CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-012

STATISTICAL REVIEW(S)

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 #:	22-012
DRUG NAME:	Carvedilol
INDICATION:	Reduce blood pressure in essential hypertensive patients
APPLICANT:	GlaxoSmithKline
DATE OF RECEIPT:	12/21/2005
REVIEW PRIORITY:	Standard
BIOMETRICS DIVISION:	Division of Biometrics I
STATISTICAL REVIEWER:	Steve Bai, Ph.D. (HFD-710)
CONCURRENT REVIEWER:	John Lawrence, Ph.D. (HFD-710)
	H.M. James Hung, Ph.D. (HFD-710)
MEDICAL DIVISION:	Division of Cardio-Renal Drug Product (HFD-110)
CLINICAL TEAM:	Akinwole Williams (HFD-110)
PROJECT MANAGER:	Melissa Robb (HFD-110)

KEY WORDS: Carvedilol, Coreg and ABPM

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The current submission is to compare the effects on DBP of three different doses of Carvedilol CR to placebo as measured by changes from baseline in mean 24hr DBP using ABPM. The target population is the group of subjects with a history of, or current essential hypertension (sitting diastolic blood pressure $\geq$ 90mmHg and $\leq$ 109mmHg). The data in this study supports the Carvedilol CR, alone or in combination with other therapies, at doses of 20mg, 40mg, and 80mg once daily yields a clinically and statistically significant reduction in blood pressure compared to placebo.

1.2 Brief Overview of Clinical Studies

COREG has been demonstrated in well-controlled clinical trials to be effective in reducing blood pressure in essential hypertensive patients. The immediate-release (IR) formulation of COREG, administered twice daily, is approved and marketed in the United States as well as other countries under different brand names for the treatment of essential hypertension, alone or in combination with other hypertensive agents. An effective once daily formulation for COREG in the long-term management of essential hypertension would represent an important advance in how this antihypertensive agent could be utilized in this patient population. Therefore, GSK submitted this submission to evaluate the safety and efficacy of the Carvedilol Controlled Release (CR) once daily formulation.

Protocol SK&F-105517 is a phase III study was a double-blind, randomized, placebo-controlled, parallel group, multicenter study conducted in subjects who have essential hypertension. Subjects who satisfied all screening and inclusion criteria for entry were randomized 1:1:1:1 to one of three doses of once-daily Carvedilol CR (20mg, 40mg or 80mg) or placebo for six weeks of treatment followed by a two-week Down-titration phase. A total of 338 subjects from 67 Canada and US centers were enrolled into the study and 273 (81%) completed the study.

1.3 Statistical Issues and Findings

In the ITT efficacy population, the primary efficacy endpoint, mean changes from baseline in mean DBP at the end of up-titration, among the four treatment groups was analyzed based on the Tukey's Trend test; the following hypotheses were tested:

a) $H_{04}: \mu_p = \mu_{20} = \mu_{40} = \mu_{80}$ at level 0.05
b) $H_{03}: \mu_p = \mu_{20} = \mu_{40}$ at level 0.05
c) $H_{02}: \mu_p = \mu_{20}$ at level 0.05

Based the results in Table 4, we can concluded that the trend in mean model-adjusted reductions in DBP with Carvedilol CR 80mg, 40mg, 20mg and placebo; Carvedilol CR 40mg, 20mg and placebo; Carvedilol CR 20mg and placebo were all statistically significant ($p<0.0001$, $p<0.0001$ and $p=0.0010$, respectively). Hence, we can declare that CR 80mg, 40mg, and 20mg are statistically significant from placebo.

2 INTRODUCTION

2.1 Overview

Protocol SK&F-105517 was designed to evaluate the safety and efficacy of the Carvedilol Controlled Release (CR) once daily formulation. The current submission is a double-blind, randomized, placebo-controlled, parallel group, multicenter study conducted in subjects who have essential hypertension. Subjects who satisfied all screening and inclusion criteria for entry were randomized 1:1:1:1 to one of three doses of once-daily Carvedilol CR (20mg, 40mg or 80mg) or placebo for six weeks of treatment followed by a two-week Down-titration phase. A total of 338 subjects from 67 Canada and US centers were enrolled into the study and 273 (81%) completed the study.

2.2 Data Sources

The sponsor's SAS datasets were stored in the directory of \\Cdsesub1\n22012\N_000\2005-12-21 of the center's electronic document room.

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The study description in this section is based on the sponsor's study report, any discrepancy between the study report and the study protocol will be discussed in the section of statistical reviewer's findings and comments.

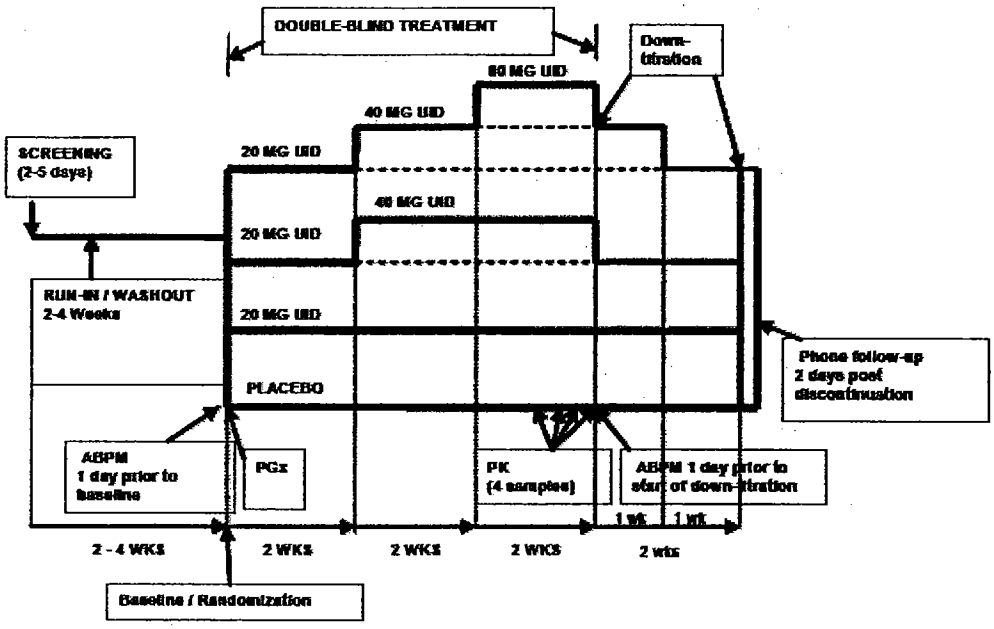
3.1.1 STUDY OBJECTIVES OF SK&F-105517/367

The primary objective of the trial was to compare the effects on DBP of three different doses of Carvedilol CR to placebo as measured by changes from baseline in mean 24hr DBP using ABPM.

3.1.2 STUDY DESIGN

This phase III study was a double-blind, randomized, placebo-controlled, parallel group, multicenter study conducted in subjects who have essential hypertension. The study consisted of five phases: screening; placebo run-in/washout; baseline/randomization; double-blind treatment (up-titration); and down-titration, see Figure 1.

Figure 1: Study Schematic Diagram



Subjects who satisfied all screening and inclusion criteria for entry were randomized 1:1:1:1 to one of three doses of once-daily Carvedilol CR (20mg, 40mg or 80mg) or placebo for six weeks of treatment followed by a two-week Down-titration phase.

3.1.3 Efficacy Measures

The primary efficacy measure was the change from baseline to end of up-titration in mean DBP measured by 24 hr ABPM.

The secondary efficacy variables were:

- Blood Pressure (DBP and SBP) Changes at Trough (20-24hr) Measured by ABPM
- Blood Pressure (DBP and SBP) Changes at Trough Measured by Cuff
- DBP trough to peak ratios
- Blood Pressure (DBP and SBP) Changes in the morning, afternoon and night
- The proportion of responders ($\geq$ 10 mmHg drop in sDBP from baseline)

3.1.4 Statistical Analysis Plan

The primary efficacy variable was analyzed via an Analysis of Covariance (ANCOVA) model with treatment, baseline, and disease history and center effects. The primary efficacy analysis was adjusted for multiplicity by the Tukey trend test. Three ordinal contrasts were defined in the primary efficacy analysis, the first contrast tested for a trend in response with all Carvedilol CR doses and placebo. The second contrast tested a trend in response with Carvedilol CR 40mg, Carvedilol CR 20mg and placebo and the last contrast compared the response of Carvedilol CR 20mg versus placebo.

Tukey's trend test was adopted for generating the sample size. Multiplicity was addressed by a step down procedure to identify the highest dose with no evidence of trend in the response. The sample size computations assumed a type I error rate of 5%. A sample size of 56 per group would provide 90% power to detect significant dose related trend for the highest dose (80mg) under the above assumptions. The power was 50% for the test of trend for the mid-dose (40mg) and 19% for the lowest dose (20mg).

Secondary efficacy variables were not adjusted for multiplicity. Main effects were tested at a 0.05 significance level and interactions at a 0.10 significance level. Least squares means (LSmeans) and 95% confidence intervals (CI) for Carvedilol CR dose group comparisons with placebo were presented.

Primary efficacy analysis comprised all data with Last Observation Carried Forward (LOCF) for non-completers. No interim data analysis was performed.

3.1.5 PATIENT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Sixty-seven centers randomized subjects into the study: 12 centers in Canada and 55 centers in the United States. A total of 338 subjects were randomized to receive treatment and 337 subjects received at least one dose of study medication. Of the 337 subjects who received study medication, 273 (81%) completed the study and 64 (19%) were withdrawn prematurely (Table 1).

Table 1 Summary of Subject Disposition

	Number (%) of Subjects				
		Carvedilol CR			
Subject Disposition	Placebo	20mg	40mg	80mg	Total
Randomized	85	87	78	88	338
Completers	61 (73)	74 (85)	65 (83)	73 (83)	273 (81)
Prematurely withdrawn	23 (27)	13 (15)	13 (17)	15 (17)	64 (19)
Missing	1 (1)	0	0	0	1 (1)

[Source: Sponsor's study report Table 6]

The distribution of subjects throughout the treatment groups was similar with respect to age, ethnicity, height, weight, BMI, baseline sDBP, sSBP, and diabetic status. There are more male subjects than female subjects in this study.

Table 2 Summary of Demographic Characteristics

VARIABLE	PLACEBO	CARVEDILOL CR		
	N=84	20mg N=87	40mg N=78	80mg N=88
Age (years) Mean±SD	52.6±9.05	54.3±9.65	51.7±9.34	52.9±8.70
Age Categories (n[%]) <65 years ≥65 years	75 (89) 9 (11)	76 (87) 11 (13)	72 (92) 6 (8)	82 (93) 6 (7)
Gender n (%) Female Male	28 (33) 56 (67)	23 (26) 64 (74)	35 (45) 43 (55)	28 (32) 60 (68)
Ethnicity n (%) Hispanic/Latino Not Hispanic/Latino	8 (10) 76 (90)	9 (10) 78 (90)	8 (10) 70 (90)	8(9) 80 (91)
Height (cm)1 Mean±SD	171.3±13.41	172.9±12.70	164.9±22.50	167.7±17.80
Weight (kg) 2 Mean±SD	91.5±22.83	95.2±19.81	96.4±60.142	97.1±91.013
Body Mass Index3 Mean ± SD	33.1±25.03	32.8±15.31	40.4±43.06	36.7±36.02
Baseline sSBP (mmHg) Mean±SD	149.8±11.43	149.5±11.86	151.4±13.60	150.7±12.69
Baseline sDBP (mmHg) Mean±SD	99.5±5.28	98.3±4.59	98.9±5.36	99.2±5.41

[Source: Sponsor's Study report Table 10]

3.1.6 PRIMARY EFFICACY RESULTS

In the ITT population, the trend in mean model-adjusted reductions of 24hr ABPM DBP with Carvedilol CR 80mg, 40mg, 20mg and placebo; Carvedilol CR 40mg, 20mg and placebo; Carvedilol CR 20mg and placebo were all statistically significant ($p<0.0001$, $p<0.0001$ and $p=0.0010$, respectively).

Table 3 Analysis of Change in Mean DBP Measured by 24hr ABPM (ITT with LOCF)

DBP, mmHg	Placebo N=76	Carvedilol CR 20mg N=82	Carvedilol CR 40mg N=76	Carvedilol CR 80mg N=86
n	58	69	63	69
Change from Baseline, Mean±SD	0.23 ± 5.60	-4.53 ± 5.42	-7.57 ± 6.49	-9.06 ± 7.07
Model-Adjusted Change from Baseline LSMean±SE	-0.36± 0.93	-4.39 ± 0.86	-7.92 ± 0.90	-9.56 ± 0.86
Difference from Placebo, LSMean	--	-4.03	-7.56	-9.19
95% CI	--	-6.41, -1.65	-9.95, -5.16	-11.59, -6.79
p-value	--	0.001	<0.0001	<0.0001

[Source: Sponsor's study report Table 16, verified by the reviewer]

Based on the Tukey's Trend test and p-values in the Table 3, the following hypotheses are all statistically significant:

(4) $H_{04}: \mu_p = \mu_{20} = \mu_{40} = \mu_{80}$ at level 0.05
(3) $H_{03}: \mu_p = \mu_{20} = \mu_{40}$ at level 0.05
(2) $H_{02}: \mu_p = \mu_{20}$ at level 0.05

Furthermore, we can declare that CR 80mg, 40mg, and 20mg are statistically significant from placebo.

On August 8, 2006, DSI finished the inspection of data audit in site 7791. There were discrepancies observed between the ABPM values reported in the data listing versus that ABPM values reported in the ——— report. This reviewer subsequently ran the same analysis with the values of ——— report; the results showed that those discrepancies had little effect on the final analysis results. See Table 4.

Table 4 Analysis of Change in Mean DBP Measured by 24hr ABPM (based on ——— report data)

DBP, mmHg	Placebo N=76	Carvedilol CR 20mg N=82	Carvedilol CR 40mg N=76	Carvedilol CR 80mg N=86
Change from Baseline, Mean±SD	0.23 ± 5.60	-4.50 ± 5.49	-7.58 ± 6.50	-9.03 ± 7.04
Model-Adjusted Change from Baseline LSMean±SE	-0.37± 0.93	-4.36 ± 0.86	-7.93 ± 0.90	-9.53 ± 0.86
Difference from Placebo, LSMean	--	-3.99	-7.56	-9.15
95% CI	--	-6.37, -1.61	-9.96, -5.17	-11.55, -6.75
p-value	--	0.0011	<0.0001	<0.0001

[Reviewer's result]

3.1.7 SECONDARY EFFICACY RESULTS

The sponsor analyzed all the continuous secondary efficacy variables, which listed in Section 3.1.3, by the same model as used for the primary efficacy analysis. However, there is no adjustment for multiplicity among the secondary variables; hence all of the following results are considered exploratory at best.

Table 5 Comparative Secondary Efficacy Evaluation of Three Doses of Carvedilol CR

Change from Baseline, (Mean±SD)	Placebo	Carvedilol CR		
		20mg	40mg	80mg
20-24hr DBP at Trough	0.94 ± 8.600	-3.01 ± 7.170	-5.75 ± 8.004	-7.01 ± 9.750
20-24hr SBP at Trough	0.99 ± 11.61	-3.48 ± 9.584	-5.73 ± 10.87	-7.24 ± 14.23
Cuff DBP at Trough	-1.64 ± 7.761	-5.78 ± 7.341	-7.27 ± 7.264	-8.29 ± 9.633
Cuff SBP at Trough	-0.78 ± 11.88	-4.07± 13.69	-8.25 ± 14.24	-7.44± 15.686
Morning DBP	0.39 ± 7.672	-4.40 ± 7.958	-7.82 ± 7.890	-9.99 ± 7.653
Afternoon DBP	0.50 ± 8.007	-4.58± 7.820	-9.37 ± 8.572	-11.08 ± 8.754
Night DBP	0.03 ± 6.335	-4.44 ± 6.078	-6.43 ± 6.985	-7.82 ± 8.789
Morning SBP	0.30 ± 11.35	-7.23 ± 12.67	-11.32± 11.378	-13.24± 11.83
Afternoon SBP	0.21 ± 10.74	-7.20± 11.352	-11.77± 12.594	-13.68 ± 13.68
Night SBP	-0.03 ± 9.076	-5.85 ± 8.241	-7.28 ± 10.931	-8.99 ± 12.697
Responder n(%)	16 (19.51)	35 (42.638)	40 (42.68)	42 (48.84)

[Source: Agency's results]

All of above exploratory results in Table 5 are numerically in favor of the three Carvedilol CR doses when compare with the placebo group.

3.1.8 CONCLUSIONS

The reviewer validated the sponsor's results according to the protocol. Following once daily administration of Carvedilol CR (20mg, 40mg or 80mg), ABPM measured mean reduction from baseline in mean 24hf DBP were statistically significantly different from that seen following administration of placebo.

3.2 Evaluation of Safety

Please read Dr. Williams's review for safety assessment.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age, Gender and Ethnic group

The exploratory analysis of the primary efficacy variable was performed for gender, race and age. The results are generally aligned with the inferences from the primary efficacy analysis. There are some exceptions in some subgroups, such as back or other race groups, subjects older than 65 years of age. These could be due to the small number of subjects in those groups.

Table 6 Subgroup analysis for change from baseline in Mean DBP

Subgroup DBP, mmHg (change from baseline)	Placebo	Carvedilol CR		
		20mg N=82	40mg N=76	80mg N=86
Gender				
Female, (n)	0.05 (14)	-5.91 (17)	-7.14 (27)	-10.6 (22)
Male, (n)	0.29 (44)	-4.08 (52)	-7.89 (36)	-8.34 (47)
Race				
Black, (n)	-1.29 (10)	-6.05 (12)	-8.02 (12)	-3.17 (6)
White/Caucasian, (n)	0.72 (46)	-4.13 (54)	-7.33 (47)	-9.78 (58)
Other, (n)	-3.25 (2)	-5.80 (3)	-9.08 (4)	-7.78 (5)
Age Group				
Age <65 years, (n)	0.03 (54)	-4.43 (61)	-7.49 (58)	-9.14 (64)
Age ≥65 years, (n)	3.05 (4)	-5.34 (8)	-8.52 (5)	-8.06 (5)

[Source: reviewer's results]

4.2 Other Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

In the ITTE population, the primary efficacy endpoint, mean changes from baseline in mean DBP at the end of up-titration, among the four treatment groups was analyzed based on the Tukey's Trend test; the following hypotheses were tested:

a) $H_{04}: \mu_p = \mu_{20} = \mu_{40} = \mu_{80}$ at level 0.05
b) $H_{03}: \mu_p = \mu_{20} = \mu_{40}$ at level 0.05
c) $H_{02}: \mu_p = \mu_{20}$ at level 0.05

Based the results in Table 4, we can concluded that the trend in mean model-adjusted reductions in DBP with Carvedilol CR 80mg, 40mg, 20mg and placebo; Carvedilol CR 40mg, 20mg and placebo; Carvedilol CR 20mg and placebo were all statistically significant ($p<0.0001$, $p<0.0001$ and $p=0.0011$, respectively). Hence, we can declare that CR 80mg, 40mg, and 20mg are statistically significant from placebo.

5.2 Conclusions and Recommendations

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

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