CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-012

MEDICAL REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: October 20, 2006

FROM: Abraham Karkowsky, M.D., Ph.D. Division of Cardiovascular and Renal Products HFD-110

THROUGH: Norman Stockbridge, Director, Division of Cardiovascular and Renal Products HFD-110

SUBJECT: Review of EIRs Covering NDA 22-012 Coreg CR (Carvedilol Phosphate) capsules.

This memo attempts to put into a context the concerns raised by Dr. Jagan Mohan R. Parepally, Ph.D., in his memo of 29 September 2006, with regards to serious deviations from protocol at the site of [redacted]. Although the memo notes several substantial deviations from good clinical practice, I think the data can still be relied upon as sufficiently accurate for the purposes of that particular study.

Study SK &F 105517/369 was a pharmacokinetic study in which patients with heart failure received in a cross-over manner either Coreg IR or Coreg CR. The study enrolled 187 subjects in 32 study sites. The study served as the source for defining the pharmacokinetics of Coreg CR and Coreg IR as similar.

The key measurement of the study was the measurement of carvedilol concentrations performed by a core laboratory. The kinetic patterns of the Coreg IR and Coreg CR differ substantially for any given individual and it appears implausible that the kinetic profiles could somehow be altered by procedures at the study site.

We relied on this study to assess the comparative concentrations in a heart failure population. Since this was the only study for which such data was obtained, the study is pivotal to the rationale for including the use of the CR formulation in that population. The extent, to which the population that was enrolled in this site deviated from the protocol stipulated population, did not appear to be sufficiently large to negate the overall study conclusion.

Some deviations that were observed by Dr. Parepally at this site worked to the detriment of the conclusion that the peaks and troughs of drugs comparing IR and CR were equivalent. They include lack of standardization of procedures which would have

made it more difficult to assert equivalence of these measurements for the two formulations.

I will go through each of Dr. Parapelly's comments, below and append my analysis.

a. Five (5) out of 17 subjects who received at least one dose of study drug did not meet eligibility criteria in that 3 subjects had left ventricular ejection fraction (LVEF) greater than the protocol allowed limit, one subject received protocol prohibited medication and another subject's creatinine level was greater than that allowed by the protocol.

Of the 17 subjects, three subjects were ineligible based on LVEF. The remaining 14 of those enrolled were appropriately enrolled. The majority of enrolled subjects, therefore, were eligible for the study and their pharmacokinetic measurements were informative for the conclusion. The subject with abnormal creatinine levels and the other subject who received prohibited medications could only increase the variance of the kinetic measurements and make it more difficult to establish equivalence between Coreg IR and Coreg CR.

b. There is no documentation of the completion of physical exams, as required by the protocol, for the study visits 1, 3, and 4 for 20 out of 20 subjects who completed at least study visit 1.

This protocol deviation, the lack of physical exams, should not alter the conclusion that the kinetic measurements of the two carvedilol formulations have similar excursions during a 24-hour period.

c. Pharmacokinetic day meal standardization was not followed according to the protocol for visits 3 and 4. There is no documentation for all the subjects who received study drug in the following areas: an eight hour fast prior to PK sampling day, calorie (<25% from fat) content of breakfast or dinner, consumption of breakfast and dinner within 30 minutes, administration of study drug within 5 min of meal consumption, lunch after 4 hours PK sample and abstention from water for 2 hours after dosing and from soft drinks and fruit juice for 4 hours after dosing.

These protocol deviations, the lack of standardization, should increase the variance of the concentration measurements and make it more difficult to establish that the peak and trough measurements of the two formulations are the same.

d. Ten (10) out of 17 subjects who received at least one dose of study drug did not have a chest X-ray done prior to receiving study drug. The protocol requires that chest x-rays be completed during visit 1 or within 6 months prior to visit 1.

These deviations should have no effect on the concentration measurement.

e. It cannot be determined if two (2) subjects met the protocol eligibility criteria as blood chemistries were not evaluated prior to administration of study drug due to hemolysis of the specimens and blood chemistries were not repeated prior to study drug administration. The chemistries were not conducted for subjects 001111 and 001117.

These protocol deviations do not impact on the measurements or on defining the population as heart failure patients.

f. The site did not comply with the IRB's SAE reporting requirement, as required by the protocol in that they did not report a SAE (intracranial hemorrhage resulting in death) that occurred in a study subject receiving study drug.

The specific individual who died was reported in the NDA. The deviation from informing the IRB is serious, but there appears no reason to believe that pertinent information was deleted from the NDA.

g. There is no documentation of routine urinalysis results, performed at the site via dipstick as required by the protocol for study visit 1, for 20 out of 20 subjects.

The absence of a routine urinalysis would not change the primary measurement or conclusion of this study.

h. There is no documentation of sample preparation and storage, including sample chilling and centrifuging, plasma transfer, and storage at -20°C for all the subject samples in both PK sampling periods.

This deviation would likely make the measurement of concentrations more variable and make it less likely to conclude that the two formulations have similar concentration excursions during a 24-hour period.

i. Site failed to document LVEF values for 2 subjects within one year according to the protocol.

Dr. Parapelly's report indicates that heart failure was documented at some previous time based on LVEF. It is unlikely that the two involved subjects were ineligible for the study. The deviation should not alter the conclusions derived from the measurement of drug concentrations.

2. The Investigator did not retain a reserve sample of the test article and reference standard used in this study.

This deviation would be extremely important if the two formulations had similar pharmacokinetic profiles. Since the CR formulation had a single peak and the IR had two peaks during pharmacokinetic measurements, it is possible to definitely identify that the appropriate medication was administered. The pharmacokinetic is sufficiently different that the deviation from GLP methods does not alter the conclusion of the study.

3. Investigational drug disposition records are not adequate with respect to quantity and use by subjects in that there is no documentation for 2 subjects dosed with Coreg MR and 8 subjects with Coreg IR.

Again, there is independent verification from the pharmacokinetic profiles that the correct formulation was administered.

4. Failure to prepare and maintain adequate case histories with respect to observations and data pertinent to the investigation in that there were no subject identifiers for ECGs for 2 subjects and ECG was not recorded for a subject 001113.

This is clearly a protocol deficiency but the deficiency does not impact on the pharmacokinetic conclusions.

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/s/

Abraham Karkowsky
10/23/2006 12:51:47 PM
MEDICAL OFFICER

Norman Stockbridge
10/24/2006 08:27:51 AM
MEDICAL OFFICER
I concur.

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memorandum

NDA: 22-012 (carvedilol phosphate; Coreg CR))

Sponsor: GSK

Review date: 13 October 2006

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Distribution: NDA 22-012

HFD-110/Robb
HFD-110/Williams
HFD-860/Garnett

The sponsor is seeking approval of a new salt of carvedilol and a controlled-release formulation to support once-daily use across the spectrum of indications for which immediate-release carvedilolol is approved—hypertension, heart failure, and post-MI left ventricular dysfunction.

Primary reviews were written by Drs. Williams (clinical; 30 August 2006, 5 September 2006), Bai (Statistics; 16 August 2006) DeFelice (pharmacology; 27 September 2006), Nashed (chemistry; 14 August 2006, 25 September 2006), and Garnett (clinical pharmacology and biopharmaceutics; 15 September 2006).

The development program was conducted under IND 27,114. There were numerous meetings with the sponsor, and there was general agreement that the development program would inherit the indications of immediate-release carvedilol on the basis of sustained effects on blood pressure (demonstrated in one ABPM study) and a demonstration of beta-blockade throughout the interdosing interval. For the latter, the degree of similarity in pharmacodynamic properties with IR carvedilol was never pinned down.

The pharmacokinetic properties of sustained-release carvedilol were shown to be similar to those of immediate-release carvedilol with respect to AUC and Cmax, after suitable adjustments were made in total dose.

The ABPM study was able to demonstrate effects of once-daily sustained-release carvedilol on systolic and diastolic pressure throughout the interdosing interval.

Beta-blockade, as assessed by effects on exercise heart rate in hypertensive subjects, fell within 80-125% confidence limits of the immediate-release formulation for both AUC and maximum effect.

Even if all of carvedilol's clinical benefits in heart failure and MI are not attributable to beta-blockade, the concordance in pharmacokinetic and pharmacodynamic properties between immediate- and sustained-release formulations gives me high confidence that the clinical effects will be preserved with the new formulation.

In addition, I note that the intra-subject variability in pharmacokinetics has been carefully assessed, and the new formulation appears to perform satisfactorily.

At this hour, a few CMC issues remain to be resolved. These may make their way into the action letter, as will our dissolution specifications.

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/s/

Norman Stockbridge
10/13/2006 08:22:28 AM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-012
Submission Code	000

Letter Date	December 21, 2005
Stamp Date	December 23, 2005
PDUFA Goal Date	October 21, 2006

Reviewer's Name	A.O.Williams, M.D.
Review Completion Date	August 30, 2006

Established Name	Carvedilol phosphate (Controlled Release)
Trade Name	COREG CR
Therapeutic Class	β-blocker
Applicant	GlaxoSmithKline
Priority Designation	S
Formulation	Capsules
Dosing Regimen	Individualized
Indications	Hypertension, Congestive Heart Failure
Intended Population	Patients with Essential Hypertension

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1 EXECUTIVE SUMMARY

GlaxoSmithKline(GSK) the sponsor, undertook development of controlled release (CR) formulation of carvedilol phosphate capsules having obtained approval for its immediate release formulation in 1995 under NDA 20-297. For this CR formulation, that will allow for once daily (OD) dosing the sponsor is seeking NDA approval for similar indications for which the twice daily (BID) dosing immediate release formulation (NDA 20-297) had been approved (See CAPRICORN Study Section 8.8). The indications include the treatment of essential hypertension, mild to severe chronic heart failure (CHF) , and the reduction of cardiovascular mortality in clinically stable patients who have survived the acute phase of a myocardial infarction and have a left ventricular ejection fraction of less than or equal to 40% (with or without symptomatic heart failure).

In this submission, there are no clinical trials for CHF and reduction of cardiovascular mortality but there are trials for efficacy and safety for the indication of hypertension, To claim similar indications as the IR formulation, the sponsor had discussions with the Division in July 2005. The sponsor was advised on the need to focus on the statistical framework for evaluating the threshold for comparisons of the PK and PD effects of the IR and CR formulations. The sponsor solicited the agreement of the Division on the proposed strategy for assessing the similarity of the IR and CR formulation. To achieve this, the sponsor agreed to perform simulation work to assess the robustness of the modeling and simulation procedures and establish final threshold margins for their supportive analyses (Study 902). Similar claims with IR formulation can only be justified by showing similarities between the PK/PD between the two formulations.

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. The sponsor suggested that availability of a once a day dosing formulation of carvedilol would provide a clinical advantage as it would improve treatment compliance and thereby improve clinical effectiveness. The CR capsules are recommended to be taken with food once daily in the morning.

There are no clinical data on the blood-pressure-lowering effects of a modified-release formulation of carvedilol phosphate. Therefore, the Division is interested in evaluating the time course of the drug effect using both systolic and diastolic blood pressures and ensuring that the effect lasts the entire inter-dosing interval. In addition the Division is interested in evaluating inter-subject variability, drug effect and time course.

Carvedilol is an immediate release tablet marketed in the US as COREG (and in other countries under various brand names) for the management of essential hypertension used either as monotherapy or in combination with other antihypertensive agents. The approved starting dose for the immediate release product in the US is 6.25 mg (as the free base) BID and can then be titrated to 12.5mg and then 25mg twice daily if tolerated and needed. The full antihypertensive effect of COREG is seen within 7 to 14 days. In an effort to provide the convenience of once daily dosing, a modified release carvedilol formulation (carvedilol CR) has been developed. The purpose of the present study is to determine whether carvedilol CR can effectively control blood

pressure with a once daily dosing regimen and to demonstrate the dose response of the targeted dose strengths of 20mg, 40mg and 80mg.

The current NDA application contains data from a well-controlled, randomized, double blinded, parallel-group trial, placebo-controlled clinical study. Subjects were administered the study drug at dose strengths of 20 mg, 40 mg, 80 mg and placebo. This study was conducted to establish the efficacy and safety of carvedilol CR formulation (carvedilol CR was referred to as carvedilol phosphate MR or modified release COREG in the protocol). Carvedilol is a racemic mix.

For the development program, the sponsor carried out 15 PK/PD studies, one clinical study, and there is still an ongoing clinical study, Protocol COR 100216, (Tables of clinical studies in Section 4.2). One of the PK/PD studies (902) evaluated the comparability of the CR and IR formulations in terms of their β-receptor blockade effect using heart rate during bicycle ergometry in patients with essential hypertension. The two studies (902 and 369) found that the PK and predicted pharmacodynamic effect (AUEC, PDmin, and PDmax) was equivalent for carvedilol CR compared to COREG IR (Tables 46-48, Figure 6 and Section 3.2 from Dr Christine Garnett of Clinical Pharmacology Division). Carvedilol CR was found to be equivalent to COREG IR with regard to R- and S-carvedilol AUC, Ct, and Cmax (Section 5). On average, the carvedilol CR formulation exhibited a maximum PD effect similar to the COREG IR formulation, with a point estimate of 0.97 and corresponding 90% confidence interval within 20% of unity for PD max in the comparison CR:IR in the analysis pooled across dose groups. Similar results were obtained in the analyses by dose group. The point estimates and 90% confidence intervals for observed PD max are presented in Tables 52 and 53 (Section 5). In effect, the indications for which the IR formulation had been approved can therefore be inferred and claimed for the CR formulation.To claim the indication for lowering blood pressure efficacy and safety of the drug in the clinical trial, 367, was also met (Sections 6 and 7).

The sponsor submitted data from a single phase III clinical study No. 367. This was a double-blind, randomized, placebo-controlled, parallel group, multicenter study conducted in 338 randomized subjects with essential hypertension. The study design consisted of five phases: screening; placebo run-in/washout; baseline/randomization; double-blind treatment (up-titration); and down-titration (Figure 7).

The subjects were screened over a 2 to 5 day period for eligibility prior to entering the 2 to 4 week Placebo Run-in/Washout phase during which subjects were monitored weekly for blood pressure. Subjects taking ß-blockers or clonidine were tapered off the medication during the Placebo Run-in/Washout phase. All subjects eligible for randomization based on the 12hr daytime ABPM measurements performed on the day prior to the baseline visit entered the baseline/randomization phase. Subjects who satisfied all screening and inclusion criteria for entry were randomized 1:1:1:1 to one of three doses of once-daily carvedilol CR (20mg, 40mg or 80mg) or placebo for six weeks of treatment followed by a two-week down-titration phase. The primary efficacy variable was the mean change from baseline in DBP measured by 24 hr ABPM. The exploratory/subgroup analyses for this primary endpoint included the following prognostic and demographic characteristics: gender, race, age <65, >65, BMI <27 >27, diabetes mellitus status at baseline (yes or no) and 2D6 status.

Protocol Title: Study 367: "A Randomized, Double-Blind, Multicenter Study Comparing the Effects of Administration of Modified Release COREG or Placebo on Blood Pressure in Essential Hypertension Patients".

Investigators: This was a multicenter study with several investigators.

Study centers: There were 12 centers in Canada and 55 centers in the United States that randomized subjects into clinical study No. 367.

Publications: None at the time of this NDA submission.

Study Period: 03 Sep 2004 – 28 Jun 2005.

A total of 338 subjects were randomized to four treatment arms in Study 367 (Table 1). A total of 273 out of 338 (81%) randomized subjects completed the study, 34 (19%) subjects withdrew, 10 (3%) had adverse events, 10 (3%) had lack of efficacy, and 44 (13 %) withdrew for other reasons. More than 25% of patients randomized to the placebo did not complete the study compared to less than 18 % in the treated group.

Table 1: Disposition of patients- Study 367

	Placebo	Carvedilol CR		
		20mg	40mg	80mg
Number of Subjects Planned, N	71	71	71	71
Randomized, N	85[1]	87	78	88
Completed, n (%)	61 (73)	74 (85)	65 (83)	73 (83)
Total Number of Subjects Withdrawn, n (%)	23 (27)	13 (15)	13 (17)	15 (17)
Withdrawn due to Adverse Events, n (%)	3 (4)	1 (1)	3 (4)	3 (3)
Withdrawn due to Lack of Efficacy, n (%)	5 (6)	4 (5)	0	1 (1)
Withdrawn for other reasons, n (%)	15 (18)	8 (9)	10 (13)	11 (13)

1. One subject (#2263) was randomized but failed to provide informed consent and did not receive study medication.

The subjects assigned to one of the three carvedilol CR arms started with 20 mg once daily dosing. At two-week intervals, the subjects were blindedly up-titrated to their assigned dose or to the highest tolerated dose if the randomized target could not be reached. At the end of six weeks of treatment, 24hr ABPM was performed on the final day of dosing before the start of down-titration. Following completion of the final 24hr ABPM, subjects in the 40 mg and 80 mg carvedilol CR daily dosing treatment groups were down-titrated over two weeks to 20mg daily: subjects randomized to 20 mg carvedilol CR UID and placebo subjects remained on their respective treatments. At the end of the two-week down titration phase double blind study medication was discontinued for all subjects. After completion of the down-titration phase, subjects were treated for hypertension at the investigators' discretion.

Objectives of the study

Primary: In a group of patients with a history of, or current essential hypertension (sitting diastolic blood pressure [DBP] =90mmHg and =109mmHg) 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).

An effective once daily formulation for COREG CR in the long-term management of essential hypertension would represent an important advance in how this antihypertensive agent could be utilized in this patient population. Some of the secondary objectives below addressed this once daily dosing regimen.

Secondary: Secondary objectives include:
• Comparison of mean DBP measured by ABPM at the drug-trough blood levels (20-24hr) for carvedilol CR compared to placebo treatment;

• Trough (20-24hr) to peak (3-7hr) DBP ratios using 24-hour ABPM;

• The dose-response relationship between incremental doses of carvedilol CR and mean 24hr ABPM DBP;

• Blood pressure changes in the morning, afternoon, and at night using ABPM;

• Office/clinic DBP and systolic blood pressure (SBP) measurements by cuff assessments at drug-trough (20-24hr) blood levels to evaluate the effect of different doses of carvedilol CR, compared to placebo;

• Comparisons between treatment groups in the percentage of responders (response was defined as a sitting diastolic blood pressure (sDBP) reduction from baseline of =10mmHg);

• Safety of the CR formulation in this subject population;

• Population pharmacokinetics after administration of the carvedilol CR formulation.

Criteria for evaluation
ABPM monitoring was completed at baseline and at the end of treatment or early withdrawal by standard electronic ambulatory monitoring equipment worn by the subject for 24 hours.

Efficacy was determined by the mean change from baseline at study end in mean 24 hour DBP as measured by ABPM. Data collected by the ABPM devices included mean DBP, SBP, and heart rate at various intervals.

Blood pressure was also measured at specified study visits using a sphygmomanometer.

Safety assessments on all randomized subjects included AEs, vital signs, ECG and clinical laboratory evaluations.

The following populations were defined for analysis:

• All Randomized: All subjects who were randomized to receive study medication. The randomized population was used for accounting purposes and was not used for summary or analysis.

• Intent to Treat Safety (ITTS or Safety Population): All randomized subjects who received at least one dose of study medication.

• Intent to Treat Efficacy (ITTE): All randomized subjects with efficacy data after a minimum of 2 weeks on treatment.

There were three primary comparisons of interest. The comparisons assessed if there was evidence of a dose related response on the primary efficacy variable within the range of doses in this study, i.e. 80mg, 40mg, 20mg of carvedilol CR and placebo.

The Tukey trend test was employed to identify the highest dose with no statistical evidence of a trend. Inferences based on the Tukey trend test were treated as primary. In addition **pairwise** comparisons of treatment doses and placebo were also performed along with corresponding 95% confidence intervals for the difference in mean change from baseline in mean DBP measured by ABPM for summary purposes.

The Tukey trend test was not applied to secondary variable analyses. Pairwise comparisons between carvedilol CR doses and placebo were performed for all secondary analyses.

Analyses were adjusted for disease status corresponding to treatment naïve and DBP controlled or DBP uncontrolled. Treatment by strata interaction was explored for the primary efficacy variable and was not significant. This interaction was not included in the analysis model.

Baseline was included as a covariate in the analysis of blood pressure related measures. For the primary efficacy variable of mean change from baseline in DBP measured by 24hr ABPM, treatment by baseline interaction was explored, and was not significant. This interaction was not included in the analysis model.

The efficacy analyses were based on the ITT efficacy population. The primary time point of interest or study endpoint was the end of treatment up-titration. This corresponded to the last available efficacy assessment in the up-titration phase which was Week 6 (or longer depending on the subjects re-challenge schedule) for completers and early withdrawal for non-completers.

Two efficacy analyses were performed for the end of treatment up-titration, one comprising all data with Last Observation Carried Forward (LOCF) for non-completers, and one without LOCF, comprising only the data at end of treatment up-titration (i.e., Observed Case [OC] analysis). Primary inference was based on the LOCF analysis.

Primary Efficacy variable
The primary efficacy variable was analyzed using Analysis of Covariance (ANCOVA) model with treatment, baseline, disease history (summarizing hypertension status as treatment naïve, DBP controlled or DBP uncontrolled) and center effects.

The primary efficacy analysis was adjusted for multiplicity using the Turkey trend test. Three ordinal contrasts were defined in the primary efficacy analysis, the first contrast tested for a trend in response with all carvedilol CR doses and placebo. The second contrast tested a trend in response with carvedilol CR 40 mg, carvedilol CR 20 mg and placebo and the last contrast compared the response of carvedilol CR 20 mg versus placebo.

Secondary efficacy variables were not adjusted for multiplicity.

- Continuous secondary efficacy variables were analyzed using the same model that was used for the primary efficacy analysis.
- Trough to peak ratio in DBP measured by ABPM was summarized by treatment.
- The proportion of responders (=10mmHg drop in sDBP from baseline) was analyzed via logistic regression with a model adjusting for treatment group and disease history.
- A sigmoid E-max model was used to describe the dose-response relationship in 24hr ABPM of mean DBP.

Efficacy Results
A reduction in mean model-adjusted DBP measured by 24hr ABPM was observed at the end of up-titration in the ITTE population with LOCF, at all carvedilol CR doses.
The trend in mean model-adjusted reductions in Diastolic Blood Pressure

- with carvedilol CR 80mg, 40mg, 20mg and placebo;
- carvedilol CR 40mg, 20mg and placebo;
- carvedilol CR 20mg and placebo were all significant

($p<0.0001$, $p<0.0001$ and $p=0.0010$, respectively [Tukey trend test])

Table 2: Model adjusted reductions in Diastolic Blood Pressure-Study 367

DBP, mmHg	Placebo N=76	Carvedilol CR 20mg N=82	Carvedilol CR 40mg N=76	Carvedilol CR 80mg N=86
n[1]	58	69	63	69
Model-Adjusted DBP Change from Baseline, LSMean±SE	-0.36 ± 0.932	-4.39 ± 0.861	-7.92 ± 0.900	-9.56 ± 0.862
Difference from Placebo, Mean[2]	--	-4.03	-7.56	-9.19
95% CI[2]	--	-6.41, -1.65	-9.95, -5.16	-11.59, -6.79
p-value	--	0.0010[5]	<0.0001[4]	<0.0001[3]

1. Number of subjects with a value at baseline and at the study endpoint (end of up-titration).
2. Based on ANCOVA: Change=Treatment+Center+Baseline+Disease History.
3. Based on Tukey trend test of carvedilol CR 80mg, 40mg and 20mg and placebo
4. Based on Tukey trend test of carvedilol CR 40mg and 20mg and placebo
5. Based on Tukey trend test of carvedilol CR 20mg and placebo

In the same population, ABPM measured trough (20-24hr) DBP and SBP levels for subjects in the carvedilol CR 40mg and 80mg groups were significantly lower than DBP and SBP levels for subjects in the placebo group.

At the carvedilol CR 20mg dose however, trough DBP and SBP changes by ABPM were not statistically significantly different (p= 0.0834 and 0.1500, respectively) to those seen with placebo. (Table 3 below) Figures 1 and 2.

Table 3: Mean adjusted change from baseline and Placebo subtracted by ABPM -DiastolicBP –Study 367

Trough (20-24hr), DBP and SBP, mmHg	Placebo N=76	Carvedilol CR 20mg N=82	Carvedilol CR 40mg N=76	Carvedilol CR 80mg N=86
n[1]	58.	66	63	69
Model-Adjusted **DBP** Change from Baseline, LSmean±SE	0.04 ± 1.223	-2.75 ± 1.161	-5.12 ± 1.183	-7.33 ± 1.132
Difference from Placebo, Mean[2]	-	-2.79	-5.15	-7.37
95% CI[2]	-	-5.95, 0.37	-8.31, -2.00	-10.53, -4.21
p-value[3]	-	0.0834	0.0015	<0.0001
Model-Adjusted **SBP** Change from Baseline, LSMean±SE	0.09 ± 1.746	-3.22 ± 1.653	-4.77 ± 1.685	-8.35 ± 1.619
Difference from Placebo, Mean[2]	-	-3.30	-4.85	-8.44
95% CI[2]	-	-7.81, 1.20	-9.35, -0.36	-12.94, -3.94
p-value[3]	-	0.1500	0.0346	0.0003

1. Number of subjects with a value at baseline and at specified visit (after LOCF).
2. Based on ANCOVA: change=treatment+center+baseline+disease history.
3. Based on pairwise comparisons.

Figure 1: Placebo-subtracted model-adjusted DBP/SBP change from baseline – study 367- Source Reviewer

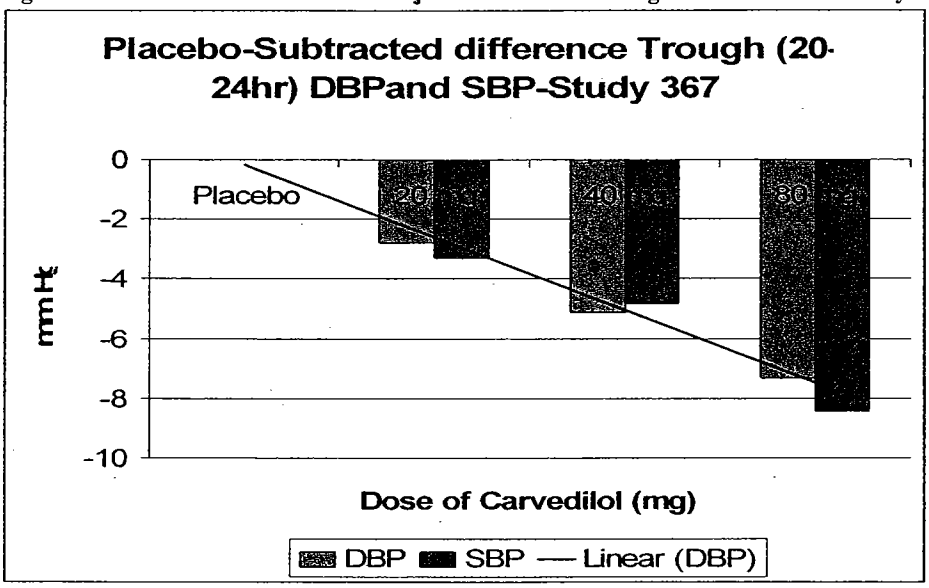
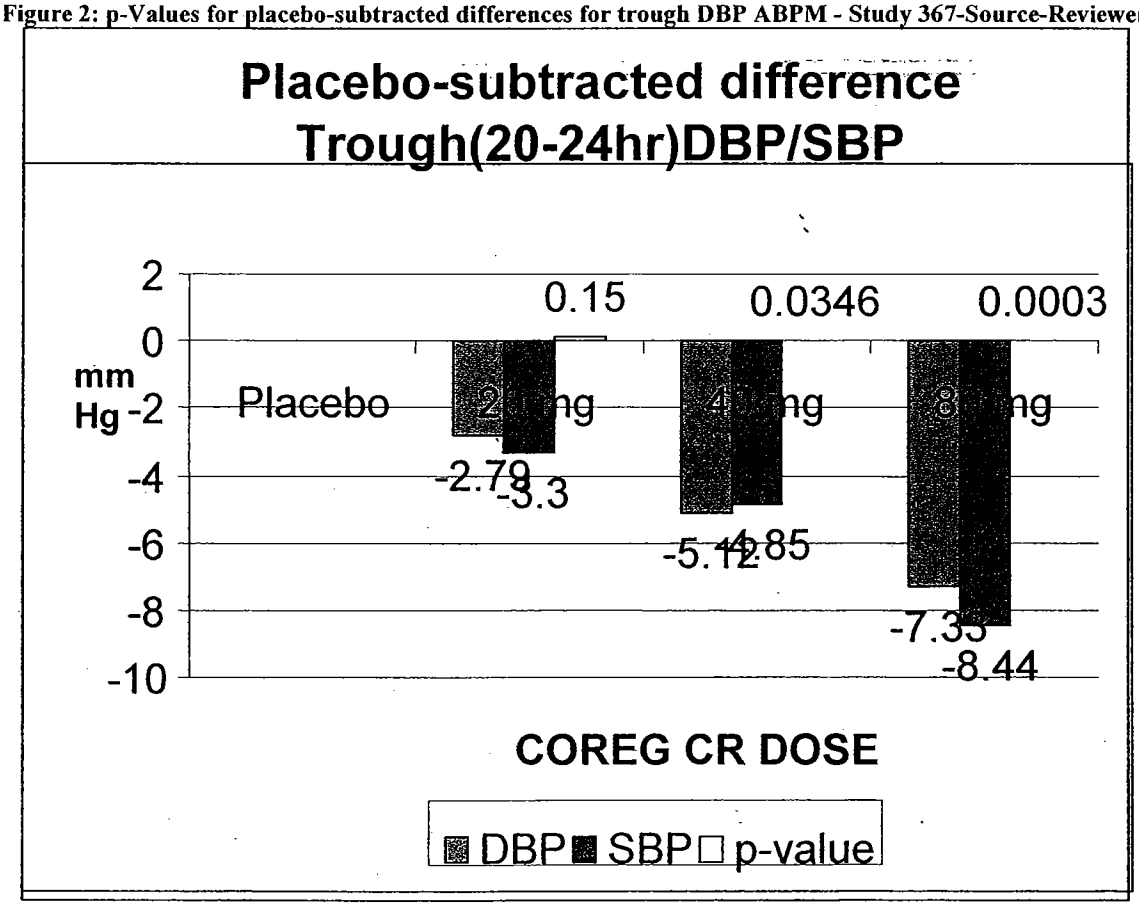


Figure 2: p-Values for placebo-subtracted differences for trough DBP ABPM - Study 367-Source-Reviewer.



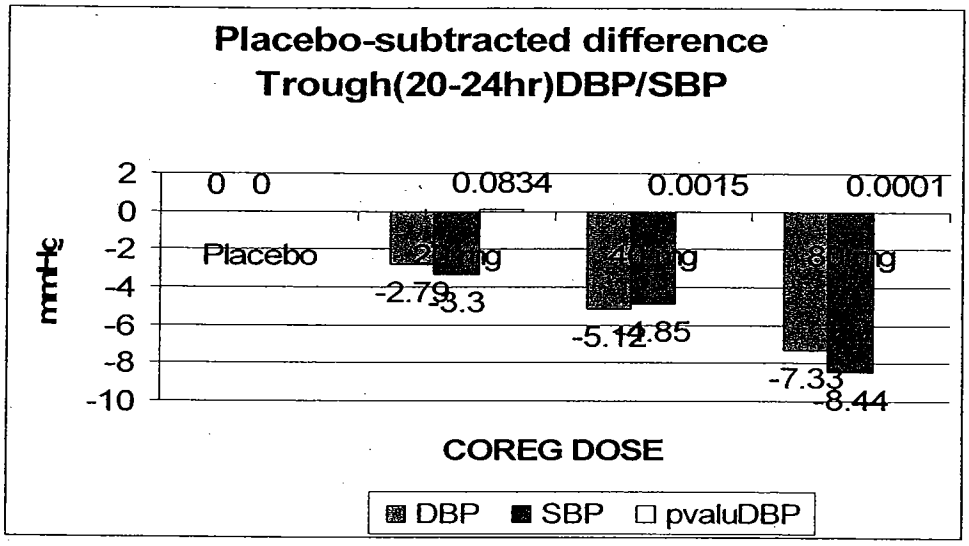
p-values for SBP are at the top of graph (0-2).

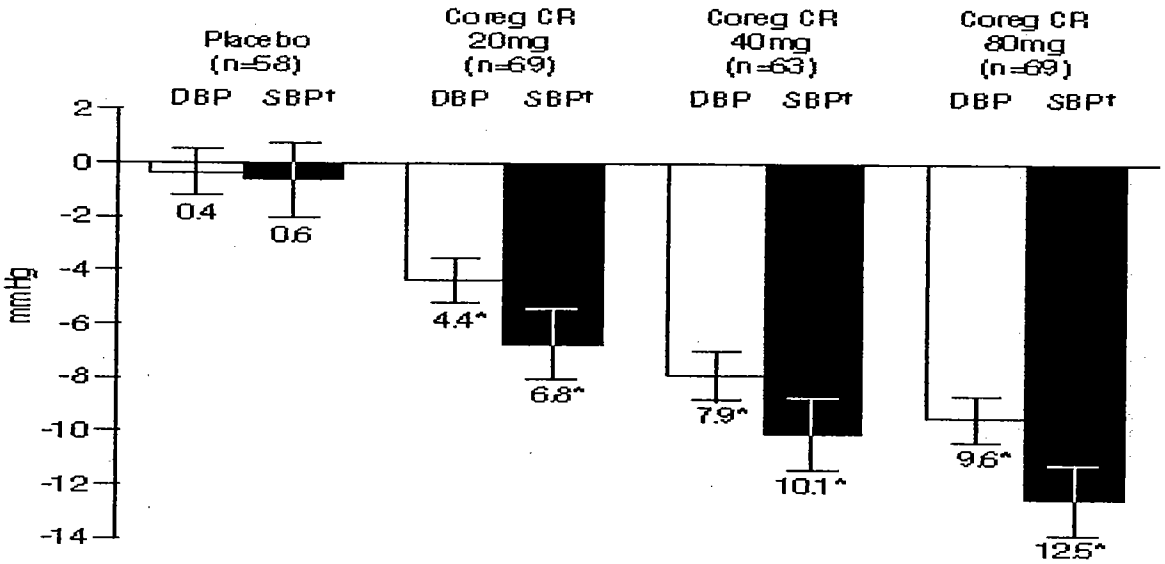
The fact that the ABPM measured changes in systolic and diastolic pressures at trough for the carvedilol CR 20 mg group failed to reach statistical significance, (p=0.15) despite the fact that the trough to peak efficacy ratio was in the same range as that of the other two treatment groups and of that seen with the IR tablet given BID, shows that 20 mg of CR likely represents the bottom of the clinically useful portion of the dose response curve.

The study achieved its primary endpoint of reduction of the 24-hour mean diastolic pressure. Furthermore, the reduction in the 24-hour mean diastolic pressure was dose related over the range tested, with mean changes from baseline (95% CIs) of -4.39mmHg (-6.41, -1.65), -7.92mmHg (-9.95, -5.16), and -9.56 mmHg (-11.59, -6.79) for the 20mg, 40mg, and 80mg carvedilol CR groups, respectively, compared to -0.36mmHg for the placebo group. Carvedilol CR also produced a similar dose-related decrease in 24-hour mean systolic blood pressure (Figures 1-5).

The reduction in both systolic and diastolic blood pressure was maintained over the entire 24 hour period as evidenced by changes from baseline pressures in the morning, afternoon, and night; the changes from baseline pressures at trough; and the trough to peak effect ratios. It is important to note that the placebo corrected trough to peak effect ratios of 0.730, 0.641 and 0.649 for the 20mg, 40mg, and 80mg carvedilol CR groups, respectively, compare favorably to the trough to peak effect ratios of 0.47, 0.65, and 0.55 previously reported for carvedilol IR tablets 6.25 mg, 12.5 mg, and 25 mg BID, respectively

Figure 3: p-values for Placebo-subtracted difference Trough (20-24hr) SBP – Source-Reviewer.





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 above histogram in black and white is based on ad hoc analysis for systolic blood pressure. The Reviewer's histogram in Figure 2 reflects the data from study 367.

Figure 4: ABPM - Study 367 Mean Change from BaselineinDBPMeasuredby24hrABPM by treatment

(ITTE Population with LOCF)

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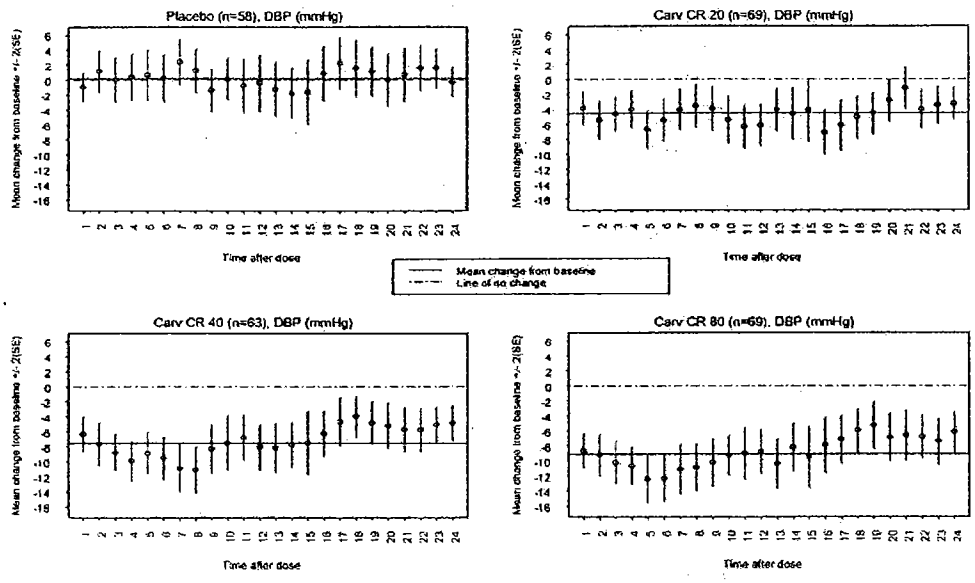
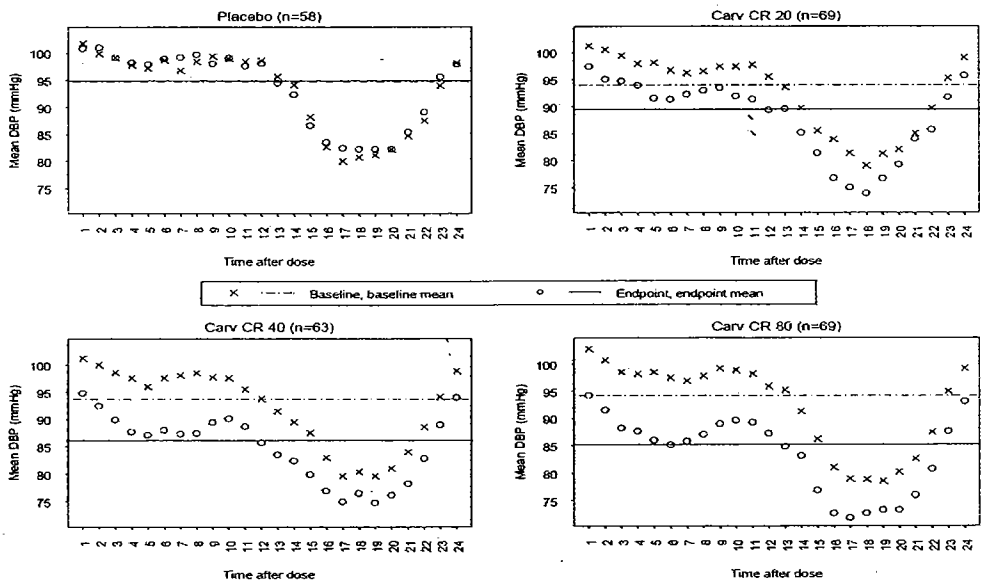


Figure 5: ABPM Study-Study 367 The mean baseline and study endpoint DBP values measured by ABPM hourly over 24 hours following study drug administration are shown by treatment group in Figure 4.



Treatment Effects using Cuff Sphygmanometer

In addition to ABPM, cuff measurements were also taken for secondary efficacy endpoint. Mean model-adjusted changes from baseline in trough sDBP at the end of up-titration were -6.19mmHg, -7.90mmHg and -8.87mmHg for the carvedilol CR 20mg, 40mg and 80mg treatment groups, respectively, compared to a -1.85 mmHg change observed for the placebo group (Table 4). The difference from placebo in mean change in sDBP at trough was statistically

significant for all three carvedilol CR doses. For all treatment groups, the trough sDBP changes measured by cuff were slightly greater than the DBP changes measured by ABPM (Tables1&4).

Table 4: Mean model-adjusted changes from baseline trough DBP – Study 367

sDBP, mmHg	Placebo N=76	Carvedilol CR 20mg N=82	Carvedilol CR 40mg N=76	Carvedilol CR 80mg N=86
n[1]	76	82	76	86
Baseline, Mean±SD	99.30 ± 5.324	98.56 ± 4.557	98.79 ± 5.411	99.16 ± 5.418
Study Endpoint, Mean±SD	98.14 ± 7.945	92.78 ± 7.437	91.53 ± 8.662	90.87 ± 8.751
Change from Baseline, Mean±SD	-1.16 ± 7.491	-5.78 ± 7.341	-7.27 ± 7.264	-8.29 ± 9.633
Model-Adjusted Change from Baseline, LSmean±SE	-1.85 ± 0.926	-6.19 ± 0.884	-7.90 ± 0.941	-8.87 ± 0.879
Difference from Placebo, Mean[2]	-	-4.33	-6.05	-7.02
95% CI[2]	-	-6.76, -1.91	-8.49, -3.61	-9.43, -4.62
p-value[3]	-	0.0005	<0.0001	<0.0001

Data Source: Table 7.21

1. Number of subjects with a value at baseline and at specified visit (after LOCF).
2. Based on ANCOVA: change=treatment+center+baseline+disease history.
3. Based on pairwise comparisons.

Responder analysis

The proportion of responders was 30.5%, 39.5% and 40.7% for the carvedilol CR 20mg, 40mg and 80mg groups, respectively, compared to 9.2% for the placebo group. The odds-ratios (95% confidence intervals) for response were 4.52 (1.8, 11.34), 6.39 (2.56, 15.99) and 7.43 (3.01, 18.34) for the 20mg, 40mg and 80mg carvedilol CR groups, respectively, versus placebo.

Coreg CR was 4 to 7 times more likely than placebo to achieve a reduction from baseline in sDBP of at least 10mmHg at doses of 20 mg, 40 mg, and 80 mg (Table 5).

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Table 5: Responder analyses - Study 367

Responder Analysis	Placebo N=76	Carvedilol CR 20mg N=82	Carvedilol CR 40mg N=76	Carvedilol CR 80mg N=86
n[1]	76	82	76	86
Responders[2] at Study Endpoint, n (%)	7 (9.2)	25 (30.5)	30 (39.5)	35 (40.7)
Odds Ratio[3]	-	4.52	6.39	7.43
95% CI	-	(1.8, 11.34)	(2.56, 15.99)	(3.01, 18.34)
p-value	-	0.0013	0.0001	<0.0001

Data Source: Table 7.28.

1. Number of subjects with an sDBP value at baseline and at study endpoint (end of up-titration).
2. Response was defined as an sDBP reduction from baseline of ≥10mmHg.
3. Odds {logistic regression: odds= treatment+disease history} of having ≥10mmHg reduction from baseline in sDBP at week 6 compared to placebo. Odds ratio>1 indicates favorable effect of treatment over placebo.

Safety

Few subjects were withdrawn for an AE (10 subjects). Hypertension related AEs were the most frequent to result in withdrawal overall; the preferred terms hypertension and hypertensive crisis together resulted in withdrawal of 3 subjects in the placebo group (Section 7 for more details).

Table 6: Adverse events leading to withdrawal - Study 367

AEs Leading to Withdrawal				
	Placebo	Carvedilol CR		
Preferred Term	N=84	20mg N=87	40mg N=78	80mg N=88
Any Adverse Event	3 (4)	1 (1)	3 (4)	3 (3)
Fatigue	0	0	1 (1)	1 (1)
Non-cardiac chest pain	0	0	0	1 (1)
Edema peripheral	0	0	1 (1)	0
Hypertension	2 (2)	0	0	0
Hypertensive crisis	1 (1)	0	0	0
Myocardial infarction	0	0	1 (1)	0
Pneumonia	0	1 (1)	0	0
Headache	0	0	0	1 (1)
Depression	0	0	0	1 (1)
Proteinuria	0	0	1 (1)	0

The number of adverse events reported in this study was relatively low, and the frequency and types of adverse events were similar across all treatment groups, including placebo. The percent of subjects reporting any adverse events was 32%, 24%, 24%, and 32% for the placebo, 20mg, 40mg, and 80mg carvedilol CR groups, respectively. These numbers compare favorably to the 30%, 41%, and 53% previously reported for carvedilol IR 6.25, 12.5, and 25mg BID groups, respectively [Carvedilol IR New Drug Application, Integrated Summary of Safety].

Dizziness, which was reported by 3%, 4%, and 5% of the hypertensive subjects who received 12.5, 25, or 50mg of carvedilol IR per day, was reported in only one subject (1%) in the placebo group, one subject (1%) in the carvedilol CR 40mg, four subjects (5%) in the carvedilol CR 80mg group, and no subjects (0%) in the carvedilol CR 20 mg group.

Table 7: Adverse events for >2% subjects in any treatment group-Study 367

AEs Reported for ≥2% of Subjects in Any Treatment Group					
	Number (%) of Subjects				
	Placebo	Carvedilol CR			
Preferred Term	(N=84)	20mg (N=87)	40mg (N=78)	80mg (N=88)	Total Carvedilol CR (N=253)
Up-Titration Phase					
Any Adverse Event	32 (38)	22 (25)	23 (29)	33 (38)	78 (31)
Headache	5 (6)	5 (6)	5 (6)	5 (6)	15 (6)
Fatigue	3 (4)	2 (2)	1 (1)	4 (5)	7 (3)
Dizziness	1 (1)	0	1 (1)	4 (5)	5 (2)
Cough	2 (2)	1 (1)	2 (3)	3 (3)	6 (2)
Nausea	0	0	1 (1)	3 (3)	4 (2)
Upper Respiratory Tract Infection	5 (6)	1 (1)	2 (3)	2 (2)	5 (2)
Nasopharyngitis	0	4 (5)	3 (4)	2 (2)	9 (4)
Influenza	1 (1)	0	0	2 (2)	2 (1)
Nasal Congestion	0	1 (1)	0	2 (2)	3 (1)
Paresthesia	0	0	1 (1)	2 (2)	3 (1)
Edema Peripheral	1 (1)	2 (2)	1 (1)	2 (2)	5 (2)
Depression	1 (1)	0	1 (1)	2 (2)	3 (1)
Sinus Congestion	0	0	0	2 (2)	2 (1)
Diarrhea	0	0	0	2 (2)	2 (1)
Dyspnea Exertional	2 (2)	0	0	0	0
Arthralgia	1 (1)	2 (2)	0	0	2 (1)
Insomnia	0	1 (1)	2 (3)	0	3 (1)
Hypertension	2 (2)	0	0	0	0
Down-Titration Phase					
Any Adverse Event	7 (8)	11 (13)	12 (15)	6 (7)	29 (11)
Headache	0	0	2 (3)	1 (1)	3 (1)
Peripheral Edema	0	2 (2)	1 (1)	0	3 (1)
ALT Increased	0	0	1 (1)	2 (2)	3 (1)

Three SAEs were reported during the treatment phase of the study. One subject in the placebo group had a hypertensive crisis (considered by the investigator to be related to study medication), one subject in the carvedilol CR 20mg group had pneumonia (unrelated to study medication) and one subject in the carvedilol CR 40mg group had a myocardial infarction (unrelated to study medication) all of which were reported as SAEs. In each case the subject was withdrawn from the study. There were no fatal events during the study.

1.1 Recommendations on Regulatory Action

In accordance with federal regulations (US Code of Federal Regulations CFR 300.50), this study was designed to test the antihypertensive effect of Coreg CR compared to placebo. Using ABPM Coreg CR at 40 and 80 mg dose levels showed superiority to placebo in the capacity to lower blood pressure (Study 367). Coreg CR 20 mg showed no statistically significant superiority to placebo. However, using cuff sphygmanometer, Coreg 20 was superior to placebo at DBP and SBP measurements.

This reviewer recommends that the Coreg 40 and 80 mg be approved for the treatment of essential hypertension. For the other indications sought, namely congestive heart failure and reduction of cardiovascular mortality, the two studies 369 and 902 showed similarity between the IR and CR formulations. Detailed results of these two studies are in Section 5 below. Data from these two studies appear to justify on statistical grounds the PK and PD similarities between the IR and CR formulations (Table 34).

This study was not powered to determine differences in responses between races. While the percentage of black subjects in the ITTE population (14.0%) is slightly higher than that in the United States population (12.3%), the number of black subjects in the ITTE population (40) is too small to expect to see a treatment effect. Based on previous experience with carvedilol, in general, as is true for other ß-blockers, antihypertensive responses are smaller in black than non-black patients.

Based on the data and the model used to evaluate and compare the data between the IR and CR formulations, there is evidence to support the inferential claims for congestive heart failure and reduction of cardiovascular mortality for the controlled release formulation. This inferential conclusion and claim may not hold for the races.

On average, the ß1-adrenergic blocking effect of the carvedilol CR formulation was similar to the ß1-adrenergic blocking effect of the COREG formulation at trough plasma concentrations (Ct). For the pooled analysis, as well as for the high and low dose groups separately, the point estimates for the ratio CR:IR for the comparison of observed PDmin were at or near unity, with corresponding lower bound of the 90% confidence interval within 20% of unity (Tables 46-48).

Recommendations and Conclusions:
• Carvedilol CR, alone at doses of 20mg, 40mg, and 80mg once daily causes a clinically and statistically significant reduction in blood pressure compared to placebo.
• The effects of once daily dosing of carvedilol CR on blood pressure last for the entire 24 hour period.
• Carvedilol CR at doses of 20mg, 40mg, or 80mg once daily was safe and well-tolerated.

• The results of this study support the use of carvedilol CR as a once daily treatment for essential hypertension.

This reviewer recommends the approval of this NDA application for the indications sought subject to Postmarketing actions and risk management activity.

1.2 Recommendation on Post Marketing actions

See risk management activity below.

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✓ Trade Secret / Confidential

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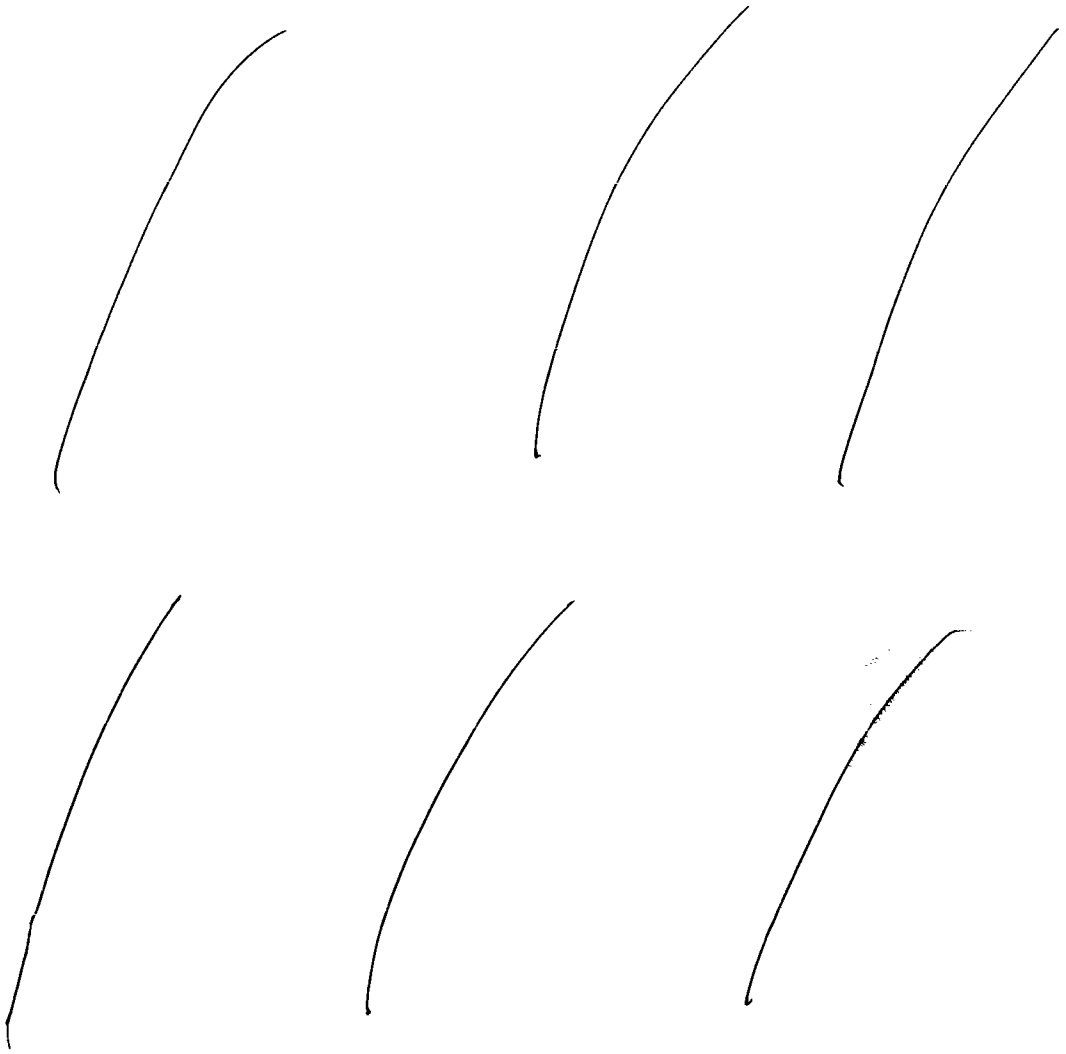


1.2.2 Required Phase 4 Commitments

Not required

1.2.3 Other Phase 4 Requests

Not required

1.3 Summary of Clinical Findings

There were 3 major studies out of 15 studies in the development program that are considered relevant for evaluation of clinical benefits in this NDA (Section 4.2) namely, 367, 369 and 902. The other 12 studies are nevertheless very useful in evaluating safety of the new formulation.

- Study 367 was for efficacy and safety of the CR formulation when compared to placebo. The data from this study have been described above under the executive summary.

Using ABPM Coreg CR at 40 and 80 mg dose levels showed superiority to placebo in the capacity to lower blood pressure (Study 367). Coreg CR 20 mg showed no statistically significant superiority to placebo. However, using cuff sphygmanometer, Coreg 20 was superior to placebo at DBP and SBP measurements.

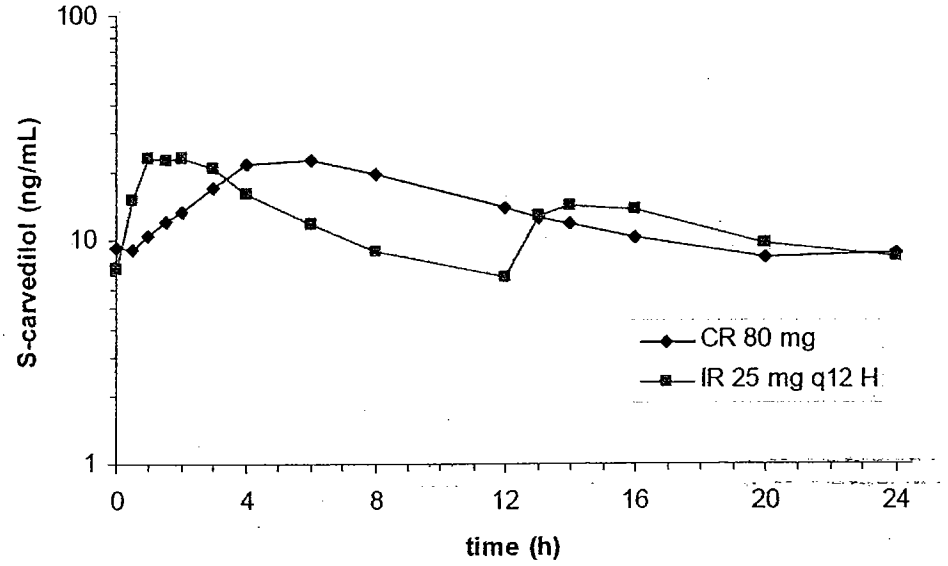
- Study 369 was to establish linkage between the IR and CR formulations using PK modeling. For the CR formulation to lay claim to the IR formulation there must be a linkage using the PK parameters. A clinical review of the PK findings is described below. A more detailed review of the PK will be carried out by Biopharm division. There was no PD evaluation in this study. This study will be described under section 5-Pharmacokinetics.

- Study 902 was the study to establish similarities in beta-1 blockade effect between the IR and CR formulations in patients with essential hypertension. By so doing the pharmacodynamic data will be assessed and clinical benefits of beta blockade will be shown by inference to impact the treatment of CHF which in turn leads to reduction in cardiovascular mortality. This study will be described under section 5-Pharmacokinetics. A more detailed review will be carried out by Biopharm Reviewer.

Based on an analysis of pooled data for comparisons of the CR and IR formulations, point estimates (CR: IR) and corresponding 90% CIs for AUC, Cmax, and Ct for R- and S-carvedilol were within the acceptable bioequivalence limits of 80% to 125%. Thus, bioequivalence criteria were achieved for the CR and IR formulations of carvedilol. In general, similar results were observed across all dose groups (Figures 6 and 10).

Figure 6: Mean steady state concentration-time profiles for S (-) – Carvedilol after administration of IR (25 mg /12hr) and CR (80 mg /24 hours-Study 369

Figure 14 Mean Steady-state Concentration-Time Profiles for S(-)-Carvedilol After Administration of IR (25 mg every 12 hours) and CR (80mg every 24hrs) Carvedilol (Study 369)



Data Source: m2.7.2 Figure 10.

Conclusions:
A once-daily formulation of carvedilol would be highly advantageous in the treatment of hypertension and long-term treatment of chronic heart failure since ease of administration would facilitate better compliance and therefore, better efficacy.

• 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 ß1- 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, Ct, and Cmax.
• 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 (Table 54).

• The relationship between plasma concentrations of S (-)-carvedilol and changes in exercise-induced heart rate were described with an Emax model. Due to large variability in the HR data and the limited data at or above Emax, 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 IR 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.

1.3.1 Brief Overview of Clinical Program

This study population includes three subsets of subjects – those who had essential hypertension (diastolic pressure =90 and =109 mmHg) and were not on antihypertensive treatment at screening; those who had a history of hypertension and whose hypertension was controlled (diastolic pressure <90 mmHg) on antihypertensive treatment; and those who were hypertensive (diastolic pressure =90 and =109 mmHg) despite being on one or two antihypertensive agents, neither of which was a beta adrenergic blocking agent. The subset whose hypertension was controlled on antihypertensive treatment at screening had their existing medications discontinued. If after two weeks off medication, their diastolic pressure was =90 and =109 mmHg, they were eligible to be randomized. The subjects who were still hypertensive despite antihypertensive treatment continued their pre-existing antihypertensive treatment throughout the study.

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.

Using ABPM Coreg CR at 40 mg and 80 mg dose levels showed superiority to placebo in the capacity to lower blood pressure. Coreg CR 20 mg showed no superiority to placebo.

A reduction in mean model-adjusted DBP measured by 24hr ABPM was observed at the end of up-titration in the ITTE population with LOCF, at all carvedilol CR doses.

The trend in mean model-adjusted reductions in Diastolic Blood Pressure

- with carvedilol CR 80mg, 40mg, 20mg and placebo;
- carvedilol CR 40mg, 20mg and placebo;
- carvedilol CR 20mg and placebo were all significant ($p<0.0001$, $p<0.0001$ and $p=0.0010$, respectively [Tukey trend test])(Table 1).

In the same population, ABPM measured trough (20-24hr) DBP and SBP levels for subjects in the carvedilol CR 40mg and 80mg groups were significantly lower than DBP and SBP levels for subjects in the placebo group.
At the carvedilol CR 20mg dose however, trough DBP and SBP changes by ABPM were not statistically significantly different ($p= 0.0834$ and 0.1500, respectively) to those seen with placebo.
• Carvedilol CR, alone **or in combination with other therapies,** at doses of 20mg, 40mg, and 80mg once daily causes a clinically and statistically significant reduction in blood pressure compared to placebo.
• The effects of once daily dosing of carvedilol CR on blood pressure last for the entire 24 hour period.
• Carvedilol CR at doses of 20mg, 40mg, or 80mg once daily was safe and well-tolerated.

• The data from this study support the use of carvedilol CR as a once daily treatment for essential hypertension.
There was one clinical study for evaluating the efficacy of antihypertensive activity of COREG CR.

Title of Study 367:
A Randomized, Double-Blind, Multicenter Study Comparing the Effects of Administration of Modified Release COREG or Placebo on Blood Pressure in Essential Hypertension Patients

The subjects were screened over a 2 to 5 day period for eligibility prior to entering the 2 to 4 week Placebo Run-in/Washout phase during which subjects were monitored weekly for blood pressure. Subjects taking ß-blockers or clonidine were tapered off the medication during the Placebo Run-in/Washout phase. All subjects eligible for randomization based on the 12hr daytime ABPM measurements performed on the day prior to the baseline visit entered the baseline/randomization phase. Subjects who satisfied all screening and inclusion criteria for entry were randomized 1:1:1:1 to one of three doses of once-daily carvedilol CR (20mg, 40mg or 80mg) or placebo for six weeks of treatment followed by a two-week down-titration phase.

The subjects assigned to one of the three carvedilol CR arms started with 20mg once daily dosing. At two-week intervals, the subjects were blindedly up-titrated to their assigned dose or to the highest tolerated dose if the randomized target could not be reached. At the end of six weeks of treatment, 24hr ABPM was performed on the final day of dosing before the start of down-titration. Following completion of the final 24hr ABPM, subjects in the 40mg and 80mg carvedilol CR daily dosing treatment groups were down-titrated over two weeks to 20mg daily: subjects randomized to 20mg carvedilol CR UID and placebo subjects remained on their

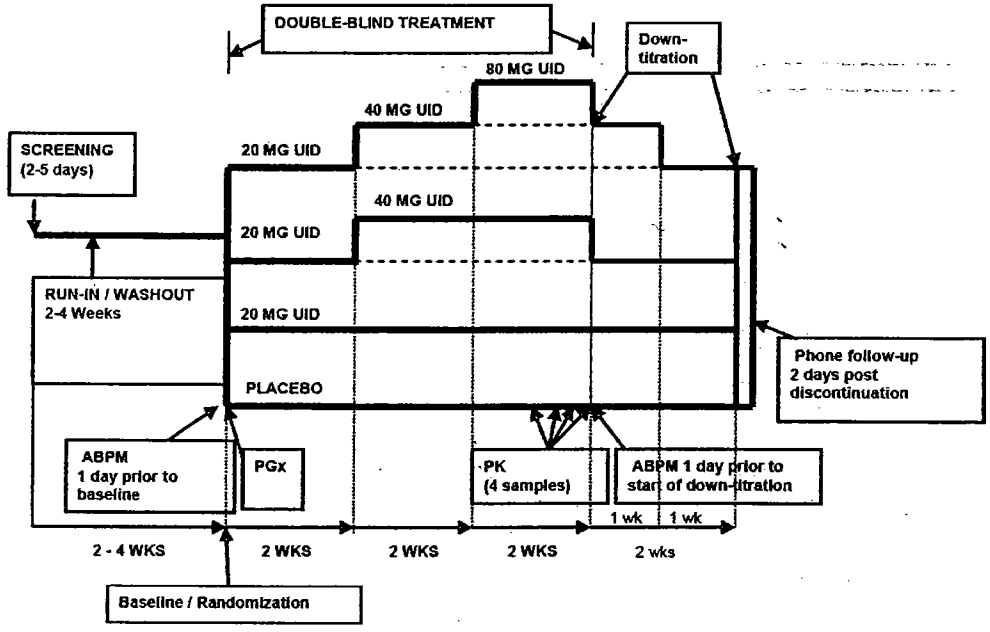
respective treatments. At the end of the two-week down titration phase double blind study medication was discontinued for all subjects. After completion of the down-titration phase, subjects were treated for hypertension at the investigators discretion.

Study design

This phase III study was a double-blind, randomized, placebo-controlled, parallel group, multicenter study conducted in subjects who have essential hypertension. The study consisted of five phases: screening; placebo run-in/washout; baseline/randomization; double-blind treatment (up-titration); and down-titration (Figure 6).

As part of the PK evaluation, an optional PGx blood sample was taken at baseline for determination of CYP2D6 metabolizer status (alleles: *3, *4, *5, *6, *7 and *8). Blood samples (6 mL) were collected into vacutainers containing EDTA and stored at approximately -20°C or lower until collected by a courier for , stored the frozen samples for monthly shipment to , which was responsible for processing the samples.

Figure 7: Study design - 367



The study assessments performed during these phases are described in Table 11 below

Table 8: Schedule of assessments -Study 367

Procedure	Screen Visit	Run-In/ Washout	Run-In/ Washout	Run-In/ Washout	Run-In/ Washout	End of Run-In (1 Day Prior to Baseline)	Optional Repeat End of Run-In (1 Day Prior to Baseline)	Baseline/ Start of Treatment (Up-Titration)
		Week -4	Week -3	Week -2	Week -1	Day -1	Repeat Day -1	Visit 1
Complete Physical Exam, Medical History, Cardio-Pulmonary Exam, Body Weight & Height	X							
Clinical Labs	X							X
HbA1c	X							
Urinalysis	X							X
Pregnancy Test (urine)	X							X
Vital Signs (cuff BP & HR)	X	X	X	X	X	X		X
24hr ABPM						X[1]	X[1]	
ECG	X							
AE assessment		X	X	X	X	X	X	X
PGx Sample								X[2]
Medication Dispensed		X						X
Concomitant Medication	X	X	X	X	X	X		X
Chest X-ray	X[3]							

continued

Procedure	Treatment (Up-Titration)	Optional Interim[1] Visits	Treatment (Up-Titration)	PK Visit (5-7 Days Post Visit 3)	Optional Interim[2] Visits	End of Treatment ABPM	Repeat End of Treatment ABPM	Start of Down Titration	Down Titration	End of Study	Early Withdrawal	Phone Follow-up
	Visit 2	Visits 2a,b,c	Visit 3		Visits 3a,b,c	Day prior to Visit 4 (down-titration)	Day prior to Visit 4 (down-titration)	Visit 4	Visit 5	Day of last dose		Within 2 days post study
Clinical Labs								X		X	X	
Urinalysis								X		X	X	
Vital signs (cuff BP & HR)	X	X	X		X			X	X	X	X	
24 hr. ABPM						X[4]	X[4]				X[5]	
ECG								X			X	
AE assessment	X	X	X	X	X	X	X	X	X	X	X	X
PK Assessment			X[6]	X[7]		X[8]						
PGx Sample												
Medication Dispensed	X	X	X		X			X	X			
Medication Compliance	X		X					X	X	X	X	
Concomitant Medication	X	X	X		X			X	X	X	X	
Chest X-ray												

1. ABPM device placed on the day prior to baseline visit, data checked at the baseline visit (included 12hr ABPM qualification); repeat allowed for ABPM data capture failure
2. Optional sample
3. Only if not done within previous 12months
4. ABPM device was placed on day prior to start of down-titration and data was checked at start of down-titration; repeat allowed for data capture failure
5. ABPM not required if subject has been off medication for greater than 3 days
6. 1 draw pre-dose and 1 draw (1-2 hours) post-dose for a total of 2 draws
7. 1 draw (4-8 hours) post-dose
8. 1 draw immediately prior to the last dose of the treatment period

Subjects were screened over a 2 to 5 day period for eligibility prior to entering the 2 to 4 week Placebo Run-in/Washout phase during which subjects were monitored weekly for blood pressure. Subjects taking ß-blockers or clonidine were tapered off the medication during the Placebo Run-in/Washout phase. All subjects eligible for randomization based on the 12hr daytime ABPM measurements performed on the day prior to the baseline visit entered the baseline/randomization phase. Subjects who satisfied all screening and inclusion criteria for entry were randomized 1:1:1:1 to one of three doses of once-daily carvedilol CR (20mg, 40mg or 80mg) or placebo for six weeks of treatment followed by a two-week Down-titration phase.

Subjects assigned to one of the three carvedilol CR arms started dosing at 20mg once daily (UID). At two-week intervals, subjects were up-titrated to their assigned dose (up-titration was blinded), or to the highest tolerated dose if the randomized target could not be reached. At the

end of six weeks of treatment, 24hr ABPM was performed on the final day of dosing before the start of down-titration. Following completion of the final 24hr ABPM, subjects in the 40mg and 80mg carvedilol CR UID treatment groups were down-titrated over two weeks to 20mg UID; subjects randomized to 20mg carvedilol CR UID and placebo subjects remained on their respective treatments. At the end of the two-week down titration phase double blind study medication was discontinued for all subjects. After completion of the down-titration phase, subjects were treated for hypertension at the investigators discretion.

Inclusion Criteria

1. Signed written, informed consent was obtained;

2. The subject was =18yrs of age (females must have been post-menopausal (i.e., no menstrual period for a minimum of six months), surgically sterilized, using a double barrier method contraceptive, or using oral Depo-Provera or implanted contraceptives for at least one month prior to the baseline/randomization visit and agreed to continue to use the same contraceptive method during the study;

3. At initial screening, the subject had a history of or presented with untreated essential hypertension (sitting DBP =90 and =109mmHg by repeat sitting office-cuff measurements) and met one of the following criteria:

• The subject was newly diagnosed and/or previously untreated (if newly diagnosed, must have had their qualifying blood pressure confirmed on two consecutive visits with the average sitting DBP (sDBP) value not differing more than 8mmHg); or

• the subject had DBP controlled (=90mmHg) at initial screening while receiving no more than two antihypertensive medications (one of which could have been a ß blocker) and the therapy could be safely withdrawn for the duration of the study (Note: A combination drug containing two antihypertensive agents was considered to represent two antihypertensive medications); note any subject who was receiving ß blockers or clonidine must have had the dose tapered down during the Run-in/Washout phase to avoid rebound hypertension); or

• the subject had DBP not controlled (>90, but =109 mmHg) at initial screening while receiving no more than two antihypertensive medications (neither of which was a ß blocker) and these would be continued during washout and the remainder of the study;

4. At Randomization, the subject had an office-cuff measurement for sDBP that was =95 but =109mmHg and the following ABPM (both 12hr and 24hr) data at final Placebo Run-in/Washout visit:

• Mean 12hr daytime (9AM to 9PM) DBP =90 but =109mmHg;

• At least 75% of the programmed readings actually recorded over 24hr monitoring period;

• No more than two nonconsecutive hours with less than two successful readings per hour while awake, and no more than two consecutive hours with less than one successful reading per hour during the sleep period over the 24hr monitoring period;

• At least two successful readings per hour for three of the last four hours of recording (trough period, i.e. 20-24hr during which subjects were awake) with a total of at least seven successful readings over this period.

Exclusion criteria

A subject was not eligible for inclusion in this study if any of the following criteria applied:

1. Female subjects who had a positive pregnancy test or were known to be pregnant, lactating, or using an unreliable form of birth control.

2. Malignant (accelerated) hypertension, history of malignant hypertension, secondary forms of hypertension, or hypertension secondary to use of hormonal contraceptive agents.

3. Average sitting SBP =180mmHg;

4. Known contraindications to ß blocker therapy;

5. Advanced hypertensive retinopathy (Keith Wagener grade IV);

6. Type 1 diabetes mellitus, or type 2 diabetes mellitus having HbA1c =9% at screening;
7. Unstable angina;
8. Uncorrected primary obstructive or severe regurgitative valvular disease, nondilated (restrictive) or hypertrophic cardiomyopathies;
9. Significant ventricular arrhythmias requiring therapy;
10. History of sick sinus syndrome unless a pacemaker was in place;
11. Second or third degree heart block unless a pacemaker was in place;
12. Congestive heart failure (NYHA Class II–IV CHF);

13. Heart rate less than 60 beats per minute (sitting);

14. Atrial fibrillation;

15. Current clinical evidence of obstructive pulmonary disease (e.g. asthma or bronchitis) requiring inhaled or oral bronchodilator or steroid therapy; or a history of bronchospastic disease not undergoing active therapy in whom, in the investigator's opinion, treatment with study medication could provoke bronchospasm;

16. Evidence of significant disease that could impair absorption, metabolism, or excretion of orally-administered medication, i.e., renal disease (serum creatinine >221µmol/L [2.5mg/dL] or

creatinine clearance <25mL/min); clinically significant hepatic disease (i.e., by laboratory alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels greater than three times upper limit of normal (ULN) range, due to hepatic impairment, or by clinical assessment); or chronic biliary disorders;
17. History of myocardial infarction;
18. Stroke in the six months prior to initial screening;
19. History or likelihood of poor compliance;
20. Cancer or other systemic disease with reduced life expectancy (<12 months);
21. History of drug sensitivity or allergic reaction to a or ß blockers;
22. Use of an investigational drug within 30 days of entry into the study or five half-lives of the investigational drug (the longer was applied);
23. Ongoing or anticipated treatment with any of the following medications during treatment with double blind study medication:
• Monoamine oxidase inhibitors;
• Any Class I or III antiarrhythmic; • a-Blockers; • Labetalol; • ß2-agonists;
• ß-Blockers (must have been discontinued at screening if the subject was to be randomized to study medication);
• Levitra or Cialis for erectile dysfunction
24. Any condition which, in the opinion of the investigator and/or the GSK Medical Monitor placed the subject at an unacceptable risk as a participant in this trial.

Other criteria

To assess any potential impact on subject eligibility with regard to safety, the investigators were referred to the approved product label and/or Clinical Investigator Brochure for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to carvedilol CR.

Drug Supply

Table 9: Drug Supply

Investigational Product	Description[1]	Batch ID Numbers
Carvedilol Phosphate 20mg CR capsule	— capsules with white opaque body and yellow opaque cap	041031967 041039312
Carvedilol Phosphate 40mg CR capsule	— capsules with yellow opaque body and green opaque cap	041031968 041039316
Carvedilol Phosphate 80mg CR capsule	— capsules with white opaque body and cap	041039318 041031970
Placebo to match 20mg CR capsule		041035708 041055665
Placebo to match 40mg CR capsule		041035707
Placebo to match 80mg CR capsule		041053597 041035706

1. All capsules are

Dosages and Administration
Subjects were randomized to one of three doses of once-daily carvedilol CR (20mg, 40mg or 80mg) or placebo for six weeks of treatment followed by a two-week down-titration phase Thus, subjects received blinded study medication for a total of eight weeks.

Subjects assigned to one of the three carvedilol CR arms started dosing at 20mg UID. At two-week intervals, subjects were up-titrated to their assigned randomized dose or the highest tolerated dose if the randomized target could not be reached. At the end of six weeks of treatment, subjects were down-titrated over two weeks to 20mg UID. Subjects randomized to 20mg carvedilol CR UID or placebo continued to take 20mg or placebo during the down-titration phase. At the end of the two week down-titration phase, double blind study medication was discontinued for all subjects.

Dose Rationale
The carvedilol CR doses (20mg, 40mg, and 80mg UID) were selected to provide exposure levels of carvedilol CR that correspond to those achieved following administration of the previously approved carvedilol IR tablets (6.25mg, 12.5mg, and 25mg BID, respectively) for the hypertension indication.

Blinding
All double-blind study medication was blinded to both the investigator and the subject. All study procedures were the same, independent of whether the subject received active or placebo medication.

Investigators: This was a multicenter study.

Study centers: Twelve centers in Canada and 55 centers in the United States randomized subjects into the study.

Publications: None at the time of this report.

Study Period: 03 Sep 2004 – 28 Jun 2005.

Phase of Development: III

Objectives:
Primary: In a group of subjects with a history of, or current essential hypertension (sitting diastolic blood pressure [DBP] =90mmHg and =109mmHg) 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). Carvedilol CR was referred to as carvedilol phosphate MR or modified release COREG in the protocol.

Secondary: Secondary objectives included: • Comparison of mean DBP measured by ABPM at the drug-trough blood levels (20-24hr) for carvedilol CR compared to placebo treatment;

• Trough (20-24hr) to peak (3-7hr) DBP ratios using 24-hour ABPM;

• The dose-response relationship between incremental doses of carvedilol CR and mean 24hr ABPM DBP;

• Blood pressure changes in the morning, afternoon, and at night using ABPM;

• Office/clinic DBP and systolic blood pressure (SBP) measurements by cuff assessments at drug-trough (20-24hr) blood levels to evaluate the effect of different doses of carvedilol CR, compared to placebo;

• Comparisons between treatment groups in the percentage of responders (response was defined as a sitting diastolic blood pressure (sDBP) reduction from baseline of =10mmHg);

• Safety of the CR formulation in this subject population;

• Population pharmacokinetics after administration of the carvedilol CR formulation.

Methodology:
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: 20 mg carvedilol CR (20 mg 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.
Treatment administration:

Subjects were assigned to receive either placebo or carvedilol CR 20mg, 40mg or 80mg. Each dose level of active carvedilol CR had a matching placebo. Subjects received three bottles at each dispensing period according to their assigned dose and took one capsule from each bottle of blinded study medication daily.

Disposition of Subjects
The study was conducted at 32 centers; 4 in Canada and 28 in the United States. A total of 188 subjects were enrolled into the study. Although 188 subjects were enrolled, 1 subject did not receive study medication and is not included in the ITT Population. The ITT Population was synonymous with the Safety Population. A total of 174 subjects (92.6%) completed the study.

Table 10: Disposition of subjects - Study 367

	Placebo	Carvedilol CR		
		20mg	40mg	80mg
Number of Subjects Planned, N	71	71	71	71
Randomized, N	85[1]	87	78	88
Completed, n (%)	61 (73)	74 (85)	65 (83)	73 (83)
Total Number of Subjects Withdrawn, n (%)	23 (27)	13 (15)	13 (17)	15 (17)
Withdrawn due to Adverse Events, n (%)	3 (4)	1 (1)	3 (4)	3 (3)
Withdrawn due to Lack of Efficacy, n (%)	5 (6)	4 (5)	0	1 (1)
Withdrawn for other reasons, n (%)	15 (18)	8 (9)	10 (13)	11 (13)

1. One subject (#2263) was randomized but failed to provide informed consent and did not receive study medication.

A summary of subject disposition by heart failure strata (mild, moderate, severe) and asymptomatic post MI LVD is shown in Table 10 and summary disposition of subjects stratified by heart failure is in Table 11 below..

Table 11: Summary of Subject disposition stratified by heart failure - Study 367

Table 5 Summary of Subject Disposition

Subject Disposition	Mild CHF	Moderate CHF	Severe CHF	Post MI LVD	Total
Enrolled[1]	53	54	51	30	188
ITT Population (Safety)[2]	52	54	51	30	187
PK Population[3]	49	48	48	28	173
Completed[4]	49	49	48	28	174

Data Source: Table 6.02

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

Distribution of Subjects by Heart Failure Strata and Dose

The numbers of subjects who enrolled and completed the study were comparable for mild, moderate, and severe CHF strata, as well as dosage group. There were however, fewer subjects in the asymptomatic post MI LVD stratum who enrolled and completed the study. In addition, no subjects in the asymptomatic post MI LVD stratum received COREG in the 3.125mg/10mg dose group.

Table 12: Subject disposition by Heart Failure and dose group-Study 367

e 6 Summary of Subject Disposition by Heart Failure Strata and Dose Group

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

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Table 13: Reasons for premature withdrawal - ITT/Safety population - Study 367

ıle 7 Summary of Reasons of Premature Withdrawal from the Study (ITT Safety Population)

Reason for Withdrawal, n (%)	Total N=187
Prematurely withdrawn	**13 (7)**
Adverse event	5 (3)
Lost to follow-up	0
Protocol violation	0
Subject decided to withdraw	8 (4)
Sponsor terminated study	0
In sufficient therapeutic effect	0
Did not meet eligibility criteria	0
Other	0

Data Source: Table 6.01

Table 14: Protocol Deviation - Study 367

le 8 Summary of Inclusion/Exclusion Criteria Deviations (ITT Safety Population)

Criterion, n (%)	Total N=187
Any criteria deviations	25 (13)
Inclusion criteria	
Signed written, informed consent	1 (<1)
Males or females 18 to 85 years of age. Must use contraceptive method	1 (<1)
Have been diagnosed with clinically stable mild, moderate, or severe CHF	17 (9)[1]
Exclusion criteria	
Evidence of significant disease that could impair absorption, metabolism or excretion of the study medication	2 (1)
Ongoing (at Screening/Baseline) or anticipated treatment with the prohibited medications during the treatment phase	5 (3)
Acute myocardial infarction within 2 weeks prior to Screening	1 (<1)
Current clinical evidence of chronic obstructive pulmonary disease requiring long term use of inhaled oral bronchodilator or steroid therapy	1 (<1)

Data Source: Table 6.12

1. The full wording of the inclusion criteria was "Diagnosed with clinically stable mild, moderate or severe heart failure of ischemic or nonischemic origin, had left ventricular ejection fraction <35% and received background medications for HF which may have included ACE inhibitors, beta blockers, diuretics, AII antagonists, aldosterone antagonists, hydralazine, nitrates, digoxin and devices (biventricular pacing and implantable defibrillators, must have been implanted >60 days before enrollment); subjects who were recent (within 2 weeks to 2 months of index MI) survivors of an MI having LVD (LVEF ≤40%) and were asymptomatic for heart failure were receiving standard background agents which may have included ACE inhibitors and/or beta blockers and antithrombotic agents. Stable heart failure was defined as no change in NYHA Class and no hospitalization for heart failure or addition of IV diuretics, vasodilators or positive inotropes during the two weeks prior to Screening evaluation. Of the 17 subjects flagged as a

Table 15: History / Duration of CHF or asymptomatic post-MI LVD - Study 367

Table 11 Summary of Disease History- Duration of Congestive Heart Failure or Asymptomatic Post MI LVD (ITT Safety Population)

Duration (years)	Mild CHF N=52	Moderate CHF N=54	Severe CHF N=51	Post MI LVD N=30	Total N=187
n	42	50	46	20	158
Mean	3.88	6.07	4.55	1.10	4.42
SD	3.67	8.56	5.37	2.17	6.13
Median	3.11	2.88	2.64	0.11	2.35
Min.	0.04	0.04	0.04	0.00	0.00
Max.	17.13	48.92	24.62	7.26	48.92

Data Source: Table 6.06

Table 16: Demographics - Study 367

Table 9 Summary of Demographic Characteristics (ITT Safety Population)

Demographic Strata		Mild CHF N=52	Moderate CHF N=54	Severe CHF N=51	Post MI LVD N=30	Total N=187
Age (yrs)	n	52	54	51	30	187
	Mean	62.6	62.9	61.5	56.2	61.4
	SD	11.86	13.23	12.23	10.95	12.36
	Median	62.0	63.0	61.0	55.0	61.0
	Min.	35	25	35	33	25
	Max.	85	85	85	80	85
Sex, n (%)	n	52	54	51	30	187
	Female	13 (25)	16 (30)	19 (37)	2 (7)	50 (27)
	Male	39 (75)	38 (70)	32 (63)	28 (98)	137 (73)
Ethnicity, n (%)	n	52	54	51	30	187
	Hispanic/ Latino	1 (2)	3 (6)	3 (6)	3 (10)	10 (5)
	Not Hispanic/ Latino	51 (98)	51 (94)	48 (94)	27 (90)	177 (95)
Diabetes status	n	52	54	51	30	187
At baseline, n (%)	No	32 (62)	30 (56)	38 (75)	22 (73)	122 (65)
	Yes	20 (38)	24 (44)	13 (25)	8 (27)	65 (35)
Height (cm)	n	52	54	51	30	187
	Mean	169.5	170.1	167.4	174.4	169.9
	SD	10.85	12.73	12.60	8.21	11.70
	Median	171.5	172.0	168.0	175.0	172.0
	Min.	127	143	141	154	127
	Max.	193	201	193	190	201
Weight (kg)	n	52	54	51	30	187
	Mean	90.5	86.1	90.7	94.6	89.9
	SD	20.53	20.03	26.71	18.15	21.93
	Median	85.8	84.1	88.2	94.6	87.0
	Min.	62	49	46	61	46
	Max.	159	135	180	129	180
Body Mass	n	52	54	51	30	187
Index (kg/m²)	Mean	31.7	29.7	32.6	31.1	31.3
	SD	7.67	5.81	9.44	5.76	7.49
	Median	29.7	28.0	30.1	32.4	29.7
	Min.	20	21	17	18	17
	Max.	60	47	57	42	60
Baseline Sitting	n	52	54	51	30	187
Systolic BP	Mean	121.8	122.6	122.9	120.5	122.1
(mmHg)	SD	16.95	20.37	18.09	21.24	18.87
	Median	121.5	120.0	121.0	117.0	120.0
	Min.	86	90	87	90	86
	Max.	160	180	173	178	180
Baseline Sitting	n	52	54	51	30	187
Diastolic BP	Mean	72.5	72.9	72.9	73.1	72.8
(mmHg)	SD	10.96	11.87	13.68	10.57	11.87
	Median	71.0	71.0	70.0	77.0	71.0
	Min.	49	48	45	57	45
	Max.	96	98	126	98	126

continued

Demographic Strata		Mild CHF N=52	Moderate CHF N=54	Severe CHF N=51	Post MI LVD N=30	Total N=187
Hear Rate (beats/minute)	n	52.0	54.0	51.0	30	187
	Mean	69.0	73.6	73.9	73.9	72.4
	SD	7.40	12.82	11.97	7.41	10.65
	Median	68.0	72.0	74.0	73.5	72.0
	Min.	52	54	58	60	52.0
	Max.	88	120	112	100	120

Data Source: Table 6.03

Racial characteristics

The majority of subjects who received at least one dose of study medication were Caucasian (137/185 subjects, 74%) and the remainder were primarily African American or of African heritage (41/185 subjects, 22%) (Table 15).

Table 17: Demogaphics - Racial groups - Study 367

Table 10 Summary of Race and Racial Combination Details (ITT Safety Population)

Race, n (%)	Mild CHF N=52	Moderate CHF N=54	Severe CHF N=51	Post MI LVD N=30	Total N=187
n	52	53	51	29	185[1]
African American/African Heritage	11 (21)	13 (25)	14 (27)	3 (10)	41 (22)
American Indian or Alaska Native	1 (2)	2 (4)	1 (2)	0	4 (2)
Asian-Central/South Asian Heritage	0	0	1 (2)	0	1 (<1)
Asian-East Asian Heritage	0	0	0	0	0
Asian-Japanese Heritage	0	0	0	0	0
Asian-South East Asian Heritage	0	0	0	0	0
Asian- Mixed Asian Heritage	0	0	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0	0	0
White-Arabic/North African Heritage	2 (4)	0	0	0	2 (1)
White/Caucasian/European Heritage	38 (73)	38 (72)	35 (69)	26 (90)	137 (74)
White-Mixed Race	0	0	0	0	0
Mixed Race	0	0	0	0	0

Data Source: Table 6.05

1. Racial determination was missing for 2 subjects

Table 18: Cardiovascular/Cerebrovascular Medical conditions in randomized subjects – Study 367

Table 12 Summary of Cardiovascular Medical Conditions (ITT Safety Population)

Classification, n (%)	Mild CHF N=52	Moderate CHF N=54	Severe CHF N=51	Post MI LVD N=30	Total N=187
Any Condition	51 (98)	54 (100)	51 (100)	30 (100)	186 (>99)
Cardiac Disorders					
Any Condition	51 (98)	54 (100)	51 (100)	30 (100)	186 (>99)
Cardiomyopathy	48 (92)	47 (87)	50 (98)	17 (57)	162 (87)
Heart failure	39 (75)	42 (78)	46 (90)	18 (60)	145 (78)
Left ventricular dysfunction	42 (81)	35 (65)	41 (80)	21 (70)	139 (74)
Myocardial infarction	29 (56)	29 (54)	27 (53)	30 (100)	115 (61)
Valvular heart disease	23 (44)	22 (41)	21 (41)	8 (27)	74 (40)
Arrhythmia	10 (19)	12 (22)	5 (10)	4 (13)	31 (17)
Vascular Disorders					
Any Condition	32 (62)	30 (56)	33 (65)	29 (97)	124 (66)
Atherosclerosis	31 (60)	30 (56)	31 (61)	28 (93)	120 (64)
Peripheral vascular disease	11 (21)	3 (6)	7 (14)	6 (20)	27 (14)
Nervous System Disorders					
Any Condition	10 (19)	3 (6)	7 (14)	5 (17)	25 (13)
Cerebrovascular disease	7 (13)	3 (6)	5 (10)	4 (13)	19 (10)
Stroke	7 (13)	2 (4)	4 (8)	2 (7)	15 (8)

Data Source: Table 6.08

Table 19: Prior medications in >/= 3% of subjects -Study 367

Table 13 Summary of Prior Medications Reported by at Least >/= 3% of Subjects in Any Dosage Group by Generic Term (ITT Safety Population)

ATC Level 1 Ingredient, Generic Term, n (%)	3.125mg/ 10mg N=38	6.25mg/ 20mg N=54	12.5mg/ 40mg N=51	25mg/ 80mg N=44	Total N=187
Any Medication	23 (61)	41 (76)	46 (90)	41 (93)	151 (81)
Carvedilol	21 (55)	30 (56)	44 (86)	40 (91)	135 (72)
Metoprolol	2 (5)	8 (15)	2 (4)	1 (2)	13 (7)
Furosemide	1 (3)	2 (4)	2 (4)	0	5 (3)
Atenolol	0	1 (2)	2 (4)	0	3 (2)
Acetylsalicylic Acid	1 (3)	0	1 (2)	0	2 (1)
Enalapril	0	2 (4)	0	0	2 (1)
Carisoprodol	1 (3)	0	0	0	1 (<1)
Celecoxib	1 (3)	0	0	0	1 (<1)
Perindopril	1 (3)	0	0	0	1 (<1)

Data Source: Table 6.19

Table 20: Ongoing prior medications by >/=12% of subjects -Study 367

Table 14 Summary of Ongoing Prior Medications Reported by at Least >/= 12% of Subjects in Any Dosage Group by Generic Term (ITT Safety Population)

ATC Level 1 Ingredient, Generic Term, n (%)	3.125mg/ 10mg N=38	6.25mg/ 20mg N=54	12.5mg/ 40mg N=51	25mg/ 80mg N=44	Total N=187
Any Medication	38 (100)	54 (100)	51 (100)	44 (100)	187 (100)
Furosemide	25 (66)	33 (61)	39 (76)	32 (73)	129 (69)
Acetylsalicylic Acid	24 (63)	37 (69)	25 (49)	22 (50)	108 (58)
Lisinopril	13 (34)	19 (35)	25 (49)	16 (36)	73 (39)
Digoxin	15 (39)	18 (33)	18 (35)	18 (41)	69 (37)
Potassium NOS	13 (34)	15 (28)	22 (43)	15 (34)	65 (35)
Warfarin	13 (34)	17 (31)	21 (41)	12 (27)	63 (34)
Atorvastatin	6 (16)	19 (35)	16 (31)	13 (30)	54 (29)
Spironolactone	12 (32)	14 (26)	11 (22)	14 (22)	51 (27)
Clopidogrel	5 (13)	17 (31)	13 (25)	9 (20)	44 (24)
Simvastatin	4 (11)	13 (24)	15 (29)	5 (11)	37 (20)
Glyceryl Trinitrate	5 (13)	11 (20)	10 (20)	6 (14)	32 (17)
Vitamins NOS	4 (11)	8 (15)	9 (18)	6 (14)	27 (14)
Isosorbide Dinitrate	6 (16)	6 (11)	6 (12)	6 (14)	24 (13)
Metformin	0	7 (13)	7 (14)	7 (16)	21 (11)
Ramipril	6 (16)	5 (9)	3 (6)	5 (11)	19 (10)
Allopurinol	2 (5)	1 (2)	5 (10)	10 (23)	18 (10)
Levothyroxine	2 (5)	5 (9)	5 (10)	6 (14)	18 (10)
Amiodarone	3 (8)	7 (13)	1 (2)	4 (9)	17 (9)
Metoprolol	2 (5)	13 (24)	0	0	15 (8)
Enalapril	5 (13)	2 (4)	5 (10)	2 (5)	14 (7)
Valsartan	1 (3)	3 (6)	4 (8)	6 (14)	14 (7)
Glibenclamide	1 (3)	4 (7)	6 (12)	2 (5)	13 (7)
Folic Acid	5 (13)	2 (4)	3 (6)	2 (5)	12 (6)
Salbutamol	0	3 (6)	7 (14)	2 (5)	12 (6)

Data Source: Table 6.20

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Table 21 : Most frequent concomitant medications reported by at least >/=3% of subjects - Study 367

Table 15 **Summary of Most Frequent Concomitant Medications Reported by at Least >/= 3% of Subjects in Any Dosage Group by Generic Term (ITT Safety Population)**

ATC Level 1 Ingredient, Generic Term, n (%)	3.125mg/ 10mg N=38	6.25mg/ 20mg N=54	12.5mg/ 40mg N=51	25mg/ 80mg N=44	Total N=187
Any Medication	16 (42)	17 (31)	13 (25)	7 (16)	53 (28)
Paracetamol	3 (8)	2 (4)	5 (10)	0	10 (5)
Furosemide	4 (11)	3 (6)	1 (2)	0	8 (4)
Acetylsalicylic Acid	2 (5)	1 (2)	2 (4)	1 (2)	6 (3)
Metoprolol	0	6 (11)	0	0	6 (3)
Chlorpheniramine maleate	2 (5)	0	1 (2)	0	3 (2)
Dextropropoxyphene	1 (3)	1 (2)	1 (2)	0	3 (2)
Hydrocodone bitartrate	1 (3)	0	2 (4)	0	3 (2)
Pseudoephedrine HCl	1 (3)	0	2 (4)	0	3 (2)
Cefalexin	1 (3)	0	1 (2)	0	2 (1)
Glyceryl Trinitrate	2 (5)	0	0	0	2 (1)
Ibuprofen	1 (3)	0	1 (2)	0	2 (1)
Benzylpenicillin	1 (3)	0	0	0	1 (<1)
Citalopram	1 (3)	0	0	0	1 (<1)
Clarithromycin	1 (3)	0	0	0	1 (<1)
Epoetin alfa	1 (3)	0	0	0	1 (<1)
Glucose	1 (3)	0	0	0	1 (<1)
Heparin	1 (3)	0	0	0	1 (<1)
Hyoscine methonitrate	1 (3)	0	0	0	1 (<1)
Meloxicam	1 (3)	0	0	0	1 (<1)
Methylphenidate HCl	1 (3)	0	0	0	1 (<1)
Metoclopramide	1 (3)	0	0	0	1 (<1)
Morphine sulfate	1 (3)	0	0	0	1 (<1)
Perindopril	1 (3)	0	0	0	1 (<1)
Phenylephrine HCl	1 (3)	0	0	0	1 (<1)
Phenylpropanolamine bitartrate	1 (3)	0	0	0	1 (<1)
Ramipril	1 (3)	0	0	0	1 (<1)
Rosiglitazone	1 (3)	0	0	0	1 (<1)
Warfarin	1 (3)	0	0	0	1 (<1)
Zolpidem	1 (3)	0	0	0	1 (<1)

Data Source: Table 6.21

Table 22: Study medication compliance data - Study 367

Table 16 Summary of Study Medication Compliance (ITT Safety Population)

	COREG IR BID				
Compliance since last visit	**3.125mg (N=38)**	**6.25mg (N=54)**	**12.5mg (N=51)**	**25mg (N=44)**	**Total N=187**
n	38	54	50	43	185
>0% and <80%	3 (8)	4 (7)	4 (8)	3 (7)	14 (7)
≥80% and ≤120%	34 (89)	45 (83)	42 (82)	38 (86)	159 (85)
>120%	1 (3)	5 (9)	3 (6)	2 (5)	11 (6)
Missing	0	0	1 (2)	0	1 (<1)
	carvedilol CR UID				
Compliance since last visit	**10mg (N=38)**	**20mg (N=54)**	**40mg (N=51)**	**80mg (N=44)**	**Total N=187**
n	38	50	47	43	178
>0% and <80%	1 (3)	0	1 (2)	1 (2)	3 (2)
≥80% and ≤120%	36 (95)	50 (93)	45 (88)	42 (95)	173 (93)
>120%	2 (5)	0	1 (2)	0	3 (2)
Missing	0	0	0	0	0

Data Source: Tables 6.09

1.3.2 Efficacy

ABPM monitoring was completed at baseline and at the end of treatment or early withdrawal by standard electronic ambulatory monitoring equipment worn by the subject for 24 hours. Efficacy was determined by the mean change from baseline at study end in mean 24 hour DBP as measured by ABPM. Data collected by the ABPM devices included mean DBP, SBP, and heart rate at various intervals. Blood pressure was also measured at specified study visits using a sphygmomanometer. Safety assessments on all randomized subjects included AEs, vital signs, ECG and clinical laboratory evaluations.
Statistical methods:

The primary efficacy variable was analyzed via an Analysis of Covariance (ANCOVA) model with treatment, baseline, disease history (summarizing hypertension status as treatment naïve, DBP controlled or DBP uncontrolled) and center effects. The primary efficacy analysis was adjusted for multiplicity via the Tukey trend test. Three ordinal contrasts were defined in the primary efficacy analysis, the first contrast tested for a trend in response with all carvedilol CR doses and placebo. The second contrast tested a trend in response with carvedilol CR 40mg, carvedilol CR 20mg and placebo and the last contrast compared the response of carvedilol CR 20mg versus placebo. Secondary efficacy variables were not adjusted for multiplicity.

Continuous secondary efficacy variables were analyzed via the same model used for the primary efficacy analysis. Trough to peak ratio in DBP measured by ABPM was summarized by treatment. The proportion of responders (=10mmHg drop in sDBP from baseline) was analyzed

via logistic regression with a model adjusting for treatment group and disease history. A sigmoid E-max model was used to describe the dose-response relationship in 24hr ABPM of mean DBP.

All safety (non-efficacy) data were presented by appropriate statistical summaries.

Ad hoc analysis of the mean change from baseline in mean SBP via ABPM was analyzed by the same model used for the primary efficacy variable. Multiplicity was adjusted similarly via the Tukey trend test.

Efficacy Results: A reduction in mean model-adjusted DBP measured by 24hr ABPM was observed at the end of up-titration in the ITTE population with LOCF, at all carvedilol CR doses. The trend in mean model-adjusted reductions in DBP with carvedilol CR 80mg, 40mg, 20mg and placebo; carvedilol CR 40mg, 20mg and placebo; carvedilol CR 20mg and placebo were all significant ($p<0.0001$, $p<0.0001$ and $p=0.0010$, respectively [Tukey trend test]).
Table ABPM -367

DBP, mmHg	Placebo N=76	Carvedilol CR 20mg N=82	Carvedilol CR 40mg N=76	Carvedilol CR 80mg N=86
n[1]	58	69	63	69
Model-Adjusted DBP Change from Baseline, LSMean±SE	-0.36 ± 0.932	-4.39 ± 0.861	-7.92 ± 0.900	-9.56 ± 0.862
Difference from Placebo, Mean[2]	--	-4.03	-7.56	-9.19
95% CI[2]	--	-6.41, -1.65	-9.95, -5.16	-11.59, -6.79
p-value	--	0.0010[5]	<0.0001[4]	<0.0001[3]

1. Number of subjects with a value at baseline and at the study endpoint (end of up-titration).
2. Based on ANCOVA: Change=Treatment+Center+Baseline+Disease History.
3. Based on Tukey trend test of carvedilol CR 80mg, 40mg and 20mg and placebo
4. Based on Tukey trend test of carvedilol CR 40mg and 20mg and placebo
5. Based on Tukey trend test of carvedilol CR 20mg and placebo

In the same population, ABPM measured trough (20-24hr) DBP and SBP levels for subjects in the carvedilol CR 40mg and 80mg groups were significantly lower than DBP and SBP levels for subjects in the placebo group. At the carvedilol CR 20mg dose however, trough DBP and SBP changes by ABPM were not statistically significantly different to those seen with placebo.

Table ABPM-367

Trough (20-24hr), DBP and SBP, mmHg	Placebo N=76	Carvedilol CR 20mg N=82	Carvedilol CR 40mg N=76	Carvedilol CR 80mg N=86
n[1]	58	66	63	69
Model-Adjusted **DBP** Change from Baseline, LSmean±SE	0.04 ± 1.223	-2.75 ± 1.161	-5.12 ± 1.183	-7.33 ± 1.132
Difference from Placebo, Mean[2]	-	-2.79	-5.15	-7.37
95% CI[2]	-	-5.95, 0.37	-8.31, -2.00	-10.53, -4.21
p-value[3]	-	0.0834	0.0015	<0.0001
Model-Adjusted **SBP** Change from Baseline, LSMean±SE	0.09 ± 1.746	-3.22 ± 1.653	-4.77 ± 1.685	-8.35 ± 1.619
Difference from Placebo, Mean[2]	-	-3.30	-4.85	-8.44
95% CI[2]	-	-7.81, 1.20	-9.35, -0.36	-12.94, -3.94
p-value[3]	-	0.1500	0.0346	0.0003

1. Number of subjects with a value at baseline and at specified visit (after LOCF).
2. Based on ANCOVA: change=treatment+center+baseline+disease history.
3. Based on pairwise comparisons.

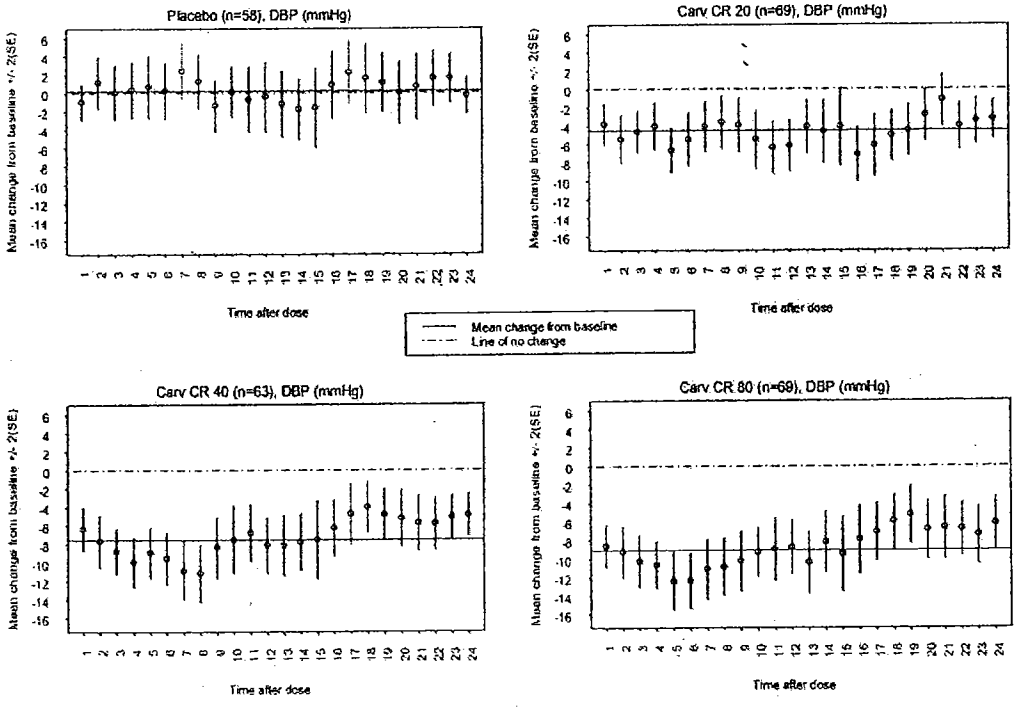


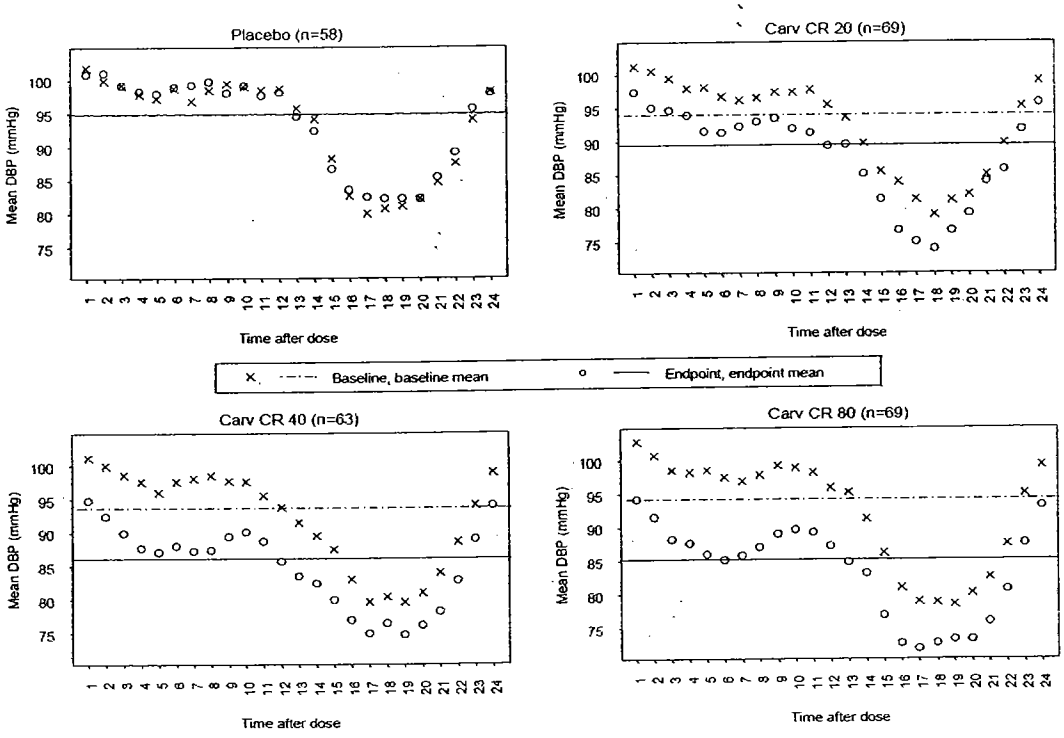
Table 23: Ad hoc analysis of change from baseline in mean SBP by 24 hr ABPM – ITTE - 367

Table 32 Analysis of Change from Baseline in Mean SBP Measured by 24hr ABPM (ITTE Population with LOCF)

SBP, mmHg	Placebo N=76	Carvedilol CR 20mg N=82	Carvedilol CR 40mg N=76	Carvedilol CR 80mg N=86
n[1]	58	69	63	69
Baseline, Mean±SD	146.05 ± 9.32	146.31 ± 11.48	145.64 ± 11.04	145.06 ± 10.06
Study Endpoint, Mean±SD	146.18 ± 11.75	139.79 ± 11.99	136.27 ± 12.69	134.07 ± 12.18
Change from Baseline, Mean±SD	0.13±8.63	-6.52±8.04	-9.37±10.40	-11.00±11.26
Model-Adjusted Change from Baseline, LSMean±SE	-0.63 ± 1.42	-6.75 ± 1.31	-10.06 ± 1.37	-12.48 ± 1.32
Difference from Placebo, Mean[2]	–	-6.12	-9.43	-11.84
95% CI[2]	–	(-9.75, -2.50)	(-13.07, -5.79)	(-15.50, -8.18)
p-value	–	0.0010[5]	<0.0001[4]	<0.0001[3]

Data Source: Ad hoc Table 7.77

1. ABPM population - Number of subjects with a value at baseline and at the study endpoint (end of up-titration).
2. Based on ANCOVA: change=treatment+center+baseline+disease history.
3. Based on Tukey trend test of carvedilol CR 80mg, 40mg and 20mg and placebo
4. Based on Tukey trend test of carvedilol CR 40mg and 20mg and placebo
5. Based on Tukey trend test of carvedilol CR 20mg and placebo



Cuff DBP and SBP trough data (measured using a sphygmomanometer) were similar and supportive of data measured by ABPM, except that SBP measured by cuff was significantly different to placebo in the 20mg group.

Using ABPM measured DBP values, placebo corrected trough to peak ratios were 0.730, 0.641 and 0.649 for the 20mg, 40mg and 80mg carvedilol CR groups, respectively. At trough (20-24hr), the mean change from baseline in mean DBP was greater than 60% of the mean change from baseline in mean DBP at peak (3-7hr) for all carvedilol CR treatment groups.

Mean morning, afternoon and night reductions from baseline to study endpoint in mean SBP and DBP as measured by ABPM were statistically significant for subjects in all three carvedilol CR treatment groups when compared to placebo. The mean reduction in DBP and SBP increased with dose.

Responder analyses

The proportion of responders was 30.5%, 39.5% and 40.7% for the carvedilol CR 20mg, 40mg and 80mg groups, respectively, compared to 9.2% for the placebo group. The odds-ratios (95% confidence intervals) for response were 4.52 (1.8, 11.34), 6.39 (2.56, 15.99) and 7.43 (3.01, 18.34) for the 20mg, 40mg and 80mg carvedilol CR groups, respectively, versus placebo.

Table 24: Responder analysis - ITTE - 367

Table 30 Analysis of Proportion of Responders (ITTE Population With LOCF)

Responder Analysis	Placebo N=76	Carvedilol CR 20mg N=82	Carvedilol CR 40mg N=76	Carvedilol CR 80mg N=86
n[1]	76	82	76	86
Responders[2] at Study Endpoint, n (%)	7 (9.2)	25 (30.5)	30 (39.5)	35 (40.7)
Odds Ratio[3]	-	4.52	6.39	7.43
95% CI	-	(1.8, 11.34)	(2.56, 15.99)	(3.01, 18.34)
p-value	-	0.0013	0.0001	<0.0001

Data Source: Table 7.28.

1. Number of subjects with an sDBP value at baseline and at study endpoint (end of up-titration).
2. Response was defined as an sDBP reduction from baseline of ≥10mmHg.
3. Odds {logistic regression: odds= treatment+disease history} of having ≥10mmHg reduction from baseline in sDBP at week 6 compared to placebo. Odds ratio>1 indicates favorable effect of treatment over placebo.

Secondary efficacy Measures

Trough DBP measured by ABPM

Mean model-adjusted changes from baseline in trough DBP measured by ABPM at the end of up-titration were -2.75mmHg, -5.12mmHg and -7.33mmHg for subjects in the carvedilol CR 20mg, 40mg and 80mg treatment groups, respectively, compared to a 0.04mmHg change observed for subjects in the placebo group (Table 25). Mean model-adjusted changes in DBP were statistically significantly different ($p<0.05$) at the carvedilol CR 40mg and 80mg doses compared to placebo. At the carvedilol CR 20mg dose, however, the mean reduction in DBP at trough was not significant compared to placebo ($p=0.0834$).

Trough SBP measured by ABPM

Mean model-adjusted changes from baseline in trough SBP at the end of up-titration were -3.22mmHg, -4.77mmHg and -8.35mmHg for subjects in the 20mg, 40mg and 80mg carvedilol CR treatment groups, compared to a 0.09mmHg change observed for subjects in the placebo group (Table 26). Mean reductions from baseline in trough SBP were similar to the corresponding mean reductions in trough DBP for the carvedilol CR treatment groups. As seen for trough DBP changes, mean model-adjusted changes in SBP were statistically significantly different ($p<0.05$) at the carvedilol CR 40mg and 80mg doses compared to placebo, but not at the 20mg dose ($p=0.1500$).

Table 25: 20-24 hr ABPM DBP - Study 367

20-24hr DBP, mmHg	Placebo N=76	Carvedilol CR 20mg N=82	Carvedilol CR 40mg N=76	Carvedilol CR 80mg N=86
n[1]	58	66	63	69
Baseline, Mean±SD	91.32 ± 8.618	92.33 ± 7.845	92.19 ± 7.983	91.66 ± 7.882
Study Endpoint, Mean±SD	92.27 ± 8.863	89.32 ± 9.832	86.44 ± 10.242	84.65 ± 9.345
Change from Baseline, Mean±SD	0.94 ± 8.600	-3.01 ± 7.170	-5.75 ± 8.004	-7.01 ± 9.750
Model-Adjusted Change from Baseline, LSmean±SE	0.04 ± 1.223	-2.75 ± 1.161	-5.12 ± 1.183	-7.33 ± 1.132
Difference from Placebo, Mean[2]	-	-2.79	-5.15	-7.37
95% CI[2]	-	-5.95, 0.37	-8.31, -2.00	-10.53, -4.21
p-value[3]	-	0.0834	0.0015	<0.0001

Data Source: Table 7.17

1. Number of subjects with a value at baseline and at specified visit (after LOCF).
2. Based on ANCOVA: change=treatment+center+baseline+disease history.
3. Based on pairwise comparisons.

Table 26: 20-24 hr ABPM SBP - Study 367

20-24hr SBP, mmHg	Placebo N=76	Carvedilol CR 20mg N=82	Carvedilol CR 40mg N=76	Carvedilol CR 80mg N=86
n[1]	58	66	63	69
Baseline, Mean±SD	140.43 ± 12.774	142.86 ± 13.101	142.58 ± 12.793	140.79 ± 13.325
Study Endpoint, Mean±SD	141.42 ± 14.050	139.38 ± 15.479	136.85 ± 16.684	133.55 ± 16.586
Change from Baseline, Mean±SD	0.99 ± 11.612	-3.48 ± 9.584	-5.73 ± 10.870	-7.24 ± 14.228
Model-Adjusted Change from Baseline, LSMean±SE	0.09 ± 1.746	-3.22 ± 1.653	-4.77 ± 1.685	-8.35 ± 1.619
Difference from Placebo, Mean[2]	-	-3.30	-4.85	-8.44
95% CI[2]	-	-7.81, 1.20	-9.35, -0.36	-12.94, -3.94
p-value[3]	-	0.1500	0.0346	0.0003

Data source: Table 7.19

1. Number of subjects with a value at baseline and at specified visit (after LOCF).
2. Based on ANCOVA: change=treatment+center+baseline+disease history.
3. Based on pairwise comparisons.

Trough DBP measured by cuff (sDBP)

Mean model-adjusted changes from baseline in trough sDBP at the end of up-titration were -6.19mmHg, -7.90mmHg and -8.87mmHg for the carvedilol CR 20mg, 40mg and 80mg treatment groups, respectively, compared to a -1.85 mmHg change observed for the placebo group (Table 27). The difference from placebo in mean change in sDBP at trough was statistically significant for all three carvedilol CR doses. For all treatment groups, the trough sDBP changes measured by cuff were slightly greater than the DBP changes measured by ABPM (Figure 5).

Table 27: DBP using Cuff - change from baseline at trough -Study 367

sDBP, mmHg	Placebo N=76	Carvedilol CR 20mg N=82	Carvedilol CR 40mg N=76	Carvedilol CR 80mg N=86
n[1]	76	82	76	86
Baseline, Mean±SD	99.30 ± 5.324	98.56 ± 4.557	98.79 ± 5.411	99.16 ± 5.418
Study Endpoint, Mean±SD	98.14 ± 7.945	92.78 ± 7.437	91.53 ± 8.662	90.87 ± 8.751
Change from Baseline, Mean±SD	-1.16 ± 7.491	-5.78 ± 7.341	-7.27 ± 7.264	-8.29 ± 9.633
Model-Adjusted Change from Baseline, LSmean±SE	-1.85 ± 0.926	-6.19 ± 0.884	-7.90 ± 0.941	-8.87 ± 0.879
Difference from Placebo, Mean[2]	-	-4.33	-6.05	-7.02
95% CI[2]	-	-6.76, -1.91	-8.49, -3.61	-9.43, -4.62
p-value[3]	-	0.0005	<0.0001	<0.0001

Data Source: Table 7.21

1. Number of subjects with a value at baseline and at specified visit (after LOCF).
2. Based on ANCOVA: change=treatment+center+baseline+disease history.
3. Based on pairwise comparisons.

By repeated measures analysis, mean model adjusted changes from baseline in trough sDBP were -6.47mmHg, -8.08mmHg and -9.54mmHg for the carvedilol CR 20mg, 40mg and 80mg treatment groups compared to a -1.73mmHg change for the placebo group (Table 28). The change in sDBP at trough was significantly different from placebo ($p<0.05$) for the three carvedilol CR dose groups.

Repeated Measures Analysis of Change from Baseline in sDBP Measured by Cuff at Drug Trough (20-24hr Mean) Blood Levels at the End of Treatment Up-titration (ITTE Population without LOCF)

Table 28; Cuff measurement of DBP at Trough (20-24hr) blood levels at end of treatment

sDBP, mmHg	Placebo N=76	Carvedilol CR 20mg N=82	Carvedilol CR 40mg N=76	Carvedilol CR 80mg N=86
n[1]	67	76	66	75
Baseline, Mean±SD	99.65±5.15	98.69±4.35	99.03±5.50	98.95±5.36
Study Endpoint, Mean±SD	98.15±7.56	92.37±7.38	91.46±8.36	89.80±8.42
Change from Baseline, Mean±SD	-1.50±7.24	-6.32±7.16	-7.56±6.85	-9.15±9.56
Model-Adjusted Change from Baseline, LSMean±SE	-1.73±0.93	-6.47±0.87	-8.08±0.94	-9.54±0.88
Difference from Placebo, Mean[2]		-4.74	-6.35	-7.82
95% CI[2]		(-7.20, -2.28)	(-8.87, -3.83)	(-10.29, -5.35)
p-value[2]		0.0002	<0.0001	<0.0001

Data Source: Table 7.30

1. Number of subjects with a value at baseline and on therapy.
2. Based on ANCOVA: change=treatment+center+baseline+disease history+time+treatment by time.

Trough SBP measured by cuff (sSBP)

Mean model-adjusted changes from baseline in trough sSBP at the end of up-titration were -4.40mmHg, -9.14mmHg and -8.86mmHg for the carvedilol CR 20mg, 40mg and 80mg groups, compared to a -1.mmHg change observed for the placebo group (Table 29). The change in sSBP at trough was statistically significant at the carvedilol CR 40mg and 80mg doses compared to placebo ($p<0.05$), but not significant at the 20mg carvedilol dose ($p=0.2030$). For all treatment groups, trough sSBP changes measured by cuff were slightly larger than the SBP changes measured by ABPM (Figure 5).

Table 29: Cuff measurement of SBP at Trough (20-24hr) blood levels at end of treatment uptitration

sSBP, mmHg	Placebo N=76	Carvedilol CR 20mg N=82	Carvedilol CR 40mg N=76	Carvedilol CR 80mg N=86
n[1]	76	82	76	86
Baseline, Mean±SD	149.17 ± 11.012	149.93 ± 11.956	151.16 ± 13.247	150.58 ± 12.706
Study Endpoint, Mean±SD	149.39 ± 14.783	145.86 ± 15.704	142.90 ± 16.357	143.15 ± 15.760
Change from Baseline, Mean±SD	0.22 ± 11.397	-4.07 ± 13.691	-8.25 ± 14.243	-7.44 ± 15.686
Model-Adjusted Change from Baseline, LSMean±SE	-1.48 ± 1.726	-4.40 ± 1.645	-9.14 ± 1.751	-8.86 ± 1.637
Difference from Placebo, Mean[2]	-	-2.92	-7.66	-7.38
95% CI[2]	-	-7.44, 1.59	-12.21, -3.11	-11.86, -2.91
p-value[3]	-	0.2030	<0.0011	<0.0013

Data Source: Table 7.23

1. Number of subjects with a value at baseline and at specified visit (after LOCF).
2. Based on ANCOVA: change=treatment+center+baseline+disease history.
3. Based on pairwise comparisons.

By repeated measures analysis, mean model adjusted changes from baseline in trough sSBP were -5.23mmHg, -9.47mmHg and -9.82mmHg for the carvedilol CR 20mg, 40mg and 80mg treatment groups compared to a -1.86mmHg change for the placebo group (Table 30). The change in sSBP at trough was significantly different from placebo ($p<0.05$) for the carvedilol CR 40mg and 80mg dose groups, but not for the carvedilol CR 20mg dose group.

Repeated Measures Analysis of Change from Baseline in sSBP Measured by Cuff at Drug Trough (20-24hr Mean) Blood Levels at the End of Treatment Up-titration (ITTE Population without LOCF)

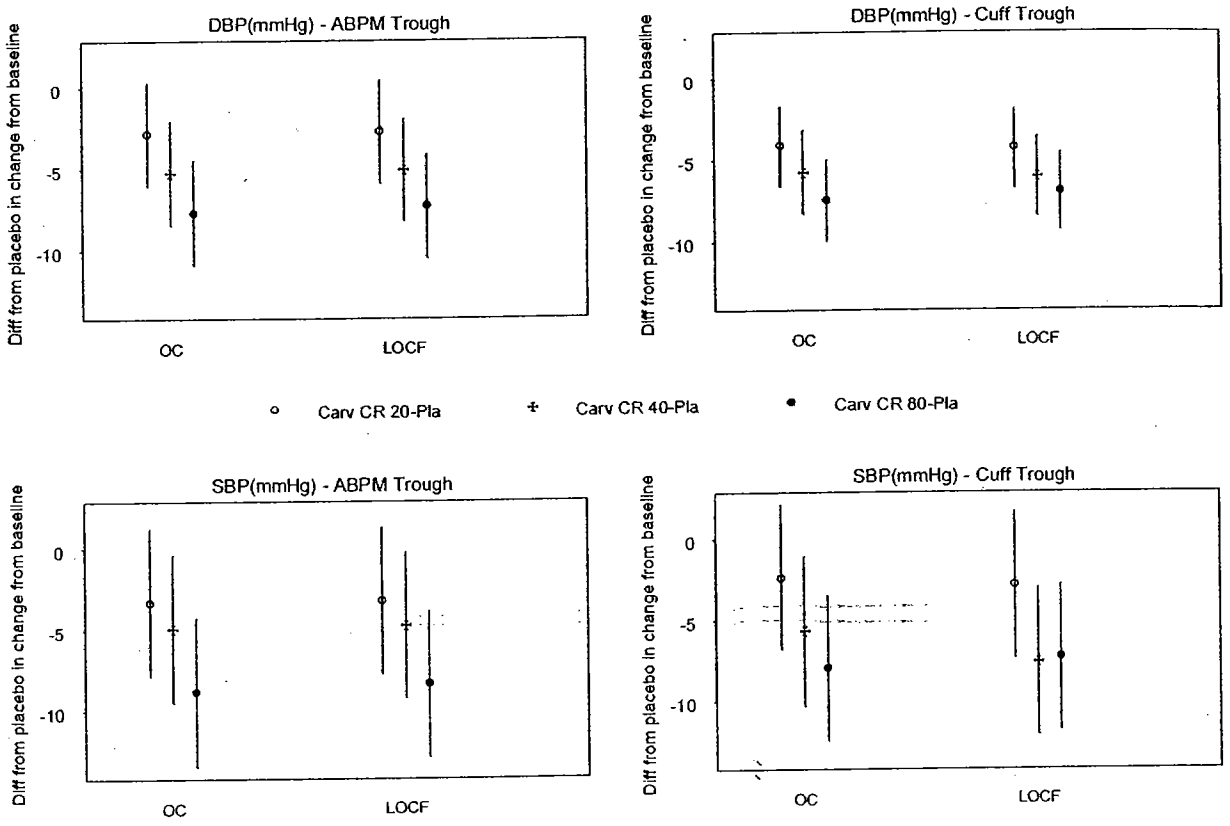
Table 30: Cuff measurement of SBP Trough (20-24hr) blood levels at end of treatment uptitration

sDBP, mmHg	Placebo N=76	Carvedilol CR 20mg N=82	Carvedilol CR 40mg N=76	Carvedilol CR 80mg N=86
n[1]	67	76	66	75
Baseline, Mean±SD	148.80±11.41	149.88±12.25	152.09±13.05	149.93±12.22
Study Endpoint, Mean±SD	148.40±14.14	144.81±14.58	143.16±16.71	140.96±14.50
Change from Baseline, Mean±SD	-0.40±10.64	-5.06±12.83	-8.93±14.36	-8.97±15.54
Model-Adjusted Change from Baseline, LSMean±SE	-1.86±1.63	-5.23±1.54	-9.47±1.66	-9.82±1.55
Difference from Placebo, Mean[2]		-3.37	-7.61	-7.96
95% CI[2]		(-7.69, 0.94)	(-12.03, -3.19)	(-12.28, -3.64)
p-value[2]		0.1248	0.0008	0.0003

Data Source: Table 7.32

1. Number of subjects with a value at baseline and on therapy.
2. Based on ANCOVA: change=treatment+center+baseline+disease history+time+treatment by time.

Figure 8: Comparisons of ABPM using electronic and cuff at Trough - DBP and SBP



Trough to Peak Ratios

Placebo corrected trough to peak ratios were 0.730, 0.641 and 0.649 for the 20mg, 40mg and 80mg carvedilol CR groups, respectively (Table 31). At trough (20-24hr) the mean DBP change from baseline was greater than 60% of the DBP change seen at peak (3-7hr) for all carvedilol CR treatment groups.

Table 31 Change from Baseline in Trough (20-24hr) to Peak (3-7hr) Mean Ratios of DBP Measured By 24hr ABPM (ITTE Population LOCF)

DBP, mmHg	Placebo N=76	Carvedilol CR 20mg N=82	Carvedilol CR 40mg N=76	Carvedilol CR 80mg N=86
n[1]	57	65	62	69
Baseline Trough Mean	91.3	92.4	92.2	91.7
Baseline Peak Mean	97.7	97.2	97.1	97.6
Endpoint Trough Mean	92.3	89.3	86.4	84.7
Endpoint Peak Mean	98.5	92.2	87.5	86.2
Trough to Peak Ratio	1.2	0.6	0.6	0.6
Change from Baseline Trough Mean	0.943	-3.012	-5.751	-7.010
Change from Baseline Peak Mean	0.802	-4.614	-9.648	-11.454
Change Trough Mean to Change Peak Mean Ratio	1.176	0.653	0.596	0.612
Placebo Corrected Trough to Peak Ratio	NA	0.730	0.641	0.649

Data Source: Table 7.25
1. Number of subjects with a value at baseline and at the study endpoint (end of up-titration)

Table 32: Morning ABPM above
Table 33: Afternoon ABPM data below

Table 24 Analysis of Change from Baseline in Mean Morning DBP Measured by 24hr ABPM (ITTE Population with LOCF)

Morning DBP, mmHG	Placebo N=76	Carvedilol CR 20mg N=82	Carvedilol CR 40mg N=76	Carvedilol CR 80mg N=86
n[1]	58	69	63	69
Baseline, Mean±SD	99.78 ± 6.756	99.99 ± 6.885	99.50 ± 5.987	100.50 ± 5.632
Study Endpoint, Mean±SD	100.16 ± 7.950	95.60 ± 9.384	91.68 ± 8.222	90.51 ± 7.805
Change from Baseline, Mean±SD	0.39 ± 7.672	-4.40 ± 7.958	-7.82 ± 7.890	-9.99 ± 7.653
Model-Adjusted Change from Baseline, Mean±SE	-0.28 ± 1.153	-4.07 ± 1.067	-8.27 ± 1.114	-10.36 ± 1.069
Difference from Placebo, Mean[2]	-	-3.78	-7.99	-10.08
95% CI[2]	-	-6.73, -0.84	-10.95, -5.03	-13.06, -7.11
p-value[3]	-	0.0121	<0.0001	<0.0001

Data Source: Table 7.05
1. Number of subjects with a value at baseline and at specified visit (after LOCF):
2. Based on ANCOVA: change=treatment+center+baseline+disease history.
3. Based on pairwise comparisons.

Table 25 Analysis of Change from Baseline in Mean Afternoon DBP Measured by 24hr ABPM (ITTE Population with LOCF)

Afternoon DBP, mmHG	Placebo N=76	Carvedilol CR 20mg N=82	Carvedilol CR 40mg N=76	Carvedilol CR 80mg N=86
n[1]	58	69	63	69
Baseline, Mean±SD	98.19 ± 6.561	96.91 ± 5.760	97.36 ± 5.488	98.10 ± 6.345
Study Endpoint, Mean±SD	98.69 ± 7.485	92.20 ± 8.537	87.99 ± 8.451	87.02 ± 8.950
Change from Baseline, Mean±SD	0.50 ± 8.007	-4.71 ± 7.820	-9.37 ± 8.572	-11.08 ± 8.754
Model-Adjusted Change from Baseline, Mean±SE	-0.07 ± 1.183	-4.58 ± 1.094	-9.66 ± 1.142	-11.41 ± 1.095
Difference from Placebo, Mean[2]	-	-4.51	-9.58	-11.34
95% CI[2]	-	-7.53, -1.48	-12.62, -6.55	-14.38, -8.30
p-value[3]	-	0.0037	<0.0001	<0.0001

Data Source: Table 7.07
1. Number of subjects with a value at baseline and at specified visit (after LOCF).
2. Based on ANCOVA: Change=Treatment+center+baseline+disease history.
3. Based on Pairwise Comparisons.

Table 34: ABPM Mean Night DBP -Study 367

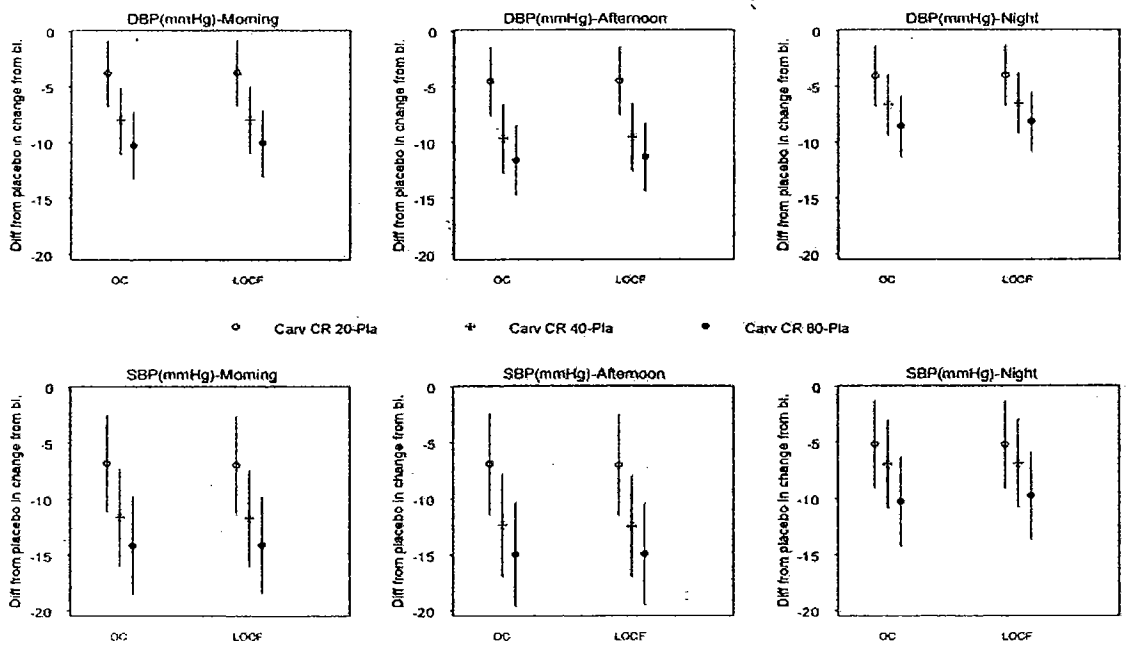
Table 32 shows Analysis of Change from Baseline in Mean Night DBP Measured by 24hr ABPM (ITTE Population with LOCF)

Night DBP, mmHG	Placebo N=76	Carvedilol CR 20mg N=82	Carvedilol CR 40mg N=76	Carvedilol CR 80mg N=86
n[1]	58	69	63	69
Baseline, Mean±SD	91.21 ± 6.704	90.33 ± 6.832	89.77 ± 5.964	90.01 ± 6.477
Study Endpoint, Mean±SD	91.24 ± 7.607	85.89 ± 7.923	83.33 ± 7.712	82.19 ± 8.041
Change from Baseline, Mean±SD	0.03 ± 6.335	-4.44 ± 6.078	-6.43 ± 6.985	-7.82 ± 8.789
Model-Adjusted Change from Baseline, LSMean±SE	-0.36 ± 1.047	-4.04 ± 0.966	-6.90 ± 1.010	-8.50 ± 0.968
Difference from Placebo, Mean[2]	-	-4.04	-6.54	-8.15
95% CI[2]	-	-6.71, -1.37	-9.23, -3.85	-10.85, -5.45
p-value[3]	-	0.0032	<0.0001	<0.0001

Data Source: Table 7.09

1. Number of subjects with a value at baseline and at specified visit (after LOCF).
2. Based on ANCOVA: change=treatment+center+baseline+disease history.
3. Based on pairwise comparisons.

Figure 9 : ABPM- morning, afternoon and night - study 367



Above: The 95% confidence intervals associated with the mean change from baseline in mean morning, afternoon and night SBP and DBP are shown graphically in Figure above

Morning, Afternoon and Night SBP - ABPM

Mean changes from baseline in SBP measured by 24hr ABPM at the end of up-titration were similar in the morning, afternoon and at night for subjects who received carvedilol CR (mean reduction in SBP increased with dose) (Tables 35-37). As observed for DBP, the mean reduction from baseline in SBP for all three carvedilol CR doses was statistically significant compared to the change from baseline for the placebo group throughout the 24hr period. In the morning, afternoon and at night, the mean reduction in SBP increased with carvedilol CR dose.

Table 35: Analysis of Change from Baseline in Mean Morning SBP Measured by 24hr ABPM (ITTE Population with LOCF)-367

Morning SBP, mmHg	Placebo N=76	Carvedilol CR 20mg N=82	Carvedilol CR 40mg N=76	Carvedilol CR 80mg N=86
n[1]	58	69	63	69
Baseline, Mean±SD	151.38 ± 10.610	152.32 ± 13.035	151.80 ± 12.600	151.60 ± 10.728
Study Endpoint, Mean±SD	151.68 ± 13.313	145.09 ± 14.033	140.49 ± 13.850	138.36 ± 12.281
Change from Baseline, Mean±SD	0.30 ± 11.355	-7.23 ± 12.667	-11.32 ± 11.378	-13.24 ± 11.826
Model-Adjusted Change from Baseline, Mean±SE	-0.74 ± 1.683	-7.73 ± 1.556	-12.48 ± 1.627	-14.86 ± 1.559
Difference from Placebo, Mean[2]	-	-6.98	-11.73	-14.12
95% CI[2]	-	-11.28, -2.68	-16.06, -7.41	-18.44, -9.79
p-value[3]	-	0.0016	<0.0001	<0.0001

Data Source: Table 7.11

1. Number of subjects with a value at baseline and at specified visit (after LOCF).
2. Based on ANCOVA: change=treatment+center+baseline+disease history.
3. Based on pairwise comparisons.

Table 36: Change from baseline in mean afternoon SBP by 24 hr ABPM-367

Table 28 Analysis of Change from Baseline in Mean Afternoon SBP Measured by 24hr ABPM (ITTE Population With LOCF)

Afternoon SBP, mmHg	Placebo N=76	Carvedilol CR 20mg N=82	Carvedilol CR 40mg N=76	Carvedilol CR 80mg N=86
n[1]	58	69	63	69
Baseline, Mean±SD	151.14 ± 10.446	149.63 ± 11.230	148.87 ± 11.297	148.61 ± 11.099
Study Endpoint, Mean±SD	150.35 ± 12.266	142.43 ± 13.395	137.10 ± 13.672	134.93 ± 13.970
Change from Baseline, Mean±SD	0.21 ± 10.741	-7.20 ± 11.352	-11.77 ± 12.594	-13.68 ± 13.684
Model-Adjusted Change from Baseline, LSMean±SE	-0.45 ± 1.755	-7.49 ± 1.623	-12.91 ± 1.696	-15.40 ± 1.629
Difference from Placebo, Mean[2]	-	-7.04	-12.46	-14.95
95% CI[2]	-	-11.52, -2.56	-16.96, -7.96	-19.47, -10.42
p-value[3]	-	0.0022	<0.0001	<0.0001

Data Source: Table 7.13

1. Number of subjects with a value at baseline and at specified visit (after LOCF).
2. Based on ANCOVA: change=treatment+center+baseline+disease history.
3. Based on pairwise comparisons.

Table 37: Change from baseline in mean night SBP by 24 hr ABPM-367

Table 29 Analysis of Change from Baseline in Mean Night SBP Measured by 24hr ABPM (ITTE Population With LOCF)

Night SBP, mmHg	Placebo N=76	Carvedilol CR 20mg N=82	Carvedilol CR 40mg N=76	Carvedilol CR 80mg N=86
n[1]	58	69	63	69
Baseline, Mean±SD	142.18 ± 10.341	142.46 ± 12.742	141.74 ± 11.596	140.98 ± 11.551
Study Endpoint, Mean±SD	142.15 ± 12.546	136.61 ± 12.842	134.46 ± 13.494	131.99 ± 13.696
Change from Baseline, Mean±SD	-0.03 ± 9.076	-5.85 ± 8.241	-7.28 ± 10.931	-8.99 ± 12.697
Model-Adjusted Change from Baseline, LSMean±SE	-0.77 ± 1.516	-5.99 ± 1.403	-7.66 ± 1.465	-10.55 ± 1.411
Difference from Placebo, Mean[2]	-	-5.22	-6.89	-9.78
95% CI[2]	-	-9.09, -1.35	-10.78, -3.00	-13.69, -5.87
p-value[3]	-	0.0085	<0.0006	<0.0001

Data Source: Table 7.15
1. Number of subjects with a value at baseline and at specified visit (after LOCF).
2. Based on ANCOVA: change=treatment+center+baseline+disease history.
3. Based on pairwise comparisons.

1.3.3 Safety

Extent of Exposure

The mean number of days of exposure to study medication was similar between the treatments (Table 38). The majority of subjects were exposed to study medication for 11 to 17 days; the mean duration of total exposure was 28.3 days with a minimum exposure of 1 day and a maximum of 51 days (Table 39).

Table 38: Extent of Exposure - ITT safety population

Table 26 Extent of Exposure (ITT Safety Population)

Subject Exposure, Days, n (%)	COREG IR BID N=187	carvedilol CR UID N=187
≤10	5 (2.7)	2 (1.1)
11-17	163 (87.2)	172 (92)
18-24	17 (9.1)	4 (2.1)
24-35	1 (0.5)	0
>35	1 (0.5)	0
Missing	0	9 (4.8)
Mean	15.82	14.10
SD	3.31	1.67
Median	16.00	14.00
Min.	1	1
Max.	38	22
Total Exposure in Subject Years	8.1	6.87

Data Source: Table 9.01

Table 39: The mean number of days of exposure to study drug-Study 367
The mean number of days of exposure to study drug was similar in all groups.

	Number (%) of Subjects				
	Placebo	Carvedilol CR			Total
Subject Exposure (days)	(N=84)	20mg (N=87)	40mg (N=78)	80mg (N=88)	N=337
≤14 [n (%)]	7 (8)	5 (6)	1 (1)	4 (5)	17(5)
15-28	5 (6)	3 (3)	2 (3)	4 (5)	14 (4)
29-56	40 (48)	30 (34)	40 (51)	42 (48)	152(45)
57-84	32 (38)	49 (56)	35 (45)	38 (43)	154(46)
Mean±SD	49.75±17.254	54.06±15.541	54.95±11.635	53.56±14.922	53.06±15.097
Median	56	57	56	56	56
Minimum-maximum	1-84	1-78	6-77	1-77	1-84
Total exposure in subject years	11.44	12.88	11.73	12.9	48.96

Data Source: Table 8.01

Overall, the most frequently reported AE in each of the carvedilol CR treatment groups was headache (6%, 9% and 7% of subjects in the carvedilol CR 20mg, 40mg and 80mg treatment groups, respectively) In the placebo group, headache and upper respiratory infection were equally frequent, each experienced by 6% of subjects. Dizziness was reported in only one subject (1%) in the placebo group, no subjects (0%) in the carvedilol CR 20mg group, one subject (1%) in the carvedilol CR 40mg group, and four subjects (5%) in the carvedilol CR 80mg group Table 40 summarizes adverse events for more than 2% in any treatment group.

Table 40: Adverse events for >2% in any treatment group-Study 367

AEs Reported for ≥2% of Subjects in Any Treatment Group					
	Number (%) of Subjects				
	Placebo	Carvedilol CR			
Preferred Term	(N=84)	20mg (N=87)	40mg (N=78)	80mg (N=88)	Total Carvedilol CR (N=253)
Up-Titration Phase					
Any Adverse Event	32 (38)	22 (25)	23 (29)	33 (38)	78 (31)
Headache	5 (6)	5 (6)	5 (6)	5 (6)	15 (6)
Fatigue	3 (4)	2 (2)	1 (1)	4 (5)	7 (3)
Dizziness	1 (1)	0	1 (1)	4 (5)	5 (2)
Cough	2 (2)	1 (1)	2 (3)	3 (3)	6 (2)
Nausea	0	0	1 (1)	3 (3)	4 (2)
Upper Respiratory Tract Infection	5 (6)	1 (1)	2 (3)	2 (2)	5 (2)
Nasopharyngitis	0	4 (5)	3 (4)	2 (2)	9 (4)
Influenza	1 (1)	0	0	2 (2)	2 (1)
Nasal Congestion	0	1 (1)	0	2 (2)	3 (1)
Paresthesia	0	0	1 (1)	2 (2)	3 (1)
Edema Peripheral	1 (1)	2 (2)	1 (1)	2 (2)	5 (2)
Depression	1 (1)	0	1 (1)	2 (2)	3 (1)
Sinus Congestion	0	0	0	2 (2)	2 (1)
Diarrhea	0	0	0	2 (2)	2 (1)
Dyspnea Exertional	2 (2)	0	0	0	0
Arthralgia	1 (1)	2 (2)	0	0	2 (1)
Insomnia	0	1 (1)	2 (3)	0	3 (1)
Hypertension	2 (2)	0	0	0	0
Down-Titration Phase					
Any Adverse Event	7 (8)	11 (13)	12 (15)	6 (7)	29 (11)
Headache	0	0	2 (3)	1 (1)	3 (1)
Peripheral Edema	0	2 (2)	1 (1)	0	3 (1)
ALT Increased	0	0	1 (1)	2 (2)	3 (1)

Few subjects were withdrawn for an AE (10 subjects). Hypertension related AEs were the most frequent to result in withdrawal overall; the preferred terms hypertension and hypertensive crisis together resulted in withdrawal of 3 subjects in the placebo group.

Table 41: Adverse events leading to withdrawal-Study 367

AEs Leading to Withdrawal				
	Placebo	Carvedilol CR		
Preferred Term	N=84	20mg N=87	40mg N=78	80mg N=88
Any Adverse Event	3 (4)	1 (1)	3 (4)	3 (3)
Fatigue	0	0	1 (1)	1 (1)
Non-cardiac chest pain	0	0	0	1 (1)
Edema peripheral	0	0	1 (1)	0
Hypertension	2 (2)	0	0	0
Hypertensive crisis	1 (1)	0	0	0
Myocardial infarction	0	0	1 (1)	0
Pneumonia	0	1 (1)	0	0
Headache	0	0	0	1 (1)
Depression	0	0	0	1 (1)
Proteinuria	0	0	1 (1)	0

Table 42: Summary of Treatment emergent adverse events in at least 2% of subjects in any treatment group-Study 367

Table 27 Summary of Treatment Emergent Adverse Events Occurring in at Least 3% of Subjects in Any Treatment Strata Regardless of Causality (ITT Safety Population)

	COREG IR BID				
Preferred Term, n (%)	**3.125mg N=38**	**6.25mg N=54**	**12.5mg N=51**	**25mg N=44**	**Total N=187**
Any Event	8 (21)	10 (19)	8 (16)	5 (11)	31 (17)
Dizziness	1 (3)	1 (2)	1 (2)	0	3 (2)
Toothache	2 (5)	0	0	0	2 (1)
Blood creatinine increased	1 (3)	0	0	1 (2)	2 (1)
Cardiac failure congestive	2 (5)	0	0	0	2 (1)
Nasopharyngitis	1 (3)	0	0	0	1 (<1)
Non-cardiac chest pain	1 (3)	0	0	0	1 (<1)
Edema peripheral	1 (3)	0	0	0	1 (<1)
Epistaxis	1 (3)	0	0	0	1 (<1)
	carvedilol CR UID				
Preferred Term, n (%)	**10mg N=38**	**20mg N=54**	**40mg N=51**	**80mg N=44**	**Total N=187**
Any Event	10 (26)	12 (22)	7 (14)	10 (23)	38 (20)
Dizziness	1 (3)	1 (2)	1 (2)	2 (5)	5 (3)
Headache	1 (3)	0	2 (4)	1 (2)	4 (2)
Non-cardiac chest pain	1 (3)	1 (2)	0	0	2 (1)
Diarrhea	1 (3)	0	1 (2)	0	2 (1)
Cardiac failure congestive	0	2 (4)	0	0	2 (1)
Coordination abnormal	1 (3)	0	0	0	1 (<1)
Diabetic gastroparesis	1 (3)	0	0	0	1 (<1)
Nausea	1 (3)	0	0	0	1 (<1)
Vomiting	1 (3)	0	0	0	1 (<1)
Sinusitis	1 (3)	0	0	0	1 (<1)
Cough	1 (3)	0	0	0	1 (<1)
Angina pectoris	1 (3)	0	0	0	1 (<1)
Bradycardia	1 (3)	0	0	0	1 (<1)
Hypoglycemia	1 (3)	0	0	0	1 (<1)
Anemia	1 (3)	0	0	0	1 (<1)
Hypotension	1 (3)	0	0	0	1 (<1)

Data Source: Tables 9.03

Table 43: Treatment Emergent AEs considered related for at least 2% in any treatment group-Study 367

Table 28 Summary of Emergent Adverse Events Considered Related by the Investigator in at least 2% of Subjects in Any Treatment Strata (ITT Safety Population)

	COREG IR BID				
Preferred Term n (%)	**3.125mg N=38**	**6.25mg N=54**	**12.5mg N=51**	**25mg N=44**	**Total N=187**
Any Event	0	3 (6)	2 (4)	0	5 (3)
Drug intolerance	0	1 (2)	0	0	1 (<1)
Fatigue	0	0	1 (2)	0	1 (<1)
Abdominal distention	0	1 (2)	0	0	1 (<1)
Fall	0	0	1 (2)	0	1 (<1)
Dizziness	0	1 (2)	0	0	1 (<1)
Rash	0	1 (2)	0	0	1 (<1)
	carvedilol CR UID				
Preferred Term n (%)	**10mg N=38**	**20mg N=54**	**40mg N=51**	**80mg N=44**	**Total N=187**
Any Event	2 (5)	3 (6)	3 (6)	4 (9)	12 (6)
Dizziness	1 (3)	0	1 (2)	1 (2)	3 (2)
Fatigue	0	1 (2)	1 (2)	1 (2)	3 (2)
Cardiac failure congestive	0	1 (2)	0	0	1 (<1)
Headache	0	0	1 (2)	0	1 (<1)
Dyspnea	0	0	0	1 (2)	1 (<1)
Dyspnea, exacerbated	0	0	1 (2)	0	1 (<1)
Bradycardia	1 (3)	0	0	0	1 (<1)
Abdominal discomfort	0	1 (2)	0	0	1 (<1)
Insomnia	0	0	0	1 (2)	1 (<1)
Hypotension	1 (3)	0	0	0	1 (<1)

Data Source: Tables 9.04

Serious Adverse Events (SAE)

Three SAEs were reported during the treatment phase of the study. One subject in the placebo group had a hypertensive crisis (considered by the investigator to be related to study medication), one subject in the carvedilol CR 20mg group had pneumonia (unrelated to study medication) and one subject in the carvedilol CR 40mg group had a myocardial infarction (unrelated to study medication) all of which were reported as SAEs. In each case the subject was withdrawn from the study. There were no fatal events during the study considered to be drug related.

Fatal Events

There were 3 fatal events reported for this study none of which was considered to be related to the study drug as determined by the investigator:

- Subject 1119 in the COREG 12.5mg/40mg dose group died of intracranial hemorrhage 27 days after the 1st dose of 40mg carvedilol CR.
- Subject 1278 in the COREG 25mg/80mg dose group died of respiratory distress 58 days after the 1st dose of 25mg COREG IR and 43 days after withdrawing from the study due to a cerebrovascular accident.
- Subject 576 died of complications due to an intervertebral disc disorder prior to receiving any study medication.

Non-Fatal Events

Four subjects (2%) during the COREG IR treatment period and 5 subjects (3%) during the carvedilol CR treatment period experienced non-fatal emergent SAEs (Table 44). None of the on-therapy non-fatal SAEs occurred in the COREG IR 6.25mg and 25mg or carvedilol CR 40mg dosage groups. One subject during the carvedilol CR 20 period, Subject 733, experienced worsening cardiac failure congestive and was subsequently withdrawn from the study. The investigator determined that this event was related to the study medication. Subject 1105 withdrew consent prior to receiving study medication due to pneumonia. Subject 1878 experienced an SAE of anemia during the carvedilol CR 10mg period also experienced cardiac failure congestive 5 days after the end of treatment. The investigator determined this was not related to the study medication. Subject 1658 experienced an SAE of a cerebrovascular accident during the COREG IR 12.mg period which was determined by the investigator not to be related to the study medication.

Table 44: Summary of serious Non Fatal emergent AEs- ITT safety population-Study 367

Table 29 Summary of Serious Non-Fatal Emergent Adverse Events (ITT Safety Population)

COREG IR Period					
Preferred Term, n (%)	**3.125mg N=38**	**6.25mg N=54**	**12.5mg N=51**	**25mg N=44**	**Total N=187**
Any Event	2 (5)	0	2 (4)	0	4 (2)
Cardiac failure congestive	2 (5)	0	0	0	2 (1)
Non-cardiac chest pain	1 (3)	0	0	0	1 (<1)
Gastroenteritis	0	0	1 (2)	0	1 (<1)
Cerebrovascular accident	0	0	1 (2)	0	1 (<1)
carvedilol CR Period					
Preferred Term, n (%)	**10mg N=38**	**20mg N=54**	**40mg N=51**	**80mg N=44**	**Total N=187**
Any Event	2 (5)	2 (4)	0	0	5 (3)
Cardiac failure congestive	0	2 (4)	0	0	2 (1)
Angina pectoris	1 (3)	0	0	0	1 (<1)
Ventricular tachycardia	0	0	0	1 (2)	1 (<1)
Anemia	1 (3)	0	0	0	1 (<1)

Data Source: Tables 9.05

Adverse Events Leading to Premature Discontinuation of Investigational Product and/or Study

Five subjects were withdrawn due to AEs; however for 1 subject the AE leading to withdrawal start date was after the last day of study medication.

Three subjects (1.6%) in the COREG 6.25mg/20mg dose group were withdrawn. Subject 230 was withdrawn 2 days after the 1st dose of 6.25mg COREG IR due to abdominal distension and drug intolerance of mild intensity determined by the investigator to be related to the study medication. Subject 1452 was withdrawn 7 days after the 1st dose of 6.25mg COREG IR due to a rash of moderate intensity and was determined by the investigator to be related to the study medication. Subject 733 was withdrawn 29 days after the 1st dose of 20mg carvedilol CR due to congestive cardiac failure of moderate intensity and was determined by the investigator to be related to the study medication

Subject 1119 was withdrawn due to intracranial hemorrhage of severe intensity 27 days after the 1st dose of 40mg carvedilol CR and was determined by the investigator not to be related to the study medication.

Subject 1278 was withdrawn 13 days after the 1st dose of 25mg ~~COREG IR~~ due to a cerebrovascular accident of severe intensity and was determined by the investigator not to be related to the study medication.

Laboratory Values of Potential Clinical Concern

Laboratory values considered to be clinically significant by the investigator were to be recorded as AEs in the eCRF. The proportions of subjects with on-therapy laboratory values of potential clinical concern were low and generally similar between treatment periods. A summary of the number of subjects with laboratory values of potential clinical concern is presented in Table 30.

Summary statistics of change from baseline in laboratory evaluations and the summary of laboratory evaluations outside the reference range by heart failure strata (mild, moderate, or severe) and asymptomatic post MI LVD are shown in Tables 45.

Table 45: Summary of Laboratory values of clinical concern - Study 367

Table 30 Summary of Laboratory Values of Potential Clinical Concern (ITT Safety Population)

COREG IR BID Period (Week 2)						
Lab Test	**Strata**	**3.125mg N=38**	**6.25mg N=54**	**12.5mg N=51**	**25mg N=44**	**Total N=187**
Calcium (mmol/L)	n	34	45	42	35	156
	Low	0	0	0	1 (3)	1 (<1)
Chloride (mmol/L)	n	34	48	44	36	162
	High	0	0	1 (2)	0	1 (<1)
Creatinine (µmol/L)	n	34	48	44	36	162
	High	1 (3)	0	0	1 (3)	2 (1)
Hemoglobin (g/L)	n	36	51	43	39	169
	Low	2 (6)	0	2 (5)	0	4 (2)
Hematocrit (%)	n	36	51	43	39	169
	Low	2 (6)	0	3 (7)	1 (3)	6 (4)
Sodium (mmol/L)	n	34	48	44	36	162
	Low	0	0	1 (2)	0	1 (<1)
Neutrophils (GI/L)	n	36	51	43	39	169
	Low	0	0	1 (2)	1 (3)	2 (1)
Platelets (GI/L)	n	36	51	42	36	165
	High	0	1 (2)	0	0	1 (<1)
	Low	0	0	0	1 (3)	1 (<1)
Urea (mmol/L)	n	34	48	44	36	162
	High	3 (9)	4 (8)	7 (16)	6 (17)	20 (12)
carvedilol CR UID Period (Week 4)						
Lab Test	**Strata**	**10mg N=38**	**20mg N=54**	**40mg N=51**	**80mg N=44**	**Total N=187**
Creatinine (µmol/L)	n	30	48	39	35	152
	High	2 (7)	0	0	1 (3)	3 (2)
Hemoglobin (G/L)	n	34	49	45	43	171
	Low	2 (6)	0	2 (4)	2 (5)	6 (4)
Hematocrit (%)	n	34	49	45	43	171
	Low	2 (6)	0	2 (4)	2 (5)	6 (4)
Potassium (mmol/L)	n	30	47	36	31	144
	High	1 (3)	2 (4)	1 (3)	0	4 (3)
Sodium (mmol/L)	n	30	48	39	35	152
	Low	0	0	1 (3)	0	1 (<1)
Neutrophils (GI/L)	n	34	49	45	43	171
	Low	0	0	1 (2)	0	1 (<1)
Platelets (GI/L)	n	34	49	43	41	167
	Low	1 (3)	0	1 (2)	1 (2)	3 (2)
Urea (mmol/L)	n	30	48	39	35	152
	High	5 (17)	3 (6)	4 (10)	8 (23)	20 (13)
White blood cell count (GI/L)	n	34	49	45	43	171
	Low	1 (3)	0	0	0	1 (<1)

Data Source: Table 9.17

ECG Findings

The majority of subjects, based on all strata at Week -1 and Week 0 did not have clinically significant abnormal ECG findings (Table 46). Twelve subjects (6%) at Week -1 and 3 subjects (2%) at Week 0 had abnormal clinically significant ECG findings.

Table 46: ECG findings at baseline-367

ECG finding, n/*N* (%)	Placebo (N=84)	Carvedilol CR 20mg (N=87)	Carvedilol CR 40mg (N=78)	Carvedilol CR 80mg (N=88)
Baseline				
Normal	48/84 (57)	55/86 (63)	47/77 (60)	56/88 (64)
Abnormal, not clinically significant	36/84 (43)	30/86 (34)	29/77 (37)	30/88 (34)
Abnormal, clinically significant	0	1/86 (1)	1/77 (1)	2/88 (2)
Any visit post-baseline				
Normal	45/76 (54)	49/80 (56)	46/70 (59)	39/80 (44)
Abnormal, not clinically significant	31/76 (37)	31/80 (36)	23/70 (29)	41/80 (47)
Abnormal, clinically significant	0	0	1 (1)	0

Data Source: Table 8.31
n/*N*=number of subjects with normal or abnormal readings/number of subjects with an ECG reading at that visit

Table 47: Summary of abnormal clinically significant ECG findings - ITT population - Study 367

Table 31 Summary of Abnormal/Clinically Significant ECG Findings (ITT Safety Population)

ECG Finding, n (%)	3.125mg/ 10mg N=38	6.25mg/ 20mg N=54	12.5mg/ 40mg N=51	25mg/ 80mg N=44	Total N=187
Week -1					
n	36	52	51	44	183
Normal	4 (11)	2 (4)	4 (8)	3 (7)	13 (7)
Abnormal, not clinically significant	30 (79)	45 (83)	44 (86)	39 (89)	158 (84)
Abnormal, clinically significant	2 (5)	5 (9)	3 (6)	2 (5)	12 (6)
Week 0					
n	16	17	18	11	62
Normal	0	1 (2)	2 (4)	0	3 (2)
Abnormal, not clinically significant	15 (39)	14 (26)	16 (31)	11 (25)	56 (30)
Abnormal, clinically significant	1 (3)	2 (4)	0	0	3 (2)

Data Source: Table 9.24

A summary of ECG findings of potential clinical concern by heart failure strata (mild, moderate, or severe) and asymptomatic post MI LVD is shown in Table 47. ////////////////////////

Table 48: Summary of vital signs of potential clinical concern- ITT - Study 367

Table 32 Summary of Vital Signs of Potential Clinical Concern (ITT Safety Population)

COREG IR BID Period (Week 2)							
Vital Sign	**Subject Position**	**Category**	**3.125mg N=38**	**6.25mg N=54**	**12.5mg N=51**	**25mg N=44**	**Total N=187**
Diastolic BP (mmHg)	Sitting	n	38	53	48	42	181
		High	0	1 (2)	0	0	1 (<1)
	Standing	n	36	49	47	41	173
		High	0	1 (2)	0	0	1 (<1)
Systolic BP (mmHg)	Sitting	n	38	53	48	42	181
		High	0	0	0	1 (2)	1 (<1)
Heart Rate (beats/minute)	Sitting	n	38	53	48	42	181
		Low	0	1 (2)	0	0	1 (<1)
	Standing	n	36	49	47	41	173
		Low	1 (3)	0	1 (2)	0	2 (1)
carvedilol CR UID Period (Week 4)							
Vital Sign	**Subject Position**	**Category**	**10mg N=38**	**20mg N=54**	**40mg N=51**	**80mg N=44**	**Total N=187**
Heart Rate (beats/minute)	Sitting	n	36	49	46	42	173
		Low	0	1 (2)	0	1 (2)	2 (1)
	Standing	n	35	49	42	37	163
		Low	1 (3)	0	0	0	1 (<1)

Data Source: Table 9.21

Safety Conclusion(s)

• Carvedilol, when administered as either immediate release or controlled release formulations, was generally safe and well-tolerated in this study.

• In these subjects, who received COREG IR followed by carvedilol CR, the observed safety profiles of the two formulations were similar.

• Carvedilol CR, alone **or in combination with other therapies,** at doses of 20mg, 40mg, and 80mg once daily causes a clinically and statistically significant reduction in blood pressure compared to placebo.

• The effects of once daily dosing of carvedilol CR on blood pressure last for the entire 24 hour period.

• Carvedilol CR at doses of 20mg, 40mg, or 80mg once daily was safe and well-tolerated.

• The results of this study support the use of carvedilol CR as a once daily treatment for essential hypertension.

1.3.4 Dosing Regimen and Administration

Dosages and Administration
Subjects were randomized to one of three doses of once-daily carvedilol CR (20mg, 40mg or 80mg) or placebo for six weeks of treatment followed by a two-week down-titration phase Thus, subjects received blinded study medication for a total of eight weeks.

Subjects assigned to one of the three carvedilol CR arms started dosing at 20mg UID. At two-week intervals, subjects were up-titrated to their assigned randomized dose or the highest tolerated dose if the randomized target could not be reached. At the end of six weeks of treatment, subjects were down-titrated over two weeks to 20mg UID. Subjects randomized to 20mg carvedilol CR UID or placebo continued to take 20mg or placebo during the down-titration phase. At the end of the two week down-titration phase, double blind study medication was discontinued for all subjects.

Carvedilol will be administered orally as the commercial formulation (COREG immediate release; Regimen A) and the new modified release formulation (carvedilol phosphate MR Capsules; Regimen B). Four dose levels of each study medication formulation will be employed in the Treatment Phase i.e. COREG IR 3.125 mg bid; or carvedilol phosphate MR 10 mg uid; COREG IR 6.25 mg bid or carvedilol phosphate MR 20 mg uid; COREG IR 12.5 mg bid or carvedilol phosphate MR 40 mg uid; COREG IR 25 mg bid or carvedilol phosphate MR 80 mg uid).

Patients are to be instructed to take study medication with food throughout the study with the morning dose being taken between 7-10 am and at that same time each day ± 30 minutes, thereafter. Patients are to be instructed also to not drink grapefruit juice or consume grapefruit during the entire study dosing period. The evening dose for COREG IR should be taken approximately 12 hours after the morning dose that day.

Many eligible patients will already be receiving COREG IR for their heart failure or post MI condition. These patients must have been receiving this dose for at least two consecutive weeks prior to Screening. These patients will begin the study receiving the same dose of COREG IR study medication that they were receiving just prior to entering the trial.

Patients may also enter the study if they are not receiving any beta blocker for heart failure or post-MI treatment. In the latter instance, chronic heart failure patients will begin the study by receiving COREG IR 3.125 mg bid, an initiating dose of COREG IR, while post MI patients will begin the study with COREG IR 6.25 mg bid. NOTE: Patients deemed by the investigator not to tolerate a 3.125 mg bid dose of COREG following the first or repeated doses accompanied by appropriate background medication changes will be withdrawn.

Dose Rationale
The carvedilol CR doses (20mg, 40mg, and 80mg UID) were selected to provide exposure levels of carvedilol CR that correspond to those achieved following administration of the previously approved carvedilol IR tablets (6.25mg, 12.5mg, and 25mg BID, respectively) for the hypertension indication.

1.3.5 Drug-Drug Interactions

Pharmacokinetic Drug-Drug Interactions: Since carvedilol undergoes substantial oxidative metabolism, the metabolism and pharmacokinetics of carvedilol may be affected by induction or inhibition of cytochrome P450 enzymes.

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 (1000 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.

1.3.6 Special Populations

Elderly: Plasma levels of carvedilol average about 50% higher in the elderly compared to young subjects.

Hepatic Impaired Patients: Compared to healthy subjects, patients with cirrhotic liver disease exhibit significantly higher concentrations of carvedilol (approximately 4- to 7-fold) following single-dose therapy.

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

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

See Clinical pharmacology review for additional information.

2 INTRODUCTION AND BACKGROUND

Chronic heart failure is an important contributing cause of cardiovascular morbidity and mortality. It is a common reason for hospital admissions in the Western World and thus, a major cost factor in total health care in developed countries. Several classes of therapeutic agents are used, often in combination, in the long term management of chronic heart failure. In recent years, the use of a variety of beta adrenergic receptor blocking agents have been demonstrated to be effective in reducing mortality and morbidity in mild to severe chronic heart failure patients [Packer, 1996a; Colucci, 1996; Bristow, 1996; Packer, 1996b; Packer, 2001; Fowler, 2002; Packer, 2002; MERIT-HF Study Group, 1999; MERIT-HF Study Group, 2000; CIBIS –II Investigators and Committees, 1999].

Carvedilol (COREG™) is a competitive adrenoreceptor antagonist, which inhibits activity not only at ß1- and ß2-adrenergic receptors but also a1-adrenergic receptors [Ruffle, 1997]. In addition to nonselective ß and a1 blocking properties, COREG exhibits a number of ancillary pharmacological activities, including antioxidant effects, inhibition of vascular smooth muscle proliferation, and calcium channel blocking activity [Ruffolo, 1997; Feuerstein, 1995; Feuerstein, 1997].

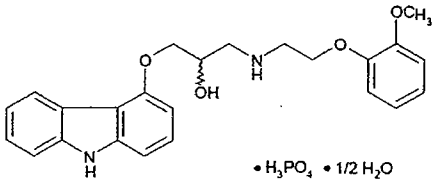
COREG has been demonstrated in well-controlled clinical trials to be effective in reducing blood pressure in essential hypertensive patients [Moser, 1998; Moser, 2000]. The mechanism by which ß-blockade produces an antihypertensive effect has not been established. COREG possesses vascular a1-receptor blockade which results in dilation of peripheral arterioles and a decrease in total peripheral vascular resistance [McTavish, 1993; Lessem, 1993]. Simultaneous ß-receptor blockade (ß1 and ß2) is generally believed to enhance the antihypertensive action of COREG produced via vasodilatation by mitigating some of the a1 receptor-blockade related actions such as reflex heart rate increases and activation of the renin-angiotensin-aldosterone system [Feuerstein, 1995]. This complementary action of a1-mediated vasodilatation and nonselective ß-receptor blockade has been demonstrated as a rational and successful approach for therapeutic management of essential hypertension [Moser, 1998].

The immediate-release (IR) formulation of COREG, administered twice daily, is approved and marketed in the United States as well as other countries under different brand names for the treatment of essential hypertension, alone or in combination with other hypertensive agents. It is also indicated in the US to improve survival in patients with mild to severe heart failure of ischemic or cardiomyopathic origin. In addition, COREG is approved for use in the US to reduce cardiovascular mortality in clinically stable subjects who have survived the acute phase of myocardial infarction and have a left ventricular ejection fraction of =40% (with or without symptomatic heart failure).

An effective once daily formulation for COREG in the long-term management of essential hypertension would represent an important advance in how this antihypertensive agent could be utilized in this patient population.

2.1 PRODUCT INFORMATION

The investigational product in this study is carvedilol phosphate MR capsules.

Structural Formula	
Molecular Formula	$C_{24}H_{26}N_2O_4 \bullet H_3PO_4 \bullet ½ H_2O$
Molecular Weight	406.5 g/mol (carvedilol free base)
	[redacted]
	513.5 g/mol (carvedilol phosphate hemihydrate)
Isomerism and Stereoisomerism	The drug substance possesses one chiral center and therefore has two potential enantiomers. SK&F-105517-D is being developed as a racemate.

Carvedilol (SK&F 105517) is (±)-1-(carbazol-4-yloxy)-3[[2-(o-methoxy-phenoxy) ethyl] amino]-2-propanol. The Carvedilol Phosphate [redacted] Modified Release (MR) Capsules (10 mg, 20 mg, 40 mg, 80 mg) contain drug layered carvedilol phosphate [redacted] IR microparticles, [redacted], and carvedilol phosphate [redacted] MR microparticles in an active drug content ratio of [redacted] and in a combined quantity sufficient to provide the label claim strength expressed in carvedilol phosphate [redacted]

Carvedilol will be administered orally as the commercial formulation (COREG immediate release; Regimen A) and the new modified release formulation (carvedilol phosphate MR Capsules; Regimen B). Four dose levels of each study medication formulation will be employed in the Treatment Phase i.e. COREG IR 3.125 mg bid; or carvedilol phosphate MR 10 mg uid; COREG IR 6.25 mg bid or carvedilol phosphate MR 20 mg uid; COREG IR 12.5 mg bid or carvedilol phosphate MR 40 mg uid; COREG IR 25 mg bid or carvedilol phosphate MR 80 mg uid).

2.2 Currently Available Treatment for Indication - Hypertension

There are several treatments available for the treatment of hypertension. These include different classes of drugs including ARBS, β-blockers, thiazide, angiotensin-converting enzyme (ACE) inhibitors or calcium channel blockers (Hansson et al 1999). A number of other trials have also evaluated clinical outcomes in hypertensive patients treated with diuretics plus beta-blockers including the North American ALLHAT trial. This 33,357 patient trial found that a regimen

based upon the thiazide diuretic chlorthalidone, and which allowed for the addition of a beta-blocker as well as other agents, was as effective as antihypertensive regimens based on ACE inhibitors or calcium channel blockers in reducing the risk for fatal/nonfatal myocardial infarction (ALLHAT Officers and Coordinators 2002).

2.3 Availability of Proposed Active Ingredient in the United States

All ingredients for this product are available in the United States.

2.4 Important Issues with Pharmacologically Related Products

Not applicable. There are no important issues with pharmacologically related products known to this reviewer.

2.5 Pre-submission Regulatory Activity

There were several meetings between the Agency and the sponsor. The minutes of these meetings are available in the Division files. The Agency suggested including an arm of the MR formulation bid in the study but this was not effected. The Agency believes that it is important to understand the relationship between plasma concentrations of carvedilol and effect as measured by beta blockade along with concentrations achieved with the two formulations. To this end the PK profile of the MR formulation will be very useful to assess the beta blockade effect. The Agency believed that PK/PD effects of the drug with several doses could be done in healthy individuals as they are more likely to give beta measures of beta blockade. The Agency encouraged the sponsor to carry out PK studies in patients with heart failure and to consult with clinical pharmacology reviewers regarding this aspect of development. The Division reminded the sponsor of analyses of patients with 2D6 as previously discussed.

Other Relevant Background Information

See Section 8.8

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

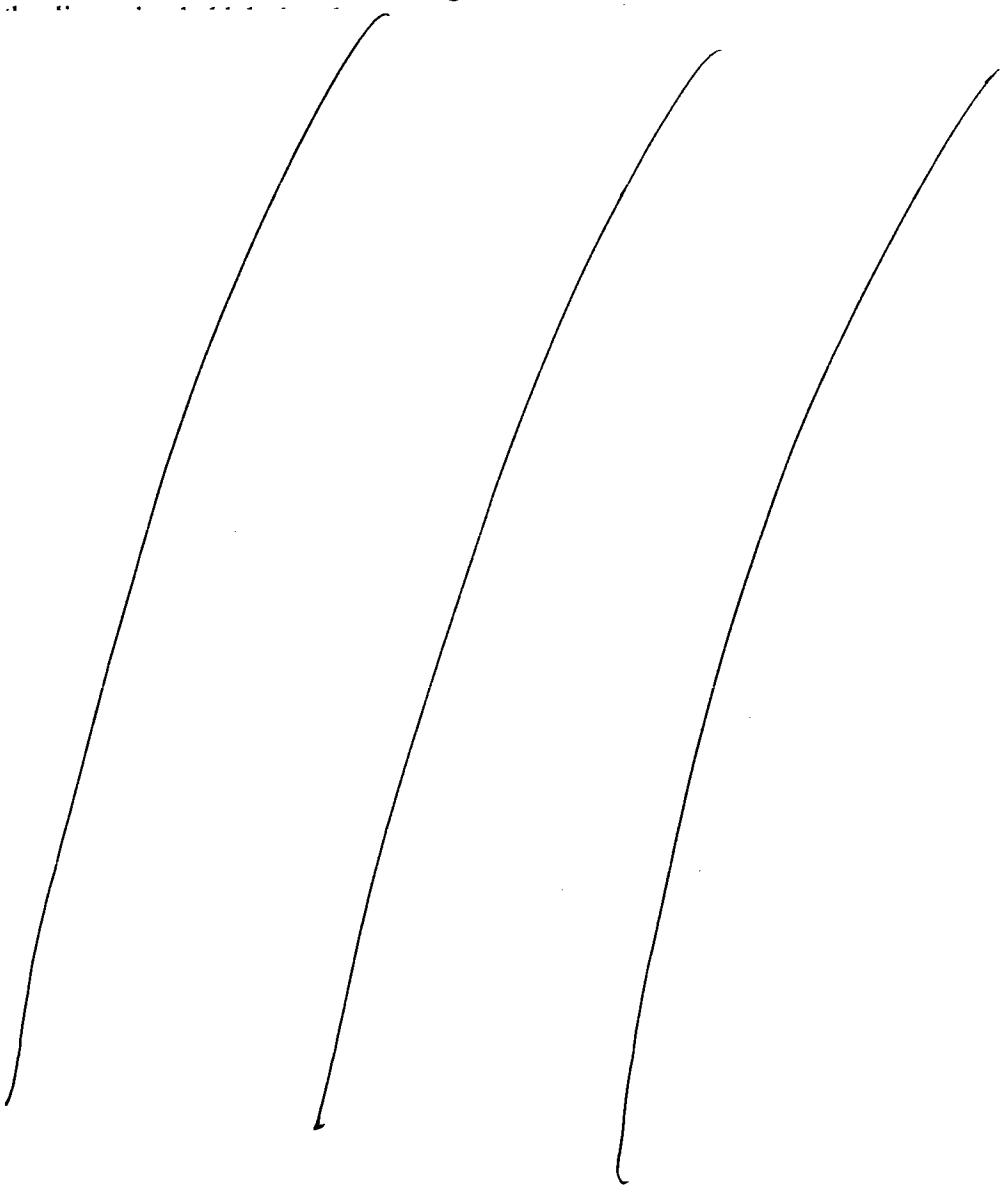
Not applicable.

3.2 Clinical Pharmacology/Biopharm

Based on pre-submission regulatory activities, the sponsor had been in consultation with clinical pharmacology Division of the Agency. This reviewer has had discussions with this division and

a draft review from Dr Christine Garnett of the clinical pharmacology division is appended below, unedited. This was discussed by both reviewers.

Draft Review from Dr C Garnett 23 Aug 2006



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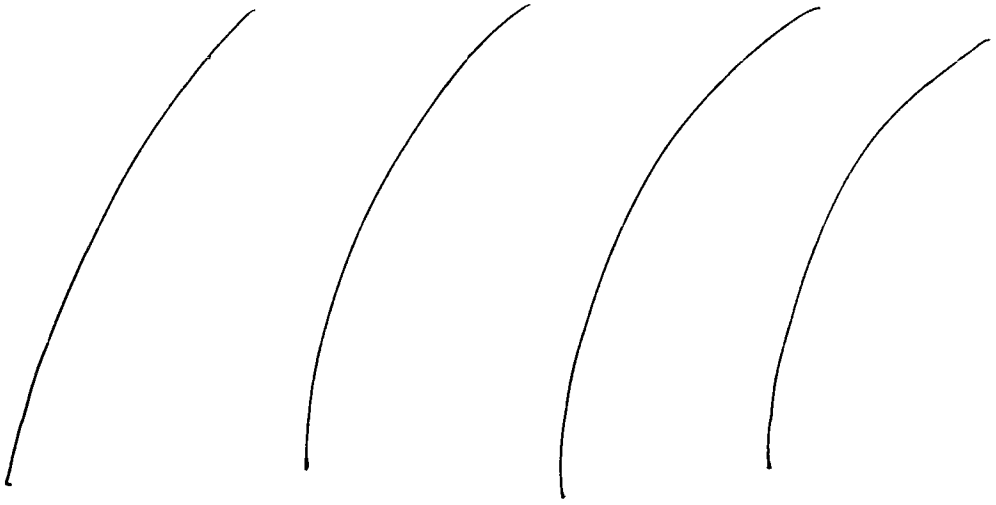

3.3 Animal Pharmacology/Toxicology

The acute oral LD50 doses in male and female mice and male and female rats are over 8000 mg/kg. Overdosage may cause severe hypotension, bradycardia, cardiac insufficiency, cardiogenic shock, and cardiac arrest. Respiratory problems, bronchospasms, vomiting, lapses of consciousness, and generalized seizures may also occur.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical data

The sources of data are from
IND 27,114 and 70,154
NDA 20,297 and 22, 012 from the EDR.

4.2 Tables of Clinical Studies

Table 1 Listing of Clinical Studies

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects: Gender M/F: Mean Age (Range)	Treatment Details (Drug/Dose/Form/ Route/Frequency/ Duration)	Study Status: Type of Report	Location of Study Report
SK&F-105517/376	Pharmacokinetic	PK following fasting conditions and high fat meal	Open-label, single-dose, four-period, period-balanced study	Healthy volunteers	22; 18M, 4F; 35 (19-53)	Carvedilol CR; 80 mg; capsule; oral; QD; one day	Completed; Final	m5.3.1.1.1
SK&F-105517/393	Pharmacokinetic	Relative Bioavailability	Open-label, single dose, randomized, three period crossover study	Healthy volunteers	33; 18M, 15F; 32 (21-51)	COREG IR; 25 mg; tablet; oral; Q12H; one day 6 various combinations of carvedilol IR, MR capsule; oral; QD; one day	Completed; Final	m5.3.1.1.2
SK&F-105517/903	Pharmacokinetic	Dose Proportionality	Non-randomized, open-label, single dose, dose-rising, four period study	Healthy volunteers	40; 22M, 18F; 33 (18-54)	Carvedilol CR; 10, 20, 40 and 80 mg; capsule; oral; QD; one day	Completed; Final	m5.3.1.1.3

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects: Gender M/F: Mean Age (Range)	Treatment Details (Drug/Dose/Form/ Route/Frequency/ Duration)	Study Status: Type of Report	Location of Study Report
SK&F-105517/906	Pharmacokinetic	Comparison of PK following morning and evening dosing	Open-label, single dose partially randomized, three-period, crossover study	Healthy volunteers	22; 15M, 7F; 32 (18-50)	Carvedilol CR; 80 mg; capsule; oral; QD; one day	Completed; Final	m5.3.1.1.4
SK&F-105517/907	Pharmacokinetic	Determine relative bioavailability and dose proportionality of two MR formulations of carvedilol phosphate at steady state	Randomized, repeat dose, open-label, parallel group study	Hypertensive patients	35; 17M, 18F; 50 (39-60)	COREG IR; 6.25, 12.5 and 25 mg; tablet; oral; Q12H; 7 days (25 mg), 4 days (12.5 mg) and 3 days (6.25 mg) MR carvedilol; 16.25, 32.5 and 65 mg; tablet; oral; QD; 7 days (per dose level) MR carvedilol; 15, 30, and 60 mg; capsule; oral; QD; 7 days (per dose level)	Completed; Final	m5.3.1.1.5

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects: Gender M/F: Mean Age (Range)	Treatment Details (Drug/Dose/Form/ Route/Frequency/ Duration)	Study Status: Type of Report	Location of Study Report
SK&F-105517/399	Pharmacokinetic	Dose proportionality Relative Bioavailability	Open-label, single dose, randomized, four-period, crossover study	Healthy volunteers	40; 26M, 14F; 32 (18-53)	COREG IR; 25 mg; tablet; oral; Q12H; one day carvedilol phosphate; 12 mg; capsule; oral; Q12h; one day CR carvedilol phosphate; 10, 20 and 40 mg; capsule; oral; QD; one day CR carvedilol phosphate; 10, 20 and 40 mg; capsule; oral; QD; one day	Completed; Final	m5.3.1.1.6

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects: Gender M/F: Mean Age (Range)	Treatment Details (Drug/Dose/Form/ Route/Frequency/ Duration)	Study Status: Type of Report	Location of Study Report
SK&F-105517/402	Pharmacokinetic	Dose proportionality Relative bioavailability	Partially randomized (with respect to COREG IR), open-label, dose-rising, 6 period cross-over study	Healthy volunteers	26; 17M, 9F; 33 (18-54)	COREG IR; 25 mg; tablet; oral; Q12H; one day carvedilol phosphate; 12 mg; capsule; oral; Q12h; one day CR carvedilol phosphate; 15, 30 and 60 mg; capsule; oral; QD; one day IR carvedilol + CR carvedilol phosphate; 60 mg (MR); single capsule (containing IR and CR); oral; QD; one day	Completed; Final	m5.3.1.1.7
SK&F-105517/386	Pharmacokinetic	PK following fasting conditions and high fat meal	Randomized, two-period, period-balanced, open-label, crossover study	Healthy volunteers	20; 8M, 12F; 36 (18-63)	MR carvedilol; 50 mg; capsule; oral; QD; one day	Completed; Final	m5.3.1.1.8

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects: Gender M/F: Mean Age (Range)	Treatment Details (Drug/Dose/Form/ Route/Frequency/ Duration)	Study Status: Type of Report	Location of Study Report
SK&F-105517/388	Pharmacokinetic	Dose proportionality	Randomized, open-label, single dose, 4 period, period balanced, crossover study	Healthy volunteers	23; 23M, 0F; 37 (22-51)	[redacted] MR carvedilol; 6.25 mg, 12.5 mg, 25 mg and 50 mg; capsule; oral; QD; one day	Completed; Final	m5.3.1.1.9
SK&F-105517/400	Pharmacokinetic	Relative Bioavailability	Open-label, single dose, randomized, three-period, crossover study	Healthy volunteers	36; 31M, 5F; 30 (18-53)	COREG IR; 25 mg; tablet; oral; Q12H; one day 6 various combinations of carvedilol IR and CR microparticles; 60 mg; capsule; oral; QD; one day	Completed; Final	m5.3.1.2.1
SK&F-105517/387	Pharmacokinetic	Effect of repeat dose pantoprazole on single dose of carvedilol [redacted] MR capsule	Open-label, non-randomized, 2 period, fixed sequence study	Healthy volunteers	24; 12M, 12F; 29 (19-53)	[redacted] MR carvedilol; 25 mg; capsule; oral; QD; one day Pantoprazole; 40 mg; tablet; oral; QD; 7 days	Completed; Final	m5.3.3.4.1

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects: Gender M/F: Mean Age (Range)	Treatment Details (Drug/Dose/Form/ Route/Frequency/ Duration)	Study Status: Type of Report	Location of Study Report
SK&F-105517/395	Pharmacokinetic/ Pharmacodynamic	To describe relationship between changes in heart rate and the concentration of S(-) carvedilol following oral doses of carvedilol	Single blind, five-period, dose-rising study	Healthy volunteers	24; 23M, 1F; 27 (19-33)	COREG IR; 6.25, 12.5, 25 and 50 mg; tablet; oral; QD (except 25 mg was Q12H); one day [redacted] MR carvedilol; 65 mg; tablet; oral; QD; one day [redacted] MR carvedilol; 50 mg; capsule; oral; QD; one day	Completed; Final	m5.3.4.1.1
SK&F-105517/908	Pharmacokinetic/ Pharmacodynamic	To describe the relationship between the changes in heart rate and the concentration of S(-)-carvedilol following oral doses of carvedilol.	2 part (Part 1, 2 sessions; Part 2, 3 sessions), randomized, single blind, placebo-controlled, parallel group study	Healthy volunteers	Part 1: 17; 16M, 1F; 24 (19-35) Part2: 17; 14M, 3F; 24 (20-35)	Coreg IR (or placebo); 50 mg; tablets; oral; QD; one day	Completed; Final	m5.3.4.1.2

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects: Gender M/F: Mean Age (Range)	Treatment Details (Drug/Dose/Form/ Route/Frequency/ Duration)	Study Status: Type of Report	Location of Study Report
SK&F-105517/302	Pharmacokinetic/ Pharmacodynamic	Establish the steady state PK/PD relationship between β 1-blockade and S(-)-carvedilol concentration using heart rate during bicycle ergometry in patients with essential hypertension	Randomized, double-blind, repeat dose, crossover study, in 3 parallel dose groups.	Patients with mild to moderate essential hypertension		Carvedilol CR (or placebo); 20, 40 and 80 mg; capsules; oral; QD; see below COREG IR (or placebo); 6.25, 12.5 and 25 mg; tablet; oral; QD; see below Duration: Patients received carvedilol phosphate CR (or placebo) capsules for 22 days followed by COREG IR (or placebo) tablets for 15 days	Completed; Final	m5.3.4.2.2
SK&F-105517/367	Safety and Efficacy Population PK	Safety and efficacy in essential hypertension	Randomized, double blind, placebo controlled, parallel group	Patients with essential hypertension	337 (84 placebo, 87 carvedilol CR 20 mg, 78 carvedilol 40 mg, 88 carvedilol 80 mg); 223M 114F; 53 (24 – 85)	Carvedilol CR 20 mg Carvedilol CR 40 mg Carvedilol CR 80 mg or Placebo once daily 6 weeks	Completed Full Completed; Final	m5.3.5.1.1 m5.3.3.5.1

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects: Gender M/F: Mean Age (Range)	Treatment Details (Drug/Dose/Form/ Route/Frequency/ Duration)	Study Status: Type of Report	Location of Study Report
SK&F-105517/369	Pharmacokinetics and Pharmacodynamics	Comparison of the steady-state pharmacokinetic and pharmacodynamic profile of carvedilol immediate tablets given twice daily to an equivalent dose of carvedilol CR capsules given once daily in patients with heart failure or left ventricular dysfunction	Open-labelled, nonrandomized, crossover	Patients with congestive heart failure or left ventricular dysfunction following acute myocardial infarction	187 (38 3.125/10 mg, 54 6.25/20 mg, 51 12.5/40 mg, 44 25/80 mg); 137M 50F; 61 (25 – 85)	COREG 3.125 mg / carvedilol CR 10 mg; COREG 6.25 mg / carvedilol CR 20 mg; COREG 12.5 mg / carvedilol CR 40 mg; COREG 25 mg / carvedilol CR 80 mg; Patients received COREG (IR) tablets twice daily for two weeks followed by carvedilol CR tablets once daily for two weeks.	Completed Full	m5.3.5.1.2

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects: Gender M/F: Mean Age (Range)	Treatment Details (Drug/Dose/Form/ Route/Frequency/ Duration)	Study Status: Type of Report	Location of Study Report
COR100216	Safety and Efficacy	Comparison of the effect of carvedilol CR + lisinopril to atenolol + lisinopril, and to lisinopril administered without β-blockade on left ventricular mass regression	Randomized, double blind, active controlled, parallel group	Patients with left ventricular hypertrophy and a history of or current hypertension	488 (122 per treatment group) planned	carvedilol CR (20 mg, 40 mg, or 80 mg), atenolol (50 mg, 75 mg, or 100 mg), or lisinopril (10 mg, 20 mg, or 40 mg) in combination with background open-label lisinopril 20 mg once daily 18 months.	Ongoing	

4.3 Review Strategy

The purpose of this review is to evaluate the efficacy of the controlled release formulation and to justify the claims for treating hypertension, congestive heart failure and reduction of cardiovascular mortality. The reviewer ascertained that the treatment effect of the controlled release formulation exceeded that of placebo in Study 367. Furthermore the reviewer ascertained through PK and PD studies (Studies 369 and 902) that there is similarity in the PK and PD profiles of the controlled release and immediate release (IR) formulations.
Although the IR formulation is an approved drug for the treatment of hypertension, congestive heart failure and reduction of cardiovascular mortality, the sponsor has not carried out any studies for congestive heart failure and reduction of cardiovascular mortality.
The small study, 902, established a steady state relationship between β1-blockade and S (-) carvedilol concentration using heart rate during bicycle ergometry in patients with hypertension. This was the basis for the CHF and reduction of cardiovascular mortality claims. This was discussed with the clinical pharmacology division (See sections 3 and 5).

4.4 Data Quality and Integrity

The data quality was found to be very good and of high integrity.

The study incorporated the following key clinical design features to generate high quality data:

• Randomized allocation of subjects to treatment groups assured that treatment comparisons were based on subjects sampled from the same population and that statistics were valid.

• Double-blind study conduct minimized the risk for study endpoint ascertainment bias and differential clinical patient management. This was important given the known risk for observer bias in recording cuff BP readings.

• A placebo control group allowed quantification of treatment-related BP reductions after adjusting for placebo effect.

• A placebo run-in period minimized variability in baseline BP determination and also assured washout of potentially confounding antihypertensive medication.

This study used GSK's Remote Data Management Integrated (RDMi) System. RDMi is a computerized clinical trials data management system which provides investigational sites a standardized and validated, remote, electronic data entry system for the collection of clinical trial data. Activities performed using RDMi include data entry, modification, review and validation. Each activity performed carries a unique user identification code and a date-time stamp. The system was fully validated using test data, prior to distributing the application to sites for use.

Clinical data were transmitted from the site to a firewall protected network server and then via an application server into the clinical database.

An electronic audit trail of all changes made to the electronic Case Report Form (eCRF) was kept by the eCRF system. This audit trail identified the person making the change by their user ID and the date and time that the change was made.

Consistency checks were run in the eCRF system to identify inconsistencies in data. Pre-defined consistency checks were run on the data being entered by authorized site staff and these initiated immediate query generation for resolution.

Quality control was carried out internally within the system for RDMi (eCRFs are printed off and checked against the SAS datasets). Adverse events and concomitant medications were coded by the autoencoder using company standard dictionaries or industry standard dictionaries.

4.5 Compliance with Good Clinical Practices

There was reasonable compliance and good clinical practice based on the quality of the case report forms.

Table 49: Compliance Study- 367

	Number (%) of Subjects			
	Placebo	Carvedilol CR		
Compliance interval	N=84	20mg N=87	40mg N=78	80mg N=88
< 80%	2 (2)	0	0	0
80% ≤120%	72 (86)	81 (93)	75 (96)	81 (92)
> 120%	10 (12)	6 (7)	3 (4)	7 (8)

Data Source: Table 6.10

Table 50: Study Medication compliance- study 367

Table 16 Summary of Study Medication Compliance (ITT Safety Population)

	COREG IR BID				
Compliance since last visit	**3.125mg (N=38)**	**6.25mg (N=54)**	**12.5mg (N=51)**	**25mg (N=44)**	**Total N=187**
n	38	54	50	43	185
>0% and <80%	3 (8)	4 (7)	4 (8)	3 (7)	14 (7)
≥80% and ≤120%	34 (89)	45 (83)	42 (82)	38 (86)	159 (85)
>120%	1 (3)	5 (9)	3 (6)	2 (5)	11 (6)
Missing	0	0	1 (2)	0	1 (<1)
	carvedilol CR UID				
Compliance since last visit	**10mg (N=38)**	**20mg (N=54)**	**40mg (N=51)**	**80mg (N=44)**	**Total N=187**
n	38	50	47	43	178
>0% and <80%	1 (3)	0	1 (2)	1 (2)	3 (2)
≥80% and ≤120%	36 (95)	50 (93)	45 (88)	42 (95)	173 (93)
>120%	2 (5)	0	1 (2)	0	3 (2)
Missing	0	0	0	0	0

Data Source: Tables 6.09

Investigators were advised that it was essential that all medication was accounted for by the investigator or institution, and that any discrepancies were explained and documented.

Patients were required to return all unused medication and empty containers to the investigator. The number of tablets dispensed and returned, dates when dispensed and returned, and dates of first and last dose were recorded, and this information was used to determine patient compliance and study drug accountability.

The investigator retained the returned medication until the sponsor authorized personnel collected it, along with any study treatments not dispensed. At the termination of the study or at the request of the Sponsor, the investigator returned any unused supplies to the sponsor. This return was documented by using an Investigational Product Return Invoice or equivalent.

At the end of the study, study drug delivery records and records of usage and returned stock were reconciled with full accountability for any discrepancies. Certificates of delivery and return were signed. Drug Accountability forms reside in the Sponsors Study Master File.

4.6 Financial Disclosures

Certificate of financial disclosure were submitted.
In compliance with the "Final Rule" on Financial Disclosure by Clinical Investigators, the financial interest information from all the clinical investigators participating in studies covered by the rule included in this New Drug Application for Coreg (carvedilol phosphate) Controlled

Release (CR) is acceptable. A copy of the requisite Form OMB 0396 duly executed by the sponsor is appended below as Figure 11.

Figure 11: Certification of Financial Interests by investigators for carvedilol CR

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006.

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	(See Attached List)	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
David M. Cocchetto	Vice Pres., U.S. Regulatory Affairs
FIRM / ORGANIZATION: GlaxoSmithKline	
SIGNATURE: David M. Cocchetto	DATE: December 14, 2005

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