

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

19-777/S-044

Statistical Review(s)

**STATISTICAL REVIEW AND EVALUATION**

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

NDA No./SUPPLEMENT: 19-777/ SE5
SERIAL NO.: 044
DATE RECEIVED BY THE CENTER: November 5, 2001
DRUG NAME: ZESTRIL™ (Lisinopril)
INDICATION: Children with Hypertension
SPONSOR: AstraZeneca Pharmaceuticals LP
DOCUMENTS REVIEWED: Vol. 1

BIOMETRICS DIVISION: **DIVISION OF BIOMETRICS I (HFD-710)**
REVIEWING STATISTICIAN: Peiling Yang, Ph.D.
TEAM LEADER: HM James Hung, Ph.D.
DIVISION DIRECTOR: George Chi, Ph.D.

MEDICAL DIVISION: **CARDIO-RENAL DRUG PRODUCTS (HFD-110)**
PROJECT MANAGER: Ms. Quynh Nguyen
MEDICAL OFFICER: Shari Targum, M.D.

DISTRIBUTION: NDA 19777/SE5

HFD-110/Quynh Nguyen
HFD-110/Dr. Shari Targum
HFD-110/Dr. Norm Stockbridge
HFD-710/Dr. Peiling Yang
HFD-710/Dr. HM James Hung
HFD-710/Dr. George Chi
HFD-700/Dr. Charles Anello

TABLE OF CONTENTS

1	EXECUTIVE SUMMARY AND STATISTICAL FINDINGS	1
1.1	OVERVIEW OF THE STUDIES REVIEWED	1
1.2	PRINCIPAL FINDINGS IN DOSE RESPONSE	1
1.3	CONCLUSIONS	3
2	STATISTICAL REVIEW AND EVALUATION OF EVIDENCE	3
2.1	INTRODUCTION	3
2.2	STUDY P115C1	3
2.2.1	<i>Background and Study Design</i>	3
2.2.2	<i>Data Analyzed and Sources</i>	4
2.2.3	<i>Sponsor's Study Objectives</i>	4
2.2.4	<i>Sponsor's Efficacy Endpoints</i>	5
2.2.5	<i>Sponsor's Sample Size and Power Considerations</i>	5
2.2.6	<i>Sponsor's Stratification</i>	5
2.2.7	<i>Sponsor's Efficacy Analysis Methods</i>	5
2.2.8	<i>Analysis Results and Statistical Reviewer's Findings/Comments</i>	6
2.2.8.1	Baseline Characteristics	6
2.2.8.2	Primary Efficacy Endpoint	7
2.2.8.3	Secondary Efficacy Endpoint	10
3	EFFICACY FINDINGS IN SPECIAL/SUBGROUP POPULATIONS	11
4	CONCLUSIONS	12

TABLE OF TABLES

TABLE 1: SUMMARY OF SLOPE ANALYSIS IN PERIOD I (ITT POPULATION)	2
TABLE 2: SUMMARY OF GROUP DIFFERENCES IN PERIOD II	2
TABLE 3: DEMOGRAPHIC CHARACTERISTICS BY TREATMENT GROUP	7
TABLE 4: MEAN CHANGE IN TROUGH SiDBP (MM HG) IN PERIOD I (ITT POPULATION)	7
TABLE 5: PRIMARY ANALYSIS OF SLOPE (ITT POPULATION)	8
TABLE 6: MEAN CHANGE IN TROUGH SiDBP (MM HG) BY WEIGHT STRATA IN PERIOD I (ITT POPULATION)	8
TABLE 7: FDA EXPLORATORY ANALYSIS OF SLOPE BY WEIGHT STRATA (ITT POPULATION)	9
TABLE 8: RESULTS OF MEAN CHANGE IN SiDBP (MM HG) IN PERIOD II (ITT POPULATION)	11
TABLE 9: PRIMARY ANALYSIS OF GROUP DIFFERENCE: LISINAPRIL VERSUS PLACEBO IN PERIOD II (ITT POPULATION)	11
TABLE 10: SUBGROUP ANALYSIS FOR SLOPE IN PERIOD I (ITT POPULATION)	12
TABLE 11: SUBGROUP ANALYSIS FOR GROUP DIFFERENCE IN PERIOD II (ITT POPULATION)	12

TABLE OF FIGURES

FIGURE 1: STUDY DESIGN	4
FIGURE 2: MEAN CHANGES IN TROUGH SiDBP (MM HG) BY WEIGHT STRATA IN PERIOD I (ITT POPULATION)	9

1 EXECUTIVE SUMMARY AND STATISTICAL FINDINGS

This review was reproduced from the statistician's review dated 2/27/2002 for NDA 19-558/SE5 PRINIVIL™ (Lisinopril). According to the sponsor's letter in this submission, the study reviewed for NDA 19-558 was used to support this NDA supplement.

1.1 OVERVIEW OF THE STUDIES REVIEWED

ZESTRIL™ (Lisinopril) is proposed to be used for the treatment of hypertension in pediatric patients. It is an oral angiotension converting enzyme inhibitor. ZESTRIL™ has been approved in adult patients for the treatment of hypertension, heart failure and acute myocardial infarction. The current NDA supplement includes two studies conducted in pediatric patients: an open-label pharmacokinetic study (reference no. P114C1) in hypertensive infants and toddlers, pre-school children, school-aged children and adolescents and a double-blind, dose response (reference no. P115C1) study in hypertensive school-aged and adolescent patients. In addition, it also includes an open, two period, crossover study (reference no. P037) to determine the relative bioavailability of the lisinopril suspension formulation and the marketed ZESTRIL™ tablets in healthy adults. This statistical reviewer only evaluated the dose response study P115C1.

The dose response study P115C1 in children with hypertension was a phase IV study. It consisted of 2 periods: a 14-day (Period I), randomized, multicenter study, followed by another 14-day (Period II) randomized double-blind placebo-controlled washout period. Patients were randomized, stratified by weight (< vs. ≥ 50 kg), to receive one of the 3 lisinopril treatment arms once daily for 14 days: Low (0.625/1.25 mg), Middle (2.5/5 mg) and High (20/40 mg). Patients who weighed < 50 kg received the lower dose in the respective treatment group (i.e., 0.625, 2.5, or 20 mg), and patients who weighed ≥ 50kg received the higher dose (i.e., 1.25, 5, or 40 mg). Patients in the high-dose group (20/40 mg) received a half dose, respectively, for the first 2 days, and the full dose for the rest of the 14-day in Period I, unless limited by an adverse experience or excessive hypotension. Following the 14-day treatment period (i.e., Period I), patients were randomly assigned to either continue the double-blind medication for an additional 14 days or placebo for 14 days (Period II). Following Periods I and II, patients were able to enter an optional, open-label 6-month extension. The primary objectives were (a) to define a dose-response relationship for lisinopril in the end of Period I and (b) to investigate safety and tolerability of lisinopril in the dose range 0.625 to 40 mg in hypertensive children aged 6 to 16 years. The primary efficacy endpoint was the slope of change in trough SiDBP (sitting diastolic blood pressure) at the end of Period I, as compared to baseline, as a function of dose. A negative slope indicates a positive dose-response relationship with increasing doses of the lisinopril treatment. The secondary efficacy endpoint was the group difference of mean change in trough SiDBP between the treatment and placebo groups for each assigned dose level in Period II. A positive difference (placebo – lisinopril) indicates that the SiDBP effect of lisinopril was lost in the associated dose level when patients were switched to placebo in Period II.

1.2 PRINCIPAL FINDINGS IN DOSE RESPONSE

The primary efficacy endpoint was the slope of change in trough SiDBP (sitting diastolic blood pressure) at the end of Period I, as compared to baseline, as a function of dose. A negative slope

indicates a positive dose response with increasing doses of the lisinopril treatment. Analysis of covariance with different intercepts but a common slope for the two weight strata was pre-specified in the statistical analysis plan in the protocol. In summary, there was statistically strong evidence for a positive dose-response relationship when a common slope was assumed between the two weight strata. However, it is to be noted that in the heavy-weight stratum the relationship was not statistically significant at significance level of 0.05, but trended in the favored direction. These findings are summarized in Table 1.

Table 1: Summary of Slope Analysis in Period I (ITT Population)

[Source: FDA Statistical Reviewer's Analysis]

Analysis	Weight Strata	Slope ^a ± SE ^b (mm Hg per unit increase in dose ratio)	P-value
Primary: common slope	--	-0.29 ± 0.06	<0.001
Exploratory: different slopes between weight strata	Light (< 50 kg)	-0.42 ± 0.09	<0.001
	Heavy (≥ 50 kg)	-0.16 ± 0.09	0.0727

^a A negative slope indicates a positive dose-response relationship.

^b Standard error of the estimated slope.

The secondary efficacy endpoint was the group difference of mean change in trough SiDBP between the treatment and placebo groups for each assigned dose level in Period II. The sponsor's primary analysis was on the average group difference across the three dose levels; analysis on the individual group difference for each assigned dose level was considered supportive. Results of both analyses are summarized in Table 2. Although the p-value (= 0.001) for the primary analysis was significant, statistically strong evidence was seen in only the middle and high dose levels that discontinuation of lisinopril treatment by switching to placebo was associated with an increase in SiDBP.

Table 2: Summary of Group Differences in Period II

[Source: FDA Statistical Reviewer's Analysis]

Treatment in Periods I/II	Mean Change ^a ± SE ^b	Supportive Analysis		Primary Analysis	
		Group Diff ^c ± SE ^d	P-value	Average Group Diff ^e ± SE	P-value
Low/Low	1.7 ± 2.3	-0.2 ± 3.3	0.96	6.19 ± 1.86	0.001
Low/Placebo	1.5 ± 2.4				
Middle/Middle	-1.2 ± 2.7	9.7 ± 3.7	0.01		
Middle/Placebo	8.5 ± 2.6				
High/High	1.4 ± 1.7	9.1 ± 2.5	<0.001		
High/Placebo	10.4 ± 1.8				

^a Last dose – Day 15.

^b Standard error of the estimated mean change.

^c A group difference (Placebo – treatment) greater than 0 indicates an increase in SiDBP when patients discontinued the lisinopril treatment by switching to placebo.

^d Standard error of the estimated group difference.

^e Average group difference across the three dose levels.

1.3 CONCLUSIONS

There was statistically strong evidence for a positive dose-response relationship when a common slope was assumed between the two weight strata. However, the data suggested that the slope seemed to differ between the light and heavy patients. It is to be noted that in the heavy-weight stratum the relationship was not statistically significant at significance level of 0.05, but trended in the favored direction.

Strong statistical evidence was seen in the middle and high dose levels that discontinuation of lisinopril treatment by switching to placebo was associated with an increase in SiDBP.

All point estimates from results of the primary analyses with respect to slope (in Period I) and average group difference (across the three dose levels in Period II) trended in the favored direction in subgroup analysis by age, race, gender, tanner stage and country.

2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 INTRODUCTION

ZESTRIL™ (Lisinopril) is proposed to be used for the treatment of hypertension in pediatric patients. It is an oral angiotension converting enzyme inhibitor. ZESTRIL™ has been approved in adult patients for the treatment of hypertension, heart failure and acute myocardial infarction. This NDA supplement includes two studies conducted in pediatric patients and one study conducted in adult patients:

- (a) an open-label pharmacokinetic study (reference no. P114C1) in hypertensive infants and toddlers, pre-school children, school-aged children and adolescents;
- (b) a double-blind, dose response (reference no. P115C1) study in hypertensive school-aged and adolescent patients;
- (c) an open, two period, crossover study (reference no. P037) to determine the relative bioavailability of the lisinopril suspension formulation and the marketed ZESTRIL™ tablets in healthy adults.

This statistical reviewer only evaluated the dose-response relationship study P115C1.

2.2 STUDY P115C1

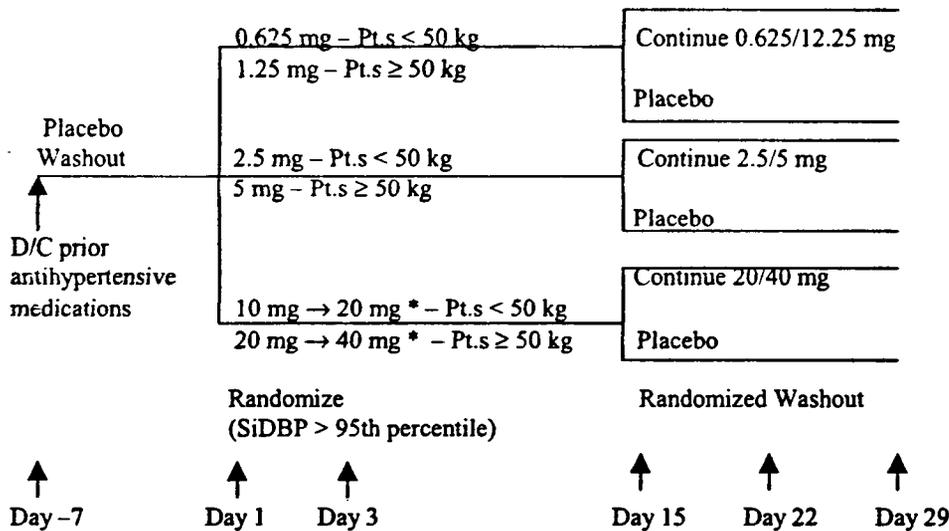
2.2.1 *Background and Study Design*

The dose-response relationship study in children with hypertension was a phase IV study. It was conducted by 22 investigators, of those 13 were in the Unites States, 1 in Belgium, 1 in Canada, 2 in Mexico and 5 in South America. The study began with an up to 7-day washout period in which patients discontinued their prior antihypertensive medication. Lisinopril placebo suspension and lisinopril placebo tablets were administered once daily during this period. If patients became hypertensive (mean trough SiDBP > 95th percentile for gender, height, and age) and met all other entry criteria and did not meet any of the exclusion criteria, they qualified to enter a 14-day randomized double-blind treatment phase (Period I). It was then followed by

another 14-day randomized double-blind placebo-controlled washout period (Period II). A total of 115 patients entered Period I and were randomized, stratified by weight (< vs. ≥ 50 kg), to receive one of the three lisinopril treatment arms once daily for 14 days: Low (0.625/1.25 mg), Middle (2.5/5 mg) and High (20/40 mg). Patients who weighed < 50 kg received the lower dose in the respective treatment group (i.e., 0.625, 2.5, or 20 mg), and patients who weighed ≥ 50 kg received the higher dose (i.e., 1.25, 5, or 40 mg). Patients in the high-dose group (20/40 mg) received a half dose, respectively, for the first 2 days, and the full dose for the rest of the 14-day in Period I, unless limited by an adverse experience or excessive hypotension. Following the 14-day treatment period (i.e., Period I), patients were randomly assigned to either continue the double-blind medication for an additional 14 days or placebo for 14 days (Period II). Following Periods I and II, patients were able to enter an optional, open-label 6-month extension. In the low dose treatment group, the study drug was administered in a suspension formulation. In the other treatment groups, dosing was with tablets. The Study design is described in the following figure.

Figure 1: Study Design

[Source: Figure 1 of Sponsor's Study Report and FDA Statistical Reviewer]



* All patients titrate at Day 3 unless limited by an adverse experience or excessive hypotension.

2.2.2 Data Analyzed and Sources

Data used for review are from the electronic submission received on 9/24/01. The network path is “\\Cdsub1\n19558\S_043\2001-09-24\crt\Datasets\115c1” in the EDR.

2.2.3 Sponsor's Study Objectives

The primary objectives were (a) to define a dose-response relationship for lisinopril in the end of Period I, and (b) to investigate safety and tolerability of lisinopril in the dose range 0.625 to 40 mg in hypertensive children aged 6 to 16 years. If the dose-response relationship was established, the secondary objective was to determine whether discontinuation of active lisinopril treatment

was associated with return of hypertension. Otherwise, the secondary objective would be to show a positive average difference of mean change between placebo-treated groups versus lisinopril-treated groups across the three dose levels.

2.2.4 Sponsor's Efficacy Endpoints

The primary efficacy endpoint was the slope of change in trough SiDBP (sitting diastolic blood pressure) at the end of Period I, as compared to baseline, as a function of dose. A negative slope indicates a positive dose-response relationship with increasing doses of the lisinopril treatment.

The secondary efficacy endpoint was the group difference of mean change in trough SiDBP between the treatment and placebo groups for each assigned dose level in Period II. The change was defined as the difference between the blood pressures at the end of Period I and of Period II. A positive difference (placebo – lisinopril) indicates that the SiDBP effect of lisinopril was lost when patients were switched to placebo in Period II.

2.2.5 Sponsor's Sample Size and Power Considerations

For the dose-response analysis at the end of Period I, with a total of 100 children, the power to detect a significant common trend (with 3 lisinopril dose levels) at a significant level of 0.05 was estimated to be 85% for a 50-mm Hg difference between the extreme doses (assuming a standard deviation of 8 mm Hg). The power calculation was based on a simple regression model of dose-ratio (1, 4 and 32).

With a total of 100 children entering Period II, the power to detect an average difference of 5 mm Hg between lisinopril-treated groups versus placebo-treated groups across the 3 dose levels at a significance level of 0.05 was estimated to be 82.3% (assuming a standard deviation of 8-mm Hg for the change). The power calculation was based on the t-test, formed by the mean of 3 differences of the mean changes (lisinopril – placebo) for the 3 dose groups.

2.2.6 Sponsor's Stratification

Patients were stratified by weight: < 50 kg and \geq 50 kg.

2.2.7 Sponsor's Efficacy Analysis Methods

The primary objective was to show a positive dose-response relationship in Period I. The primary analysis was under the assumption that the response (change in trough SiDBP in Period I) was a linear function of dose within each weight stratum. The dose was considered continuous and dose ratio (1:4:32 within each stratum) was used in predicting the response. It was also assumed that the two linear functions (one in each stratum) were parallel to each other. These assumptions translated to a statistical model of stratified simple linear regression with weight strata as stratified intercepts and a common slope. The response was defined as the change in trough SiDBP on Day 15 minus that on Day 1 in Period I. A statistically significantly negative slope would provide strong evidence for a positive dose-response relationship.

The last-measurement-carried-forward approach was used for patients who did not have measurements on Day 15. However, baseline measurements were not carried forward. The primary analysis was performed on the intent-to-treat (ITT) population. In addition, 3 supportive analyses were also performed by the sponsor:

- **Per-Protocol Analysis:** same analysis as the primary analysis except that patients with protocol violations were excluded from this analysis.
- **ANOVA (Analysis of Variance) Model:** An ANOVA model was performed with terms including dose (low/middle/high), weight (light/heavy) and the interaction between dose and weight. In the ANOVA model, dose was considered discrete; i.e., each dose level had equal weight unlike the model in the primary analysis, where dose ratio was used.
- **Longitudinal Model:** The mixed model was performed with terms including period (I/II), weight (light/heavy), and dose ratio as the continuous covariate.

The secondary objective was to show that discontinuation of active lisinopril treatment by switching to placebo was associated with an increase in blood pressure. The corresponding efficacy endpoint was the group difference (treatment – placebo) of mean change (end of Period II – end of Period I) in trough SiDBP for each assigned dose level in Period II; i.e., mean change in placebo group – mean change in treatment group. A statistically significantly positive group difference would provide strong evidence that discontinuation of lisinopril treatment by switching to placebo was associated with an increase in SiDBP in the associated dose level. The primary analysis was to estimate the average group difference across the three dose levels using the statistical model of one-way ANOVA with a factor of 6 treatments (low/low, low/placebo, middle/middle, middle/placebo, high/high, high/placebo) on change in trough SiDBP. The primary analysis was performed on the intent-to-treat population. Analyses performed on the per-protocol population and/or based on the ANOVA model with the weight factor (< 50 kg / ≥ 50 kg) included was considered supportive. Analysis of individual group difference at each dose level was also considered supportive.

2.2.8 Analysis Results and Statistical Reviewer's Findings/Comments

2.2.8.1 Baseline Characteristics

The distributions of demographic characteristics are summarized in Table 3. The three treatment dose groups appeared to be comparable in most demographic composition. However, it is noted that, for patients in the heavy-weight stratum, the mean weight in the middle dose level group was considerably larger compared with the other two groups.

APPEARS THIS WAY
ON ORIGINAL

Table 3: Demographic Characteristics by Treatment Group

[Source: Tables 4, 7 – 9 of Sponsor's Study Report and FDA Statistical Reviewer's Analysis.]

Characteristics	Low dose 0.625/1.25 mg N = 33	Middle dose 2.5/5 mg N = 24	High dose 20/40 mg N = 58	Total N = 115
Frequency				
Gender (M/ F)	21 / 12	15 / 9	39 / 19	75 / 40
Race (White/ Black/ Asian/ Hispanic)	15 / 4 / 0 / 14	11 / 3 / 0 / 10	25 / 5 / 1 / 27	51 / 12 / 1 / 51
Weight by strata (< 50/ ≥50 kg)	20 / 13	10 / 14	25 / 33	55 / 60
Tanner Stage (≤ 3/ > 3)	26 / 7	12 / 12	31 / 27	69 / 46
Country (U.S. / Non-U.S.)	13 / 20	10 / 14	18 / 40	41 / 74
Mean (Standard Deviation)^a				
Age (yrs)	11.9 (2.8)	12.2 (3.1)	11.9 (2.9)	12.0 (2.9)
Weight (kg)	49.1 (19.0)	66.1 (34.3)	56.0 (27.2)	56.1 (27.3)
Weight (kg) in < 50-kg stratum in ≥ 50-kg stratum	36.3 (9.0) 68.9 (11.7)	32.7 (10.3) 89.8 (23.2)	33.5 (8.4) 73.0 (23.9)	34.4 (8.9) 76.1 (22.8)
Baseline SiDBP (mm Hg)	87.9 (8.7)	91.0 (9.4)	90.4 (7.7)	89.8 (8.4)
Baseline SiSBP (mm Hg)	125.5 (12.7)	134.3 (15.1)	128.6 (11.6)	128.9 (12.9)

^a Standard deviation of the sample distribution.

2.2.8.2 Primary Efficacy Endpoint

The primary objective was to demonstrate a positive dose-response relationship, shown by a negative slope as a function of dose ratio in Period I. 115 patients were included in the intent-to-treat (ITT) population. Table 4 summarizes the mean changes (Day 15 – baseline) along with their standard errors in trough SiDBP at each of the 3 dose levels in Period I.

Table 4: Mean Change in Trough SiDBP (mm Hg) in Period I (ITT Population)

[Source: Table 16 of Sponsor's Study Report and FDA Statistical Reviewer]

Dose Level	Sample Size	Day 1	Day 15	Mean Changes ± SE ^a
Low (0.625/1.25 mg)	33	87.9	80.3	-7.6 ± 1.8
Middle (2.5/5 mg)	24	91.0	81.6	-9.3 ± 2.1
High (20/40 mg)	58	90.4	74.1	-16.4 ± 1.4

^a Standard error of the estimated mean change.

Table 5 summarizes results of the primary slope analysis. In this analysis, a common slope as a function of dose ratio (1: 4: 32) was assumed but allowing for different intercepts between the two weight strata. The results showed a significantly negative slope at a significance level of 0.05 (p-value < 0.001), indicating a positive dose-response relationship. Results of supportive analyses performed on the per-protocol population and/or the ANOVA model were consistent with this finding.

Table 5: Primary Analysis of Slope (ITT Population)

[Source: Table 18 of Sponsor's Study Report, confirmed by FDA Statistical Reviewer]

Parameter	Estimate ± SE ^a	P-value
Slope (mm Hg per unit increase in dose ratio)	-0.29 ± 0.06	<0.001
Difference in mean change (mm Hg) between weight groups (<50kg vs. ≥ 50 kg)	-3.84 ± 1.93	0.049

^a Standard error of the estimated mean change.

The primary analysis was under the assumption of no interaction between dose and weight strata (i.e., a common slope between the two weight strata). In order to investigate whether there were consistent results between the two weight strata, some exploratory analyses were pursued. Table 6 summarizes the mean changes in SiDBP by weight strata (Day 15 – baseline) at each of the 3 dose levels. Figure 2 is the corresponding graphic representation. It can be seen from this figure that the mean change appeared to be a linear relationship with dose for patients in the light-weight stratum, whereas it appeared to be a quadratic relationship for patients in the heavy-weight stratum.

Table 6: Mean Change in Trough SiDBP (mm Hg) by Weight Strata in Period I (ITT Population)

[Source: Table 17 of Sponsor's Study Report and FDA Statistical Reviewer]

Weight Strata	Statistics	Dose Level		
		Low (0.625/1.25 mg)	Middle (2.5/5 mg)	High (20/40 mg)
Light	N ^a	20	10	25
	Mean Change ± SE ^b	-6.4 ± 2.3	-12.4 ± 3.2	-20.6 ± 2.0
Heavy	N	13	14	33
	Mean Change ± SE	-9.5 ± 2.8	-7.1 ± 2.7	-13.2 ± 1.8

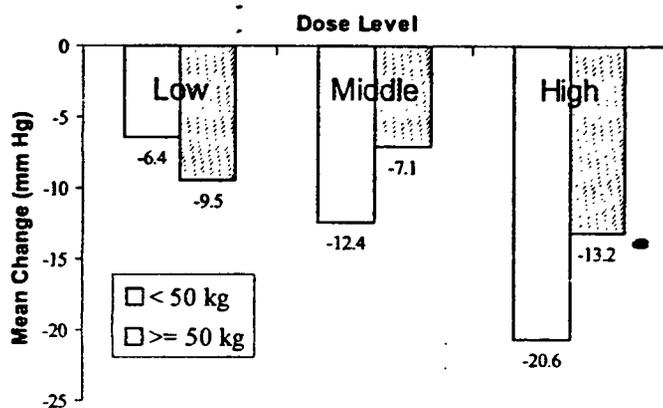
^a Number of patients.

^b Standard error of the estimated mean change.

**APPEARS THIS WAY
ON ORIGINAL**

Figure 2: Mean Changes in Trough SiDBP (mm Hg) by Weight Strata in Period I (ITT Population)

[Source: Figure 3 of Sponsor's Study Report and FDA Statistical Reviewer]



In order to investigate if the dose-response relationship exists in the heavy-weight stratum, this reviewer repeated the primary slope analysis, but allowing for different slopes between weight strata; i.e., including the interaction of slope with weight strata in the model (full model of ANCOVA). The results based on this analysis indicated that the interaction effect on the slope appeared to be evident (p-value = 0.0502). However, no qualitative interaction effect was observed. The slope in the light-weight stratum was significantly negative (p-value < 0.0001). The slope in the heavy-weight stratum was not statistically significant, but trended in the favored direction. Table 7 summarizes results of this reviewer's exploratory slope analysis on the intent-to-treat population. Exploratory analysis performed on the per-protocol population gave consistent results.

Table 7: FDA Exploratory Analysis of Slope by Weight Strata (ITT Population)

[Source: FDA Statistical Reviewer]

Weight Strata	Slope ± SE ^a (mm Hg per unit increase in dose ratio)	P-value
Light (< 50 kg)	-0.42 ± 0.09	<0.001
Heavy (≥ 50 kg)	-0.16 ± 0.09	0.0727

^a Standard error of the estimated slope.

In addition, this reviewer performed analysis of variance (ANOVA) where dosage was no longer considered continuous, but rather discrete. Full model was used to explore whether linear or quadratic relationship was statistically significant in the heavy-weight stratum. The results based on the intent-to-treat population showed neither statistically significant linear relationship (p-value = 0.2715) although trended in the favored direction, nor quadratic relationship (p-value = 0.19). Exploratory analysis performed on the per-protocol population led to consistent results.

In summary, results of these exploratory analyses were consistent: a numerically positive dose-response relationship in the heavy-weight stratum was not statistically significant but trended in the favored direction.

It is noted that, in the heavy-weight stratum, patients randomized to the middle dose group had a considerably larger mean weight as compared to the other two dose groups. The following question was then raised: was the lack of significantly positive dose-response relationship in the heavy-weight stratum associated with the imbalance in patients weight among the three dose groups? An exploratory analysis of ANCOVA with baseline weight considered as a covariate and three discrete dose levels (i.e., considering change in SiDBP as a continuous linear function of baseline weight for each of the three dose levels with a common slope) was performed on the heavy-weight stratum. Results did not suggest statistically significant dose-response relationship even after adjusting for baseline weight as a covariate (p-value = 0.2694 as compare to 0.2715 without considering weight as a covariate). This suggested that the lack of dose-response relationship in the heavy-weight stratum could not be explained by the imbalance in patients weight among the three dose groups. In addition, the term for weight in the model (mm Hg/kg) was not statistically significantly different from 0 (p-value = 0.81), suggesting that there was no strong statistical evidence that baseline weight was a good predictor of change in SiDBP.

It is unknown whether or not the lack of significantly positive dose-response finding in the heavy-weight stratum was associated with insufficient power in allowing for different slopes in the reviewer's exploratory analysis. The puzzle might be solved with more patients included in the heavy-weight stratum.

Reviewer's Summary:

- There was statistically strong evidence for a positive dose-response relationship when a common slope was assumed between the two weight strata. However, the data suggested that slope seemed to differ between the light and heavy patients. It is to be noted that in the heavy-weight stratum the relationship was not statistically significant at significance level of 0.05, but trended in the favored direction.

2.2.8.3 Secondary Efficacy Endpoint

The secondary objective was to see whether discontinuation of lisinopril treatment by switching to placebo was associated with an increase in blood pressure. 104 of the 115 patients entered Period II and had postrandomization blood pressure measurements in Period II.

Results of mean change in SiDBP at each dose level in Period II are summarized in Table 8. The results suggested that statistically strong evidence was seen in the middle and high dose levels that discontinuation of lisinopril treatment by switching to placebo was associated with an increase in SiDBP. The estimated mean [median] starting dose of lisinopril received by patients randomized to the middle/middle dose level in Period II was 0.07 [0.06] mg/kg.

Table 8: Results of Mean Change in SiDBP (mm Hg) in Period II (ITT Population)*[Source: Table 23 of Sponsor's Report and FDA Statistical Reviewer]*

Treatment in Periods I/II	N ^a	Day 15	Last Dose	Mean Change ^b ± SE ^c	Group Difference ^d (Plac. – trt.) ± SE ^e	P-value
Low/Low	15	77.4	79.1	1.7 ± 2.3	-0.2 ± 3.3	0.96
Low/Placebo	14	76.9	78.4	1.5 ± 2.4		
Middle/Middle	11	77.5	76.3	-1.2 ± 2.7	9.7 ± 3.2	0.01
Middle/Placebo	12	83.2	91.7	8.5 ± 2.6		
High/High	27	71.1	72.5	1.4 ± 1.7	9.1 ± 2.6	<0.001
High/Placebo	25	74.5	85.0	10.4 ± 1.8		

^a Number of patients.^b SiDBP in last dose – Day 15 (i.e., end of Period II – end of Period I).^c Standard error of the estimated mean change.^d Placebo – treatment. A group difference greater than 0 indicates an increase in SiDBP when patients discontinued the lisinopril treatment by switching to placebo.^e Standard error of the estimated group difference.

The sponsor's primary analysis was the average group difference across the three dose levels, results of which are summarized in Table 9. Although the p-value (= 0.001) was significant, results should be interpreted with caution because the effect was seen in only the middle and high, not the low, dose levels (see Table 8). Analysis results based on the per-protocol population were consistent with those based on the intent-to-treat population.

Table 9: Primary Analysis of Group Difference: Lisinopril Versus Placebo in Period II (ITT Population)*[Source: Table 24 of Sponsor's Study Report, Confirmed by FDA Statistical Reviewer]*

	Estimate ± SE ^a	P-value
Group Difference (mm Hg) (Placebo – Treatment)	6.19 ± 1.86	0.001

^a Standard error of the estimated group difference.**Reviewer's Summary:**

- Strong statistical evidence was seen in the middle and high dose levels that discontinuation of lisinopril treatment by switching to placebo was associated with an increase in SiDBP.

3 EFFICACY FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Results of subgroup analyses of the primary and secondary efficacy endpoints by age, tanner stage, gender, race and country are summarized in Table 10 and Table 11, respectively. All the point estimates trended in the favored direction.

Table 10: Subgroup Analysis for Slope in Period I (ITT Population)*[Source: Table 22 of Sponsor's Study Report, Confirmed by FDA Statistical Reviewer]*

Factor	Strata	# of Patients	Slope \pm SE ^a
Age	\leq 12 years	54	-0.35 \pm 0.10
	> 12 years	61	-0.22 \pm 0.08
Tanner Stage	\leq 3	69	-0.35 \pm 0.08
	> 3	46	-0.20 \pm 0.10
Gender	Male	75	-0.26 \pm 0.08
	Female	40	-0.32 \pm 0.12
Race	White	51	-0.28 \pm 0.11
	Black	12	-0.07 \pm 0.10
	Others	52	-0.36 \pm 0.09
Country	U.S.	41	-0.19 \pm 0.09
	Non-U.S.	74	-0.32 \pm 0.09

^a Standard error of the estimated slope.**Table 11: Subgroup Analysis for Group Difference in Period II (ITT Population)***[Source: Table 27 of Sponsor's Study Report, Confirmed by FDA Statistical Reviewer]*

Factor	Strata	Number of Patients	Group Difference \pm SE ^a
Age	\leq 12 years	48	8.27 \pm 2.55
	> 12 years	56	4.36 \pm 2.64
Tanner Stage	\leq 3	63	6.71 \pm 2.21
	> 3	41	5.40 \pm 3.67
Gender	Male	69	4.42 \pm 2.46
	Female	35	8.71 \pm 3.38
Race	White	44	5.88 \pm 2.86
	Black	12	3.33 \pm 4.49
	Others	48	7.69 \pm 2.67
Country	U.S.	39	6.24 \pm 3.55
	Non-U.S.	65	5.84 \pm 2.13

^a Standard error of the estimated slope.

4 CONCLUSIONS

There was statistically strong evidence for a positive dose-response relationship when a common slope was assumed between the two weight strata. However, the data suggested that the slope seemed to differ between the light and heavy patients. It is to be noted that in the heavy-weight stratum the relationship was not statistically significant at significance level of 0.05, but trended in the favored direction.

Strong statistical evidence was seen in the middle and high dose levels that discontinuation of lisinopril treatment by switching to placebo was associated with an increase in SiDBP.

All point estimates from results of the primary analyses with respect to slope (in Period I) and average group difference (across the three dose levels in Period II) trended in the favored direction in subgroup analysis by age, race, gender, tanner stage and country.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Peiling Yang
3/7/02 06:19:06 PM
BIOMETRICS

James Hung
3/7/02 06:31:16 PM
BIOMETRICS

George Chi
3/8/02 11:12:51 AM
BIOMETRICS