CLINICAL PHARMACOLOGY REVIEW

NDA Number:	21-286
Submission Type; Code:	Pediatric supplement, S_018
Applicant Name:	Daiichi Sankyo Pharma Development
Submission Dates:	08/05/09, 09/22/09, 12/14/09
Brand Name:	Benicar
Generic Name:	Olmesartan medoxomil
Dosage Form:	Tablet
Dosage Strengths:	20 and 40 mg
Proposed Indication:	Treatment of hypertension in children 1 to < 17 years
Proposed dosing regimen:	(b) (4) 10 mg if TBW < 35 Kg 20 mg if TBW ≥ 35 Kg
OCP Division:	DCP I
OND Division:	DCRP
Primary Reviewer:	Divya Menon-Andersen, Ph.D.
OCP Team Leader:	Rajanikanth Madabushi, Ph.D.

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EXECUTIVE SUMMARY

Olmesartan medoxomil (Benicar®) is a selective angiotensin II receptor antagonist, approved for use in the treatment of hypertension in adults at a starting dose of 20 mg given once daily. Depending on the response, the dose may be increased to 40 mg given once daily. Olmesartan is commercially available as 5, 20 or 40 mg film coated tablets. In this pediatric supplement Daiichi Sankyo Pharma Development is seeking approval of olmesartan for use in the treatment of hypertension in children 1 to < 17 years of age.

The application contains three studies in support of sponsor's claim for efficacy.

- The relative bioavailability of an extemporaneously compounded suspension to 40 mg Benicar® tablet was assessed in healthy adults in study CS0866-A-U101.
- The pharmacokinetics of olmesartan in hypertensive children 2 to < 17 years of age was characterized in study CS0866-A-U102.
- The efficacy and safety of olmesartan in pediatric patients were evaluated in study CS0866-A-U301.

The primary aim of this review was to assess the effectiveness of olmesartan in pediatrics 1 < 6y years of age and provide the necessary dosing recommendations.

Recommendations

The Office of Clinical Pharmacology (OCP/DCP1) reviewed sNDA 21-286 and finds it acceptable from a clinical pharmacology perspective, provided that a satisfactory agreement is reached between the sponsor and the Agency regarding language in the package insert.

The Office of Clinical Pharmacology recommends approval of olmesartan in children 1 < 17 years of age.

Phase 4 Commitments

None.

Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The key clinical pharmacology and biopharmaceutics findings are listed below.

1. The extemporaneously compounded olmesartan suspension was bioequivalent to the marketed tablet. Following administration of 10 mL of a 4 mg/mL suspension (Test) and a 40 mg Benicar® tablet (Ref), the mean geometric ratio (Test/Ref) for AUC_{0-t}, and C_{max} were 1.05 (0.97, 1.13) and 1.06 (0.97, 1.16), respectively.
2. Results of the population pharmacokinetic analyses showed that total body weight was the only predictor of clearance of olmesartan in pediatrics. When adjusted for total body weight, olmesartan exposure in children 1 to < 17 years of age was comparable to that observed in adults.
3. The blood pressure lowering effect of olmesartan is exposure dependent in pediatric patients 1 to < 17 years of age. A 15 fold increase in exposure resulted in about a 7 mm Hg decrease in seated systolic blood pressure (seSBP), indicating a shallow

exposure-response relationship. The shape of this relationship is similar to that observed in adults.

4. Olmesartan is effective in reducing blood pressure in children 1 to < 17 years of age.
    - The magnitude of change in seSBP from baseline for pediatric patients 1 - < 6 years (-13.3 mm Hg) was similar to that observed in older children (-12.57 mm Hg). This effect is comparable to that observed in adults at the approved starting dose of 20 mg (-14.5 mm Hg).
    - During the placebo controlled randomized withdrawal phase of the study, the treatment effect (ΔΔ - change from baseline and placebo corrected) was similar between pediatric patients 1 - < 6 years of age (4.2 mm Hg) and older children (3.8 mm Hg).
5. Blood pressure lowering effect of olmesratan was similar in children < 6 y of age with primary hypertension (-11.7 mm Hg) and secondary hypertension due to renal disease (-13.3 mm Hg)($p>0.6$).
6. The dosing recommendation proposed by the sponsor for olmesartan in hypertensive children is acceptable.
    - For pediatric patients the proposed starting dose is 10 mg (if total body weight < 35 Kg) or 20 mg (if total body weight ≥ 35 Kg). The doses may be increased to 20 or 40 mg depending on response.
    - (b) (4)

Clinical Pharmacology Briefing
A required office level briefing was held on January 15, 2010; and attended by Drs. Islam Younis, Norman Stockbridge, Tom Marciniak, Mehul Mehta, Sally Chung, John Lazor, Sudarshan Hariharan, Chinmay Shukla, Xinning Yang, Immo Zdrowjewski, Kristina Dimova, Mike Pacanowski, Ramana Uppoor, Rajanikanth Madabushi, Gil Burkhart, Atiq Rahman, Shen Xiao, Shirley Lu, Dillara Jappar, and Divya Menon-Andersen.

QUESTION BASED REVIEW

This is an abridged version of the question based review.

General Attributes of the Drug

Olmesratan medoxomil (Benicar®) is hydrolyzed during absorption in the gastrointestinal tract to form olmesartan (OM), a selective angiotensin II receptor antagonist. Olmesartan was approved for use in the treatment of hypertension in adults in 2002, at a starting dose of 20 mg given once daily. Depending on the response, the dose may be increased to 40 mg given once daily. Olmesartan is commercially available as 5, 20 or 40 mg film coated tablets. It has a bioavailability of about 26%, and peak plasma OM concentrations are attained within 1 to 2 h following administration. Olmesartan is not metabolized and is eliminated unchanged. About 50% of the absorbed dose is eliminated via renal excretion and the remainder in feces via the bile. The terminal elimination half-life of OLM is about 13 h. Olmesartan exhibits linear pharmacokinetics up to 80 mg.[1]

General Clinical Pharmacology

What are the design features of the clinical pharmacology and the clinical studies used to support dosing or claims?

Three clinical studies were conducted with OM to support dosing and claims.

Table 1: Key design features of the clinical studies.

Study number	Design	Study population	Treatments
CS0866-A-U101 Relative BA	Open label, crossover, single dose study	Healthy adults (n=26)	Suspension, tablet (40 mg)
CS0866-A-U102 Pharmacokinetics	Open label, single dose study	Hypertensive subjects 1-<2y (n=0), 2-5y (n=4), 6-12y (n=10), >12y (n=10)	2-5y: 0.3 mg/kg For >6yr: If TBW<35 Kg: 20mg* If TBW>35 Kg: 40 mg
CS0866-A-U301 PK, Exposure-response, dose-response	Randomized, double blind, placebo controlled study with a 1-year clinical follow-up	Hypertensive subjects 1-<6y (n=59, 9 <2y), 6-<17y (n=300)	1-5y: 0.3 mg/Kg For >6y: If TBW<35 Kg: 2.5/20 If TBW>35 Kg: 5/40

*One individual received this dose.

Study **CS0866-A-U301** consisted of a three week long dose – response phase (period II), followed by a two week placebo controlled randomized withdrawal phase (period III), and a year long open label phase. Hypertensive children 6 to < 17 years (y) of age were enrolled in cohorts A and B (all black), while children < 6y of age were enrolled in cohort C.

[1] *Package insert – Benicar tablets*

What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

The primary efficacy variable for cohorts A and B was the change in trough seated systolic blood pressure (seSBP) and seated diastolic blood pressure (seDBP) from baseline to end of period II (week 3/LOCF), and from period III baseline to end of period III (week 2/LOCF).

Olmesartan is an antihypertensive agent; therefore change in blood pressure is an appropriate measure of its effect. Trough blood pressure was measured (in triplicate) using an electronic blood pressure measuring instrument or a sphygmomanometer at each visit before the patient took the study medication.

Are the active moieties in plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Olmesartan is the only active moiety. Please refer to section 2.6.

Exposure-Response

What are the characteristics of the exposure-response relationships for efficacy?

Dose-Response

A dose dependent reduction in blood pressure was observed in children 6 to < 17 y (**Figure 1**).

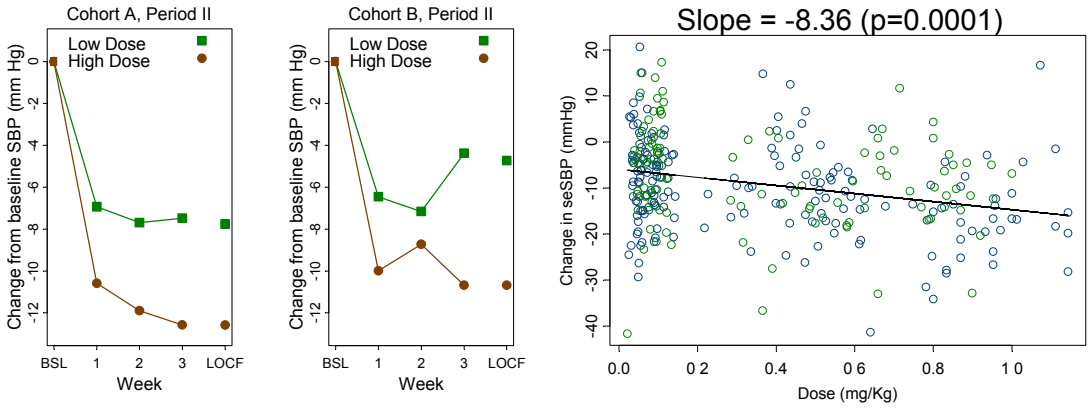


Figure 1: Olmesartan produces a dose dependent reduction in blood pressure. The observed decrease in seSBP is presented in the left panel and the dose-response analysis is presented in the right panel.

Dose – response data are notavailable in children 1 to< 6y of age, as only a single dose of 0.3 mg/kg was studied in **CS0866-A-U301**. Other data supporting effectiveness of olmesartan in reducing blood pressure in children in this age group are presented in the Pharmacometrics review (Please follow link for details Pharmacometrics review).

Exposure-response

A statistically significant ($p<0.00001$), linear relationship was observed for change from baseline in seSBP to end of period II (week 3) and AUC at steady state in children 1 to < 17 y (**Figure 2**). The shape of the relationship was similar to that seen in adults.

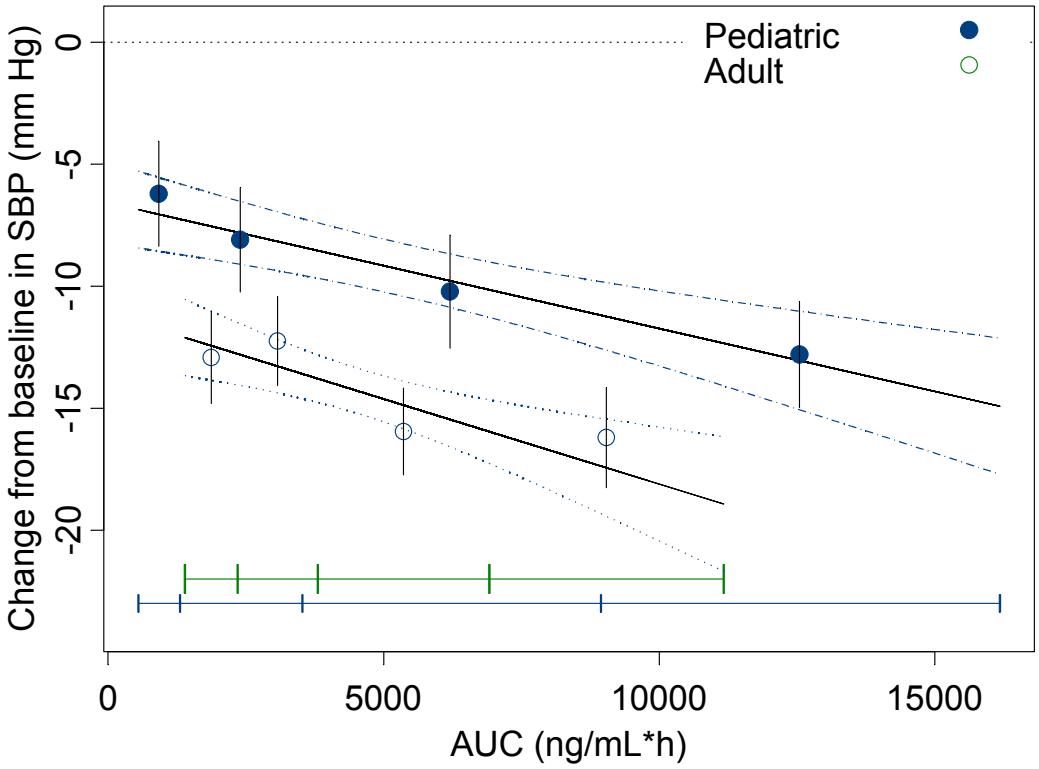


Figure 2: Change in seSBP from baseline is dependent on OM exposure in hypertenisve children 1 to < 17 y. The closed and open circles represent observed mean (± 2*SE) change in seSBP from baseline in children and adults, respectively. The solid line represents the mean prediction from the linear regression. The broken lines represent the 95% confidence interval.

As seen in **Figure 2**, a 15 fold increase in exposure resulted in about a 7 mm Hg decrease in seSBP, indicating a shallow exposure-response relationship.

What are the characteristics of the exposure-response relationships for safety?

Exposure-response relationships for safety were not evaluated. Mild to moderate headache was the most commonly reported adverse event in study **CS0866-A-U301**, and was not dose dependant.

Is the dose and dosing regimen selected by the sponsor consistent with the known E-R relationship?

Yes. The proposed starting doses in children 6 to < 17y (10 mg if TBW < 35 Kg, 20 mg if TBW ≥ 35 Kg) will provide mean exposures similar to that in adults at the approved starting dose of 20 mg. (b) (4) (**Figure 2**).

What are the PK characteristics of the drug?

What are the single and multiple dose PK parameters?

The pharmacokinetics of OLM in hypertensive children 1 to < 17 y of age were evaluated using a population PK approach (studies U102 and U301). Total body weight was the only significant predictor of CL/F and V/F. The pharmacokinetic parameters along with the estimated between subject variability are presented in Table.

Table 2: Parameter estimates from the final PPK model (Ref: Pharmacokinetic and exposure-response analysis for CS0866-A-U102 and CS0866-A-U301).

Parameter	Point estimate (% CV)	Inter-individual variability (%CV)
CL (L/h)	5.11 (6)	16.4 (173)
V1 (L)	34.6 (10)	19.6 (206)
V2 (L)	19.9 (34)	Not estimated
Q (L/h)	0.64 (24)	Not estimated
ka	1.44 Fixed	Not estimated
Residual error (proportional)	0.821 (24)	Not estimated

Please refer to the individual study review for a more detailed review of **CS0866-A-U102**.

General Biopharmaceutics

What is the relative bioavailability of the extemporaneously compounded suspension to the immediate release formulation?

The extemporaneously compounded OM suspension (OM 20 mg tablet + Ora-Sweet + Ora-Plus, **CS0866-A-U101**) is bioequivalent to the immediate release tablet. The plasma OM concentration-time profiles for the suspension (TRT A) and tablet (TRT B), and point estimate of the geometric means and the associated 90% confidence intervals are presented in **Figure 3**.

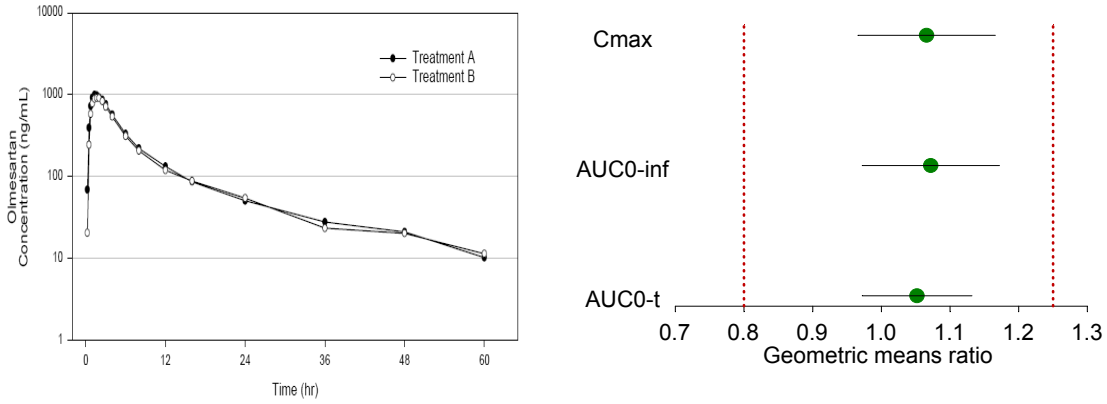


Figure 3: The extemporaneously compounded OM suspension is bioequivalent to the marketed 40 mg Benicar® tablet.

Analytical Section

What bioanalytical methods are used to assess concentrations?

Table 3 provide the details of the bioanalytical method used to support the pharmacokinetic studies. The method satisfied all criteria for 'method validation' and 'application to routine analysis' set by the Bioanalytical Guidance, and was therefore acceptable.

Table 3: Summary of the bio-analytical methods used.

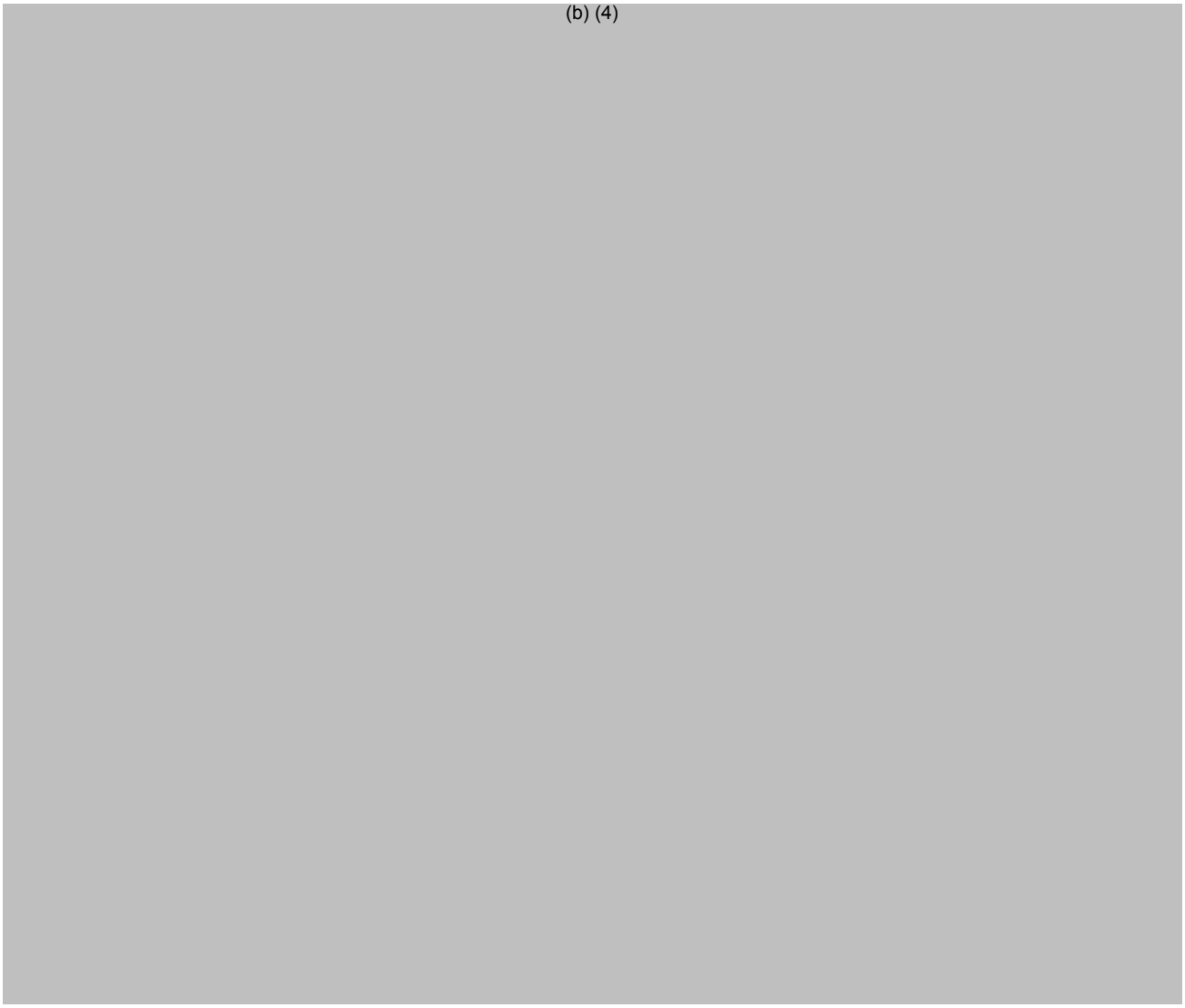
Report #/ study	Method	Range	Matrix	Validation	In-study validation
PKGR-0406 / U101 (BE)	LC/MS/MS	1 - 1000	plasma	Acceptable	Acceptable
PKGR-0506 / U102 (PK)	LC/MS/MS	1 - 1000	plasma	Acceptable	Acceptable
PKGR-0501 / U102 (PK)	LC/MS/MS	5 - 2000	urine	Acceptable	Acceptable
PKGR-0407 / U301 (Efficacy)	LC/MS/MS	1 - 1000	plasma	Acceptable	Acceptable

DETAILED LABELING RECOMMENDATIONS

The Office of Clinical Pharmacology (OCP/DCP-1) has reviewed the package insert labeling for sNDA 21-286 and finds it acceptable pending the following revisions. ~~Strikethrough text~~ is recommended to be deleted and underlined text is recommended to be added. Labeling discussions are currently ongoing.

DOSAGE AND ADMINISTRATION

(b) (4)



APPENDICES

Pharmacometrics Review

Summary of Findings

Key Review Questions

The purpose of this review is to address the following key questions.

Is olmesartan exposure in pediatrics at the studied doses comparable with exposure in adults?

The observed systemic OM exposures (**Figure 1**) at the studied doses in pediatrics span the mean AUC observed in adults. In children 6 to < 17 y of age, the mean exposures with high dose, and low dose olmesartan were about 70 % higher and lower, respectively, than that observed in adults receiving the approved starting dose of 20 mg. The mean exposure in children 1 to <6y was about 30% lower.

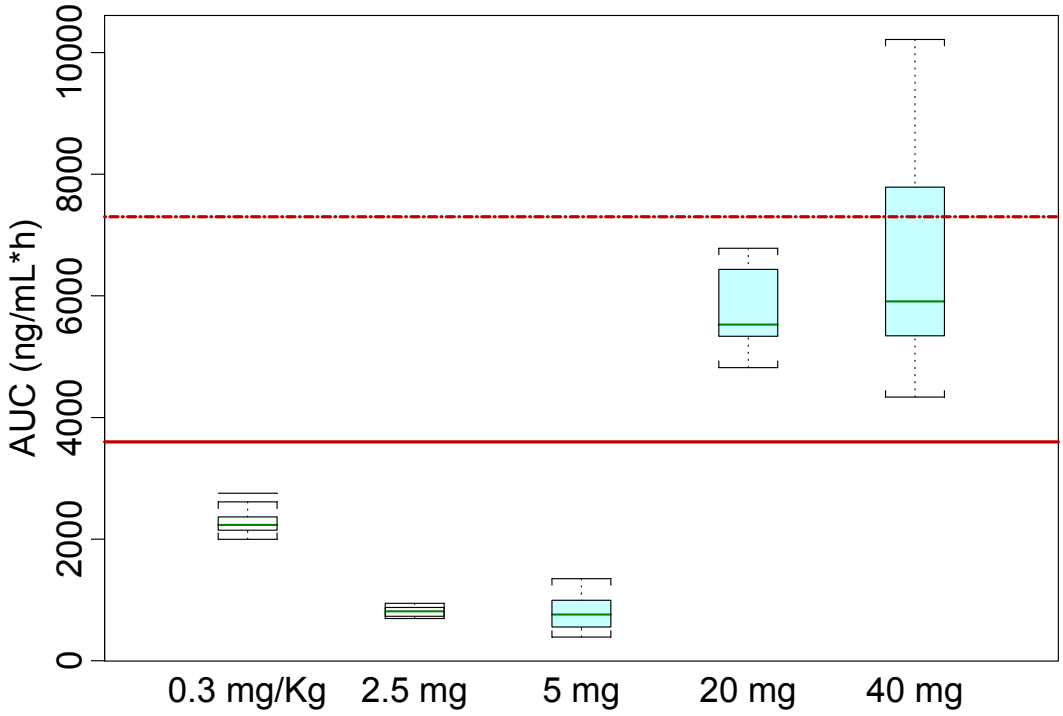


Figure 1: Observed exposure to olmesartan at the studied doses span the mean AUC observed in adults. Children < 6y received 0.3 mg/Kg OM. Children 6 to 16 y received a low dose of 2.5 mg (if TBW < 35 Kg) / 5 mg (if TBW ≥ 35 Kg) or a high dose of 20 mg (if TBW < 35 Kg) / 40 mg (if TBW ≥ 35 Kg). The horizontal lines represent the mean adult AUC at 20 mg (solid) and 40 mg (broken), respectively.

A dose of 10 mg (if TBW < 35 Kg) or 20 mg (if TBW ≥ 35 Kg) in children 6 to < 17 y, will result in exposures comparable to the mean exposure in adults following administration of 20 mg of OM (**Figure 2**).

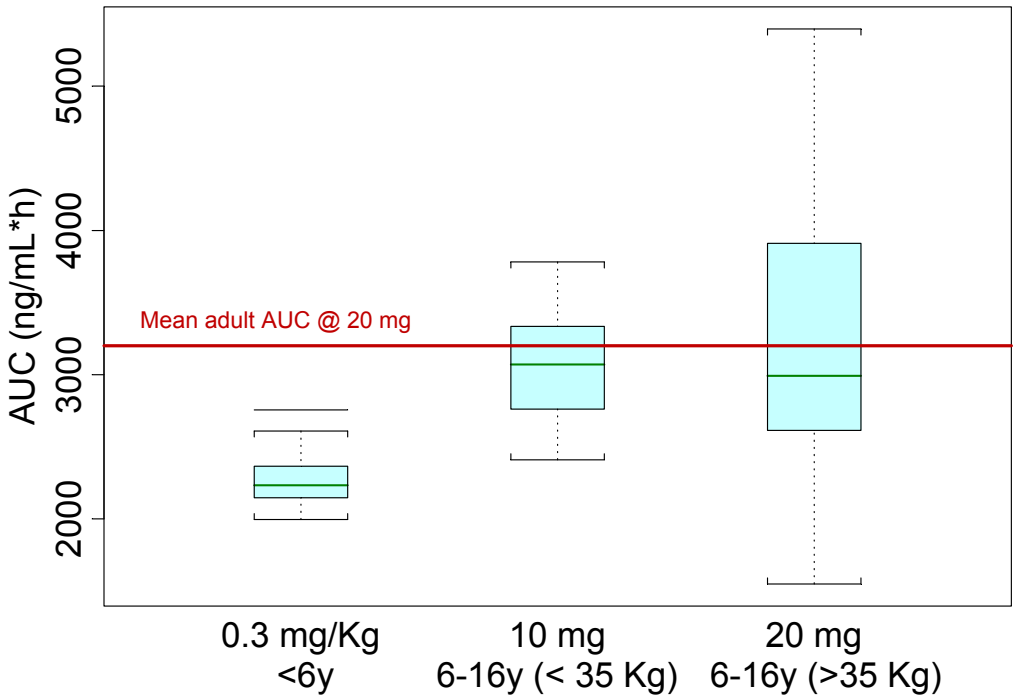


Figure 2: Olmesartan systemic exposure in children < 6 y, and standardized to a dose of 10 mg (TBW < 35 Kg) or 20 mg (TBW ≥ 35 Kg) in children 6 to <17y.

The lower exposure in children <6 y is acceptable based on the shape of the exposure-response relationship, as described under Sec 1.1.2.

What is the exposure-response relationship for olmesartan in pediatrics?

The blood pressure lowering effect of olmesartan is concentration dependent in pediatric patients 1 to < 17 y of age (**Figure 3)**. As seen in the figure, a 15 fold increase in exposure resulted in about a 7 mm Hg decrease in SBP, indicating a shallow exposure-response relationship. The shape of this relationship is similar to that observed in adults (**Figure 3**).

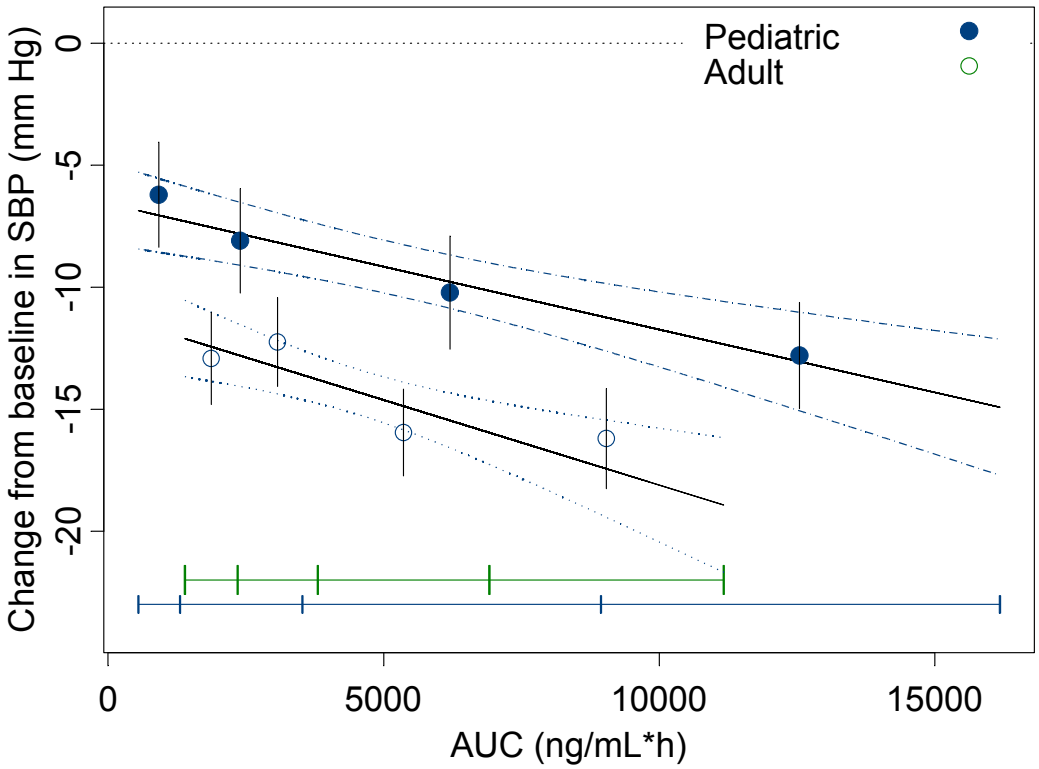


Figure 3: Change in SBP from baseline is dependent on OM exposure in hypertenisve children 1 to < 17 y. The closed and open circles represent observed mean (± 2*SE) change in SBP from baseline in children and adults, respectively. The solid line represents the mean prediction from the linear regression. The broken lines represent the 95% confidence interval.

As seen in **Figure 3**, a greater mean decrease in seSBP is predicted in adults than in children at equivalent OM exposures. Baseline seSBP in adults is higher than that in children (160 mm Hg in vs. 130 mm Hg), possibly explaining the the larger observed effect size in adults.

Is olmesartan effective in lowering blood pressure in hypertensive children 1 to < 6y of age?

Yes. The following data substantiate effectiveness of OM in children 1 to <6 y of age.

1. The magnitude of change in SBP from baseline for children < 6 y (-13.3 mm Hg) was similar to that observed in older children receiving high dose olmesartan (-12.57 mm Hg), as seen in **Figure 4**.

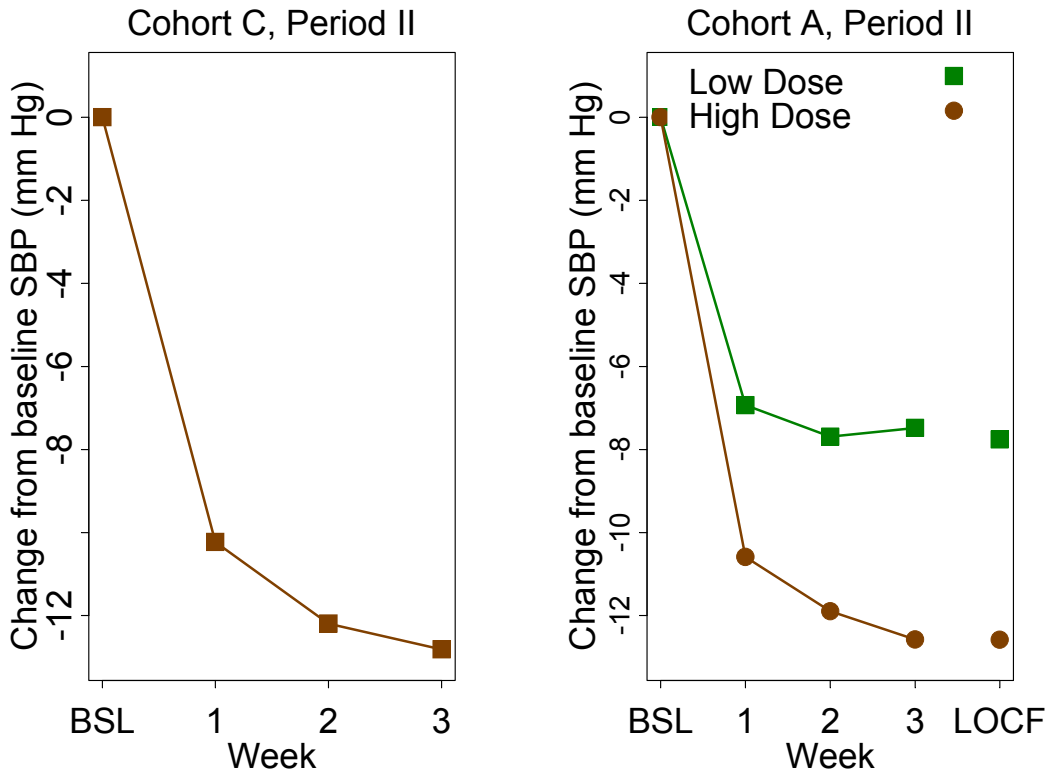


Figure 4: The magnitude of the mean change from baseline in SBP in children < 6y (cohort C) is similar to that observed in children 6 to < 17y (cohort A), during period II.

2. During the placebo controlled randomized withdrawal phase of the study, the treatment effect (ΔOM - ΔPLC) was similar between the younger (4.23 mm Hg) and older children (3.8 mm Hg) (**Table 1** and **Figure 5**).

Table 1: Treatment effect at the end of the placebo controlled randomized withdrawal phase (period III, week 2 w/ LOCF).

	LS means OM	**LS means PLC**	**Difference**	**p-value**
6 to < 17y n=181	0.33	3.92	-3.58	0.0093
< 6 y n=57	1.32	4.84	-3.52	0.1965

The mean observed treatment effect with 0.3 mg/Kg in the younger children is lower than that seen in the older children receiving high dose OM. However, at the proposed lower starting dose of 10 / 20 mg, the treatment effects in the two groups would be comparable.

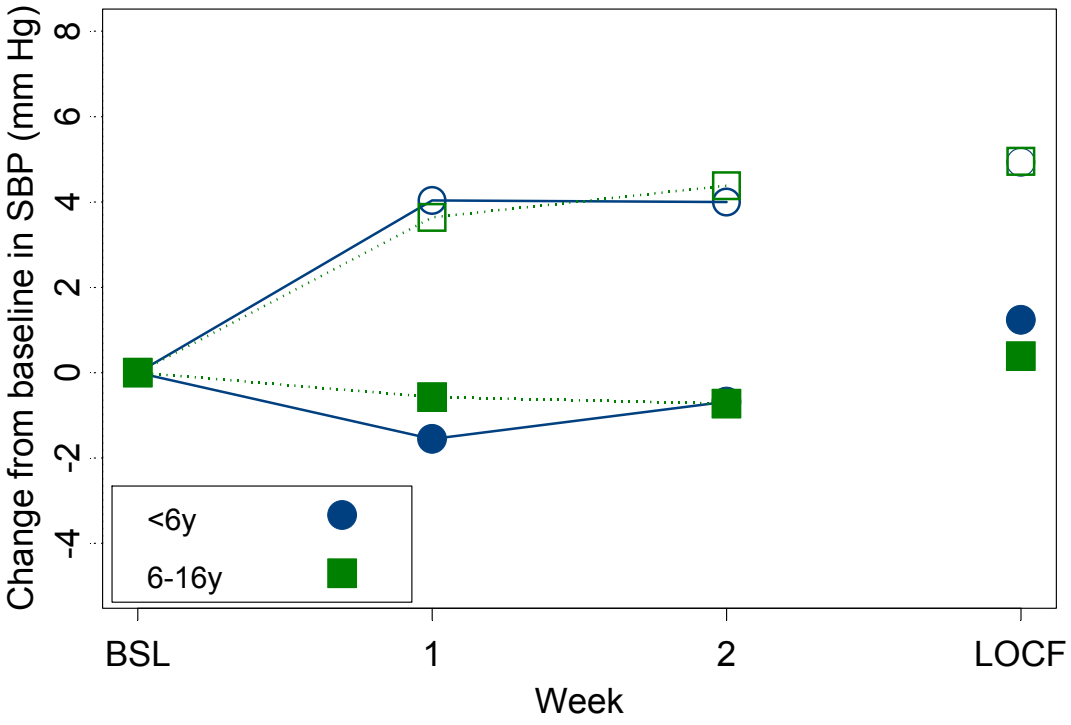


Figure 5: Mean observed treatment effect in younger children is comparable to that in older children. The closed symbols represent OM and the open symbols represent placebo.

3. Further, as seen in **Figure 3**, at the studied doses, OM exhibits a monotonic, exposure dependent lowering of blood pressure in pediatrics 1 to <17 y of age; indicating no obvious age dependent differences (1 to < 6 y vs 6 to <17 y) in response.
4. Finally, as seen in **Figure 6**, the mean decrease in seSBP observed during Period II (weeks 1 to 3) appears to be maintained throughout the open label phase of the study.

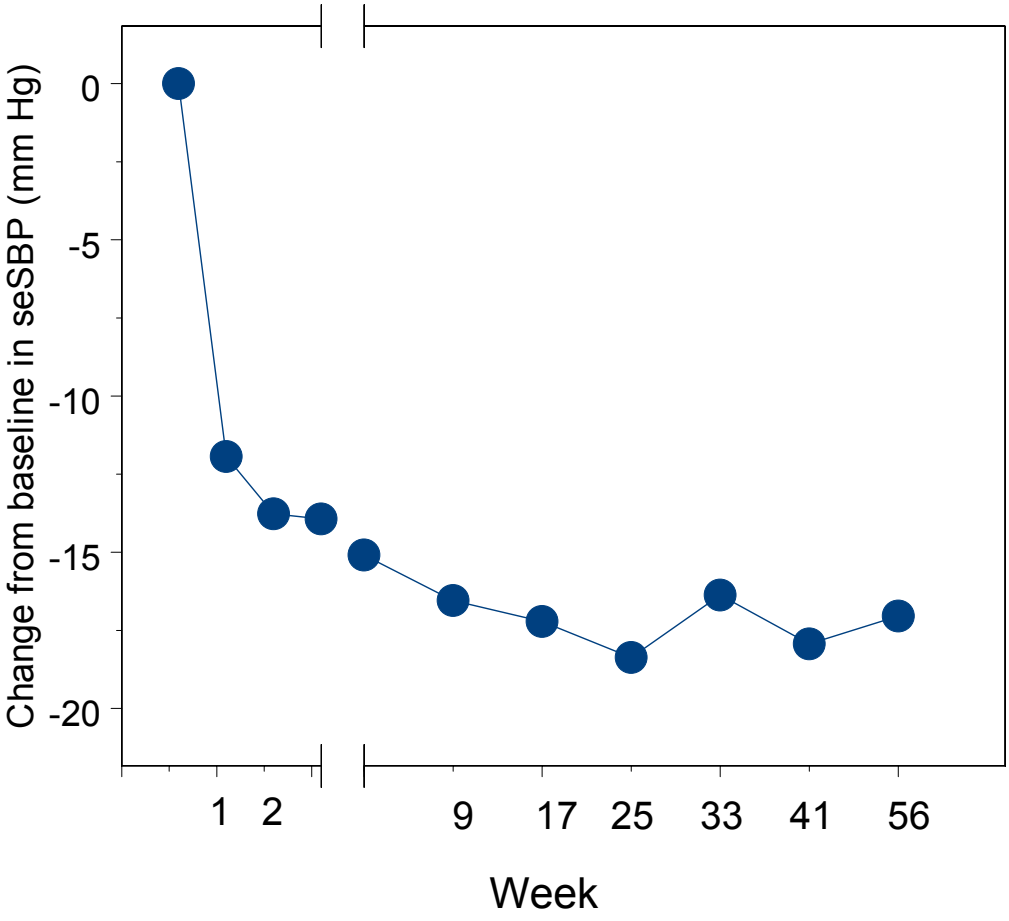


Figure 6: The observed mean change from baseline in seSBP is robust. The closed symbols represent the mean change from baseline seSBP (n=41).

Is the dosing recommendation in the proposed labeling acceptable?

Yes. The proposed starting doses in children 6 to < 17y (10 mg if TBW < 35 Kg, 20 mg if TBW ≥ 35 Kg) will provide mean exposures similar to that in adults at the approved starting dose of 20 mg. (b) (4) (**Table 2**).

Table 2: Blood pressure reduction at the proposed doses in children.

	Change from baseline seSBP Predicted (95% CI)
10/20 mg (6 to < 17y)	-8.38 (-9.5,-7.22)
20 mg, adult	-13.5 (-14.59,-12.55)

The proposed dosing regimen provides an option for up-titration based on the response. Additionally, no major adverse reactions were observed at the doses studied in **CS0866-A-U301**.

Recommendations

Approval of OM for use in the treatment of hypertension in children 1 to < 17y of age is recommended.

PERTINENT REGULATORY BACKGROUND

Olmesratan medoxomil (Benicar®) is hydrolyzed during absorption in the gastrointestinal tract to form olmesartan (OM), a selective angiotensin II receptor antagonist. Olmesartan was approved for use in the treatment of hypertension in adults in 2002, at a starting dose of 20 mg given once daily. Depending on the response, the dose may be increased to 40 mg given once daily. Olmesartan is commercially available as 5, 20 or 40 mg film coated tablets. In the current pediatric supplement the sponsor is seeking approval of OM for use in the treatment of hypertension in children 1 to < 17 y.

Results of Sponsor's Analysis

The sponsor conducted a population pharmacokinetic analysis to characterize the disposition of OM in hypertensive children 1 to < 17 y of age, and an exposure-response analysis to characterize the change in blood pressure with change in systemic exposure to OM.

Population pharmacokinetics (PPK)

The data for the PPK analysis came from a dedicated PK study (U102) conducted in hypertensive children 2 to 16 y, and from the efficacy study (U301) conducted in children 1 to < 17 y.

CS0866-A-U102 was a randomized, multi-center, single dose, open label study conducted to characterize the PK of olmesartan in hypertensive children 2 to < 17 y of age. In this study, children < 6 y of age received 0.3 mg/Kg of olmesartan administered as an exptemporaneously compounded suspension. Children 6 to < 17 y, with TBW < 35 Kg received 20 mg of olmesartan and children with TBW ≥ 35 Kg received 40 mg of olmesartan. Pharmacokinetic samples were collected at pre-dose and at 1, 2, 4, 8, 12, 24, and 48 h post dosing.

CS0866-A-U301was a randomized, multi-center, double blind, parallel group, dose ranging study designed to evaluate the effectiveness of olmesartan in children 1 to < 17 y of age with primary or secondary hypertension, with a 3 week dose-response phase, followed by a two placebo controlled randomized withdrawal phase, and a 1 year open label phase. Children 6 to < 17 y of age were randomized to receive a low (2.5 mg if TBW < 35 Kg and 5 mg if TBW ≥ 35 Kg) or a high (20 mg if TBW < 35 Kg and 40 mg if TBW ≥ 35 Kg) dose of olmesartan. Children < 6 y of age (Cohort C) received 0.3 mg/Kg. All children were administered olmesartan in the form of a suspension. Three PK samples (one sample taken at 2-4, 6-10h post dose during week 2, and a trough sample and a second sample between 1-3 h post dose during week 3) were collected in children who consented to participate in the PK portion of the study. Further, children 6 to <17 y

of age were enrolled into two cohorts – Cohort A and B. Cohort A was considered to be a typical American population with ~ 18% blacks, and Cohort B enrolled all black subjects.

Data

A total of 405 concentration records, 163 were from the 24 subjects in **CS0866-A-U102**, and 242 from 89 subjects in **CS0866-A-U301** were available for the PPK analysis. Eighty nine subjects in study U 301had at least one PK sample and a trough blood pressure measurement. Hence data from 89 subjects were used in the exposure-response analysis.

Analysis methods

Log-transformed olmesartan concentration versus time data were modeled in NONMEM V, Level 1.1 (b) (4)), using the first order conditional estimation method for parameter estimation. A two-compartment pharmacokinetic model with first order elimination from the central compartment, parameterized in terms of clearance (CL) and volume of distribution (V), and inter-compartmental distribution (Q) was selected as the base structural model. The absorption rate constant was fixed to the value estimated in adults [2]. Random effects were modeled on CL and V1, and assumed to follow a log normal distribution. The random residual error was modeled by an exponential error model (additive on the log scale).

Covariate relationships were evaluated following the stepwise forward addition and backward deletion method, informed by the findings in adults. Of the correlated covariates age and weight, weight had a higher impact on CL/F and V/F and was the only covariate found to significantly affect CL/F and V/F. The parameter estimates from the final model are presented in **Table 3**.

Table 3: Parameter estimates from the final PPK model (Ref: Pharmacokinetic and exposure-response analysis for CS0866-A-U102 and CS0866-A-U301).

Parameter	Point estimate (% CV)	Inter-individual variability (%CV)
CL (L/h)	5.11 (6)	16.4 (173)
V1 (L)	34.6 (10)	60.4 (206)
V2 (L)	19.9 (34)	Not estimated
Q (L/h)	0.64 (24)	Not estimated
Ka (h^{-1})	1.44 Fixed	Not estimated
Residual error (proportional)	0.821 (24)	Not estimated

The goodness of fit plots for the final PPK model are presented in **Figure 7.**

[2] *Yoshihara et al, Clin PK, 2005; 44(12): 1329-1342*

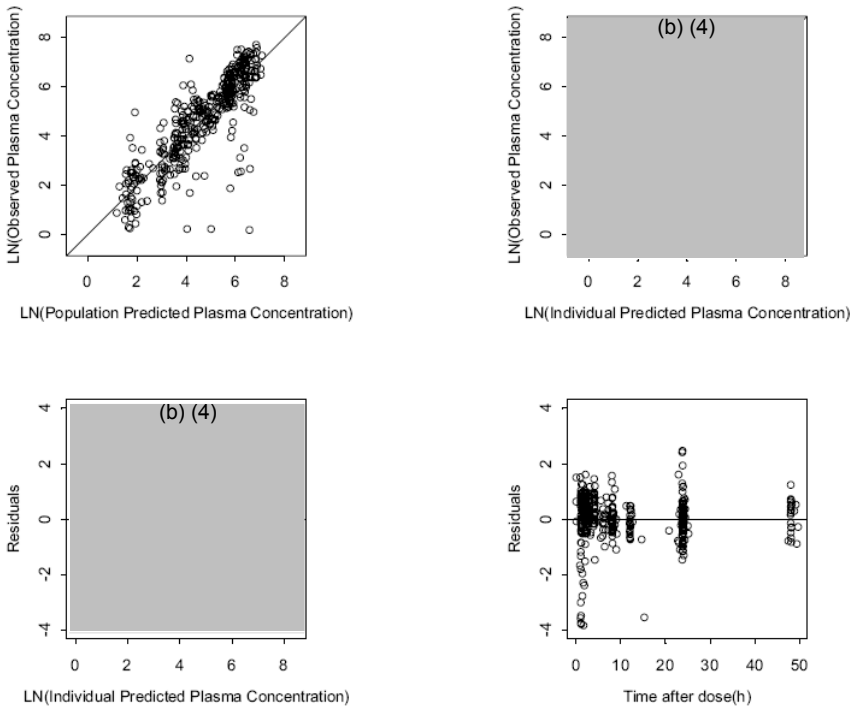


Figure 7: Goodness of fit plots for the final model (Ref: Pharmacokinetic and exposure-resposne analysis for CS0866-A-U102 and CS0866-A-U301).

Exposure-response (ER)

The relationship between change from baseline SBP and DBP at the end of period II (week 3) for children 1 to < 17 y, was investigated using linear regression. The results of the analysis are presented in **Figure 8**.

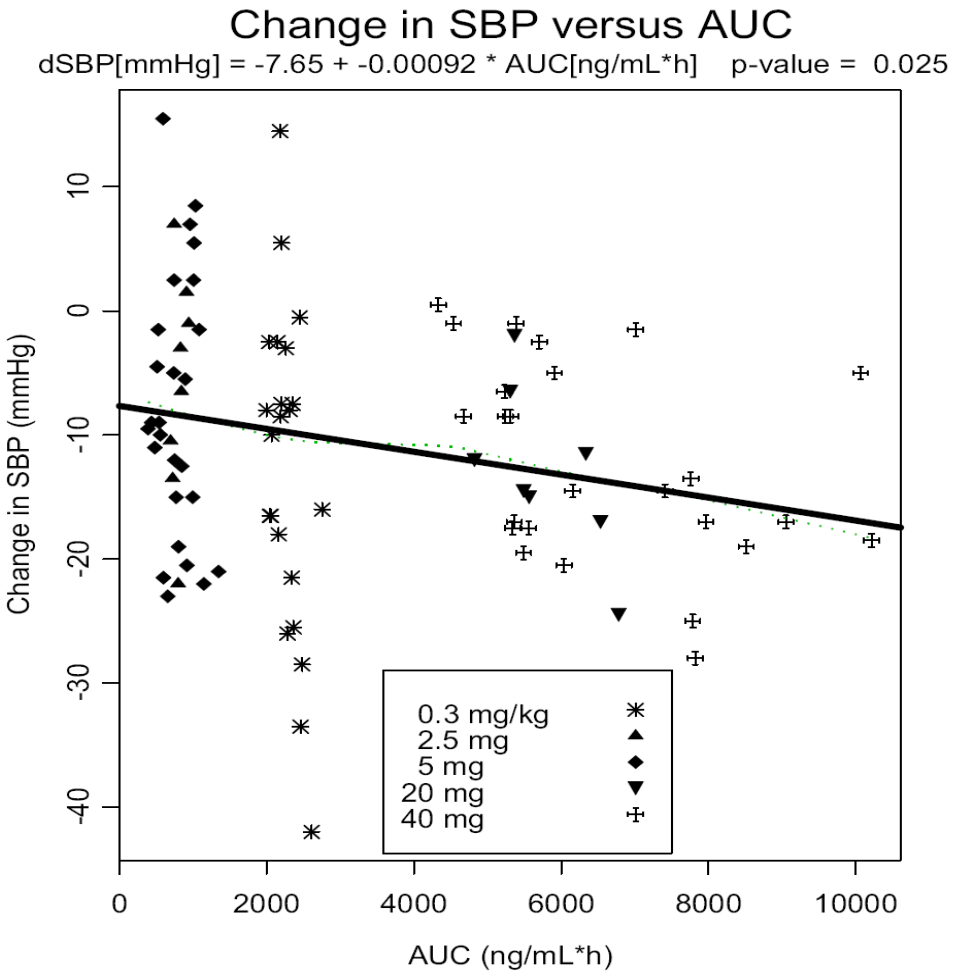


Figure 8: Plot of linear relationship between change from baseline SBP and olmesartan exposure in children 1 to < 17 y. (Ref: Pharmacokinetic and exposure-response analysis for CS0866-A-U102 and CS0866-A-U301).

Reviewer's Analysis

Introduction

Data from the dose – response period in **CS0866-A-U301**provide evidence for the antihypertensive effect of OM in children 6 to < 17 y. Such data are lacking in children < 6y of age, as only a single dose of 0.3 mg/kg was studied. The only formal analysis testing for antihypertensive effect of olmesartan in children of this age (cohort C) comes from the placebo-controlled randomized withdrawal period in **CS0866-A-U301**. While the magnitude of the observed effects in children 1 to < 6y during periods II and III were similar to those observed in older children, the results do not attain statistical significance. Hence, one of the main aims of this analysis was to examine all available data for evidence for effectiveness of OM in hypertensive children 1 to < 6 y of age.

A secondary aim of this analysis was to re-examine the data collected during period III for all cohorts. The blood pressure measurements for patients, who moved on to the open

label phase of the study after 1 week in period III, were incorrectly recorded under week 2. While this did not impact the sponsor's analysis (all analysis were performed on week2 w/LOCF), it is an incorrect representation of the data and is likely to affect the sensitivity analyses.

Objectives

Analysis objectives are stated below.

1. To characterize the pharmacokinetics of olmesartan across all the age groups
2. To characterize the exposure-response relationship of olmesartan across all the age groups and provide basis for evidence of effectiveness in children 1 – 16 yrs
3. To evaluate the proposed dosing recommendations.

Methods

Data Sets

Data sets used are summarized in **Table 4**.

Table 4: Analysis Data Sets

Study Number	Name	Link to EDR
CS0866-A-U301	vita-ab.xpt	\\Cdsesub1\evsprod\NDA021286\0000\m5\datasets\cs0866-a-u301\analysis\vita-ab.xpt
CS0866-A-U301	eval.xpt	\\Cdsesub1\evsprod\NDA021286\0000\m5\datasets\cs0866-a-u301\analysis\eval.xpt
CS0866-A-U301	Demog.xpt	\\Cdsesub1\evsprod\NDA021286\0000\m5\datasets\cs0866-a-u301\listings\demog.xpt
CS0866-A-U301	Vitals.xpt	\\Cdsesub1\evsprod\NDA021286\0000\m5\datasets\cs0866-a-u301\listings\vitals.xpt

Software

NONMEM VI, S-plus 7.0, and SAS 9.1 were used for this analysis.

Methods

A new dataset containing blood pressure data for all subjects across all periods of **CS0866-A-U301** was created by merging relevant columns from vitals.xpt, eval.xpt, phy.xpt, medhist1.xpt, and demog.xpt.

Results

Population pharmacokinetics

Results of the reviewer's PPK analysis concur with those of the sponsor's, and hence are not described here in detail. Total body weight was the only significant predictor of CL/F in this population, and accounted for a major portion of the observed between subject variability (reduced between subject variability from 42 to 16 %). As seen in **Figure 9** (right panel), no trends were observed between age and variability in CL/F following inclusion of weight in the model.

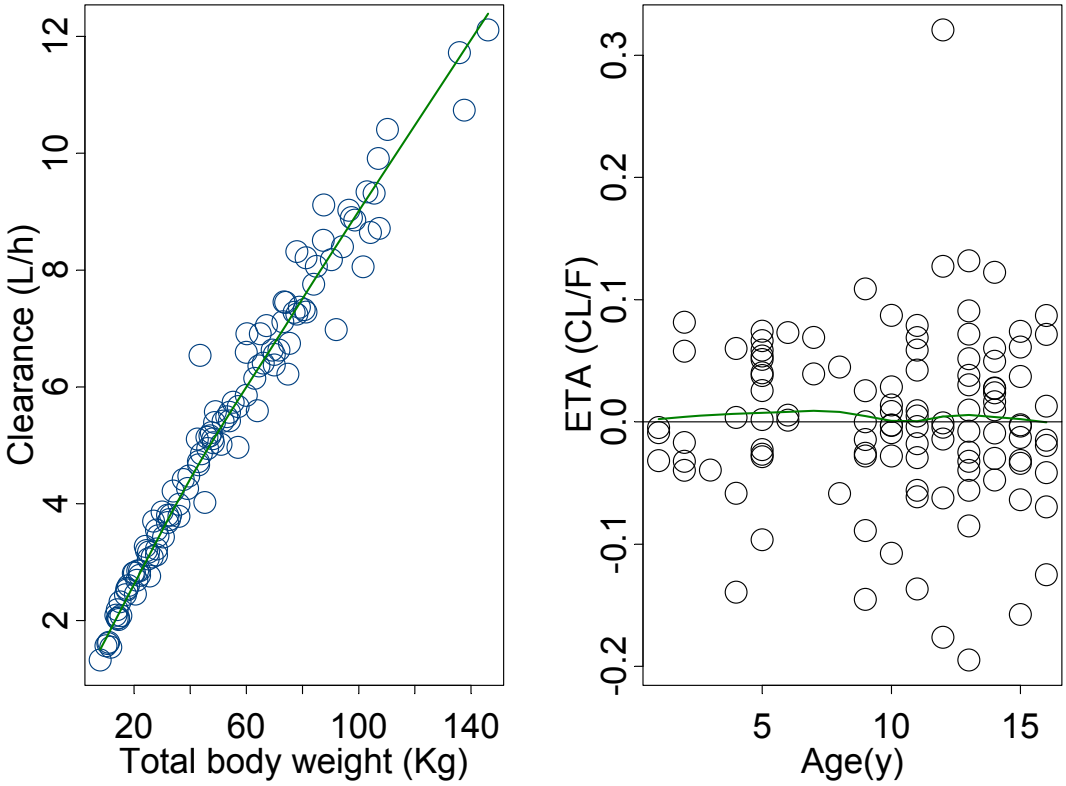


Figure 9: Total body weight is a significant predictor of CL/F. *Left panel:*Plot of CL/F versus weight. *Right panel:* Plot of random effects on CL/F versus age. The solid line represents the lowess.

The limited data available in the absorption phase did not permit adequate characterization of the absorption rate constant, and the value was fixed to that reported in the literature (ka=1.44 h^{-1}). The large residual error in the final model was therefore predominantly driven by lack of information in the absorption phase.

Antihypertensive effect in children 1 to < 6y

The antihypertensive effect of olmesartan was studied in children 1 to < 6y of age at a single dose of 0.3 mg/Kg. As seen in **Figure 3**, during the dose-response phase, the magnitude of change in seSBP from baseline for children 1 to < 6 y (-13.3 mm Hg) was similar to that observed in older children receiving high dose olmesartan (-12.57 mm Hg). This observed drop in seSBP in children 1 < 6y of age is similar to that previously reported with candesartan (same class of antihypertensive, -12 mm Hg).

Olmesartan was shown to be effective in lowering blood pressure in children 6 to < 17 y of age. A statistically significant dose-response relationship was demonstrated for OM in this group. Hence, with a similar magnitude of effect, it follows that OM is effective in children 1 to < 6y, assuming similar placebo effects.

In period III (placebo controlled randomized withdrawal phase) the effect of treatment withdrawal was assessed in children 1 to < 6y. As seen in **Table 5** and **Figure 5,** the

observed mean treatment effect (ΔOM - ΔPLC) was similar between the younger (4.23 mm Hg) and older children (3.8 mm Hg).

The blood pressure measurements for patients who moved on to the open label phase of the study after 1 week in period III, were incorrectly recorded under week 2. While this did not impact the results of the sponsor's analysis (all analysis were performed on week2 w/LOCF), it is an incorrect representation of the data and is likely to affect the sensitivity analyses. Hence the data was corrected, and an ANCOVA was performed on the corrected data. In addition, the data were also examined using mixed model repeated measures (MMRM). Results from the analysis are presented in **Table 5**.

Table 5: Results of the statistical analysis of period III data in cohort C. (Ref for sponsor's analysis: CSR CS0866-A-U301, Table C7.2.2.3)

	Observed mean *		**Sponsor's analysis**			**Reviewer's Analysis***					
			ANCOVA LS Means		**p-value for diff**	**ANCOVA LS Means**		**p-value for diff**	**MMRM LS Means**		**p-value for diff**
	Olm	**Plc**	**Olm**	**Plc**		**Olm**	**Plc**		**Olm**	**Plc**	
Week 1	-1.55	4.03	-2.86	2.92	0.0019	-1.45	3.93	0.0077	-1.43	3.98	0.0075
Week 2	-0.68	4.0	1.54	4.36	0.2113	-0.47	3.76	0.0458	0.877	4.52	0.0944
LOCF	1.36	4.95	1.54	4.36	0.2113	1.32	4.84	0.1965	-	-	Overall 0.0151

* Corrrected data.

Exposure – response

Exposure – response relationship for change from baseline SBP was evaluated using data from all patients in study U 301 (1 to < 17 y). Steady state exposure (AUC) to olmesartan was predicted for all patients in study U 301 using the CL/F model ($CL/F_I = 5.11 * (WT/Median\ WT)^{**0.75}$). Since the between subject variability in CL/F was low (16%), population estimates for CL/F were used to predict exposure. The relationship between change from baseline SBP and exposure was evaluated using linear regression.

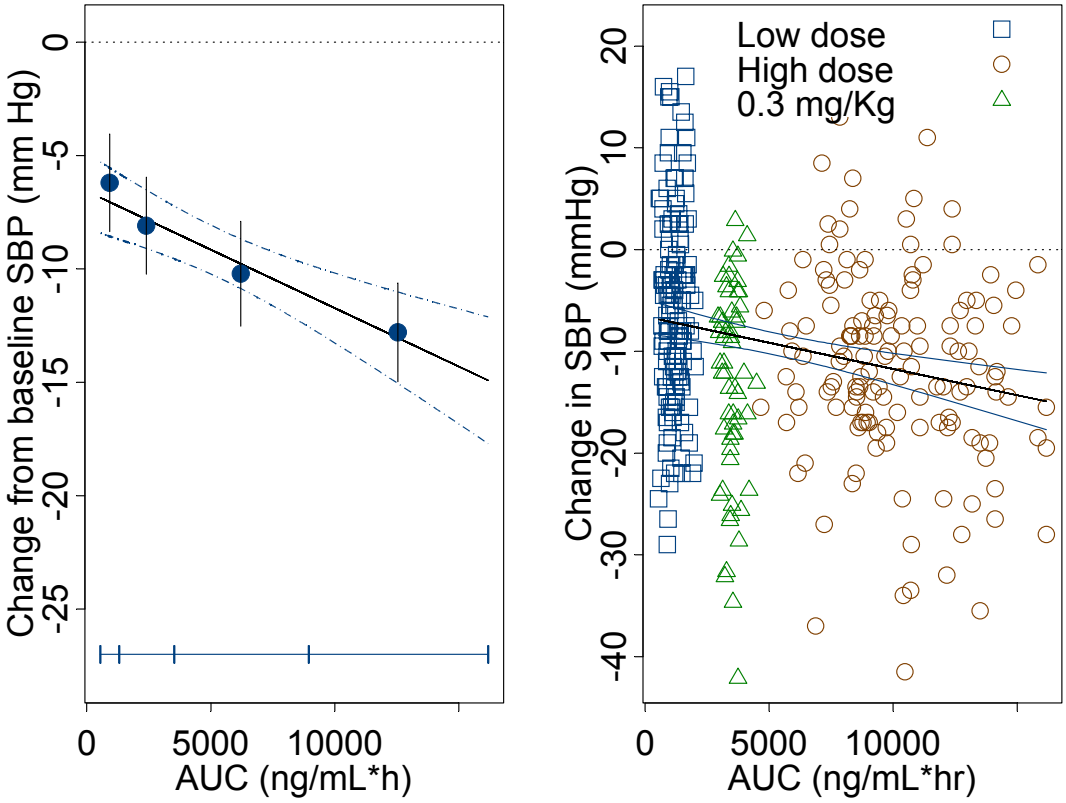


Figure 11: Change in SBP from baseline is dependent on OM exposure in hypertenisve children 1 to < 17 y. The solid line represents the mean prediction from the linear regression. The broken lines represent the 95% confidence interval. Left panel: The range of olmesratan exposures (AUC) is represented by the horizontal solid line. The filled circles represent the mean change in SBP within a given quartile of AUC. Right panel: Observed change from baseline SBP.

As seen in **Figure 11**, there is a significant linear ($p<0.00001$) exposure-response relationship for change from baseline SBP in children 1 to < 17 y. A mean decrease in SBP of about 6mm Hg was predicted at the low dose (AUC ~ 1st quartile), while at the high dose (AUC ~ 4th quartile) a mean decrease in SBP of about 13 mm Hg is predicted. An increase in effect by about 7 mm Hg across over a 15 fold increase in exposure is indicative of a shallow exposure-response relationship. The shape of the relationship is similar to that observed in adults (**Figure 3**). The observed decrease in SBP for children 1 to < 6y who received 0.3 mg/Kg of olmesartan was consistent with that observed in older children. Therefore, it is reasonable to expect a similar effect of olmesartan in younger children.

Open label phase

In the open label phase of the study, 16 out of the 57 subjects had their dose increased to 0.6 mg/Kg for various durations. Forty one subjects continued to receive 0.3 mg/Kg of

olmesartan till week 56. As seen in **Figure 6**, the mean decrease in seSBP observed during Period II (weeks 1 to 3) is maintained throughout the study.

Comparison between primary and secondary hypertension

About 33% (n=20) of the children < 6 y of age had primary hypertension. Of the children with secondary hypertension, nephrotic syndrome was the most predominant cause. None of the subjects in this group had hypertension secondary to diabetes. A graphical comparison of blood pressure reduction in these two sub-populations is presented in **Figure 10**.

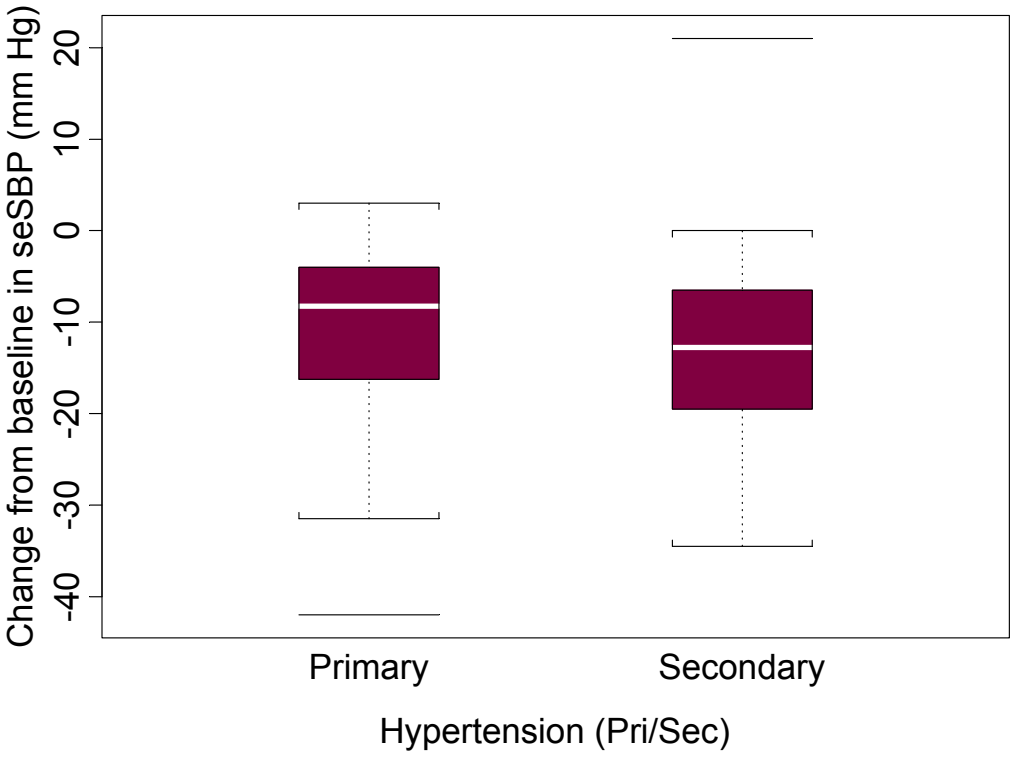


Figure10: Blood pressure reduction effect of olmesartan at the end of Period II in children < 6y of age with secondary hypertension (n=38) appears to be similar to that in children < 6y of age with primary hypertension (n=20).

There was no significant difference in the mean change from baseline in seSBP at the end of Period II between the two groups (primary hypertension: -11.7 vs. secondary hypertension: -13.3, p>0.6).

Dosing recommendation

At the studied doses, the observed mean change from baseline in seSBP in children (~ -13 mm Hg at 20/40 mg and 0.3 mg/Kg), were comparable to that observed in adults at the

approved starting dose of 20 mg (-14.5 mm Hg including placebo effect[3]). The observed effect of OM is exposure dependent, and the shape of the exposure – response relationship is similar to that seen in adults (**Figure 3**). A greater decrease in change from baseline in SBP was observed at equivalent exposures in adults compared to children. This, along with the effect at the studied doses would support dosing of OM in children at the doses studied in **CS0866-A-U301**. However, as seen from the observed mean reduction in seSBP in **Figure 3**, there is considerable overlap between values observed in children and adults. In addition, the exposure-response relationship for OM is shallow, suggesting that increasing exposure may result in only a marginal increase in effect. Hence, starting doses aimed at matching men adult exposure following administration of 20 mg is reasonable.

The proposed starting doses in children (10 mg if TBW < 35 Kg, 20 mg if TBW ≥ 35 Kg) will provide mean exposures similar to that in adults at the approved starting dose of 20 mg. (b) (4) **Table 2)**. The proposed dosing regimen provides an option for up-titration based on the response, and no major adverse reactions were observed in **CS0866-A-U301**. Also, since the median weight in a 6 year old is 20 Kg and it also covers the 90% confidence interval for children 4 to 8 years of age, using 20 Kg as a cut off is reasonable.

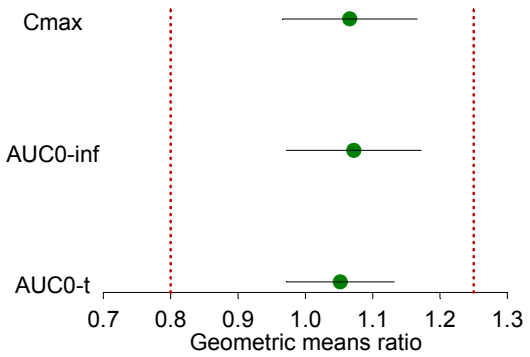
The proposed dosing recommendation is therefore acceptable.

Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
BPtimecourse.ssc	Change in seSBP time course	\\Olmesartan_NDA21286_dma\\ERAnalyses
ExpResp.ssc	Dose-Response and Exposure-Response	\\Olmesartan_NDA21286_dma\\ERAnalyses
CohC.ssc	Dose changes, etiology	\\Olmesartan_NDA21286_dma\\ERAnalyses
ANCOVACohC.sas	ANCOVA, Cohort C	\\Olmesartan_NDA21286_dma\\ERAnalyses

[3] *Benicar package insert*

Study CS0866-A-U101 (Bioequivalence)

Study Report # CS0866-A-U101	**Protocol #** CS0866-A-U101
Title	A comparative, randomized, single dose, two way crossover bioavailability study of a compounded 4 mg/mL olmesratan medoximil suspension (total dose 40 mg) and 40 mg olmesartan medoximil tablets (Benicar®) in healthy adult volunteers under fasting conditions.
Objectives	Bioequivalence ☒ Bioavailability ☐
Study Design	Parallel ☐ Crossover ☒
Formulation	**Test** / **Reference** Dosage Form: Suspension / Tablet Dosage Strength: 4 mg/mL x 10 mL / 40 mg Batch #.: Benicar 20 mg:441869, OraPlus: 3419563, OraSweet: 4211216 / 441847
PK Sampling	pre-dose, and at 0.25h, 0.5h, 0.75h, 1.0h, 1.33h, 1.67h, 2.0h, 2.5h, 3h, 4h, 6h, 8h, 12h, 16h, 24h, 36h, 48h and 60h post dosing
Statistical Method	A mixed-effect ANOVA model on log transformed parameters. Two-sided 90% CI for the intra-subject test to reference ratio (as estimated by the ratio of the geometric means) of each of AUC $_{0\text{-}t}$, AUC$_{0\text{-}\infty}$ and C$_{max}$.
Population	Total randomized: 26 / Completed: 24 / Withdrawn: 2
Results:	
Site Inspection	Performed: Yes ☐ No ☒ -
Assay Method	The performance of the assay method during study sample analysis is summarized in the table below

	Method: LC/MS/MS		**LOQ:** 1 ng/mL
	Calibration Curve		Range: 1 to 1000 ng/mL
	QC	Accuracy	%RE: < ± 15%, < ± 20% at LOQ
	(1, 40, 1000 ng/mL)	Precision	%CV = < ± 15%, < ± 20% at LOQ
Safety	Death/SAE: None		
Conclusion	The extemporaneously compounded suspension is bioequivalent to the tablet.		

Detailed Results:

		Geometric Mean (%CV)		
Parameter	**N**	**Test**	**N**	**Reference**
C_{max} (ng/mL)	24	1036.9 (27.3)	26	949.6 (27.9%)
t_{max} (h)*	24	1.7 (1.0 – 4.0)	26	1.7 (1.0 - 4.0)
$AUC_{0\text{-last}}$ (ng/mL*h)	24	6812.6 (24.3)	26	6358.5 (27.0)
$AUC_{0\text{-}\infty}$ (ng/mL*h)	20	7184.2 (26.6)	23	6594.3 (28.0)
$t_{1/2}$ (h)**	20	12.4 ± 4.6	23	12.2 ± 3.5

**Median (range) ** Mean ± SD*

Concentration time-course

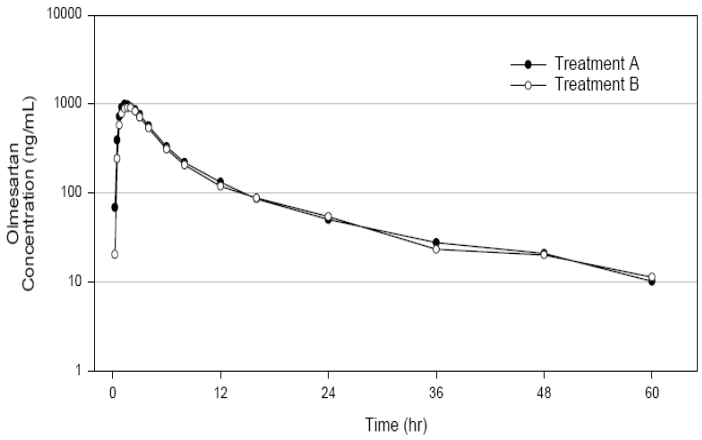


Figure 2: Plasma olmesartan concentration versus time profile following administration of a 40 mg tablet (Reference, open circles) or 10 mL of 4 mg/mL suspension (Test, closed circles).

Study CS0866-A-U102 (Pharmacokinetics)

<table>
<tr><td colspan="2">Study Report # CS0866-A-U102</td><td>Protocol # CS0866-A-U102</td></tr>
<tr><td>Title</td><td colspan="2">An Open-Label Study of the Single-Dose Pharmacokinetics of Olmesartan Medoxomil in Pediatric Patients with Hypertension.</td></tr>
<tr><td>Objectives</td><td colspan="2">To characterize the pharmacokinetics of olmesartan (OM) following administration of a single dose of 0.3 mg/Kg, 20 or 40 mg in hypertensive children.</td></tr>
<tr><td>Study Design</td><td colspan="2">This was a single dose, open-label, parallel design study.</td></tr>
<tr><td>Dose and Formulation</td><td colspan="2">
<table>
<tr><th></th><th>< 6 y</th><th>6 to < 17 y
TBW < 35 Kg</th><th>6 to < 17 y
TBW ≥ 35 Kg</th></tr>
<tr><td>Dose</td><td>0.3 mg/Kg</td><td>20 mg</td><td>40 mg</td></tr>
<tr><td>Dosage Form</td><td>Suspension</td><td>Tablet</td><td>Tablet</td></tr>
<tr><td>Batch no.</td><td colspan="2">444003, B0004, B0095</td><td>444013</td></tr>
</table>
</td></tr>
<tr><td>PK Sampling</td><td colspan="2">Plasma: Pre-dose, and at 1.0h, 2.0h, 4h, 8h, 12h, 18h, 24h, and 48h post dosing
Urine: 0-6h, 6-12h,12-24h</td></tr>
<tr><td>Pharmacokinetic analysis</td><td colspan="2">The following pharmacokinetic measures and parameters were estimated using non-compartmental methods – Cmax, tmax, AUC, t1/2, CL/F, V/F.</td></tr>
<tr><td>Population</td><td colspan="2">
<table>
<tr><th></th><th>12-23 months</th><th>2-5 years</th><th>6-12 years</th><th>13-16 years</th></tr>
<tr><td></td><td>N=0</td><td>N=4</td><td>N=10</td><td>N=10</td></tr>
<tr><td>Age*</td><td>-</td><td>4.8 (0.5)</td><td>10.2 (1.03)</td><td>14.8 (1.03)</td></tr>
<tr><td>Weight*</td><td>-</td><td>32.0 (16.3)</td><td>70.3 (20.5)</td><td>86.3 (29.5)</td></tr>
<tr><td colspan="5">**Mean (SD)*</td></tr>
</table>
</td></tr>
<tr><td>Results</td><td colspan="2"></td></tr>
</table>

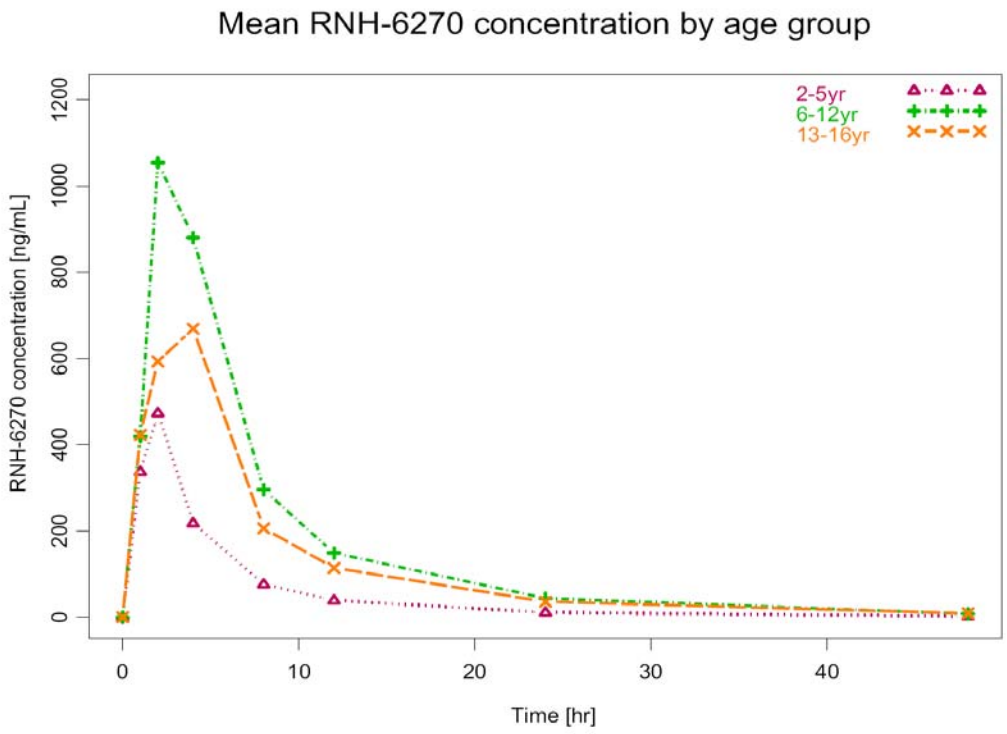


Figure 1: Plot of mean plasma OM concentration versus time, following administration of a single dose of 0.3 mg/Kg, 20 or 40 mg of olmesratan (Ref: Abbreviated technical report, PK analysis for CS866-A-U102).

Table1: Mean pharmacokinetic measures and parameters for OM (Ref: Abbreviated technical report, PK analysis for CS866-A-U102).

Age	**AUC_{0-t} (ng/mL*h)**	**C_{max} (ng/mL)**	**t_{max} (h)**	**CL/F (L/h)**	**V/F (L)**	**CLr**	**$t_{1/2}$ (h)**
2 to 5y n=4	2552 ± 894	473 ± 237	2	2.9 ± 0.7	38.2 ± 21	0.23 ±0.1	9.35 (4.1-17.1)
6 to 12y n=10	7874 ± 2913	1227 ± 451	2.8 (1-4)	4.3 ± 1.9	50.9 ± 20.7	0.48 ± 0.3	8.4 (4.5-11.4)
13 to 16y n=10	5851 ± 2083	895 ± 262	2.5 (1-4)	6.1 ± 2.6	81.3 ± 42.1	0.53 ± 0.4	9.1 (6.6-12.2)

Assay Method

The performance of the assay method during study sample analysis is summarized in the table below

Method: LC/MS/MS **LOQ:** 1 ng/mL

Calibration Curve	Range: 1 to 1000 ng/mL

	QC (2, 40, 800 ng/mL)	Accuracy	%RE: < ± 15%, < ± 20% at LOQ
		Precision	%CV = < ± 15%, < ± 20% at LOQ
Safety	Death/SAE: None		
Discussion	• The plasma sampling times used in this study ranges over four adult elimination half-lives, and is therefore adequate for characterizing PK. • Olmesartan exhibits bi-exponential kinetics with a short distributional half-life of about 3 h and a longer elimination half-life of about 10 h. This is consistent with the prior information in adults. • Clearance of OM appears to increase with age. As seen in **Table 1**, the mean observed clearance of OM in children 13 to 16 y was about 30% higher than that in children 6 to 12 y. Except for one child in the 6 to 12 y group, all children received an absolute dose of 40 mg. It should be noted that older children are heavier and body weight could be the true predictor of olmesartan clearance. In a previously conducted PPK analysis in adults, total body weight was found to be a significant predictor of CL/F. A lower CL/F was reported in subjects with lower body weight[4]. Given this, and that the renal elimination pathways mature within the first year of life, olmesartan clearance increase with an increase weight. • Approximately 3 to 15% of the administered dose was recovered in urine (compared to a mean of 12.6% in adults).		
Conclusions	The pharmacokinetics of OM were characterized in hypertensive children 2 to 16 y, and appear to be consistent with prior knowledge in adults[4].		

[4] *Yoshihara et al, Clin PK, 2005; 44(12): 1329-1342*

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/

DIVYA MENON ANDERSEN
01/21/2010

RAJANIKANTH MADABUSHI
01/21/2010
Concur