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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21-286/S-018

Drug Name: Benicar® (olmesartan medoxomil)
Indication(s): Pediatric Hypertension
Applicant: Daiichi-Sankyo
Date(s): Letter Date: 08-05-2009
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Biometrics Division: DB1
Statistical Reviewer: Valeria Freidlin, Ph.D.
Concurring Reviewers: James Hung, Ph.D.

Medical Division: Cardio-Renal
Clinical Reviewer: Shen Xiao, M.D.

Project Manager: Quynh Nguen

Keywords: Written Request**,** dose response.

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The design of the single Study CS0866-A-U301 in this submission was consistent with the amended Pediatric Written Request issued by the FDA on 05/19/2009. In hypertensive pediatric patients aged 6 to 16 years, Study CS0866-A-U301 showed that Benicar (olmesartan medoxomil) is effective. A statistically significant dose response was observed for both sitting systolic (SeSBP) and sitting diastolic (SeDBP) blood pressure ($p<0.001$) in Period II. In randomized placebo withdrawal Period III, a statistically significant difference was shown between Benicar and placebo relative to both SeSBP and SeDBP ($p<0.003$).
In the subgroup of 59 patients aged 1 to 5 years, only one dose (0.3 mg/kg) of Benicar was used in Period II. In placebo withdrawal Period III for this subgroup, Benicar was only numerically better than placebo ($p>0.2$).
Safety of Benicar is a matter of clinical judgment of the medical division.

1.2 Brief Overview of Clinical Studies

A single clinical study, CS0866-A-U301, was submitted to demonstrate efficacy and safety of olmesartan medoxomil (OM) in hypertensive pediatric population. For brevity this study will be called Study 301.

1.3 Statistical Issues and Findings

The design of Study 301 is consistent with the Written Request (WR) from the FDA. This reviewer agrees with the statistical methods used by the sponsor. The primary efficacy results in Study 301 were verified and confirmed by this reviewer.

2. INTRODUCTION

2.1 Overview

2.2 Data Sources and Data Integrity

The sponsor has submitted an electronic NDA. Electronic submission and SAS datasets can be found at the following link: \\CDSESUB1\EVSPROD\NDA21286\0000.
This reviewer looked for high treatment responses in large sites. The US site # 631 with 26 randomized patients and mean change of -13.9 mm Hg in sitting systolic blood pressure (SeSBP) from baseline to the end of Period II was recommended for DSI inspection.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy in Study CS0866-A-U301

Reviewer's comment: For Study 301, the sponsor used the Trial B design suggested in the Written Request (WR). Trial B is a two-stage trial where the first stage is randomization to the two doses of active drug and the second stage is randomization to continuation of the original dose or to placebo (randomized withdrawal study).
According to the WR, "the analysis of Trial B would first be a slope analysis for the first phase. If the first phase failed to reveal a statistically significant non-zero slope, an analysis of the second phase would determine whether there was, or was not, a blood pressure effect. No alpha adjustment would be required for testing these two hypotheses. This design would allow to distinguish between failure to see dose-response because all doses were similarly effective and failure to see a dose-response because none of the doses had an effect."

Study CS0866-A-U301301 was a randomized, multicenter, double-blind, parallel-group, prospective dose-ranging study in subjects 1 to 16 years of age with primary or secondary hypertension. Subjects were enrolled into one of three cohorts based on age and race. Subjects 6 to 16 years of age were enrolled into Cohort A. Subjects enrolled into Cohort A were stratified by age with approximately half aged 6 to 12 years and the remainder aged 13 to 16 years. Approximately 15% of the subjects in Cohort A were to be of Black or African descent. When a minimum of 28 Black subjects were randomized into Cohort A, enrollment in Cohort B was started. Black subjects only, 6 to 16 years of age, were enrolled into Cohort B. Subjects 1 to 5 years of age were enrolled into Cohort C regardless of race. Approximately 340 subjects were planned for the study with 180 in Cohort A, 100 in Cohort B, and 60 in Cohort C.

The study had four periods. Period I was a wash-out period from Week -1 to randomization. Subjects were randomized to treatment sequences carried through the remainder of the study. Period II was a double-blind, dose-ranging period for Cohorts A and B, where subjects received either low-dose or high-dose OM once daily. In Cohort C, all subjects received 0.3 mg/kg OM per day. Period III was a placebo-controlled withdrawal period beginning at Week 4 and ending after 1 or 2 weeks, depending on the sitting blood pressure (SeBP) measurement at each weekly study visit. Subjects either continued their Period II OM regimen or switched to placebo based on the initial randomization scheme.

Statistical Plan
Descriptive statistics used for summarizing results included mean, median, standard deviation, minimum, and maximum for continuous variables. Frequency count and percentage of subjects were presented for categorical variables.

For BP, the visit value was the mean of three measurements taken during the visit. Study baseline for BP was defined as the average of the visit values for the randomization visit and the

visit prior to randomization. For all other assessments, study baseline was the value determined at the beginning of Period II before subjects received the first dose of OM.

The Period III baseline was defined as the value at the end of Period II and before receiving Period III study medication.

Study baseline characteristics such as age, gender, race, height, weight and vital signs (SeSBP, SeDBP, and heart rate) were summarized within each cohort for all subjects. They were also summarized and compared for subjects who received at least one dose of OM or placebo during Period III.

In order to provide useful information for physicians who might prescribe the drug based on body weight, the baseline-body-weight-adjusted dose (mg/kg) the subjects received were calculated and summarized.

Analysis Sets

ITT Populations
The ITT population for Period II of the study was defined as subjects who took at least one dose of study medication for Period II and had study baseline and at least one SeSBP or SeDBP measurement after taking study medication.
For the randomized withdrawal phase of the study (Period III), the ITT population was defined as subjects who finished Period II, had the end of Period II SeSBP or SeDBP measurement, took the Period III study medication for at least one week, and had the end of Period III SeSBP or SeDBP measurement.

Per-Protocol Populations
If more than 10% of the subjects in a cohort had a major violation of the protocol, a per-protocol analysis was to be performed for that cohort. The criteria for a subject to be included in the per-protocol evaluation were defined prior to unblinding the database.

Efficacy
All comparisons were performed at 2-sided 5% significance level.
For handling missing data at Week 3 in Period II and Week 5 in Period III, the LOCF method was used in the analyses of efficacy variables.

Primary Efficacy Analysis for Cohorts A, B, and A + B
The primary analysis was to assess the dose response in SeSBP or in SeDBP for subjects 6 to 16 years of age at the end of Period II. The change in SeSBP or SeDBP from study baseline to the end of Period II was calculated for all subjects. The primary analysis was carried out using a linear regression model:
Change from baseline in SeSBP (or SeDBP) = a + bDose + e,

where "a" is the intercept, "b" is the slope, and "e" is the random error. In the model, "Dose" was either the fixed OM dose (low or high) or the weight-adjusted OM dose (mg/kg). The null hypothesis of b=0 was tested. The analysis was performed on the BP data for Cohorts A, B (all Black population), and A+B.

If a subject had missing BP data at Week 3, the last observed post study baseline BP measurement was carried forward to replace the missing value at Week 3.

If any of the SeSBP or SeDBP null hypotheses for fixed OM dose or weight-adjusted OM dose was rejected and if the treatment effect was larger as the dose increased, it was to be concluded that there was a dose response of OM treatment in subjects 6 to 16 years of age and OM was efficacious in this subject population.

Secondary Efficacy Analysis for Cohorts A, B, and A + B
An ANCOVA using Period III baseline as a covariate and treatment and country as main effects was to be performed for the change from Period III baseline to the end of Period III in SeSBP and SeDBP. In this analysis, all OM-treated subjects were combined as one group and all placebo-treated subjects were combined as one group. Therefore, treatment effect had two levels: OM and placebo. In addition, a 95% confidence interval (CI) for the difference between least-squares means of OM and placebo was calculated. For subjects with missing BP data at Week 5, the LOCF approach was used.
If the results showed that there was a statistically significant difference between the OM and placebo groups in Period III, the results were to be considered interpretable.

Efficacy Analysis for Cohort C
For Cohort C Period III blood pressure, ANCOVA for change from Period III baseline to the end of Period III was performed using Period III baseline as a covariate, and treatment as factor. A 95% CI was calculated for the least-squares mean difference between OM and placebo. The analysis was carried out at Week 5 for SeSBP and SeDBP with and without LOCF for missing values.

Determination of Sample Size
Reviewer's comment: According to the WR, for the Trial B design, the trial needs to have at least 200 patients in the 6-16 year old group and at least 50 patients in the younger group. In Study 301, the sponsor had slightly more patients than was recommended in the WR.

The sponsor's sample size calculation was based on an assumed treatment effect in Cohort A. For the primary analysis, using a dose ratio of 1:8 and assuming a 0.41 mm Hg drop in SeSBP per dose unit increase, a total of 129 subjects would have been needed to have 80% power to test the null hypothesis of slope=0 with a two-sided type I error of 5%.

In case the primary analysis did not demonstrate a dose response during Period II and a Period III ANCOVA was needed, the following assumptions were made in the sample size calculation: the difference between the OM-treated and the OM-withdrawn placebo group would be 4 mm Hg in SeSBP at the end of Period III with a standard deviation (SD) of 12 mm Hg; 80% power; and 2-sided alpha of 0.05. Based on these assumptions 143 subjects per group was needed. In effect, the sample size requirement was 286 subjects, which is consistent with the combined number of subjects in Cohort A and Cohort B (n = 280).

The number of subjects planned for Cohorts B and C was based on FDA requests. The WR specified 40% to 60% of subjects be Black. To ensure compliance with this request, Cohort B was planned as an all-Black cohort of 100 Black subjects. The WR also specified at least 25% of subjects be 6 years of age. Cohort C was planned as a cohort of 60 pediatric subjects 1 to 5 years of age (25% of 240).

Results of Study 301

Data Sets Analyzed

The analysis sets included ITT, per protocol, and safety populations. Table 1 presents the data sets analyzed for all cohorts.

Table 1: Data Analysis Sets

	Cohort A n (%)[a]	Cohort B n (%)[a]	Cohort A +B n (%)[a]	Cohort C n (%)[a]
Screened[b]	282	140	422	80
Randomized	190	112	302	60
Safety population[c]	190 (100.0)	112 (100.0)	302 (100.0)	59 (98.3)
ITT population[d]	188 (99.0)	112 (100.0)	300 (99.3)	59 (98.3)
Per Protocol population	152 (80.0)	75 (67.0)	227 (75.2)	54 (90.0)

ITT = intent-to-treat
[a:] Percentage is based on the number of subjects randomized to each group.
[b:] Subjects who completed at least one screening procedure.
[c:] Subjects who took at least one dose of study medication.
[d:] Subjects who took at least one dose of study medication, had a baseline and at least one post baseline efficacy assessment.

One randomized subject in Cohort C was excluded from both the safety and ITT populations because no drug was taken. This subject was discontinued from the study for not meeting the entry criteria before any drug was provided or study procedures performed. Two subjects randomized into Cohort A were excluded from the ITT population because both were lost to follow-up immediately after Day 1. All randomized subjects in Cohort B were included in the safety and ITT populations.
A total of 80 subjects were excluded from the per protocol population, 38 in Cohort A, 37 in Cohort B, and 5 in Cohort C.

Disposition of Subjects

A total of 502 subjects were screened for the study. There were 65 centers located in the US, Africa, Latin America/South America, and India. Among the 502 subjects screened, 362 (72%) were randomized into the three cohorts (Cohort A: 190, Cohort B: 112, Cohort C: 60).

Table 2. Key Demographic and Baseline Characteristics. All Randomized Subjects.

	Cohort A (N=190)	Cohort B (N=112)	Cohort A + B (N=302)	Cohort C (N=60)
Age (years)				
Mean (SD)	12.2 (2.97)	12.5 (2.64)	12.3 (2.85)	3.4 (1.45)
Median (Min – Max)	13.0 (6.0-17.0)	13.0 (6.0-16.0)	13.0 (6.0-17.0)	4.0 (1.0-5.0)
Height (cm)				
Mean (SD)	154.2 (18.76)	155.2 (16.08)	154.6 (17.79)	98.3 (12.92)[a]
Median (Min – Max)	159.0 (111.0-187.0)	156.0 (110.0-190.0)	158.0 (110.0-190.0)	98.0 (73.0-120.0)
Weight (kg)				
Mean (SD)	73.4 (38.51)	67.2 (33.25)	71.1 (36.72)	16.9 (6.61)[a]
Median (Min – Max)	72.8 (18.0-200.0)	60.1 (20.0-232.9)	66.2 (18.0-232.9)	15.5 (8.0-44.0)
	n (%)	n (%)	n (%)	n (%)
Race[b]				
White	118 (62.1)	1 (0.9)[c]	119 (39.4)	27 (45.0)
Black/African heritage	35 (18.4)	112 (100.0)	147 (48.7)	7 (11.7)
Asian	19 (10.0)	0 (0.0)	19 (6.3)	21 (35.0)
Hawaiian	1 (0.5)	0 (0.0)	1 (0.3)	0 (0.0)
Other	25 (13.2)	1 (0.9)[b]	26 (8.6)	5 (8.3)
Gender				
Male	122 (64.2)	57 (50.9)	179 (59.3)	34 (56.7)
Female	68 (35.8)	55 (49.1)	123 (40.7)	26 (43.3)
Primary hypertension				
Yes	128 (67.4)	97 (86.6)	225 (74.5)	20 (33.3)
No	62 (32.6)	15 (13.4)	77 (25.5)	40 (66.7)
Family hypertension				
Yes	112 (58.9)	76 (67.9)	188 (62.3)	17 (28.3)
No	78 (41.1)	36 (32.1)	114 (37.7)	43 (71.7)
Baseline SeSBP (mm Hg) Mean (SD)	129.3 (8.70)	131.2 (9.40)	130.0 (9.00)	115.2 (8.74)
Baseline SeDBP (mm Hg) Mean (SD)	77.2 (8.16)	79.3 (8.09)	78.0 (8.18)	72.7 (8.74)

OM = olmesartan medoxomil; SD = standard deviation; SeDBP = seated diastolic blood pressure; SeSBP = seated systolic blood pressure

[a:] n=59

[b:] More than one race could have been checked.

[c:] All subjects in this cohort were black; however, two were of mixed race and more than a single race could be checked.

Demographic and Other Baseline Characteristics

Key demographic and baseline characteristics for the randomized subject population are summarized by cohort in Table 2. Differences in demographic and other baseline characteristics between all randomized subjects and the ITT population were minor.

Overall, mean age was appropriate for the defined age range per cohort. As shown in Table 2, race distribution met the protocol specifications in Cohorts A and B. The various races were equally represented in the high and low OM dose groups in Cohort A.

In Cohort A there were more males than females (64.2% versus 35.8%). In Cohort B, there was an approximately equal distribution of males and females (50.9% and 49.1%, respectively). Distribution of males and females was comparable in the low and high OM dose groups in Cohort A. In Cohort B, there were more males than females in the low dose OM group (64.3% versus 35.7%), while there were more females than males in the high dose OM group (62.5% versus 37.5%)

EFFICACY RESULTS in STUDY 301

All analyses presented here are based on the ITT population. The efficacy results for the per protocol population were generally consistent with the results for the ITT population and are not shown here.

Period II Efficacy – Cohorts A, B, and A+B

The primary efficacy analyses were based on the changes from baseline in trough SeSBP and SeDBP to the end of Period II in Cohort A, Cohort B, and Cohort A + B.

Table 3. Primary Efficacy Results. Effect of OM Dose on Change from Study Baseline in SeSBP at Week 3 with and without LOCF
Cohorts A, B, A+B, Period II

		Cohort A		Cohort B		Cohort A + B	
Visit	Effect	Estimate (SE)	p-value	Estimate (SE)	p-value	Estimate (SE)	p-value
Week 3 observed values	Intercept	-6.76 (1.189)	< 0.0001	-3.48 (1.635)	0.0356	-5.53 (0.967)	< 0.0001
	Dose (Slope)	-0.73 (0.206)	0.0005	-0.90 (0.286)	0.0021	-0.79 (0.168)	< 0.0001
End of Period II With LOCF	Intercept	-7.07 (1.150)	< 0.0001	-3.88 (1.605)	0.0172	-5.88 (0.941)	< 0.0001
	Dose (Slope)	-0.69 (0.202)	0.0008	-0.85 (0.282)	0.0032	-0.75 (0.165)	< 0.0001

LOCF = last observation carried forward; SE = standard error; SeSBP = seated systolic blood pressure
Regression model: Change from baseline in SeSBP or SeDBP = a + bDose + e, where "a" is the intercept, "b" is the slope, and "e" is the random error.

Systolic Blood Pressure Analysis

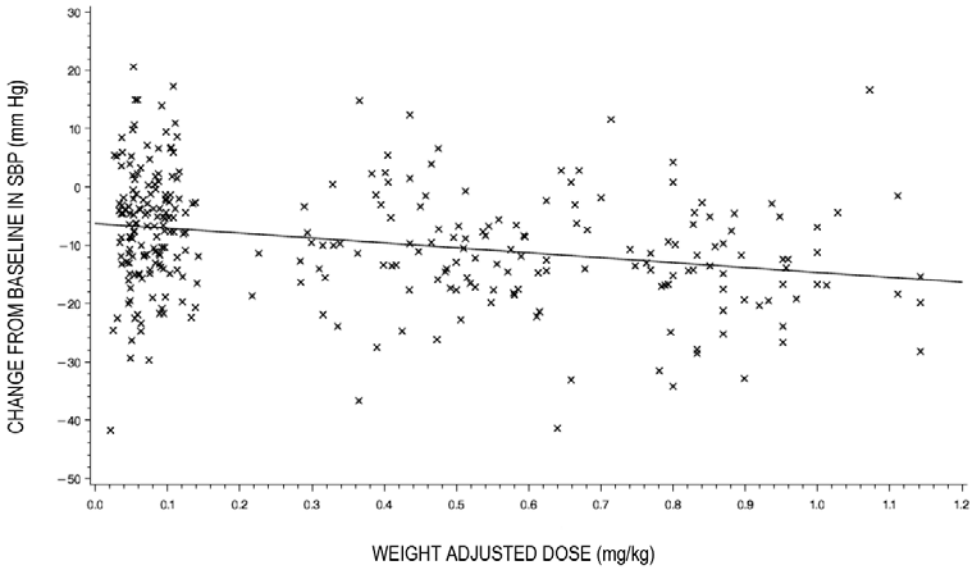
Table 3 summarizes the linear regression analysis for SeSBP. A statistically significant OM dose response for SeSBP was observed in all cohorts ($p<0.0032$). The dose response remained statistically significant ($p<0.027$) when the analysis adjusted the OM dose for baseline body weight (Table 4). Results for the weight-adjusted analysis are shown graphically in Figure 1 for Cohort A + B.

Table 4. Effect of OM Dose (Baseline Weight-Adjusted) on Change from Study Baseline in SeSBP at Week 3 with and without LOCF
Cohorts A, B, A+B, Period II

		Cohort A		Cohort B		Cohort A + B	
Visit	Effect	Estimate (SE)	p-value	Estimate (SE)	p-value	Estimate (SE)	p-value
Week 3 observed values	Intercept	-6.65 (1.045)	< 0.0001	-4.79 (1.561)	0.0028	-5.94 (0.877)	< 0.0001
	Dose (Slope)	-9.36 (2.096)	< 0.0001	-7.59 (3.235)	0.0209	-8.77 (1.780)	< 0.0001
End of Period II With LOCF	Intercept	-6.93 (1.014)	< 0.0001	-5.12 (1.525)	0.0011	-6.24 (0.854)	< 0.0001
	Dose (Slope)	-8.97 (2.054)	< 0.0001	-7.17 (3.190)	0.0265	-8.36 (1.750)	< 0.0001

LOCF = last observation carried forward; SE = standard error; SeSBP = seated systolic blood pressure
Regression model: Change from baseline in SeSBP or SeDBP = a + bDose + e, where "a" is the intercept, "b" is the slope, and "e" is the random error

Figure 1. Linear regression Analysis on Weight-Adjusted Dose for Change from Baseline in SeSBP in Cohort A+B at the End of Period II with LOCF



Diastolic Blood Pressure

Table 5 summarizes the linear regression analysis for SeDBP. A statistically significant OM dose response for SeDBP was observed in each of the three cohorts ($p<0.013$). The dose response remained statistically significant ($p<0.0084$) when the analysis adjusted the OM dose for baseline body weight (Table 6). Results for the weight adjusted analysis are shown graphically in Figure 2 for Cohort A + B.

Table 5. Effect of OM Dose on Change from Study Baseline in SeDBP at Week 3 with and without LOCF Cohorts A, B, A+B, Period II

		Cohort A		Cohort B		Cohort A + B	
Visit	Effect	Estimate (SE)	p-value	Estimate (SE)	p-value	Estimate (SE)	p-value
Week 3 observed values	Intercept	-4.81 (1.090)	< 0.0001	-3.03 (1.353)	0.0270	-4.15 (0.851)	< 0.0001
	Dose (Slope)	-0.59 (0.189)	0.0021	-0.61 (0.236)	0.0112	-0.60 (0.148)	< 0.0001
End of Period II With LOCF	Intercept	-4.95 (1.063)	< 0.0001	-2.91 (1.310)	0.0286	-4.19 (0.829)	< 0.0001
	Dose (Slope)	-0.57 (0.186)	0.0026	-0.58 (0.230)	0.0125	-0.57 (0.145)	< 0.0001

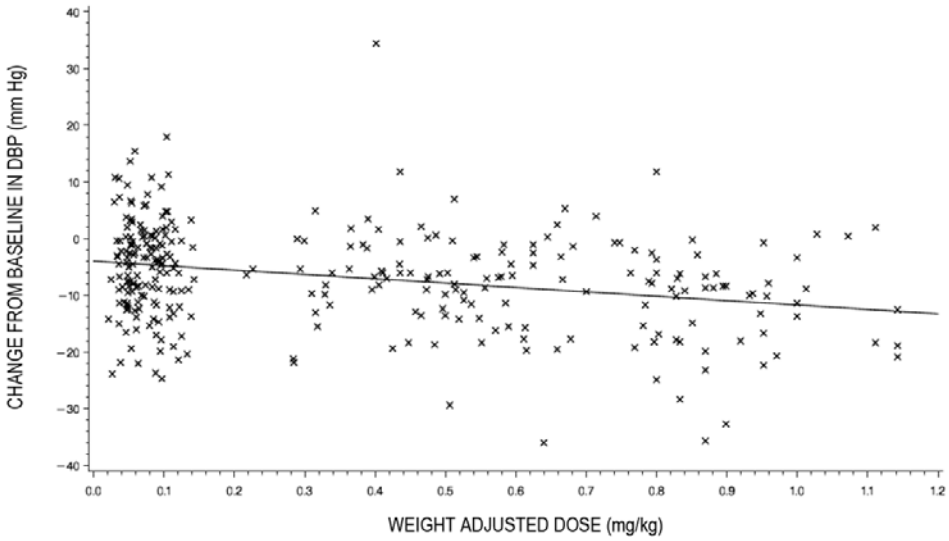
LOCF = last observation carried forward; SE = standard error; SeDBP = seated diastolic blood pressure
Regression model: Change from baseline in SeSBP or SeDBP = a + bDose + e, where "a" is the intercept, "b" is the slope, and "e" is the random error

Table 6. Effect of OM Dose (Baseline Weight-adjusted) on Change from Study Baseline in SeDBP at Week 3 with and without LOCF Cohorts A, B, A+B, Period II

		Cohort A		Cohort B		Cohort A + B	
Visit	Effect	Estimate (SE)	p-value	Estimate (SE)	p-value	Estimate (SE)	p-value
Week 3 observed values	Intercept	-4.44 (0.953)	< 0.0001	-3.31 (1.266)	0.0104	-4.00 (0.762)	< 0.0001
	Dose (Slope)	-8.40 (1.911)	< 0.0001	-6.82 (2.624)	0.0107	-7.87 (1.547)	< 0.0001
End of Period II With LOCF	Intercept	-4.57 (0.933)	< 0.0001	-3.07 (1.220)	0.0134	-3.99 (0.743)	< 0.0001
	Dose (Slope)	-8.15 (1.890)	< 0.0001	-6.85 (2.551)	0.0084	-7.71 (1.522)	< 0.0001

LOCF = last observation carried forward; SE = standard error; SeDBP = seated diastolic blood pressure
Regression model: Change from baseline in SeSBP or SeDBP = a + bDose + e, where "a" is the intercept, "b" is the slope, and "e" is the random error

Figure 2. Linear regression Analysis on Weight-Adjusted Dose for Change from Baseline in SeDBP in Cohort A+B at the End of Period II with LOCF



Period III (Withdrawal Period) Efficacy – Cohorts A, B, and A + B

Although an OM dose response was demonstrated in the primary analysis, the secondary efficacy analysis was performed. This analysis examined BP changes from the Period III baseline to the end of Period III.

Table 7. Treatment Comparison for Change in SeSBP and SeDBP in Period III For Cohorts A, B, A+B

Change in BP	LS Mean OM	LS Mean Placebo	Difference in LS Means	95% CI for Difference	p-value
Cohort A					
SBP	0.33	3.92	-3.58	(-6.27, -0.89)	0.0093
DBP	0.14	3.63	-3.49	(-5.92, -1.05)	0.0052
Cohort B					
SBP	1.30	3.86	-2.57	(-5.93, 0.79)	0.1330
DBP	1.93	3.32	-1.38	(-4.27, 1.50)	0.3442
Cohort A + B					
SBP	-0.05	3.12	-3.16	(-5.24, -1.09)	0.0029
DBP	0.04	2.84	-2.80	(-4.65, -0.95)	0.0032

LS = least squares; OM = olmesartan medoxomil: SeDBP = seated diastolic blood pressure, SeSBP = seated systolic blood pressure
Note: Analysis was based on the ANCOVA model with treatment and country as factors and end of dose-ranging BP value as covariate.

Analyses of Cohort A and the combined Cohort A+B during Period III showed that subjects continuing on OM (low dose or high dose) maintained the lower mean SeSBP and SeDBP values achieved at the end of Period II. However, subjects switched to placebo did not. The LS mean for changes in SeSBP and SeDBP for subjects continuing on OM compared with subjects on placebo are shown in Table 7. In Cohort A, the results from ANCOVA for the change in SeSBP showed a statistically significant difference (-3.58 mm Hg) between OM and placebo (p=0.009). This statistically significant result was also shown for Cohort A+B: (-3.16 mm Hg, p=0.0029). Results for SeDBP showed a similar OM treatment benefit for Cohorts A and A+B.

For Cohort B, Table 7 shows that during Period III, the treatment effect of OM was not maintained. Increases in mean SeSBP values were shown in both subjects continuing OM and those on placebo withdrawal. The difference of LS mean in SeSBP between OM and placebo was not statistically significant (p=0.13). Increases in mean SeDBP values were also noted in both subjects continuing OM and those on placebo withdrawal. The difference in LS mean in SeDBP between OM and placebo was not statistically significant (p=0.34).

Cohort C (age 1-5 years old)

Period II

In Cohort C, in Period II all patients were on the same dose (0.3 mg/kg) of Benicar.

Period III (Placebo Withdrawal Period)

Efficacy

Table 8 summarizes mean BP changes in Cohort C during Period III.
From Period III baseline to the end of the period with LOCF, mean increases in SeSBP were noted for subjects continuing on OM (1.36 mm Hg) and subjects on placebo (4.95 mm Hg). The mean increase in SeSBP was only numerically (p=0.21) larger for the placebo withdrawal subjects compared with the subjects continuing on OM.
Similar results were observed for SeDBP. Mean SeDBP values increased for both subjects continuing on OM and subjects on placebo. The mean increase in SeDBP was only numerically larger for the placebo withdrawal subjects compared with the subjects continuing on OM (p=0.15).

Table 8. Change from Period III Baseline in SESBP and SeDBP y Visit and Treatment Group for Cohort C

	Dose group	N	SeSBP		SeDBP	
			BP at start of Period III Mean (SD)	Change from start of Period III Mean (SD)	BP at start of Period III Mean (SD)	Change from start of Period III Mean (SD)
Week 4 observed values	OM	25	102.0 (11.06)	-3.83 (7.72)	61.3 (9.23)	-2.45 (4.90)
	Placebo	22	100.7 (10.95)	2.91 (7.14)	62.0 (9.18)	3.42 (7.50)
Week 5 observed values	OM	29	101.8 (11.87)	1.36 (8.99)	60.9 (9.16)	0.31 (8.56)
	Placebo	28	101.4 (10.09)	4.95 (8.57)	61.9 (8.56)	3.77 (7.20)
End of Period III with LOCF	OM	29	101.8 (11.87)	1.36 (8.99)	60.9 (9.16)	0.31 (8.56)
	Placebo	28	101.4 (10.09)	4.95 (8.57)	61.9 (8.56)	3.77 (7.20)

BP = blood pressure; LOCF = last observation carried forward; SD = standard deviation; SeSBP = seated systolic blood pressure; SeDBP = seated diastolic blood pressure

Statistical/Analytical Issues

Handling of Dropouts or Missing Data

Subjects who discontinued were not replaced. For analysis of data by visit, observed data were used. For analyses involving the end of a study period, the LOCF approach was used.

Interim Analyses and Data Monitoring

There was no interim analysis in Study 301

Multiple Comparisons/Multiplicity

There were no adjustments for multiplicity or for multiple comparisons.
Reviewer's comment: WR specified that no alpha adjustment would be required for testing the two hypotheses (dose response in Period II and comparison to placebo in Period III).
As the labeling does not show results for the two doses, no adjustment is needed for the two doses.

Examination of Subgroups

Subgroup analyses were not part of the statistical analysis plan.

Efficacy Conclusions
In Study 301, hypertensive pediatric subjects were enrolled in three cohorts: Cohort A, 6 to 16 years and any race; Cohort B, Black subjects, 6 to 16 years of age; and Cohort C, 1 to 5 years of age and any race.

In Period II, a statistically significant OM dose response was observed for SeSBP and SeDBP in Cohort A ($p = 0.0008$ and 0.0026, respectively), Cohort B ($p = 0.0032$ and 0.0125, respectively), and A + B ($p < 0.001$).

When the analysis adjusted the OM dose for subject baseline body weight, the results were similar. A statistically significant OM dose response was observed for SeSBP and SeDBP in Cohort A ($p < 0.001$ for SBP and DBP), Cohort B ($p = 0.027$ and 0.0084, respectively), and A + B ($p < 0.001$) in Period II.

In placebo withdrawal Period III, the results from the ANCOVA in Cohort A for the change in SeSBP showed a statistically significant difference between OM and placebo (-3.58 mm Hg, $p = 0.0093$). A statistically significant effect of OM was also shown for Cohort A + B (-3.16 mm Hg, $p = 0.0029$). Results for SeDBP were similar.

For Cohort B (100% Black), in placebo withdrawal Period III, mean SeSBP increase for subjects on OM was only numerically less than for subjects on placebo ($p=0.13$). Results for SeDBP were similar ($p=0.34$).

For Cohort C (pediatric subjects 1 to 5 years of age), in Period II, all patients took the same dose (0.3 mg/kg) of OM. In placebo withdrawal Period III, subjects who continued on their OM regimen had only numerically ($p>0.2$) smaller mean increases in BP than subjects who switched to placebo.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Race

In Period II, both Black and Non-black subjects in Cohort A+B demonstrated a dose response. For Non-black subjects the SeSBP reductions from baseline were -7.8 mm Hg for the low dose and -13.2 mm Hg the high dose. For Black subjects, the SeSBP reductions were -5.5 mm Hg for the low dose and -10.4 mm Hg for the high dose.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence
There were no statistical issues in this submission.

5.2 Conclusions and Recommendations

The design of the single Study CS0866-A-U301 in this submission was consistent with the amended Pediatric Written Request issued by the FDA on 05/19/2009. In hypertensive pediatric patients aged 6 to 16 years, Study CS0866-A-U301 showed that Benicar (olmesartan medoxomil) is effective. A statistically significant dose response was observed for both sitting systolic (SeSBP) and sitting diastolic (SeDBP) blood pressure ($p<0.001$) in Period II. In randomized placebo withdrawal Period III, a statistically significant difference was shown between Benicar and placebo relative to both SeSBP and SeDBP ($p<0.003$).
In the subgroup of 59 patients aged 1 to 5 years, only one dose (0.3 mg/kg) of Benicar was used in Period II. In placebo withdrawal Period III for this subgroup, Benicar was only numerically better than placebo ($p>0.2$).
Safety of Benicar is a matter of clinical judgment of the medical division.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21286	SUPPL-18	DAIICHI SANKYO INC	BENICAR(OLMESARTAN MEDOXOMIL)5/20/40M

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/s/

VALERIA FREIDLIN
12/16/2009

HSIEN MING J J HUNG
12/16/2009