CLINICAL PHARMACOLOGY REVIEW

Division of Pharmaceutical Evaluation I

NDA 20297 N (#022) **SUBMISSION DATE:** September 1, 2006

Type: Pediatric Exclusivity Submission of Supplement #22 to NDA 20297
Brand Name: Coreg® Tablets and Coreg® CR Capsules
Dosage Strength: 3.125, 6.25, 12.5 and 25 mg IR tablets
10, 20,40, 80 mg CR caspules

Indication: Treatment of mild to severe heart failure of ischemic or cardiomyopathic origin, left ventricular dysfunction following myocardial infarction or hypertension
Sponsor: GlaxoSmithKline
Research Triangle Park, NC

Reviewing Division: Division of Cardiovascular and Renal Products, HFD-110

Reviewers: Peter H. Hinderling, MD
Pravin Jadhav, PhD

Team Leaders: Patrick J. Marroum, PhD
Joga Gobburu, PhD

Reference is made to the approved NDA 20297 for Coreg Immediate release Tablets of 3.125, 6.25, 12.5 and 25 mg strengths tablets. (b) (4) Coreg® is a non-selective β–adrenergic blocking agent, devoid of intrinsic sympathomimetic activity with α1-blocking activity and indicated in adults for the treatment of:

- Mild to severe heart failure of ischemic or cardiomyopathic origin, usually in addition to diuretics, ACE inhibitors, and digitalis, to increase survival and, also, to reduce the risk of hospitalization

- Left ventricular dysfunction following myocardial infarction: to reduce cardiovascular mortality in clinically stable patients who survive the acute phase of a myocardial infarction and have a left ventricular ejection fraction of ≤ 40%

- Hypertension alone or in combination with other anti-hypertensives

In adults the maximum tolerated dose of carvedilol is 50 mg bid in patients with essential hypertension and mild to moderate heart failure and 25 mg bid in patients with left ventricular dysfunction resulting from myocardial infarction. The carvedilol tablets are to be taken with food to slow the absorption of the drug to minimize orthostatic side effects.

Supplement Type SE-5 to NDA 20297 dated September 1, 2006 includes the reports of:

1. Study SK&F-105517/321: A multi-center, placebo controlled, 8 month study of the effect of twice daily carvedilol in children with congestive heart failure due to systemic ventricular systolic dysfunction

2. Study SK&F-105517/396: A multi-center, open-label extension study to evaluate the safety of twice daily oral carvedilol in pediatric subjects with chronic heart failure.

3. Study COG103639: A multi-center, observational study of oral carvedilol in pediatric subjects with dilated cardiomyopathy: A report from the North American Pediatric Cardiomyopathy registry (PCMR)

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Table of Content

1. Executive Summary

Stipulations of the Written Request

The Witten Request (WR) stipulated the performance of an outcome/safety trial in which carvedilol and placebo are added to standard therapy in pediatric patients with congestive heart failure (CHF) due to systemic left ventricular dysfunction. The outcome trial must be a randomized, double-blind, parallel comparison of carvedilol and placebo of at least 6 month duration in a population judged to be of adequate size. A 1-year (nominal) open treatment phase should follow the controlled trial phase. The study is to be analyzed by looking for a treatment-related reduction in endpoint events (e.g. death or cause specific hospitalizations) or other indications of clinical benefit (e.g. NYHA class or growth) in the entire randomized population.

The subjects enrolled should be diagnosed with heart failure according to the standards of local practice.

The subjects to be enrolled in the trial were to be in Tanner stage 3 to < 18 years (up to 50%) with the remainder less than Tanner Stage 3. The enrollment strategy should ensure a mixture of black and non-black subjects. The study should enroll at least 150 subjects with 75 patients having >1 year of exposure.

The pharmacokinetics of carvedilol should be determined in pediatric patients either in a separate study or in a sub-study of the outcome trial. The PK data must be obtained over the dose range studied for effectiveness and the patients should have grossly normal metabolic function. AUC, half life, oral apparent clearance, volume of distribution, Cmax and tmax should be determined for S(-) and R(+) carvedilol. (b) (4)

Studies Performed by the Sponsor

Pivotal Trial

The sponsor performed an efficacy and safety study using a randomized, placebo controlled, double-blind, parallel group design in 161 children with congestive heart failure due to systemic ventricular systolic dysfunction with a one year open label extension. The primary endpoint was a composite measure of heart failure outcomes of "worsened", "unchanged" or "improved". The composite outcome included death, hospitalization or discontinuation for worsening heart failure, NYHA or Ross' heart failure classification and/or global assessment. The children received a low or high dose of carvedilol or placebo bid for 8 months. The study used a suspension formulation allowing body weight adjusted dosing of 0.025, 0.05, 0.1, 0.2 mg/kg (low dose) or 0.05, 0.1, 0.2, 0.4 mg/kg (high dose) in subjects weighing <62.5 kg and the immediate release tablets 3.125, 6.25, 12.5 (low dose) or 3.125, 6.25, 12.5, 25 mg (high dose) for children weighing ≥ 62.5 kg. Children weighing ≥ 62.5 kg randomized to the low dose 1.563 mg treatment received a suspension, because there is no equivalent strength tablet available. The study medications were administered with a small amount of food to slow the absorption of carvedilol. Following a screening phase the pediatric patients were randomized in a blinded fashion to receive placebo, low-dose or high-dose carvedilol in a 1:1:1 randomized schedule. In a 2 month up-titration phase the doses of carvedilol were titrated every 2 weeks, as tolerated, through four dose levels. The subjects continued on the dose level achieved during the up-titration phase during the 6 months maintenance phase. During this period, if the subject was unable to reach the target dose during the up-titration phase, the investigator had the option to intermittently continue to increase the dose level to achieve dose level 4, i.e. for children weighing < 62.5 kg 0.2 mg/kg (low dose level) or 0.4 mg/kg (high dose level) and for children weighing ≥ 62.5 kg 12.5 mg (low dose level) and 25 mg (high dose level)
Patients were stratified at the time of randomization as having a left ventricle or non-left ventricle according to the anatomic substrate of the patients' ventricular dysfunction.

As shown below the efficacy of carvedilol in the pediatric target population could not be demonstrated:

Outcome	Treatment Group			
	Placebo (N=54)	Low-Dose Carvedilol (N=51)	High-Dose Carvedilol (N=52)	Combined Carvedilol (N=103)
	n (%)	n (%)	n (%)	n (%)
Improved	30 (55.6)	27 (52.9)	31 (59.6)	58 (56.3)
Unchanged	8 (14.8)	11 (21.6)	9 (17.3)	20 (19.4)
Worsened	16 (29.6)	13 (25.5)	12 (23.1)	25 (24.3)

The pre-specified primary analysis of the CHF composite outcome showed no statistically significant difference in the distributions or proportions of the outcomes between placebo and the combined active treatments (p= 0.740, Wilcoxon rank-sum test). Possible reasons for the negative result include high placebo effect, too small sample size or ineffectiveness of carvedilol.

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Compliance with Stipulations of Written Request

A comparison of the Clinical Pharmacology methods used by the sponsor in performing the studies with the stipulations of the Written Request (WR) shows the following:

The POPPK analysis used data from 80 children, who constituted the large majority of the subjects on active treatment. They included 43 males and 37 females, with median age 4 (0.33-18) years and median weight 16.5 (5-127) kg. There were 47 Caucasians, 18 blacks and 15 of other origin. Fifteen, 54 and 11 had Class I, Class II, and Class III heart failure, respectively. The demographics of the children were in accordance with the WR which requested that up to 50 % of the children were to be in Tanner Stage 3 to up to 18 years and at least 50% of the population should be younger, and there should be a mixture of black and non-black subjects.

The plasma concentrations of the active enantiomers S(-) carvedilol with nonselective β blocking activity and α1-blocking activity, and R(+) carvedilol with α1- blocking activity were measured. The sponsor did not measure the plasma concentrations of 4-hydroxyphenyl-carvedilol, an active metabolite whose contributions to the overall β-blocking activity equals that of the parent drug. This was in accordance with the revised WR which did not stipulate any longer that " ….. carvedilol and any metabolite that makes substantial contributions to its efficacy and/or toxicity should be measured". In agreement with the WR the protocol excluded subjects with abnormal metabolic function. As requested by the WR the plasma concentrations of the carvedilol enantiomers were measured over the range of doses tested for efficacy. The PK parameters CL/F and AUC were reported. The WR requested additional reporting of V/F, Cmax, tmax and t1/2. However, these latter parameters were to be obtained if a data rich approach was applied.

In accordance with the WR the tablet and suspension formulations used were appropriate to the age of the patients and the clinical setting. (b) (4)

The WR indicated specifically that a suspension would be acceptable. (b) (4)

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Pharmaceutical Evaluation I (OCP/DPE1) has reviewed the study reports of the population pharmacokinetic analysis of the clinical trial data in the target pediatric population (study 321), (b) (4) the corresponding assay validation reports (b) (4)

A comparison of the Clinical Pharmacology studies and methods used by the sponsor with the stipulations of the Written Request (WR) shows agreement. The Clinical Pharmacology database compiled by the sponsor is acceptable. Therefore, from a Clinical Pharmacology view point the sponsor should be granted 6 month pediatric exclusivity. (b) (4)

Peter H. Hinderling, MD
DPE 1
OCP
RD Initialed by Patrick Marroum, Ph.D. _____

Briefing held on January 23, 2007 (Drs. Jadhav, Marroum, K. Kumi, Rahman, Tornoe, Uppoor, Bashaw, Reynolds, Gobburu, Madabushi, Stockbridge, Mehta, Sahajwalla, Huang, Hinderling)

2. Question Based Review

What is the pediatric target population for carvedilol?

Children in the age between birth and 18 years with chronic symptomatic congestive heart failure due to systemic ventricular systolic dysfunction.

What are the studies stipulated by the Written Request and what are their design features?

The Written Request asked for the performance of:

1. An efficacy and safety study in the pediatric target population in which carvedilol or placebo was added to standard therapy during the controlled phase and carvedilol during the open phase.

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The efficacy and safety study used a randomized, placebo controlled, double-blind, parallel group design. The sponsor determined the PK of carvedilol in the children participating in the clinical trial. (b) (4)

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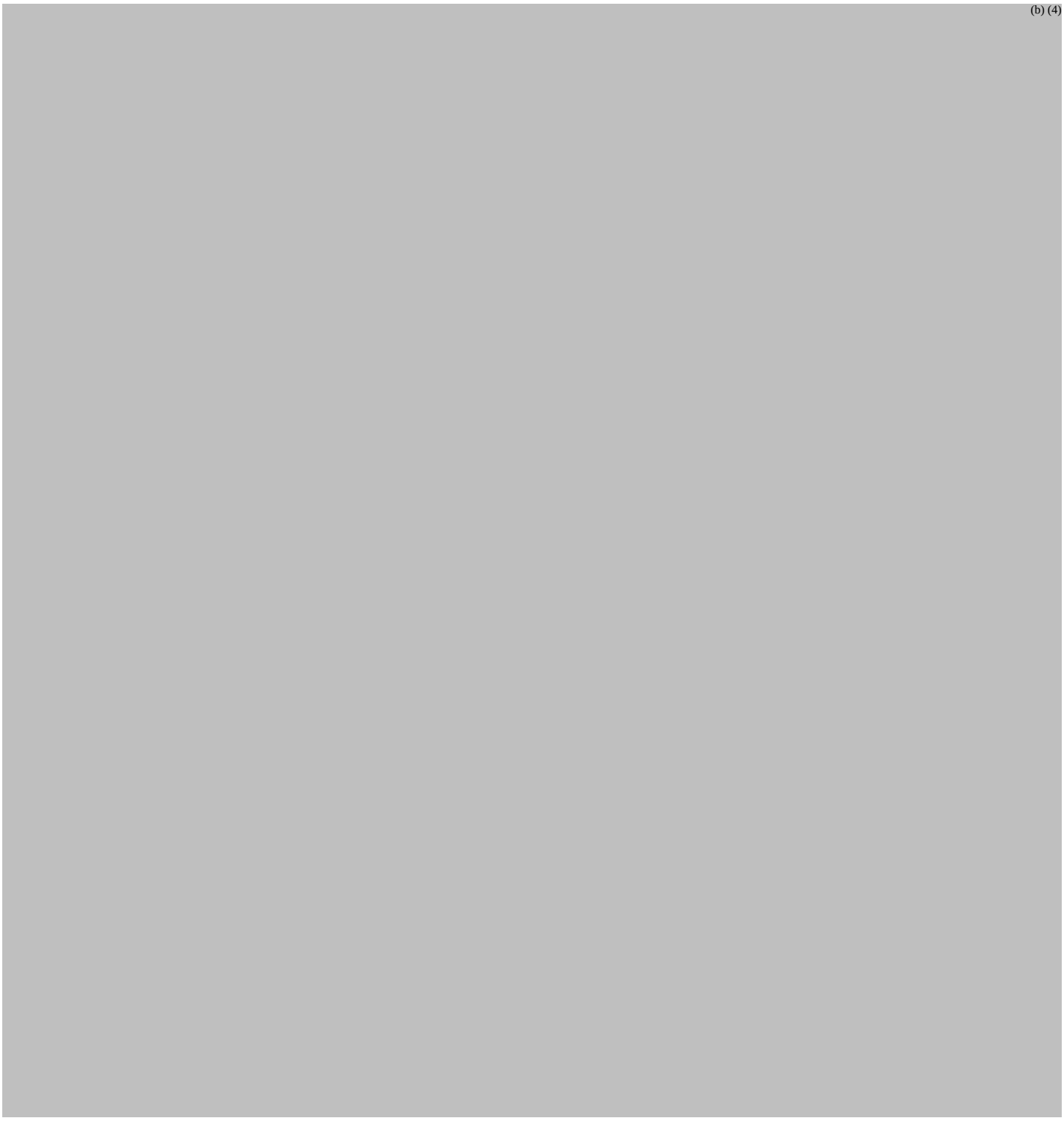

What are the outcome variables of the efficacy trial?

The primary endpoint of the study is a composite CHF outcome of "worsened", "improved" or "unchanged":

Worsened: Subject died, was hospitalized for at least 24 hours for worsening heart failure requiring intravenous heart failure medication; permanently discontinued double-blind treatment due to worsening heart failure, treatment failure or lack of/insufficient therapeutic response; permanently discontinued double-blind treatment due to withdrawal of consent or other administrative reason and had worsening heart failure at the time of study discontinuation; demonstrated worsening in NYHA Class or Ross' Classification for CHF in children at last observation carried forward (LOCF) or moderate-marked worsening of physician or subject/parent global assessment score at LOCF.

Improved: Subject did not worsen (as defined above), and demonstrated improvement in NYHA Class or Ross' Classification for CHF in children at LOCF and/or moderate-marked improvement in physician or subject/parent global assessment score at LOCF

Unchanged: Subject was neither improved nor worsened

The secondary efficacy parameters included: selected individual components of the CHF composite of clinical outcomes, ventricular function and remodeling parameters (echocardiographically derived), pharmacokinetics of carvedilol exposure, and plasma brain natriuretic peptide (BNP) levels. Safety was assessed by adverse events, laboratory tests, vital signs, cardiopulmonary examinations, height and weight (for growth assessment), and ECGs.

The primary comparison of interest is between the placebo group and the combined carvedilol groups.

What are the major findings of the efficacy and safety trial in the pediatric target population?

There is no statistically significant difference between placebo and the combined carvedilol groups for the protocol specified primary endpoint of the CHF composite response.

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Were the formulations used adequate for the age of the population and the clinical setting and were they adequately characterized?

The available four fixed strengths of the tablets and the flexible strengths of the suspensions allowed the required dose adjustment for the children who displayed a wide range of body

weights (5-127 kg). (b) (4)

Can the cause for the negative result of the carvedilol trial in children be identified?

The negative outcome could be due to a difference in disease, efficacy/pharmacodynamics of carvedilol, or exposure to carvedilol between the two populations, or alternatively caused by an insufficient power of the study or a combination of these factors.

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5. Validation of Assays

A HPLC ass ay with fluorescence detection of the derivatized carvedilol enantiomers was used for analyzing the serum samples from the clinical study 321 in the pediatric population with the target disease. (b) (4)

The below table summarizes the performance characteristics of the assays:

Assay	Study	Matrix	Analyte	LLOQ	Precision	Accuracy
				ng/mL	%	%
HPLC-Fluorescence	321	Serum	R(+) Carvedilol	0.5	3.2 - 6.8	1.9- 10.0
			S(-) Carvedilol	0.5	3.5 -16.7	0.05 - 10.0
HPLC/MS/MS	(b) (4)	Plasma	R(+) Carvedilol	0.2	3.6- 6.3	-6.2- (-)10.3
			S (-) Carvedilol	0.2	3.1- 4.4	-8.2- (-)11.1
HPLC/MS/MS	(b) (4)	Plasma	R(+) Carvedilol	0.2	5.3-9.5	-2.8-0.3
			S (-) Carvedilol	0.2	4.9- 9.7	-2.7- 0.7

The precision and accuracy obtained with the both assays are adequate. Cross validation of the HPLC method with fluorescence detection and the HPLC/MS/MS method was not performed. The small bias in accuracy of both assays is not likely to have biased the comparison of the comparative exposure of carvedilol in the 2 patient populations.

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7. Pharmacometrics Review

NDA Number:	N20297
Generic Name:	Carvedilol
Brand Name:	Coreg
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Sponsor:	GlaxoSmithKline
Type of Submission:	Pediatric supplement
Pharmacometrics (PM) Reviewer:	Pravin Jadhav Ph.D.
Primary Reviewer:	Peter Hinderling MD
PM Team Leader:	Jogarao Gobburu Ph.D.

Exective summary

Coreg is indicated in adults for the treatment of mild-to-severe heart failure of ischemic or cardiomyopathic origin, left ventricular dysfunction following myocardial infarction and hypertension. GlaxoSmithKline submitted a pediatric supplement for coreg (carvedilol) in response to FDA written request.

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The pre-specified primary analysis of the CHF composite outcome showed that there was no statistically significant difference in the distribution or proportions of the outcome responses between placebo and the combined carvedilol group (p=0.740, Wilcoxon rank-sum test). The failure of the study could be attributed to the following major reasons (1) high placebo response (2) insufficient sample size to demonstrate significant difference at such low effect size. Further, there are no measurements available that would allow us to study the time course of drug action and relate back to the CHF composite outcome. Thus, the quest to develop exposure response relationship is likely to be difficult.

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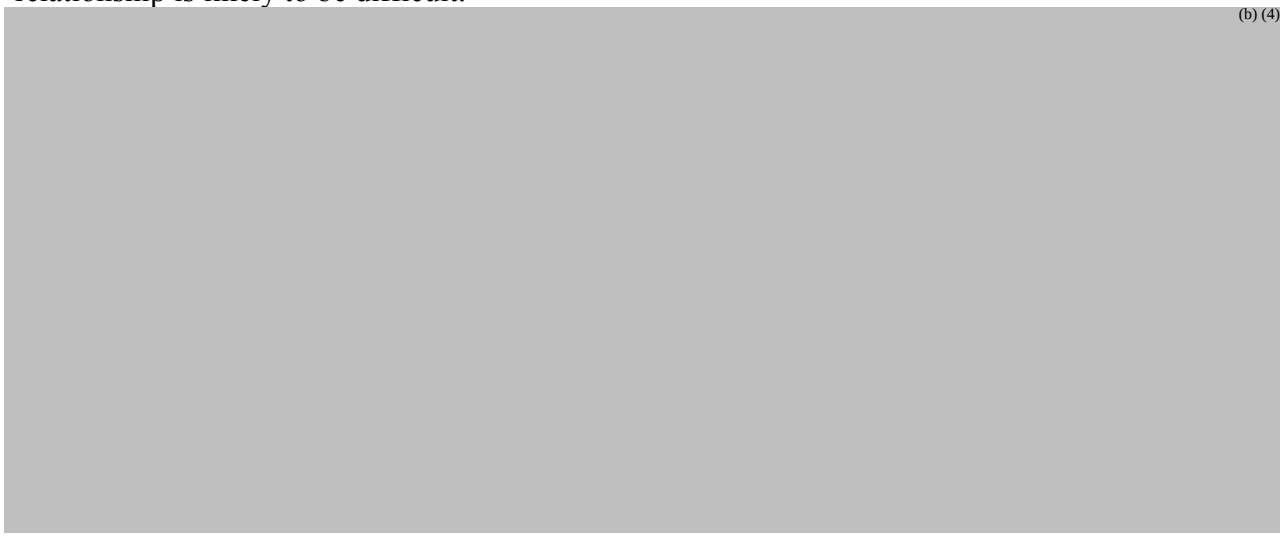

Recommendations

1. Future pediatric trial designs should consider improving trial success through careful consideration of endpoints, trial design and optimal sample size.
    a. Clinical trial simulations based on adult data and literature knowledge in pediatric patients can be used to assess the above design aspects.
    b. If the drug has established effectiveness in adults and sample size in a pediatric study is limited, scientifically valid but less stringent endpoints should be investigated.

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List of Figures

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List of Tables

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Introduction

Coreg is indicated in adults for the treatment of mild-to-severe heart failure of ischemic or cardiomyopathic origin, left ventricular dysfunction following myocardial infarction and hypertension. GlaxoSmithKline submitted a pediatric supplement for coreg (carvedilol) in response to FDA written request. The primary purpose of this review was to investigate the reasons of the failure of the primary analysis and gain insights into exposure response of coreg based on 321 (double blind) and 396 (open label extension) studies.

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For the 321 study, the primary effectiveness parameter was the CHF composite outcome. Subjects were determined to have an outcome response of "Worsened", "Improved", or "Unchanged". Table 1 illustrates the response rates observed in the study by dose groups.

Table 1: Distribution of Primary CHF Composite Outcomes

	Treatment Group			
Outcome	Placebo (N=54) n (%)	Low-Dose Carvedilol (N=51) n (%)	High-Dose Carvedilol (N=52) n (%)	Combined Carvedilol (N=103) n (%)
Improved	30 (55.6)	27 (52.9)	31 (59.6)	58 (56.3)
Unchanged	8 (14.8)	11 (21.6)	9 (17.3)	20 (19.4)
Worsened	16 (29.6)	13 (25.5)	12 (23.1)	25 (24.3)

Low-dose carvedilol: target dose 0.2mg/kg bid if weight was <62.5 kg, or 12.5mg bid if weight was ≥ 62.5 kg); High-dose carvedilol: target dose 0.4mg/kg bid if weight was <62.5 kg, or 25mg bid if weight was ≥ 62.5 kg

The pre-specified primary analysis of the CHF composite outcome showed that there was no statistically significant difference in the distribution or proportions of the outcome responses between placebo and the combined carvedilol group (p=0.740, Wilcoxon rank-sum test). There are reasons that could have lead to the failure of the study (1) high placebo response (2) insufficient sample size to demonstrate significant difference at such low effect size.

Given the high placebo response, the power of exposure (concentration or dose)-response analysis for the CHF composite outcome is limited. In addition, there are no measurements available that would allow us to study the time course of drug action and relate back to the CHF composite outcome. Thus, the quest to develop exposure response relationship is likely to be difficult.

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Conclusion

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However, these results are of less significance due to an inability to establish effectiveness in pediatric patients in a controlled clinical trial (321).

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Peter Hinderling
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Patrick Marroum
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