NDA #20297

Supplement amendment: 022 dated September 1, 2006

Sponsor: GlaxoSmithKline

Name of Finished Product: Coreg®

Name of Active Ingredient: carvedilol

(b) (4)

Conclusion:

There is no indication that the use of carvedilol in doses up to 25 mg bid is efficacious in children with heart failure. There were no unexpected safety events reported in this NDA supplement. (b) (4)

Summary:

The data base (b) (4) consists of one efficacy study (105517/321) and the extension study (105517/396), a report from the North American Pediatric Cardiomyopathy Registry (COG103639), and a review of the published literature.

Introduction:

Protocol number: SK&F-105517/321

Title: A multicenter, placebo-controlled, 8-month study of the effect of twice daily carvedilol in children with congestive heart failure due to systemic ventricular systolic dysfunction.

Study center(s): Twenty-six centers in the United States contributed subjects to this study.

Study period: 5-Jun-2000 - 13-Jun-2005

Objectives

The primary objective of this protocol was to compare the efficacy of placebo and carvedilol administered twice daily for 8 months as assessed by a composite measure of clinical congestive heart failure (CHF) outcomes in children with symptomatic systemic ventricular systolic dysfunction and CHF.

Methods

The screening phase was up to 14 days. Those subjects meeting the entry criteria were randomized, in a blinded fashion, to placebo, low-dose carvedilol, or high dose carvedilol in a 1: 1: 1 randomization schedule. At the time of randomization, subjects were stratified according to the anatomic substrate of the subject's ventricular dysfunction[1]. Subjects received the first dose of double-blind study medication (Level l) at the Randomization Visit.

[1] the investigator determined whether the patient would be stratified as left ventricle (LV) or non left ventricle (NLV) according to the anatomic substrate of the subject's ventricular dysfunction, i.e., those with systemic left ventricular dysfunction or those with right ventricular or single ventricular physiology. Patients with tricuspid atresia and a single left ventricle were to be randomized as LV if a left ventricular morphology was present and left ventricular systolic function could be analyzed using normal echocardiographic analyses.

Doses of study medication were titrated every 2 weeks, as tolerated, through four dose levels. Within the low-dose[2] and high-dose carvedilol groups[3], the mg/kg administered for each of these four levels was assigned according to weight (above or below 62.5 kg). Suspensions or tablets were supplied.

Subjects continued taking the dose level achieved during up-titration and returned to the clinic at 1, 2, 3, 4.5, and 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 Level 4. Subjects who completed the study and did not enter open-label studies and those who were prematurely withdrawn entered into the 4 week Down-Titration Phase and returned 2 weeks later for final safety assessments. Premature withdrawals were followed for the duration of the study period (randomization to one day after the planned last maximum dose of study medication, approximately eight months) for the collection and documentation of study endpoints.

Diagnosis and main criteria for inclusion

Subjects who
-were male or female children from birth through 17 years,
-had chronic symptomatic CHF (NYHA Class II-IV, if > 5 years-of-age or Ross' Classification of CHF Class II-IV if <5 years-of-age),
-had left ventricular ejection fraction (LVEF) <40%,
-had systemic left ventricular dysfunction or qualitative evidence of a dilated ventricle with moderate systemic ventricular systolic dysfunction in subjects with right ventricular or single ventricular physiology (i.e., NL V),
-were receiving standard heart failure therapy.

Excluded subjects included those with protocol defined medical conditions, were actively listed for transplantation or corrective heart surgery during the eight month period of the study, required protocol defined prior or concomitant medications, or were unwilling to practice acceptable contraceptive measures.

The planned sample size was 150.

Criteria for evaluation

The primary efficacy variable was a CHF composite outcome response. Subjects were determined to have a CHF composite outcome response[4] of "Worsened", "Improved", or "Unchanged" determined 12 hours after the last dose of study medication. The definitions of the categories were:

Worsened

-subject died,
-was hospitalized for at least 24 hours for worsening heart failure requiring intravenous heart failure medication;

[2] Target dose 0.2 mg/kg bid if weight was < 62.5 kg or 12.5 mg bid if weight was ≥ 62.5 kg
[3] Target dose 0.4 mg/kg bid if weight was < 62.5 kg or 25 mg bid if weight was ≥ 62.5 kg

[4] An Endpoint Committee, consisting of six participating investigators, adjudicated independently before unblinding, all deaths, hospitalizations, and permanent withdrawals to determine which events were associated with worsening heart failure.

-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.

Secondary efficacy parameters included selected individual components of the CHF composite of clinical outcomes, ventricular function and remodeling parameters (derived from that echocardiogram), 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.

Statistical methods

Sample size calculations were based on the primary endpoint of composite CHF composite outcome response of Worsened, Improved, or Unchanged. The primary comparison of interest was between the placebo group and the combined carvedilol group.

Results

A total of 161 subjects were randomized: 55 to placebo, 53 to low-dose carvedilol, and 53 to high-dose carvedilol. The following table shows the outcomes for these subjects by treatment group.

Number and (percent) of subjects

	Placebo	**Low dose Carv**	**High dose Carv**
Subjects Enrolled	55	53	53
Subjects Completed	44	40	42
Subjects Withdrawn	11	13	11
Reasons for Withdrawal			
Adverse Event+	9	9	8
Lack of Efficacy	0	0	0
Other^	2	4	3

+includes those who died during treatment.

^includes those who were discontinued because they took prohibited medication (1), started on commercial carvedilol (2), had elective transplantation (2), were lost to follow up (2), were terminated by sponsor, deviated from protocol (2)

The treatment groups were similar for the percentages of subjects who completed or withdrew from the study (including the specific reasons for withdrawal).

Demographics

Demographics for the subject population are shown below.

Number and (percent) of subjects

		Placebo n=55	Low-Dose Carv n=53	High-Dose Carv n=53
Gender, n (%)	Male	30 (55)	28 (53)	25 (47)
Age, (months)	Mean	56	83	71
Age category, %	Birth to Tanner Stage 2	87	76	85
	Tanner Stage 3 to <18 years	13	25	15
Race, %	White	36	59	59
	Black or African American	26	19	26
	other	38	23	15
Weight category, %	<62.5 kg	95	83	91
	≥ 62.5 kg	6	17	9
Ventricular Stratifier[a], %	LV	71	76	74
	NLV	29	25	26
NYHA/Ross CHF Class %	II	69	68	77
	III	31	30	21
	IV	0	2	2
Ejection Fraction %	n	42	42	39
	Mean (SD)	25.1 (±8.42)	27.0 (±7.06)	27.3 (±7.43)

[a]Ventricular stratifier is based on the ventricular status assigned during re-evaluation of echocardiographic data.

A small majority of subjects were male. Mean age was lower for the placebo group (56 months) compared to the active treatment groups (83 and 71 months for low dose and high dose carvedilol, respectively). Over 80% of all subjects were birth to Tanner Stage 2. About one quarter of subjects were black and most were less than 62.5 kg in weight. The majority of subjects were NYHA/Ross CHF classification II and the mean LV ejection fractions were around 27%. The groups were similar in the type of patient population.

As expected, all subjects had heart failure. The next most common cardiovascular conditions were cardiomegaly, primary cardiomyopathy, and cardiac murmurs. Commonly taken cardiac medications included digoxin, diuretics and ACE inhibitors/angiotensin receptor blockers. Commonly taken non cardiac medications included analgesics and antibiotics. Anti-asthmatic medication was taken by more than 20% of the study population.

Efficacy Results

Primary Efficacy Variable

The results of the primary endpoint (the CHF composite response being improved, unchanged, or worsened) for placebo and the combined as well as individual dose groups of carvedilol are shown below.

Number and (percent) of subjects

	Placebo	Low-Dose Carv	High-Dose Carv	Combined Car
Outcome	**n=54**	**n=51**	**n=52**	**n=103**
Improved	30 (56)	27 (53)	31 (60)	58 (56)
Unchanged	8 (15)	11 (22)	9 (17)	20 (19)
Worsened	16 (30)	13 (26)	12 (23)	25 (24)

There were small, irrelevant differences between placebo and the combined carvedilol group for the protocol specified primary endpoint of the CHF composite response (p=0.740, Wilcoxon rank sum).

The table below shows the results when the response categories are collapsed into improved or not improved as well as worsened and not worsened. (See statistical review).

Number and (percent) of subjects

	Placebo	**Low-Dose Carv**	**High-Dose Carv**	**Combined Car**
Outcome	**n=54**	**n=51**	**n=52**	**n=103**
Improved	30 (56)	27 (53)	31 (60)	58 (56)
Not improved[a]	24 (44)	24 (47)	21 (40)	45 (44)

[a] consists of the categories "unchanged" and "worsened"

Regarding the comparison of placebo and combined carvedilol groups, the odds ratio is 1.04 and the p value for the odds ratio is 0.9.

Number and (percent) of subjects

	Placebo	**Low-Dose Carv**	**High-Dose Carv**	**Combined Car**
Outcome	**n=54**	**n=51**	**n=52**	**n=103**
worsened	16 (30)	13 (26)	12 (23)	25 (24)
Not worsened[a]	38 (70)	38 (75)	40 (77)	78 (76)

[a] consists of the categories "improved" and "unchanged"

Regarding the comparison of placebo and combined carvedilol groups, the odds ratio is 0.80 and the p value for the odds ratio is 0.5.

Secondary Efficacy Variables

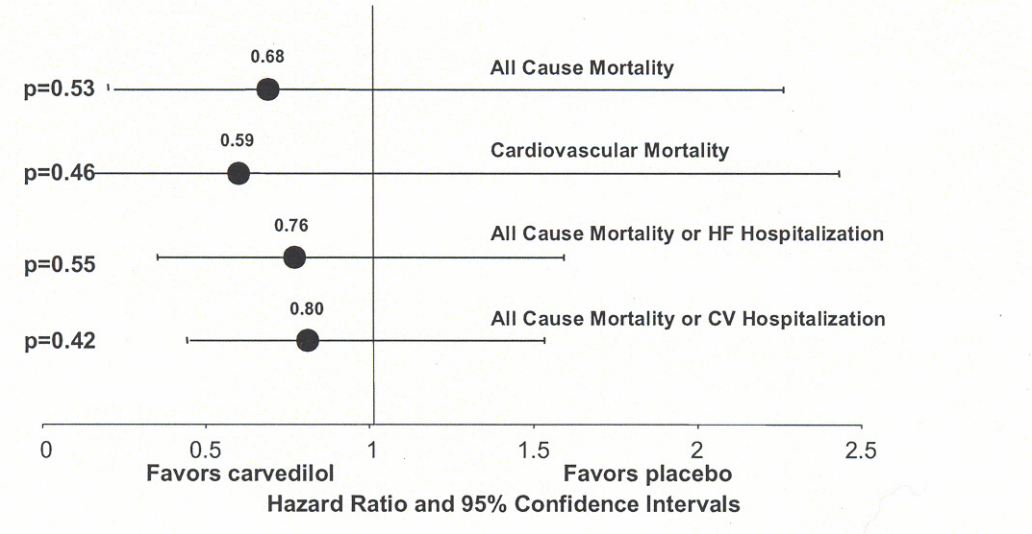
There were small, irrelevant differences between placebo and carvedilol groups for any of the individual components of the CHF composite (shown below).

Number and (percent) of subjects

	Placebo	**Low-Dose Carv**	**High-Dose Carv**	**Combined Car**
Outcome	**n=55**	**n=53**	**n=53**	**n=106**
All cause mortality+	5 (9)	3 (6)	3 (6)	6 (6)
Cardiovascular mortality	4 (7)	2 (4)	2 (4)	4 (4)
Cardiovascular hospitalizations	13 (24)	10 (19)	9 (17)	19 (18)
Worsening heart failure hospitalization	10 (18)	6 (11)	8 (15)	14 (13)

+excludes 3 subjects: 2 subjects (placebo and low dose carvedilol) who died post cardiac transplant and 1 who died > 30 days (low dose carvedilol) after receiving last dose of study drug.

Figure 2 **Hazard Ratio Plot for Time to Event Analyses of Mortality, and Mortality or Hospitalizations**



There is no evidence from the hazard ratios for mortality rate and hospitalization rate that the use of carvedilol in this patient population is harmful.

Safety Results

The mean durations of exposure to placebo, low dose carvedilol, and high dose carvedilol were 231, 220, and 230 days, respectively. The majority of subjects were able to tolerate the highest titrated dose (placebo 93%, low dose carvedilol 76%, high dose carvedilol 83% determined at the end of maintenance phase).

Serious safety

Deaths

There were 14 reported deaths during the trial period (6 placebo, 5 low dose carvedilol, and 3 high-dose carvedilol). Of the 14 deaths, 5 occurred during the treatment phase and 9 occurred post treatment.

Subjects who died

	Subject number	Age/sex	Days on drug	Preferred term
On therapy				
placebo	321.001.00001	11years/m	128	arrhythmia
Low dose carvedilol	321.001.00267	9months/f	111	pneumonia
	321.014.00223	15years/f	45	Ventricular fibrillation
	321.021.00074	16years/m	108	Cardiac arrest
High dose carvedilol	321.003.00293	8years/f	133	Cardiac failure
Post therapy				

Placebo	321.001.00268	11years/m	36P	Cardiac failure
	321.003.00047	16years/m	28P	Arrhythmia post transplant
	321.014.00026	10months/f	2P	Respiratory distress
	321.016.00297	19months/m	49P	Cardiac failure
	321.025.00192	6years/m	56P	Ventricular arrhythmia
Low dose carvedilol	321.014.00030	7years/f	36P	Renal failure and cerebral hemorrhage post transplant
	321.039.00324	14months/f	52P	Bone marrow disorder
High dose carvedilol	321.001.00004	27months/f	105P	Respiratory distress
	321.021.00276	13years/f	19P	Arrhythmia

P=post therapy

The subjects listed above are discussed in the following table (grouped by study drug assignment).

Placebo	
00001	This 12 year old male received placebo for 127 days. The subject was in the down titration phase when he had sudden collapse. He was found to be in ventricular fibrillation and was unable to be resuscitated.
00268	This 11 year old male was discontinued from study drug on day 84 because of fatigue and cough. On chest x-ray, he had increased cardiomegaly, bilateral pulmonary edema and pleural effusion. The subject suffered a cardiac arrest during insertion of pacemaker 13 days post study drug therapy. He recovered and was awaiting cardiac transplantation when he became systolic and expired.
00047	This 16 year old male was hospitalized for worsening heart failure and was withdrawn from study drug on day 194. He died 11 days post cardiac transplant.
00026	This 13 month old female died on day 153 secondary to respiratory distress considered to be caused by acute viral syndrome.
00297	This 24 month old male was discontinued from study drug on day 140 because of syncope resulting from “torsades de pointes” (v tach). He had a difficult hospital course during which he received open label carvedilol. He died of cardiac failure following an episode of acute hypotension, ventricular tachycardia and ventricular fibrillation.
00192	This 7 year old male died because of a ventricular arrhythmia 56 days after the last dose of study drug. He had been withdrawn from study drug because of worsening heart failure.
Low dose carvedilol	
00267	This 12 moth old female with complex medical history died of pneumonia on study day 108.
00030	This 7 year old female complained of dyspnea 4 hours after starting study drug. She was treated for heart failure and withdrawn from study medication on day 7 She underwent a cardiac transplant the next day. Post op, she developed positive blood cultures for candida, thrombocytopenia, acute respiratory distress syndrome, renal failure, and subarachnoid hemorrhage. She died about 5 weeks after study drug was discontinued.

00223	This 15 year old female with a history of myocarditis and dilated cardiomyopathy collapsed with ventricular fibrillation 44 days after starting study drug. She was unable to be resuscitated.
00074	This 16 year old male with cardiomegaly and dilated cardiomyopathy. He was hospitalized for worsening heart failure about 2 months after starting study drug and his dose was reduced. His study drug course was complicated by an episode of sepsis. He had sudden cardiac arrest on day 106 and died one day later
00324	This 22 month old female with a medical history that included dilated cardiomyopathy and pansystolic murmur developed resistant otitis media with positive blood cultures for strep viridans and staph about 7 months after the start of study drug. She was found to be positive for influenza B infection and her clinical course, including a diagnosis of bone marrow failure, continued to decline. Study drug was discontinued and she died about 2 months later.
High dose carvedilol	
00004	This 28 month old female had loss of consciousness and sinus bradycardia with a heart rate of 35 bpm one day after starting study drug. (It was noted that this type of event had occurred in the past). Study drug was discontinued and she died of congestive heart failure, dilated cardiomyopathy associated with neonatal myocarditis about 5 months later.
00293	This 8 year old female with numerous medical conditions including tetralogy of Fallot developed worsening heart failure 102 days after starting study drug. She was deemed not to be a candidate for transplant and she was withdrawn from study medication. The subject died of congestive heart failure about 1 month later.
00276	This 13 year old female with congenital heart disease had complaints of edema, vomiting and shortness of breath 8 days after start of study drug. She was diagnosed with worsening heart failure, discontinued study drug on day 29. Death thought to be secondary to an arrhythmia occurred 19 days after the last dose of study drug.

Serious adverse events

Serious adverse events reported by at least 2 carvedilol subjects are shown below by treatment group.

Number and (percent) of subjects

	Placebo N=55	Low dose carv N=53	High dose carv N=53	Combined carv N=106
Subjects with at least one report	24 (44)	19 (36)	19 (36)	38 (36)
Anemia	0	2	0	2
Bradycardia	1	1	1	2
Worsening heart failure+	10^	7	7^	14
Vomiting	0	0	2	2
Pyrexia	1	1	1	2
Bronchiolitis	2	1	1	2
Pneumonia	0	1	1	2
URTI	0	2	1	3
Viral infection	2	1	4	5
Dehydration	1	2	3	5
Failure to thrive	1	2	0	2
Septic shock	0	2	0	2

+reported as cardiac failure or cardiac failure congestive
^excluding one death

There were 38 subjects (36%) randomized to carvedilol who reported a serious adverse events compared to 24 (44%) of subjects randomized to placebo. The most commonly reported event was worsening heart failure followed by viral infection and dehydration. Nothing seems to indicate an association with carvedilol.

Withdrawals because of adverse events
There were 22 subjects who withdrew from the study because of adverse events (7 placebo, 7 low dose carvedilol, 8 low dose carvedilol). The most frequent adverse event resulting in withdrawal was worsening heart failure (cardiac failure and cardiac failure congestive combined) with 6 subjects in each group.

Number of withdrawals from study drugs

	Placebo	Low-Dose Carvedilol	High-Dose Carvedilol	Combined Carvedilol
	N=55	N=53	N=53	N=106
Number of subjects with events leading to withdrawal	7	7	8	15
Bradycardia	0	0	1	1
Cardiac failure+	6	6	6	12
Congenital coronary artery malformation	0	1	0	1
Chest pain	0	0	1	1
Fatigue	0	0	1	1
Respiratory tract infection	0	1	0	1
Viral infection	0	0	1	1
Decreased ejection fraction	1	0	0	0
Muscle cramp	0	0	1	1
Loss of consciousness	0	0	1	1

Exertional dyspnea	0	0	1	1

+includes cardiac failure congestive

All adverse events

Most of the adverse events occurring in > 10% of subjects in any treatment group and the incidence rate for the combined carvedilol groups was higher than the incidence rate for placebo are shown below:

The number and (percent) of subjects

	Placebo	Low-Dose Carvedilol	High-Dose Carvedilol	Combined Carvedilol	Placebo subtracted[b] (%)
	N=55	N=53	N=53	N=106	
Subjects with Events	54 (98)	50 (94)	53 (100)	103 (97)	
Dizziness	1 (2)	7 (13)	7 (13)a	14 (13)	11
Dyspnea	0	7 (13)	5 (9)	12 (11)	11
Chest Pain	3 (6)	9 (17)	9 (17)	18 (17)	9
Headache	6 (11)	10 (19)	9(17)	19 (18)	7
Dehydration	1 (2)	4 (8)	4 (8)	8 (8)	6
Nausea	5 (9)	6(11)	9 (17)	15 (14)	5
Pneumonia	2 (4)	6 (11)	2 (4)	8 (8)	4
Anemia	2 (4)	5 (9)	3 (6)	8 (8)	4
Bradycardia	1 (2)	3 (6)	3 (6)	6 (6)	4
Upper Respiratory Tract Infection	25 (46)	30 (57)	22 (43)	52 (49)	3
Hypotension	3 (6)	6 (11)	4 (8)	10 (9)	3
Syncope	0	3 (6)	0	3 (3)	3
Fatigue	9 (16)	15 (28)	4 (8)	19(18)	2
Cardiac murmur	2 (4)	3 (6)	3 (6)	6 (6)	2
Abdominal Pain Upper	6 (11)	7 (13)	6 (11)	13 (12)	1

a. Includes subject 321.014.00224

b Combined carvedilol with placebo rate subtracted

Table 48

Adverse Events: The placebo subtracted rates for dizziness and dyspnea were 11%. The rates for chest pain and headache were 9% and 7%, respectively. All the other events were 5% or less.

There is no evidence for a dose relationship for any of the adverse events.

Clinical laboratory

There were no reported study drug withdrawals because of abnormal laboratory values in any of the drug groups.

Hematology

Change from baseline at endpoint

	Placebo n=55+	Low dose carv n=53+	High dose carv n=53+
Hemoglobin (G/dl)	0.4	-0.2	-0.1

Hematocrit (%)	1.6	0	-0.2
White blood count ($/mm^3$)	0.5	-0.8	-0.1
Platelets ($/mm^3$)	29.1	-24.0	-8.8

+most but not all randomized subjects had baseline and post baseline values

There were small changes from baseline in all treatment groups.

Liver and kidney

Change from baseline at endpoint

	Placebo n=55+	Low dose carv n=53+	High dose carv n=53+
ALT (U/L)	-2.7	0.2	5.2
AST (U/L)	-3.1	3.1	1.5
Serum creatinine (mg/dl)	0	0.1	0

There were similar changes in the treatment groups for these laboratory values with the exception of ALT. A total of 6 subjects randomized to high dose carvedilol had normal baseline values but elevated levels at the end of maintenance compared to 3 placebo and 1 low dose carvedilol subjects. There was only 1 subject in the high dose carvedilol group (and none in the placebo and low dose carvedilol groups) with a normal baseline AST value that was elevated at end of maintenance. There were 3 subjects (1 placebo, 2 high dose carvedilol) with abnormal liver function tests that were reported as non serious adverse event[5].

The abnormal laboratory tests reported as adverse events by more than 2 carvedilol subjects are shown below.

Number and (percent) of subjects with abnormality

	Placebo n=55	Low dose carv n=53	High dose carv n=53
Anemia	2 (4)	5 (9)	3 (6)
O_2 sat decreased	1 (2)	0	3 (6)
Hyperkalemia	0	(4)	2 (4)

There were 8 subjects with abnormal laboratory values that were reported as serious. Only the adverse event anemia was reported by more than 1 subject (2 subjects on low dose carvedilol).

There is no evidence that carvedilol is associated with life-threatening changes in clinical laboratory parameters. There could be a minor effect of carvedilol on decreasing hemoglobin.

Vital signs

As expected, there were decreases in heart rate in the carvedilol groups compared to placebo.

[5] Tables 79 and 80.

Change from baseline at endpoint, placebo subtracted (bpm)

	Low dose carv n=53	High dose carv n=52
Heart rate	-4.1	-5.5

Bradycardia was reported as serious adverse event in 3 subjects, 1 per drug group. There was one withdrawal in the high dose carvedilol group. In addition, there was one report of serious bradycardia associated with junctional rhythm. The subject completed the study.

Blood pressure, on the other hand, was slightly elevated in the high dose carvedilol group.

Change from baseline at endpoint (mmHg)

	Placebo n=55	Low dose carv n=53	High dose carv n=53
systolic	0.3	0.4	1.6
diastolic	2.1	0.5	3.5

There was one report of serious hypotension ((low dose carvedilol). The subject was not withdrawn from the study. There were other reports of hypotension/orthostatic hypotension/syncope not deemed to be serious and none resulted in study drug withdrawal.

Growth and Development

Adverse events associated with growth and development include failure to thrive, weight decreased, and hydrocephalus. There were two reports of failure to thrive in subjects randomized to low dose carvedilol. One subject continued in the study and the event was reported as resolved. The other subject received a gastrostomy tube and remained in the study. This event also was reported as resolved. One subject (placebo) had ongoing hydrocephalus at screening. The shunt was revised and the subject remained in the study. There also was a report of failure to thrive for this subject. No change in study drug was made.

The numbers of subjects who received a cardiac transplant are shown below by treatment group.

Number and (percent) of subjects

	Placebo n=55	Low dose carv n=53	High dose carv n=53
Up titration	0	1	0
Maintenance	1	1	2
On therapy	1	2	2
Post therapy	4	4	5

There are minor differences among the treatment groups regarding the numbers of subjects who underwent transplantation.

ECG abnormalities

There were no study withdrawals because of abnormal ECG. There were 2 reports of serious safety: atrioventricular block (lose dose carvedilol) and nodal arrhythmia (high dose carvedilol).

The reports of abnormalities with the highest frequencies in the carvedilol groups include ventricular tachycardia (placebo 3, low dose carvedilol 2, high dose carvedilol 2), ventricular extrasystoles (placebo 0, low dose carvedilol 2, high dose carvedilol 1), extrasystoles (placebo 0, low dose carvedilol 1, high dose carvedilol 1), atrioventricular block (placebo 0, low dose carvedilol 1, high dose carvedilol 1), sinus bradycardia (placebo 0, low dose carvedilol 1, high dose carvedilol 1) cardiac flutter (placebo 0, low dose carvedilol 2, high dose carvedilol 0).

Missed school days
A large percentage of the study subjects did not attend school so this parameter was disregarded in this safety review.

Protocol number 396

Title: A multicenter, open label extension study to evaluate the safety of twice daily oral carvedilol in pediatric subjects with chronic heart failure.

Study center(s): eighteen centers in the United States contributed subjects to this study.

Study period: 15-Oct-2003 - 16-Dec-2005

Objectives: The primary objective of this protocol was to evaluate the long term safety of carvedilol in pediatric subjects with heart failure who completed the study 321.

Methods: The screening phase was the maintenance month 6 visit in the 321 study. There was an 8-week phase of simultaneous down-titration of study drug from 321 and up titration of open label carvedilol. During the maintenance phase, subjects continued on the maximum dose of carvedilol achieved during up-titration for at least 6 months. Subjects who were not to receive commercial carvedilol after the completion of the study were down titrated over 4 weeks. Dose schedule is shown below.

All subjects, categorized by weight (< 62.5 kg and ≥ 62.5 kg), were up-titrated using the following 4 visit, 6 week schedule:

Week of Up-Titration Phase	0	2	4	6
Carvedilol (mg/kg b.i.d.)	0.05	0.1	0.2	0.4

Subjects weighing ≥62.5 kg were up-titrated using the following 4 visit, 6 week schedule:

Week of Up-Titration Phase	0	2	4	6
Carvedilol (mg b.i.d.)	3.125	6.25	12.5	25

Main criterion for inclusion: subjects who completed the maintenance period of study 321.

Disallowed concomitant medications included monoamine oxidase (MAO) inhibitors, calcium entry blockers, alpha-blockers, labetalol, disopyramide, flecainide, encainide, moricizine, propafenone, intravenous (IV) inotropes or intravenous vasodilator agents, IV CHF medications, or beta-blockers other than double-blind carvedilol.

No efficacy analyses were planned.

This safety review includes 102 subjects, 66 subjects who were enrolled in study 396 and 36 subjects who participated in the 321 OL phase but did not enter study 396.

Table 5 Number and Percentage of Subjects Who Received Open-Label Carvedilol

	Treatment Group of Origin in Study 321		
	Plac/Carv	Carv/Carv	Total
Number of Subjects Planned: 130	n (%)	n (%)	n (%)
Total Number of Subjects Receiving Open-Label Carvedilol	39 (38.2)	63 (61.8)	102 (100.0)
Subjects Enrolled in Study 396 (Either Directly or After 321OL Phase[a])	28 (27.5)	38 (37.3)	66 (64.7)
Subjects Enrolled in 321OL Phase Who Did Not Enter Study 396	11 (10.8)	25 (24.5)	36 (35.3)

a. Of the 66 subjects in Study 396, 36 transitioned into Study 396 after the 321OL phase, and 30 enrolled directly into 396.
Percentage is based on total number of subjects receiving open-label carvedilol
Source: Table 6.01

Demographics: the 102 subjects who received open label carvedilol (66 from study 396 and 36 from open label use of carvedilol) were primarily white (49%), male (55%), and were in the age category of birth to Tanner stage 2 (86%). The mean age was 66.7 month and 36% were NYHA/Ross Class I.

Commonly used medications: The most often used cardiovascular medications were ACE inhibitors (72%), digoxin (60%), and diuretics (55%). Non cardiovascular medications included analgesics and vitamins.

Duration of treatment: there were 84 subjects (82%) who received carvedilol for $\geq$ 366 days. The mean duration of exposure was 719 days (range 12 to 1812 days).

Serious safety

Deaths

There were 7 reported deaths.

Table 32 Subjects with Serious Adverse Events Resulting in Death

PID	Age[a]	Sex	Dose Level at Onset of SAE	Onset Day[b]	Treatment Group	Phase[e]	Preferred Term
					On-Therapy		
321OL.003.00007	36 mo	F	4	1093	Plac/Carv	Maintenance	Cardiac Arrest
321OL.003.00048	10 mo	M	2	39	Plac/Carv	Up-titration	Cardio-Respiratory Arrest
396.035.00207[c]	8 yr	F	4	578	Carv/Carv	Maintenance	Arrhythmia
					Post-Therapy		
321OL.007.00082	26 mo	M	...	353 (14P)	Carv/Carv	Post-therapy	Cardio-Respiratory Arrest
321OL.014.00222	13 yr	M	2	440(1P)[d]	Carv/Carv	Post-therapy	Multi-Organ Failure
396.003.00272	6 yr	M	...	722 (8P)	Carv/Carv	Post-therapy	Sudden Death
396.021.00171	9 yr	F	...	623 (29P)	Carv/Carv	Post-therapy	Cardiac Arrest (Post Transplant)

a. Age at screening in Study 321
b. Onset day relative to start date of carvedilol
c. Subject was withdrawn and died the next day
d. Subject was withdrawn and died 7 days post-therapy
e. Phase at time of death
Source: Listing D.04 (Attachment 1)

The subjects in the previous table are discussed in detail below.

00007	This 6 year old female with dilated cardiomyopathy died suddenly after 4 years of treatment with carvedilol (in addition to other cardiac medications). The preliminary autopsy results included thrombus, pulmonary embolism or an infarct. With biventricular dilation, left ventricular hypertrophy and left ventricular endocardial fibroelastosis.
00048	This 10 month old male with various anomalies secondary to mitochondrial abnormalities (including dilated cardiomyopathy) had a cardiac arrest 40 days after starting blind medication. He died after undergoing attempts to resuscitate him. Autopsy showed severe cardiomegaly.
00272	This 7 year old male with numerous cardiac abnormalities including T wave abnormalities, cardiomegaly, dilated cardiomyopathy, died suddenly after taking carvedilol for about 2 years. His course in the study had been complicated by an episode of syncope (day 534) and hospitalization for a viral infection and worsening cardiac function (2 months prior to death). No autopsy results are known.
00082	This 3 year old male with complex congenital heart disease died 2 weeks after receiving last dose of carvedilol. He experienced asystole shortly after a follow up cardiac catheterization and could not be resuscitated.
00222	This 14 year old male developed ventricular tachycardia/ventricular fibrillation. He was hospitalized and withdrawn from the study. The subject went on to have multi-organ failure and died about 1 week later.
00171	This 10 year old female with a history of severe congenital heart disease underwent a heart transplant after 19 months of treatment with carvedilol. The study drug was discontinued and the subject experienced a cardiac arrest about 27 days post transplant. No autopsy results were available at the time of the report.
00207	This 9 year old female with multiple congenital heart abnormalities including aortic coarctation cardiomegaly, right ventricular dysfunction, and diffuse ST and T wave changes experienced collapse and then death 2 days later. She had been taking carvedilol about 19 months with several serious adverse events.

It appears unlikely that carvedilol contributed to the death of any of these subjects. All had complex medical histories that included severe (congenital) cardiac abnormalities and seemed to be able to tolerate long term use of carvedilol.

Serious adverse events

Nonfatal serious events are shown below.

Table 33 Number and Percentage of Subjects with Non-Fatal Serious Adverse Events during the On-Therapy Period (Up-Titration, Maintenance, Down-Titration Combined) – All Subjects Enrolled

System Organ Classification Preferred Term	Treatment Group of Origin in Study 321 Plac/Carv (N=39) n (%)	 Carv/Carv (N=63) n (%)	 Total (N=102) n (%)
Subjects with Non-Fatal SAEs	**10 (25.6)**	**20 (31.7)**	**30 (29.4)**
Blood and Lymphatic System Disorders	**0**	**1 (1.6)**	**1 (<1)**
Anaemia	0	1 (1.6)	1 (<1)
Cardiac Disorders	**4 (10.3)**	**12 (19.0)**	**16 (15.7)**
Worsening Heart Failure[a]	3 (7.7)	10 (15.9)	13 (12.7)
Cardiomyopathy	1 (2.6)	2 (3.2)	3 (2.9)
Atrial Fibrillation	0	1 (1.6)	1 (<1)
Atrial Flutter	0	1 (1.6)	1 (<1)
Bradycardia	0	1 (1.6)	1 (<1)
Ventricular Fibrillation	0	1 (1.6)	1 (<1)
Ventricular Tachycardia	0	1 (1.6)	1 (<1)
Electromechanical Dissociation	1 (2.6)	0	1 (<1)
Gastrointestinal Disorders	**0**	**2 (3.2)**	**2 (2.0)**
Vomiting	0	2 (3.2)	2 (2.0)
General Disorders and Administration Site Conditions	**2 (5.1)**	**1 (1.6)**	**3 (2.9)**
Pyrexia	1 (2.6)	1 (1.6)	2 (2.0)
Hypothermia	1 (2.6)	0	1 (<1)
Immune System Disorders	**0**	**1 (1.6)**	**1 (<1)**
Anaphylactic Reaction	0	1 (1.6)	1 (<1)
Infections and Infestations	**6 (15.4)**	**6 (9.5)**	**12 (11.8)**
Bacteraemia	0	1 (1.6)	1 (<1)
Croup Infectious	0	1 (1.6)	1 (<1)
Gastroenteritis	1 (2.6)	1 (1.6)	2 (2.0)
Lobar Pneumonia	0	1 (1.6)	1 (<1)
Otitis Media	0	1 (1.6)	1 (<1)
Pneumonia	2 (5.1)	1 (1.6)	3 (2.9)
Respiratory Tract Infection Viral	0	1 (1.6)	1 (<1)
Shigella Infection	0	1 (1.6)	1 (<1)
Upper Respiratory Tract Infection	0	1 (1.6)	1 (<1)
Viral Infection	0	1 (1.6)	1 (<1)
Bronchiolitis	1 (2.6)	0	1 (<1)
Respiratory Syncytial Virus Infection	1 (2.6)	0	1 (<1)
Viral Upper Respiratory Tract Infection	1 (2.6)	0	1 (<1)
Injury, Poisoning and Procedural Complications	**0**	**2 (3.2)**	**2 (2.0)**
Head Injury	0	1 (1.6)	1 (<1)
Therapeutic Agent Toxicity	0	1 (1.6)	1 (<1)
Investigations	**0**	**1 (1.6)**	**1 (<1)**
International Normalised Ration Decreased	0	1 (1.6)	1 (<1)
Metabolism and Nutrition Disorders	**2 (5.1)**	**1 (1.6)**	**3 (2.9)**
Dehydration	1 (2.6)	1 (1.6)	2 (2.0)
Hypoglycaemia	1 (2.6)	0	1 (<1)
Nervous System Disorders	**1 (2.6)**	**2 (3.2)**	**3 (2.9)**
Syncope	1 (2.6)	2 (3.2)	3 (2.9)
Complex Partial Seizures	0	1 (1.6)	1 (<1)
Respiratory, Thoracic and Mediastinal Disorders	**1 (2.6)**	**0**	**1 (<1)**
Asthma	1 (2.6)	0	1 (<1)
Vascular Disorders	**1 (2.6)**	**2 (3.2)**	**3 (2.9)**
Hypotension	1 (2.6)	1 (1.6)	2 (2.0)
Pharyngeal Haemorrhage	0	1 (1.6)	1 (<1)

a. Cardiac failure and cardiac failure congestive combined (based on Listing D.02 [Attachment 1])
Source: Table 8.22

Worsening heart failure, cardiomyopathy, pneumonia, and syncope were the most often reported serious adverse events.

Withdrawals for adverse events

There were 11 subjects (11%) who with drew from the open label treatment because of an adverse event.

Table 27 Number and Percentage of Subjects with Adverse Events Leading to Withdrawal during the On-Therapy Period[a] by Prior Treatment Group – Subjects in 321OL Phase Who Did Not Transition Into Study 396

	Treatment Group of Origin in Study 321		
	Plac/Carv (N=11)	Carv/Carv (N=25)	Total (N=36)
Preferred Term	n (%)	n (%)	n (%)
Subjects with AEs	**1 (9.1)**	**5 (20.0)**	**6 (16.7)**
Worsening Heart Failure[b]	1 (9.1)	3 (12.0)	4 (11.1)
Cardiomyopathy	0	1 (4.0)	1 (2.8)
Ventricular Fibrillation	0	1 (4.0)	1 (2.8)

a. For withdrawals, on-therapy is defined as up-titration and maintenance periods only.
b. Cardiac failure and cardiac failure congestive combined (based on Listing D.05 [Attachment 1])
Source: Table 8.24

Table 28 Number and Percentage of Subjects with Adverse Events Leading to Withdrawal during the On-Therapy Period[a] by Prior Treatment Group – Subjects Enrolled in Study 396

	Treatment Group of Origin in Study 321		
	Plac/Carv (N=28)	Carv/Carv (N=38)	Total (N=66)
Preferred Term	n (%)	n (%)	n (%)
Subjects with AEs	**3 (10.7)**	**2 (5.3)**	**5 (7.6)**
Worsening Heart Failure[b]	2 (7.1)	1 (2.6)	3 (4.5)
Arrhythmia	0	1 (2.6)	1 (1.5)
Fatigue	1 (3.6)	0	1 (1.5)
Nausea	1 (3.6)	0	1 (1.5)

a. For withdrawals, on-therapy is defined as up-titration and maintenance periods only.
b. Cardiac failure and cardiac failure congestive combined (based on Listing D.05 [Attachment 1])
Source: Table 8.24

The 11 subjects are shown in the table below.

Table 27 Number and Percentage of Subjects with Adverse Events Leading to Withdrawal during the On-Therapy Period[a] by Prior Treatment Group – Subjects in 321OL Phase Who Did Not Transition Into Study 396

	Treatment Group of Origin in Study 321		
	Plac/Carv (N=11)	Carv/Carv (N=25)	Total (N=36)
Preferred Term	n (%)	n (%)	n (%)
Subjects with AEs	**1 (9.1)**	**5 (20.0)**	**6 (16.7)**
Worsening Heart Failure[b]	1 (9.1)	3 (12.0)	4 (11.1)
Cardiomyopathy	0	1 (4.0)	1 (2.8)
Ventricular Fibrillation	0	1 (4.0)	1 (2.8)

a. For withdrawals, on-therapy is defined as up-titration and maintenance periods only.
b. Cardiac failure and cardiac failure congestive combined (based on Listing D.05 [Attachment 1])
Source: Table 8.24

Table 28 Number and Percentage of Subjects with Adverse Events Leading to Withdrawal during the On-Therapy Period[a] by Prior Treatment Group – Subjects Enrolled in Study 396

	Treatment Group of Origin in Study 321		
	Plac/Carv (N=28)	Carv/Carv (N=38)	Total (N=66)
Preferred Term	n (%)	n (%)	n (%)
Subjects with AEs	**3 (10.7)**	**2 (5.3)**	**5 (7.6)**
Worsening Heart Failure[b]	2 (7.1)	1 (2.6)	3 (4.5)
Arrhythmia	0	1 (2.6)	1 (1.5)
Fatigue	1 (3.6)	0	1 (1.5)
Nausea	1 (3.6)	0	1 (1.5)

a. For withdrawals, on-therapy is defined as up-titration and maintenance periods only.
b. Cardiac failure and cardiac failure congestive combined (based on Listing D.05 [Attachment 1])
Source: Table 8.24

Overall, there were 7 withdrawals for worsening heart failure. In addition, there was one withdrawal for ventricular fibrillation and one arrhythmia**.**

Adverse events (limited to study 396) reported by at least 5 subjects (8%) are shown below.

Table 20 **Number and Percentage of Subjects with Adverse Events that Occurred in > 5% of Subjects in the Total Group during the On-Therapy Period by Descending Order of Preferred Term Incidence of Total Group by Prior Treatment Group – Subjects Enrolled in Study 396**

	Treatment Group of Origin in Study 321		
	Plac/Carv (N=28)	Carv/Carv (N=38)	Total (N=66)
Preferred Term	n (%)	n (%)	n (%)
Subjects with AEs	**27 (96.4)**	**38 (100.0)**	**65 (98.5)**
Pyrexia	15 (53.6)	18 (47.4)	33 (50.0)
Upper Respiratory Tract Infection	12 (42.9)	21 (55.3)	33 (50.0)
Cough	14 (50.0)	15 (39.5)	29 (43.9)
Vomiting	15 (53.6)	13 (34.2)	28 (42.4)
Diarrhoea	11 (39.3)	9 (23.7)	20 (30.3)
Fatigue	7 (25.0)	8 (21.1)	15 (22.7)
Rhinorrhoea	5 (17.9)	10 (26.3)	15 (22.7)
Nasopharyngitis	6 (21.4)	7 (18.4)	13 (19.7)
Otitis Media	6 (21.4)	7 (18.4)	13 (19.7)
Ear Infection	4 (14.3)	6 (15.8)	10 (15.2)
Headache	3 (10.7)	7 (18.4)	10 (15.2)
Pharyngolaryngeal Pain	2 (7.1)	8 (21.1)	10 (15.2)
Chest Pain	4 (14.3)	5 (13.2)	9 (13.6)
Decreased Appetite	7 (25.0)	2 (5.3)	9 (13.6)
Dizziness	2 (7.1)	7 (18.4)	9 (13.6)
Pneumonia	6 (21.4)	3 (7.9)	9 (13.6)
Abdominal Pain Upper	5 (17.9)	3 (7.9)	8 (12.1)
Viral Infection	2 (7.1)	6 (15.8)	8 (12.1)
Worsening Heart Failure[a]	3 (10.7)	5 (13.2)	8 (12.1)
Epistaxis	3 (10.7)	4 (10.5)	7 (10.6)
Gastroenteritis	1 (3.6)	6 (15.8)	7 (10.6)
Hypotension	5 (17.9)	2 (5.3)	7 (10.6)
Hyperhidrosis	0	6 (15.8)	6 (9.1)
Pain in Extremity	3 (10.7)	3 (7.9)	6 (9.1)
Bronchitis	3 (10.7)	2 (5.3)	5 (7.6)
Croup Infectious	1 (3.6)	4 (10.5)	5 (7.6)
Dyspnoea	2 (7.1)	3 (7.9)	5 (7.6)
Nausea	2 (7.1)	3 (7.9)	5 (7.6)
Rash	2 (7.1)	3 (7.9)	5 (7.6)
Sinusitis	1 (3.6)	4 (10.5)	5 (7.6)
Syncope	1 (3.6)	4 (10.5)	5 (7.6)

[a] includes cardiac failure and cardiac failure congestive.

The most commonly reported adverse events included pyrexia and URTI (50%), followed by cough (44%), vomiting (42%), and diarrhea (30%).

There were 13 reported cases of hypotension/procedural hypotension/syncope. These subjects are shown below.

Table 39 Subjects with Hypotension and Syncope During the On-Therapy Period – Subjects Enrolled in Study 396

Study Drug	PID	Age[a]	Sex	Dose Level at Onset	Preferred Term	Relday[b]	Dur (days)	Sev[c]	Rel	WD	SAE	Bsl BP (mmHg)	Event BP (mmHg)[b]
Placebo/Carvedilol	396.001.00163	9 mo	M	4	Hypotension	412	7	Mod	Not	No	No	99/72	...
Placebo/Carvedilol	396.001.00266	55 mo	M	2	Hypotension	29	1	Mil	Susp	No	No	94/53	74/48
Placebo/Carvedilol	396.007.00079	12 mo	M	4	Hypotension	226	7	Sev	Unl	No	Yes	82/57	...
Placebo/Carvedilol	396.009.00246	10 yr	F	3	Hypotension	43	1	Mod	Prob	No	No	117/50	94/26
Placebo/Carvedilol	396.011.00176	21 mo	M	4	Hypotension	392	8	Mod	Not	No	No	105/59	...
Placebo/Carvedilol	396.021.00078	57 mo	M	4	Procedural Hypotension	733	1	Mod	Not	No	No	96/58	...
Carvedilol/Carvedilol	396.011.00011	23 mo	M	2	Hypotension	386	41	Mil	Not	No	No	101/44	...
				2	Hypotension	1027	2	Mod	Not	No	No	101/44	...
Carvedilol/Carvedilol	396.021.00172	10 yr	M	3	Hypotension	272	15	Mil	Not	No	No	106/36	...
				4	Hypotension	286	1	Mod	Not	No	No	106/36	...
Placebo/Carvedilol	396.001.00163	9 mo	M	4	Syncope	412	1	Sev	Unl	No	Yes	99/72	...
Carvedilol/Carvedilol	396.003.00272	6 yr	M	4	Syncope	535	2	Mil	Unl	No	Yes	101/47	...
Carvedilol/Carvedilol	396.003.00273	24 mo	M	3	Syncope	269	1	Sev	Unl	No	No	134/68	...
				4	Syncope	334	1	Mil	Unl	No	Yes	134/68	...
Carvedilol/Carvedilol	396.021.00077	14 yr	F	4	Syncope	680	1	...	Unl	No	No	122/60	...
Carvedilol/Carvedilol	396.027.00218	23 mo	M	3	Syncope	309	1	Mil	Susp	No	No	70/42	...
				3	Syncope	316	1	Mil	Susp	No	No	70/42	...

a. Age at screening in Study 321
b. Onset day relative to start of carvedilol
c. Missing severity is summarized as severe per worst case.
Source: Listing D.02 , E.01 (Attachment 1)

Of the 13 cases, 4 were considered serious. No subject was withdrawn from the trial because of this event.

Clinical laboratory parameters

Abnormal laboratory values reported by more than 1 carvedilol subject included anemia, digoxin level increased, hyperkalemia (3 reports each), bicarbonate decreased, BUN increased, hepatic enzyme increased, hypocalcemia, hyponatremia, and WBC abnormal (2 reports each).

There were 5 subjects with reports of serious laboratory abnormalities. These are shown below. No subject was withdrawn for this reason.

Table 55 Laboratory Value Adverse Events That Were Serious or Were Determined Related by Investigator

Study Drug	PID	Age[a]	Sex	Dose Level at Onset of AE	Preferred Term	Relday[b]	Dur (days)	Sev	Rel	WD	SAE	Event Value (Unit)	Post-event Lab Value (Unit)
Placebo/Carvedilol	396.007.00079	12 mo	M	4	Hypoglycaemia	226	7	Sev	Unl	No	Yes	...	...
Carvedilol/Carvedilol	396.014.00224	5 yr	F	4	Cardioactive Drug Level Increased (Digoxin)	533	99	Mil	Prob	No	No	2.818 nmol/L	1.281 nmol/L
Carvedilol/Carvedilol	396.021.00077	14 yr	F	4	International Normalised Ratio Decreased	930	10	Sev	Not	No	Yes	...	...
Carvedilol/Carvedilol	396.021.00277	21 mo	M	3	Anaemia	227	6	Mod	Not	No	Yes	Hgb 63 G/L Hct 0.192 pro of 1	Hgb 126 G/L, Hct 0.373 pro of 1
Carvedilol/Carvedilol	396.027.00218	23 mo	M	3	Therapeutic Agent Toxicity (Digoxin)	626	6	Mod	Susp	No	Yes	2.69 nmol/L	1.025 nmol/L

a. Age at screening in Study 321
b. Onset day relative to start of carvedilol
Source: Listing D.02, Listing D.06, Listing F.01 (Attachment 1)

Only the event “digoxin level increased” was reported more than once.

Physical growth, functional assessments, left ventricular ejection fraction

Without a control group it is difficult to assess these parameters. That said, there appears to be nothing to indicate a large effect of carvedilol, either positive or negative.

Conclusions: there is no indication from this review that the use of carvedilol in this patient population is different from the safety conclusion derived from the sponsor supported clinical trials (321 and 396)

Summary

The literature review[6] included 55 citations (14 manuscripts, 23 unique abstracts, 5 partial data reviews and 13 case reports). The approximate number of patients included in the review was 273 patients. The patients' ages were between 2 weeks and 20 years and they were treated with carvedilol for indications of heart failure (53 citations) or hypertension (2 citations). The duration of the studies ranged from 6 months to 5 years. Most of the trials included patients with diagnoses of cardiomyopathy, including chemotherapy-induced cardiomyopathy and idiopathic dilated cardiomyopathy, as well as non-specified diagnoses of heart failure. In addition, there were 10 trials that included patients with heart failure based on congenital heart disease, and a small number of patients with Duchenne's muscular dystrophy.

The citations in the pediatric literature review reported an initial dose of approximately 0.1 mg/kg/day up-titrated to about 1.0 mg/kg/day.

Safety results

The deaths reported in the articles are shown below.

Author/date	Deaths as reported
Rusconi/2003-4	1 death not further explained (see below)
Rusconi/2000	1 death from v fib while awaiting transplant (could be the same as above)
Rusconi/2002	4 deaths: 1 while awaiting transplant, 3 with Duchenne's muscular dystrophy
Azeka/2002	4 deaths (not further explained)
Bruns/2001	1 death from congenital heart disease
Blume/2006	1 death (not further explained)
Williams/2002	5 deaths or transplantations (not further explained)
Giardini/2003	1 death 5 days after discontinuation of carvedilol from end stage heart failure and anuria.
Laer/2002	1 death 4 weeks after carvedilol was discontinued because of severe infection
Greenway/2006	1 death following cardiac transplantation
Mir/2004	1 death 4 weeks after carvedilol was discontinued because of severe infection

Despite a paucity of details, the deaths appear to be expected in this patient population and not dissimilar to those reported in the sponsor studies.

There were 24 patients including 2 placebo patients who were reported to have undergone cardiac transplantation.

The list below shows the discontinuations of study drug because of an adverse event.

Asthma	l
Worsening CHF	7
Serious infection	l
Surgery for ventricular septal defect	1

[6] through June 2006

Cardiac transplant	6
Needed ventricular assist device	l
Hypotension/syncope	3

There were reports of increased digoxin serum concentration in 2 children.

REGISTRY REVIEW

Conclusions
There is no evidence from this study that the use of carvedilol is harmful in pediatric patients with dilated cardiomyopathy enrolled in the North American Pediatric Cardiomyopathy Registry (PCMR).

Introduction
Study Number: COG103639

Title: A Multicenter Observational Study of Oral Carvedilol in Pediatric Subjects with Dilated Cardiomyopathy: A Report from the North American Pediatric Cardiomyopathy Registry.

12 centers in the United States contributed subjects to Study COG103639. These 12 sites represent 50 5% of the total PCMR.

Study Period: Observational data have been collected in the PCMR since October 25, 1990. For this report, data are recorded on the use of carvedilol in patients included in the PCMR from June, 1997 to September 20, 2005. The first record of a patient receiving carvedilol in the PCMR occurred on October 6, 1997.

Objectives: The objective of this study was to assess the experience of pediatric subjects with dilated cardiomyopathy in the PCMR receiving carvedilol.

Methodology: This was an open-label, uncontrolled, registry designed to assess the long-term experience of pediatric subjects with dilated cardiomyopathy enrolled in the PCMR who were receiving carvedilol. Carvedilol was prescribed by, and doses were determined by, patients' physicians. All relevant data were extracted from patient charts dating from June, 1997 (the date of availability of carvedilol for prescription in the US) through September 20, 2005.

Diagnosis and Main Criteria for Inclusion: Data in this study came from male and female children with who were included in the PCMR and who were receiving carvedilol.

The data for the study were categorized into the following phases:

1. Baseline (Registry entry)
2. At carvedilol initiation
3. At first post-initiation assessment
4. 1 year post-initiation
5. 2 years post-initiation
6. 3 years post-initiation
7. Last dose assessment

Treatment Administration: No study medication was provided; carvedilol was prescribed by the subjects' physicians and provided as a tablet or suspension.

Criteria for Evaluation: Data were assessed for the following categories: carvedilol therapy, demographic characteristics, vital signs, CHF status, growth parameters, etiology of cardiomyopathy, hematology, blood chemistry, echocardiographic and electrocardiographic measurements, hospitalizations, and clinical outcomes.

Statistical Methods: No efficacy analyses were planned or performed.

Results

Demographics and medical history: There were 118 subjects. These subjects were predominately female (52%) and white (58%) with a mean age of 7 years. The percent of the population that was reported as black was 23%. The etiology of the dilated cardiomyopathy was identified as idiopathic in 66 % of the cases. For cases with a known etiology, 14 % had myocarditis and 12 % had Familial isolated cardiomyopathy. Nearly all of patients were receiving either medication including ACE inhibitors at initiation of carvedilol.

The mean carvedilol dose at initiation was 2.84 mg BID (mean range 0.18 mg to 2 mg BID). The mean maximum dose was 8.81 mg BID. Half of the subjects received carvedilol for at least 360 days and 36 (31 %) subjects received carvedilol for more than 720 days.

Safety

A total of 41/118 patients (35%) stopped using carvedilol during the study period.

	Number of subjects
Total withdrawals	41
Cardiac transplant	25
Death	5[7]
Resolution of cardiac disease	5
Adverse event	4
Switch to another beta blocker	1
Unknown	1

The majority of subjects withdrew from carvedilol therapy because of heart transplant. There were 5 reported deaths, 5 subjects were withdrawn because of resolution of disease, and 4 subjects withdrew because of an adverse event (bradycardia (1), fatigue (1), pallor and decreased ejection fraction (1, later successfully restarted carvedilol), increase BUN and creatinine (1). None of these resulted in hospitalization or death during the study period.

Details of the 4 reported deaths are shown below.

Pt no./age/sex	comments
2/58 months/m	Cardiomyopathy secondary to inborn errors of metabolism. Cardiac arrest occurred 75 days after start of carvedilol.
8/7 months/m	Idiopathic dilated cardiomyopathy and CHF. Underwent cardiac transplant and died 5 days later. Course was marked with hospitalizations for failure to thrive, worsening heart failure, sepsis,

[7] Includes patient #8 who died 5 days after cardiac transplantation

	pneumonia.
10/16 years/m	Cardiomyopathy secondary to inborn errors of metabolism. After more than 2 years of treatment with carvedilol, patient was hospitalized for respiratory distress and congestive cardiomyopathy. He experienced a cardiac arrest and could not be resuscitated.
13/8 years/m	Idiopathic dilated cardiomyopathy and CHF. Hospitalized for hyponatremia and dehydration. Patient died of congestive cardiomyopathy more than 6 weeks after starting carvedilol.
79/13 years/f	Idiopathic dilated cardiomyopathy. Developed congestive cardiomyopathy and died 19 days after starting carvedilol.

There were four deaths on-therapy (congestive cardiomyopathy, 2 patients; cardiac arrest, 1 patient; and respiratory distress, 1 patient) and 1 post-therapy death (cardiac failure). The mean age at death was 9.76 years, and the mean carvedilol dose at death was 7.05 mg. There is no evidence of an unsafe effect of carvedilol on these patients.

There were no hospital admissions for hypotension or bradycardia. Twenty-six patients received heart transplants; 24 while on carvedilol.

Clinical laboratory evaluation

Less than half of patients had any laboratory assessment during the Registry. There were 7 subjects who developed hematocrit $\leq$ 30% at the first post drug initiation visit and 6 patients who were still anemic at the last on-drug assessment. There were no patients who had an elevated LFT or serum creatinine during carvedilol treatment but did not have the elevation at baseline.

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