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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 19-787/S30

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA:	**19,787 SE5 030**
Submission Dates:	September 14, 2001, January 25, and February 5, 2002
Drug Name:	Norvasc (amlodipine besylate) tablets
Applicant:	Pfizer Pharmaceutical Group
Submission:	Supplemental NDA, pediatric exclusivity
Reviewer:	Elena V. Mishina, Ph.D.

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EXECUTIVE SUMMARY

Background:

Pfizer Pharmaceutical is seeking approval of Norvasc (amlodipine besylate) in pediatric population and is requesting an additional six months of marketing exclusivity based on submission of the information in the supplemental NDA 19,787. Norvasc (amlodipine besylate) is a long-acting dihydropyridine calcium channel blocker, which is approved for use in adults in the treatment of hypertension, chronic stable angina, and confirmed or suspected vasospastic angina. The approved adult doses for these indications are 5 to 10 mg once daily.

Amlodipine inhibits the transmembrane influx of calcium ions into vascular smooth muscle cells and cardiac muscle without altering serum calcium concentration. It is a peripheral vasodilator that acts on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure. Absolute bioavailability of amlodipine is about 90%. The terminal half-life in adults is approximately 35-50 hours.

Basic pharmacokinetic parameters in children are unknown. Literature reports (FDA search revealed 72 publications for the key words combination 'amlodipine and children') indicate that amlodipine is effective and well tolerated in the treatment of hypertension in children between ages of 15 months and 18 years. In pediatric population, the doses ranged from 0.06 to 1.54 mg/kg/day. The 5 mg doses of amlodipine used in on average 70 kg adults, lead to the daily dose of 0.07 mg/kg/day. The dose recommendation for children has not been properly established.

Submission:

The primary objective of this Application was to obtain Pediatric Exclusivity for Norvasc, to evaluate the efficacy and safety of amlodipine in pediatric population, and to provide the labeling changes related to the amlodipine use in children. In this Application, NDA 19,787 SE5-030, the sponsor included 2 studies. These were a clinical study Protocol A0531018 "A randomized, double-blind, placebo-controlled parallel group dose-ranging study to evaluate the efficacy and safety of amlodipine in the treatment of hypertension in children" and a pharmacokinetic study Protocol A0531023 "The pediatric use of amlodipine in the treatment of hypertension: a population pharmacokinetic trial".
The main elements included in this submission are:

- proposed labeling,
- two study reports (copies of the text of the report, including the analytical reports and the population pharmacokinetic data analysis report),
- summary from published literature.

Additionally, the annotated case report forms, statistical data, and pharmacokinetic data were submitted in electronic format.

REVIEWER COMMENTS

1. The Agency considered that the information provided in the Supplement No. SE5 030 to NDA 19,787 dated September 14, 2001, January 25, and February 5, 2002 for Norvasc (amlodipine besylate) was appropriate to fulfill the pediatric exclusivity requirements described in the FDA Written Request and Written Agreement letters. The Agency granted an additional six months of marketing exclusivity.

CLINICAL PHARMACOLOGY COMMENTS

2. From the Clinical Pharmacology and Biopharmaceutics point of view, study A0531023 was submitted in support of the labeling changes for the pediatric patients. The primary objective of this study was to obtain estimates of amlodipine pharmacokinetic parameters in hypertensive children six months to 17 years of age. Secondary objectives include an assessment of the safety of amlodipine when used in hypertensive children and describing blood pressure control in hypertensive children receiving amlodipine by using 24-hours ambulatory blood pressure monitoring (ABPM). Clinical study Protocol A0531018 included

efficacy and safety data of amlodipine administration to children (6 to 17 years old) in the dose range of 2.5 and 5 mg per day.

3. Seventy three patients have completed study A0521023. The plasma concentrations of amlodipine were measured by LC/MS/MS method in [redacted]. This method has been properly validated for amlodipine over the concentration range of 0.1 to 50.0 ng/mL. The method was found to be sensitive, specific, precise and accurate. The limit of quantitation of amlodipine in plasma using LC/MS/MS was 0.1 ng/mL.

4. The sponsor analyzed the plasma concentration data from the study A0521023 using mixed effect modeling. A population pharmacokinetic model with multiple covariates was developed and population as well as individual pharmacokinetic parameters were estimated. The developed model adequately described the typical and individual pharmacokinetic parameters of amlodipine. The typical values for clearance for a subject with median weight of 45 kg were 23.7 L/hr for males and 17.6 L/hr for females. The typical value for volume of distribution for a subject with median weight of 45 kg was 1130 L. These values are comparable with the published estimates for clearance (24.8 L/hr) and volume of distribution (1120 L) in typical 70 kg adult. Out of 73 patients, seventeen subjects had ambulatory blood pressure monitoring (ABPM) for 24 hours. In this study, PK/PD relationship has not been established by the sponsor. Many patients received additional antihypertensive agents and the pharmacodynamic information relative to amlodipine was very unlikely to obtain.

5. Although the pharmacokinetics of amlodipine was studied in 11 patients younger than 6 years of age, the clinical study (Protocol A0531023) assessing the safety of amlodipine in children did not have any data on children younger than 6 years. Therefore, the proposed labeling changes will affect only patients 6 years of age and older. Mean clearance value estimated for children older than 6 years of age of 26.2 L/hr (0.53 L/hr/kg) and volume of distribution value of 1321 L (24.5 L/kg) were in the same range as published values for adults. The clinical pharmacology data provided in the study A0531018 are appropriate to support the pediatric information included in the proposed labeling.

6. The FDA reviewer performed the PK/PD analysis of data from study A0531018. The developed population PK/PD model allowed to describe the relationship between the effect (lowering of systolic (SBP) and diastolic (DBP) blood pressure) and the average steady-state amlodipine plasma concentrations (CAVG).

7. The PK/PD relationship was best described with the linear model. Both systolic and diastolic blood pressure changes were dependent on the CAVG with the slopes of –1.22 mmHg/ng/mL (SBP) and –0.68 mmHg/ng/mL (DBP). The slope seems to be steeper for SBP.

8. Statistically significant influence of gender was shown for the covariate model of SBP. Female subjects had on average 4.89 mmHg higher baseline SBP value.

9. The only covariate, which influenced the DBP baseline was body weight. The model includes this covariate as a power function.

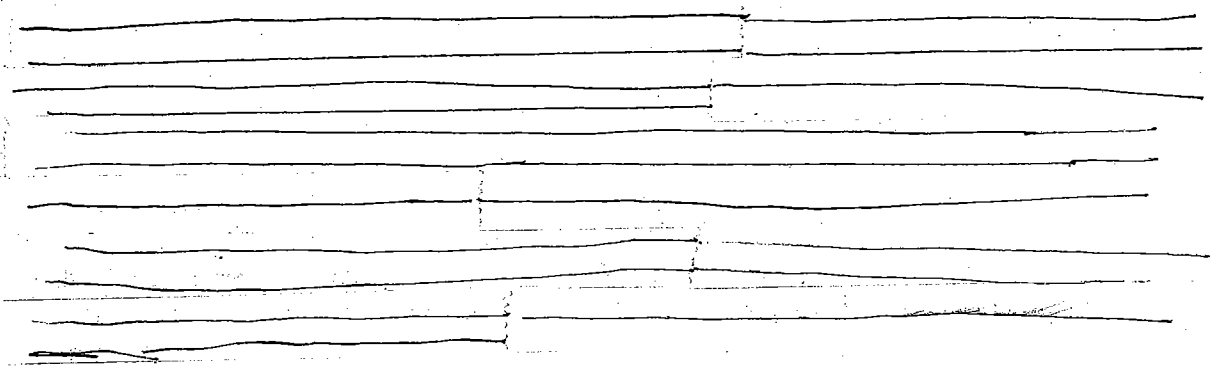
10. The population model has considerable unexplained variability.

11. The difference in the effect – concentration curve slopes for adults (historical published data) and children could be statistically significant and clinically relevant. For example, amlodipine plasma concentration of 10 ng/mL will cause a 31 mmHg reduction of SBP in adults and 12 mmHg reduction of SBP in children. Therefore, systolic blood pressure changes in children were found to be less sensitive to amlodipine than in adults.

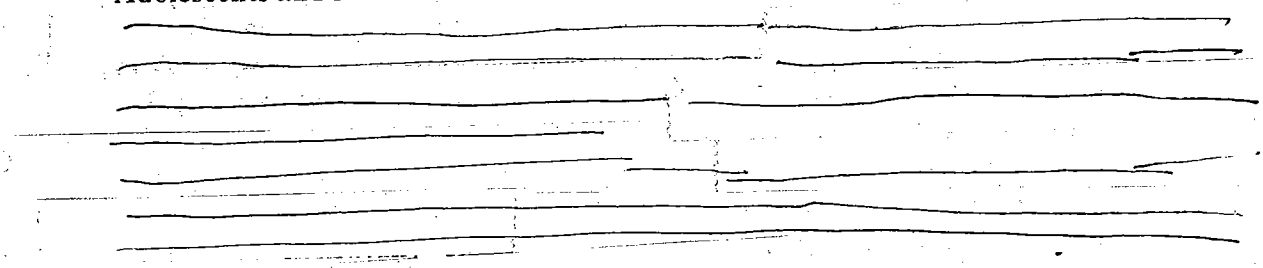
12. The sponsor proposed the starting dose of 2.5 mg in children. Considering that an average 70 kg adult taking the starting dose of 5 mg receives daily approximately 0.07 mg/kg/day. The dose of 2.5 mg per day in average 45 kg child will lead to an approximate daily dose of 0.056 mg/kg/day. This dose adjustment for children seems to be acceptable.

LABELING COMMENTS:

In the CLINICAL PHARMACOLOGY Section,
Pediatric Patients:



Effects in Hypertension:
Adolescents and Pediatric Patients Ages 6 to 17 years:



Pediatric Use:

This sentence should be changed to:
The study assessing the efficacy of amlodipine in pediatric patients less than 6 years of age has not been performed.

DOSAGE AND ADMINISTRATION
Children
The effective antihypertensive oral dose in pediatric patients ages 6-17 years is 2.5 mg to 5 mg once daily. Doses in excess of 5 mg daily have not been studied in pediatric patients.

The labeling changes proposed by the sponsor are acceptable with minor correction.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation I has reviewed the pediatric information included in the Supplement SE5 030 to NDA 19,787 dated September 14, 2001, January 25, and February 5, 2002 for Norvasc (amlodipine besylate) tablets. If the Division of Cardio-Renal Drug Products opts to include a description of amlodipine pharmacokinetics in pediatrics in the Package Insert, the Office of Clinical Pharmacology and Biopharmaceutics recommends adopting the above proposed language. The recommended starting dose of 2.5 mg for an average 45 kg child appears to be adequate and comparable with the recommended staring dose of 5 mg for an average 70 kg adult.
Please forward the Clinical Pharmacology Comments to the sponsor.

_____ Date_____
Elena Mishina, Ph. D.
Clinical Pharmacology Reviewer

_____
Joga Gobburu, Ph. D.
Pharmacometrics Team Leader

cc list: NDA 19787, MehulM, MishinaE, HFD 110 BIOPHARM

APPENDIX I

NDA 19787

PROPOSED PEDIATRIC LABELING CHANGES

APPENDIX II

NDA 19787

Review of individual studies

Study No.: A0531023

Study Title: The Pediatric Use of Amlodipine in the Treatment of Hypertension. A Population Pharmacokinetic Trial (PATH-2)

Volumes: 7 & 8

Principal Investigators:
J Flynn, MD; J Mahan, MD; J Goebel, MD; J Lemire, MD; P Brophy, MD; A Sakarcan, MD; R Hogg, MD; C Hovinta, Pharm D; T Nevins, MD, R Potman, MD; JP Saul, MD; D Jones, MD; G Arbus, MD; W Tenney, MD.

Sites: Eleven Clinical sites in the US and Canada

Monitoring Organization:

Safety Tests:

Analytical:

Data Analysis:

Random SPONSOR'S ANALYSIS

OBJECTIVES:

- The primary objective of this study was to obtain estimates of amlodipine pharmacokinetic parameters in hypertensive children six months to 17 years of age.

Secondary objectives include an assessment of

- the safety of amlodipine when used in hypertensive children, and
- blood pressure control in hypertensive children receiving amlodipine by using 24-hours ambulatory blood pressure monitoring (ABPM).

METHODS:

Study Design:

This was an open-label, multicenter study. Subjects from 6 months to 17 years of age who were receiving amlodipine for the treatment of hypertension were included. There was a two-week screening period, amlodipine was administered daily at a stable dose during this period. The second period was four-week pharmacokinetic sampling phase, which consisted of 4 weekly visits. Plasma samples were obtained for up to 24 hours following drug administration (visit 2). Plasma sampling was sparse (2-3 time points per subject). Through amlodipine concentrations were obtained at visits 3 and 4. When possible, subjects participated in ABPM for 24 hours at visit 3.

The sparse data set from 73 patients and 10 study sites included 405 non-zero plasma amlodipine concentration measurements. Demographic characteristics are shown in Table 1.

Table 1. Demographic characteristics.

Statistic	Infant and toddler (1 month to 2 years)	Pre-school (2 to <6 years)	School Age (≥ 6 to < 13 years)	Adolescent (≥ 13 to < 17 years)	≥ 17 years
Age (months)					
N	2	9	34	23	5
Mean	17.6	53.7	115.8	178.3	210.0
Min	12.2	33.3	73.6	156.7	204.6
Max	23.0	69.3	152.4	201.3	213.0
Median	17.6	50.1	118.6	177.6	211.6
SD	7.6	12.6	25.3	13.6	3.6
%CV	43.37	23.37	21.82	7.65	1.70
Weight (kg)					
N	2	9	34	23	5
Mean	9.8	21.2	46.1	74.8	65.6
Min	6.5	11.1	19.6	33.8	46.7
Max	13.2	42.9	105.2	142.0	80.9
Median	9.8	18.4	38.3	67.1	63.3
SD	4.8	9.9	24.5	32.9	13.8
%CV	48.29	46.81	53.10	44.05	21.07
Height (cm)					
N	2	9	34	23	5
Mean	76.1	102.0	137.5	164.2	165.4
Min	64.1	84.0	110.5	139.2	151.5
Max	88.0	120.7	166.0	190.6	184.4
Median	76.1	99.9	137.0	166.5	161.2
SD	16.9	11.5	16.2	15.4	13.9
%CV	22.18	11.23	11.79	9.41	8.41
Gender					
Male	1	6	21	19	2
Female	1	3	13	4	3
Race (Number)					
Caucasian	1	5	21	10	4
Black	1	3	12	9	1
Other	0	0	1	1	0
Hispanic	0	1	0	3	0

This population included about 30% of females who were slightly younger than males. Of the 73 subjects, 32 were classified as obese. The majority of the subjects were Caucasian (56%) or Black (36%).

Formulations and dose administration:

Dosage form: 2.5 mg tablets (9QP132A-G1, 9QP277A-G1), 5 mg tablets (9QP135A-G1), 10 mg tablets (9QP164A-G1, 9QP156A-G1).
Dosing: Stable oral dose determined by previous medical needs of the subject. Daily doses of 1.3 to 20 mg given either once or twice daily.
Duration of the study: Up to eight weeks.

Assay:

The plasma samples were assayed for amlodipine using a validated LC/MS method with multiple reaction monitoring detection.
Specificity: satisfactory, chromatorgams present.
Linearity: satisfactory. Linearity covered the range of concentrations between 0.1 and 50 mcg/L.
Limit of quantitation was set to 0.1 mcg/mL.
Precision and accuracy: satisfactory.

Intra-assay

At the limit of quantitation (0.3 mcg/L):			
CV	4.99%	Difference from theoretical	3.66%
All other concentrations:			
CV	between 2.04 and 13.7%	Difference from theoretical	-3.45-4.74%.

Inter-assay

At the limit of quantitation (0.3 mcg/L):			
CV	13.2%	Difference from theoretical	4.97%
All other concentrations			
CV	between 5.20 and 7.52%	Difference from theoretical	1.12-7.04%.

Data Analysis: Plasma amlodipine concentrations were used in a population pharmacokinetic analysis using NONMEM. Multiple covariates were tested for relationship to amlodipine exposure. Pharmacokinetic parameters were calculated based on the developed population PK model. Population data analysis was performed by

Seventeen subjects participated in ABPM for 24 hours but PK/PD data analysis using these data was not attempted due to confounding effect of a number of anti-hypertensive co-medications.

Population PK Data Analysis Report

Population pharmacokinetic model was built using NONMEM (Version V, level 1.1) and NM-TRAN pre-processor. Models were run using the Digital Visual Fortran Compiler (Version 5.0D0 on a personal computer under the Microsoft Windows NT 4.0 operating system. The population data analysis consisted of several steps:

Base model building;
Covariance model building;
Model reduction;
Model refinement;
Evaluation of the final model.

For the base model, one-compartmental pharmacokinetic model was assumed (information from the literature: Meredith PA and Elliott HL. Clinical pharmacokinetics of amlodipine. Clin. Pharmacokinet. 1992, 22(1) 22-31).. Initially, interindividual variability was included in all fixed effect pharmacokinetic parameters: clearance (CL/F), volume of distribution (V/F), and the first order absorption rate constant (KA).

$$CL_j = TVCL \cdot \exp(\eta_{jCL})$$

where η_{jCL} denotes the proportional difference between the true parameter (CL_j) of individual j and the typical value TVCL. The method of estimation, first order conditional estimation with interaction (FOCEI) was found to be the most suitable for this analysis. Initial residual error model consisted of both an additive and a proportional component.

$$Cp_{ij} = \tilde{C}\, p_{ij}(1+\varepsilon_{1ij}) + \varepsilon_{2ij}$$

where Cp_{ij} and Cp_{ij} are the i-th measured and modeled predicted concentrations for patient j and ε_{1ij} and ε_{2ij} denote the residual intra-patient random error for constant coefficient of variations (CCV) part and the additive part with respective variances σ_1^2 and σ_2^2. Later in the process of model development, the additive part of residual error was omitted.

The relationship between covariates and individual parameters obtained with the base model were graphically explored. All body size parameters, demographic parameters (age, gender, race), creatinine clearance (CrCL), serum creatinine (SCR), aspartate aminitransferase (AST), alanine aminitransferase (ALT), alkaline phosphatase (ALKP), total protein (PROT), albumin (ALB) were tested as covariates. Only body size parameters, creatinine clearance, and gender showed an influence on CL and/or V. The effects of covariates on KA were not tested due to the lack of the data in the absorption phase. Body size parameters are usually highly correlated, and the sponsor has chosen the body weight (BW) as the best representative for both CL and V. The sponsor described each step of model building as a statistical test of individual covariate on the appropriate

parameter (CL or V) in a separate run. Gender and race (Black) were expressed as the categorical covariates, all others as the continuous covariates (BW was centered). When comparing alternative hierarchial 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. At the screening stage, the level of sensitivity was assumed as p=0.05 (Δ in OFV 3.8).

After the finalizing of the full model, the significance of each of the covariates was tested by removing them from the model one by one. At the high level of sensitivity (p=0.001), 10.83 unit difference in the objective function was required for the test of statistical significance.

The sponsor summarized the parameter estimates obtained with the base model in Table 2.

Table 2. Results of the Base Model Run

Base Model Parameter Estimates - FOCEI Method		
Structural Model and Interindividual Variance Parameters		
Parameter	**Typical Value (%RSE*)**	**Interindividual %CV (%RSE*)**
CL/F (L/hr)	22.2 (6%)	50.89% (19%)
V/F (L)	1300 (12%)	60.50% (44%)
k_a (hr^{-1})	0.850 (47%)	44.83% (45%)
Residual Error		
Parameter	**Estimate (%RSE*)**	**Interindividual %CV (%RSE*)**
$\sigma^2 1_{prop}$	%CV=22.14% (14%)	

*%RSE: percent relative standard error of the estimate = SE/parameter estimate * 100
Abbreviations: FOCEI = first order conditional estimation with interaction, CL/F = Apparent oral clearance, V/F = Apparent volume of distribution, ka = absorption rate constant, $\sigma^2 1_{prop}$ = proportional residual error.

The process of model building is shown in Table 3.

Table 3. Covariate model building steps.

Step	Amlodipine Stepwise Covariate Model Building Run No.	Covariate-Parameter Model	OFV	Change in OFV*
Base Model	301	-	1426.007	-
Step One – Significant Covariates on Clearance*				
	310	Centered Weight	1410.314	15.693
	311	Centered Age	1419.854	6.153
	312	Centered Height	1410.235	15.772
	313	Centered IBW	1411.421	14.586
	314	Centered BSA	1408.991	17.016
	316	Sex	1419.22	6.787
	325	Centered Protein	1420.949	5.058
	326	Centered Albumin	1422.166	3.841
	333	Race = Black	1421.94	4.067
	335	Centered CRCL	1405.618	20.389
	337	Centered BMI	1415.473	10.534
Step Two – Significant Covariates on Volume*				
	346	Centered Weight	1414.176	11.831
	347	Centered Age	1420.636	5.371
	348	Centered Height	1418.873	7.134
	349	Centered IBW	1418.211	7.796
	350	Centered BSA	1414.906	11.101
	356	Centered ALT	1420.236	5.771
	365	Centered CRCL	1421.112	4.895
	369	Centered BMI	1414.115	11.892

Abbreviations: OFV = objective function value, IBW = ideal body weight, BSA = body surface area, CRCL = creatinine clearance, BMI = body mass index, ALT = alanine aminotransferase
*Significance defined *a priori* at 0.05 (equivalent to a change in OFV of 3.84)

Table 4 illustrates the results of model reduction.

Table 4. Model reduction steps.

Step	Amlodipine Stepwise Covariate Model Reduction Run No.	Covariate Removed	OFV	Change in OFV*
Full Model	402	-	1367.828	-
One	411	Centered Height on Volume	1367.867	0.039
Two	414	Centered Height on Clearance	1368.004	0.137
Three	428	Centered Creatinine Clearance on Volume	1368.512	0.508
Four	434	Centered Protein on Clearance	1371.327	2.815
Five	440	Race = Black on Clearance	1374.297	2.97
Six	447	Centered ALT on Volume	1377.185	2.888
Seven	448	Centered Weight on Clearance	1382.497	5.312
Eight	452	Centered CrCL on Clearance	1407.500	25.003*
Nine	453	Sex on Clearance	1394.005	11.508*
Ten	454	Centered Weight on Volume	1393.709	11.212*

*Significance defined *a priori* at 0.001 (equivalent to a change in OFV of 10.83)

kg clearance values were 23.7 L/hr (males) and 17.6 L/hr (females). These estimates are similar with the published estimates of CL/F of 24.8 L/hr for a typical 70 kg adult. The average estimates of volume of distribution for the subject of median weight of 45 kg was 1130 L (25.11 L/kg). In typical 70 kg adult V/F of 1120 L (16 L/kg) was published.

Figure 1 represents the trends in clearance and volume of distribution estimates depending on body weight.

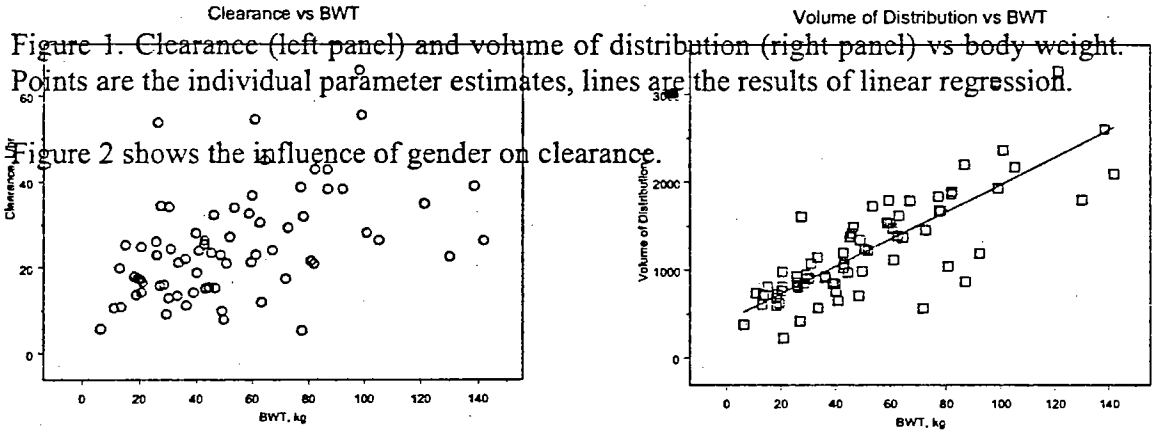


Figure 1. Clearance (left panel) and volume of distribution (right panel) vs body weight. Points are the individual parameter estimates, lines are the results of linear regression.

Figure 2 shows the influence of gender on clearance.

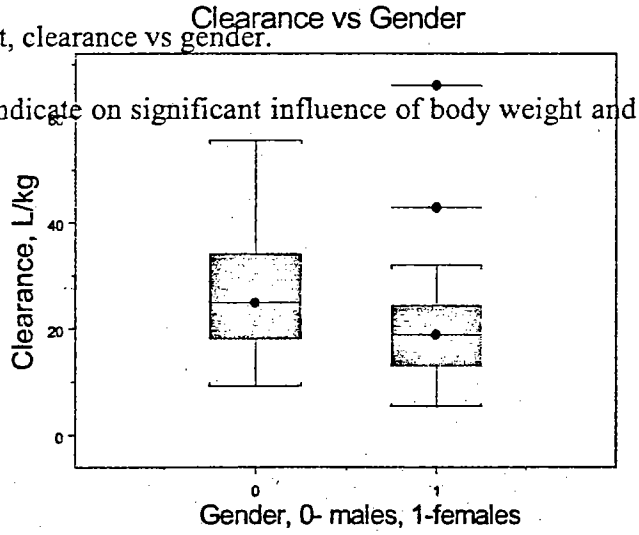


Figure 2. Box plot, clearance vs gender.

Figures 1 and 2 indicate on significant influence of body weight and gender on clearance values.

The resulting model was the final PK model. Parameter estimations are shown in Table 5.

Table 5. Parameter estimates for the final model.

Structural Model and Interindividual Variance Parameters		
Parameter	**Typical Value (%RSE*)**	**Interindividual %CV (%RSE*)**
CL/F (L/hr)	CL = θ1 + θ4*(WT-45) - θ5*SEX	43.24% (22%)
θ1	23.7 (6%)	-
θ4	0.176 (29%)	-
θ5	6.09 (36%)	-
V/F (L)	V = θ2 + θ6*(WT-45)	48.68% (52%)
θ2	1130 (11%)	-
θ6	16 (35%)	-
k_a (hr^{-1})	ka = θ3	50.60% (52%)
θ3	0.807 (62%)	-
Residual Error		
Parameter	**Estimate (%RSE*)**	**Interindividual %CV (%RSE*)**
σ^2_{1prop}	%CV=22.07% (14%)	-

*%RSE: percent relative standard error of the estimate = SE/parameter estimate * 100
FOCEI = first order conditional estimation with interaction, CL/F = Apparent oral clearance, V/F = Apparent volume of distribution, ka = absorption rate constant, σ^2_{1prop} = proportional residual error

The validation of the final model by splitting the data set was not possible due to the small size of the data set. The sponsor simulated data for approximately 2500 subjects and evaluated the precision of parameter estimates over the several time intervals.
All diagnostics plots (IPRED vs OBS; PRED vs OBS; weighted residuals vs predicted amlodipine plasma concentrations or time) indicate on the marked improvement of model fit to the data in comparison with the base model (Table 6).

Table 6. Comparison of parameter estimates of the base model, final models and literature values in adults:

RE'		CL/F (L/hr)*	CL/F (L/hr/kg)*	V/F (L)*	V/F (L/kg)*	
	Base Model	22.2	0.317	1300	18.57	
The	Model with CrCL on CL/F -females	19.3	0.275	1535	21.93	he
pop	Model with CrCL on CL/F -males	26.5	0.379	1535	21.93	ler
abs	Model with Wt on CL/F -females	22.0	0.314	1530	21.86	he
sam	Model with Wt on CL/F -males	28.1	0.401	1530	21.86	
Onl	Literature Estimates	24.8	0.354	1120	16	to
cha	*All estimates have been normalized for a 70 kg individual					45

Study No.: A0531018

Study Title: The Pediatric Use of Amlodipine in the Treatment of Hypertension I. (PATH-I). A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Dose-Ranging Study to Evaluate the Efficacy and Safety of Amlodipine in the Treatment of Hypertension in Children

Volumes: 2-6

This study was designed to measure effectiveness and safety. No plasma concentration data were obtained. The reviewer used the measurements of manual systolic and diastolic blood pressure at baseline and during the treatment phases to develop a population pharmacokinetic/ pharmacodynamic model.

OBJECTIVES:

- The primary objective of this study was to compare the effect of amlodipine versus placebo on systolic blood pressure in hypertensive children ages 6 to less than 17 years.

Secondary objectives were

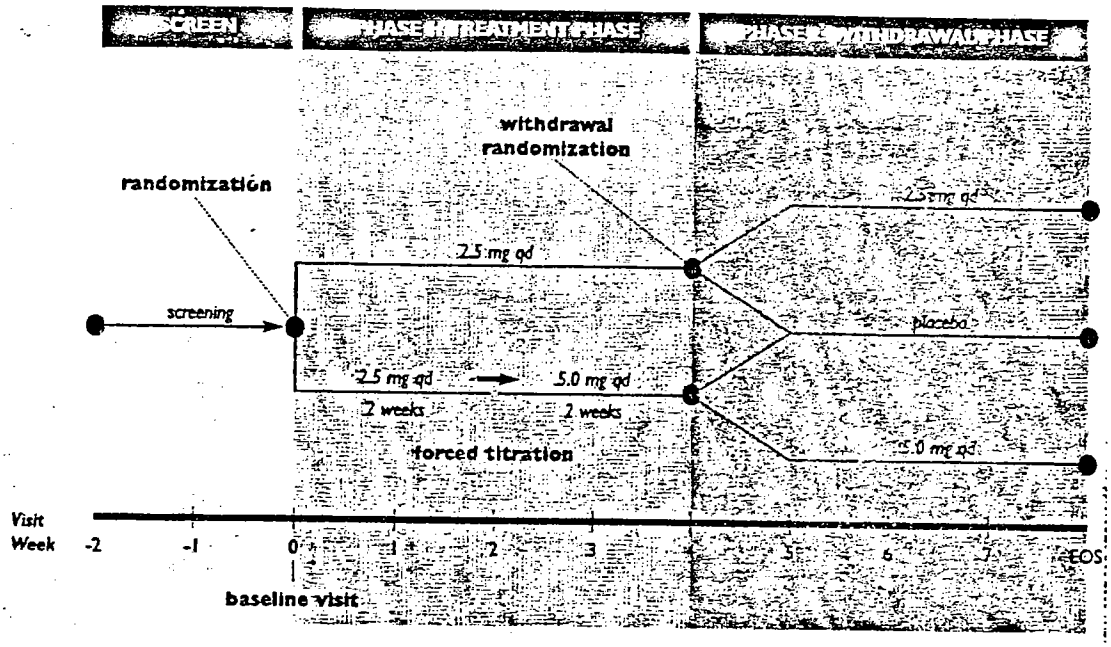
- To compare the effect of amlodipine versus placebo on diastolic blood pressure in hypertensive children,
- To evaluate the effect of amlodipine of systolic and diastolic blood pressure as a function of dose and body size, and
- To evaluate the safety of amlodipine in hypertensive children.

METHODS:

Study Design:

This was a randomized, double-blind, placebo-controlled, parallel group dose-ranging multicenter study consisting of a two week screening period followed by 4 week 2 treatment phases (See the chart).

In treatment Phase I of the study, the subjects were randomized to receive oral amlodipine QD (2.5 mg for 4 weeks or 2.5 mg for 2 weeks followed by 5 mg for 2 weeks). In treatment Phase II of the study, subjects were randomized to continue on oral amlodipine at a dose of 2.5 mg or 5 mg for 4 weeks; or were randomized to withdrawal to oral placebo QD for 4 weeks. Randomization was stratified by age range into two stratums: stratum 1, (6 years old)<AGE<(13 years old); stratum 2 (13 years old)<AGE<(17 years old). Subjects were evaluated at screening, baseline, and weeks 1, 2, 3, 4, 5, 6, 7, and 8.



Demographic characteristics by the treatment phase are shown in Table1.

Table 1. Demographic characteristics.

	Amlodipine 2.5 mg/2.5 mg			Amlodipine 2.5 mg/Placebo		
	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL
Number of Subjects	52	32	84	23	20	43
Age (years):						
<2	0	1	1	0	0	0
2-5	0	1	1	2	0	2
6-12	20	11	31	11	14	25
13-16	27	17	44	10	6	16
>=17	5	2	7	0	0	0
Mean	12.9	12.0	12.6	11.5	11.3	11.4
SD	3.0	3.9	3.4	3.5	2.9	3.2
Range	6-17	1-17	1-17	5-16	7-16	5-16
Race:						
WHITE	34	21	55	13	10	23
BLACK	11	8	19	6	8	14
ASIAN	0	0	0	0	0	0
HISPANIC	4	1	5	4	1	5
OTHER	3	2	5	0	1	1
Weight (kg):						
Mean	73.5	64.5		63.9	58.1	
SD	31.0	28.5		31.5	27.6	
Range	19-161	11-125		17-128	20-109	
N	52	32		23	20	
Height (cm):						
Mean	160.8	150.4		151.5	146.7	
SD	19.9	20.0		23.8	18.6	
Range	108-195	80-178		103-183	120-173	
N	52	32		23	20	

Table 1, continued.

	Amlodipine 5 mg/Placebo			Amlodipine 5.0 mg/5.0 mg		
	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL
Number of Subjects	33	14	47	69	25	94
Age (years):						
<2	0	0	0	0	0	0
2-5	0	1	1	1	2	3
6-12	12	10	22	32	12	44
13-16	19	2	21	32	9	41
>=17	2	1	3	4	2	6
Mean	12.9	10.9	12.3	12.2	11.2	12.0
SD	2.8	3.5	3.1	3.1	4.0	3.4
Range	6-17	5-17	5-17	4-17	2-17	2-17
Race:						
WHITE	17	7	24	48	13	61
BLACK	8	7	15	16	6	22
ASIAN	0	0	0	0	2	2
HISPANIC	7	0	7	4	4	8
OTHER	1	0	1	1	0	1
Weight (kg):						
Mean	70.2	62.5		66.8	58.1	
SD	25.3	30.8		28.6	31.2	
Range	24-114	16-109		20-139	15-136	
N	33	14		69	25	
Height (cm):						
Mean	156.4	145.4		156.2	144.6	
SD	22.8	19.0		20.6	20.1	
Range	68-185	104-170		110-191	95-172	
N	33	14		69	25	

The number of patients entered, evaluated for efficacy and safety, and completed the study are shown below:

	Phase 1 Amlodipine		Phase 2 Amlodipine		Placebo
	2.5mg	5mg	2.5mg	5mg	
Entered Study	127	141	83	88	87
Completed Study	125	133	81	84	85
Evaluated for Efficacy	0	0	83	86	87
Assessed for Safety					
Adverse Events	127	141	83	88	87
Laboratory Tests	3	5	83	86	85

Formulations:

Dosage form: 2.5 mg tablets: FID# QC1652; Lots: N9059G1, N0011G1.
Placebo tablets: FID# QC1653, Lot N9058G1

Duration of the study: Eight weeks.

PHARMACOKINETIC/PHARMACODYNAMIC DATA ANALYSIS

Objectives:

1. To develop a basic pharmacokinetic/pharmacodynamic (PK/PD) model to correlate amlodipine plasma concenrations at steady state with manual systolic and diastolic blood pressure.
2. To evaluate the effect of covariates (demographics, history of family hypertension, kidney transplantation, etc.).

Data:

The population pharmacokinetic model developed by the sponsor (study A0531023) was used. In this model, the expression for the clearance with the covariates of weight and gender was established. Based on the estimated individual values of clearance obtained from the posthoc table for each patient, the daily average amlodipine plasma concentrations (CAVG) were calculated (Dose/CL). The measurements of systolic and diastolic blood pressure were obtained at screening and during the treatment with amlodipine. The data set included a total of 268 patients with 6309 effect measurements. Each subject has on average 3 blood pressure measurements at each of 8 visits. In the new data set, the variable CAVG was included to drive the PD model.

Methods:

Both Emax and linear models were tested. The Emax model could not achieve the convergence even for the basic model most likely due to insufficient data points to describe a plateau (the convergence was terminated due to the rounding errors). Additionally, graphical data exploration indicate the plausibility of the linear model. Information from the literature confirms the plausibility of the linear PD model for amlodipine (Donelly R, Meredith PA et al Clin Pharmacol Ther 1993; 54(3): 303-310). Therefore, the population PK/PD model with linear relationship between the amlodipine plasma concentration (CAVG values) and effect was proposed for both systolic and diastolic blood pressure.

$$EFFECT_{ij} = BSL_i + SLP_i * CAVG_{ij}$$

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 $CAVG_{ij}$ is the j^{th} daily average amlodipine plasma concentration in the i^{th} patient.

The placebo effect was estimated as a linear function and the final expression for the effect model was:

$$EFFECT_{ij} = BSL_i + SLP_i * CAVG_{ij} + PL_i * PLCB_{ij}$$

where PL_i was the placebo effect and $PLCB_{ij}=0$ when the dose of drug was given and $PLCB_{ij}=1$ when placebo was given (for the subjects in Phase II of the study)

Interindividual variability for the baseline was modeled as

$$BSL_j = TVBSL_j \exp(\eta_{jBSL})$$

where η_{jBSL} denotes the proportional difference between the true parameter (BSL_j) of individual j and TVBSL is the typical value of baseline.
Interindividual variability for both slope and placebo effect were modeled using the additive error model.
The residual error model consisted of an additive component.

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

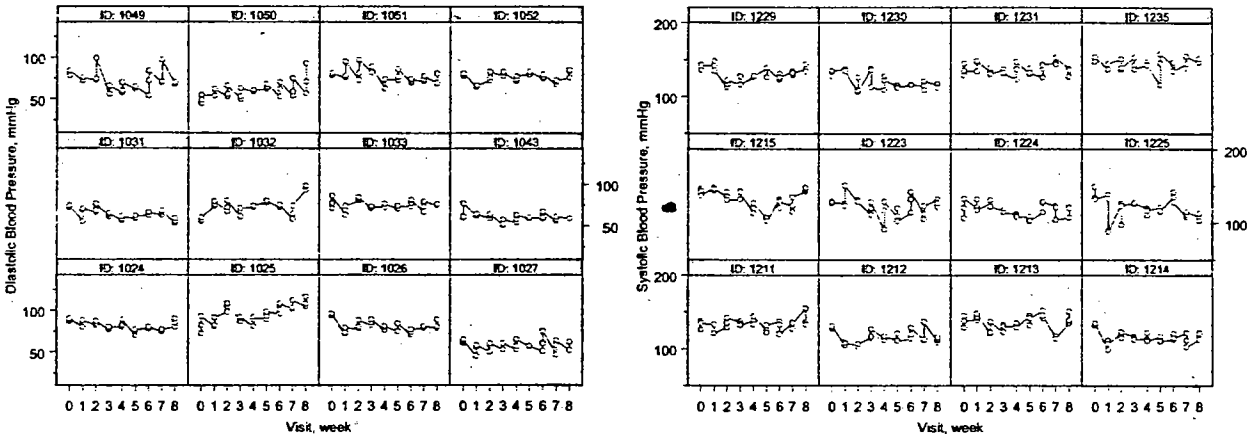
where $EFFECT_{ij}$ and $TVEFFECT_{ij}$ are the i-th measured and modeled predicted effects for patient j and ε_{ij} denotes the residual intra-patient random error with variance σ_1^2.
The first order conditional estimation (FOCE) method of estimation was used for this analysis. Nonlinear mixed effects modeling was performed using NONMEM (ver. 5, level 1.1). All data manipulations were conducted using SAS (ver 6.12). S-plus was used for graphical display.

Relationship between covariates and individual parameters obtained from the base model were graphically explored. The following covariates were tested: body weight, age, gender, race, family history of hypertension, kidney transplantation. 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 hierarchial 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. At the screening stage, the level of sensitivity was assumed as p=0.01 (Δ in OFV 6.8). After the finalizing of the full model, the significance of each of the covariates was tested by removing them from the model one by one. At the high level of sensitivity (p=0.001), 10.83 unit difference in the objective function was required for the test of statistical significance. The final model was refined by the test of possible covariance between the random effects (use of OMEGA BLOCK function).

Results and Discussion

The plots of amlodipine systolic and diastolic (Figure 1) blood pressure vs the average amlodipine plasma concentrations in representative patients are shown below. Both systolic and diastolic blood pressure seems to decrease in all patients from visit 1 to visit 4. Some patients have an increase of the blood pressure reaching the baseline (withdrawal to placebo groups).

Figure 1. Systolic (right panel) and diastolic (left panel) blood pressure vs visit in representative patients. The patient numbers are identified on top of each graph.



Both Emax and linear pharmacodynamic models were tested for systolic and diastolic blood pressure relationship with amlodipine plasma concentrations. Emax model was rejected due to insufficient data to describe a hyperbolic function (the convergence was terminated due to the rounding errors, objective function value was 497 units larger). Same finding for amlodipine antihypertensive PD model was published in literature (Donelly R, Meredith PA et al Clin Pharmacol Ther 1993; 54(3): 303-310).
Simple linear model with placebo effect was used to describe the relationship between average amlodipine plasma concentrations and systolic/diastolic blood pressure.
Base model parameter estimates for systolic blood pressure are shown in Table 1.

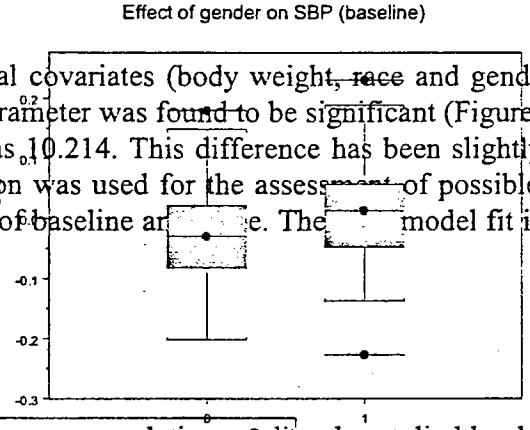
Table 1. Pharmacodynamic parameter estimates with base model for SBP.

PARAMETER	BASELINE, mmHg	SLOPE mmHg/ng/mL	PLACEBO mmHg
Typical value	37	-1.21	-4.61
RSE%	0.6	8.5	18.6
Interindividual %CV	8.29	87.8	126.0
RSE%	9.2	23.7	21.4
ERR (SD)	9.67		
RSE%	3.6		

The effect of drug was tested by assigning the value of the slope equal to zero. This run led to the increase of the objective function by 546 units, indicating that the effect of the drug was very significant.

The covariate influences were tested graphically for both baseline and slope random effects, exploring plots of ETAs vs the parameter. Only the covariates, which showed the effect graphically, were included in the covariate analysis.

Figure 2. Box plot of the effect of gender (0 states for females, 1 states for males) on ETA for baseline (ETBL).



From the tested individual covariates (body weight, race and gender) only the effect of gender on the baseline parameter was found to be significant (Figure 2). The difference in the objective function was 10.214. This difference has been slightly improved when the OMEGA BLOCK function was used for the assessment of possible covariance between ETAs for the parameters of baseline and slope. The model fit is illustrated in Figure 3.

Figure 3. Relationship between population predicted systolic blood pressure and average daily amlodipine plasma concentrations. Light color circles are the values for females and dark color circles are the values for males.

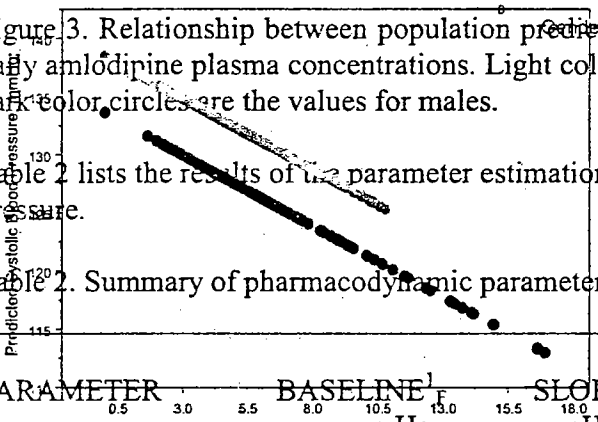


Table 2 lists the results of the parameter estimation with the final model for systolic blood pressure.

Table 2. Summary of pharmacodynamic parameters for SBP.

PARAMETER	BASELINE[1]$_F$ mmHg	SLOPE mmHg/ng/mL	PLACEBO mmHg	SEX mmHg
Typical value	134	-1.22	-4.55	4.89
RSE%	0.9	8.5	18.9	30.9
Interindividual %CV	8.26	89.0	126.8	
RSE%	10.5	23.7	21.6	
ETAR12	-0.101			
ERR (SD)	9.67			
RSE%	3.6			

[1]Baseline$_F$ is Baseline SBP in females; [2]Baseline$_F$ + SEX is Baseline SBP in males.

Therefore, the population predicted mean baseline systolic blood pressure in females was 134 mmHG, and in males was 138.89 mmHg. In the presence of amlodipine, SBP was

decreasing in the linear manner with the slope of –1.22 mmHg/ng/mL. In case of withdrawal to placebo, SBP was increasing on average on 4.55 mmHg.

EFFECT = 134 + 4.85*SEX - 1.22*CAVG - 4.55*PLCB

Figures 4 and 5 illustrate the diagnostics plots for the final model.

Figure 4. Diagnostics plots for the final model. Left panel, population predicted vs observed systolic blood pressure, line is a line of identity. Right panel, individual predicted vs observed systolic blood pressure, line is a line of identity.

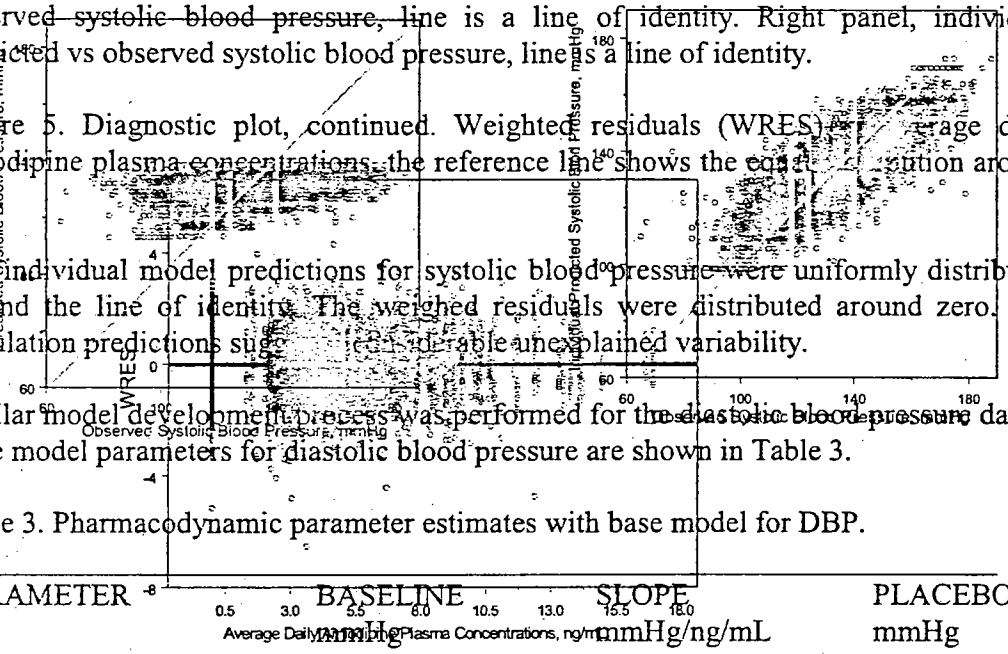


Figure 5. Diagnostic plot, continued. Weighted residuals (WRES) vs average daily amlodipine plasma concentrations, the reference line shows the equidistribution around zero.

The individual model predictions for systolic blood pressure were uniformly distributed around the line of identity. The weighed residuals were distributed around zero. The population predictions suggested considerable unexplained variability.

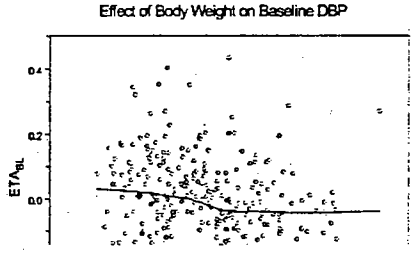
Similar model development process was performed for the diastolic blood pressure data. Base model parameters for diastolic blood pressure are shown in Table 3.

Table 3. Pharmacodynamic parameter estimates with base model for DBP.

PARAMETER	BASELINE mmHg	SLOPE mmHg/ng/mL	PLACEBO mmHg
Typical value	73.3	-0.68	-1.58
RSE%	0.9	12.5	41.0
Interindividual %CV	13.11	83.01	404.9
RSE%	10.4	35.4	30.8
ERR (SD)	7.16		
RSE%	4.0		

The effect of drug on DPB was tested by assigning the value of the slope equal to zero. This run led to the increase of the objective function on 361 units, indicating that the effect of the drug was very significant.

Effect of covariates on the parameters of the base model was explored graphically. The effects of weight and gender on the baseline were admitted and tested in the model. Figure 6 demonstrates the effects of the covariates, which were found to be significant.



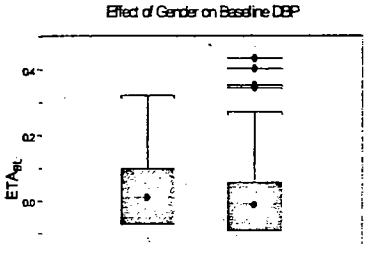


Figure 6. Influence of body weight (left panel, circles are the observed diastolic blood pressure, line is Loess smoothing curve) and gender (right panel, 0 states for males, 1 states for females) on baseline parameter.

Gender effect was not statistically significant (change in the objective function 2.8 units in comparison with the base model). Body weight effect was tested using both centered weight linear model and power model. Only the latter led to a 7.2 units decrease of the objective function (statistically significant change for $p<0.01$). The best fit was obtained with the consideration of possible covariance between ETAs (OMEGA BLOCK function), change in OFV was –41 units.

Table 4 lists the final pharmacodynamic parameter estimates.

Table 4. Summary of pharmacodynamic parameters for DBP.

PARAMETER	BASELINE mmHg	SLOPE mmHg/ng/mL	PLACEBO mmHg	WEIGHT kg
Typical value	74	-0.687	-1.46	-0.039
RSE%	1.1	12.4	45.7	40.8
Interindividual %CV	13.9	122.2	252.3	
RSE%	10.9	33.1	30.8	
ETAR12	-0.458			
ERR (SD)	7.14			
RSE%	4.0			

These parameters indicate that in an average subject the population predicted diastolic blood pressure at baseline was 74 mmHg and decreases with the increase of CAVG according to the equation:

$$EFFECT = 74 * (WT/45)^{-0.039} - 0.687 * CAVG - 1.46 * PLCB$$

The effect of withdrawal to placebo for DBP was 1.46 mmHg, smaller than the same for SBP (4.55 mmHg).

Figure 7 presents the model diagnostics plots.

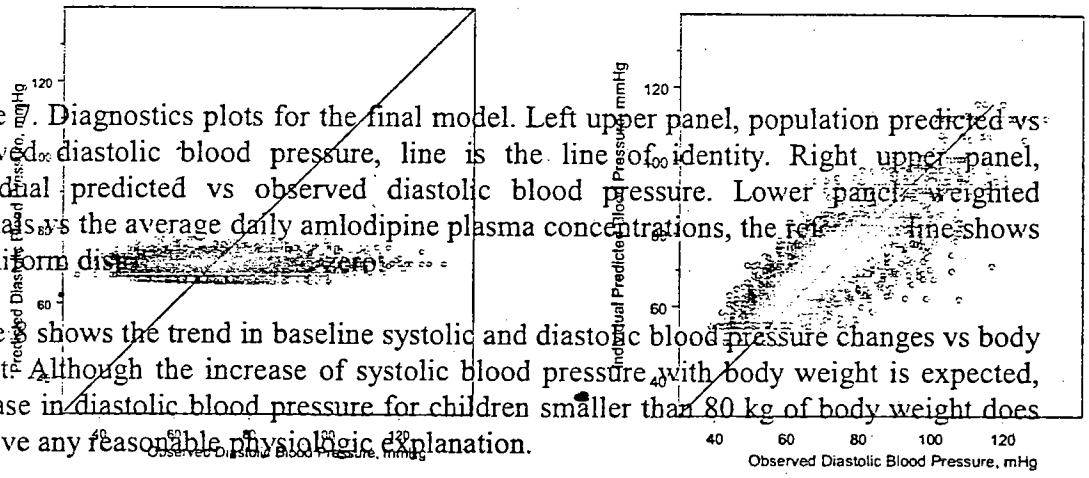


Figure 7. Diagnostics plots for the final model. Left upper panel, population predicted vs observed diastolic blood pressure, line is the line of identity. Right upper panel, individual predicted vs observed diastolic blood pressure. Lower panel, weighted residuals vs the average daily amlodipine plasma concentrations, the red line shows the uniform distribution zero.

Figure 8 shows the trend in baseline systolic and diastolic blood pressure changes vs body weight. Although the increase of systolic blood pressure with body weight is expected, decrease in diastolic blood pressure for children smaller than 80 kg of body weight does not have any reasonable physiologic explanation.

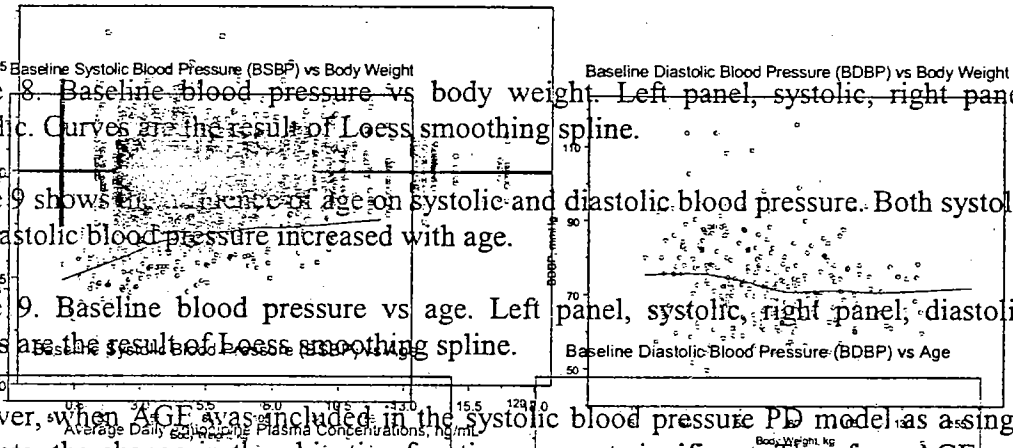


Figure 9 shows the influence of age on systolic and diastolic blood pressure. Both systolic and diastolic blood pressure increased with age.

Figure 9. Baseline blood pressure vs age. Left panel, systolic, right panel, diastolic. Curves are the result of Loess smoothing spline.

However, when AGE was included in the systolic blood pressure PD model as a single covariate, the change in the objective function was not significant. Therefore, AGE as a covariate was not included in the model. For the same reasons, AGE as a covariate was not included in the final model for the diastolic blood pressure.

Pharmacodynamic modeling of the antihypertensive effect of amlodipine in adults was described in the literature (Donelly R, Meredith PA et al Clin Pharmacol Ther 1993; 54(3): 303-310). Twelve patients received 5 mg once daily dose of amlodipine for 6 weeks. Drug concentration – effect relationship was described with the linear model for each individual separately. Mean value (SD) of the slope for the systolic blood pressure changes was -3.1(0.9) mmHg/ng/mL. The value of the slope of the effect-concentration curve was larger in adults in comparison with the same value for children estimated by the reviewer (-1.21 mmHg/ng/mL). The precision of the population model estimation in children was reasonable (RSE 8.5%), and the difference between the slopes for adults and children could be statistically significant and clinically relevant. For example, amlodipine plasma concentration of 10 ng/mL will cause a 31 mmHg reduction of SBP in adults and

12 mmHg reduction of SBP in children. Therefore, systolic blood pressure changes in children were found to be less sensitive to amlodipine than in adults.

COMMENTS:

1. The developed population PK/PD model allowed to describe the relationship between the effect (lowering of systolic (SBP) and diastolic (DBP) blood pressure) and the average amlodipine plasma concentrations (CAVG).

2. The PK/PD relationship was described by linear model. Both systolic and diastolic blood pressure declines were dependent on the CAVG with the slopes of –1.22 mmHg/ng/mL (SBP) and –0.68 mmHg/ng/mL (DBP). The slope was steeper for the SBP.

3. The effect of withdrawal to placebo for the patients randomized to this step in Phase II of the study A0531023 was included in the model. For the SBP, it led to a population average increase of 4.55 mmHg, and for DPB it was 1.46 mmHg.

4. Statistically significant influence of gender was shown for the covariate model of SBP. Female subjects have on average 4.55 mmHg higher baseline SBP value.

5. For DBP the only covariate, which influenced the baseline parameter was body weight. The model includes this covariate as a power function.

6. Time course of the effect could not be taken into account due to the lack of adequate data.

7. The population model has considerable unexplained variability.

8. The difference in the effect – concentration curve slopes for adults and children could be statistically significant and clinically relevant. For example, amlodipine plasma concentration of 10 ng/mL will cause a 31 mmHg reduction of SBP in adults and 12 mmHg reduction of SBP in children. Therefore, systolic blood pressure changes in children were found to be less sensitive to amlodipine than in adults.

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Elena Mishina
4/10/02 02:55:54 PM
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Jogarao Gobburu
4/11/02 05:20:22 PM
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3 Clinical studies

3.1 Protocol A0531018 (PATH-I): Pediatric use of amlodipine in the treatment of hypertension; a randomized, double-blind, placebo-controlled, parallel group dose-ranging study to evaluate the efficacy and safety of amlodipine in the treatment of hypertension in children.

3.1.1 Study dates

28 October 1999 to 10 November 2000

3.1.2 Source materials reviewed

Final study report: Vol 77.1, page 19

Fully amended protocol and amendments: Vol 77.1, page 253.

3.1.3 Protocol

The study population was to be 240 children under age 17 with a baseline systolic pressure above the 95th percentile for gender, age, and height. Subjects were to be drawn equally from strata age 6 to 13[1] and 13 to 17 years. Subjects previously receiving amlodipine must have been receiving a dose less than 2.5 mg. Other concomitant antihypertensive therapy was permitted, but had to remain constant during the study. Exclusion criteria included previous intolerance to dihydropyridines, unstable or malignant hypertension, and any unstable clinical disease.

Subjects were randomized to amlodipine 2.5 or 5 mg and followed for 4 weeks. At that time, a second randomization placed 1/3 of subjects on placebo and the remainder kept the original randomized dose for the final 4 weeks of study. Subjects were followed at weekly intervals. Blood pressure assessments were by an automated oscillometric device. Symptomatic hypotension in the first 2 weeks resulted in withdrawal. Subsequent symptomatic hypotension was treated by dose reduction. Significant blood pressure elevation (10 mmHg) was to be treated by discontinuation. Routine clinical laboratory assessments were performed at screening and at the end of study.

Study drug was commercial amlodipine 2.5 mg tablets and matching placebo.

The primary analysis was a one-sided comparison of the change in systolic pressure on placebo and amlodipine 5 mg. The analysis was LOCF with a linear model incorporating terms for gender, age, weight, height, and etiology. Two administrative interim analyses were planned. The first interim analysis was after 40 subjects completed phase I; its purpose was to allow the study to be resized based on observed variability[2]. The second interim analysis was to accommodate the cutoff date for a report meeting the goals of the Written Request. No statistical penalty was contemplated for either interim analysis.

3.1.4 Results

3.1.4.1 Conduct

The study was conduced at sites in the US (46), Canada (2), Brazil (2), and Argentina (1). These centers enrolled 1 (3 sites) to 20 subjects (2 sites). Two-hundred sixty-eight subjects were enrolled, of whom 258 completed phase I and started phase II. Two-hundred fifty completed phase II, but all 258 entering phase II were evaluable for the primary analysis.

Phase II demographics are summarized in Table 1.

---

[1] *An amendment permitted subjects under age 6 if they could ingest the tablets.*

[2] *This interim analysis resulted in increasing the sample size from 200 to 240 subjects.*

Table 1. Demographics in phase II (PATH-I)

	2.5 mg - Plcbo N=43	2.5 mg - 2.5 mg N=84	5 mg - Plcbo N=47	5 mg - 5 mg N=94
Male (%)	53	62	70	73
Caucasian (%)	53	65	51	65
Black (%)	33	23	32	23
Tanner 1 (M/F)	41/35	33/26	16/36	31/42
Tanner 2	18/10	6/7	19/21	18/4
Tanner 3	14/20	8/19	19/0	4/8
Tanner 4	14/5	12/16	19/29	19/17
Tanner 5	14/30	41/32	28/14	28/23

Discrepancies among treatment groups were about what was to be expected in a study of this size. The placebo groups tended to have more females and more Blacks.

The most common presenting condition was obesity (n=78). Thirty-four subjects had history of renal transplants, Fourteen had history of cardiac transplant. One-hundred eighteen (46%) had prior antihypertensive treatment, most commonly with ACE inhibitors.

Ten subjects discontinued from phase I and 8 subjects discontinued during phase II, for various reasons.

3.1.4.2 Effectiveness

Effects on blood pressure are summarized in Table 2.

Table 2. Change in systolic pressure (PATH-I)

Delta SBP	2.5 mg		5 mg	
Change from	mmHg	P	mmHg	P
Baseline	-3.3±1.9[3]	0.04	-5.1±1.9	0.005[4]
End phase I	-2.3±1.8	0.01	-3.9±1.8	0.01

Blood pressures by week of study are shown in Figure 1.

Appears This Way
On Original

[3] *Mean ± SE*

[4] *Primary end point*

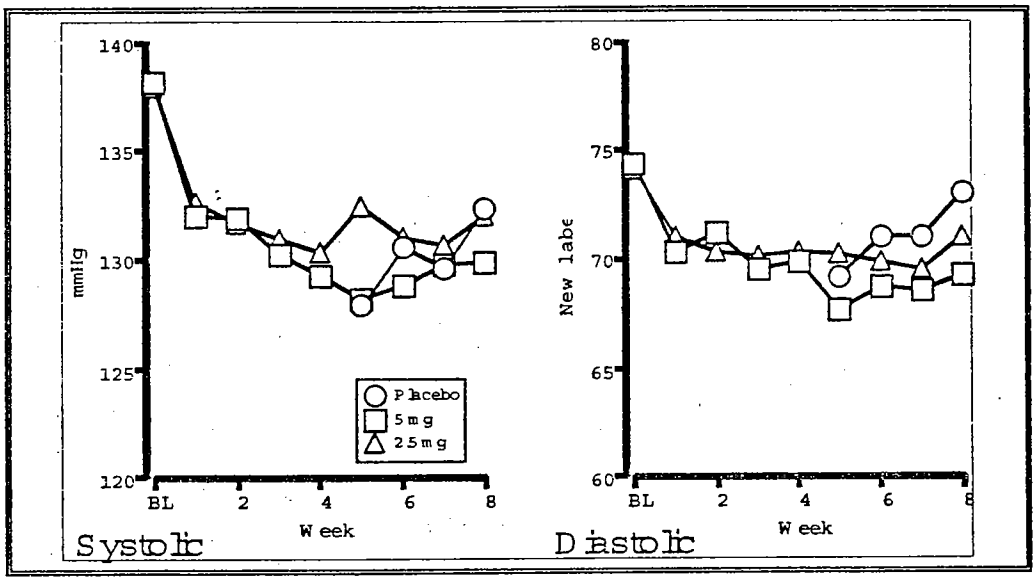

Figure 1. Systolic and diastolic pressures by week (PATH-I)

Data from sponsor's tables 5.2.1, 5.2.3, 5.3.1, and 5.3.3. Sponsor's LOCF analysis; reviewer's graph.

Change from the end of phase I to the end of phase II is a better indication of the magnitude of treatment effect. Four weeks does not allow time to achieve steady-state. The data also suggest that 2.5- and 5-mg doses are not much different and that much of the change from baseline represents a placebo effect.

There was a statistically significant interaction by gender, with females having larger effects than males. By the sponsor's analyses, this was independent of statistically significant effects by weight. There was no significant interaction with Tanner stage.

3.1.4.3 Safety

There were no deaths.

Eight subjects withdrew (6 from active treatment) for worsening hypertension, coded as an adverse event. One subject discontinued for facial edema, one for rash and edema of the fingers, and one for pulmonary edema and shortness of breath, the latter of which was considered serious.

There were a total of 5 serious adverse events, all on active study drug, and none considered treatment-related. All events resolved.

Subject 5038-1209 was a 10-year old male with a renal transplant, hospitalized for urinary tract infection.

Subject 5037-3003 was a 13-year old male hospitalized for gastroenteritis.

Subject 5020-1133 was a 9-year old female who developed pancreatitis 13 days after completion of the study (not clear is subject was still receiving amlodipine).

Subject 5022-3134 was a 13-year old female who was hospitalized for pulmonary edema during week 7.

Subject 5022-3135 was a 13-year old male developed pneumonia, sepsis, and acute tubular necrosis.

Adverse events were reported for 60-80% of subjects per group, with no trend by dose group. Of adverse events reported for more than 2 subjects per group, the only ones

more common on active drug than on placebo were headache (24% vs. 18%) and asthenia (8% vs. 7%).

Four to 8% of subjects per group had treatment-emergent laboratory abnormalities, but the only such abnormality in more than 2 subjects per arm was hematuria (3 subjects on 2.5 mg and 1 subject on 5 mg).

3.2 Protocol A0531023 (PATH-II): Pediatric use of amlodipine in the treatment of hypertension; a population pharmacokinetic trial.

3.2.1 Study dates

14 January 2000 to 10 November 2000

3.2.2 Source materials reviewed

Final study report: Vol 77.7, page 2968.

Fully amended protocol and amendments: Vol 77.7, page 3066.

3.2.3 Protocol

This was an open-label, multicenter study in 70 subjects age 6 months to 17 years, on a stable dose of amlodipine for hypertension. Subjects could be receiving any dose, morning, evening, or twice daily. Formal monitoring for dosing compliance began 1 week prior to the first PK sampling (collected 3, 5, 8, 10, 15, 18, 20, and 24 hours after a dose). There was a second PK sampling series the following day; some subjects had 24-hour ABPM beginning with that visit. There was an optional third PK sampling series 3 weeks later. NONMEM analyses of PK were specified.

3.2.4 Results

3.2.4.1 Conduct

Nine sites in the US and one in Canada enrolled a total of 74 subjects (3 to 20 per site), of whom 72 completed study. One subject underwent renal transplant prior to the first PK sampling visit.

Three subjects were under age 2 years, 9 were age 2-5, 34 were age 6-12, 23 were age 13-16, and 5 were age >17. Sixty-six percent were male. Fifty-seven percent were Caucasian and 35% were Black. Weight ranged from 6 to 142 kg.

3.2.4.2 Pharmacokinetics and pharmacodynamics

Model-estimated clearance was dependent on age and gender. By 45 kg, the median mass in the study, clearance was indistinguishable from rates published for adults, including the approximately 50% higher clearance in males. Clearance in the two subjects under age 2 years was about half the adult value.

Model-estimated volume of distribution was dependent on mass alone. Volume of distribution per unit mass was about 2-fold higher in the youngest subjects than in the oldest, and values in subjects >45 kg were similar to values reported in adults.

Seventeen subjects at one center underwent ABPM, but there was no control group and no baseline assessment, so these data are difficult to interpret.

3.2.4.3 Safety

There were no deaths.

One subject was lost to follow-up and one discontinued permanently following an adverse event of dehydration and hyperglycemia, not attributed to study drug. One subject missed several days' treatment because of grand mal seizure, also not believed to be related to study drug. The few other serious adverse events—infections (2) and progression of renal failure (2) were not considered treatment-related.

Headache was the most commonly reported adverse event.

3.3 Other published data

The sponsor summarized 22 literature reports of exposure to amlodipine in the pediatric population, with ages similar to sponsor's studies. A few of these were reviews or were reports of overdose. Other experience worth noting follows:

Flynn et al. have 4 publications across which it is difficult to count the number of distinct subjects or patients, but the largest number cited is 55. Dosing by mass was similar to recommended levels in adults. Dizziness, fatigue, flushing, and edema were reported by no more than 3 subjects.

Von Vigier reported on 43 pediatric renal failure patients dosed on a per-meter-squared basis; 15% of these subjects withdrew for edema, flushing, or headache.

Various smaller series are reported for doses from about half to twice the adult dose on a mass-adjusted basis; safety experience is fairly consistent.

Several publications report that levels of cyclosporine are not affected by amlodipine.

4 Summary and recommendations

The studies clearly satisfy the terms of the Written Request. Thus, the decision to grant exclusivity is appropriate.

What, if anything, should be said about the results in labeling for use in children is more difficult. The effectiveness study—randomization first to one of two doses and then again to the same dose versus placebo—did not have an initial randomization to placebo, so the magnitude of treatment effect at the end of 4 weeks is difficult to ascertain. Attainment of steady-state took somewhat longer than 4 weeks, so the second phase placebo control is also not adequate to determine the real treatment effect, but it probably less than 5 mmHg for the 5-mg dose. If the treatment effect were larger, then titration steps should be only after 6 or 8 weeks.

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