CLINICAL REVIEW

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Division / Office	DCRP/ODEI/OND
Reviewer Name(s)	Shen Xiao M.D, Ph.D
Review Completion Date	December 4, 2009
Established Name	Olmesartan Medoxomil
(Proposed) Trade Name	Benicar®
Therapeutic Class	Angiotensin II receptor blocker
Applicant	Daiichi Sankyo
Formulation(s)	Tablets
Dosing Regimen	Once daily
Indication(s)	Hypertension
Intended Population(s)	Children aged 1-16 years old

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of olmesartan (OM) for the treatment of hypertension in the pediatric population at ages between 1 to 16 years old. In the provide clinical studies, a statistically and clinically meaningful OM dose response was observed for both systolic and diastolic blood pressure reductions in children at the ages from 6 to 17 years old. In addition, in the double-blind and randomized withdraw study, there is also a statistically significant difference of systolic and diastolic blood pressure reductions between OM and placebo at this age group.

In the children at the ages between 1 and 5 years old, a 0.3 mg/kg/day OM treatment decreased systolic blood pressure by 13.3 mm Hg and decreased mean diastolic pressure by 10.4 mm Hg compared to baseline. In the randomized withdraw study, subjects who continued on their OM regimen had numerically smaller mean increases in BP than subjects who switched to placebo. However, the difference in this small cohort was not statistically significant. In the long-term (46 weeks) open label study with OM treatment, both systolic blood pressure and diastolic blood pressure were reduced relative to study baseline at all visits. Considering the small sample size, the similar trend, frequency and magnitude of the reduction of blood pressure in this age group compared to the older children group, and the long-term open label study data, I suggest that OM should also be approved for the treatment of hypertension in this age group although there was not statistically significant for the reduction of blood pressures in this group in the phase of randomized withdraw study.

Regarding the difference of black and non-black population, overall, Non-Blacks appeared to have a greater response to OM treatment than Blacks in children at the ages between 6 to 16 years old based on above studies.

In the safety data analysis, headache was the predominant treatment emergent adverse event (TEAE). The incidence of headache was higher in subjects taking the high OM dose. There were no difference of other TEAEs between the low dose and high dose, between and treatment and placebo groups. There was one SAE, a relapse in SLE, is considering to be drug related. Overall, the safety data suggest that olmesartan in children exhibits the same adverse effects as seen in adults, including decreases in hemoglobin, hematocrit and increases in potassium and creatinine.

The sponsor's proposed dosing recommendation is as outlined below and appears acceptable.

- For pediatric patients who weigh ≥20 kg, the usual recommended starting dose of Benicar is 10 mg (body weight <35 kg) or 20 mg (body weight ≥35 kg) once daily.
- For patients requiring further reduction in blood pressure after 2 weeks of therapy, the dose of Benicar may be increased to 20 mg (body weight <35 kg) or 40 mg (body weight ≥35 kg) once daily.

(b) (4)

1.2 Risk Benefit Assessment

In this whole study program, transient minor to moderate headache was the major adverse event with this product in pediatric population. Other than that, there does not appear to be any other unexpected adverse events in children compared to adults. Based on review of the submitted clinical studies and the post-marketing data available regarding the olmesartan use in adult and pediatric populations, olmesartan appears to have a favorable risk-benefit profile considering the long-term outcome of hypertension in adults. However, there were no data available for the long-term outcome of hypertension in pediatric population.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Since this product has been approved for many years and has a clear safety profile in adult, the submitted post-marketing data in children from sponsor and my own literature search did not indicate any new safety concerns, I don't have any recommendations for postmarket risk evaluation and mitigation strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

I don't have any recommendations for post market requirements and commitments.

2 Introduction and Regulatory Background

2.1 Product Information

Olmesartan medoxomil (OM, marketed as Benicar® in the US) is an orally active selective AT1 subtype angiotensin receptor blocker (ARB). It has been approved for the treatment of hypertension in adults in 2002. For adults, the usual recommended starting dose is 20 mg once daily when used as monotherapy in patients who are not volume-contracted. For patients requiring further reduction in blood pressure after 2 weeks of therapy, the dose may be increased to 40 mg. This supplement reports pharmacokinetic (PK) and clinical safety and efficacy studies in hypertensive children in response to a pediatric written request.

2.2 Tables of Currently Available Treatments for Proposed Indications

Treatment of hypertension in children has been more elusive than treatment of hypertension in adults. While most older children may have essential hypertension like their adult counterparts, younger children frequently have secondary hypertension, most commonly related to renal

disease. Prior to the Food and Drug Administration Modernization Act (FDAMA) of 1997, most available anti-hypertensives were use in treating children but none were specifically approved for use in children. Since FDAMA, calcium channel blockers, beta blockers, ACE inhibitors, ARBs, and aldosterone receptor blocker have been studied in hypertensive children. However, some of these drugs have been tested to be ineffective in children. The currently approved treatments for hypertension in children were summarized in the following table 1. Please also refer to the NHLBI fourth report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents for additional details.

Table 1: Approved anti-hypertensive drugs for treatment of hypertension in pediatric population (by the end of 2008)

Drug name	Drug category	Dose
Amlodipine	Calcium channel blocker	2.5 mg to 5 mg once daily for ages 6-17 years.
Fenoldopam	dopamine D1-like receptor agonist	i.v. use, 0.2 μg/kg/min up to 0.3 to 0.5 μg/kg/min every 20 to 30 minutes.
Benazepril	ACEI	0.2 mg/kg to 0.6 mg/kg once daily (or up to 40mg daily) for ages 6-17 years.
Enalapril	ACEI	0.08mg/kg up to 0.6mg/kg once daily for age $\geq$ 6 years old
Fosinopril	ACEI	5 to 10 mg once daily for children weighting more than 50kg
Lisinopril	ACEI	0.07 mg/kg up to 5 mg total once daily for age $\geq$ 6 years old
Losartan	ARB	0.7 mg/kg once daily (up to 50 mg total)
Valsartan	ARB	1.3-2.7 mg/kg once daily (up to 40-160 mg total)

2.3 Availability of Proposed Active Ingredient in the United States

OM has been marketed in US in 2002 and the combination product of OM with hydrochlorothiazide has been marketed in US in 2003 for the treatment of hypertension in adult patients.

2.4 Important Safety Issues with Consideration to Related Drugs

OM, like other ACEI and ARBs, may cause hypotension in patients with an activated renin-angiotensin aldosterone system, such as volume- and/or salt-depleted patients (e.g., those being treated with high doses of diuretics), changes in renal function susceptible individuals. In addition, as a consequence of inhibiting the renin-angiotensin-aldosterone system, OM may also raise the serum level of potassium, especially in patients with renal insufficiency.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

- On March 6, 2001, the Division issued a formal written request for pediatric studies to the sponsor.

- On November 25, 2002, the Division issued a revised Written Request to the sponsor for conducting pediatric studies.
- On September 20, 2004, a new protocol for Study CS0866-A-U301 "Dose-Ranging Study to Evaluate the Safety and Efficacy of Olmesartan Medoxomil in Children and Adolescents with Hypertension" is submitted. The Division had the meeting with Sponsor to discuss the Study CS0866-A-U301 on March 4, 2005.
- On August 19, 2005, a new protocol for Study CS0866-A-U102 "An Open-Label Study of the Single-Dose Pharmacokinetics of Olmesartan Medoxomil in Pediatric Patients with Hypertension" is submitted.
- On May 24, 2007, the Division had meeting with Sponsor on the status of the pediatric program.
- On March 31, 2009, the Division had pre-NDA meeting with Sponsor. The Division agreed that CS0866-A-U301 is sufficient to fulfill the final written request and also agreed the proposal the Sponsor proposed for safety evaluation of olmesartan in pediatric population. The safety proposal will include conducting a review of the internal safety database, including post-marketing reports of adverse events in children, and a comprehensive literature search, in addition to the safety analysis based on the clinical studies conducted in response to the Written Request..
- On May 19, 2009, the Division issued a final written request based on the Section 505A of the Federal Food, Drug, and Cosmetic Act, as amended by the Food and Drug Administration Amendments Act of 2007. In this final written request, the Division highlighted the following issues:

Submitted studies should include pharmacokinetic sampling in patients, a dose-response trial of effectiveness in hypertensive pediatric patients; and safety data derived from a 1-year study including a controlled phase assessing effectiveness and safety, followed by an open treatment phase, and a summary of all available information on the safety of the drug in hypertensive pediatric patients. The safety evaluation in children must include a summary of the published literature and formal analyses of published and unpublished data.

For pharmacokinetic study, data must be obtained over the range of doses and ages studied for effectiveness. Patient must have grossly normal metabolic function. Data must be collected with respect to olmesartan and any metabolites that make substantial contribution to its efficacy or toxicity. For the parent and each metabolite followed, the data collected must provide estimates of the exposure (AUC), half-life, oral apparent clearance, volume of distribution, Cmax, and Tmax in pediatric subjects of the various age groups.

For the dose-ranging trial, the trial must be performed in patients of both sexes. If adolescents are included, at least one additional age group must be included, and 50% of the patients in the trial must be 12 years old. They must not be recruited if other interventions known to affect blood pressure (e.g., repair of arterial anomalies) are likely to occur during the expected course of the trial or if their blood pressures are so high as to need immediate treatment. The dose-ranging study must be double-blind in design and it must evaluate at least two dose levels of olmesartan. Based on the evaluation of the pharmacokinetic data, you must obtain agreement from the Division on the doses to be incorporated into this study. The duration of the parallel portion of the study must be at least 2 weeks after titration to target doses is completed.
The primary end point must be either absolute or percentage change in systolic or diastolic pressure. The primary analysis must include all patients with data on randomized treatment. If

the pharmacokinetics of the drug in children, derived from the pharmacokinetic trial described above, differs substantially from the reported pharmacokinetics in adults, such that the serum half-life is appreciably altered, the trial must include an assessment of the effect of varying dosing interval on trough antihypertensive effect. This must include measurement of the effects of the drug at peak and trough.

For blood pressure measurement, both systolic pressure and diastolic pressure must be measured in all patients. Systolic and/or diastolic blood pressure should be used as the primary end point. For the trial designs other than randomized withdrawal from active drug (see above), the primary efficacy measurement must be the change in blood pressure from baseline to the time of the last dose plus the inter-dosing interval. For randomized withdrawal trial designs, the primary efficacy measurement must be the change in blood pressure at the inter dosing interval from the last on-treatment visit to the end of the withdrawal period, or to the time at which an acceptable blood pressure is exceeded.

For drug information, an age-appropriate formulation must be used in the studies described above. If an age-appropriate formulation is not currently available, the Sponsor must develop and test one, and, if it is found safe and effective in the studied pediatric populations, the Sponsor must seek marketing approval for that age-appropriate formulation. If the Sponsor demonstrated that reasonable attempts to develop a commercially marketable formulation have failed, the Sponsor must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If the Agency agrees that the Sponsor has valid reasons for not developing a commercially marketable, age-appropriate formulation, then the Sponsor must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If the Sponsor conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information. In addition, bioavailability of any formulation used in the studies must be characterized.

For statistical considerations, the trial must be designed to detect a treatment effect of conventional ($p<0.05$) statistical significance. If the “Trial A” design is chosen, the study must be powered to be able to detect a "clinically meaningful" treatment benefit on the primary end point. This requires the study to show that if the true treatment effect for one of the treatment groups were minimally "clinically meaningful", the pre-planned analysis would have at least 90% power to infer that at least one dose or the high dose is significantly different from placebo, under the “Trial A” design.

For labeling, under section 505A(j) of the Act, regardless of whether the studies demonstrate that olmesartan is safe and effective, or whether such study results are inconclusive in the studied pediatric population, the Sponsor must submit labeling to include information about the results of the studies.

Regarding the data reporting and timeframe for reports, the Sponsor must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. Under section 505A(d)(2)(B) of the Act, when submitting the study reports, the Sponsor must submit all postmarketing adverse event reports regarding this drug that are available at that time. Reports of the above studies must be submitted to the Agency on or before September 30, 2009.

2.6 Other Relevant Background Information

I am not aware of any other relevant background information.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

I have requested Division of Scientific Investigations (DSI) to audit two clinical site (Study Sites 601 and 631) based on the large number of patient enrollment and large treatment effect size. In the preliminary report from DSI, there were no significant regulatory deviations.

I reviewed case report forms and the data sets using JMP software to verify that source documents were consistent with the reports and tabulations. However, the table to describe the changes of creatine phosphokinase (CPK) in the safety summary is inconsistent with the same table in the study report. I have checked the dataset and confirmed that the table in the safety summary is correct. In addition, the sponsor reported that the protocol deviations in some study sites were not finalized before they submitted this supplement. They are conducting a full quality control process now and will provide a new amendment in the middle of December.

3.2 Compliance with Good Clinical Practices

The clinical overview states that the studies were conducted in compliance with ethical principles that have their origin in the Declarations of Helsinki and in accordance with the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP). The studies in the pediatric population were also conducted in compliance with the Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations.

3.3 Financial Disclosures

There are three clinical studies for this supplemental NDA. The sponsor claimed that all of the investigators did not enter into any financial arrangements with Daiichi Sankyo whereby the value of compensation to the investigators could be affected by the outcome of the studies. The investigators were required to disclose to Daiichi Sankyo whether they have a proprietary

interest in the product or a significant equity in Daiichi Sankyo and they did not disclose any such interests. The investigators were not recipients of significant payments of other sorts.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The sponsor proposed using Benicar® Tablets 20 mg as Benicar® Tablets, for Oral Suspension. Oral Suspension is an extemporaneously-prepared formulation for oral administration for pediatric use. The suspension is prepared at the pharmacy site using Benicar® 20 mg tablets and commercially-available suspension compounding vehicles Ora-Sweet® and Ora-Plus® supplied by the pharmacy. Concentration of the suspension is 2 mg/ml in a total volume of 200 ml. Benicar® Tablets with the active ingredient of olmesartan medoxomil is fully described in Type II Drug Master File 14953. Please see Dr. Bartholomew Ho's chemistry review for details.

4.2 Clinical Microbiology

The submission does not include microbiology data.

4.3 Preclinical Pharmacology/Toxicology

The submission does not include new animal pharmacology or toxicology data.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Olmesartan medoxomil, a prodrug, is hydrolyzed to olmesartan during absorption from the gastrointestinal tract. Olmesartan is a selective AT_1 subtype angiotensin II receptor antagonist. Olmesartan blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in vascular smooth muscle.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and circulating angiotensin II levels do not overcome the effect of olmesartan on blood pressure.

4.4.2 Pharmacodynamics

The submission does not include studies of pharmacodynamic parameters other than the effects on blood pressure discussed in the efficacy below.

4.4.3 Pharmacokinetics

The PK data in pediatric population were analyzed in two studies including an open-label study of a single-dose pharmacokinetics of olmesartan medoxomil in pediatric patients with hypertension (Study CS0866-A-U102) and multiple-dose, safety, efficacy, and population PK study (Study CS0866-A-U301). The following is the sponsor's summary of the most pertinent findings: Plasma half lives and Tmax were similar across all of the age groups in the pediatric studies. Total body clearance and volume of distribution are proportional to subject body weight. Unadjusted for covariate status, typical clearance in the adult dataset was 44% higher than pediatric subjects. When pediatric subjects' clearances were weight normalized to 73 kg based on to the clearance-weight relationship, the adult/pediatric ratio for clearance was 0.95 [0.92, 0.97], well within the bioequivalence range of 80% to 125%.

Within the "low dose" arm, subjects were randomized to 2.5 mg and 5 mg based on a weight cut point of 35kg. Similarly, within the "high dose" arm, subjects were randomized to 20 mg and 40 mg based on a weight cut point of 35 kg. Within both arms, AUC and Cmax were similar between the high and low weight subjects confirming the validity of the dose-adjustment by weight and appropriateness of the 35 kg as the cut-point weight for dose adjustment. When exposures were normalized to weight of 73 kg, estimated AUC and Cmax showed near dose proportional increase at dose ranges of 2.5 mg to 40 mg further supporting body weight being the influential factor for the pharmacokinetics of olmesartan in pediatric populations. Overall, the plasma PK parameters for the 6-16 year old subjects of this study were similar to those estimated in prior studies in adults, whose body weights were within the body weights range of adults in previous studies. Please see Dr. Divya Menon-Andersen's clinical pharmacology review for a detailed review of the PK studies.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2: Summary of clinical studies of olmesartan medoxomil in pediatric program (Sponsor's table)

Study ID	Number of Study Centers Locations(s)	Study Start date Completion date Number of Subjects Planned, Actual	Study Design including Control Type	Study Drugs Dose, Route, Regimen	Study Objective and Duration	Subject Demography	Inclusion Criteria Study Assessments
CS0866-A-U101	1 site US	Started: 14 Nov 2004 Completed: 13 Dec 2004 Number of subjects: Planned: 26 Actual: 26	Comparative, randomized, open-label, 2-way crossover, single-dose, PK study	OM 4 mg/mL suspension (10 mL for a total dose of 40 mg) OM tablets, 1 x 40 mg Single dose, administered orally with 240 mL water	To determine if the compounded suspension formulation of OM was bioequivalent to the marketed tablet formulation. Single dose with 60-hour follow-up.	26 subjects 22 males 4 females Age (years): Median: 28.0 Minimum: 18.0 Maximum: 38.0	Healthy adults, 18 to 45 years of age with a BMI between 19 and 32 kg/m^2, drug and alcohol free at the time of the study. Women could not be pregnant or breast-feeding. PK: AUC_{0-t}, AUC_{inf}, AUC/AUC_{inf}, C_{max}, t_{max}, k_{el}, $t_{1/2}$ Safety: AEs, clinical laboratory measurements, vital signs, physical examinations, ECG
CS0866-A-U102	6 sites US	Started: 27 Sep 2005 Completed: 06 Feb 2008 Total number of subjects: Planned: 40 Actual: 24 Subjects in group (Subject age) **Group 1**: (12 to 23 months): Planned: 10 Actual: 0 **Group 2**: (2 to 5 years): Planned: 10 Actual: 4 **Group 3**: (6 to 12 years): Planned: 10 Actual: 10 **Group 4**: (13 to 16 years): Planned: 10 Actual: 10	Open-label, single-dose, PK study	All subjects received a single oral dose of OM. **Subjects < 6 years old**: 0.3 mg/kg suspension, not to exceed 20 mg. **Subjects ≥ 6 years old** 20 mg tablet if < 35 kg 40 mg tablet if ≥ 35 kg The suspension was also offered as an alternative to subjects ≥ 6 years old who could not swallow tablets	To determine the single-dose PK of OM in hypertensive pediatric subjects between the ages of 12 months and 16 years.	24 subjects 11 males 13 females Age (years): Median: 11.0 Minimum: 4.0 Maximum: 16.0	Female or male subjects treated for hypertension or with systolic blood pressure (SBP) ≥ 95th percentile or SBP or diastolic blood pressure (DBP) ≥ 90th percentile for diabetics or those with a family history of hypertension. PK plasma: AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, $t_{1/2}$, k_{el}, CL/F PK urine: A_{et}, A_e, Xu, CL_r Safety: AEs, clinical laboratory measurements, vital signs, physical examinations, ECG
CS0866-A-U301	65 sites US (25) Africa (17) Latin America/South America (14) India (9)	Started: 27 Apr 2005 Completed: 15 Sep 2008 Total number of subjects: Planned: 340 Actual: 362 Subjects/cohort **Cohort A**: 6 to 16 years old, all races Planned: 180 Actual: 190 **Cohort B**: 6 to 16 years old, all Black Planned: 100 Actual: 112 **Cohort C**: 1 to 5 years old, all races Planned: 60 Actual: 60	Randomized, double-blind, placebo-controlled, with an open-label extension **Period I**: Screening **Period II**: Double-blind dose ranging for subjects aged 6 to 16 years, open-label for subjects aged 1-5 years **Period III**: Double-blind placebo withdrawal **Period IV**: Open-label	OM suspension and matching placebo suspension or tablet[a] **Period II**: **Subjects 6-16 years old**: ≥ 35 kg, 5 or 40 mg < 35 kg, 2.5 or 20 mg **Subjects < 6 years old**: 0.3 mg/kg **Period III**: Continue on Period II dose or switch to placebo **Period IV**[a]: **Subjects 6-16 years old**: ≥ 35 kg, 10 or 20[b] mg < 35 kg, 20 or 40[b] mg **Subjects < 6 years**: 0.3 or 0.6[b] mg/kg	Effect of OM on SeSBP and SeDBP of subjects 6 to 16 years with high blood pressure or hypertension Period I: 2 weeks Period II: 3 weeks Period III: up to 2 weeks Period IV: 46 weeks Entire study: Up to 53 weeks	**Cohort A**: 122 (64.2%) males 68 (35.8%) females Median Age (min – max): 13.0 years (6.0-17.0 years) **Cohort B**: 57 (50.9%) males 55 (49.1%) females Median Age (min – max): 13.0 years, (6.0-16.0 years) **Cohort C**: 34 (56.7%) males 26 (43.3%) females Median Age (min – max): 4.0 years (1.0-5.0 years)	Female or male subjects with seated systolic blood pressure (SeSBP) ≥ 95th percentile but ≤ 2 standard deviations (SDs) above the 99th percentile for gender and height-for-age (or ≥ 90th percentile for diabetic subjects, subjects with glomerular kidney disease, or family history of hypertension) after required washout of antihypertensive medications. Subjects had to be between the ages of 6 and 16 years, inclusive for Cohort A and Cohort B and between 1 and 5 years of age, inclusive, for Cohort C. Efficacy: SeSBP, SeDBP Safety: AEs, clinical laboratory measurements, vital signs, physical examinations

Ae = total amount of olmesartan excreted in urine over all periods, AE = adverse event, Aet – amount olmesartan excreted in urine during each collection interval, AUC = area under the concentration time curve, BMI = body mass index, BP = blood pressure, CL/F = apparent oral clearance, CL_r = renal clearance, C_{max} = maximum plasma concentration, DBP = diastolic blood pressure, ECG = electrocardiogram, k_{el} = elimination rate constant, OM = olmesartan medoxomil, PK = pharmacokinetic, SBP = systolic blood pressure, SD = standard deviation, SeDBP = seated diastolic blood pressure, SeSBP = seated systolic blood pressure, Vd/F = apparent oral volume of distribution, Xu = percent of dose recovered as olmesartan in urine.

[a] Suspension was given for all periods except during the open-label extension when tablets could be substituted for suspension if preferred. All doses were taken once daily.

[b] Higher dose given if target BP was not achieved on lower dose

5.2 Review Strategy

I initially verified that the sponsor's reports of the studies were consistent with the final revised WR. I discussed with the statistician to confirm whether the sponsor's efficacy analyses were appropriate. I check the data sets using JMP software to analyze the adverse events, vital signs and laboratory test data for safety signals.

5.3 Discussion of Individual Studies/Clinical Trials

Three studies were conducted with olmesartan medoxomil (OM) suspension and tablets to determine suitability for a hypertensive pediatric population, aged 1 to 16 years.

Study CS0866-A-U101 was a randomized, open-label, single-dose, two-arm crossover, pharmacokinetic (PK), bioequivalence/bioavailability study in healthy adult volunteers at ages of 18 to 45 years old. The objective of the study was to determine if the compounded suspension formulation of OM (4 mg/ml x 10 mL, for a total dose of 40 mg) was bioequivalent to the marketed formulation of a 40-mg Benicar tablet. Analysis of the data was also completed to determine the appropriate dosage strengths of the suspension formulation for the further development of olmesartan in pediatric hypertensive patients.

Study CS0866-A-U102 was a single-dose study in hypertensive subjects 1 to 16 years of age, the objective of which was to determine the PK profile of OM in the pediatric population. The purpose of this study was to determine the pharmacokinetic behavior of OM in pediatric hypertension patients in the age range of 1-16 years. Subjects aged 1 to 5 years received a single 0.3 oral mg/kg dose. Subjects aged 6 to 16 years, weighing < 35 kg received a single oral 20-mg dose. Subjects aged 6 to 16 years, weighing ≥ 35 kg received a single oral 40-mg dose. The pharmacokinetic samples were taken before dosing and at 1, 2, 4, 8, 12, 24, and 48 hours postdose.

Study CS0866-A-U301 was to evaluate the blood pressure-lowering effect and safety of OM in pediatric subjects. Specifically, the effects of OM, at high-dose and low-dose regimens, on seated systolic blood pressure (SeSBP) and seated diastolic blood pressure (SeDBP) were studied in subjects 1 to 16 years of age, inclusive, with hypertension. The long-term clinical efficacy and safety of OM in this population was assessed in a 46-week, open-label extension period. In addition, PK sampling was completed in a subset of subjects of this study. Study CS0866-A-U301 evaluated three cohorts of subjects with hypertension. Cohort A consisted of subjects 6 to 16 years old, approximately 15% of whom were black. Cohort B consisted of subjects 6 to 16 years old, all of whom were black. Cohort C consisted of subjects aged 1 to 5 years from any race.

All studies were consistent with the final Written Request. The clinical pharmacology reviewer discusses the two PK studies CS0866-A-U101 and CS0866-A-U102 in detail as well as the population PK analysis combining the data from CS0866-A-301. I discuss primarily the efficacy and the safety study CS0866-A-U301.

6 Review of Efficacy

Efficacy Summary

In this study, hypertensive pediatric subjects were enrolled in three cohorts: Cohort A, 6 to 16 years of age regardless of race; Cohort B, Black subjects, 6 to 16 years of age; and Cohort C, 1 to 5 years of age regardless of race.

In study with Cohorts A and B, both low and high doses of OM were effective in reducing seated systolic blood pressure (SeSBP) and seated diastolic blood pressure (SeDBP) in pediatric subjects 6 to 16 years old, regardless of race. A statistically significant OM dose response was observed for SeSBP and SeDBP in Cohort A and Cohort B with and without adjustment of baseline body weight. Both Black and Non-black subjects demonstrated a dose response. However, mean reductions in SeSBP and SeDBP were numerically greater in Non-black subjects compared with Black subjects.

In Period III, pediatric subjects in Cohort A and Cohort B either continued on their Period II OM treatment or took placebo in a double-blind fashion for up to two weeks. Results showed a statistically significant difference between OM and placebo in Cohort A and Cohort A + Cohort B. The difference in LS means between OM and placebo was -3.6 mm Hg ($p = 0.0093$) in Cohort A and -3.2 mm Hg ($p = 0.0029$) in Cohort A +Cohort B. However, there was no statistically significant difference in Cohort B.

In Period IV, pediatric subjects in Cohort A and Cohort B took open-label OM (10, 20, or 40 mg per day with up and down titrations allowed) for up to 46 weeks. Compared with study baseline, mean SeSBP and mean SeDBP were reduced at all visits for Cohorts A, B, and A + B. Numerically, at almost all visits, the magnitude of BP reduction was greater for Cohort A than Cohort B.

Regarding the difference of black and non-black population, overall, Non-Blacks appeared to have a greater response to OM treatment than Blacks in the children at the ages between 6 to 16 years old based on above studies.

For Cohort C (pediatric subjects 1 to 5 years of age), results showed that 0.3 mg/kg/day OM treatment decreased SeSBP by 13.3 mm Hg and decreased mean SeDBP by 10.4 mm Hg. Subjects who continued on their OM regimen in Period II had numerically smaller mean increases in BP during Period III than subjects who switched to placebo. However, the difference in this small cohort was not statistically significant. This may be due to the small sample size. Over 46 weeks of open-label OM treatment (0.3 to 0.6 mg/kg/day with up and down titrations allowed) in Period IV, mean SeSBP and mean SeDBP were reduced relative to study baseline at all visits. Mean SeSBP reduction from study baseline ranged from 13.6 to 16.4 mm Hg and mean SeDBP reduction from study baseline ranged from 11.0 to 14.0 mm Hg. Overall, the trend, frequency and magnitude of the reduction of blood pressure in this group is similar to the older age group.

6.1 Indication

The targeted indication is the treatment of hypertension in children.

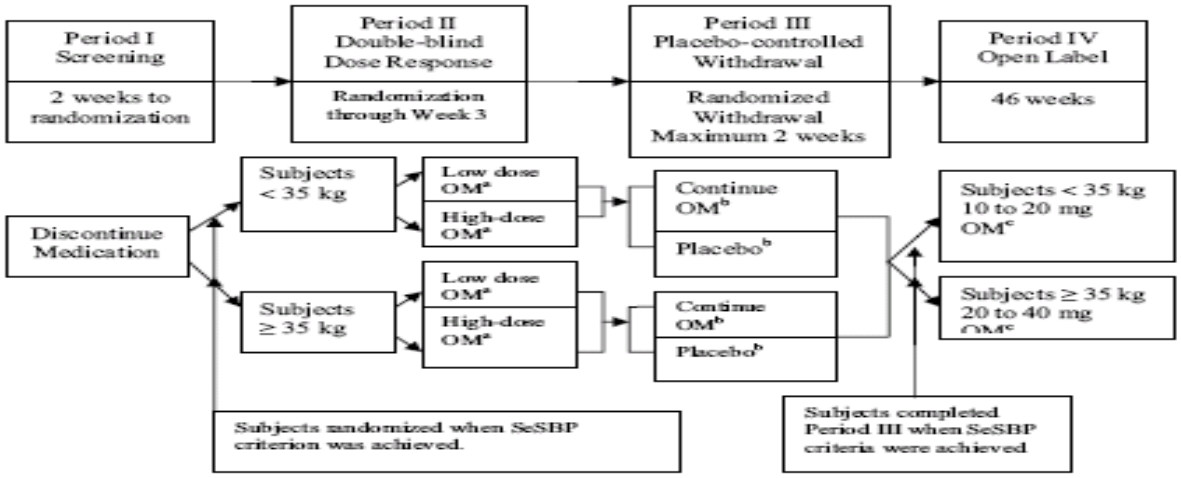
6.1.1 Methods

This submission provides one pivotal efficacy study, Study CS0866-A-U301. This 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. The efficacy objectives are the changes of seated systolic blood pressure (SeSBP) and seated diastolic pressure (SeDBP). This study trial design was based on the options described in the Written Request (WR). The primary efficacy endpoints were the changes from baseline in trough SeSBP and SeDBP to the end of Period II (a period of dose-response study: low dose group vs high dose group) in children at the ages between 6 to 16 years old. The sponsor picked the dosages to cover the range from lower than the approved adult starting dose to the approved adult maximum dosage.

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. In Cohort A, subjects were stratified by age with approximately half aged 6 to 12 years and the remainder aged 13 to 16 years. 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. The BP entry criterion was SeSBP $\geq$ 95th percentile but $\leq$ 2 standard deviations (SDs) above the 99^{th} percentile for gender and height-for-age or SeSBP $\geq$ 90th percentile for subjects who had type 1 or 2 diabetes mellitus, glomerular kidney disease, or a family history of hypertension. The blood pressures representing these percentiles were defined by the National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents.

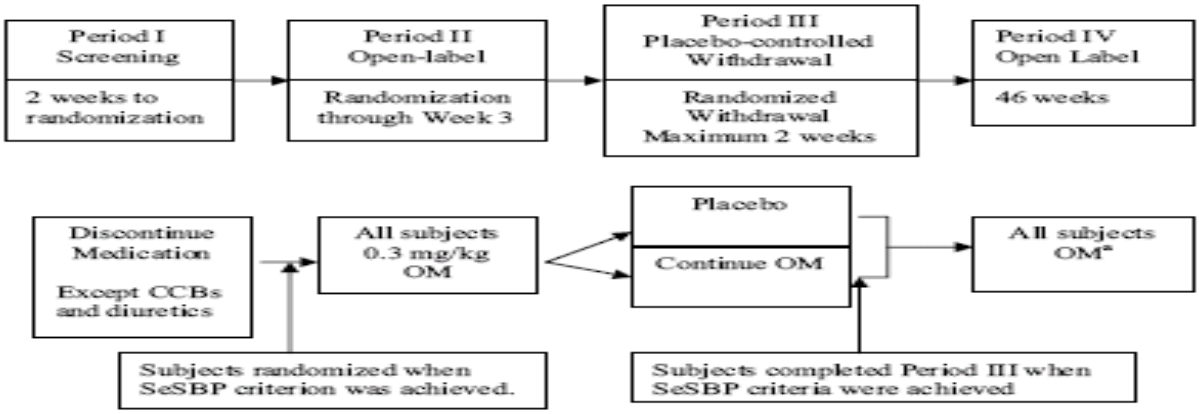
The study comprised four periods. Period I was a wash-out period from Week -1 to randomization. Subjects were randomized to treatment sequences carried through the remainder of the study. Period II was a three-week, double-blind, dose-ranging period. In Cohorts A and B, subjects received either low-dose 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 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. Period IV was a 46-week open-label extension period. The study design including treatment sequences is illustrated in Figure 1 and Figure 2. OM doses were given once daily.

Figure 1: Study Design for Cohort A and Cohort B (Subjects 6 to 16 Years Old)



a: Half of the subjects in both weight categories took low-dose OM and half took high-dose OM. For subjects weighing > 20 kg and < 35 kg, low-dose OM was 2.5 mg qd and high-dose OM was 20 mg qd. For subjects weighing > 35 kg, low-dose OM was 5.0 mg qd and high-dose OM was 40 mg qd.
b: In Period III, subjects either continued their OM dose or were switched to placebo.
c: In Period IV, subjects weighing > 20 kg and < 35 kg began at the 10 mg dose of OM. After 2 weeks, if hypertension was not controlled (SeSBP > 95th percentile for gender and height-for-age, or > 90th percentile for subjects with diabetes, glomerular kidney disease or family history of hypertension), the dose was doubled to 20 mg. Subjects weighing > 35 kg began at the 20 mg dose of OM. After 2 weeks if hypertension was not controlled, the dose was doubled to 40 mg. Subjects had the option in Period IV of taking their dosage in tablets, instead of suspension. If BP still exceeded the indicated level, additional hypertension medication other than an angiotensin receptor blocker or angiotensin converting enzyme inhibitor was allowed. Back titration of OM was also permitted.

Figure 2: Study Design for Cohort C (Subjects 1 to 5 Years Old)



CCB = calcium channel blocker; a: In Period IV, subjects started at the 0.3 mg/kg qd dose of OM. After 2 weeks, if hypertension was not controlled (SeSBP > 95th percentile for gender and height-for-age, or > 90th percentile for subjects with diabetes, glomerular kidney disease or family history of hypertension), the dose was doubled to 0.6 mg/kg qd. If BP still exceeded the indicated level, additional antihypertensive medication other than an angiotensin receptor blocker or angiotensin converting enzyme inhibitor was allowed. Back titration was also permitted.

Concomitant antihypertensive agents that are part of the patient's regimen at screening will be discontinued for the duration of the washout (Period I), the dose-response (Period II) and randomized withdrawal (Period III). During the 46-week open label period (Period IV), antihypertensive agents except for other angiotensin II receptor blockers and ACE inhibitors, may be used as needed to reach blood pressure goals. **Note that Cohort C may use CCB and or**

diuretics during the course of the study. One or both of these drugs may be optionally discontinued to meet study entry criteria.

6.1.2 Demographics

Demographic and baseline characteristics for the randomized subject population are summarized by cohort in the following table 3. As shown in the following table, overall, mean age was appropriate for the defined age range per cohort. In Cohort A, 47.4% of subjects were ≤ 12 years old and 52.6% were > 12 years old. In Cohort B, 41.1% of subjects were ≤ 12 years old and 58.9% were > 12 years old. Mean age and age distribution were similar in the low OM and high OM dose groups for both cohorts. 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%). Mean SBP was comparable in Cohorts A and B at baseline (129.3 and 131.2 mm Hg, respectively) as was mean DBP (77.2 and 79.3 mm Hg, respectively). A greater percentage of subjects in Cohort B had primary hypertension and a family history of hypertension (86.6% and 67.9%, respectively) compared with Cohort A (67.4% and 58.9%, respectively). Mean weight at baseline was only slightly greater in Cohort A compared with Cohort B (73.4 kg versus 67.2 kg). White (45.0%) and Asian (35.0%) were the primary races in Cohort C, and there were more males (56.7%) than females (43.3%). In contrast to Cohorts A and B, approximately two thirds of subjects in Cohort C did not have primary hypertension, and the majority (71.7%) did not have a family history of hypertension.

Table 3: Demographic and Baseline Characteristics – All Randomized Subjects – Period I (Screening, sponsor's table)

	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.

In Cohort A, 88.4% of all randomized subjects had previous or concurrent medical conditions at screening. The most frequently reported system organ class was cardiovascular disorders (41.1%) which primarily reflected hypertension. The next most frequently reported disorders were endocrine/metabolic disorders (36.8%) and eyes, ears nose, and throat disorders (35.3%). In Cohort B, 65.2% of all randomized subjects had previous or concurrent medical conditions at screening. After cardiovascular disorders (34.8%), the most frequently observed disorders were in the respiratory (20.5%) system organ class. In Cohort C, 88.1% of all randomized subjects had previous or concurrent medical conditions at screening. Genitourinary abnormalities were the most prevalent, and were reported in 59.3% of subjects. Cardiovascular was the second highest system organ class with reported history in Cohort C (30.5%). Data were summarized in the following tables. (A: number of patients with abnormality, B: number of patients with either "normal" or "abnormal" response).

Table 4: Medical history abnormalities in Cohort A (all randomized patients, Sponsor's table).

	LOW DOSE (N = 95)			HIGH DOSE (N = 95)			OVERALL (N = 190)		
MEDICAL HISTORY	A	B	(%)[1]	A	B	(%)[1]	A	B	(%)[1]
PATIENTS WITH ABNORMALITIES	89	95	(93.7%)	79	95	(83.2%)	168	190	(88.4%)
EYES, EARS, NOSE AND THROAT	36	95	(37.9%)	31	95	(32.6%)	67	190	(35.3%)
RESPIRATORY	29	95	(30.5%)	23	95	(24.2%)	52	190	(27.4%)
CARDIOVASCULAR	40	95	(42.1%)	38	95	(40.0%)	78	190	(41.1%)
GASTROINTESTINAL	16	95	(16.8%)	14	95	(14.7%)	30	190	(15.8%)
MUSCULOSKELETAL	13	95	(13.7%)	18	95	(18.9%)	31	190	(16.3%)
NEUROLOGICAL	12	95	(12.6%)	15	95	(15.8%)	27	190	(14.2%)
ENDOCRINE/METABOLIC	36	95	(37.9%)	34	95	(35.8%)	70	190	(36.8%)
HEMATOPOIETIC/LYMPHATIC	5	95	(5.3%)	6	95	(6.3%)	11	190	(5.8%)
DERMATOLOGIC	30	95	(31.6%)	22	95	(23.2%)	52	190	(27.4%)
PSYCHOLOGICAL	12	95	(12.6%)	13	95	(13.7%)	25	190	(13.2%)
GENITOURINARY	27	95	(28.4%)	30	95	(31.6%)	57	190	(30.0%)
SURGICAL	30	95	(31.6%)	32	95	(33.7%)	62	190	(32.6%)
ALLERGY	18	95	(18.9%)	25	95	(26.3%)	43	190	(22.6%)
OTHER	33	95	(34.7%)	33	95	(34.7%)	66	190	(34.7%)

Table 5: Medical history abnormalities in Cohort B (all randomized patients, Sponsor's table)

	LOW DOSE (N = 56)			HIGH DOSE (N = 56)			OVERALL (N = 112)		
MEDICAL HISTORY	A	B	(%)[1]	A	B	(%)[1]	A	B	(%)[1]
PATIENTS WITH ABNORMALITIES	36	56	(64.3%)	37	56	(66.1%)	73	112	(65.2%)
EYES, EARS, NOSE AND THROAT	8	56	(14.3%)	11	56	(19.6%)	19	112	(17.0%)
RESPIRATORY	15	56	(26.8%)	8	56	(14.3%)	23	112	(20.5%)
CARDIOVASCULAR	18	56	(32.1%)	21	56	(37.5%)	39	112	(34.8%)
GASTROINTESTINAL	4	56	(7.1%)	1	56	(1.8%)	5	112	(4.5%)
MUSCULOSKELETAL	4	56	(7.1%)	5	56	(8.9%)	9	112	(8.0%)
NEUROLOGICAL	13	56	(23.2%)	6	56	(10.7%)	19	112	(17.0%)
ENDOCRINE/METABOLIC	5	56	(8.9%)	7	56	(12.5%)	12	112	(10.7%)
HEMATOPOIETIC/LYMPHATIC	2	56	(3.6%)	2	56	(3.6%)	4	112	(3.6%)
DERMATOLOGIC	9	56	(16.1%)	9	56	(16.1%)	18	112	(16.1%)
PSYCHOLOGICAL	5	56	(8.9%)	2	56	(3.6%)	7	112	(6.3%)
GENITOURINARY	7	56	(12.5%)	6	56	(10.7%)	13	112	(11.6%)
SURGICAL	11	56	(19.6%)	8	56	(14.3%)	19	112	(17.0%)
ALLERGY	9	56	(16.1%)	11	56	(19.6%)	20	112	(17.9%)
OTHER	12	56	(21.4%)	13	56	(23.2%)	25	112	(22.3%)

Table 6: Medical history abnormalities in Cohort C (all randomized patients, Sponsor's table)

	COHORT C (N = 60)		
MEDICAL HISTORY	A	B	(%)[1]
PATIENTS WITH ABNORMALITIES	52	59	(88.1%)
EYES, EARS, NOSE AND THROAT	12	59	(20.3%)
RESPIRATORY	11	59	(18.6%)
CARDIOVASCULAR	18	59	(30.5%)
GASTROINTESTINAL	5	59	(8.5%)
MUSCULOSKELETAL	2	59	(3.4%)
NEUROLOGICAL	2	59	(3.4%)
ENDOCRINE/METABOLIC	7	59	(11.9%)
HEMATOPOIETIC/LYMPHATIC	5	59	(8.5%)
DERMATOLOGIC	2	59	(3.4%)
PSYCHOLOGICAL	1	59	(1.7%)
GENITOURINARY	35	59	(59.3%)
SURGICAL	13	59	(22.0%)
ALLERGY	8	59	(13.6%)
OTHER	15	59	(25.4%)

6.1.3 Subject Disposition

A total of 502 subjects were screened for the study. There were 65 centers located in the US (25 [20 of the 25 sites actively screened subjects and 18 sites randomized subjects into the study]), Africa (17 [15 of the 17 sites actively screened subjects and 12 sites randomized subjects into the study]), Latin America/South America (14 [all 14 sites actively screened and 13 sites randomized subjects into the study]), and India (9 [all 9 sites actively screened and 6 sites randomized subjects into the study]). Among the 502 subjects screened, 362 (72%) were randomized into the three cohorts (Cohort A: 190, Cohort B: 112, Cohort C: 60). The disposition of subjects in Cohorts A, B, and C during Periods I through IV of the study are summarized in the following tables.

Table 7: Data analysis sets (sponsor's table)

	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)

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.

For each cohort, the percentage of subjects completing each study period is calculated using the number of subjects that entered that study period as the denominator. All randomized subjects in Cohorts A and B entered Period II. One subject in Cohort C did not receive any study drug and did not enter Period II. Most subjects who entered Period II completed all 3 weeks, Cohort A: 95.8%, Cohort B: 95.5%, Cohort C: 96.7%. A total of 14 subjects withdrew (Cohort A, n = 8; Cohort B, n = 5; Cohort C, n = 1) during Period II and did not continue into Period III. Most subjects who entered Period III continued to Period IV, Cohort A: 98.4%, Cohort B: 97.2%, Cohort C: 98.3%. A total of seven subjects withdrew from Period III (Cohort A, n = 3; Cohort B, n = 3; Cohort C, n =1) and did not continue into Period IV, the 46-week open-label extension period. Among the subjects who continued into Period IV, 83.2% and 79.8% completed from Cohort A and Cohort B, respectively, and 100.0% completed from Cohort C.

Eight subjects in Cohort A discontinued in Period II. In the low dose OM group, four subjects withdrew due to a protocol violation, and two due to an AE. Of the two subjects who withdrew in the high dose OM group, one withdrew due to an AE and the other for unknown reasons. Three subjects in Cohort A withdrew during Period III. All subjects were in the placebo group and there was one withdrawal each for AE, protocol violation, and reason unknown. A total of 30 (16.8%) of the 179 subjects in Period IV withdrew. More than half (n = 17) were lost to follow-up. Most of the subjects who withdrew from Period IV were lost to follow-up (n = 17) or non-compliant (n = 4). One subject discontinued due to a SeSBP or SeDBP > 99th percentile. Five subjects in Cohort B discontinued in Period II. In the low dose OM group, one subject each withdrew due to SeSBP/SeDBP criteria failure, lost to follow-up, and other (unspecified). Of the

two subjects who withdrew in the high dose OM group, one was at the discretion of the investigator and the other was due to non-compliance. Three subjects withdrew during Period III. These were one incidence each: SeSBP/SeDBP criteria failure in the low dose OM group, subject request in the high dose OM group and other (unspecified) in the placebo group. A total of 21 (20.2%) of the 104 subjects in Period IV withdrew. Most subject who withdrew during Period IV were lost to follow-up (n = 6) or non-compliant (n = 4). One subject discontinued due to a SeSBP or SeDBP > 99th percentile. One subject in Cohort C discontinued in Period II, due to SeSBP or SeDBP > 99th percentile. One subject withdrew during Period III; reason unknown and there were no discontinuations during Period IV.

Table 8: Subject Completion/Withdrawal Cohort A - Periods II, II, and IV (Sponsor's table)

Randomized Population						
	Period II			Period III		Period IV
	Low OM dose[a] (N=95) n (%)	High OM dose[a] (N= 95) n (%)	Total OM (N=190) n (%)	Total OM (N=93) n (%)	Placebo (N=89) n (%)	Total OM (N=179) n (%)
Completed[b]	89 (93.7)	93 (97.9)	182 (95.8)	93 (100.00)	86 (96.6)	149 (83.2)
Early termination	6 (6.3)	2 (2.1)	8 (4.2)	0 (0.0)	3 (3.4)	30 (16.8)
Reasons for termination						
Subject request	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (2.8)
Subject had a mean SeSBP and/or SeDBP > 99th percentile for subject's gender/age/height	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	17 (9.5)
Non-compliance or lack of cooperation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.2)
Adverse event	2 (2.1)	1 (1.1)	3 (1.6)	0 (0.0)	1 (1.1)	1 (0.6)
Protocol violation	4 (4.2)	0 (0.0)	4 (2.1)	0 (0.0)	1 (1.1)	1 (0.6)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.6)
Missing[c]	0 (0.0)	1 (1.1)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)

a: Low dose: 2.5 mg (> 20 < 35 kg) or 5.0 mg (35 kg); high dose: 20.0 mg (> 20 < 35 kg) or 40.0 mg (≥35 kg)
b: Percentage of randomized subjects
c: No reason was provided.

Table 9: Subject Completion/Withdrawal Cohort B - Periods II, II, and IV (Sponsor's table)

Randomized Population						
	Period II			Period III		Period IV
	Low OM dose[a] (N=56) n (%)	High OM dose[a] (N=56) n (%)	Total OM (N=112) n (%)	Total OM (N=53) n (%)	Placebo (N=54) n (%)	Total OM (N=104) n (%)
Completed[b]	53 (94.6)	54 (96.4)	107 (95.5)	51 (96.2)	53 (98.1)	83 (79.81)
Early termination	3 (5.4)	2 (3.6)	5 (4.5)	2 (3.8)	1 (1.9)	21 (20.2)
Reasons for termination						
Subject request	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	2 (1.9)
Subject had a mean SeSBP and/or SeDBP > 99th percentile for subject's gender/age/height	1 (1.8)	0 (0.0)	1 (0.9)	1 (1.9)	0 (0.0)	1 (1.0)
Investigator judgment	0 (0.0)	1 (1.8)	1 (0.9)	0 (0.0)	0 (0.0)	2 (1.9)
Lost to follow-up	1 (1.8)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	6 (5.8)
Non-compliance or lack of cooperation	0 (0.0)	1 (1.8)	1 (0.9)	0 (0.0)	0 (0.0)	4 (3.8)
Adverse event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.9)
Other	1 (1.8)	0 (0.0)	1 (0.9)	0 (0.0)	1 (1.9)	3 (2.9)
Missing[c]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)

a: Low dose: 2.5 mg (> 20 < 35 kg) or 5.0 mg (35 kg); high dose: 20.0 mg (> 20 < 35 kg) or 40.0 mg (≥ 35 kg)
b: Percentage is of randomized subjects.
c: No reason was provided.

Table 10: Subject Completion/Withdrawal Cohort C - Periods II, III, and IV (Sponsor's table)

Randomized Population				
	Period II	Period III		Period IV
	OM 0.3 mg.kg (N=60) n (%)	OM 0.3 mg/kg (N=29) n (%)	Placebo (N=29) n (%)	Total OM (N= 57) n (%)
Completed[a]	58 (96.7)	29 (100.00)	28 (96.6)	57 (100.00)
Early termination	2 (3.3)[b]	0 (0.0)	1 (3.4)	0 (0.0)
Reasons for termination				
Subject had a mean SeSBP and/or SeDBP > 99th percentile for subject's gender/age/height	1 (1.7)[c]	0 (0.0)	0 (0.0)	0 (0.0)
Missing[d]	1 (1.7)	0 (0.0)	1 (3.4)	0 (0.0)

a: Percentage of randomized subjects.
b: One of these subjects was discontinued for failure to meet protocol criteria prior to receiving study drug
c: This subject was discontinued prior to receiving study drug for failure to meet the per protocol BP criteria
d: No reason was provided.

6.1.4 Analysis of Primary Endpoint(s)

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 in Cohort A, Cohort B, and Cohort A + B (all of the patients). 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.

In Period II, low and high doses of OM were effective in reducing SeSBP and SeDBP in pediatric subjects 6 to 16 years old overall. Change from baseline for all of these cohorts in Period II is shown in the following tables. The mean changes in SeSBP from the study baseline to the end of Period II with the last observation carried forward (LOCF) were -7.76 mmHg and -12.58 mmHg for low and high OM doses, respectively, in Cohort A and -4.73 mmHg and –10.68 mmHg for low and high OM doses, respectively, in Cohort B. The mean changes in SeDBP from the study baseline to the end of Period II with the LOCF were -5.52 mmHg and -9.50 mmHg for low and high OM doses, respectively, in Cohort A, and -3.49 mmHg and -7.58 mmHg for low and high doses, respectively, in Cohort B.

Table 11: Mean Change From Baseline in SeSBP (mm Hg) for Cohorts A, B and A + B (ITT population, Sponsor's table)

		Cohort A			Cohort B			Cohort A +B		
Visit	OM dose group	N	Baseline BP Mean (SD)	Change from baseline Mean (SD)	N	Baseline BP Mean (SD)	Change from baseline Mean (SD)	N	Baseline BP Mean (SD)	Change from baseline Mean (SD)
Week 1 (Period II)	Low dose	91	129.4 (9.00)	-6.93 (7.858)	55	131.6 (9.18)	-6.46 (9.937)	146	130.3 (9.10)	-6.75 (8.669)
	High dose	94	129.1 (8.35)	-10.59 (10.503)	54	130.8 (9.45)	-9.99 (8.855)	148	129.7 (8.77)	-10.37 (9.907)
Week 2 (Period II)	Low dose	89	129.5 (9.07)	-7.69 (8.662)	53	131.1 (8.96)	-7.16 (9.579)	142	130.1 (9.03)	-7.49 (8.985)
	High dose	94	129.1 (8.35)	-11.89 (10.000)	55	131.2 (9.87)	-8.73 (11.364)	149	129.9 (8.97)	-10.72 (10.597)
Week 3 (Period II)	Low dose	89	129.5 (9.07)	-7.48 (9.233)	53	131.1 (8.96)	-4.38 (11.187)	142	130.1 (9.03)	-6.33 (10.081)
	High dose	93	129.3 (8.24)	-12.57 (10.212)	54	130.8 (9.45)	-10.68 (9.431)	147	129.8 (8.70)	-11.88 (9.942)
End of Period II with LOCF	Low dose	94	129.7 (9.03)	-7.76 (9.180)	56	131.7 (9.12)	-4.73 (11.483)	150	130.4 (9.09)	-6.63 (10.170)
	High dose	94	129.1 (8.35)	-12.58 (10.157)	56	131.0 (9.93)	-10.68 (9.259)	150	129.8 (8.98)	-11.87 (9.843)

LOCF – last observation carried forward; SD – standard deviation; SeSBP – seated systolic blood pressure

Table 12: Mean Change From Baseline in SeDBP (mm Hg) for Cohorts A, B and A + B (ITT population, Sponsor's table)

		Cohort A			Cohort B			Cohort A + B		
Visit	OM dose group	N	Baseline BP Mean (SD)	Change from baseline Mean (SD)	N	Baseline BP Mean (SD)	Change from baseline Mean (SD)	N	Baseline BP Mean (SD)	Change from baseline Mean (SD)
Week 1 (Period II)	Low dose	91	78.2 (7.95)	-4.64 (8.003)	55	79.6 (9.05)	-5.32 (9.045)	146	78.7 (8.38)	-4.89 (8.387)
	High dose	94	76.3 (8.13)	-8.23 (9.162)	54	79.0 (6.84)	-7.81 (8.128)	148	77.3 (7.77)	-8.08 (8.773)
Week 2 (Period II)	Low dose	89	78.1 (7.99)	-5.92 (7.417)	53	79.6 (9.12)	-5.14 (8.951)	142	78.6 (8.43)	-5.63 (8.001)
	High dose	94	76.3 (8.13)	-9.30 (9.483)	55	79.2 (6.91)	-6.93 (7.924)	149	77.4 (7.80)	-8.43 (8.986)
Week 3 (Period II)	Low dose	89	78.1 (7.99)	-5.40 (7.925)	53	79.6 (9.12)	-3.64 (8.996)	142	78.6 (8.43)	-4.75 (8.353)
	High dose	93	76.4 (8.15)	-9.54 (9.803)	54	79.0 (6.84)	-7.91 (8.100)	147	77.4 (7.78)	-8.94 (9.219)
End of Period II with LOCF	Low dose	94	78.1 (8.21)	-5.52 (8.058)	56	79.4 (9.05)	-3.49 (8.844)	150	78.6 (8.53)	-4.76 (8.389)
	High dose	94	76.3 (8.13)	-9.50 (9.757)	56	79.2 (6.87)	-7.58 (8.172)	150	77.4 (7.78)	-8.78 (9.216)

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

A statistically significant OM dose response for both SeSBP and SeDBP with and without baseline body weight adjustment was observed in all cohorts shown in the following tables and figures.

Table 13: Effect of Olmesartan Medoxomil on Change from Baseline in SeSBP (mm Hg) at Week 3 with and without LOCF (ITT population, Sponsor's table)

		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.

Table 14: Effect of Olmesartan Medoxomil (Baseline Weight adjusted) on Change from Baseline in SeSBP (mmHg) at Week 3 with and without LOCF (ITT population, Sponsor's table)

		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

Table 15: Effect of Olmesartan Medoxomil on Change from Baseline in SeDBP (mm Hg) at Week 3 with and without LOCF (ITT population, Sponsor's table)

		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 16: Effect of Olmesartan Medoxomil (Baseline Weight adjusted) on Change from Baseline in SeDBP (mmHg) at Week 3 with and without LOCF (ITT population, Sponsor's table)

		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 3: Linear Regression Analysis on Weight-adjusted Dose for Change from Baseline in SeSBP in Cohort A + B at End of Period II with LOCF (ITT population, Sponsor's figure)

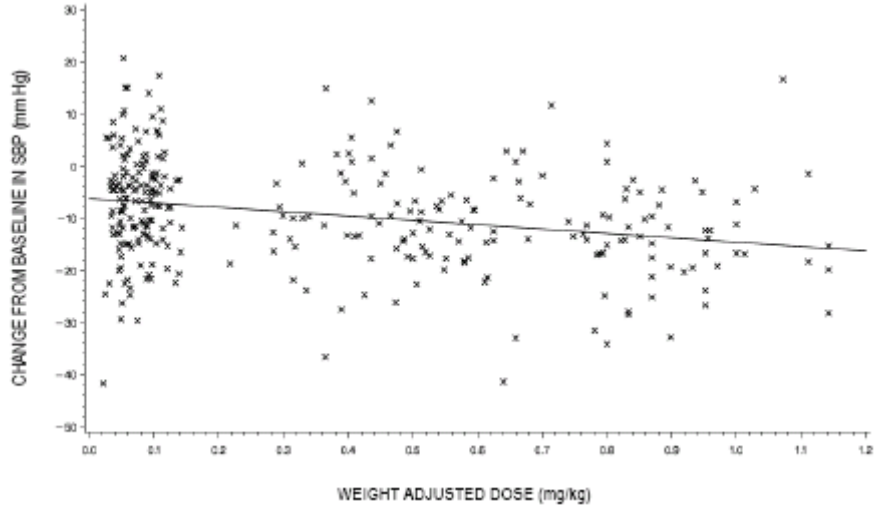
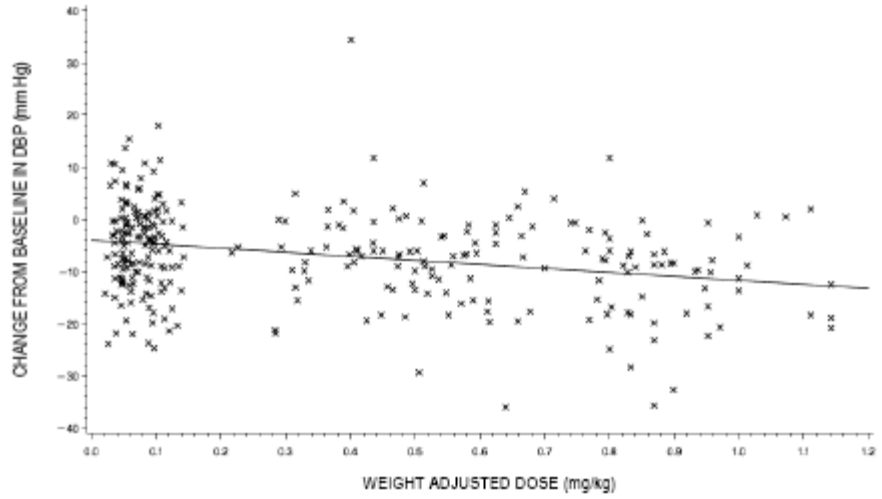


Figure 4: Linear Regression Analysis on Weight-adjusted Dose for Change from Baseline in SeDBP in Cohort A + B at End of Period II with LOCF (ITT population, Sponsor figure)



6.1.5 Analysis of Secondary Endpoints(s)

The secondary endpoints were to examine the BP changes from the Period III baseline to the end of Period III. Data were summarized in the following tables. During Period III, analyses of Cohort A and the combined Cohort A+B 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 whereas subjects switched to placebo did not. For Cohort A and Cohort A+B, there were no clinically relevant or statistically significant changes in mean SeSBP and SeDBP during Period III in the OM group. In contrast, mean SeSBP increased by 4.93 mm Hg and 4.50 mm Hg for placebo withdrawal subjects in Cohort A and Cohort A+B, respectively. Mean SeDBP increased by 4.43 mm Hg and 3.99 mm Hg for placebo withdrawal subjects in Cohort A and Cohort A+B,

respectively. The difference of LS mean in both SeSBP and SeDBP between OM and placebo was statistically significant in both Cohort A and Cohort A+B.

During Period III, the treatment effect of OM was not maintained for Cohort B. Increases in mean SeSBP and SeDBP values were noted in subjects continuing OM (SeSBP/SeDBP: 1.37/1.94 mm Hg) and those on placebo withdrawal (SeSBP/SeDBP: 3.79/3.25 mm Hg); the difference of LS mean in both SeSBP and SeDBP between OM and placebo was not statistically significant.

Table 17: Treatment Comparison for Change in SeSBP and SeDBP (mmHg) in Period III for Cohorts A, B and A + B (ITT population, Sponsor's table)

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

Analysis was based on the ANCOVA model with treatment and country as factors and end of dose ranging BP value as covariate.

Table 18: Mean Change From Start of Period III in SeSBP (mm Hg) by Visit and Treatment Group During Period III for Cohorts A, B, and A + B (ITT population, Sponsor's table)

		Cohort A			Cohort B			Cohort A + B		
Visit	Dose group[a]	N	BP at start of Period III Mean (SD)	Change from start of Period III Mean (SD)	N	BP at start of Period III Mean (SD)	Change from start of Period III Mean (SD)	N	BP at start of Period III Mean (SD)	Change from start of Period III Mean (SD)
Week 4 observed values	OM	77	119.1 (12.61)	-1.86 (8.684)	29	117.7 (9.35)	-1.11 (9.361)	106	118.7 (11.79)	-1.66 (8.836)
	placebo	62	115.8 (12.83)	2.59 (10.230)	27	121.9 (12.36)	-1.02 (9.904)	89	117.6 (12.93)	1.49 (10.213)
Week 5 observed values	OM	93	120.4 (12.49)	0.43 (9.459)	51	123.2 (12.87)	1.34 (9.590)	144	121.4 (12.65)	0.75 (9.482)
	placebo	86	117.7 (13.22)	4.98 (9.442)	53	123.8 (11.81)	3.79 (10.002)	139	120.0 (13.00)	4.53 (9.641)
End of Period III with LOCF	OM	93	120.4 (12.49)	0.43 (9.459)	52	123.4 (12.86)	1.37 (9.498)	145	121.5 (12.66)	0.77 (9.451)
	placebo	88	118.0 (13.25)	4.93 (9.620)	53	123.8 (11.81)	3.79 (10.002)	141	120.2 (13.00)	4.50 (9.745)

LOCF = last observation carried forward; OM = olmesartan medoxomil; SD = standard deviation; SeSBP = seated blood pressure
[a] OM dose was continued from Period II or switched to placebo based on the initial randomization scheme.
NOTE: The Week 5 visit included all patients who completed Period III treatment, including patients who completed Period III after 1 week of treatment due to BP measurements exceeding pre-specified percentiles for gender and height-for-age, as per protocol

Table 19: Mean Change From Start of Period III in SeDBP (mm Hg) by Visit and Treatment Group During Period III for Cohorts A, B, and A + B (ITT population, Sponsor's table)

		Cohort A			Cohort B			Cohort A + B		
Visit	Dose group[a]	N	BP at start of Period III Mean (SD)	Change from start of Period III Mean (SD)	N	BP at start of Period III Mean (SD)	Change from start of Period III Mean (SD)	N	BP at start of Period III Mean (SD)	Change from start of Period III Mean (SD)
Week 4 observed values	OM	77	69.8 (9.88)	-1.53 (7.559)	29	71.7 (8.07)	0.18 (8.709)	106	70.3 (9.42)	-1.06 (7.885)
	placebo	62	68.6 (10.32)	1.35 (9.000)	27	72.5 (11.03)	0.19 (7.209)	89	69.8 (10.64)	1.00 (8.473)
Week 5 observed values	OM	93	70.1 (10.34)	0.24 (8.122)	51	73.2 (7.96)	1.90 (7.163)	144	71.2 (9.65)	0.82 (7.811)
	placebo	86	68.7 (9.95)	4.77 (9.980)	53	73.7 (10.18)	3.25 (8.741)	139	70.6 (10.29)	4.19 (9.523)
End of Period III with LOCF	OM	93	70.1 (10.34)	0.24 (8.122)	52	73.4 (8.09)	1.94 (7.101)	145	71.3 (9.70)	0.85 (7.790)
	placebo	88	69.1 (10.23)	4.43 (10.146)	53	73.7 (10.18)	3.25 (8.741)	141	70.8 (10.42)	3.99 (9.627)

BP = blood pressure; LOCF = last observation carried forward; OM = olmesartan medoxomil; SD = standard deviation; SeDBP = seated diastolic blood pressure
[a] OM dose was continued from Period II or switched to placebo based on the initial randomization scheme.
NOTE: The Week 5 visit included all patients who completed Period III treatment, including patients who completed Period III after 1 week of treatment due to BP measurements exceeding pre-specified percentiles for gender and height-for-age, as per protocol

6.1.6 Other Endpoints

6.1.6.1. Period IV results for Cohort A and B: mean changes from study baseline in SeSBP and SeDBP were analyzed for Period IV. At all Period IV visits, for all cohorts, mean SeSBP and mean SeDBP were reduced relative to study baseline. The mean reduction from study baseline in SeSBP for Period IV in Cohort A and Cohort A + B was consistently ≥ 10 mm Hg at all visits during the 46-week treatment period, and ranged from 11.1 to 12.7 mm Hg for Cohort A and from 10.2 to 12.9 mm Hg for Cohort A + B. In Cohort B, the mean reduction from study baseline ranged from 7.5 mm Hg to 13.1 mm Hg. The mean reduction from study baseline in SeDBP in Cohort A was similar to that observed for Cohort A + B in Period IV. At Period IV visits, Cohort A mean reductions in SeDBP ranged from 7.3 mm Hg to 9.8 mm Hg and in the combined Cohort A + B, mean reductions in SeDBP were between 6.6 mm Hg and 9.2 mm Hg. As noted for SeSBP, the magnitude of mean reductions from study baseline was smaller in Cohort B (5.2 mm Hg to 8.2 mm Hg) compared with either Cohort A or Cohort A + B. Data were summarized in the following tables.

Table 20: Mean Change from Study Baseline in SeSBP (mm Hg) by Visit and Treatment Group during Period IV for Cohorts A, B, and A + B (ITT population, Sponsor table)

	Cohort A			Cohort B			Cohort A + B		
Visit	N	Study Baseline BP Mean (SD)	Change from baseline Mean (SD)	N	Study Baseline BP Mean (SD)	Change from baseline Mean (SD)	N	Study Baseline BP Mean (SD)	Change from baseline Mean (SD)
Week 2	177	129.1 (8.43)	-12.0 (9.50)	102	131.0 (9.11)	-8.5 (9.98)	279	129.8 (8.72)	-10.7 (9.81)
Week 4	175	129.1 (8.47)	-12.6 (9.23)	98	131.0 (9.12)	-7.5 (9.44)	273	129.8 (8.75)	-10.8 (9.61)
Week 12	167	128.9 (8.54)	-11.5 (9.90)	95	131.1 (9.06)	-8.1 (11.82)	262	129.7 (8.78)	-10.3 (10.73)
Week 20	162	128.8 (8.63)	-11.1 (9.60)	90	131.2 (9.00)	-11.7 (10.70)	252	129.7 (8.82)	-11.3 (9.99)
Week 28	156	128.9 (8.67)	-12.7 (8.41)	88	131.6 (8.71)	-13.1 (10.82)	244	129.9 (8.76)	-12.9 (9.33)
Week 36	151	128.8 (8.84)	-12.3 (9.37)	84	131.8 (8.74)	-11.4 (11.37)	235	129.8 (8.90)	-12.0 (10.12)
Week 46	149	128.6 (8.80)	-11.3 (9.50)	83	131.6 (8.62)	-8.3 (13.44)	232	129.7 (8.83)	-10.2 (11.14)
End of Study	178	129.1 (8.41)	-10.8 (9.75)	103	130.9 (9.09)	-7.7 (12.71)	281	129.8 (8.69)	-9.7 (11.01)

BP = blood pressure; LOCF = last observation carried forward; OM = olmesartan medoxomil; SD = standard deviation; SeSBP = seated systolic blood pressure

Table 21: Mean Change From Study Baseline in SeDBP (mm Hg) by Visit and Treatment Group during Period IV for Cohorts A, B, and A + B (ITT population, Sponsor table)

	Cohort A			Cohort B			Cohort A +B		
Visit	N	Study Baseline BP Mean (SD)	Change from baseline Mean (SD)	N	Study Baseline BP Mean (SD)	Change from baseline Mean (SD)	N	Study Baseline BP Mean (SD)	Change from baseline Mean (SD)
Week 2	177	76.9 (7.93)	-8.6 (8.76)	102	79.0 (7.95)	-6.2 (9.11)	279	77.7 (7.99)	-7.7 (8.95)
Week 4	175	76.9 (7.97)	-8.9 (9.24)	98	78.8 (8.00)	-5.8 (10.39)	273	77.6 (8.02)	-7.7 (9.76)
Week 12	167	77.1 (7.90)	-8.4 (10.10)	95	78.8 (8.06)	-5.4 (9.92)	262	77.7 (7.98)	-7.3 (10.12)
Week 20	162	77.1 (7.79)	-8.5 (9.84)	90	78.6 (7.97)	-8.0 (8.71)	252	77.6 (7.87)	-8.3 (9.44)
Week 28	156	77.0 (7.86)	-9.8 (9.37)	88	78.6 (8.04)	-8.2 (8.79)	244	77.6 (7.95)	-9.2 (9.18)
Week 36	151	76.9 (7.85)	-8.2 (9.71)	84	78.5 (8.12)	-7.1 (8.07)	235	77.4 (7.97)	-7.8 (9.16)
Week 46	149	76.9 (7.80)	-7.3 (9.21)	83	78.3 (7.89)	-5.2 (9.38)	232	77.4 (7.84)	-6.6 (9.30)
End of Study	178	76.9 (7.93)	-7.4 (9.31)	103	79.1 (7.93)	-5.1 (9.45)	281	77.7 (7.98)	-6.6 (9.41)

BP = blood pressure; LOCF = last observation carried forward; OM = olmesartan medoxomil; SD = standard deviation; SeDBP = seated diastolic blood pressure

6.1.6.2. Period II and III results for Cohort C

Mean changes from study baseline in SeSBP and SeDBP in Cohort C during Period II and Period III are shown in the following tables. In this open-label period II study, the mean reduction from study baseline Cohort C at the end of Period II with the last observation carried forward was -13.31 mmHg for SeSBP and - 10.42 mmHg for SeDBP. Like the results in Cohorts A and B. The antihypertensive effect was largely manifest within one week and reached the peak levels after 2 weeks.

In this withdrawal Period III study, 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 numerically larger for the placebo withdrawal subjects compared with the subjects continuing on OM. However, the differences in the LS means were not statistically significant. This could be due to the small sample size. Similar results were observed for SeDBP. Mean SeDBP values increased for both subjects continuing on OM (0.31 mm Hg) and subjects on placebo (3.77 mm

Hg). The mean increase in SeDBP was numerically larger for the placebo withdrawal subjects compared with the subjects continuing on OM but not statistically significant.

Table 22: Mean Change from Study Baseline in SeSBP and SeDBP (mm Hg) by Visit During Period II for Cohort C (ITT population, Sponsor table)

	SeSBP			SeDBP		
Visit	N	Study Baseline BP Mean (SD)	Change from baseline Mean (SD)	N	Study Baseline BP Mean (SD)	Change from baseline Mean (SD)
Week 1	58	114.8 (7.25)	-10.68 (9.12)	58	72.1 (7.77)	-8.17 (10.01)
Week 2	58	114.8 (7.25)	-12.68 (10.07)	58	72.1 (7.77)	-9.91 (9.78)
Week 3	58	114.8 (7.25)	-13.32 (11.03)	58	72.1 (7.77)	-10.65 (9.70)
End of Period II with LOCF	59	115.4 (8.62)	-13.31 (10.94)	59	72.6 (8.80)	-10.42 (9.78)

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

Table 23: Change from Period III Baseline in SeSBP and SeDBP (mmHg) by Visit and Treatment Group for Cohort C (ITT population, Sponsor table)

			SeSBP		SeDBP	
	Dose group	N	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

6.1.6.3. Period IV results for Cohort C: Mean changes from study baseline in SeSBP and SeDBP in Cohort C were analyzed for Period IV and the data are shown in the following table. At all visits, mean BP values were reduced relative to study baseline. The mean reduction from study baseline in SeSBP in Cohort C ranged between 13.6 and 16.4 mm Hg. The mean reduction from study baseline in SeDBP in Cohort C ranged between 11.0 and 14.0 mm Hg.

Table 24: Mean Change From Study Baseline in SeSBP and SeDBP (mm Hg) by Visit During Period IV for Cohort C (ITT population, Sponsor table)

		SeSBP		SeDBP	
Visit	N	Study Baseline BP Mean (SD)	Change from baseline Mean (SD)	Study Baseline BP Mean (SD)	Change from baseline Mean (SD)
Week 2	57	114.7 (7.24)	-13.6 (10.17)	72 (7.79)	-11.0 (10.77)
Week 4	57	114.7 (7.24)	-15.1 (8.59)	72 (7.79)	-13.0 (8.71)
Week 12	57	114.7 (7.24)	-16.3 (10.23)	72 (7.79)	-14.0 (10.40)
Week 20	57	114.7 (7.24)	-16.4 (10.78)	72 (7.79)	-13.3 (11.50)
Week 28	57	114.7 (7.24)	-14.3 (11.80)	72 (7.79)	-11.7 (11.07)
Week 36	57	114.7 (7.24)	-16.4 (10.11)	72 (7.79)	-14.0 (11.88)
Week 46	57	114.7 (7.24)	-15.7 (9.83)	72 (7.79)	-13.3 (11.18)
End of Study	57	114.7 (7.24)	-15.7 (9.83)	72 (7.79)	-13.3 (11.18)

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

6.1.7 Subpopulations

The difference of black and non-black population were analyzed. In the Period II study, the mean reductions for both SeSBP and SeDBP were consistently greater in the high-dose OM group than in the low-dose OM group for both subgroups. Non-Blacks appeared to have a greater response to OM treatment than Blacks. Data were summarized in the following tables.

Table 25: Black and Non-Black Mean Change from Baseline in SeSBP (mm Hg) for Cohort A + B (ITT population, Sponsor table)

		Black			Non-Black		
Visit	OM dose group	N	Baseline BP Mean (SD)	Change from baseline Mean (SD)	N	Baseline BP Mean (SD)	Change from baseline Mean (SD)
Week 1 (Period II)	Low dose	72	130.9 (8.98)	-6.40 (9.015)	74	129.6 (9.23)	-7.09 (8.365)
	High dose	69	129.5 (9.28)	-9.79 (8.900)	79	129.9 (8.36)	-10.87 (10.741)
Week 2 (Period II)	Low dose	69	130.7 (8.79)	-7.31 (9.111)	73	129.5 (9.27)	-7.66 (8.924)
	High dose	70	129.9 (9.66)	-9.35 (10.567)	79	129.9 (8.36)	-11.95 (10.539)
Week 3 (Period II)	Low dose	69	130.7 (8.79)	-5.03 (10.875)	73	129.5 (9.27)	-7.55 (9.176)
	High dose	68	129.8 (9.14)	-10.35 (9.922)	79	129.9 (8.36)	-13.19 (9.831)
End of Period II with LOCF	Low dose	76	131.2 (8.93)	-5.51 (10.872)	74	129.6 (9.23)	-7.78 (9.327)
	High dose	71	129.7 (9.69)	-10.39 (9.713)	79	129.9 (8.36)	-13.19 (9.831)

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

Table 26: Black and Non-black Mean Change from Baseline in SeDBP (mm Hg) for Cohort A + B (ITT population, Sponsor table)

		Black			Non-Black		
Visit	OM dose group	N	Baseline BP Mean (SD)	Change from baseline Mean (SD)	N	Baseline BP Mean (SD)	Change from baseline Mean (SD)
Week 1 (Period II)	Low dose	72	80.1 (8.94)	-5.58 (8.879)	74	77.4 (7.61)	-4.23 (7.881)
	High dose	69	77.7 (7.36)	-6.98 (8.576)	79	77.0 (8.14)	-9.04 (8.884)
Week 2 (Period II)	Low dose	69	80.1 (9.05)	-5.70 (9.183)	73	77.3 (7.61)	-5.55 (6.762)
	High dose	70	77.9 (7.44)	-6.92 (8.362)	79	77.0 (8.14)	-9.76 (9.355)
Week 3 (Period II)	Low dose	69	80.1 (9.05)	-4.17 (8.754)	73	77.3 (7.61)	-5.29 (7.977)
	High dose	68	77.8 (7.37)	-6.97 (9.422)	79	77.0 (8.14)	-10.65 (8.745)
End of Period II with LOCF	Low dose	76	79.8 (9.22)	-4.17 (8.806)	74	77.4 (7.61)	-5.37 (7.951)
	High dose	71	77.8 (7.39)	-6.71 (9.344)	79	77.0 (8.14)	-10.65 (8.745)

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

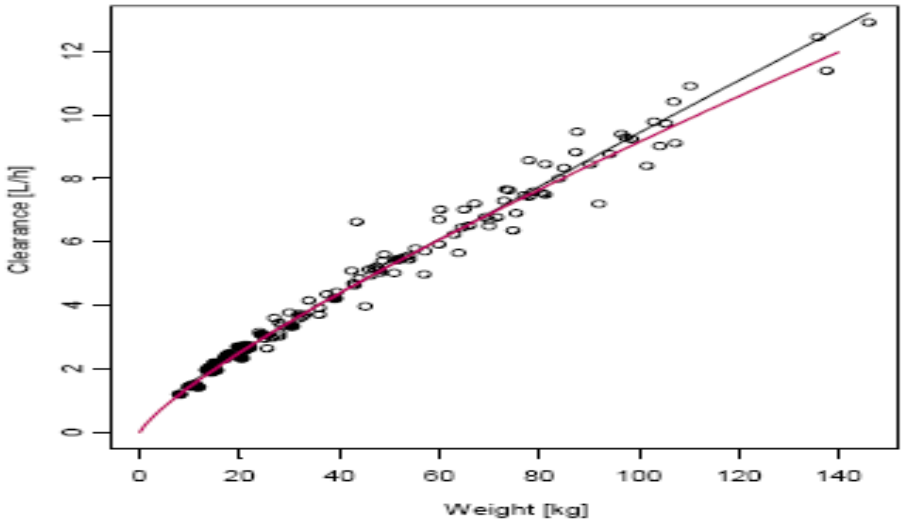
Regarding the Period III study, in Cohort A, there were total 181 patients at the end of Phase III study. The race distribution was 62% white, 18% black, 10% Asia, and 14% other races (subject could check more than one race). In Cohort A+B, there were total 286 patients. The race distribution was changed to 39% white, 48% black, 6% Asia, and 9% other races. In both Cohort A and Cohort A+B study, the differences of LS mean in both SeSBP and SeDBP between OM and placebo were statistically significant. However, the difference was not statistically significant in black people only in Cohort B. Please see details in 6.1.5 secondary endpoint discussion.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

As weight is the only covariate that influences the PK characteristics of OM, it is reasonable using weight as the cut-off for defining the dose.

The highest dose approved in adults is 40 mg qd. At this dose, the BP lowering effect is close to the maximal. In the population pharmacokinetic analysis of the pooled dataset, clearance of OM in pediatric subjects weighing 35 kg is approximately 57% of the clearance of a 70 kg individual (the reference adult weight) and approximately 49% of the clearance of an adult weighing 86 kg. A simulation based on the population PK model, using the individual post hoc clearances from the pediatric data set supported 35 kg as an appropriate body weight cutoff to achieve similar olmesartan exposure in children as with a 20 mg dose in adults. Data were shown in the following figure.

Figure 5: Relationship between Individual Post-hoc Clearances and Weight in Pediatric Population Pharmacokinetic Model



Based on all of the data to date, including the PK/PD modeling and simulation, the Sponsor provided the following dose recommendation:

- Body weight between 5 and 20 kg (above 1 year of age): OM 0.3mg/kg/day, to be increased to OM 0.6 mg/kg/day if there is an insufficient effect on BP when 0.3 mg/kg/day is given.

- Body weight between 20 and 35 kg: OM 10 mg/day, to be increased to OM 20 mg if there is an insufficient effect on BP when 10 mg/day is given.
- Body weight ≥ 35 kg: OM 20 mg/day, to be increased to OM 40 mg if there is an insufficient effect on BP when 20 mg/day is given.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

In Cohort A and Cohort A+B in Period III, analyses showed that subjects continuing on OM maintained the lower mean SeSBP and SeDBP values achieved at the end of Period II whereas subjects switched to placebo did not. In Cohort B, however, there was only a numeric reduction of SeSBP and SeDBP in OM maintained compared to placebo without statistical difference.

There was no indication of a tolerance effect during the study. During the 46-week open-label OM period of the study, BP was consistently lower than study baseline with no clear reduction in the magnitude of BP lowering over time. However, since this is an open label study and there are patients dropouts, it is hard to make the final conclusion based on these data.

6.1.10 Additional Efficacy Issues/Analyses

N/A

7 Review of Safety

Safety Summary

There were no deaths in the study. One SAE, a relapse in SLE, was considered to be drug related. The majority of TEAEs were mild or moderate. Headache was the predominant TEAE for Cohorts A and B. The incidence of headache was higher in subjects taking the high OM dose. Otherwise, the incidence of Period II (dose-response period) TEAEs was similar for the high and low dose OM groups within Cohort A and within Cohort B. During Period III (randomized withdrawal study), the incidence rate of TEAEs for subjects on the low OM dose was similar to that for subjects taking placebo for Cohorts A and B. For Cohort C, Period II TEAE incidence rate was similar to that observed for Cohort B in Period II, and in Period III, the placebo group had a higher incidence of TEAEs compared with subjects continuing OM.

During Period IV (46-week long-term open label study), the TEAE incidence was highest in Cohort C (80.7%) compared with Cohort A (71.9%) and Cohort B (54.4%). The higher incidence rate of Period IV TEAEs observed in Cohort C is considering the pre-existing co-morbidities in Cohort C subjects. Infections and infestations was the dominant system organ class for TEAEs in all cohorts in Period IV; however, headache remained the most frequently reported TEAE for Cohorts A and B. Reports of syncope were limited to one TEAE in one subject, and hypotension was one time each for four subjects. No subjects discontinued from the study for syncope or hypotension.

Hematological laboratory values for hemoglobin and hematocrit shifted from normal at study start to low at the end of the study. This was not unexpected, as this is seen in the adult population as well. Also like the findings in the adult, there were shifts in potassium from normal at study baseline to high at the end of the study. TEAEs of hyperkalemia were reported 5 times for 4 subjects in Cohort A and a total of four reports of pseudo-hyperkalemia in four subjects (Cohort A, n = 3; Cohort C, n = 1) occurred. The increase in potassium for the subjects with hyperkalemia and those with pseudo-hyperkalemia were similar (0.4 – 1.1mmol/L and 0.1 – 1.0 mmol/L above the normal range of 5.0 mmol/L, respectively). There were no AEs of increased potassium in Cohort B and no specific trend or dose relationship was seen. Laboratory values for some serum chemistry parameters such as CPK and ALT were elevated during the study for some subjects. In the majority of cases, these values were high at study entry and were not considered clinically relevant. No causative factor was readily identifiable for either the CPK or ALT abnormalities. Increased BUN and creatinine were also seen but there were no clinically relevant changes from baseline as some subjects had increased serum concentrations for BUN and creatinine at study entry and/or these changes were minor. One patient had significant change of serum level of creatinine. However, this patient had recurrent urinary tract infections, vesicoureteral reflux, ureterocele, and ongoing moderate chronic renal insufficiency, and therefore, was not considered as a drug-related change.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

There are three studies including Study CS0866-A-U101, U102, and U301 with OM suspension and tablets to determine suitability for a hypertensive pediatric population, 1 to 16 years of age. Studies in which safety was assessed are provided in the following table. As discussed in the section 5.3, Study CS0866-A-U301 is the pivotal study for both efficacy and safety analysis.

7.1.2 Categorization of Adverse Events

Adverse events reported during each of the studies were classified using the Medical Dictionary for Regulatory Activities (MedDRA). For study C S0866-A-U101 MedDRA version 7.1 was used. For studies CS0866-A-U102 and CS0866-A-U301, MedDRA version 8.1 was used.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

Since the designs of the three studies were different, the incidence of adverse events is not pooled and compared across the studies. The safety data were listed and described by individual study.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Three studies were evaluated for safety in children. In the Study CS0866-A-U101, the 24 subjects who completed both arms of the study received a single oral 40-mg OM tablet and a single oral 40-mg OM dose in suspension for a total of 80 mg over the entire study period. Two subjects received only one treatment (tablet) of the crossover study. In Study CS0866-A-U102, all enrolled subjects received a single dose of OM based on age and weight. Subjects ≤ 6 years of age (n = 4) received a single 0.3 mg/kg OM dose. One subject in the 6 to 12 year-old age group weighed 33.0 kg received a single 20-mg OM dose. All (n = 19) other subjects that were 6 to 16 years old weighed ≥ 35 kg received a single 40-mg OM dose.

In the pivotal Study CS0866-A-U301, a total of 361 subjects were included in the safety population, defined as subject who took at least one dose of study drug. The number of subjects in each cohort and received treatments are shown by period in the following tables. All subjects received OM and a total of 194 subjects also received placebo during the 2-week placebo-withdrawal period of the study.

Table 27: Number of Subjects in Study CS0866-A-U301 (Sponsor's table)

	Randomized N	Safety population N (%)[a]	Completed Period II N (%)[a]	Completed Period III N (%)[a]	Completed Period IV N (%)[a]
Cohort A	190	190 (100)	182 (95.79)	179 (94.21)	149 (78.42)
Cohort B	112	112 (100)	107 (95.54)	104 (92.86)	83 (74.11)
Cohort C	60	59 (98.33)	58 (96.67)	57 (95.00)	57 (5.00)

[a] percent is calculated using the number of patients assigned to each cohort as denominator.

Table 28: Treatments Administered in Study CS0866-A-U301 (Sponsor's table)

Cohort A and Cohort B				
		Period II Double-blind	**Period III Placebo-withdrawal**	**Period IV[a] Open-label**
Weight	**Period II OM Assignment**	**Dosing Regimen**		
> 20 kg but < 35 kg	Low dose	2.5 mg OM, p.o., daily	2.5 mg OM or placebo, p.o., daily	10 or 20 mg[b] OM, p.o., daily
	High dose	20 mg OM, p.o., daily	20 mg OM or placebo, p.o., daily	
≥ 35 kg	Low dose	5.0 mg OM, p.o., daily	5.0 mg OM or placebo, p.o., daily	20 or 40 mg[b] OM, p.o., daily
	High dose	40 mg OM, p.o., daily	40 mg OM or placebo, p.o., daily	
Cohort C				
All Subjects		**Period II Open-label**	**Period III Placebo-withdrawal**	**Period IV[a] Open-label**
		Dosing Regimen		
		0.3 mg/kg OM	0.3 mg/kg OM or placebo	0.3 or 0.6 mg/kg

a: Subjects could titrate to double the initial dose, provided they were not intolerant and had not reachedthe SeSBP goal after 2 weeks. Additional antihypertensives (except another ARB or an ACE inhibitor) could be added to reach BP goals as assessed by and at the discretion of the investigator. Back titration of OM also could be performed.
b : During Period IV, the 10 mg dose could be administered as 2 x 5 mg tablets and the 20 mg dose could be administered as a 20 mg tablet. The 40 mg dose could be administered as 2 x 20 mg tablets.

Overall, the extent of exposure was consistent with the Written Request. In Cohort A and Cohort B, mean extents of exposure to the low and high OM doses were similar in Period III. During Period IV, mean extents of exposure to OM 10 mg, 20mg, and 40 mg, once a day, were 254.2, 202.6, and 234.8 days, respectively for Cohort A and mean extents of exposure to OM 10mg, 20mg, and 40mg, once a day were 212.5, 176.3, and 280.9 days, respectively for cohort B. In Cohort C, mean extents of exposure of OM 0.3 mg/kg were comparable to that of placebo during Period III. Mean exposures to OM 0.3 mg/kg and 0.6mg/kg were similar in Period IV. Data were summarized in the following table.

Table 29: CS0866-A-U301: Extent of Exposure (days) – Safety Population (Sponsor's table)

	Cohort A					
	Period II		**Period III**		**Period IV**	
OM Dose	N	Mean (SD) Min - Max	N	Mean (SD) Min - Max	N	Mean (SD) Min - Max
OM 2.5 mg	16	19.6 (3.77) 8 - 24	7	14.6 (1.13) 13 - 16	0	---
OM 5 mg	78	21.0 (4.03) 2 - 32	38	13.8 (5.11) 5 - 36	0	---
OM 10 mg	0	---	0	---	26	254.2 (106.54) 14 - 333
OM 20 mg	15	21.1 (1.46) 18 - 24	3	11.7 (4.93) 6 - 15	133	202.6 (130.22) 11 - 341
OM 40 mg	79	22.3 (4.27) 18 - 53	45	13.9 (5.31) 5 - 42	74	234.8 (99.83) 28 - 336
placebo	0	---	89	12.4 (5.73) 2 - 50	0	---
	Cohort B					
	Period II		**Period III**		**Period IV**	
OM Dose	N	Mean (SD) Min - Max	N	Mean (SD) Min - Max	N	Mean (SD) Min - Max
OM 2.5 mg	5	21.2 (2.95) 18 - 26	3	11.3 (3.79 7 - 14	0	---
OM 5 mg	51	20.6 (3.56) 6 - 28	24	11.1 (4.88) 4 - 22	0	---
OM 10 mg	0	---	0	---	11	212.5 (137.91) 14 - 329
OM 20 mg	10	21.9 (3.96) 15 - 28	6	12.3 (3.27) 7 - 16	63	176.3 (142.02) 7 - 346
OM 40 mg	46	21.4 (2.67) 17 - 31	20	11.0 (4.40) 5 - 18	55	280.9 (78.66) 10 - 338
placebo	0	---	54	11.0 (4.43) 4 - 29	0	---
	Cohort C					
	Period II		**Period III**		**Period IV**	
OM Dose	N	Mean (SD) Min - Max	N	Mean (SD) Min - Max	N	Mean (SD) Min - Max
OM 0.3 mg/kg	59	20.6 (3.23) 1 - 26	29	13.5 (2.82) 7 - 18	51	261.7 (114.17) 14 - 336
OM 0.6 mg/kg	0	---	0	---	19	261.1 (89.79) 14 - 334
Placebo	0	---	28	12.5 (4.01) 4 - 21	0	---

Subject demographics and other characteristics at study baseline are provided by study in the following tables. For studies CS0866-A-U101 and CS0866-A-U102 demographics were

summarized for all enrolled subjects and for study CS0866-A-U301 the demographics were summarized for all randomized subjects.

In Study CS0866-A-U101, the majority of healthy adult subjects in this study were male (22/26, 84.6%) and White (19/26, 73.1%). In Study CS0866-A-U102, the mean age of all subjects in the study was 11.2 years, with a range of 4 to 16 years. Exactly 50% of the subjects in the 6 to12 (Group 3, n = 10) and 13 to 16 (Group 4, n = 10) year age groups were male and half were female. In the 2 to 5 (Group 2, n = 4) year age group, there were three females and one male. The majority of subjects (66.7%) were Black. No subjects were enrolled in the 12 to 23 month (Group 1) age group. In Groups 3 and 4, all subjects except one weighed ≥ 35 kg. Six subjects in the 13 to 16 year age group and four in the 6 to 12 year age group weighed over 80 kg.

In Study CS0866-A-U301, overall, mean age was appropriate for the protocol-specified age ranges in Cohorts A and B. Mean age and age distribution were similar for subjects receiving low and high OM doses. Race distribution met the Written Request specifications for Cohorts A and B. The various races were equally represented in subjects receiving low and high OM doses in Cohort A. In Cohort A, there were more males than females; whereas in Cohort B, there was an approximately equal distribution of males and females. Distribution of males and females was comparable in subjects receiving low and high OM doses within each cohort. Mean BP was comparable in Cohorts A and B at baseline. A greater percentage of subjects in Cohort B had primary hypertension and a family history of hypertension compared with Cohort A. White (45.0%) and Asian (35.0%) were the primary races in Cohort C (1 to 5 years old), and there were more males than females. Most subjects in Cohort C did not have primary hypertension and did not have a family history of hypertension. Unlike Cohort A or Cohort B, comorbid kidney abnormalities such as nephrotic syndrome were present in 59.3% of subjects.

Table 30: CS0866-A-U101 and CS0866-A-U102 - Key Demographic and Baseline Characteristics (Sponsor's table)

	CS0866-A-U101 Healthy adults (N = 26)	CS0866-A-U102 2-16 years old (N = 24)
Age (years)		
Mean (SD)	28.8 (5.90)	11.2 (3.76)
Median (Min – Max)	28.0 (18.0 - 38.0)	11.0 (4 – 16)
Height (cm)		
Mean (SD)	175.2 (6.97)	151.6 (19.44)
Median (Min – Max)	176.5 (152.4 - 188.0)	155.7 (106 - 178)
Weight (kg)		
Mean (SD)	79.0 (11.65)	70.6 (30.09)
Median (Min – Max)	77.8 (61.3 - 98.4)	66.1 (18 - 136)
	n (%)	n (%)
Race[a]		
White	2 (7.7)	9 (37.5)
Black/African heritage	19 (73.1)	16 (66.7)
Asian	1 (3.8)	--
Hispanic	2 (7.7)	2 (8.3)
Other	2 (7.7)	--
Gender		
Male	22 (84.6)	11 (45.8)
Female	4 (15.4)	13 (54.2)
Primary hypertension		
Yes	N/A	24 (100.0)
No	N/A	0 (0.0)
Familial hypertension		
Yes	N/A	N/A
No	N/A	N/A

a: Subjects were allowed to check more than one race.

Table 31: CS0866-A-U301 - Key Demographic and Baseline Characteristics (Sponsor's table)

	Cohort A 6-16 years old (N = 190)	Cohort B 6-16 years old (N = 112)	Cohort C 1-5 years old (N = 60)
Age (years)			
Mean (SD)	12.2 (2.97)	12.5 (2.64)	3.4 (1.45)
Median (Min – Max)	13.0 (6.0-17.0)	13.0 (6.0-16.0)	4.0 (1.0 - 5.0)
Height (cm)			
Mean (SD)	154.2 (18.76)	155.2 (16.08)	98.3 (12.92)[a]
Median (Min – Max)	159.0 (111.0-187.0)	156.0 (110.0-190.0)	98.0 (73.0 - 120.0)
Weight (kg)			
Mean (SD)	73.4 (38.51)	67.2 (33.25)	16.9 (6.61)[a]
Median (Min – Max)	72.8 (18.0-200.0)	60.1 (20.0-232.9)	15.5 (8.0 - 44.0)
	n (%)	n (%)	n (%)
Race[b]			
White	118 (62.1)	1 (0.9)[c]	27 (45.0)
Black/African heritage	35 (18.4)	112 (100.0)	7 (11.7)
Asian	19 (10.0)	0 (0.0)	21 (35.0)
Hawaiian	1 (0.5)	0 (0.0)	0 (0.0)
Other	25 (13.2)	1 (0.9)[c]	5 (8.3)
Gender			
Male	122 (64.2)	57 (50.9)	34 (56.7)
Female	68 (35.8)	55 (49.1)	26 (43.3)
Primary hypertension			
Yes	128 (67.4)	97 (86.6)	20 (33.3)
No	62 (32.6)	15 (13.4)	40 (66.7)
Familial hypertension			
Yes	112 (58.9)	76 (67.9)	17 (28.3)
No	78 (41.1)	36 (32.1)	43 (71.7)

a: n=59
b: Subjects were allowed to check more than one race.
c: All subjects in this cohort were black; however, two were of mixed race and more than one race could be checked.

Subject completion information by study period is summarized in the following tables for the study Cohorts A, B, and C. Most subjects who entered Period II completed all 3 weeks, Cohort A: 95.8%, Cohort B: 95.5%, Cohort C: 96.7%. A total of 14 subjects withdrew (Cohort A, n = 8; Cohort B, n = 5; Cohort C, n = 1) during Period II and did not continue into Period III. Most subjects who entered Period III continued to Period IV, Cohort A: 98.4%, Cohort B: 97.2%, Cohort C: 98.3%. A total of seven subjects withdrew from Period III (Cohort A, n = 3; Cohort B, n = 3; Cohort C, n =1) and did not continue into Period IV, the 46-week open-label extension period. Among the subjects who continued into Period IV, 83.2% and 79.8% completed from Cohort A and Cohort B, respectively, and 100.0% completed from Cohort C.

Table 32: CS0866-A-U301: Subject Completion/Withdrawal Cohort A in Periods II, III, and IV (Sponsor's table)

Randomized Population						
	Period II			Period III		Period IV
	Low OM dose[a] (N=95) n (%)	High OM dose[a] (N= 95) n (%)	Total OM (N=190) n (%)	Total OM (N=93) n (%)	Placebo (N=89) n (%)	Total OM (N=179) n (%)
Completed[b]	89 (93.7)	93 (97.9)	182 (95.8)	93 (100.0)	86 (96.6)	149 (83.2)
Early termination	6 (6.3)	2 (2.1)	8 (4.2)	0 (0.0)	3 (3.4)	30 (16.8)
Reasons for termination						
Subject request	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (2.8)
Subject had a mean SeSBP and/or SeDBP > 99th percentile for subject's gender/age/height	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	17 (9.5)
Non-compliance or lack of cooperation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.2)
Adverse event	2 (2.1)	1 (1.1)	3 (1.6)	0 (0.0)	1 (1.1)	1 (0.6)
Protocol violation	4 (4.2)	0 (0.0)	4 (2.1)	0 (0.0)	1 (1.1)	1 (0.6)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.6)
Missing[c]	0 (0.0)	1 (1.1)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)

a: Low dose: 2.5 mg (> 20 but < 35 kg) or 5.0 mg (≥35 kg); high dose: 20.0 mg (> 20 but < 35 kg) or 40.0 mg (≥ 35 kg)
b: Percentage of subjects at the start of each period
c: No reason was provided.

Table 33: CS0866-A-U301 - Subject Completion/Withdrawal Cohort B - Periods II, III, and IV (Sponsor's table)

Randomized Population						
	Period II			Period III		Period IV
	Low OM dose[a] (N=56) n (%)	High OM dose[a] (N=56) n (%)	Total OM (N=112) n (%)	Total OM (N=53) n (%)	Placebo (N=54) n (%)	Total OM (N=104) n (%)
Completed[b]	53 (94.6)	54 (96.4)	107 (95.5)	51 (96.2)	53 (98.1)	83 (79.8)
Early termination	3 (5.4)	2 (3.6)	5 (4.5)	2 (3.8)	1 (1.9)	21 (20.2)
Reasons for termination						
Subject request	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	2 (1.9)
Subject had a mean SeSBP and/or SeDBP > 99th percentile for subject's gender/age/height	1 (1.8)	0 (0.0)	1 (0.9)	1 (1.9)	0 (0.0)	1 (1.0)
Investigator judgment	0 (0.0)	1 (1.8)	1 (0.9)	0 (0.0)	0 (0.0)	2 (1.9)
Lost to follow-up	1 (1.8)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	6 (5.8)
Non-compliance or lack of cooperation	0 (0.0)	1 (1.8)	1 (0.9)	0 (0.0)	0 (0.0)	4 (3.8)
Adverse event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.9)
Other	1 (1.8)	0 (0.0)	1 (0.9)	0 (0.0)	1 (1.9)	3 (2.9)
Missing[c]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)

a: Low dose: 2.5 mg (> 20 but < 35 kg) or 5.0 mg (≥ 35 kg); high dose: 20.0 mg (> 20 but < 35 kg) or 40.0 mg (≥ 35 kg)
b: Percentage of subjects at the start of each period
c: No reason was provided.

Table 34: CS0866-A-U301 - Subject Completion/Withdrawal Cohort C -Periods II, III, and IV (Sponsor's table)

Randomized Population				
	Period II	Period III		Period IV
	OM 0.3 mg/kg (N=60) n (%)	OM 0.3 mg/kg (N=29) n (%)	Placebo (N=29) n (%)	Total OM (N= 57) n (%)
Completed[a]	58 (96.7)	29 (100.0)	28 (96.6)	57 (100.0)
Early termination	2 (3.3)[b]	0 (0.0)	1 (3.4)	0 (0.0)
Reasons for termination				
Subject had a mean SeSBP and/or SeDBP > 99th percentile for subject's gender/age/height	1 (1.7)[b]	0 (0.0)	0 (0.0)	0 (0.0)
Missing[c]	1 (1.7)	0 (0.0)	1 (3.4)	0 (0.0)

a: Percentage of randomized subjects.
b: One subject was discontinued for failure to meet protocol criteria prior to receiving study drug.
c: No reason was provided.

7.2.2 Explorations for Dose Response

Dose-response study was conducted in Study CS0866-A-U301. Overall, there was no clear relationship between the dose and adverse events other than the headache which showed a high incidence rate in high dose group.

In the dose-ranging period of study (period II), the percentages of subjects with treatment emergent adverse event (TEAEs) were similar for the low- and high-dose OM groups. There were more subjects with TEAEs in Cohort A (43.2 % OM low dose and 47.4% OM high dose) than in Cohort B (33.9% and 28.6%, respectively). There were three subjects with SAEs (low OM dose [n = 1], high OM dose [n = 2]) from Cohort A, and there were no SAEs in Period II in Cohort B. Two subjects discontinued due to TEAEs in the low OM dose group of Cohort A no discontinuations due to TEAEs in Cohort B. Data were summarized in the following table.

Table 35: Overview of TEAEs for Cohorts A and B during Period II – All Randomized Subjects (Sponsor's table)

Category		Period II treatment n (%) of subjects[a]			
		Cohort A		Cohort B	
		Low OM dose[b] N=95	High OM dose[b] N=95	Low OM dose[b] N=56	High OM dose[b] N=56
Number of subjects (%) with at least one TEAE		41 (43.16)	45 (47.37)	19 (33.93)	16 (28.57)
Drug-related[c] TEAEs		3 (3.16)	8 (8.42)	0 (0.00)	1 (1.79)
TEAEs by maximum intensity	Mild	33 (34.74)	30 (31.58)	15 (26.79)	11 (19.64)
	Moderate	8 (8.42)	14 (14.74)	4 (7.14)	5 (8.93)
	Severe	0 (0.00)	1 (1.05)	0 (0.00)	0 (0.00)
Deaths		0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
SAEs	All	1 (1.05)	2 (2.11)	0 (0.00)	0 (0.00)
	Drug-related[c]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Discontinuations due to TEAEs	All	2 (2.11)	0 (0.00)	0 (0.00)	0 (0.00)
	Drug-related[c]	1 (1.05)	0 (0.00)	0 (0.00)	0 (0.00)

a: Percentage is based on the number of subjects in each OM treatment group.
b: Low dose OM is 2.5 mg qd for subjects weighing > 20 kg and < 35 kg and 5.0 mg qd for subjects weighing > 35 kg.
c: High dose OM is 20 mg qd for subjects weighing > 20 kg and < 35 kg and 40 mg qd for subjects weighing > 35 kg

During the withdrawal study of Period III in Cohort A, the incidence of TEAEs was greater for subjects taking the high OM dose compared with either subjects taking the low OM dose or placebo. Within Cohort B, the incidence of TEAEs was slightly greater for subjects taking the high OM dose compared with subjects taking the low OM dose and slightly greater or the same compared with subjects taking placebo. The majority of TEAEs in both cohorts were mild or moderate. Data were summarized in the following table. There was one SAE (pyelonephritis) in the high OM dose group in Cohort B which resolved with treatment.

Table 36: Overview of TEAEs for Cohorts A and B During Period III – All Randomized Subjects (Sponsor's table)

Category		Period III treatment n (%) of subject[a]							
		Cohort A				Cohort B			
		Low dose[b]		High dose[b]		Low dose[b]		High dose[b]	
		OM[c] N=45	Placebo[c] N=44	OM[c] N=48	Placebo[c] N=45	OM[c] N=27	Placebo[c] N=26	OM[c] N=26	Placebo[c] N=28
Number of. subjects (%) with at least one TEAE		14 (31.11)	13 (29.55)	19 (39.58)	14 (31.11)	3 (11.11)	4 (15.38)	4 (15.38)	4 (14.29)
Drug-related[d] TEAEs		1 (2.22)	0 (0.00)	2 (4.17)	2 (4.44)	0 (0.00)	0 (0.00)	1 (3.85)	0 (0.00)
TEAEs by maximum intensity	Mild	11 (24.44)	8 (18.18)	16 (33.33)	9 (20.00)	2 (7.41)	3 (11.54)	3 (11.54)	3 (10.71)
	Moderate	3 (6.67)	5 (11.36)	2 (4.17)	3 (6.67)	1 (3.70)	1 (3.85)	1 (3.85)	1 (3.57)
	Severe	0 (0.00)	0 (0.00)	0 (0.00)	1 (2.22)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Deaths		0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
SAEs	All	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (3.85)	0 (0.00)
	Drug-related[d]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Discontinuations due to TEAEs	All	0 (0.00)	0 (0.00)	0 (0.00)	1 (2.22)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
	Drug-related[d]	0 (0.00)	0 (0.00)	0 (0.00)	1 (2.22)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

a: Percentage is based on the number of subjects in each OM or placebo treatment group.
b: This reflects the treatment received during Period II (low or high dose OM).
c: During Period III, subjects were randomized to continue on the Period II dose of OM (low or high dose) or to begin placebo treatment. Low dose OM is 2.5 mg qd for subjects weighing > 20 kg and < 35 kg and 5.0 mg qd for subjects weighing > 35 kg. High dose OM is 20 mg qd for subjects weighing > 20 kg and < 35 kg and 40 mg qd for subjects weighing > 35 kg.
d: Drug-related events were those considered to be possibly, probably, or definitely related to study medication.

7.2.3 Special Animal and/or In Vitro Testing

Neither special animal nor in vitro testing was done.

7.2.4 Routine Clinical Testing

The routine clinical testing including adverse event data collection in both short-term and long-term studies, monitoring laboratory parameters, vital signs, and physical examinations are adequate. In addition, the specific tests for children including the height, weight and developmental assessments were considered adequate according to the Written Request Protocol.

7.2.5 Metabolic, Clearance, and Interaction Workup

The pharmacokinetic workup in children appears adequate. Please see the FDA clinical pharmacology review for a detailed discussion.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Several ACEI/ARB products such as Enalapril, Fosinopril, Quinapril, losartan, and Irbesartan have been evaluated in children. Adverse events are similar to the adults. No new additional adverse events were discovered.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in the studies.

7.3.2 Nonfatal Serious Adverse Events

There were no SAEs in either study CS0866-A-U101 or study CS0866-A-U102. In Study C S0866-A-U301, Cohort A, 12 subjects had a total of 23 SAEs. In Cohort B, four subjects had a total of eight SAEs. One of these SAEs, relapse of systemic lupus erythematosus (SLE) was severe, considered possibly related to study drug, and resulted in the subject discontinuing study drug. The SAE was ongoing at the time of discontinuation. In a post study follow-up 33 months after the subject discontinued (February 2009), SLE was in remission but still required treatment. In Cohort C, five subjects had a total of six SAEs. SAEs are shown by cohort in the following table.

Table 37: CS0866-A-U301 - Serious Treatment Emergent Adverse Events during the Study for All Cohorts - Safety Population (Sponsor's table)

Subject No.	Treatment[a]	MedDRA Preferred Term	Severity/ Relationship (Study Day at Onset of SAE)	Outcome at the last study visit
Cohort A				
11116	OM 40 mg	Vomiting	Moderate/Unrelated (249)	Recovered
		Sinusitis	Moderate/Unrelated (280)	Continuing[b]
		Vomiting	Moderate/Unrelated (280)	Recovered
		Ophthalmoplegia	Severe/Unrelated (286)	Recovered
		Sinusitis	Severe/Unrelated (286)	Recovered
		Systemic lupus erythematosus	Severe/Unrelated (287)	Unknown[c]
10400	OM 10 mg	Ureteric stenosis	Moderate/Unrelated (132)	Recovered
11167	OM 20 mg	Upper respiratory tract infection	Moderate/Unrelated (15)	Recovered
	OM 10 mg	Anasarca	Moderate/Unrelated (64)	Recovered
		Hypoproteinemia	Mild/Unrelated (83)	Recovered
10398	OM 20 mg	Laparoscopy	Mild/Unrelated (176)	Recovered
10185	OM 40 mg	Bronchopneumonia	Moderate/Unrelated (71)	Recovered
	OM 20 mg	Bronchitis	Severe/Unrelated (139)	Recovered
	OM 40 mg	Bronchopneumonia	Moderate/Unrelated (401)	Recovered
11173	OM 20 mg	Metabolic disorder	Severe/Unrelated (38)	Recovered with sequelae
10140	OM 20 mg	Coarctation of the aorta	Moderate/Unlikely (311)	Recovered
11155	OM 20 mg	Depression	Severe/Unlikely (36)	Recovered
		Suicide attempt	Severe/Unlikely (36)	Recovered
11182	OM 5 mg	Diabetic ketoacidosis	Moderate/Unlikely (18)	Recovered
11205	OM 40 mg	Mental disorder	Severe/Unrelated (19)	Recovered
10151	OM 40 mg	Arthralgia	Severe/Unrelated (206)	Recovered with sequelae
		Arthralgia	Severe/Unrelated (223)	Recovered with sequelae
10124	OM 10 mg	Bronchopneumonia	Moderate/Unrelated (35)	Recovered
Cohort B				
20108	OM 20 mg	Pyelonephritis	Moderate/Unrelated (34)	Recovered
	OM 10 mg	Systemic lupus erythematosus	Severe/Possible (52)	Continuing[d]
		Epistaxis	Moderate/Unrelated (79)	Recovered
20109	OM 20 mg	Nephrotic syndrome	Moderate/Unlikely (55)	Continuing[d]
		Nephrotic syndrome	Severe/Unlikely (62)	Continuing[d]
		Peritonitis	Severe/Unrelated (263)	Recovered
20187	OM 40 mg	Abscess limb	Moderate/Unrelated (252)	Recovered
20388	OM 20 mg	Asthma	Severe/Unrelated (212)	Recovered

Cohort C				
30153	OM 0.6 mg/kg	Bronchopneumonia	Moderate/Unrelated (238)	Recovered
		Nephrotic syndrome	Moderate/Unrelated (241)	Recovered
30154	OM 0.6 mg/kg	Bronchopneumonia	Moderate/Unrelated (238)	Recovered
30132	OM 0.3 mg/kg	Pneumonia	Moderate/Unrelated (165)	Recovered
30138	OM 0.6 mg/kg	Eye hemorrhage	Moderate/Unrelated (245)	Continuing[f]
30106	OM 0.3 mg/kg	Ovarian cyst	Moderate/Unlikely (300)	Recovered

a: Dose assigned at the time the SAE occurred
b: Follow-up showed improvement; not resolved at the time of the last follow-up.
c: Investigations into the systemic lupus erythematosis relapse were ongoing at the time of the last follow-up.
d: Follow-up on 12 February 2009 shows subject in remission but still requiring treatment.
e: Follow-up on 12 February 2009 shows subject in remission but still requiring treatment.
f: At the last follow-up during the study the SAE was improving, however subsequent follow-up showed remnant lesion: blindness.

7.3.3 Dropouts and/or Discontinuations

No subjects discontinued due to TEAEs in either study CS0866-A-U101 or study CS0866-A-U102. In stud y C S0866-A-U301, four subjects discontinued due to TEAEs in Cohort A (2 on OM 5 mg qd during Period II, 1 on placebo during Period III, and 1 on OM 20 mg qd during Period IV) and one subject discontinued due to a TEAE in Cohort B (OM 10 mg qd during Period IV). There were no discontinuations due to TEAEs in Cohort C. For two of the subjects, the events leading to discontinuation were also SAEs. In Cohort A, one subject was hospitalized for laparoscopic band placement surgery due to a metabolic disorder. In Cohort B, one subject had a SLE relapse. The following table lists all subjects who discontinued due to an AE by study cohort.

Table 38: CS0866-A-U301 - Subjects Who Discontinued Due to Treatment Emergent Adverse Events by Cohort - Safety Population (Sponsor's table)

Subject No.	Treatment	Period	MedDRA Preferred Term	Severity/ Relationship	Outcome at the last study visit
Cohort A					
10160	OM 5 mg	II	Hypertension	Moderate/ Unlikely	Recovered
11102	OM 5 mg	II	Hypoaesthesia	Moderate/ Possible	Recovered
10139	Placebo	III	Blood pressure increased	Severe/ Possible	Recovered
		III	Dizziness	Moderate/ Possible	Recovered
11173	OM 20 mg	IV	Body mass index increased	Severe/ Unrelated	Recovered with sequelae
		IV	Metabolic disorder	Severe/ Unrelated	Recovered with sequelae
Cohort B					
20108	OM 10 mg	IV	Systemic lupus erythematosus	Severe/ Possible	Continuing[a]

a: Follow-up on 12 February 2009 shows subject in remission but still requiring treatment.

7.3.4 Significant Adverse Events

There were no significant AEs other than discussed above. However, as expected, minor reduced hemoglobin and hematocrit, increased serum levels of potassium, blood urea nitrogen and creatinine in some subjects were observed. In addition, increased CPK (creatine phosphokinase)

and liver enzymes were found in some subjects. These changes were not considered clinically meaningful changes. Please see the detailed discussion in the section of 7.4.2 laboratory findings.

Increased CPK was reported in one subject in study CS0866-A-U101. The subject had a CPK at screening of 282 U/L (normal range, 0 to 215 U/L). At the post-study assessment, the CPK had increased to 1,059 U/L. During follow-up approximately 2.5 months later, the CPK was reached to 13,647 U/L without any other clinical manifestations. The patient claimed that he had moved heavy furniture the previous day. The CPK was 230 U/L at the subsequent follow-up after 3 months post-study.

7.3.5 Submission Specific Primary Safety Concerns

There were no primary safety concerns from this particular study.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In studies of CS0866-A-101 and 102, all TEAEs were considered mild in intensity and all subjects recovered from all events. In Study CS0866-A-101, one of 24 subjects reported fatigue after taking the OM suspension and one of 26 subjects reported fatigue after taking the OM tablet. Asthenia and dizziness occurred after taking the OM tablet and headache occurred after taking the OM suspension. Nausea and joint sprain occurred each. In Study CS0866-A-102, four (16.7%) of the 24 subjects experienced six TEAEs. One subject in the 2 to 5 year age group experienced headache and fatigue. In the 6 to 12 year age group, TEAEs were somnolence and diarrhea (one subject) and abdominal pain (one subject). In the 13 to 16 year age group one subject had a high white blood cell count (WBC) in the urine (12/high power field at the end-of-study laboratory assessment). Data were summarized in the following tables.

Table 39: CS0866-A-U101 - Treatment Emergent Adverse Events

MedDRA system organ class Preferred term	40 mg OM Healthy Adults N = 26[a]
No. of subjects (%) with at least one TEAE[b]	**4 (15.4)**
	n (%) of subjects
Gastrointestinal disorders	**1 (3.8)**
Nausea	1 (3.8)
General disorders and administration site conditions	**2 (7.7)**
Asthenia	1 (3.8)
Fatigue	2 (7.7)
Injury, poisoning, and procedural complications	**1 (3.8)**
Joint sprain	1 (3.8)
Nervous system disorders	**2 (7.7)**
Dizziness	1 (3.8)
Headache	1 (3.8)

a: This study was a crossover design with a total N of 26 subjects. All 26 received the tablet formulation and 24 received the suspension.
b: Subjects could have more than one TEAE.

Table 40: CS0866-A-U102 - Treatment Emergent Adverse Events

MedDRA system organ class Preferred term	CS0866-A-U102		
	2-5 years old 0.3 mg/kg OM N = 4	6 – 12 years old 40 mg OM[a] N = 10	13 - 16 years old 40 mg OM N =10
No. of subjects (%) with at least one TEAE[c]	**1 (25.0)**	**2 (20.00)**	**1 (10.0)**
	n (%) of subjects		
Gastrointestinal disorders	**0 (0.0)**	**2 (20.0)**	**0 (0.0)**
Abdominal pain	0 (0.0)	1 (10.0)	0 (0.0)
Diarrhea	0 (0.0)	1 (10.0)	0 (0.0)
General disorders and administration site conditions	**1 (25.0)**	**0 (0.0)**	**0 (0.0)**
Fatigue	1 (25.0)	0 (0.0)	0 (0.0)
Investigations	**0 (0.0)**	**0 (0.0)**	**1 (10.0)**
Urine analysis abnormal	0 (0.0)	0 (0.0)	1 (10.0)
Nervous system disorders	**1 (25.0)**	**1 (10.0)**	**0 (0.0)**
Headache	1 (25.0)	0 (0.0)	0 (0.0)
Somnolence	0 (0.0)	1 (10.0)	1 (5.0)

a: Subjects in this study were given 20 mg or 40 mg OM based on body weight. One of the subjects was given the 20-mg dose and did not report any TEAEs. All other subjects in this group received the 40 mg dose.

In Study CS0866-A-U301, during the dose-ranging period of the study (Period II), the incidence of TEAEs was greater in Cohort A (45.3%) than in Cohort B (31.3%), but comparable for subjects taking low and high OM doses within each of these cohorts. During the placebo withdrawal period of the study (Period III), the incidence of TEAEs was also greater in Cohort A (33.0%) than in Cohort B (14.0%) and greatest in subjects taking the high OM dose within each cohort. The incidence of TEAEs in subjects taking the low OM dose was not different from that for subjects taking placebo in either cohort. In Cohort C, the incidence rates of TEAEs was 28.6% in placebo and 17.2% in OM treated group, respectively.

Overall during the study in all cohorts, the majority of TEAEs was mild or moderate in intensity. Headache was the most frequently reported TEAE in Cohorts A and B and the incidence of headache was higher in subjects taking the high OM dose. Dizziness was a commonly reported TEAE. There were reports of dizziness in 23 subjects during the entire study in Cohort A (Period II, n = 11; Period III, n = 2; Period IV, n = 10). In Cohort B there were three reports of dizziness overall in three subjects. There was one report of dizziness in Cohort C during Period III for a subject taking placebo. One subject in Cohort A discontinued the study due to dizziness while taking placebo in Period III. Reports of syncope were limited to one TEAE in one subject in Cohort A during Period IV while taking 20 mg OM. Hypotension was reported one time each for four subjects, one subject in Cohort A in Period IV (40 mg OM) and three subjects in Cohort B, one in Period III (20 mg OM) and two in Period IV (20 mg and 40 mg OM). No reports of syncope or hypotension were reported for Cohort C. No subjects discontinued from the study due to syncope or hypotension in any cohort. Data were summarized in the following table.

Table 41: CS0866-A-U301 - Treatment Emergent Adverse Events Reported by≥ 2% of Subjects in Cohorts A, B, or C During Period II-Safety Population (sponsor's table)

MedDRA system organ class Preferred term	Period II treatment n (%) of subjects		
	Cohort A N = 190	Cohort B N = 112	Cohort C N = 59
Number of subjects (%) with at least one TEAE	**86 (45.26)**	**35 (31.25)**	**18 (30.51)**
Gastrointestinal disorders	**21 (11.05)**	**9 (8.04)**	**3 (5.08)**
Abdominal pain upper	8 (4.21)	1 (0.89)	0 (0.0)
Toothache	0 (0.0)	3 (2.68)	1 (1.69)
Vomiting	4 (2.11)	1 (0.89)	0 (0.0)
General disorders and administration site conditions	**16 (8.42)**	**4 (3.57)**	**3 (5.08)**
Fatigue	3 (1.58)	3 (2.68)	0 (0.0)
Pyrexia	8 (4.21)	1 (0.89)	3 (5.08)
Infections and infestations	**27 (14.21)**	**14 (12.50)**	**9 (15.25))**
Nasopharyngitis	5 (2.63)	3 (2.68)	1 (1.69)
Pharyngitis	6 (3.16)	0 (0.0)	0 (0.0)
Upper respiratory tract infection	11 (5.79)	2 (1.79)	1 (1.69)
Musculoskeletal and connective tissue disorders	**9 (4.74)**	**3 (2.68)**	**1 (1.69)**
Back pain	4 (2.11)	1 (0.89)	0 (0.0)
Nervous system disorders	**32 (16.84)**	**8 (7.14)**	**1 (1.69)**
Dizziness	11 (5.79)	1 (0.89)	0 (0.0)
Headache	21 (11.05)	8 (7.14)	1 (1.69)
Somnolence	4 (2.11)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	**17 (8.95)**	**6 (5.36)**	**5 (8.47)**
Pharyngolaryngeal pain	7 (3.68)	0 (0.0)	0 (0.0)
Cough	0 (0.0)	1 (0.89)	3 (5.08)
Rhinitis allergic	0 (0.0)	0 (0.0)	2 (3.39)
Rhinorrhea	5 (2.63)	1 (0.89)	0 (0.0)

7.4.2 Laboratory Findings

In Study CS0866-A-101, increased creatine phosphokinase (CPK) was reported in one subject. The subject had a CPK at screening of 282 U/L (normal range, 0 to 215 U/L). At the post-study assessment, the CPK had increased to 1,059 U/L. During follow-up approximately 2.5 months later, the CPK was 13,647 U/L reportedly due to moving heavy furniture the previous day. This issue was resolved at the subsequent follow-up, 3 months post-study, at which time the CPK was 230 U/L. In Study CS0866-A-102, increased was reported in one subject. The subject had increased WBCs in the urine (n = 12/high power field [hpf], normal range, 0 – 5/hpf) at the end-of-study laboratory assessment. No laboratory assessment was done at screening; therefore, there is no comparison with baseline.

Like the studies conducted in adults, in the pivotal study of Study CS0866-A-301, 7.1% subjects in Cohort A and 8.4% in Cohort B had shifts from normal at the beginning of the study to low at the end of the study in hemoglobin, and 7.1% subjects in Cohort A and 7.5% in Cohort B had shifts from normal at the beginning of the study to low at the end of the study in hematocrit. Four

patients in Cohort A and 2 patients in Cohort B had more than 10% hemoglobin reductions from baseline with the lowest level of 9.1g/dl (normal low range was 11.5g/dl). Three patients in Cohort A and 2 patients in Cohort B are below the normal range. No patients had hemoglobin reductions more than 30% compared to baseline. The frequency and magnitude of these changes are similar to the adult studies. No hematological shifts were seen in Cohort C. Data were summarized in the following tables. Overall these changes are not considered, clinically meaningful change.

Table 42: Changes of Hemoglobin, Hematocrit, and Red Blood Cells in Cohort A (Sponsor's table)

		END OF STUDY							
LABORATORY VARIABLE	BASELINE	LOW		NORMAL		HIGH		TOTAL	
HEMOGLOBIN(GM/L)	LOW	8	(4.3%)	2	(1.1%)	0	(0.0%)	10	(5.4%)
	NORMAL	13	(7.1%)	143	(77.7%)	2	(1.1%)	158	(85.9%)
	HIGH	0	(0.0%)	10	(5.4%)	6	(3.3%)	16	(8.7%)
	TOTAL	21	(11.4%)	155	(84.2%)	8	(4.3%)	184	
HEMATOCRIT(%)	LOW	7	(3.8%)	2	(1.1%)	0	(0.0%)	9	(4.9%)
	NORMAL	13	(7.1%)	141	(76.6%)	2	(1.1%)	156	(84.8%)
	HIGH	0	(0.0%)	12	(6.5%)	7	(3.8%)	19	(10.3%)
	TOTAL	20	(10.9%)	155	(84.2%)	9	(4.9%)	184	
RED BLOOD CELLS(X 10^12/L)	LOW	4	(2.2%)	2	(1.1%)	0	(0.0%)	6	(3.3%)
	NORMAL	10	(5.4%)	158	(85.9%)	3	(1.6%)	171	(92.9%)
	HIGH	0	(0.0%)	5	(2.7%)	2	(1.1%)	7	(3.8%)
	TOTAL	14	(7.6%)	165	(89.7%)	5	(2.7%)	184	
MCV(FL)	LOW	6	(3.3%)	2	(1.1%)	0	(0.0%)	8	(4.3%)
	NORMAL	1	(0.5%)	139	(75.5%)	7	(3.8%)	147	(79.9%)
	HIGH	0	(0.0%)	6	(3.3%)	23	(12.5%)	29	(15.8%)
	TOTAL	7	(3.8%)	147	(79.9%)	30	(16.3%)	184	
MCH(PG)	LOW	1	(0.5%)	2	(1.1%)	0	(0.0%)	3	(1.6%)
	NORMAL	0	(0.0%)	180	(97.8%)	1	(0.5%)	181	(98.4%)
	HIGH	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
	TOTAL	1	(0.5%)	182	(98.9%)	1	(0.5%)	184	

[1]ONLY PATIENTS HAVING BOTH BASELINE AND POST BASELINE MEASUREMENTS ARE INCLUDED AT EACH TIME POINT.

Table 43: Changes of Hemoglobin, Hematocrit, and Red Blood Cells in Cohort B (Sponsor's table)

		END OF STUDY							
LABORATORY VARIABLE	BASELINE	LOW		NORMAL		HIGH		TOTAL	
HEMOGLOBIN(GM/L)	LOW	7	(6.5%)	5	(4.7%)	0	(0.0%)	12	(11.2%)
	NORMAL	9	(8.4%)	80	(74.8%)	1	(0.9%)	90	(84.1%)
	HIGH	0	(0.0%)	3	(2.8%)	2	(1.9%)	5	(4.7%)
	TOTAL	16	(15.0%)	88	(82.2%)	3	(2.8%)	107	
HEMATOCRIT(%)	LOW	7	(6.5%)	5	(4.7%)	0	(0.0%)	12	(11.2%)
	NORMAL	8	(7.5%)	78	(72.9%)	0	(0.0%)	86	(80.4%)
	HIGH	0	(0.0%)	6	(5.6%)	3	(2.8%)	9	(8.4%)
	TOTAL	15	(14.0%)	89	(83.2%)	3	(2.8%)	107	
RED BLOOD CELLS(X 10^12/L)	LOW	5	(4.7%)	1	(0.9%)	0	(0.0%)	6	(5.6%)
	NORMAL	7	(6.5%)	92	(86.0%)	0	(0.0%)	99	(92.5%)
	HIGH	0	(0.0%)	2	(1.9%)	0	(0.0%)	2	(1.9%)
	TOTAL	12	(11.2%)	95	(88.8%)	0	(0.0%)	107	
MCV(FL)	LOW	3	(2.8%)	1	(0.9%)	0	(0.0%)	4	(3.7%)
	NORMAL	1	(0.9%)	75	(70.1%)	5	(4.7%)	81	(75.7%)
	HIGH	0	(0.0%)	10	(9.3%)	12	(11.2%)	22	(20.6%)
	TOTAL	4	(3.7%)	86	(80.4%)	17	(15.9%)	107	
MCH(PG)	LOW	1	(0.9%)	1	(0.9%)	0	(0.0%)	2	(1.9%)
	NORMAL	0	(0.0%)	104	(97.2%)	1	(0.9%)	105	(98.1%)
	HIGH	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
	TOTAL	1	(0.9%)	105	(98.1%)	1	(0.9%)	107	

[1]ONLY PATIENTS HAVING BOTH BASELINE AND POST BASELINE MEASUREMENTS ARE INCLUDED AT EACH TIME POINT.

Table 44: CS0866-A-U301: Patients with more than 10% Reduction of Hemoglobin from Baseline for All Cohorts and All Periods (Reviewer's table)

Subject No.	Visit	Dosage	Hemoglobin (g/L)	Normal low value of Hemoglobin (g/L)
Cohort A				
11187	1.0	N/A	124	120
	2.3	40 mg	112	120
	4.7	20 mg	101	120
10158	1.0	N/A	138	120
	2.3	5 mg	134	120
	4.7	40 mg	118	120
11205	1.0	N/A	133	120
	2.3	40 mg	128	120
	4.7	40 mg	110	120
10119	1.0	N/A	136	115
	2.3	20 mg	122	115
	4.7	20 mg	113	115
Cohort B				
20136	1.0	N/A	137	115
	2.3	5 mg	135	115
	4.7	40 mg	109	115
20176	1.0	N/A	113	115
	2.3	5 mg	119	115
	4.7	40 mg	91	115

As expected, there were shifts in serum potassium from normal at study baseline to high at the end of the study in Cohort A (5.0%), Cohort B (7.9%), and Cohort C (8.9%). TEAEs of hyperkalemia were reported five times for four subjects in Cohort A. There were a total of four reports of pseudohyperkalemia in four subjects (Cohort A, n = 3; Cohort C, n = 1). The increase in potassium for the subjects with hyperkalemia and those with pseudohyperkalemia was similar (0.4 – 1.1 mmol/L and 0.1 – 1.0 mmol/L above the upper limit of the normal range of 5.0 mmol/L, respectively). There were no TEAEs of increased potassium in Cohort B. No specific trends or dose relationship was seen. Data were summarized in the following table.

Table 45: Hyperkalemia reported as TEAEs for all Cohorts and All Periods (Sponsor's table)

Subject No.	TEAE	Visit	Dosage	Serum potassium mmol/L (normal range: 3.5 – 5.0 mmol/L)
Cohort A				
11120	--	1.0	N/A	4.8
	Hyperkalemia	2.3	OM 40 mg	6.1
	--	4.7	OM 20 mg	--
11187	--	1.0	N/A	4.7
	Pseudohyperkalemia	2.3	OM 40 mg	6.0
	Hyperkalemia	USV	OM 20 mg	unk
	Hyperkalemia	USV	OM 20 mg	unk
	--	4.7	OM 20 mg	5.2
11193	--	1.0	N/A	4.8
	Pseudohyperkalemia	2.3	OM 5 mg	5.7
	Hyperkalemia	USV	OM 40 mg	unk
	--	4.7	OM 40 mg	4.9
10158	--	1.0	N/A	4.5
	--	2.3	OM 5 mg	4.4
	Hyperkalemia	2.3.1	OM 40 mg	5.4
	--	4.7	OM 40 mg	4.9
10175	--	1.0	N/A	4.0
	Pseudohyperkalemia	2.3	OM 2.5 mg	5.1
	--	4.7	OM 10 mg	5.4
Cohort C				
30134	--	1.0	N/A	5.0
	Pseudohyperkalemia	2.3	OM 0.3 mg/kg	5.6
	--	4.7	OM 0.3 mg/kg	4.1

N/A = not applicable; USV = unscheduled visit; unk = unknown
a: Dosage at the time of laboratory testing

Laboratory values for some serum chemistry parameters such as CPK and alanine aminotransferase (ALT) were elevated during the study for some subjects. In the majority of cases, these values were high at study entry and were not considered clinically relevant. No causative factor was readily identifiable for either the CPK or ALT abnormalities. The changes of CPK may be related to normal growth or physical activity in this pediatric population. Laboratory (CPK and ALT) abnormalities are shown in the following tables for all study cohorts.

Table 46: CS0866-U-301 - Abnormalities in CPK for All Cohorts and All Periods (Sponsor's table)

Subject No.	Visit	Dosage[a]	Serum CPK IU/L	Normal Range IU/L[b]
Cohort A				
11161	1.0 2.3 4.7	N/A OM 5 mg OM 20 mg	126.0 58.0 772.0	30 - 180
11109	1.0 2.3 4.7	N/A OM 5 mg OM 40 mg	87.0 88.0 726.0	30 - 180
11148	1.0 2.3 4.7	N/A OM 5 mg OM 20 mg	177.0 122.0 263.0	20-120
11137	1.0 ET	N/A OM 5 mg	144.0 753.0	30-180
11167	1.0 1.01 2.3 ET	N/A N/A OM 20 mg OM 10 mg	51.0 47.0 43.0 753.0	30 -180
11123	1.0 1.01 2.3	N/A N/A OM 40 mg	378.0 406.0 378.0	30 - 180
Cohort B				
20171	1.0 2.3 2.31 4.7	N/A OM 40 mg OM 40 mg OM 40 mg	253.0 373.0 97.0 138.0	30 - 180
20174	1.0 2.3 2.31 4.7	N/A OM 40 mg OM 40 mg OM 20 mg	135.0 540.0 274.0 215.0	30 - 180
20163	1.0 2.3 4.7	N/A OM 5 mg OM 20 mg	321.0 373.0 506.0	30 - 180
20118	1.0 2.3 4.7	N/A OM 5 mg OM 40 mg	158.0 206.0 948.0	30 - 180
20162	1.0 2.3 ET ET.01	N/A OM 40 mg OM 20 mg OM 20 mg	225.0 338.0 708.0 795.0	20 - 120
20198	1.0 2.3 4.7	N/A OM 40 mg OM 40 mg	609.0 412.0 480.0	30 - 180
20149	1.0 2.3 4.7	N/A OM 40 mg OM 20 mg	101.0 105.0 309.0	20-120
20105	1.0 1.01 2.3 2.31 ET	N/A N/A OM 5 mg OM 5 mg OM 20 mg	125.0 180.0 209.0 213.0 340.0	20-120

a: Dosage at the time of laboratory testing
b: Normal range is 20 to 120 IU/L for females 6 to 17 years of age and 30 to 180 IU/L for males 6 to 17 years of age.
Note: Visits beginning with 1 are visits during screening, (Period I). Visits beginning with 2 are visits during Period II. Visit 4.7 = the last visit of the study during Period IV.

Table 47: CS0866-A-U301 - Abnormalities in ALT for All Cohorts and All Periods (Sponsor's table)

Subject No.	Visit	Dosage	Serum ALT IU/L (normal range: 5 – 25 IU/L)
Cohort A			
11147	1.0	N/A	32
	2.3	OM 5 mg	51
	4.7	OM 40 mg	42
11113	1.0	N/A	41
	2.3	OM 5 mg	51
	4.7	OM 20 mg	28
11164	1.0	N/A	62
	1.0	N/A	62
	4.7	OM 40 mg	80
11189	1.0	N/A	79
	2.3	OM 5 mg	59
	2.3.1	OM 5 mg	67
	4.7	OM 20 mg	110
10391	1.0	N/A	38
	1.1	N/A	45
	2.3	OM 5 mg	52
	4.7	OM 20 mg	15
11167	1.0	N/A	15
	1.1	N/A	13
	2.3	OM 20 mg	21
	ET	OM 10 mg	57
11126	1.0	N/A	25
	2.3	OM 40 mg	21
	4.7	OM 20 mg	60
11191	1.0	N/A	23
	2.3	OM 5 mg	26
	4.7	OM 40 mg	57
Cohort B			
20163	1.0	N/A	28
	2.3	OM 5 mg	22
	4.7	OM 20 mg	55
Cohort C			
30123	1.0	N/A	22
	2.3	OM 0.3 mg/kg	58
	4.7	OM 0.3 mg/kg	16

Twelve patients had elevated BUN and creatinine concentrations from baseline and higher than normal values. Five of twelve patients had normal values of serum creatinine at baseline with 3 patients in Cohort A and 2 patients in Cohort C. Seven of twelve patients had abnormal high values of serum creatinine at baseline with 6 patients in Cohort A and 1 patient in Cohort C. All of these increases from baseline were minor except the patients 10119 who had significant increase of serum level of creatinine. This patient had recurrent urinary tract infections, vesicoureteral reflux, ureterocele, and ongoing moderate chronic renal insufficiency. Data were shown in the following table. Changes of BUN were similar to the creatinine.

Table 48: CS0866-A-U301 - Abnormalities in Serum Creatinine for All Cohorts and All Periods (Reviewer's table)

Subject No.	Visit	Dosage	Serum Creatinine (μmol/L)	Normal high value of Serum creatinine (μmol/L)
Cohort A				
10394	1.0	N/A	150	80
	2.3	20 mg	177	80
	2.31	20 mg	159	80
	4.7	20 mg	168	80
10395	1.0	N/A	133	106
	2.3	5 mg	124	106
	4.7	20 mg	159	106
11203	1.0	N/A	159	106
	2.3	40 mg	141	106
	2.31	40 mg	133	106
	4.7	40 mg	194	106
11161	1.0	N/A	106	106
	2.3	5 mg	115	106
	4.7	20 mg	124	106
10174	1.0	N/A	88	80
	2.3	20 mg	88	80
	4.7	20 mg	97	80
10184	1.0	N/A	124	80
	2.3	40 mg	124	80
	4.7	40 mg	141	80
11193	1.0	N/A	106	106
	2.3	5 mg	115	106
	4.7	20 mg	115	106
11205	1.0	N/A	88	106
	2.3	40 mg	115	106
	4.7	40 mg	115	106
10119	1.0	N/A	186	80
	2.3	20 mg	230	80
	2.31	20 mg	239	80
	4.7	20 mg	283	80
Cohort C				
30137	1.0	N/A	44	62
	2.3	0.3 mg/kg	44	62
	4.7	0.3 mg/kg	80	62
30164	1.0	N/A	53	62
	2.3	0.3 mg/kg	53	62
	4.7	0.3 mg/kg	71	62
30106	1.0	N/A	168	62
	2.3	0.3 mg/kg	203	62
	2.31	0.3 mg/kg	186	62
	2.32	0.3 mg/kg	230	62
	4.7	0.3 mg/kg	186	62

7.4.3 Vital Signs

Changes of blood pressure have been discussed in the efficacy section. There were no consistent differences in heart rate in these clinical studies for the different groups and phases. Physical examination findings that were clinically relevant changes from baseline were reported as TEAEs.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not done routinely in these pediatric studies.

7.4.5 Special Safety Studies/Clinical Trials

The WR specified that the long term safety study include assessments of growth (change in head circumference, weight, and length or height), and development (milestones, school performance, or neurocognitive testing) assessed at baseline and at one year. The sponsor measure height and weight and did neurocognitive testing in a sub study. Please see the section of 7.6.3: pediatric and assessment of effect on growth.

7.4.6 Immunogenicity

The sponsor did not evaluate immunogenicity nor is there any theoretical or empirical evidence suggesting that it should be studied.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

In the pivotal study, headache was the predominant TEAE during Period II in both Cohort A and Cohort B. The incidence of headache was greater in the high OM dose groups than in the low OM dose groups (14.7% and 7.4%, respectively for Cohort A) and (9.0 % and 5.4%, respectively). Headache occurred in one subject only (1.7%) in Cohort C during Period II. During the Period III, headache was also the predominant TEAE for subjects treated with OM and occurred in more than 5% of OM-treated subjects in both Cohort A and Cohort B with the highest incidence rates for subjects taking the high OM dose.

7.5.2 Time Dependency for Adverse Events

There is no clear relationship between the time of dose administration and the adverse events.

7.5.3 Drug-Demographic Interactions

There is no clear relationship between the safety signals and the demographic factors.

7.5.4 Drug-Disease Interactions

Drug-disease interactions are not analyzed.

7.5.5 Drug-Drug Interactions

Drug-drug interactions were not studied in this submission. Sponsor claimed that no significant drug interactions were reported in studies in which OM was co-administered with digoxin or warfarin in healthy adult volunteers.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The exposure in children is too limited to evaluate human carcinogenicity.

7.6.2 Human Reproduction and Pregnancy Data

Subjects in the pediatric clinical trials were excluded if they were pregnant or lactating or not taking appropriate birth control if female and of child-bearing potential.

7.6.3 Pediatrics and Assessment of Effects on Growth

The height, weight, and developmental assessments were conducted in the pivotal study.

Height was measured at the beginning of the study (Screening) and at every visit during Period IV. Subjects in Cohort A and Cohort B were similar in overall baseline and end-of-study heights. Heights were similar in subjects receiving low dose OM and high dose OM regardless of cohort. Subjects in Cohort A grew slightly more than those in Cohort B. The subjects in Cohort C had the greatest mean increase in height (7.4 cm) when compared with Cohort A (4.1 and 4.0 cm for the low and high OM doses respectively) and Cohort B (3.4 and 2.8 cm for the low and high OM doses, respectively). This is expected given the young age of the pediatric subjects in Cohort C compared with Cohorts A and B. There did not appear to be any effect of 1 year of OM treatment on height in any cohort. Data were summarized in the following table.

Note: reduced height at the end of study compared to the baseline has been observed in 4 patients (2 in Cohort A with low and high dose each and 2 in Cohort B with low dose). The maximal reduction was ≤ 2 cm. These could be due to the measurement errors. Data were show in the following table 50.

Table 49: CS0866-A-U301 - Height Assessments (cm) at Baseline and End of Study-All Cohorts (Sponsor's table)

	Cohort A					
	Low Dose OM			High Dose OM		
	Baseline N = 95	Period 4 End of Study N = 73	Change from Baseline N = 73	Baseline N = 95	Period 4 End of Study N = 76	Change from Baseline N = 76
Mean (SD)	155.1 (19.12)	158.2 (17.79)	4.1 (3.32)	153.3 (18.46)	155.2 (16.75)	4.0 (2.84)
Min - Max	111.0 – 187.0	116.7 – 187.5	-1.2 – 12.0	118.0 – 186.0	118.0 – 186.1	-2.0 – 10.0
	Cohort B					
	Low Dose OM			High Dose OM		
	Baseline N = 56	Period 4 End of Study N = 43	Change from Baseline N = 43	Baseline N = 56	Period 4 End of Study N = 38	Change from Baseline N = 38
Mean (SD)	156.1 (14.21)	158.9 (13.17)	3.4 (3.02)	154.2 (17.83)	161.2 (14.16)	2.8 (2.48)
Min - Max	114.0 – 186.0	119.0 – 191.0	-2.0 – 9.0	110.0 – 190.0	115.5 - 189.7	0.0 – 10.0
	Cohort C					
	Baseline N = 59		Period 4 End of Study N = 57		Change from Baseline N = 57	
Mean (SD)	98.3 (12.92)		105.6 (13.06)		7.4 (2.76)	
Min - Max	73.0 – 120.00		82.0 – 129.0		0.5 – 15.0	

Table 50: Patients with Reduction of Height at End of Study Compared to Baseline (Reviewer's table)

Subject No.	Visit	Dosage Group	Height (cm)
Cohort A			
11116	Baseline	N/A	157
	End of Study	High dose	155
11168	Baseline	N/A	169.3
	End of Study	Low dose	168.5
Cohort B			
20170	Baseline	N/A	154
	End of Study	Low dose	152
20183	Baseline	N/A	158
	End of Study	Low dose	156

Weight was measured at the beginning of the study (Screening) and at every visit during Period IV. subjects receiving low dose OM in Cohort A had a higher mean weight (78.9 kg) than subjects receiving high dose OM in Cohort A (68.0 kg) or those in either group in Cohort B (68.1 and 66.2 kg, respectively) at study start. Changes from baseline at the end of the study were similar across all treatment groups for Cohorts A and B. The subjects in Cohort C had the lowest mean increase in weight (2.6 kg) when compared with Cohort A (5.4 and 5.5 kg for the low and high OM doses respectively) and Cohort B (5.9 and 4.8 kg for the low and high OM doses, respectively). According to CDC growth charts, children in the age range between 2 and 6 years usually gain approximately 2 kg of weight per year, while children in the age range between 10 and 16 usually gain approximately 5 kg of weight per year. There did not appear to be any effect

of 1 year of OM treatment on weight in any cohort. Data were summarized in the following table.

Table 51: CS0866-A-U301 - Weight Assessments (kg) at Baseline End of Study – All Cohorts (Sponsor's table)

	Cohort A					
	Low Dose OM			High Dose OM		
	Baseline N = 95	Period 4 End of Study N = 72	Change from Baseline N = 72	Baseline N = 95	Period 4 End of Study N = 76	Change from Baseline N = 76
Mean (SD)	78.9 (41.85)	79.7 (41.58)	5.4 (4.74)	68.0 (34.22)	65.2 (27.31)	5.5 (4.43)
Min - Max	18.0 – 200.0	21.0 – 189.9	- 4.5 – 20.0	20.0 – 183.8	21.0 – 136.0	-4.5 – 18.3
	Cohort B					
	Low Dose OM			High Dose OM		
	Baseline N = 56	Period 4 End of Study N = 43	Change from Baseline N = 43	Baseline N = 56	Period 4 End of Study N = 40	Change from Baseline N = 40
Mean (SD)	68.1 (34.36)	70.6 (28.83)	5.9 (5.86)	66.2 (32.39)	78.3 (33.35)	4.8 (5.32)
Min - Max	20.5 – 232.9	22.8 – 150.2	-7.7 – 21.6	20.0 – 140.8	20.1 – 150.2	- 11.3 – 22.3
	Cohort C					
	Baseline N = 59		Period 4 End of Study N = 57		Change from Baseline N = 57	
Mean (SD)	16.9 (6.61)		19.5 (7.66)		2.6 (1.69)	
Min - Max	8.0 –44.0		9.0 – 51.0		-0.6 – 7.0	

Assessments of development in pediatric subjects were completed at the beginning of the study and at the end of the long-term safety extension or upon early withdrawal. For Cohorts A and B, the questionnaire was based on school performance. For Cohort C, the questionnaire was based on developmental milestones for age and region. Results were consistent for Cohorts A, B, and A+B. The majority of subjects in all three cohorts were rated at the end of study as doing equally well or better than at baseline. The majority of subjects in each cohort showed no shifts from baseline when compared with their peers at the end of the study. Subjects in Cohorts A and B primarily stayed at their same level when compared with their peers or improved, with few going from better than peers at baseline to worse (Cohort A, n = 1 [0.5%]) or from equal to their peers at baseline to worse (Cohort A, n = 6 [3.2%] or Cohort B, n = 3 [2.7%]). In Cohort C, no subjects scored less advanced than their peers. Overall, it appears that there is no negative effect from 1 year of treatment with OM on either development or school performance. Data were summarized in the following tables.

Table 52: Study CS0866-A-U301 - Developmental Assessments for All Cohorts: End of Study Compared With Study Baseline – All Randomized Subjects (sponsor's table)

Achievement at End of Study Relative to Baseline[a]	Cohort A N = 190 n (%)	Cohort B N = 112 n (%)	Cohort A + B N = 302 n (%)	Cohort C N = 60 n(%)
Better	23 (12.1)	25 (22.3)	48 (15.9)	--
Equally well	113 (59.5)	60 (53.6)	173 (57.3)	--
Worse	16 (8.4)	9 (8.0)	25 (8.3)	--
More than expected	--	--	--	10 (16.7)
According to expectations	--	--	--	30 (50.0)
Less than expected	--	--	--	0 (0.0)

[a] Only subjects with both baseline and end of study assessments were included.

Table 53: Study CS0866-A-U301 - Comparison with Peers at End of Study All Randomized Subjects (Sponsor's table)

End of Study				
Cohort A (N = 190)				
Baseline	**Better n (%)**	**Equal n (%)**	**Worse n (%)**	**Missing n (%)**
Better	35 (18.4)	14 (7.4)	1 (0.5)	4 (2.1)
Equal	9 (4.7)	77 (40.5)	6 (3.2)	23 (12.1)
Worse	0 (0.0)	4 (2.1)	11 (5.8)	2 (1.1)
Missing	0 (0.0)	0 (0.0)	1 (0.5)	3 (1.6)
Cohort B (N = 112)				
Better	7 (6.3)	12 (10.7)	0 (0.0)	4 (3.6)
Equal	10 (8.9)	41 (36.6)	3 (2.7)	13 (11.6)
Worse	0 (0.0)	7 (6.3)	9 (8.0)	0 (0.0)
Missing	0 (0.0)	2 (1.8)	1 (0.9)	3 (2.7)
Cohort C (N = 60)				
	More advanced n (%)	**Equal n (%)**	**Less Advanced n (%)**	**Missing n (%)**
More advanced	1 (1.7)	2 (3.3)	0 (0.0)	3 (5.0)
Equal	4 (6.7)	32 (53.3)	0 (0.0)	7 (11.7)
Less advanced	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	11 (18.3)

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no overdoses reported in the pediatric studies. This submission does not provide data regarding abuse potential nor is there any theoretical or empirical evidence that suggests an abuse potential. During the randomized withdrawal there was no evidence of withdrawal rebound or unusual AEs.

7.7 Additional Submissions / Safety Issues

There are no additional submissions/safety issues.

8 Postmarket Experience

With December 31, 2008 as the cut-off date, the Sponsor's global safety database was searched for post-marketing cases involving OM (including olmesartan, olmesartan/hydrochlorothiazide, and olmesartan/amlodipine) in patients ≤ 18 years of age. A total of six (6) post-marketing cases were identified; three of these cases reported accidental exposure with no adverse events, and the other three cases reported nonserious adverse events. A summary of each report of exposure in the pediatric population is given in the following table. There were no additional unknown safety findings of OM.

Table 54: Post-marketing Adverse Events Reported with OM Usage in the Pediatric Population

Adverse Events Report ID#	Patient Info OM dose Therapy Duration	Additional information	Event Outcome
Accidental Exposure			
Accidental exposure; No adverse events DSM-2009-00020 [Germany]	18-month-old boy 10 mg 1 dose	The child also ingested a 5 mg tablet of escitalopram. The child was hospitalized for 1 night and no adverse events were observed.	NA (no adverse events)
Accidental drug intake by child; No adverse events SU-2006-004969 [USA]	22-month-old boy Up to 120 mg 1 dose	Possible ingestion.	NA (no adverse events)
Accidental exposure; No adverse events DSM-2009-00033 [Germany]	2-year-old boy 10 mg 1 dose	Possible ingestion.	NA (no adverse events)
Approved Use			
Muscle spasms, hyperhidrosis SU-2005-002972 [USA]	18-year-old male 20 mg daily 3 weeks	Indication = hypertension	Resolved after d/c
Unapproved Use			
Asthenia DSJ-2007-04232 [Japan]	3-year-old boy 1 mg daily 8 days	This is a literature report.[5] Indication = pulmonary valve incompetence cardiac failure; Co-suspect drug = carvedilol 2.5 mg daily (5 months of treatment at time of event).	Resolved after d/c
Vomiting Decreased lamotrigine level DSU-2008-01403 [USA]	9-year-old boy Olmesartan 20 mg / hydrochlorothiazide 12.5 mg Approximately 1 month	Indication = tics due to seizure; Co-suspect drug = lamotrigine 125 mg twice daily Experienced adverse events with lamotrigine: breakthrough seizures, anger, social withdrawal, suicidal ideation, decreased interest.	Unknown

9 Appendices

9.1 Literature Review/References

I searched Pubmed and found 517 references to olmesartan. However, "olmesartan and pediatric" and " olmesartan and children" yielded no references.

9.2 Labeling Recommendations

Labeling recommendations will be discussed separately.

9.3 Advisory Committee Meeting

N/A

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

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

/s/

SHEN XIAO
01/06/2010