U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 19-851/SE5-028

Drug Name: Lotensin (benazepril HCl). 5, 10, 20, 40 mg tablets

Indication(s): Treatment of hypertension in children aged 6 to 16 years

Applicant: Novartis Pharmaceuticals Corporation

Date(s): Submitted on April 25, 2003.

Review Priority: Priority

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Keywords: ANOVA, t-test, LOCF.

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EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

In order to obtain an additional 6-month market exclusivity for Lotensin, the Sponsor conducted a pediatric study, Study CIB824E US01, which is intended to fulfill the requirements by the Written Reguest from the FDA dated November 2, 1999. The study consisted of 4 phases: a screening phase, a dose-escalation phase, a double-blind randomized withdrawal phase, and an optional open-label treatment phase. At the beginning of the randomized withdrawal phase, subjects were randomly assigned in a ratio of 1:1:1:1 to receive low, medium, high-dose benazepril or placebo. This reviewer considered the changes in the randomized withdrawal phase in seated systolic blood pressure (SSBP) and seated diastolic blood pressure (SDBP) as the primary endpoints.

For subjects in the ITT population, the mean SSBP and SDBP were increased from the beginning to the end of the randomized withdrawal phase in all treatment groups. The mean increases were significantly greater in the placebo group than in the medium-dose group in SSBP and SDBP. The significance was maintained after multiplicity adjustment. However, the high-dose group failed to achieve statistical significance for either SSBP or SDBP. Although the reviewer's analyses showed positive slopes (in the right direction) for the dose-response lines of SSBP and SDBP, statistical significance was not attained at the 0.05 level.

It should be noted that the dose responses were not consistent with the dose strength. For both SSBP and SDBP, the medium-dose group did better than the high-dose group in terms of mean changes during the randomized withdrawal phase.

1.2 Brief Overview of Clinical Studies

The pediatric study (CIB824E US01) was fully reviewed. A single dose pharmacokinetic sub-study was included in the study, which was not reviewed here. The study had 4 phases, a screening phase (3 weeks), a dose-escalation phase (4 weeks), a double-blind withdrawal phase (2 weeks) and an optional open-label phase (6 months). A total of 107 children aged 6 to 16 years entered the dose-escalation phase. Each subject took low-dose medication for 8 days, then medium-dose medication for 7 days and high-dose medication for 14 days. Subjects who completed the dose-escalation phase entered the randomized withdrawal phase for 2 weeks. Eighty-five subjects were randomized in the withdrawal phase with 24, 23, 19 and 19 subjects in the low, medium, high-dose and placebo group, respectively. At the completion of the withdrawal phase, subjects entered an optional 6-month extension phase with open-label benazepril. Seventy-six subjects entered the open-label phase.

1.2 Statistical Issues and Findings

The Sponsor defined the primary endpoint as the change from baseline to the end of dose-escalation phase in SSBP. However, as indicated by the FDA's Written Request, the focus should be on the randomized withdrawal phase. Therefore, this reviewer used the changes in SSBP and SDBP from the beginning to the end of the randomized withdrawal phase as the primary endpoints. The intent-to-treat (ITT) population was used for the primary analyses, where ITT was defined as all the subjects who entered the randomized withdrawal phase, took at least one dose of medication and had at least one blood pressure assessment.

A dose-response analysis was conducted to test if the dose-response line was flat (slope = 0) for the primary endpoints. If the analysis revealed a flat dose-response curve, ANOVA was used to compare the difference between the active and placebo group.

The estimated slopes were positive (in the right direction) for the two primary endpoints. However, both slopes were not statistically differentiable from zero with p-values = 0.053 and 0.071 for SSBP and SDBP, respectively. ANOVA analyses showed that the medium-dose group achieved statistical significance over placebo group for both SSBP and SDBP, with p-values = 0.015 and 0.013, respectively. The significance was maintained after multiplicity adjustment. The high-dose group obtained nominal statistical significance for SDBP with p-value = 0.025. For SSBP, the high-dose group did not achieve statistical significance. The low-dose group did not achieve statistical significance for either SSBP or SDBP.

It should be noted that the dose responses were not consistent with the strength of the medication between the medium and high-dose groups. The mean SSBP and SDBP were increased during the randomized withdrawal phase in all treatment groups. The mean increases in SSBP were 7.5, 3.9, 1.0 and 2.2 mm Hg in placebo, low, medium and high-dose group, respectively. The mean increases in SDBP were 7.9, 3.9, 1.9 and 2.3 mm Hg in placebo, low, medium and high-dose group, respectively. For both SSBP and SDBP, the mean increases in the high-dose group were higher than those in the medium-dose group.

2. INTRODUCTION

2.1 Overview

Lotensin (benazepril HCI), an angiotensin converting enzyme (ACE) inhibitor, was approved to treat mild and moderate hypertension in adults. Its US patent 4,410,520 was due to expire on August 11, 2003. This submission was intended to fulfill the requirements described in the Written Reguest by the FDA dated November 2, 1999. The Sponsor requested an additional 6-month market exclusivity for Lotensin based on this submission. In the FDA's Written Request, the Division requested that a dose-ranging trial in hypertensive pediatric patients to be conducted, and the details about the design and analysis of the trial were suggested. In particular, four choices were provided for the design of the trial, and suggestions for the data analysis were given for each case. The Sponsor conducted the dose-ranging trial (Study

CIB824E US01) in children. It seems that the design of Trial D was chosen, but the primary analysis was not performed as suggested. These issues will be addressed in details in Section 3.

This reviewer reviewed Study CIB824E US01 in detail. The study was conducted based on Protocol CCIB824 US01 titled 'A Multicenter Study to Evaluate the Pharmacokinetics, Dose-Response, Efficacy, and Safety of Benazepril in Pediatric Subjects'. The main objective of the study was to evaluate the efficacy and dose-response relationship of benazepril in children aged 6 to 16 years with hypertension. It consisted of a screening phase (21 days), a dose-escalation phase (28 days), a double-blind randomized withdrawal phase (14 days), and an optional open-label treatment phase (6 months). A total of 107 patients were recruited in the dose-escalation phase. Among them, 85 patients entered the double-blind randomized withdrawal phase (low dose 24, medium dose 23, high dose 19, and placebo 19). There were 76 patients in the optional open-label phase. Twenty-seven centers in the US were used to enroll patients.

2.2 Data Sources

This submission was submitted electronically. The final report is located at \\CDSESUB1\N19851 \S_028\2003-04-25. SAS data sets are located at \\CDSESUB1\N19851\S_028\2003-04-25\crt\datasets\US01. This reviewer confirmed the Sponsor's primary analyses and conducted dose-response analyses and subgroup analyses for the primary endpoints.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoint

As mentioned before, Study CIB824E US01 consisted of 4 phases: a screening phase, a dose-escalation phase, a double-blind randomized withdrawal phase, and an optional open-label treatment phase. The dose-escalation phase also included a single-dose pharmacokinetic sub-study, which was not reviewed here. At the screening visit (Visit 1), eligible subjects were to discontinue use of any antihypertensive medications and start morning home blood pressure monitoring using blood pressure monitors provided by the study sites. Subjects whose home blood pressure measurements were $\geq$ 95th percentile for age, sex, and height, were to return to the study site. If the subject's hypertension was confirmed in the clinic, the subject was eligible to enter the dose-escalation phase of the study. Hypertension was confirmed in the clinic by two sets of seated blood pressure measurements at least one hour apart. Each set of measurements was the average of three measurements at least 5 minutes apart. Hypertension was confirmed when both sets of measurements for either mean SSBP or the mean SSDP were $\geq$ 95th percentile for age, sex, race and height. The dose-escalation phase started at Visit 2 (Day 0) with low-dose benazepril. After 7 days of active treatment (Visit 3), medium-dose treatment began. Seven days later (Visit 4), the dose increased to high-dose benazepril. Subjects remained on the high dose for 14 days. The dosages depended on the body weight of the patients. For patients with weight between 20 to 50 kg, the low, medium and high doses were 5, 10, and 20 mg,

respectively. For patients with weight > 50kg, the low, medium and high doses were 10, 20 and 40 mg, respectively. At Visit 5 (Day 28), subjects who completed the dose-escalation phase and whose mean SSBP and SDBP were < 95th percentile for age, sex, and height entered the double-blind randomized withdrawal phase, and were randomly assigned in a ratio of 1:1:1:1 (regardless of their body weight) to receive low, medium, or high-dose benazepril, or placebo for 2 weeks. No stratification by weight was considered for randomization, and the actual dose was given according to the subject's weight. After 7 days of treatment in the randomized withdrawal phase, subjects returned to the clinic for blood pressure assessment (Visit 6). If hypertension was confirmed at this visit, subjects were to be discontinued from the study. Those subjects who remained in the randomized withdrawal phase for the full 14 days returned to the clinic for Visit 7 (Day 42). At the discretion of the Investigator and the subject's parent/guardian, subjects who completed the randomized withdrawal phase or discontinued earlier from the study could enter the optional 6-month open-label extension phase. In this phase, subjects were to continue on their maximum tolerated dose of benazepril and return to the clinic for assessment every 3 months for 6 months.

Subjects were screened and enrolled at 27 centers in the United States. The first subject was enrolled on February 2, 2000 and the last subject was completed on October 14, 2002.

The primary objective of the study was to evaluate the efficacy and dose-response relationship of benazepril in children with hypertension. The Sponsor originally defined the primary endpoint as the change in SDBP from Visit 2 to Visit 5 (Day 28). In Protocol amendment 5, the primary endpoint was switched to the change in SSBP from Visit 2 to Visit 5.

Reviewer's Comments

The design of the trial seems to follow the design of Trial D as suggested in the FDA's Written Request. According to the Written Request, the analysis should be built around the randomized withdrawal phase. In the Written Request, it was stated that ' It would be possible to build the entire trial around randomized withdrawal (Trial D). Patients would be force-titrated to maximal tolerated doses of benazepril HCI and then randomly withdrawn to lower doses (including placebo), with the same close follow-up, discretionary withdrawal to open-label therapy, and analysis as in Trial C'. Since the analysis should be focused on the withdrawal phase, this reviewer used the changes in SSBP and SDBP from Visit 5 to Visit 7 as the primary endpoints. The Sponsor designated these two variables as secondary variables.

3.1.2 Patient Disposition, Demographic and Baseline Characteristics

The study included male and female children 6 to 16 years of age with a mean SSBP or SDBP $\geq$ 95th percentile for age, sex, and height that could be treated with a single medication. A total of 107 subjects entered the dose-escalation phase and received at least one dose of benazepril. Among them, eight-five (79.4%) entered the double-blind randomized withdrawal phase.

Table 1 summarizes patient disposition for the randomized withdrawal phase. Discontinuation rate in the placebo group (42.1%) was higher than the active treatment groups (5.3% to 8.7%).

All discontinuations in the benazepril groups and 6 out of 8 discontinuations in the placebo group were due to an unsatisfactory therapeutic response.

Table 1. Patient disposition, randomized withdrawal phase

	Low Dose	Medium Dose	High Dose	Placebo
Total number of subjects , N(%)				
Entered randomized withdrawal phase	24	23	19	19
Completed randomized withdrawal phase	22 (91.7)	21 (91.3)	18 (94.7)	11 (57.9)
Discontinued, N (%)	2 (8.3)	2 (8.7)	1 (5.3)	8 (42.1)
Adverse events	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)
Unsatisfactory therapeutic effect	2 (8.3)	2 (8.7)	1 (5.3)	6 (31.6)
Protocol violation	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)

Source: Post-text Table 1 of the Sponsor's final report

Table 2 presents patient disposition in the dose-escalation phase. Nineteen subjects (17.8) discontinued the study in this phase. Among them, five subjects were due to adverse events and 11 were because of unsatisfactory therapeutic response.

Table 2. Patient disposition, dose-escalation phase

Total number of subjects, N(%)	
Screened and did not take study medication	36
Enrolled	107
Completed dose-escalation phase	88 (82.2)
Entered randomized withdrawal phase	85 (79.4)
Entered optional open-label phase	76 (71.0)
Discontinued, dose-escalation phase, N (%)	19 (17.8)
Adverse events	5 (4.7)
Unsatisfactory therapeutic response	11 (10.3)
Protocol violation	2 (1.9)
Subject withdrew with consent	1 (0.9)

Source: Post-text Table 1 of the Sponsor's final report

Demographic and background characteristics by treatment group are presented in Table 3 for the randomized withdrawal phase. Subjects in the four treatment groups were not significantly different with respect to mean weight, sex or race distribution. The treatment groups differed with respect to the mean height of subjects. It seems that they also differed in age with a borderline p-value = 0.0501. The reason could be that the randomization was not stratified by any variables and the sample size was not very large.

Table 3. Demographic and background characteristics by treatment group, for randomized withdrawal phase

	Low Dose N = 24	Medium Dose N = 23	High Dose N = 19	Placebo N = 19	Overall N = 85	P-value
Age (years)						
Mean	11.8	13.3	13.4	13.5	12.9	0.0501
S.D.	2.9	1.6	2.6	2.1	2.5	
Range	7 - 16	10 - 16	7 - 16	8 - 16	7 - 16	
Sex (N, %)						
Male	10 (41.7)	16 (69.6)	15 (78.9)	10 (52.6)	51 (60.0)	0.0610
Female	14 (58.3)	7 (30.4)	4 (21.1)	9 (47.4)	34 (40.0)	
Race (N, %)						
Caucasian	14 (58.3)	15 (65.2)	9 (47.4)	10 (52.6)	48 (56.5)	0.7650
Black	3 (12.5)	5 (21.7)	6 (31.6)	5 (26.3)	19 (22.4)	
Oriental	1 (4.2)	1 (4.3)	2 (10.5)	1 (5.3)	5 (5.9)	
Other	6 (25.0)	2 (8.7)	2 (10.5)	3 (15.8)	13 (15.3)	
Weight (kg)						
Mean	61.5	76.7	80.2	75.3	72.9	0.0935
S.D.	22.2	27.7	30.5	25.1	26.9	
Range	28 - 128	30 - 132	36 - 147	25 - 124	25 - 147	
Height (cm)						
Mean	151.9	163.4	163.1	160.0	159.3	0.0252
S.D.	14.0	12.1	15.7	15.6	14.9	
Range	126 - 173	139 - 187	121 - 181	122 - 192	121 - 192	

Source: Post-text Table 2.2 of the Sponsor's final report. Independently confirmed by this reviewer

3.1.3 Statistical Methodologies

The Sponsor defined the primary endpoint as the change from baseline to Visit 5 (end of dose-escalation phase) in SSBP. The hypothesis of no mean change from baseline to Visit 5 in SSBP was tested using a paired t-test. The analysis was based on the ITT1 population, where ITT1 included all subjects enrolled in the study that received at least one dose of benazepril and had at least one post-dose blood pressure measurement.

This reviewer used the changes from Visit 5 to Visit 7 in SSBP and SDBP as the primary endpoints. To be consistent with the Written Request (test of a positive slope), the change from Visit 5 to Visit 7 was defined as value at Visit 5 – value at Visit 7. Based on the Written Request, a regression analysis was performed with the primary endpoint as the dependent variable, and dosage as the independent variable. The hypothesis of flat line (slope = 0) was tested. If the dose-response line was horizontal, then an ANOVA was conducted. The hypothesis of no difference among treatment groups in the mean change from Visit 5 to Visit 7 was tested using an ANOVA with treatment as factors. The analysis was based on the ITT2 population, where ITT2 included all subjects that entered the randomized withdrawal phase, received at least one dose of study medication, and had at least one blood pressure measurement.

A last observation carried forward was used to impute missing data for the analyses of the primary endpoints. Covariates such as sex, race, age and weight were evaluated separately to determine if they had any effect on the outcome.

It should be noted that the Sponsor conducted the analyses of the changes from Visit 5 to Visit 7 in SSBP and SDBP using ANOVA. These analyses were designated as secondary analyses in the final report.

The Sponsor stated that sample size and power considerations were based on the randomized withdrawal phase. An expected difference of 11 mmHg in the change in SSBP between the high dose of benazepril and placebo was considered clinically important to detect. A conservative standard deviation of 12 mmHg was assumed. To detect a difference between any of the three dose groups and placebo with 80% power, while controlling for type I error of 0.05, 20 evaluable subjects per group were needed.

3.1.4 Results and Conclusions

Table 4 presents the results of the dose-response analyses of the changes in SSBP and SDBP from Visit 5 to Visit 7. It can be seen that both slopes were positive, but they were not statistically differentiable from zero at the 0.05 level. The p-value for the slope of SSBP is 0.053, which is quite close to the 0.05 level.

Table 4. Dose-response analyses of changes in SSBP and SDBP from Visit 5 to Visit 7, randomized withdrawal phase, ITT population

Parameter	Estimator	S.E. of Estimator	T-value	P-value
SSBP				
Intercept	-5.61	1.40	-3.99	0.0001
Slope	0.13	0.07	1.96	0.053
SDBP				
Intercept	-5.62	1.26	-4.45	< 0.0001
Slope	0.11	0.06	1.83	0.071

Source: Reviewer's analysis. The dependent variable is the change from Visit 5 to Visit 7 in SSBP or SDBP, the independent variable is dosage

Tables 5 and 6 give the ANOVA analysis results for the changes from Visit 5 to Visit 7 in SSBP and SDBP, respectively. The p-values were from the contrast statement using SAS PROC GLM and the confidence intervals were from Dunnett's 2-sided t-test. The Dunnett's test controls the Type I error for comparisons of all active treatment groups against placebo. The p-values for the medium-dose group were 0.015 and 0.013 for SSBP and SDBP, respectively. Both were < 0.017 = 0.05/3 using the conservative Bonferroni method. Dunnett's t-test confirmed the significance results. Therefore, the medium-dose group achieved statistical significance for both SSBP and SDBP. The high-dose group obtained statistical significance with a nominal p-value = 0.025. But significance was not maintained after multiplicity adjustment.

Table 5. Change in SSBP (mm Hg) from Visit 5 to Visit 7 by treatment, randomized withdrawal phase, ITT population

	Low Dose N = 24	Medium Dose N = 23	High Dose N = 19	Placebo N = 19
Visit 5				
Mean	117.9	124.0	121.2	121.0
Standard Deviation	11.5	11.9	10.2	13.4
Visit 7				
Mean	121.8	124.9	123.4	128.5
Standard Deviation	11.1	10.9	10.6	9.2
Change: Visit 5 to Visit 7				
Mean	-3.9	-1.0	-2.2	-7.5
Standard Deviation	8.8	8.7	6.8	9.5
P-value	0.171	0.015*	0.058	
Difference in Change (vs. Placebo)				
Mean	3.6	6.6	5.3	
Confidence Interval	(-2.6 – 9.8)	(0.3 – 12.9)**	(-1.3 – 11.9)	

Source: Post-text Table 8.1 of the Sponsor's final report and reviewer's analysis
*Significantly different from placebo, after adjusting for multiplicity using the conservative Bonferroni method
** Significantly different from placebo using Dunnett's 2-sided t-test

Table 6. Change in SDBP (mm Hg) from Visit 5 to Visit 7 by treatment, randomized withdrawal phase, ITT population

	Low Dose N = 24	Medium Dose N = 23	High Dose N = 19	Placebo N = 19
Visit 5				
Mean	69.1	71.0	67.6	69.7
Standard Deviation	8.0	8.1	11.6	9.2
Visit 7				
Mean	73.0	73.0	69.8	77.6
Standard Deviation	8.7	9.9	9.9	12.4
Change: Visit 5 to Visit 7				
Mean	-3.9	-1.9	-2.3	-7.9
Standard Deviation	6.4	7.9	7.4	8.7
P-value	0.089	0.013*	0.025	
Difference in Change (vs. Placebo)				
Mean	4.0	6.0	5.6	
Confidence Interval	(-1.6 – 9.6)	(0.4 – 11.6)**	(-0.3 – 11.5)	

Source: Post-text Table 10.1 of the Sponsor's final report and reviewer's analysis
*Significantly different from placebo, after adjusting for multiplicity using the conservative Bonferroni method
** Significantly different from placebo using Dunnett's 2-sided t-test

Table 7 summarizes the analyses for the changes from baseline to Visit 5 in SSBP and SDBP for the ITT population. It should be noted that although the change from baseline to Visit 5 in SSBP was defined as the primary endpoint by the Sponsor, it was considered to be one of the secondary endpoints by this reviewer. Therefore, the results in Table 7 were secondary efficacy results. It can be seen that both SSBP and SDBP were reduced significantly (p-value < 0.0001) in the dose-escalation phase.

Table 7. Changes in SSBP and SDBP (mm Hg) from baseline to Visit 5, dose-escalation phase, ITT population

Change from Baseline to Visit 5	**SSBP**			**SDBP**		
	20-50 kg N = 26	> 50 kg N = 81	All N = 107	20-50 kg N = 26	> 50 kg N = 81	All N = 107
Mean	-10.8	-10.8	-10.8	-10.5	-9.0	-9.3
Standard deviation	9.4	10.0	9.8	11.0	10.3	10.4
P-value*	< 0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Source: Post-text Tables 7.1 and 9.1 of the Sponsor's final report. Independently confirmed by this reviewer
* P-values were obtained from within each group comparison using paired t-test

In summary, the analyses revealed a positive slope to the dose-response line for the changes from Visit 5 to Visit 7 (randomized withdrawal phase) in both SSBP and SDBP, but they were not significantly different from zero at the 0.05 level, with p-values = 0.053 and 0.071 for SSBP and SDBP, respectively. However, the medium-dose group achieved statistical significance over placebo group for both SSBP and SDBP in the double-blind randomized withdrawal phase. The significance was maintained after adjusting multiplicity. Tables 5 and 6 revealed that the dose responses were not consistent with the strength of the medication between the medium and high-dose groups.

3.2 Evaluation of Safety

Adverse events were coded using MedDRA (Medical Dictionary for Drug Regulatory Activities) dictionary. Table 7 summarizes adverse events of all causalities for any body system and any adverse event within a body system that occurred for at least 2 subjects in any treatment group. The two most frequently reported adverse events were headache and cough.

Table 8. Number (%) of subjects with most frequent adverse events (> 2 subjects in any treatment group), randomized withdrawal phase, safety population

	Low Dose	**Mediu m Dose**	**High Dose**	**Placebo**	**p-value**
Subjects studied					
Total number of subjects	24	23	19	19	
Total number with AEs	10(41.7)	11(47.8)	5(26.3)	6(31.6)	0.48
Body system affected					
Eye disorders	2 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0.24

Nervous system disorders	4 (16.7)	3 (13.0)	1 (5.3)	3 (15.8)	0.77
Headache	3 (12.5)	2 (8.7)	1 (5.3)	2 (10.5)	
Respiratory, thoracic, and mediastinal Disorders	5 (20.8)	6 (26.1)	3 (15.8)	0 (0.0)	0.08
Cough	3 (12.5)	6 (26.1)	1 (5.3)	0 (0.0)	
Pharyngolaryngeal pain	1 (4.2)	0 (0.0)	2 (10.5)	0 (0.0)	
Sneezing	0 (0.0)	2 (8.7)	0 (0.0)	0 (0.0)	
Skin and subcutaneous tissue disorders	2 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0.24

Source: Post-text Table 15.2.1 of the Sponsor's final report

The Sponsor reported that the overall incidence of adverse events and the incidence of adverse events for any body system were not significantly different across the treatment (Post-text Table 15.2.1, Table 10.3 of the Sponsor's final report).

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, Weight and Tanner Stage

Table 9 presents the subgroup estimates of the slopes of the dose-response lines for the changes in SSBP and SDBP from Visit 5 to Visit 7 (randomized withdrawal phase). Most of the slopes were positive and in the right direction except for SDBP in the subgroups of weight from 20 to 50 kg, age from 7 to 11 years old and tanner stage from 1 to 2. The slopes were negative in the three subgroups but they were very close to zero and not significantly different from zero.

Table 9. Subgroup dose-response analyses of changes in SSBP and SDBP from Visit 5 to Visit 7, randomized withdrawal phase, ITT population

	Subgroup	N	Slope Estimator (S.E.)	P-value
SSBP	**Gender**			
	Male	51	0.06 (0.08)	0.496
	Female	34	0.29 (0.13)	0.029
	Race			
	Caucasian	48	0.19 (0.11)	0.078
	Non-Caucasian	37	0.07 (0.08)	0.383
	Weight			
	20-50 kg	20	0.15 (0.27)	0.588
	> 50 kg	65	0.14 (0.08)	0.079
	Age			
	7 – 11 Years Old	18	0.16 (0.21)	0.460
	12 – 16 Years Old	67	0.15 (0.07)	0.045
	Tanner Stage			
	1 to 2	22	0.24 (0.16)	0.162
	3 to 5	63	0.12 (0.08)	0.127

	Subgroup	N	Slope Estimator (S.E.)	P-value
SDBP	**Gender**			
	Male	51	0.02 (0.07)	0.768
	Female	34	0.32 (0.12)	0.014
	Race			
	Caucasian	48	0.13 (0.09)	0.180
	Non-Caucasian	37	0.10 (0.08)	0.238
	Weight			
	20-50 kg	20	-0.02 (0.27)	0.950
	> 50 kg	65	0.17 (0.06)	0.008
	Age			
	7 – 11 Years Old	18	-0.06 (0.20)	0.752
	12 – 16 Years Old	67	0.15 (0.07)	0.026
	Tanner Stage			
	1 to 2	22	-0.04 (0.20)	0.858
	3 to 5	63	0.15 (0.06)	0.020

Source: Reviewer's analysis. The dependent variable is the change from Visit 5 to Visit 7 in SSBP or SDBP, the independent variable is dosage.

The subgroup analyses of SSBP and SDBP among treatment groups are presented in Table 10. In all the subgroups, the active groups did better than placebo group in terms of keeping the blood pressure low for both SSBP and SDBP. It seemed that there was a trend for the dose-response among most of the subgroups with relative large sample sizes.

Table 10. Changes from Visit 5 to Visit 7 in SSBP and SDBP (mm Hg) by subgroup, randomized withdrawal phase, ITT population

		Low Dose	Medium Dose	High Dose	Placebo
SSBP	**Gender**				
	Male (N)	10	16	15	10
	Mean (S.D.)	-1.0 (10.1)	-0.5 (9.8)	-3.7 (5.6)	-7.1 (7.8)
	P-value	0.112	0.058	0.333	
	Female (N)	14	7	4	9
	Mean (S.D.)	-6.0 (7.5)	-2.0 (5.7)	3.5 (8.6)	-8.0 (11.5)
	P-value	0.589	0.175	0.033	
	Race				
	Caucasian (N)	14	15	9	10
	Mean (S.D.)	-2.9 (8.8)	-0.87 (8.9)	-1.9 (8.1)	-10.5 (11.3)
	P-value	0.053	0.015	0.050	
	Non-Caucasian (N)	10	8	10	9
	Mean (S.D.)	-5.4 (9.0)	-1.1 (8.8)	-2.5 (5.7)	-4.2 (5.9)
	P-value	0.734	0.400	0.620	
	Weight				
	20-50 kg (N)	9	3	4	4
	Mean (S.D.)	-1.2 (7.2)	-6.7 (6.7)	-3.5 (6.4)	-10.5 (11.2)
	P-value	0.069	0.535	0.229	
	> 50 kg (N)	15	20	15	15
	Mean (S.D.)	-5.5 (9.5)	-0.1 (8.7)	-1.9 (7.0)	-6.7 (9.2)
	P-value	0.706	0.029	0.130	
	Age				
	7 – 11 Years Old (N)	10	2	3	3
	Mean (S.D.)	-5.0 (6.5)	16.5 (4.9)	-4.0 (5.6)	-1.0 (3.5)
	P-value	0.321	0.006	0.544	
	12 – 16 Years Old (N)	14	21	16	16
	Mean (S.D.)	-3.1 (10.3)	-2.6 (6.9)	-1.9 (7.1)	-8.8 (9.8)
	P-value	0.076	0.033	0.025	
	Tanner Stage				
	1 to 2 (N)	8	6	4	4
	Mean (S.D.)	-5.1 (5.8)	-0.2 (9.2)	-2.5 (5.4)	-7.5 (10.1)
	P-value	0.619	0.155	0.368	
	3 to 5 (N)	16	17	15	15
	Mean (S.D.)	-3.3 (10.1)	-1.2 (8.7)	-2.1 (7.2)	-7.5 (9.7)
	P-value	0.198	0.053	0.106	
SDBP	**Gender**				
	Male (N)	10	16	15	10
	Mean (S.D.)	-1.9 (4.2)	-2.2 (7.8)	-3.4 (6.2)	-6.9 (9.0)
	P-value	0.120	0.105	0.231	
	Female (N)	14	7	4	9
	Mean (S.D.)	-5.3 (7.4)	-1.3 (8.7)	2.0 (11.0)	-9.0 (8.8)

		Low Dose	Medium Dose	High Dose	Placebo
	P-value	0.312	0.080	0.039	
	Race				
	Caucasian (N)	14	15	9	10
	Mean (S.D.)	-2.9 (5.9)	-3.0 (7.3)	-1.3 (9.2)	-9.5 (10.3)
	P-value	0.051	0.053	0.032	
	Non-Caucasian (N)	10	8	10	9
	Mean (S.D.)	-5.3 (7.1)	0.1 (9.1)	-3.1 (5.7)	-6.1 (6.7)
	P-value	0.807	0.083	0.368	
	Weight				
	20-50 kg (N)	9	3	4	4
	Mean (S.D.)	1.9 (3.6)	-5.0 (12.3)	-2 (10.1)	-5.3 (9.9)
	P-value	0.152	0.968	0.569	
	> 50 kg (N)	15	20	15	15
	Mean (S.D.)	-7.3 (5.1)	-1.5 (7.4)	-2.3 (7.0)	-8.6 (8.6)
	P-value	0.630	0.005	0.020	
	Age				
	7 – 11 Years Old (N)	10	2	3	3
	Mean (S.D.)	-2.0 (6.7)	6.0 (15.5)	-6.7 (4.6)	-8.0 (7.8)
	P-value	0.251	0.064	0.833	
	12 – 16 Years Old (N)	14	21	16	16
	Mean (S.D.)	-5.2 (6.1)	-2.7 (7.0)	-1.4 (7.7)	-7.9 (9.1)
	P-value	0.340	0.042	0.019	
	Tanner Stage				
	1 to 2 (N)	8	6	4	4
	Mean (S.D.)	-0.4 (6.4)	0.5 (11.5)	-8.0 (4.6)	-7.8 (9.2)
	P-value	0.169	0.146	0.967	
	3 to 5 (N)	16	17	15	15
	Mean (S.D.)	-5.6 (5.8)	-2.8 (6.4)	-0.7 (7.4)	-7.9 (8.9)
	P-value	0.375	0.047	0.008	

Source: Reviewer's analysis. P-values were from ANOVA. The dependent variable is the change from Visit 5 to Visit 7 in SSBP or SDBP, the independent variable is treatment group.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The Sponsor seemed to follow the study design of Trial D as described in the FDA's Written Request. While the Written Request stated that the analyses should be focused on the double-blind randomized withdrawal phase, the Sponsor's analyses was focused on the dose-escalation phase. The Sponsor defined their primary endpoint as the change from baseline to Visit 5 (escalation phase) in SSBP. A paired t-test was used for the analysis of their primary endpoint.

Based on the recommendation of the Written Request, this reviewer used the changes from Visit 5 to Visit 7 (randomized withdrawal phase) in SSBP and SDBP as the primary endpoints. A dose-response analysis was conducted for SSBP and SDBP. If the slope of the dose-response line was not statistically significant from zero, then ANOVA was used to analyze the difference between the active treatment and placebo group. The Sponsor's primary endpoint was considered as a secondary endpoint by this reviewer.

Both slopes of the dose-response lines were positive, but they were not statistically differentiable from zero, with p-values = 0.053 and 0.071 for SSBP and SDBP in the randomized withdrawal phase, respectively. They did not achieve significance at the 0.05 level, although the p-values were quite close to 0.05. The ANOVA analyses showed that the medium-dose group achieved statistical significance over the placebo group for both SSBP and SDBP, with p-values = 0.015 and 0.013, respectively. The significance was maintained after multiplicity adjustment. It should be noted that the high-dose group did not obtain statistical significance for SSBP. The high-dose group had a nominal p-value = 0.025 for SDBP. But it was not statistically significant after multiplicity adjustment. The mean changes in the active treatment groups were not consistent with the dose strength for both SSBP and SDBP. The mean changes in SSBP from Visit 5 to Visit 7 were -3.9, -1.0, -2.2and -7.5 for the low, medium, high-dose and placebo group, respectively. The mean changes in SDBP from Visit 5 to Visit 7 were -3.9, -1.9, -2.3 and -7.9 for the low, medium, high-dose and placebo group, respectively. The high-dose group did not do as well as the medium-dose group.

5.2 Conclusions and Recommendations

Following treatment with high-dose benazapril for two weeks in the dose-escalation phase, the study has demonstrated that the mean SSBP and SDBP increased over the 2-week randomized withdrawal phase. The active treatment groups increased less than the placebo group, with the medium-dose group achieving statistical significance over the placebo group. The significance was maintained after multiplicity adjustment for both SSBP and SDBP. The dose-response analyses showed that there seemed to be positive slopes (in the right direction) for SSBP and SDBP. However, both slopes failed to be statistically significant.

It should be noted that the mean changes in SSBP and SDBP were not consistent with dose strength between the medium and high-dose groups. The high-dose group did not do as well as the medium-dose group.

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