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RESEARCH**

APPLICATION NUMBER:

22-012

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Addendum to QBR
Date: 12-October 2006

NDA Number:	22-012
Submission Type; Code:	Original
Applicant Name:	GlaxoSmithKline
Submission Dates:	15-Sep-2006 26-Sep-2006
Brand Name:	Coreg CR (proposed)
Generic Name:	Carvedilol phosphate
Dosage Form:	Controlled release capsules
Dosage Strengths:	10, 20, 40 and 80 mg
Proposed Indication:	Treatment of essential hypertension, mild to severe chronic heart failure, and to reduce cardiovascular mortality in clinically stable post-MI and LVD patients
OCP Division:	DPE I
CP and PM Reviewer:	Christine Garnett, PharmD
CP Team Leader:	Patrick Marroum, PhD
PM Team Leader:	Joga Gobburu, PhD

Recommendations

- A review of the in vitro dissolution data showed that a paddle speed of 100 rpm is discriminatory and therefore, the dissolution method is found to be acceptable. The following dissolution method and specification are recommended:

The dissolution method is USP Apparatus II, paddle speed of 100 rpm, in 0.1N HCL dissolution medium at 37°C. The vessel volume is 900 ml. The four time point specification expressed as % label claim is not more than — at 1-h, not less than — and not more than — at 8-h, not less than — and not more than — at 18-h, and not less than — at 24-h.
- A biowaiver for the level II site change can be granted for all capsules strengths.

I. Dissolution Method and Specification

Two teleconferences (12-Sept and 20-Sept 2006) were held with the sponsor to discuss the Agency's recommendations for the dissolution method and specification.

FDA Comment #1: The sponsor has proposed a rotation speed of 100 rpm for USP Apparatus II.

Sponsor's Response: The sponsor believes that, as was depicted in Table 3 below that the paddle rotation speed of 100 rpm results in appropriate discrimination. The sponsor stated that the higher paddle rotation speed is appropriate with a controlled release formulation

Table 3 Dissolution of Coreg CR Capsule Batch 041031970 using Different Paddle Rotation Speed (M100393)

Rotation Speed (rpm)	100		100	
Time (min)	% Drug Release (Average of 6 vessels)		% RSD	
30		9		8.7
60		11		7.2
120		16		7.2
240		28		7.5
360		40		6.2
480		51		4.8
720		68		3.5
1080		83		2.1
1440		89		1.8

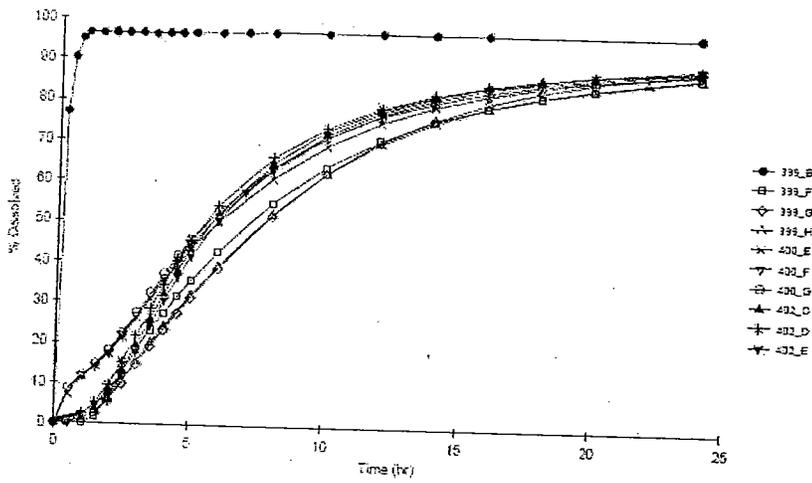
Tested at N=6.

FDA's Response: Figure 4 below shows the mean in vitro dissolution data for 14 controlled-release formulations using a paddle speed of 100 rpm. The in vivo PK parameters for three of the formulations are presented in the Table. The dissolution method was able to detect small in vivo differences in formulations. Therefore, it was concluded that a paddle speed of 100 rpm is discriminatory.

Geometric Mean (Range) of PK Parameters for R(+) Carvedilol

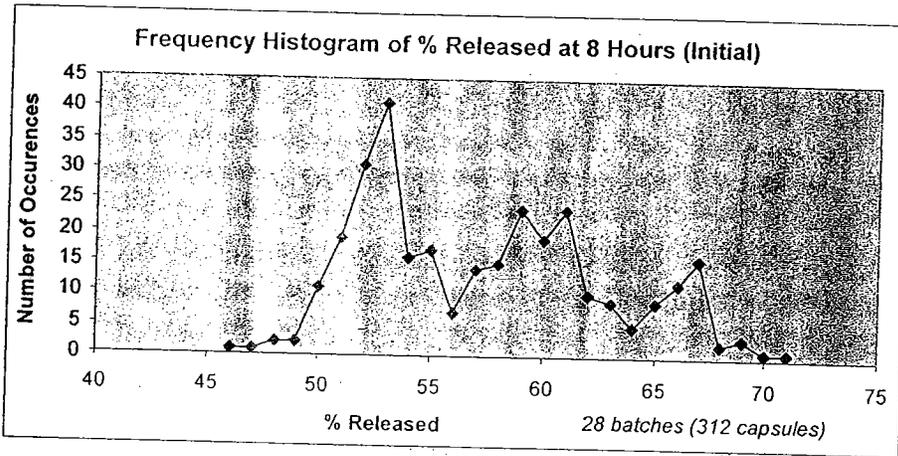
Formulation	Dose	C _{max} , ng/ml	AUC, ng•h/ml
399-G	20 mg	5.38 (2.10-12.2)	48.8 (23.2-101)
402-D	30 mg	26.2 (7.16-67.7)	159 (56.4-659)
400-E	60 mg	40.0 (16.8- 108.9)	322 (138-649)

Figure 4 Mean in vitro dissolution data



FDA Comment #2: The recommended range at any dissolution time point is _____ deviation from the mean dissolution profile obtained from the clinical lots. The sponsor has proposed a _____ for the 8-h time point. Without support from in vivo BE data, the reviewer recommends a specification of NLT _____ and NMT _____.

Sponsor's Response: The sponsor stated that most individual values were _____ after scale-up some were as high as _____. The sponsor confirmed that the commercial batches were not tested clinically and the changes in the batches were related to scale-up and a new manufacturing building.

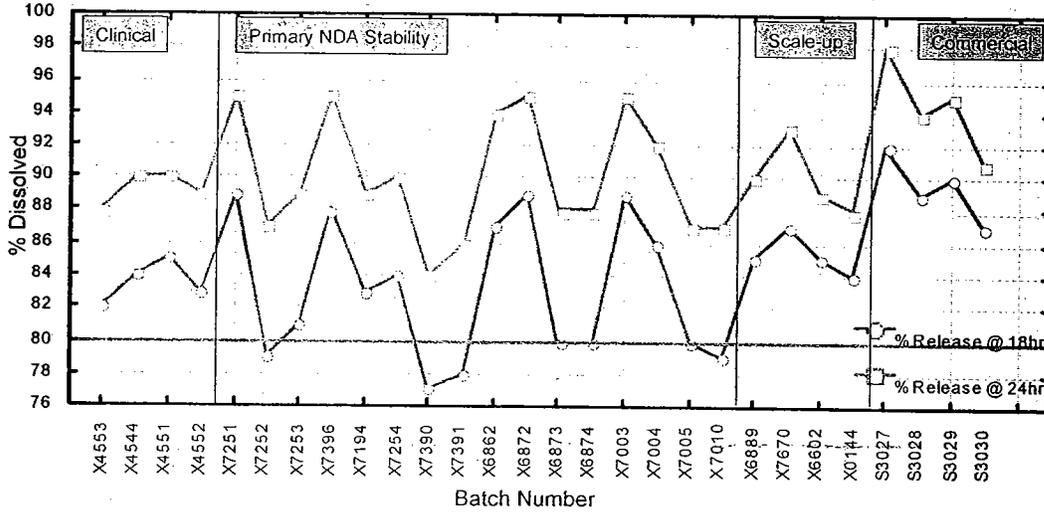


The sponsor proposed an interim range of _____ with a post-marketing commitment to tighten that range based on the results of the _____ commercial batches.

FDA's Response: The sponsor's specification is acceptable.

FDA Comment #3: The last time point should be the time point where at least 80% of the drug has dissolved. Based on the dissolution profiles for the biobatches and commercial batches, it is recommended

Sponsor's Response: The sponsor proposed adding an additional 18-h time point with a specification of \approx , to control release rates across formulations.



FDA's Response: The sponsor's proposal is acceptable.

2. Dose Amount for Population PK Analyses of R(+) and S(-) Carvedilol

During labeling discussions with the sponsor it was revealed that the dose amount was incorrect in the data files used for population PK analysis. GSK re-ran the model with the correct dose amount for each enantiomer and is reporting a population CL/F estimate of 90 L/h and 213 L/h for R(+) and S(-) carvedilol, respectively, for label. These values are acceptable as the ratio of the CL/F values for the enantiomers are comparable to ratio previously reported.

It is important to note that this dose error does not have any impact on the pivotal PKPD analysis to assess the relationship between plasma S(-) carvedilol concentrations and beta-blockade.

3. Study report for Alcohol Interaction Study

The report submitted by the sponsor is considered preliminary. Therefore, labeling statements about alcohol will remain until a final clinical study report has been received and reviewed.

4. Bioanalytical Reports

Bioanalytical reports to support the pivotal pharmacokinetic studies are acceptable.

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this page is the manifestation of the electronic signature.**

/s/

Christine Garnett
10/12/2006 02:53:26 PM
PHARMACOLOGIST

Patrick Marroum
10/12/2006 05:36:34 PM
BIOPHARMACEUTICS

Jogarao Gobburu
10/12/2006 06:07:58 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY REVIEW

NDA Number:	22-012
Submission Type; Code:	Original
Applicant Name:	GlaxoSmithKline
Submission Dates:	21-Dec-2005 07-Feb-2006 24-Mar-2006 31-Mar-2006 21-Apr-2006 30-Jun-2006
Brand Name:	Coreg CR (proposed)
Generic Name:	Carvedilol phosphate
Dosage Form:	Controlled release capsules
Dosage Strengths:	10, 20, 40 and 80 mg
Proposed Indication:	Treatment of essential hypertension, mild to severe chronic heart failure, and to reduce cardiovascular mortality in clinically stable post-MI and LVD patients
OCP Division:	DPE I
CP and PM Reviewer:	Christine Garnett, PharmD
CP Team Leader:	Patrick Marroum, PhD
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1 EXECUTIVE SUMMARY

GlaxoSmithKline has developed a controlled-release (CR) capsule formulation of carvedilol that allows for once daily dosing. The capsules are filled with drug-layered immediate release (IR) microparticles _____ CR microparticles that are drug-layered and then coated with _____ niethacrylic acid copolymer. The capsule strengths of 10 mg, 20 mg, 40 mg and 80 mg provide similar exposure levels of carvedilol over a 24-h interval as those achieved with BID dosing of immediate release (IR) tablets at 3.125 mg, 6.25 mg, 12.5 mg, and 25 mg, respectively.

The sponsor is seeking approval of the CR formulation for the treatment of essential hypertension, mild to severe chronic heart failure (CHF), and to reduce mortality in clinically stable survivors of the acute phase of a myocardial infarction who have a left ventricular ejection fraction $\leq 40\%$. The sponsor submitted seven clinical studies with the final CR formulation: one efficacy and safety study in patients with essential hypertension; one pharmacokinetic-pharmacodynamic study in patients with essential hypertension; one pharmacokinetic study in patients with CHF or post-MI LVD, and four pharmacokinetic studies in healthy volunteers.

To support the hypertension indication, the sponsor conducted a double-blind, placebo-controlled, 8-week trial to evaluate the antihypertensive effects of 20 mg, 40 mg, and 80 mg carvedilol CR administered once daily to patients with essential hypertension. There was a dose-related blood pressure response: mean (90% CI) differences in diastolic BP from placebo were -4.03 (-6.41, -1.65), -7.56 (-9.95, -5.16), and -9.19 (-11.59, -6.79) for the 20 mg, 40 mg and 80 mg dose groups, respectively. The sponsor also conducted an exposure-response analysis for the mean change in blood pressure vs. model-predicted, steady state AUC values.

To support the heart failure and mortality indications, the sponsor demonstrated that 1) exercise-induced heart rate at trough concentrations (PD_{min}) observed with carvedilol CR capsules was equivalent to those observed with IR tablets; 2) the input rate carvedilol CR has no effect on the concentration-effect model; and 3) the steady state exposure to R(+) and S(-) carvedilol observed with carvedilol CR capsules are comparable to those observed with IR tablets in patients with mild to severe CHF or post-MI LVD.

1.1 Recommendations

The office of Clinical Pharmacology / Division of Clinical Pharmacology 1 (OCP/DCP 1) has reviewed the information contained in NDA 22-012. This NDA is considered acceptable from a clinical pharmacology perspective.

A biowaiver for the level II site change cannot be granted for all capsules strengths until the sponsor has submitted multipoint dissolution data in several media using methodology which incorporates the following recommendations:

- The recommended range at any dissolution time point is _____ deviation from the mean dissolution profile obtained from the clinical lots. Without support from in vivo BE data, the reviewer recommends a specification of NLT _____ and NMT _____ for the 8-h time point.

- The last time point should be the time point where at least 80% of the drug has dissolved. Based on the dissolution profiles for the biobatches and commercial batches, it is recommended
- The sponsor has proposed a rotation speed of 100 rpm for USP Apparatus II.

The sponsor did not include instructions for switching patients currently maintained on the immediate release tablets. It is recommended that the following language be included in the Dosage and Administration section of the label.

Patients controlled on conventional tablets lone or in combination with other medications may be switched to COREC CR capsules at the total daily doses shown in the table below. Subsequent titration to higher or lower doses may be necessary as clinically warranted.

Total Daily Dose of Conventional Tablets	Total Daily Dose of COREC CR Capsules
6.25 mg	10 mg
12.5 mg	20 mg
25 mg	40 mg
50 mg	80 mg

There should be satisfactory agreement between the sponsor and the Agency on language in the package insert.

Comments to be conveyed to the sponsor:

- The sponsor is required to submit a bioanalytical report for each pharmacokinetic study as described in the Guidance for Industry, Bioanalytical Method Validation (May 2001). The bioanalytical report documents the application of the validated bioanalytical methods to routine drug analysis.
- When submitting NONMEM data sets as XPT data files, please consider verifying that data formats do not change. Your submitted datasets supporting the population pk analysis could not be run because the formats of the date and time columns were incorrect and could not be corrected without access to the original data file.
- In future submissions please consider providing a model development decision tree and/or table which give an overview of major modeling steps and decisions.

1.2 Phase 4 Commitments

No Phase 4 commitments are recommended.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Exposure (Dose)-Response Relationship

Exercise heart rate and concentration data collected in patients with essential hypertension showed that carvedilol CR has the same blocking effects as the immediate release formulation. The exercise-induced heart rate at trough concentrations (PD_{min}) observed with 20 mg and 80 mg once daily carvedilol CR capsules was equivalent to those observed with 6.25 mg and 25 mg BID dosing of IR tablets. The 90% confidence intervals of the CR:IR ratio fell within the 80 to 125% equivalence interval. Similar findings were observed for PD_{max} and AUEC.

A direct effect E_{max} PKPD model was used to describe the relationship between steady state plasma concentrations of S(-) carvedilol and changes in exercise-induced heart rate in patients with essential hypertension. The population estimates for E₀, EC₅₀, and E_{max} were 126 bpm (BSV of 8%), 4.25 ng/ml, and 15.1 bpm, respectively. When the same model was applied to plasma concentration and heart rate data for the CR and IR formulations separately, the distribution of parameter estimates from 1000 bootstrap datasets was similar. This provides evidence that the concentration-effect relationships for the CR and IR formulations are the same.

When carvedilol CR was administered to patients with essential hypertension, there was a trend for dose-related blood pressure response: mean (90% CI)-differences in diastolic BP from placebo were -4.03 (-6.41, -1.65), -7.56 (-9.95, -5.16), and -9.19 (-11.59, -6.79) for the 20 mg, 40 mg and 80 mg dose groups, respectively. The sponsor also conducted an exposure-response analysis for the mean change in blood pressure vs. model-predicted, steady state AUC values. The decrease in both mean systolic and diastolic BP was described by an E_{max} model.

Pharmacokinetics in Heart Failure Patients and Post-MI Patients with LVD

The steady-state pharmacokinetics of carvedilol CR was characterized in patients with mild to severe heart failure and post-MI patients with LVD. Patients received IR tablets (3.125 mg, 6.25 mg, 12.5 mg, and 25 mg) for 14 days then received an equivalent CR dose (10 mg, 20 mg, 40 mg and 80 mg). At all dose levels, exposure to R(+) and S(-) carvedilol observed with carvedilol CR capsules were comparable to the exposure observed with IR tablets. Using pooled data across dose groups, the 90% confidence intervals of the CR:IR ratios for C_{max}, AUC, and C_{tau} fell within the 80% to 125% equivalence interval.

General Pharmacokinetic Properties

Following single-dose administration of a 60 mg CR capsule and 25 mg q12h IR tablets under fed conditions, mean and CV% values for C_{max} and AUC were comparable for R(+) and S(-) carvedilol. The relative bioavailability of carvedilol CR is approximately 81% for R(+) and 89% for S(-) carvedilol. T_{max} values were 3 to 4 hours longer with the CR capsule. Due to stereoselective first-pass metabolism, plasma levels of R(+) carvedilol were higher than those observed for S(-) carvedilol.

Steady-state exposure to R(+) and S(-) carvedilol following once daily administration of 20 mg and 80 mg CR capsules were equivalent to the exposure with 6.25 mg and 25 mg q12h IR tablets, respectively. The 90% confidence intervals for the geometric mean CR:IR ratios for AUC, Cmax and Ctau fell within the equivalence bounds of 80-125%. Tmax values were 3 to 4 hours longer with CR capsules. The fluctuation between peak and trough concentrations was comparable between the CR and IR formulations.

Evening administration of 80 mg CR capsule with food resulted in an approximate 10% decrease in AUC of both R(+) and S(-) carvedilol and a decrease in Cmax of 15% to 19% compared to morning administration with food. There was also a decrease in rate of absorption with evening administration as Tmax values were 1.5 hours longer. Diurnal variation in the pharmacokinetics of carvedilol is also observed with the IR formulation.

With repeat administration of 80 mg CR capsule in healthy subjects, the within-subject variability for AUC and Cmax was less than 30%. These values are similar to IR carvedilol (study 271, historical data).

There is an approximate dose proportional increase in Cmax and AUC of R(+) and S(-) carvedilol following single dose administration of 10 mg, 20 mg, 40 mg and 80 mg CR capsules with food.

There is no evidence of dose dumping when carvedilol CR is administered with a high fat meal, or sprinkled with applesauce. Administration of 80 mg CR capsule with a high-fat meal increased AUC and Cmax by 20% compared to a standard meal. Administration of 80 mg CR capsule with sprinkled over applesauce following a standard meal did not affect AUC but decreased Cmax by 20% compared to administration with a standard meal. Compared to the administration of carvedilol CR under fasting conditions, a high fat meal increased AUC and Cmax by 60% and 107%, respectively, as well as increased Tmax by 1 hour.

Concomitant administration of a proton-pump inhibitor, pantoprazole, with a pilot formulation of carvedilol CR did not increase the exposure to carvedilol. The 90% confidence intervals for the geometric mean ratios for AUC and Cmax fell within the equivalence range of 80% to 125% when comparing administration of carvedilol CR with and without pantoprazole. The formulation used in this study consisted of microparticles

There is some evidence of potential dose dumping if carvedilol CR is administered with alcohol. An in vitro dissolution study has shown that ethanol over the concentration range of 4% to 24% causes a concentration-related increase in the rate of release from the CR capsules. The sponsor recommends that patients be instructed to take carvedilol CR in the morning with food and to separate the ingestion of any alcohol-containing products by at least two hours. The sponsor is also conducting a randomized, open-label, single-dose, four-period crossover study to determine the effects of alcohol on the pharmacokinetics of carvedilol CR.

Biopharmaceutics Highlights

The controlled-release capsules containing 10 mg, 20 mg, 40 mg and 80 mg of carvedilol phosphate are filled with drug-layered immediate release (IR) microparticles

CR microparticles that are drug-layered and then coated with methacrylic acid copolymer

The proposed dissolution method is USP Apparatus II, paddle speed of 100 rpm, in 0.1N HCL dissolution medium at 37°C. The vessel volume is 900 ml. The

Clinical Pharmacology NDA Briefing

A required office-level briefing was held on 11 September and attended by Femi Williams (MO), Eugenia Nash (Chemist), Larry Lesko, Shiew Mei Huang, Mehul Mehta, John Lazor, Dennis Bashaw, Atik Rahman, Felix Frueh, Patrick Marroum, Kellie Reynolds, Joga Gobburu, Peter Hinderling, Lydia Velazquez, Wei Qiu, Lei Zhang, Seong Jang, Vikram Ayra, Chistoffer Tornoe, Gilbert Burckart, and Christine Garnett.

Christine Garnett, Pharm.D. _____

RD/FT Initialed by Patrick Marroum, Ph.D. _____

Joga Gobburu, Ph.D. _____

Mehul Mehta, Ph.D. _____

cc:

Division File: NDA 22-012

HFD-110 (CSO/Robb)

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HFD-860 (Garnett, Marroum, Gobburu, Mehta),

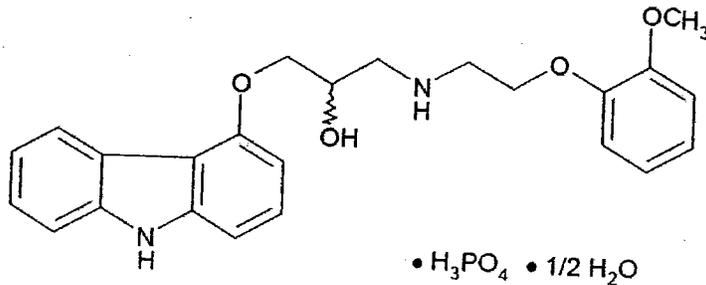
Central Documents Room (CDR-Clinical Pharmacology)

2 QUESTION BASED REVIEW

2.1 General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Carvedilol phosphate is identified structurally as 1-(9H-Carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-2-propanol dihydrogen phosphate. Carvedilol is a nonselective β -adrenergic blocking agent with α 1-blocking activity. It is a racemic mixture with the following structure:



Carvedilol has molecular weight of 513.5 (406.5 carvedilol free base) and a molecular formula of C₂₄H₂₆N₂O₄•H₃PO₄•½H₂O. There is one chiral center and therefore has two potential enantiomers.

The sponsor has formulated once-daily controlled-release capsules containing 10 mg, 20 mg, 40 mg and 80 mg of carvedilol phosphate. The capsules are filled with drug-layered immediate release (IR) microparticles and _____ CR microparticles that are drug-layered and then coated with _____ methacrylic acid copolymer

microparticles _____. The capsules contain IR microparticles, _____ in a combined quantity sufficient to provide the label claim strength expressed as carvedilol phosphate _____ (Table 1).

Table 1. Composition of Carvedilol CR Capsules

Capsule Component	Carvedilol CR Capsule Strengths (expressed as carvedilol phosphate)			
	10 mg	20 mg	40 mg	80 mg
Immediate Release Microparticles				
_____ Microparticles				

2.1.2 What are the proposed mechanism of action and therapeutic indications?

Carvedilol is a competitive adrenoreceptor antagonist which inhibits activity at β_1 - and β_2 -adrenergic receptors as well as α_1 receptors. The mechanism by which β -blockade produces an antihypertensive effect has not been established.

Carvedilol (Coreg®) is currently approved as an immediate release (IR), twice-daily (BID) formulation for the treatment of essential hypertension, mild to severe chronic heart failure (HF), and to reduce cardiovascular mortality in clinically stable survivors of the acute phase of a myocardial infarction (MI) who have a left ventricular ejection fraction of $\leq 40\%$ (with or without symptomatic heart failure).

Carvedilol Phosphate CR capsule strengths (expressed as carvedilol phosphate) of 10 mg, 20 mg, 40 mg, and 80 mg were selected to provide similar exposure levels of carvedilol over a 24 hour period as those achieved with BID administration of COREG tablets at 3.125 mg, 6.25 mg, 12.5 mg, and 25 mg, respectively.

2.1.3 What are the proposed dosages and routes of administration?

The proposed starting dosage regimen of carvedilol phosphate CR for adults with essential hypertension or with left ventricular dysfunction following myocardial infarction is 20 mg po once daily in the morning with food. The dose can be titrated for clinical response. Total daily dose should not exceed 80 mg.

For adult patients with heart failure, the proposed starting dose is 10 mg po once daily in the morning with food. The dose must be individualized based on tolerability.

The administration of carvedilol CR with alcohol should be separated by 2 h.

The capsules may be sprinkled over a spoonful of applesauce.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and the clinical studies used to support dosing or claims?

Seven clinical studies were conducted using the final CR formulation to support the proposed indications (Table 2). Individual reviews of these studies can be found in Appendix 4.2. An in vivo interaction study with pantoprazole using a pilot formulation with microparticles was reviewed; however, eight additional studies that utilized pilot controlled-release formulations were not reviewed.

Table 2. Summary of Clinical Studies Using the Commercial Formulation

Study	Design	Treatment	Endpoints
400 Relative Bioavailability	O, SD, R, 3 period XO study in 36 [5F/31M] adult volunteers	A. 25 mg Coreg IR Q12H x 2 E. Final 60 mg CR B,C,D,F, and G were pilot formulations	Pharmacokinetics
376 Food Effect	O,SD, R, 4 period, XO study in 22 [4F/18M] adult volunteers	A. 80 mg CR fasting B. 80 mg CR standard meal C. 80 mg CR high-fat meal D. 80 mg CR sprinkle with applesauce	Pharmacokinetics
903 Dose- proportionality	O, SD, NR, 4 period XO study in 40 [18F/22M] adult volunteers	A. 10 mg CR B. 20 mg CR C. 40 mg CR D. 80 mg CR	Pharmacokinetics
906 Diurnal variation	O, SD, PR, 3 period XO study in 22 [7F/15M] adult volunteers	A. 80 mg CR in AM B. 80 mg CR in PM	Pharmacokinetics
902 Steady-state PK and PD	DB, R, PLC, MD, 5 period XO study in 121 mild to moderate essential hypertension patients [59F/62M]	A. Placebo B. 6.25 mg IR BID vs. 20 mg CR QD C. 12.5 mg IR BID vs. 40 mg CR QD D. 25 mg IR BID vs. 80 mg CR QD	Pharmacokinetics, Pharmacodynamics, PKPD
367 Phase III in patients with hypertension	DB, R, PLC, P study in subjects with a history of or current essential hypertension	Placebo 84[28F/56M] CR 20 mg QD 87 [23F/64M] CR 40 mg QD 78 [35F/43M] CR 80 mg QD 88 [28F/60M]	Blood pressure PopPK PKPD
369 Phase III in patients with heart failure and post- MI LVD	O, NR, MD, 2 period XO study in 187 [50F/137M] subjects with stable, chronic heart failure and post- MI LVD	A. 3.125 mg IR BID vs. 10 mg CR QD B. 6.25 mg IR BID vs. 20 mg CR QD C. 12.5 mg IR BID vs. 40 mg CR QD	Pharmacokinetics

O = open label, SD = single-dose, R = randomized, NR = Not randomized, PR=partially randomized, XO = crossover study, F = female, M = male, PLC = placebo-controlled, P = parallel, MD = multiple-dose

2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

The primary endpoint for the phase III trial (367) in essential hypertension patients was to compare the effects of carvedilol CR to placebo as measured by changes from baseline in mean 24-h DBP using ambulatory blood pressure monitoring.

The primary endpoint for the phase III trial (369) in heart failure and post-MI LVD patients was to compare the PK profiles of Coreg IR BID regimen and carvedilol CR QD regimen.

The primary endpoint for the PKPD trial (902) in essential hypertension patients was to describe the relationship between changes in ergometric heart rate and plasma concentrations of S(-) carvedilol.

2.2.3 Are the active moieties in plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

The known active moiety of carvedilol in plasma consist of R(+) and S(-) carvedilol. Nonselective β -adrenoreceptor blocking activity is present in the S(-) enantiomer and α 1-adrenergic blocking activity is present in both R(+) and S(-) enantiomers at equal potency.

2.2.4 Exposure-Response

2.2.4.1 What are the characteristics of the exposure-response relationships for efficacy?

β 1-Blocking Effects

Study 902 was a randomized, double-blind, placebo controlled, multicenter study to compare the β 1-blocking effects of carvedilol CR capsule formulation to COREG IR tablets at steady state in 122 adult patients with essential hypertension, by evaluating heart rate response to bicycle ergometry (study 902, Appendix 4.2.5).

Exercise heart rate and concentration data shows that carvedilol CR has the same blocking effects as the immediate release formulation (Figure 1). The exercise-induced heart rate at trough concentrations (PDmin) observed with carvedilol CR capsules was equivalent to those observed with IR tablets (Table 3. The 90% confidence intervals of the CR:IR ratio fell within a 80 to 125% equivalence interval. Similar findings were observed for PDmax and AUEC (Table 4 and Table 5, respectively).

Figure 1. Time Course of Mean S(-) Concentration Time Profile and Change in Exercise-Induced Heart Rate from Baseline (study 902)

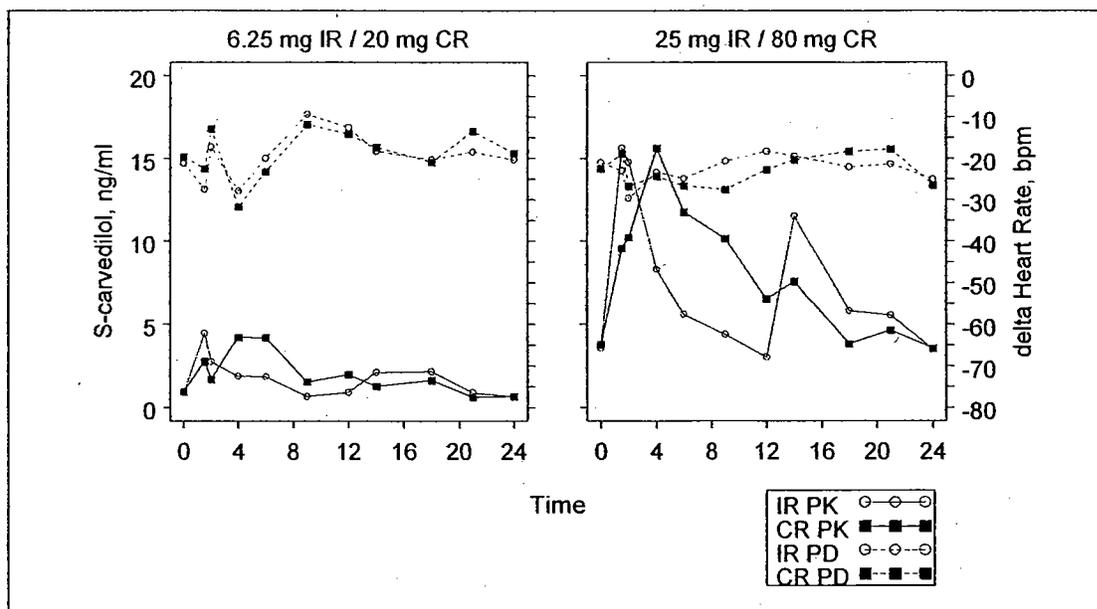


Table 3. Beta-Blocking Effects in Patients with Essential Hypertension (study 902): Statistical Analysis of PDmin% (Reference Table 20/Section 7.1/Study 902)

Parameter	Comparison of Interest CR:IR	Point Estimate	90% CI	Within subject SD ⁴
PDmin	Pooled Group ¹	1.00	(0.94, 1.07)	3.86
PDmin	High Dose Group ²	1.06	(0.97, 1.15)	
PDmin	Low Dose Group ³	0.94	(0.84, 1.05)	

1. High and Low Dose Groups combined
2. COREG 25mg BID and carvedilol CR 80mg OD
3. COREG 6.25mg BID and carvedilol CR 20mg OD
4. Within-subject standard deviation

Source: Table 7.1

**Table 4. Beta-Blocking Effects in Patients with Essential Hypertension (study 902):
Statistical Analysis of PDmax%**
(Reference Table 22/Section 7.3/Study 902)

Parameter	Comparison of Interest	Point Estimate	90% CI	SDw
PDmax	CR:IR (Pooled) ¹	0.97	(0.92, 1.02)	3.82
PDmax	CR:IR (High Dose Group) ²	1.02	(0.95, 1.08)	
PDmax	CR:IR (Low Dose Group) ³	0.92	(0.84, 1.00)	

1. High and Low Dose Groups combined
 2. COREG 25mg BID and carvedilol CR 80mg OD
 3. COREG 6.25mg BID and carvedilol CR 20mg OD
- Source: Table 7.5

**Table 5. Beta-Blocking Effects in Patients with Essential Hypertension (study 902):
Statistical Analysis of AUEC%**
(Reference Table 21/Section 7.2/Study 902)

Parameter	Comparison of Interest	Median	90% Bootstrap CI (5th percentile, 95th percentile)
AUEC	CR:IR (Pooled) ¹	1.02	(0.93, 1.10)
AUEC	CR:IR (High Dose Group) ²	1.03	(0.96, 1.10)
AUEC	CR:IR (Low Dose Group) ³	1.00	(0.92, 1.09)

1. High and Low Dose Groups combined
 2. COREG 25mg BID and carvedilol CR 80mg OD
 3. COREG 6.25mg BID and carvedilol CR 20mg OD
- Source: data on file, GSK

A direct effect Emax PKPD model was used to describe the relationship between steady state plasma concentrations of S(-) carvedilol and changes in exercise-induced heart rate in patients with essential hypertension (Table 6). The population estimates for E0, EC50, and Emax were 126 bpm (BSV of 8%), 4.25 ng/ml, and 15.1 bpm, respectively. Due to large variability in the HR data and the limited data at or above Emax, the PKPD model did not support estimation of interindividual variability for most parameters.

Table 6. Population PKPD Parameters
(Reference Table 28/Section 10)

	Population Mean (% se ¹)	Inter-Individual Variability as % CV (% se ¹)
E0 (bpm)	126 (1.3)	7.7 (23.2)
EC50 (ng/mL)	4.25 (44.9)	NE
E _{max} (bpm)	15.1 (11.5)	NE
Amplitude	0.013 (15.4)	NE
T _{max} (h)	11.6 (7.2)	NE
Residual Variability % CV (% se ¹)	4.9 (13.1)	

1. % se – percent standard error

NE – Not Evaluated

Source: Table 10.1

The change in exercise heart rate from baseline vs. S(-) carvedilol concentrations are presented in Figure 2. This figure illustrates that the IR and CR formulations have comparable concentration range and beta-blocking effects. When the same model was applied to plasma concentration and heart rate data for the CR and IR formulations separately, the distribution of parameter estimates from 1000 bootstrap datasets was similar (Table 7). This provides evidence that the concentration-effect relationship for the CR and IR formulations is the same.

Figure 2. Change from Baseline Exercised-Induced Heart Rate vs. S(-) Carvedilol Concentrations

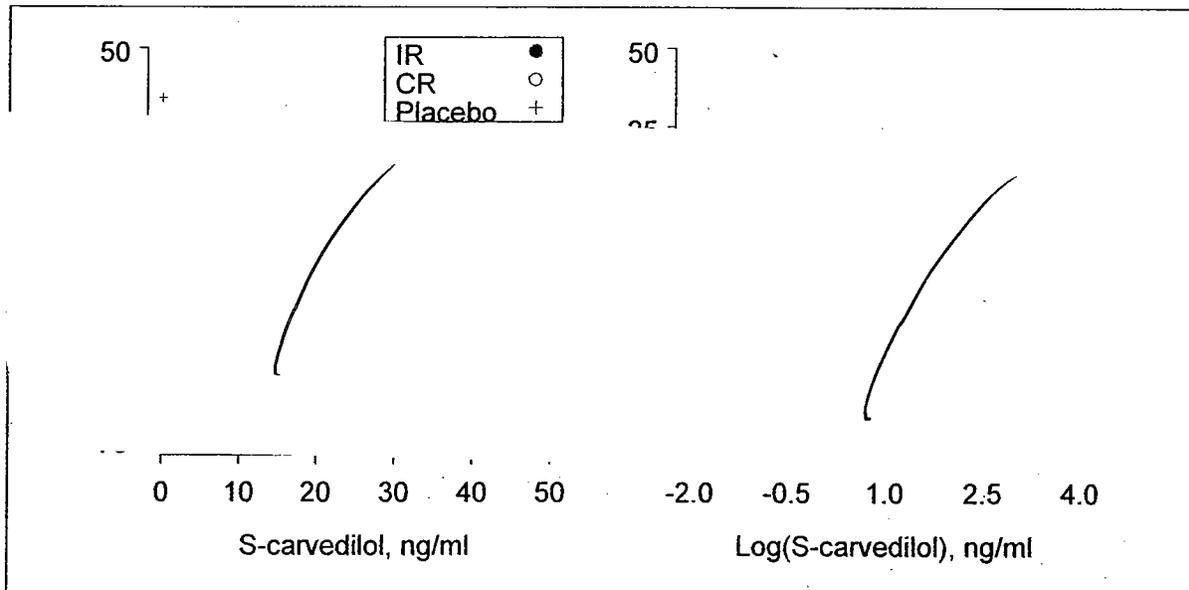


Table 7. Median (5th, 95th percentiles) for Model Parameters Calculated from 1000 Bootstrap Datasets

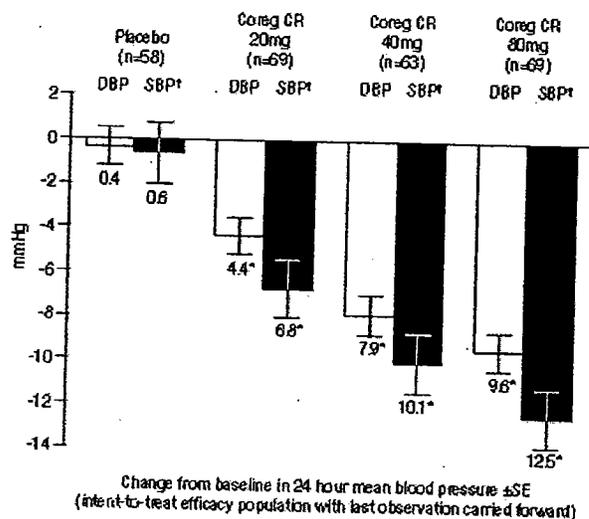
Parameter	IRCR Data	IR Data Alone	CR Data Alone
E0	126 (123, 129)	127 (123, 131)	128 (123, 132)
EC50	4.1 (1.86, 9.66)	2.87 (0.920, 2694)	2.04 (0.470, 2116)
E _{max}	15.5 (12.6, 18.5)	16.5 (13.2, 1240)	16.6 (12.7, 1112)
Amplitude	0.0123 (0.0101, 0.0168)	0.0165 (0.0125, 0.0207)	.00947 (3.74E-11, 0.0135)
T _{max}	11.6 (10.3, 13.3)	10.9 (9.80, 124)	11.3 (2.08, 58.5)
BSV for E0 (expressed as CV)	0.0781 (0.0631, 0.0981)	0.0777 (0.0637, 0.0948)	0.0796 (0.0635, 0.0983)
Residual error (expressed as CV)	0.0483 (0.0431, 0.0536)	0.0462 (0.0401, 0.0525)	0.0436 (0.0392, 0.0484)
% runs with successful convergence	99.6	99.2	97.8

Blood Pressure Effects

Study 367 was a double-blind, randomized, placebo-controlled, parallel group, multicenter trial comparing 3 doses of carvedilol CR administered once daily (20 mg, 40 mg, and 80 mg) in 284 patients with essential hypertension.

Mean reductions from baseline in mean 24-h diastolic and systolic BP by ABPM was statistically different from placebo (Figure 3). There is trend for dose-related blood pressure response.

Figure 3. Mean Blood Pressure Changes from Baseline Measured by 24-h ABPM (Reference Figure 7 /2.5 Clinical Overview)



¹ SBP inferences are based on an ad-hoc analysis
^{*} P values < 0.001 for dose related trend tests for change from baseline in mean DBP and SBP

The sponsor also conducted an exposure-response analysis for the mean change in blood pressure vs. model-predicted, steady state AUC values. The decrease in both mean systolic and diastolic BP was described by an Emax model (Figure 4 and Figure 5).

Figure 4. PKPD Model for R-Carvedilol
(Reference Figures 3 and 4/ Section 11/POPPK/Study 367)

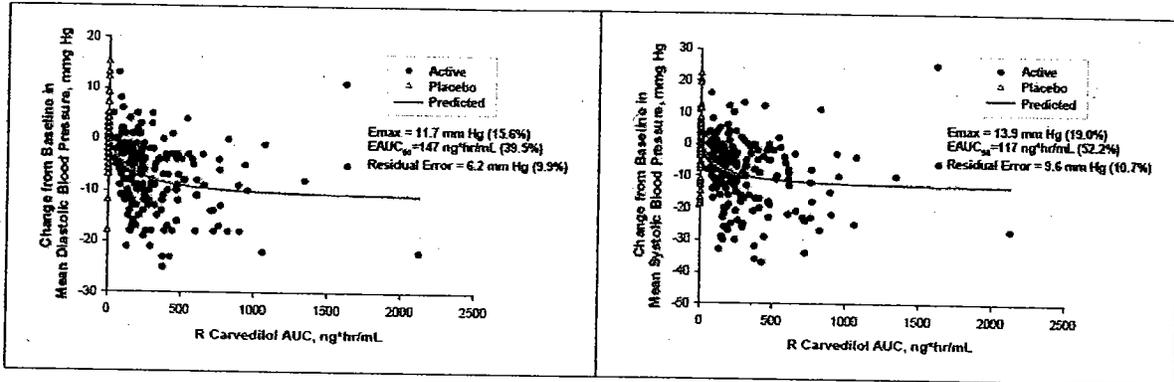
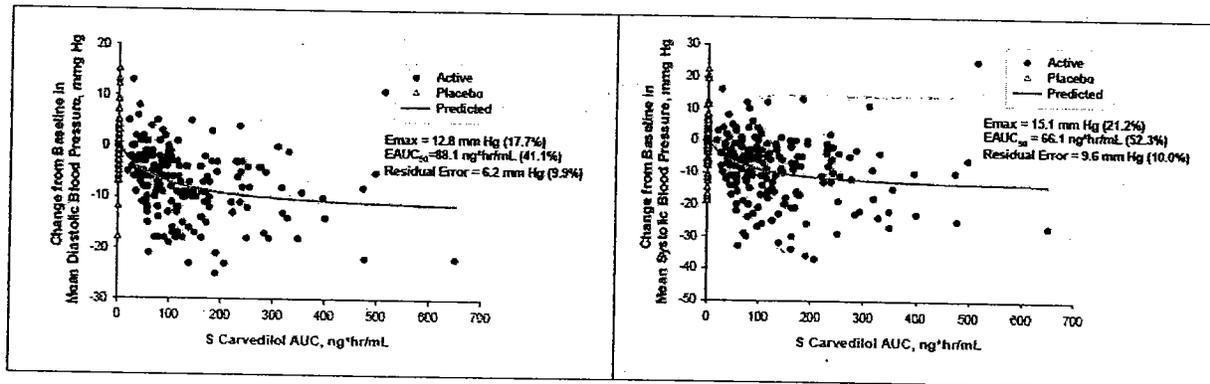


Figure 5. PKPD Model for S-Carvedilol
(Reference Figures 5 and 6/ Section 11/POPPK/Study 367)



2.2.4.2 What are the characteristics of the exposure-response relationships for safety?

The range of R(+) and S(-) carvedilol concentrations observed after the administration of once daily 10 mg, 20 mg, 40 mg and 80 mg CR capsules is equivalent to the concentrations following BID dosing of 3.125 mg, 6.25 mg, 12.5 mg, and 25 mg IR tablets. Therefore, the AE profile of the carvedilol is related to the known pharmacology of the drug and is similar to the IR formulation.

2.2.4.3 Does this drug prolong QT/QTc Interval?

The sponsor did not evaluate the effect of carvedilol CR on cardiac repolarization.

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known E-R relationship?

The proposed dosing regimens are consistent with the ER relationship (described in detail in section 2.2.4.1).

2.2.5 What are the PK characteristics of the drug?

2.2.5.1 What are the single and multiple dose PK parameters?

Single Dose Pharmacokinetics

The single-dose pharmacokinetics of R(+) and S(-) carvedilol were assessed in healthy male and female volunteers following administration of 60 mg (1 x 60 mg Q24H) carvedilol CR capsules and 50 mg (2 x 12.5 mg Q12H) IR tablets (Study 400, Appendix 4.2.1).

The controlled release formulation (regimen E) provides comparable total daily exposure to carvedilol compared to the immediate release formulation (Figure 6, Table 8). Median T_{max} values were 3 to 4 hours longer than conventional tablets.

Figure 6. Mean Concentration-Time Profile Following Single-Dose Administration of 60 mg Carvedilol CR and 50 mg Immediate-Release Carvedilol (Study 400)

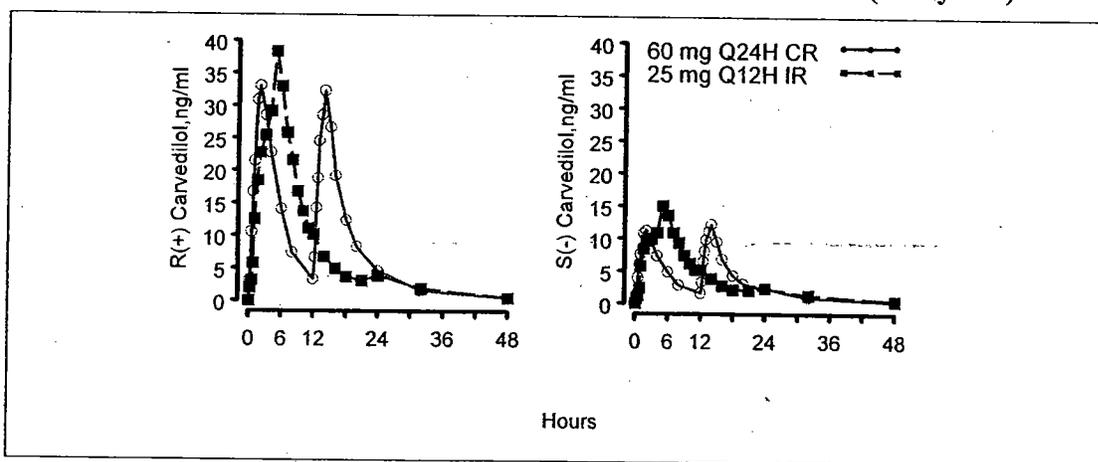


Table 8. Summary of Single Dose Pharmacokinetic Parameters (Reference Table 13/Section 7.0/Study 400)

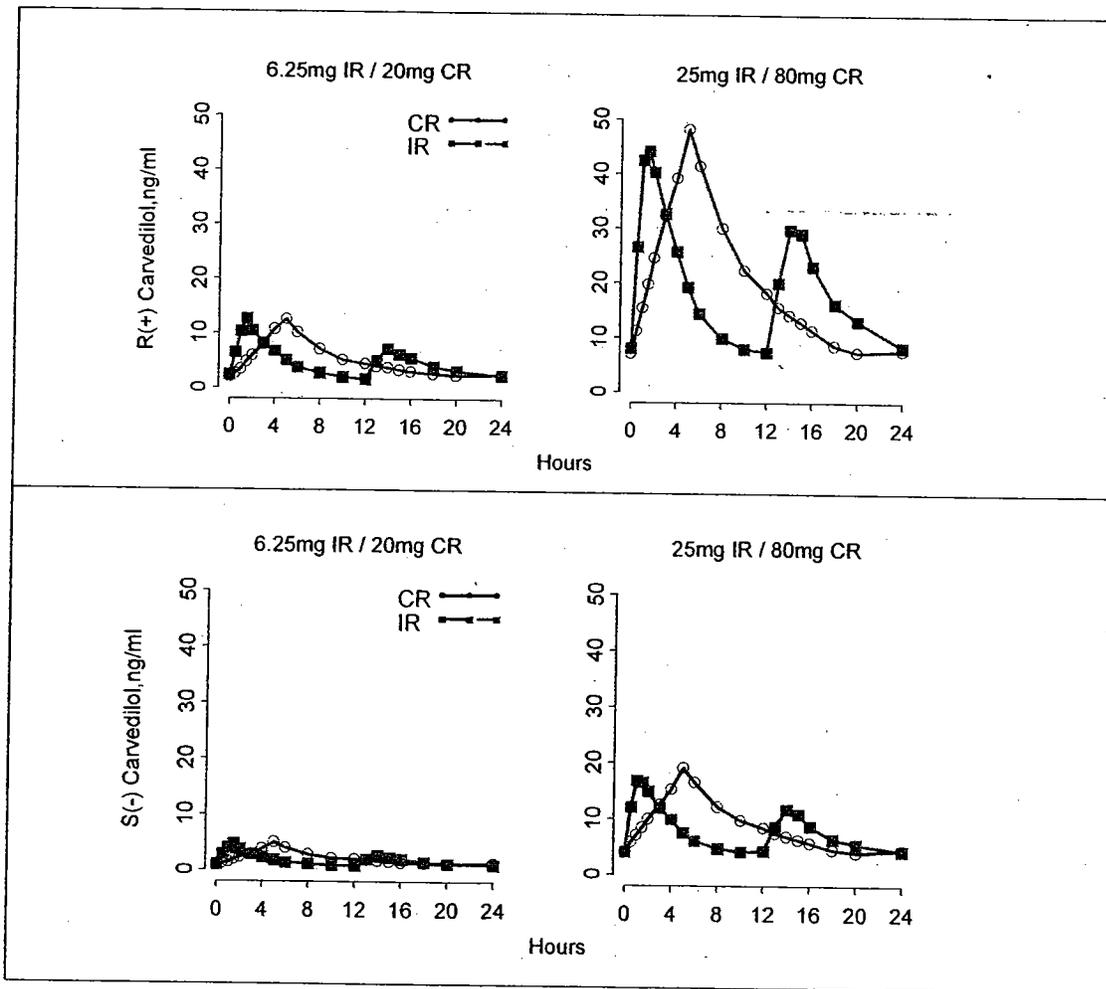
Parameter	Mean (CVb%)		CR:IR Ratio	90% CI
	60 mg q24h CR	25 mg q12h IR		
<i>R(+)-carvedilol</i>				
C _{max} , ng/ml	46.62 (62.7%)	46.12 (49.8%)	1.09	0.91, 1.30
AUC, ng.h/ml	350 (45.7%)	375 (51.7%)	1.10	0.98, 1.23
T _{max} , h	5.0 (1.5, 6.0)	1.5 (0.5, 3.0)	3.24	2, 4.3
<i>S(-)-carvedilol</i>				
C _{max} , ng/ml	19.75 (67.9%)	17.82 (49.2%)	1.09	0.90, 1.33
AUC, ng.h/ml	165 (43.0%)	143 (42.0%)	1.19	1.05, 1.35
T _{max} , h	5.0 (1.5, 6.0)	1.5 (0.5, 4.0)	3.50	2.01, 4.13

Multiple Dose Pharmacokinetics in Patients with Essential Hypertension

The multiple-dose pharmacokinetics of R (+) and S(-) carvedilol were assessed in male and female patients with essential hypertension following administration of low (6.25 mg IR q12 h / 20 mg CR q24h) and high (25 mg IR q12h or 80 mg CR q24h) dose carvedilol regimens in a crossover fashion (study 902, Appendix 4.2.5). Figure 7, Table 9, and Table 10 summarizes the steady state pharmacokinetics of R(+) and S(-) carvedilol.

Steady-state exposure to R(+) and S(-) carvedilol following once daily administration of 20 mg and 80 mg CR capsules were equivalent to the exposure with 6.25 mg and 25 mg q12h IR tablets, respectively. The 90% confidence intervals for the geometric mean CR:IR ratios for AUC, C_{max} and C_{tau} fell within the equivalence bounds of 80-125%. T_{max} values were 3 to 4 hours longer with CR capsules. The fluctuation between peak and trough concentrations was comparable between the CR and IR formulations.

Figure 7. Mean Concentration-Time Profile Following Multiple-Dose Administration of Carvedilol CR and Immediate-Release Carvedilol



**Table 9. Summary of Multiple-Dose Pharmacokinetic Parameters for R(+)
Carvedilol in Patients with Essential Hypertension
(Reference Table 9.5/ 105517/ Study 902)**

Parameter	Mean (CVb%)		Geometric Mean Ratio (CR/IR)	90% CI
	CR	IR		
Low Dose Regimen (6.25 mg Q12H IR / 20 mg Q24H CR)				
Cmax, ng/ml	14.5 (73.8%)	15.5 (71.8%)	0.94	0.82, 1.09
AUC, ng.h/ml	122 (80.4%)	111 (71.7%)	1.06	1.00, 1.12
Ctau, ng/ml	2.32 (153%)	2.43 (124%)	0.94	0.81, 1.10
Tmax, h	5 (1 – 20)	1.5 (0.5 – 4.0)	3.44	3.00, 3.94
% Fluctuation	268 (35%)	249 (33.4%)	--	--
High Dose Regimen (25 mg Q12H IR / 80 mg Q24H CR)				
Cmax, ng/ml	53.3 (65.5%)	54.5 (54.4%)	0.94	0.86, 1.03
AUC, ng.h/ml	457 (67.3%)	420 (61.2%)	1.05	1.00, 1.11
Ctau, ng/ml	7.32 (99.7%)	7.95 (92.0%)	0.85	0.74, 0.97
Tmax, h	5 (1 – 10)	1.13 (0.08 – 3.0)	3.5	3.00, 3.99
% Fluctuation	264 (23.6%)	282 (43.0%)	--	--

**Table 10. Summary of Multiple-Dose Pharmacokinetic Parameters for S(-)
Carvedilol in Patients with Essential Hypertension
(Reference Table 9.5/ 105517/ Study 902)**

Parameter	Mean (CVb%)		Geometric Mean Ratio (CR/IR)	90% CI
	CR	IR		
Low Dose Regimen (6.25 mg Q12H IR / 20 mg Q24H CR)				
Cmax, ng/ml	5.61 (65.7%)	5.93 (72.3%)	1.00	0.86, 1.16
AUC, ng.h/ml	49.9 (63.9%)	41.3 (57.2%)	1.18	1.10, 1.27
Ctau, ng/ml	1.16 (113%)	1.01 (85.4%)	1.08	0.94, 1.23
Tmax, h	5 (1.5 – 13)	1.2 (0.5 – 4.0)	3.5	3.00, 4.00
% Fluctuation	219 (35.7%)	218 (28.5%)	--	--
High Dose Regimen (25 mg Q12H IR / 80 mg Q24H CR)				
Cmax, ng/ml	21.6 (56.4%)	22.1 (53.6)	0.97	0.85, 1.10
AUC, ng.h/ml	200 (54.0%)	175 (49.7%)	1.12	1.05, 1.19
Ctau, ng/ml	4.32 (84.6%)	4.24 (62.0%)	0.91	0.81, 1.02
Tmax, h	5.0 (1.0 – 10.0)	1.0 (0.08 – 3.0)	3.5	3.21, 4.00
% Fluctuation	223 (24.8%)	243 (41.9%)	--	--

The steady state exposure to the active metabolite, 4'-hydroxyphenyl (M4), was assessed in study 902 at the high dose level. After administration of each formulation, the M4 concentrations were in parallel with total carvedilol concentrations (Figure 8). AUC and Cmax were similar for the CR and IR formulations (Table 11). The mean metabolite to total carvedilol ratio was 9 to 10% for both formulations.

Figure 8. Mean Steady-State Concentration-Time Profiles of Carvedilol and 4'-hydroxyphenyl Carvedilol (M4) Following Administration of 25 mg BID IR Tablets and 80mg QD CR Capsules

(Reference Figure 12/ Summary of Clinical Pharmacology)

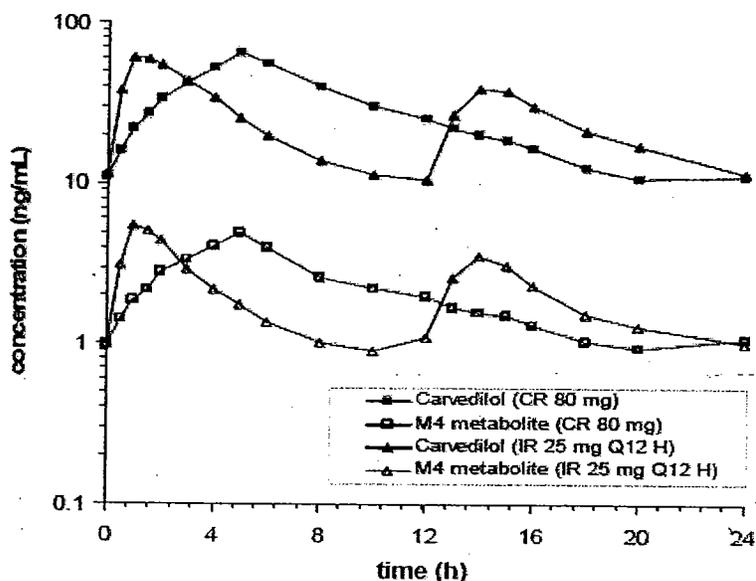


Table 11. Summary of Multiple-Dose Pharmacokinetic Parameters for the 4'-Hydroxyphenyl (M4) Carvedilol Metabolite in Patients with Essential Hypertension
(Reference Table 26/Study 902)

Parameter	Mean (CVb%)	
	80 mg QD CR	25 mg BID IR
Cmax, ng/ml	5.53 (43.0%)	6.16 (47.2%)
AUC, ng.h/ml	46.9 (42.6%)	44.2 (35.5%)
Tmax, h	5.0 (1.0 – 10.0)	1.5 (0.5 – 4.0)

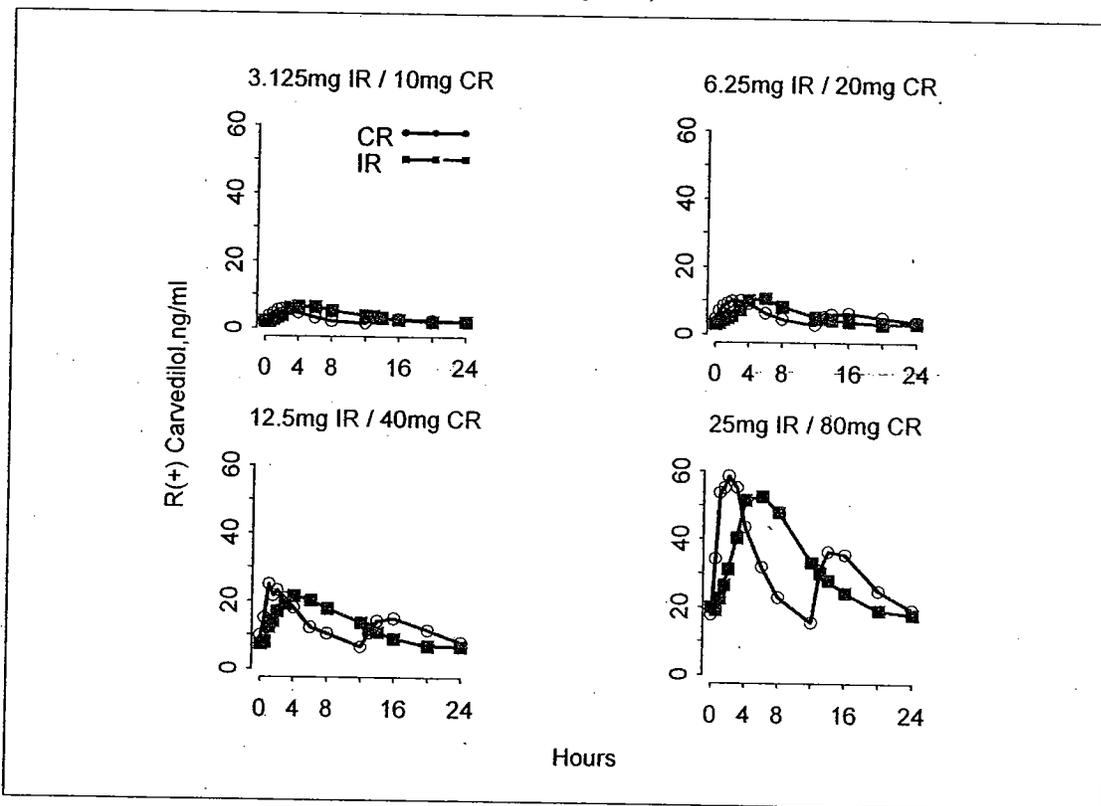
Multiple Dose Pharmacokinetics in Patients with Mild to Severe Heart Failure and Post-MI Patients with LVD

The multiple-dose pharmacokinetics of R(+) and S(-) carvedilol were assessed in male and female patients with mild to severe heart failure and post-MI patients with LVD (study 369, Appendix 4.2.7). Patients received IR tablets (3.125 mg, 6.25 mg, 12.5 mg,

and 25 mg) for 14 days then received an equivalent CR dose (10 mg, 20 mg, 40 mg and 80 mg) for 14 days. Figure 9, Figure 10, and Table 12 summarize the steady state pharmacokinetics of R(+) and S(-) carvedilol in this patient population.

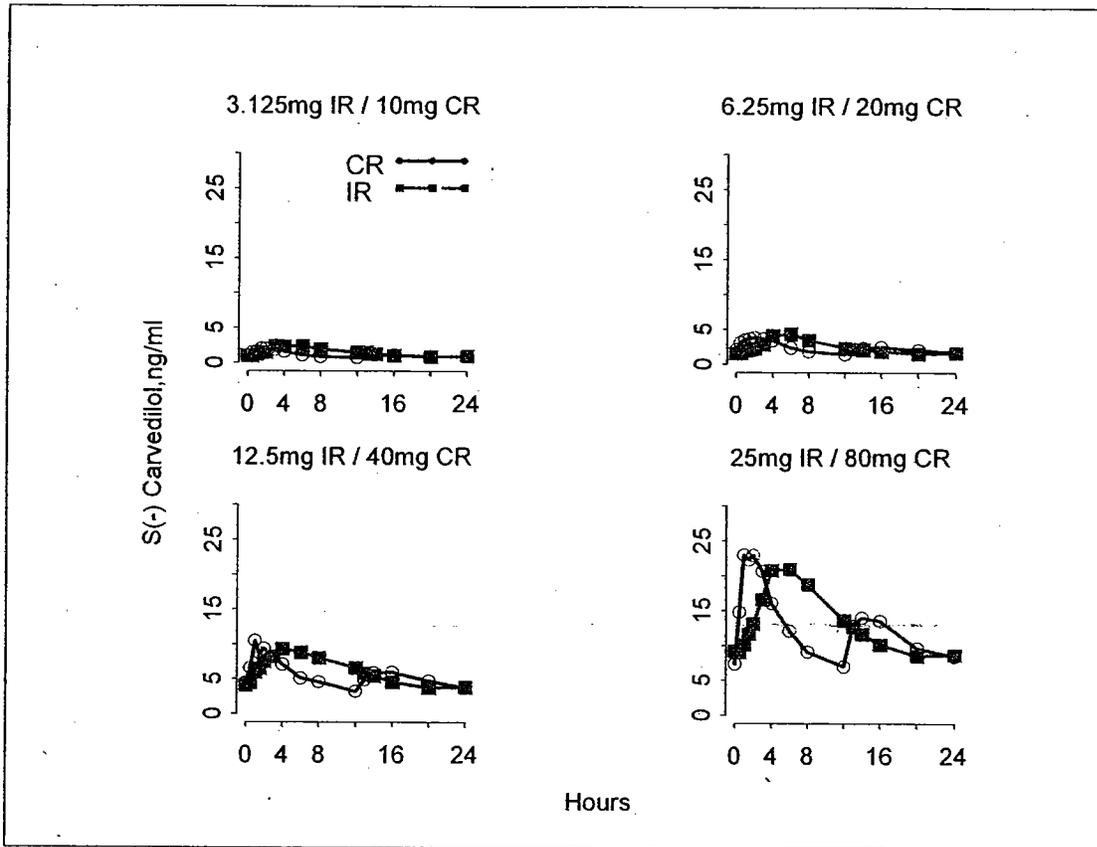
At all dose levels, exposure to R(+) and S(-) carvedilol observed with carvedilol CR capsules were similar to the exposure observed with IR tablets. Using pooled data across dose groups, the 90% confidence intervals of the CR:IR ratios for C_{max}, AUC, and C_{tau} fell within an 80% to 125% equivalence interval.

Figure 9. Mean R(+) Carvedilol Concentration-Time Profile Following Multiple-Dose Administration of Carvedilol CR Capsules and Immediate-Release Tablets to Patients with CHF and Post-MI LVD (Study 369)



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Figure 10. Mean S(-) Carvedilol Concentration-Time Profile Following Multiple-Dose Administration of Carvedilol CR Capsules and Immediate-Release Tablets to Patients with CHF and Post-MI LVD (Study 369)



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Table 12. Summary of Multiple-Dose Pharmacokinetic Parameters for R(+) and S(-) Carvedilol in Patients with CHF and Post-MI LVD
(Reference Table 22/ 2.7.2 Clinical Pharmacology Summary)

Analyte	Regimen	N	AUC(0-t) ¹ (ng-hr/mL)	C _{max} ¹ (ng/mL)	T _{max} ² (hr)	C _τ ¹ (ng/mL)
R(+)-	IR 3.125mg bid	36	53.5 (79.4)	6.10 (67.1)	1.95 (0.00-6.00)	1.13 (140)
	IR 6.25mg bid	49	103 (73.4)	11.0 (61.2)	1.92 (0.00-6.03)	2.43 (107)
	IR 12.5mg bid	46	252 (63.6)	26.8 (58.9)	1.51 (0.00-11.75)	6.24 (97.0)
	IR 25mg bid	42	552 (94.0)	60.6 (70.3)	1.51 (0.50-12.00)	11.6 (144)
	CR 10mg uid	36	64.9 (85.8)	6.48 (92.0)	4.04 (1.00-24.00)	1.37 (114)
	CR 20mg uid	49	109 (70.0)	10.6 (58.6)	5.67 (1.00-8.00)	2.28 (106)
	CR 40mg uid	46	248 (70.3)	23.0 (69.0)	4.00 (0.50-12.00)	4.71 (119)
	CR 80mg uid	42	551 (104)	53.8 (84.6)	6.00 (3.00-16.00)	9.91 (169)
S(-)-	IR 3.125mg bid	36	20.9 (73.6)	2.27 (72.1)	1.95 (0.00-6.00)	0.519 (123)
	IR 6.25mg bid	49	43.0 (66.5)	4.33 (60.0)	1.52 (0.00-6.03)	1.24 (88.1)
	IR 12.5mg bid	46	108 (59.4)	11.0 (59.9)	1.50 (0.00-11.75)	3.02 (85.9)
	IR 25mg bid	42	242 (70.5)	25.9 (61.1)	1.50 (0.50-12.00)	6.12 (97.6)
	CR 10mg uid	36	27.7 (76.8)	2.68 (91.3)	4.04 (1.00-24.00)	0.671 (105)
	CR 20mg uid	49	48.9 (66.9)	4.35 (61.4)	5.67 (0.98-8.00)	1.24 (91.1)
	CR 40mg uid	46	122 (63.9)	10.2 (66.4)	4.00 (0.50-24.00)	2.82 (105)
	CR 80mg uid	42	254 (80.2)	22.7 (71.0)	6.00 (3.00-16.00)	5.72 (119)

1. Geometric mean (CVb%)
2. Median (range)

2.2.5.2 How does the PK of the drug and its major metabolites in healthy adults compare to that in patients?

Figure 11 and Figure 12 presents a cross-study comparison of steady state exposure to R(+) and S(-) carvedilol following administration of the CR capsules. Patients with heart failure and post-MI patients with LVD have higher exposure to carvedilol (as measured by AUC and C_τ) compared to patients with essential hypertension.

The steady state pharmacokinetics of carvedilol CR was not studied in healthy volunteers.

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Figure 11. Mean (95% CI) of R(+) Carvedilol PK Parameters Stratified by Patient Population

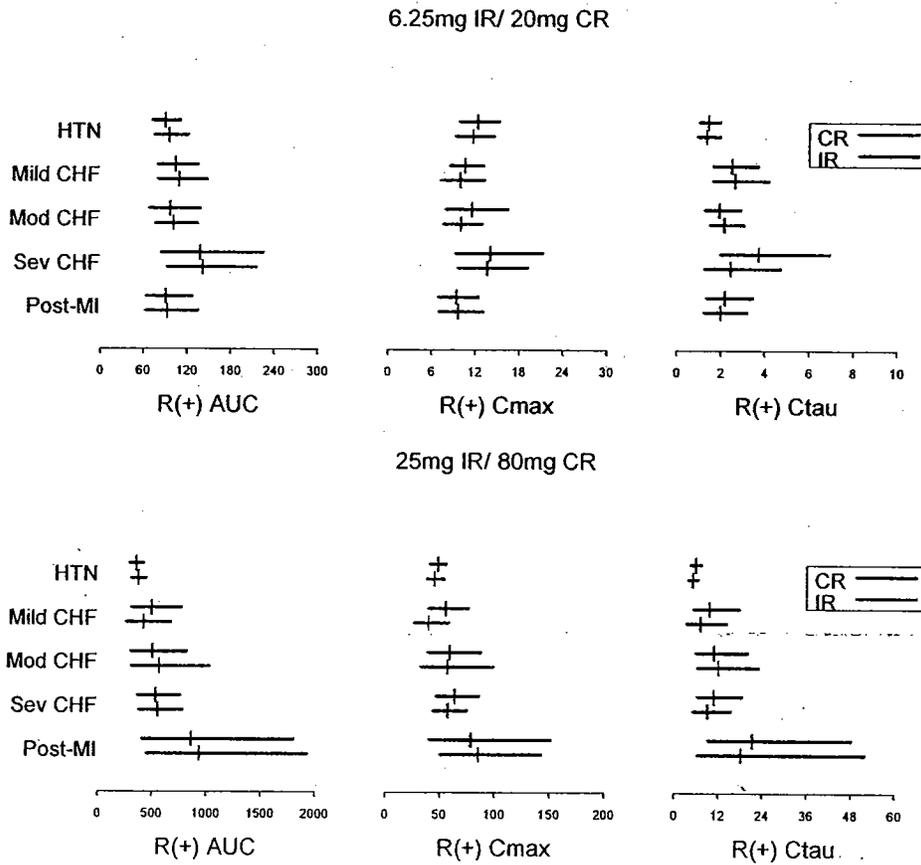
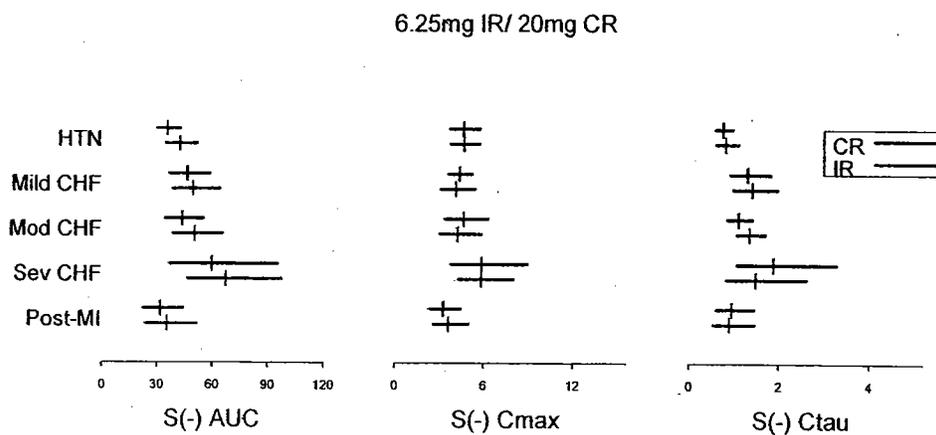
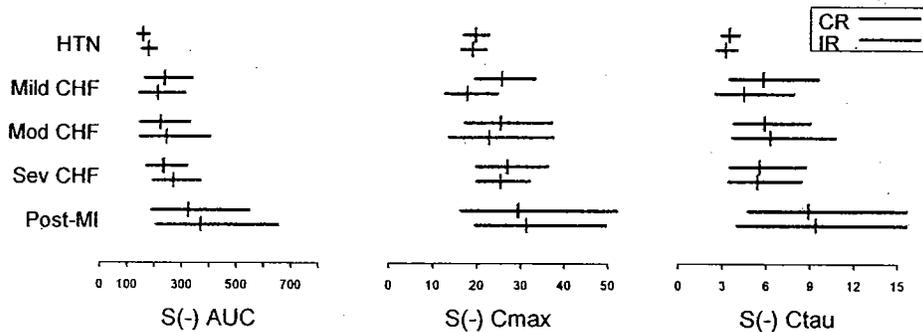


Figure 12. Mean (95% CI) of S(-) Carvedilol PK Parameters Stratified by Patient Population



25mg IR/ 80mg CR



2.2.5.3 What are the characteristics of drug absorption?

According to the label, carvedilol is rapidly and extensively absorbed following oral administration of immediate release tablets, with absolute bioavailability of approximately 25% to 35% due to first-pass metabolism.

The absorption of carvedilol CR is slower than the IR formulation with peak concentrations occurring approximately 5 hours after dosing.

2.2.5.4 What are the characteristics of drug distribution?

According to the label, carvedilol is more than 98% bound to plasma proteins, primarily albumin. The plasma-protein binding is independent of concentration over the therapeutic range.

According to the population PK model, the V/F is 1000 L for R-carvedilol and 3050 L for S-carvedilol, indicating substantial distribution into extravascular tissues.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Carvedilol is extensively metabolized. Following oral administration of radiolabelled carvedilol to healthy volunteers, less than 2% of the dose was excreted unchanged in the urine.

2.2.5.6 What are the characteristics of drug metabolism?

Carvedilol is metabolized by aromatic ring oxidation and glucuronidation.

The primary P450 enzymes responsible for the metabolism of both R- and S-carvedilol in human liver microsomes were CYP2D6 and CYP2C9 and to a lesser extent CYP3A4, 2C19, 1A2, and 2E1. CYP2D6 is thought to be the major enzyme in the 4'- and 5'-hydroxylation of carvedilol.

Carvedilol undergoes stereoselective first-pass metabolism with plasma levels of R-carvedilol approximately 2 to 3 times higher than S-carvedilol following oral administration of carvedilol CR. Plasma clearance values are 176 L/h and 399 L/h for the R(+) and S(-) enantiomers, respectively.

2.2.5.7 What are the characteristics of drug elimination?

The metabolites of carvedilol are excreted primarily via the bile into the feces.

2.2.5.8 Based on PK parameters, what is the degree of linearity in the dose-concentration relationship?

The dose-proportionality of R(+) and S(-) carvedilol were assessed in healthy male and female volunteers following administration of 10 mg, 20 mg, 40 mg and 80 mg carvedilol CR with food (study 903, Appendix 4.2.3). The mean C_{max} and AUC increased proportionally with dose. Table 13 summarizes the pharmacokinetic parameters.

Table 13. Statistical Analyses of PK Parameters: Power Model
(Reference Table 7/Section 7.3/Study 903)

Parameter	Effect	Point Estimate	90% CI
R(+)-carvedilol			
AUC(0-t)	Log (dose)	1.11	(1.08, 1.14)
AUC(0-t')	Log(dose)	1.06	(1.03, 1.09)
C _{max}	Log (dose)	1.06	(1.02, 1.11)
S(-)-carvedilol			
AUC(0-t)	Log (dose)	1.20	(1.17, 1.23)
AUC(0-t')	Log (dose)	1.08	(1.05, 1.11)
C _{max}	Log(dose)	1.09	(1.05, 1.14)

2.2.5.9 How do the PK parameters change with time following chronic dosing?

Study 906 (Appendix 4.2.4) evaluated the effect of evening dosing on the single dose pharmacokinetics of R(+) and S(-) carvedilol compared to morning dosing. Evening administration of 80 mg CR capsule resulted in an approximate 10% decrease in AUC of both R(+) and S(-) carvedilol and a decrease in C_{max} of 15% to 19% compared to morning administration. There was also a decrease in rate of absorption with evening administration as T_{max} values were 1.5 hours longer. Diurnal variation in the pharmacokinetics of carvedilol is also observed with the IR formulation.

Based on population pharmacokinetic analysis of plasma R(+) and S(-) carvedilol concentration from studies 902 and 367, there is no evidence to suggest that clearance changes over time.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients?

In the phase I studies where poor metabolizers of CYP2D6 were excluded, the percent coefficient of variation for C_{max} and AUC were approximately 50%.

Based on population pharmacokinetic analysis of plasma R(+) and S(-) carvedilol concentration from studies 902 and 367, the between subject variability for CL/F and V_c/F are 50% and 100%, respectively.

In patient with CHF or Post-MI, coefficient of variation for C_{max} and AUC ranged from 60% to 100%.

The within-subject variability which was computed for all studies is summarized in Table 14. The within-subject variability after replicate administration of the CR formulation (study 903) was comparable to the variability observed with the IR formulation (Study 271, historical data).

Table 14. Within-Subject Variability in Volunteers and Patients

Study	Within-Subject Variability (%CV)	Inter-Day Variability (%CV)
400 Relative Bioavailability	R-carvedilol: 17.6% to 34.9% S-carvedilol: 19.8% to 34.9%	
376 Food Effect	Total carvedilol: 24.5% to 29.1%	
903 Dose-proportionality	R-carvedilol: 18.4% to 26.7% S-carvedilol: 18.5% to 27.7%	
906 Diurnal variation	R-carvedilol: 23.8% to 31.3% S-carvedilol: 24.5% to 32.0%	R-carvedilol: 14.7% to 26.0% (vs. 16.5% to 24.3% for IR in Study 271) S-carvedilol: 15.9% to 29.9% (vs. 22.4% to 29.7% for IR in Study 271)
902 Steady-state PK and PD	R-carvedilol: 14.6% to 38.5% S-carvedilol: 16.7% to 37.4%	
369 Phase III in patients with CHF and Post-MI LVD	R-carvedilol: 28.0% to 49.4% S-carvedilol: 27.6% to 46.7%	

Within-subject variability: $CV_w (\%) = \sqrt{[\exp(MSE) - 1]} \times 100$

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The impact of heart failure and hypertension on the steady state pharmacokinetics of carvedilol were assessed in studies 369 and 902, respectively. The impact of these covariates is discussed in section 2.2.5.1.

2.3.2 Based upon what is known about E-R relationships and their variability, what dosage regimen adjustments are recommended for each group?

2.3.2.1 Elderly

No dose adjustment in the elderly.

2.3.2.2 Pediatric Patients

The assessment of the safety and effectiveness of carvedilol in pediatric patients is ongoing under investigational IND 58,999 in Protocol 105517/321 entitled "A Multicenter, Placebo-Controlled, 8-Month Study of the Effect of Twice Daily Carvedilol in Children with Congestive Heart Failure Due to Systemic Ventricular Systolic Dysfunction."

2.3.2.3 Race

No dose adjustment for race.

2.3.2.4 Renal Impairment

No dose adjustment for renal impairment.

2.3.2.5 Hepatic Impairment

The use of carvedilol CR in patients with clinically manifest hepatic impairment is not recommended. Administration of immediate release carvedilol to patients with cirrhotic liver disease caused a 4- to 7-fold increase in exposure to carvedilol.

2.3.3 What pregnancy and lactation use information is there in the label?

Pregnancy Category C.

It is not known whether this drug is excreted in breast milk.

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2.4 Extrinsic Factors

2.4.1 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The sponsor performed the following in vivo drug interaction studies with the immediate release tablets: rifampin, cimetidine, glyburide, hydrochlorothiazide, digoxin, torsemide, and warfarin.

2.4.2 What are the drug-drug interactions?

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

The primary P450 enzymes responsible for the metabolism of both R(+) and S(-) carvedilol in human liver microsomes were CYP2D6 and CYP2C9 and to a lesser extent CYP3A4, 2C19, 1A2, and 2E1. CYP2D6 is thought to be the major enzyme in the 4' and 5' hydroxylation of carvedilol, with a potential contribution from 3A4. CYP2C9 is thought to be of primary importance in the O methylation pathway of S() carvedilol.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Carvedilol is subject to the effects of genetic polymorphism with poor metabolizers of debrisoquin (a marker for cytochrome P450 2D6) exhibiting 2 to 3 fold higher plasma concentrations of R(+) carvedilol compared to extensive metabolizers. In contrast, plasma levels of S(-) carvedilol are increased only about 20% to 25% in poor metabolizers, indicating this enantiomer is metabolized to a lesser extent by cytochrome P450 2D6 than R(+) carvedilol. The pharmacokinetics of carvedilol do not appear to be different in poor metabolizers of S mephenytoin (patients deficient in cytochrome P450 2C19).

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

According to the literature, carvedilol is not an inhibitor and/or inducer of CYP enzymes.

2.4.2.4 Is the drug an inhibitor and/or an inducer of PGP transport processes?

There is some evidence in the literature that carvedilol is a substrate and an inhibitor of PGP (Bachmakov I et al. Characterization of beta-adrenoceptor antagonists as substrates and inhibitors of the drug transporter P-glycoprotein. *Fundamental & Clinical Pharmacology* 2006; **20(3)**:1472-82). The IC₅₀ for P-gp inhibition is 0.16 μM. The sponsor has already conducted in vivo drug-interaction studies with digoxin-carvedilol and cyclosporine-carvedilol.

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

It is not known if there are other metabolic/transporter pathways.

2.4.2.6 Does the label specify co-administration of another drug?

This drug is not to be co-administered with another drug.

2.4.2.7 What other co-medications are likely to be administered to the target population?

Pharmacodynamic interactions are described in section 2.4.2.8.

2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Proton Pump Inhibitors: There is no clinically meaningful increase in AUC and C_{max} with concomitant administration of carvedilol CR with pantoprazole (study 387).

Inhibitors of CYP2D6: Interactions of carvedilol with strong inhibitors of CYP2D6 (such as quinidine, fluoxetine, paroxetine, and propafenone) have not been studied, but these drugs would be expected to increase blood levels of the R(+) enantiomer of carvedilol.

The following drug interaction studies were performed with the conventional carvedilol tablet.

Rifampin: In a pharmacokinetic study conducted in 8 healthy male subjects, rifampin (600 mg daily for 12 days) decreased the AUC and C_{max} of carvedilol by about 70%.

Cimetidine: In a pharmacokinetic study conducted in 10 healthy male subjects, cimetidine (1,000 mg/day) increased the steady-state AUC of carvedilol by 30% with no change in C_{max} .

Glyburide: In 12 healthy subjects, combined administration of carvedilol (25 mg once daily) and a single dose of glyburide did not result in a clinically relevant pharmacokinetic interaction for either compound.

Hydrochlorothiazide: A single oral dose of carvedilol 25 mg did not alter the pharmacokinetics of a single oral dose of hydrochlorothiazide 25 mg in 12 patients with hypertension. Likewise, hydrochlorothiazide had no effect on the pharmacokinetics of carvedilol.

Digoxin: Following concomitant administration of carvedilol (25 mg once daily) and digoxin (0.25 mg once daily) for 14 days, steady-state AUC and trough concentrations of digoxin were increased by 14% and 16%, respectively, in 12 hypertensive patients.

Torsemide: In a study of 12 healthy subjects, combined oral administration of carvedilol 25 mg once daily and torsemide 5 mg once daily for 5 days did not result in any significant differences in their pharmacokinetics compared with administration of the drugs alone.

Warfarin: Carvedilol (12.5 mg twice daily) did not have an effect on the steady-state prothrombin time ratios and did not alter the pharmacokinetics of R(+) and S(-) warfarin following concomitant administration with warfarin in 9 healthy volunteers.

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

Catecholamine-depleting agents: 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.

Clonidine: 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.

Cyclosporine: Modest increases in mean trough cyclosporine concentrations were observed following initiation of carvedilol treatment in 21 renal transplant patients suffering from chronic vascular rejection. In about 30% of patients, the dose of cyclosporine had to be reduced in order to maintain cyclosporine concentrations within the therapeutic range, while in the remainder no adjustment was needed. On the average for the group, the dose of cyclosporine was reduced about 20% in these patients. Due to wide interindividual variability in the dose adjustment required, it is recommended that cyclosporine concentrations be monitored closely after initiation of carvedilol therapy and that the dose of cyclosporine be adjusted as appropriate.

Digoxin: Digoxin concentrations are increased by about 15% when digoxin and carvedilol are administered concomitantly. Both digoxin and carvedilol slow AV conduction. Therefore, increased monitoring of digoxin is recommended when initiating, adjusting, or discontinuing COREG CR.

Calcium channel blockers: Isolated cases of conduction disturbance (rarely with hemodynamic compromise) have been observed when carvedilol is co administered with diltiazem. As with other agents with β -blocking properties, if COREG CR 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.

Insulin or oral hypoglycemics: Agents with β -blocking properties may enhance the blood sugar reducing effect of insulin and oral hypoglycemics. Therefore, in patients taking insulin or oral hypoglycemics, regular monitoring of blood glucose is recommended.

2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

There are no unresolved questions.

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

Based on in vitro data, concomitant administration of COREG CR with alcohol may affect the modified release properties, potentially resulting in a faster rate of release and

higher than expected peak and lower than expected trough plasma concentrations of carvedilol phosphate (in vitro study described section 4.2.8.5)

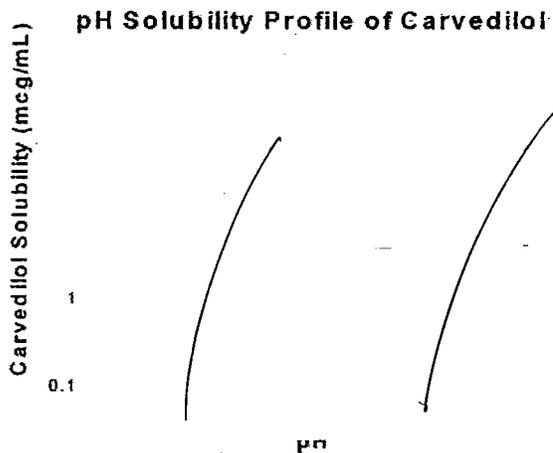
The sponsor recommends that patients be instructed to take carvedilol CR in the morning with food and to separate the ingestion of any alcohol-containing products by at least two hours. The sponsor is also conducting a randomized, open-label, single-dose, four-period crossover study to determine the effects of alcohol on the pharmacokinetics of carvedilol CR.

2.5 General Biopharmaceutics

2.5.1 Based on the biopharmaceutics classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Hence, there was a concern that absorption might be compromised in a formulation that released drug slowly,

Figure 13. Carvedilol Solubility



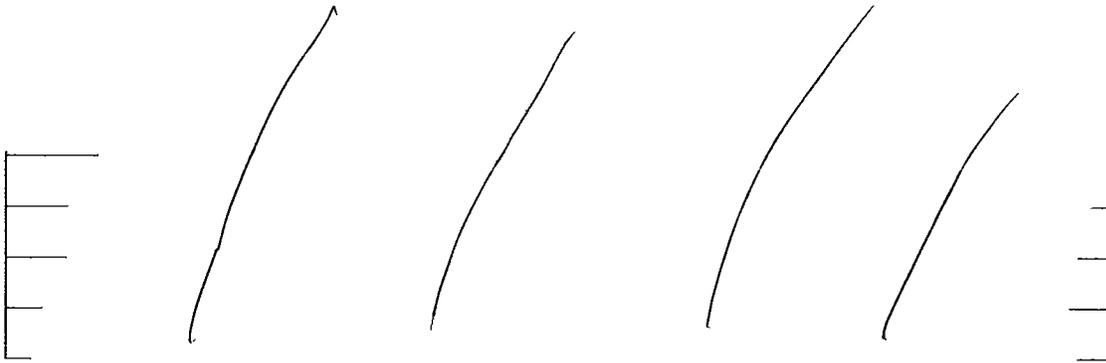
Permeability (in vitro) of a 60 μ M solution of carvedilol across stripped rabbit ileum and distal colon (mucosal-serosal) is compared below with that for mannitol. The values indicate that carvedilol absorptive flux across ileal tissue is low and is moderate in the distal colon. These findings suggest that solubility and permeability might be limiting factors in intestinal absorption but that some absorption in the lower GI tract is feasible if solubility in that region could be improved.

	Carvedilol	Mannitol
Ileum	0.009 \pm 0.003 cm/h	0.004 \pm 0.002 cm/h
Distal Colon	0.065 \pm 0.032 cm/h	0.010 \pm 0.012 cm/h

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the immediate release formulation?

Based on the geometric mean AUC values, the steady-state relative bioavailability (normalized to mg of carvedilol free base, Table 15) of R(+) and S(-) carvedilol is approximately 82% and 89%, respectively (data obtained from Table 9 and Table 10, study 902).

The single dose relative bioavailability () is approximately 81% for R(+) carvedilol and 89% for S(-) carvedilol (Table 8, study 400). This study used the final formulation of carvedilol CR but with a slightly lower amount of drug substance ().



2.5.2.1 What data support or do not support a waiver of *in vivo* BE study?

To compare the commercial batches (SUPAC MR level 2 scale-up and level 2 site change) to the clinical biobatches, multipoint dissolution profiles were obtained in the proposed dissolution media (0.1N HCl) and three other media ().

The similarity factor (F2) ranged from 55 to 97 when comparing the biobatches (test) to the commercial batch (reference) providing evidence that the dissolution curves are similar in the four media.

A biowaiver for the level II site change can be granted for all capsules strengths once the sponsor has submitted multipoint dissolution data in several media using methodology which incorporates the following recommendations:

- The recommended range at any dissolution time point is () deviation from the mean dissolution profile obtained from the clinical lots. Without support from *in vivo* BE data, the reviewer recommends a specification of NLT () and NMT () for the 8-h time point.
- The last time point should be the time point where at least 80% of the drug has dissolved. Based on the dissolution profiles for the biobatches and commercial batches, it is recommended to ().
- The sponsor has proposed a rotation speed of 100 rpm for USP Apparatus II. ()

2.5.2.2 What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

A bioequivalence trial comparing clinical to the to-be-marketed formulation was not required for this submission.

2.5.2.3 If the formulation does not meet the standard criteria for bioequivalence, what clinical pharmacology and/or safety and efficacy data support the approval of the to-be-marketed product?

A bioequivalence trial comparing clinical to the to-be-marketed formulation was not required for this submission.

2.5.3 What is the effect of food on the bioavailability of the drug from the dosage form?

The sponsor conducted a randomized, open-label, single-dose, four-period crossover study (Study 376, Appendix 4.2.2) to assess the effect of food on the bioavailability of 80 mg of carvedilol CR. Study medication was administered under fasting conditions; within 30 minutes of a high-fat breakfast (meal was equivalent to 1020 calories; 58g carbohydrates, 33g protein, 58-75 g fat); within 30 minutes of a standard breakfast (meal was equivalent to approximately 490 calories, 77g carbohydrates, 28g protein, and 13g of fat), and sprinkled with applesauce administered 30 minutes after the start of a standard breakfast.

There is no evidence of dose dumping when carvedilol CR is administered with a high fat meal, or sprinkled with applesauce (Table 16). Administration of 80 mg CR capsule with a high-fat meal increased AUC and C_{max} by 20% compared to a standard meal. Administration of 80 mg CR capsule with sprinkled over applesauce following a standard meal did not affect AUC but decreased C_{max} by 20% compared to administration with a standard meal.

Compared to the administration of carvedilol CR under fasting conditions, a high fat meal increased AUC and C_{max} by 60% and 107%, respectively, as well as increased T_{max} by 1 hour.

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Table 16. Food Increases the Bioavailability of Carvedilol
(Reference Table 7/Section 7.3/Study 376)

Parameter	Comparison	Point Estimate	90% CI
Fasted vs Standard Meal			
AUC(0-t) ¹	A:B	0.73	(0.64, 0.83)
AUC(0-t) ¹	A:B	0.73	(0.64, 0.83)
C _{max} ¹	A:B	0.57	(0.49, 0.67)
T _{max} ² (hr)	A-B	-1.00	(-2.00, 0.00)
High-fat Meal vs Standard Meal			
AUC(0-t) ¹	C:B	1.18	(1.04, 1.35)
AUC(0-t) ¹	C:B	1.19	(1.04, 1.35)
C _{max} ¹	C:B	1.19	(1.02, 1.39)
T _{max} ² (hr)	C-B	0.00	(-0.50, 0.50)
High-fat Meal vs Fasted			
AUC(0-t) ¹	C:A	1.62	(1.42, 1.84)
AUC(0-t) ¹	C:A	1.64	(1.44, 1.87)
C _{max} ¹	C:A	2.07	(1.78, 2.42)
T _{max} ² (hr)	C-A	1.00	(-0.50, 2.13)
Applesauce + Standard Meal vs Standard Meal			
AUC(0-t) ¹	D:B	0.99	(0.87, 1.12)
AUC(0-t) ¹	D:B	0.99	(0.87, 1.13)
C _{max} ¹	D:B	0.82	(0.70, 0.96)
T _{max} ² (hr)	D-B	0.00	(-0.50, 1.00)

1. Point estimate represents the ratio of adjusted geometric means between regimens
2. Point estimate represents the estimated median difference between regimens

Regimen:

- A: 80 mg intact carvedilol phosphate CR under fasting conditions
- B: 80 mg intact carvedilol phosphate CR following a standard meal
- C: 80 mg intact carvedilol phosphate CR following a high fat meal
- D: 80 mg carvedilol phosphate CR sprinkled on applesauce following a standard meal

Source Data: Table 7.1, Table 7.2 and Table 7.5 to Table 7.9.

2.5.4 When would a fed BE study be appropriate and was one conducted?

Not applicable.

2.5.5 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

The proposed product dissolution method and proposed specification for the carvedilol CR capsules are shown in Table 17. The CR component of the capsules or CR microparticles is designed to release carvedilol phosphate based on pH and time dependent mechanisms. In 0.1N HCl dissolution media, the release profile presents a delayed release for approximately 2 hours and a gradual release of carvedilol phosphate in the next 22 hours from the CR components (Figure 14).

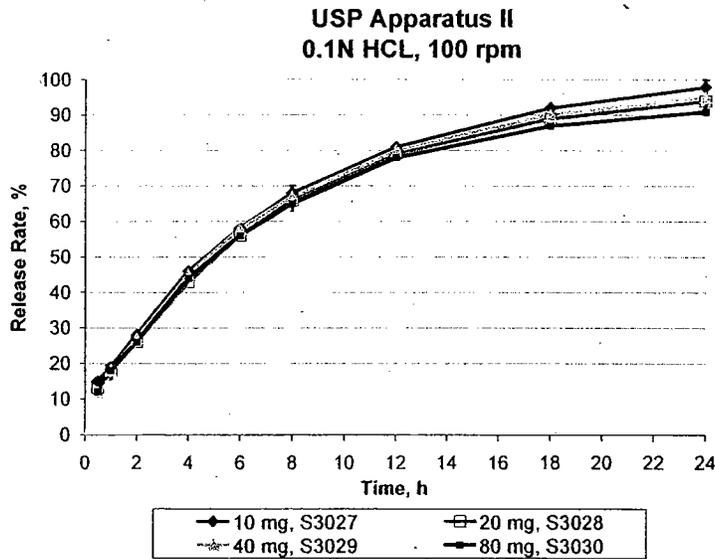
Based on the review of the submitted data, it is recommended to tighten the 8-h time point to \bar{x} mean dissolution value for commercial and clinical batches, to change the

last time point where at least 80% of drug has dissolved

Table 17. Proposed Product Dissolution Method and Specification (described in section 2.4.2.3.4/ m3.2.P.2. Pharmaceutical Development)

Dosage Form:	Capsule
Strengths:	10 mg, 20 mg, 40 mg, 80 mg
Apparatus Type:	USP Apparatus II (paddle)
Media:	0.1 N hydrochloric acid (HCl), pH 1.1-1.2
Media Volume	900 mL at 37°C
Rotation Speed	100
Sampling Times:	
Brief Description of the Dissolution Analytical Method:	
Dissolution Specification:	/ / / /

Figure 14. Dissolution Profiles of Commercial Batches of Carvedilol CR.
(Reference Table 16 in section m3.2.P.5.4. Batch Analyses)



2.5.6 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support approval of the various strengths of the to-be-marketed product?

A bioequivalence trial was not required for this submission.

2.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PKPD relationship?

Refer to the response to Section 2.2.4 for further details.

2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate BE?

No active controls were used in phase 3 trials.

2.5.9 What are significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed.

Not applicable.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma?

A total of four validated bioanalytical methods were used to support the pivotal pharmacokinetic studies (Table 18).

Table 18. Analytical Methods Utilized for Pivotal PK Studies

Studies	Validation Report No.	Validation Type	Reference Method Summary of Changes	Validation Procedure	Facility
376	CD2005-00085-00	Partial	RSD-101SNO/1 1. Simplify the assay procedure by utilizing an mass spectrometer	Selectivity, sensitivity, and linearity Bias and precision Processed samples Dilution above ULQ	GSK 709 Swedeland Rd. King of Prussia, PA 19406
400, 903	CD2003-00592-00	Partial	SKF105517-HUPLVALA	Selectivity, sensitivity, and linearity Bias and precision Processed samples	GSK 709 Swedeland Rd. King of Prussia, PA 19406

367, 369, 902, 906	CD2004- 01420-00	Partial	CD2003-00592-00 1. Reduce plasma volume 2. EDTA vs. Heparin human plasma	Selectivity, sensitivity, and linearity Bias and precision	GSK 709 Swedeland Rd. King of Prussia, PA 19406
902	CD2005/010 57/00	Full	--	Selectivity, sensitivity, and linearity Bias and precision Stability in analytical solution Stability at RT Free-thaw Processed samples Dilution above ULQ	GSK 709 Swedeland Rd. King of Prussia, PA 19406

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2.6.2 Which metabolites have been selected for analysis and why?

The active metabolite, M4 (SB-203231), was selected for analysis in study 902 only.

2.6.3 For all moieties measured, is free, bound, or total measured?

Total carvedilol as well as its enantiomers, R(+) and S(-) carvedilol, were measured.

2.6.4 What bioanalytical methods are used to assess concentrations?

Table 19 summarizes the bioanalytical methods used for analysis.

Table 19. Summary of Bioanalytical Methods

Studies	Validation Report No.	Extraction from Plasma	Method	Analytes	Plasma Concentration Range
376	CD2005-00085-00	using acetonitrile containing an isotopically labeled internal standard, [2H5]-skf-105517. Plasma volume: 50µl	HPLC-M/MS using an	SKF-105517	/ -
400, 903	CD2003-00592-00	using acetonitrile containing an isotopically labeled internal standard, [2H5]-skf-105517 followed by derivation using GITC Plasma volume: 150µl	HPLC-MS/MS using a TurboIonSpray interface and	SKF-105517-S SKF-105517-R	/
367, 369, 902, 906	CD2004-01420-00	using acetonitrile containing an isotopically labeled internal standard, [2H5]-skf-105517 followed by derivation using GITC Plasma volume: 100µl	HPLC-MS/MS using a TurboIonSpray interface	SKF-105517-S SKF-105517-R	/
902	CD2005-01057-00	using an isotopically labeled internal standard, [2H6]-sb-203231 Plasma volume: 100µl	HPLC-MS/MS using a TurboIonSpray interface	SB-203231	/

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Draft Labeling

Deliberative Process

3 DETAILED LABELING RECOMMENDATIONS

The Office of Clinical Pharmacology (OCP/DPE-1) has reviewed the package insert labeling for carvedilol CR capsules and finds it acceptable pending the following revisions shown in appendix 4.1. ~~Strikethrough text~~ is recommended to be deleted and underlined text is recommended to be added.

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 / Draft Labeling

 Deliberative Process

4.2 Individual Study Reviews

4.2.1 Study 400 (Relative Bioavailability)

A Randomized, Single Dose, Three Period Crossover Study of the Bioavailability of Six Carvedilol Modified Release Formulation Capsules in Relation to COREG Immediate Release Formulation (TILTAB) Tablets in Healthy Adult Subjects

Protocol Number: SK&F-105517/400

Investigator: _____

Study Site: The study was conducted at a single site.

/ / / /

Study dates: 16 December 2003 – 08 March 2004

4.2.1.1 Objectives

Study objective was to estimate the relative bioavailability of six different modified-release formulations of 60 mg carvedilol compared to 1 x 25 mg q12h COREG

4.2.1.2 Study Design

This was a randomized, open-label, single-dose, three-period crossover study. Each subject was randomized to one of 33 sequences to receive three of the seven regimens under fed conditions (high fat meal).

Table A 1. Study Treatments

REGIMEN	TREATMENT	MICROPARTICLES	
		IR	
A	50 mg (2 x 12.5 mg q12h) COREG	--	
B	60 mg carvedilol CR		
C	60 mg carvedilol CR		
D	60 mg carvedilol CR		
E	60 mg carvedilol CR		
F	60 mg carvedilol CR		
G	60 mg carvedilol CR		

Healthy adult male and female subjects were included in the study. Subject who were poor metabolizers of CYP2D6 were excluded from participation.

4.2.1.2.1 Formulations

The pilot CR formulations _____

Table A 2. Products used in SK&F-105517/400

TREATMENT	DRUG PRODUCT BATCH NUMBER	DRUG SUBSTANCE BATCH NUMBER	FORMULATION
carvedilol IR	4263V41	--	12.5 mg COREG® tablet
carvedilol CR	031014116	03K9-002 & 1055A1-02	60 mg CR capsule
carvedilol CR	031014138	03K9-002 & 1055A1-02	60 mg CR capsule
carvedilol CR	031014140	03K9-002 & 1055A1-02	60 mg CR capsule
carvedilol CR	031014145	03K9-002 & 1055A1-02	60 mg CR capsule
carvedilol CR	031014147	03K9-002 & 1055A1-02	60 mg CR capsule
carvedilol CR	031014149	03K9-002 & 1055A1-02	60 mg CR capsule

4.2.1.2.2 Pharmacokinetic Assessments

Blood samples were collected in heparinized tubes pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 21, 24, 32, and 48 hours after administration of the CR formulations. For the IR formulation (regimen A), blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 12.25, 12.5, 12.75, 13, 13.5, 14, 15, 16, 18, 20, 24, 32 and 48 hours after administration.

Plasma R(+) and S(-) carvedilol concentrations were analyzed at GSK (Upper Merion, PA) using a validated method based on HPLC-MS/MS (validation report CD2003/00592/00). The performance of the assays is shown in Table A 3.

Table A 3. Performance of Analytical Methodology (collection in heparin)

ANALYTE	METHOD	RANGE ¹ (NG/ML)	LINEARITY (CORRELATION COEFFICIENT)	LLOQ (NG/ML)	QC SAMPLES (NG/ML)	INTER- BATCH PRECISION (%CV)	INTRA- BATCH ACCURACY (%RE)
SKF-105517-S	HPLC-MS/MS						
SKF-105517-R	HPLC-MS/MS						

¹ Calibration range consisted of 10 spiked samples over the specified range.

Plasma concentrations were analyzed by standard noncompartmental methods. Following log_e-transformation, AUC(0-t), AUC(0-t') and C_{max} of carvedilol were analyzed separately by an ANOVA model, fitting subject, period and regimen. Point estimates and 90% confidence intervals for the ratios for the difference between B:A, C:A, D:A, E:A, F:A and G:A were computed.

The within-subject coefficients of variation (CV_w) for AUC(0-t), AUC(0-t') and C_{max} were calculated based on the log_e-normal distribution:

$$CV_w (\%) = \sqrt{[\exp(MSE) - 1] \times 100}$$

where MSE was the mean squared error obtained from the ANOVA.

4.2.1.2.3 Safety Assessments

Assessments of safety included adverse events, clinical laboratory evaluations, and concomitant medications. No formal statistical tests were performed for safety.

4.2.1.3 Study Results

4.2.1.3.1 Subjects

A total of 36 subjects were enrolled and 30 (83%) completed the study. Four subjects withdrew consent, one subject was withdrawn for positive urine test, and the other subject was withdrawn due to decreased blood pressure. A summary of demographic data is presented (Table 4A).

Table A 4. Demographic Summary (Reference Table 10/Section 6.4.1/Study 400)

	Parameter	Age (years)	Height (m)	Weight (kg)
Subjects n=36	Mean	30	1.75	80.4
	SD	9.1	0.08	12.8
	Range	18 – 53	1.61 - 1.91	61.8 – 110.7

86% Male, 14% Female; 75% White, 19% Black, 6% Other

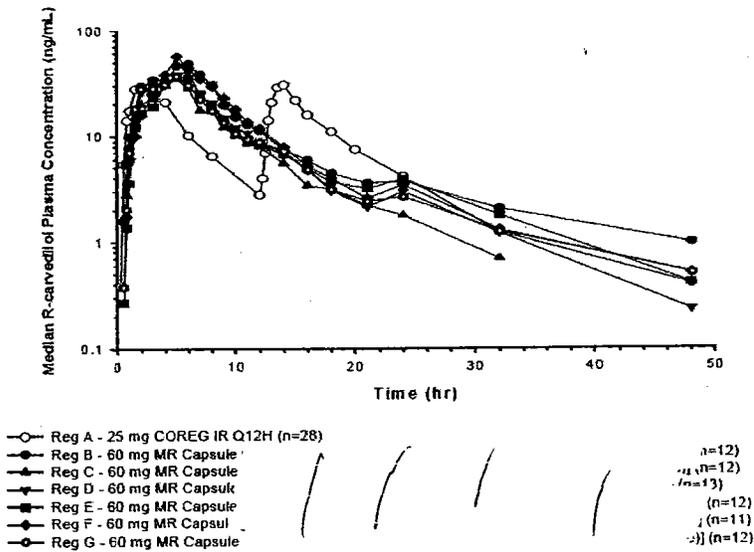
Source: Section 12, Table 12.2

4.2.1.3.2 Pharmacokinetic Results

The results of pharmacokinetic analysis are presented in Figures A1-A2 and Tables A5-A7.

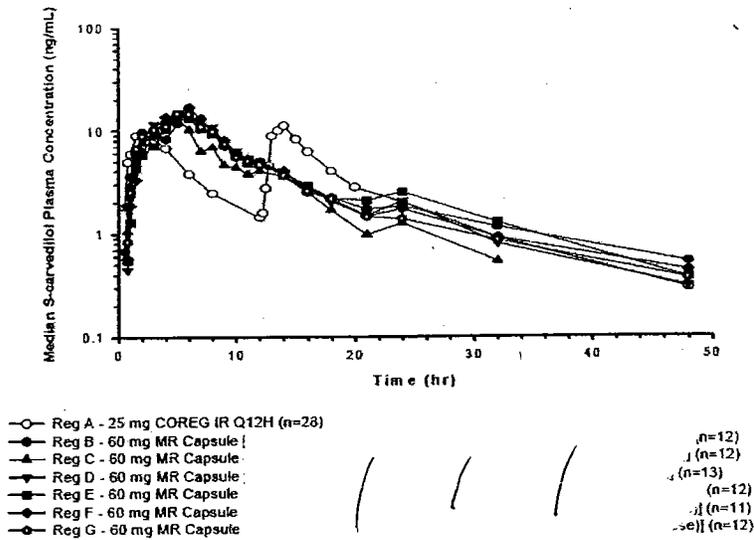
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Figure A 1. Median Time Course of R-Carvedilol Plasma Concentrations (Reference Figure 1/Section 7.0/Study 400)



Source: Section 13, Table 13.8 – Table 13.14

Figure A 2. Median Time Course of S-Carvedilol Plasma Concentrations (Reference Figure 2/Section 7.0/Study 400)



Source: Section 13, Table 13.24 – Table 13.30

Table A 5. Summary of PK Parameters for R- and S-Carvedilol (Reference Table 13/Section 7.0/Study 400)

(R)-Parameter							
	A (n=28)	B (n=12)	C (n=12)	D (n=13)	E (n=12)	F (n=11)	G (n=12)
AUC ₍₀₋₈₎ (ng*hr/mL)	336 (133-801)	480 (196-1272)	300 (160-716)	353 (182-839)	322 (138-649)	373 (156-701)	343 (173-1041)
AUC ₍₀₋₂₄₎ (ng*hr/mL)	334 (133-801)	478 (196-1272)	300 (160-715)	350 (182-839)	313 (138-649)	367 (153-701)	342 (173-1041)
C ₂₄ (ng/mL)	3.84 (1.28-11.55)	4.49 (1.64-15.41)	2.19 (0.83-5.26)	2.62 (0.84-7.25)	3.41 (1.32-7.06)	3.16 (1.29-6.40)	2.82 (0.80-12.26)
C _{max} (ng/mL)	41.7 (15.7-92.5)	56.1 (16.7-161.5)	44.3 (25.8-92.9)	47.8 (19.4-156.7)	40.0 (16.8-108.9)	52.9 (21.5-128.2)	48.4 (28.8-116.4)
t _{max} (hr) ¹	1.50 (0.50-3.02)	6.00 (3.00-6.03)	4.50 (2.00-6.00)	5.02 (1.50-8.00)	5.00 (1.52-6.00)	5.00 (2.00-6.17)	5.00 (2.00-6.00)
HVD (hr) ²	3.45 (1.88-4.95)	5.82 (3.53-8.26)	4.46 (2.57-6.57)	5.67 (3.10-11.1)	5.68 (2.11-9.43)	4.90 (3.51-6.86)	5.05 (2.23-8.41)
Retard Quotient ²	-	1.49 ³ (1.14-2.20)	1.29 ⁴ (0.96-1.72)	2.10 ⁴ (1.12-3.45)	1.84 ⁴ (0.79-2.74)	1.26 ³ (0.73-2.15)	1.53 ⁴ (0.68-2.77)
(S)-Parameter							
AUC ₍₀₋₈₎ (ng*hr/mL)	133 (63-278)	172 (96-413)	127 (68-281)	152 (72-263)	153 (71-273)	166 (89-273)	147 (89-321)
AUC ₍₀₋₂₄₎ (ng*hr/mL)	131 (63-278)	171 (96-412)	127 (68-281)	150 (72-263)	147 (65-273)	160 (89-273)	146 (85-321)
C ₂₄ (ng/mL)	2.02 (1.07-5.59)	2.18 (0.97-6.12)	1.30 (0.70-2.93)	1.62 (0.45-4.45)	2.11 (0.68-3.79)	1.94 (1.07-4.45)	1.77 (1.08-5.39)
C _{max} (ng/mL)	16.1 (6.67-36.9)	18.9 (6.69-61.0)	16.6 (9.52-35.8)	18.6 (8.03-48.9)	16.3 (7.22-62.2)	20.8 (9.60-39.9)	18.7 (8.35-54.8)
t _{max} (hr) ¹	1.50 (0.50-4.00)	6.00 (1.50-6.03)	5.00 (2.00-6.00)	5.03 (1.50-8.00)	5.02 (1.52-6.00)	5.00 (2.00-6.17)	5.00 (2.00-6.40)
HVD (hr) ²	3.20 (1.62-4.48)	5.76 (3.47-10.03)	4.65 (2.97-7.06)	5.58 (2.66-10.28)	6.32 (2.35-14.17)	4.81 (2.70-8.04)	5.39 (1.62-9.33)
Retard Quotient ²	-	1.70 ³ (1.10-3.06)	1.41 ⁴ (1.06-1.68)	2.29 ⁴ (1.10-4.02)	2.19 ⁴ (0.80-4.41)	1.21 ³ (0.74-2.44)	1.81 ⁴ (0.58-2.50)

1. Presented as median (range)
2. Presented as arithmetic mean (range); HVD = Half-value duration
3. n=8
4. n=9

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Table A 6. Statistical Analyses of PK Parameters for R-Carvedilol (Reference Table 14/Section 7.0/Study 400)

Parameter	Comparison	Point Estimate ¹	90% CI	CV _w %
AUC ₍₀₋₈₎	B:A	1.12	(1.00, 1.26)	17.6
AUC ₍₀₋₈₎	B:A	1.13	(1.00, 1.26)	17.0
C _{max}	B:A	1.19	(0.99, 1.44)	28.3
C ₂₄ ²	B:A	0.83	(0.65, 1.06)	37.1
t _{max}	B-A	3.00h ³	(1.50h, 4.50h)	-
AUC ₍₀₋₈₎	C:A	1.00	(0.89, 1.12)	
AUC ₍₀₋₈₎	C:A	1.00	(0.90, 1.12)	
C _{max}	C:A	1.17	(0.98, 1.40)	
C ₂₄ ²	C:A	0.69	(0.55, 0.87)	
t _{max}	C-A	3.24h ³	(2.25h, 4.38h)	
AUC ₍₀₋₈₎	D:A	1.10	(0.98, 1.23)	
AUC ₍₀₋₈₎	D:A	1.10	(0.99, 1.23)	
C _{max}	D:A	1.16	(0.97, 1.39)	
C ₂₄ ²	D:A	0.86	(0.68, 1.08)	
t _{max}	D-A	4.00h ³	(2.50h, 5.01h)	
AUC ₍₀₋₈₎	E:A	1.10	(0.98, 1.23)	
AUC ₍₀₋₈₎	E:A	1.08	(0.96, 1.20)	
C _{max}	E:A	1.09	(0.91, 1.30)	
C ₂₄ ²	E:A	0.98	(0.78, 1.24)	
t _{max}	E-A	3.24h ³	(2.00h, 4.27h)	
AUC ₍₀₋₈₎	F:A	1.01	(0.90, 1.14)	
AUC ₍₀₋₈₎	F:A	1.00	(0.89, 1.12)	
C _{max}	F:A	1.16	(0.97, 1.40)	
C ₂₄ ²	F:A	0.74	(0.58, 0.95)	
t _{max}	F-A	2.92h ³	(1.12h, 3.52h)	
AUC ₍₀₋₈₎	G:A	1.04	(0.93, 1.16)	
AUC ₍₀₋₈₎	G:A	1.05	(0.94, 1.17)	
C _{max}	G:A	1.14	(0.95, 1.36)	
C ₂₄ ²	G:A	0.71	(0.56, 0.90)	
t _{max}	G-A	2.63h ³	(1.75h, 3.50h)	

1. Represents the ratio of adjusted geometric means between regimens
2. R-carvedilol concentration at 24 hours post-dose
3. Represents the estimated median difference between regimens

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Table A 7. Statistical Analyses of PK Parameters for S-Carvedilol (Reference Table 15/Section 7.0/Study 400)

Parameter	Comparison	Point Estimate ¹	90% CI	CV _w %
AUC ₍₀₋₉₎	B:A	1.22	(1.07, 1.39)	19.8
AUC _(0-t)	B:A	1.23	(1.08, 1.39)	18.7
C _{max}	B:A	1.20	(0.98, 1.48)	31.6
C ₂₄ ²	B:A	1.02	(0.81, 1.28)	34.9
t _{max}	B:A	2.50h ³	(1.00h, 4.50h)	-
AUC ₍₀₋₉₎	C:A	1.04	(0.92, 1.19)	
AUC _(0-t)	C:A	1.06	(0.94, 1.19)	
C _{max}	C:A	1.10	(0.90, 1.34)	
C ₂₄ ²	C:A	0.78	(0.62, 0.97)	
t _{max}	C:A	3.38h ³	(2.75h, 4.50h)	
AUC ₍₀₋₉₎	D:A	1.16	(1.02, 1.31)	
AUC _(0-t)	D:A	1.16	(1.03, 1.31)	
C _{max}	D:A	1.14	(0.94, 1.40)	
C ₂₄ ²	D:A	0.95	(0.76, 1.18)	
t _{max}	D:A	3.75h ³	(2.50h, 4.76h)	
AUC ₍₀₋₉₎	E:A	1.19	(1.05, 1.35)	
AUC _(0-t)	E:A	1.15	(1.02, 1.30)	
C _{max}	E:A	1.09	(0.90, 1.33)	
C ₂₄ ²	E:A	1.02	(0.82, 1.27)	
t _{max}	E:A	3.50h ³	(2.01h, 4.13h)	
AUC ₍₀₋₉₎	F:A	1.09	(0.95, 1.24)	
AUC _(0-t)	F:A	1.06	(0.94, 1.21)	
C _{max}	F:A	1.16	(0.94, 1.43)	
C ₂₄ ²	F:A	0.86	(0.68, 1.09)	
t _{max}	F:A	3.03h ³	(1.12h, 3.75h)	
AUC ₍₀₋₉₎	G:A	1.09	(0.96, 1.24)	
AUC _(0-t)	G:A	1.11	(0.98, 1.25)	
C _{max}	G:A	1.07	(0.88, 1.31)	
C ₂₄ ²	G:A	0.81	(0.65, 1.01)	
t _{max}	G:A	2.95h ³	(2.00h, 4.00h)	

1. Represents the ratio of adjusted geometric means between regimens
2. S-carvedilol concentration at 24 hours post-dose
3. Represents the estimated median difference between regimens

4.2.1.3.3 Safety Results

Twenty-two of 36 subjects (61.1%) experienced 57 adverse events. A summary of adverse events is presented in Table A8. The investigator considered 37 of the AEs to be related to study medication with orthostatic hypotension being the most frequently reported.

Table A 8. Summary of Adverse Events (Reference Table 11/Section 9.2)

Adverse Event (preferred term)	Number of Subjects							
	Regimen							Total
	A	B	C	D	E	F	G	
Orthostatic hypotension ²	5	2	1	0	3 ¹	0	2	9
Headache ²	3	4	1	0	1	0	1	7
Dizziness	2	0	0	0	1	0	0	3
Hypotension ²	2	0	0	1	1	0	0	3
Nasal congestion	0	1	1	1	0	0	0	3
Epistaxis	0	0	0	0	1	0	1	2
Anaemia	0	0	0	1	0	0	0	1
Blood pressure fluctuation	0	0	0	0	0	1	0	1
Depressed mood	0	0	0	1	0	0	0	1
Dizziness postural ²	1	0	0	1	0	0	0	1
Dry mouth	0	0	0	0	1	0	0	1
Excoriation	0	0	1	0	0	0	0	1
Fatigue	0	0	0	0	0	0	1	1
Hyperuricaemia	0	0	0	1	0	0	0	1
Lower respiratory tract infection	1	0	0	0	0	0	0	1
Muscle cramp	0	0	0	1	0	0	0	1
Muscle Spasms	0	1	0	0	0	0	0	1
Neutrophilia	0	0	0	1	0	0	0	1
PCO2 abnormal	0	0	0	1	0	0	0	1
Pharyngolaryngeal pain	1	0	0	0	0	0	0	1
Pyuria	0	0	0	1	0	0	0	1
Renal insufficiency	0	0	0	1	0	0	0	1
Somnolence	0	0	0	0	1	0	0	1
Tendonitis	0	0	0	0	1	0	0	1
Venipuncture site bruise	0	0	0	0	1	0	0	1
Venipuncture site haemorrhage	0	0	0	0	0	1	0	1
Venipuncture site inflammation	1	0	0	0	0	0	0	1
Total Number of AEs	16	8	4	11	11¹	2	5	57¹
Number of Subjects with AEs	13	6	3	4	6	1	3	22
Number of Subjects Exposed	28	12	12	13	12	11	12	36

1. One subject had orthostatic hypotension twice following administration of Regimen E. This AE is only counted once for the purpose of this table.

2. At least one subject reported this treatment-emergent AE in more than one session.

Twenty-three subjects experienced 121 instances of vital sign changes with decreases in BP being most frequently reported. A total of 9 subjects met the criteria for orthostatic hypotension as defined in the protocol (a reduction in SBP of 20mmHg or more and/or a reduction of DBP of 10mmHg or more for standing vs. supine measurements). Decreases in blood pressure is an expected finding based on the pharmacology of the drug.

4.2.1.4 Sponsor's Conclusions

- Based on AUC, R-carvedilol exposure following administration of a single 60 mg carvedilol MR capsule was generally comparable to that from a 25 mg COREG IR tablet given Q12H, while C_{max} was, on average, approximately 9-19% higher for the 60 mg carvedilol MR capsules.
- Based on AUC and C_{max}, S-carvedilol exposure following administration of a single 60 mg carvedilol MR capsule was, on average, approximately 4 to 23% and 7 to 20% higher, respectively, compared to a 25 mg COREG IR tablet given Q12H.

- Median tmax was approximately 3 to 4 hours longer for both R- and S-carvedilol following administration of a single 60 mg carvedilol MR capsule compared to a 25 mg COREG IR tablet given Q12H.
- The COREG IR tablet formulation and the six MR capsule formulations were tolerated by healthy adult males and females.
- Decreases in blood pressure and orthostatic hypotension are consistent with the known pharmacology of carvedilol in normotensive volunteers.

4.2.1.5 Reviewer's Comments on Study 400

The single dose relative bioavailability _____ is approximately 81% for R(+) carvedilol and 89% for S(-) carvedilol. This study used the final formulation (Regimen E) of carvedilol CR but with a slightly lower amount of drug substance. _____

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4.2.2 Study 376 (Food Effect)

A Study To Investigate The Effect Of Food And The Effect Of A Sprinkle Dose Regimen On The Pharmacokinetics Of The Carvedilol Phosphate Modified Release Capsule In Healthy Adult Subjects

Protocol Number: SK&F-105517/376

Investigator: / /

Study Site: The study was conducted at a single site.

Study dates: 24 January – 22 March 2005

4.2.2.1 Objectives

Following administration of a single dose of 80 mg of carvedilol CR to healthy volunteers, study objectives were to describe the pharmacokinetics under fasting conditions, with a high fat meal, and in a sprinkle-dose regimen using applesauce.

4.2.2.2 Study Design

This was a randomized, open-label, single-dose, four-period study. Each subject received one the following regimens:

- 80 mg carvedilol CR under fasting conditions.
- 80 mg carvedilol CR 30 minutes after the start of a high fat meal. The high fat breakfast (meal was equivalent to 1020 calories; 58g carbohydrates, 33g protein, 58-75 g fat) consisted of the following: 2 eggs cooked in butter, 2 strips of bacon, 2 pieces of toast, 2 teaspoons of butter, 4 ounces of hash brown potatoes and 8 ounces of whole milk.
- 80 mg carvedilol CR 30 minutes after the start of a standard meal. The standard moderate calorie breakfast (meal was equivalent to approximately 490 calories, 77g carbohydrates, 28g protein, and 13g of fat) consisted of the following: cereal (Corn Flakes or Special K), 200 ml skim milk, 1 strip of bacon (grilled), 1 egg scrambled in milk, 2 slices of toast, 1 teaspoon of butter and ½ cup of fruit juice (apple or orange).
- 80 mg carvedilol CR sprinkled with applesauce administered 30 minutes after the start of a standard meal. The contents of one 80 mg carvedilol phosphate CR capsule were sprinkled on 1 tablespoon of applesauce in a dish. The capsule was opened by slightly squeezing the capsule cap and body and carefully pulling them apart over the applesauce. A second tablespoon of applesauce was then added to the dish and the particles were folded into the applesauce. Subjects were to have swallowed the applesauce without chewing, along with 240 mL of tepid water.

Healthy adult male and female subjects were included in the study.

4.2.2.2.1 Formulations

Table A 9. Products used in SK&F-105517/376

FORMULATIONS	DRUG PRODUCT BATCH NUMBER	DRUG SUBSTANCE BATCH NUMBER	CR FORMULATION
carvedilol CR	X7194	SK&F105517-D 03K9-003	80 mg CR capsule

4.2.2.2.2 Pharmacokinetic Assessments

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 18, 24, 32, and 48 hours after administration.

Plasma total carvedilol concentrations were analyzed at GSK (Upper Merion, PA) using a validated method based on HPLC-MS/MS (validation report CD2005/00085/00). The performance of the assays is shown in Table A 10.

Table A 10. Performance of Analytical Methodology

ANALYTE	METHOD	RANGE ¹ (NG/ML)	LINEARITY (CORRELATION COEFFICIENT)	LLOQ (NG/ML)	QC SAMPLES (NG/ML)	INTER- BATCH PRECISION (%CV)	INTER- BATCH ACCURACY (%RE)
SKF- 105517	HPLC- MS/MS						

¹ Calibration range consisted of 10 spiked samples over the specified range.

Plasma concentrations were analyzed by standard noncompartmental methods.

Following log_e-transformation, AUC(0-t), AUC(0-t') and C_{max} of carvedilol for the carvedilol CR capsule were analyzed separately by analysis of variance (ANOVA) using a mixed effects model fitting fixed effect terms for sequence, period and regimen, and fitting subject (sequence) as a random effect.

The within-subject coefficients of variation (CV_w) for AUC(0-t), AUC(0-t') and C_{max} were calculated based on the loge-normal distribution:

$$CV_w (\%) = \sqrt{[\exp(MSE) - 1]} \times 100$$

where MSE was the mean squared error obtained from the ANOVA.

4.2.2.2.3 Safety Assessments

Assessments of safety included adverse events, clinical laboratory evaluations, and concomitant medications. No formal statistical tests were performed for safety.

4.2.2.3 Study Results

4.2.2.3.1 Subjects

A total of 22 subjects were enrolled and 19 (86.4 %) completed the study. The 3 subjects who did not complete the study withdrew voluntarily. A summary of demographic data is presented in the following table.

Table A 11. Demographic Summary (Reference Table 4/Section 6.4.1/Study 376)

Group	Parameter	Age (years)	Height (cm)	Weight (kg)
All Subjects n = 22	Mean	34.6	174.3	85.7
	SD	11.5	9.75	15.56
	Range	19-53	152.0-193.0	55.0-114.5

18% Female, 82% Male; 73% White, 23% Black, 5% Mixed Race.

Source: Table 6.4 and Table 6.5.

No enrolled subjects were poor metabolizers of CYP2D6.

4.2.2.3.2 Pharmacokinetic Results

Food increases the exposure to carvedilol as shown in Table A 12 and Table A 13.

Table A 12. Summary of PK Parameters (Reference Table 6/Section 7.2/Study 376)

Regimen/ Condition	N	AUC(0-t) (ng-hr/mL)	AUC(0-∞) (ng-hr/mL)	C _{max} (ng/mL)	T _{max} (hr) ²
A Fasted	19	430 (45.4)	419 (44.8)	40.1 (47.6)	4.00 (0.50-7.00)
B Standard Meal	19	584 (45.5)	574 (45.8)	69.5 (50.4)	5.00 (2.00-7.00)
C High Fat Meal	20	703 (48.4)	695 (48.1)	82.9 (52.1)	4.50 (2.00-8.02)
D Sprinkled with Standard Meal	20	585 (43.5)	577 (43.6)	57.6 (49.9)	5.00 (1.50-9.00)

1. Geometric mean (CVb%)

2. Median (range)

Table A 13. Statistical Analyses of PK Parameters (Reference Table 7/Section 7.3/Study 376)

Parameter	Comparison	Point Estimate	90% CI
Fasted vs Standard Meal			
AUC(0-t) ¹	A:B	0.73	(0.64, 0.83)
AUC(0-t) ¹	A:B	0.73	(0.64, 0.83)
C _{max} ¹	A:B	0.57	(0.49, 0.67)
T _{max} ² (hr)	A-B	-1.00	(-2.00, 0.00)
High-fat Meal vs Standard Meal			
AUC(0-t) ¹	C:B	1.18	(1.04, 1.35)
AUC(0-t) ¹	C:B	1.19	(1.04, 1.35)
C _{max} ¹	C:B	1.19	(1.02, 1.39)
T _{max} ² (hr)	C-B	0.00	(-0.50, 0.50)
High-fat Meal vs Fasted			
AUC(0-t) ¹	C:A	1.62	(1.42, 1.84)
AUC(0-t) ¹	C:A	1.64	(1.44, 1.87)
C _{max} ¹	C:A	2.07	(1.78, 2.42)
T _{max} ² (hr)	C-A	1.00	(-0.50, 2.13)
Applesauce + Standard Meal vs Standard Meal			
AUC(0-t) ¹	D:B	0.99	(0.87, 1.12)
AUC(0-t) ¹	D:B	0.99	(0.87, 1.13)
C _{max} ¹	D:B	0.82	(0.70, 0.96)
T _{max} ² (hr)	D-B	0.00	(-0.50, 1.00)

1. Point estimate represents the ratio of adjusted geometric means between regimens

2. Point estimate represents the estimated median difference between regimens

Regimen:

- A: 80 mg intact carvedilol phosphate CR under fasting conditions
- B: 80 mg intact carvedilol phosphate CR following a standard meal
- C: 80 mg intact carvedilol phosphate CR following a high fat meal
- D: 80 mg carvedilol phosphate CR sprinkled on applesauce following a standard meal

Source Data: Table 7.1, Table 7.2 and Table 7.5 to Table 7.9.

Within-subject variability for pharmacokinetic parameters was less than 30%.

4.2.2.3.3 Safety Results

Thirteen of 22 subjects (59%) experienced 32 adverse events. A summary of adverse events is presented in Table A 14. The investigator considered 11 of the AEs to be related to study medication with dizziness being the most frequently reported.

Table A 14. Summary of Adverse Events (Reference Table 9/Section 8.2/Study 376)

Adverse Event (Preferred Term)	Number of Subjects				
	Regimen				Total
	A Fasted	B Standard Meal	C High Fat Meal	D Sprinkled with Meal	
Dizziness	2	1	3 ³	3	6 ¹
Headache	1	1	0	1	3
Abnormal Dreams	1	0	0	0	1
Chapped Lips	1	0	0	0	1
Constipation	0	0	1 ²	0	1
Contusion	1	0	0	0	1
Dysmenorrhea	0	0	1	0	1
Erythema	1	0	0	0	1
Flatulence	0	0	0	1	1
Hematoma	0	0	0	1	1
Nasopharyngitis	0	0	1	0	1
Nausea	0	1	0	0	1
Paranasal Sinus Hypersecretion	1	0	0	0	1
Pyrexia	1	0	0	0	1
Sinus Congestion	1	0	0	0	1
Throat Irritation	1	0	0	0	1
Upper Respiratory Tract Infection	0	0	0	1	1
Ventricular Hypertrophy	1 ⁵	0	0	0	1
Vision Blurred	1	0	0	0	1
Vomiting	0	1	0	0	1
Total Number of AEs	13	4	8^{2,3}	7	32^{2,3}
Number of Subjects with AEs	7	2	6	5	13
Number of Subjects Exposed	20	20	20	20	22⁴

Regimen A: 80 mg intact carvedilol phosphate CR under fasting conditions; Regimen B: 80 mg intact carvedilol phosphate CR following a standard meal; Regimen C: 80 mg intact carvedilol phosphate CR following a high fat meal; Regimen D: 80 mg carvedilol phosphate CR sprinkled on applesauce following a standard meal.

Fifteen subjects had 38 instances of sitting vital sign changes. Decreases in blood pressure is an expected finding based on the pharmacology of the drug.

4.2.2.4 Sponsor's Conclusions

- Administration of carvedilol CR with a high fat meal increased AUC and Cmax by 20% compared to administration of a standard meal.
- Administration of carvedilol CR under fasting conditions resulted in a 27% and 43% decrease in AUC and Cmax, respectively, compared to administration of a standard meal.
- Administration of carvedilol CR with applesauce following a standard meal did not effect AUC by decreased Cmax by 20% compared to administration of a standard meal.
- Carvedilol CR when administered under fasting and fed conditions is well tolerated. The most frequent reported events were dizziness and headache which are known AEs of carvedilol IR.

4.2.2.5 Reviewer's Comments on Study 376

The current label for Coreg states that immediate release formulation should be taken with food to slow the rate of absorption and reduce the incidence of orthostatic effects. The bioavailability of the IR formulation does not change in the presence of food.

It is recommended that the CR formulation is administered with food even though the median time to peak concentrations with the CR formulation is 5 hours after dosing. Peak concentrations increase by 20% when carvedilol CR is administered with a high fat meal and decrease by 40% when administered under fasting conditions. To minimize the inter-fluctuation in plasma concentrations, the reviewer concurs that carvedilol should be taken with food.

This study provides evidence that dose dumping does not occur when carvedilol CR is administered with a high-fat meal, or sprinkled with applesauce.

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4.2.3 Study 903 (Dose Proportionality)

A Single Oral Dose Study to Assess the Dose Proportionality of Carvedilol Phosphate CR Capsules in Healthy Adult Subjects

Protocol Number: SK&F-105517/903

Investigator: _____

Study Site: The study was conducted at a single site.

/ /

Study dates: 06 October 2004 – 13 January 2005

4.2.3.1 Objectives

Study objective was to assess the dose proportionality of carvedilol CR capsules at doses of 10 mg, 20 mg, 40 mg and 80 mg.

4.2.3.2 Study Design

This was a randomized, open-label, single-dose, dose-rising, four-period study. Each subject received one the following regimen. Each subject received 10 mg, 20 mg, 40 mg and 80 mg under fed conditions (moderate calorie breakfast, standard meal) in a crossover fashion.

Healthy adult male and female subjects were included in the study. Subject who were poor metabolizers of CYP2D6 were excluded from participation.

4.2.3.2.1 Formulations

The carvedilol phosphate CR capsules are filled with carvedilol phosphate drug layered immediate release microparticles (IRp) and carvedilol phosphate CR microparticles that were layered then coated with a _____

Table A 15. Products used in SK&F-105517/903

FORMULATIONS	DRUG PRODUCT BATCH NUMBER	DRUG SUBSTANCE BATCH NUMBER	CR FORMULATION
carvedilol CR	X4553	03K9-004 & 03K9-005	10 mg CR capsule (✓)
	X4544	03K9-004 & 03K9-005	20 mg CR capsule (✓)
	X4551	03K9-004 & 03K9-005	40 mg CR capsule (✓)
	X4552	03K9-004 & 03K9-005	80 mg CR capsule (✓)

4.2.3.2.2 Pharmacokinetic Assessments

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, 32, and 48 hours after administration.

Plasma R- and S-carvedilol concentrations were analyzed at GSK (Upper Merion, PA) using a validated method based on HPLC-MS/MS (validation report CD2003/00592/00). The performance of the assays is shown in Table A 16.

Table A 16. Performance of Analytical Methodology

ANALYTE	METHOD	RANGE ¹ (NG/ML)	LINEARITY (CORRELATION COEFFICIENT)	LLOQ (NG/ML)	QC SAMPLES (NG/ML)	INTER- BATCH PRECISION (%CV)	INTER- BATCH ACCURACY (%RE)
SKF-105517-S	HPLC-MS/MS						
SKF-105517-R	HPLC-MS/MS						

¹ Calibration range consisted of 10 spiked samples over the specified range.

Plasma concentrations were analyzed by standard noncompartmental methods. Following log_e-transformation, AUC(0-t), AUC(0-t') and C_{max} of carvedilol were analyzed separately by a power model to assess dose-proportionality. Point estimates and associated 90% confidence intervals were constructed for slopes.

An ANOVA model was also considered. A mixed effects model fitting fixed effect terms for sequence, period and regimen, and fitting subject (sequence) as a random effect was used to compute point estimates and 90% confidence intervals for the ratios of dose-normalized AUC(0-t), AUC(0-t') and C_{max}.

The within-subject coefficients of variation (CV_w) for AUC(0-t), AUC(0-t') and C_{max} were calculated based on the loge-normal distribution:

$$CV_w (\%) = \sqrt{[\exp(MSE) - 1] \times 100}$$

where MSE was the mean squared error obtained from the ANOVA.

4.2.3.2.3 Safety Assessments

Assessments of safety included adverse events, clinical laboratory evaluations, and concomitant medications. No formal statistical tests were performed for safety.

4.2.3.3 Study Results

4.2.3.3.1 Subjects

A total of 40 subjects were enrolled and 38 (95%) completed the study. One subject had a positive UDS and was withdrawn from the study and the other subject was withdrawn since enrollment goal was reached. A summary of demographic data is presented in the following table.

Table A 17. Demographic Summary (Reference Table 9/Section 6.4.1/Study 903)

Group	Parameter	Age (years)	Height (m)	Weight (kg)
All Subjects n = 40	Mean	32.9	1.68	74.5
	SD	9.5	0.09	10.2
	Range	18-54	1.49-1.84	60.1-98.0

55% Male, 45% Female

60% Non Hispanic or Latino, 40% Hispanic or Latino

15% African American, 78% White, 8% Mixed race

Source: Table 6.1, Table 6.5, Table 6.6

4.2.3.3.2 Pharmacokinetic Results

The exposure to R- and S-carvedilol increases proportionally with dose. The results of pharmacokinetic analysis is shown in Table A 18 to Table A 21. Within-subject variability for pharmacokinetic parameters was less than 30%.

Table A 18. Summary of PK Parameters for R-Carvedilol (Reference Table 10/Section 7.2/Study 903)

Dose ²	N	AUC(0-t) (ng-h/mL)	AUC(0-t') (ng-h/mL)	Cmax (ng/mL)	tmax (h) ³
10 mg	39	33.4 (72.0)	33.4 (72.0)	4.91 (62.7)	5.00 (2.00-8.03)
20 mg	39	73.5 (64.1)	68.4 (66.5)	9.90 (58.1)	5.00 (2.00-8.00)
40 mg	39	158 (60.0)	141 (67.1)	20.8 (56.6)	5.00 (1.50-6.02)
80 mg	38	328 (56.2)	291 (63.4)	43.5 (54.4)	5.00 (2.00-8.00)

Source: Table 7.4

1. Geometric mean (between subject CV%)
2. Single oral dose of carvedilol phosphate CR capsule
3. Median (range)

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Table A 19. Summary of PK Parameters for S-Carvedilol (Reference Table 11/Section 7.3/Study 903)

Dose ²	N	AUC(0-t) (ng·h/mL)	AUC(0-t') (ng·h/mL)	Cmax (ng/mL)	tmax (h) ³
10 mg	39	13.0 (56.6)	13.0 (56.6)	1.86 (54.6)	6.00 (2.00-8.03)
20 mg	39	32.6 (45.4)	27.5 (50.5)	3.97 (50.4)	5.00 (2.00-8.00)
40 mg	39	74.0 (44.1)	58.2 (54.5)	8.42 (50.5)	5.00 (1.50-7.00)
80 mg	38	155 (37.9)	120 (50.7)	17.8 (45.1)	5.00 (2.00-8.00)

Source: Table 7.5

1. Geometric mean (between subject CV%)
2. Single oral dose of carvedilol phosphate CR capsule
3. Median (range)

Table A 20. Statistical Analyses of PK Parameters: Power Model (Reference Table 7/Section 7.3/Study 903)

Parameter	Effect	Point Estimate	90% CI
R(+)-carvedilol			
AUC(0-t)	Log (dose)	1.11	(1.08, 1.14)
AUC(0-t')	Log(dose)	1.06	(1.03, 1.09)
Cmax	Log (dose)	1.06	(1.02, 1.11)
S(-)-carvedilol			
AUC(0-t)	Log (dose)	1.20	(1.17, 1.23)
AUC(0-t')	Log (dose)	1.08	(1.05, 1.11)
Cmax	Log(dose)	1.09	(1.05, 1.14)

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Table A 21. Statistical Analyses of PK Parameters:ANOVA Model (Reference Table 7/Section 7.3/Study 903)

Parameter	Comparison	Point Estimate	90% CI	CV _w (%)
R(+)-carvedilol				
AUC(0-t) ¹	B/A	1.10	(1.03, 1.18)	18.4%
	C/A	1.19	(1.11, 1.27)	
	D/A	1.27	(1.18, 1.36)	
AUC(0-t) ²	B/A	1.02	(0.96, 1.10)	18.0%
	C/A	1.06	(0.99, 1.13)	
	D/A	1.13	(1.05, 1.20)	
Cmax ¹	B/A	1.01	(0.91, 1.11)	26.7%
	C/A	1.06	(0.96, 1.17)	
	D/A	1.13	(1.03, 1.25)	
tmax ¹	B-A	0.00	(-0.04, 0.50)	
	C-A	-0.50	(-1.00, -0.02)	
	D-A	-0.49	(-0.51, 0.00)	
S(-) carvedilol				
AUC(0-t) ¹	B/A	1.25	(1.17, 1.34)	18.5%
	C/A	1.42	(1.33, 1.52)	
	D/A	1.52	(1.42, 1.63)	
AUC(0-t) ²	B/A	1.06	(0.99, 1.13)	17.6%
	C/A	1.12	(1.05, 1.19)	
	D/A	1.18	(1.11, 1.26)	
Cmax ¹	B/A	1.07	(0.96, 1.18)	27.7%
	C/A	1.13	(1.02, 1.25)	
	D/A	1.22	(1.10, 1.35)	
tmax ²	B-A	0.00	(-0.04, 0.49)	
	C-A	-0.51	(-1.00, 0.07)	
	D-A	-0.50	(-0.53, 0.00)	

Source: Table 7.2 and Table 7.3

1. Point estimate represents ratio of adjusted geometric means between regimens.
 2. Point estimate represents estimated median difference between regimens.
- Regimen A: Single oral dose of carvedilol phosphate CR capsule 10 mg
 Regimen B: Single oral dose of carvedilol phosphate CR capsule 20 mg
 Regimen C: Single oral dose of carvedilol phosphate CR capsule 40 mg
 Regimen D: Single oral dose of carvedilol phosphate CR capsule 80 mg

4.2.3.3.3 Safety Results

Nineteen of 40 subjects (47.5%) experienced 39 adverse events. A summary of adverse events is presented in Table A 22. The investigator considered 26 of the AEs to be related to study medication with headache being the most frequently reported.

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Table A 22. Summary of Adverse Events (Reference Table 15/Section 8.2/Study 903)

Adverse Event (Preferred Term)	Number of Subjects				
	Regimen (mg CR carvedilol)				
	A (10)	B (20)	C (40)	D (80)	Total
Headache	2	4	5	3	10
Dizziness	2	2 ¹	1	1	5
Elevated Mood	0	1	0	2	3
Nausea	0	1	0	2	2
Abdominal Pain	0	1	1 ¹	0	2
Myalgia	1	1	0	0	2
Anxiety	1	0	0	0	1
Cough	0	1	0	0	1
Diarrhoea	0	1	0	0	1
Fatigue	0	1	0	0	1
Laceration	0	1	0	0	1
Nasal Congestion	0	1	0	0	1
Nasopharyngitis	0	0	1	0	1
Pollakiuria	0	0	0	1	1
Venipuncture Site Pain	1	0	0	0	1
Total Number of AEs	7	15	8	9	39
Number (%) of Subjects with AEs	6 (15)	9 (23)	6 (15)	8 (21)	19 (47.5)
Number of Subjects Exposed	40	39	39	38	40

1. One subject experienced this AE more than once after administration of this same regimen. For the purposes of this table, no AE was counted more than once for each subject per treatment, but each AE is listed individually in the source of this table.

Source: Table 6.7, Table 8.1 and Table 8.2

Eleven subjects experienced 38 instances of sitting vital sign changes. No subject met the criteria for orthostatic hypotension. Decreases in blood pressure is an expected finding based on the pharmacology of the drug.

4.2.3.4 Sponsor's Conclusions

- There was approximate dose proportional increases in C_{max} and AUC of R- and S-carvedilol enantiomers with increasing single oral doses of the CR formulation.

4.2.3.5 Reviewer's Comments on Study 903

This study provides evidence of dose proportionality.

4.2.4 Study 906 (Diurnal Variation)

An Open-Label, Single Dose, Three Session, Partially Randomized, Crossover Study to Assess Morning and Evening Dosing of Carvedilol Phosphate MR Capsules in Healthy Adult Subjects

Protocol Number: SK&F-105517/906

Investigator: _____

Study Site: The study was conducted at a single site.

/ /

Study dates: 10 January 2005 – 28 February 2005

4.2.4.1 Objectives

Study objective was to assess the diurnal variation in the pharmacokinetics of 80 mg carvedilol CR capsule administered as a single dose under fed conditions.

4.2.4.2 Study Design

This was a partially-randomized, open-label, single-dose, dose-rising, three-period crossover study. Each subject was randomized to ABA or BAA:

- A. 80 mg carvedilol CR administered under fed conditions in the morning
- B. 80 mg carvedilol CR administered under fed conditions in the evening

Healthy adult male and female subjects were included in the study. Subject who were poor metabolizers of CYP2D6 were excluded from participation.

4.2.4.2.1 Formulations

The carvedilol phosphate CR capsules are filled with carvedilol phosphate drug layered immediate release microparticles (IRp) and carvedilol phosphate CR microparticles that were layered then coated with _____

The formulation used in this study is the final CR formulation.

Table A 23. Products used in SK&F-105517/906

FORMULATIONS	DRUG PRODUCT BATCH NUMBER	DRUG SUBSTANCE BATCH NUMBER	CR FORMULATION
carvedilol CR	X7194	03K9-003	80 mg CR capsule

4.2.4.2.2 Pharmacokinetic Assessments

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 18, 24, 32, and 48 hours after administration.

Plasma R- and S-carvedilol concentrations were analyzed at GSK (Upper Merion, PA) using a validated method based on HPLC-MS/MS (validation report CD2004/01420/00). The performance of the assays is shown in Table A 24.

Table A 24. Performance of Analytical Methodology (collection in EDTA)

ANALYTE	METHOD	RANGE ¹ (NG/ML)	LINEARITY (CORRELATION COEFFICIENT)	LLOQ (NG/ML)	QC SAMPLES (NG/ML)	INTRA- BATCH PRECISION (%CV)	INTRA- BATCH ACCURACY (%RE)
SKF-105517-S	HPLC-MS/MS						
SKF-105517-R	HPLC-MS/MS						

¹ Calibration range consisted of 10 spiked samples over the specified range.

Plasma concentrations were analyzed by standard noncompartmental methods. A mixed effects model fitting fixed effect terms for sequence, period and regimen, and fitting subject as a random effect was used to compute point estimates and 90% confidence intervals for the ratios for the difference PM-AM dosing for AUC(0-∞) AUC(0-t), AUC(0-t') and Cmax.

The within-subject coefficients of variation (CVw) for AUC(0-t), AUC(0-t') and Cmax were calculated based on the loge-normal distribution:

$$CVw (\%) = \sqrt{\exp(MSE) - 1} \times 100$$

where MSE was the mean squared error obtained from the ANOVA.

4.2.4.2.3 Safety Assessments

Assessments of safety included adverse events, clinical laboratory evaluations, and concomitant medications. No formal statistical tests were performed for safety.

4.2.4.3 Study Results

4.2.4.3.1 Subjects

A total of 22 subjects were enrolled and 20 (91%) completed the study. One subject withdrew consent and the other subject was withdrawn due to a pre-dose SBP < 110 mmHg. A summary of demographic data is presented (Table A 25).

Table A 25. Demographic Summary (Reference Table 5/Section 6.4.1/Study 906)

	Parameter	Age (years)	Height (m)	Weight (kg)
Subjects n=22	Mean	32.2	1.74	81.1
	SD	11.25	0.08	11.4
	Range	18 – 50	1.61 – 1.92	64.5 – 101.8

68% Male, 32% Female; 86% White, 14% African American; 5% Hispanic or Latino, 95% Not Hispanic or Latino

1. Table 6.4 incorrectly reports that the weight of Subject 017 was 30.9 kg. The actual weight of Subject 017, which was used in these calculations, was 95.9 kg.

Source: Table 6.3, Table 6.4, Table 6.5

4.2.4.3.2 Pharmacokinetic Results

The exposure to R- and S-carvedilol was decreased by approximately 10% for AUC and <20% for C_{max} when administered as a single oral dose in the evening compared to morning administration. There was also a delay in T_{max}. The results of pharmacokinetic analysis are shown in Table A 26 to Table A 29. Overall, within-subject variability for pharmacokinetic parameters was less than 32%.

Table A 26. Summary of PK Parameters for R-Carvedilol (Reference Table 6/Section 8.1/Study 906)

Regimen	N	AUC(0-t) (ng-hr/mL)	AUC(0-t') (ng-hr/mL)	C _{max} (ng/mL)	t _{max} (hr) ²
A (Admin 1)	22	378 (67.6)	369 (69.3)	43.9 (57.8)	5.00 (1.50-8.00)
A (Admin 2)	20	398 (67.6)	393 (68.7)	47.9 (64.7)	5.00 (3.00-8.00)
B	22	347 (58.6)	343 (60.5)	37.3 (66.5)	7.00 (3.00-10.00)

1. Geometric mean (CVb%)

2. Median (range)

Regimen A: 80 mg carvedilol phosphate CR administered in morning under fed conditions

Regimen B: 80 mg carvedilol phosphate CR administered in evening under fed conditions

Source Data: Table 8.3

Table A 27. Summary of PK Parameters for S-Carvedilol (Reference Table 7/Section 8.2/Study 906)

Regimen	N	AUC(0-t) (ng-hr/mL)	AUC(0-t') (ng-hr/mL)	C _{max} (ng/mL)	t _{max} (hr) ²
A (Admin 1)	22	157 (57.2)	151 (59.0)	16.6 (55.0)	5.00 (1.50-8.00)
A (Admin 2)	20	168 (57.0)	166 (57.4)	18.7 (62.4)	5.00 (3.00-6.00)
B	22	143 (50.8)	140 (54.8)	13.5 (58.6)	7.00 (3.00-10.00)

1. Geometric mean (CVb%)

2. Median (range)

Regimen A: 80 mg carvedilol phosphate CR administered in morning under fed conditions

Regimen B: 80 mg carvedilol phosphate CR administered in evening under fed conditions

Source Data: Table 8.4

Table A 28. Statistical Analyses of PK Parameters: Assessment of Evening to Morning Administration (Reference Table 8/Section 8.3/Study 906)

Parameter	Comparison of Interest	Point Estimate ¹	90% CI	CVw%
R(+)-CARVEDILOL				
AUC(0-t)	B : A	0.92	(0.81, 1.04)	23.8
AUC(0-t')	B : A	0.93	(0.82, 1.05)	23.8
C _{max}	B : A	0.85	(0.72, 1.00)	31.3
t _{max}	B - A	1.50 hr ²	(1.00, 2.50)	
S(-)-CARVEDILOL				
AUC(0-t)	B : A	0.91	(0.80, 1.03)	24.5
AUC(0-t')	B : A	0.92	(0.81, 1.05)	25.0
C _{max}	B : A	0.81	(0.69, 0.96)	32.0
t _{max}	B - A	1.50 hr ²	(0.56, 2.50)	

1. Point estimate represents ratio of adjusted geometric means between regimens.
 2. Point estimate represents estimated median difference between regimens.
- Regimen A: 80 mg carvedilol phosphate CR administered in morning under fed conditions
 Regimen B: 80 mg carvedilol phosphate CR administered in evening under fed conditions
 Source Data: Table 8.5, Table 8.6, and Table 8.9

Table A 29. Statistical Analyses of PK Parameters: Assessment of Within-Subject Inter-Day Variability (Reference Table 9/Section 8.3/Study 906)

Parameter	Comparison of Interest	Point Estimate ¹	90% CI	CVw%
R(+)-carvedilol				
AUC(0-t)	Admin2 : Admin1 ²	1.00	(0.93, 1.09)	14.7
AUC(0-t')	Admin2 : Admin1 ²	1.02	(0.94, 1.11)	14.8
C _{max}	Admin2 : Admin1 ²	1.07	(0.93, 1.23)	26.0
t _{max}	Admin2 - Admin1 ²	0.00 hr ³	(-0.50, 0.51)	
S(-)-carvedilol				
AUC(0-t)	Admin2 : Admin1 ²	1.03	(0.95, 1.13)	15.9
AUC(0-t')	Admin2 : Admin1 ²	1.05	(0.96, 1.15)	16.5
C _{max}	Admin2 : Admin1 ²	1.11	(0.95, 1.31)	29.9
t _{max}	Admin2 - Admin1 ²	0.00 hr ³	(-1.00, 0.01)	

1. Point estimate represents ratio of adjusted geometric means between regimens.
 2. Admin1 and Admin2 represent the first and second dosing occasions, respectively of 80 mg carvedilol phosphate CR dosed in morning under fed conditions (Regimen A).
 3. Point estimate represents estimated median difference between regimens.
- Source Data: Table 8.7, Table 8.8, and Table 8.10

4.2.4.3.3 Safety Results

Sixteen of 22 subjects (72.7%) experienced 57 adverse events. A summary of adverse events is presented in Table A 30. The investigator considered 16 of the AEs to be related to study medication with headache being the most frequently reported. All treatment-related AEs resolved before the completion of the study.

Table A 30. Summary of Adverse Events (Reference Table 11/Section 9.2)

Adverse Event (preferred term)	Number of Subjects		
	Time of Administration (Regimen)		
	Morning Regimen A ¹	Evening Regimen B	Total
Headache	6 ^{2,3}	3	8
Blood pressure fluctuation	3	4 ²	6
Nausea	2	5	5
Dizziness	3	2	4
Dyspepsia	2	1	3
Chest discomfort	2	0	2
Arthropod bite	0	1	1
Asthenia	1	0	1
Chest wall pain	1	0	1
Constipation	1	0	1
Cough	1	0	1
Dizziness postural	0	1	1
Erythema	1	0	1
Excoriation	0	1	1
Gastroesophageal reflux disease	1	0	1
Hyperhidrosis	1	0	1
Myalgia	1	0	1
Neck pain	1	0	1
Nocturia	1	0	1
Orthostatic hypotension	0	1	1
Pharyngolaryngeal pain	1	0	1
Pyrexia	1	0	1
Rhinorrhoea	0	1	1
Sinus congestion	0	1	1
Tinnitus	1 ²	0	1
Vomiting	1	0	1
Total Number of AEs	36	21	57
Number of Subjects with AEs	13	11	16
Number of Subjects Exposed	22	22	22
Number of Subject Sessions	42	22	64

- Subjects were administered Regimen A in two sessions
 - One or more subjects reported this AE more than once in the same session. For the purposes of this table, AEs reported by one subject in the same session are counted once.
 - One or more subjects reported this AE following dosing with this regimen in more than one session. For the purposes of this table, AEs reported by one subject in different sessions are counted separately.
- Regimen A: 80 mg carvedilol phosphate CR administered in morning under fed conditions
 Regimen B: 80 mg carvedilol phosphate CR administered in evening under fed conditions

Twelve subjects experienced 52 instances of sitting vital sign changes with decreases in BP being most frequently reported. A total of 6 subjects met the criteria for orthostatic hypotension as defined in the protocol (a reduction in SBP of 20mmHg or more and/or a reduction of DBP of 10mmHg or more for standing vs. supine measurements). Only one of these subjects was symptomatic and the other five were considered asymptomatic. Decreases in blood pressure is an expected finding based on the pharmacology of the drug.

4.2.4.4 Sponsor's Conclusions

- Evening administration of carvedilol CR resulted in an approximate 10% decrease in AUC of both R(+)- and S(-)-carvedilol and a 15% to 19% decrease in Cmax of both R(+)- and S(-)-carvedilol compared to morning administration. Additionally, there was a decrease in the rate of absorption of both R(+)- and S(-)-carvedilol with evening administration (Tmax delayed approximately 1.5 hours)

- The within-subject inter-day variability for AUC and Cmax following morning (fed) administration for CR carvedilol [both R(+)- and S(-)-carvedilol] was similar to IR carvedilol (compared to historical data).
- The 80 mg dose of the carvedilol phosphate CR capsule formulation was generally safe and well tolerated by healthy adult males and females when administered in both the morning and evening in the fed state.

4.2.4.5 Reviewer's Comments on Study 906

This study provides evidence that the drug product's formulation provide consistent pharmacokinetic performance between individual dosage units: upon repeat administration the within-subject variability was less than 30% for AUC and Cmax parameters. There was a small difference between PK parameters when comparing evening to morning administration; this is thought to be related to diurnal variation.

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4.2.5 Study 387 (Pantoprazole Interaction Study)

Investigation of the effect of repeat oral doses of pantoprazole on a single oral dose of the modified release capsule formulation of carvedilol in healthy adult subjects

Protocol Number: SK&F-105517/387

Investigator: David Hoelscher, MD

Study Site:

Study dates: 12 September 2003 – 31 October 2003

4.2.5.1 Objectives

To evaluate the effect of repeat oral doses of pantoprazole on the pharmacokinetics of a single oral dose of the modified release capsule formulation of carvedilol in healthy subjects

4.2.5.2 Study Design

4.2.5.2.1 Formulations

The carvedilol phosphate CR capsules are filled with carvedilol phosphate drug layered immediate release microparticles (IRp) and carvedilol phosphate CR microparticles that were layered then coated with a
The formulation used in this study is a pilot CR formulation.

Table A 31. Products used in SK&F-105517/387

FORMULATIONS	DRUG PRODUCT BATCH NUMBER	DRUG SUBSTANCE BATCH NUMBER	CR FORMULATION
25 mg carvedilol CR	U03096	SK&F-105517 03K8-007 and SK&F-105517-D 1055A1-02	Pilot formulation

4.2.5.2.2 Pharmacokinetic Assessments

Blood samples (approximately 3mL) were collected prior to dosing (Time 0) and at nominal times of 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, 32, and 48 h after administration.

Total carvedilol concentrations were analyzed at GSK (Upper Merion, PA) using a validated method based on HPLC-MS/MS (validation report RSD-101SN0/1).

Plasma concentrations were analyzed by standard noncompartmental methods. Following loge-transformation, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, and C_{max} of carvedilol were separately analyzed by analysis of variance (ANOVA), fitting terms for subject and regimen. Point estimates and 90% confidence intervals for the difference of interest (B-A) were constructed using the residual variance. Point and interval estimates were then exponentially backtransformed to construct point and interval estimates for the ratio of interest (B:A).

The within-subject coefficients of variation (CVw) for AUC(0-t), AUC(0-t') and Cmax were calculated based on the loge-normal distribution:

$$CVw (\%) = \sqrt{[\exp(MSE) - 1]} \times 100$$

where MSE was the mean squared error obtained from the ANOVA.

4.2.5.2.3 Safety Assessments

Assessments of safety included adverse events, clinical laboratory evaluations, and concomitant medications. No formal statistical tests were performed for safety.

4.2.5.3 Study Results

4.2.5.3.1 Subjects

A total of 24 subjects were enrolled and 23 (96%) completed the study. One subject was withdrawn from this study due to an AE. A summary of demographic data is presented (Table A 32).

Table A 32. Demographic Summary (Reference Table 6/Section 6.4.1/Study 387)

Group	Parameter	Age (years)	Height (cm)	Weight (kg)
All Subjects n = 24	Mean	29	174	81.7
	SD	9.9	8.9	17.75
	Range	19-53	159-191	60.4-123.9
Male Subjects n = 12	Mean	29	180	88.6
	SD	9.3	7.7	18.64
	Range	21-48	169-191	66.5-123.9
Female Subjects n = 12	Mean	29	168	74.8
	SD	10.8	5.4	14.39
	Range	19-53	159-176	60.4-103.8

50% Male, 50% Female; 87.5% White, 12.5% Black

Source: Section 12, Table DS1

4.2.5.3.2 Pharmacokinetic Results

Compared to carvedilol alone (Regimen A), subjects receiving pantoprazole + carvedilol (Regimen B) had AUC values approximately 3 to 4% higher while C_{max} was approximately 10% higher. The corresponding 90% confidence intervals for the ratios of AUC(0-t), AUC(0-t'), AUC(0-∞), and C_{max} for B:A were within 20% of unity. Median t_{max} was identical for both treatment regimens. The results of pharmacokinetic analysis are shown in Figure A 3, Table A 33 to Table A 34. Overall, within-subject variability for pharmacokinetic parameters was less than 24%.

Figure A 3. Median Carvedilol Time Course (Reference Figure/Section 7 /Study 387)

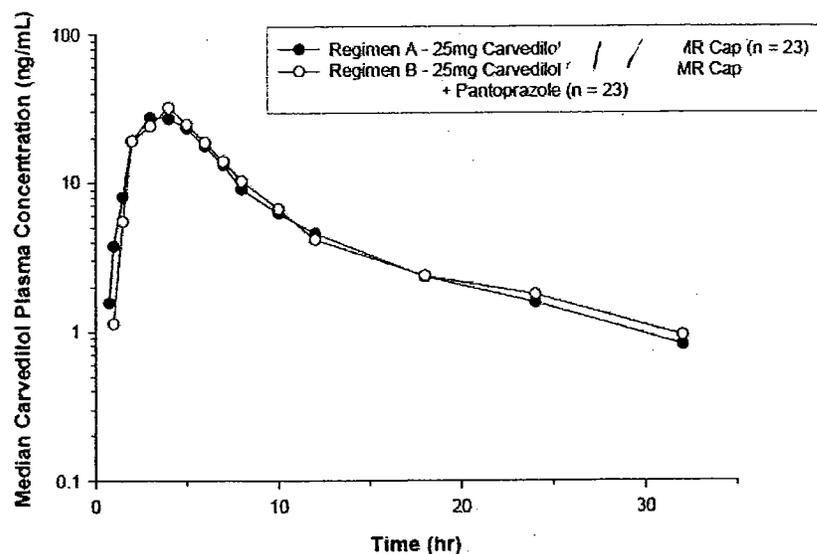


Table A 33. Summary of PK Parameters for total Carvedilol (Reference Table 8/Section 7/Study 387)

Parameter	Regimen A (carvedilol alone)	Regimen B (pantoprazole + carvedilol)
N	23	23
AUC ₍₀₋₉₎ (ng*hr/mL)	225 (90 - 564)	233 (81 - 642)
AUC ₍₀₋₁₎ (ng*hr/mL)	223 (86 - 564)	231 (81 - 642)
AUC _(0-∞) (ng*hr/mL)	234 (93 - 485) ²	243 (84 - 599) ²
C _{max} (ng/mL)	35.9 (15.9 - 101.7)	39.5 (17.7 - 135.1)
t _{max} (hr) ¹	4.00 (1.00 - 8.00)	4.00 (1.50 - 5.00)
t _{1/2} (hr) ¹	8.02 (4.09 - 14.09) ³	8.84 (3.29 - 17.73) ⁴

1. Presented as median (range)
2. n = 14,
3. n = 19,
4. n = 15

Source: Attachment 2, Table 1 - Table 8

Table A 34. Statistical Analyses of PK Parameters: (Reference Table 8/Section 8.3/Study 906)

Parameter	Comparison	Point Estimate ¹	90% CI	CV%
AUC ₍₀₋₄₎	B:A	1.03	(0.98, 1.10)	11.31
AUC ₍₀₋₇₎	B:A	1.03	(0.98, 1.09)	10.54
AUC _(0-∞)	B:A	1.04	(0.98, 1.11)	9.66
C _{max}	B:A	1.10	(0.98, 1.24)	23.77
t _{max} (hr)	B - A	0 ²	(-0.50, 0.50)	--

1. Point estimates represents ratio of adjusted geometric means between regimens
 2. Point estimate represents estimated median difference between regimens
 Regimen A: a single oral 25 mg dose of the — MR capsule formulation of carvedilol
 Regimen B: 40 mg of pantoprazole once daily for 7 days with a single concomitant oral 25 mg dose of the — MR capsule formulation of carvedilol on Day 7.
 Source: Attachment 1, Table 1 – Table 5

4.2.5.3.3 Safety Results

Thirteen of 24 subjects (54.2%) experienced 14 adverse events. A summary of adverse events is presented in Table A 35. The investigator considered 9 of the AEs to be related to study medication with headache being the most frequently reported.

Table A 35. Summary of Adverse Events (Reference Table 11/Section 9.2)

Adverse Event (Preferred Term)	Number of Subjects		
	A	B	Total
Headache	2	1	3
Constipation	0	2	2
Dyspepsia	1	1	2
Acne	0	1	1
Blood Creatine Phosphokinase Increase	1	0	1
Cough	0	1	1
Dizziness	0	1	1
Dry Mouth	0	1	1
Fatigue	0	1	1
Somnolescence	1	0	1
Total Number of AEs	5	9	14
Number of Subjects with AEs	5	8	13
Number of Subjects Exposed	24	23	24

Regimen A: a single oral 25 mg dose of the — MR capsule formulation of carvedilol
 Regimen B: 40 mg of pantoprazole once daily for 7 days with a single concomitant oral 25 mg dose of the — MR capsule formulation of carvedilol on Day 7
 Source: Section 12, Table DS6

A total of 10 subjects experienced 24 changes in vital signs of potential clinical concern during this study (Section 14, Table DS11). All changes in vital signs were decreases in blood pressure. All of the vital signs of potential clinical concern were asymptomatic and not considered clinically significant by the investigator. Decreases in blood pressure is an expected finding based on the pharmacology of the drug.

4.2.5.4 Sponsor's Conclusion

Concomitant pantoprazole therapy had no clinically relevant effect on the single dose pharmacokinetic profile of a 25 mg carvedilol — MR capsule

4.2.5.5 Reviewer's Comments on Study 387

With _____, thus potentially altering the absorption rate of carvedilol. This study provides evidence that there is not dose dumping when carvedilol CR is co-administered with a proton-pump inhibitor.

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4.2.6 Study 902 (Multiple-Dose PK and PKPD)

A randomized, double-blind, placebo controlled, PKPD modeling, multicenter study to compare the β 1-blocking effects of carvedilol CR capsule formulation to COREG IR tablets at steady state in adult patients with essential hypertension, by evaluating heart rate response to bicycle ergometry

Protocol Number: SK&F-105517/902

Investigator: This was a multicenter study.

Study Site: The study was conducted at 9 clinical sites.

Study dates: 30 December 2004 – 27 June 2005

4.2.6.1 Objectives

Following administration placebo and 6.25 mg/20 mg or 20mg/80 mg of IR/CR to patients with essential hypertension, study objectives were to

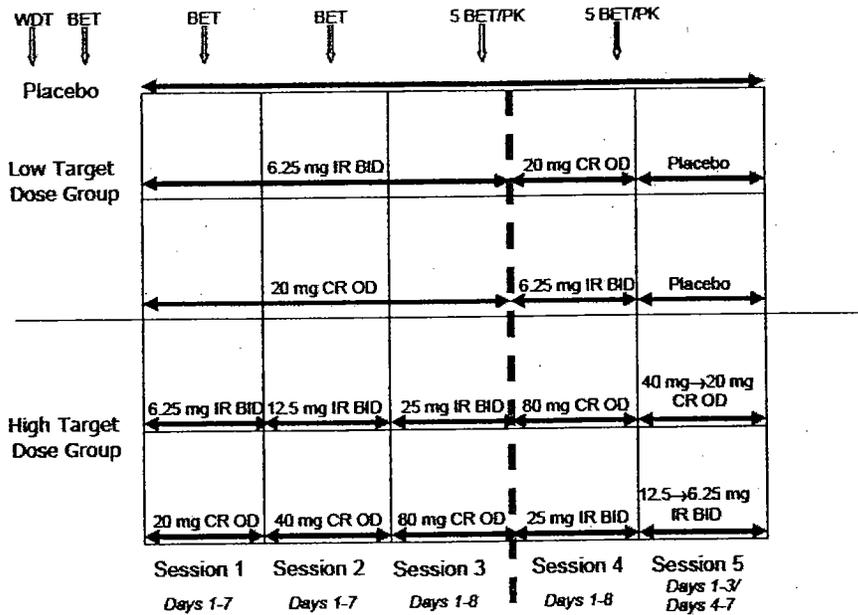
1. Establish the steady state PKPD relationship between β 1-blockade and S(-)-carvedilol concentration using heart rate during bicycle ergometry
2. Compare the β 1-blockade between the IR and CR formulations
3. Describe the pharmacokinetics of R(+) and S(-) carvedilol
4. Evaluate the safety and tolerability

4.2.6.2 Study Design

The design was double-blind, placebo controlled, repeat-dose crossover study in three parallel groups. The study consisted of five phases: screening; down titration/washout, drug-free run-in, double-blind treatment (consisting of five sessions as shown in Figure A 4), and follow-up.

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Figure A 4. Study Design of 902



Healthy male and non-pregnant female subjects were included in the study if they had a history of, or presented with, mild to moderate essential hypertension (sitting DBP ≥ 90 mmHg and ≤ 109 mmHg) and met one of the following criteria:

- Was newly diagnosed and/or previously untreated; or
- Had DBP controlled at initial screening while receiving no more than 2 medications and could be safely withdrawn; or
- Had DBP not controlled at initial screening while receiving no more than 2 medications (no beta-blockers) and these would be continued during the study

Subjects who were poor metabolizers of CYP2D6 were excluded from participation.

4.2.6.2.1 Formulations

During inpatient dosing, subjects took study drug 30 minutes after completion of a standard/moderate calorie meal.

Table A 36. Products used in SK&F-105517/902

TREATMENT	DRUG PRODUCT BATCH NUMBER	DRUG SUBSTANCE BATCH NUMBER	FORMULATION
carvedilol CR	X4544	03K9-004 & 03K9-005	20 mg CR capsule
carvedilol CR	X4551	03K9-004 & 03K9-005	40 mg CR capsule
carvedilol CR	X4552	03K9-004 & 03K9-005	80 mg CR capsule
carvedilol IR	041034504	--	6.25 mg IR tablet
carvedilol IR	041050106	--	12.5 mg IR tablet
carvedilol IR	041034506	--	25 mg IR tablet

4.2.6.2.2 Pharmacodynamic Assessments

Subjects were randomized to 1 of 6 sequences for bicycle ergometric tests (BET) as follows:

B1: Pre-dose, and 1.5, 6, 12, 18 hours post AM dose on Day 7

B2: Pre-dose, and 1.5, 4, 14, 21 hours post AM dose on Day 7

B3: Pre-dose, and 1.5, 4, 14, 24 hours post AM dose on Day 7

B4: Pre-dose, and 2, 6, 12, 18 hours post AM dose on Day 7

B5: Pre-dose, and 2, 9, 14, 21 hours post AM dose on Day 7

B6: Pre-dose, and 2, 9, 12, 24 hours post AM dose on Day 7

The supine BET was performed for a total of 6 minutes with a 1 minute warm-up, 4 minute exercise period, and 1 minute cool down. Heart rate was collect via continuous dual-lead ECG.

Pharmacodyamic Response Metrics

PD%	$100 \cdot (\text{EHR0-HER}) / \text{EHR0}$
PDmin%	The pre-dose effect on Day 7 (effect at Ctau)
PDmax%	Maximal effect obtained during 0-24 h dosing interval
AUEC%	AUC during 0-24 h dosing interval

Bootstrap analyses were performed to estimate the mean and 90% confidence interval for AUEC% between IR and CR formulations since full PD% curves were not collected in each subject. This was performed by sampling ID with replacement to generate 3000 bootstrap datasets. Each dataset was analyzed by a mixed effects model and LSM estimates were obtained for each formulation and dose group at each time point. AUEC values were calculated from the LSM PD% profile. The median value and corresponding 90% confidence intervals (5th and 95th percentiles) for the ratio of AUEC between the two formulations were constructed from the distribution of ratio estimates from the 3000 simulated datasets.

Observed PDmin% and PDmax% were analyzed by a mixed effects model, fitting fixed effect terms for dose group, sequence, period, formulation, and dose*formulation, and subject (dose group) as random effect.

4.2.6.2.3 Pharmacokinetic Assessments

Blood samples were collected in EDTA tubes at times corresponding to BET (described in Pharmacodynamic Assessments). Pre-dose samples were obtained within approximately 10 min prior to dosing.

Plasma concentrations were analyzed by standard noncompartmental methods. Following log_e-transformation, AUC(0-t), AUC(0-t') and Cmax of carvedilol were analyzed separately by an ANOVA model, fitting fixed effect terms for dose group, sequence, period, formulation and dose group*formulation, and subject(dose group) as random

effects.. Point estimates and 90% confidence intervals for the ratios for the difference between CR:IR were computed.

The within-subject coefficients of variation (CVw) for AUC(0-t), AUC(0-t') and Cmax were calculated based on the loge-normal distribution:

$$CVw (\%) = \text{sqrt} [\text{exp}(\text{MSE}) - 1] \times 100$$

where MSE was the mean squared error obtained from the ANOVA.

4.2.6.2.4 Bioanalytical Assay

Plasma R- and S-carvedilol concentrations were analyzed at GSK (Upper Merion, PA) using a validated method based on HPLC-MS/MS (validation report CD2004/01420/00 for R- and S-carvedilol and CD2005/01057/00 for metabolite). The performance of the assays is shown in Table A 37.

Table A 37. Performance of Analytical Methodology (EDTA Plasma)

Analyte	Method	Range ¹ (ng/ml)	Linearity (correlation coefficient)	LLOQ (ng/ml)	QC Samples (ng/ml)	Intra- batch precision (%CV)	Intra-batch accuracy (%RE)
S-	HPLC- MS/MS						
R-	HPLC- MS/MS						
M4- metabolite							

¹ Calibration range consisted of 10 spiked samples over the specified range.

4.2.6.2.5 PKPD Assessments

The relationship between changes from baseline in mean DBP and predicted AUC for R- and S- carvedilol was explored. Linear, log-linear, and Emax models were explored. A complete review of the PKPD model is presented in the Pharmacometrics Review (Appendix 4.3, QBR).

4.2.6.2.6 Safety Assessments

Assessments of safety included adverse events, clinical laboratory evaluations, and concomitant medications. No formal statistical tests were performed for safety.

4.2.6.3 Study Results

4.2.6.3.1 Subjects

The study was conducted at 9 centers (all in US). A total of 122 subjects were enrolled and 105 (86%) completed the study. Table A 38 presents disposition of subjects by treatment group and sequence.

Table A 38. Disposition of Subjects (Reference Table 15/Section 6.1)

Subject Disposition		Number of Subjects				
Total Screened		242				
Total Screened but Not Used		120				
Total Randomized/Enrolled		122				
	Target Dose Level	Low Dose Groups		High Dose Groups		Placebo
	Total	41		55		26
	Treatment Sequence	COREG / Carvedilol CR ¹	Carvedilol CR / COREG ²	COREG / Carvedilol CR ³	Carvedilol CR / COREG ⁴	Placebo
	Total	20	21	27	28	26
Total Withdrawn Prior to Dosing		0				
Total Withdrawn After Dosing		17				
	Target Dose Level	Low Dose Groups		High Dose Groups		Placebo
	Total	5		8		4
	Treatment Sequence	COREG / Carvedilol CR ¹	Carvedilol CR / COREG ²	COREG / Carvedilol CR ³	Carvedilol CR / COREG ⁴	Placebo
	Adverse Event	1	1	1	2	2
	Protocol Deviation	0	1	0	0	1
	Other	1	1	2	3	1
	Total	2	3	3	5	4
Total Completed		105				
	Target Dose Level	Low Dose Groups		High Dose Groups		Placebo
	Total	36		47		22
	Treatment Sequence	COREG / Carvedilol CR ¹	Carvedilol CR / COREG ²	COREG / Carvedilol CR ³	Carvedilol CR / COREG ⁴	Placebo
	Total	18	18	24	23	22

- Subjects received COREG 6.25 mg in Sessions 1-3, carvedilol CR 20 mg in Session 4, and placebo in Session 5.
- Subjects received carvedilol CR 20 mg Sessions 1-3, COREG 6.25 mg in Session 4, and placebo in Session 5.
- Subjects received COREG 6.25 mg in Session 1, COREG 12.5 mg in Session 2, COREG 25 mg in Session 3, carvedilol CR 80 mg in Session 4, and carvedilol CR 40 mg followed by carvedilol CR 20 mg in Session 5.
- Subjects received carvedilol CR 20 mg in Session 1, carvedilol CR 40 mg in Session 2, carvedilol CR 80 mg in Session 3, COREG 25 mg in Session 4, and COREG 12.5 mg followed by COREG 6.25 mg in Session 5.

Source: Table 6.1 - Table 6.5

Demographic characteristics are summarized in Table A 39.

Table A 39. Summary of Demographics (Reference Table 16 and 17/Section 6.4.1)

Group	Parameter	Age (years)	Height (m)	Weight (kg)
All subjects n = 121 ¹	Mean	45	1.70	86.8
	SD	7.6	0.09	13.2
	Range	22 - 55	1.50 - 1.92	57.0 - 130.0

- Subject 069 is not included in the summary data, as this subject's diary card was lost prior to transcription, so dosing data for this subject was not recorded. This subject was a 53 year old female of 'other' race, 1.65 m height, 96.3 kg weight.

Source: Table 6.1

Number (Percentage) of Subjects ¹			
Gender		Race	
Male	62 (51)	White	53 (44)
		Black	33 (27)
		American Hispanic	17 (14)
Female	59 (49)	American Indian	1 (1)
		Japanese	1 (1)
		Other	16 (13)

1. Subject 069 is not included in the summary data, as this subject's diary card was lost prior to transcription, so dosing data for this subject was not recorded. This subject was a 53 year old female of 'other' race, 1.65 m height, 96.3 kg weight.

Source: Table 5.1

4.2.6.3.2 Pharmacodynamic Results

Similar trough, peak, and overall pharmacodynamic effect were observed for the carvedilol CR and IR formulations (Table A 40 to Table A 42).

Table A 40. Summary of PD_{min}% (Reference Table 20/Section 7.1)

Parameter	Comparison of Interest CR:IR	Point Estimate	90% CI	Within subject SD ⁴
PD _{min}	Pooled Group ¹	1.00	(0.94, 1.07)	3.86
PD _{min}	High Dose Group ²	1.06	(0.97, 1.15)	
PD _{min}	Low Dose Group ³	0.94	(0.84, 1.05)	

- High and Low Dose Groups combined
- COREG 25mg BID and carvedilol CR 80mg OD
- COREG 6.25mg BID and carvedilol CR 20mg OD
- Within-subject standard deviation

Source: Table 7.1

Table A 41. Summary of PD_{max}% (Reference Table 22/Section 7.3)

Parameter	Comparison of Interest	Point Estimate	90% CI	SDw
PD _{max}	CR:IR (Pooled) ¹	0.97	(0.92, 1.02)	3.82
PD _{max}	CR:IR (High Dose Group) ²	1.02	(0.95, 1.08)	
PD _{max}	CR:IR (Low Dose Group) ³	0.92	(0.84, 1.00)	

- High and Low Dose Groups combined
- COREG 25mg BID and carvedilol CR 80mg OD
- COREG 6.25mg BID and carvedilol CR 20mg OD

Source: Table 7.5

Table A 42. Summary of AUEC% (Reference Table 21/Section 7.2)

Parameter	Comparison of Interest	Median	90% Bootstrap CI (5th percentile, 95th percentile)
AUEC	CR:IR (Pooled) ¹	1.02	(0.93, 1.10)
AUEC	CR:IR (High Dose Group) ²	1.03	(0.96, 1.10)
AUEC	CR:IR (Low Dose Group) ³	1.00	(0.92, 1.09)

1. High and Low Dose Groups combined
2. COREG 25mg BID and carvedilol CR 80mg OD
3. COREG 6.25mg BID and carvedilol CR 20mg OD

Source: data on file, GSK

4.2.6.3.3 Pharmacokinetic Results

Carvedilol CR was equivalent to COREG with regard to R(+)- and S(-)-carvedilol AUC, C_τ, and C_{max} (Tables A38-A40). On average, steady state plasma concentrations of the metabolite M4 were less than 10% of the plasma concentrations observed for carvedilol following administration of both the COREG IR and carvedilol CR formulations (Table A 46).

Table A 43. Summary of PK Parameters for R-Carvedilol (Reference Table 23/Section 9.1)

Regimen	N	AUC(0-t) (ng-hr/mL)	AUC(0-t') (ng-hr/mL)	C _{max} (ng/mL)	t _{max} (hr) ²	C _τ (ng/mL)
A	33	89.7 (71.7)	89.5 (72.2)	12.4 (71.8)	1.50 (0.50-4.00)	1.41 (124)
C	45	362 (61.2) ³	362 (61.2) ³	48.6 (54.4)	1.13 (0.08-3.00)	5.97 (92.0)
D	33	94.7 (80.4)	94.7 (80.4)	11.6 (73.8)	5.00 (1.50-20.00)	1.33 (153)
F	45	382 (67.3)	382 (67.3)	45.5 (65.5)	5.00 (1.00-10.00)	5.06 (100)

1. Geometric mean (CVb%)
2. Median (range)
3. N=44

Regimen A: COREG 6.25 mg every 12 hours

Regimen C: COREG 25 mg every 12 hours

Regimen D: Carvedilol CR 20 mg OD

Regimen F: Carvedilol CR 80 mg OD

Source Data: Table 9.5

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Table A 44. Summary of PK Parameters for S-Carvedilol (Reference Table 24/Section 9.2)

Regimen	N	AUC(0-t) (ng-hr/mL)	AUC(0-∞) (ng-hr/mL)	Cmax (ng/mL)	tmax (hr) ²	Cτ (ng/mL)
A	33	35.6 (57.2)	35.4 (57.7)	4.65 (72.3)	1.17 (0.50-4.00)	0.748 (85.4)
C	45	159 (49.7) ³	159 (49.7) ³	19.7 (53.6)	1.00 (0.08-3.00)	3.64 (62.0)
D	33	42.1 (63.9)	42.1 (63.9)	4.64 (65.7)	5.00 (1.50-13.00)	0.807 (113)
F	45	178 (54.0)	178 (54.0)	19.0 (56.4)	5.00 (1.00-10.00)	3.33 (84.6)

1. Geometric mean (CVb%)
2. Median (range)
3. N=44

Regimen A: COREG 6.25 mg every 12 hours

Regimen C: COREG 25 mg every 12 hours

Regimen D: Carvedilol CR 20 mg OD

Regimen F: Carvedilol CR 80 mg OD

Source: Table 9.5

Table A 45. Summary of Statistical Analysis (Reference Table 25/Section 9.3)

Parameter	Group	Comparison ¹	PE	90% CI	CVw% ³
R(+)-carvedilol					
AUC(0-t)	Pooled	CR:IR	1.06	(1.02, 1.10)	14.6
	High Dose		1.05	(1.00, 1.11)	
	Low Dose		1.06	(1.00, 1.12)	
AUC(0-∞)	Pooled	CR:IR	1.06	(1.02, 1.10)	14.5
	High Dose		1.05	(1.00, 1.11)	
	Low Dose		1.06	(1.00, 1.13)	
Cmax	Pooled	CR:IR	0.94	(0.86, 1.03)	35.3
	High Dose		0.94	(0.83, 1.06)	
	Low Dose		0.94	(0.82, 1.09)	
Cτ	Pooled	CR:IR	0.89	(0.81, 0.99)	38.5
	High Dose		0.85	(0.74, 0.97)	
	Low Dose		0.94	(0.81, 1.10)	
tmax (hr)	Pooled	CR – IR ²	3.50	(3.13, 3.75)	
	High Dose		3.50	(3.00, 3.99)	
	Low Dose		3.44	(3.00, 3.94)	
S(-)-carvedilol					
AUC(0-t)	Pooled	CR:IR	1.15	(1.10, 1.20)	16.7
	High Dose		1.12	(1.05, 1.19)	
	Low Dose		1.18	(1.10, 1.27)	
AUC(0-∞)	Pooled	CR:IR	1.15	(1.10, 1.21)	16.3
	High Dose		1.12	(1.06, 1.18)	
	Low Dose		1.19	(1.11, 1.27)	
Cmax	Pooled	CR:IR	0.98	(0.89, 1.09)	37.4
	High Dose		0.97	(0.85, 1.10)	
	Low Dose		1.00	(0.86, 1.16)	
Cτ	Pooled	CR:IR	0.99	(0.91, 1.08)	33.7
	High Dose		0.91	(0.81, 1.02)	
	Low Dose		1.08	(0.94, 1.23)	
tmax (hr)	Pooled	CR – IR ²	3.50	(3.25, 3.78)	
	High Dose		3.50	(3.21, 4.00)	
	Low Dose		3.50	(3.00, 4.00)	

1. Point estimate is the ratio of adjusted geometric means between regimens.
 2. Point estimate is the estimated median difference between regimens.
 3. CVw% represents a pooled estimate of within-subject variability across regimens.
- Source: Table 9.1 – Table 9.4

Table A 46. Summary of PK Parameters for M4-Metabolite (Reference Table 26/Section 9.4)

Treatment Regimen	N	AUC(0-t) (ng-hr/mL) ¹	C _{max} (ng/mL) ¹	t _{max} (hr) ²
C: COREG 25 mg BID	45	44.2 (35.5%)	6.16 (47.2%)	1.50 (0.50 - 4.00)
F: Carvedilol CR 80 mg OD	45	46.9 (42.6%)	5.53 (43.0%)	5.00 (1.00 - 10.00)

1. Geometric mean (CV%)

2. Median (range)

Source: Table 9.25

4.2.6.3.4 PKPD Results

The relationship between plasma concentrations of S(-)-carvedilol and changes in exercise-induced heart rate were described with an E_{max} model (Table A 47). Due to large variability in the HR data and the limited data at or above E_{max}, the PK/PD model did not support estimation of interindividual variability for most parameters.

Table A 47. Population PKPD Parameters (Reference Table 28/Section 10)

	Population Mean (% se) ¹	Inter-Individual Variability as % CV (% se) ¹
E ₀ (bpm)	126 (1.3)	7.7 (23.2)
EC ₅₀ (ng/mL)	4.25 (44.9)	NE
E _{max} (bpm)	15.1 (11.5)	NE
Amplitude	0.013 (15.4)	NE
T _{max} (h)	11.6 (7.2)	NE
Residual Variability % CV (% se) ¹	4.9 (13.1)	

1. % se – percent standard error

NE – Not Evaluated

Source: Table 10.1

4.2.6.3.5 Safety Results

The number of patients with hypertension who received the carvedilol CR or COREG and reported adverse events regardless of causality are described in Table A 48. The percentages of subjects who reported AEs while receiving carvedilol CR (55/93 = 59.1%) was, in general, less than the percentages of subjects reporting AEs while receiving a comparable dosage of COREG (69/89 = 77.5%). Headache was commonly reported with both formulations and as well with placebo.

Table A 48. Summary of Adverse Events (Reference Table 31/Section 11.2.1)

Adverse Event (preferred term)	Number (%) Subjects						
	Regimen						
	COREG ³			Carvedilol CR ³			Placebo ²
	6.25 mg BID	12.5 mg BID	25 mg BID	20 mg QD	40 mg QD	80 mg QD	
Headache	20 (30.8)	7 (26.9)	16 (32.0)	14 (20.9)	5 (19.2)	10 (19.6)	12 (19.0)
Dizziness	6 (9.2)	2 (7.7)	5 (10.0)	5 (7.5)	0 (0)	2 (3.9)	4 (6.3)
Orthostatic Hypotension	3 (4.6)	2 (7.7)	2 (4.0)	3 (4.5)	0 (0)	2 (3.9)	5 (7.9)
Fatigue	2 (3.1)	0 (0)	0 (0)	3 (4.5)	0 (0)	0 (0)	5 (7.9)
Nausea	2 (3.1)	1 (3.8)	2 (4.0)	0 (0)	1 (3.8)	1 (2.0)	4 (6.3)
Diarrhea	4 (6.2)	0 (0)	1 (2.0)	2 (3.0)	0	0	2 (3.9)
Total Number of AEs	72	17	51	54	14	28	74
Number (%) of Subjects With AEs	34 (52.3)	9 (46.9)	26 (52.0)	28 (41.8)	8 (30.8)	19 (37.2)	26 (41.3)
Number of Subjects Exposed ⁴	65	26	50	67	26	51	63

1. Only the most commonly reported adverse events are listed in this table. Adverse events are presented regardless of causality.
2. In this table, the placebo grouping includes the run-out periods [Session 5] for the two low-target dose groups who previously received carvedilol in Sessions 1 – 4 in addition to subjects receiving placebo in Sessions 1 – 4.
3. In this table, AEs attributed to any dosage of COREG or carvedilol CR include events that were reported by subjects in any treatment group who were receiving the designated regimen (Sessions 1 – 4); AEs that occurred in the down-titration period are not included (Session 5).
4. Includes subjects exposed to the designated regimen at any time in Sessions 1 – 4; AEs that occurred in the down-titration period are not included (Session 5). Although Table 6.3 does not include exposure data for Subject 069, this table does include this subject in number of subjects exposed.

Source: Table 11.1

A total of 57 subjects had vital sign changes that met the protocol-specified criteria for orthostatic hypotension during this study (Table A 49). There did not appear to be any difference in the number of subjects who had orthostatic changes in SBP or DBP between the COREG IR regimens and carvedilol CR regimens.

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Table A 49. Summary of Adverse Events (Reference Table 38/Section 11.6.2)

Number (%) ¹ of Subjects with Occurrences of Orthostatic Hypotension		
Regimen	Systolic Blood Pressure	Diastolic Blood Pressure
A: COREG 6.25 mg PO Q12H	14 (21.5)	5 (7.7)
B: COREG 12.5 mg PO Q12H	5 (19.2)	2 (7.7)
BA: COREG 12.5 mg, then COREG 6.25 mg PO Q12H	1 (4.0)	0 (0)
C: COREG 25 mg PO Q12H	13 (26.0)	4 (8.0)
<i>COREG IR total</i>	33	11
D: Carvedilol CR 20 mg PO QD	16 (23.9)	8 (11.9)
E: Carvedilol CR 40 mg PO QD	1 (3.8)	0 (0)
ED: Carvedilol CR 40 mg, then 20 mg PO QD	3 (12.5)	0 (0)
F: Carvedilol CR 80 mg PO QD	10 (19.6)	8 (15.7)
<i>Carvedilol CR Total</i>	30	16
Placebo	12 (19.0)	8 (12.7)
<i>Total</i>	75	35

1. The calculated percentage is the number of subjects with an orthostatic change in the parameter (DBP or SBP) divided by the total number of subjects exposed to that regimen.

Source: Table 11.6

4.2.6.4 Sponsor's Conclusions

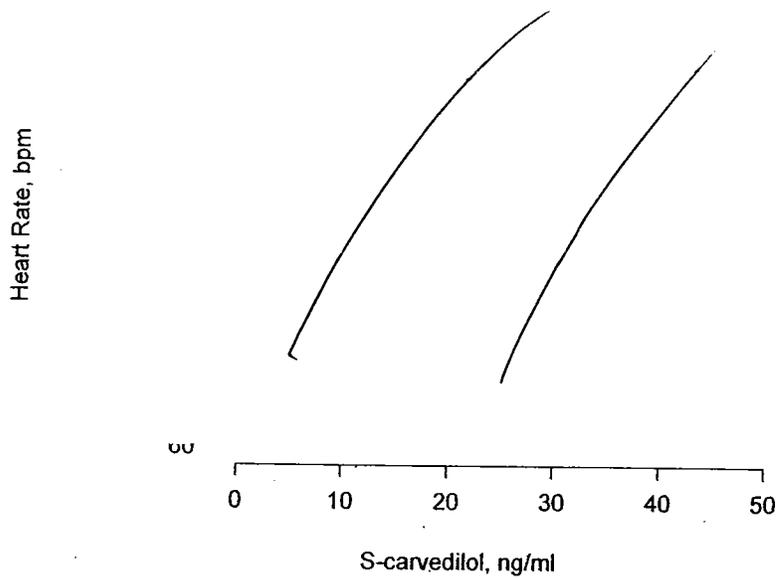
- On average, for carvedilol CR, the reduction of exercise-induced heart rate in patients with hypertension was maintained over the entire 24 hour period.
- Compared to COREG, the carvedilol CR formulation provided equivalent β_1 -adrenergic blockade at trough plasma concentrations.
- Similar peak pharmacodynamic effect and similar overall effect (based on AUEC) were observed for the carvedilol CR formulation compared to the COREG formulation.
- Carvedilol CR was equivalent to COREG with regard to R(+)- and S(-)-carvedilol AUC, C_{τ} , and C_{max} .
- After administration of each formulation, M4 metabolite concentrations declined in parallel with carvedilol concentrations, suggesting that M4 metabolite elimination is formation-rate limited. On average, steady state plasma concentrations of the metabolite M4 were less than 10% of the plasma concentrations observed for carvedilol following administration of both the COREG IR and carvedilol CR formulations.
- The relationship between plasma concentrations of S(-)-carvedilol and changes in exercise-induced heart rate were described with an E_{max} model. Due to large variability in the HR data and the limited data at or above E_{max} , the PK/PD model did not support estimation of interindividual variability for most parameters.

- There appeared to be a greater number of AEs of any causality and those that were considered related to study medication following administration of the COREG regimens compared to the carvedilol CR regimens.
- Administration of COREG and the carvedilol CR formulation to male and female patients with essential hypertension was generally safe.

4.2.6.5 Reviewer's Comments

The data presented in this report provides evidence that IR and CR formulations provide equivalent beta-blocking effects. Evaluation of the concentration-heart rate relationship (Figure A 5) is presented in the pharmacometrics review.

Figure A 5. Concentration and Exercise-Induced Heart Rate Data



4.2.7 Study 369 (PK in CHF and Post-MI LVD Patients)

An open, nonrandomized comparison of pharmacokinetic profiles of carvedilol (SK&F-105517) MR and IR on repeat dosing in chronic CHF patients and survivors of an acute MI and LVD

Protocol Number: SK&F-105517/369

Investigator: This was a multicenter study.

Study Site: The study was conducted at 32 clinical sites.

Study dates: 08 October 2004 – 05 August 2005

4.2.7.1 Objectives

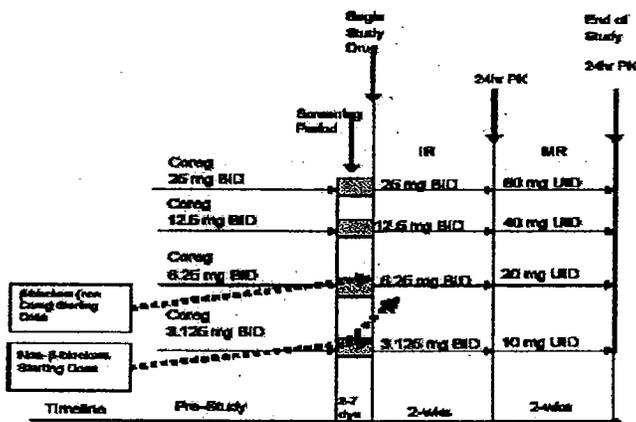
Following multiple-dose administration of twice-daily immediate release and once-daily controlled-release carvedilol formulations to patients with congestive heart failure and asymptomatic survivors of a recent acute myocardial infarction with left ventricular dysfunction, study objectives were to

- Compare the pharmacokinetic profiles
- Assess safety and tolerability of the CR formulation

4.2.7.2 Study Design

This was an open, nonrandomized, multicenter, cross-over PK study in a group of 188 subjects with stable, chronic heart failure (mild, moderate or severe symptoms) and recent asymptomatic survivors of an acute myocardial infarction who had LVD. This study was divided into 3 phases: a screening/baseline phase, a treatment phase, and a safety follow-up phase as illustrated in the following figure. Subject enrollment was stratified for dose of COREG IR at study entry as well as heart failure and post MI LVD group allowing approximately equal numbers of subjects in each strata.

Figure 1 Schematic of Study Design



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Four dose levels of each study formulation was administered in the morning with food: COREG IR 3.125mg bid; or carvedilol CR 10mg qd; COREG IR 6.25mg bid or carvedilol CR 20mg qd; COREG IR 12.5mg bid or carvedilol CR 40mg qd; COREG IR 25mg bid or carvedilol CR 80mg qd).

4.2.7.2.1 Formulations

Table A 50. Products used in SK&F-105517/369

FORMULATIONS	DRUG PRODUCT BATCH NUMBER	DRUG SUBSTANCE BATCH NUMBER	CR FORMULATION
carvedilol CR	X4553	03K9-004 & 03K9-005	10 mg CR capsule (/
	X4544	03K9-004 & 03K9-005	20 mg CR capsule (/
	X4551	03K9-004 & 03K9-005	40 mg CR capsule (/
	X4552	03K9-004 & 03K9-005	80 mg CR capsule (/

To be enrolled, male and female subjects (18-85 y/o) had been diagnosed with clinically stable mild, moderate or severe CHF of ischemic or nonischemic origin and had left ventricular ejection fraction <35% and received background medications for HF. Stable heart failure was defined as no change in New York Heart Association (NYHA) Class and no hospitalization for heart failure or addition of intravenous (IV) diuretics, vasodilators or positive inotropes during the two weeks prior to Screening evaluation).

Subjects must have been euvolemic (the dose of diuretic must have been adjusted so that the subject was neither volume overloaded nor volume contracted. Sitting (resting) heart rate of ≥ 55 BPM if subject was receiving β -blocker agent ≥ 68 BPM if no β -blocker agent was being used; sitting (resting) systolic blood pressure ≥ 85 mmHg. Subjects may have been receiving a β -blocker drug (other than COREG) as CHF or post MI LVD treatment, however, only at dose levels below the total daily equivalent of 200 mg Toprol XL.

4.2.7.2.2 Pharmacokinetic Assessments

Blood samples were collected at 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 13, 14, 16, 20, and 24 hours after dose administration on visit 3 and visit 4. As part of the PK evaluation, all subjects who complete eligibility requirements successfully, had a blood sample withdrawn at Screening for determination of CYP2D6 metabolizer status (alleles *3, *4, *5, *6, *7, and *8).

PK analyses of plasma R-carvedilol and S-carvedilol concentration-time data were conducted using non-compartmental Model 200 of WinNonlin Professional Edition version 4.1 (Pharsight Corporation, Mountain View, CA) according to the standard operating procedures.

4.2.7.2.3 Bioanalytical Assay

Plasma R- and S-carvedilol concentrations were analyzed at GSK (Upper Merion, PA) using a validated method based on HPLC-MS/MS (validation report CD2004/01420/00). Both analytes are extracted from 100 μ l of human plasma by protein precipitation using acetonitrile containing the internal standard. Extracts are analyzed by HPLC-MS/MS. The performance of the assays is shown in Table A 51.

Table A 51. Performance of Analytical Methodology

Analyte (Protocol)	Method	Range ¹ (ng/ml)	Linearity (correlation coefficient)	LLOQ (ng/ml)	QC Samples (ng/ml)	Inter-batch precision (%CV)	Inter-batch accuracy (%RE)
S-	HPLC-MS/MS						
R-	HPLC-MS/MS						

¹ Calibration range consisted of 10 spiked samples over the specified range.

4.2.7.2.4 Pharmacodynamic Assessments

S-carvedilol (the enantiomer with β 1-blocking activity) concentration-time data obtained in the current study and a previously developed PKPD model in healthy volunteers (Study 395) were used to predict the β 1-blocking effect (change in exercise-induced heart rate) of carvedilol in heart failure subjects.

4.2.7.2.5 PK-PD Assessments

β 1-blocking effect at each time point was defined as the percent change from baseline in the predicted exercise-induced heart rate (EHR):

$$PD(\%) = 100 \times (EHR_0 - EHR)/EHR_0$$

where EHR₀ was the predicted exercise heart rate for a given subject at baseline (baseline = 146 bpm) and EHR was the predicted exercise heart rate at each of the postdose measurements for that subject.

The PD(%)-time data were analyzed by non-compartmental methods using the computer program WinNonlin Professional, version 4.0 [WinNonlin, 2003] The following pharmacodynamic parameters were computed:

PD_{max} (%) = maximal pharmacodynamic effect obtained over 24 hours on Day 14

PD_{min} (%) = pharmacodynamic effect at 24 hours postdose on Day 14

AUEC(%·h) = area under the effect curve during the 24 hour dosing interval on Day 14

4.2.7.2.6 Statistical Evaluation

The predicted AUEC, PD_{min}, and PD_{max} data were separately analyzed by a mixed effects model, fitting fixed effect terms for disease strata (mild heart failure, moderate heart failure, severe heart failure, or asymptomatic post MI LVD), dose group (level 1: IR 3.125mg bid or CR 10mg uid, level 2: IR 6.25mg bid or CR 20mg uid, level 3: IR 12.5mg bid or CR 40mg uid, level 4: IR 25mg bid or CR 80mg uid), formulation (IR or CR), group-by-formulation interaction, and dose group-by-formulation interaction. Subject was treated as a random effect. Point estimates and corresponding 90% confidence intervals for the difference of interest (CR-IR) were constructed using the

residual variance. Point and interval estimates for the ratio CR:IR were constructed by expressing the point and interval estimates for the difference normalized to the mean IR response. Point estimates and corresponding 90% confidence intervals for the ratio CR:IR were also constructed by dose group for descriptive purposes.

4.2.7.2.7 Safety Assessments

Assessments of safety included daily recordings of adverse events, clinical laboratory evaluations, and concomitant medications. No formal statistical tests were performed for safety.

4.2.7.3 Study Results

4.2.7.3.1 Subjects

The study was conducted at 32 centers (28 in US and 4 in Canada). A total of 188 subjects were enrolled and 174 (92.6%) completed the study. Of the 14 subjects who did not complete the study 1 was never dosed and excluded from the ITT population, 5 discontinued due to AEs and 8 withdrew voluntarily.

The distribution of subjects by heart failure status and dose group was comparable with the exception of the 3.125mg/10mg dose group of which there were no post-MI patients (Table A 52).

Table A 52. Disposition of Patients (Reference Table 6/Section 6.1.1)

Subject Disposition	3.125mg/ 10mg	6.25mg/ 20mg	12.5mg/ 40mg	25mg/ 80mg	Total
Mild CHF					
Enrolled ¹	-	-	-	-	53
ITT Population (Safety) ²	12	14	13	13	52
PK Population ³	12	12	12	13	49
Completed ⁴	12	12	12	13	49
Moderate CHF					
Enrolled ¹	-	-	-	-	54
ITT Population (Safety) ²	14	13	15	12	54
PK Population ³	12	12	13	11	48
Completed ⁴	12	12	13	12	49
Severe CHF					
Enrolled ¹	-	-	-	-	51
ITT Population (Safety) ²	12	13	13	13	51
PK Population ³	12	12	12	12	48
Completed ⁴	12	12	12	12	48
Post MI LVD					
Enrolled ¹	-	-	-	-	30
ITT Population (Safety) ²	-	14	10	6	30
PK Population ³	-	13	9	6	28
Completed ⁴	-	13	9	6	28
Total					
Enrolled ¹	-	-	-	-	188
ITT Population (Safety) ²	38	54	51	44	187
PK Population ³	36	49	46	42	173
Completed ⁴	36	49	46	43	174

Data Source: Table 6.17

1. Enrolled: Subjects assigned to study medication
2. Intent-to-Treat: Enrolled subjects who received at least one dose of study medication
3. PK Population: Subjects evaluable for PK
4. Completed: As determined by the investigator

Demographic characteristics were balanced between heart failure status. The sponsor did not provide demographic summary by dose group.

4.2.7.3.2 Pharmacokinetics

Mean concentration-time profiles are presented Figure A 6 and Figure A 7. A summary of R- and S-carvedilol PK parameters are shown in Table A 53 and Table A 54. The results of the statistical analysis of PK parameters are shown in Table A 55 and Table A 56. Based on the pooled analysis, the 90% confidence intervals for geometric mean parameters (AUC, C_{max}, C_{min}) fell within the 80% to 125% equivalence range.

Figure A 6. Time Course of Mean (95% CI) R-Plasma Carvedilol Concentrations Stratified by Dose Group (original dataset)

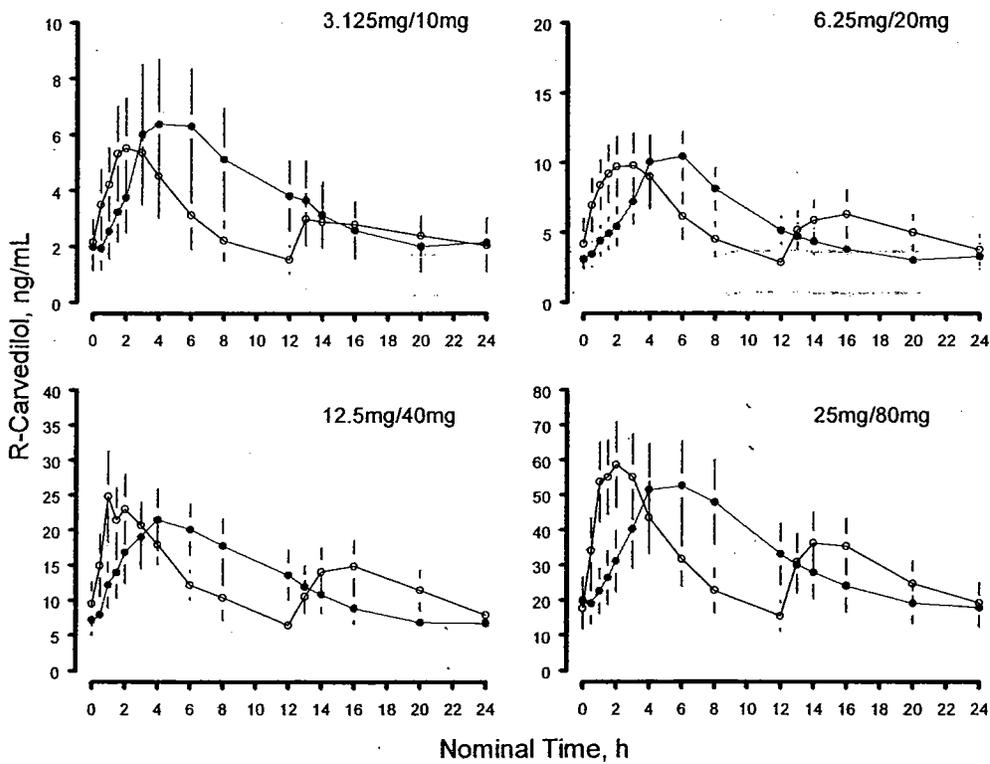


Figure A 7. Time Course of Mean (95% CI) S-Plasma Carvedilol Concentrations Stratified by Dose Group (original dataset)

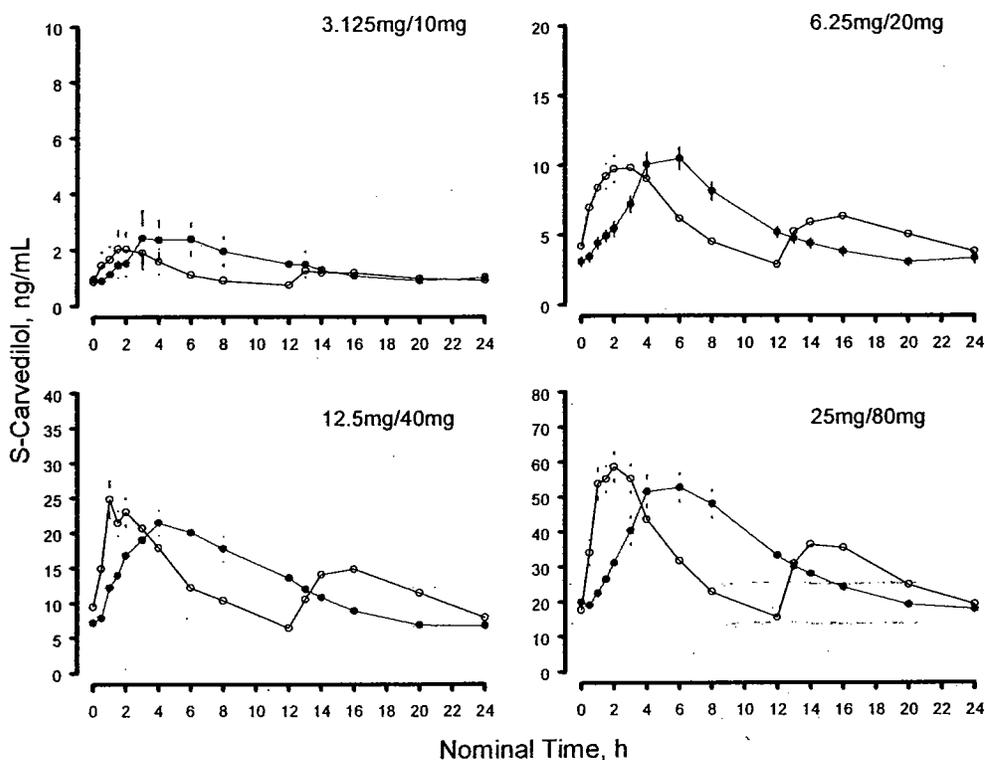


Table A 53. Pharmacokinetic Parameters for R(+) Carvedilol (Reference Table 17/Section 8.2)

Regimen	N	AUC(0-t) ¹ (ng-hr/mL)	C _{max} ¹ (ng/mL)	T _{max} ² (hr)	C _t ¹ (ng/mL)
IR 3.125mg bid	36	53.6 (79.4)	6.10 (67.1)	1.95 (0.00-6.00)	1.13 (140)
IR 6.25mg bid	49	103 (73.4)	11.0 (61.2)	1.92 (0.00-6.03)	2.43 (107)
IR 12.5mg bid	46	252 (63.6)	26.8 (58.9)	1.51 (0.00-11.75)	6.24 (97.0)
IR 25mg bid	42	552 (94.0)	60.6 (70.3)	1.51 (0.50-12.00)	11.6 (144)
CR 10mg uid	36	64.9 (85.8)	6.48 (92.0)	4.04 (1.00-24.00)	1.37 (114)
CR 20mg uid	49	109 (70.0)	10.6 (58.6)	5.67 (1.00-8.00)	2.28 (106)
CR 40mg uid	46	248 (70.3)	23.0 (69.0)	4.00 (0.50-12.00)	4.71 (119)
CR 80mg uid	42	551 (104)	53.8 (84.6)	6.00 (3.00-16.00)	9.91 (169)

Data Source: Tables 8.05 and 8.06

1. Geometric mean (CVb%)

2. Median (range)

Table A 54. Pharmacokinetic Parameters for S(-) Carvedilol (Reference Table 18/Section 8.3)

Regimen	N	AUC(0-t) ¹ (ng-hr/mL)	C _{max} ¹ (ng/mL)	T _{max} ² (hr)	C _τ ¹ (ng/mL)
IR 3.125mg bid	36	20.9 (73.6)	2.27 (72.1)	1.95 (0.00-6.00)	0.519 (123)
IR 6.25mg bid	49	43.0 (66.5)	4.33 (60.0)	1.52 (0.00-6.03)	1.24 (88.1)
IR 12.5mg bid	46	108 (59.4)	11.0 (59.9)	1.50 (0.00-11.75)	3.02 (85.9)
IR 25mg bid	42	242 (70.5)	25.9 (61.1)	1.50 (0.50-12.00)	6.12 (97.6)
CR 10mg uid	36	27.7 (76.8)	2.68 (91.3)	4.04 (1.00-24.00)	0.671 (105)
CR 20mg uid	49	48.9 (66.9)	4.35 (61.4)	5.67 (0.98-8.00)	1.24 (91.1)
CR 40mg uid	46	122 (63.9)	10.2 (66.4)	4.00 (0.50-24.00)	2.82 (105)
CR 80 mg uid	42	254 (80.2)	22.7 (71.0)	6.00 (3.00-16.00)	5.72 (119)

Data Source: Tables 8.07 and 8.08

1. Geometric mean (CVb%)
2. Median (range)

Table A 55. Statistical Analysis of R-Carvedilol PK Parameters (Reference Table 19/Section 8.4)

Parameter	Dose Group	Comparison of Interest	Point Estimate	90% CI	CVw% ³
AUC(0-t) ¹ ng.hr/mL	Pooled	CR:IR	1.06	(1.01, 1.12)	28.0
	3.125mg IR/ 10mg CR	CR:IR	1.21	(1.09, 1.35)	
	6.25mg IR/ 20mg CR	CR:IR	1.06	(0.97, 1.16)	
	12.5mg IR/ 40mg CR	CR:IR	0.98	(0.89, 1.08)	
	25mg IR/ 80mg CR	CR:IR	1.00	(0.90, 1.10)	
C _{max} ¹ ng/mL	Pooled	CR:IR	0.95	(0.89, 1.02)	38.2
	3.125mg IR/ 10mg CR	CR:IR	1.06	(0.92, 1.23)	
	6.25mg IR/ 20mg CR	CR:IR	0.97	(0.85, 1.09)	
	12.5mg IR/ 40mg CR	CR:IR	0.87	(0.76, 0.98)	
	25mg IR/ 80mg CR	CR:IR	0.90	(0.79, 1.03)	
C _τ ¹ ng/mL	Pooled	CR:IR	0.92	(0.85, 1.01)	49.4
	3.125mg IR/ 10mg CR	CR:IR	1.21	(1.01, 1.45)	
	6.25mg IR/ 20mg CR	CR:IR	0.94	(0.80, 1.10)	
	12.5mg IR/ 40mg CR	CR:IR	0.75	(0.64, 0.89)	
	25mg IR/ 80mg CR	CR:IR	0.86	(0.72, 1.02)	
t _{max} (hr) ²	Pooled	CR:IR	3.00	(2.59, 3.25)	
	3.125mg IR/ 10mg CR	CR:IR	3.02	(2.25, 4.25)	
	6.25mg IR/ 20mg CR	CR:IR	2.74	(2.21, 3.25)	
	12.5mg IR/ 40mg CR	CR:IR	2.25	(1.50, 2.77)	
	25mg IR/ 80mg CR	CR:IR	4.00	(3.50, 4.48)	

Data Source: Tables 8.01 and 8.03

1. Point estimate is the ratio of adjusted geometric means between regimens.
2. Point estimate is the estimated median difference between regimens.
3. CVw% represents a pooled estimate of within-subject variability across regimens.

Table A 56. Statistical Analysis of S-Carvedilol PK Parameters (Reference Table 20/Section 8.4)

Parameter	Dose Group	Comparison of Interest	Point Estimate	90% CI	CVw% ³
AUC(0-t) ¹ ng.hr/mL	Pooled	CR:IR	1.16	(1.10, 1.22)	27.6
	3.125mg IR/ 10mg CR	CR:IR	1.33	(1.19, 1.47)	
	6.25mg IR/ 20mg CR	CR:IR	1.14	(1.04, 1.24)	
	12.5mg IR/ 40mg CR	CR:IR	1.13	(1.03, 1.24)	
	25mg IR/ 80mg CR	CR:IR	1.05	(0.95, 1.16)	
C _{max} ¹ ng/mL	Pooled	CR:IR	1.00	(0.94, 1.08)	39.0
	3.125mg IR/ 10mg CR	CR:IR	1.18	(1.02, 1.37)	
	6.25mg IR/ 20mg CR	CR:IR	1.00	(0.88, 1.14)	
	12.5mg IR/ 40mg CR	CR:IR	0.94	(0.82, 1.07)	
	25mg IR/ 80mg CR	CR:IR	0.89	(0.78, 1.02)	
C _τ ¹ ng/mL	Pooled	CR:IR	1.03	(0.95, 1.12)	46.7
	3.125mg IR/ 10mg CR	CR:IR	1.29	(1.09, 1.54)	
	6.25mg IR/ 20mg CR	CR:IR	1.01	(0.87, 1.17)	
	12.5mg IR/ 40mg CR	CR:IR	0.93	(0.80, 1.09)	
	25mg IR/ 80mg CR	CR:IR	0.94	(0.80 ⁴ , 1.10)	
t _{max} (hr) ²	Pooled	CR:IR	3.00	(2.73, 3.25)	
	3.125mg IR/ 10mg CR	CR:IR	3.03	(2.25, 4.04)	
	6.25mg IR/ 20mg CR	CR:IR	2.76	(2.25, 3.49)	
	12.5mg IR/ 40mg CR	CR:IR	2.25	(1.50, 3.00)	
	25mg IR/ 80mg CR	CR:IR	3.86	(3.50, 4.25)	

Data Source: Tables 8.02 and 8.04

1. Point estimate is the ratio of adjusted geometric means between regimens.
2. Point estimate is the estimated median difference between regimens.
3. CVw% represents a pooled estimate of within-subject variability across regimens.
4. 0.796.

There were 6 patients (776, 876, 1284, 1285, 1658, and 1659) who provided anomalous PK data. ID 776, 876, 1284, 1285 had their CR-IR treatments switched and ID 1658 and 1659 had 3 h and 24 h samples switched. The sponsor performed statistical analyses on the original dataset (ITT analysis) as well as a modified dataset (changing treatments) and by excluding these patients. There was little impact of the anomalous PK data on the statistical analyses.

4.2.7.3.3 Pharmacodynamics

The sponsor used a PKPD model to predict the beta-blocking effects from the observed plasma concentrations. A summary of parameters calculated from the predicted response data is shown in Table A 57. The sponsor concluded that the predicted pharmacodynamic effect (AUEC, PD_{min}, and PD_{max}) was equivalent for carvedilol CR compared to COREG IR.

Table A 57. Summary of Predicted Responses (Reference Table 23/Section 9.1)

Dose Group	N	AUEC (%.h) ¹	PDmin (%) ¹	PDmax (%) ¹
IR 3.125mg bid	36	36.1 (60.8%)	1.15 (92.7%)	3.26 (48.6%)
IR 6.25mg bid	49	62.8 (49.5%)	2.11 (66.2%)	4.89 (32.9%)
IR 12.5mg bid	46	113 (33.6%)	3.96 (48.1%)	7.75 (19.8%)
IR 25mg bid	42	168 (28.2%)	5.92 (40.8%)	10.0 (13.3%)
CR 10mg uid	36	45.4 (57.7%)	1.35 (76.8%)	3.69 (52.9%)
CR 20mg uid	49	68.5 (44.6%)	2.14 (61.7%)	4.86 (34.3%)
CR 40mg uid	46	121 (33.6%)	3.91 (50.5%)	7.41 (24.6%)
CR 80mg uid	42	171 (30.0%)	5.76 (46.3%)	9.59 (16.8%)

Data Source: Table 8.24

1. Arithmetic mean (CVb%).

4.2.7.3.4 Safety

The frequency and types of adverse experiences were similar across both treatment periods, and each of the strata. The percentage of subjects reporting any adverse experience was 26%, 22%, 14% and 20% for the 10mg, 20mg, 40mg, and 80mg carvedilol CR groups, respectively. These numbers were comparable to the 21%, 19%, 16%, and 11% reported for COREG IR 3.125mg, 6.25mg, 12.5mg, and 25mg bid groups, respectively.

4.2.7.4 Sponsor's Conclusions

- At all dose levels, the pharmacokinetic parameters for R(+)- and S(-)-carvedilol were similar for the two formulations. Based on the pooled analysis, AUC, C_{max}, and C_{tau} for R(+)- and S(-)-carvedilol were equivalent for the CR and IR formulations as point estimates and corresponding 90% confidence intervals for the pharmacokinetic parameters were within bioequivalence limits of 80%-125%.
- Based on the pooled analysis, carvedilol CR had an equivalent predicted overall effect (AUEC), maximum effect (PD_{max}), and minimum effect (PD_{min}) compared to COREG IR.

4.2.7.5 Reviewer's Comments

1. This study provides evidence that the steady-state pharmacokinetics of the CR and IR formulations are equivalent in the target population.
2. Assessment of the individual concentration-time profiles confirmed the sponsor's claim of anomalous PK data for IDs 776, 876, 1284, 1285, 1658, and 1659.

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4.2.8 Dissolution Methodology

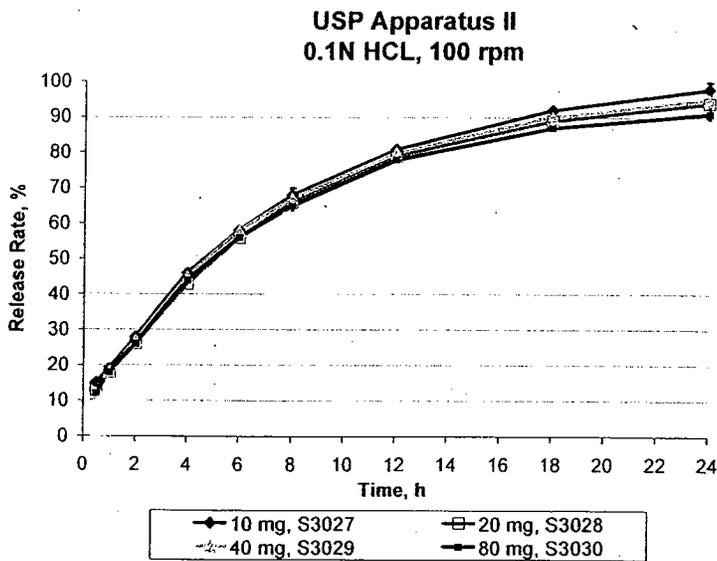
4.2.8.1 Dissolution Methodology and Specification

Table A 58 shows the product dissolution method and proposed specification for the carvedilol CR capsules. The CR component of the capsules or CR microparticles is designed to release carvedilol phosphate based on pH and time dependent mechanisms. In 0.1N HCl dissolution media, the release profile presents a delayed release for approximately 2 hours and a gradual release of carvedilol phosphate in the next 22 hours from the CR components (Figure A 12).

Table A 58. Product Dissolution Method and Specification (described in section 2.4.2.3.4/ m3.2.P.2. Pharmaceutical Development)

Dosage Form:	Capsule
Strengths:	10 mg, 20 mg, 40 mg, 80 mg
Apparatus Type:	USP Apparatus II (paddle)
Media:	0.1 N hydrochloric acid (HCl),
Media Volume	900 mL at 37°C
Rotation Speed	100
Sampling Times:	1
Brief Description of the Dissolution Analytical Method:	
Dissolution Specification:	

Figure A 12. Dissolution Profiles of Commercial Batches of Carvedilol CR (Reference Table 16 in section m3.2.P.5.4. Batch Analyses)



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- **24 hour, Not less than 80%**

The limit at 24 hours ensures that the bulk of carvedilol phosphate in the dosage form is adequately released from the dosage form during the test period.

4.2.8.4 Release Rates of Final Formulation: Biobatches vs. Commercial Batches

To compare the commercial batches (SUPAC MR level 2 scale-up and level 2 site change) to the biobatches (Table A 61), multipoint dissolution profiles were obtained in the proposed dissolution media (0.1N HCl) and three other media (____). The similarity factor (f2) ranged from 55 to 97 when comparing the biobatches (test) to the commercial batch (reference) providing evidence that the dissolution curves are similar in the four media.

Table A 61. Batch Analyses (m3.2.P.5.4. Batch Analyses)

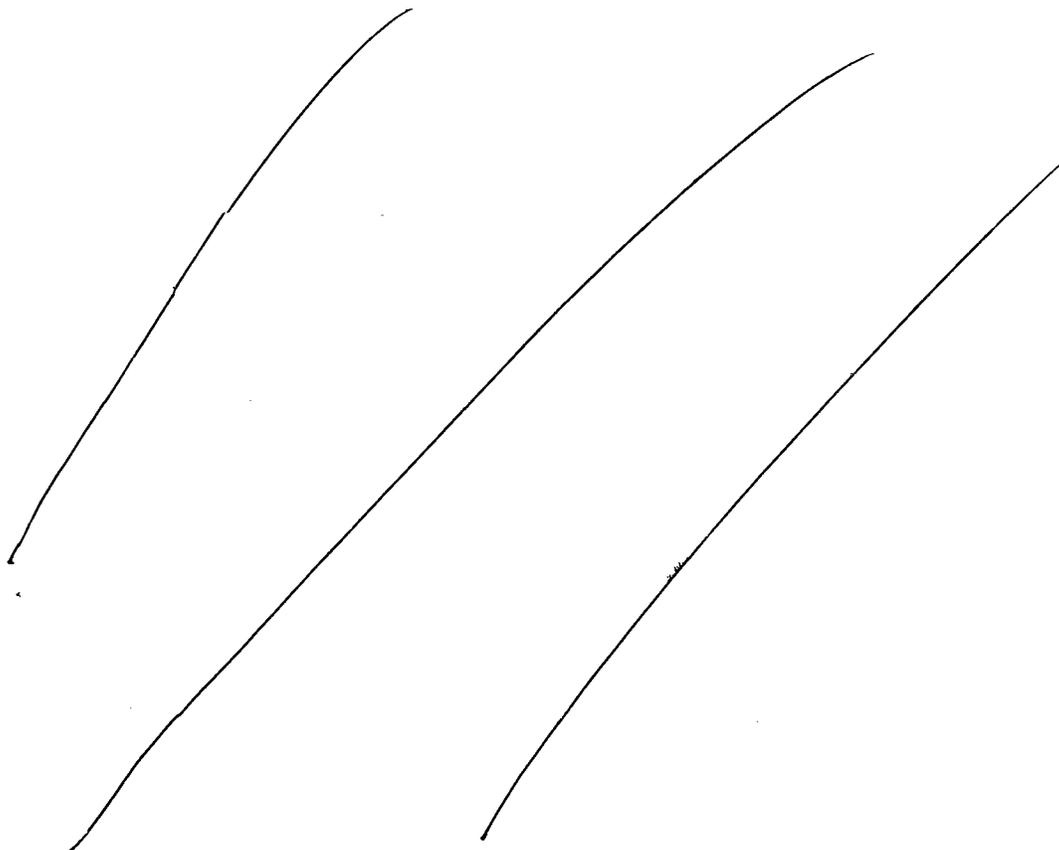
	10 mg Capsules	20 mg Capsules	40 mg Capsules	80 mg Capsules
Batch No. Batch Size Scale Use Date	<u>XS3027</u> Production Commercial March 2006	<u>XS3028</u> Production Commercial March 2006	<u>XS3029</u> Production Commercial March 2006	<u>XS3030</u> Production Commercial March 2006
Batch No. Batch Size Scale Use Date	<u>X4553</u> Pilot Clinical February 2004	<u>X4544</u> Pilot Clinical February 2004	<u>X4551</u> Pilot Clinical February 2004	<u>X4552</u> Pilot Clinical February 2004
Batch No. Batch Size Scale Use Date	<u>X7251</u> Pilot Stability & Clinical March 2004	<u>X6862</u> Pilot Stability & Clinical March 2004	<u>X7004</u> Pilot Stability & Clinical March 2004	<u>X7194</u> Pilot Stability & Clinical March 2004

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4.2.8.5 *In Vitro* Ethanol Interaction (Reference: Attachment II, 24-March Submission Cover Letter)

A dissolution study was performed to assess the potential for ethanol to affect in-vitro drug release from carvedilol CR capsules. For this analysis, the proposed commercial release method was employed (USP Apparatus II, 900 mL dissolution media, 100 rpm) with the exception that varying levels of ethanol were incorporated into the medium.

A concentration-related increase in the rate of release of carvedilol was observed, with release rate increasing with ethanol content (Figure A 21, Table A 62). Based on these data, the sponsor is conducting a clinical study to more accurately assess the impact of ethanol on the drug release profile.

Figure A 21. Mean Release Rates as a Function of Ethanol Concentration

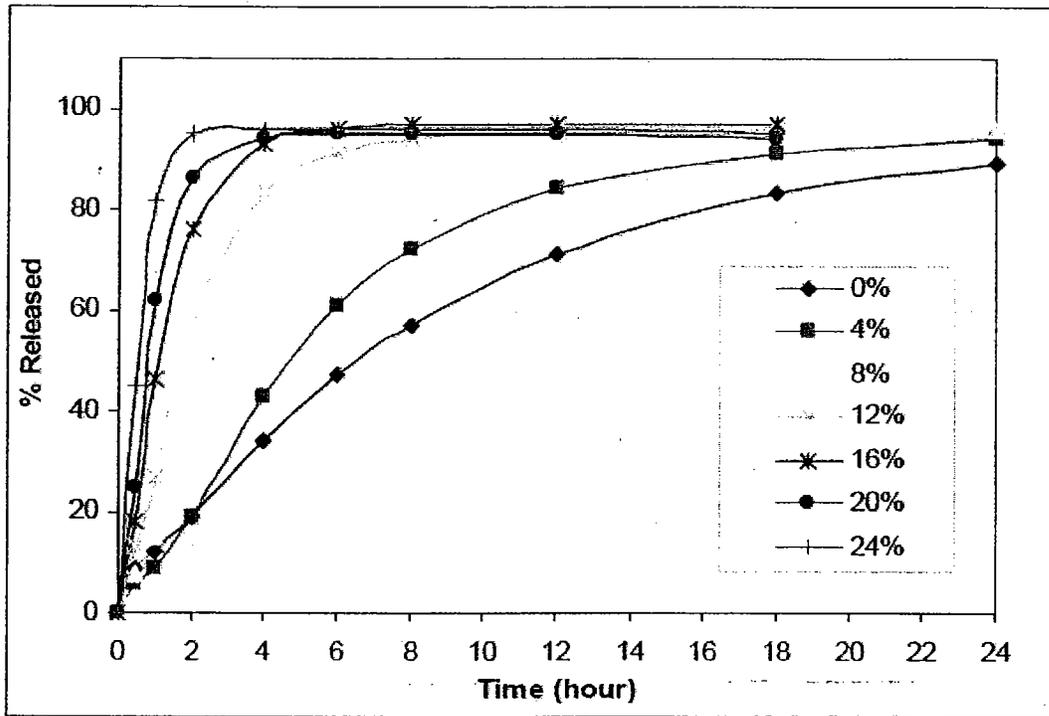


Table A 63. Mean Release Rates as a Function of Ethanol Concentration

Time (hour)	Level of Ethanol						
	0%	4%	8%	12%	16%	20%	24%
0	0	0	0	0	0	0	0
0.5	9	6	8	13	18	25	45
1	12	9	15	27	46	62	82
2	19	19	35	59	76	86	95
4	34	43	67	83	93	94	96
6	47	61	81	91	96	95	96
8	57	72	88	94	97	95	96
12	71	84	94	96	97	95	96
18	83	91	96	96	97	94	95
24	89	94	96	NP	NP	NP	NP

Note: NP = not performed

4.2.8.6 Reviewer's Comments

- The recommended range at any dissolution time point is $\pm 5\%$ deviation from the mean dissolution profile obtained from the clinical lots. The sponsor has proposed a $\pm 10\%$ for the 8-h time point. Without support from in vivo BE data, the reviewer recommends a specification of NLT $\pm 5\%$ and NMT $\pm 5\%$.

The last time point should be the time point where at least 80% of the drug has dissolved. Based on the dissolution profiles for the biobatches and commercial batches, it is recommended 24 hours.

The sponsor has proposed a rotation speed of 100 rpm for USP Apparatus II.

Capsule Strength	Mean % Release at 8-h in 0.1 N HCl			Mean
	Commercial Batch	Clinical Batch	Stability Batch	
10 mg	68	57	63	63
20 mg	66	58	62	62
40 mg	67	58	62	62
80 mg	65	57	61	61

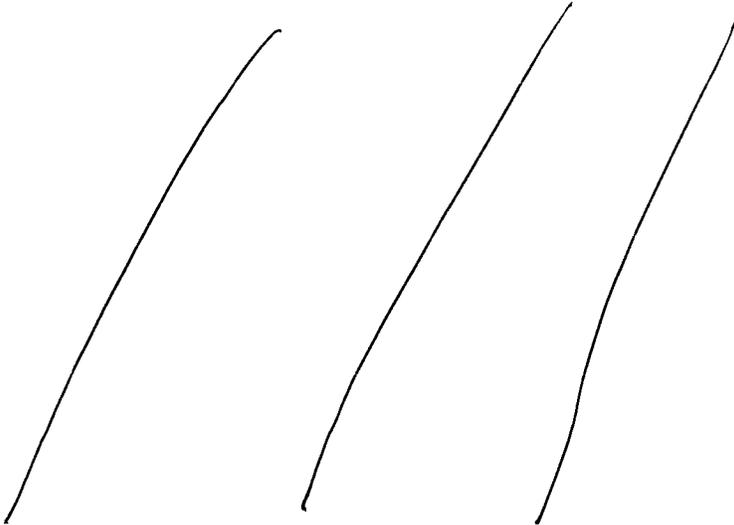
- 
2. A biowaiver for the SUPAC level 2 site change and scale up for the commercial batches cannot be granted until additional dissolution data is submitted using the recommended method and specification.
 3. The coefficient of variation for the mean dissolution profiles in the proposed dissolution media is less than 10% for the commercial and pivotal biobatches. Table A 64 to Table A 66 present these data. The same tables will need to be generated with the recommended dissolution method and specification.

Table A 64. Mean (%CV) Dissolution Data for the Commercial Batches

Time	S3027 10 mg Capsule		S3028 20 mg Capsule		S3029 40 mg Capsule		S3030 80 mg Capsule	
	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV
0.1 N HCl (Commercial Dissolution Media)								
0.5	14.6	7.4	12.7	6.1	12.1	9.6	12.3	6.3
1	19.4	5.1	17.6	4.5	17.8	3.5	17.7	2.8
2	28.5	3.8	26.2	3.6	26.9	2.9	26.4	2.5
4	45.4	2.6	43.4	2.7	44.6	2.2	43.7	2.0
6	58.1	2.7	56.2	2.1	57.5	1.7	56.2	1.3
8	67.6	2.4	65.6	2.3	67.1	1.5	65.4	1.2
12	81.3	2.2	78.8	2.2	80.3	1.3	77.8	1.6
18	92.4	2.0	89.2	2.1	90.3	1.2	86.8	1.4
24	97.8	2.4	94.1	2.0	95.3	1.1	90.8	1.3

0.5	12.8	7.6	12.1	7.5	12.5	5.4	12.3	8.7
1	15.8	5.5	14.8	4.2	15.3	4.2	15.0	4.0
2	20.4	3.3	19.2	4.4	19.9	2.6	19.5	4.1
4	33.2	2.5	31.4	3.2	32.3	2.4	31.2	3.0
6	45.8	2.4	44.0	2.7	44.9	1.5	42.7	2.5
8	56.8	2.2	54.7	2.4	55.7	1.4	52.5	2.1
12	70.0	2.1	68.3	2.2	69.0	0.9	64.8	1.5
18	78.8	2.2	76.6	2.4	77.0	0.8	72.0	1.5
24	82.6	2.2	80.3	2.1	80.0	0.8	74.2	1.0

0.5	17.7	6.5	18.8	4.4	18.4	4.9	17.3	3.8
1	31.8	5.5	35.6	3.0	35.4	3.7	35.0	1.2
2	49.8	4.8	51.8	2.7	52.4	1.9	51.8	1.2
4	63.3	3.2	63.2	1.5	63.8	0.9	62.8	1.0
6	69.6	2.8	68.9	1.4	69.4	1.0	67.9	1.0
8	74.6	2.5	73.9	1.8	74.2	1.3	72.3	0.9
10	79.4	2.5	78.6	1.8	78.4	0.9	76.4	1.2
12	83.5	2.2	82.9	1.6	82.4	0.8	80.2	0.7
14	87.0	2.5	86.8	1.7	85.9	1.0	83.6	1.1
16	89.9	2.4	90.1	1.8	89.0	1.0	86.4	1.0
18	92.5	2.2	92.7	1.9	91.5	1.1	88.9	1.1

0.5	22.1	11.0	21.0	18.8	17.3	6.2	17.2	4.2
1	40.6	5.3	39.8	4.9	38.3	2.8	37.8	1.6
1.5	53.7	3.4	52.4	3.6	51.6	1.7	50.6	1.0
2	63.7	3.0	62.3	2.4	61.5	1.5	60.3	1.5
3	75.4	2.7	73.8	1.8	73.2	0.8	71.7	1.8
4	83.7	2.8	81.8	1.7	79.8	2.8	79.3	1.2
5	88.5	2.3	86.8	1.6	85.5	0.9	84.8	0.7
6	91.8	2.2	90.2	1.5	89.1	0.8	88.1	0.9
8	95.7	2.1	93.6	1.5	91.7	1.2	91.2	0.6

Table A 65. Mean (%CV) Dissolution Data for the Biobatches: Clinical Batches

Time	X4553		X4544		X4551		X4552	
	10 mg Capsule		20 mg Capsule		40 mg Capsule		80 mg Capsule	
	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV
0.1 N HCl (Commercial Dissolution Media)								
0.5	13.3	5.8	12.3	5.1	12.2	6.9	12.0	9.4
1	15.6	4.3	15.0	2.8	15.1	5.3	14.5	6.2
2	21.3	4.1	20.3	3.7	20.4	4.9	19.8	3.6
4	35.3	3.9	34.9	3.1	35.2	3.6	34.4	2.9
6	47.5	3.6	47.0	2.6	48.0	2.5	46.8	2.0
8	57.5	3.6	57.6	2.6	58.4	2.7	57.3	1.5
12	72.5	3.7	73.4	2.5	74.0	2.6	72.4	1.2
18	84.7	3.5	85.9	2.7	87.3	2.4	84.5	1.2
24	90.4	3.8	92.5	2.6	93.6	2.5	90.2	1.2
<hr/>								
0.5	9.8	20.1	10.0	12.8	11.8	8.7	11.2	7.5
1	11.9	10.4	12.4	6.4	13.3	5.8	13.0	3.3
2	15.4	5.8	15.8	3.6	16.4	4.8	15.7	3.1
4	26.1	6.6	27.1	2.5	27.4	2.4	26.2	1.5
6	38.1	5.8	39.2	2.8	39.2	1.0	37.1	1.8
8	48.8	5.4	50.2	2.7	50.0	1.5	47.2	1.5
12	62.9	4.5	64.3	2.2	64.1	1.0	60.3	1.0
18	72.3	4.2	73.5	2.6	73.3	1.2	68.3	1.0
24	76.4	4.1	77.5	2.5	76.9	1.3	71.1	0.7
<hr/>								
0.5	20.0	8.8	20.6	7.3	18.8	3.3	18.3	3.4
1	36.1	5.5	37.6	4.5	36.1	2.2	35.8	2.3
2	53.5	4.0	55.1	4.1	53.5	1.3	52.9	1.3
4	64.1	3.7	65.4	4.5	65.0	1.6	64.1	1.4
6	70.1	3.6	71.7	4.5	70.2	1.6	69.2	1.5
8	75.4	4.0	77.6	4.3	75.1	1.7	73.7	0.9
10	80.9	4.0	82.5	4.6	79.4	1.7	77.8	0.9
12	85.1	3.6	87.4	4.5	83.3	1.6	81.8	0.8
14	89.0	3.5	91.1	4.8	87.3	1.6	84.9	0.8
16	92.2	3.8	94.3	4.9	90.1	1.7	87.8	0.7
18	93.8	3.8	96.4	4.9	93.0	2.1	90.7	2.6
<hr/>								
0.5	19.3	12.0	18.2	11.0	21.1	9.1	20.6	7.9
1	38.4	5.9	36.3	5.7	39.3	4.0	38.5	3.4
1.5	53.5	4.7	51.1	3.3	53.8	2.6	51.9	2.2
2	65.0	4.4	62.3	3.4	64.7	2.3	62.4	1.4
3	78.3	3.8	75.3	2.8	77.3	1.5	73.3	1.2
4	84.8	3.6	82.6	2.7	85.2	1.4	80.5	1.1
5	88.6	3.4	86.7	2.6	89.5	1.1	84.9	0.9
6	90.6	3.3	89.4	2.4	92.4	1.2	87.7	1.0
8	92.9	3.4	92.0	2.7	95.0	1.2	90.1	1.0

Table A 66. Mean (%CV) Dissolution Data for the Biobatches: Clinical & Stability Batches

Time	X7251 10 mg Capsule		X6862 20 mg Capsule		X7004 40 mg Capsule		X7194 80 mg Capsule	
	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV
0.1 N HCl (Commercial Dissolution Media)								
0.5	13.8	6.3	12.6	5.3	12.7	3.9	12.1	4.3
1	16.8	6.6	15.6	4.3	16.3	2.8	15.8	2.5
2	24.3	5.1	22.3	4.0	24.1	2.1	23.2	2.5
4	40.9	3.2	39.3	2.9	40.4	1.3	39.4	1.7
6	53.0	2.8	51.6	2.7	52.5	1.0	51.6	1.3
8	62.8	2.7	61.6	2.6	62.1	1.1	60.9	0.8
12	76.4	2.5	76.2	2.5	75.9	1.3	74.7	1.0
18	89.3	1.9	88.4	2.5	88.3	1.4	86.0	1.0
24	95.4	2.1	94.6	2.6	94.3	1.5	91.3	1.0

0.5	12.5	8.0	11.6	6.8	12.1	6.6	11.8	5.3
1	14.3	6.8	13.1	5.1	13.7	4.8	13.6	3.8
2	17.8	5.8	16.7	3.0	17.3	3.8	16.6	3.1
4	29.9	4.1	28.8	4.0	28.8	3.0	27.1	2.5
6	42.8	3.7	41.5	4.0	41.3	2.6	38.4	2.6
8	53.9	3.3	52.6	4.1	52.2	2.0	48.8	2.5
12	67.8	2.4	66.7	3.0	66.1	1.5	61.9	2.0
18	77.1	2.4	75.8	2.2	74.8	1.6	70.0	1.1
24	81.0	2.4	79.9	2.0	78.3	1.3	72.8	1.0

0.5	17.7	6.5	19.2	6.2	18.6	3.6	18.0	4.7
1	31.8	5.5	37.9	2.1	36.0	3.9	35.3	5.8
2	49.8	4.8	55.0	1.6	52.7	2.8	51.8	3.8
4	63.3	3.2	65.6	1.4	64.2	1.6	63.1	1.1
6	69.6	2.8	71.1	1.5	69.4	1.4	68.3	0.7
8	74.6	2.5	76.1	1.4	74.2	1.8	72.7	0.9
10	79.4	2.5	80.9	1.5	78.2	1.5	76.8	1.1
12	83.5	2.2	85.1	1.5	82.2	1.5	80.6	1.1
14	87.0	2.5	88.8	1.5	85.7	1.8	83.8	1.2
16	89.9	2.4	92.1	1.7	88.8	1.5	86.8	1.0
18	92.5	2.2	94.1	1.8	91.3	1.7	89.4	1.2

0.5	23.0	8.5	20.5	9.2	19.8	6.4	19.3	7.0
1	44.3	4.4	40.8	4.3	40.5	4.3	42.8	1.9
1.5	58.5	3.0	54.1	2.9	53.1	3.3	55.3	1.7
2	69.4	3.0	63.9	2.5	62.8	2.2	64.3	1.7
3	81.8	2.1	75.8	2.3	74.3	2.2	76.0	1.3
4	88.5	2.1	83.4	2.4	81.8	1.7	82.8	1.5
5	93.3	2.1	88.4	2.2	86.8	1.6	86.8	1.4
6	96.0	1.9	91.8	2.3	90.0	1.5	89.6	0.9
8	98.8	1.6	95.7	2.2	93.5	1.4	91.8	1.3

4.3 Pharmacometrics Review

4.3.1.1 Regulatory Background

During the pre-NDA meeting with the sponsor (21 July 2005), it was agreed that to support the heart failure / mortality indication the sponsor will have to demonstrate that both the PK and PD after administration of carvedilol CR capsules are equivalent to those obtained from the IR tablets. These data includes (1) observed PK data (C_{tau}, C_{max}, AUC) from study 369, (2) observed PD data (PD_{min}, PD_{max}, AUEC) from study 902, and (3) the concentration-effect data.

4.3.1.2 Question-Based Review

4.3.1.2.1 *Is the observed β -blocking effect following administration of carvedilol CR capsules equivalent to those observed with IR tablets?*

Exercise heart rate and concentration data collected in patients with essential hypertension (study 902) shows that carvedilol CR has the same blocking effects as the immediate release formulation. The exercise-induced heart rate at trough concentrations (PD_{min}) observed with carvedilol CR capsules was equivalent to those observed with IR tablets (Table A 67). The 90% confidence intervals of the CR:IR ratio fell within a 80 to 125% equivalence interval. Similar findings were observed for PD_{max} and AUEC (Table A 68 and Table A 69, respectively).

Table A 67. Beta-Blocking Effects in Patients with Essential Hypertension (study 902): Statistical Analysis of PD_{min}%
(Reference Table 20/Section 7.1/Study 902)

Parameter	Comparison of Interest CR:IR	Point Estimate	90% CI	Within subject SD ⁴
PD _{min}	Pooled Group ¹	1.00	(0.94, 1.07)	3.86
PD _{min}	High Dose Group ²	1.06	(0.97, 1.15)	
PD _{min}	Low Dose Group ³	0.94	(0.84, 1.05)	

1. High and Low Dose Groups combined
2. COREG 25mg BID and carvedilol CR 80mg OD
3. COREG 6.25mg BID and carvedilol CR 20mg OD
4. Within-subject standard deviation

Source: Table 7.1

**Table A 68. Beta-Blocking Effects in Patients with Essential Hypertension (study 902):
Statistical Analysis of PDmax%
(Reference Table 22/Section 7.3/Study 902)**

Parameter	Comparison of Interest	Point Estimate	90% CI	SDw
PDmax	CR:IR (Pooled) ¹	0.97	(0.92, 1.02)	3.82
PDmax	CR:IR (High Dose Group) ²	1.02	(0.95, 1.08)	
PDmax	CR:IR (Low Dose Group) ³	0.92	(0.84, 1.00)	

1. High and Low Dose Groups combined
 2. COREG 25mg BID and carvedilol CR 80mg OD
 3. COREG 6.25mg BID and carvedilol CR 20mg OD
- Source: Table 7.5

**Table A 69. Beta-Blocking Effects in Patients with Essential Hypertension (study 902):
Statistical Analysis of AUEC%
(Reference Table 21/Section 7.2/Study 902)**

Parameter	Comparison of Interest	Median	90% Bootstrap CI (5th percentile, 95th percentile)
AUEC	CR:IR (Pooled) ¹	1.02	(0.93, 1.10)
AUEC	CR:IR (High Dose Group) ²	1.03	(0.96, 1.10)
AUEC	CR:IR (Low Dose Group) ³	1.00	(0.92, 1.09)

1. High and Low Dose Groups combined
 2. COREG 25mg BID and carvedilol CR 80mg OD
 3. COREG 6.25mg BID and carvedilol CR 20mg OD
- Source: data on file, GSK

4.3.1.2.2 Do the CR capsules and IR tablets have the same concentration-effect relationship?

Administration of carvedilol CR capsules and IR tablets to patients with essential hypertension have the same concentration-effect relationship. This relationship is shown graphically in Figure A 22. An Emax model was applied to the concentration-heart rate data for each formulation separately. The median and 90% confidence intervals for model parameters show that this relationship is the same (Table A 73). Therefore, it can be concluded that the PKPD relationship for carvedilol is not dependent on the input rate.

4.3.1.2.3 Is the observed exposure to R(+) and S(-) carvedilol following administration of carvedilol CR capsules equivalent to the exposure with IR tablets?

The steady-state pharmacokinetics of carvedilol CR was characterized in patients with mild to severe heart failure and post-MI patients with LVD. Patients received IR tablets (3.125 mg, 6.25 mg, 12.5 mg, and 25 mg) for 14 days then received an equivalent CR dose (10 mg, 20 mg, 40 mg and 80 mg). At all dose levels, exposure to R(+) and S(-) carvedilol observed with carvedilol CR capsules were similar to the exposure observed with IR tablets (Table A 70 to Table A 72). Using pooled data across dose groups, the 90% confidence intervals of the CR:IR ratios for Cmax, AUC, and Ctau fell within the 80% to 125% equivalence interval.

Table A 70. Summary of Steady-State Pharmacokinetic Parameters for R(+) and S(-) Carvedilol in Patients with CHF and Post-MI LVD
(Reference Table 22/ 2.7.2 Clinical Pharmacology Summary)

Analyte	Regimen	N	AUC(0-t) ¹ (ng-hr/mL)	C _{max} ¹ (ng/mL)	T _{max} ² (hr)	C _τ ¹ (ng/mL)
R(+)-	IR 3.125mg bid	36	53.5 (79.4)	6.10 (67.1)	1.95 (0.00-6.00)	1.13 (140)
	IR 6.25mg bid	49	103 (73.4)	11.0 (61.2)	1.92 (0.00-6.03)	2.43 (107)
	IR 12.5mg bid	46	252 (63.6)	26.8 (58.9)	1.51 (0.00-11.75)	6.24 (97.0)
	IR 25mg bid	42	552 (94.0)	60.6 (70.3)	1.51 (0.50-12.00)	11.6 (144)
	CR 10mg uid	36	64.9 (85.8)	6.48 (92.0)	4.04 (1.00-24.00)	1.37 (114)
	CR 20mg uid	49	109 (70.0)	10.6 (58.6)	5.67 (1.00-8.00)	2.28 (106)
	CR 40mg uid	46	248 (70.3)	23.0 (69.0)	4.00 (0.50-12.00)	4.71 (119)
	CR 80mg uid	42	551 (104)	53.8 (84.6)	6.00 (3.00-16.00)	9.91 (169)
S(-)-	IR 3.125mg bid	36	20.9 (73.6)	2.27 (72.1)	1.95 (0.00-6.00)	0.519 (123)
	IR 6.25mg bid	49	43.0 (66.5)	4.33 (60.0)	1.52 (0.00-6.03)	1.24 (88.1)
	IR 12.5mg bid	46	108 (59.4)	11.0 (59.9)	1.50 (0.00-11.75)	3.02 (85.9)
	IR 25mg bid	42	242 (70.5)	25.9 (61.1)	1.50 (0.50-12.00)	6.12 (97.6)
	CR 10mg uid	36	27.7 (76.8)	2.68 (91.3)	4.04 (1.00-24.00)	0.671 (105)
	CR 20mg uid	49	48.9 (66.9)	4.35 (61.4)	5.67 (0.98-8.00)	1.24 (91.1)
	CR 40mg uid	46	122 (63.9)	10.2 (66.4)	4.00 (0.50-24.00)	2.82 (105)
	CR 80mg uid	42	254 (80.2)	22.7 (71.0)	6.00 (3.00-16.00)	5.72 (119)

1. Geometric mean (CVb%)
2. Median (range)

Table A 71. Statistical Analysis of R(+) Carvedilol PK Parameters
(Reference Table 19/Section 8.4/Study 369)

Parameter	Dose Group	Comparison of Interest	Point Estimate	90% CI	CVw% ³
AUC(0-t) ¹ ng-hr/mL	Pooled	CR:IR	1.06	(1.01, 1.12)	28.0
	3.125mg IR/ 10mg CR	CR:IR	1.21	(1.09, 1.35)	
	6.25mg IR/ 20mg CR	CR:IR	1.06	(0.97, 1.16)	
	12.5mg IR/ 40mg CR	CR:IR	0.98	(0.89, 1.08)	
	25mg IR/ 80mg CR	CR:IR	1.00	(0.90, 1.10)	
C _{max} ¹ ng/mL	Pooled	CR:IR	0.95	(0.89, 1.02)	38.2
	3.125mg IR/ 10mg CR	CR:IR	1.06	(0.92, 1.23)	
	6.25mg IR/ 20mg CR	CR:IR	0.97	(0.85, 1.09)	
	12.5mg IR/ 40mg CR	CR:IR	0.87	(0.76, 0.98)	
	25mg IR/ 80mg CR	CR:IR	0.90	(0.79, 1.03)	
C _τ ¹ ng/mL	Pooled	CR:IR	0.92	(0.85, 1.01)	49.4
	3.125mg IR/ 10mg CR	CR:IR	1.21	(1.01, 1.45)	
	6.25mg IR/ 20mg CR	CR:IR	0.94	(0.80, 1.10)	
	12.5mg IR/ 40mg CR	CR:IR	0.75	(0.64, 0.89)	
	25mg IR/ 80mg CR	CR:IR	0.86	(0.72, 1.02)	
t _{max} (hr) ²	Pooled	CR:IR	3.00	(2.59, 3.25)	
	3.125mg IR/ 10mg CR	CR:IR	3.02	(2.25, 4.25)	
	6.25mg IR/ 20mg CR	CR:IR	2.74	(2.21, 3.25)	
	12.5mg IR/ 40mg CR	CR:IR	2.25	(1.50, 2.77)	
	25mg IR/ 80mg CR	CR:IR	4.00	(3.50, 4.48)	

Data Source: Tables 8.01 and 8.03

1. Point estimate is the ratio of adjusted geometric means between regimens.
2. Point estimate is the estimated median difference between regimens.
3. CVw% represents a pooled estimate of within-subject variability across regimens.

Table A 72. Statistical Analysis of S(-) Carvedilol PK Parameters
(Reference Table 20/Section 8.4/Study 369)

Parameter	Dose Group	Comparison of Interest	Point Estimate	90% CI	CVw% ³
AUC(0-t) ¹ ng.hr/mL	Pooled	CR:IR	1.16	(1.10, 1.22)	27.6
	3.125mg IR/ 10mg CR	CR:IR	1.33	(1.19, 1.47)	
	6.25mg IR/ 20mg CR	CR:IR	1.14	(1.04, 1.24)	
	12.5mg IR/ 40mg CR	CR:IR	1.13	(1.03, 1.24)	
	25mg IR/ 80mg CR	CR:IR	1.05	(0.95, 1.16)	
C _{max} ¹ ng/mL	Pooled	CR:IR	1.00	(0.94, 1.08)	39.0
	3.125mg IR/ 10mg CR	CR:IR	1.18	(1.02, 1.37)	
	6.25mg IR/ 20mg CR	CR:IR	1.00	(0.88, 1.14)	
	12.5mg IR/ 40mg CR	CR:IR	0.94	(0.82, 1.07)	
	25mg IR/ 80mg CR	CR:IR	0.89	(0.78, 1.02)	
C _t ¹ ng/mL	Pooled	CR:IR	1.03	(0.95, 1.12)	46.7
	3.125mg IR/ 10mg CR	CR:IR	1.29	(1.09, 1.54)	
	6.25mg IR/ 20mg CR	CR:IR	1.01	(0.87, 1.17)	
	12.5mg IR/ 40mg CR	CR:IR	0.93	(0.80, 1.09)	
	25mg IR/ 80mg CR	CR:IR	0.94	(0.80*, 1.10)	
t _{max} (hr) ²	Pooled	CR:IR	3.00	(2.73, 3.25)	
	3.125mg IR/ 10mg CR	CR:IR	3.03	(2.25, 4.04)	
	6.25mg IR/ 20mg CR	CR:IR	2.76	(2.25, 3.49)	
	12.5mg IR/ 40mg CR	CR:IR	2.25	(1.50, 3.00)	
	25mg IR/ 80mg CR	CR:IR	3.86	(3.50, 4.25)	

Data Source: Tables 8.02 and 8.04

1. Point estimate is the ratio of adjusted geometric means between regimens.
2. Point estimate is the estimated median difference between regimens.
3. CVw% represents a pooled estimate of within-subject variability across regimens.
4. 0.796.

4.3.1.3 PKPD Analysis

4.3.1.3.1 Beta-Blocking Effects

4.3.1.3.1.1 Data

Data from study 902 were used in the PKPD analysis. The design of 902 is shown in Figure A 4. A description of the data is presented in Table A 73. The dataset used for this analysis was obtained from the 30-March submission and located in \\crt\datasets\902\4.

Table A 73. Data Used in PKPD Analysis

Study	Population	Treatments	Sampling Times	No. Subjects and Samples
902	Patients with hypertension Enrolled: 122 Completed: 105	Low Dose: 6.25 mg bid IR and 20 mg qd CR High Dose: 20 mg bid IR and 80 mg qd CR Placebo	B1: 0, 1.5, 6, 12, 18 B2: 0, 1.5, 4, 14, 21 B3: 0, 1.5, 4, 14, 24 B4: 0, 2, 6, 12, 18 B5: 0, 2, 9, 14, 21 B6: 0, 2, 9, 12, 24	Low Dose: 36 subjects contributing 365 observations High Dose: 47 subjects contributing 513 observations Placebo: 22 subjects contributing 239 observations

4.3.1.3.1.2 Graphical Exploration of Observed Data

The change in exercise heart rate from baseline vs. S(-)carvedilol concentrations are presented in Figure A 22 and Figure A 23. These figures illustrate that the IR and CR formulations have

comparable concentration range and beta-blocking effects. There were four individuals with very low exercise induced heart rates (change from baseline >50 bpm): 2, 91, 102, and 126 (Figure A 24). With the exception of subject 91, low heart rates were observed with both the CR and IR formulations.

Figure A 22. Change from Baseline Exercised-Induced Heart Rate vs. S(-)Carvedilol Concentrations

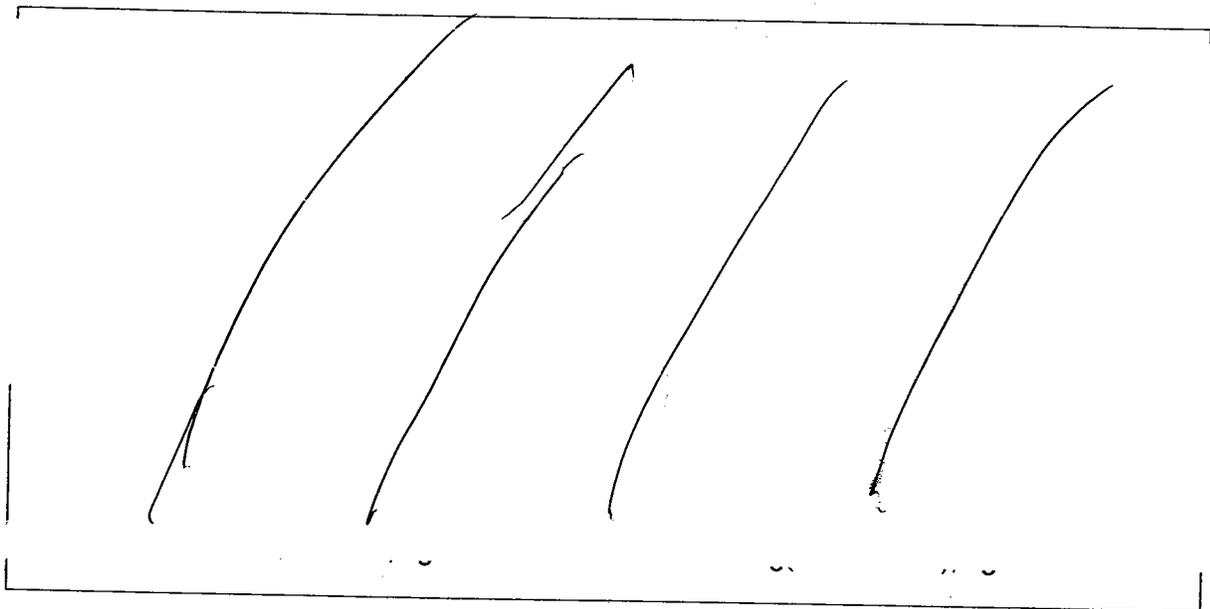


Figure A 23. Change from Baseline Heart Rate vs. S(-)Carvedilol Concentrations Stratified by Dose Group (with subject ID as indicator)

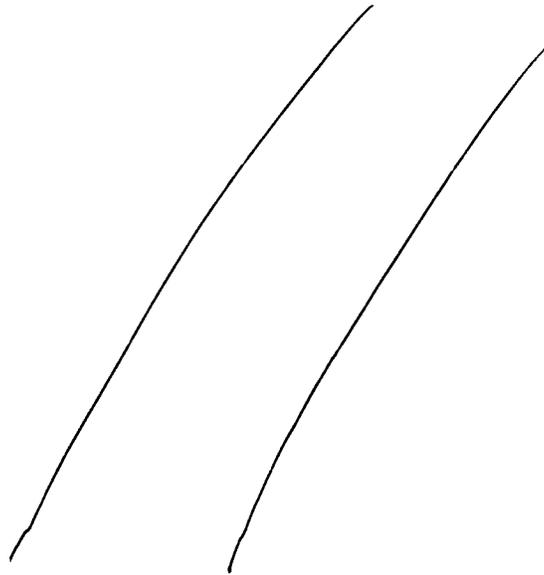
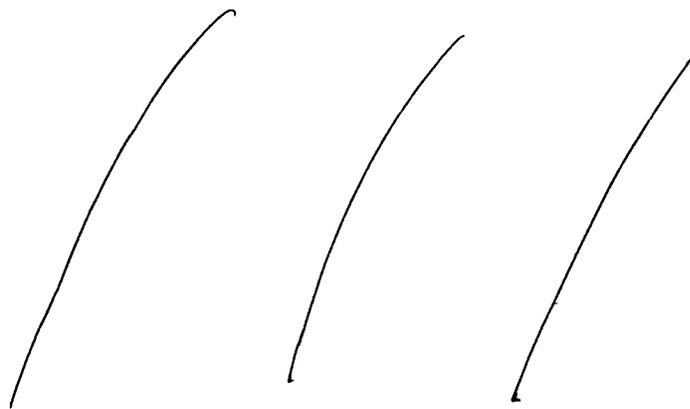
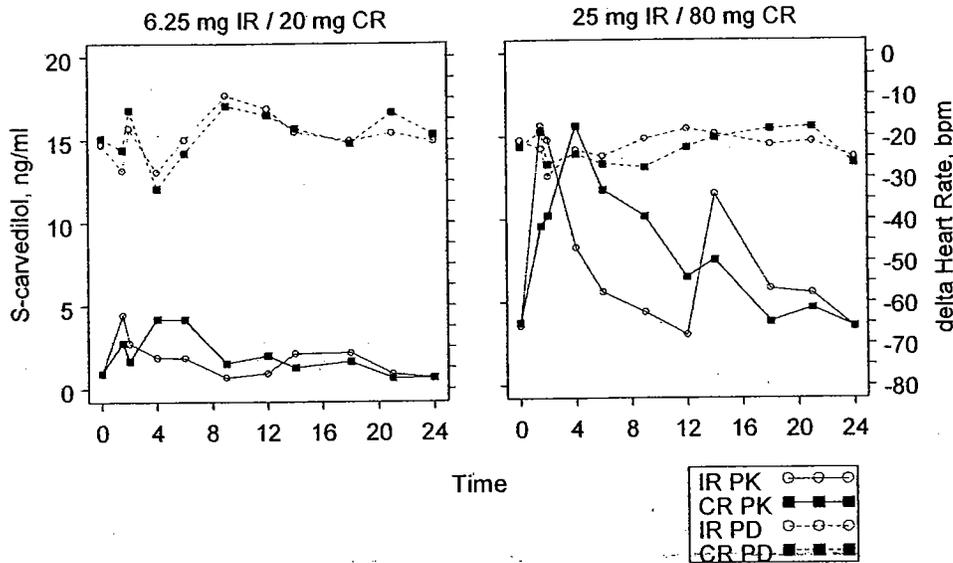


Figure A 24. Individual Plots of Subjects with Low Exercise Induced Heart Rate



The mean time-course of change in exercise heart rate from baseline by dose group is presented in Figure A 25, with individual profiles presented in Appendix A 3. These plots show that mean and individual beta-blockade is comparable between the CR and IR formulations.

Figure A 25. Mean PK and PD Time Course.



4.3.1.3.2. PKPD Model

An Emax model best described the relationship between exercise heart rate and S(-) carvedilol concentrations (refer to individual study 902 for details, Appendix 4.2.5). This model was based on the combined data for the IR and CR formulations. Model parameters are shown in Table A 74. Between-subject variability could not be estimated for EC50 and Emax (Appendix A 4 for reviewer's analysis of data). Parameter estimates are similar to an Emax developed using PKPD data obtained in healthy volunteers who received doses up to 50 mg with IR tablets and two pilot CR formulations (Appendix A 5).

Table A 74. Parameters for the Emax Model Describing the S(-) Carvedilol and Beta Blocking Effects of Carvedilol Administered as CR Capsules and IR Tablets (Reference Table 28/Section 10/Study 902)

	Population Mean (% se) ¹	Inter-Individual Variability as % CV (% se ¹)
E0 (bpm)	126 (1.3)	7.7 (23.2)
EC50 (ng/mL)	4.25 (44.9)	NE
Emax (bpm)	15.1 (11.5)	NE
Amplitude	0.013 (15.4)	NE
Tmax (h)	11.6 (7.2)	NE
Residual Variability % CV (% se ¹)	4.9 (13.1)	

1. % se – percent standard error

NE – Not Evaluated

Source: Table 10.1

To determine if the PKPD model was different between formulations, the data was split by formulation and re-analyzed using the Emax model. If the two formulations have similar beta-blocking effects, then model parameters should be the same. The median and 90% confidence intervals for model parameters were obtained using bootstrap techniques. The dataset was re-sampled by subject ID with replacement and the resulting dataset was fit to the Emax model. This procedure was repeated 1000 times each for three datasets: IR data alone, CR data alone and combined IR and CR data.

Table A 75 lists the median parameter estimates and the 90% confidence interval computed from the bootstrap distribution. Model parameters for the IR and CR formulations are the same. The 90% confidence intervals for Emax and EC50 are much wider when the individual formulations were fit to the Emax model compared to the combined dataset. This most likely reflects instability in the Emax model due to insufficient data at or around Emax.

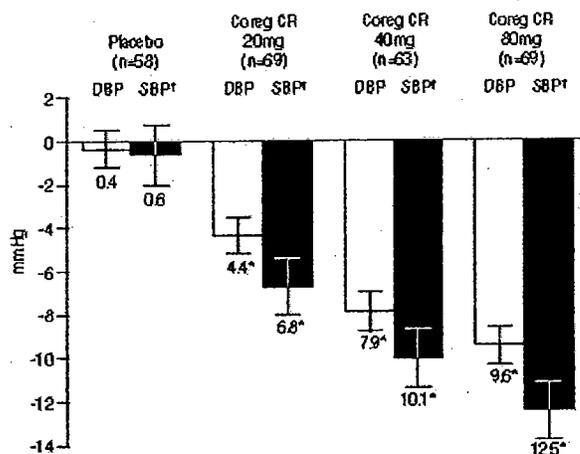
Table A 75. Median (5th, 95th percentiles) for Model Parameters Calculated from 1000 Bootstrap Datasets

Parameter	IRCR Data	IR Data Alone	CR Data Alone
E0	126 (123, 129)	127 (123, 131)	128 (123, 132)
EC50	4.1 (1.86, 9.66)	2.87 (0.920, 2694)	2.04 (0.470, 2116)
Emax	15.5 (12.6, 18.5)	16.5 (13.2, 1240)	16.6 (12.7, 1112)
Amplitude	0.0123 (0.0101, 0.0168)	0.0165 (0.0125, 0.0207)	.00947 (3.74E-11, 0.0135)
Tmax	11.6 (10.3, 13.3)	10.9 (9.80, 124)	11.3 (2.08, 58.5)
BSV for E0 (expressed as CV)	0.0781 (0.0631, 0.0981)	0.0777 (0.0637, 0.0948)	0.0796 (0.0635, 0.0983)
Residual error (expressed as CV)	0.0483 (0.0431, 0.0536)	0.0462 (0.0401, 0.0525)	0.0436 (0.0392, 0.0484)
% runs with successful convergence	99.6	99.2	97.8

4.3.1.3.3 Dose-Response for Blood Pressure

The sponsor conducted a double-blind, placebo-controlled, 8-week trial to evaluate the antihypertensive effects of 20 mg, 40 mg, and 80 mg carvedilol CR administered once daily to patients with essential hypertension (study 367, schematic shown in Appendix A 2). The mean (\pm SE) change from baseline in 24 h mean SBP and DBP for each treatment is shown in Figure A 26. Evident in this figure is a dose-response with the carvedilol CR.

Figure A 26. Mean Blood Pressure Changes from Baseline Measured by 24-h ABPM (Reference Figure 7 /2.5 Clinical Overview)



Change from baseline in 24 hour mean blood pressure ±SE (intent-to-treat efficacy population with last observation carried forward)

*SBP inferences are based on an ad-hoc analysis
 *P values < 0.001 for dose related trend tests for change from baseline in mean DBP and SBP

The sponsor also assessed the exposure-response relationship between model-predicted steady state AUC values and mean blood pressure changes. Table A 76 summarizes the results of this analysis.

Table A 76. Summary of the Results of the Exposure Response Analysis for Antihypertensive Effects of Carvedilol CR (Reference Tables E2 and E3/ Study 367 PopPK)

Dose	AUC ng.h/ml	Mean Change in Diastolic BP		Mean Change in Systolic BP	
		Observed Effect	Emax Model-Predicted	Observed Effect	Emax Model-Predicted
<i>R(+)</i> Carvedilol					
20 mg	128	-4.4	-5.5	-6.8	-7.3
40 mg	231	-7.9	-7.2	-10.1	-9.2
80 mg	479	-9.6	-9.0	-12.5	-11.2
<i>S(-)</i> Carvedilol					
20 mg	54	-4.4	-5.1	-6.8	-6.8
40 mg	101	-7.9	-7.1	-10.1	-9.1
80 mg	211	-9.6	-9.2	-12.5	-11.5

The immediate release tablets were studied in placebo-controlled trials that utilized twice-daily dosing, at total daily doses of 12.5 to 50 mg (Coreg label). These trials showed a dose-related blood pressure response.

4.3.1.3.4 Population PK Analysis

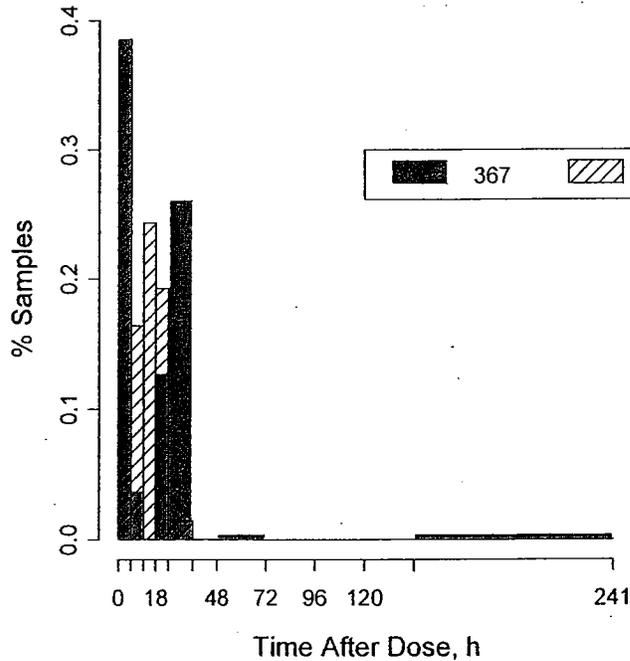
4.3.1.3.4.1 Data

Data from studies 902 and 367 were used in the analysis of R(+) and S(-) carvedilol (Table A 77). The design of 902 and 367 is shown in Appendix A 1 and Appendix A 2, respectively. The distribution of sampling times is shown in Figure A 27.

Table A 77. Data Used in PopPK Analysis

Study	Population	CR Treatments	Sampling Times	No. Samples
902	122 patients with hypertension	20 mg qd CR 80 mg qd CR Placebo	5 samples per treatment (10 total)	81 patients contributing 1920 R(+) and S(-)carvedilol observations
367	338 patients with hypertension	20 mg qd CR 40 mg qd CR 80 mg qd CR Placebo	4 samples	223 patients contributing 861 R(+) and S(-) carvedilol observations

Figure A 27. Histogram of Sampling Times



4.3.1.3.4.2 Demographics

Table A 78. Summary of Demographics
(data source: 902_367_scar_mr_nonmem_lndata_finalc.csv)

Covariate	Study 902 (N = 81)	Study 367 (N = 223)	Total (N = 304)
Age (y)	46 (22 – 55)	53 (24 – 85)	51 (22 – 85)
Weight (kg)	84 (57 – 118)	90 (47 – 173)	88 (57 – 118)
Sex	38 M / 43 F	144 M / 79 F	182 M / 122 F
Race	33 (Caucasian), 24 (African American), 24 (other)	173 (Caucasian), 36 (African American), 14 (other)	206 (Caucasian), 60 (African American), 38 (other)
CYP2D6 Metabolizers	81 EM	211 EM / 12 PM	292 EM / 12 PM

4.3.1.3.4.3 Pharmacokinetic Models

Model parameters were estimated using nonlinear mixed effects modeling as implemented by NONMEM (Version V, level 1.0) with FOCE-interaction.

NMTRAN code for the base and final models are presented in Appendices A 6 to A 9.

4.3.1.3.4.3.1 Fixed Effects

Due to limited sampling in study 367, the sponsor developed the structural models for R(+) and S(-) carvedilol using data from study 902. Once the structural model was defined, data from study 367 was included in the analysis.

A two-compartment model with first order absorption and elimination and a lag was selected for the base structural model. The absorption phase consisted of two change points with different k_a values which is consistent with the microparticle CR formulation. These change points were 0-2 h, >2-4 h, and >4 h post-dose.

For the combined data, the NONMEM parameters V3/F, Q/F, ALAG, and the three change point k_a values were fixed.

4.3.1.3.4.3.2 Random Effects

Between-subject variability was included on CL/F, V/F and k_a , it was assumed that these parameters were log-normally distributed.

Residual variability was described by a constant coefficient of variation model.

Inter-occasional variability (IOV) was included on k_a and F.

4.3.1.3.4.4 Results

4.3.1.3.4.4.1 Base Structural Model

R(+) Carvedilol

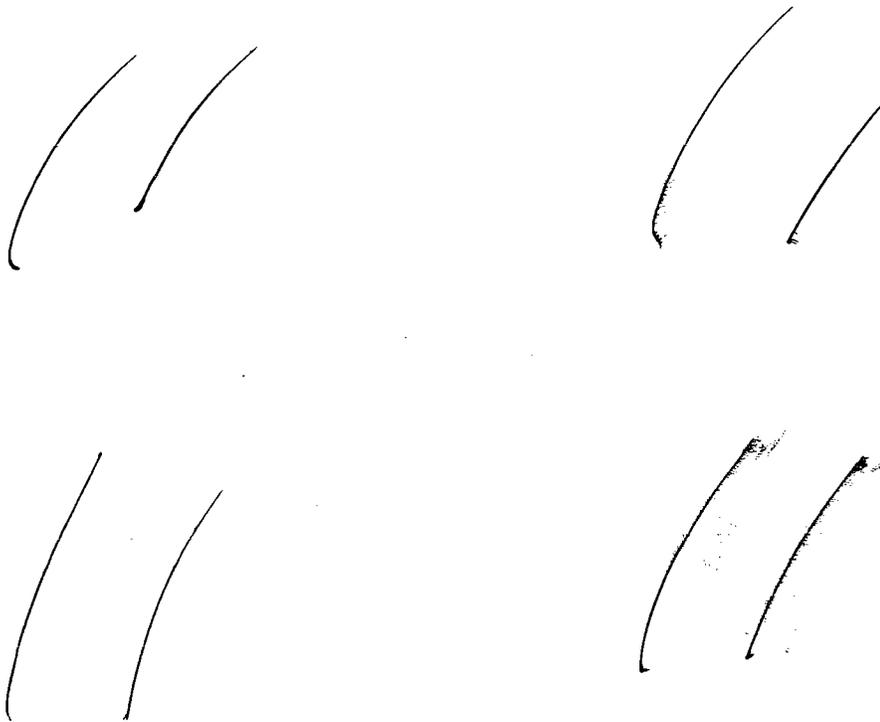
The population PK parameters for the final base model for R(+)carvedilol are presented in Table A 79 and goodness-of-fit plots in Figure A 28.

Table A 79. Model Parameters for R(+) Carvedilol: Base Model

	Inter-Individual	
	Pop. Mean (% CV ¹)	Variability % ² (% CV ¹)
ka (Ka at time ≤ 2 hours (h ⁻¹)	0.211	N.E.
ka (Ka between 2-4 hours (h ⁻¹)	0.491 fixed	N.E.
Ka at time > 4 hours (h ⁻¹)	10.1 fixed	N.E.
CL/F (L/h)	176 (3.9)	59.7 (10.8)
V ₂ /F (L)	1010 (7.2)	106 (10.3)
V ₃ /F (L)	2970 fixed	N.E.
Q (L/h)	75.4 fixed	N.E.
Alag (h)	0.693 fixed	N.E.
IOV% in ka *(%CV)	122 fixed	
IOV% in F *(%CV)	50.3 (13.2)	
Random Residual Variability** (%CV)	27.9 (9.9)	

1. precision expressed as % coefficient of variation
 2. expressed as % coefficient of variation
- N.E. - Not estimated

Figure A 28. Goodness-of-Fit Plots for R(+) Carvedilol: Base Model



S(-) Carvedilol

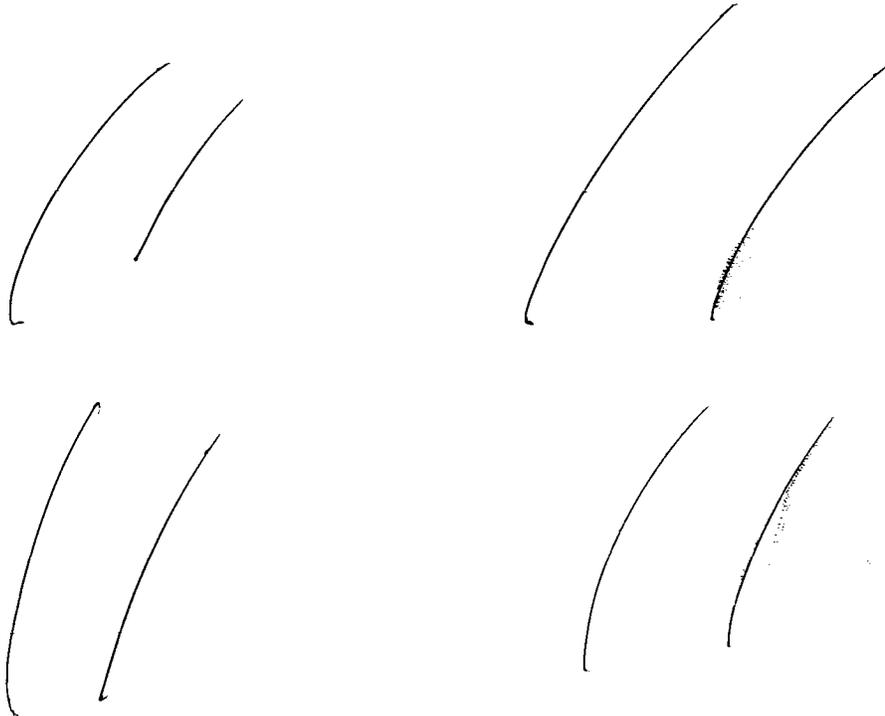
The population PK parameters for the final base model for R(+)carvedilol are presented in Table A 80 and goodness-of-fit plots in Figure A 29.

Table A 80. Model Parameters for S(-)Carvedilol: Base Model

	Pop. Mean	Inter-Individual
	(% CV ¹)	Variability % ² (% CV ¹)
ka (Ka at time ≤ 2 hours (h ⁻¹)	0.150 fixed	N.E.
ka (Ka between 2-4 hours (h ⁻¹)	0.425 fixed	N.E.
Ka at time > 4 hours (h ⁻¹)	11.7 fixed	N.E.
CL/F (L/h)	399 (3.4)	50.9 (11.7)
V ₂ /F (L)	3050 (7.1)	10.4 (14.0)
V ₃ /F (L)	8360 fixed	N.E.
Q (L/h)	231 fixed	N.E.
Lag (h)	0.329 fixed	N.E.
IOV% in ka * (%CV)		128 fixed
IOV% in F * (%CV)		47.3 (11.7)
Random Residual Variability* (%CV)		23.8 (9.9)

1. precision expressed as % coefficient of variation
 2. expressed as % coefficient of variation
- N.E. - Not estimated

Figure A 29. Goodness-of-Fit Plots for S(-)Carvedilol: Base Model



4.3.1.3.4.4.2 Covariate Model

The influence of weight, age, sex, race and CYP2D6 metabolizer status on CL/F and V/F were evaluated in a stepwise modeling approach, with a change in objective function of 10 as evidence of statistical significance. The sponsor identified sex and 2D6 metabolizer status as statistically significant covariates for CL/F. These covariates, however, did not decrease the between-subject variability in CL/F (Table A 81).

Table A 81. Evaluation of the Sponsor’s Covariate Models

Covariate	Model	OFV	DOFV	IIV CL
<i>S(-)Carvedilol</i>				
Base (#74)	--	-2025.659	--	50.9
SEX (#81)	CL* θ *Female	-2037.379	-11.72	49.5
<i>R(+)-Carvedilol</i>				
Base (#77)	--	-1216.506	--	59.7
2D6 (#105)	CL* θ *PM	-1233.075	-16.57	57.3

Figure A 30. Distribution of CL/F Values for CYP2D6 EM and PM

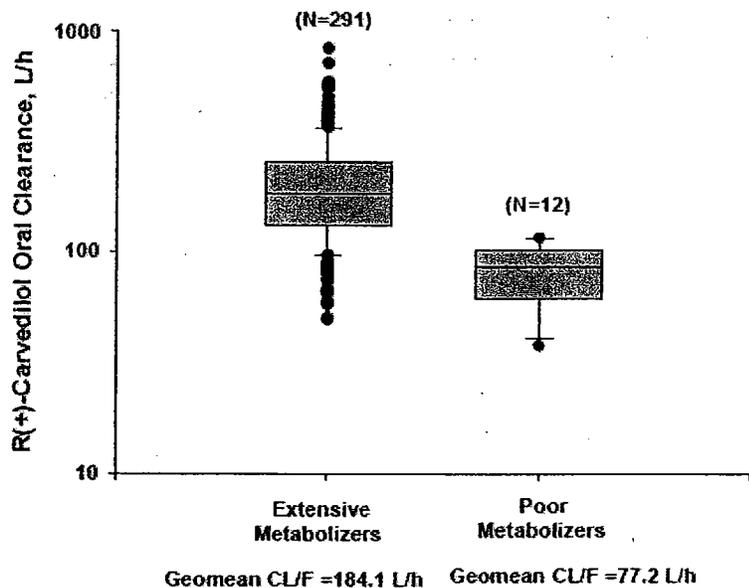
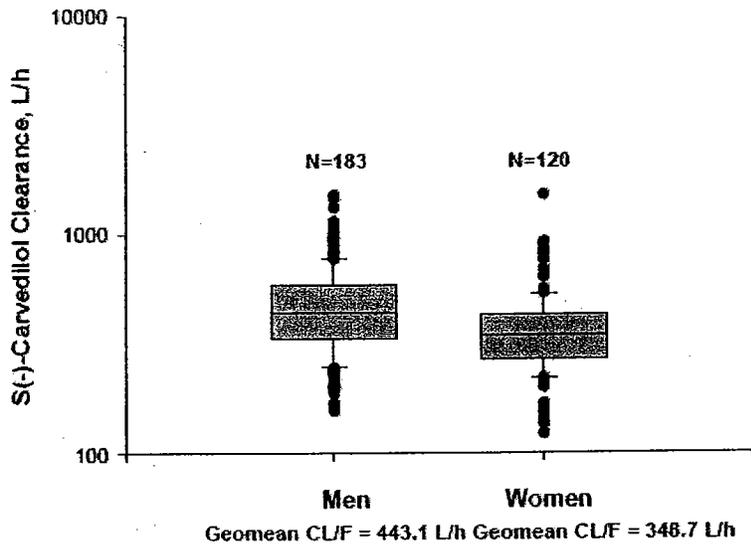


Figure A 31. Distribution of CL/F Values for Male and Female Patients



4.3.1.3.4.5 Final PK Models

The final population model for R(+) carvedilol is shown in Table A-82. Poor metabolizers have approximately 45% lower clearance compared to extensive metabolizers (Figure A 30). Despite the large change in CL/F values, this covariate did not reduce the BSV for CL/F.

Table A 82. Final Model Parameters for R(+)Carvedilol

	Pop. Mean	Inter-Individual
	(% CV ¹)	Variability % ² (% CV ¹)
ka (Ka at time ≤ 2 hours (h ⁻¹)	0.211 fixed	N.E.
ka (Ka between 2-4 hours (h ⁻¹)	0.491 fixed	N.E.
Ka at time > 4 hours (h ⁻¹)	10.1 fixed	N.E.
CL/F (L/h)	181 (3.8)	57.3 (11.1)
Φ ₂ for CYP on CL/F (L/h)	0.545 (12.0)	-
V ₂ /F (L)	1020 (7.0)	106 (13.0)
V ₃ /F (L)	2970 fixed	N.E.
Q (L/h)	75.4 fixed	N.E.
Alag (h)	0.693 fixed	N.E.
IOV% in ka *(%CV)	122 fixed	
IOV% in F *(%CV)	50.3 (12.8)	
Random Residual Variability** (%CV)	27.9 (9.3)	

1. precision expressed as % coefficient of variation

2. expressed as % coefficient of variation

N.E. – Not estimated

CL_{CYP2D6} = Φ₂ * CL_{CYP2D6}; 1=Extensive metabolizer of CYP2D6 or missing genotype status, 2=poor metabolizer of CYP2D6.

The final population model for S(-) carvedilol is shown in Table A 83. Females had a 15% lower CL/F compared to males (Figure A 31). These differences are not considered to be clinically relevant.

Table A 83. Final Model Parameters for S(-) Carvedilol

	Pop. Mean	Inter-Individual
	(% CV ¹)	Variability % ² (% CV ¹)
ka (Ka at time ≤ 2 hours (h ⁻¹)	0.150 fixed	N.E.
ka (Ka between 2-4 hours (h ⁻¹)	0.425 fixed	N.E.
Ka at time > 4 hours (h ⁻¹)	11.7 fixed	N.E.
CL/F (L/h)	427 (3.7)	49.5 (12.6)
θ ₂ for gender on CL/F (L/h)	0.846 (5.0)	-
V ₂ /F (L)	3040 (7.0)	104 (14.9)
V ₃ /F (L)	8360 fixed	N.E.
Q (L/h)	231 fixed	N.E.
Lag (h)	0.329 fixed	N.E.
IOV% in ka *(%CV)	128 fixed	
IOV% in F *(%CV)	47.3 (11.5)	
Random Residual Variability** (%CV)	23.8 (9.8)	

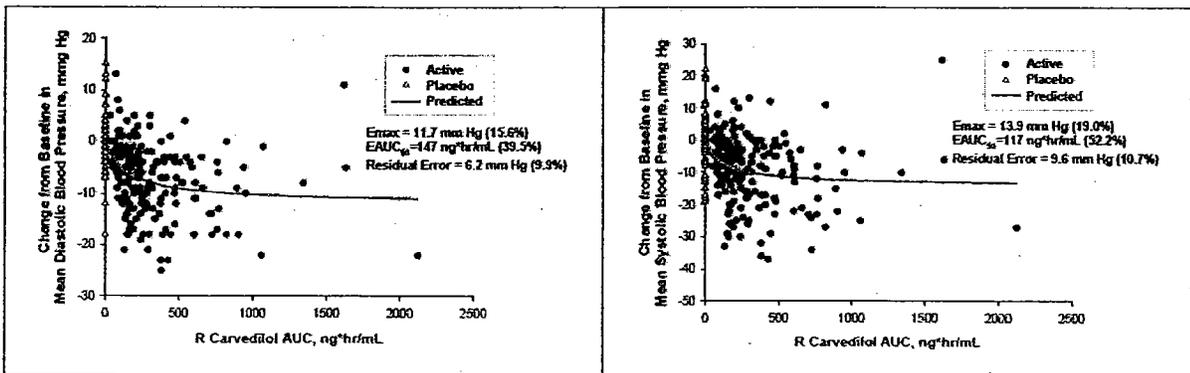
1. precision expressed as % coefficient of variation
 2. expressed as % coefficient of variation
- N.E. - Not estimated
CL_{women} = θ₂ * CL_{men}

4.3.1.3.5 Exposure-Response Analysis of Mean Blood Pressure Changes

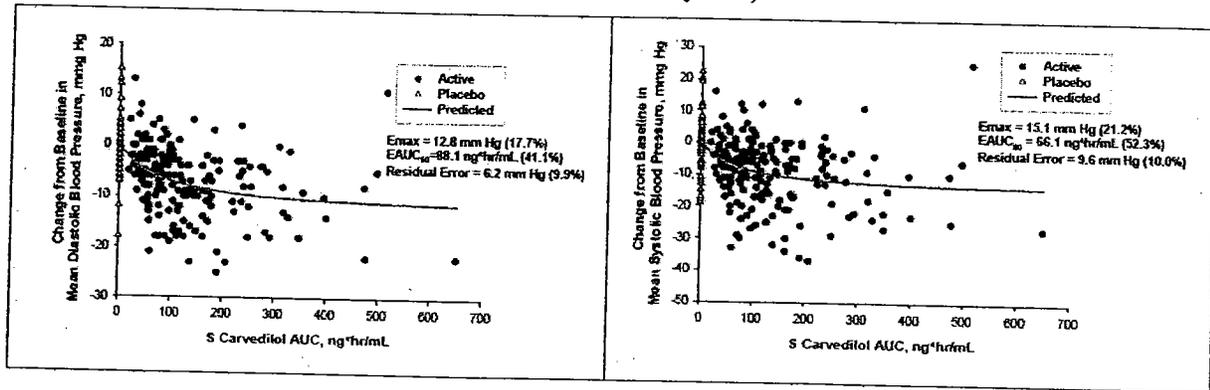
R(+) and S(-) carvedilol model-predicted AUC values were used to assess the relationship between PK and the change from baseline in mean systolic and diastolic blood pressure for patients in study 367 (N=193, representing 79% of carvedilol-treated patients).

An Emax model best described the PKPD relationship for both R(+) and S(-) carvedilol. Plots are shown in Figure A 32 to Figure A 33. This analysis supports the dose-related reduction in blood pressure response (Figure A 26).

Figure A 32. PKPD Model for R(+) Carvedilol
(Reference Figures 3 and 4/ Section 11/POPPK/Study 367)



**Figure A 33. PKPD Model for S(-) Carvedilol
(Reference Figure 5 and 6/ Section 11/POPPK/Study 367)**



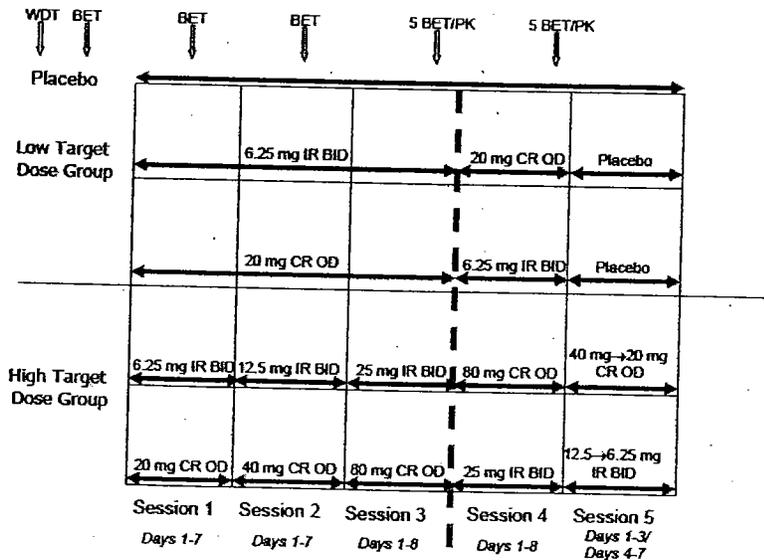
4.3.1.3.6 Reviewer's Comments

- DSI inspection of the _____ clinical site (enrolled 14 subjects) for study 367 found that there were several subjects that had protocol violations with respect to pharmacokinetic sampling times. The reviewer determined that these protocol violations have no impact on the population analysis of data because actual sampling times were recorded and missing data were treated as missing.

4.3.1.3.7 PM Appendices

A 1. Design of Study 902

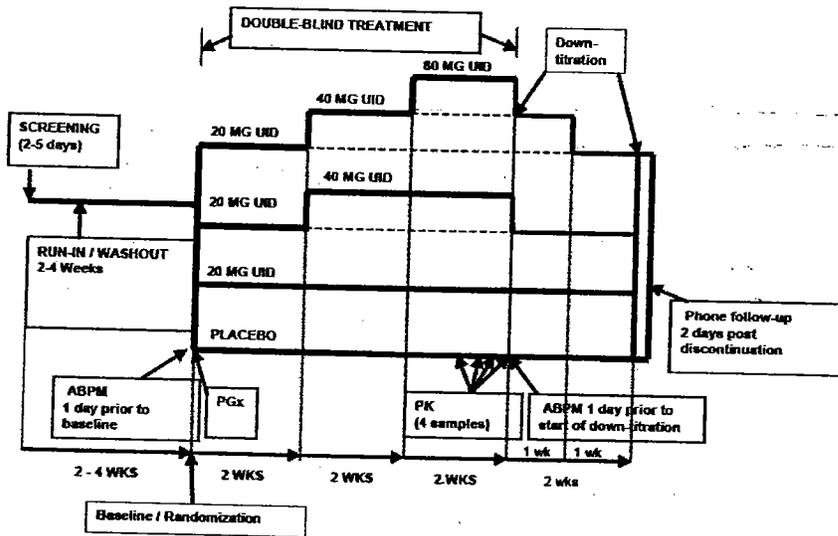
Study 902 was double-blind, placebo controlled, repeat-dose crossover study in three parallel groups. The study consisted of five phases: screening, down titration/washout, drug-free run-in, double-blind treatment (consisting of five sessions as shown below), and follow-up.



A 2. Design of Study 367

This was a double-blind, randomized, placebo-controlled, parallel group, multicenter study comparing three doses of carvedilol CR with placebo in subjects with essential hypertension. Following a four-week run-in/washout phase, eligible subjects were randomized in a 1:1:1:1 ratio to one of four treatment arms for double-blind treatment as follows: 20mg carvedilol CR (20mg once daily for six weeks); 40mg carvedilol CR (20mg once daily carvedilol CR for 2 weeks, up-titrated at Week 2 to 40mg once daily for 4 weeks); 80mg carvedilol CR (20mg carvedilol CR for 2 weeks, up-titrated to 40mg at Week 2 for 2 weeks, and up-titrated to 80mg at Week 4 for 2 weeks); or placebo for six weeks. At the end of six weeks of treatment, subjects receiving doses >20mg once daily were down-titrated over a two week period to 20mg once daily while subjects in the carvedilol CR 20mg group continued to receive 20mg once daily and subjects randomized to placebo remained on placebo. At the end of the two-week down-titration phase, double-blind study medication was discontinued for all subjects. Thus, subjects received blinded study medication for a total of eight weeks.

STUDY DESIGN SCHEMATIC
Coreg 367



The primary objective was to compare the effects on DBP of three different doses of carvedilol controlled release (carvedilol CR) to placebo as measured by changes from baseline in mean 24hr DBP using ambulatory blood pressure monitoring (ABPM).

4 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Model	METHOD	OBV	E0	EC50	EMAX	σ	S0
control.ct <u>Sponsor's Final Model</u>	FO	4927.579	126 (CV% = 7.7)	4.25	15.1	CV=0.0485	
controlFOCE	FOCE	4934.427	126 (CV% = 8.0)	4.15	15	CV=0.0486	
controlFOCEI	FOCEI	4990.293	125 (CV% = 8.0)	4.49	14.2	CV=0.0503	
control_AddRE	FOCE	4938.460	126 (CV% = 8.0)	3.88	14.7	SD = 5.865	
control_IR	FOCE	3045.9	127 (CV% = 7.9)	2.83	15.7	CV = 0.0464	
control_CR	FOCE	2983.087	128 (CV% = 8.0)	2.01	16	CV = 0.0439	
Ratio	FOCE	4934.427	126 (CV% = 8.0)	--	15	CV = 0.0486	3.62
Ratio_2ETA	FOCE	4934.316	126 (CV% = 8.0)	--	14.9 (CV% = 16.2)	CV = 0.0486	3.69
Ratio_3ETA	FOCE	4931.188	127 (CV% = 7.0)	--	15.1 (CV% = 28.9)	CV = 0.0481	4.88 (CV%=126)

A 5. Study 395

This was a single-blind, five-period, dose-rising study conducted in healthy subjects. Sessions 1 through 4, subjects received the immediate release (IR) formulation in ascending doses. In Session 5, subjects were randomly allocated to receive either the pilot controlled release (CR) formulation or the pilot MR formulation. Study sessions were separated by a minimum washout period of at least 7 days. Ergometric bicycle tests were carried out in all 5 sessions with the target workload for exercise testing determined during screening. Plasma concentrations of R(+)- and S(-)-carvedilol were measured at the same timepoints as the exercise tests.

The results of the PKPD model are shown in the following table.

	Population Mean (% s.e. ¹)	Inter-Individual Variability as % CV (% s.e. ¹)
E0 (bpm)	146 (1.0)	5.7 (32.2)
EC50 (ng/mL)	7.71 (25.2)	44.2 (82.1)
Emax (bpm)	19.2 (9.2)	21.8 (49.5)
Baseline slope ¹³	0.017 (10.8)	NE ²
Baseline slope ²⁴	0.005 (34.1)	NE
24h Θ (bpm)	6.3 (14.7)	NE
Interoccasional Variability in E0		2.1 (19.4)
Residual Variability % CV (% s.e.)	3.0 (13.2)	

1. % s.e. = percent standard error

2. NE = Not Evaluated

3. slope1 for study 395 data

4. slope2 for de Mey data

Source: Data on file, GSK

16 Page(s) Withheld

✓ Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

4.4 Cover Sheet and OCP Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics				
New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
NDA Number	22-012	Brand Name	CoREG	
OCPB Division (I, II, III)	I	Generic Name	Carvedilol	
Medical Division	Cardiorenal	Drug Class	Beta-blocker	
OCPB Reviewer	Christine Garnett	Indication(s)	Hypertension, mild to severe chronic heart failure, and post-MI LVD	
OCPB Team Leader	Patrick Marroum	Dosage Form	Carvedilol Phosphate — IR capsules (10mg, 20mg, 40mg, and 80mg)	
		Dosing Regimen	Once daily	
Date of Submission	December 21, 2005	Route of Administration	Oral	
Estimated Due Date of OCPB Review	August 29, 2006	Sponsor	GSK	
PDUFA Due Date	October 20, 2006	Priority Classification	1S	
Division Due Date	September 20, 2006			
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				Cross reference to IR
Isozyme characterization:				Cross reference to IR
Blood/plasma ratio:				Cross reference to IR

Plasma protein binding:				Cross reference to IR
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	10	6	Pivotal: 376, 903, 906, 400, 387, 395, 908, 902, 367, 369 Supporting: 393, 907, 399, 388, 386, 402 (pilot formulations)
multiple dose:	X	3	2	Pivotal: 395, 908 Supporting: 402 (pilot formulations)
Patients-				
single dose:	X			
multiple dose:	X	4	3	Pivotal: 902, 367, 369 Supporting: 907 (pilot formulations)
Dose proportionality -				
fasting / non-fasting single dose:	X	1	1	903
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1	1	387 (effect of pantoprazole, gastric pH)
In-vivo effects of primary drug:				Cross reference to IR
In-vitro:	X	1	1	Alcohol
Subpopulation studies -				
ethnicity:				Cross reference to IR
gender:				Cross reference to IR
pediatrics:				Cross reference to IR
geriatrics:				Cross reference to IR
renal impairment:				Cross reference to IR
hepatic impairment:				Cross reference to IR
PD:				
Phase 2:				
Phase 3:	X	1	1	367 (hypertension trial)
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	2	2	395 (PK-PD in HV) 908 (PK-PD in HV)

Phase 3 clinical trial:	X	2	2	369 (heart failure PK-PD) 902 (hypertension PK-PD)
Population Analyses -				
Data rich:				
Data sparse:	X	1	1	367 population PK
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X (IR)	3	3	400 (SD), 369 (MD), 902 (MD) are pivotal studies for BA.
Bioequivalence studies -				
traditional design; single / multi dose:				Registration lot used in phase III study.
replicate design; single / multi dose:				
Food-drug interaction studies:	X			376 (Food effect at 80 mg)
Dissolution:	X			
(IVIVC):				//
Bio-wavier request based on BCS				Not submitted
BCS class				Not submitted
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics	X	1	1	906: AM vs. PM dosing
Pediatric development plan	X	1	0	Study on-going
Literature References				
Total Number of Studies		16	10	6 studies were conducted with pilot formulations and are considered supporting.
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		

Comments sent to firm ?	X	<p>1) Please submit the following data to support the population PK-PD analyses for studies 367, 395, 908, and 902:</p> <ul style="list-style-type: none"> •All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. •Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt). •A model development decision tree and/or table which gives an overview of modeling steps. <p>2) Please submit dissolution data to support alcohol interaction with drug product.</p>
QBR questions (key issues to be considered)		<p>Does the CR formulation provide comparable exposure to the IR formulation?</p> <p>How does the intra- and inter-subject variability between the IR and CR formulations compare?</p> <p>Are the PK and beta-blocking effects of CR equivalent to IR formulation in hypertension and heart failure patients?</p> <p>If answer to Q3 is yes, can we grant the indication for survival in post-MI LVD patients?</p>
Other comments or information not included above		<p>The assessment of the safety and effectiveness of carvedilol in pediatric patients is ongoing _____ n Protocol 105517/321 entitled "A Multicenter, Placebo-Controlled, 8-Month Study of the Effect of Twice Daily Carvedilol in Children with Congestive Heart Failure Due to Systemic Ventricular Systolic Dysfunction."</p>
Primary reviewer Signature and Date		Christine Garnett
Secondary reviewer Signature and Date		<p>Patrick Marroum (clinical pharmacology)</p> <p>Joga Gobburu (pharmacometrics)</p>

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this page is the manifestation of the electronic signature.**

/s/

Christine Garnett
9/15/2006 04:26:34 PM
PHARMACOLOGIST

Patrick Marroum
9/15/2006 04:38:35 PM
BIOPHARMACEUTICS