfate and transfer to a 2-liter volumetric flask. Add 150 mL of the potassium phosphate/triethylamine solution using a graduated cylinder. Shake the mixture well by hand for about one minute, sonicate until dissolved, and then allow the contents of the flask to return to room temperature. Add 700 mL of acetonitrile, and then dilute to volume with water. Mix thoroughly by hand, filter through a 0.2 µm Nylon 66 filter, and allow to return to room temperature. Final concentrations of KH₂PO₄, TEA, and SDS are

approximately 0.75 mM, 10.4 mM, and 1.8 mM, respectively, and the organic content is 35%.

Mobile Phase B: Weigh approximately 1.04 grams of sodium dodecyl sulfate and transfer to a 2-liter volumetric flask. Add 150 mL of the potassium phosphate/triethylamine solution using a graduated cylinder. Shake the mixture well by hand for about one minute, sonicate until dissolved, and then allow the contents of the flask to return to room temperature. Add 900 mL of acetonitrile, and then dilute to volume with water. Mix thoroughly by hand, filter through a 0.2 μ m Nylon 66 filter, and allow to return to room temperature. Final concentrations of KH_2PO_4 , TEA, and SDS are approximately 0.75 mM, 10.4 mM, and 1.8 mM, respectively, and the organic content is 45%.

Mobile Phase C: Mobile Phase C is for use with a single pump HPLC system. To a 2 liter volumetric flask, add 1.68 liters of Mobile Phase A and dilute to volume with Mobile Phase B. Mix thoroughly by hand and allow to return to room temperature. Organic content is 36.6%.

HPLC Wash Solution: Add 500 mL of acetonitrile and 500 mL of water to a 1-liter flask. Mix thoroughly by hand, filter through a 0.2 μ m Nylon 66 filter, and allow to return to room temperature. (The HPLC wash solution is to be used to wash the column after the run is complete.)

1 M Hydrochloric Acid: Prepare 1 M hydrochloric acid solution according to the instructions on the Dilut-it package. To prepare the 1 M hydrochloric acid solution from concentrated acid, add approximately 800 mL of water to a 1-liter volumetric flask. Add 83 mL of concentrated hydrochloric acid and mix well by hand. Dilute to volume with water and mix well by hand.

Extraction Solvent: Fill a 2-liter volumetric flask to approximately 50% capacity with methanol. Add 200 mL of 1 M hydrochloric acid and mix. Dilute the solution to volume with methanol and mix thoroughly by hand.

Standard Preparation

Standard Stock Solution (0.25 mg/mL): Prepare standard in duplicate. Accurately weigh approximately 25 mg of carvedilol analytical standard into a 100 mL volumetric flask. Add 10 mL of water to the flask using a graduated cylinder, shake by hand for about 30 seconds, and sonicate for fifteen minutes. Add approximately 70 mL of extraction solvent to the flask, shake by hand for about 30 seconds, sonicate for fifteen minutes, and then allow the contents of the flask to return to room temperature. Dilute to volume with extraction solvent and mix well by hand. Concentration of the resulting standard stock solution is 0.25 mg/mL.

Working Standard Solution: Further dilute each standard stock solution (0.25 mg/mL) by pipetting 10.0 mL to a 200 mL volumetric flask, add 70 mL of methanol followed by

100 mL of water and dilute to volume with methanol. Mix well by hand. Final concentration of carvedilol is approximately 0.0125 mg/mL. During the assay, the HPLC vials should be tightly sealed.

Sample Preparation

Prepare samples in duplicate. Place the tablet or tablets to be assayed into a volumetric flask of the appropriate size (See Dilution Table below). Add the designated quantity of water to the flask using a graduated cylinder, shake by hand for about 30 seconds, and sonicate for fifteen minutes. Add the approximate designated quantity of extraction solvent to the flask, shake by hand for about 30 seconds, sonicate for fifteen minutes, shake on a mechanical shaker for thirty minutes, and then allow the contents of the flask to return to room temperature. Dilute to volume with extraction solvent and mix well by hand. The concentration of the resulting solution is 0.25 mg/mL. Transfer 50 mL of the resulting solution to a centrifuge tube. Centrifuge at 2400 rpm for ten minutes. Pipette 10.0 mL of the supernatant to a 200 mL volumetric flask. Add 70 mL of methanol followed by 100 mL of water, dilute to volume with methanol and mix well by hand. Filter the final solution with a 20 mL disposable syringe fitted with a Gelman Acrodisc-CR disposable filter, 0.45 μ m porosity and discard the first 5 mL of filtrate. Transfer an aliquot of the filtrate to an HPLC vial for injection and tightly seal the vial. Final concentration of carvedilol is 0.0125 mg/mL.

Dilution Table

Strength	12.5 mg	12.5 mg	25 mg	25 mg
Number of Tablets for Assay	1	10	1	10
Size of Volumetric Flask	50 mL	500 mL	100 mL	1 Liter
Volume of Water	5 mL	50 mL	10 mL	100 mL
Approximate Volume of Extraction Solvent	35 mL	350 mL	70 mL	700 mL

Chromatographic Conditions

Chromatograph:

Column Temperature:	40°C
Flow Rate for Mobile Phase A:	Approximately 0.84 mL/min adjusted as required to meet system suitability
Flow Rate for Mobile Phase B:	Approximately 0.16 mL/min adjusted as required to meet system suitability
Flow Rate for Single Pump System using Mobile Phase C:	1.0 mL/min
UV Detection Wavelength:	240 nm
Injection Volume:	25 µL
Analysis Time:	30 min

System Suitability

The following criteria must be met for the carvedilol peak in chromatograms recorded as part of this determination (see sample chromatogram):

1. Using a computerized data acquisition system, k' must be between 30 and 35 when t_0 is taken as the first deviation off the baseline. For non-computerized data acquisition systems where t_0 cannot be accurately calculated, use t_0 as the top of the first peak. The k' for non-computerized systems must be between 21 and 26.
2. The tailing factor at 5% peak height must be less than 2.
3. The number of theoretical plates must be greater than 1200.
4. The relative standard deviation of the response factors for the carvedilol peak in five replicate injections of the working standard solution should not be more than 2%.

In a two pump HPLC system, the ratio of the flow rates of Mobile Phases A and B may need to be adjusted to meet system suitability, but the total flow rate for the combined mobile phases must be 1.0 mL/min. For a single pump system, Mobile Phase C may need to be adjusted with either Mobile Phase A or B to meet system suitability. Note that small changes in the flow rates of the individual pumps, or small additions of Mobile Phases A or B to Mobile Phase C, result in large changes in the capacity factor. Calculations for k' , the tailing factor, the number of theoretical plates and the relative standard deviation are described in the current USP.

Procedure

Inject standard and sample solutions and record the response factor of the peak of interest.

Calculations

1. Response Factor, K:

$$K = \frac{W_s}{A_s}$$

where:

W_s = Weight of the analytical standard (carvedilol) in mg

A_s = Area response of a single standard injection

2. Quantification of Carvedilol in Tablet Formulations:

$$A_u \times \frac{K_{av}}{N} \times \frac{D_s}{D_u} \times P = \text{mg carvedilol/tablet}$$

where:

A_u = Average area response of the sample

K_{av} = Average response factor over all injections of standard

N = Number of tablets used for sample preparation

D_s = Dilution factor for the standard (1/100 X 10/200 = 0.0005)

D_u = Dilution factor for the sample
(1/50 X 10/200 = 0.001 for single 12.5 mg tablet,
1/500 X 10/200 = 0.0001 for composite 12.5 mg tablet,
1/100 X 10/200 = 0.0005 for single 25 mg tablet or
1/1000 X 10/200 = 0.00005 for composite 25 mg tablet)

P = Purity of the analytical standard (decimal)

3. Identification of Carvedilol

The presence of carvedilol in a tablet is confirmed if the peak present in the sample solution has a retention time corresponding to the retention time of the peak present in the standard solution $\pm 5\%$.

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SPECIFICATIONS AND ANALYTICAL METHODS

b. Analytical Methods

5. Degradation Product Profiling by High Performance Liquid Chromatography

Summary

A degradation product profiling procedure by HPLC has been developed for carvedilol in tablet formulations. This method is a high sensitivity variation of the stability indicating assay method, and therefore, uses the same chromatographic system and conditions (with the exception of injection volume). The analysis is performed using a C-8 column at 40°C and UV detection wavelength set at 240 nm. Because slight changes in the acetonitrile percentage in the mobile phase make a critical difference in the retention time and peak shape of the carvedilol peak, an isocratic two pump system consisting of low (35%) and high (45%) percentage organic mobile phases on individual pumps is utilized. The flow rates of the two pumps are adjusted in order to maintain a k' for the carvedilol peak between 30 and 35 under the conditions specified in this method. As an alternative, a procedure using a single pump system with manual adjustment of mobile phase composition to meet system suitability criteria is presented.

Validated Applications and Sample Requirements

This method has been validated for carvedilol 12.5 mg and 25 mg tablets. Ten tablets are required for each composite sample preparation.

Safety Precautions, Equipment, Reagents, Solutions

Refer to Stability Indicating Assay Method

Standard Preparation

Standard Stock Solution (0.25 mg/mL): Prepare standard in duplicate. Accurately weigh approximately 25 mg of carvedilol analytical standard into a 100 mL volumetric flask. Add 10 mL of water to the flask using a graduated cylinder, shake by hand for about 30 seconds, and sonicate for fifteen minutes. Add approximately 70 mL of extraction solvent to the flask, shake by hand for about 30 seconds, sonicate for fifteen minutes, and then allow the contents of the flask to return to room temperature. Dilute to volume with extraction solvent and mix well by hand. Concentration of the resulting standard stock solution is 0.25 mg/mL.

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Working Standard Solution: Pipette 1.0 mL of the standard stock solution (0.25 mg/mL) into a 200 mL volumetric flask, add 70 mL of extraction solvent followed by 100 mL of purified water and dilute to volume with extraction solvent. Mix well by hand. Final concentration of carvedilol is approximately 1.25 µg/mL. During the assay, the HPLC vials should be tightly sealed.

Sample Preparation

Sample Solution for 12.5 mg Strength: Place ten tablets into a 500 mL volumetric flask. Add 50 mL of purified water to the flask using a graduated cylinder, shake by hand for about 30 seconds, and sonicate for fifteen minutes. Add approximately 350 mL of extraction solvent to the flask, shake by hand for about 30 seconds, sonicate for fifteen minutes, shake on a mechanical shaker for thirty minutes, and then allow the contents of the flask to return to room temperature. Dilute to volume with extraction solvent and mix well by hand. The concentration of the resulting solution is 0.25 mg/mL. Pipette 25.0 mL of this solution into a 50 mL volumetric flask, dilute to volume with purified water and mix well by hand. Filter the sample solution with a 20 mL disposable syringe fitted with a Gelman Acrodisc-CR disposable filter, 0.45 µm porosity and discard the first 5 mL of filtrate. Transfer an aliquot of the filtrate to an HPLC vial for injection and tightly seal the vial.

Sample Solution for 25 mg Strength: Place ten tablets into a one liter volumetric flask. Add 100 mL of purified water to the flask using a graduated cylinder, shake by hand for about 30 seconds, and sonicate for fifteen minutes. Add approximately 700 mL of extraction solvent to the flask, shake by hand for about 30 seconds, sonicate for fifteen minutes, shake on a mechanical shaker for thirty minutes, and then allow the contents of the flask to return to room temperature. Dilute to volume with extraction solvent and mix well by hand. The concentration of the resulting solution is 0.25 mg/mL. Pipette 25.0 mL of this solution into a 50 mL volumetric flask, dilute to volume with purified water and mix well by hand. Filter the sample solution with a 20 mL disposable syringe fitted with a Gelman Acrodisc-CR disposable filter, 0.45 µm porosity and discard the first 5 mL of filtrate. Transfer an aliquot of the filtrate to an HPLC vial for injection and tightly seal the vial.

Chromatographic Conditions

The chromatographic conditions are as specified for the Stability Indicating Assay Method, except that the injection volume is 15 µL instead of 25 µL.

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System Suitability

The following criteria must be met for the carvedilol peak in chromatograms recorded as part of this determination (see sample chromatogram):

1. Using a computerized data acquisition system, k' must be between 30 and 35 when t_0 is taken as the first deviation off the baseline. For non-computerized data acquisition systems where t_0 cannot be accurately calculated, use t_0 as the top of the first peak. The k' for non-computerized systems must be between 21 and 26.
2. The tailing factor at 5% peak height must be less than 2.
3. The number of theoretical plates must be greater than 1200.

In a two pump HPLC system, the ratio of the flow rates of Mobile Phases A and B may need to be adjusted to meet system suitability, but the total flow rate for the combined mobile phases must be 1.0 mL/min. For a single pump system, Mobile Phase C may need to be adjusted with either Mobile Phase A or B to meet system suitability. Note that small changes in the flow rates of the individual pumps, or small additions of Mobile Phases A or B to Mobile Phase C, result in large changes in the capacity factor. Calculations for k' , the tailing factor, the number of theoretical plates and the relative standard deviation are described in the current USP.

Procedure

Inject the standard and sample solutions.

Calculations

1. Response Factor, K:

$$K = \frac{W_s}{A_s}$$

where:

W_s = Weight of the analytical standard (carvedilol) in mg

A_s = Area response of a single standard 15 μ L injection

000120

Calculations (continued)

2. Calculation of Nominal Area of Carvedilol, A_n :

$$\frac{L}{K_{av}} \times \frac{N}{P} \times \frac{D_u}{D_s} = A_n$$

Selection of degradation products:

Select peaks in the chromatogram which appear above $\alpha = 0.04$, in other words, peaks which elute beyond the solvent elution peak. Peaks with less than 0.05% of the nominal peak area of carvedilol (A_n) should not be included. Identify each selected peak by its α value.

Degradation Product Quantitation (as Area of Nominal Carvedilol Area):

$$\frac{A_w}{A_n} \times 100 = \text{Area \%}$$

where:

A_w = Area of a single degradation product peak obtained from a 15 μL injection of sample solution

L = Label claim of carvedilol (12.5 mg or 25 mg)

N = Number of tablets used for sample preparation (10)

K_{av} = Average response factor over all 15 μL injections of standard

D_s = Dilution factor for the standard (1/100 X 1/200 = 0.00005)

D_u = Dilution factor for the sample
(1/500 X 10/200 = 0.0001 for 12.5 mg tablet,
1/1000 X 10/200 = 0.00005 for 25 mg tablet)

P = Purity of the analytical standard (decimal)

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SPECIFICATIONS AND ANALYTICAL METHODS

b. Analytical Methods

6. Dissolution Method

Summary

A dissolution assay procedure has been developed to monitor the dissolution of carvedilol in 12.5 mg and 25 mg tablets. The dissolution medium is simulated gastric fluid (USP XXII). The dissolution samples are assayed by HPLC using a C-18 column and an isocratic mobile phase. The mobile phase is a 50:50 v/v mixture of 0.10 M phosphate buffer, pH 2.0 and methanol. The detection wavelength is 285 nm. This method resolves carvedilol from its formulation excipients.

Validated Applications and Sample Requirements

This method is validated for the dissolution of 12.5 mg and 25 mg tablets of carvedilol. Six tablets are required for each sample assay.

Safety Precautions

Consult current material safety data sheets or equivalent for the safe handling and disposal of carvedilol. Methanol is toxic. Avoid skin contact or vapor inhalation. Concentrated hydrochloric acid is hazardous. Use protective clothing and proper ventilation. Routine laboratory safety practices must be followed.

Equipment (as stated below or equivalent)

Dissolution Apparatus:	Hanson Model 72RL-1115
Chromatograph:	Isocratic, single pump liquid chromatograph with a variable wavelength detector and a general purpose integrator.
Column:	Beckman Ultrasphere ODS, 4.6 mm id x 15 cm, 5 micron particle size.
Data Acquisition System:	A general purpose chromatographic integrator

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Filters:	Alltech Nylon-66 filters, 0.45 μm (stock #2024) Gelman Acrodisc 13 CR PTFE filters, 0.45 μm (polytetrafluoroethylene membrane- product #4423)
pH Meter:	Orion model SA 520
Balance:	Mettler PE 3600 top loading balance Cahn 29 electro balance
Sonicator:	Bransonic Model B-52
Syringe:	5 mL disposable syringe

Reagents (as stated below or equivalent)

Carvedilol:	Analytical standard
Pepsin:	Reagent grade
Sodium chloride:	Reagent grade
Hydrochloric Acid, concentrated (HCl):	Reagent grade
1 M Hydrochloric Acid:	Reagent Grade, DILUT-IT concentrate for 1.0 M solution or Reagent Grade, concentrated acid
Sodium Hydroxide	Pellets, Reagent Grade or DILUT-IT concentrate for 1.0 M solution
Potassium phosphate, monobasic, (KH_2PO_4):	Reagent grade
Phosphoric acid (85%): (H_3PO_4)	Reagent grade
Water:	Milli-Q or HPLC grade
Methanol:	HPLC grade

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Solutions

Simulated gastric fluid (Dissolution Medium): Accurately weigh 24.0 grams of sodium chloride and transfer to a two liter volumetric flask. Dissolve and dilute to volume with water. Accurately weigh 38.4 grams of pepsin and transfer to a two liter volumetric flask. Dissolve and dilute to volume with water. Accurately measure 84 mL of concentrated HCl into a two liter volumetric flask containing approximately 500 mL of water. Dilute to volume with water and mix. Transfer these three solutions to a suitable container. Fill each volumetric flask with water, transfer to the same container and mix. The container should now contain 12 liters of solution. The pH of this solution must be 1.45 ± 0.2 . Adjust the pH if necessary with 1N HCl and/or 1N NaOH.

1 M Hydrochloric Acid: Prepare 1 M hydrochloric acid solution according to the instructions on the DILUT-IT package. To prepare the 1 M hydrochloric acid solution from concentrated acid, add approximately 800 mL of water to a 1 liter volumetric flask. Add 83 mL of concentrated hydrochloric acid and mix well by hand. Dilute to volume with water and mix well by hand.

1 M Sodium Hydroxide: Add one DILUT-IT to water as directed, or dissolve 40 grams sodium hydroxide pellets in 1 liter of water. Mix thoroughly. Allow the solution to return to room temperature.

0.1 M Phosphoric acid: Accurately measure 13.6 mL of phosphoric acid, 85%, into approximately one liter of water in a two liter volumetric flask and mix. Dilute to volume with water and mix well. The pH of this solution is approximately 1.8.

0.1 M Potassium phosphate, monobasic: Accurately weigh 27.2 grams of potassium phosphate, monobasic into a two liter volumetric flask. Dissolve and dilute to volume with water. Mix well.

Buffer solution (Mobile Phase): Adjust the pH of the 0.1M phosphoric acid to 2.00 ± 0.05 by adding 0.1M potassium phosphate, monobasic (approximately 1 L).

Mobile phase: Mix buffer solution:methanol::50:50 v/v and filter with vacuum through a 0.45 μm Nylon-66 filter. Degas before use.

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Standard Solution Preparation

25 mg Tablet: Accurately weigh approximately 7.0 mg of carvedilol analytical standard and quantitatively transfer to a 250 mL volumetric flask. Add 3 mL of methanol and sonicate until dissolved. Dilute to volume with dissolution medium and mix well. The final concentration is approximately 28 µg/mL.

12.5 mg Tablet: Accurately weigh approximately 7.0 mg of carvedilol analytical standard and quantitatively transfer to a 500 mL volumetric flask. Add 5 mL of methanol and sonicate until dissolved. Dilute to volume with dissolution medium and mix well. The final concentration is approximately 14 µg/mL.

Duplicate standards should be prepared for each analysis.

Dissolution Conditions

Medium:	900 mL simulated gastric fluid at 37.0 ± 0.5°C, degas immediately before use
Apparatus:	USP 2 (paddle), 50 ± 2 rpm
Sample Aliquot:	3 mL
Sampling Time:	<del> </del>

Sample Solution Preparation

The test is performed as described in USP <711>, using the conditions described above. A single tablet is placed into each of the six dissolution vessels, one at a time. The time interval for placing the tablets into each of the vessels should be sufficient to pull the sample aliquot at the specified time interval. At the end of the time interval, a 3 mL aliquot is withdrawn from each vessel using a 5 mL syringe. The sample is filtered through a 0.45 µm Acrodisc 13 CR or equivalent, discarding the first 2 mL and collecting the next 1 mL for HPLC analysis.

Chromatographic Conditions

Chromatograph:

Column Temperature:	ambient
Flow Rate:	1.5 mL/min
UV Detection Wavelength:	285 nm
Injection Volume:	50 μ L
Analysis Time:	7.0 minutes

System Suitability

The following criteria must be met for the carvedilol peak in chromatograms recorded as part of this determination (see Figure 6.4):

1. Each k' must be between 4.0 and 6.0 where the time of the unretained peak (t_0) is taken as the first observed deviation from the baseline on the chromatogram.
2. The tailing factor at 5% peak height must be less than 2.6.
3. The number of theoretical plates for the carvedilol must be greater than 1000.

Calculations for k' , the tailing factor and the number of theoretical plates are described in the current USP. If any test fails, instrument conditions and/or mobile phase composition must be modified to meet the designated parameters.

Procedure

Inject working standard and filtered samples and record the response factor of the peaks of interest.

Calculations

1. Response Factor, K:

$$K = \frac{W_s}{A_s}$$

where:

W_s = weight of standard (mg)

A_s = area response of single standard injection

2. Quantification of Carvedilol:

$$\frac{A_u}{L} \times K_{av} \times V \times D_s \times P \times 100 = \% \text{ carvedilol dissolved}$$

where:

A_u = Average peak area response of the sample

V = Volume of dissolution medium (900 mL)

K_{av} = Average response factor over all injections of standard

L = Label claim of sample (mg)

D_s = Dilution factor for standard:
1/500 = 0.002 for 12.5 mg tablet
1/250 = 0.004 for 25 mg tablet

P = Purity of the analytical standard as a decimal

100 = Factor to convert to percent dissolved

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SPECIFICATIONS AND ANALYTICAL METHODS

b. Analytical Methods

7. Content Uniformity

Performed according to the USP using the Stability Indicating Assay Method presented in Section 6.b.(4).

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