CENTER FOR DRUG EVALUATION AND RESEARCH

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Statistical Review(s)

STATISTICAL REVIEW AND EVALUATION

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

NDA No./ SUPPLEMENT:	19-787/SE5
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INDICATION:	Children with Hypertension
SPONSOR:	Pfizer
DOCUMENTS REVIEWED:	S 77.1, 77.3, 77.4, and 77.7
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STATISTICAL REVIEW AND EVALUATION

1 Executive Summary and Statistical Findings

1.1 Overview of the Studies Reviewed

Amlodipine is a dihydropyridine calcium channel blocker which is approved for use in adults in the treatment of hypertension, chronic stable angina, and confimed or suspected vasospatic angina. The approved adult doses for these indications are 5 to 10mg once daily. This NDA supplement included results of two studies conducted in pediatric patients: a population pharmacokinetic trial (A023), and a dose-ranging study of amlodipine in children with hypertension (A018). This reviewer evaluated the dose-ranging study (A018).

Study A018 was a double-blind, randomized, placebo-conrolled, parallel group, multicenter, dose ranging study (2.5mg – 5mg) evaluating the efficacy and safety of amlodipine in the treatment of hypertension in children. 268 patients received at least one dose of the study drug, and 250 patients completed the study.

The study consisted of a 2 week screening period followed by two 4 week treatment phases. In treatment Phase 1 of the study, all patients were randomized to receive amlodipine (2.5mg for 4 weeks; or 2.5mg for 2 weeks followed by 5mg for 2 weeks). In treatment Phase 2 of the study patients were randomized to continue on amlodipine at a dose of 2.5mg or 5mg for 4 weeks; or were randomized to withdraw to placebo for 4 weeks. Randomization was stratified by age range into two stratums (Stratum 1: ages greater than or equal to 6 years and less than but not equal to 13 years; Stratum 2: ages greater than or equal to 13 years and less than but not equal to 17 years).

1.2 Principal Findings

The primary endpoint was change in seated systolic blood pressure (SBP) at the end of study compared to baseline. The null hypothesis tested was that for given values of the covariates (treatment, bseline SBP, age, gender, race, weight, height, and etiology), the means of change in SBP were equal in the groups randomized to 5mg and placebo. The alternative hypothesis was that there was a greater mean decrease in the 5mg group. A linear model with the covariates was fitted, and the primary hypothesis was tested using least squares means from the model with a 0.05 level of significance

Patients who received 5.0mg amlodipine had statistically significantly greater reductions in seated SBP from baseline to the end of the study than those in the placebo group (p=0.005). The difference between the two amlodipine treatment groups was not statistically significant. The estimated difference of treatment effect from the placebo for change in SBP was approximately 5.1mmHg for the 5mg and 3.3mmHg for the 2.5mg group. There appeared to be a gender effect on

SBP (p=0.0143) suggesting greater reductions among females than males. The following table summarizes the results.

Table 1: Results of Comparisons between Treatment Groups

	Estimated Mean Difference	p-value
5.0mg vs. Placebo	-5.054	0.0046
2.5mg vs. Placebo	-3.287	0.0449
5.0mg vs. 2.5mg	-1.768	0.1803

The secondary objectives of the study were to compare the effect of amlodipine vs. placebo on diastolic blood pressure (DBP) in the hypertensive children; to evaluate the effect of amlodipine on SBP and DBP as a function of dose and body size; and to evaluate the safety of amlodipine in hypertensive children.

The treatment effect for DBP achieved a p-value=0.047 for the overall comparison of treatment groups, but its interpretation is complicated by an apparent treatment by gender interaction. A correlation was shown between mg/kg dose and change in SBP (p=0.031) and DBP (p=0.023). There was a pattern of greater reductions in both SBP and DBP in females than males. Tanner stage was not shown to be associated with treatment effect.

1.3 Conclusions

There was a statistically significant reductions in seated SBP among patients who received 5.0mg amlodipine compared to the patients in the placebo group (p=0.005). The change of DBP, relation between mg/kg dose and the reduction of blood pressure, and the blood pressure reduction during Phase 1 also confirmed that the amlodipine had significant efficacy on treatment for pediatric hypertension.

2 Statistical Review and Evaluation of Evidence

2.1 Introduction

Amlodipine is a dihydropyridine calcium channel blocker which is approved for use in adults in the treatment of hypertension, chronic stable angina, and confimed or suspected vasospatic angina. The approved adult doses for these indications are 5 to 10mg once daily.

This NDA supplement includes two studies conducted in pediatric patients and a summary from published literature:

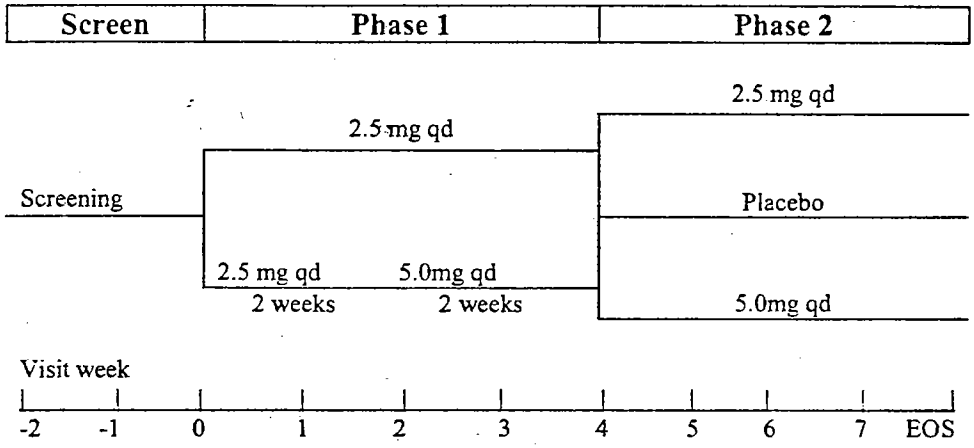
a) A0531018 Clinical Study Report – The Pediatric Use of Amlodipine in the Treatment of Hypertension
b) A0531023 Clinical Study Report – The Pediatric Use of Amlodipine in the Treatment of Hypertension: A Population Pharmacokinetic Trial
c) Summary From Published Literature of Clinical Experience With Amlodipine in Children

This statistical reviewer evaluated the dose-ranging study (A018)

2.2 Study Design

This study was a randomized, double-blind, dose-ranging, placebo controlled, parallel group, multicenter study conducted in the United States, Canada, Argentina, and Brazil. It consisted of a screening visit, followed by an 8-week treatment phase. There are two treatment phases: Phase I, a 4-week randomized double-blind period with patients receiving amlodipine and Phase II, a 4-week randomized amlodipine-placebo withdrawal period. During the fist phase, patients are randomized to one of 2 daily doses of amlodipine, either 2.5mg for 4 weeks; or 2.5mg for 2 weeks followed by 5mg for 2 weeks. During the second phase, a randomized amlodipine-placebo withdrawal phase, 1/3 of the patients will be randomized to withdraw to placebo while other patients continue on their treatment from the latter part of the first phase.

Figure 1 : Design of the Study



2.3 Data Analyzed and Sources

Data used for review is from the electronic submission received on 9/28/01. The network path is " CDSESUB1\N19787\S_030\2001-09-14\\crt\datasets\1018 " in the EDR. The following volumes were reviewed: 77.1, 77.3, 77.4, and 77.7

2.4 Study Objectives

The primary objective of the study was to compare the effect of amlodipine versus placebo on seated SBP in hypertensive children ages 6 to less than 17 years.

The secondary objectives of the study were to compare the effect of amlodipine versus placebo on DBP in these hypertensive children; to evaluate the effect of amlodipine on systolic and diastolic blood pressure as a function of dose and body size; and to evaluate the safety of amlodipine in hypertensive children.

2.5 Efficacy Endpoints

The primary efficacy endpoint was change in seated SBP at the end of study treatment in Phase 2 compared to baseline.

The secondary efficacy endpoints included 1) the change in seated DBP at the end of study treatment in Phase 2 compared to baseline, 2) relationship between the mg/kg exposure and the blood pressure response (SBP&DBP), 3) influence of Tanner Stage of blood pressure response (SBP&DBP), and 4) change in blood pressure (SBP&DBP) during Phase 1.

2.6 Sample Size Considerations

At a sample size of 240 subjects initially randomized to Phase I, assuming a 25% dropout rate between the beginning of Phase I and the end of Phase II, it was estimated that the power to detect treatment effects of 5 mmHg between the group randomized to amlodipine 5 mg and placebo will be approximately 80% for the primary comparison of the study.

Reviewer's Comments:

1. 268 patients enrolled in the study, and 256 patients were included in the primary analysis. The actual dropout rate was 6.7%, which was significantly lower than anticipated dropout rate, which was 25%. The sample size of this study was larger than initially planned sample size.

2.7 Stratification

The study was stratified by age range. Stratum 1 consisted of younger patients, less than but not equal to 13 years. Stratum 2 consisted of older patients, aged greater than or equal to 13 years and less than but not equal to 17 years.

2.8 Interim Analysis

An interim analysis was planned and conducted for the purpose of re-estimating blood pressure variability after approximately 40 patients had completed Phase 1. As this analysis was to utilize only Phase 1 data, no primary efficacy data were involved, and no decision other than to increase sample size based on the re-estimate of variability, no adjustment to planned levels of significance was required. The sample size for the study was subsequently increased from 200 to 240 after the interim analysis.

Reviewer's Comments:

1. It was stated in the protocol that two administrative interim analyses were planned. However, there was no record about the second interim analysis in the study report.

2.9 Efficacy Analysis Methods

The null hypothesis tested was that for given values of the covariates, the means of the distribution of the primary variable were equal in the groups randomized to 5mg and placebo. The alternative hypothesis was that there was a greater mean decrease in the 5mg group. Four readings of SBP were taken at each visit. To calculate the SBP associated with a given visit, all non-physiologic readings were

discarded, the first reading was discarded, and an average of the remaining readings was taken as the patients' SBP for the visit. For patients who discontinued during Phase 2, the last mean blood pressure was carried forward for comparison to baseline. The primary analysis employed a linear model with terms for treatment, baseline SBP, gender, race, etiology, age, weight, and height. The primary hypothesis was tested using least squares means from this model with a 0.05 level of significance (one-sided with amlodipine providing the greater reduction).

Diastolic responses were analyzed in the same manner as for the primary analysis of systolic responses. For the estimation of the relationship between the mg/kg exposure and the blood pressure response, a linear model with the covariates (treatment, baseline, age, gender, height, and etiology) and mg/kg as predictors was fitted to blood pressure responses. Influence of Tanner Stage was analyzed by employing a linear model with the covariates (treatment, baseline, gender, height, weight, and etiology) and Tanner Stage as predictors to blood pressure responses.

2.10 Sponsor's Results and Statistical Reviewer's Findings/Comments

This section will summarize the results of the study.

2.10.1 Baseline Characteristics

The distribution of baseline demographic characteristics including age, sex, races, weight, and height and Tanner Stages of sexual development are summarized in the following Tables. The treatment groups appeared to be comparable in most demographic composition. However, each treatment group had a higher number of male patients than female patients.

Table 2: Demography and Baseline Characteristics

Demographic Characteristics				
	2.5mg / 2.5mg	2.5mg / Placebo	5.0mg / 5.0mg	5.0mg / Placebo
Number of Subjects	84	43	94	47
Sex				
Male	52 (61.9%)	23 (53.5%)	69 (73.4%)	33 (70.2%)
Female	32 (38.1%)	20 (46.5%)	25 (26.6%)	14 (29.8%)
Race				
White	55	23	61	24
Black	19	14	22	15
Asian	0	0	2	0
Hispanic	5	5	8	7
Other	5	1	1	1
Weight (kg) Male/female	73.5/64.5	63.9/58.1	66.8/58.1	70.2/62.5
Height (cm) Male/female	160.8/150.4	151.5/146.7	156.2/144.6	156.4/145.4
Baseline B.P. (mmHg) Male/female				
SBP	141.9/137.3	136.3/130.3	139.5/136.0	137.5/136.7
DBP	74.7/76.8	72.6/70.0	72.1/78.2	74.7/76.8

• Sponsor's analysis

Table 3 : Baseline Characteristics (Tanner Stage)

Tanner Stages of Sexual Development				
	2.5mg/ 2.5mg	2.5mg / Placebo	5.0mg / 5.0mg	5.0mg / Placebo
Male Subjects: Pubic Hair	51	22	68	32
Stage 1	17 (33.3%)	9 (40.9%)	21 (30.9%)	5 (15.6%)
Stage 2	3 (5.9%)	4 (18.2%)	12 (17.6%)	6 (18.8%)
Stage 3	4 (7.8%)	3 (13.6%)	3 (4.4%)	6 (18.8%)
Stage 4	6 (11.8%)	3 (13.6%)	13 (19.1%)	6 (18.8%)
Stage 5	21 (41.2%)	3 (13.6%)	19 (27.9%)	9 (28.1%)
Female Subjects Breast/Pubic Hair	31	20	24	14
Stage 1	8 (25.8%) / 7 (22.6%)	7 (35.0%) / 9 (45.0%)	10 (41.7%) / 12 (50.0%)	5 (35.7%) / 6 (42.9%)
Stage 2	2 (6.5%) / 4 (12.9%)	2 (10.0%) / 0 (0.0%)	1 (4.2%) / 1 (4.2%)	3 (21.4%) / 2 (14.3%)
Stage 3	6 (19.4%) / 4 (12.9%)	4 (20.0%) / 4 (20.0%)	2 (8.3%) / 0 (0.0%)	0 (0.0%) / 0 (0.0%)
Stage 4	5 (16.1%) / 5 (16.1%)	1 (5.0%) / 1 (5.0%)	4 (16.7%) / 3 (12.5%)	4 (28.6%) / 4 (28.6%)
Stage 5	10 (32.3%) / 11 (35.5%)	6 (30.0%) / 6 (30.0%)	7 (29.2%) / 8 (33.3%)	2 (14.3%) / 2 (14.3%)

• Sponsor's analysis

2.10.2 Primary Efficacy Analyses

The primary endpoint was the change of SBP from the start of Phase I to the end of Phase 2, and the endpoint was analyzed by employing a linear model with covariates; treatment, baseline SBP, age, gender, race, weight, height, and etiology. Least squares means from the model were used for testing the primary hypothesis. Patients in the 5.0mg group had statistically significantly greater reductions in SBP (-8.7mmHg) than those in the placebo group (-3.6mmHg; p=0.005). The estimate of the treatment effect for change in SBP between the two groups was 5.1mmHg. Uncorrected for multiple comparisons, the patients in the 2.5mg group also had statistically significantly greater reductions in SBP (-6.9mmHg) than the patients in the placebo group (-3.6mmHg; p=0.045). The estimate of the treatment effect for change in SBP between the 2.5mg group and the placebo was approximately 3.3mmHg. The difference between the two amlodipine treatment groups (2.5mg vs. 5.0mg) was not statistically significant (p=0.180). The following table summarizes the results.

Table 4: Results of Comparisons between Treatment Groups

	Estimated Mean Difference	p-value
5.0mg vs. Placebo	-5.054	**0.0046**
2.5mg vs. Placebo	-3.287	0.0449
5.0mg vs. 2.5mg	-1.768	0.1803

• Sponsor's results confirmed by the reviewer's analysis

As shown in the Table below, there were statistically significant differences in change from baseline among the patients assigned to the three different Phase 2 treatments (p=0.03).

Table 5: Result from Linear Model of Changes in Systolic Blood Pressure

Covariates	Coefficient	P-value
Treatment		**0.0303**
Baseline systolic bp	-0.430	0.0001
Age	0.510	0.1915
Gender	4.192	0.0143
Race		0.2743
Weight	0.011	0.8128
Height	0.017	0.8173
Etiology		0.0735

• Sponsor's results confirmed by the reviewer's analysis

The p-value for the gender effect on SBP was 0.014, which indicates greater reductions among females than males. The mean changes by gender from

baseline to the end of Phase 2 were: amlodipine 2.5mg: males, -6.9mmHg; females, -8.9mmHg; amlodipine 5.0mg: males, -6.6mmHg; females, -14.0mmHg; placebo: males, -2.5mmHg; females, -3.8mmHg. The following table summarizes the mean changes by gender from baseline to the end of Phase 2.

Table 6: Mean of Systolic Blood Pressure Change from Baseline by Gender

	Treatment					
	Placebo		2.5mg		5.0mg	
Gender	N	Mean	N	Mean	N	Mean
Male	54	-2.5mmHg	51	-6.9mmHg	63	-6.6mmHg
Female	33	-3.8mmHg	32	-8.9mmHg	23	-14.0 mmHg

• Sponsor's analysis

The placebo group was broken down by Phase 1 treatment, and unadjusted mean changes of SBP and DBP were computed. The mean changes were seen to be similar for the two Phase 1 treatment groups with mean changes in SBP of -3.6mmHg and –2.4mmHg in the 2.5mg and 5.0mg groups, respectively; and mean changes in DBP of –0.1mmHg and –0.8mmHg in the 2.5mg and 5.0mg groups, respectively. The following Table summarizes the mean change of systolic and diastolic blood pressure for placebo treatment group.

Table 7: Change in Blood Pressure of 2.5/Placebo and 5.0/Placebo Treatment Arms

	N	Mean change of SBP	Mean change of DBP
2.5/Placebo	42	-3.6	-0.1
5.0/Placebo	45	-2.4	-0.8

• Sponsor's analysis

Reviewer's Comments:

1. No procedure for multiple comparison adjustment was proposed. Therefore, the result of comparison between the 2.5mg group and the placebo group should be interpreted with caution since α-level was not adjusted for multiple comparisons.

2. The mean of SBP changes in each gender reported in the previous table (Table 6) were not adjusted for covariates unlike the means for combined gender. The adjusted means of SBP changes from baseline by gender are shown in the table below.

Table 8: Adjusted Mean of Systolic Blood Pressure Change from Baseline by Gender

	Treatment					
	Placebo		2.5mg		5.0mg	
Gender	N	Mean	N	Mean	N	Mean
Male	54	-3.0mmHg	51	-6.3mmHg	63	-6.7mmHg
Female	33	-6.5mmHg	32	-8.2mmHg	23	-11.1mmHg

• Reviewer's analysis

As shown in the table above, the reduction of SBP was greater in female group across the treatment groups. In addition, the mean of change of females in the placebo group was similar to the mean changes of males in the amlodipine- treated groups (6.5mmHg vs. 6.3mmHg and 6.7mmHg). The mean changes between two amlodipine- treated groups among males were very similar (6.3mmHg vs. 6.7mmHg).

3. As an exploratory analysis, this reviewer fitted a linear model which included interaction term between gender and treatment. This model showed there was no statistical evidence for qualitative interaction of treatment by gender in this model. (p-value=0.6367)

4. The protocol specified stratification by age at randomization. Younger patients were defined as age < 13, and older patients were defined as ≥ 13. The following table presents the adjusted mean change of SBP stratified by the age at the randomization.

Table 9: Adjusted Mean of Changes in Systolic Blood Pressure by Age Stratum

	Treatment					
	Placebo		2.5mg		5.0mg	
Age	N	Mean	N	Mean	N	Mean
<13	48	-3.8mmHg	33	-8.0mmHg	43	-7.1mmHg
≥13	39	-2.4mmHg	50	-6.9mmHg	43	-10.3mmHg

• Reviewer's analysis

The primary analysis model showed that age of patients did not affect the mean of changes of SBP (p-value = 0.1915 in Table 5). However, above table suggested that the younger patients (<13) did not appear to have treatment effect from high dose of amlodipine (5.0mg) as much as the older patients. The mean of changes in SBP were increased as the dose of amlodipine

increased among the older patients; however, the mean of changes in SBP in 5.0mg treatment group appeared to be smaller than the one of 2.5mg treatment group among the younger patients. However, the above subgroup analysis results should be interpreted with caution.

5. This reviewer compared the mean changes of SBP and DBP among the patients who received the same treatment during Phase 1. The patients in the 5.0mg group (5.0/5.0) were compared with the patients who received 5.0mg during Phase 1, and switched to the placebo group in Phase 2 (5.0/Placebo). The patients in the 2.5mg group were compared with the patients who received 2.5mg during Phase 1, and switched to the placebo group in Phase 2 (2.5/Placebo). The results of the analyses are summarized in Table 10.

Table 10: Results of Comparisons between 5.0/5.0 and 5.0/Placebo groups, and between 2.5/2.5 and 2.5/placebo groups.

	Estimated Mean Difference	p-value
SBP		
5.0/5.0 vs. 5.0/Placebo	-6.058	0.0046
2.5/2.5 vs. 2.5/Placebo	-2.166	0.1828
DBP		
5.0/5.0 vs. 5.0/Placebo	-4.499	0.0059
2.5/2.5 vs. 2.5/Placebo	-1.976	0.1417

• Reviewer's analysis

As shown in the above table, the analysis result for SBP was consistent with the one for DBP. The difference of mean changes in SBP and DBP between 5.0/5.0 group and 5.0/placebo group were statistically significant (SBP, p=0.0046; DBP, p=0.0059). The estimated mean differences between the two groups were –6.058 for SBP, and –4.499 for DBP. However, the difference of mean changes between the 2.5/2.5 group and the 2.5/placebo group were smaller and insignificant (SBP, p=0.1828; DBP, p=0.1417). And the estimated mean differences between the groups were only –2.166 for SBP and –1.976 for DBP. However, the results need to be interpreted cautiously since the sample sizes of the placebo groups (2.5/placebo and 5.0/placebo) are about a half of the amlodipine treated groups (2.5/2.5; 83 vs. 2.5/placebo; 42, and 5.0/5.0; 88 vs. 5.0/placebo; 45).

2.10.3 Secondary Efficacy Analyses

The secondary analyses for the study include DBP response, regression vs. mg/kg, relationship to Tanner Stage, and Phase I.

Diastolic Blood Pressure:

For the mean change of DBP, a linear model with terms for treatment, baseline DBP, gender, race, age, weight, height, etiology, and an interaction terms between covariates and treatment was fitted. This model showed that the overall treatment effect was highly significant (p-value=0.005). Baseline DBP was a significant variable that affected the mean change of hypertensive pediatric patients.

Table 11: Results of Linear Model for Changes in Diastolic Blood Pressure

Covariates	Coefficient	P-value
Treatment		**0.005**
Baseline diastolic b.p.	-0.499	0.0001
Age	0.489	0.3056
Gender	-2.534	0.2722
Race		0.1490
Weight	-0.047	0.4864
Height	-0.047	0.5266
Etiology		0.8630
Treatment*Gender		0.0343

• Sponsor's results confirmed by the reviewer's analysis

The p-value for treatment by gender interaction for change from baseline to end Phase 2 in DBP was p=0.034. Therefore, the data were further analyzed separately by gender. For males, although both active treatments yielded lower point estimates for mean blood pressure reduction than did placebo (mean changes: 5.0mg, -3.2mmHg; 2.5mg, -3.4mmHg, placebo, -1.1mmHg), the overall differences among treatments were not statistically significant (p=0.438). For females, there were treatment effects evident (p=0.023), and the 5.0mg dose group reduced blood pressures more than placebo (mean changes: 5.0mg, -8.0mmHg; 2.5mg, -3.2mmHg; and placebo, -0.7mmHg). The following table summarizes the results.

Table 12: Analysis of Diastolic Blood Pressure for Each Gender

	Overall Treatment Effect (p-value)	Adjusted Mean Changes		
		Placebo	2.5mg	5.0mg
Male	0.438	-1.1mmHg	-3.4mmHg	-3.2mmHg
Female	0.023	-0.7mmHg	-3.2mmHg	-8.0mmHg

• Sponsor's results confirmed by the reviewer's analysis

Reviewer's Comment:

1. The meaning of overall treatment effect in an analysis of DBP should be

cautiously interpreted due to the apparent treatment by gender interaction.

Regression vs. mg/kg:

When the changes in systolic and diastolic blood pressures were regressed on assigned dose divided by patients' weights after accounting for baseline, age, gender, race, height, and etiology, there was a correlation between mg/kg dose and change in blood pressure: p=0.031 for systolic, and p=0.023 for diastolic. Predicted mean changes in SBP and DBP from baseline to the end of Phase 2 by tertiles of study drug exposure are provided in Tables below (predicted mean change for zero mg/kg exposure: -3.7mmHg systolic –0.7mmHg diastolic; predicted mean change for greater than zero mg/kg exposure to 0.05869mg/kg: -6.3mmHg systolic; -3.1mmHg diastolic; and predicted mean change for greater than 0.05869mg/kg exposure: -9.2mmHg systolic; -4.9mmHg diastolic)

Table 13: Predicted Mean Change in Systolic Blood Pressure by Tertiles of Study Drug Exposure (mg/kg)

Exposure	Adjusted Mean	Standard Error
< 0 mg/kg	-3.660	1.337
> 0 – 0.05869 mg/kg	-6.309	1.444
> 0.05869 mg/kg	-9.247	1.423

• Sponsor's results confirmed by the reviewer's analysis

Table 14: Predicted Mean Change in Diastolic Blood Pressure by Tertiles of Study Drug Exposure (mg/kg)

Exposure	Adjusted Mean	Standard Error
< 0 mg/kg	-0.746	1.027
> 0 – 0.05869 mg/kg	-3.096	1.111
> 0.05869 mg/kg	-4.922	1.097

• Sponsor's results confirmed by the reviewer's analysis

Reviewer's Comment:

1. Mean of dose divided by patients' weight was computed separately by gender to see whether drug exposure can explain the greater reduction of blood pressure among females or not. The means of mg/kg for each gender were about same (male : 0.048mg/kg, female: 0.049 mg/kg).

Relationship to Tanner Stage:

When Tanner stage was substituted for age in the primary model and the two active treatment groups were pooled, the analytic results were consistent with the primary model. As for age in the primary model, the evidence is insufficient to conclude that Tanner stage is associated with response (Tanner stage effect: SBP, p=0.253; DBP, p=0.466). There was no evidence of any interaction between treatment (amlodipine, placebo) and Tanner stage.

Reviewer's Comment:

1. The results of analysis for the effect of Tanner stage on blood pressure were consistent when the two amlodipine-treated groups were not pooled. The p-value for Tanner stage effect on the SBP was 0.2762, and the one for DBP was 0.5198.

Phase I

During Phase I, blood pressures were reduced in both amlodipine treatment groups, but there was not enough difference between the groups to conclude that the effects of group assignment were different, with a p-value for a treatment effect for SBP of p=0.234. The p-value for a treatment effect for DBP was p=0.486. Point estimates for the amlodipine 5.0mg group were lower than the amlodipine 2.5mg group. The mean changes of systolic and diastolic blood pressure in Phase I are summarized in the table below.

Table 15: Mean Changes of Blood Pressure in Phase I

	Dose Group	
	2.5 mg	5.0 mg
Mean change of SBP	-7.3 mmHg	-9.0 mmHg
Mean change of DBP	-3.7 mmHg	-4.4 mmHg

• Sponsor's results confirmed by the reviewer's analysis

3 Statistical Evaluation of Collective Evidence

In both phases of the study, blood pressures were reduced in both amlodipine treatment groups, although the difference between the two treatment groups was not significant.

In Phase 2 of the study, patients in the 5.0mg treatment group had significantly greater reductions in SBP from baseline than those in the placebo group (p=0.005). Uncorrected for multiple comparisons, the comparisons between two amlodipine-treated groups showed an insignificant difference of mean change in SBP between two amlodipine-treated groups (-1.8mmHg, p=0.180). The mean changes in SBP between the 2.5mg group and the placebo group was -3.3mmHg

with p=0.045. There appeared to be a gender effect on SBP suggesting greater reductions among females than males.

The treatment effect for DBP achieved a p-value less than 0.05 for the overall comparison of treatment groups, but it's interpretation is complicated by an apparent treatment by gender interaction.

A correlation was shown between mg/kg dose and change in systolic and diastolic blood pressure with a predicted mean change for zero mg/kg exposure.

Tanner stage was not shown to be associated with treatment effect.

4 Conclusion

There was a statistically significant reductions in seated SBP among patients who received 5.0mg amlodipine compared to the patients in the placebo group (p=0.005). The change of DBP, relation between mg/kg dose and the reduction of blood pressure, and the blood pressure reduction during Phase 1 also confirmed that the amlodipine had significant efficacy on treatment for pediatric hypertension.

Jasmine Choi, M.S.
Mathematical Statistician
Date:

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