STATISTICAL REVIEW AND EVALUATION

NDA NUMBER:	19-915
SERIAL NUMBER:	S-037
DATE RECEIVED BY CENTER:	November 27, 2002
DRUG NAME:	Monopril (fosinopril sodium)
INDICATION:	Treatment of hypertension
SPONSOR:	Bristol-Myers Squibb Co.
DOCUMENTS REVIEWED:	Electronic submission and data sets
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TABLE OF CONTENTS

Page

1 Executive Summary

1.1 Conclusions and Recommendations

According to the terms of the written request, this trial is interpretable and has the interpretation “line flat, withdrawal slower on active treatment”. There was no dose response relationship shown between the three doses in the first period of the study (Period B). During the randomized-withdrawal period (Period C), the patients radnomized to placebo were distinguished from the remainder when all patients were pooed into two large groups (placebo versus monopril). However, no individual dose group successfully distinguished patients who cintinued monopril from the patients from that group randomized to placebo in the withdrawal phase.

1.2 Brief Overview of Clinical Studies

One clinical study was conducted in support of the sNDA in children and adolescents with elevated blood pressure that could tolerate a test dose of the study drug. Three doses were compared over a 4-week period. A total of 253 patients entered the initial 4-week double-blind treatment phase of the study. Patients who completed the initial 4-week phase then entered a 2-week randomized withdrawal period. A total of 235 patients entered this 2-week randomized withdrawal phase.

1.3 Statistical Issues and Findings

The primary analysis used the observed cases and ignored data from patients who discontinued from the study for any reason. This analysis violates the intent-to-treat principle that is widely advocated for analysis of randomized clinical trials (see for example, ICH Topic E 9 "Statistical Principles for Clinical Trials"). Nonetheless, the last-observation carried forward analysis was done in addition to the primary analysis and the results were similar to the observed case analysis. A significant difference between the three doses studied was not found during the 4-week treatment period (p-value for overall trend test = 0.5266). In order to satisfy the interpretability clause of the written request, a 2-week randomized withdrawal phase commenced at the end of the 4 weeks of treatment. A significant difference was found between these two groups- placebo and three monopril arms combined (p-value = 0.0132).

2 Introduction

2.1 Overview

One clinical study, CV118028, in children and adolescents with hypertension or high-normal BP was conducted in support of this sNDA. A significant difference between the three doses studied was not found during the 4-week treatment period (p-value for overall trend test = 0.5266). In order to satisfy the interpretability clause of the written request, a 2-week randomized withdrawal phase commenced at the end of the 4 weeks of treatment. A significant difference was found between these two groups- placebo and three monopril arms combined

(p-value = 0.0132). According to the terms of the written request, this trial is interpretable and has the interpretation "line flat, withdrawal slower on active treatment" (see Written Request).

2.2 Data Sources

One clinical study, CV118028, in children and adolescents with hypertension or high-normal BP was conducted in support of this sNDA. The trial commenced in April 2001 at 78 study centers located in the United States, Israel, and Russia. Two hundred fifty-three subjects were randomized to receive treatment with monopril target doses of 0.1 mg/kg, 0.3 mg/kg, or 0.6 mg/kg. This multicenter, randomized, double-blind, dose-ranging study evaluated the safety and effectiveness of a range of monopril doses in the treatment of children and adolescents with hypertension or high-normal blood pressure (BP). To qualify for study participation, each child or adolescent was to have either hypertension or high-normal BP with an associated clinical condition requiring medical treatment or intervention. Hypertension was defined as seated systolic BP (SeSBP) or seated diastolic BP (SeDBP) $\geq 95^{th}$ percentile for gender, age, and height, on at least 3 sequential occasions. High-normal BP was defined as SeSBP or SeDBP $\geq 90^{th}$ percentile and $< 95^{th}$ percentile for gender, age, and height, on at least 3 sequential occasions. All subjects received a test-dose of monopril 0.1 mg/kg during Period A. Subjects who tolerated this test dose were eligible to receive randomized treatment with monopril at target doses of 0.1 mg/kg, 0.3 mg/kg or 0.6 mg/kg during the four week double-blind period of the study (Period B). A total of 253 patients entered Period B. The demographic characteristics of the 253 patients appear in Table 1.

Table 1 Patient Demographic Characteristics for Initial 4-week Treatment Period (Period B)

Demographic Characteristic	Fosinopril 0.1/0.1 mg/kg N = 83	Fosinopril 0.1/0.3 mg/kg N = 87	Fosinopril 0.3/0.6 mg/kg N = 83	Total Subjects N = 253
Age (years)				
N	83	87	83	253
Mean (SD)	12.0 (2.8)	12.0 (2.6)	12.3 (2.5)	12.1 (2.6)
Range	6 - 16	7 - 16	6 - 16	6 - 16
Age Group: n (%)[a]				
6 - 12 years	46 (55.4)	47 (54.0)	47 (56.6)	140 (55.3)
13 - 16 years	37 (44.6)	40 (46.0)	36 (43.4)	113 (44.7)
Gender: n(%)				
Male	51 (61.4)	63 (72.4)	52 (62.7)	166 (65.6)
Female	32 (38.6)	24 (27.6)	31 (37.3)	87 (34.4)
Race; n (%)				
White	49 (59.0)	53 (60.9)	50 (60.2)	152 (60.1)
Black	12 (14.5)	20 (23.0)	20 (24.1)	52 (20.6)
Asian	2 (2.4)	1 (1.1)	2 (2.4)	5 (2.0)
Hispanic	17 (20.5)	9 (10.3)	9 (10.8)	35 (13.8)
Native American	1 (1.2)	0	0	1 (0.4)
Other	2 (2.4)	4 (4.6)	2 (2.4)	8 (3.2)
Hypertensive Status: n (%)				
High-normal BP	12 (14.5)	15 (17.2)	9 (10.8)	36 (14.2)
Hypertension	71 (85.5)	72 (82.8)	74 (89.2)	217 (85.8)
Height (cm)				
N	83	87	83	253
Mean (SD)	156.0 (17.4)	157.4 (16.5)	158.9 (15.8)	157.4 (16.6)
Range	103.0 - 193.5	117.0 - 186.7	112.3 - 189.0	103.0 - 193.5
Weight (kg)				
N	83	87	83	253
Mean (SD)	71.1 (30.4)	75.8 (32.9)	73.8 (28.5)	73.6 (30.6)
Range	22.2 - 178.8	24.3 - 168.6	18.0 - 165.4	18.0 - 178.8
Hypertension Duration (months)				
N	78	83	75	236
Mean (SD)	15.3 (25.9)	18.4 (29.0)	18.4 (28.9)	17.4 (27.9)
Range	0.1 - 168.3	0.2 - 142.2	0.4 - 152.1	0.1 - 168.3
Region: n (%)				
North America	52 (62.7)	61 (70.1)	55 (66.3)	168 (66.4)
Europe	31 (37.3)	26 (29.9)	28 (33.7)	85 (33.6)

Source: Table 11.1.3.2 on p. 80 of Study Report.

The overall mean duration of treatment during Period B was 26.9 days and was similar across treatment groups. Subjects who completed Period B were eligible to enter Period C; a two-week, double-blind, placebo withdrawal phase. During this period, subjects were randomly assigned to receive either placebo or to continue treatment with monopril at the assigned target dose taken during Period B. The mean duration of treatment during Period C was 13.9 days in both the placebo arm and in the three arms of monopril combined.

3 Statistical Evaluation

3.1 Evaluation of Statistical Efficacy

According to the sponsor's study report, the primary analysis was based on an ANCOVA model with terms for dose and baseline blood pressure using the data for patients that had a week 4 observation. In several places, the study report states that this is an intent-to-treat analysis and that all randomized subjects are included in the analysis. However, this is wrong because the actual analysis used only the patients with observed SeSBP after 4 weeks of treatment (in other words, an observed case analysis). The primary endpoint was change in SeSBP from baseline. The results for the primary analysis appear in Table 2. The results for the intent-to-treat analysis using last observation carried forward were similar to the observed-case analysis. For SeSBP, adjusted mean changes from baseline were -10.2, -11.2, and -11.3 mmHg, and for SeDBP were -4.2, -4.2, and -5.0 mmHg, for the low, medium, and high-dose regimens, respectively. The tests

for trend revealed no evidence for a dose-response relationship, with p = 0.49 and p = 0.39 for SeSBP and SeDBP, respectively (*Source: p. 45 of Study Report and confirmed by reviewer*).

Table 2 Change in SeSBP and SeDBP during 4-week Treatment Period (Period B).

	Fosinopril 0.1/0.1 mg/kg N = 83	**Fosinopril 0.1/0.3 mg/kg N = 87**	**Fosinopril 0.3/0.6 mg/kg N = 83**
Trough SeSBP (mmHg)			
n	73	86	79
Baseline Mean (SD)	134.3 (11.1)	133.1 (12.0)	133.7 (10.6)
Adj. Mean On-Therapy Change from Baseline (SE)	-10.9 (1.2)	-11.3 (1.1)	-11.9 (1.1)
95% Confidence Interval	(-13.2, -8.6)	(-13.4, -9.1)	(-14.2, -9.7)
P-value for the overall trend test			0.5266
Trough SeDBP (mmHg)			
n	73	86	79
Baseline Mean (SD)	71.1 (11.3)	70.8 (9.4)	72.7 (9.2)
Adj. Mean On-Therapy Change from Baseline (SE)	-4.5 (0.8)	-4.2 (0.7)	-5.1 (0.8)
95% Confidence Interval	(-6.0, -3.0)	(-5.7, -2.8)	(-6.6, -3.6)
P-value for the overall trend test			0.5158

Source: Table 11.1.5.1 on p. 84 of Study Report and confirmed by reviewer.

Since no dose response relationship was found in Period B, the analysis of the 2-week randomized withdrawal phase (Period C) is needed to assess the interpretability of the study. The model for the primary analysis for Period C was similar to the primary analysis in Period B, i.e. an ANCOVA mode with terms for baseline (of Period C) and treatment group (placebo vs. all doses of monopril). A significant difference was found between placebo and monopril in the observed case analysis (see Table 3).

Table 3 Change in SeSBP and SeDBP during 2-week Randomized Withdrawal Period.

	Any Placebo N = 127	Any Fosinopril N = 108
Trough SeSBP (mmHg)		
n	115	106
Baseline Mean (SD)	122.3 (11.1)	120.6 (12.6)
Adj. Mean On-Therapy Change from Baseline (SE)	5.2 (1.0)	1.5 (1.1)
Est. Difference between treatment and placebo with 95% CI		-3.7 (-6.6, -0.8)
P-value for the difference between treatment and placebo		0.0132
Trough SeDBP (mmHg)		
n	115	106
Baseline Mean (SD)	67.1 (8.1)	66.2 (7.1)
Adj. Mean On-Therapy Change from Baseline (SE)	1.7 (0.7)	0.1 (0.7)
Est. Difference between treatment and placebo with 95% CI		-1.6 (-3.5, 0.3)
P-value for the difference between treatment and placebo		0.1036

Source: Table 11.1.5.3 on p. 89 of Study Report and confirmed by reviewer.

The results of last-observation-carried forward analysis were similar to the observed-case results. In the placebo group, the adjusted mean increase in SeSBP from the end of Period B, after subtracting monopril, was a statistically significant 3.9 mmHg (p = 0.007). For SeDBP, the adjusted increase was a non-significant 1.7 mmHg (p = 0.066). Hence, according to the terms of the written request, this trial is interpretable and has the interpretation "line flat, withdrawal slower on active treatment" (see Written Request).

The analysis of the data from Period C shown above pools all patients in Period C into two groups regardless of which dose they were taking in Period B. It is possible to analyze the data in Period C within the three cohorts defined by the doses given in Period B. These three analyses are independent and therefore, one way to adjust for the three comparisons is to make use of this independence and test each comparison at $\alpha = 1 - \sqrt[3]{0.95} \approx 0.01695$. Although there is no legitimate way to make post hoc adjustments for multiple comparisons, this approach would have been a reasonable way to do it as a pre-specified analysis plan. For the patients

randomized to the low dose in Period B, the adjusted mean changes in Period C were 5.34 (placebo) and 5.07 (monopril) and the adjusted p-value is 0.99. For the patients randomized to the middle dose in Period B, the adjusted mean changes in Period C were 5.46 (placebo) and -0.47 (monopril) and the adjusted p-value is 0.08. For the patients randomized to the high dose in Period B, the adjusted mean changes in Period C were 4.91 (placebo) and –0.41 (monopril) and the adjusted p-value is 0.09. This demonstrates that there is insufficient evidence to conclude that any particular dose is different from placebo in the randomized withdrawal phase.

3.2 Evaluation of Safety

In order for a patient to enter Period B, the patient first had to tolerate a test dose of monopril. Hence, it is possible that monopril may appear better tolerated among the patients who were randomized into Period B than it would in the general pediatric population. The most frequently reported AEs in subjects receiving any monopril during Period B were headache (13.9%), hypotension (4.8%), cough (3.6%) and elevated blood potassium or hyperkalemia (3.6%). In 19 subjects with headache, the event was considered by the investigator as unrelated or not likely related to the study drug. In 4 subjects, headache was severe in intensity. There were no discontinuations because of headache and in the majority of the subjects, headache resolved within 1 to 11 days of onset. In 1 subject headache continued for 48 days. All incidences of hypotension were deemed by the investigator as certainly or probably related to the study drug.

4 Findings in Special Subgroups/Populations

Since this sNDA is for a special population (pediatric patients), no special subgroup analyses were done.

4.1 Gender

Not applicable for this sNDA.

4.2 Race

Not applicable for this sNDA.

4.3 Age

Not applicable for this sNDA.

4.4 Other Special Subgroup/Populations

Not applicable for this sNDA.

5 Summary and Conclusions

The trial failed to show a significant difference in change from baseline in SeSBP between the three doses studied (p-value = 0.5266). However, the analysis of the data from the randomized withdrawal period demonstrated a difference in change in SeSBP during the withdrawal period between the pooled monopril groups and pooled placebo groups (p-value = 0.0132). Hence, the study is interpretable by the terms of the Written Request. However, no single dose group was significantly different than placebo in the randomized withdrawal phase.

6 Appendices

Not applicable.

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