

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

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

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

Carvedilol is more than 98% bound to plasma proteins, primarily with albumin. The plasma-protein binding is independent of concentration over the therapeutic range. Carvedilol is a basic, lipophilic compound with a steady-state volume of distribution of approximately 115 L, indicating substantial distribution into extravascular tissues. Plasma clearance ranges from 500 to 700 mL/min.

To date, the carvedilol phosphate modified release (CR/MR) capsule formulation has not been evaluated in any manner in heart failure patients or survivors of acute myocardial infarction with LVD. Evaluation of specific pharmacokinetic characteristics on repeat dosing between the current marketed IR formulation and the MR formulation in concert with model-generated estimates of β -1 receptor blockade post dosing will define important pharmacokinetic/pharmacodynamic relationship(s) in chronic CHF and post MI survivors with LVD. The current study will be conducted to evaluate and compare the PK characteristics of the carvedilol phosphate CR and COREG IR formulations. Specifically, the study will enroll patients with symptoms of mild, moderate and severe heart failure as well as asymptomatic patients who have survived a the acute phase of a recent myocardial infarction and have LVD. Additionally, the safety and tolerability of the carvedilol phosphate MR and COREG IR formulation will be evaluated in this patient population (Study 369).

Pharmacodynamic effect (change in heart rate as a measure of β -1 receptor blockade) after administration of IR and MR carvedilol will be estimated in CHF patients based on a PK/PD model initially developed in healthy volunteers. Comparison of the estimated PD effects between the two formulations will, however, be the basis of a claim for similar indications between the IR and CR formulation (Study 902)

A total of 15 PK and PD studies was carried out during the development program (Tables of clinical studies Section 4.2. Studies 369 and 902 are described in some detail below.

Study 369 - OBJECTIVE(S)

Primary

The primary objective of this study is to evaluate and compare the pharmacokinetic profiles of the COREG immediate release (BID regimen) and carvedilol phosphate MR (UID regimen) formulations after repeat dosing in chronic CHF patients (mild, moderate and severe symptoms) and asymptomatic survivors of a recent acute myocardial infarction with LVD.

Secondary

Evaluation of tolerability and safety with the MR formulation is a secondary objective of this study.

ENDPOINT(S)

Primary

The primary measures of interest are the pharmacokinetic (PK) parameters AUC, Cmax, Tmax, and Ctau for each formulation.

Secondary

The secondary measures of interest are safety assessments for each formulation.

STUDY DESIGN

This was an open, non-randomized, multicenter, cross-over pharmacokinetic study in a group of at least 128 patients with stable, chronic heart failure (mild, moderate and severe symptoms) or recent asymptomatic survivors of an acute MI who have LVD. A total of approximately 140 patients was enrolled to achieve at least 128 completed patients. A significant number of the patients enrolled in the study are expected to receive COREG IR (3.125-25 mg BID) as part of their CHF or post MI treatment. Patients who meet the study requirements and are not receiving beta blockers may be enrolled. Additionally, eligible patients receiving another beta blocker for CHF or post MI treatment may also be enrolled.

Enrollment will be stratified and, thus, controlled in order to ensure that the study enrolls a similar number of patients from each heart failure/post MI group at each of the four dose levels of COREG IR (3.125 mg bid, 6.25 mg bid, 12.5 mg bid, 25 mg bid; NOTE: Post MI doses are 6.25 mg bid, 12.5 mg bid and 25 mg bid only

Study Phases: The study was divided into three phases:

- Screening/Baseline Phase (up to 1 week)-Patients will be screened for eligibility based on inclusion and exclusion criteria. Screening and final Baseline assessments may take up to 1 week for completion of all procedures and tests needed (prior to being enrolled).

- Treatment Phase (4 weeks): Following Screening, signed Informed Consent and Baseline assessments, eligible patients will be enrolled and begin receiving open study medication (COREG® IR) for two weeks followed by cross-over to receiving carvedilol phosphate MR once daily for two weeks. PK profiles over 24 h will be determined at the end of each two week period (± 2 days). Safety and tolerability will be monitored throughout this 4 week treatment period.
- Safety Follow up Phase (1 week)-Any patient who requires permanent down-titration during or at study end will undergo a Safety Follow-up visit 4-7 days following the last dose of study medication.

Eligible patients who have signed a written informed consent and have met all inclusion/exclusion criteria and baseline assessments will be enrolled and begin taking study medication (COREG IR: Regimen A). The study medication will be added to the drugs (except non-protocol defined beta blockers) the patients are already receiving for management of chronic heart failure or post-infarction state. The doses of the background medications may be changed or adjusted as deemed necessary by the investigator to care for the patient. Patients are to take COREG IR study medication (3.125 mg, 6.25 mg, 12.5mg or 25 mg) twice daily for two weeks. Patients will return to the clinic on the last day of this two week period (± 2 days) for a 24 hr pharmacokinetic profiling. Three days prior to the scheduled clinic visit, patients will be contacted and reminded of the time of administration of their daily carvedilol doses (the time of administration for these days should be consistent with the time of administration on the scheduled PK sampling day). They will also be instructed to not take their morning dose before coming to the clinic (Note: visits will need to be rescheduled if the patient takes their morning dose and come to the clinic). Patients will remain in the clinic overnight.

Following completion of the 24 hr PK procedures, patients will be crossed-over to carvedilol phosphate MR (Regimen B) and receive the first dose in the clinic where they will be observed for a three hour period. The dose of carvedilol phosphate MR will be the equivalent dose of IR (i.e. 10 mg, 20 mg, 40 mg, 80 mg) taken during the two previous weeks. Patients will take carvedilol phosphate MR once daily for two weeks and then return to the clinic on the last day of therapy (± 2 days) for a 24 hr PK profile assessment. Three days prior to the scheduled clinic visit, patients will be contacted and reminded of the time of administration of their daily carvedilol dose (the time of administration for these days should be consistent with the time of administration on the scheduled PK sampling day). Patients will also be instructed to not take their morning dose before coming to the clinic (Note: visits will need to be rescheduled if the patient takes their morning dose and comes to the clinic). Patients will remain in the clinic overnight and then have a final study visit the next day before completing the study.

At this last clinic study visit, patients will be offered the opportunity to receive a one-month supply of commercial COREG IR at the equivalent COREG MR dose they were receiving at study end. Should the patient choose not to receive these GSK provided supplies, the investigator will treat the patient at their discretion. In those instances where down-titration from study medication at the study end may be needed, study medication should be discontinued over a 1-3 week period depending on the dose the patient is receiving and a Safety Follow-up visit performed within 4-7 days following the last dose of study medication.

Pharmacokinetic Sampling: Full 24 hour pharmacokinetic profiles at steady state will be generated for all patients in each treatment group on the last day of each two week treatment period (see Section 6.4).

As part of the pharmacokinetic evaluation, all patients who complete eligibility requirements successfully will have a blood sample withdrawn at Screening for determination of CYP2D6 metabolizer status (alleles*3,*4,*5,*6,*7, and*8). Blood samples (6 mL) will be collected into vacutainers containing EDTA, inverted several times and will be immediately frozen and stored at approximately -20°C or lower until collected by a courier for _____ will store (-20°C or colder) the frozen samples and will ship them (in batches every month) to _____

STUDY POPULATION: Number of Subjects

A total of 140 patients who are either male or female and 18-85 years of age who have been diagnosed with stable mild, moderate or severe CHF or are recent (within 2 months) asymptomatic survivors of an acute MI who have LVD receiving CHF or Post MI background medications will be enrolled to ensure at least 128 patients will be studied.

Only patients who are expected to comply with the requirements of the protocol should be included in the study.

Patients to be enrolled may be already receiving COREG IR for their chronic heart failure (3.125 mg, 6.25mg, 12.5 mg, 25 mg bid) or post MI (6.25 mg, 12.5 mg or 25 mg bid) treatment regimen. Patients must have been receiving this dose for at least two consecutive weeks. These patients, once enrolled, will continue on with carvedilol IR as their initial study medication (Regimen A) for two weeks before crossing-over to the equivalent doses of carvedilol phosphate MR (Regimen B: 10 mg, 20 mg, 40mg, 80 mg).

Eligible patients, who at the time of Screening, are not receiving a beta blocker for treatment of their heart failure condition may also be enrolled and will begin taking the lowest dose of COREG IR (3.125 mg bid) as their initial study medication (Regimen A) for the initial 2 week treatment period before being crossed-over to the equivalent dose (10 mg uid) of carvedilol phosphate MR. Post MI patients not receiving a beta-blocker for their condition will begin COREG IR at 6.25 mg bid at their initial study medication (Regimen A) for the initial two week treatment period before being crossed-over to the equivalent dose (20 mg uid) of carvedilol phosphate MR.

Finally, eligible patients who are taking beta blockers, other than COREG IR, may be enrolled. Patients must have been receiving this dose for at least two consecutive weeks. Patients who are receiving moderate to high doses of a beta blocker for treatment of their heart failure or post MI condition would have their dose reduced by 50% at the Baseline visit and begin receiving COREG IR (6.25 mg, bid). Patients would continue this dose for two weeks at which time the 24 hr PK assessment would be performed and crossed-over to the equivalent dose of carvedilol phosphate MR (20 mg uid). The reduced dose of the concomitant beta blocker would continue

throughout the entire 4 week treatment period to the end of the study. This would ensure the patients PK assessments were being done under the same study conditions. Patients receiving low initiating doses of beta blockers for heart failure or post MI treatment would have their dose discontinued at the time of enrollment. These patients would also begin the study by receiving COREG IR(6.25 mg bid) for the first two weeks before being crossed-over to the carvedilol phosphate MR dose equivalent (20 mg uid). [NOTE: Low initiating doses are defined as: Metoprolol IR = 25 mg/day; Bisoprolol = 2.5 mg/day; Toprol XL =25 mg/day; Atenolol = 25 mg/day; Propranolol = 40 mg/day].

Eligibility Criteria: Inclusion Criteria

A patient will be eligible for inclusion in this study only if all of the following criteria apply:

Key inclusion criteria for eligibility and enrollment are as follows:

- Males or females 18 to 85 years of age. Females must be 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 Enrollment/Baseline visit and agree to continue to use the same contraceptive method during the study;
- Have been diagnosed with clinically stable mild, moderate or severe CHF.

Definition of Mild, Moderate, Severe Chronic Heart Failure) of ischemic or non-ischemic origin, have left ventricular ejection fraction < 35% and currently receiving background medications for HF which may include ACE inhibitors, beta blockers, diuretics, AII antagonists, aldosterone antagonists, hydralazine, nitrates, digoxin and devices (biventricular pacing and implantable defibrillators, must be implanted >60 days before enrollment); patients who are recent (within 2 weeks to 2 months of index MI) survivors of an MI having LVD (LVEF = 40%) and are asymptomatic for heart failure are to be receiving standard background agents which may include ACE inhibitors and/or beta blockers and antithrombotic agents. Stable heart failure is 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);

- Patients must be euvolemic (the dose of diuretic must be adjusted so that the patient is neither volume overloaded nor volume contracted. Specifically, the patient should have no physical evidence of fluid retention (pleural effusion, rales, ascites, or leg edema) except for trace leg edema or minimal pleural effusions that are not believed to be cardiac in origin. In addition, physicians should ensure that patients with orthostatic hypotension or pre-renal azotemia are not volume depleted.
- Sitting (resting) heart rate of = 55 BPM if receiving beta blocker agent; =68 BPM if no beta blocker agent is being used; sitting (resting) systolic blood pressure = 85 mmHg

- Patients may be receiving a beta-blocker drug (other than COREG) as CHF or Post MI treatment, however, only at dose levels below the total daily equivalent of 200 mg Toprol XL

Exclusion Criteria

A patient will not be eligible for inclusion in this study if any of the following criteria apply:

Key exclusion criteria making the patient NOT eligible for enrollment:

- Uncorrected primary obstructive or severe regurgitative valvular disease; nondilated (restrictive) or hypertrophic cardiomyopathies; women with heart failure during the 12 months following childbirth;
- Patients must have been free of symptomatic or sustained VT or ventricular fibrillation for at least 3 months prior to Screening (patients who have an ICD in place for at least 60 days and not fired in last 30 days may be enrolled);
- Acute myocardial infarction within two weeks prior to Screening;
- Unstable angina or coronary artery bypass grafting (CABG) within 2 months prior to Screening;
- Likely heart transplant within the next 3 months following Screening/Enrollment;
- History of sick sinus syndrome or second or third degree heart block unless a non-fixed rate pacemaker is in place;
- Type I Diabetes Mellitus
- Documented CVA within the two months prior to Screening;
- Current clinical evidence of chronic obstructive pulmonary disease (i.e. asthma or severe bronchitis) requiring long term use of inhaled oral bronchodilator or steroid drug therapy; also patients with a history of bronchospastic disease not undergoing active therapy in whom, in the investigator's opinion, treatment with the study medication could provoke bronchospasm;
- Sitting systolic blood pressure less than 85 mmHg (with or without beta blocker agents); uncontrolled hypertension (i.e. SBP>180 mmHg or DBP > 114 mmHg);
- Sitting (resting) heart rate < 55BPM if receiving a beta blocker; < 68 BPM in the absence of a beta blocker;

- Evidence of significant disease that could impair absorption, metabolism or excretion of study medication, i.e. renal disease defined as serum creatinine > 2.5 mg/dl; clinically significant hepatic disease defined by laboratory values of ALT or AST greater than three times upper limit of normal; chronic biliary disorders;
- Cancer or other systemic disease with reduced life expectancy (< 6 months)
- Likelihood of poor compliance;
- Known history of intolerance to initiating doses of β blocker agents;
- Known history of drug allergy to alpha or beta-blocker agents;
- Use of an investigational drug within 30 days of Screening/Randomization into the study or five half-lives of the study drug whichever is longer;

Ongoing (at Screening/Baseline) or anticipated treatment with the following medications during treatment phase:

- Monoamine oxidase (MAO) inhibitors;
- Calcium channel blockers
- α blocker, combined α and β blockers
- Any Class I or III antiarrhythmic agents (amiodarone may be used if daily maintenance doses are = 200 mg/day)
- β -2 agonist therapy
- β -Blockers where total daily doses equivalent to > 200 mg Toprol XL used
- Metoprolol tartrate (>150 mg)
- Bisoprolol (>10 mg)
- Atenolol (>150 mg) • propranolol (>160 mg) Clonidine 19. Patients with a history of heparin-induced thrombocytopenia and/or heparin allergy

Other Eligibility Criteria Considerations

To assess any potential impact on subject eligibility with regard to safety, the investigator must refer to the following document(s) for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the investigational product(s) being used in this study: Clinical Investigator Brochure and COREG Product Label.

NOTE: Patients should discontinue use of the PDE5 inhibitors Levitra and Cialis prior to enrolling into the study.

STUDY ASSESSMENTS AND PROCEDURES

This trial is an open, non-randomized, cross-over design and has no up-titration phase. Assessments will be performed at initial Screening/Baseline visits, at scheduled visits during the 4 week constant dose Treatment Phase and at a final visit at the end of a 2-3 week dose-Down-titration phase in those special cases where down-titration of dose is necessary (e.g. early permanent withdrawal from the study or at the end of the study). There are no efficacy assessments planned.

Demographic, Screening and Baseline Assessments

Potentially eligible male and female patients will be evaluated during Screening for demographic criteria as well as clinical criteria for study entry. Screening assessments for eligibility may last 2-7 days. Following enrollment, final Baseline assessments will occur just prior to beginning COREG IR study medication dosing. Screening and initial Baseline assessments at the initial study visit(s) will satisfy any remaining Inclusion/Exclusion criteria for study entry.

Screening/Baseline Visit Assessments/Procedures:

- Complete Medical History- including a review of all medications taken in the prior three months
- Complete Physical Exam-including cardiopulmonary exam • Serum pregnancy testing for females of childbearing potential • ECG (12 lead) • Vital signs (sitting)
- Height and body weight • NYHA Class
- Chest X ray (if not done in last 6 months) • Safety Laboratory Tests • CYP 2D6 sample collection Patients may be enrolled anytime during the 2-7 days Screening period provided they have satisfied all Inclusion/Exclusion criteria.

Safety

Safety evaluation will be conducted at Screening/Baseline visits and at each study visit during the Treatment Phase of each study medication. Additionally, safety assessments will be done within 4-7 days following any necessary or elective down-titration of study medication.

The following will be assessed at Screening/Baseline visits:

- Chest X ray if not done in last 6 months • Complete Physical Exam • Safety Clinical Laboratory Assessments • Urinalysis • Vital signs (systolic and diastolic blood pressure and heart rate) in sitting position • ECG (12 lead) • Height/Body Weight • Cardiopulmonary exam
- The following will be conducted at all subsequent scheduled visits after enrollment and beginning study medication:

• Interim Physical Exam • Vital Signs (sitting and standing) and Body Weight • Tolerability Assessment • Safety Clinical Laboratory Assessments (includes at follow-up visit following early

Efficacy

Efficacy evaluations were not carried out in this trial as the primary measure was an assessment of the pharmacokinetic profiles of each of the two study drug formulations.

Statistics: Interim Analysis

No interim analysis is planned for this study. Statistical analyses of the pharmacokinetic data were performed after the completion of the study.

Sample Size Considerations

The target sample size is 128 patients. Patients will be enrolled from each heart failure and post MI group such that approximately equal numbers from each group will be enrolled at each of the four dose levels...

Sample Size Assumptions: Sample size is based on feasibility. However, some justification is provided below.

Based on the largest estimate of within-subject variability (35.9% for C_{max} of S-carvedilol in the MR formulation) and a sample size of 128 (i.e., 32 patients per dose level), it is estimated that the precision for the comparison of interest (MR: IR) will be no more than 16% of the observed point estimate, where precision is expressed as the half-width of the 90% confidence interval. That is, the lower and upper bounds of the 90% confidence interval for the ratio of Modified Release: Immediate Release will be within approximately 16% of the observed ratio. Calculations are based on a symmetric two-tailed procedure on the loge-scale and a type I error rate of 10%.

Any changes to the planned statistical analyses will be described in the clinical study report.

The pharmacokinetic parameter data will not be dose-normalized prior to statistical analysis. Additionally, the oral clearance (CL/F) after IR administration may be fit as a covariate in the model.

Pharmacokinetics

Sample Collection: Three days prior to the scheduled clinic visit, patients will be contacted and reminded of the time of administration of their daily carvedilol dose (the time of administration for these days should be consistent with the time of administration on the scheduled PK sampling day). Patients will also be instructed to not take their morning dose before coming to the clinic. On the morning of the last day of dosing study medication (day 14), all patients will be admitted to the hospital or CRC unit for 24 hr PK workup. Patients will remain in the unit overnight. On this day, patients will not take their morning dose before being admitted to the unit. Following admission, blood samples (approximately 3 mL) will be collected into vacutainer tubes containing EDTA prior to the morning dose of study medication (time 0) and then at nominal

times of 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 13, 14, 16, 20, and 24 hours after administration. The same timepiece (watch/clock) should be used to record the time of dose administration and time of PK sample collection for an individual patient.

Sample Preparation: After the blood specimens are collected into vacutainer tubes containing EDTA, the tubes will immediately be chilled on crushed ice. Plasma will be separated by centrifugation at approximately 1000-1500 x g for 10-15 minutes. Centrifuge sleeves will be frozen prior to centrifugation. Plasma will be transferred to polypropylene specimen containers labeled with study number, subject number, date and nominal time of collection. Specimens will be immediately frozen and stored at approximately -20°C or lower until collected by a courier for _____ will store (-20°C or colder) the frozen pharmacokinetic samples and will ship them (in batches every month) to DMPK, Department of World Wide Bioanalysis, GSK, King of Prussia, PA. The pharmacokinetic plasma samples will be stored frozen (-20°C or colder) until analysis.

Assay Methodology: Plasma specimens were assessed for concentrations of R- and S-carvedilol using the currently validated methodology (on file at the Department of World Wide Bioanalysis, GlaxoSmithKline Pharmaceuticals, King of Prussia, Pennsylvania).

As part of the pharmacokinetic evaluation, all patients who complete eligibility requirements successfully will have a blood sample withdrawn at Screening for determination of CYP2D6 metabolizer status (alleles*3,*4,*5,*6,*7, and*8). Blood samples (6 mL) will be collected into vacutainers containing EDTA, inverted several times and will be immediately frozen and stored at approximately -20°C or lower until collected by a courier for _____ will store (-20°C or colder) the frozen samples and will ship them (in batches every month) to _____

Pharmacodynamics

Evaluations of pharmacodynamic effects were not conducted in this trial.

Description of Investigational Product

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

Dosage and Administration

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). 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.

Patients may be enrolled if they are receiving acceptable doses of a beta blocker other than COREG. Patients must have been receiving this dose for at least two consecutive weeks prior to Screening. These otherwise eligible patients will begin the study by receiving COREG IR 6.25 mg bid. Patients who are on moderate to high stable doses of beta blockers will reduce their dose of concomitant beta blocker by 50% at study entry (Baseline visit) and continue to receive the concomitant beta blocker for the entire treatment phase in combination with both study medications. Those patients receiving low (initiating) doses of a concomitant beta blocker will have their dose stopped at study entry before starting COREG IR study medication (NOTE: Initiating doses are defined as: Metoprolol IR = 25 mg/day; Bisoprolol = 2.5 mg/day; Toprol XL = 25 mg/day; Atenolol = 25 mg/day; Propranolol = 40 mg/day].

Patients will take COREG IR study medication at one of four dose levels (i.e. 3.125 mg, 6.25 mg, 12.5 mg or 25 mg) twice daily for two weeks. On the last day of the two week treatment period, patients are to return to the clinic between 6-8 am for safety, tolerability and compliance assessments and the 24 hr steady state pharmacokinetic assessment. Prior to dosing an intravenous cannula for collection of blood samples may be inserted into one antecubital vein and kept patent with a dilute heparin solution (= 10 U/ml) for up to 24 hours. Three days prior to the scheduled clinic visit, patients will be contacted and reminded of the time of administration of their daily carvedilol doses (the time of administration for these days should be consistent with the time of administration on the scheduled PK sampling day). They will also be instructed to not take their morning dose before coming to the clinic. Patients will remain overnight as part of the pharmacokinetic assessment.

On the morning after completing the pharmacokinetic assessments and completion of all assessments and procedures, patients will receive the first dose of carvedilol phosphate MR capsules (study medication B). This once daily dose will be the equivalent to the twice daily dose they had received the previous two weeks (i.e. 10 mg, 20 mg, 40 mg, or 80 mg MR equivalent to 3.125 mg, 6.25 mg, 12.5 mg or 25 mg bid IR respectively). Patients will be observed for three hours following this initial dose. Patients will be instructed to take the study medication once daily in the morning for two weeks. On the last day of the two week treatment phase, patients are to return to the clinic between 6-8 am for safety, tolerability and compliance assessments and the 24 hr steady state pharmacokinetic assessment which will require an overnight stay. Prior to dosing, an intravenous cannula for collection of blood samples may be inserted into one antecubital vein and kept patent with a dilute heparin solution (= 10U/ml) for up to 24 hours. Three days prior to the scheduled clinic visit, patients will be contacted and reminded of the time

of administration of their daily carvedilol doses (the time of administration for these days should be consistent with the time of administration on the scheduled PK sampling heir morning dose before coming to the clinic.

On the morning of the day after completion of the pharmacokinetic assessments, the patient has completed study medication dosing and has completed the study. At this last clinic visit, patients will be offered open label COREG IR at the equivalent MR dose they were receiving at study end for one additional month. Patients choosing not to receive the GSK provided COREG will be treated as deemed necessary by the investigator. If down titration is required in those rare cases, this is to be conducted over a 1-3 week time period to prevent rebound effects from occurring. A Safety Follow-up visit will occur 4- 7 days after the last dose of down titrated study medication. No study specific data will be collected during the post-study time period when commercial COREG is provided to patients.

Dose Rationale

The dosing for the COREG IR study medication is as specified in current labeling for treatment of chronic heart failure i.e. 3.125 mg, 6.25 mg, 12.5 mg and 25 mg bid. The duration of 2 weeks dosing ensures reaching steady state levels. The final doses of the carvedilol phosphate MR formulation (10 mg, 20 mg, 40 mg, and 80 mg uid) were chosen to approximate the equivalent dose of the IR formulation based on AUC, Cmax, Tmax and Ctau.

COREG IR mg	COREG MR mg
3.125 mg	10 mg
6.25 mg	20 mg
12.5 mg	40 mg
25 mg	80 mg

Blinding

This study was not blinded in any way.

Treatment Assignment

All patients will receive COREG immediate release (Regimen A) followed by the new modified release formulation carvedilol phosphate MR Capsules (Regimen B). They will then be eligible for open label COREG IR at the equivalent MR dose they were receiving at study end for one additional month.

All patients will be assigned to the sequence AB in accordance with the schedule generated by Clinical Pharmacology Statistics and Programming, GlaxoSmithKline, using validated internal software (RandAll), prior to the start of the study. The assignment schedule will be stratified by patient group and IR dose level.

GSK's RAMOS system, in accordance with the assignment schedule, was used to assign the patients to treatment and to order open label study medication. It did not assign containers to the patients since the study is open label. The level of study medication is assigned by the

investigator. The pharmacist or designee assigned the appropriate containers of study medication based on the investigator's order.

Efficacy Analyses

No efficacy analyses are planned for this study.

Primary Analysis

No efficacy analyses are planned for this study.

Secondary Analyses

No efficacy analyses are planned for this study.

Safety Analyses

No formal statistical analyses of the safety data are planned for this study. Safety data will be summarized using descriptive statistics (i.e., means, standard deviations, percentages, wherever applicable). Additional details of summaries of safety data will be included in the reporting and analysis plan. All summaries of safety data will be performed on the intent-to-treat safety population.

Extent of Exposure

The number and percentage of subjects exposed to treatment along with descriptive statistics (mean, median, standard deviation, minimum, and maximum) for overall exposure (i.e., number of days on treatment) will be provided.

Pharmacokinetic Analyses

The primary focus of the statistical analysis of the pharmacokinetic data was to compare the modified release formulation of carvedilol (MR) to the immediate release formulation (IR), pooled across all heart failure and post MI groups.

Following log-transformation, AUC, C_{max}, and C_{tau} of R- and S-carvedilol will be separately analyzed using a mixed effects model, fitting fixed effect terms for group (mild heart failure, moderate heart failure, severe heart failure, or post MI), dose (level 1: IR 3.125 mg bid or MR 10 mg uid, level 2: IR 6.25 mg bid or MR 20 mg uid, level 3: IR 12.5 mg bid or MR 40 mg uid, level 4: IR 25 mg bid or MR 80 mg uid), group-by-dose interaction, formulation (IR or MR), group-by-formulation interaction, and dose-by-formulation interaction. Subject (dose*group) will be treated as a random effect. The oral clearance (CL/F) after IR administration may be fit as a covariate in the model. Point estimates and 90% confidence intervals for the difference of interest (MR-IR) will be constructed using the appropriate error term. These point and interval estimates will then be exponentially back-transformed to construct point and interval estimates for the ratio of interest (MR: IR).

The interaction terms (group-by-dose, group-by-formulation, and dose-by-formulation) in the above model will be tested. If the interaction terms are significant, then a descriptive analysis

will be undertaken to characterize the nature of the interaction. This will be interpreted in the context of clinical relevance.

Study 902 Title

“ A Randomized, Double-Blind, Placebo Controlled, PK/PD Modeling, Multicenter Study to Compare the β 1-Blocking Effects of Carvedilol Phosphate CR Capsule Formulation to COREG® Immediate Release Tablets at Steady State in Adult Patients with Essential Hypertension, by Evaluating Heart Rate Response to Bicycle Ergometry “

Pharmacodynamic Analyses

Pharmacodynamic effect (change in heart rate as a measure of β -1 receptor blockade) after administration of IR and MR Carvedilol will be predicted in CHF patients in the current study based on a PK/PD model developed in healthy volunteers and PK data from this trial. Comparison of the predicted PD effect between formulations will be reviewed by Biopharm Division.

The following is a brief report of Study 902.

Investigator(s): This was a multi-center study.

Study center(s): The study was conducted at a total of 9 sites in the United States. Seven of the 9 sites enrolled subjects.

Publication(s): None as of the date of this report.

Study Period: 30 December 2004 – 27 June 2005

Phase of Development: I

Objectives:

1. 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
2. Estimate the β 1-blocking effects of the carvedilol CR formulation relative to the COREG IR formulation by comparing pharmacodynamic parameters in patients with essential hypertension
3. Describe the pharmacokinetics of the carvedilol phosphate CR capsule formulation and COREG IR at steady state [R (+) and S (-) enantiomers]
4. To evaluate the safety and tolerability of the carvedilol phosphate CR capsule formulation and COREG IR following repeat dose administration in patients with essential hypertension

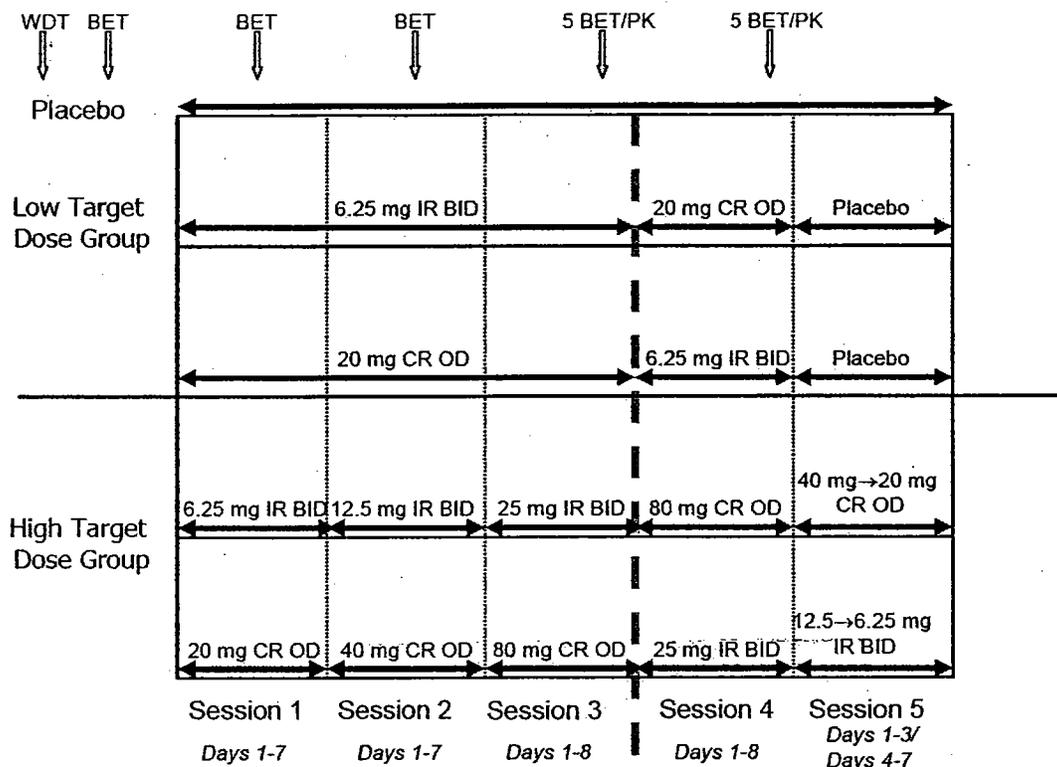
Methodology:

This was a randomized, double-blind, repeat dose, crossover study, in 3 parallel dose groups. The study consisted of 5 phases: screening, down titration/washout, drug free run-in, double-blind treatment, and follow-up.

In the screening phase, subjects were screened over approximately 1 week for eligibility prior to entering the down titration/washout phase. The screening phase included outpatient visits. If the subject was determined eligible for inclusion into the study during the screening phase, the subject entered the down titration/washout phase and was down-titrated or withdrawn from prescribed antihypertensive medications over a time period determined safe per the investigator. Following down titration or cessation of prescribed antihypertensive medication(s), subjects entered the drug free run-in phase and were without antihypertensive treatment for at least 2 weeks but no more than 4 weeks prior to qualifying for and being randomized to the double-blind treatment phase. Subjects could not be without antihypertensive medication(s) for more than 6 weeks prior to entering the double-blind treatment phase.

In the double-blind treatment phase, subjects were randomized to 1 of 5 treatment groups. Subjects in Group 1 received placebo; Groups 2 and 3 received the low dose of carvedilol (target dose of 6.25 mg of COREG IR Q12H; 20 mg of carvedilol CR capsules QD); Groups 4 and 5 were up-titrated to the high dose (target dose of 25 mg of COREG IR Q12H; 80 mg of carvedilol CR capsules QD) of carvedilol.

The double-blind treatment phase consisted of 5 sequential study sessions (Sessions 1 through 5). Subjects randomized to the carvedilol treatment groups began dosing with one of the COREG IR or carvedilol CR formulations (at random) in Session 1 at the lowest dose level, and either remained on the low dose level in Sessions 2 and 3 (Groups 2 and 3; Low Target Dose Level) or were titrated up to the high dose level (Groups 4 and 5; High Target Dose Level) by Session 3. In Session 4, subjects receiving the carvedilol IR formulation (COREG) in Sessions 1 through 3 were switched to receive the corresponding carvedilol CR formulation, while subjects receiving the carvedilol CR formulation in Sessions 1 through 3 were switched to receive the corresponding carvedilol IR formulation (COREG). Doses administered in Session 4 were at a dose equivalent to that administered in Session 3. In Session 5, subjects in Groups 4 and 5 receiving the high dose were down-titrated; down-titration in Session 5 reduced the risk of rebound hypertension that may occur following abrupt discontinuation of beta-blockers. Subjects in Groups 1, 2, and 3 (the placebo and low dose treatment groups) received placebo in Session 5 to maintain the blind. At the conclusion of the last dosing session and at the discretion of the investigator, subjects resumed their prescribed antihypertensive medication(s). Approximately 7 – 10 days following the completion of Session 5, subjects returned for the follow-up visit. The study design is summarized in the following figure.



Subjects participated in a minimum of 3 bicycle exercise orientations to become familiarized with the study environment and the supine bicycle ergometry techniques prior to entering the drug free run-in phase. One of these orientations was completed during the screening phase while the other 2 could have been completed at anytime prior to the drug free run-in phase. During the drug free run-in phase, following cessation of the antihypertensive medication(s), subjects participated in a Workload Determination Test during which the workload (measured in watts) calculated to achieve a heart rate of 140 bpm was determined. The workload determined from the results of this test was used in the remaining bicycle ergometric tests for the study [baseline bicycle exercise test (BET), the BET on Day 4 of Sessions 1 and 2, and the 5 BETs on Day 7 of Sessions 3 and 4].

Within approximately 5 days prior to dosing, subjects underwent a baseline BET according to the ergometry protocol (although prior to randomization to study medication, this was considered the start of double-blind treatment phase). The subject was permitted to be dosed on Day 1, Session 1, if the heart rate at any time during the 5th minute of the baseline BET was at or above 130 bpm. If all heart rate values were below 130 bpm, the subject may have returned to the clinic within 2 days to perform another baseline BET. If during this second test the heart rate during minute 5 did not reach at least 130 bpm, the subject was withdrawn from the study and began receiving his/her prior antihypertensive medication(s) at the discretion of the investigator.

Upon satisfactory completion of the baseline BET, additional BETs were completed in Sessions 1 – 4 during the double-blind treatment phase. In Sessions 1 and 2, a single bicycle orientation was performed prior to morning dosing on Day 4. The purpose of this bicycle orientation was to provide the subject and clinical research unit (CRU) additional familiarization with the study environment and the supine bicycle ergometry techniques. In addition, subjects were monitored for safety via blood pressure and heart rate. On Day 7 in Sessions 3 and 4, a total of 5 BETs were conducted prior to and up to 24 hours following morning study drug administration according to the ergometry protocol. Subjects were randomized to 1 of 6 sequences of times for the BETs.

On Day 7 of Sessions 3 and 4, PK/PD evaluations (heart rate during BET) occurred. Pharmacokinetic samples were obtained immediately following each prescribed BET.

On Day 8 of Sessions 3 and 4, pharmacokinetic blood samples were obtained pre-dose and periodically over the 24 hours following dosing (last sample 24 hours post-dose) to provide a thorough assessment of pharmacokinetic parameters.

Safety and tolerability of protocol-specified treatments were assessed from spontaneous and elicited AE reporting, vital signs, electrocardiograms (ECGs), and nursing/physician observations throughout the study. Data obtained were summarized and clinically relevant abnormalities described.

The total study duration for each subject (including screening, treatment, and follow-up procedures) was approximately 10 to 14 weeks.

Pharmacokinetics

Blood samples for pharmacokinetic (PK) assessment were collected over a 24-hour period following carvedilol CR and COREG multiple dosing on Days 7 and 8 of Sessions 3 and 4. Plasma concentrations of R (+) - and S (-)-carvedilol and M4 (high dose groups only) were measured using a method based upon HPLC-MS/MS analysis using a Turbo IonSpray interface. R(+)- and S(-)-carvedilol plasma concentration-time data were analyzed by noncompartmental methods to determine the peak concentration (C_{max}), time to peak concentration (t_{max}), area under the curve to time t where t is the last quantifiable concentration [AUC(0-t)], area under the curve to time t' where t' is the last time of a quantifiable concentration within a subject across treatments [AUC(0-t')], Fluctuation Index, and 24 hour trough concentration (C_t) values as appropriate. M4 and combined (total) R (+) - and S (-) - carvedilol plasma concentration-time data were analyzed by noncompartmental methods to determine C_{max}, t_{max}, and AUC (0-t).

Pharmacokinetics/Pharmacodynamics

The relationship between plasma concentrations of S (-)-carvedilol and changes in exercise-induced heart rate (HR) were described. Based on a previous PK/PD model in healthy volunteers, the E_{max} model was evaluated to describe the relationship. Population PK/PD modeling was performed using NONMEM (Version V). The statistical model included two components of variability: interindividual variability (IIV) and random residual variability. The

stability of the parameter estimates was examined using the bootstrap technique based on 1000 resampled data sets.

A total of 122 subjects were randomized and enrolled in this study and received study medication, 17 subjects were withdrawn from the study, and 105 subjects completed the study.

Diagnosis and main criteria for inclusion:

Subjects were male or female patients with mild to moderate essential hypertension, between the ages of 20 and 55 years.

Treatment administration:

In order to maintain the double blinded nature of this study, and because both the tablets and the capsules had different sizes and/or colors for each dose, each subject took 6 tablets and 3 capsules every day [3 capsules (carvedilol CR or matched placebo) and 3 tablets (COREG IR formulation or matched placebo) in the morning, and 3 tablets (COREG IR formulation or matched placebo) in the evening].

During outpatient dosing, subjects took study drug following meals (moderate calorie breakfast for AM dose). Subjects were provided with detailed instructions on how and when to take the study medications.

Criteria for evaluation:

The primary pharmacodynamic endpoints were area under the effect curve (AUEC), pharmacodynamic effect at Ct (PDmin), and maximum pharmacodynamic effect (PDmax).

The primary pharmacokinetic endpoints were AUC, Cmax, tmax, and Ct.

Safety assessments were made throughout the study including heart rate, blood pressure, laboratory safety tests, adverse event questioning, and clinical monitoring.

For both carvedilol CR and COREG, the blunting of exercise-induced heart rate (EHR) in patients with hypertension was maintained over the entire 24-hour period. In those subjects receiving placebo, it was noted that EHR decreased from Session 1 through 4 as compared to baseline. This observation probably reflects an increased familiarity with the exercise technique rather than a training effect given the short timeframe. Importantly, this time-related occurrence did not alter the interpretation of the pharmacodynamic comparisons in the study as carvedilol-treated subjects showed more pronounced effects on EHR.

Results:

The mean baseline and pre-dose EHR measurements for each treatment group are provided in Table 51 below including point estimates for comparisons of PDmin. Tables 52 and 53 summarize comparison of AUEC and PD max for CR : IR with bootstrap confidence intervals in Study 902. This provides evidence of bioequivalence between the two formulations.

Table 51: Mean Exercise-induced heart rate and % change from baseline; point estimates -Study 902

Mean Exercise-induced Heart Rate ¹ (bpm) And Percent Change from Baseline [PD(%)]				
Treatment Group	N	Baseline	Steady State Trough [PDmin]	
Low Dose	36		Carvedilol CR 20mg OD	COREG 6.25mg BID
		140 (6.9)	120 (12.5)	119 (12.1)
			14.0% (8.46)	14.8% (7.56)
High Dose	45		Carvedilol CR 80mg OD	COREG 25mg BID
		139 (7.1)	117 (10.7)	118 (9.9)
			16.0% (7.30)	15.0% (6.18)
Placebo	22		Placebo Session 3	Placebo Session 4
		140 (7.5)	127 (10.8)	125 (10.9)
			8.9% (7.71)	9.8% (10.34)

1. Mean (SD) presented for EHR and PD%

Point estimates and 90% confidence intervals (CI) for the comparisons of observed PDmin are presented in the table below.

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

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

The summary of the comparisons of AUEC for CR: IR across the bootstrap datasets indicate that for both dose groups pooled as well as for the low and high dose groups separately, the carvedilol CR formulation provided similar results to the COREG IR formulation. Based on summary statistics of AUEC by dose group from the bootstrap datasets, for either formulation, the four-fold increase in dose results is only a modest increase in AUEC as the median AUEC for the high dose groups were approximately 20% greater than the median AUEC for the respective low dose groups. The point estimates and 90% confidence intervals for the comparisons of the AUEC bootstrap estimates are presented in Table 52 below.

Table 52: Comparison of AUEC for CR : IR with bootstrap confidence intervals - Study 902

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

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

Table 53: Comparison of PD max for CR:IR with point estimates and confidence intervals- Study 902

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

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

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 the table 53 above.

Pharmacokinetic Results

On average, the Fluctuation Index for both R(+)- and S(-)-carvedilol was approximately one, indicating that the peak to trough fluctuation in plasma concentration for carvedilol after administration of the carvedilol CR formulation once daily was similar to that of the COREG IR formulation after the AM dose of twice daily administration. PK parameters are summarized in the table below.

After administration of each formulation, M4 metabolite concentrations declined in parallel with total carvedilol concentrations. On average, steady state plasma levels of metabolite M4 were less than 10% of those observed for carvedilol for both COREG and carvedilol CR. M4 PK parameters are summarized in the table below.

Table 54: PK of M4 metabolite concentrations for 2 dose strengths of Coreg- Study 902

Analyte	Regimen	N	AUC(0-t) (ng-hr/mL)	Cmax (ng/mL)	tmax (hr) ²
M4	C	45	44.2 (35.5%)	6.16 (47.2%)	1.50 (0.50 - 4.00)
M4	F	45	46.9 (42.6%)	5.53 (43.0%)	5.00 (1.00 -10.00)

1. Geometric mean (CVb%)

2. Median (range)

Regimen C: COREG 25 mg PO Q12H

Regimen F: Carvedilol CR capsule formulation 80 mg PO QD

Conclusions

On average, the β_1 -adrenergic blocking effect of the carvedilol CR formulation was similar to the β_1 -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.

Pharmacokinetic/Pharmacodynamic

The population estimates for E0, EC50, and Emax were 126 bpm, 4.25 ng/mL, and 15.1 bpm (a 12% decrease in heart rate), respectively. To account for an apparent fluctuation in placebo HR data over the course of the day, a cosine function was added to the model for E0. The parameter estimate for the amplitude of the variation in HR at baseline was 0.013 (representing an approximate 2 bpm change in HR) while the parameter estimate for the time of peak HR at baseline was 11.6 hours post-dose. The population parameters for the final model were estimated with reasonable precision with standard errors less than 50% of the mean for all parameters (typically, 15% or less). Due to large variability in the HR data and limited data at or above Emax, the PK/PD model did not support estimation of inter- individual variability for most parameters. Nevertheless, the stability of the PK/PD model parameter estimates was demonstrated using the bootstrap technique showing that the bootstrap estimates were essentially the same as the population estimates.

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.

Table 55: Selected plasma R-carvedilol PK parameters (PK population) -Study 367

Table 17 Summary of Selected Plasma R-carvedilol Pharmacokinetic Parameters (PK Population)

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

Data Source: Tables 8.05 and 8.06

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

Plasma concentrations of R-carvedilol were typically measurable over the 24 hour dose interval at each dose level for both formulations. Generally, with increasing dose of COREG IR and carvedilol CR, R-carvedilol exposure increased in an approximate dose proportional manner, while there was little change in t_{max}. The mean (standard deviation) Fluctuation Index (CR/IR) for R-carvedilol was 1.06 (0.49).

Table 56: Selected plasma S-carvedilol PK parameters (PK population) -Study 367

Table 18 Summary of Selected Plasma S-carvedilol Pharmacokinetic Parameters (PK Population)

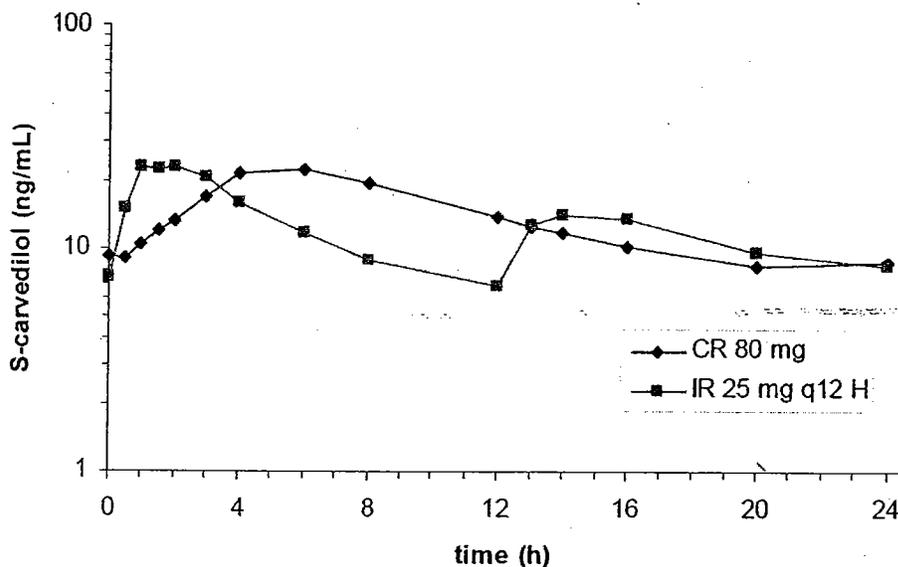
Regimen	N	AUC(0-t) ¹ (ng·hr/mL)	C _{max} ¹ (ng/mL)	T _{max} ² (hr)	C _τ ¹ (ng/mL)
IR 3.125mg bid	36	20.9 (73.6)	2.27 (72.1)	1.95 (0.00-6.00)	0.519 (123)
IR 6.25mg bid	49	43.0 (66.5)	4.33 (60.0)	1.52 (0.00-6.03)	1.24 (88.1)
IR 12.5mg bid	46	108 (59.4)	11.0 (59.9)	1.50 (0.00-11.75)	3.02 (85.9)
IR 25mg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

Data Source: Tables 8.07 and 8.08

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

Plasma concentrations of S-carvedilol were typically measurable for 24 hours at each dose level for both formulations. Generally, with increasing dose of COREG IR and carvedilol CR, S-carvedilol exposure increased in an approximately dose proportional manner, while there was little change in tmax. The mean (standard deviation) Fluctuation Index (CR/IR) for S-carvedilol was 1.04 (0.62).

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.

Table 57: Selected plasma R-carvedilol PK parameters

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Table 19 Comparisons of Interest for R-Carvedilol Pharmacokinetic Parameters (Original Dataset) (PK Population)

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

Data Source: Tables 8.01 and 8.03

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

Table 58: Selected plasma S-carvedilol PK parameters (PK population)

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Table 20 Comparisons of Interest for S-carvedilol Pharmacokinetic Parameters (Original Dataset) (PK Population)

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

Data Source: Tables 8.02 and 8.04

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

Based on the pooled analysis, R-carvedilol AUC (0-t) was, on average, 6% higher for carvedilol CR compared to COREG IR, while C_{max} and C_t were 5% and 8% lower, respectively. For the pooled analysis and in general for all dose groups, 90% intervals were within the 80%-125% equivalence range for AUC, C_t, and C_{max}. **Median R-carvedilol t_{max} was delayed by approximately 3 hours following CR dosing relative to COREG IR.**

Based on the pooled analysis, S-carvedilol AUC (0-t), C_{max}, and C_t were, on average, 16%, 0%, and 3% higher, respectively, for carvedilol CR compared to COREG IR. For the pooled analysis and in general for all dose groups, 90% confidence intervals were within the 80%-125%

equivalence range for AUC, Ct, and Cmax. Median S-carvedilol tmax was delayed by approximately 3 hours following CR dosing relative to COREG

Table 59: Comparisons between CR and IR formulation-PK population parameters

Table 21 Comparisons of Interest for R-Carvedilol Pharmacokinetic Parameters (Modified Dataset) (PK Population)

Parameter	Dose Group	Comparison of Interest	Point Estimate	90% CI	CVw% ³
AUC(0-t) ¹ ng.hr/mL	Pooled	CR:IR	1.07	(1.02, 1.12)	25.5
	3.125mg IR/ 10mg CR	CR:IR	1.19	(1.08, 1.31)	
	6.25mg IR/ 20mg CR	CR:IR	1.06	(0.98, 1.15)	
	12.5mg IR/ 40mg CR	CR:IR	1.02	(0.93, 1.11)	
	25mg IR/ 80mg CR	CR:IR	1.04	(0.95, 1.14)	
Cmax ¹ ng/mL	Pooled	CR:IR	0.95	(0.89, 1.01)	36.0
	3.125mg IR/ 10mg CR	CR:IR	1.01	(0.88, 1.15)	
	6.25mg IR/ 20mg CR	CR:IR	0.96	(0.85, 1.07)	
	12.5mg IR/ 40mg CR	CR:IR	0.89	(0.79, 1.00)	
	25mg IR/ 80mg CR	CR:IR	0.93	(0.82, 1.06)	
Ct ¹ ng/mL	Pooled	CR:IR	0.93	(0.86, 1.01)	44.8
	3.125mg IR/ 10mg CR	CR:IR	1.13	(0.96, 1.34)	
	6.25mg IR/ 20mg CR	CR:IR	0.94	(0.81, 1.08)	
	12.5mg IR/ 40mg CR	CR:IR	0.81	(0.70, 0.94)	
	25mg IR/ 80mg CR	CR:IR	0.90	(0.77, 1.05)	
	Mild CHF	CR:IR	0.92	(0.80, 1.06)	
	Moderate CHF	CR:IR	1.14	(0.99, 1.32)	
	Severe CHF	CR:IR	0.81	(0.70, 0.93)	
	Post MI LVD	CR:IR	0.85	(0.70, 1.02)	
	tmax (hr) ²	Pooled	CR:IR	3.03	
3.125mg IR/ 10mg CR		CR:IR	3.49	(2.54, 4.50)	
6.25mg IR/ 20mg CR		CR:IR	2.76	(2.28, 3.46)	
12.5mg IR/ 40mg CR		CR:IR	2.50	(1.75, 3.00)	
25mg IR/ 80mg CR		CR:IR	4.00	(3.50, 4.50)	

Data Source: Tables 8.46 and 8.48

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

Table 60: Comparisons between CR and IR formulation-PK population parameters

Table 22 Comparisons of Interest for S-carvedilol Pharmacokinetic Parameters (Modified Dataset) (PK Population)

Parameter	Dose Group	Comparison of Interest	Point Estimate	90% CI	CVw% ³
AUC(0-t) ¹ ng.hr/mL	Pooled	CR:IR	1.17	(1.12, 1.23)	24.5
	3.125mg IR/ 10mg CR	CR:IR	1.29	(1.17, 1.41)	
	6.25mg IR/ 20mg CR	CR:IR	1.14	(1.06, 1.24)	
	12.5mg IR/ 40mg CR	CR:IR	1.18	(1.08, 1.28)	
	25mg IR/ 80mg CR	CR:IR	1.10	(1.01, 1.20)	
C _{max} ¹ ng/mL	Pooled	CR:IR	1.00	(0.93, 1.06)	36.6
	3.125mg IR/ 10mg CR	CR:IR	1.09	(0.95, 1.25)	
	6.25mg IR/ 20mg CR	CR:IR	0.99	(0.88, 1.12)	
	12.5mg IR/ 40mg CR	CR:IR	0.96	(0.85, 1.09)	
	25mg IR/ 80mg CR	CR:IR	0.92	(0.81, 1.05)	
C _τ ¹ ng/mL	Pooled	CR:IR	1.07	(1.00, 1.15)	40.0
	3.125mg IR/ 10mg CR	CR:IR	1.21	(1.04, 1.40)	
	6.25mg IR/ 20mg CR	CR:IR	1.07	(0.94, 1.22)	
	12.5mg IR/ 40mg CR	CR:IR	1.02	(0.89, 1.16)	
	25mg IR/ 80mg CR	CR:IR	0.99	(0.86, 1.14)	
	Mild CHF	CR:IR	1.00	(0.88, 1.14)	
	Moderate CHF	CR:IR	1.27	(1.12, 1.45)	
	Severe CHF	CR:IR	0.93	(0.82, 1.06)	
	Post MI LVD	CR:IR	1.07	(0.90, 1.27)	
	t _{max} (hr) ²	Pooled	CR-IR	3.20	
3.125mg IR/ 10mg CR		CR-IR	3.49	(2.54, 4.49)	
6.25mg IR/ 20mg CR		CR-IR	2.98	(2.49, 3.50)	
12.5mg IR/ 40mg CR		CR-IR	2.30	(1.74, 3.00)	
25mg IR/ 80mg CR		CR-IR	4.00	(3.50, 4.46)	

Data Source: Tables 8.47 and 8.49

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

Statistical Analysis Details

Statistical analyses of PK data were performed under the direct auspices of Clinical Pharmacology Statistics and Programming (CPSP), GlaxoSmithKline Pharmaceuticals, Philadelphia.

Data was released to CPSP on 21-SEP-2005 by — via Harmonization of Analysis Reporting Process (HARP). Main results of the statistical analyses (point estimates and 90% confidence intervals) are presented to 2 decimal places; however, all calculations were carried out with greater precision. All statistical analyses were carried out using SAS 8.02 for UNIX running under the HARP environment.

All 173 subjects provided evaluable PK parameter data for statistical analysis and were included in the PK parameter analysis population. However, 6 subjects (776, 876, 1284, 1285, 1658 and 1659) provided anomalous PK data. It appears that the samples from these subjects were potentially mis-labeled as the corresponding concentration profiles do not reflect the characteristic IR or CR profiles. Thus, two sets of statistical analyses were performed, the first based on the original dataset, and the second based on modified treatment assignments for subjects 776, 876, 1284, and 1285, and modified 3hr and 24hr sample assignments for subjects 1658 and 1659 as it is believed this would more accurately represent the true CR and IR time course profiles for these subjects.

Statistical analyses based on the original dataset indicated that for all endpoints, with the exception of R(+) carvedilol Cmax, the dose group-by-formulation interaction term was statistically significant at the $\alpha=0.10$ significance level. To examine this, comparative plots of geometric least squares means for each formulation by dose group were generated (data on file, GSK). The graphical displays showed a similar relationship between CR and IR for each dose group (i.e., the plots by dose group generally appeared parallel to one another), suggesting that due to the large sample size, the model was sensitive to minor differences in the CR:IR comparison between the dose groups.

For the statistical analysis based on the original dataset: subject 1285 appeared as a potential statistical outlier in the analyses of AUC (0-t) for both enantiomers, while subjects 1284 and 1656 appeared as potential statistical outliers in the analyses of AUC (0-t) for S (-) carvedilol, and subject 1658 appeared as a potential statistical outlier in the analyses of Ct for S (-) carvedilol. Statistical analyses with these subjects removed from the analyses of the affected endpoints did not generally result in changes that impacted the statistical inference or notable changes to point estimates. For R (+) carvedilol AUC (0-t), analysis with the outlier excluded did not result in change to inference or notable change in the point estimate (data on file, GSK). For the S(-) enantiomer, analyses excluding the potential outliers resulted in an increase in the point estimates for the comparisons in the 12.5mg IR/40mg CR dose group from 13% higher to 21% higher and from 7% lower to no difference for AUC(0-t) and Ct, respectively (data on file, GSK). No other gross distributional assumption violations were noted.

In the statistical analyses with modified treatment assignments for subjects 776, 876, 1284 and 1285, and modified 3hr and 24hr sample assignments for subjects 1658 and 1659, the dose group-by-formulation interaction terms was no longer statistically significant for any endpoint. However, in this analysis, the strata-by-formulation interaction term was statistically significant (at the 5% level of significance) in the analyses of Ct for both enantiomers. Comparative plots of geometric least squares means for each formulation by subject group were generated to examine the nature of this interaction (data on file, GSK). For S(-) carvedilol Ct, this graphical display

showed that, on average, for moderate heart failure subjects, higher Ct concentrations were obtained following dosing with the CR formulation, while for the other subject groups, Ct concentrations were more similar between the two formulations. For R(+) carvedilol Ct, comparative plots of geometric least squares means for each formulation by subject group indicated that, on average, for the asymptomatic post MI LVD and severe CHF strata, concentrations were higher following dosing with the IR formulation, while in the moderate CHF group, concentrations were higher following dosing with the CR formulation. Statistical analysis results are presented pooled across all subject and dose groups, as well as by dose group for descriptive purposes. No outliers or gross distributional assumption violations were noted in the statistical analyses on this dataset.

Pharmacokinetic Conclusion

- Carvedilol CR was equivalent to COREG IR with regard to R- and S-carvedilol AUC, Ct, and Cmax.

5.2 Pharmacodynamics

RESULTS: Pharmacodynamic Parameters

Predicted pharmacodynamic parameters for the CR and IR formulations are summarized in Table 61.

Table 61: Predicted Pharmacodynamic parameters (PK population)

Table 23 Summary of Predicted Pharmacodynamic Parameters (PK Population)

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

Data Source: Table 8.24

1. Arithmetic mean (CVb%)

For both the IR and CR formulations, there was an increasing pharmacodynamic effect with increasing dose. As expected for this pharmacodynamic measurement, pharmacodynamic effect tended to plateau with increasing dose.

Statistical Analysis of Pharmacodynamic Parameters

Statistical analysis results for carvedilol predicted PD parameters based on the original PD parameter dataset are presented in Table 34 below.

Table 62: Comparisons of predicted PD parameters between CR and IR- Study 902

Table 24 Comparisons of Interest for Carvedilol Predicted Pharmacodynamic Parameters (Original Dataset) (PK Population)

Parameter	Dose Group	Comparison of Interest	PE	90% CI ²	SDw ³
AUEC ¹	Pooled	CR:IR	1.07	(1.04, 1.10)	16.9
	3.125mg bid IR/10mg CR	CR:IR	1.27	(1.08, 1.46)	
	6.25mg bid IR/20mg CR	CR:IR	1.00	(1.00, 1.18)	
	12.5mg bid IR/40mg CR	CR:IR	1.08	(1.03, 1.13)	
	25mg bid IR/80mg CR	CR:IR	1.02	(0.98, 1.05)	
PDmax ¹	Pooled	CR:IR	0.99	(0.96, 1.02)	1.02
	3.125mg bid IR/10mg CR	CR:IR	1.14	(1.01, 1.27)	
	6.25mg bid IR/20mg CR	CR:IR	0.99	(0.92, 1.06)	
	12.5mg bid IR/40mg CR	CR:IR	0.96	(0.91, 1.00)	
	25mg bid IR/80mg CR	CR:IR	0.96	(0.92, 1.00)	
PDmin ¹	Pooled	CR:IR	1.01	(0.95, 1.06)	0.97
	3.125mg bid IR/10mg CR	CR:IR	1.18	(0.84, 1.51)	
	6.25mg bid IR/20mg CR	CR:IR	1.01	(0.86, 1.17)	
	12.5mg bid IR/40mg CR	CR:IR	0.99	(0.90, 1.07)	
	25mg bid IR/80mg CR	CR:IR	0.98	(0.92, 1.04)	

Data Source: Table 8.25

1. Point estimate is the point estimate for the difference normalized to the mean IR response
2. Lower and upper interval estimates are the lower and upper interval estimates for the difference normalized to the mean IR response
3. SDw represents a pooled estimate of within-subject variability across regimens

For the pooled analysis, AUEC and PDmin were, on average, 7% and 1% higher, respectively, for the CR formulation relative to the IR formulation while PDmin was 1% lower. Corresponding 90% confidence intervals were within the equivalence range of (0.80-1.25). By dose group, all except the 3.125mg IR/10mg CR dose group comparison for the three parameters had 90% confidence intervals within this same equivalence range.

Statistical analysis results for predicted PD parameters based on a modified PD parameter dataset are presented in Table 19. The modified dataset had treatment assignments switched for subjects 776, 876, 1284, and 1285 and S(-)-carvedilol concentration values (at 3 and 24 hours) switched for subjects 1658 and 1659 as it is believed this would more accurately represent the true CR and IR time course profiles for these subjects (see Section 5.8.5). For PDmin, a statistically significant subject group-by-formulation interaction was detected in the analysis of this dataset (at the 5% level of significance), suggesting differences in the CR:IR comparison across the subject groups. Thus, for PDmin, treatment comparisons by subject group are also included in the Table 25.

Safety

Safety evaluation will be conducted at Screening/Baseline visits and at each study visit during the Treatment Phase of each study medication. Additionally, safety assessments will be done within 4-7 days following any necessary or elective down-titration of study medication.

The following will be assessed at Screening/Baseline visits:

• Chest X ray if not done in last 6 months • Complete Physical Exam • Safety Clinical Laboratory Assessments • Urinalysis • Vital signs (systolic and diastolic blood pressure and heart rate) in sitting position • ECG (12 lead) • Height/Body Weight • Cardiopulmonary exam The following will be conducted at all subsequent scheduled visits after enrollment and beginning study medication:

• Interim Physical Exam • Vital Signs (sitting and standing) and Body Weight • Tolerability Assessment • Safety Clinical Laboratory Assessments (includes at follow-up visit following early

5.3 Exposure-Response Relationships

A sigmoid E-max model was used to describe the dose-response relationship in 24hr ABPM of mean DBP.

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

6 INTEGRATED REVIEW OF EFFICACY

There is no integrated review of efficacy as there was only one study.

6.1 Indication

Treatment of essential hypertension, congestive heart failure and reduction of cardiovascular mortality.

6.1.1 Methods

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.

6.1.2 General Discussion of Endpoints

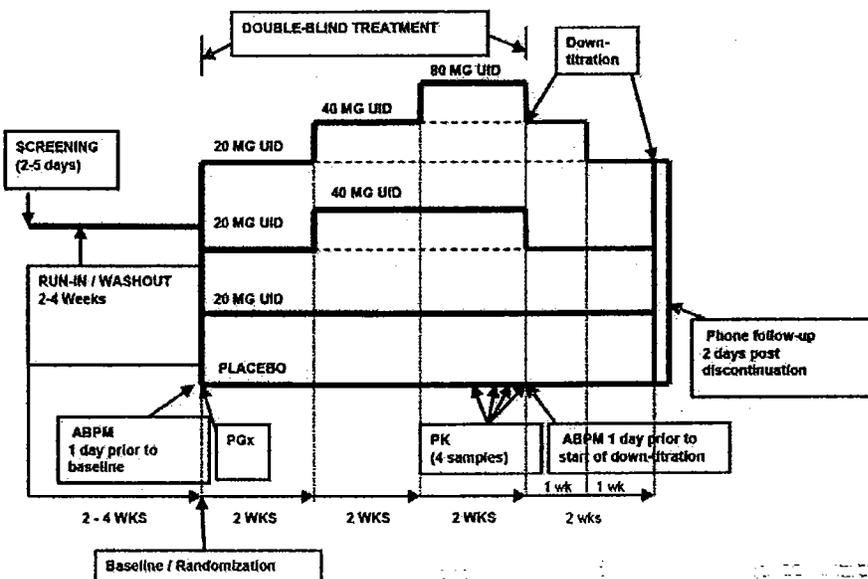
The efficacy analyses were based on the ITT efficacy population. The primary time point of interest or study endpoint was the end of treatment up-titration. This corresponded to the last available efficacy assessment in the up-titration phase which was Week 6 (or longer depending on the subjects re-challenge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

SiDBP determined at trough (24±2 hrs, Visit 8) served as the primary efficacy measure. The primary measure of effect was the placebo-corrected change from baseline to Week 8 in trough SiDBP. This was acceptable.

Secondary efficacy measures of effect included change from baseline in trough SiSBP, peak sitting BPs, and trough StSBP and StDBP. These were also acceptable.
Statistics for endpoints- See Statistical review by Dr Steve Bai.

6.1.3 Study Design - 367



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

Table 63: Study Assessments - 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 ²							

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

6.1.4 Efficacy Findings

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])

Following once daily administration of carvedilol CR (20mg, 40mg or 80mg), ABPM measured mean reductions from baseline in mean 24hr DBP were significantly different from that seen following administration of placebo. Ad hoc analysis indicated that mean reductions from baseline in mean 24hr SBP by ABPM following once daily administration of carvedilol CR (20mg, 40mg or 80mg), were significantly different from that seen following administration of placebo.

- Trough (20-24hr) DBP and SBP levels by ABPM for subjects in the 40mg and 80mg carvedilol CR groups were significantly lower than those for subjects in the placebo group. In the 20mg carvedilol CR group however, DBP and SBP changes were not statistically significantly different to those seen with placebo. Cuff DBP and SBP were similar and supportive of data measured by ABPM.

- At trough (20-24hr) the mean DBP change from baseline measured by ABPM was greater than 60% of the mean DBP change at peak (3-7hr) for all carvedilol CR treatment groups.

- A consistent and similar reduction from baseline in both SBP and DBP was maintained over the entire 24hr period following administration of carvedilol CR.
- Coreg CR is 4 to 7 times more likely than placebo to achieve a reduction from baseline in sDBP of at least 10mmHg at doses of 20mg, 40mg, and 80mg. Table 5 above reproduced below.

DBP, mmHg	Placebo N=76	Carvedilol CR		
		20mg N=82	40mg N=76	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 4 above reproduced below)

Trough (20-24hr), DBP and SBP, mmHg	Placebo N=76	Carvedilol CR		
		20mg N=82	40mg N=76	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.

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 [GlaxoSmithKline Document Number MP/0007/SKF-105517/1].

Trough to Peak ratio for SiDBP

Table 64: Trough to Peak ratio of SiDBP at baseline and week 8/LOCF - ITT- Study 367
Table 23 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	40mg N=76	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)

Subgroup analyses: Age, Gender and Race

The sponsor applied the same model used for analysis of primary efficacy end point for secondary efficacy variables. The sponsor however did not adjust for multiplicity among the secondary variables. This makes the analyses of all secondary variables rather difficult to interpret. For example, females given 20 mg had a mean adjusted change from baseline of -8.04mmHg compared to males with -3.39 mmHg while blacks given 80mg of the drug had a mean adjusted change of -1.58 mmHg compared to White/Caucasians given the same dose with -10.70 mmHg. These several fold differences may be due to small numbers and other factors. (Table 65). In the case of blacks, there was no statistically significant difference between them and placebo for all three doses (p=0.1607; p=0.2351, and p=0.7785 for 20mg, 40 mg, and 80 mg COREG CR, respectively. This observed trend is suggestive of the drug not being as effective in blacks compared to Whites/Caucasians. There were very few patients over the age of 65 years.

Table 65: Subgroup analyses for change from baseline in mean DBP by ABPM ITTE and LOCF - 367

Subgroup DBP, mmHg	Placebo N=76	Carvedilol CR		
		20mg N=82	40mg N=76	80mg N=86
Gender				
Female, n ¹	14	17	27	22
Model-Adjusted Change from Baseline, LSMean±SE	0.75±2.94	-7.29±2.48	-8.46±1.95	-11.94±2.06
Difference from Placebo, Mean		-8.04	-9.21	-12.69
95% CI ²		(-16.53, 0.44)	(-16.88, -1.53)	(-20.01, -5.38)
p-value ³		0.0624	0.0203	0.0013
Male, n ¹	44	52	36	47
Model-Adjusted Change from Baseline, LSMean±SE	-0.73±1.12	-4.12±1.01	-8.61±1.25	-8.90±1.05
Difference from Placebo, Mean		-3.39	-7.89	-8.17
95% CI ²		(-6.28, -0.51)	(-11.11, -4.67)	(-11.15, -5.20)
p-value ³		0.0215	<0.0001	<0.0001
Race				
Black, n ¹	10	12	12	6
Model-Adjusted Change from Baseline, LSMean±SE	-2.24±3.34	-8.45±2.85	-7.80±2.80	-3.81±4.45
Difference from Placebo, Mean		-6.21	-5.56	-1.58
95% CI ²		(-15.22, 2.81)	(-15.21, 4.09)	(-13.43, 10.28)
p-value ³		0.1607	0.2351	0.7785
White/Caucasian, n ¹	46	54	47	58
Model-Adjusted Change from Baseline, LSMean±SE	0.57±1.04	-3.47±0.98	-6.85±1.04	-10.13±0.92
Difference from Placebo, Mean		-4.03	-7.42	-10.70
95% CI ²		(-6.75, -1.32)	(-10.15, -4.69)	(-13.24, -8.00)
p-value ³		0.0039	<0.0001	<0.0001
Other, n ^{1,4}	2	3	4	5
Age Group				
Age <65 years, n ¹	54	61	58	64
Model-Adjusted Change from Baseline, LSMean±SE	-0.43±0.95	-3.91±0.90	-7.58±0.92	-9.52±0.88
Difference from Placebo, Mean		-3.49	-7.16	-9.09
95% CI ²		(-5.97, -1.01)	(-9.65, -4.67)	(-11.56, -6.63)
p-value ³		0.0061	<0.0001	<0.0001
Age ≥65 years, n ^{1,4}	4	8	5	5

continued

Subgroup DBP, mmHg	Placebo N=76	Carvedilol CR		
		20mg N=82	40mg N=76	80mg N=86
BMI Category				
BMI <27kg/m ² , n ¹	17	17	16	15
Model-Adjusted Change from Baseline, LSMean±SE	-0.68±2.63	-9.62±2.56	-2.85±3.21	-8.72±2.43
Difference from Placebo, Mean		-8.95	-2.17	-8.04
95% CI ²		(-16.93, -0.97)	(-11.15, 6.81)	(-16.10, 0.02)
p-value ³		0.0297	0.6212	0.0504
BMI ≥27kg/m ² , n ¹	41	52	47	54
Model-Adjusted Change from Baseline, LSMean±SE	0.17±1.07	-4.05±0.94	-8.32±1.01	-8.89±0.95
Difference from Placebo, Mean		-4.22	-8.49	-10.06
95% CI ²		(-6.98, -1.47)	(-11.27, -5.71)	(-12.80, -7.32)
p-value ³		0.0029	<0.0001	<0.0001
Diabetes Status at Baseline				
Non-diabetic, n ¹	55	65	58	64
Model-Adjusted Change from Baseline, LSMean±SE	0.03±0.97	-4.59±0.89	-7.86±0.96	-9.71±0.91
Difference from Placebo, Mean		-4.61	-7.89	-9.74
95% CI ²		(-7.11, -2.12)	(-10.39, -5.39)	(-12.28, -7.20)
p-value ³		0.0004	<0.0001	<0.0001
Diabetic, n ^{1,4}	3	4	5	5

Data Source: Table 7.34, Table 7.35, Table 7.36, Table 7.37 and Table 7.38

1. n=number of subjects with ABPM data at baseline and at the study endpoint (end of up-titration).
2. Based on ANCOVA: change=treatment+center+baseline+disease history.
3. Based on pairwise comparisons.
4. Insufficient subjects in this subgroup for 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.

Table 66: Number (%) responders at week 8 - ITTE- Study 367

Responder Analysis	Placebo N=76	Carvedilol CR		
		20mg N=82	40mg N=76	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 ≥ 10 mmHg.
3. Odds (logistic regression: odds= treatment+disease history) of having ≥ 10 mmHg reduction from baseline in sDBP at week 6 compared to placebo. Odds ratio>1 indicates favorable effect of treatment over placebo.

6.1.5 Clinical Microbiology

Not applicable

6.1.6 Efficacy Conclusions

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])

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 20 mg, 40 mg, and 80 mg carvedilol CR groups, respectively, compared 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

Results of secondary objectives: 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.

Secondary: Results of Secondary objectives

- Comparison of mean DBP measured by ABPM at the drug-trough blood levels (20-24hr) for carvedilol CR compared to placebo treatment - See Table 28
- Trough (20-24hr) to peak (3-7hr) DBP ratios using 24-hour ABPM; See Table 31
- The dose-response relationship between incremental doses of carvedilol CR and mean 24hr ABPM DBP; See Table 25
- Blood pressure changes in the morning, afternoon, and at night using ABPM; See Tables 35-37.
- 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; See Tables 28-29.
- Comparisons between treatment groups in the percentage of responders (response was defined as a sitting diastolic blood pressure (sDBP) reduction from baseline of ≥ 10 mmHg); See Tables 24 and 65.
- Safety of the CR formulation in this subject population; See Tables 40 - 44
- Population pharmacokinetics after administration of the carvedilol CR formulation. See Biopharm review.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

See Section 1.3.3

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Safety results: The mean duration of each period was:

Table 67 : Drug Exposure-367

Subject Exposure (days)	Number (%) of Subjects				Total N=337
	Placebo (N=84)	Carvedilol CR			
		20mg (N=87)	40mg (N=78)	80mg (N=88)	
≤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

During the down-titration phase, more AEs were reported in the carvedilol CR 40mg treatment group (15% of subjects) than the other groups. No pattern of AEs by study phase was observed. 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.

Adverse events

AEs reported for the carvedilol CR groups were similar in nature, intensity and relationship to study medication to those reported for the placebo group.

A low percentage of subjects in all treatment groups experienced AEs during the study and few subjects withdrew as a result of an AE.

There was a low incidence of SAEs, only one of which was considered related to treatment with study medication, and there were no deaths during the study.

Carvedilol CR was safe in this subject population

Summary of safety: See Section 1.3.3 and Section 9

7.1.1 Deaths Nil

7.1.2 Other Serious Adverse Events

See Section 1.3.3

7.1.3 Dropouts and Other Significant Adverse Events

See Section 12

7.1.3.1 Overall profile of dropouts-See Table 7

In Study 369, dizziness (3%) and headache (2%) were the most frequently reported AEs for the carvedilol CR treatment period; for COREG IR, only dizziness was reported in >1% of subjects (reported incidence of 2%). The incidence of emergent AEs considered by the investigator to be related to treatment with the study medication was low (=2%) for any single event for both COREG IR and carvedilol CR. Emergent AEs considered by the investigator to be related to treatment with the study medication were reported for 5 subjects (3%) during the COREG IR treatment period and 12 subjects (6%) during the carvedilol CR treatment period.

7.1.3.2 Adverse events associated with dropouts - Table 7

7.1.3.3 Other significant adverse events See section 1.3 and case narratives in Section 12.

7.1.4 Other Search Strategies

There is no evidence that treatment with carvedilol CR at doses of 20mg, 40mg, or 80mg OD was associated with any significant safety issues compared to treatment with placebo.

7.1.5 Common Adverse Events

The most common side effects associated with COREG IR for HF, based on the experience from controlled trials and as reflected in the current USPI are dizziness, fatigue, weight increase, hypotension, and bradycardia (reported in =10% of patients [both mild-to-moderate and severe populations] and more frequently on COREG IR).

Worsening HF symptoms were also reported, but with equal or greater frequency in placebo-treated patients. In the CAPRICORN trial that enrolled patients with LVD post-MI the only additional common AEs (reported in >3% of patients and more frequently on COREG IR) were

dyspnea, lung edema and anemia. The most common side effect of COREG IR in hypertension trials was dizziness (6%) which was comparable to the placebo incidence of 5%.

See Section 1.3.3 and Section 9.

7.1.5.1 Eliciting adverse events data in the development program

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

7.1.5.3 Incidence of common adverse events See table 7

7.1.5.4 Common adverse event tables

7.1.5.5 Identifying common and drug-related adverse events

7.1.5.6 Additional analyses and explorations

7.1.6 Less Common Adverse Events

7.1.7 Laboratory Findings

A small number of treatment emergent AEs related to laboratory values was recorded. None of the lab-related AEs led to withdrawal of the subjects from the study and only one AE describing an increased ALT for a subject in the carvedilol CR 80mg treatment group was considered by the investigator to be related to treatment with study medication. In this particular subject, the ALT was normal at baseline and week 6 but increased to $<1.5x$ upper limit of normal at week 8 and resolved on follow-up. The AST, total bilirubin and alkaline phosphatase were within normal limits. Of the remaining subjects in which treatment emergent AEs were recorded, one subject in the carvedilol CR 20mg treatment group had an isolated elevated bilirubin which was $<3x$ upper limit of normal and had not resolved at week 8. ALT, AST and alkaline phosphatase were within normal limits. Four subjects had increased ALT and AST (two subjects in the carvedilol CR 80mg treatment group and two subjects in the carvedilol CR 40mg treatment group) with normal total bilirubin and alkaline phosphatase. One subject in the 80 mg treatment group had elevations $<2x$ upper limit of normal which were reported only at baseline. The AST and ALT were normal at weeks 6 and 8. The other subject in the 80mg treatment group had an elevated ALT $<2.5x$ upper limit of normal which persisted at follow up and an elevated AST $<2x$ upper limit of normal at weeks 6 and 8 that resolved at follow up. One of the subjects in the 40 mg treatment group had an ALT $<3x$ upper limit of normal and an AST $<4x$ upper limit of normal that

persisted at follow up. The other subject in the 40 mg treatment group had an elevated ALT <3x upper limit of normal and an AST <4x upper limit of normal only at week 8 with normal ALT and AST at baseline and week 6 (Table 67).

Table 68 Abnormal laboratory values of potential concern - 367

Laboratory Parameter	Phase	Range of Clinical Concern	Number (%) ¹ of Subjects			
			Placebo N=84	Carvedilol CR		
				20mg N=87	40mg N=78	80mg N=88
ALT (IU/L)	End Up-Titration	High	0	0	0	1/69 (1)
	Study End	High	0	0	0	1/69 (1)
AST (IU/L)	End Up-Titration	High	0	0	0	1/73 (1)
	Study End	High	0	0	2/62 (3)	1/69 (1)
	Follow-Up	High	0	0	1/3 (33)	0
BUN (mmol/L)	Baseline	High	0	0	0	1/85 (1)
Hematocrit	End Up-Titration	Low	0	1/73 (1)	0	0
	Study End	Low	0	1/72 (1)	0	0
Hemoglobin	Baseline	Low	1/80 (1)	0	0	0
	Week 2	Low	1/6 (17)	0	0	0
	End Up-Titration	Low	0	1/73 (1)	0	0
	Study End	Low	0	1/72 (1)	0	0
Platelets (GI/L)	End Up-Titration	High	0	1/72 (1)	0	0
		Low	0	1/72 (1)	0	0
Potassium (mmol/L)	Baseline	High	0	1/82 (1)	1/75 (1)	1/85 (1)
	End Up-Titration	High	0	0	1/64 (2)	1/73 (1)
	Week 7	High	0	1/2 (50)	0	0
	Study End	High	2/57 (4)	0	0	3/69 (4)
WBC	Baseline	Low	0	1/79 (1)	2/74 (3)	0
	Week 2	Low	0	1/5 (20)	0	0
	End Up-Titration	Low	0	1/73 (1)	0	0
	Study End	Low	0	0	0	1/68 (1)

Data Source: Table 8.26

1. Percent=number of subjects in the high or low category for a specified laboratory test /number of subject with values for that specified laboratory test.

Table 69: Laboratory values and ranges ITT - 367

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Population

Laboratory Parameter	Phase	Reference Range	Number (%) ¹ of Subjects			
			Placebo N=84	Carvedilol CR		
				20mg N=87	40mg N=78	80mg N=88
ALT (IU/L)	Baseline	High	7/83 (8)	4/82 (5)	5/76 (7)	6/85 (7)
	End Up-Titration	High	5/66 (8)	5/74 (7)	2/64 (3)	6/74 (8)
	Study End	High	7/57 (12)	2/73 (3)	5/62 (8)	7/69 (10)
Alk. Phos. (IU/L)	Baseline	High	2/83 (2)	1/82 (1)	3/76 (4)	2/85 (2)
	End Up-Titration	High	2/66 (3)	1/74 (1)	3/64 (5)	1/74 (1)
	Study End	High	1/57 (2)	1/73 (1)	2/62 (3)	1/69 (1)
AST (IU/L)	Baseline	High	4/83 (5)	4/82 (5)	1/75 (1)	7/85 (8)
	End Up-Titration	High	3/66 (5)	2/74 (3)	2/64 (3)	3/73 (4)
	Study End	High	4/57 (7)	2/72 (3)	3/62 (5)	2/69 (3)
BUN (mmol/L)	Baseline	High	0	1/82 (1)	0	1/85 (1)
	End Up-Titration	High	1/66 (2)	0	1/64 (2)	0
		Low	1/66 (2)	0	0	0
	Study End	High	0	1/73 (1)	3/62 (5)	1/69 (1)
Calcium (mmol/L)	Baseline	High	2/83 (2)	1/82 (1)	2/75 (3)	6/85 (7)
	End Up-Titration	High	1/66 (2)	1/74 (1)	0	1/73 (1)
	Study End	High	2/57 (4)	1/72 (1)	2/62 (3)	0
		Low	1/57 (2)	0	0	1/69 (1)
Chloride (mmol/L)	Baseline	High	6/83 (7)	6/82 (7)	7/76 (9)	6/85 (7)
	End Up-Titration	High	5/66 (8)	7/74 (9)	8/64 (13)	9/74 (12)
	Study End	High	5/57 (9)	8/73 (11)	5/62 (8)	10/69 (14)
Creatinine (umol/L)	Baseline	High	1/83 (1)	2/82 (2)	0	3/85 (4)
	End Up-Titration	High	2/66 (3)	3/74 (4)	1/64 (2)	3/74 (4)
	Study End	High	0	1/73 (1)	1/62 (2)	2/69 (3)
Hematocrit	Baseline	High	5/80 (6)	8/79 (10)	6/74 (8)	5/83 (6)
		Low	5/80 (6)	2/79 (3)	5/74 (7)	5/83 (6)
	End Up-Titration	High	3/66 (5)	5/73 (7)	5/63 (8)	3/71 (4)
		Low	4/66 (6)	5/73 (7)	2/63 (3)	8/71 (11)
	Study End	High	4/55 (7)	5/72 (7)	5/61 (8)	3/68 (4)
		Low	2/55 (4)	2/72 (3)	4/61 (7)	3/68 (4)
Hemoglobin (g/L)	Baseline	High	6/80 (8)	4/79 (5)	4/74 (5)	5/83 (6)
		Low	6/80 (8)	3/79 (4)	3/74 (4)	6/83 (7)
	End Up-Titration	High	0	5/73 (7)	2/63 (3)	0
		Low	4/66 (6)	5/73 (7)	2/63 (3)	9/71 (13)
	Study End	High	2/55 (4)	4/72 (6)	2/61 (3)	0
		Low	2/55 (4)	3/72 (4)	2/61 (3)	10/68 (15)
Platelets (G/L)	End Up-Titration	High	1/66 (2)	1/72 (1)	1/63 (2)	0
		Low	1/70	0	0	0
	Study End	Low	0	2/71 (3)	0	0
Potassium (mmol/L)	Baseline	High	0	2/82 (2)	1/75 (1)	1/85 (1)
		Low	1/83 (1)	1/82 (1)	0	0
	End Up-Titration	High	0	1/74 (1)	1/64 (2)	1/73 (1)
		Low	1/66 (2)	1/74 (1)	1/64 (2)	0
	Study End	High	2/57 (4)	0	0	4/69 (6)
		Low	1/57 (2)	2/72 (3)	2/62 (3)	0
RBC (T/L)	Baseline	High	1/80 (1)	5/79 (6)	2/74 (3)	3/83 (4)
		Low	2/80 (3)	2/79 (3)	4/74 (5)	2/83 (2)

Continued

Laboratory Parameter	Phase	Reference Range	Number (%) ¹ of Subjects			
			Placebo N=84	Carvedilol CR		
				20mg N=87	40mg N=78	80mg N=88
RBC (T/L)	End Up-Titration	High	0	5/73 (7)	3/63 (5)	0
		Low	3/66 (5)	3/73 (4)	2/63 (3)	2/71 (3)
	Study End	High	1/55 (2)	3/72 (4)	4/61 (7)	1/68 (1)
		Low	2/55 (4)	3/72 (4)	3/61 (5)	2/68 (3)
Sodium (mmol/L)	Baseline	High	1/83 (1)	1/82 (1)	2/76 (3)	1/85 (1)
		Low	0	2/82 (2)	0	0
	End Up-Titration	High	2/66 (3)	0	1/64 (2)	1/74 (1)
		Study End	High	3/57 (5)	0	0
Study End	Low	0	1/73 (1)	0	0	
	Low	0	1/73 (1)	0	0	
Bilirubin (umol/L)	Baseline	High	2/83 (2)	1/82 (1)	2/76 (3)	3/85 (4)
	End Up-Titration	High	1/66 (2)	1/74 (1)	2/64 (3)	1/74 (1)
	Study End	High	1/57 (2)	2/73 (3)	1/62 (2)	2/69 (3)
Urine Albumin/ Creatinine Ratio (mg/mmol)	Baseline	High	11/78 (14)	10/75 (13)	14/71 (20)	15/72 (21)
	End Up-Titration	High	12/63 (19)	9/67 (13)	10/58 (17)	10/65 (15)
	Study End	High	9/53 (17)	7/63 (11)	9/61 (15)	10/63 (16)
WBC (G/L)	Baseline	High	0	2/79 (3)	2/74 (3)	1/83 (1)
		Low	4/80 (5)	2/79 (3)	3/74 (4)	2/83 (2)
	End Up-Titration	Low	2/66 (3)	5/73 (7)	1/63 (2)	1/71 (1)
		Study End	High	0	2/72 (3)	0
Study End	Low	1/55 (2)	2/72 (3)	1/61 (2)	2/68 (3)	

Data Source: Table 8.25

1. Percent=number of subjects in the high or low category for a specified laboratory test /number of subject with values for that specified laboratory test.

7.1.7.1 Overview of laboratory testing in the development program

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities

7.1.7.4 Additional analyses and explorations

7.1.7.5 Special assessments

Urinalysis at screening, baseline, Visit 4, end of study and early withdrawal measured the following: glucose, total protein, blood, ketones, albumin and creatinine. At Visit 4 (Week 6) results for occult blood, glucose and ketones were similar across the treatment groups with at least 94% of samples negative in all cases. Samples were negative for urine protein for 78% of subjects in the placebo group compared to 90%, 84% and 86% of subjects in the 20mg, 40mg and 80mg carvedilol CR groups, respectively. One subject in the carvedilol CR 40mg group was withdrawn for proteinuria.

7.1.8 Vital Signs

Few subjects had vital signs of potential clinical concern during the study. Subjects with vital signs of potential clinical concern during the treatment period are summarized in Table 69.

Table 70: Vital signs in the range of potential clinical concern while subjects were on therapy

Laboratory Parameter, n ¹ /n ² (%)	High/Low	Placebo N=84	Carvedilol CR			
			20mg N=87	40 mg N=84	80mg N=87	
Standing SBP, mmHg	Week 2	High	1/82 (1)	1/81 (1)	0	0
Sitting DBP, mmHg	Week 8	High	1/60 (2)	0	0	0
	Week 6	High	1/67 (1)	0	0	0
Standing DBP, mmHg	Week 0	High	1/84 (1)	0	0	0
Standing Heart Rate, bpm	Week 2	High	0	0	1/76 (1)	0
	Week 6	High	1/67 (1)	0	0	0
	Week 8	High	1/60 (2)	0	0	0
	Week 8	High	0	0	0	1/72 (1)

Data Source: Table 8.29

1. Number of subject in High/Low categories.
2. Number of subject with specified laboratory test value.

7.1.8.1 Overview of vital signs testing in the development program

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

7.1.8.4 Additional analyses and explorations

Nil.

7.1.9 Electrocardiograms

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

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 71 below.

ECGs were performed at the screening visit and at the start of down-titration, Visit 4, after removal of the ABPM device, or at early withdrawal. Only one subject (in the carvedilol CR 40mg treatment group) had a clinically significant abnormal ECG value

Table 71: Abnormal clinically significant ECG findings -367

ECG finding, n/N (%)	Placebo (N=84)	Carvedilol CR		
		20mg (N=87)	40mg (N=78)	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

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

Adverse events

Discontinuations due to adverse events
See Tables 13 and 41.

7.1.10 Immunogenicity

Not applicable

7.1.11 Human Carcinogenicity

Not applicable because both products have been approved.

7.1.12 Special Safety Studies

Not applicable.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Not applicable.

7.1.14 Human Reproduction and Pregnancy Data

Not applicable

7.1.15 Assessment of Effect on Growth

Not applicable

7.1.16 Overdose Experience

Symptoms of an overdose of carvedilol phosphate include severe hypotension, bradycardia, heart failure, cardiogenic shock and cardiac arrest. There may also be respiratory problems, bronchospasm, vomiting, disturbed consciousness, and generalized seizures.

Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication (suspected or confirmed, intentional or unintentional) were to be communicated to GSK within 24 hours and were to be fully documented as a serious adverse event (SAE). Details of any signs or symptoms and their management were to be recorded including details of any antidote administered.

In addition to general procedures, the vital signs were to be monitored and corrected, if necessary, under intensive care conditions. The following could be given as antidotes:

- Atropine: 2mg, intravenous (i.v.) (for excessive bradycardia).
- Glucagon: initially 5mg to 10mg i.v. rapidly over 30seconds, then 5mg/hr continuous infusion (to support cardiovascular function).
- Sympathomimetics according to body weight and effect: dobutamine, isoprenaline, orciprenaline or adrenaline.
- If peripheral vasodilatation dominated the intoxication profile then norepinephrine or noradrenaline were to be administered with continuous monitoring of the circulatory conditions.
- In the case of drug-resistant bradycardia, pacemaker therapy was to be initiated. In the case of bronchospasm, β -sympathomimetics (as aerosol, or if ineffective, also as an i.v.) or aminophylline i.v. were to be given. In the event of seizures, slow i.v. injection of diazepam or clonazepam was recommended.

In the event of severe intoxication with symptoms of shock, treatment with antidotes was to be continued for a sufficiently long period of time since prolonged elimination half-life and redistribution of carvedilol CR from deeper compartments was to be expected.

Not applicable.

7.1.17 Postmarketing Experience

Not applicable.

7.2 Adequacy of Patient Exposure and Safety Assessments

This is considered to be adequate for a drug of this class, however, it is inadequate for subgroup analyses as it is not powered enough for such analyses.

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

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

For description see overview of clinical program on pages 25- 42 and section 6 on safety. These studies are considered adequate to evaluate safety by this reviewer.

7.2.1.1 Study type and design/patient enumeration

Study type is acceptable and patients' enumeration is accurate as every patient was accounted for.

**APPEARS THIS WAY
ON ORIGINAL**

See Section 1.3

7.2.1.2 Demographics

See Section 1.3 Tables 15-16.

7.2.1.3 Extent of exposure (dose/duration)

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)
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Min.	1	1
Max.	38	22
Total Exposure in Subject Years	8.1	6.87

Data Source: Table 9.01

See Section 1.3

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

See Section 1.3 Tables 31- 40

7.2.2 Other studies

7.2. Postmarketing experience

Not applicable as combination product is not yet on the market.

7.2. Literature

See section 11

7.2.3 Adequacy of Overall Clinical Experience

See section 1.3

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

7.2.5 Adequacy of Routine Clinical Testing

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

This is adequate.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

7.2.8 Assessment of Quality and Completeness of Data

This is adequate and acceptable

7.2.9 Additional Submissions, Including Safety Update

Not required as all studies have been completed.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

7.4 General Methodology

This was acceptable.

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Parameter	Comparison of Interest	PE	90% CI ¹
AUEC ²	CR:IR	1.07	(1.04, 1.10)
PDmax ²	CR:IR	0.99	(0.96, 1.02)
PDmin ²	CR:IR	1.01	(0.95, 1.06)

Data source: m2.7.2 Table 30

1. Lower and upper interval estimates are the lower and upper interval estimates for the difference normalized to the mean IR response.
2. Point estimate is the point estimate for the difference normalized to the mean IR response

Based on the statistical analysis of data pooled across all subject and dose groups, carvedilol CR had equivalent predicted PD effects (AUEC, PDmin, and PDmax) compared to IR carvedilol.

7.4.1.2 Combining data

Not applicable.

7.4.2 Explorations for Predictive Factors

S(-)-carvedilol concentration-time data obtained in Study 369 and the PK/PD model developed in healthy volunteers were used to predict the β_1 -blocking effect of carvedilol in these subjects. Statistical analysis results for the predicted PD parameters of carvedilol are presented in Table 61.

7.4.2.1 Explorations for dose dependency for adverse findings

7.4.2.2 Explorations for time dependency for adverse findings

7.4.2.3 Explorations for drug-demographic interactions

7.4.2.4 Explorations for drug-disease interactions

7.4.2.5 Explorations for drug-drug interactions

7.4.3 Causality Determination

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Subjects will receive blinded study medication for a total of 8 weeks, which includes 6 weeks during the up-titration phase and 2 weeks during the down-titration phase. Both the investigator and subject will be blinded to the dose. The investigator or study coordinator will call RAMOS and will be given the subject's randomization number and three container numbers which correspond to the next bottles of study medication that the subject is to receive. The investigator will be required to enter the dose level of study medication that the subject is to receive. If a subject is on dose level 2 and needs to downtitrate, the investigator will enter dose level 1 into the RAMOS system. Further instructions will be provided in the RAMOS worksheets which will be sent to the site with the study medication.

Carvedilol phosphate MR: It is intended that the 20 mg, 40 mg, and 80 mg once daily dose strengths in the carvedilol phosphate MR formulation are approximately equivalent to the 6.25 mg, 12.5 mg and 25 mg bid immediate release dose, respectively. Subjects will be titrated to the assigned randomized target dose or to the maximally tolerated dose. Each strength of MR is different in size and color.

8.2 Drug-Drug Interactions

Drug Interactions See Section 1.3.5

8.3 Special Populations

No special populations were studied.

8.4 Pediatrics

Pediatric age group was not studied.

8.5 Advisory Committee Meeting

Not required

8.6 Literature Review

Allhat Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. JAMA 2002;288(23):2981-97.

August P. Initial treatment of hypertension. N Engl J Med 2003; 348(7):610-17.

See references Section 11.

8.7 Postmarketing Risk Management Plan

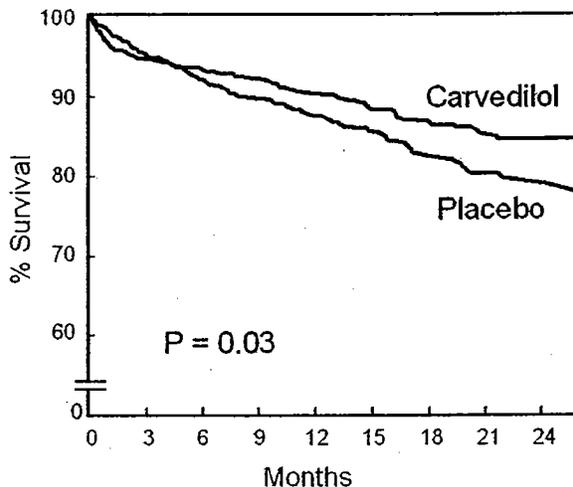
See Section 1.2.1

8.8 Other Relevant Materials

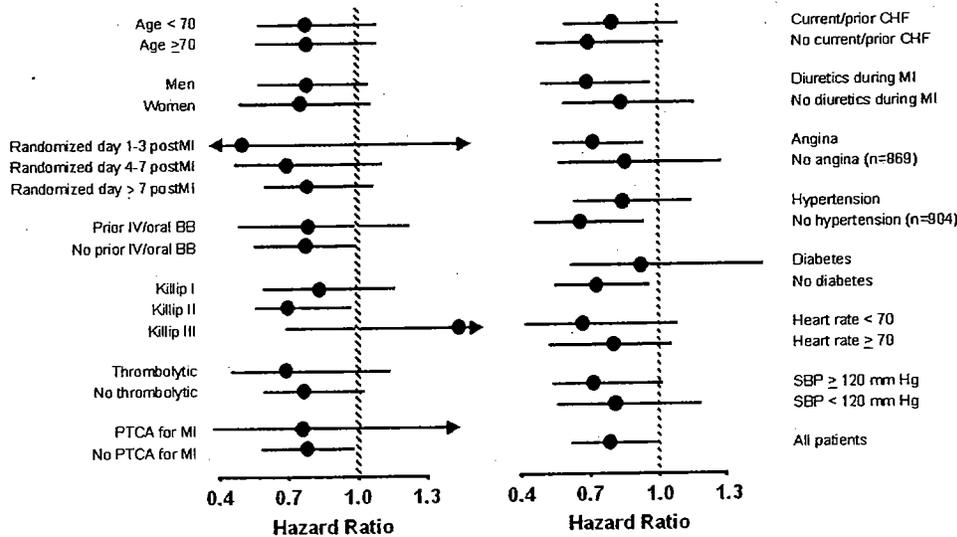
COREG IR is the only β -blocker that has:

- received a specific indication for treatment of the post-MI patients with LVD based on the Carvedilol Post-Infarct Survival Control in LVD (CAPRICORN) trial [Dargie, 2001], in which additional survival benefit was demonstrated compared to placebo when added to standard post MI treatment with ACE-I, aspirin, and lipid-lowering agents.
- shown to be effective and is indicated for reducing mortality and morbidity in mild to severe chronic heart failure [Packer, 1996(a); Packer, 1996(b); Packer, 2002; Fowler, 2002].

Survival analysis curve for CAPRICORN STUDY (IR formulation) and NDA 20297. •



Effects on mortality for subgroups in CAPRICORN



9 OVERALL ASSESSMENT

The number of patients who completed the pivotal study is rather small. However it was powered enough to show a statistical difference compared to placebo.

The number of blacks who participated in this study is very small. As a result subgroup analyses of data are difficult to interpret particularly regarding the contentious opinion as to whether blacks benefit as much from β -blockers as whites.

The sponsor did not adjust for multiplicity for the secondary objectives including the once daily dosing claim that the sponsor wishes to claim.

Reviewing the statistical review, the reviewer stated that all the results for continuous efficacy variables are "considered exploratory at best"

The sponsor has met all the requirements for the primary efficacy endpoint and the drug should be approved for the treatment of hypertension. By virtue of the bioequivalence shown between the IR and CR, the claims already approved for IR can be conferred on the CR formulation. Overall the sponsor has targeted the claims they wish to have and they have met the criteria agreed upon with the Division. Claims _____ should be looked at carefully.

Chronic heart failure is rapidly becoming one of the most prevalent cardiovascular disorders in industrialized countries [O'Connell, 2000; Zannad, 1999]. Its prevalence is projected to increase as the population ages. In the United States, CHF the most common Medicare diagnosis-related group (i.e., hospital discharge diagnosis), and more Medicare dollars are spent for the diagnosis and treatment of HF than for any other diagnosis [Massie, 1997]. The total estimated direct and indirect costs for HF in 2005 were \$27.9 billion [AHA, 2005].

Several classes of therapeutic agents are used, often in combination, in the long term management of chronic heart failure. With regards to β -blockers:

- In recent years, the use of three β -adrenergic receptor blocking agents (bisoprolol, long-acting metoprolol, and COREG IR) have been demonstrated to be effective in reducing mortality and morbidity in mild to severe chronic heart failure subjects [Packer, 1996(a); Packer, 1996(b); Packer, 2001; Packer, 2002; Bristow, 1996; CIBIS II Investigators, 1999; Colucci, 1996; Fowler, 2002; The MERIT Group, 1999; Hjalmarson, 2000].
- β -blockers have a class I indication [Hunt, 2001; AHA, 2002] for any patient with MI or ischemic heart disease who does not have a contraindication to this class of medications.
- COREG IR is the only β -blocker that has:
 - received a specific indication for treatment of the post-MI patients with LVD based on the Carvedilol Post-Infarct Survival Control in LVD (CAPRICORN) trial [Dargie, 2001], in which additional survival benefit was demonstrated compared to placebo when added to standard post MI treatment with ACE-I, aspirin, and lipid-lowering agents.
 - shown to be effective and is indicated for reducing mortality and morbidity in mild to severe chronic heart failure [Packer, 1996(a); Packer, 1996(b); Packer, 2002; Fowler, 2002].

A once-daily formulation of COREG will enhance the long-term management of patients with chronic heart failure through better compliance and, therefore, improved efficacy.

Efficacy

The clinical pharmacology program designed to support the approval of carvedilol CR consisted of several studies that were submitted in the carvedilol phosphate modified release IND. The pivotal studies include 367 in support of the indication of hypertension, and Studies 369 and 902 in support of the indications for HF and post-MI LVD by establishing PK and PD bioequivalence. Additionally, the information from the clinical trials program and post-marketing experience of COREG IR will also support the approval of the carvedilol CR program.

Hypertension

Study 367 demonstrated that a consistent and similar reduction from baseline in both SBP and DBP was maintained over the entire 24hr period following administration of carvedilol CR compared with COREG IR. The reduction in both SBP and DBP was maintained by carvedilol CR over the entire 24 hour period as evidenced by changes from baseline pressures at the end of the dosing interval as well as in the afternoon and night.

Heart Failure and Post-MI LVD

Study 369 demonstrated, across all dose groups, that carvedilol CR was equivalent to COREG IR with regard to R- and S-carvedilol AUC, Ct, and Cmax. Based on the statistical analysis of data pooled across all subject and dose groups, carvedilol CR had an equivalent predicted PD effect (AUEC, PDmin, and PDmax) compared to COREG IR. Based on these findings it is expected that carvedilol CR would result in efficacy which is comparable to that which has been demonstrated in the clinical trials with COREG IR and which are the basis of the current indications in the COREG IR USPI.

These major trials are:

COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival Study), which showed that COREG IR reduced all cause mortality by 35% among subjects with severe CHF and LVEF <25% [Packer, 2001; Packer, 2002],

COMET (Carvedilol or metoprolol European Trial) [Poole-Wilson, 2003], in which COREG IR reduced all cause mortality by 17% relative to metoprolol tartrate in subjects with mild to severe CHF, and

CAPRICORN (Carvedilol Post-Infarct Survival Control in LV Dysfunction) trial, which demonstrated that cardiovascular mortality was reduced by 25% with COREG IR (p=0.024) in subjects with a proven acute MI and LVEF of =40%, with or without symptoms of heart failure.

Study 367 provides information as to the expected treatment responses by important sub-populations. Women tended to respond somewhat better than men but these treatments by gender differences were small.

The safety findings in Study 367

The safety profile of carvedilol CR is expected to be similar to that of COREG IR, which has exhibited an excellent safety profile in an extensive patient exposure (greater than — patient years experience) since it was first approved in Belgium in 1990. This includes subjects with all three current COREG IR indications. Light headedness, orthostatic hypotension, and syncope (related to an exaggerated PD effect of carvedilol) have been seen in clinical trials as well as the post-marketing experience. The incidence of these complications has been reduced by dose titration (especially in subjects being treated for CHF). Additionally, administration of carvedilol with food also mitigates this effect and is recommended in the COREG IR USPI.

The most common side effects associated with COREG IR for HF, based on the experience from controlled trials and as reflected in the current USPI are dizziness, fatigue, weight increase, hypotension, and bradycardia (reported in =10% of patients [both mild-to-moderate and severe populations] and more frequently on COREG IR).

Worsening HF symptoms were also reported, but with equal or greater frequency in placebo-treated patients. In the CAPRICORN trial that enrolled patients with LVD post-MI the only

additional common AEs (reported in >3% of patients and more frequently on COREG IR) were dyspnea, lung edema and anemia. The most common side effect of COREG IR in hypertension trials was dizziness (6%) which was comparable to the placebo incidence of 5%.

Hypertension

In Study 367, very few AEs were reported and the frequency and types of adverse experiences were similar across all treatment groups, including placebo. The percentage of subjects reporting any adverse experience during the up-titration treatment period was 38%, 25%, 29%, and 38% 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, 1993]. 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, two subjects (2%) in the carvedilol CR 80mg group, and no subjects (0%) in the carvedilol CR 20mg or 40mg groups.

There is no evidence that treatment with carvedilol CR at doses of 20mg, 40mg, or 80mg OD was associated with any significant safety issues compared to treatment with placebo.

Heart Failure and Post-MI LVD

In Study 369, dizziness (3%) and headache (2%) were the most frequently reported AEs for the carvedilol CR treatment period; for COREG IR, only dizziness was reported in >1% of subjects (reported incidence of 2%). The incidence of emergent AEs considered by the investigator to be related to treatment with the study medication was low (=2%) for any single event for both COREG IR and carvedilol CR. Emergent AEs considered by the investigator to be related to treatment with the study medication were reported for 5 subjects (3%) during the COREG IR treatment period and 12 subjects (6%) during the carvedilol CR treatment period.

There were 3 fatal events reported in Study 369, none of which were reported as related to the study drug as determined by the investigator. Four subjects (2%) during the COREG IR treatment period and 3 subjects (2%) during the carvedilol CR treatment period experienced non-fatal emergent SAEs. None of the on-therapy non-fatal SAEs in the 3.125mg/10mg, 12.5mg/40mg, and 25mg/80mg dose groups were reported as related to the study medication. One subject in the 6.25mg/20mg dose group experienced worsening of CHF that was reported as related to the study medication and was subsequently withdrawn from the study.

In clinical studies of greater than 3000 subjects with CHF of whom more than 2100 participated in placebo-controlled clinical trials, COREG IR was associated with an increased incidence of dizziness, hypotension, edema, abnormal vision, bradycardia and atrioventricular block,

hyperglycemia, reversible renal dysfunction, thrombocytopenia, and increased digoxin levels; each of the aforementioned events are listed in the USPI for COREG IR.

Overall, carvedilol, when administered as either immediate release or controlled release formulations, was generally safe and well-tolerated in Study 369.

Dosage Regimen

The dose strengths of the CR formulation are 10, 20, 40 and 80mg and are expressed as carvedilol phosphate. The dosing recommendations for carvedilol CR are specific for each indication and based upon the corresponding dosage recommendations for all three COREG IR approved indications, for which carvedilol is taken twice daily and the corresponding dose strengths are 3.125, 6.25, 12.5 and 25mg based on the free base (carvedilol), respectively. Carvedilol CR should be taken in the morning with food. Additionally, the proposed label for carvedilol CR will advise patients to separate the ingestion of carvedilol CR from the ingestion of any ethanol-containing product (including prescription and over-the-counter medications that contain ethanol) by at least two hours, based on preliminary in vitro dissolution profiles suggesting that the ingestion of alcohol may affect the release of carvedilol from carvedilol CR. (m1.16)

Benefit: Risk Profile

Based on the pivotal studies conducted in the carvedilol CR development program, the clinical development program for COREG IR, and from the post-marketing experience with COREG IR, carvedilol CR has a favorable benefit:risk profile for the indicated patient populations with essential hypertension, mild-to-severe chronic heart failure, and post-MI LVD.

When co-administered with a high fat meal compared to a standard meal, mean AUC and C_{max} for carvedilol CR were increased approximately 20% and no 'dose-dumping' was observed. Although patients taking carvedilol CR with a high fat meal may have an increase in exposure, it is not expected that this will have an effect on the safety profile. Safety profiles were similar for subjects following the administration of carvedilol CR in the absence and presence of food, including a high fat meal. In all clinical trials with carvedilol CR in patients to date, this formulation has been taken with food (with no restriction as to type of food), and the observed safety profile was not different from that observed in clinical trials of COREG-IR.

Preliminary in vitro dissolution profiles suggest that the ingestion of alcohol may affect the release of carvedilol from carvedilol CR. This could result in the potential for higher peak and lower trough plasma carvedilol concentrations. Therefore, although no clinical data are available, patients will be asked to separate the ingestion of carvedilol CR from the ingestion of any ethanol-containing product by at least two hours (m3.2.P.2 and Risk Management Plan, m1.16).

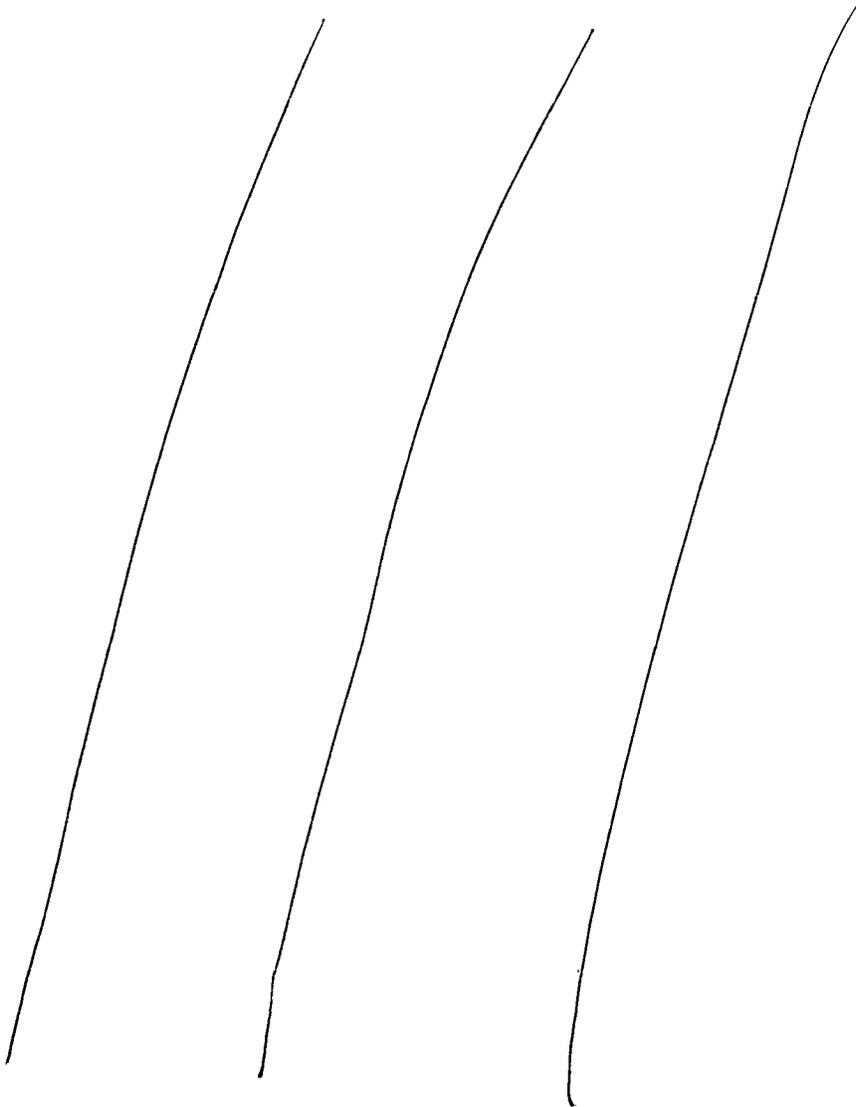
9.3.2 Required Phase 4 Commitments

Not required

9.3.3 Other Phase 4 Requests

Not applicable

9.4 Labeling Review



1 Page(s) Withheld

 Trade Secret / Confidential

 ✓ Draft Labeling

 Deliberative Process

Consistent with its high degree of plasma protein binding, carvedilol does not appear to be cleared significantly by hemodialysis. [COREG Prescribing Information, CO:L10, June 2005]

10 APPENDICES

10.1 Review of Individual Study Reports

See review of clinical study reports above

11 REFERENCES

Allhat Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. JAMA 2002;288(23):2981-97.

August P. Initial treatment of hypertension. N Engl J Med 2003; 348(7):610-17.

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Coreg (Carvedilol) Product Information. October, 2003.

Feuerstein GZ, Poste G, Ruffolo RR Jr. Carvedilol Update III: Rationale for use in congestive heart failure. Drugs of Today. 1995;31(5):307-26.

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McTavish D., Campoli-Richards D, Sorkin E.M. Carvedilol: A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. Drugs 45:232-258 (1993).

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Moser M, Frishman WH. Beta-blockers with vasodilating activity: focus on carvedilol. In: Messerli FH, Editor. The ABC's of antihypertensive therapy. 2nd ed. Philadelphia:Lippincott Williams and Wilkins, 2000:78-92.

Ruffolo RR Jr., and Feuerstein GZ. Pharmacology of carvedilol: rationale for use in hypertension, coronary artery disease, and congestive heart failure. Cardiovasc Drugs Ther. 1997;11:247-56.

12 CASE NARRATIVES

There may be minor discrepancies in the details of the SAEs included in the clinical narratives compared with the safety tabulations. This is because the data come from two different databases (i.e., a locked clinical trials database and a dynamic SAE database) and have been collected at different points in time. However, all key data points are reconciled. It is considered that these minor discrepancies do not change the overall clinical significance or understanding of the SAE.

Serious Adverse Events

Protocol Id: 105517 367 Investigator Number: 8406 Subject Number: 58 Treatment Number: 1116 Case Id: A0557426A Suspect Drugs: Carvedilol Serious Events: Myocardial infarction

This 44-year-old male subject was enrolled in a blinded study for the treatment of hypertension. Medical conditions at the time of the event included obesity and smoking. The subject received oral blinded trial medication once per day from

The subject was randomized to Carvedilol MR 40 mg.

On _____, 54 days after the first dose of investigational product, the subject experienced chest pain. The subject was hospitalised and the events were life threatening. He was diagnosed with myocardial infarction. The subject was treated with aspirin (ASA), ramipril (Altace), clopidogrel bisulphate (Plavix), atorvastatin calcium (Lipitor) and nitroglycerine (Tnt). He underwent coronary dilatation on _____. Treatment with investigational product was discontinued due to these events and the subject was withdrawn from the study. The events resolved on 08 May 2005. The investigator considered there was no reasonable possibility that the myocardial infarction may have been caused by investigational product. The investigator also considered the event to be possibly associated with concurrent medical conditions smoking and obesity.

Protocol Id: 105517 367 Investigator Number: 7578 Subject Number: 405 Treatment Number: 1208 Case Id: A0542043A Suspect Drugs: Carvedilol Serious Events: Pneumonia

This 45-year-old male subject was enrolled in a blinded study for the treatment of hypertension. The subject's past medical history included drug abuse. Medical conditions at the time of the

event included alcohol use, chronic sinusitis, overweight and smoking. The subject received oral investigational product from _____

The subject was randomized to Carvedilol MR 20 mg.

On _____ 19 days after the start of investigational product, the subject developed community acquired pneumonia with symptoms of shortness of breath. He was diagnosed with chronic obstructive pulmonary disease (COPD) and sleep apnea after a chest x-ray, computerized axial tomography (CAT) scan, ultrasound and CO2 pulmonary testing was performed. The subject was hospitalised and treated with oxygen, airway intubation, intravenous antibiotics (unspecified), nebulizing treatments, albuterol, ipratropium bromide (Atrovent) and moxifloxacin hydrochloride (Avelox). Treatment with investigational product was discontinued due to these events on _____ and the subject was withdrawn from the study. The community acquired pneumonia resolved on 30 January 2005. The investigator considered there was no reasonable possibility that the community acquired pneumonia may have been caused by investigational product.

Investigator Number: 7739 Subject Number: 1728 Treatment Number: 1325 Case Id:
A0544037A Suspect Drugs: Placebo Serious Events: Hypertensive crisis

This 39-year-old female subject was enrolled in a blinded study for the treatment of essential hypertension. The subject's past medical history included migraine headaches. Medical conditions at the time of the event included hypertension and upper respiratory infection (URI). Concomitant medications included ibuprofen, guaiphenesin (Mytussin) and oseltamivir phosphate (Tamiflu).

The subject received oral placebo from 01 February 2005 to 03 February 2005.

On 3 February 2005, two days after the start of investigational product, the subject presented to clinic with an elevated blood pressure of 196/120 (taken earlier that day), upper chest pain/muscle pain which was dull and non-radiating, neck pain, fatigue, facial flushing and moderate nausea. The events were clinically significant (or requiring intervention). Relevant test results included an electrocardiogram which showed normal sinus rhythm, chest x-ray was showed no evidence of acute cardiopulmonary process and an influenza antibody screen was negative. All laboratory values were within normal limits with the exception of an elevated blood urea nitrogen, low potassium, and elevated carbon dioxide. There were no signs or symptoms of viral meningitis. Blood culture on 03 February 2005 produced no growth. The subject was diagnosed with hypertensive crisis. The subject was treated with furosemide (Lasix) and clonidine. Later that day at 21:00 the subject reported less facial flushing and no cardiac symptoms. Treatment with investigational product was discontinued due to these events on 3 February 2005 and the subject was withdrawn from the study. On 04 February 2005, at a follow-up clinical visit, the subject's blood pressure was reduced, but still elevated with an average sitting diastolic blood pressure of 93 mmHg. The subject had less facial flushing and reduced fatigue, but lateral neck pain was still present. The subject resumed taking ramipril (Altace), furosemide (Lasix) and clonidine if systolic blood pressure was greater than 150 mmHg. On 15

February 2005, the subject had a follow-up visit and denies chest tightness/pain, palpitations, dizziness, leg edema, or diaphoresis. Blood pressure is 135/92 mmHg. The subject continued to complain of fatigue which gets worse by the end of the day. The subject will discontinue furosemide (Lasix), continue clonidine, increase ramipril (Altace), and begin triamterene+hydrochlorothiazide. The events resolved on 15 February 2005. The investigator considered there was reasonable possibility that the hypertensive crisis may have been caused by investigational product. The investigator also considered the event to be possibly associated with the disease under study hypertension, and/or a possible viral illness.

Adverse Events Leading to Withdrawal

Protocol Id: 105517 367 Investigator Number: 7777 Subject Number: 440 Suspect Drugs:
Carvedilol CR 80 mg Adverse Events: Depression

This 51 year old white male subject was enrolled in a randomized, double-blind study for the treatment of essential hypertension. Physical examination and medical history at screening revealed current hypertension, grade I hypertensive retinopathy, grade 1/6 systolic murmur at apex, impotence, an enlarged prostate, and lower back pain, and a past history of a head injury and hyperlipidemia. His concomitant medications at baseline were diltiazem hydrochloride 240 mg daily (which was discontinued on February 23, 2005), valsartan 320 mg daily (which was discontinued on March 14, 2005), and hydrochlorothiazide 12.5 mg daily (which was discontinued on March 21, 2005). On April 5, 2005, the patient was randomized to the carvedilol CR 80 mg treatment group, and began receiving carvedilol 20 mg daily. The plan was to increase his carvedilol CR dose to 40 mg daily on April 19, and to 80 mg daily on May 2; however, on April 11, 2005, while he was still receiving carvedilol CR 20 mg daily, he was diagnosed with depression and was withdrawn from treatment.

Protocol Id: 105517 367 Investigator Number: 7782 Subject Number: 498 Suspect Drugs:
Carvedilol CR 40 mg Adverse Events: Proteinuria

This 26 year old white male was enrolled in a randomized, double-blind study for the treatment of essential hypertension. His medical history included a current diagnosis of hypertension, eczema, and right axillary lymphadenitis and a past history of epistaxis. His screening clinical laboratory and urinalysis values on December 9, 2004 were all within normal limits with the exception of a urine albumin/creatinine ratio of 9.153 mg/mmol creatinine. His concomitant medications at baseline were hydrochlorothiazide 25 mg and valsartan 160 mg daily, which he was taking to treat his hypertension and cefalexin monohydrate 500 mg twice daily, which he was taking to treat the axillary lymphadenitis. On December 15, 2004, his antihypertensive medications were discontinued, and on December 18, 2004, the cefalexin was discontinued. On December 20, he was randomized to the carvedilol CR 40 mg treatment group and received carvedilol CR 20 mg daily until January 11, 2005, then carvedilol CR 40 mg daily. On December 28, 2004, his urine protein by dipstick was 2+, and his urine albumin/creatinine ratio was 24.295 mg/mmol, and on February 3, 2005, he was withdrawn from treatment. On February 11, 2005, his urine protein by dipstick was 2+ and his urine albumin/creatinine ratio was 26.216.

Protocol Id: 105517 367 Investigator Number: 7793 Subject Number: 611 Suspect Drugs:
Placebo Adverse Events: Exacerbation of hypertension

This 50 year old white male, a newly diagnosed hypertensive patient who was not receiving any antihypertensive treatment, was enrolled in a randomized, double-blind study for the treatment of essential hypertension. His sitting blood pressures during the baseline period were 141/104 mmHg, 142/108 mmHg, and 162/106 mmHg on January 13, 2005, January 20, 2005, and January 25, 2005, respectively. Following the blood pressure assessment on January 25, an ABPM apparatus was placed on him. The following morning, his sitting blood pressure was 150/104 mmHg, and his mean 24 hour pressures were within the prescribed range to be randomized. He was randomized to placebo on January 26, 2005. On February 10, 2005, his sitting blood pressure was 174/119 mmHg, and he was withdrawn from the study due to exacerbation of his hypertension. By February 17, 2005, the exacerbation of his hypertension was said to have resolved.

Protocol Id: 105517 367 Investigator Number: 7828 Subject Number: 948 Suspect Drugs:
Carvedilol CR 80 mg Adverse Events: Non-cardiac chest pain

This 49 year old white male subject was newly diagnosed with hypertension and enrolled in a randomized, double-blind study for the treatment of essential hypertension. Other than a current diagnosis of hypertension, his physical exam and medical history did not reveal any significant findings. At baseline he was not receiving any concomitant medication. On December 1, 2004, he was randomized to the carvedilol CR 80 mg treatment group and began receiving carvedilol 20 mg daily. The plan was to increase his carvedilol CR dose to 40 mg daily on December 15, and to 80 mg daily on December 29; however, on December 1, 2004, while he was still receiving carvedilol CR 20 mg daily, he complained of chest pain, which was determined to be non-cardiac in nature. He was withdrawn from treatment following his dose on December 14, and the non-cardiac chest pain had resolved by December 15, 2004.

Protocol Id: 105517 367 Investigator Number: 7658 Subject Number: 1615 Suspect Drugs:
Placebo Adverse Events Worsening of hypertension

This 39 year old African American female subject was enrolled in a randomized, double-blind study for the treatment of essential hypertension. On December 2, 2004, while receiving lisinopril 20 mg and hydrochlorothiazide 12.5 mg daily, her sitting blood pressure was 133/86 mmHg. As defined by the protocol, her antihypertensive medications were withdrawn. Her sitting blood pressures were 173/112 mmHg, 160/104 mmHg, and 161/94 mmHg on December 10, 2004, December 14, 2004, and January 3, 2004, respectively. Following the blood pressure assessment on January 3, an ABPM apparatus was placed on her. The following morning, her sitting blood pressure was 163/106 mmHg, and her mean 24 hour pressures were within the prescribed range to be randomized. She was randomized to placebo on January 4, 2005. Her sitting blood pressures were 173/109 mmHg, 163/105 mmHg, and 181/124 mmHg on January 18, 2005, February 1, 2005, and February 15, 2005, respectively. On February 15, 2005 she was withdrawn from the study because of her worsening hypertension and was started on lisinopril 40 mg and hydrochlorothiazide 12.5 mg per day. On February 16, 2005, her sitting blood pressure

had dropped to 131/90 mmHg, and by February 18, 2005, her worsening hypertension was said to be resolved.

Protocol Id: 105517 367 Investigator Number: 8389 Subject Number: 2142 Suspect Drugs: Carvedilol CR 80 mg Adverse Events: Tiredness and headache

This 48 year old African American female subject was enrolled in a randomized, double-blind study for the treatment of essential hypertension. At screening, she had uncontrolled hypertension despite treatment with amlodipine besilate 10 mg daily. Her other medications at baseline consisted only of aspirin as needed for occasional headaches. Other than the current diagnosis of uncontrolled hypertension, she had no significant findings on physical examination or medical history. Her screening clinical laboratory and urinalysis values were within normal limits with the exception of 3+ occult blood by dipstick in her urine, 10 to 15 red blood cells and 0 to 1 white blood cell per high power field on the microscopic examination of the urine. On the day of randomization (prior to the first dose of carvedilol), her urinary albumin to creatinine ratio was 26.216 mg/mmol of creatinine, occult blood in the urine was 3+, protein in the urine was 1+, and there were few bacteria, 15 to 25 red blood cells, and 3 to 5 white blood cells per high power field. Amlodipine besilate 10 mg daily was continued through the baseline period and on March 18, 2005 she was randomized to the carvedilol CR 80 mg treatment group. From March 18, 2005 until March 31, 2005, she received carvedilol CR 20 mg daily; from March 31, 2005 until April 15, 2005, she received carvedilol CR 40 mg daily and on April 15, 2005 she began receiving carvedilol CR 80 mg daily. On April 14, 2005 she complained of tiredness and headache and following her dose on April 16, she was withdrawn from treatment. By April 20, 2005, her tiredness and headache had resolved and the urinalysis was normal.

Protocol Id: 105517 367 Investigator Number: 8389 Subject Number: 2144 Suspect Drugs: Carvedilol CR 40 mg Adverse Events: Peripheral Edema and Tiredness

This 42 year old African American female subject was enrolled in a randomized, double-blind study for the treatment of essential hypertension. Her medical history included a current diagnosis of hypertension, and a past history of endometriosis and an abdominal hysterectomy. Her concomitant medications at baseline were hydrochlorothiazide 12.5 mg and losartan potassium 50 mg daily to treat her hypertension. Her screening laboratory and urinalysis values were all within normal limits with the exception of urinary protein by dipstick of 1+, and 3 to 5 red blood cells per high power field on the microscopic urine exam. On March 1, 2005, her antihypertensive medication was discontinued, and on March 15, 2005 she was randomized to receive carvedilol CR 20 mg daily until March 31, 2005, then carvedilol 40 mg daily. On April 1, 2005, she was noted to have peripheral edema, and on April 13, 2005 she reported tiredness. On April 17, 2005, she was withdrawn from treatment, and on April 18, 2005, her edema and tiredness had resolved.

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CLINICAL REVIEW- 120 day safety update

Application Type NDA
Submission Number 22-012
Submission Code 000

Letter Date December 21, 2005
Stamp Date December 23, 2005
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Reviewer's Name A.O. Williams, M.D.
Review Completion Date September 5, 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

Summary

This 120 day Safety Update provides all safety information reported from the data cut-off date for the COREG CR NDA (09 September 2005) to the data cut-off date for this safety update (15 February 2006). Safety data from four ongoing studies (COR100216, COG103560, COR103561, COG104851) employing the carvedilol CR formulation are included. Although the ongoing studies with COREG CR have added approximately 24% to the total number of subjects exposed to COREG CR from the time of NDA filing, these ongoing studies are blinded. The sponsor claims that there are no safety signals to suggest a change in the safety profile of COREG CR by the additional data obtained

A total of 544 subjects are enrolled in these ongoing studies, and safety data are available for 327 (60%) of these subjects. These studies have added approximately 24% to the total number of subjects exposed to COREG CR from the time of NDA filing.

However this 120 day Safety Update provides all safety information reported from the data cut-off date for the COREG CR NDA (09 September 2005) to the data cut-off date for this safety update (15 February 2006).

There are currently four ongoing studies employing the carvedilol controlled release formulation:

- Study COR100216 (the CLEVER study) is a randomized, double-blind, multi-center study comparing the effects of carvedilol modified release formulation (COREG MR) and atenolol in combination with and compared to an angiotensin converting enzyme inhibitor (lisinopril) on left ventricular mass regression in hypertensive patients with left ventricular hypertrophy (LVH).
- Study COR103560 is a randomized, double-blind, positive-controlled, multicenter study comparing the efficacy of carvedilol phosphate modified release formulation (COREG MR) and metoprolol succinate extended release (Toprol-XL™) on the reduction of microalbuminuria in patients with hypertension and microalbuminuria.
- Study COR103561 is a randomized, double-blind, multicenter study comparing the effects of carvedilol phosphate modified release formulation (COREG-MR) with metoprolol succinate (Toprol-XL) on the lipid profile in normolipidemic, or mildly dyslipidemic hypertensive patients.
- Study COG104851 (the CASPER study) is a prospective, randomized, controlled assessment of once-daily controlled release COREG CR versus twice-daily COREG immediate release (IR) on measures of compliance and quality of life in patients with heart failure and left ventricular systolic dysfunction.

Clinical Studies

As of the data cut-off date, there are four ongoing studies employing the carvedilol CR formulation (COR100216, COG103560, COR103561, and COG104851). The following information is provided for each ongoing study based on the clinical trials database cut-off of 15 February 2006: subject disposition, demographic characteristics, adverse events (AEs), AEs assessed by the investigator as being related to study drug, serious adverse events (SAEs), SAEs assessed by the investigator as being related to study drug, Listing of non-fatal SAEs, and a Listing of AEs leading to subject withdrawal from the study. All serious adverse events (SAEs) reported from these ongoing studies were also obtained from a search of the _____

_____ GSK's global safety database, _____ with a database cut-off of 15 February 2006. Adverse events were coded using the ICH MedDRA (Medical Dictionary for Regulatory Activities) coding dictionary [Medical Dictionary for Regulatory Activities, 2001].

COR100216 (the CLEVER study) is a randomized, double-blind, multi-center study with an 18-month maintenance Phase comparing the effects of carvedilol modified release formulation (COREG MR) and atenolol in combination with and compared to an angiotensin converting enzyme inhibitor (lisinopril) on left ventricular mass regression in hypertensive subjects with left ventricular hypertrophy (LVH). There have been 91 subjects enrolled. Three subjects on blinded trial medication experienced SAEs up to the time of database cutoff. These events included atrial fibrillation, peripheral neuropathy, and asthma. None of the events were related to investigational product according to the study investigators.

A summary of subject disposition, demographic characteristics, AEs, AEs assessed by the investigator as being related to study drug, SAEs, SAEs assessed by the investigator as being related to study drug, a Listing of non-fatal SAEs, and a Listing of AEs leading to subject withdrawal from Study COR100216 are provided.

COR103560 is a randomized, double-blind, positive-controlled, multicenter study with a 6-month maintenance Phase comparing the efficacy of carvedilol phosphate modified release formulation (COREG MR) and metoprolol succinate extended release (Toprol-XL) on the reduction of microalbuminuria in subjects with hypertension and microalbuminuria. There have been 33 subjects enrolled. One patient reported an SAE up to the time of database cutoff. This event (ruptured cerebral aneurysm) occurred prior to the subject receiving investigational product but after the subject began open-label lisinopril during the run-in phase of the study.

A summary of subject disposition, demographic characteristics, AEs, AEs assessed by the investigator as being related to study drug, SAEs, SAEs assessed by the investigator as being related to study drug, a Listing of non-fatal SAEs, and a Listing of AEs leading to subject withdrawal from Study COR103560 are provided.

COR103561 is a randomized, double-blind, multicenter study with a 5-month maintenance Phase comparing the effects of carvedilol phosphate modified release formulation (COREG-MR) with metoprolol succinate (Toprol-XL) on the lipid profile in normolipidemic, or mildly dyslipidemic hypertensive subjects. There have been 15 subjects enrolled. There were no SAEs reported at the time of database cutoff.

A summary of subject disposition, demographic characteristics, AEs, AEs assessed by the investigator as being related to study drug, SAEs, SAEs assessed by the investigator as being related to study drug, a Listing of non-fatal SAEs, and a Listing of AEs leading to subject withdrawal from Study COR103561 are provided.

COG104851 (the CASPER study) is a prospective, multi-center, 3-arm, parallel-group, randomized 5-month clinical trial to evaluate and compare compliance and quality of life with the COREG IR immediate release (BID regimen) and carvedilol phosphate CR controlled release (COREG CR; QD regimen) formulations in subjects with chronic heart failure (CHF) and LVD with mild to severe symptoms of heart failure. Subjects were currently receiving a stable dose of COREG IR as part of their chronic heart failure (6.25mg, 12.5mg, 25mg BID) treatment regimen. Eligible subjects were randomized in a 1:1:1 distribution to receive: A) their usual twice daily dose of COREG IR (double-blind), or B) be switched to the analogous once-daily dose of COREG CR with a placebo being substituted for the second daily dose, or C) be switched to an open label once daily regimen of COREG CR.

A total of 405 subjects have been enrolled. There were 84 events in 21 subjects reported up to the time of OCEANS database cutoff; these events are summarized by System/Organ/Class (SOC) in Table below.

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Table of adverse events in 21 subjects summarized by system organ- Safety update

Blood and lymphatic system disorders	
Coagulopathy	1
Iron deficiency anaemia	1
Thrombocytopenia	1
Cardiac disorders	
Arrhythmia	1
Cardiac arrest	1
Cardiac failure congestive	2
Congestive cardiomyopathy	1
Electromechanical dissociation	1
Myocardial infarction	1
Ventricular fibrillation	2
Ventricular tachycardia	1
Gastrointestinal disorders	
Acute abdomen	1
Colonic obstruction	1
Constipation	1
Faecaloma	1
Umbilical hernia	1
General disorders and administration site conditions	
Abasia	1
Asthenia	6
Chest discomfort	3
Chest pain	2
Fatigue	2
Pyrexia	2
Sudden death	1
Hepatobiliary disorders	
Cholecystitis	1
Infections and infestations	
Arthritis bacterial	1
Bronchitis acute	1
Lower respiratory tract infection	1
Osteomyelitis	1
Respiratory tract infection	1
Sepsis	1
Septic shock	2
Injury, poisoning and procedural complications	
Fall	2
Joint injury	1
Pelvic fracture	1
Investigations	
Pulse absent	1
White blood cell count increased	1

(cont'd)

Metabolism and nutrition disorders	
Hyperkalaemia	1
Hypoglycaemia	1
Musculoskeletal and connective tissue disorders	
Arthralgia	2
Joint swelling	1
Pain in extremity	1
Rhabdomyolysis	2
Nervous system disorders	
Dysstasia	1
Headache	1
Hypoaesthesia	2
Loss of consciousness	1
Syncope	1
Psychiatric disorders	
Mental status changes	1
Renal and urinary disorders	
Renal failure acute	1
Renal failure chronic	1
Respiratory, thoracic and mediastinal disorders	
Cough	1
Dyspnoea	3
Dyspnoea exacerbated	2
Epistaxis	1
Haemoptysis	1
Hypoxia	1
Wheezing	1
Skin and subcutaneous tissue disorders	
Erythema	1
Hyperhidrosis	1
Onychomadesis	1
Skin discolouration	1
Vascular disorders	
Circulatory collapse	1
Hypotension	2
REPORT EVENT TOTALS:	84
REPORT CASE TOTALS:	21

Two events (syncope and asthenia) in one subject were related to investigational product according to the study investigator; these events are listed, based on the reference safety information for carvedilol.

There have been two fatal SAE cases reported in COG104851 up to the time of database cutoff. One subject died due to sepsis secondary to a perforated viscus. One subject died due to cardiac arrest and ventricular fibrillation. Neither fatal SAE case was related to treatment with carvedilol, according to the investigator.

Enrollment in this study began on 18 October 2005 and was completed on 31 January 2006, 15 days before the data cutoff date for this update. With this short recruitment

period and proximity of the data cut to the completion of enrollment, data are available on only 185 of the 405 subjects enrolled. The study is ongoing and only pooled, blinded data are presented based on the clinical data base.

A summary of subject disposition, demographic characteristics, AEs, AEs assessed by the investigator as being related to study drug, a Listing of SAEs assessed by the investigator as being related to study drug, a Listing of non-fatal SAEs, and a Listing of AEs leading to subject withdrawal from Study COG104852 are provided.

CONCLUSIONS

In summary, the ongoing studies with COREG CR, as of the 15 February 2006 cut-off date for this 120 day update, have added approximately 24% to the total number of subjects exposed to COREG CR from the time of NDA filing. From the additional data obtained and a review of the frequencies of adverse events there is neither evidence to suggest that any unusual events had occurred, albeit blinded, nor to suggest a change in the safety profile of COREG CR.

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