DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	20-297 / S_022
Drug Name:	COREG® (carvedilol) Tablets
Indication(s):	Treatment of Heart Failure (b) (4)
Applicant:	GSK
Date(s):	Date of Document: September 01, 2006 PDUFA Due Date: March 01, 2006
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Biometrics Division:	Biometrics I, HFD-710
Statistical Reviewer:	Ququan Liu, M.D., M.S.
Concurring Reviewers:	James Hung, Ph.D.
Medical Division:	Division of Cardio-Renal Drug Products, HFD-110
Clinical Team:	Maryann Gordon, M.D. Norman Stockbridge, M.D., Ph.D.
Project Manager:	Melissa Robb
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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The efficacy of carvedilol in children with heart failure is inconclusive. For some reasons the result of the study seems to suggest that carvedilol is not effective. A larger study with a carefully planned sample size and targeted population may be needed to demonstrate the efficacy of carvedilol in children with heart failure.

1.2 Brief Overview of Clinical Study

This sNDA consists of clinical studies in complete response to a Written Request (WR) for Pediatric Studies issued by FDA on September 17, 2004. The package includes four studies (Study 321, Study 396, Study COG103639, and Study CRV104257) and a comprehensive review of literature. This review only pertains to the dose-ranging trial of Study 321.

The primary objective of the dose-ranging trial was to compare the efficacy of carvedilol administered twice daily for 8 months as compared to placebo, on a composite measure of clinical congestive heart failure (CHF) outcomes in children with symptomatic systemic ventricular systolic dysfunction and CHF. The primary efficacy variable was the CHF composite outcome. Subjects were determined to have an outcome response of "worsened", "improved", or "unchanged".

1.3 Statistical Issues and Findings

The efficacy has not been shown in children with heart failure. The agency in the WR letter suggests that a 10% treatment effect be used for planning the study, however, the sponsor used a bigger effect, about 20%. The negative result of the study may be due to insufficient power. However, the trial results (see Tables 2-4) seem to suggest that carvedilol has only little effect in this pediatric population.

2. INTRODUCTION

2.1 Overview

COREG® (carvedilol), which provides nonselective β-adrenergic blockade with α_1-blocking activity, is currently approved in adults for the treatment of essential hypertension, mild to severe chronic heart failure, and the reduction of cardiovascular mortality in clinically stable patients who have survived the acute phase of a myocardial infarction (MI) and have a left ventricular ejection fraction (LVEF) of $\leq$ 40% (with or without symptomatic heart failure). Congestive heart failure (CHF) due to systemic ventricular dysfunction is a significant medical problem for children and represents the reason for referral in at least 50% of all children referred for heart transplantation. The clinical studies included in this submission were conducted to support the use of carvedilol in pediatric subjects with

heart failure. In these trials, doses were titrated every 2 weeks, as tolerated, through four levels. Carvedilol was supplied to parents/subjects in the form of a suspension for children weighing <62.5 kg or tablet for children weighing ≥ 62.5 kg.

2.2 Data Sources

The sponsor's SAS datasets were stored in the directory of \\Cdsesub1\n20297\N_000\2006-09-01 of the Center's electronic document room.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 STUDY 321

3.1.1.1 Study Objectives

The primary objective of this study was to assess the efficacy of carvedilol administered twice daily for 8 months as compared to placebo on a composite measure of clinical CHF outcomes in children with symptomatic systemic ventricular systolic dysfunction and CHF.

3.1.1.2 Study Design

This was a multicenter, randomized, double-blind, placebo-controlled study. The study was conducted in two phases:

Phase I: Initial screening phase (initial screening visit and randomization visit).

Phase II: Double-blind treatment phase (up-titration period and double-blind maintenance period).

3.1.1.3 Efficacy Measures

(1) Primary Efficacy Endpoint

The primary efficacy endpoint was a CHF composite outcome response: worsened, improved and unchanged.

(2) Secondary Efficacy Endpoints

- Individual components of the CHF composite (mortality and hospitalizations, alone and combined)
- CHF functional classification (NYHA/Ross' CHF Class)
- Global assessment scores and subject symptom assessment scores
- Permanent withdrawal, all-cause death, and all-cause hospitalization according to the endpoint committee
- Left ventricular function and remodeling parameters –echocardiographic measures

- Qualitative assessment of ventricular function and systemic atrioventricular regurgitation in subjects with non-left ventricle dysfunction

3.1.1.4 Patient Disposition, Demographic and Baseline Characteristics

Table 1 summarizes patient disposition, demographic and baseline characteristics. A smaller percentage of children in the placebo group (36.4%) were white compared with children in the carvedilol groups (58.5%), and the mean age was lower in the placebo group (55.6 ±60.75 months) than in both carvedilol groups (low-dose carvedilol 82.6 ±73.75 months, high-dose carvedilol 70.8 ±69.13 months). More than 70% of the subjects in each group were identified as having left ventricular anatomy.

Table 1 Patient Disposition, Demographic and Baseline Characteristics

	Total of Number	**Treatment Group**			
		Placebo	Low Dose	High Dose	Combined
Disposition					
Enrolled	176				
Randomized	161	55	53	53	106
Demographic					
Age (months)					
Mean		55.6	82.6	70.8	76.7
Gender (%)					
Male	83	30 (54.5)	28 (52.8)	25 (47.2)	53 (50.0)
Female	78	25 (45.5)	25 (47.2)	28 (52.8)	53 (50.0)
Race (%)					
Caucasian		20 (36.4)	31 (58.5)	31 (58.5)	62 (58.5)
Black		14 (25.5)	10 (18.9)	14 (26.4)	24 (22.6)
Asian		4 (7.3)	0	0	0
Hispanic		14 (25.5)	10 (18.9)	9 (17.0)	19 (17.9)
American Indian or Alaska native		1 (1.8)	0	1 (1.9)	1 (<1)
Other		16 (29.1)	12 (22.6)	7 (13.2)	19 (17.9)
Baseline					
Weight (KG)					
Mean		20.2	30.8	23.5	27.1
Original Ventricular Status					
NLV		14 (25.5)	9 (17.0)	12 (22.6)	21 (19.8)
LV		41 (74.5)	44 (83.0)	41 (77.4)	85 (80.2)

(Source: Sponsor's Table 6.07)

3.1.1.5 Sponsor's Primary Efficacy Results

1. The CHF composite outcome responses were categorized as: worsened, improved, or unchanged:

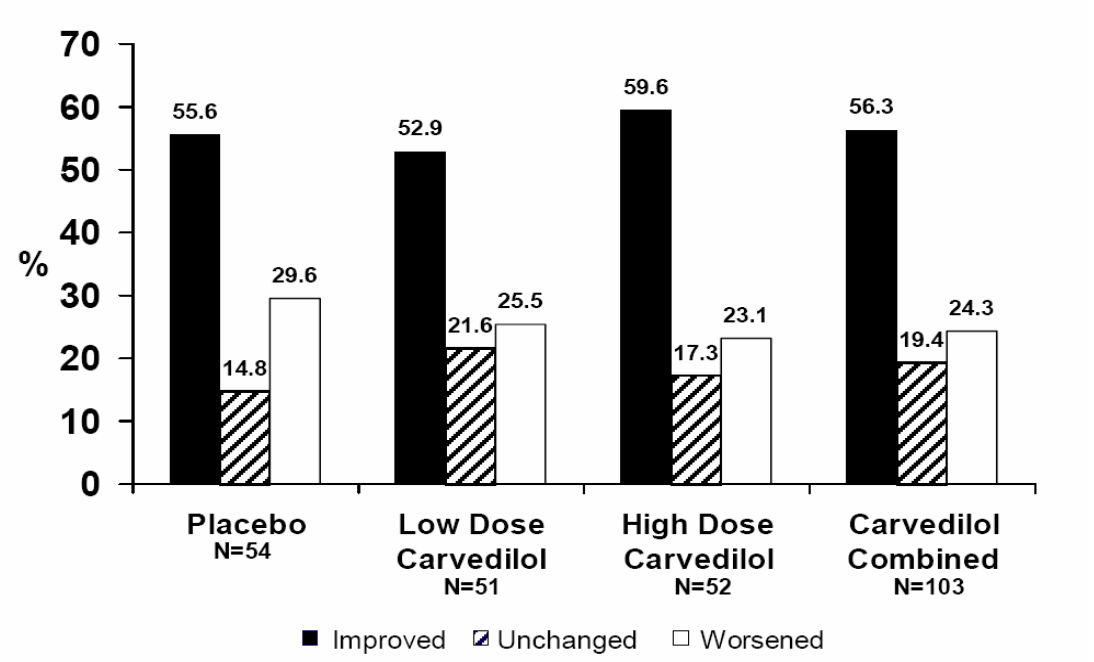
   The primary analysis showed that there was no statistically significant difference in the distribution or proportions of the outcome responses between placebo and the combined carvedilol group (p=0.740, Wilcoxon ranksum test, Table 2 and Figure 1). The other two supportive analyses of the CHF composite outcome also showed that there was no overall treatment effect across the three randomized groups based on the Kruskal-Wallis test, p=0.799 and the Cochran-Mantel-Haenzel chi-square test, p=0.739).

Table 2 Distribution of Primary CHF Composite Outcomes (ITT)

	Placebo	Low-Dose	High -Dose	Combined-Dose
Outcome	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)
P-value	0.740			

(Source: Sponsor's Table 7.01)

Figure 1 CHF Composite Response Rates for the Treatment Groups at LOCF



2. The CHF composite outcome responses were categorized as: improved vs. not improved (worsened + unchanged) or worsened vs. not worsened (improved + unchanged):

Secondary analyses of the primary endpoint showed that no significant difference between placebo and the combined carvedilol group in the proportion of subjects categorized as improved vs. not improved (OR=1.04, 95% CI: 0.53 to 2.05, p=0.900, Table 3) or categorized as worsened vs. not worsened (OR=0.80, 95% CI: 0.38 to 1.68, p=0.548, Table 4).

Table 3 Distribution of Primary CHF Composite Outcomes (Improved vs. Not improved)

	Placebo	Low-Dose	High -Dose	Combined-Dose
Outcome	n (%)	n (%)	n (%)	n (%)
Improved	30 (55.6)	27 (52.9)	31 (59.6)	58 (56.3)
Not improved	24 (44.4)	24 (47.1)	21 (40.4)	45 (43.7)
Odds Ratio (95% CI)	1.04 (0.53-2.05)			
P-value for odds ratio	0.900			

(Source: Sponsor's Table 24)

Table 4 Distribution of Primary CHF Composite Outcomes (Worsened vs. Not worsened)

	Placebo	Low-Dose	High -Dose	Combined-Dose
Outcome	n (%)	n (%)	n (%)	n (%)
Worsened	16 (29.6)	13 (25.5)	12 (23.1)	25 (24.3)
Not worsened	38(70.4)	38 (74.5)	40 (76.9)	78 (75.7)
Odds Ratio (95% CI)	0.8 (0.38-1.68)			
P-value for odds ratio	0.548			

(Source: Sponsor's Table 26)

3.1.1.6 Sponsor's Secondary Efficacy Results

The secondary efficacy analysis results were presented in the section 7.2, Tables 30-43 respectively.

3.1.1.7 Reviewer's Results

The statistical reviewer verified the sponsor's analyses and agreed that this was a negative study and the efficacy of carvedilol has not been shown in children with heart failure.

In view of the negative result, in addition to the considerations of age and status of left ventricle discussed by the sponsor, another factor may be also considered:

- The study may not be powered: The sponsor did not power the study based on a 10% effect on outcome events or a 20% effect (difference from placebo) on symptoms or global assessment score specified in the WR letter. A different treatment effect specified as the expected frequencies of 0.39, 0.375 and 0.235 for improved, unchanged and worsened in the combined carvedilol group; 0.19, 0.35 and 0.46 in the placebo group, was used instead for powering the study. It is not clear that how the 10% treatment effect on a binary outcome specified by FDA in the WR letter was translated into an overall effect on a three categories outcome specified by the sponsor. The sponsor also chose to not perform an interim analysis offered by FDA which may allow the sample size adjusted based on the observed variability from the study.

3.1.1.8 Conclusions

The efficacy of carvedilol has not been shown in children with heart failure. The study was only considered responsive to the WR since the requirement of a minimal of 150 subjects enrolled was met.

3.2 Conclusions and Recommendations

The efficacy of carvedilol in children with heart failure is inconclusive. For some reasons the result of the study seems to suggest that carvedilol is not effective. A larger study with a carefully planned sample size and targeted population may be needed to demonstrate the efficacy of carvedilol in children with heart failure.

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/s/

Ququan Liu
12/19/2006 08:19:51 AM
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James Hung
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