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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

19-777/S-044

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 19-777, SE5-044

SUBMISSION DATES: November 2, 2001

BRAND NAME: Zestril™

GENERIC NAME: Lisinopril tablets

DOSAGE STRENGTH: 2.5 mg, 5 mg, 10 mg, 20 mg, 30 mg and 40 mg

SPONSOR: AstraZeneca Pharmaceuticals LP

PRIMARY REVIEWER: Joga Gobburu, Ph.D.

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EXECUTIVE SUMMARY

Lisinopril (Zestril®) is an ACE inhibitor approved for use in adults for hypertension and as adjunctive therapy in the management of heart failure in patients who are not responding adequately to diuretics and digitalis.

Study 037 - a study demonstrating bioequivalence of lisinopril suspension (formulation used in pediatric population) and marketed tablets in healthy adults that demonstrated bioequivalence. **Study 114/117** - A steady state lisinopril pharmacokinetic study in children 6 months to 16 years of age with a history of hypertension. Children in the different age groups received between 0.12 mg/kg/day to 0.15 mg/kg/day for 7 days, a dose which is similar to the adult starting dose of 0.14 mg/kg/day. The sponsor concluded that the pharmacokinetics of lisinopril in children was similar to adults on a mg/kg basis. The reviewer's population pharmacokinetic modeling indicated that the apparent oral clearance (CL/F) of lisinopril was influenced by body weight raised to function 0.642 which is equivalent to body surface area.

$$\frac{CL}{F} = 9.99\left(\frac{L}{h}\right)*\left(\frac{Body\ Weight}{30}(kg)\right)^{0.642}$$ The typical CL/F value for a child weighing 30 kg would be 9.99 L/h.

Study 115/116 – A double-blind, randomized, multicenter dose-response study in 115 hypertensive pediatric patients between 6 years and 16 years of age, with doses to elucidate the dose-response relationship of lisinopril in children between 6 and 16 years of age. The sponsor analysis demonstrated that lisinopril decreases sitting systolic blood pressure and that increasing effect was seen with increasing doses with a slope of -0.29 mmHg/mg, which does not account for the placebo effect with time. A substantially larger decrease in SiSBP in the <50 kg group for the low, medium and high doses of –6.4 mmHg, -12.4 mmHg and –20.6 mmHg, respectively, was observed compared to a smaller decrease in the >50 kg group of –9.5 mmHg, -7.1 mmHg and –13.2 mmHg, respectively. The effect of the highest dose in the >50 kg group is similar to the response to the middle dose in the <50 group.

The reviewer's PK/PD modeling indicated that the effect of lisinopril was best fit to a linear model. There was a significant placebo effect on sitting and standing systolic and diastolic blood pressure. Body weight influenced both baseline SiSBP, StSBP, SiDBP and StDBP and their respective slopes of concentration-effect relationships. In a 30 kg child, typical values of baseline SiSBP, StSBP, SiDBP and StDBP were, 127 mmHg, 126 mmHg, 87.5 mmHg and 88.2 mmHg, respectively, and their respective typical values for slope of concentration-effect relationship were -0.134 mmHg/(ng/ml), -0.168 mmHg/(ng/ml), -0.147 mmHg/(ng/ml) and -0.147 mmHg/(ng/ml), respectively. The slope of the concentration-blood pressure reduction relationship decreased with increasing body weight indicating lower sensitivity at higher body weight. For a 30 kg child, the slope of lisinopril concentration-effect relationship for SiSBP, StSBP, SiDBP and StDBP were, -0.181 mmHg/(ng/ml), -0.205 mmHg/(ng/ml), -0.182 mmHg/(ng/ml) and –0.211 mmHg/(ng/ml), respectively, which would decrease for a child weighing 40

kg to –0.144 mmHg/(ng/ml), -0.177 mmHg/(ng/ml), -0.156 mmHg/(ng/ml) and –0.101 mmHg/(ng/ml) for SiSBP, StSBP, SiDBP and StDBP, respectively.

SPONSOR PROPOSED LABELING:
CLINICAL PHARMACOLOGY

[

]

COMMENTS:

1. The proposed description of the pharmacokinetics of lisinopril should be moved to the [
and should be modified to read [

2. The Clinical Study portion of sponsor proposed label should include the following sentence. [

Office of Clinical Pharmacology and Biopharmaceutics briefing for the lisinopril pediatric submission was held on June 13, 2002 and was attended by Mishina, Mehta, Lawrence, Boladian, Viswanathan, Gobburu and Marroum.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the pediatric supplement for lisinopril and finds the studies acceptable. The above comments (#1-2) are to be conveyed to the sponsor. No further action is warranted at this time.

Joga Gobburu, Ph.D.

RD/FT initialed by Patrick J. Marroum, Ph.D.

cc: NDA 19-777, HFD 110, HFD 860 (Mehta,Marroum,Gobburu,Robbie), CDER document room: Attn: Biopharm (CDER)

APPENDIX I

PROPOSED PACKAGE INSERT

34 page(s) of draft labeling was redacted from the approval package

APPENDIX II

REVIEW OF INDIVIDUAL STUDIES

AN OPEN, TWO-PERIOD CROSSOVER STUDY TO DETERMINE THE RELATIVE BIOAVAILABILITY OF LISINOPRIL SUSPENSION 20 MG AND MARKETED PRINIVIL™ 20-MG TABLETS

STUDY #: 037

STUDY INVESTIGATOR & SITE: [

]

OBJECTIVES:

1. To assess the relative bioavailability of lisinopril suspension 20 mg and the marketed PRINIVIL™ 20-mg tablet.
2. To evaluate the serum concentration profile of lisinopril following administration of lisinopril suspension 20 mg and the 20 mg marketed PRINIVIL™ tablet.

FORMULATIONS:

20 mg PRINIVIL™ tablet – Formulation # J8365
20 mg lisinopril suspension – 20 mg PRINIVIL™ tablet suspended in 5% sterile water, 15% BICITRA™ (sodium citrate and citric acid solution)
80% ORA-Sweet (SF syrup vehicle).

STUDY DESIGN:

This was an open-label, randomized, single-dose, 2-period crossover, single center study in 25 healthy adult male (14) and female (11) volunteers between 20 and 45 years of age and body weight between 110 and 205 lb. Twenty-two of 25 subjects were Hispanic. Subjects received single doses of lisinopril according to a randomization schedule as either Treatment A = 20 mg PRINIVIL™ tablet, or Treatment B = 20 ml of 1 mg/ml lisinopril suspension, following an overnight fast. Each period was separated by a washout interval of 21 days.

Sample Collection:
Blood samples for pharmacokinetic analyses of lisinopril were collected predose and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, 36, 48, 60, 72, 84 and 96 hours post dose.
Urine samples for lisinopril analysis were collected predose and at intervals 0-6, 6-12, 12-18, 18-24, 24-36, 36-48, 48-60, 60-72, 72-84 and 84-96 hours postdose.

ASSAY:

Compound	Matrix	Method	LOQ (ng/ml)	Range (ng/ml)	QC (ng/ml)	CV%	Accuracy (% Bias)
Lisinopril	Plasma	Radioimmunoassay	[				]

Lisinopril	Urine	Radioimmunoassay	[ ]

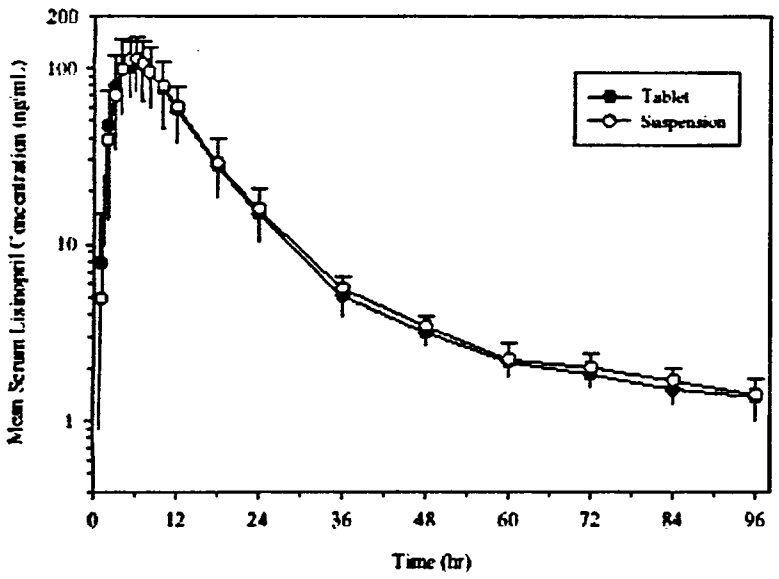
RESULTS

Mean pharmacokinetic parameters of lisinopril obtained following administration of 20 mg lisinopril suspension and 20 mg PRINIVIL™ tablet in a crossover fashion to 24 subjects are listed below.

Geometric Mean Pharmacokinetic Parameters of Lisinopril

Parameter	Suspension	Tablet	MSE	Point Estimate Susp./Tablet	90% CI
Cmax (ng/ml)	112.46	110.50	0.086	1.02	0.88, 1.18
Tmax (h)	6.00	6.00	-	-	
$AUC_{0\text{-}96}$ (ng.h/ml)	1488.41	1452.72	0.074	1.02	0.90, 1.17
Urinary Recovery (% Dose)	27.30	28.83	0.182	0.95	0.77, 1.17

Mean (SD) Serum Lisinopril Concentration Following Administration of Single Oral Doses of Lisinopril 20-mg Marketed Tablet (PRINIVIL™) and 20 mL of 1 mg/mL Lisinopril Suspension (Error Bars With No Caps)



Cmax and $AUC_{0\text{-}96}$ of lisinopril when administered as a suspension or as PRINIVIL™ tablet were bioequivalent. The point estimates for both Cmax and AUC of lisinopril were 1.02 and the 90% confidence intervals were contained within the bioequivalence goal posts of 0.80 and 1.25. About 27% and 29% of administered dose were recovered in the urine following suspension and tablet administration over 96 h, respectively.

CONCLUSIONS:

The 20-mg suspension formulation used for pediatric dosing and the 20-mg PRINIVIL™ tablet formulations of lisinopril were bioequivalent. The 90% confidence limits for Cmax and AUC were contained within the bioequivalence limits of 0.8 and 1.25.

AN OPEN LABEL STUDY TO INVESTIGATE THE PHARMACOKINETICS OF LISINOPRIL IN HYPERTENSIVE CHILDREN AND INFANTS

STUDY #: 114/117

STUDY INVESTIGATORS & SITES: Multicenter (5 investigators in US; 1 in Chile; 1 in Peru)

OBJECTIVES:

1. To estimate the serum pharmacokinetic parameters of lisinopril at steady state in hypertensive children aged 1 month to <16 years.
2. To estimate urinary recovery of lisinopril at steady state in hypertensive children aged 1 month to <16 years

FORMULATIONS:

Lisinopril Tablet – 2.5 mg – Lot # WP-G691, WP-H014
Lisinopril Tablet – 5 mg – Lot # WP-G692, WP-H015
Lisinopril Tablet – 10 mg – Lot # WP-G693, WP-H016
Lisinopril Tablet – 20 mg – Lot # WP-G690, WP-H013
Bicitra – Lot # WP-G694, WP-H017
Ora-Sweet SF – Lot # WP-G695, WP-H018

STUDY DESIGN:

This was an open-label, multicenter study of lisinopril steady state (Day 7) pharmacokinetics in children 1 month to 16 years of age with a history of hypertension and GFR >30 ml/min/1.73 m^2.

The patient demographics are presented in the following table.

	Group I (1 mo to <2 Yr)	Group II (2 to <6 Yr)	Group III (6 to <12 Yr)	Group IV (12 to <16 Yr)
Total No. of Patients	11	12	12	17
Males (n)	8	3	6	11
Actual age range	6 to 22 mo	2 to 3 yr	6 to 11 yr	12 to 15 yr
Females (n)	3	9	6	6
Actual age range	22 to 23 mo	2 to 5 yr	7 to 10 yr	12 to 15 yr
Caucasian (n)	3	3	5	10
Black (n)	0	0	4	5
Hispanic (n)	6	5	1	0
Mixed race (n)	2	4	2	2
Weight range (kg)	8.5 - 12.0	13.0 - 29.0	24.0 - 54.0	36.0 - 140.0
Patients with PK (n)	9	8	12	17

Children <6 years who could not swallow tablets received lisinopril suspension (prepared from lisinopril 20-mg tablets suspended in buffer/water/syrup) dose of 0.15 mg/kg/day for 7 days.
Children 6 yr and older, weighing <25 kg, received lisinopril 2.5-mg tablets once daily for 7 days.
Children 6 yr and older, weighing =25 kg but <45 kg, received lisinopril 5-mg tablets once daily for 7 days.
Children 6 yr and older, weighing =>45 kg, received lisinopril 10-mg tablets once daily for 7 days.

Sample Collection:
Blood samples for pharmacokinetic analyses of lisinopril were collected predose and at 2, 4, 6, 8, 10, 12, 16 and 24 hours post dose on Day 7.
Urine samples for lisinopril analysis were collected predose and at intervals 0-6, 6-12, and 12 to 24 hours postdose on Day 7.

ASSAY:

Bioanalytical report of lisinopril assays in plasma and urine were not provided in the submission.

Compound	Matrix	Method	LOQ (ng/ml)
Lisinopril	Plasma	Radioimmunoassay	—
Lisinopril	Urine	Radioimmunoassay	—

RESULTS

SPONSOR'S ANALYSIS:

The recommended starting dose of lisinopril for uncomplicated hypertensive adults is 10 mg (0.14 mg/kg for a 70-kg adult). The actual mean dosages in children in this study were 0.15, 0.15, 0.15, and 0.12 mg/kg/day in Groups I through IV, respectively, which is similar to recommended starting dose in adults based on a mg/kg basis.

In order to directly compare the pharmacokinetics of lisinopril across all 4 age groups, the sponsor dose-adjusted AUC_{0-24} hr and C_{max} based on patient weight to 0.15 mg/kg (the dose given to Groups I and II) and based on patient BSA to 1.0 mg/m^2. Body surface area was calculated based on patient height and weight using the Gehan-George method :

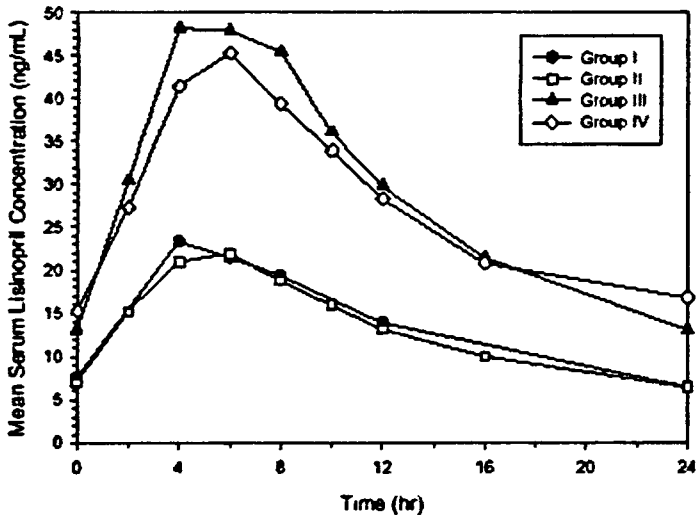
$$BSA = 0.02350(WT\ kg)^{0.51456}\ (HT\ cm)^{0.42246}$$

Mean steady state pharmacokinetic parameters of lisinopril obtained in the 4 age groups in pediatric hypertensive patients is listed in the following table.

	Group I (1 mo to <2 Yr)	Group II (2 to <6 Yr)	Group III (6 to <12 Yr)	Group IV (12 to <16 Yr)
N	9	8	12	17
Mean dose- mg/kg	0.15	0.15	0.15	0.12
Mean dose- mg/m^2	3.07	3.59	4.50	4.78
Geometric Mean (95% CI)				
^{AUC}0-24 hr (ng.hr/mL)	311.04	301.13	570.29	549.82
	(218.47, 442.83)	(207.03, 438.01)	(419.98, 774.39)	(425.20, 710.97)
^{AUC}0-24 hr - per 1.0 mg/m^2 BSA	101.35	83.91	128.97	116.89
	(72.13, 142.41)	(58.50, 120.36)	(96.07, 173.15)	(91.26, 149.71)
C_{max} (ng/mL)	22.12	21.85	44.70	43.50
	(16.14, 30.32)	(15.64, 30.53)	(34.02, 58.73)	(34.58, 54.72)
^{C}max - per 1.0 mg/m^2 BSA	7.21	6.09	10.11	9.25
	(5.36, 9.69)	(4.45, 8.34)	(7.82, 13.06)	(7.45, 11.47)
Median T_{max} (hour)	5.06	5.04	5.06	5.98
	(4.03, 6.99)	(4.03, 6.00)	(4.01, 6.18)	(5.02, 6.10)
Apparent half-life (hour)	N=7	N=8	N=12	N=16
Harmonic mean (95% CI)	10.45	10.35	9.59	8.83
	(8.64, 13.23)	(8.66, 12.84)	(8.36, 11.25)	(7.90, 10.00)
Geometric Mean (95% CI) Steady State Urinary Recovery				
		N=4	N=9	N=15
Lisinopril (% Dose)	NA	20.41	35.68	26.74
		(14.33, 29.07)	(28.18, 45.17)	(22.27, 32.10)

NA = urine collections were incomplete or not performed, so analysis was not performed

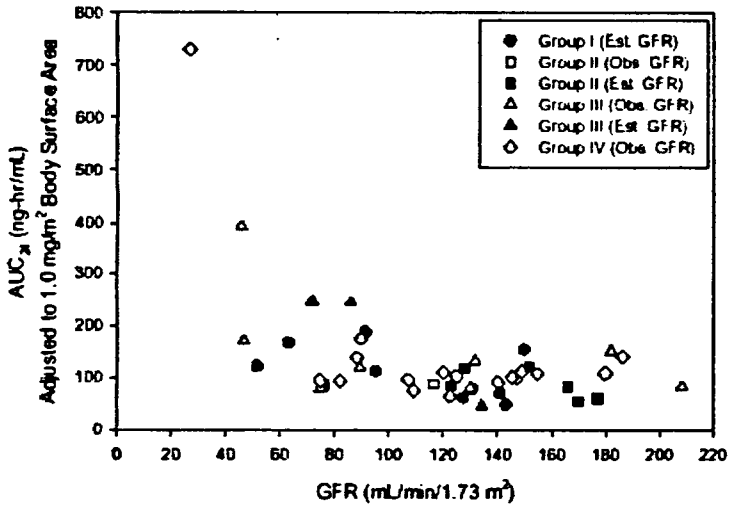
Mean Steady State Serum Lisinopril Concentrations (ng/mL) in Hypertensive Infants and Toddlers, Pre-School Children, School-Age Children, and Adolescents Following Daily Doses of 0.15 mg/kg Lisinopril Suspension (Groups I, II, III) or 2.5- or 5- or 10-mg Lisinopril Tablet (Groups III, IV)



Mean serum concentrations, C_{max} and AUC of lisinopril in Groups III and IV were about 80% higher than Groups I and II consistent with a higher dose, the dose per m^2 BSA was about 50% higher on average in Groups III and IV than in Groups I and II.

When AUC_{0-24} and C_{max} values were dose-adjusted for BSA, both AUC_{0-24} and C_{max} values were similar across the age range indicating that CL/F is similar across the age groups when adjusted for BSA. Since GFR and BSA are correlated, this finding is expected for lisinopril, which is primarily renally excreted through filtration.

Steady State Lisinopril AUC_{24} (ng•hr/mL) Adjusted to 1.0 mg/m^2 Dose Versus Observed GFR (Observed Creatinine Clearance, Where Available; Open Symbols) or Estimated GFR (Schwartz Formula; Closed Symbols) in Hypertensive Infants and Toddlers, Pre-School Children, School-Age Children, and Adolescents



The sponsor compared mean pharmacokinetic parameters from the 4 groups to historical adult pharmacokinetic data for lisinopril.

Comparison of PK in Hypertensive Infants and Toddlers, Pre-School Children, School-Age Children, and Adolescents With Historical Data in Adults

	Group I (n=9)	Group II (n=8)	Group III (n=12)	Group IV (n=17)	Adults (n=8)
Geometric Mean Steady State Lisinopril					
Mean dose (mg/kg)	0.15	0.15	0.15	0.12	0.14†
Mean dose (mg/m^2)	3.07	3.59	4.50	4.78	4.75†
AUC_{0-24} hr (ng.hr/mL)	311.04	301.13	570.29	549.82	493.5†
AUC_{0-24} hr (per 1.0 mg/m^2 BSA)	101.35	83.91	128.97	116.89	93.3
Cmax (ng/mL)					
Cmax (per 1.0 mg/m^2 BSA)					

Median Tmax (h)	5.06	5.04	5.06	5.98	6.5‡
Geometric Mean Steady-State Urinary Recovery					
		N=4	N=9	N=15	N=8
Lisinopril (% dose)	NA	20.41	35.68	26.74	25.1‡

NA = urine collections were incomplete or not performed, analysis was not done.
† Adjusted to simulate 10-mg dose, consistent with pediatric study; ‡ Result for adults is the arithmetic mean.

In the present study, median T_{max} in children and infants was 5 to 6 hours, consistent with the adult mean T_{max} of 6.5 hours. Similarly, the extent of absorption of orally administered lisinopril based on urinary recovery was similar in children and adults, 20% to 36% compared to 25%, respectively. The half-life in infants and toddlers, and pre-school patients was slightly longer (10 h) compared to school age and adolescents (9 h). The sponsor concludes that the pharmacokinetics of lisinopril is similar across infants and toddlers, pre-school children, school age children and adolescents. Moreover, the pharmacokinetics of lisinopril in pediatric patients is similar to adult patients.

CONCLUSIONS:

The sponsor concludes that,

1. Pharmacokinetics of lisinopril following oral administration are generally similar in infants and toddlers, pre-school children, school-age children, and adolescents, and are generally comparable to historical values in adults.
2. Lisinopril can be administered in a suspension formulation, with an acceptable pharmacokinetic profile, to hypertensive children and infants who are unable to swallow tablets or who require a lower dose than is available in tablet form.

A DOUBLE-BLIND, RANDOMIZED, DOSE-RESPONSE STUDY OF LISINOPRIL IN CHILDREN WITH HYPERTENSION

STUDY #: 115/116

STUDY INVESTIGATORS & SITES: Multicenter (13 in US; 1 in Belgium & Canada; 2 in Mexico ; 5 in S. America)

OBJECTIVES:

1. To define the dose-response relationship for lisinopril in children aged 6 to 16 years with hypertension, after a 14-day double-blind treatment period..
2. To investigate the safety and tolerability of lisinopril in the dose range 0.625 to 40 mg in hypertensive children aged 6 to 16 years.
3. To define the mean change in blood pressure during a 14-day, double-blind, randomized, placebo-controlled washout period following the 14-day double-blind treatment period.

FORMULATIONS:

Lisinopril Tablet – 2.5 mg, 5 mg, 10 mg, 20 mg and 40 mg
Placebo matching 2.5 mg, 5 mg, 10 mg, 20 mg and 40 mg lisinopril tablets
Bicitra
Ora-Sweet SF

STUDY DESIGN:

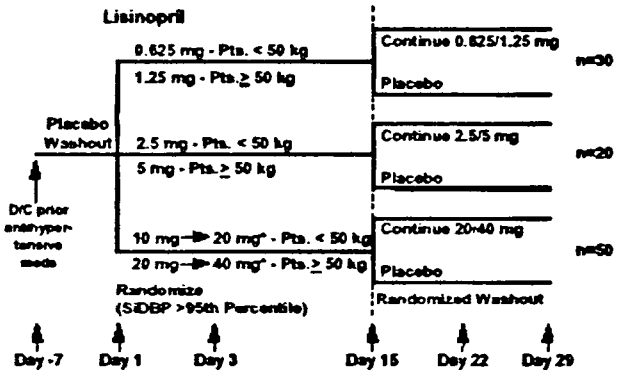
This was a double-blind, randomized, multicenter dose-response study in 115 hypertensive pediatric patients between 6 years and 16 years of age, with body weight >20 kg and, GFR ≥30 ml/min/1.73 m^2. The recommended starting dose of lisinopril for hypertensive adults is 10 mg (0.14 mg/kg for a 70-kg adult). The doses in this study ranged from 0.625 mg, which was expected to be a minimally effective dose, to 40 mg, the maximum dose in the usual adult dosage range.

After a 7-day washout period in which patients discontinued their prior antihypertensive medication, patients who became hypertensive (mean trough SiDBP >95th percentile for gender, height, and age) qualified to enter the double-blind treatment phase, which consisted of 2 periods. Period I was the double-blind 2-week treatment period. Period II was the randomized, placebo-washout period.

In Period I, patients were randomized to 1 of 3 treatment arms, Low Dose; 0.625/1.25 mg (suspension), Middle Dose 2.5/5.0 mg (tablet), High Dose 20/40 mg (tablet). Patients were assigned to receive a starting dose of lisinopril 0.625, 2.5, or 10 mg (patients <50 kg) and 1.25, 5, or 20 mg (patients ≥50 kg) once daily.

On Day 3, patients who started on 10 mg who weighed <50 kg had their dose increased in a double blind manner to 20 mg (no adverse event or excessive hypotension). Patients who started on 20 mg (≥50 kg) had their dose increased to 40 mg in double blind manner (no adverse event or excessive hypotension). All patients remained on the randomly assigned dose of lisinopril from Day 3 through Day 14. Following the 14-day double-blind treatment period, patients underwent a randomized washout to placebo or continued active treatment (1:1) for up to 14 days. Following the randomized washout period, patients could enter an optional open-label 6-month extension.

Study Design



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

The patient demographics is presented in the following table.

	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)
	n	n	n	n
GENDER				
Male	21	15	39	75
Female	12	9	19	40
RACE				
White	15	11	25	51
Black	4	3	5	12
Asian	0	0	1	1
Hispanic	14	10	27	51
Age (Years)				
<6'	1	0	1	2
6 to 12.9	16	11	25	52
13 to 16	16	13	32	61
Range	5 to 16	6 to 16	5 to 16	5 to 16
DOSE				
Weight-adjusted Dose (mg/kg)	0.02	0.07	0.61	
BSA-adjusted Dose (mg/m^2)	0.61	2.42	20.76	
Duration of Hypertension (Years)				
≤1.01	10	8	19	37
1.02 to 2	7	5	16	28
2.01 to 4	10	5	9	24
4.01 to 8	4	4	11	19

8.01 to 12	1	2	2	5
12.01 to 16	1	0	1	2
Range	0.08 to 15.6	0.08 to 10.8	0.08 to 15	0.08 to 15.6

Sample Collection:
Blood and urine samples were not collected for pharmacokinetic analyses of lisinopril.

RESULTS

SPONSOR'S ANALYSIS:

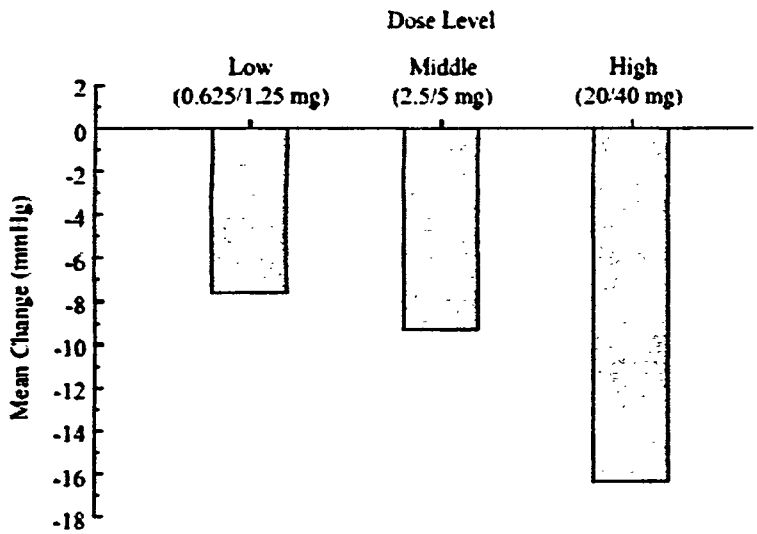
In Period I, which was a double-blind, randomized, parallel dose-ranging study, increasing doses of lisinopril resulted in greater reductions in blood pressure. After 2 weeks of lisinopril therapy taken once daily (Period I), when sitting diastolic blood pressure was measured 24 hours postdose (trough), there was a strong dose-response relationship across the low (0.625 mg/1.25 mg), middle (2.5 mg/5 mg), and high (20 mg/40 mg) doses, resulting in slope of -0.29 mm Hg per unit increase in dose ratio 1:4:32 ($p<0.001$) for the combined light and heavy pediatric patient populations. The lowest effective dose was not determined because there was no placebo group in Period I.

Baseline to Day 15 Mean Change in Trough SiDBP (mm Hg) in Period I (Intent-to-Treat)

	N	Day 1	Day 15	Mean Change	SD	95% Confidence Interval (for Mean Change)	
Low (0.625/1.25 mg)	33	87.9	80.3	-7.6	9.3	-10.9,	-4.3
Middle (2.5/5 mg)	24	91.0	81.6	-9.3	8.7	-13.0,	-5.7
High (20/40 mg)	58	90.4	74.1	-16.4	11.7	-19.5,	-13.3

N = Patients with both baseline (on Day 1) and postdose measurements.
SD=Standard deviation
Mean Change = Measurement on Day 15 minus measurement on Day 1.

Mean Changes in Trough SiDBP (mm Hg) in Period I (Day 15 Versus Day 1)
Intention-to-Treat Approach
Dose Level



Primary Hypothesis—Primary Slope Analysis (Intent-to-Treat Analysis)

	Estimate	Standard Error	p-Value
— Slope (β) (mm Hg per unit increase in dose ratio)	-0.29	0.06	<0.001
— Difference in mean change (mm Hg) between weight Groups: (<50 kg versus ≥50 kg)	-3.84	1.93	0.049
Adjusted SD (mm Hg)	10.31		

SD=standard deviation

The mean changes (Day 15 vs. Day 1) were all negative (-7.6, -9.3, and -16.4 mm Hg), at the three dose levels of lisinopril, with increasing doses producing greater reductions. The difference of the mean changes between High dose and Low dose was -8.8 mm Hg.

The mean changes in trough SiDBP were reduced in both weight groups <50 kg and ≥50 kg.

Mean Changes in Trough SiDBP (mm Hg) and Standard Deviation (SD) in Period I by Weight Stratum (Intent-to-Treat Analysis)

	Low (0.625/1.25 mg)		Middle (2.5/5 mg)		High (20/40 mg)	
	<50 kg	≥50 kg	<50 kg	≥50 kg	<50 kg	≥50 kg
N	20	13	10	14	25	33
Mean Changes (SD) mm Hg	-6.4 (9.1)	-9.5 (9.7)	-12.4 (9.2)	-7.1 (7.9)	-20.6 (11.4)	-13.2 (11.1)

N = Patients with both baseline (on Day 1) and postdose measurements.
Mean Change = Measurement on Day 15 minus measurement on Day 1.

At the middle- and high-dose levels, patients with body weight <50 kg had a numerically greater reduction in trough SiDBP than heavier patients. In general, increasing doses of lisinopril were associated with greater reductions in trough SiDBP with the exception of the heavier children who received the middle dose.

The stratified simple linear regression model was applied for the evaluation of change in trough SiDBP (Day 15 versus Day 1) with weight group as the stratified intercepts and dose ratio (1:4:32) as the continuous covariate. The slope for lighter patients was -0.42 mm Hg per unit increase in dose; this was steeper than the slope for heavier patients (-0.16 mm Hg per unit increase in dose). The test for interaction between slope and weight was almost significant with p-value = 0.0502. The pediatric patients with weight <50 kg had a slightly greater mean change (-3.84 mm Hg with p-value = 0.049) in trough SiDBP from baseline than those patients with weight ≥50 kg. The model-adjusted standard deviation for change in trough SiDBP from baseline at Day 15 was 10.3 mm Hg. The p-

value for the normality test for the regression model was 0.558, indicating normal distribution of the observations around the regression line.

The most common adverse experience was headache, which occurred similarly across the 3 dose groups.

In Period II where half of the patients continued lisinopril treatment while the other half switched to placebo treatment in a blinded fashion, blood pressure increased after discontinuation of lisinopril indicating that the Period I blood pressure effect was lost when switched to placebo, The overall mean increase was 6.19 mm Hg when switched to a placebo (p=0.001). Blood pressure response following discontinuation of lisinopril in patients who received the low dose (0.02 mg/kg) was similar to that in patients who received placebo.

Analysis of Group Differences Using ANOVA: Lisinopril vs. Placebo in Period II (Per-Protocol Approach)

	Estimate	Standard Error	p-Value
— Group Difference δ (mm Hg)	6.19	1.87	0.001
— Adjusted SD (mm Hg)	8.98		

SD = Standard deviation.

Note: 103 patients were included in the analysis, 12 patients were excluded from the per-protocol analysis in Period II

Mean Changes and Standard Deviations (SD) in Trough SiDBP (mm Hg) in Period II

Treatment Group	N	Mean Change (SD)		Group Difference
Low/Low	15	1.7	(8.2)	-0.2
Low/Placebo	14	1.5	(9.3)	
Middle/Middle	11	-1.2	(7.3)	9.7
Middle/Placebo	12	8.5	(8.2)	
High/High	27	1.4	(9.1)	9.1
High/Placebo	25	10.4	(9.5)	

N = Patients with both baseline (on Day 15) and postdose measurements.
Mean Change = Last Measurement - measurement on Day 15.
Group Difference = Placebo - lisinopril.

These differences of -0.2, 9.7, and 9.1 mm Hg, respectively, for the low, middle and high dose levels indicated a loss of antihypertensive effect of lisinopril when switched to placebo.

Near maximal antihypertensive effect was observed within 2 weeks of treatment; patients who continued treatment during the randomized washout period (Period II) had no additional, clinically important, or statistically significant reduction in blood pressure.

This indicates that 2 weeks of therapy produces steady-state antihypertensive effect at a particular dose of lisinopril in children.

The sponsor recommends a starting dose of 2.5 mg (in patients <50 kg) and 5 mg (in patients ≥50 kg), ~0.07 mg/kg once daily. The low doses of 0.625 mg and 1.25 mg (0.02 mg/kg) once daily were found not to offer consistent antihypertensive efficacy.

PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSIS PERFORMED BY CLINICAL PHARMACOLOGY REVIEWER

The clinical pharmacology reviewer performed population pharmacokinetic (PK) and pharmacodynamic (PD) modeling on submitted lisinopril PK and PD data from 2 studies (114-117 and 115-116) and tested the influence of various covariates on apparent oral clearance and sitting and standing systolic and diastolic blood pressures.

AN OPEN LABEL STUDY TO INVESTIGATE THE PHARMACOKINETICS OF LISINOPRIL IN HYPERTENSIVE CHILDREN AND INFANTS

STUDY – 114-117

OBJECTIVES:

1. To estimate lisinopril CL/F from steady-state concentrations in a dosing interval (24 hours) in pediatric subjects aged 1 month to <16 years.
2. Evaluate the influence of patient covariates, age, body weight and race, and treatment on CL/F of lisinopril.

METHODS:

Data from 52 pediatric patients from the open-label, steady state pharmacokinetic study 114-117 was analyzed using NONMEM version V, level 1.1, Compaq Digital Ver 6.1 fortran compiler. Compartmental modeling of the sparse data at steady-state was attempted. The 1-compartment or 2-compartment pharmacokinetic models yielded poor fits of observed lisinopril concentrations and were unable to fit the long terminal half-life of lisinopril. The 3-compartment model with absorption lag time fit the data well with a typical value for CL/F of 19.7 L/h and a typical value for absorption lag time of 1.1 hour. The effect of body weight was significant on both CL/F and V/F; the typical value of CL/F for a 30 kg person was 9.98 L/h with a power function of 0.819. However, the 3-compartment model failed to provide post hoc estimates for CL/F. Because of the inability to obtain post hoc values of CL/F from compartmental modeling, the sparse pharmacokinetic data was used to estimate individual lisinopril CL/F as the ratio of dose to steady-state AUC (calculated using linear trapezoidal rule).

Because the pharmacokinetics of lisinopril were not modeled and since CL/F was estimated for each subject, intra-individual variability could not be estimated. Therefore, residual variability was set to zero for the fixed effect pharmacokinetic parameter CL/F.

$$\frac{CL}{F}_j = TV\frac{CL}{F} \cdot + (\eta_{j\frac{CL}{F}})$$

where $\eta_{jCL/F}$ denotes the additive difference between the true parameter (CL/F_j) of individual j and the typical value TVCL/F. The inter-individual error model was an additive error model. The method of estimation was first order (FO), which was found to be most suitable for this analysis.

RESULTS:

The estimates of the base model for apparent oral clearance of lisinopril are presented in the table below.

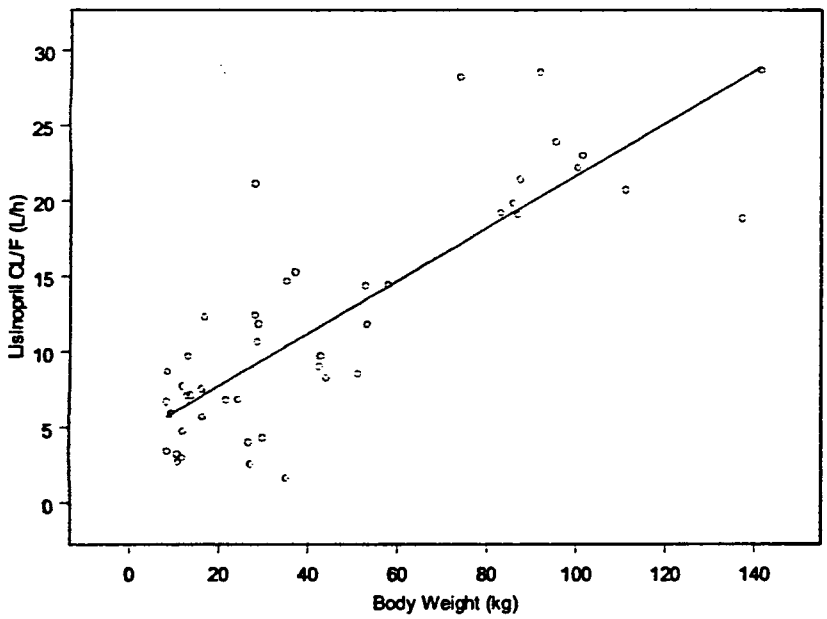
Parameter	Typical Value (SE%)
CL/F (L/h)	12.1 (9.3%)
σ^2 additive	%CV=62.89 (16.9%)

SE%:percent relative standard error of estimate = SE/parameter estimate x 100

The population predicted CL/F of lisinopril was 12.1 L/h with interindividual variability of 63%.

The covariate model building was performed on calculated CL/F. To evaluate the effect of different covariates on CL/F plots of body weight, age, gender and race vs. lisinopril CL/F was constructed. Of the different covariates plotted, only body weight demonstrated a strong correlation (r^2=0.693) with lisinopril CL/F.

Plot of Body Weight vs. Lisinopril CL/F in Children



The results of modeling the effect of the various patient covariates using the FO method is presented in the Table below.

#	MODEL FOR LISINOPRIL CL/F	OBJ FUNC	Δ OBJ FUNC	SIGNIFI-CANCE
1	Base Model (BM)	232.665		
2	Effect of Body Weight on BM (BWBM)	177.608	55.057	**
3	Effect of Age on BWBM	177.246	0.362	NS
4	Effect of Gender on BWBM	174.018	3.59	NS
5	Effect of White Race on BWBM	176.013	1.595	NS
6	Effect of Black Race on BWBM	176.829	0.779	NS
7	Effect of Hispanic Race on BWBM	175.452	2.156	NS
8	Effect of Multiracial Race on BWBM (MRBWBM)	172.841	4.767	NS
9	Effect of Treatment 1on MRBWBM	170.14	2.701	NS
10	Effect of Treatment 2on MRBWBM	171.793	1.048	NS
11	Effect of Treatment 3on MRBWBM	169.992	2.849	NS
12	Effect of Treatment 4on MRBWBM	170.851	1.99	NS

**Significance defined a priori at p=0.001 equivalent to a change in OBJ FUNC of 10.83; NS=not significant

In agreement with the covariate plots, covariate model building indicated that only body weight had a significant effect on lisinopril CL/F. The parameters of the final model are presented in the Table below.

Parameter	Typical Value (SE%)
CL/F (L/h)	$CL/F = \theta_1 * (BW/30)^{\theta 2}$
θ_1 (L/h/30 kg)	9.99 (7.6%)
θ_2	0.642 (11.1%)
Inter-individual Variability (SE%)	
%CV (additive)	41.76 (24.4%)

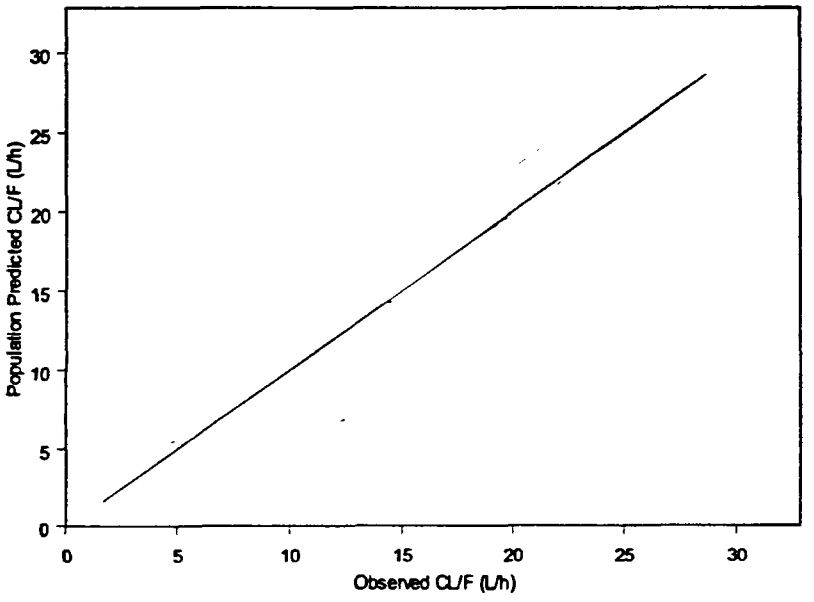
SE%:percent relative standard error of estimate = SE/parameter estimate x 100

The model predicts a typical value of lisinopril CL/F of 9.99 L/kg in a child weighing 30 kg and that CL/F increases with increasing body weight. For a child weighing twice (60 kg) that of the typical body weight (30 kg) in the model, CL/F would increase by 56%. The slope of the CL/F vs. Body weight plot is 0.642 which is in agreement with the scaling factor for body surface area. Accounting for body weight decreased the inter-individual variability of lisinopril CL/F from 63% to 42%.

FINAL PHARMACOKINETIC MODEL:

$$\frac{CL}{F} = 9.99\left(\frac{L}{h}\right) * \left(\frac{Body\ Weight}{30}(kg)\right)^{0.642}$$

Plot of Observed vs. Model Predicted CL/F of Lisinopril



CONCLUSIONS:

The base pharmacokinetic model predicted a typical value for lisinopril CL/F of 12.1 L/h. Covariate model testing indicated that body weight significantly influence lisinopril CL/F. Accounting for body weight, the population pharmacokinetic model predicted a typical value of lisinopril CL/F of 9.99 L/h in a child weighing 30 kg with an exponent of 0.642 which is in agreement with the scaling factor for body surface area. Accounting for body weight decreased the inter-individual variability of lisinopril CL/F from 63% to 42%.

PHARMACODYNAMICS:

A DOUBLE-BLIND, RANDOMIZED, DOSE-RESPONSE STUDY OF LISINOPRIL IN CHILDREN WITH HYPERTENSION

STUDY #: **115/116**

OBJECTIVES:

1. To develop a basic pharmacokinetic/pharmacodynamic (PK/PD) model to correlate lisinopril average concentration at steady state (estimated from CL/F) with sitting and standing manual systolic and diastolic blood pressure.
2. To evaluate the effect of placebo on sitting and standing systolic and diastolic blood pressure with time.
3. To evaluate the effect of covariates (body weight, age, gender and race) on the pharmacodynamic parameters, baseline and slope of concentration-effect relationship, of lisinopril.

METHODS:

Blood samples were not collected from individuals in the efficacy trial Study 115-116. Therefore, the final model for lisinopril CL/F (from Study 114-117) accounting for effect of body weight was used to estimate individual values of lisinopril CL/F for subjects in the efficacy Study 115-116. The estimated individual CL/F values were used to predict individual AUC values from which individual average plasma concentrations (CAVG) within a dosing interval was estimated using the following steady-state equation.

$$CAVG = \frac{AUC_{24}}{\tau}$$

NULL MODEL:
Baseline (BL) sitting and standing systolic and diastolic blood pressures were modeled and the effect was set to baseline to test the null model of zero slope for the concentration-effect relationship.

$$BL_i = TVBL * \exp(\eta_{iBL})$$

$$EFFECT_{ij} = BL_i + \varepsilon_{ij}$$

where, ε_{ij} denotes the residual intra-patient random error with variance σ_1^2.

PLACEBO MODEL:
Placebo effect was estimated for sitting and standing systolic and diastolic blood pressure as a linear function of time in days using the following equation:

$$EFFECT_{ij} = BL_i + PL_i * RDAY + \varepsilon_{ij}$$

Where RDAY is the dosing day relative to start of study (Day 0).

DRUG EFFECT MODEL:

Both Emax and linear models were tested. The Emax model was marginally better (based on objective function value) than the linear model. However, modeling was performed using the linear model because of the following reasons,

1) The EC_{50} of 103 ng/ml for standing systolic blood pressure was toward the higher end of the range of CAVG values (there is only one value (152 ng/ml) above 120 ng/ml).
2) The standard error of the estimates were not estimated for sitting systolic blood pressure.
3) Graphical data exploration indicated the plausibility of a linear model.

Therefore, a population PK/PD model with linear relationship between the lisinopril plasma concentration (CAVG values) and effect was proposed for both systolic and diastolic blood pressure.

$$EFFECT_{ij} = BSL_i + SLP_i * CAVG + \varepsilon_{ij}$$

Where $EFFECT_{ij}$ is j^{th} measurement of systolic or diastolic blood pressure, BSL_i is baseline blood pressure, SLP_i is the slope of the effect vs plasma concentration curve and $CAVG_i$ is the daily average lisinopril plasma concentration in the i^{th} patient.

The final expression for the effect model included the placebo effect:

$$EFFECT_{ij} = BL_i + SLP_i * CAVG_{ij} + PL_i * RDAY + \varepsilon_{ij}$$

Interindividual variability for both slope and placebo effect were modeled using the additive error model.

The first order conditional estimation (FOCE) method of estimation was used for this analysis. Nonlinear mixed effects modeling was performed using NONMEM (ver. 5, level 1.1). S-plus was used for graphical display.

The relationship between covariates - body weight, age, gender and race, and individual PD parameters, baseline and slope, were tested. Statistical significance of each covariate-parameter relationship was tested individually in a stepwise addition method in NONMEM (each in a separate run). When comparing alternative hierarchical models, differences in the NONMEM objective function are approximately chi-square distributed with n (number of parameters) degrees of freedom. The alternative models were compared based on the log likelihood test. The level of sensitivity was set a priori to

p=0.05 (Δ Objective Function of 3.84). The final model was refined by the test of possible covariance between the random effects (use of OMEGA BLOCK function), associated with baseline and slope.

RESULTS AND DISCUSSION

Modeling of sitting and standing systolic and diastolic blood pressure indicated a significant placebo effect on blood pressure with time. Placebo effect was most pronounced for sitting systolic and diastolic blood pressure with a slope of -0.202 and -0.209 mmHg/day, respectively.

Trough Sitting Systolic Blood Pressure (SiSBP):

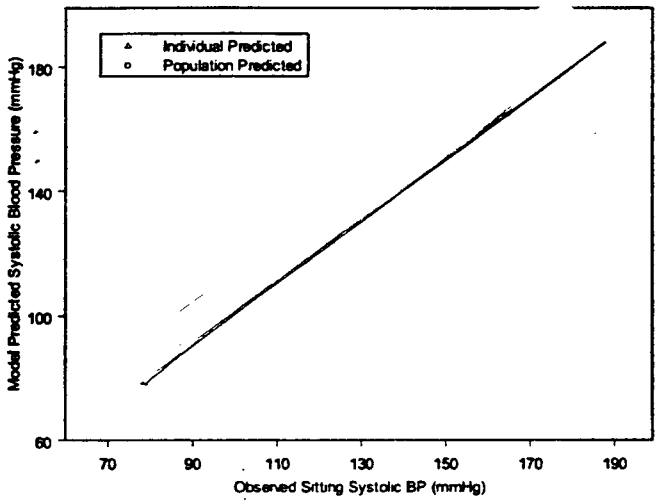
Modeling of lisinopril average concentration versus sitting systolic blood pressure indicated that lisinopril had a significant effect on blood pressure. Increasing concentrations of lisinopril produced larger decreases in SiSBP. Population pharmacodynamic modeling using the linear pharmacodynamic model predicted the decrease in SiSBP with increasing lisinopril concentrations adequately. The typical value of SiSBP was 127 mmHg with interindividual variability of 9%. The typical value for slope of the concentration-effect relationship was –0.134 mmHg/(ng/ml) (interindividual variability 64%). A significant placebo effect was observed with time with a slope of –0.197 mmHg/Rday (interindividual variability 78%). The residual variability was 7 mmHg.

BASE SITTING SYSTOLIC BLOOD PRESSURE MODEL

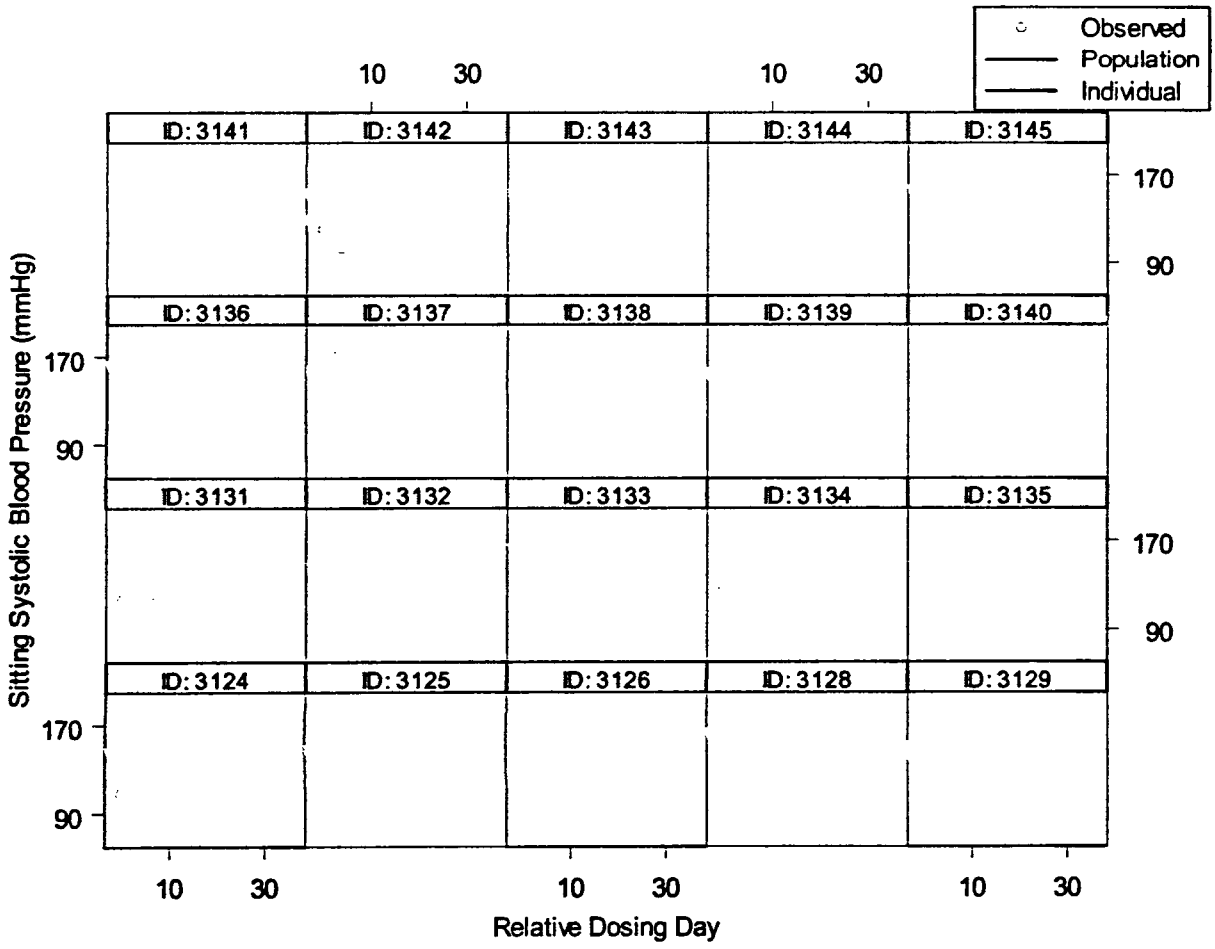
Parameter	Typical Value (SE%)
Baseline (mmHg)	127 (0.9%)
Slope of Drug Effect (mmHg/(ng/ml))	-0.134 (11.7%)
Placebo Slope (mmHg/RDAY)	-0.197 (15.3%)
Residual Variability	
σ^2 additive	6.99 (12.5%)

The results of the covariate modeling indicated that body eight had a significant effect on both baseline SiSBP and slope of the concentration-effect relationship. Baseline SiSBP increased with body weight with a slope of 0.0584 mmHg/kg. The typical value for slope of the concentration-effect relationship for a 30 kg individual was –0.181 mmHg which would decrease to –0.144 mmHg for a 40 kg individual. The slope of the body weight vs. slope of concentration-effect relationship was –0.799 mmHg/kg.

Plot of Observed vs. Model Predicted Sitting Systolic Blood Pressure

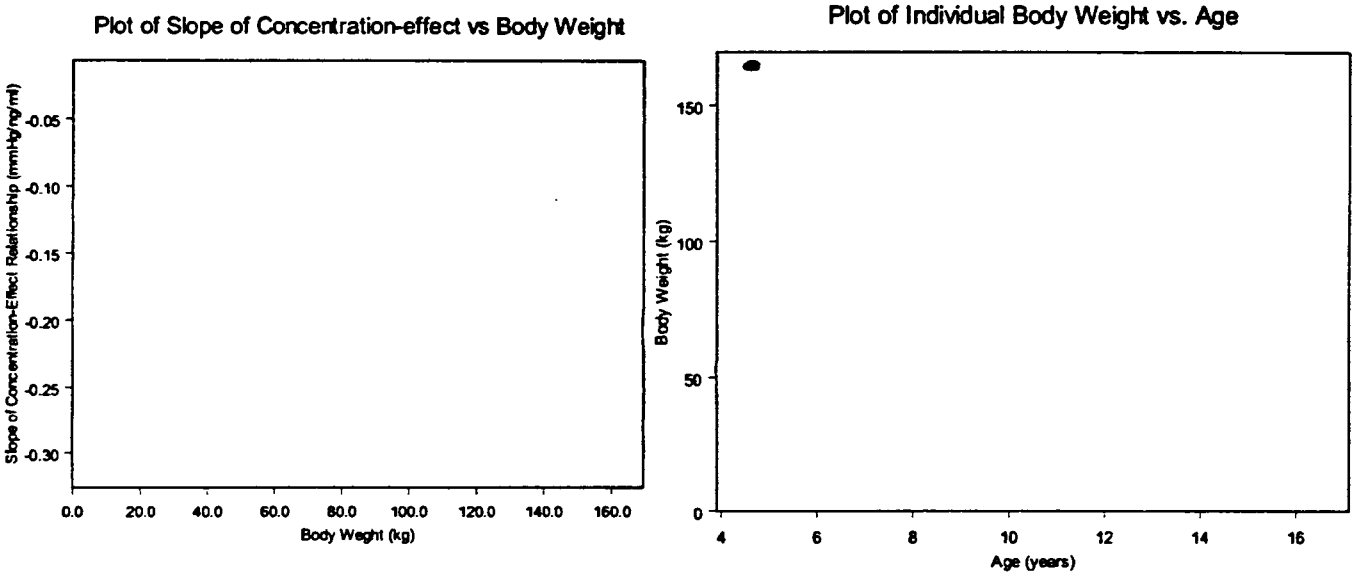


Representative blood pressure plots of individuals with population prediction and individual prediction are presented in the following figure.



The reason for the decreasing slope of the concentration-effect relationship indicates decreased sensitivity for blood pressure with increasing body weight. As seen in the figure below body weight and age are highly correlated, therefore, lisinopril might be less effective in lowering SiSBP in older children compared to younger children. The reason for the decreased sensitivity with increasing body weight is not known.

The following figure illustrates decreasing slope of concentration-SiSBP relationship with body weight.



The results of the individual covariate tests on baseline SiSBP and slope of concentration-effect relationship is presented in the following Table.

#	MODEL FOR TROUGH SITTING SBP	OBJ FUNC	Δ OBJ FUNC	SIG
1	Null Model	4648.877		
2	Null Model with Effect of Body Weight (BW)	4620.609	28.268	**
3	Effect of Placebo on Null Model	4518.303	102.306	**
4	EMAX Model	4355.031	163.272	**
5	Linear Model (LM)	4361.097	157.206	**
6	LM with effect of *BW on baseline* (BL)	4335.854	25.243	**
7	LM with effect of *BW on BL and Slope* (SP)	4321.702	14.152	**
8	LM with effect of BW on BL and SP and *Gender on BL*	4321.296	0.406	NS
9	LM with effect of BW on BL and SP and *Gender on SP*	4321.433	0.269	NS
10	LM with effect of BW on BL and SP and *Age on BL*	4321.173	0.529	NS
11	LM with effect of BW on BL and SP and *Age on SP*	4319.786	1.916	NS
12	LM with effect of BW on BL and SP and *All Races on BL*	4305.927	15.775	**
13	LM with effect of BW on BL and SP and *All Races on SP*	4316.757	4.945	NS
14	LM with effect of BW on BL and SP and *White Race on BL*	4310.577	11.125	**
15	LM with effect of BW on BL and SP and *White Race on BL and SP*	4310.427	0.15	NS
16	LM with effect of BW on BL and SP and *Black Race on BL*	4321.269	0.433	NS

17	LM with effect of BW on BL and SP and *Black Race on SP*	4318.136	3.566	NS
18	LM with effect of BW on BL and SP and *Hispanic Race on BL*	4306.114	15.588	**
19	LM with effect of BW on BL and SP and *Hispanic Race on BL and SP*	4304.696	1.418	NS
20	LM with effect of BW on BL and SP and *White and Hispanic Race on BL*	4305.933	15.769	**
21	Model 20 with block covariance	4303.436	2.497	NS

**Significance defined a priori at 0.05 (equivalent to a change in OBJ FUNC of 3.84); NS=not significant

Age and gender were not found to influence either baseline or slope of the effect relationship.

The final model incorporating effect of covariates-White and Hispanic race on baseline SiSBP and body weight on baseline and slope of concentration-effect relationship and the final parameter values are presented in the following Table.

Final Model for Sitting Systolic Blood Pressure

$RACE\_BL = \theta_1 * (1 + \theta_6 * WHITE + \theta_7 * HISPANIC)$
$TBL = RACE\_BL * (BW/30\ Kg)^{\theta_4}$
$TSLP = \theta_2 * (BW/30\ Kg)^{\theta_5}$
$TPL = \theta_3$

BASE LINE =TBL*EXP(ETA_BL)
SLOPE =TSLP + ETA_SP
PLACEBO =TPL + ETA_PL

EFFECT = BASE LINE + SLOPE*CAVG + PLACEBO*RDAY

Model	Typical Value (SE%)	Interindividual %CV (SE%)
Baseline SiSBP (mmHg)		
θ_1 (Blacks and Hispanics)	126 (2.3%)	7.43 (17%)
θ_4 (Effect of Body Weight on Baseline)	0.0584 (31.3%)	
θ_6 (Effect of White Race on Baseline SiSBP)	0.0104 (195.2%)	
θ_7 (Effect of Hispanic Race on Baseline SiSBP)	-0.0538 (34.2%)	
Slope of Concentration-effect relationship (mmHg/(ng/ml))		
θ_2 (Typical value in all races)	-0.181 (11.2%)	33.24 (45.3%)
θ_5 (Effect of Body Weight on Slope)	-0.799 (24.8%)	
Slope of Placebo-effect relationship (mmHg/(ng/ml))		
θ_3 (Typical value in all races)	-0.202 (14.9%)	77.96 (80.6%)
Residual Error		
σ standard deviation	7 mm Hg (12.6%)	

$$SiSBP = \left[126\ mmHg * (1 + 0.0104\ (White) - 0.0538\ (Hispanic)) * \left(\frac{Body\ Weight}{30}(kg)\right)^{0.0584}\right] + \left[-0.181 * Cavg * \left(\frac{Body\ Weight}{30}(kg)\right)^{-0.799}\right] - 0.202\ (RDAY)$$

Both White and Hispanic races exhibited increased SiSBP baseline by 1% and 5% respectively. However, the differences in baseline SiSBP in White and Hispanic races may not be clinically meaningful. They were included in the final model for purposes of modeling completeness.

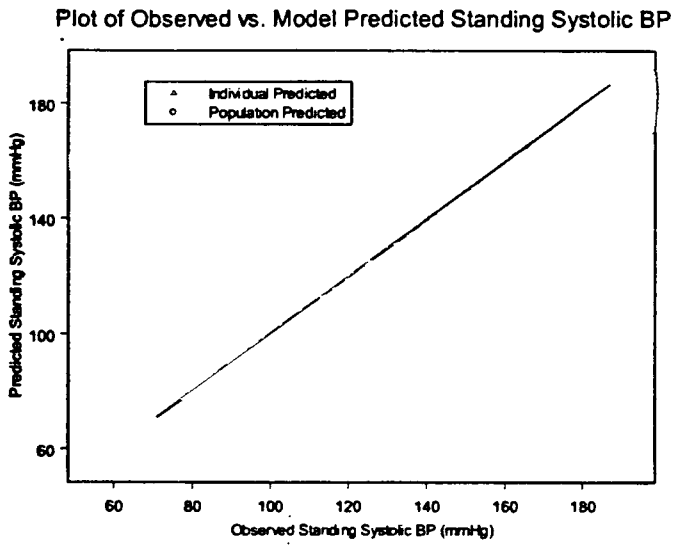
TROUGH STANDING SYSTOLIC BLOOD PRESSURE (StSBP):

Population pharmacodynamic modeling of lisinopril average concentration versus standing systolic blood pressure indicated that lisinopril had a significant effect on blood pressure. The results of modeling of StSBP were similar to SiSBP with the linear pharmacodynamic model predicting a decrease in StSBP with increasing lisinopril concentrations adequately. The typical value of StSBP was 126 mmHg with interindividual variability of 10%. The typical value for slope of the concentration-effect relationship was –0.168 mmHg/(ng/ml) (interindividual variability 63%) with a significant placebo effect with a slope of –0.164 mmHg/RDAY (interindividual variability 119%). The residual variability was 7 mmHg.

BASE STANDING SYSTOLIC BLOOD PRESSURE MODEL

Parameter	Typical Value (SE%)
Baseline (mmHg)	126 (1.0%)
Slope of Drug Effect (mmHg/(ng/ml))	-0.168 (11.1%)
Placebo Slope (mmHg/RDAY)	-0.164 (19.9%)
Residual Variability	
σ^2 additive	7.00 (11.6%)

The results of the covariate modeling of StSBP were similar to SiSBP. Body weight had a significant effect on both baseline StSBP and slope of the concentration-effect relationship. Baseline StSBP increased with body weight with a slope of 0.0713 mmHg/kg. The typical value for slope of the concentration-effect relationship for a 30 kg individual was –0.205 mmHg which would decrease to –0.177 mmHg for a 40 kg individual. The slope of the body weight vs. slope of concentration-effect relationship was –0.501 mmHg/kg.



The results of the individual covariate tests on baseline StSBP and slope of concentration-effect relationship is presented in the following Table.

#	MODEL FOR TROUGH STANDING SBP	OBJ FUNC	Δ OBJ FUNC	SIG
1	Null Model	4612.924		
2	Null Model with Effect of Body Weight (BW)	4582.883	30.041	**
3	Effect of Placebo on Null Model	4491.899	90.984	**
4	EMAX Model	4285.355	297.528	**
5	Linear Model (LM)	4294.198	288.685	**
6	LM with effect of *BW on baseline* (BL)	4266.143	28.055	**
7	LM with effect of *BW on BL and Slope* (SP)	4261.305	4.838	**
8	LM with effect of BW on BL and SP and *Gender on BL*	4260.606	0.699	NS
9	LM with effect of BW on BL and SP and *Gender on SP*	4260.909	0.396	NS
10	LM with effect of BW on BL and SP and *Age on BL*	4260.933	0.372	NS
11	LM with effect of BW on BL and SP and *Age on SP*	4257.592	3.713	NS
12	LM with effect of BW on BL and SP and *All Races on BL*	4243.962	17.343	**
13	LM with effect of BW on BL and SP and *All Races on SP*	4258.791	2.514	NS
14	LM with effect of BW on BL and SP and *White Race on BL*	4250.747	10.558	**
15	LM with effect of BW on BL and SP and *White Race on BL and SP*	4250.747	0	NS
16	LM with effect of BW on BL and SP and *Black Race on BL*	4260.878	0.427	NS
17	LM with effect of BW on BL and SP and *Black Race on SP*	4259.323	1.982	NS
18	LM with effect of BW on BL and SP and *Hispanic Race on BL*	4244.992	16.313	**
19	LM with effect of BW on BL and SP and *Hispanic Race on BL and SP*	4244.629	0.363	NS
20	LM with effect of BW on BL and SP and *White and Hispanic Race on BL*	4244.958	16.347	**
21	Model #20 with block covariance	4242.781	2.17	NS

**Significance defined a priori at 0.05 (equivalent to a change in OBJ FUNC of 3.84 per parameter); NS=not significant

Age and gender were not found to influence either baseline StSBP or slope of the concentration-effect relationship.

The final model incorporating effect of covariates-White and Hispanic race on baseline StSBP and body weight on baseline StSBP and slope of concentration-effect relationship and the final parameter values are presented in the following Table.

Standing Systolic Blood Pressure Model

RACE_BL = θ_1*(1 + θ_6 *WHITE + θ_7 * HISPANIC)
TBL = RACE_BL*(BW/30 Kg)$^{\theta_4}$
TSLP = θ_2*(BW/30 Kg)$^{\theta_5}$
TPL = θ_3

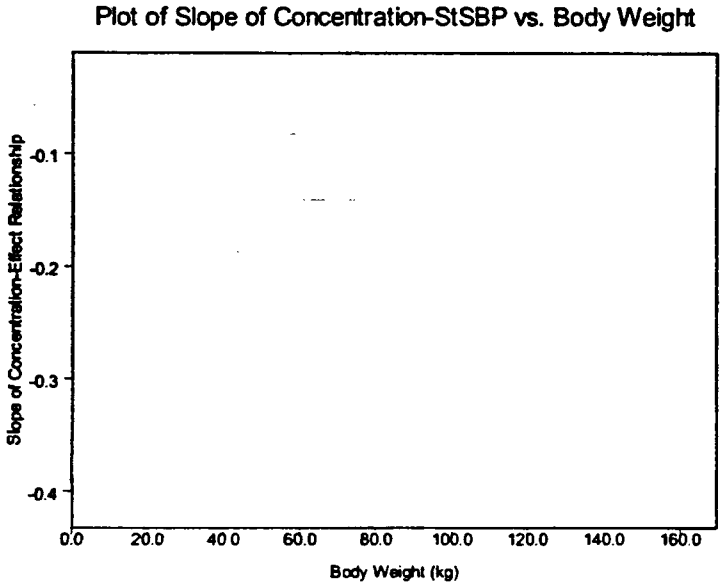
BASE LINE = TBL*EXP(ETA_BL)
SLOPE = TSLP + ETA_SP
PLACEBO = TPL + ETA_PL

EFFECT = BASE LINE + SLOPE*CAVG + PLACEBO*RDAY

Model	Typical Value (SE%)	Interindividual %CV (SE%)
Baseline StSBP (mmHg)		
θ_1 (Blacks and Hispanics)	125 (2.5%)	7.75 (15.9%)
θ_4 (Effect of Body Weight on Baseline)	0.0713 (26.9%)	
θ_6 (Effect of White Race on Baseline StSBP)	0.00473 (479.9%)	
θ_7 (Effect of Hispanic Race on Baseline StSBP)	-0.0625 (33.4%)	
Slope of Concentration-effect relationship (mmHg/(ng/ml))		
θ_2 (Typical value in all races)	-0.205 (11.9%)	44.73 (41.1%)
θ_5 (Effect of Body Weight on Slope)	-0.501 (43.5%)	
Slope of Placebo-effect relationship (mmHg/(ng/ml))		
θ_3 (Typical value in all races)	-0.17 (19.1%)	114.06 (40.4%)
Residual Error		
σ standard deviation	7 mm Hg (11.7%)	

$$StSBP = \left[125\ mmHg * (1 + 0.00473\ (White) - 0.0625\ (Hispanic)) * \left(\frac{Body\ Weight}{30}(kg)\right)^{0.0713}\right] + \left[-0.205 * Cavg * \left(\frac{Body\ Weight}{30}(kg)\right)^{-0.501}\right] - 0.170\ (RDAY)$$

The following Figure illustrates the change in slope of concentration-StSBP relationship with body weight. (Note: The Y-axis has negative values.)



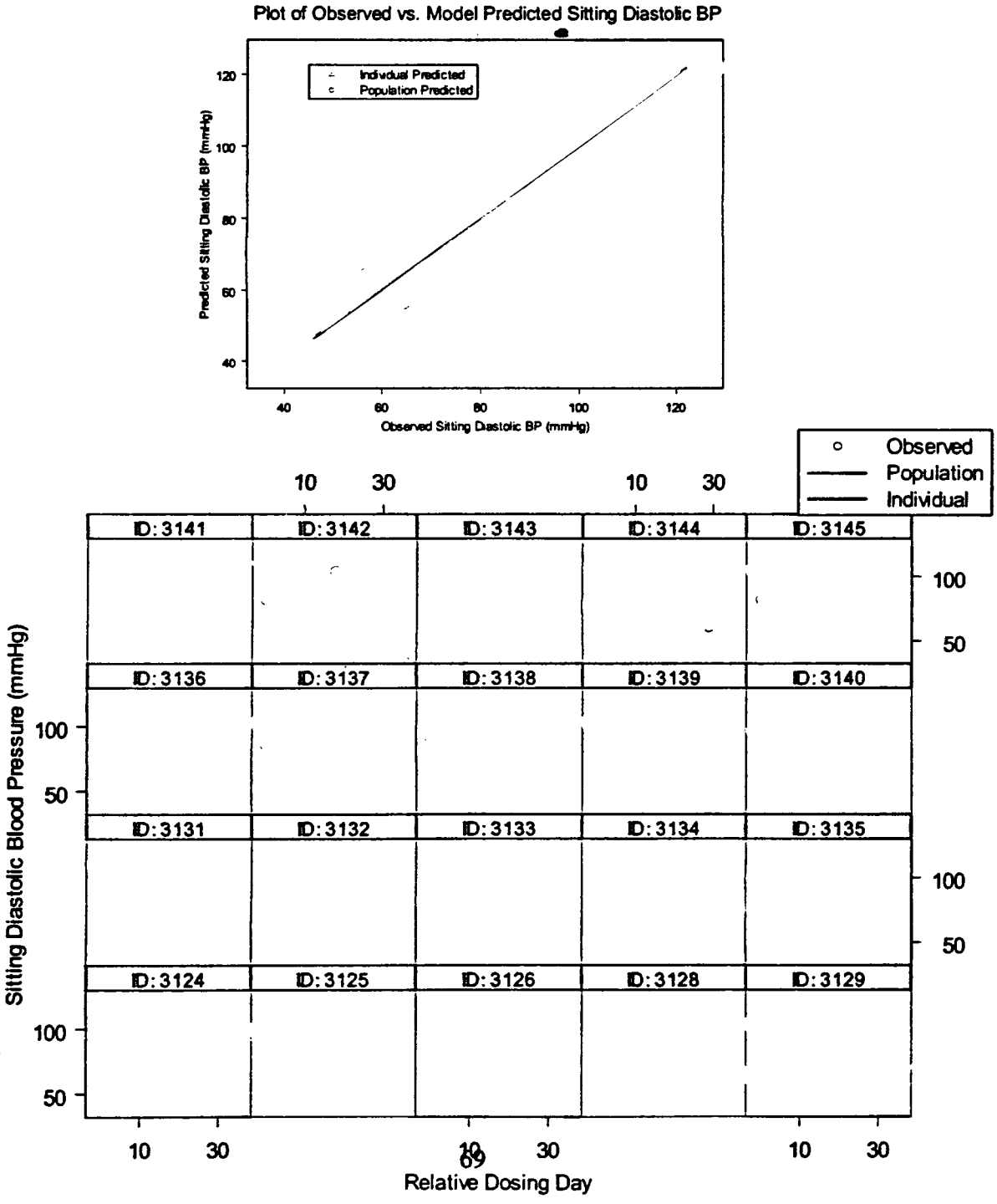
Trough Sitting Diastolic Blood Pressure (SiDBP):

Modeling of lisinopril average concentration versus sitting diastolic blood pressure indicated that lisinopril had a significant effect on blood pressure. Population pharmacodynamic modeling using the linear pharmacodynamic model predicted the decrease in SiDBP with increasing lisinopril concentrations adequately. The typical value of SiDBP was 87.5 mmHg with interindividual variability of 9%. The typical value for slope of the concentration-effect relationship was –0.147 mmHg/(ng/ml) (interindividual variability 55%) with a significant placebo effect with a slope of –0.204 mmHg/Rday (interindividual variability 117%). The residual variability was 6 mmHg.

BASE SITTING DIASTOLIC BLOOD PRESSURE MODEL

Parameter	Typical Value (SE%)
Baseline (mmHg)	87.5 (0.9%)
Slope of Drug Effect (mmHg/(ng/ml))	-0.147 (11.2%)
Placebo Slope (mmHg/RDAY)	-0.204 (16.5%)
Residual Variability	
σ^2 additive	6.04 (8.7%)

Consistent with SiSBP and StSBP, body weight had a significant effect on both SiDBP baseline and slope of the concentration-effect relationship. Baseline SiDBP increased with body weight with a slope of 0.0396 mmHg/kg. The typical value for slope of the concentration-effect relationship for a 30 kg individual was –0.182 mmHg which would decrease to –0.156 mmHg for a 40 kg individual. The slope of the body weight vs. slope of concentration-effect relationship was –0.538 mmHg/kg. Prediction of SiDBP at higher values of SiDBP (>100 mmHg) were not as good as SiDBP prediction below 100 mmHg. Above 100 mmHg SiDBP the population pharmacodynamic model under-predicted SiDBP compared to observed SiDBP values.



The results of the individual covariate tests on baseline SiDBP and slope of concentration-effect relationship is presented in the following Table.

#	MODEL FOR TROUGH SITTING DBP	OBJ FUNC	Δ OBJ FUNC	SIG
1	Null Model	4512.05		
2	Null Model with Effect of Body Weight (BW)	4503.603	8.447	**
3	Effect of Placebo on Null Model	4323.586	180.017	**
4	EMAX Model	4106.98	216.606	**
5	Linear Model (LM)	4129.777	193.809	**
6	LM with effect of *BW on baseline* (BL)	4123.514	6.263	**
7	LM with effect of *BW on BL and Slope* (SP)	4115.929	7.585	**
8	LM with effect of BW on BL and SP and *Gender on BL*	4115.829	0.1	NS
9	LM with effect of BW on BL and SP and *Gender on SP*	4115.435	0.494	NS
10	LM with effect of BW on BL and SP and *Age on BL*	4114.872	1.057	NS
11	LM with effect of BW on BL and SP and *Age on SP*	4113.641	2.288	NS
12	LM with effect of BW on BL and SP and *All Races on BL*	4113.158	2.771	NS
13	LM with effect of BW on BL and SP and *All Races on SP*	4114.977	0.952	NS
14	Final model #7 with Block Covariance	4113.351	2.578	NS

**Significance defined a priori at 0.05 (equivalent to a change in OBJ FUNC of 3.84); NS=not significant

Age, gender and race were not found to influence either baseline SiDBP or slope of the concentration-effect relationship.

The final model incorporating effect of covariate-body weight on SiDBP baseline and slope of concentration-effect relationship and the final parameter values are presented in the following Table.

Sitting Diastolic Blood Pressure Model

$TBL = \theta_1 * (BW/30\ Kg)^{\theta 4}$
$TSLP = \theta_2 * (BW/30\ Kg)^{\theta 5}$
$TPL = \theta_3$

BASE LINE = TBL*EXP(ETA_BL)
SLOPE = TSLP + ETA_SP
PLACEBO = TPL + ETA_PL

EFFECT = BASE LINE + SLOPE*CAVG + PLACEBO*RDAY

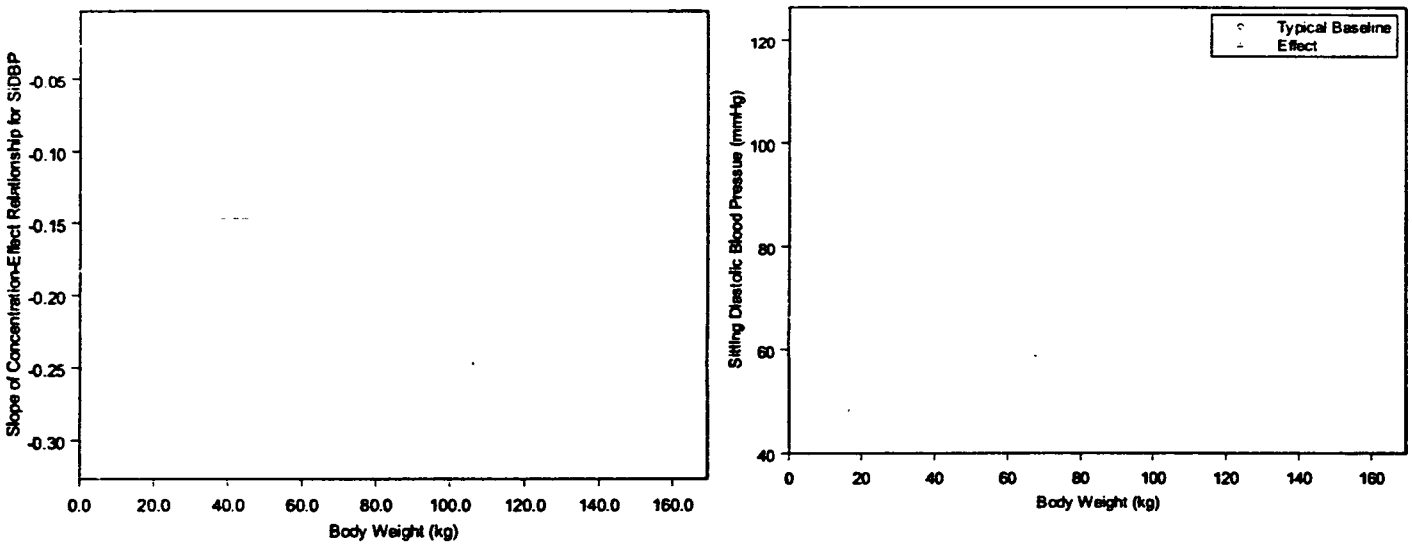
Parameter	Typical Value (SE%)	Interindividual %CV (SE%)
Baseline SiDBP (mmHg)		
θ_1 (All races)	85.7 (1.7%)	8.61 (17.9%)
θ_4 (Effect of Body Weight on Baseline)	0.0396 (54.5%)	
Slope of Concentration-effect relationship		

(mmHg/(ng/ml))		
θ_2 (Typical value in all races)	-0.182 (10.8%)	35.65 (59.1%)
θ_5 (Effect of Body Weight on Slope)	-0.538 (36.4%)	
Slope of Placebo-effect relationship (mmHg/(ng/ml))		
θ_3 (Typical value in all races)	-0.209 (15.9%)	111.49 (39.6%)
Residual Error		
σ standard deviation	6 mm Hg (8.9%)	

$$SiDBP = \left[85.7\ mmHg * \left(\frac{Body\ Weight}{30}(kg)\right)^{0.0396}\right] + \left[-0.182 * Cavg * \left(\frac{Body\ Weight}{30}(kg)\right)^{-0.538}\right] - 0.209\ (RDAY)$$

The following Figure illustrates the change in slope of concentration-SiDBP relationship with body weight.

Plot of Slope of Concentration-SiDBP Relationship vs. Body Weight



Trough Standing Diastolic Blood Pressure (StDBP):

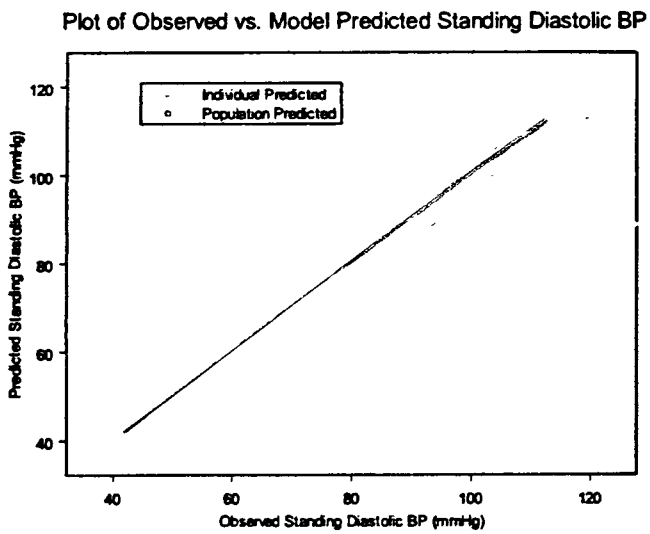
The pharmacokinetic-pharmacodynamic modeling of lisinopril average concentration versus standing diastolic blood pressure indicated that lisinopril had a significant effect on blood pressure. A linear pharmacodynamic model predicted the decrease in StDBP with increasing lisinopril concentrations adequately. The typical value of StDBP was 88.2 mmHg with interindividual variability of 10%. The typical value for slope of the concentration-effect relationship was –0.147 mmHg/(ng/ml) (interindividual variability

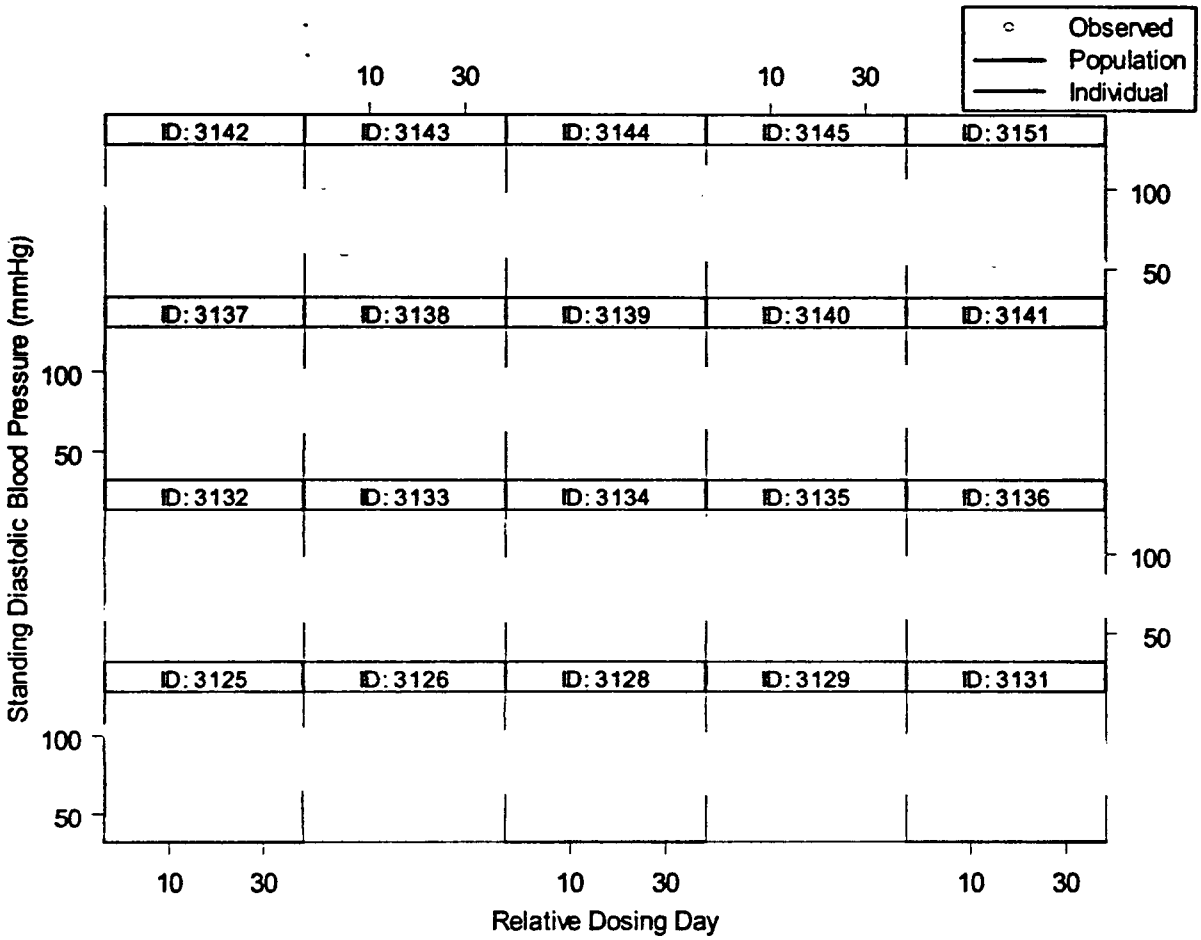
69%) with a significant placebo effect with a slope of –0.164 mmHg/Rday (interindividual variability 114%). The residual variability was 6 mmHg.

BASE STANDING DIASTOLIC BLOOD PRESSURE MODEL

Parameter	Typical Value (SE%)
Baseline (mmHg)	88.2 (1.0%)
Slope of Drug Effect (mmHg/(ng/ml))	-0.147 (12.7%)
Placebo Slope (mmHg/RDAY)	-0.164 (17.5%)
Residual Variability	
σ^2 additive	5.92 (8.8%)

Covariate modeling indicated body weight had a significant effect on both StDBP baseline and slope of the concentration-effect relationship. Baseline StDBP increased with body weight with a slope of 0.048 mmHg/kg. Both body weight and age influenced the slope of the concentration-effect in the covariate analysis. The typical value for slope of the concentration-effect relationship was –0.211 mmHg for an individual who is 10 years old weighing 30 kg. For a 15 year old individual who weighs 40 kg the slope of the concentration-effect relationship would decrease to –0.101 mmHg for a 40 kg individual. The slope of the body weight vs. slope of concentration-effect relationship was –1.18 mmHg/kg and the slope of age vs. slope of concentration-effect relationship was –0.979 mmHg/year. Prediction of StDBP at higher values of StDBP (>100 mmHg) were not as good as StDBP prediction below 100 mmHg. Above 100 mmHg StDBP the population pharmacodynamic model under-predicted StDBP compared to observed StDBP values.





The results of the individual covariate tests on baseline StDBP and slope of concentration-StDBP relationship is presented in the following Table.

#	MODEL FOR TROUGH STANDING DBP	OBJ FUNC	Δ OBJ FUNC	SIG
1	Null Model	4370.151		
2	Null Model with Effect of Body Weight (BW)	4359.869	10.282	**
3	Effect of Placebo on Null Model	4211.901	147.968	**
4	EMAX Model	3996.461	215.44	**
5	Linear Model (LM)	4012.656	199.245	**
6	LM with effect of *BW on baseline* (BL)	4005.24	7.416	**
7	LM with effect of *BW on BL and Slope* (SP)	3998.672	6.568	**
8	LM with effect of BW on BL and SP and *Gender on BL*	3998.663	0.009	NS
9	LM with effect of BW on BL and SP and *Gender on SP*	3998.669	0.003	NS
10	LM with effect of BW on BL and SP and *Age on BL*	3995.613	3.059	NS
11	LM with effect of BW on BL and SP and *Age on SP*	3994.265	4.407	**
12	LM with effect of BW on BL and SP and *All Races on BL*	3995.765	2.907	NS
13	LM with effect of BW on BL and SP and *All Races on SP*	3993.616	5.056	NS
14	Final Model #11 with Block Covariance	3991.605	2.660	NS

**Significance defined a priori at 0.05 (equivalent to a change in OBJ FUNC of 3.84); NS=not significant

Age, gender and race were not found to influence baseline SiDBP. Gender and race did not influence slope of concentration-StDBP relationship.

The final model incorporating effect of covariate-body weight on SiDBP baseline and age and body weight on slope of concentration-StDBP relationship and the final parameter values are presented in the following Table.

Standing Diastolic Blood Pressure Model

$TBL = \theta_1 * (BW/30\ Kg)^{\theta_4}$
$WSLP = \theta_2 * (BW/30\ Kg)^{\theta_5}$
$TSLP = WSLP * (AGE/10\ years)^{\theta_6}$
$TPL = \theta_3$

BASE LINE = TBL*EXP(ETA_BL)
SLOPE = TSLP + ETA_SP
PLACEBO = TPL + ETA_PL

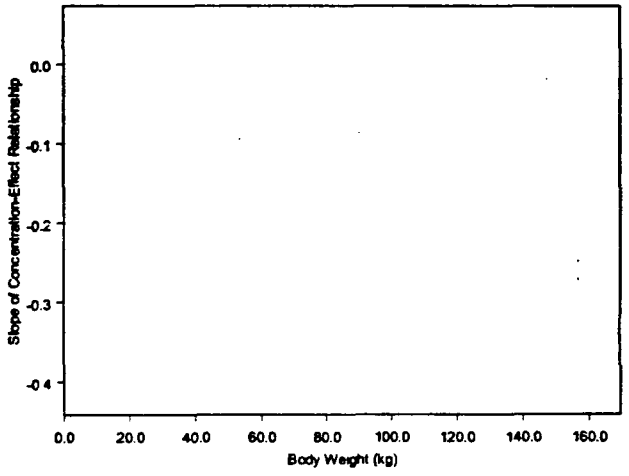
EFFECT = BASE LINE + SLOPE*CAVG + PLACEBO*RDAY

Parameter	Typical Value (SE%)	Interindividual %CV (SE%)
Baseline StDBP (mmHg)		
θ_1 (All races)	86 (1.7%)	9.42 (16.9%)
θ_4 (Effect of Body Weight on Baseline)	0.048 (46.3%)	
Slope of Concentration-effect relationship (mmHg/(ng/ml))		
θ_2 (Typical value in all races)	-0.211 (12.0%)	37.80 (57.7%)
θ_5 (Effect of Body Weight on Slope)	-1.18 (29.2%)	
θ_6 (Effect of Age on Slope)	-0.979 (39.1%)	
Slope of Placebo-effect relationship (mmHg/(ng/ml))		
θ_3 (Typical value in all races)	-0.17 (16.8%)	107.3 (37.5%)
Residual Error		
σ standard deviation	6 mm Hg (8.8%)	

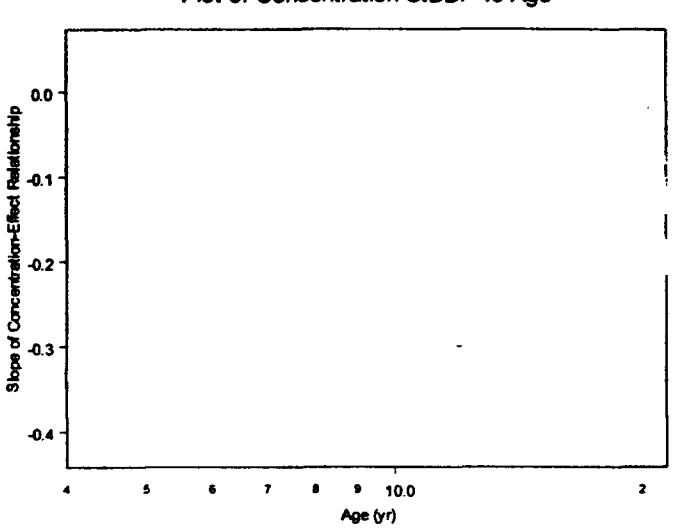
$$StDBP = \left[86\ mmHg * \left(\frac{Body\ Weight}{30}(kg)\right)^{0.048}\right] + \left[-0.211 * Cavg * \left(\frac{Age}{10}(yr)\right)^{-0.979} * \left(\frac{Body\ Weight}{30}(kg)\right)^{-1.18}\right] - 0.170\ (RDAY)$$

The following Figures illustrate the trend between **A.** Body Weight and slope of concentration-effect relationship and **B.** Age vs. slope of concentration-effect relationship.

A.



B.

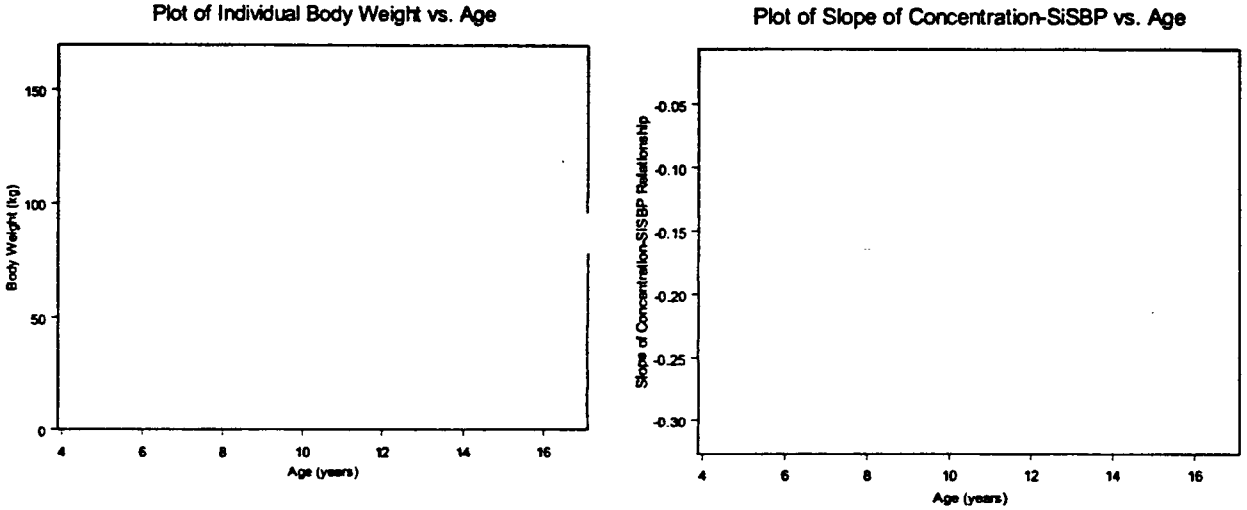


CONCLUSIONS:

1. Lisinopril decreases both sitting and standing diastolic blood pressure in children between 6 years and 16 years.
2. Increasing concentrations of lisinopril produce larger decreases in blood pressure.
3. There was a significant placebo effect for both sitting and standing diastolic blood pressure. The placebo effect was greatest for sitting systolic and diastolic blood pressure, -0.197 mmHg and –0.204 mmHg, respectively. The slope of placebo-effect with time was –0.164 mmHg for both standing systolic and diastolic blood pressure.
4. The linear pharmacodynamic model best described the pharmacokinetic/pharmacodynamic model. Typical values of baseline SiSBP, StSBP, SiDBP and StDBP were, 127 mmHg, 126 mmHg, 87.5 mmHg and 88.2 mmHg, respectively. The typical value of slope of concentration-effect relationship for SiSBP, StSBP, SiDBP and StDBP were -0.134 mmHg, -0.168 mmHg, -0.147 mmHg and -0.147 mmHg, respectively.
5. The results of the covariate modeling indicated a significant influence of body weight on both baseline and slope of concentration- SiSBP, StSBP, SiDBP and StDBP. Increasing body weight decreased the slope of the concentration-effect relationship.
6. For a 30 kg child, the slope of lisinopril concentration-effect relationship for SiSBP, StSBP, SiDBP and StDBP were, -0.181 mmHg, -0.205 mmHg, -0.182 mmHg and –0.211 mmHg, respectively. For a child weighing 40 kg, the slope of the concentration-effect relationship would decrease to –0.144 mmHg, -0.177

mmHg, -0.156 mmHg and –0.101 mmHg for SiSBP, StSBP, SiDBP and StDBP, respectively.

7. The decreasing slope of the concentration-effect relationship indicates decreased sensitivity for blood pressure. The reason for the decreased sensitivity to blood pressure lowering by lisinopril in subjects with increased body weight is not known. It can be hypothesized that because age and body weight are highly correlated, a given dose of lisinopril might be less effective in lowering SiSBP in older children compared to younger children. This lowered sensitivity might be a result of physiology peculiar to hypertensive children.



The difference in the effect – concentration curve slopes for adults and children could be significantly different and clinically relevant as evidenced by the decreasing slope with increasing body weight.

The decreased sensitivity in higher body weights is also seen in the mean SiSBP data stratified by body weight presented by the sponsor. (Note: this is dose response and therefore does not account for lower concentrations with higher body weights since this is fixed dose).

Mean Changes in Trough SiDBP (mm Hg) and Standard Deviation (SD) in Period I by Weight Stratum (Intent-to-Treat Analysis)

	Low (0.625/1.25 mg)		Middle (2.5/5 mg)		High (20/40 mg)	
	<50 kg	≥50 kg	<50 kg	≥50 kg	<50 kg	≥50 kg
N	20	13	10	14	25	33
Mean Changes (SD) mm Hg	-6.4 (9.1)	-9.5 (9.7)	-12.4 (9.2)	-7.1 (7.9)	-20.6 (11.4)	-13.2 (11.1)

N = Patients with both baseline (on Day 1) and postdose measurements.
Mean Change = Measurement on Day 15 minus measurement on Day 1.

Contrary to the substantially larger decrease in SiSBP in the <50 kg group for the low, medium and high doses of –6.4 mmHg, -12.4 mmHg and –20.6 mmHg, respectively, the

decrease in the >50 kg group was –9.5 mmHg, -7.1 mmHg and –13.2 mmHg, respectively. The effect of the highest dose in the >50 kg group is similar to the response to the middle dose in the <50 group.

8. The population model has considerable unexplained variability especially in slope of placebo effect-time relationship.

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/s/

Jogarao Gobburu
6/19/02 10:21:00 AM
UNKNOWN

Patrick Marroum
6/19/02 10:27:15 AM
BIOPHARMACEUTICS

1. NDA 19-558/S-043 - Prinivil: letter date 24-Sep-2001, Doc Type SE5, Seq No 043, Mod Type PM: An electronic version of the proposed labeling showing revisions (annotations) to the last approved labeling (Merck label reference #7825246, issued February 2001 and was approved by the division on August 7, 2001) was reviewed. No revisions were made by the sponsor to the nonclinical pharmacology/toxicology section of the label.
2. NDA 19-777/S-044 - Zestril: letter date 2-Nov-2001, Doc Type SE5, Seq No 044, Mod Type PM: An electronic version of the proposed labeling showing revisions (annotations) to the last approved labeling (on February 7, 2001) was reviewed. No revisions were made by the sponsor to the nonclinical pharmacology/toxicology section of the label.

G. Jagadeesh, Ph.D.
Pharmacology/Toxicology Reviewer
March 14, 2002

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/s/

Gowra Jagadeesh
3/14/02 02:40:34 PM
PHARMACOLOGIST

Charles Resnick
3/14/02 03:38:36 PM
PHARMACOLOGIST
Labeling revisions to Prinivil and Zestril Labeling. NAI.