Public Assessment Report for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

Olmetec®, Benicar®
Olmesartan Medoxomil

UK/021/pdWS/001

Marketing Authorisation Holder:

Daiichi Sankyo Europe GmbH

Rapporteur:	**UK**
Finalisation procedure (day 120):	**5 November 2013**

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Olmetec®, Benicar®
INN (or common name) of the active substance(s):	Olmesartan medoxomil
MAH:	Daiichi Sankyo Europe GmBH
Currently approved Indication(s)	Treatment of essential hypertension, alone or with other antihypertensive agents
Pharmaco-therapeutic group (ATC Code):	C09CA08
Pharmaceutical form(s) and strength(s):	Film-coated tablet containing 10 mg, 20 mg, or 40 mg

I. EXECUTIVE SUMMARY

This is an assessment of data for olmesartan medoxomil (OM), as part of the Article 46 EU worksharing procedure for assessment of paediatric studies completed after the Paediatric Regulation entered into force 26 Jan 2007 and thereafter. The UK is Rapporteur for this procedure.

Olmesartan medoxomil is an angiotensin II antagonist which has selective activity at the angiotensin II type 1 (AT1) receptor. OM is available as 10 mg, 20 mg and 40 mg film coated tablets in the EU. In adults the approved therapeutic indication is for mono-therapy or combined therapy for essential hypertension. OM was first approved for mono-therapy in EU in Germany in August 2002, subsequent MRP and national procedures resulted in approvals in 28 European countries, including UK. It has received paediatric indication for treatment of hypertension in children from 6-18 years old in the USA based on the results of the same paediatric data as submitted in this worksharing procedure.

The current submission includes: one adult bioavailability and two clinical paediatric studies, reports of post marketing experience, and a clinical overview. The MAH has stated that the submitted paediatric studies do influence the benefit risk for olmesartan medoxomil positively and has requested an indication for treatment of hypertension in children and adolescents from 6 to less than 18 years of age.

Based on the assessment of the paediatric data presented as part of this procedure, SmPC changes are proposed in sections 4.8, 5.1 and 5.2.

☒ Change

☒ New study data: sections 5.1 & 5.2

☐ New safety information: section 4.8

☐ Paediatric information clarified: section 4.2

☐ New indication: N/A

II. RECOMMENDATION

Based on the review of the presented paediatric data on pharmacokinetics, safety and efficacy and the assessment of the response to the list of questions raised by the Rapporteur and other MSs, it is considered that the results of these studies support a positive benefit:risk ratio for children with hypertension older than 6 years of age. The additional information has confirmed that the population pharmacokinetic model used adequately describes the pharmacokinetics of olmesartan in the paediatric population, thus the paediatric dosing used in these studies was sufficient to demonstrate an effect. The evidence of efficacy in children aged 1-5 years old is not robust enough to support the use of olmesartan in this age group, however the findings in should also be included in the SmPC.

The safety profile of olmesartan generally resembles that of adults, however higher frequency of epistaxis in children compared with adults and higher incidence of dizziness and headache with increasing dose of olmesartan have been noted.

FINAL SmPC TEXT

4.2 Posology and method of administration

Paediatric population

The safety and efficacy of olmesartan in children and adolescents below 18 years has not been established. ~~No data are available~~. **Currently available data are described in section 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.**

Olmesartan medoxomil should not be used in children below 1 years of age because of safety concerns and lack of data in this age group.

4.8 Undesirable effects

Paediatric population:

The safety of olmesartan was monitored in 361 children and adolescents, aged 1-17 years old during 2 clinical trials. Whilst the nature and severity of the adverse events are similar to that of the adults, the frequency of the following is higher in the children:

- Epistaxis is a common adverse event in children (i.e. ≥ 1/100 to < 1/10) that has not been reported in adults.
- During the 3 weeks of double blind study, the incidence of treatment emergent dizziness and headache nearly doubled in children 6-17 years of age in the high olmesartan dose group.

The overall safety profile for olmesartan in paediatric patients does not differ significantly from the safety profile in adults.

5.1 Pharmacodynamic properties

Paediatric population:

The antihypertensive effects of Olmetec in the paediatric population were evaluated in a randomized, double-blind, placebo-controlled study in 302 hypertensive patients aged 6 to 17 years. The study population consisted of an all black cohort of 112 patients and a mixed racial cohort of 190 patients, including 38 blacks. The aetiology of the hypertension was predominantly essential hypertension (87% of the black cohort and 67% of the mixed cohort). Patients who weighed 20 to <35 kg were randomized to 2.5 mg (low dose) or 20 mg (high dose) of Olmetec once daily and patients who weighed ≥35 kg were randomized to 5 mg (low dose) or 40 mg (high dose)of Olmetec once daily. Olmetec significantly reduced both systolic and diastolic blood pressure in a weight-adjusted dose-dependent manner. Olmetec at both low and high doses significantly reduced systolic blood pressure by 6.6 and 11.9 mmHg from the baseline, respectively. This effect was also observed during the 2 weeks randomized withdrawal phase, whereby both mean systolic and diastolic blood pressures demonstrated a statistically significant rebound in the placebo group compared to olmetec group. The treatment was effective in both, paediatric patients with primary and secondary hypertension. As observed in adult populations, the blood pressure reductions were smaller in black patients.

In the same study, 59 patients aged 1 to 5 years who weighed ≥5 kg received 0.3 mg/kg of Olmetec once daily for three weeks in an open label phase and then were randomized to receiving Olmetec or placebo in a double-blind phase. At the end of the second week of withdrawal, the mean systolic/diastolic blood pressure at trough was 3/3 mmHg lower in the group randomized to Olmetec; this difference in blood pressure was not statistically significant (95% C.I. -2 to 7/-1 to 7).

5.2 Pharmacokinetic properties

Paediatric population:

The pharmacokinetics of olmesartan was studied in paediatric hypertensive patients aged 1 to16 years. The clearance of olmesartan in paediatric patients was similar to that in adult patients when adjusted by the body weight.

There is no pharmacokinetic information available in renally impaired paediatric subjects.

Final PIL text:

4. Possible side effects

Children and adolescents:
In children, side effects are similar to those reported in adults. However, dizziness and headache are seen more often in children, and nose bleeding is a common side effect seen in children only.

III. INTRODUCTION

On 5th of May 2010, the MAH submitted 3 completed paediatric studies for olmesartan medoxomil finilized after January 2007, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

The current submission includes: one adult bioavailability and two clinical paediatric studies, reports of post marketing experience, and a clinical overview. These studies have been conducted in response to a written request for paediatric data from the US Food and Drug Administration (FDA) Paediatric Exclusivity Granted list. A clinical overview has also been provided. The MAH stated that the submitted paediatric studies positively influence the benefit risk for olmesartan medoxomil in the paediatric population and proposed granting an indication for treatment of hypertension in children and adolescents from 6 to less than 18 years of age.

IV. SCIENTIFIC DISCUSSION

Product characteristics

Olmesartan medoxomil is a potent angiotensin II antagonist, also known as angiotensin receptor blocker (ARB), which has selective activity at the angiotensin II type 1 (AT1) receptor. OM is a pro-drug which is converted *in vivo* to the active metabolite olmesartan. The use of the medoxomil ester pro-drug is necessary because of the low bioavailability of olmesartan itself after oral administration. OM is available as 10 mg, 20 mg and 40 mg film coated tablets in the EU. The approved adult therapeutic indication is essential hypertension.

Other drugs in this class are valsartan, azilsartan, candesartan, irbesartan, telmisartan, losartan, of which losartan and valsartan have paediatric indications within the EU.

Paediatric hypertension

Hypertension is an important risk factor for cardiovascular morbidity and mortality and occurs in 1 to 9% of children and adolescents. In younger children, hypertension is generally secondary to renal or renovascular disease. The most common cause of paediatric hypertension, accounting for between 60 and 70% of cases is renal disease, including hereditary kidney disorders, renal hypo- or dysplasia and acquired glomerulopathies. Other causes include diabetes mellitus, cardiac pathologies, coarctation of the aorta, and endocrine disease such as pheochromocytoma and hyperthyroidism. Essential hypertension is rare in infants and young schoolchildren, but is frequent in adolescents. Its increasing prevalence during childhood parallels that of obesity. In adolescents, essential hypertension is more prominent, especially in association with obesity.

Hypertension in children is defined as diastolic and/or systolic blood pressure (BP) greater than the 95th percentile for gender, age and height, measured on at least 3 occasions. The treatment goal is generally to reduce BP to below the 95th percentile, although in some cases, e.g. children with nephropathy, a lower target may be desired.

Acceptable drug classes for use in children include ACE inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, calcium channel blockers, and diuretics.

IV.1 Information on the pharmaceutical formulation used in the studies

OM was dispensed as a compounded suspension. Benicar or placebo tablets were dispersed in vehicles containing water, Ora-Plus and Ora-Sweet.

Ora-Plus and Ora-Sweet are commercially available suspending and sweetening vehicles used in the extemporaneous compounding of oral suspensions. Preparation methods for the compounded suspension of olmesartan medoxomil are described below:

Volumetric method
Add 50 mL of purified water to five Benicar 20 mg tablets (0.5 mg/mL)
Add 50 mL of purified water to forty Benicar 20 mg tablets (4 mg/mL)
Let stand for 5 min, Shake for 1 min x 4 times, Standing for 1 min
Add 100 mL of Ora-Sweet and 50 mL of Ora-Plus, Shake for 1 min

Assessor's comment: No data regarding quality aspects of the extemporaneous liquid suspension are provided. Therefore we cannot be certain that the same dose of OM was received from the compounded liquid suspension and the tablets in the efficacy study. Further information is requested on the quality control of the extemporaneous preparation.

IV.2 Clinical Aspects

1. Introduction

The MAH submitted three final report(s) for:

- **S0866-A-U101 A Comparative, Randomized, Single-Dose, 2-Way Crossover Bioavailability Study of a Compounded 4 mg/mL Olmesartan Medoxomil Suspension (Total Dose 40 mg) and 40 mg Olmesartan Medoxomil Tablets (Benicar®) in Healthy Adult Volunteers Under Fasting Conditions**

- **S0866-A-U102 An Open-Label Study of the Single-Dose Pharmacokinetics of Olmesartan Medoxomil in Paediatric Patients with Hypertension**

- **S0866-A-U301 A Dose-ranging Study to evaluate the Safety and Efficacy of Olmesartan Medoxomil in Children and Adolescents with Hypertension**

- **An expert clinical overview**

- **PSUR: Periodic safety updates Report no 15 for Olmesartan Medoxomil; Period 25 Apr 2009 to 24 Oct 2009**

Assessor's comment: A literature search/ review of the existing paediatric studies is not included.

Non-clinical Aspects

No non-clinical studies on juvenile animals were performed by the applicant. Nor a literature review has been carried out.

Assessor's comment: A literature search/ review of the existing juvenile animal studies with particular reference to renal toxicity and any effects on the adrenal and thyroid

growth and function needs to be carried out. If toxicological investigation had been undertaken within the regulatory guidelines in a rodent and non rodent species including any studies undertaken on juvenile animals, then the full data set should be submitted.

2. Clinical studies

2.1 <u>Study- CS0866-A-U10:</u> A Comparative, Randomized, Single-Dose, 2-Way Crossover Bioavailability Study of a Compounded 4 mg/mL Olmesartan Medoxomil Suspension (Total Dose 40 mg) and 40 mg Olmesartan Medoxomil Tablets (Benicar) in Healthy Adult Volunteers Under Fasting Conditions

- **Description**

The study was a randomized, open-label, 2-way crossover study to compare the pharmacokinetics of olmesartan medoxomil administered as a compounded suspension to the marketed tablet formulation in healthy subjects under fasting conditions. The compounded suspension was later utilized in paediatric population in the PK (CS0866-A-U102) and efficacy (CS0866-A-U301) studies.

- **Methods**

There was a washout period of 7 days between doses. Subjects were randomly assigned to receive one of the following two formulations on two different occasions:

- Treatment A: 4 mg/mL suspension (10 mL, for a total dose of 40 mg)
- Treatment B: OM tablets (Benicar, 1 × 40 mg tablets)

Safety monitoring included complete physical examination, vital signs, 12-lead ECG, laboratory (haematology, serum chemistry, urinalysis), and adverse events evaluation at designated times during the study.

- Objective(s)

The objective of this study was to determine if the compounded suspension formulation of olmesartan medoxomil (4 mg/mL × 10 mL, for a total dose of 40 mg) is bioequivalent to the marketed tablet formulation of Benicar (1 × 40 mg tablet).

- Study design

The study was designed as an open-label, single-dose, randomized, 2-way crossover study to compare the pharmacokinetics of olmesartan medoxomil administered as a compounded suspension to the marketed tablet formulation in healthy adult subjects under fasting conditions. An oral dose of 40 mg of olmesartan medoxomil was chosen because it is the highest recommended dose administered in clinical settings.

The study endpoints were the 90% confidence intervals of the ratio of least-squares means (LSM) of the test to reference formulation for the pharmacokinetic parameters AUC0-t, AUCinf and Cmax.

- Study population /Sample size

24 subjects (20 males and 4 females) completed the study. Subjects selected for this study were healthy, 18-45 years of age with body mass index (BMI) of 19-32 kg/m2. All female subjects had a negative pregnancy results at screening. The majority of subjects (73.1%) were black.

- Treatments

Subjects received, on two different occasions, 7 days apart, a single dose of 4 mg/mL (10 mL, for a total dose of 40 mg) or a single 40 mg OM tablet (Benicar) orally with 240 mL of water.

- Outcomes/endpoints

Pharmacokinetic parameters were calculated from the individual plasma concentrations of olmesartan using noncompartmental methods. The following PK parameters were calculated: AUC0-t, AUCinf, AUC/AUCinf, Cmax, tmax, t½ and kel.

Safety was monitored by evaluation of adverse events, clinical laboratory measurements, vital signs, physical examinations, and 12-Lead electrocardiograms (ECGs).

- Statistical Methods

Analysis of variance (ANOVA) was performed on natural log-transformed AUC0-t, AUCinf and Cmax using the SAS PROC MIXED and the SAS GLM procedures (version 8.2 executing on OpenVMS 7.2-1 platform). The SAS PROC MIXED and the SAS GLM ANOVA models included sequence, formulation, and period as fixed effects, and subject nested within sequence as a random effect. Consistent with the two one-sided tests for bioequivalence, 90% confidence intervals of the ratios of geometric means of the pharmacokinetic parameters AUC0-t, AUCinf and Cmax of the test to the reference treatment were computed.

In order to determine bioequivalence, the 90% confidence interval (CI) of the ratios of geometric means for AUC0-t, AUCinf, and Cmax of the test to reference formulation were to be within 80 to 125%.

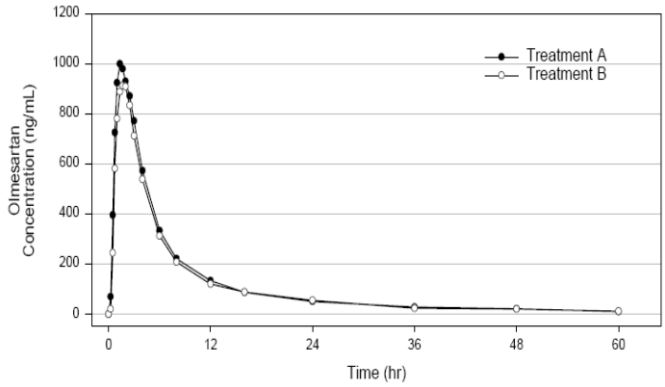
Assessor's comment:
Cmax of the metabolite is usually less sensitive to differences in the absorption rate than Cmax of the parent drug, bioequivalence should, if possible, be determined for Cmax of the parent compound (OM) as a measure of peak exposure. The applicant needs to clarify whether it was not possible to reliably measure the parent compound after single dose administration of OM.

Otherwise the design and the acceptance limits (80-125% with 90% confidence interval) for PK parameters are in compliance with the EMEA guideline on the investigation of bioequivalence, July 2008.

- **Pharmacokinetic Results**

Figure 1- below, shows the mean serum concentration-time profiles for OM in the 24 healthy subjects who received a single oral dose of a 40-mg OM tablet and a single oral dose of 24-mg OM suspension.

Figure 1- Olmesartan Plasma Concentration Profiles



Mean plasma concentration of Treatment A (4 mg/mL × 10 mL olmesartan medoxomil suspension) and Treatment B (40 mg Benicar tablet) formulations

Following oral administration, olmesartan medoxomil is rapidly transformed to the active moiety, olmesartan and the pharmacokinetics of this moiety is reported. Mean PK profiles for suspension and tablet formulations were virtually superimposible. Geometric means of the main pharmacokinetic parameters for Treatment A and Treatment B are presented in the table 1 below:

Table 1- PK parameters for treatments A and B

Parameters	Geometric Mean		Ratio (A/B)	90% CI
	Treatment A[a]	Treatment B[b]		
AUC_{0-t}	6688.8	6358.5	105.2	(97.7, 113.3)
AUC_{inf}	7032.6	6557.6	107.2	(97.5, 117.9)
C_{max}	1012.6	949.6	106.6	(97.8, 116.3)

a Treatment A = 10 mL (4 mg/mL) olmesartan medoxomil Suspension
b Treatment B = 40 mg olmesartan medoxomil (Benicar) Tablet

The 90% confidence intervals for the ratios of test to reference for AUC0-t, AUCinf and Cmax of olmesartan were all within 80 to 125% when using the SAS PROC MIXED procedure. Therefore, a claim of bioequivalence can be made between the 4 mg/mL × 10 mL olmesartan medoxomil suspension and 40 mg olmesartan medoxomil (Benicar) tablets under fasting conditions.

Assessors comment: The pharmacokinetic results show that the Olmesartan medoxomil oral suspension and the marketed 40 mg Benicar tablet are bioequivalent.

- Safety results

A total of 7 clinical TEAEs were reported by 4 (15.4%) of the 26 subjects with 2 (8.3%) of the 24 subjects taking the olmesartan medoxomil suspension and 2 (7.7%) of the 26 subjects taking the Benicar tablets. All clinical TEAEs were mild in severity and resolved at the end of the study. The Investigator considered 5 of the 7 clinical TEAEs to be possibly or probably related to study drug. All mean vital sign and clinical laboratory findings remained within normal limits and no marked changes from baseline were noted.

Assessors comment: 24 adults were recruited in this single dose study. In this small study, no unexpected or alarming adverse events were observed. The headache, fatigue and nausea are already known adverse events associated with OM.

2.2 **Study- CS0866-A-U102:** An Open-Label Study of the Single-Dose Pharmacokinetics of Olmesartan Medoxomil in Paediatric Patients with Hypertension

- Description

This was a single-dose, open-label Pharmacokinetics and Safety study of Olmesartan Medoxomil in 24 hypertensive children and adolescents of both sexes between 2 and 16 years of age.

- Methods

Subjects were stratified into four groups by age: 12-23 months (no subjects enrolled), 2-5 years (n=4), 6-12 years (n=10), and 13-16 years (n=10). On Day 1, subjects were given a single dose of OM at least 1 hour following a light breakfast.

Serial blood samples (approximately 1 mL whole blood each draw) for analysis of olmesartan were drawn prior to dosing and 1, 2, 4, 8, 12, 24, and 48 hours post dosing.

In adolescents and in children who were toilet trained, who did not have enuresis, and who could void on command, all possible voided urine was collected from each subject during 0-6, 6-12, and 12-24 hours post dose intervals.

Subjects were monitored for adverse events (AEs) throughout the 48 hours after dosing. Vital signs were checked before dosing and at 1, 2, 4, 8, 12, and 24 hours after dosing, and a final physical examination, urinalysis, and electrocardiogram (ECG) were conducted 48 hours after dosing. Blood samples for clinical laboratory testing were collected immediately before dosing and at 48 hours after dosing.

- Objective(s)

The primary objective of the study was to determine the single-dose PK of olmesartan following oral administration of a pro-drug, OM, in paediatric subjects with hypertension ages 12 months to 16 years.

- Study design

This study was designed to assess the single-dose PK of the active metabolite, olmesartan, following oral administration of the pro-drug, OM in paediatric patients. Blood samples were analysed for area under the curve (AUC), maximum plasma concentration (Cmax) and half life (t1/2). Urine samples were analysed for the PK parameters relevant to renal clearance.

- Study population /Sample size

Hypertensive children with current treatment for hypertension, Systolic blood pressure (SBP) ≥ 95th percentile SBP or diastolic blood pressure (DBP) ≥ 90th percentile if diabetic and Glomerular filtration rate (GFR) ≥ 30 mL/min/1.73 m2 were recruited. A total of 33 subjects were screened for the study at six Centres in the USA, but only 24 subjects were enrolled and completed the study.

- Treatments

OM was provided as 20 mg and 40 mg film-coated tablets (Benicar). Children 6 years of age and older received OM 40 mg (≥ 35kg) or 20 mg (< 35kg); children younger than 6 years received OM in suspension form at a dose of 0.3 mg/kg body weight, not exceeding 20 mg.

The suspension was offered to children 6 years or older who had difficulty swallowing tablets. Study drug was administered orally in the clinic with up to 8 oz (240 mL) of water. All suspension doses were measured with an oral syringe delivery system.

- Outcomes/endpoints

Pharmacokinetics:
The following PK variables were calculated from plasma analysis of olmesartan concentration data: AUC0-t and AUC0-∞ (ng·hr/mL), Cmax (ng/mL), Tmax (hr) – Tt1/2.

The following PK parameters were calculated from the olmesartan concentration in urine: Aet – Amount of olmesartan excreted in urine at each collection, Ae – The total amount of olmesartan excreted in urine over all collection periods, Fe – Fraction of dose recovered as olmesartan in urine, CLR – The renal clearance

Safety:
Line listing of all adverse events in accordance with Medra Dictionary and subsequent assessment of the nature of each event, time of onset after drug administration, duration, and intensity were documented.

Laboratory values measured include; haematology, blood chemistry and urinalysis.
Vital signs examinations included; blood pressure heart rate, body temperature, respiratory rate, ECGS and physical examination.

- Statistical Methods

Pharmacokinetics:
The PK variables were calculated using WinNonLin 5.2 for plasma data and S-PLUS 8 for urine data to perform noncompartmental analysis. Missing or unusable concentrations were removed from the data set. Concentrations that were below the quantifiable limit were set to zero.

Safety:
Summary statistics were tabulated by group to assess the continuous safety and tolerability variables of laboratory tests (chemistry and hematology), blood pressure, and pulse rate. Frequency counts were tabulated by group to assess the safety and tolerability variables of adverse events, urinalysis, ECG, and physical examinations.

➢ Results

- Recruitment/ Number analysed

A total of 24 subjects were enrolled and completed the study. Subjects were stratified into four groups by age: 12-23 months (no subjects enrolled), 2-5 years (n=4), 6-12 years (n=10), and 13-16 years (n=10).

The mean age of all subjects in the study was 11.2 years, with a range of 4 to 16 years. Overall, the number of males and females was essentially equal. Exactly half (50%) of the subjects in the 6-12 and 13-16 year age groups were male and half were female, but there was a 3:1 female to male distribution in the 2-5 year age group (n = 4). The majority of subjects (66.7%) were black, non-Hispanic. Six subjects in the oldest age group and four in the 6-12 year age group weighed over 80 kg, and therefore, the mean subject weights were greater than expected for the subjects' ages.

Assessor's Comment: Despite the study design and title there were no children enrolled in 12-23 month cohort. Furthermore in the 2-5 year old cohort (n=4), the youngest patient enrolled is 4 years old.

- Baseline data

Table 2 presents a summary of the subjects' demographic characteristics and Baseline height and weight for the subjects' age groups.

Table 2- Baseline Demographics and Characteristics (All Enrolled Subjects)

Attribute	12-23 Months N=0	2-5 Years N=4	6-12 Years N=10	13-16 Years N=10	All Groups Combined N=24
Age (years)					
Mean (SD)	0	4.8 (0.50)	10.2 (1.03)	14.8 (1.03)	11.2 (3.76)
Median		5.0	10.5	15.0	11.0
Min-Max		4-5	8-11	13-16	4-16
Gender n (%)					
Male	0	1 (25.0)	5 (50.0)	5 (50.0)	11 (45.8)
Female	0	3 (75.0)	5 (50.0)	5 (50.0)	13 (54.2)
Race[a] n (%)					
White, non-Hispanic	0	2 (50.0)	2 (20.0)	5 (50.0)	9 (37.5)
Black, non-Hispanic	0	2 (50.0)	9 (90.0)	5 (50.0)	16 (66.7)
Hispanic	0	1 (25.0)	1 (10.0)	0	2 (8.3)
Height (cm)					
Mean (SD)	0	116.7 (9.01)	151.8 (9.44)	165.5 (9.74)	151.6 (19.44)
Median		117.3	152.1	166.2	155.7
Min-Max		106-126	134-163	148-178	106-178
Weight (kg)					
Mean (SD)	0	32.0 (16.31)	70.3 (20.53)	86.3 (29.50)	70.6 (30.09)
Median		29.5	71.0	89.1	66.1
Min-Max		18-52	33-102	43-136	18-136

Assessor's Comment: Most (18 out of 20) of the 6-16 year old subjects in this study had adult body weights of 70-80 Kg.

- Pharmacokinetic results

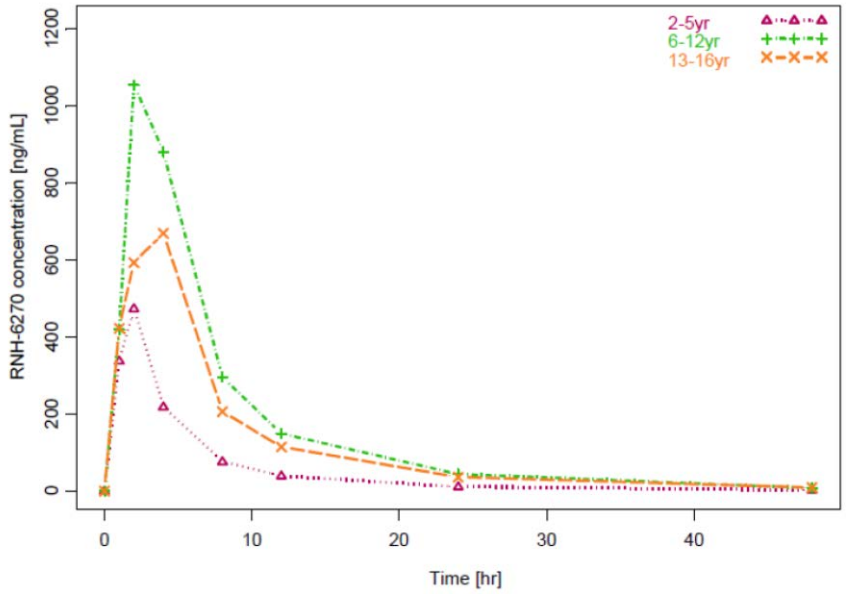
Table 3 shows the mean pharmacokinetic parameters for the 6-12 and 13-16 year age groups. The sample size of four subjects was insufficient to support calculation of summary statistics for the 2-5 age group.

Table 3- Mean Plasma Pharmacokinetic Parameters of Olmesartan

	AUC0-$_t$t ng/mL * hr	K_{el} L/hr	AUC0-∞ ng/mL* hr	Cmax ng/mL	Tmax hr	t½ hr	CL/F L/hr	Vd/F L
6-12 Year Age Group (N = 10)								
Mean	7874	0.090	7988	1227	2.8	8.4	4.3	50.9
SD	2913	0.029	2913	451	1.3	2.4	1.9	20.7
13-16 Year Age Group (N = 10)								
Mean	5851	0.079	5982	895	2.5	9.1	6.1	81.3
SD	2083	0.016	2130	262	1.1	1.9	2.6	42.1

The geometric means of AUC and Cmax of the 6-12 year age group were one-third higher than those of the 13-16 year age group. Correspondingly, the geometric means of apparent clearance (CL/F) and apparent volume of distribution (Vz/F) of the 6-12 year age group were roughly two-thirds of those of the 13-16 year age group. These relationships correspond to the roughly proportional relationships of CL/F and Vz/F with body weight. Plasma half-life (t½) and Tmax were not associated with body weight. None of the plasma parameters was statistically significant at α = 0.05 in an ANOVA with age group as a factor.

Figure 2- Study CS0866-A-U102 - Mean Olmesartan Concentration Versus Time by Age Group



Approximately 3% to 15% of administered drug was recovered in the subject's urine. Renal clearance was associated with body weight. No differences among groups in urine PK parameters were observed.

Assessor's comments: There were no children12-36 months old enrolled. In 2-5 years old group there are only four children aged 4 years and older; they were considered too few for any statistical calculation, thus no data in this age group was provided. Despite the title of it, this study only represents PK values for children between 6-17 years of age.

Few facts can be deducted from the submitted data in the 6-17 year olds, as follows:

- The children included in this study were mostly of adult weight of 70-80 Kg and with exception of one subject, all received 40 mg OM (maximum adult dose)..
- Peak concentrations (Cmax) and AUC seem to be decreasing with age. Both parameters of the 6-12 year age group were one-third higher than those of the 13-16 year age group.
- Clearance and volume of distribution increased with age. Approximately 3% to 15% of administered drug was recovered in the subject's urine.
- Plasma half-life (t½) and Tmax were similar across both age groups.

- None of the plasma or urine PK parameters were statistically significantly different within the age groups.

A proper dose may not be deducted from the results of these PK parameters. There are no data on the younger children dosed on mg/kg bases. The dose-exposure relationships needed for dosing on body weight (mg/kg) are not provided.

- Safety results

In total, 4 of the 24 subjects (16.7%) experienced 6adverse events (AE). None of the AEs was treatment-related and all were mild in severity. One subject in the 2-5 year age group experienced headache and fatigue. In the 6-12 year age group AEs were somnolence and diarrhoea (n =1) and abdominal pain (n = 1). In the 13-16 year age group 1 subject had an abnormal urinalysis (high WBC count).

There were no changes from Baseline to Endpoint in mean and individual haematology, chemistry, and urinalysis parameters. Mean heart rate, body temperature, ECGs and respiration rate were not influenced by a single dose of OM.

Assessor's comment: 24 children were recruited in this single dose study. In this small study, no unexpected or alarming adverse events were observed other than only one case of high WBC count. The headache, fatigue and gastrointestinal disorders are already known AEs associated with OM.

2.3 Population PK

➢ Description

Data from both Studies **CS0866-A-U102** (single-dose PK) and **CS0866-A-U301** (sparse sampling of high & low doses) were used for the population PK (PPK) analysis and exposure-response relationships of olmesartan in paediatric subjects. In total, 113 paediatric subjects from both studies were used in the pharmacokinetic analysis, and 89 paediatric subjects from CS0866-A-U301 were used in the exposure-response analysis.

➢ Methods

- Objective(s)

Population pharmacokinetic:
To establish the pharmacokinetic and exposure-response relationships of OM in paediatric patients and to compare it with the results observed in adults in prior studies.

- Study design

In study CS0866-A-U102 (single-dose PK) serial blood samples (approximately 1 mL whole blood each draw) for analysis of olmesartan were drawn prior to dosing and 1, 2, 4, 8, 12, 24, and 48 hours post dosing.

In study CS0866-A-U301, the PPK sampling was focused on Period II. Samples were taken at Week 2 and Week 3 of Period II. At Week 2, one sample was taken from one of the following

randomised time intervals: 2 to 4 hours, 6 to 8 hours, and 8 to 10 hours post dose. At Week 3, a trough sample and a second sample 1-3 hours postdose were drawn.

- Study population /Sample size

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 CS0866-A-U301 had at least one PK sample and a trough blood pressure measurement. Hence data from 89 subjects were used in the exposure-response analysis.

- Outcomes/endpoints

Pharmacokinetic/Pharmacodynamics endpoints
To establish the pharmacokinetic and exposure-response relationships of OM in paediatric patients and to compare it with the results observed in adults in prior studies.

To determine whether the current dataset is sufficient to evaluate the pharmacokinetic and dose/exposure-response relationships in paediatrics.

- Statistical Methods

PK Population Analysis
A previously developed population pharmacokinetic model of 472 adult olmesartan subjects determined that a two-compartment pharmacokinetic model with first-order absorption with absorption lag and first order elimination was appropriate for describing the plasma concentration profile for olmesartan. In the adult model, covariate analysis revealed that apparent oral clearance was related to weight [kg], gender, CRT [µmol/L], age [yr], and patient status. Lower clearance was associated with hypertension, female gender, increasing age, decreasing weight, and increasing serum creatinine, where the differences in demographic of healthy and hypertensive population used in dataset were age (30 vs. 54 years), body weight (70 vs. 77 kg), and serum creatinine levels (83.5 vs. 92.9 µmol/mL). The lower clearance in hypertensive population in the previous dataset may have originated in part from these demographic differences. Race (Japanese /Westerner) was not statistically significant. Similar results (hypertensive status, gender, bodyweight, and serum creatinine) were reported in a separate analysis performed with newer adult studies of olmesartan.

In the current pharmacokinetic analysis of the paediatric data alone, a stepwise covariate search, informed by biological plausibility and the adult findings, was used to select a population pharmacokinetic model. In the initial step, a two-compartment structural 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), without covariates was estimated with inter-individual variability on PK parameters to the extent supported by the dataset. Due to the absence of samples before 1 hour post-dose in the paediatric dataset, absorption lag time was set to 0 and the absorption rate was fixed at the 1.44/hr value from the adult model. In the second step, the correlated covariates weight and age were each separately tested on apparent clearance and central volume of distribution; the covariate that provided a greater reduction in objective function was retained. Subsequent steps tested for effects of formulation (i.e., the oral suspension given to those under 6 years of age) on bioavailability, ALT on clearance, serum creatinine on clearance, sex on clearance, and race on clearance.

Random effects were modelled on CL and V1, and assumed to follow a log normal distribution. The random residual error was modelled by an exponential error model (additive on the log

scale). An alpha-level of 0.01 (chi-squared distribution: 6.63 points of log-likelihood in NONMEM objective function) was used as the level of required statistical significance. Modelling was conducted with NONMEM V, Level 1.1, with method FOCE-Interaction (Globomax, LLC), and all data preparation and graphical analysis was conducted with S-PLUS 8.0 (Insightful Corp.)

Individual covariate-adjusted clearances were calculated based on the Bayesian post-hoc estimates from the population PK model, and the associated geometric means were calculated for paediatric and adult datasets.

The point estimate and corresponding 90% confidence interval for the ratio of geometric means between paediatric and adult patients were obtained using the least square mean difference between groups and the 90% CI from an ANOVA. The standard PK comparability criterion of 80-125% was used to determine comparability between paediatric and adult pharmacokinetics. Based on the post-hoc estimates of pharmacokinetic parameters, additional pharmacokinetic parameters were also calculated.

Pharmacokinetic assessor's comment: The Applicant submitted two technical reports around the population PK and PKPD modelling in paediatric patients. The results of these analyses are used to conclude similar PK behaviour to adults, a similar relationship between exposure and response and to support the recommended doses in paediatric patients. Given that the dosing strategy relies on the results of the population PK and PKPD modelling, it is important that model evaluation/qualification is rigorous. The two reports submitted by the Company provide a summary of the data, methods and results of the analyses, but lack sufficient detail for an appropriate level of assessment. The Applicant is requested to submit a full report of the analyses and simulations contained within the two technical reports. Although not possible to provide a full assessment, comments and questions resulting from review of the technical reports are included. Suggestions (not exhaustive) are made for inclusion of certain information in the requested full report.

To be included: analysis plan, electronic file of analysis dataset as comma separated and space deliminated text file, information regarding the handling of missing data and data below LOQ, deviations from analysis plan, description of all models evaluated, NONMEM input and output files for base and final models, distribution of samples (actual number per subject sorted by study, treatment group and visit), summary statistics and histograms of the continuous covariates and frequencies of categorical covariates, stratified over the relevant subpopulations.

Exposure-Response Analysis

The triplicate seated trough blood pressure readings at each visit were averaged for each subject. Per protocol, baseline was defined as the average of the randomization visit and the previous visit (either Visit 1.1 or 1.2, depending on whether the SeSBP criterion was met at Visit 1.1). "On-drug" was the trough seated BP at Visit 2.3 (week 3) at the end of Period 2. Drug exposure was represented by AUC, where AUC was calculated as dose divided by the individual post-hoc clearances of the population PK analysis using the final model. The relationships between changes from baseline and drug exposure (both as AUC and dose per body weight) were investigated using linear regression for both SBP and DBP. All steps were conducted in S-PLUS 8.0.

Comparison of Olmesartan Pharmacokinetics and Blood Pressure Lowering Effects between Adults and Paediatric Patients to Support Dosage Regimen

Simulation of the paediatric pharmacokinetics of olmesartan: Paediatric pharmacokinetics of olmesartan were simulated based on the population pharmacokinetic analysis results utilizing

CS866-102 and CS866-301 study based on the dosage regimen used in study CS866-301. The simulated observations were compared to posthoc estimated actual observations by superimposing the exposures to the simulated results. In order to evaluate maximum PD effects, the week 3 plasma concentration of olmesartan and blood pressure measurement taken 1-3 hours post-dose from CS0866-A-U301 were used.

- **PPK results**

The population pharmacokinetic analysis found weight to have a larger impact than age in the covariate selection process; weight influenced clearance and central volume of distribution in the final model. Parameters for the final model are shown in Table 4. The median weight of 48 kg was used to scale the estimates for the purpose of weight in the covariate evaluation.

In the final model, clearance was scaled to weight to the 0.803 power, similar to the allometric value of 0.75

$$C_{:i}\,[L/h] = 5.11 \cdot \left(\frac{WT[kg]_i}{48} \right)^{0.803}$$

and central volume of distribution was related to weight to the 1.17 power, again similar to the allometric value of 1.

$$V_{2,i}[L] = 34.6 \cdot \left(\frac{WT[kg]_i}{48} \right)^{1.17}$$

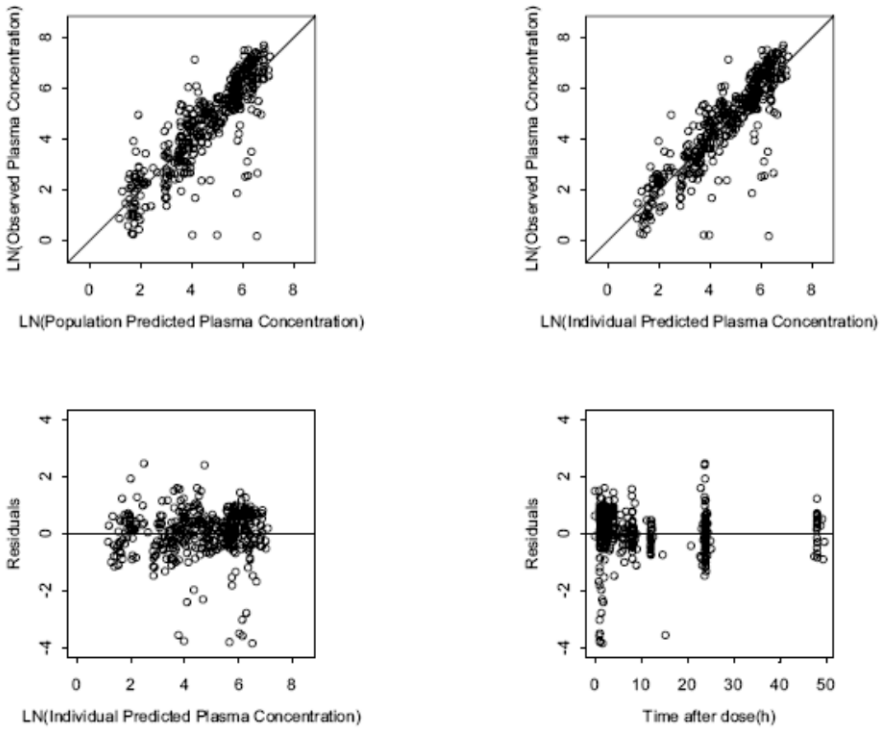
No other covariates were statistically significant, and no impact of formulation (oral suspension versus tablet) was found, similar to the results observed in a bioequivalence study. The final model reduced inter-subject variability parameters on clearance and central volume of distribution compared to the base model. Inter-subject variabilities in clearance and central volume of distribution were minimized from 40% and 60% to 16% and 20%, respectively, upon the addition of weight into the model. Parameters for the final model are shown in Table below:

Table 4- Population pharmacokinetic parameters of final paediatric model

Parameters (units)	Pediatric Dataset		
	Estimated	SE	CV (%)*
CL (L/hr)	5.11	0.299	6
V2 (hr^{-1})	34.6	3.43	10
Q (hr^{-1})	0.64	0.154	24
V3 (hr^{-1})	19.9	6.72	34
K_A (hr^{-1})	1.44	FIXED	FIXED
Lag time (hr)	0	FIXED	FIXED

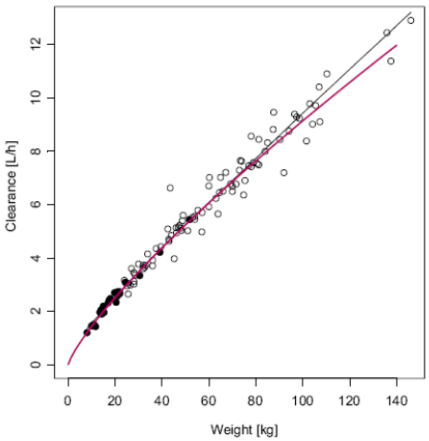
Model qualification plots in Figure 3 and Figure 4 showed the model to be appropriate. The low intersubject variability in clearance and central volume of distribution in the final model and similar prediction between individual and population predictions also supported weight being the most important covariate for determining the paediatric pharmacokinetic characteristics of olmesartan.

Figure 3- Model qualification plots for final paediatric PPK model



Pharmacokinetic assessor's comment: There appears to be an important overestimation of plasma concentration at early times for a number of patients (difference between predicted and observed concentration greater than two-fold). It is assumed that this is a result of fixing the absorption rate constant during the analysis. Similar plots for subgroups of interest would be helpful to determine if this overestimation is a general phenomenon or limited to one or more subgroups.
Additional model qualification information is necessary to demonstrate the value of using the post-hoc estimates of clearance, volume, etc, e.g. an assessment of the shrinkage of the individual estimates towards the population mean, visual predictive checks for subgroups of interest and individual plots of observed concentrations versus time with the population and individual predicted profiles overlaid.

Figure 4- Relationship between individual post-hoc clearances & weight in final model



Note: Solid, black points are from the pediatric subjects administered solution due to age under 6 years. Faint black line is loess smooth. Red, curved line is median, final model-predicted clearance based on weight (x-axis).

Pharmacokinetic assessor's comment: Assuming that the post-hoc estimates of clearance are well-estimated, the relationship between OM clearance and weight is convincing. It would be useful to see a similar graph for the central volume of distribution.

Plots generated to screen for other covariate relationships, following adjustment of clearance and volume for weight, should be provided.

Table 5 presents a summary by dose and age group for subject post-hoc estimated clearance, AUC, and C_{max} based on posthoc estimated population PK parameters using the final model. Table 6 repeats these estimates, but with posthoc estimates based on clearance and central volume of distribution normalized to a weight of 73 kg, which was the median weight in the adult dataset. The overall median of the paediatric subjects' clearances was 5.1 L/h unadjusted and 7.2 L/h when normalized to an adult body weight of 73 kg.

The paediatric subjects' clearances were compared to the earlier adult analysis, including all subjects in both datasets. Comparing all subjects in both groups unadjusted, the adult/paediatric ratio for clearance was 1.44 [1.31, 1.57], outside the bioequivalence range of 80% to 125%, in part due to the difference in weight between a typical subject in the adult dataset (median of 73 kg) and a typical subject in the paediatric dataset (median of 48 kg). When paediatric subjects' clearances were weight normalized to 73 kg based on to the clearance-weight relationship of the final model, the adult/paediatric ratio for clearance was 0.95 [0.92, 0.97], well within the bioequivalence range of 80% to 125%.

Pharmacokinetic assessor's comment: More details are needed regarding the basis of this calculation, particularly regarding the covariate distribution and variability of the simulation data set for the paediatric and adult populations.

Table 5- Paediatric subject pharmacokinetic summary by age group and dose group.

Age Group	Dose Group	N	Dose (mg) mean±SD	Clearance (L/h) [median] mean±SD	AUC (ng*h/mL) [median] mean±SD	C_{max} * (ng/mL) [median] mean±SD
12-23 mo**	0.3 mg/kg	3	2.4, 3, 3.2	1.2, 1.5, 1.5	1996, 2067, 2148	354, 366, 364
2-5 yr	0.3 mg/kg	23	6.1 ± 2.8	[2.4] 2.5 ± 0.9	[2282] 2338 ± 232	[351] 352 ± 6
6-12 yr	2.5 mg	8	2.5 ± 0	[3.1] 3.1 ± 0.3	[814] 811 ± 89	[105] 108 ± 10
	5 mg	9	5 ± 0	[5.2] 6.2 ± 1.7	[959] 854 ± 206	[108] 100 ± 28
	20 mg	7	20 ± 0	[3.6] 3.5 ± 0.4	[5489] 5814 ± 731	[719] 795 ± 128
	40 mg	20	40 ± 0	[6.6] 6.7 ± 1.3	[6098] 6197 ± 1161	[648] 704 ± 209
13-16 yr	2.5 mg	0	-	-	-	-
	5 mg	17	5 ± 0	[6.9] 7.5 ± 2.6	[748] 744 ± 264	[78] 82 ± 36
	20 mg **	2	20	3.8, 3.6	5305, 5567	758, 723
	40 mg	24	40 ± 0	[7.4] 7.3 ± 2.2	[5438] 6021 ± 1952	[587] 654 ± 252
ALL	0.3 mg/kg	26	5.8 ± 2.8	[2.3] 2.4 ± 0.9	[2234] 2307 ± 236	[352] 353 ± 7
	2.5 mg	8	2.5 ± 0	[3.1] 3.1 ± 0.4	[814] 811 ± 89	[105] 108 ± 10
	5 mg	26	5 ± 0	[6.6] 7.1 ± 2.4	[758] 782 ± 247	[83] 88 ± 34
	20 mg	9	20 ± 0	[3.6] 3.5 ± 0.4	[5489] 5730 ± 658	[723] 783 ± 114
	40 mg	44	40 ± 0	[7.0] 7.0 ± 1.8	[5701] 6101 ± 1625	[607] 677 ± 232
ALL	ALL	113	20 ± 17	[5.1] 5.4 ± 2.7	[2610] 3600 ± 2585	[360] 435 ± 303

* Based on estimated post-hoc pharmacokinetic parameters for each subject

** Due to low sample size, list of actual values shown in lieu of summary statistics

Table 6- Paediatric subject weight-normalized PK summary by age group and dose group.

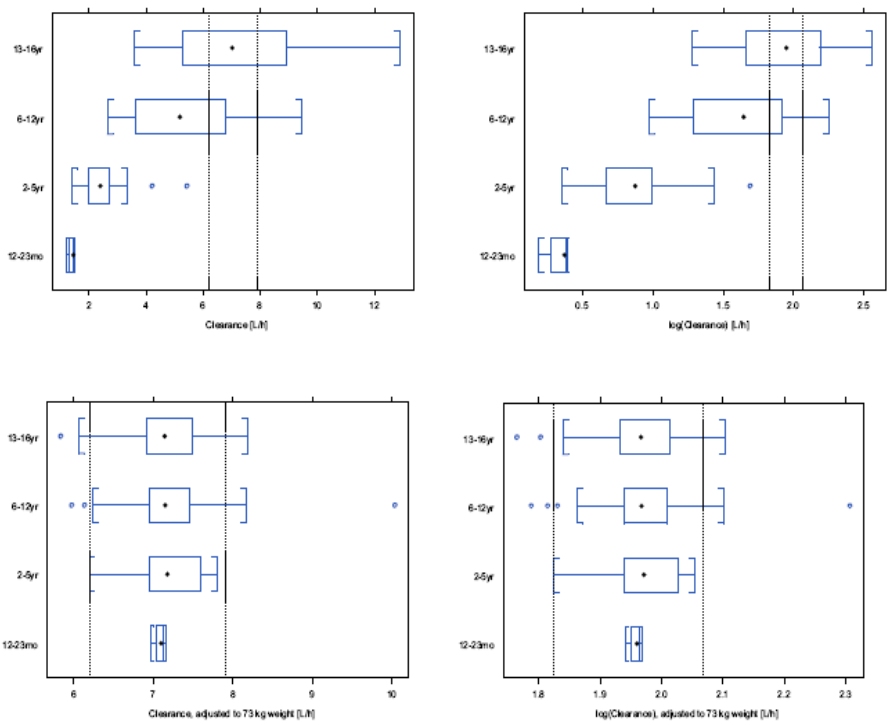
Age Group	Dose Group	N	Dose (mg) mean±SD	Clearance, weight normalized* (L/h) [median] mean±SD	AUC, weight normalized* (ng*h/mL) [median] mean±SD	C_{max}, weight normalized* (ng/mL) [median] mean±SD
12-23 mo**	0.3 mg/kg	3	2.4, 3, 3.2	7.1, 7.2, 7.0	338, 419, 459	35, 45, 48
2-5 yr	0.3 mg/kg	23	6.1 ± 2.8	[7.2] 7.2 ± 0.4	[689] 844 ± 401	[77] 90 ± 43
6-12 yr	2.5 mg	8	2.5 ± 0	[7.0] 7.0 ± 0.6	[360] 360 ± 30	[37] 37 ± 0.5
	5 mg	9	5 ± 0	[7.1] 7.3 ± 0.4	[702] 683 ± 35	[75] 74 ± 3
	20 mg	7	20 ± 0	[7.2] 7.3 ± 0.3	[2780] 2762 ± 120	[296] 296 ± 5
	40 mg	20	40 ± 0	[7.2] 7.2 ± 0.8	[5591] 5598 ± 552	[599] 600 ± 22
13-16 yr	2.5 mg	0	-	-	-	-
	5 mg	17	5 ± 0	[7.1] 7.1 ± 0.4	[709] 708 ± 44	[76] 75 ± 3
	20 mg **	2	20	7.7, 7.0	2597, 2871	294, 302
	40 mg	24	40 ± 0	[7.2] 7.3 ± 0.5	[5531] 5568 ± 446	[598] 585 ± 31
ALL	0.3 mg/kg	26	5.8 ± 2.8	[7.2] 7.2 ± 0.4	[686] 793 ± 402	[76] 85 ± 43
	2.5 mg	8	2.5 ± 0	[7.0] 7.0 ± 0.6	[360] 360 ± 30	[37] 37 ± 1
	5 mg	26	5 ± 0	[7.1] 7.2 ± 0.4	[703] 699 ± 42	[76] 75 ± 3
	20 mg	9	20 ± 0	[7.2] 7.3 ± 0.3	[2780] 2756 ± 125	[296] 297 ± 5
	40 mg	44	40 ± 0	[7.2] 7.2 ± 0.7	[5571] 5582 ± 491	[598] 592 ± 27
ALL	ALL	113	20 ± 17	[7.2] 7.2 ± 0.5	[2357] 2762 ± 981	[109] 293 ± 248

Pharmacokinetic assessor's comment: Normalisation of clearance to weight is useful for comparison across the different age groups. Normalisation of AUC and C_{max} doesn't make sense, as the administered dose was already adjusted for weight.

Assuming that the post-hoc estimates of individual pharmacokinetic parameters are valid, the applicant's position, that total body weight is likely to be the only significant predictor of CL/F in this population, is accepted. Despite the results of the single dose study (CS0866-A-U102) where Cmax and AUC decreased with age, this effect seems to have normalized by the increase in the number of subjects included in the population pharmacokinetic analysis.

The distribution of individuals' clearance, both unadjusted and normalized to weight of 73 kg, is shown by age group in Figure 5. The reference lines in Figure 5 illustrate the difference between healthy volunteer (7.9 L/h) and hypertensive status (6.2 L/h), where demographic of healthy and hypertensive population used in dataset were age (30 vs. 54 years), body weight (70 vs. 77 Kg) and serum creatinine levels (83.5 vs. 92.9 µmol/mL) (healthy vs. hypertensive populations).

Figure 5- Boxplots of variability in clearance (top) and 73 kg body weight-normalised clearance (bottom) by age group, shown on linear scale (left) and log scale (right), with vertical reference lines of typical 73 kg adult hypertensive patient and healthy volunteer clearances at 6.2 L/h and 7.9 L/h, respectively.



Note: Typical adult clearances assume 50/50 mix of genders, weight of 73 kg, serum creatinine of 80 µmol/L, and age of 50 yr.
Values are drawn from original olmesartan population pharmacokinetic analysis in adults by Gao et al.

Exposure-Response Analysis of Blood Pressure

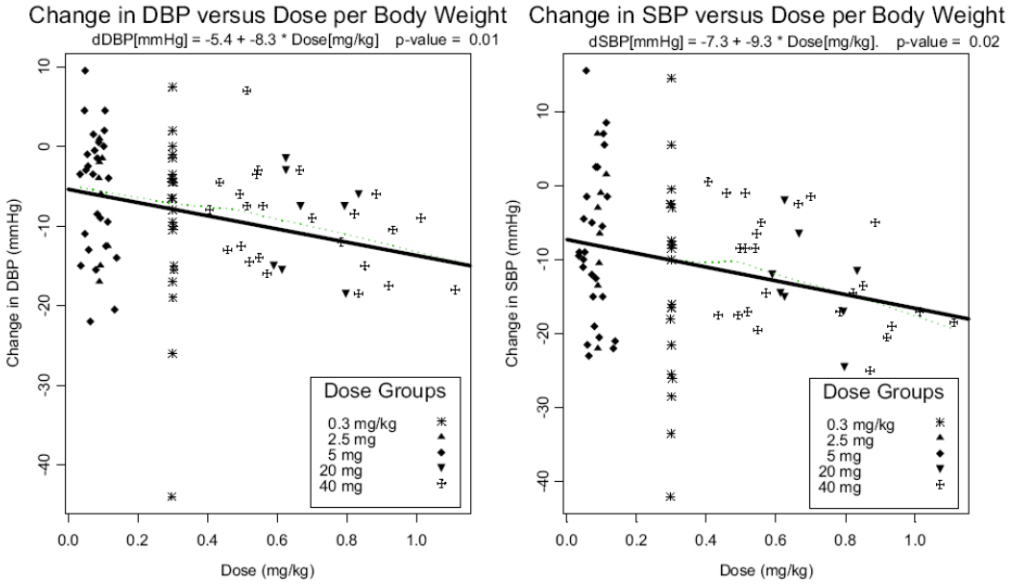
Table 6 displays the summary statistics for blood pressure reduction overall and by dose groups.

Table 6: Paediatric subject blood pressure changes from baseline by dose group.

Dose Group	N	Dose (mg) mean±SD	delta SBP (mmHg) [median] mean±SD	delta DBP (mmHg) [median] mean±SD	AUC (ng*h/mL) [median] mean±SD
0.3 mg/kg	26	5.8 ± 2.8	[-9.3] -12.8 ± 13.2	[-6.5] -9.1 ± 10.9	[2234] 2307 ± 236
2.5 mg	8	2.5 ± 0	[-4.8] -6.0 ± 9.2	[-5.0] -7.1 ± 6.8	[814] 811 ± 89
5 mg	26	5 ± 0	[-9.3] -7.9 ± 10.5	[-3.5] -5.7 ± 8.0	[758] 782 ± 247
20 mg	9	20 ± 0	[-13.3] -12.9 ± 6.8	[-7.5] -9.3 ± 6.3	[5489] 5730 ± 658
40 mg	44	40 ± 0	[-14.5] -12.3 ± 8.1	[-9.0] -10.6 ± 7.9	[5701] 6101 ± 1625
ALL	113	20 ± 17	[-10] -10 ± 10.4	[-7.5] -8.4 ± 8.6	[2610] 3600 ± 2585

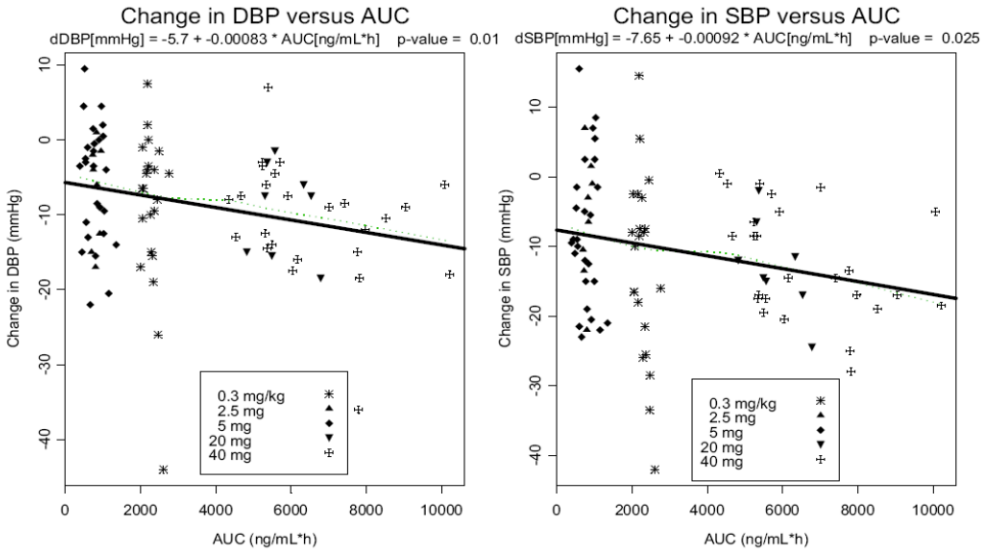
In the dose per weight analysis (Figure 6), the p-values for the slopes were 0.01 in the case of DBP and 0.02 in the case of SBP. The intercepts of the fit were -5.4 mmHg for DBP and -7.3 mmHg for SBP, and the slopes were -8.3 and -9.3 mmHg per mg/kg dose, respectively.

Figure 6- Relationship of change in blood pressure to dose per body weight



The AUC analysis (Figure 7) showed a p-value for the SBP slope was 0.025, while the p-value for the DBP slope was 0.01. Intercepts and slopes were similar to those estimated in the dose per weight analysis, -5.7 mmHg for DBP and -7.65 mmHg for SBP. Slopes were -0.00083 for DBP and -0.00092 for SBP [mmHg per ng/mL*h of AUC].

Figure 7- Relationship of change in blood pressure to drug exposure (AUC)



In the efficacy analyses, expressing exposure as dose per weight yielded a statistically significant relationship. The relationship was approximately linear. Because weight was a significant determinant of clearance, the dose per weight analysis yielded similar results to the

AUC-based exposure-response analysis of DBP. While the intercept was approximately the same 6 mmHg reduction as estimated in a prior adult analysis of SE/866-11 [6], the current slope in the AUC-DBP analysis was somewhat smaller. Nonetheless, the number of paediatric patients currently in the dataset is sufficient to conclude a dose response relationship if weight is taken into account.

Comparison of Olmesartan Pharmacokinetics and Blood Pressure Lowering Effects between Adults and Paediatric Patients to Support Dosage Regimen

Figures 8 and 9 show that observed exposure (posthoc estimated) were in line with simulated exposure of olmesartan in paediatric patients. The posthoc estimated paediatric exposures of olmesartan at doses of 10 mg (<35 Kg) and 20 mg (≥35 mg) were similar to those in adults given a 20 mg dose in the 866-318 study and the CS8663-A-U301 study. The olmesartan exposures in paediatric patients below 6 years old (0.3 mg/Kg) were slightly lower than those in the adult population (20 mg) but all of the observation were within lower 90% confidence interval.

Figure 8- Simulated and observed olmesartan exposure in paediatric subjects of age at and above 6 years old. Subjects were dosed at 10 mg (< 35 kg) and 20 mg (≥35 kg) above. Solid straight line indicates mean adult olmesartan exposure at 20 and 40 mg and dotted straight lines indicate 90 % upper and lower confidence interval at the given doses based on original adult PPK model. Points at right side indicated posthoc estimated olmesartan exposures in adults at studies of 866-318 and CS8663-a-u301 study at 20 and 40 mg.

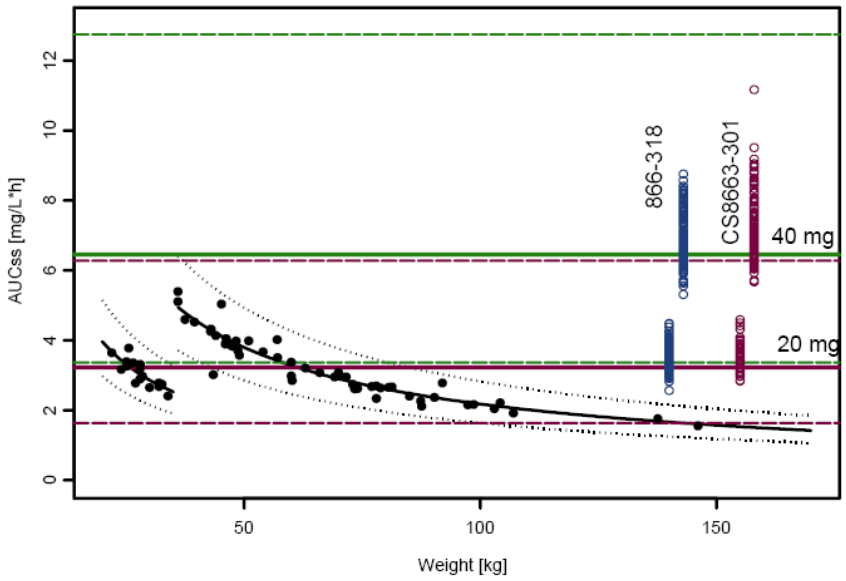
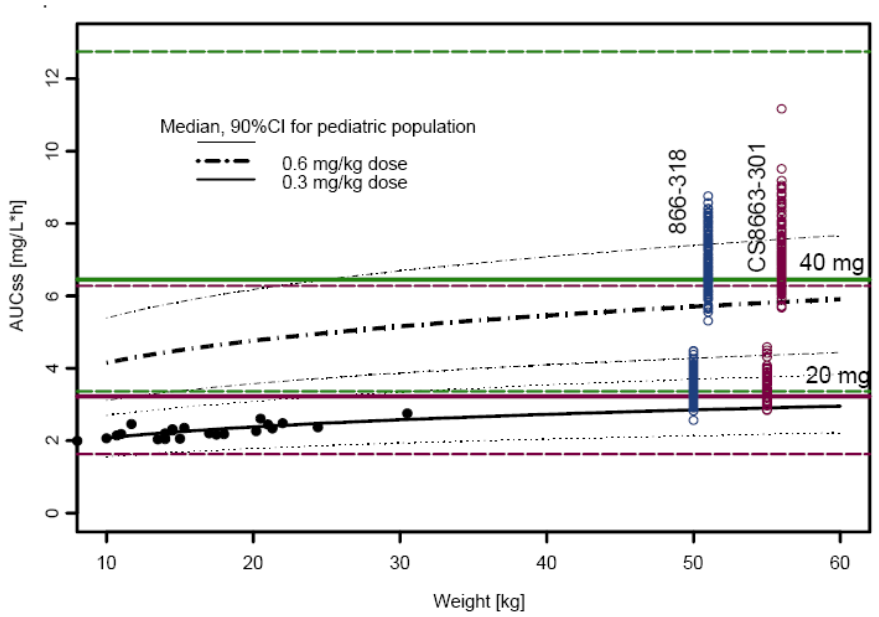


Figure 9- Simulated and observed olmesartan exposure in paediatric subjects age below 6 years old. Subjects were dosed at 0.3 mg/kg. Solid straight line indicates mean adult olmesartan exposure at 20 and 40 mg and dotted straight lines indicate 90 % upper and lower confidence interval at the given doses based on original adult PPK model. Points at right side indicated posthoc estimated olmesartan exposures in adults at studies of 866-318 and CS8663-A-U301study at 20 and 40 mg.



Pharmacokinetic assessor's comment: Assuming that the post-hoc estimates of individual pharmacokinetic parameters are valid, it is agreed that doses of 10 mg (<35 Kg) and 20 mg (≥35 Kg) result in similar olmesartan exposures between paediatric and adult patients and that exposures in paediatric patients below 6 years old (0.3 mg/Kg) were slightly lower than those in the adult population.

Figures 10 to 13 show observed blood pressure lowering effects of olmesartan between adults and paediatrics by body weight based dose and exposure. Both diastolic and systolic blood pressure showed a significant slope when regressed against olmesartan dose or exposure in adult population. Visual inspection by overlaying paediatric blood pressure to the adults' blood pressure showed similar dose-response or exposure-response pattern of higher dose or exposure to higher blood pressure lowering effects. A formal statistical comparison was not done due to the lack of a placebo arm during the primary period of the paediatric study, as well as due to different disease characteristics (such as baseline blood pressures) between hypertensive paediatric and adults. Positive slopes in both the dose and exposure response of olmesartan were demonstrated in the CS0866-A-U301 study.

Figure 10- Effect of olmesartan dose on diastolic blood pressure lowering effects in adults (top) and adult and Paediatrics (bottom). In lower figures 'p' indicates diastolic blood pressure lowering effects in paediatric population. Corresponding olmesartan doses in adults were divided by their body weights.

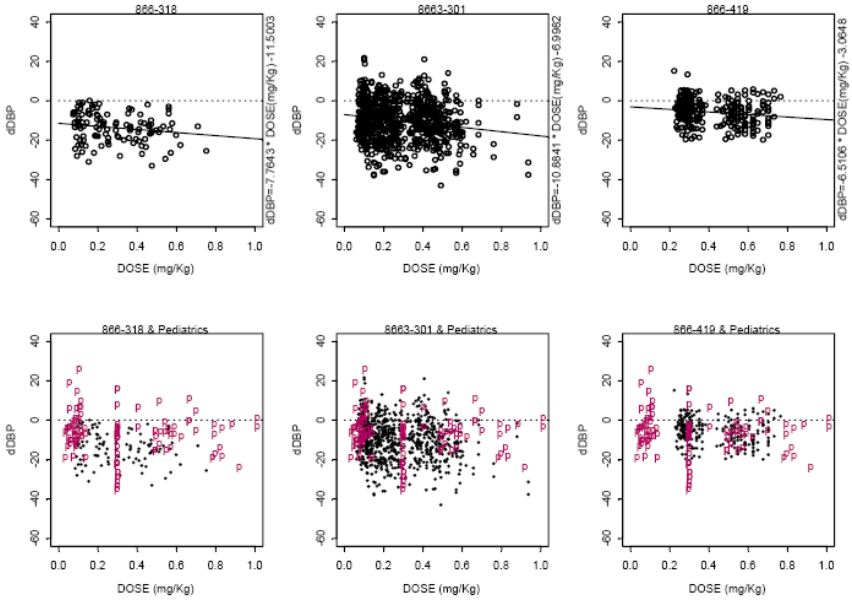


Figure 11- Effect of olmesartan dose on systolic blood pressure lowering effects in adults (top) and adult and Paediatrics (bottom). In lower figures 'p' indicates diastolic blood pressure lowering effects in paediatric population. Corresponding olmesartan doses in adults were divided by their body weights.

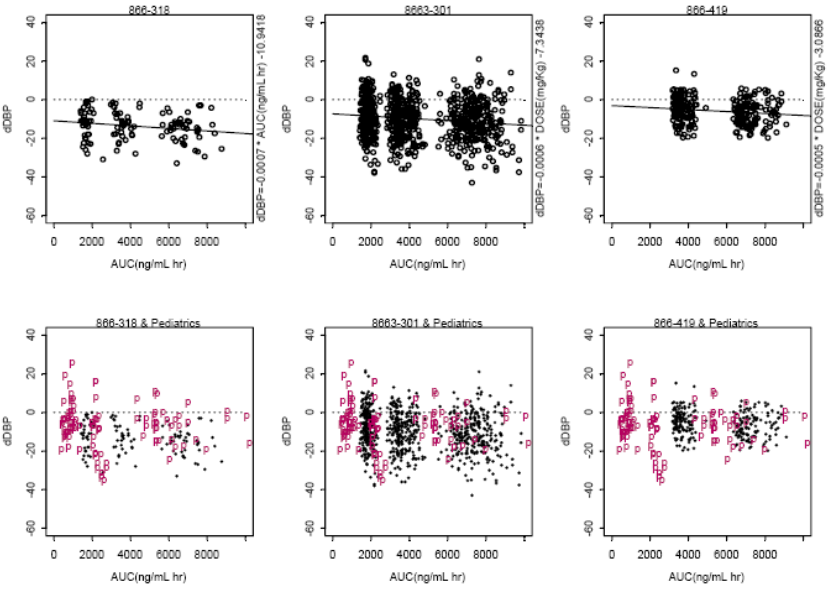


Figure 12- Effect of olmesartan exposure on diastolic blood pressure lowering effects in adults (top) and adult and Paediatrics (bottom). In lower figures 'p' indicates diastolic blood pressure lowering effects in paediatric population. Corresponding olmesartan doses in adults were divided by their body weights.

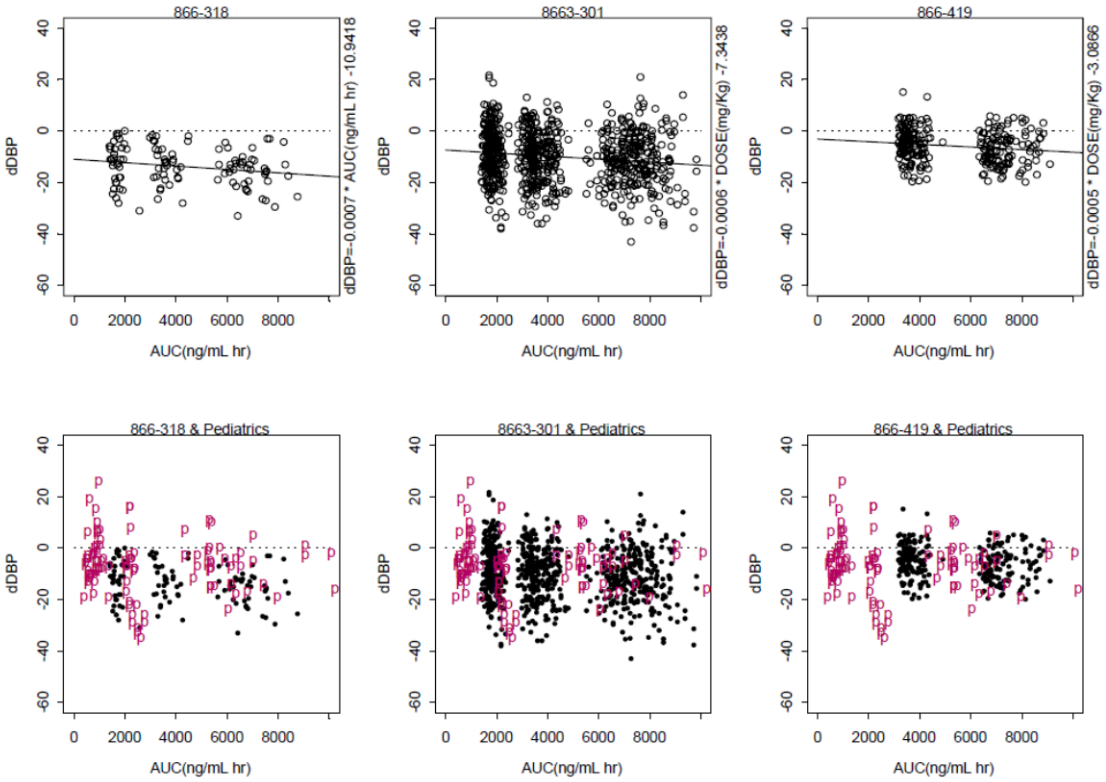


Figure 13- Effect of olmesartan exposure on systolic blood pressure lowering effects in adults (top) and adult and Paediatrics (bottom). In lower figures 'p' indicates diastolic blood pressure lowering effects in paediatric population. Corresponding olmesartan doses in adults were divided by their body weights

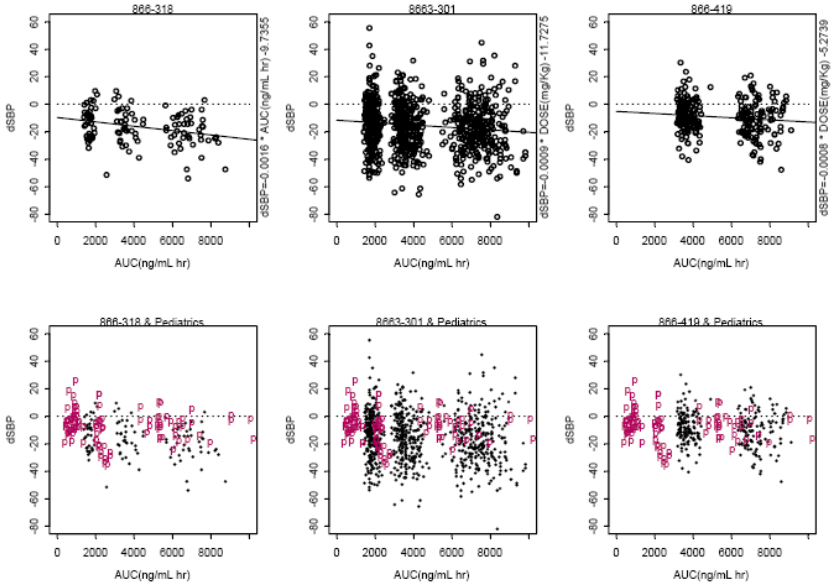


Figure 14 and Tab1e 7 show the blood pressure lowering effect at peak plasma concentration (1-3 hours post dose) compared to the baseline and steady state trough pre-dose measurements. As shown in Figure 14, olmesartan lowered systolic and diastolic blood pressure from baseline. The intra-subject changes in peak blood pressure compared to the steady state trough predose level were -2.68 ± 7.77 and -0.59 ± 9.26 mmHg for diastolic and systolic blood pressure, respectively.

Figure 14- Effect of peak olmesartan exposure on diastolic and systolic blood pressure compared to baseline and predose**.**

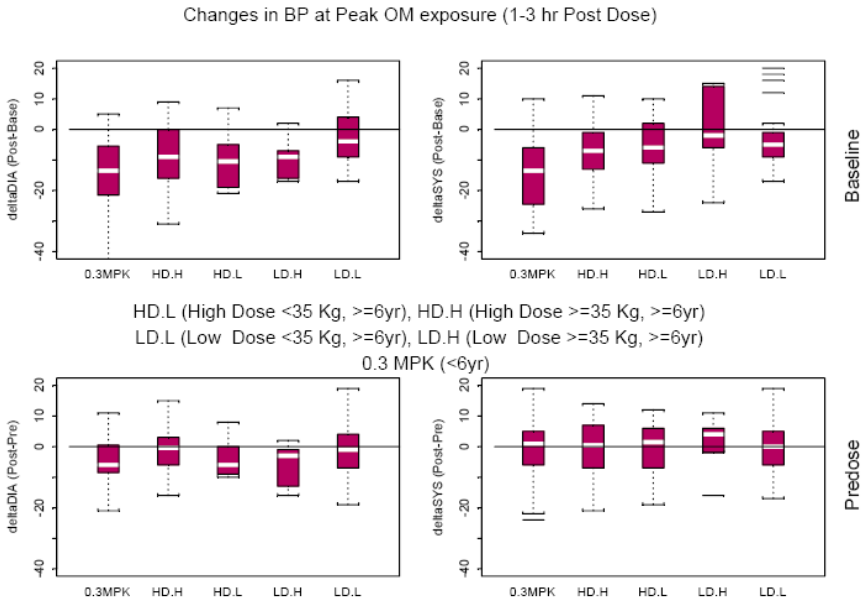


Table 7- Summary of peak, baseline and predose blood pressure and their differences in paediatric patients in cs0866-a-u301 study. Data expressed as mean (sd). The peak measurements were blood pressure at 1-3 hours post administration of the olmesartan on visit 2.2 and/or 2.3. It is noted that 28 subjects had two measurements at 1-3 hour post dose from visits of 2.2 and 2.3.

		Dose Group					
		All	0.3 mg/Kg	2.5 mg	5 mg	20 mg	40 mg
Age			< 6 yrs		≥6 yrs		
Body Weight (Kg)			all	<35	≥35	<35	≥35
Subject	n	75	18	5	26	6	20
Observation	n	103	25	7	35	10	26
Peak blood pressure (A)				(mmHg)			
	mean	65.72	58.21	65.57	70.6	63	67.15
Diastolic	(SD)	(11.64)	(9.15)	(11.21)	(12.65)	(7.45)	(10.49)
	mean	115.85	100.33	117.57	124.03	108	121.73
Systolic	(SD)	(15.05)	(13.3)	(7.68)	(12.87)	(8.59)	(10.01)
Baseline blood pressure (B)							
	mean	73.74	71.68	75.43	73.33	73.4	76
Diastolic	(SD)	(9.5)	(8.3)	(9.68)	(11.75)	(4.45)	(8.81)
	mean	122.69	115.16	117.86	127.27	114.2	128.92
Systolic	(SD)	(10.96)	(10.6)	(7.17)	(9.74)	(5.75)	(8.13)
Predose blood pressure (C)				(mmHg)			
	mean	68.46	63.6	71	72.26	66.9	67.92
Diastolic	(SD)	(9.92)	(7.8)	(14.08)	(10.34)	(7.62)	(9.05)
	mean	116.55	102.32	116.57	124.51	108.7	122.54
Systolic	(SD)	(14.47)	(13.63)	(9.71)	(11)	(11.49)	(9.42)
(A-B)				(mmHg)			
	mean	-8.32	-13.54	-9.86	-3.12	-10.4	-8.92
Diastolic	(SD)	(10.48)	(11.51)	(6.44)	(9.04)	(9.12)	(10.2)
	mean	-6.99	-14	-0.29	-3.67	-6.2	-6.84
Systolic	(SD)	(11.32)	(13.29)	(13.4)	(8.9)	(10.74)	(9.1)
(A-C)				(mmHg)			
	mean	-2.68	-4.92	-5.43	-1.66	-3.9	-0.77
Diastolic	(SD)	(7.77)	(8.13)	(6.55)	(8.44)	(6.03)	(7.06)
	mean	-0.59	-0.92	1	-0.49	-0.7	-0.81
Systolic	(SD)	(9.26)	(10.92)	(8.68)	(8.69)	(9.75)	(8.98)

cf) 2 BLQ measurements were recorded as olmesartan plasma concentrations at 1-3 hour postdose condition.

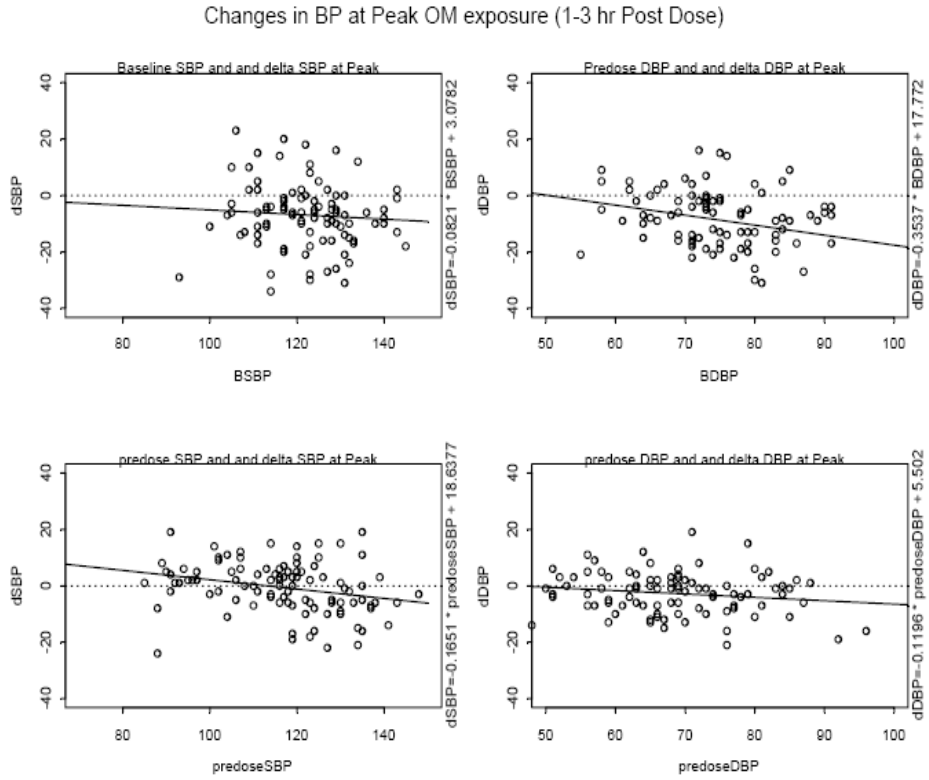
The intra-subject changes in peak blood pressure to baseline measurement were -8.32 ± 10.48 and -6.99 mmHg ± 11.32 mmHg for diastolic and systolic blood pressure, respectively (Table 7). It is noted that the blood pressure lowering effects were apparently similar in paediatric patients at 0.3 mg/kg (below 6 years old) compared to high dose in paediatric subjects ages at and above 6 years old (about or higher than 0.4 mg/kg). The observation was consistent with the saturable adult blood pressure lowering effect shown in Eq 1, which shows blood pressure lowering effect of the olmesartan in adult population.

$$DEff_{OM} = 13*(1+Black*-0.411)*\left(\frac{WTKG}{70}\right)^{-0.686}*\left(\frac{Age}{60}\right)^{-0.424}*\left(\frac{Baseline}{100}\right)^{1.73}*\frac{AUC_{OM}}{AUC_{OM}+1930} \quad \text{Eq .1}$$

Where $DEff_{om}$, Black, WTKG, AGE, Baseline and AUC_{om} represents, blood pressure lowering effect (Baseline-at the time of measurement), African American subjects, bodyweight in kilogram, age in years, baseline blood pressure measurements, and exposure of olmesartan, respectively.

Figure 15 shows the relationship between baseline, steady state predose blood pressure, and blood pressure lowering effect at the steady state peak (dSBP and dDBP). As shown in the figure, paediatric subjects with higher blood pressure at baseline and predose showed larger blood pressure decline compared to lower baseline blood pressure, which is consistent with previous observation in blood pressure lowering effects in adults (Eq.1).

Figure 15- Baseline, predose blood pressure and peak PD effects**.**



The terminal half lives of olmesartan in paediatric study was 9 hrs (mean) in range of 4.1 to 17.1 hrs while adult terminal half life was approximately 13 hours (olmesartan label). The terminal half lives of olmesartan were unlikely to be dependent upon body weight.

For calculation of clearance for each of the weights (20, 35, 70 kg) the equation below was used:

$$CL_i[L/h] = 5.11 * \left(\frac{WT[kg]_i}{48} \right)^{0.803} \qquad \text{Eq. 2}$$

To match the adult dose of 20 mg, the recommended dosage for the body weights 35 kg and above is 20 mg. The recommended dose for subjects between 20 kg and 35 kg is 10 mg. The adult-paediatric comparisons showed similar exposures at similar weights. As the mean body weight of adult population is near 70 kg, the paediatric population with body weights above 35 kg would yield similar olmesartan exposure compared to adults administered the same dose. Based on Eq 2, the clearances for 20 to 35 kg for paediatric subjects to 70 kg subjects would be 37 to 57 %. As the clearance of the paediatric population with body weight between 20 and 35 kg would be about half of the paediatric population weight 70 kg, lowering the dose by half (e.g., 20 to 10 mg) would result in similar olmesartan exposures for these subjects in comparison to the 20 mg dose in adults. This recommendation is further supported by a comparison of paediatric and adult exposures from several different studies via posthoc estimation (Fig 1). Paediatric populations with very low body weight (below 20 kg) have comparative higher body weight-adjusted clearance, and the differences become stronger as body weight declines further. In order to produce similar exposure to adults given 20 mg, paediatrics with body weight 9-20 kg should be administered about 0.4-0.5 mg/kg dosage.

No direct comparison of the blood pressure exposure-response between adult and paediatric population was feasible due to different study design. However, the paediatric blood pressure lowering effect overlapped with adult observations, indicating overall similarity of the olmesartan blood pressure lowering effect when body weight adjusted dose is taken into account. However it should be noted that the blood pressure lowering effect at dose level of 0.3 mg/kg (paediatric population with age below 6 years) showed similar lowering compared to high dose group with age above 6 years.

Pharmacokinetic assessor's comment: The applicant is not able to establish a directly comparable PKPD relationship for Olmesartan between adult and paediatric patients. The applicant has, however, provided evidence that there is a relationship between blood pressure lowering effect and weight-normalised dose for paediatric patients and that there is considerable overlap in this relationship between adult and paediatric patients.

This provides a justification for proposed starting doses of 10 mg in children ≤ 35 Kg, and 20 mg ≥ 35 Kg will provide mean exposures similar to that in adults starting dose of 20 mg. This dosing regimen provides an option for up-titration based on the response. Since the median weight in a 6 year old is about 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.

2.4 Study CS0866-A-U301- Efficacy and Safety: A Dose-ranging Study to evaluate the Safety and Efficacy of Olmesartan Medoxomil in Children and Adolescents with Hypertension

➢ Description

The BP lowering effect and safety of OM was evaluated in paediatric subjects. This was a randomized, multicenter, double-blind, parallel-group, prospective dose-ranging study in subjects 1 to 16 years of age. Specifically, the effects of OM, at high-dose and low-dose regimens, on seated systolic blood pressure (SeSBP) and seated diastolic blood pressure (SeDBP) was studied in paediatric 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 an 11-month, open label extension period.

Population pharmacokinetic and exposure-response relationships of OM in paediatric patients were evaluated.

➢ Methods

- Objective(s)

Efficacy:
The primary objective of the study was to assess a dose response relationship in SeSBP or SeDBP in subjects 6 to 16 years of age with high blood pressure or hypertension, receiving high and low doses of OM.

The secondary objectives, the efficacy of OM in subjects 1 to 5 years of age with high blood pressure were also evaluated.

Population pharmacokinetic:
To establish the pharmacokinetic and exposure-response relationships of OM in paediatric patients and to compare it with the results observed in adults in prior studies.

Safety
Safety was assessed throughout the study and included monitoring of adverse events (AEs), concomitant medications, and routine laboratory safety tests, vital signs, and physical examination findings.

- Study design

The study comprised of four periods. Period I was a wash-out period from Week -1 to randomization. Subjects were randomized to treatment sequences carried through the remainder of the study. Period II was a double-blind, dose-ranging period for Cohorts A and B, where subjects received either low-dose or high-dose OM once daily. In Cohort C, all subjects received 0.3 mg/kg OM per day. Period III was a placebo-controlled withdrawal period beginning at Week 4 and ending after 1 or 2 weeks, depending on the 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 are illustrated in Figures 16 & 17.

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

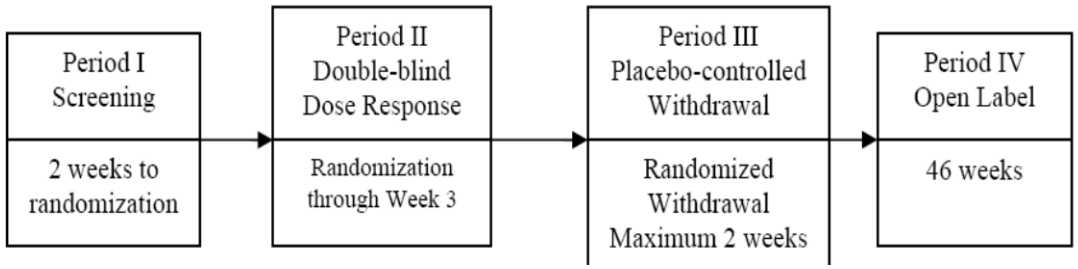
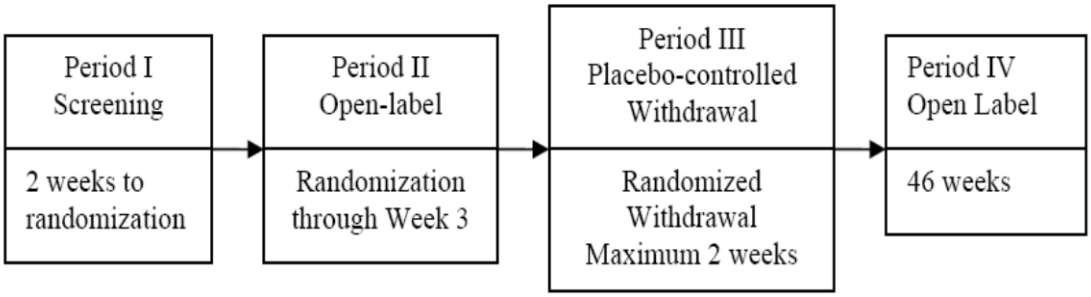


Figure 17- Study Design for Cohort C (Subjects 1 to 5 Years Old)



All other antihypertensive medications were discontinued at screening for a maximum of 14 days. For Cohort C discontinuation of calcium channel blockers and/or diuretics was optional at the discretion of the investigator.

In addition, a total of 3 blood samples were taken for population pharmacokinetic (PK) assessments from some of the subjects.

Safety was assessed throughout the study and included monitoring of adverse events (AEs), concomitant medications, and routine laboratory safety tests, vital signs, and physical examination findings.

- Study population /Sample size

Efficacy Population
Subjects were enrolled into one of three cohorts based on age and race:

Cohort A: 6-16 years old, mixed race
Cohort B: 6-12 years old, Black or African descent
Cohort C: 1-5 years old, mixed race

Approximately 15% of the subjects in Cohort A were of Black or African descent. Subjects 1 to 5 years of age were enrolled into Cohort C regardless of race. Subjects not taking any hypertension medications at the initial screening must also have met one of following 2 criteria before randomization:

• SeSBP ≥ 95th percentile but ≤ 2 standard deviations (SDs) above the 99th percentile for gender and height-for-age
• SeSBP ≥ 90th percentile for subjects who had type 1 or 2 diabetes mellitus, glomerular kidney disease, or a family history of hypertension.

Safety Population
The safety population consists of all subjects who took at least one dose of study drug.

- Treatments

Treatment was administered based on age and weight as described in the table 8.

Table 8- Treatments Administered

Cohort A and Cohort B				
		Period II	**Period III**	**Period IV[a]**
Weight	**Dose Group**	**Dosing Regimen**		
> 20 kg and < 35 kg	Low dose	2.5 mg OM, p.o., daily	2.5 mg OM or placebo, p.o. daily	10 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 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**	**Period III**	**Period IV[c]**
		Dosing Regimen		
		0.3 mg/kg	0.3 mg/kg or placebo	0.3 mg/kg

Treatments for Periods II and III were a compounded suspension of OM or matching placebo (Period III only) to be taken by mouth at the same time ± 2 hours each day. In Period IV, subjects in Cohorts A and B could substitute OM tablets for the suspension.

For subjects 1 to 5 years of age, the extemporaneous suspension was administered at a dosage of 0.3 mg/kg. In Period IV, doses could be doubled from starting daily doses of 10 mg, 20 mg or 0.3 mg/kg to 20 mg, 40 mg and 0.6 mg/kg respectively.

Assessor's comment: On both sides of the 35 kg weight cut off point, the difference between the low and high dose is very large, practically at either end of dosing spectrum with no middle dose.

- Outcomes/endpoints

The primary analysis was to assess a dose response in trough SeSBP or SeDBP after three weeks of treatment (the end of Period II) in Cohort A, Cohort B, and Cohort A + B (subjects 6 to 16 years of age).

The Secondary analyses:

- To asses the effect of withdrawal of OM on trough SeSBP and SeDBP in Cohort A, Cohort B, and Cohort A + B (subjects 6 to 16 years of age).
- To asses the efficacy of OM (and withdrawal of it) with in subjects 1 to 5 years of age with high blood pressure.

Pharmacokinetic/Pharmacodynamics endpoints

To establish the pharmacokinetic and exposure-response relationships of OM in paediatric patients and to compare it with the results observed in adults in prior studies.

To determine whether the current dataset is sufficient to evaluate the pharmacokinetic and dose/exposure-response relationships in paediatrics.

Safety endpoints

Monitoring of adverse events (AEs) throughout the study, concomitant medications, and routine laboratory safety tests, vital signs, and physical examination findings.

Developmental evaluation prior to active treatment in Period II and at the end of Period IV utilizing a standard questionnaire.

- Statistical Methods

The primary analysis was carried out using a linear regression model:
Change from baseline in SeSBP (or SeDBP) = a + bDose + e
where "a" is the intercept, "b" is the slope, and "e" is the random error. In the model, "Dose" was either the fixed OM dose (low or high) or the weight-adjusted OM dose (mg/kg). The null hypothesis of b=0 was tested. The analysis was performed on the BP data for Cohorts A (all "American" population), B (all Black population), and A+B.

If a dose response was not demonstrated in Period II, an analysis of covariance (ANCOVA) using Period III baseline as a covariate and treatment and country as main effects was to be performed for the change from Period III baseline to the end of Period III in SeSBP and SeDBP. The analysis for the change in SBP/DBP from the Period III baseline to the end of Period III utilized a planned ANCOVA model, regardless of the results from the primary analysis in Period II. Country and treatment interaction were explored. The difference between OM and placebo for the LS mean changes in SeSBP/SeDBP was estimated and the corresponding 95% CI was calculated.

Cohort C: The ANCOVA model with treatment and country as factors and the Period III baseline value as a covariate. The 95% CI for the LS means difference between OM and placebo was calculated.

- **Results**

  - Recruitment/ Number analysed

Among the 502 subjects screened, 362 (72%) were randomized into the three cohorts (Cohort A: 190, Cohort B: 112, Cohort C: 60).

  - Baseline data

Key demographic and baseline characteristics for the randomized subject population are summarized by cohort in Table 9.

Table 9- Demographic & Baseline Characteristics – All Randomized Subjects

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

Assessor's comment: The average age for cohort A+B (6-16 years old) is 12.3 years with mean body weight of 71 kg. The majority of children in this age group have adult weight or are obese, which is not surprising as obesity is a recognized comorbidity of primary hypertension.

In 6-16 years old the number of children with primary hypertension is three times more than secondary hypertension and in the 1-5 years old the number of children with secondary hypertension is double that of primary hypertension. The difference in prevalence of the two types of hypertension in different age groups is expected since primary hypertension is rare in infants and young schoolchildren, but increase as children grow in to adolescents.

- Efficacy results

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

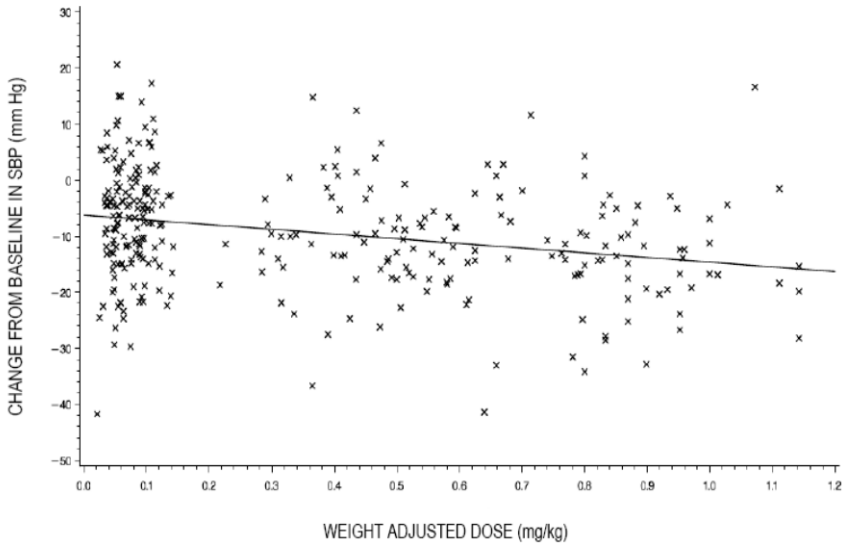
Period II, Double blind, dose response, 3 weeks; Systolic Blood Pressure Analysis

A statistically significant OM dose response for SeSBP was observed in all cohorts. The dose response remained statistically significant when the analysis adjusted the OM dose for baseline body weight (Table 10 & Figure 18).

Table 10- Effect of OM Dose (Weight adjusted) on Change From Baseline in SeSBP (mm Hg) at Week 3

		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

Figure 18- Linear Regression of Weight-adjusted Dose for Change from Baseline in SeSBP in Cohort A + B at week 3 with LOCF



For Cohort A + B, change in SeSBP from baseline to the end of Period II (at week 3) for Black and Non-black subgroups was summarized (Table 11). Mean reductions were consistently greater in the high-dose OM group than in the low-dose OM group for both subgroups. Non-Black appeared to have a greater response to OM treatment than Black.

Table 11- Black and Non-Black Mean Change From Baseline in SeSBP (mm Hg) at week 3

		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)

Assessor's comment: The efficacy results for SeSBP in the 6-17 years old can be summarized as:

- A statistically significant OM dose response was observed for SeSBP in Cohort A (mixed race, p = 0.0008), Cohort B (Black children only, p = 0.0032), and A + B (p < 0.0001) - This significance was maintained when the OM dose was adjusted for subjects baseline body weight.
- The mean changes in SeSBP from the study baseline to the end of Period II were -7.76 mm Hg and -12.58 mm Hg for low and high OM doses, respectively, in cohort A, and -4.73 mm Hg and -10.68 mm Hg for low and high Om doses, respectively, in cohort B.
- Both Black and Non-black subjects demonstrated a dose response. For Non-black subjects, the SeSBP reductions from baseline were -7.78 mm Hg for the low dose and -13.19 mm Hg the high dose. For Black subjects, the reductions were -5.51 mm Hg for the low dose and -10.39 mm Hg for the high dose.

A statistically significant OM dose response in reduction of SeSBP is clearly demonstrated in the 6-17 years old. Hence the primary objective is reached. Both the low and high doses of OM were effective in reducing SeSBP. This efficacy is also of clinical importance as the SeSBP was reduced in the range of 7-13 mmHg in this age group. The lower effect of OM in Black children, ties in with the well documented lower response of adult patient of Black /African race to ARBs (Oparil et al 2005).

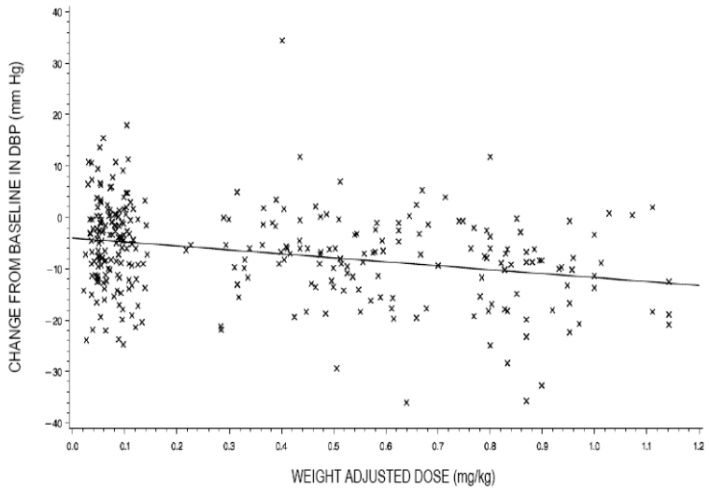
Period II, Double blind, dose response, 3 weeks; Diastolic Blood Pressure Analysis

Table 12 summarizes the linear regression analysis for SeDBP. A statistically significant OM dose response for SeDBP was observed in each of the three cohorts. The dose response remained statistically significant when the analysis adjusted the OM dose for baseline body weight (Table 12 & Figure 19).

Table 12- Effect of OM Dose (Weight adjusted) on Change from Baseline in SeDBP (mm Hg) at Week 3

		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

Figure 19- Linear Regression Analysis on Weight-adjusted Dose for Change from Baseline in SeDBP in Cohort A + B at week 3 with LOCF



For Cohort A + B, change in SeDBP from baseline to the end of Period II for Black and Non-black subgroups were summarized (Table 13). Mean reductions were consistently greater in the high-dose OM group than in the low-dose OM group. However, except for the low dose OM group at Weeks 1 and 2, Non-Black consistently appeared to have a greater response to treatment than Black.

Table 13- Black and Non-black Mean Change from Baseline in SeDBP (mm Hg) at week 3

		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)

Assessor's comment: The efficacy results for SeDBP in the 6-17 years old can be summarized as:

- A statistically significant OM dose response was observed for SeDBP in Cohort A ($p = 0.0026$), Cohort B ($p = 0.0125$), and A + B ($p < 0.0001$).
- The mean changes in SeDBP from the study baseline to the end of Period II were -5.52 mm Hg and -9.5 mm Hg for low and high OM doses, respectively, in Cohort A, and -3.49 mm Hg and -7.58 mm Hg for low and high OM doses, respectively, in Cohort B.
- Low and high doses of OM were effective in reducing SeDBP paediatric subjects 6 to 16 years old, regardless of race.

A statistically significant OM dose response in reduction of SeDBP is clearly demonstrated in the 6-17 years old. Hence the primary objective is reached. Both the low and high doses of OM were effective in reducing SeDBP. This efficacy is also of clinical importance as the SeDBP was reduced in the range of 6-10 mmHg in this age group.

Period III, Placebo control, Withdrawal, 2 weeks; Cohorts A, B, and A + B

Although an OM dose response was demonstrated in the primary analysis, a secondary efficacy analysis was performed. This analysis examined BP changes from the Period III baseline to the end of Period III. During Period III, 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 (Table 14).

Table 14- Mean Change in SeSBP & SeDBP (mm Hg) During Period III

		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)
SBP- mean changes at the end of withdrawal phase										
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)
DBP- mean changes at the end of withdrawal phase										
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)

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 (Table 14). 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. LS mean for changes in SeSBP and SeDBP for subjects continuing on OM compared with subjects on placebo are shown below in Table 15.

Table 15- Treatment Comparison for Change in SeSBP and SeDBP (mmHg) in Period III for Cohorts A, B and A + B

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

Assessor's comment: Period II, placebo control, withdrawal, 2 weeks, in the 6-17 years old, results can be summarized as:

- For Cohort A, the mean increase in SeSBP for subjects on OM was 0.43 mm Hg and for subjects on placebo was 4.93 mm Hg. There is a statistically significant rebound effect in the placebo compared to OM group. The difference in LS means between OM and placebo was -3.58 mm Hg (p = 0.0093). This statistically significant effect of OM was also observed for Cohort A + B (-3.16 mm Hg, p = 0.0029).
- For Cohort B (100% Black), mean SeSBP increase (1.37 mm Hg) for subjects on

OM was numerically less than for subjects on placebo (3.79 mm Hg). However, this difference was not statistically significant.

The rebound of BP to the baseline values in the placebo subjects is clear. It is further demonstration of the efficacy of OM in treating hypertension. The fact that cohort B shows non significant changes ties in well with the lower response observed in the Black adults too.

Period IV, Open label, 46 weeks; Cohorts A, B, and A + B

Mean changes from study baseline in SeSBP and SeDBP were analyzed for Period IV. These data are shown by cohort in Table 16 and Table 17, respectively.

Table16- Mean Change from Baseline in SeSBP (mm Hg) During 46 weeks

	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)

Table 17- Mean Change from Baseline in SeDBP (mm Hg) During 46 weeks

	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)

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.

Assessor's comment: In the long term open label phase, paediatric subjects took 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 through out the duration of the study. Numerically, the magnitude of BP reduction was greater for Cohort A than Cohort B. The long term efficacy of OM is consistent with earlier short term (3 weeks) results.

Period II, Double blind, dose response, 3 weeks; - Cohort C (1-5 years old)
Mean changes from study baseline in SeSBP and SeDBP in Cohort C during Period II are shown in Table 18 below. The mean reduction from study baseline Cohort C at the end of Period II with the last observation carried forward was -13.31 mm Hg for SeSBP and - 10.42 mm Hg for SeDBP. This was a statistically significant change from baseline.

Table 18- Mean Change From Baseline in SeSBP and SeDBP (mm Hg) at week 3- Cohort C

	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)

Assessor's comment: In children 1-5 years of age only one dose of 0.3 mg/kg/day was tested, therefore the dose/response relationship has not been investigated. Over three weeks (Period II), OM treatment decreased mean SeSBP by 13.31 & SeDBP by 10.42 mm Hg. Although it is claimed that there is statistically significant reduction from baseline the p values are not provided.

Period III, Placebo control, Withdrawal, 2 weeks; Cohort C
From Period III baseline to the end of the withdrawal phase, 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 but the differences in the LS means were not statistically significant.

Similarly the mean SeDBP values increased for both subjects continuing on OM (0.31 mm Hg) and subjects on placebo (3.77 mm Hg), but the differences in the LS means were not statistically significant due to the small sample size. The results of this phase are summarized in the table below:

Table 8.15: Change from Period III Baseline in SeSBP and SeDBP (mm Hg)- Cohort C

			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)

Assessor's comment: The mean increase in SeSBP for subjects on OM was 1.36 mm Hg and for subjects on placebo was 4.95 mm Hg. There is a slight rebound effect in the placebo compared to OM group (not statistically significant), which may be due to the small sample size. The rebound effect of high BP in the placebo patients is unclear. It does not support efficacy of the OM in this age group.

Period IV, Open label, 46 weeks; Cohorts C

Mean changes from study baseline in SeSBP and SeDBP in Cohort C were analyzed for Period IV and the data are shown in Table 19. 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 19- Mean Change from Baseline in SeSBP & SeDBP (mmHg) During 46 weeks

		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)

Assessor's comment: Over the 46 weeks of open-label treatment with OM 0.3 to 0.6 mg/kg/day (up and down titrations allowed), reduced both mean SeSBP and SeDBP relative to baseline. The magnitude of reduction is in the range of 10-15 mmHg. However it is not known if this reduction is statistically significant or not and no p values have been provided.

Statistical Assessment of Efficacy data

In general the statistical methods described for the analysis of the SeSBP and SeDBP are considered acceptable. The Statistical Analysis Plan specified that if the primary objective was achieved in Period II demonstrating a dose response, the analysis of the data from the Period III randomised withdrawal would not be conducted. However, although a dose response was seen, the Period III data were formally analysed. For Cohorts A, B and A+B the change from the Period III baseline in both SeSBP and SeDBP were analysed using a pre-specified ANCOVA model including treatment and country as factors and the baseline as a covariate. This analysis is both necessary and appropriate.

As the original randomisation of subjects into Cohort A was stratified by age into two strata (6-12 years and 13-16 years) the ANCOVA model should be adjusted by including this stratification variable as a covariate (see CPMP/EWP/2863/99: Points to consider on adjustment for baseline covariates). Although randomisation into Cohort B was not stratified in this way, the applicant obviously considered that balance in terms of age was important in the original population and the analysis should be repeated including age in the model.

Missing data at Week 5 were imputed using the LOCF (last observation carried forward) method. Although this approach has not been justified and would not usually be considered sufficient in these circumstances, as very few patients failed to complete the study, it is unlikely that this method of handling the missing data will introduce bias in favour of the active treatment.
The results of the analysis of Cohort A and the combined Cohort A+B for Period III demonstrated statistically significant differences between OM and placebo with an estimated difference in both SeSBP and SeDBP of approximately 3mmHg. As Cohort B included only 112 randomised patients there was insufficient power to demonstrate statistical significance. However it is noted that the estimated change from baseline for the OM patient group showed an increase in both SBP and DBP of 1.30 and 1.93 mmHg respectively while the change for the placebo group was similar as that seen for Cohort A. As 35 black patients are included in Cohort A, an assessment of efficacy in the black subgroup should be based on analysis of Cohort B and these additional 35 patients from Cohort A.
The analysis of change from baseline in SeSBP and SeDBP for patients in Cohort C did not achieve statistical significance probably because of the small number of patients (n=59). However, the estimated differences between OM treatment and placebo in SeSBP was -2.8 mmHg and in SeDBP -2.92 mmHg. This would suggest that the treatment effect was similar in younger children to that for the older age group.

- **Safety results**

The safety population consists of all subjects who took at least one dose of study drug.

Adverse Events during Period II (3 weeks double blind) – Cohorts A and B
Common AEs for Period II for Cohorts A and B are defined as TEAEs reported by ≥ 2% of all randomized subjects, as summarized in the Table 20 below.

Table 20- Treatment Emergent Adverse Events Reported by ≥ 2% of Subjects in Cohorts A & B during Period II - All Randomized Subjects

This table is split over 2 pages	Period II treatment n (%) of subjects[a]			
	Cohort A		Cohort B	
MedDRA system organ class Preferred term	Low OM dose[b] N=95	High OM dose[c] N=95	Low OM dose[b] N=56	High OM dose[c] N=56
Number of subjects (%) with at least one TEAE	**41 (43.16)**	**45 (47.37)**	**19 (33.93)**	**16 (28.57)**
Cardiac disorders	**0 (0.00)**	**3 (3.16)**	**0 (0.00)**	**0 (0.00)**
Tachycardia	0 (0.00)	2 (2.11)	0 (0.00)	0 (0.00)
Gastrointestinal disorders	**11 (11.58)**	**10 (10.53)**	**3 (5.36)**	**6 (10.71)**
Abdominal pain	0 (0.00)	2 (2.11)	0 (0.00)	1 (1.79)
Abdominal pain upper	5 (5.26)	3 (3.16)	0 (0.00)	1 (1.79)
Diarrhea	2 (2.11)	1 (1.05)	0 (0.00)	0 (0.00)
Nausea	1 (1.05)	2 (2.11)	0 (0.00)	1 (1.79)
Toothache	0 (0.00)	0 (0.00)	1 (1.79)	2 (3.57)
Vomiting	3 (3.16)	1 (1.05)	1 (1.79)	0 (0.00)
General disorders and administration site conditions	**6 (6.32)**	**10 (10.53)**	**2 (3.57)**	**2 (3.57)**
Chest pain	2 (2.11)	1 (1.05)	0 (0.00)	0 (0.00)
Fatigue	0 (0.00)	3 (3.16)	2 (3.57)	1 (1.79)
Pyrexia	4 (4.21)	4 (4.21)	0 (0.00)	1 (1.79)

This table is split over 2 pages MedDRA system organ class Preferred term	Period II treatment n (%) of subjects[a]			
	Cohort A		Cohort B	
	Low OM dose[b] N=95	High OM dose[c] N=95	Low OM dose[b] N=56	High OM dose[c] N=56
Infections and infestations	**15 (15.79)**	**12 (12.63)**	**8 (14.29)**	**6 (10.71)**
Influenza	0 (0.00)	1 (1.05)	2 (3.57)	0 (0.00)
Nasopharyngitis	4 (4.21)	1 (1.05)	2 (3.57)	1 (1.79)
Pharyngitis	2 (2.11)	4 (4.21)	0 (0.00)	0 (0.00)
Respiratory tract infection	1 (1.05)	2 (2.11)	0 (0.00)	0 (0.00)
Upper respiratory tract infection	4 (4.21)	7 (7.37)	2 (3.57)	0 (0.00)
Viral infection	2 (2.11)	0 (0.00)	0 (0.00)	0 (0.00)
Musculoskeletal and connective tissue disorders	**4 (4.21)**	**5 (5.26)**	**2 (3.57)**	**1 (1.79)**
Back pain	2 (2.11)	2 (2.11)	1 (1.79)	0 (0.00)
Nervous system disorders	**9 (9.47)**	**23 (24.21)**	**3 (5.36)**	**5 (8.93)**
Dizziness	2 (2.11)	9 (9.47)	0 (0.00)	1 (1.79)
Headache	7 (7.37)	14 (14.74)	3 (5.36)	5 (8.93)
Somnolence	2 (2.11)	2 (2.11)	0 (0.00)	0 (0.00)
Psychiatric disorders	**2 (2.11)**	**3 (3.16)**	0 (0.00)	0 (0.00)
Insomnia	2 (2.11)	1 (1.05)	0 (0.00)	0 (0.00)
Respiratory, thoracic and mediastinal disorders	**12 (12.63)**	**5 (5.26)**	**4 (7.14)**	**2 (3.57)**
Epistaxis	2 (2.11)	0 (0.00)	1 (1.79)	0 (0.00)
Pharyngolaryngeal pain	6 (6.32)	1 (1.05)	0 (0.00)	0 (0.00)
Productive cough	2 (2.11)	0 (0.00)	0 (0.00)	0 (0.00)
Rhinorrhea	3 (3.16)	2 (2.11)	1 (1.79)	0 (0.00)
Skin and subcutaneous tissue disorders	**1 (1.05)**	**5 (5.26)**	**1 (1.79)**	**1 (1.79)**
Rash	0 (0.00)	2 (2.11)	1 (1.79)	0 (0.00)

In Cohort A, nervous system disorders occurred more often in the high OM dose group compared with the low OM dose group (24.2% vs. 9.5%, respectively). In particular, headache and dizziness had higher incidences in the high OM dose group. The most frequently occurring TEAEs in the low OM dose group in Cohort A were upper abdominal pain (5.3%), headache (7.4%), and pharyngolaryngeal pain (6.3%). In the high OM dose group, they were headache (14.7%), dizziness (9.5%), and upper respiratory tract infection (7.4%). These events were not reported in the low OM dose group.

In Cohort B, the low and high OM groups had approximately equal percentages of subjects with TEAEs with no obvious imbalance for any system organ class. An increased incidence of headache in the high OM dose group was also seen in Cohort B, but it was not as great as in Cohort A.

Headache was the only AE that occurred in 10% or more of subjects in either dose group.

Overall during Period II, within each cohort, the percentages of subjects with 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). Overall, the majority of TEAEs were of mild or moderate intensity and considered unrelated or unlikely related to study medication.

Assessor's comment: During the 3 weeks of double blind phase (period II), the number of treatment emergent AEs were similar in both low (43.2 %) dose and high (47.4%) OM doses in cohort A. This pattern was also seen in cohort B (Low dose 33.9%) and (high dose 28.6%).

However the nervous system disorders occurred almost twice as many in the high OM dose group (24.2%) than in the low OM dose group (9.5%).

Headache was the most common AE and occurred in 10% or more of subjects in either dose group. The most frequently occurring TEAEs in Cohort A were upper abdominal pain, headache, and pharyngolaryngeal pain, dizziness, and upper respiratory tract infection, which are all known adverse events associated with olmesartan.

In Cohort B, the low and high OM doses seem to have no effect on the type or severity of the TEAEs. Interestingly the occurrence and severity of AEs in the children of Black origin seem to be half than those of the mixed race cohort.Overall, the majority of TEAEs in both cohorts were of mild or moderate intensity.

Adverse Events during Period III (2 weeks withdrawal) – Cohorts A & B

In Cohort A, TEAEs occurred in a slightly greater percentage of subjects taking high dose OM (39.6%) versus either low dose OM (31.1%) or placebo (approximately 30%). In Cohort B, the percentages of subjects with TEAEs in the OM and placebo dose groups were similar (approximately 15% for high dose OM or placebo and 11.1% for low dose OM).

In Cohort A, general disorders and administration site conditions occurred more often in the high OM dose group (8.3%) compared with its corresponding placebo withdrawal group (0%). Infections and infestations occurred more frequently in the Cohort A placebo groups (13.6% in the low dose placebo group and 11.1% in the high dose placebo group) than in either OM group or the Cohort B placebo groups.

Headache and cough were the only events that occurred in more than 5% of subjects taking either low dose or high dose OM. There were also more respiratory, thoracic and mediastinal disorders among subjects taking OM (11.1% to 14.6%) compared with subjects on placebo (2.2% to 4.6%).

Assessor's comment: The type, severity and occurrence of adverse events in both high and low doses of OM are similar to the ones seen during the 3 weeks of period II. Interestingly the number of AEs in the placebo group (30%) is rather high and close to that of the treatment groups (31-39%).

In Cohort A during Period III, one placebo-treated subject had a severe BP increase that was considered possibly related to the study drug by the investigator. The subject discontinued study drug due to this TEAE.

Adverse Events during Period IV (46 weeks open label) – Cohorts A and B
Overall during Period IV, 65.5% of subjects in combined Cohort A+B experienced a TEAE. The percentage of subjects with a TEAE was higher in Cohort A (71.9%) than in Cohort B (54.4%). The majority of TEAEs were mild or moderate in intensity. TEAEs occurring in any treatment group for Cohorts A and B during Period IV are summarized in Table 21 below.

Table 21- TEAEs Reported by ≥ 2% of Subjects for Cohorts A and B during Period IV - All Randomized Subjects

	n (%) of subjects[a]	
MedDRA system organ class Preferred term	**Cohort A N=178**	**Cohort B N=103**
Number of subjects (%) with at least one TEAE	**128 (71.91)**	**56 (54.37)**
Gastrointestinal disorders	**29 (16.29)**	**19 (18.45)**
Abdominal pain upper	10 (5.62)	9 (8.74)
Diarrhea	2 (1.12)	3 (2.91)
Nausea	4 (2.25)	4 (3.88)
Vomiting	11 (6.18)	7 (6.80)
General disorders and administration site conditions	**26 (14.61)**	**12 (11.65)**
Chest pain	5 (2.81)	4 (3.88)
Pyrexia	16 (8.99)	2 (1.94)
Infections and infestations	**76 (42.70)**	**22 (21.36)**
Ear infection	6 (3.37)	1 (0.97)
Gastroenteritis	4 (2.25)	0 (0.00)
Influenza	10 (5.62)	4 (3.88)
Malaria	0 (0.00)	3 (2.91)
Nasopharyngitis	16 (8.99)	4 (3.88)
Pharyngitis	7 (3.93)	0 (0.00)
Sinusitis	6 (3.37)	3 (2.91)
Upper respiratory tract infection	20 (11.24)	3 (2.91)
Urinary tract infection	4 (2.25)	0 (0.00)
Injury, poisoning and procedural complications	**17 (9.55)**	**3 (2.91)**
Joint sprain	5 (2.81)	1 (0.97)
Investigations	**8 (4.49)**	**5 (4.85)**
Blood creatine phosphokinase increased	1 (0.56)	3 (2.91)
Musculoskeletal and connective tissue disorders	**13 (7.30)**	**7 (6.80)**
Pain in extremity	1 (0.56)	3 (2.91)
Nervous system disorders	**35 (19.66)**	**21 (20.39)**
Dizziness	10 (5.62)	2 (1.94)
Headache	30 (16.85)	18 (17.48)
Reproductive system and breast disorders	**5 (2.81)**	**2 (1.94)**
Dysmenorrhea	4 (2.25)	2 (1.94)
Respiratory, thoracic and mediastinal disorders	**46 (25.84)**	**18 (17.48)**
Asthma	6 (3.37)	2 (1.94)
Cough	24 (13.48)	7 (6.80)
Epistaxis	3 (1.69)	5 (4.85)
Nasal congestion	9 (5.06)	2 (1.94)
Pharyngolaryngeal pain	12 (6.74)	3 (2.91)
Rhinorrhea	4 (2.25)	2 (1.94)

A greater percentage of subjects in Cohort A (42.7%) experienced infections and infestations compared with Cohort B (21.4%). Examples of these events include upper respiratory tract infection, nasopharyngitis, influenza, pharyngitis, sinusitis, ear infection, gastroenteritis, and urinary tract infections. Other conditions often associated with these infections such as cough, nasal congestion, pharyngolaryngeal pain, rhinorrhea, and pyrexia also had higher incidence rates in Cohort A compared with Cohort B. Most subjects with cough as a TEAE had comorbidities such as those listed above. None of the subjects with cough were taking ACE inhibitors. Dizziness was experienced by 5.6% of subjects in Cohort A and 1.9% of subjects in Cohort B.

Seven (3.9%) subjects in Cohort A and 3 (2.9%) subjects in Cohort B had severe TEAEs, including one report each of ophthalmoplegia, nausea, vomiting, pyrexia, bronchitis, arthralgia, systemic lupus erythematosus, headache, anxiety disorder, depression, suicide attempt, nephrotic syndrome, asthma, and epistaxis. There were two reports of severe sinusitis. Severe TEAEs in Cohort B included one report each of systemic lupus erythematosus, nephritic syndrome, and asthma.

Assessor's comment: In children 6 to 17 years old, during the 46 weeks of the open label phase more AEs have emerged in cohort A+ B, which is not surprising as the long term administration of a drug increases opportunity for the AEs to surface. There were higher number of AEs related to upper respiratory infections (n=23), including ear infection (n=7), and pyrexia (n=18), but they are all common childhood diseases and labelled in the SmPC.

There was no comparison of type, severity and frequency of AEs between high and low doses OM groups during the long term open label arm of the study.

In cohort B there were 3 cases of Malaria, which may have little to do with the OM treatment, but need to be addressed by the applicant. Similarly there were 8 cases of asthma and 6 cases of joint sprain in the combined A+B cohort that may have been confounded by the concurrent condition or accidental, but need to be clarified by the applicant.

In the 281 children that received at least one dose of OM, there are 6 cases of dysmenorrhoea and 8 cases of epistaxis in the combined A+B cohort. These adverse events have not been reported, nor included in the SmPC in adults and seem to be treatment emergent in children/adolescents only. Therefore they should be included in the section 4.8 under the paediatric heading.

Two subjects discontinued due to TEAEs (an increase in body mass index [BMI]/metabolic disorder) in Cohort A and one subject due to relapse in systemic lupus erythematosus in Cohort B. Only SLE relapse was considered by the applicant to be related to study drug. No subjects died during the study.

Adverse Events, all periods – Cohort C

During Period II, 18 (30.5%) subjects had at least one TEAE. During Period III, five (17.2%) subjects in the OM group and 8 (28.6%) subjects in the placebo group had at least one TEAE. During Period IV, 46 (80.7%) subjects had at least one TEAE. In Period IV, five (8.8%) subjects had serious AEs. Table 22 below summarizes TEAEs reported for Cohort C during the study.

Table 22- Treatment Emergent Adverse Events Reported by ≥ 2% of Subjects for Cohort C during Period II, III, and IV - Safety Population

This table splits over 2 pages MedDRA system organ class Preferred term	n (%) of subjects[b]			
	Period II OM 0.3 mg/kg N=59	Period III		Period IV N=57 OM[c]
		OM 0.3 mg/kg N=29	Placebo N=28	
Number of subjects (%) with at least one TEAE	**18 (30.51)**	**5 (17.24)**	**8 (28.57)**	**46 (80.70)**
Blood and lymphatic system disorders	**1 (1.69)**	**0 (0.00)**	**1 (3.57)**	**1 (1.75)**
Eosinophilia	0 (0.00)	0 (0.00)	1 (3.57)	0 (0.00)
Gastrointestinal disorders	**3 (5.08)**	**0 (0.00)**	**1 (3.57)**	**10 (17.54)**
Diarrhea	1 (1.69)	0 (0.00)	1 (3.57)	4 (7.02)
Vomiting	0 (0.00)	0 (0.00)	0 (0.00)	3 (5.26)
General disorders and administration site conditions	**3 (5.08)**	0 (0.00)	0 (0.00)	**9 (15.79)**
Pyrexia	3 (5.08)	0 (0.00)	0 (0.00)	7 (12.28)
Infections and infestations	**9 (15.25)**	**2 (6.90)**	**4 (14.29)**	**35 (61.40)**
Bronchitis	1 (1.69)	0 (0.00)	0 (0.00)	4 (7.02)
Bronchopneumonia	1 (1.69)	0 (0.00)	0 (0.00)	2 (3.51)
Gastroenteritis	0 (0.00)	0 (0.00)	0 (0.00)	2 (3.51)
Influenza	1 (1.69)	1 (3.45)	1 (3.57)	3 (5.26)
Laryngitis	0 (0.00)	0 (0.00)	0 (0.00)	2 (3.51)
Nasopharyngitis	1 (1.69)	0 (0.00)	2 (7.14)	2 (3.51)
Otitis media acute	1 (1.69)	0 (0.00)	0 (0.00)	3 (5.26)
Pharyngitis	0 (0.00)	0 (0.00)	0 (0.00)	2 (3.51)
Pharyngotonsillitis	0 (0.00)	0 (0.00)	0 (0.00)	2 (3.51)
Sinusitis	1 (1.69)	0 (0.00)	0 (0.00)	2 (3.51)
Tonsilitis	0 (0.00)	0 (0.00)	0 (0.00)	5 (8.77)
Upper respiratory tract infection	1 (1.69)	1 (3.45)	0 (0.00)	11 (19.30)
Urinary tract infection	0 (0.00)	0 (0.00)	0 (0.00)	4 (7.02)
Varicella	0 (0.00)	0 (0.00)	0 (0.00)	2 (3.51)
Viral infection	0 (0.00)	0 (0.00)	0 (0.00)	3 (5.26)
Viral upper respiratory tract infection	0 (0.00)	0 (0.00)	1 (3.57)	1 (1.75)
Metabolism and nutrition disorders	**0 (0.00)**	**0 (0.00)**	**2 (7.14)**	**2 (3.51)**
Pseudohyperkalemia	0 (0.00)	0 (0.00)	2 (7.14)	0 (0.00)
Nervous system disorders	**1 (1.69)**	**0 (0.00)**	**1 (3.57)**	**1 (1.75)**
Dizziness	0 (0.00)	0 (0.00)	1 (3.57)	0 (0.00)
Headache	1 (1.69)	0 (0.00)	0 (0.00)	1 (1.75)
Somnolence	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Renal and urinary disorders	**0 (0.00)**	**0 (0.00)**	**0 (0.00)**	**9 (15.79)**
Nephrotic syndrome	0 (0.00)	0 (0.00)	0 (0.00)	5 (8.77)
Proteinuria	0 (0.00)	0 (0.00)	0 (0.00)	3 (5.26)
Respiratory, thoracic and mediastinal disorders	**5 (8.47)**	**2 (6.90)**	**1 (3.57)**	**19 (33.33)**
Asthma	0 (0.00)	0 (0.00)	0 (0.00)	6 (10.53)
Cough	3 (5.08)	1 (3.45)	1 (3.57)	5 (8.77)
Epistaxis	0 (0.00)	0 (0.00)	0 (0.00)	2 (3.51)
Pharyngolaryngeal pain	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Rhinitis	0 (0.00)	1 (3.45)	0 (0.00)	4 (7.02)
Rhinitis allergic	2 (3.39)	0 (0.00)	0 (0.00)	1 (1.75)
Upper respiratory tract inflammation	0 (0.00)	0 (0.00)	0 (0.00)	2 (3.51)
Skin and subcutaneous tissue disorders	**1 (1.69)**	**1 (3.45)**	**0 (0.00)**	**5 (8.77)**
Hyperhidrosis	0 (0.00)	1 (3.45)	0 (0.00)	0 (0.00)
Vascular disorders	**0 (0.00)**	**0 (0.00)**	**0 (0.00)**	**2 (3.51)**
Hypertension	0 (0.00)	0 (0.00)	0 (0.00)	2 (3.51)

During Period II, half of the 18 subjects with TEAEs had events classified in the infections and infestations system organ class. However, no single event within this system organ class was experienced by more than one subject. The only TEAEs that occurred in 2 or more of subjects were pyrexia, cough, and allergic rhinitis.

During Period III, the percentage of subjects with TEAEs was higher in the placebo group (28.6%) than in the OM group (17.2%). No TEAE occurred in more than a single subject in the OM group. In the placebo group, only nasopharyngitis and pseudohyperkalemia were reported for more than 1 subject (n=2 each).

During Period IV, TEAEs were reported for 80.70% of subjects. The most frequently occurring TEAEs were upper respiratory tract infection (11 subjects, 19.3%) followed by pyrexia (7 subjects, 12.3%), and asthma (6 subjects, 10.5%). TEAEs experienced by 5 (8.8%) subjects include tonsilitis, nephrotic syndrome, and cough. The nephrotic syndrome TEAEs were relapses in all 5 subjects, who had a history of nephrotic syndrome at study entry. TEAEs experienced by 4 (7.0%) subjects include diarrhoea, bronchitis, urinary tract infection, and rhinitis.

Assessor's comment: In children 1-6 year old, during Period II, 18 subjects (30.5%), during Period III, five subjects (17.2%) in the OM group and 8 subjects (28.6%) in the placebo group had at least one TEAE. During Period IV, 46 subjects (80.7%) had at least one TEAE. The increased number of TEAEs in the long term arm of the study is to be expected as the length of the study (46 weeks) increased the chance of the incidence of TEAEs emerging.

There were higher numbers of AEs including upper respiratory infection (n=11), pyrexia (n=7), Asthma (n=6), urinary tract infection (n=4) and Skin and subcutaneous tissue disorder (n=5) but they are all common childhood diseases or related to the underlying cause of hypertension and are labelled in the SmPC.

Only one strength (0.3 mg/kg) of OM was studied in this cohort and therefore no comparison of AEs between high and low doses is possible.

In the 1-5 year olds there were one case of treatment emergent ovarian cyst, one case of eye haemorrhage and one case of hyperhidrosis that may have been confounded by the concurrent conditions, but need to be clarified by the applicant.

In the 57 children that completed the 46 weeks open label study, there are 2 cases of epistaxis, which is neither reported, nor included in the SmPC in adults and seems to be treatment emergent in children/adolescents only. Therefore should be included in the section 4.8 under the paediatric heading.

There were no severe TEAEs, no discontinuation and no deaths during the study for Cohort C.

Laboratory Values

Haematology

For Cohorts A and B (6 - 16 year olds), by the end of both Period II and IV haemoglobin (Hgb), hematocrit (Hct), and red blood cell (RBC) count were shifted from normal to low, conversely white blood cell (WBC) count and platelets shifted from normal to high.

Cohort A: at the End-of-Study, Hgb, Hct, and RBC values decreased in 13 (7.1%), 13 (7.1%), and 10 (5.4%) subjects, respectively. WBC counts were increased in 21 (11.4%) subjects.

Cohort B: at the End-of-Study, shifts in Hgb, Hct, and RBC were decreased in 9 (8.4%), 8 (7.5%), and 7 (6.5%) subjects, respectively. WBC and platelet counts were increased in 8 (7.5%) and 5 (5.0%) subjects, respectively
For Cohort C (1-5 years of age), there were no significant changes in haematological values at the end of Period II or at the End-of-Study evaluation.

Serum Chemistry
From baseline to both the end of Period II and the End-of-Study, shifts from normal to high were generally observed in potassium, phosphorus, creatine phosphokinase (CPK), and total protein for all cohorts. Also, Cohort C had a few additional clinically relevant shifts.

Cohort A: at the end of the study potassium and phosphorus values were increased in 9 (5.0%) subjects each and CPK in 10 (5.4%) subjects.

Cohort B: at the end of the study, potassium, chloride, calcium, and CPK values were increased in eight (7.9%), six (5.6%), eight (7.5%), and 16 (14.8%) subjects, respectively.

Cohort C: at the end-of-Study; potassium, phosphorus, blood urea nitrogen (BUN), creatinine, AST, and total protein values were increased in 5 (8.9%), 7 (15.2%), 3 (5.2%), 3 (5.2%), 4 (6.9%), and 3 (5.2%) subjects, respectively. bicarbonate values were decreased in from in 11 (19.0%) subjects.

Assessor's comment: The majority of haematology, serum chemistry, and urinalysis parameters are recognized and documented Laboratory adverse events related to OM in adults.

Vital Signs

No clinically relevant changes from baseline were observed for mean heart rate in any cohort in any period of the study.

Neurocognitive Height & Weight Assessments

Developmental milestone assessments were completed by the investigator at study baseline and at the end of the study using a standard questionnaire. 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. Comparisons with peers at the end of the study for Cohorts A and B are provided in Table 23 below:

Table 23- Neurocognitive Assessments for Cohorts A, B, and A + B: End of Study Compared With Study Baseline - All Randomized Subjects

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(%)
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)

In Cohort C, 40 of the 60 randomized subjects (66.7%) had both study baseline and end of study assessments for developmental milestones. All assessed subjects met (75%) or exceeded (25%) developmental expectations at the end of the study. In Cohort C, subjects who were assessed as equal in development to their peers at study baseline and had an end of study

assessment (n=36) were either equivalent to their peers at the end of the study (n=32) or more advanced (n=4). No subject scored worse than their peers at either assessment.

Heights were similar in subjects receiving low dose OM and high dose OM regardless of cohort. Mean increases in height were 4.0-4.1cm for Cohort A and 2.8-3.4 cm for Cohort B. Subjects in Cohort A grew slightly more than those in Cohort B. The subjects in Cohort C had a mean increase in height of 7.4 cm. Two 1-year-old subjects grew 15 cm in the 1 year on study, which may have contributed to the high mean in Cohort C.

Mean increases in weight for Cohort A were 5.4 and 5.5 kg for the low and high OM doses, respectively and for Cohort B were 5.9 and 4.8 kg for the low and high OM doses, respectively. 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 a mean increase in weight of 2.6 kg.

Assessor's comment: At the end of the study the majority of subjects in all three cohorts scored equally well or better than baseline in the standard questionnaire. 46 weeks of treatment with OM, do not appear to have a deteriorating effect on neurocognitive capability of these children. Similarly the height and weight of the children displays a normal growth pattern by the end of the study.

PSUR: Periodic safety updates Report no 15; Period 25 Apr 2009 to 24 Oct 2009

This report refers to olmesartan medoxomil monosubstance as well as to the combinations with hydrochlorothiazide and amlodipine besylate. Overall during the period covered by this report, 791 individual case safety reports were received as spontaneous reports from health care professionals or Regulatory Authorities, as reports from post-authorisation studies and as clinical trial reports or were identified in the scientific literature. No relevant safety issues were identified during this review period. No targeted new safety studies were planned, initiated or continuing during the review period.

Overall, this PSUR does not present severe, unexpected events which would signal, based on their frequency or general characterization, a new risk with olmesartan medoxomil, or the combination products with hydrochlorothiazide and amlodipine.

Discussion on clinical aspects

Efficacy

In the study CS0866-A-U301 the efficacy variables were SeSBP and SeDBP with the primary analysis of the dose response in SeSBP or in SeDBP for subjects 6 - 17 years of age at the end of the three-week, randomized, double-blind Period II. The change in SeSBP or SeDBP from study baseline to the end of Period II was analysed as a dependent variable and a linear regression was fit on both dose and weight adjusted dose to evaluate the dose response.

In children 6-17 years of age a statistically significant OM dose response was observed for SeSBP and SeDBP in Cohort A (mixed race group, $p < 0.0001$ for SBP and DBP), Cohort B (all Black group, $p = 0.0265$ and 0.0084, respectively), and A + B ($p < 0.0001$ for SBP and DBP) in weight-adjusted analysis. The magnitude of reduction in SeSBP from the study baseline to the end of Period II was 7.8 - 12.6 mm Hg, in Cohort A and 4.7 - 10.7 mm Hg, in Cohort B. Similarly the reduction in SeDBP from the study baseline to the end of Period II was 5.5 - 9.5 mm Hg in Cohort A, and 3.5 - 7.6 mm Hg, in Cohort B. Both the low and high doses of OM were effective in reducing SeSBP. This efficacy is also of clinical importance as the SeSBP and SeDBP were

reduced in the range of 4.7-13 mmHg and 3.5-9.5 mmHg respectively in this age group. Hence the primary objective is reached.

The evidence of efficacy in the 6-17 years age group is further substantiated by the statistically significant rebound high blood pressure in the placebo compared to OM group at the withdrawal phase of the study. For Cohort A, the mean increase in SeSBP was 0.43 mm Hg for subjects on OM and 4.93 mm Hg for subjects on placebo. The difference of OM versus placebo in LS mean changes was - 3.58 mm Hg (p = 0.0093). This statistically significant effect of OM was also observed for Cohort A + B (- 3.16 mm Hg, p = 0.0029). Results for SeDBP showed a similar OM treatment benefit. For Cohort B (100% black), the mean SeSBP and SeDBP increase for subjects on OM was numerically less than that for subjects on placebo, but not statistically significant.

Through out the 46 weeks open label phase, treatment with OM maintained similar levels of lowered blood pressure as seen in the phase II (3 weeks), which may rule out developing tolerance during long term use.

All through the 3 phases of this study the magnitude of BP reduction was greater for Cohort A than Cohort B. The lower effect of OM in Black children, ties in with the well documented lower response of adult patient of Black /African race to ARBs. Hypertension is more common, more severe, develops at an earlier age, and leads to more clinical sequelae in black than in white population. Suppressed activity of the renin-angiotensin-aldosterone system (RAAS) and diminished response to antihypertensive drugs that inhibit the RAAS, has been reported in black adults (Oparil et al 2005). In the safety population of this study interestingly the occurrence of AEs in the children of Black origin seems to be half that of the mixed race cohort.

The average age for cohort A+B (6-16 years old) is 12.3 years with mean body weight of 71 kg. The majority of children in this age group have adult weight or are obese, and there are a 3 fold higher number of children with primary than secondary hypertension. This is not surprising since obesity is a recognized comorbidity of primary hypertension and prevalence of primary hypertension increase as children grow in to adolescents.

The evidence of efficacy is not so compelling in the 1-5 years old children. Only one dose of OM, 0.3 mg/kg/day was tested, therefore the dose/response relationship has been not been investigated. Over three weeks (Period II), OM treatment decreased mean SeSBP by 13.31 & SeDBP by 10.42 mm Hg. During the withdrawal phase, a slight rebound of high blood pressure in the placebo compared to OM group was observed, that was not statistically significant. Over the 46 weeks of open-label OM treatment of 0.3 to 0.6 mg/kg/day (up and down titrations allowed), reduced both mean Se SBP and SeDBP relative to baseline. The magnitude of reduction is in the range of 10-15 mmHg. However it is not known if this reduction is statistically significant or not and no p values have been provided. Although the treatment effect of OM was similar in younger children to that for the older age group, but overall the data presented do not support an indication for the OM in the younger age group.

Population PK

Assuming that the post-hoc estimates of individual pharmacokinetic parameters are valid, the applicant's position, that total body weight is likely to be the only significant predictor of CL/F in this population, is accepted. Despite the results of the single dose study (CS0866-A-U102) where Cmax and AUC decreased with age, this effect seems to have normalized by the increase in the number of subjects included in the population pharmacokinetic analysis.

Based on the same assumption, it is agreed that in children 6-17 years of age doses of 10 mg (<35 Kg) and 20 mg (≥35 Kg) result in similar olmesartan exposures between paediatric and adult patients and that exposures in paediatric patients below 6 years old (0.3 mg/Kg) were slightly lower than those in the adult population.

A directly comparable PKPD relationship for Olmesartan between adult and paediatric patients has not been established. The applicant has, however, provided evidence that there is a relationship between blood pressure lowering effect and weight-normalised dose for paediatric patients and that there is considerable overlap in this relationship between adult and paediatric patients.

Safety

Safety monitoring of both PK studies CS0866-A-U101 and CS0866-A-U102 has not given rise to any major concerns, which is not surprising as they are single dose exposure in a small (n=24 each) number of adults and children respectively. The headache, fatigue and gastrointestinal disorders are already known adverse events associated with OM. Study CS0866-A-U301, however had 338 children under safety monitoring for nearly a year and has yielded a higher number and types of adverse events. During the 3 weeks of Double blind phase (period II), the number of treatment emergent AEs were similar in both low and high OM doses in children 6-17 years of age, with exception of dizziness and headache which occurred almost twice as much in the high OM dose group.

During the 46 weeks of the open label phase, in children of all cohorts there were higher numbers of AEs including upper respiratory infection (n=44), pyrexia (n=25), asthma (n=6), urinary tract infection (n=4) and Skin and subcutaneous tissue disorder (n=5). These AEs are common childhood diseases or related to the underlying cause of hypertension and are labelled in the SmPC, and of no particular concern.

In 281 children, aged 6-16 years recruited in this study, there are 6 cases of dysmenorrhoea and 8 cases of epistaxis in the combined A+B cohort. Similarly in the 57, 1-5 years old children that completed the 46 weeks open label study, there are 2 cases of epistaxis. These adverse events are neither reported, nor included in the SmPC in adults and seem to be treatment emergent in children /adolescents only. Therefore they should be included in the section 4.8 under the paediatric heading.

The majority of haematology and serum chemistry, and urinalysis parameters are recognized and documented Laboratory adverse events related to OM in adults. Long term (46 weeks) treatment with OM, does not appear to have a deteriorating effect on neurocognitive capability of these children, nor an effect on their height and weight.

V. RAPPORTEUR'S CONCLUSIONS AT DAY 70

The submitted data provide a statistically and clinically meaningful OM dose response for both systolic and diastolic blood pressure reductions in children aged 6 to 17 years. The evidence for efficacy in children of 1-5 years is not robust enough to allow granting an indication in this paediatric age range.

Assuming that the post-hoc estimates of individual pharmacokinetic parameters are valid, total body weight is likely to be the only significant predictor of CL/F in this population. In children 6-17

years old, the proposed starting doses of 10 mg in children ≤ 35 Kg, and 20 mg ≥ 35 Kg will provide mean exposures similar to that in adults starting dose of 20 mg.

The safety profile of OM in children, in the present data generally resembles that of the adults and most adverse events were of mild and moderate intensity. Adverse events of dysmenorrhoea and epistaxis should be included in the section 4.8 under the paediatric heading.

Overall the data submitted has demonstrated the benefit of olmesartan medoxomil in the 6-17 years old but has not adequately addressed the risk involved with use of OM. There is no juvenile toxicity review, nor a current literature review to address paediatric population specifically.

VI. ASSESSMENT OF RESPONSE TO QUESTIONS

Following the circulation of the preliminary assessment report and receipt of comments from Member States, the MAH was asked to provide the requested information of the first round of questions in 5 October 2010. Many issues have remained unresolved or partially resolved in particular on dosing (POP PK) and safety and a second round of questions were sent to the MAH on 18 July 2011. The clock was not restarted until the response to this was received and assessed. Below is the assessment of both sets of questions and responses:

From the Rapporteur:

Question 1- A literature search/ review of the existing juvenile toxicological studies.

APPLICANT'S RESPONSE
The applicant performed a search in the PubMed literature database. There are no existing published toxicology studies in juvenile animals with olmesartan medoxomil.

Assessor's comment: The applicant has carried out a further literature search and has not found any other toxicology studies in juvenile animals with olmesartan medoxomil.

Issue resolved.

Question 2- A full data set for a toxicological investigation which meets regulatory guidelines from a rodent and non rodent species including any studies undertaken on juveniles, if available.

APPLICANT'S RESPONSE
The applicant has submitted two pre- and postnatal toxicity studies conducted in Crj:CD rats.

Toxicity Study Tr143-010
In the first study 0, 8, 40 or 200 mg/kg of olmesartan medoxomil was administered orally by gavage to pregnant Crj:CD rats (n= 25-, 22-, 22- and 24/group respectively) from gestational day 17 to postnatal day 21 (stage of weaning) to investigate effects on the dams and the pre and postnatal development of the F1 generation. The postnatal development of the F1 offspring was monitored up until 8 weeks of age. Some of these animals were selected (n= 10/sex/group) and raised until 10 weeks of age for tests on reproductive performance. These animals were mated and the dams were allowed to undergo natural parturition. The birth index and gestation period was examined. Findings in the F_0 dams - A reduction in mean body weight gain was observed

during the lactation period in the 200 mg/kg group. Reduced food intake from the late pregnancy period to the lactational period in the 40 and 200mg/kg groups. Findings in the F_1 offspring - Reduced mean body weight at parturition which continued throughout the period of growth was observed at all doses, but statistically significant at the top dose (200mg/kg). A decline in the condition of the offspring (e.g. piloerection decreased spontaneous locomotor activity, staggering gait and tremor) was observed in the 40mg/kg (n=2) and 200 mg/kg (n=6) groups during the weaning period (PND 21- 23) with death at postnatal day (PND) 24. An increased incidence in mortality of the F1 offspring (n=5) from the top dose group was also observed prior to weaning. Histopathology analysis revealed dilatation of the renal pelvis in the intermediate (n=1) and high dose group offspring (n=5), and this treatment induced renal damage was judged to be the cause of the decline in the condition of the offspring and increased mortality. Behavioural tests were conducted to evaluate effects on motor coordination, sensory function and emotional effects. Motor coordination was the only parameter affected by treatment (prolongation of the reaction latency in the righting reflex and a decrease in the ratio of positive reaction in the negative geotaxis in the early half of the test days at >40mg/kg). This was concluded to be the result of suppression of postnatal growth. Other signs of suppressed postnatal growth which occurred at all doses tested, included separation of ear auricular, eruption of lower incisor and appearance of abdominal hair.. There was no treatment related effects on reproductive function, maintenance of pregnancy and parturition of the F1 offspring.

As a NOAEL was not identified for the suppressed postnatal growth a second study was conducted with 2 lower doses to identify a NOAEL.

Toxicity Study Tr143-278

In the second study groups of pregnant rats were treated with 0.3 and 1.6 mg/kg olmesartan from gestational day (GD) 17 to PND 21. The only treatment related finding was a reduction in body weight gain of the F1 offspring of the 1.6mg/kg group during the rearing period. The NOAEL for effects on postnatal development was considered to be 0.3 mg/kg.

Toxicological assessor's comments: In response to the RFI request the applicant submitted 2 pre-and postnatal studies. However a non-clinical overview discussing this information and its impact on the benefit risk for the proposed paediatric population was not provided. The results of the 2 studies are already reflected in the SmPC.

The most notable treatment related findings was the increased incidence in renal dilatation in the F1 offspring of the intermediate and high dose (40 and 200mg/kg) dams, and the suppression of postnatal development (e.g. reduced body weight gain, effects on motor coordination, separation of ear auricular, eruption of lower incisor) at ≥1.6 mg/kg.

The renal dilatation is a pharmacodynamic effect of exposure to an angiotensin II (AT_1) receptor antagonist during renal development. A similar phenomenon has previously been reported with angiotensin converting enzyme inhibitors. The F1 offspring were not directly dosed but were exposed to olmesartan through lactation up until weaning around PND 21 (equivalent to a 2 year old human) which is the time when the anatomical and functional development of the kidneys should have reached completion in the rat. Angiotensin II plays an important role in renal development therefore exposure to this angiotensin II (AT_1) receptor antagonist during the period of renal development in rats would be expected to have an adverse effect on renal function. The degeneration in the condition of the offspring post weaning in the

present studies was clear evidence of this. The proposed SmPC already cites adverse effects in humans following exposure and the active is contraindicated during the 2nd and 3rd trimester of pregnancy which is the period of nephrogenesis in humans.

This effect will not be relevant to the proposed paediatric population of 6-17 year olds because glomerulo-nephrogenesis occurs prenatally in humans and functional maturation of the kidneys as indicated by the glomerular filtration rate (GFR), is completed between postnatal day 45-180 in humans (review by Silva-Lima et al [2010]). Adult renal function is fully established by 6 years of age and therefore the most relevant model for potential effects on renal function in this patient population will be adult humans.

In the rodent studies the F1 offspring were monitored until adulthood. Long term effects on sexual maturation, fertility and reproductive outcome from this early postnatal exposure were evaluated, and no adverse effects were observed. However it is important to note that the F1 offspring were not directly dosed during this later postnatal period, which spans the equivalent age range of the intended paediatric population, therefore the study did not investigate the potential effect of olmesartan on the organ systems undergoing development in the intended paediatric population (sexual maturation, skeletal bone development, CNS development etc).

The applicant did not submit any juvenile toxicity studies or repeat dose toxicity studies that have been conducted in juvenile animals in their RFI response; therefore it is assumed that these data are not available.

As the age range of the intended paediatric population is 6-17 years old and the pre- and postnatal studies only models exposures up to the equivalent age of a 2 year old, the applicant is requested to provide a brief statement on effects arising from direct exposures during puberty in the intended paediatric population of 6-17 year old. The applicant should provide a discussion on the potential effects of treatment on all organs systems undergoing development in this paediatric population and the reproductive outcome, if such information exists. The findings of studies conducted with other members of this class of compounds should be included in the discussion.

Issue partially resolved.

APPLICANT'S 2ND RESPONSE

According to the FDA guideline on “Nonclinical safety evaluation of pediatric drug products” (1) and the EMA guideline “on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications” (2) and a literature (B. Silva-Lima et al), reproductive and skeletal systems are undergoing development in the intended paediatric population (6-17 year old) for olmesartan medoxomil (OM) use. As shown in Table 24, several toxicity studies conducted as preliminary studies for carcinogenicity evaluation in rats and mice can cover the corresponding period for the postnatal development in these human systems. These toxicity studies showed no significant concern about reproductive and skeletal organs in general conditions or histopathology. In human nervous system, glutamate receptors are known to decline to adult level in 2-16 year olds. However, that decline can be also be observed in rats, and the period for the event (>28 days) was covered in rat toxicity studies. Consequently, the applicant believes that OM has no potential effect on organ systems undergoing development in this intended paediatric population.

For compounds in the same drug class compounds as OM, irbesartan is the only drug which juvenile toxicity assessment has been conducted as far as applicant knows. The results obtained from the rat juvenile study was recently reported (J. Liaw et al). Except for renal lesions, irbesartan treatment of neonatal and weanling rats evoked changes similar to those noted in

Target system	Human	Rat				Mouse			
	Postnatal developmental period	Postnatal developmental period	Study conducted			Postnatal developmental period	Study conducted		
			Age for dose initiation	Dosing duration	Study No.		Age for dose initiation	Dosing duration	Study No.
Reproductive (Puberty)	11–12 years	40–60 days	5 weeks 5 weeks 5 weeks 6 weeks	7 days 14 days 90 days 2 years	TR14 1-111 TR14 2-012 TR14 2-137 TR14 6-570	35-45 days	5 weeks 5 weeks 5 weeks	7 days 14 days 90 days	TR14 1-110 TR14 2-046 TR14 3-035
Skeletal (Fusion of 2° Ossification Centers)	14-19 years	15-162 weeks				12-13 weeks			

mature rats treated with irbesartan, and the authors concluded that there appear to be no increased safety concerns in children with full renal development. Additionally, the applicant's expression of no concerns for organ systems with OM is consistent with the findings determined in this study with irbesartan.

Table 24- Target system concerned for OM, comparison between humans & animals

Toxicological assessor's comment: The applicant's response is adequate. They have provided some information (albeit very limited) from studies in rodents showing that exposures during the period of sexual maturation and skeletal development (which is relevant to the patient population) was not associated with an adverse effect on the sexual organs and skeleton of the tested animals.

Therefore the data did not indicate a potential risk to the intended patient population.
Issue resolved.

Question 3- A literature search/ review of the existing paediatric studies.

APPLICANT'S RESPONSE
The results of the study submitted in this procedure CS0866-A-U301, has been published by Hazan et al. 2010 in "Hypertension". A copy was provided. In addition, an *Adis Drug Profile of Olmesartan Medoxomil in Children and Adolescents with Hypertension* was recently been published in "Drugs" [2010; 70(18): 2439-2447]. A copy was provided.
An additional search in the PubMed literature database did not return any additional publications on paediatric studies with Olmesartan medoxomil.

Assessor's comment: The applicant has carried out a further literature search and has not found any other paediatric studies, other than the Hazan *et al.* 2010 study with olmesartan medoxomil.

Issue resolved.

Study CS0866-A-U301- Efficacy & safety

Question 4- Data regarding quality aspects of the extemporaneous liquid suspension are required in order to provide assurance that the same dose of OM was received from the compounded liquid suspension and the tablets in the efficacy & safety population.

APPLICANT'S RESPONSE

Olmesartan medoxomil (OM) film-coated tablets
The applicant has provided the list of excipients contained in OM tablets (all strengths)

Olmesartan medoxomil
OM (CAS: 144689-63-4) is approved in the EU (trade name Olmetec and other) as 10 mg, 20 mg, and 40 mg film-coated tablets and in the US (trade name Benicar) as 5 mg, 20 mg, and 40 mg film-coated tablets (see prescribing information (PI) in Appendix 5).

OM is a white to pale yellowish white powder, which melts at approximately 178°C. It is practically insoluble in water, very slightly soluble at pH 1.2 and 8.0, slightly soluble in ethanol and acetonitrile and sparingly soluble in methanol and acetone. Partition between octanol and pH 7 buffer gives log P 1.0 and the pKa is 4.3. Extensive studies show no evidence for the existence of polymorphs or other solid state forms. The molecule has no chiral centres. It is not hygroscopic.

Olmesartan medoxomil extemporaneous suspension used for clinical investigation
Depending on age and study, paediatric patients used commercially available OM film-coated tablets or an extemporaneous OM suspension derived from commercially available OM film-coated tablets in the clinical studies. The extemporaneous suspension was prepared in the pharmacy using Benicar 20 mg tablets along with other ingredients for oral administration for once daily dosing. Ora-Sweet and Ora-Plus are fully-formulated sweetening and suspending agents, commercially available in the US and widely used to compound paediatric dosage forms. In order to maintain the double blind aspect of the conducted clinical studies, suspensions of 8-fold different concentration were needed, and two different concentrations were developed for clinical use: 0.5 mg/mL and 4 mg/mL. The components and composition of these suspensions have been provided.

In the US, the preparation of an extemporaneous suspension (2 mg/ml) from Benicar 20 mg commercially available tablets is recommended for pediatric patients who are not able to swallow the film coated tablets. The concentration of 2 mg/mL was selected as this covers a broad range of possible doses that can be accurately measured using readily available dosing aids (such as oral syringes) without imposing an undue volume burden on paediatric patients .
The suspension should be refrigerated at 2-8°C (36-46°F) and can be stored for up to 4 weeks. Information on the stability program, including in-use stability was provided.

By using commercially available OM film coated tablets, the extemporaneous suspension used for the paediatric clinical study was consequently quantitatively and qualitatively identical in performance to the film-coated tablets. The bioequivalence of the tablets and the compounded liquid formulation used in the paediatric clinical investigation was demonstrated in clinical study CS0866-A-U101.

Quality assessor's comment: The applicant has provided results of a specific stability program for olmesartan oral suspension 2 mg/mL. The program included primary (registration) and supportive (in-use, thermal cycling and photo) stability studies.
The proportions of extemporaneous vehicle materials used in the 4mg/ml preparation from the bioequivalence study CS0866-A-U101; Ora-Sweet, Ora-Plus and purified water is the same as the 0.5mg/ml and 4mg/ml preparations detailed in Table 25.

Primary (registration) stability studies
The results from the primary stability study (5°C for 6 weeks and 25°C for 1 week with samples in the up-right and inverted position) for three different batches were provided by the applicant. The tests performed include appearance, redispersibility, pH, uniformity of suspension, assay and related substances. Microbial contamination was tested at the initial and final time points for each testing condition.
The analytical methods conform to ICH guidelines. All parameters were within the specification limits in both up-right and inverted positions. Given that the data provided indicate that Benicar tablets suspended in the test vehicle is stable for 6 weeks at refrigerated conditions (2-8°C), a 4-week refrigerated shelf-life is considered appropriate for a 2mg/ml product. However, efficacy & safety study CS0866-A-U301 was performed at OM strengths 0.5mg/ml and 4mg/ml.

supportive (in-use, thermal cycling, stress and photo) stability studies
The photostability studies were carried out according ICH Q1B Guideline. Olmesartan and an aluminium wrapped control sample were exposed for over 6 weeks to a D65 fluorescent lamp. The results indicate that there is no increase in related substances or decrease in assay and therefore, olmesartan medoxomil is considered photostable. The colour of the irradiated samples without immediate packaging changed slightly from pale reddish-white to pale white. However, due to the fact that the primary packaging container for oral suspension is an amber PET-bottle that provides additional protection from exposure to light, this change in the appearance is acceptable.

In-use stability study has been conducted to evaluate the effect of repeated opening and closing of patient bottles during routine use by customer and/or patient.
All samples used for the in-use stability study were stored at 5°C. Each of the bottles was opened over a fixed period of 6 weeks every day for approximately 5 minutes. Testing of samples was performed at the initial time point and after six weeks of storage at the long-term condition of 5°C. The tests performed include appearance, redispersibility, pH, uniformity of suspension, assay, related substances and microbial contamination. The results from the in-use stability study, initial and 6 weeks are showed that all parameters were within the specification limits.

A thermal cycling study has been conducted to determine the potential effect of temperature variation on the oral suspension. The samples were stored at 25°C for 1 day and then at 5°C for 1 day. This 2-day cycle of storage was repeated two more times, which resulted in total of 6 days of storage. Testing of the thermal cycling stability study samples was performed after 6 days of storage at 5°C/25°C. At the end of the 6 day testing period, all parameters were within the specification limits.

The results of the primary and supportive stability studies provided, shows that the extemporaneous suspension of 2 mg/ml quantitatively and qualitatively is stable at least 6 weeks at the refrigerated (2-8°C) condition.
Issue resolved.

Question 5- Period II, Cohort C, the p values for the change in SeSBP and SeDBP from the base line.

APPLICANT'S RESPONSE
The applicant has performed a t-test on the data and the p-values were calculated using a one-sample t-test for the change from baseline in BP at each scheduled visit in Period II for Cohort C. For Cohort C, the within-group changes from baseline in SeSBP and SeDBP were statistically significant (p<0.0001) across all visits (Weeks 1, 2, 3) in Period II and at End of Period II with LOCF. The results are presented in the table 26 below.

Table 26- Mean Change from Study Baseline in SeSBP and SeDBP (mm Hg) by Visit during Period II for Cohort C

Visit	SeSBP				SeDBP			
	N	Study Baseline Mean (SD)	Change from baseline Mean (SD)	P-value	N	Study Baseline Mean (SD)	Change from baseline Mean (SD)	P-value
Week 1	58	114.8 (7.25)	-10.68 (9.12)	<0.0001	58	72.1 (7.77)	-8.17 (10.01)	<0.0001
Week 2	58	114.8 (7.25)	-12.68 (10.07)	<0.0001	58	72.1 (7.77)	-9.91 (9.78)	<0.0001
Week 3	58	114.8 (7.25)	-13.32 (11.03)	<0.0001	58	72.1 (7.77)	-10.65 (9.70)	<0.0001
End of Period II	59	115.4 (8.62)	-13.31 (10.94)	<0.0001	59	72.6 (8.80)	-10.42 (9.78)	<0.0001

SeSBP = seated systolic blood pressure; SeDBP = seated diastolic blood pressure; SD = standard deviation;
P-value was obtained from one-sample t-test on change-from-baseline.

Assessor's comment: The applicant has provided the missing *p values*, for period II, cohort C which show highly statistically significant reductions in both diastolic and systolic blood pressure compared with the baseline. **Issue resolved**.

Question 6- Period IV, Cohort C, the p values for the change in SeSBP and SeDBP from the base line.

APPLICANT'S RESPONSE
The applicant has performed a t-test on the data and the p-values were calculated using a one-sample t-test for the change from baseline in BP at each scheduled visit for Cohort C. For Cohort C, the within-group changes from baseline in SeSBP and SeDBP were statistically significant (p<0.0001) across all visits, including those of Period IV (Weeks, 12, 20, 28, 36, and 46). The results are presented in the table 27 below.

Table 27- Mean Change from Study Baseline in SeSBP and SeDBP (mm Hg) by Visit during Period IV for Cohort C

Visit	SeSBP				SeDBP			
	N	Study Baseline Mean (SD)	Change from baseline Mean (SD)	P-value	N	Study Baseline Mean (SD)	Change from baseline Mean (SD)	P-value
Week 2	57	114.7 (7.24)	-13.6 (10.17)	<0.0001	57	72 (7.79)	-11.0 (10.77)	<0.0001
Week 4	57	114.7 (7.24)	-15.1 (8.59)	<0.0001	57	72 (7.79)	-13.0 (8.71)	<0.0001
Week 12	57	114.7 (7.24)	-16.3 (10.23)	<0.0001	57	72 (7.79)	-14.0 (10.40)	<0.0001
Week 20	57	114.7 (7.24)	-16.4 (10.78)	<0.0001	57	72 (7.79)	-13.3 (11.50)	<0.0001
Week 28	57	114.7 (7.24)	-14.3 (11.80)	<0.0001	57	72 (7.79)	-11.7 (11.07)	<0.0001
Week 36	57	114.7 (7.24)	-16.4 (10.11)	<0.0001	57	72 (7.79)	-14.0 (11.88)	<0.0001
Week 46	57	114.7 (7.24)	-15.7 (9.83)	<0.0001	57	72 (7.79)	-13.3 (11.18)	<0.0001
End of Study	57	114.7 (7.24)	-15.7 (9.83)	<0.0001	57	72 (7.79)	-13.3 (11.18)	<0.0001

SeSBP = seated systolic blood pressure; SeDBP = seated diastolic blood pressure; SD = standard deviation;
P-value was obtained from one-sample t-test on change-from-baseline.

Assessor's comment: The applicant has provided the missing *p values*, for period IV, cohort C which show highly statistically significant reductions in both diastolic and systolic blood pressure compared with the baseline.

Issue resolved.

Question 7- Period IV, Cohort A+B, summarized comparison of type, severity and frequency of AEs between high and low dose OM groups during the long term open label arm of the study.

APPLICANT'S RESPONSE
The applicant is not able to provide the requested comparison of AEs for the "high" and "low" doses for the following reasons:
As per the study design, in Period IV, the open-label OM treatment period, subjects started with 10 or 20 mg OM dose, based on body weight (<35 kg, >=35 kg, respectively), and the dose could be titrated to 20 or 40 mg by weight, respectively, after two weeks of treatment. The confounding issue is the 20 mg dose, which could be used as high dose for low body weight < 35kg, or low starting dose for high body weight >=35 kg. In addition, subjects taking the maximum dose not under control could be prescribed additional anti-hypertensive medications, at the discretion of the investigator. Subjects could also be back titrated if necessary. Therefore, there the assessment of type, severity and frequency of AES between high and low dose OM groups are not clearly possible in Period IV.

Assessor's comment: The applicant is not able to provide the comparison of AEs for the "high" and "low" doses due to olmesartan up and down titration and use of additional anti-hypertensive medications, used at the discretion of the investigator, during the 46 weeks open label phase. The applicant's position that, "the assessment of type, severity and frequency of AES between high and low dose OM groups are not clearly possible in Period IV" is acknowledged.

Issue resolved.

Question 8- Summarized, tabulated comparison of frequency of the AEs in adults Vs children.

APPLICANT'S RESPONSE
The applicant has compiled a table (Table 28 to compare the frequency of AEs in children vs. adults using treatment emergent adverse events of subjects in cohorts A, B and C during double-blind treatment compared to corresponding AEs in adults from the CS-866 Marketing Authorisation Application (MAA) (DE/H/0384/001-003). Due to the differences in sample size and the fact that the data from the MAA derive from a pooled analysis of several clinical trials with different treatment duration, the frequencies cannot be directly compared. The overall pattern of AEs however, is similar between adults and children.

Of note, in the adults the frequency of headache in the placebo group is higher than that in the OM group and in a comparable range with the high OM dose in paediatric subjects.

Assessor's comment: The applicant's argument that "*Due to the differences in sample size and the fact that the data from the MAA derive from a pooled analysis of several clinical trials with different treatment duration, the frequencies cannot be directly compared*" is unacceptable, as the AE frequency comparisons between children and adults are routinely performed in unequal sample sizes. The table

provided needs to be amended and pool all the paediatric subsets together in one column to be comparable to the adult pooled analysis of several clinical trials presented. Text for section 4.8 in accordance with the SmPC guidelines of September 2009 should be proposed, accordingly.

Issue not resolved.

APPLICANT'S 2ND RESPONSE

The requested table with all the paediatric subsets pooled together in one column is presented hereafter.

Table 28- Treatment Emergent Adverse Events Reported Subjects in Cohorts A, B and C During Period II (Pooled data) vs. TEAEs in adults (OM and placebo) from CS-866 ISS[d]

MedDRA system organ class Preferred term[c]	**CS-0866-A-U301; Period II treatment n (%) of subjects in cohorts A, B and C (low[a] and high[b] dose)**	**CS-866 ISS**	
	N=361 (%)	Placebo[c] N=582 (%)	OM[c] N=3190 (%)
Number of subjects (%) with at least one TEAE	**139 (38.50)**	**267 (45.88)**	**1625 (50.94)**
Blood and lymphatic system disorders	**1 (0.28)**		
Iron deficiency anaemia	1 (0.28)	-	-
Cardiac disorders	**3 (0.83)**		
Palpitations	1 (0.28)	0 (0.00)	13 (0.41)
Tachycardia	2 (0.55)	6 (1.03)	26 (0.82)
Ear and labyrinth disorders	**2 (0.55)**		
Ear pain *(Ear ache)*	2 (0.55)	*0 (0.00)*	*4 (0.13)*

MedDRA system organ class Preferred term[c]	**CS-0866-A-U301; Period II treatment n (%) of subjects in cohorts A, B and C (low[a] and high[b] dose)**	**CS-866 ISS**	
	N=361 (%)	Placebo[c] N=582 (%)	OM[c] N=3190 (%)
Eye disorders	**4 (1.11)**		
Eye pain	2 (0.55)	1 (0.17)	0 (0.00)
Eye pruritus	1 (0.28)	-	-
Mydriasis	1 (0.28)	-	-
Ocular discomfort	1 (0.28)	-	-
Gastrointestinal disorders	**33 (9.14)**		
Abdominal distension	1 (0.28)	-	-
Abdominal pain (incl. upper)	13 (3.60)	4 (0.69)	40 (1.25)
Dental discomfort	1 (0.28)	-	-
Diarrhea	4 (1.11)	5 (0.86)	66 (2.07)
Gastritis	2 (0.55)	1 (0.17)	16 (0.50)
Loose stools	2 (0.55)	-	-
Nausea	4 (1.11)	5 (0.86)	44 (1.38)
Oral pain	1 (0.28)	-	-
Stomach discomfort	1 (0.28)	-	-
Tooth ache	4 (1.11)	2 (0.34)	16 (0.50)
Vomiting	5 (1.39)	2 (0.34)	17 (0.53)
General disorders and administration site conditions	**23 (6.37)**		
Chest pain	3 (0.83)	4 (0.69)	52 (1.63)
Fatigue	6 (1.66)	5 (0.86)	46 (1.44)
Oedema peripheral	1 (0.28)	5 (0.86)	36 (1.13)
Pain	2 (0.55)	3 (0.52)	44 (1.38)
Pyrexia *(Fever)*	12 (3.32)	*0 (0.00)*	*7 (0.22)*
Immune system disorders	**2 (0.55)**		
Hypersensitivity *(Allergic reaction)*	1 (0.28)	*1 (0.17)*	*14 (0.44)*
Seasonal allergy *(Allergy)*	1 (0.28)	2 (0.34)	11 (0.34)
Infections and infestations	**50 (13.85)**		
Bronchitis	2 (0.55)	20 (3.44)	120 (3.76)
Bronchopneumonia *(Pneumonia)*	1 (0.28)	*1 (0.17)*	*3 (0.09)*
Cellulitis	1 (0.28)	-	-
Dental caries	1 (0.28)	-	-
Fungal infection	1 (0.28)	2 (0.34)	6 (0.19)
Gastroenteritis	1 (0.28)	1 (0.17)	38 (1.19)
Gastroenteritis viral	1 (0.28)	-	-
Gastrointestinal infection	2 (0.55)	-	-
Influenza *(Influenza-like symptoms)*	4 (1.11)	*22 (3.78)*	*128 (4.01)*
Malaria	1 (0.28)	-	-
Nasopharyngitis	9 (2.49)	-	-
Otitis media	1 (0.28)	2 (0.34)	5 (0.16)

MedDRA system organ class Preferred term[c]	**CS-0866-A-U301; Period II treatment n (%) of subjects in cohorts A, B and C (low[a] and high[b] dose)**	**CS-866 ISS**	
	N=361 (%)	Placebo[c] N=582 (%)	OM[c] N=3190 (%)
Otitis media acute	1 (0.28)	-	-
Otitis media chronic	1 (0.28)	-	-
Pharyngitis	6 (1.66)	8 (1.37)	58 (1.82)
Pharyngotonsilitis	1 (0.28)	-	-
Respiratory tract infection (incl. upper)	18 (4.99)	32 (5.50)	162 (5.08)
Sinusitis	2 (0.55)	15 (2.58)	69 (2.16)
Tonsilitis	1 (0.28)	-	-
Tracheitis	1 (0.28)	1 (0.17)	5 (0.16)
Varicela	1 (0.28)	-	-
Viral infection	2 (0.55)	3 (0.52)	9 (0.28)
Injury, poisoning and procedural complications	**6 (1.66)**		
Abdominal injury	1 (0.28)	-	-
Arthropod bite	1 (0.28)	-	-
Contusion	1 (0.28)	-	-
Excoriation	1 (0.28)	-	-
Forearm fracture	1 (0.28)	-	-
Head injury	1 (0.28)	-	-
Limb injury	1 (0.28)	-	-
Metabolism and nutrition disorders	**5 (1.39)**		
Anorexia	1 (0.28)	-	-
Decreased appetite	2 (0.55)	-	-
Diabetic ketoacidosis	1 (0.28)	-	-
Fluid retention	1 (0.28)	-	-
Musculoskeletal and connective tissue disorders	**14 (3.89)**		
Arthralgia	4 (1.11)	4 (0.69)	54 (1.69)
Aseptic necrosis bone	1 (0.28)	-	-
Back pain	5 (1.39)	9 (1.55)	70 (2.19)
Muscle spasms	1 (0.28)	-	-
Musculoskeletal stiffness *(Rigors)*	1 (0.28)	*0 (0.00)*	*3 (0.09)*
Myalgia	1 (0.28)	7 (1.20)	27 (0.85)
Neck pain	1 (0.28)	-	-
Pain in extremity *(Skeletal pain)*	2 (0.55)	*3 (0.52)*	*34 (1.07)*
Sensation of heaviness	1 (0.28)	-	-
Nervous system disorders	**41 (11.36)**		
Dizziness	12 (3.32)	6 (1.03)	118 (3.7)
Headache	30 (8.31)	56 (9.62)	244 (7.65)
Hypoaesthesia	1 (0.28)	1 (0.17)	10 (0.31)
Post-traumatic headache	1 (0.28)	-	-
Sleep apnoe syndrome	1 (0.28)	1 (0.17)	0 (0.00)

MedDRA system organ class Preferred term[c]	**CS-0866-A-U301; Period II treatment n (%) of subjects in cohorts A, B and C (low[a] and high[b] dose)**	**CS-866 ISS**	
	N=361 (%)	Placebo[c] N=582 (%)	OM[c] N=3190 (%)
Somnolence	4 (1.11)	1 (0.17)	11 (0.34)
Psychiatric disorders	**5 (1.39)**		
Insomnia	3 (0.83)	9 (1.55)	31 (0.97)
Mental disorder	1 (0.28)	-	-
Mood altered	1 (0.28)	-	-
Renal and urinary disorders	**1 (0.28)**		
Dysuria	1 (0.28)	0 (0.00)	6 (0.19)
Urinary incontinence	1 (0.28)	0 (0.00)	3 (0.09)
Reproductive system and breast disorders	**1 (0.28)**		
Dysmenorrhoea	1 (0.28)	0 (0.00)	6 (0.19)
Respiratory, thoracic and mediastinal disorders	**28 (7.76)**		
Chronic obstructive airways disease	1 (0.28)	1 (0.17)	0 (0.00)
Cough *(Coughing)*	4 (1.11)	*6 (1.03)*	*47 (1.47)*
Dyspnoe	2 (0.55)	4 (0.69)	14 (0.44)
Epistaxis	3 (0.83)	2 (0.34)	10 (0.31)
Nasal congestion	2 (0.55)	-	-
Nasal passage irritation	1 (0.28)	-	-
Pharyngolaryngeal pain	7 (1.94)	-	-
Productive cough	*2 (0.55)*	-	-
Rhinitis allergic	2 (0.55)	-	-
Rhinorrhea	6 (1.66)	-	-
Sinus pain	1 (0.28)	-	-
Upper respiratory tract congestion	1 (0.28)	-	-
Upper respiratory tract inflammation	1 (0.28)	-	-
Skin and subcutaneous tissue disorders	**9 (2.49)**		
Alopecia	1 (0.28)	1 (0.17)	2 (0.06)
Dermatitis contact	1 (0.28)	0 (0.00)	3 (0.09)
Face oedema	1 (0.28)	0 (0.00)	4 (0.13)
Heat rash	1 (0.28)	-	-
Rash	4 (1.11)	3 (0.52)	27 (0.85)
Rash pruritic *(Pruritus)*	1 (0.28)	*1 (0.17)*	*14 (0.44)*
Vascular disorders	**3 (0.83)**		
Flushing *(Hot flushes)*	1 (0.28)	*0 (0.00)*	*6 (0.19)*
Hypertension	2 (0.55)	1 (0.17)	6 (0.19)

The most common TEAEs are dizziness and headache with a similar frequency in children (3.32%, 8.31%) and adults (3.7%, 7.65%). Both terms are already listed as common adverse drug reactions in the SmPC.

Abdominal pain is slightly more frequent in children. This is a common phenomenon in children and abdominal pain is listed as an expected reaction in the SmPC with common frequency. Also signs and symptoms of common cold like fever, nasopharyngitis, pharyngeal pain and rhinorrhea seem to be slightly more frequent in children. However, this could also partly be caused by the use of two different coding systems. For example, influenza-like symptoms are more frequent in the adult population compared to the pediatric population. This general term might include some of the more specific, separately coded symptoms from the pediatric population such as nasopharyngitis or rhinorrhea.

In addition, frequencies of the previously mentioned terms dysmenorrhoea and epistaxis do not show significant differences between the pooled pediatric data and the adult cohort.

Overall, the adverse event profile for children shows no major unexpected differences form the one seen in adults.

The section 4.8 of the SmPC has been revised accordingly.

Assessor's comment: Despite several attempts, the applicant could not produce an all inclusive table of Paediatric Vs adult adverse events. The table 28 produced by the applicant excludes the long term safety data from study CS0866-A-U301 in children. Hence the assessor has merged all tables and came up with the following decisions:

There were 10 cases of epistaxis in 338 children compared with 10 cases in 3190 adults who took at least one dose of olmesartan. Nose bleed can be attributed to vasodilatory effect of olmesartan. It is the type of adverse event that could be expected from the pharmacodynamics of an angiotensin II receptor inhibitor. None the less, its frequency in children seems to be 1 in 100 compared to 1 in 1000 in adults and this information should be reflected in the section 4.8 of the SmPC.

The frequency of occurrence of abdominal pain, vomiting, pyrexia, otitis media, ear pain, tooth ache, dysuria, urinary incontinence, tracheitis, viral infection, sleep apnoea and contact dermatitis were shown to be greater in children than in adults. These adverse events are mostly common childhood diseases or growth related. There was one case of alopecia that may have been confounded by other ongoing conditions.

There were 6 cases of dysmenorrhoea in the older adolescent girls receiving olmesartan. However prevalence of dysmenorrhoea among adolescent girls ranges from 60 to 93 percent and hence it does not constitute a major concern.

There were 6 cases of joint sprain in children (6-17 years old, n=281) and none in adults. Although it may very well be due to higher play/sport activity in children, it is plausible that olmesartan may have an idiopathic effect on connective tissue during growth but not in adulthood.

Therefore events of joint sprain, and related preferred terms and/or SOCs, should be monitored in the updated risk management plan, with the view of a potential idiopathic signal. Events of eye pain, ocular discomfort and eye haemorrhage were also exclusive to paediatric population. Although the frequency of their occurrence in children is not very high at this point, but the event of eye pain, related preferred terms and/or SOCs should be monitored in the updated risk management plan, with

the view of a potential paediatric signal.
The overall safety profile for olmesartan in paediatric patients does not differ significantly from the safety profile in adults.

Issue Resolved.

PSUR covering the period 25-APR-2010 to 24-OCT-2010

The applicant submitted the 17th PSUR for olmesartan medoxomil covering the time period from 25-APR-2010 to 24-OCT-2010. This report refers to olmesartan medoxomil monosubstance and the dual combinations with hydrochlorothiazide and amlodipine besilate as well as the triple combination Olmesartan medoxomil with hydrochlorothiazide and amlodipine.

During the review period of this report it is estimated that 5,311,312 patients were exposed to olmesartan medoxomil monosubstance worldwide.

Overall, this PSUR does not present severe, unexpected events which would signal, based on their frequency or general characterization, a new risk with olmesartan medoxomil, or the combination products with hydrochlorothiazide and amlodipine. However, based on recent additional signal detection activities it was decided to include the following terms into the CCDSs of olmesartan medoxomil monosubstance and all combinations: 'diarrhoea', 'oedema peripheral' and 'anaphylactic reactions'. The CCDSs will be updated by 30-NOV-2010.

In the period of 2009-2011 there were 3 reports on neonates with serious adverse reactions ranging from skull, Renal and pulmonary hypoplasia and associated renal and respiratory failure. The events occurred in the neonate whose mother received olmesartan and in one case additional ACE-1during pregnancy.

There was one report of "Accidental drug intake by child" in 2010 and one in 2011.

Assessor's comment: The fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) of olmesartan are known and its use is not recommended during the first trimester of pregnancy and contra-indicated during the 2nd and 3rd trimester of pregnancy. These cases do not present new or unknown safety concern, relevant to the paediatric population.

Statistical point

Question 9- The original randomisation of subjects into Cohort A was stratified by age into two strata (6-12 years and 13-16 years). As described in the current guidance (CPMP/EWP/2863/99: Points to consider on adjustment for baseline covariates) the ANCOVA model should be adjusted by including this stratification variable as a covariate. Although randomisation into Cohort B was not stratified in this way, possible differences between the younger children under 12 years and those aged 13 and above should be addressed for Cohort B as well as for Cohort A and the combination of the two, Cohort A+B. The Applicant should repeat the analysis of change from baseline in SeSBP and SeDBP for these three cohorts including age in the ANCOVA model. As Cohort C included children aged 1 to 5 years only no adjustment of this kind is required.

APPLICANT'S RESPONSE
The analyses were performed by the applicant based on the request, which is to include the stratification factor, the age group (6-12, 13-16 years), in the ANCOVA model. The requested data are presented in table 29 below.
Table 29 summarizes the results from the ANCOVA model for the effect of weight-adjusted OM dose (mg/kg) on the change from baseline in BP (mm Hg) at Week 3 of Period II as well as at the End of Period II LOCF, adjusting for age at baseline (6-12 years, 13-16 years).

A statistically significant dose response was observed for SeDBP and SeSBP in each of the three cohorts A, B and A + B when the analysis adjusted for age at baseline (6-12 years, 13-16 years) for weight-adjusted OM dose (mg/kg) at Week 3 of Period II as well as at the End of Period II LOCF, as shown in Table 29.

Table 29- Effect of weight-adjusted OM Dose (mg/kg) on change from Baseline in BP (mm Hg) at week 3 (Period 2) and at end of Period 2 (with LOCF) for all intent-to-treat Patients

COHORT	BP	VISIT	Effect Of Weight-Adjusted OM Dose (mg/kg) on Change From Baseline In Bp (mm Hg)		
			(mmHg) ESTIMATE	SE	P-VALUE
A	SeSBP	Week 3 (Period 2)	-9.74	2.112	<0.0001
		End of Period 2 (With LOCF)	-9.33	2.073	<0.0001
	SeDBP	Week 3 (Period 2)	-8.42	1.935	<0.0001
		End of Period 2 (With LOCF)	-8.19	1.915	<0.0001
B	SeSBP	Week 3 (Period 2)	-8.07	3.271	0.0153
		End of Period 2 (With LOCF)	-7.69	3.225	0.0188
	SeDBP	Week 3 (Period 2)	-6.79	2.665	0.0123
		End of Period 2 (With LOCF)	-6.81	2.593	0.0098
A+B	SeSBP	Week 3 (Period 2)	-9.16	1.794	<0.0001
		End of Period 2 (With LOCF)	-8.74	1.766	<0.0001
	SeDBP	Week 3 (Period 2)	-7.86	1.565	<0.0001
		End of Period 2 (With LOCF)	-7.70	1.542	<0.0001

MODEL: CHANGE IN BP = WEIGHT-ADJUSTED DOSE + AGE GROUP (6-12 YEARS, 13-16 YEARS).
SE=Standard error of the mean.

Statistical assessor's comments: The results of the analysis provided in the response have confirmed the findings presented in the study report.

Issue resolved.

Studies CS0866-A-U102 & CS0866-A-U301 - Population PK

Question 10- The Applicant is requested to submit a full report of the analyses and simulations contained within the two technical reports, including: analysis plan, electronic file of analysis dataset as comma separated and space deliminated text file, information regarding the handling of missing data and data below LOQ, deviations from analysis plan, description of all models evaluated, NONMEM input and output files for base and final models, distribution of samples (actual number per subject sorted by study, treatment group and visit), summary statistics and histograms of the continuous covariates and frequencies of categorical covariates, stratified over the relevant subpopulations.

Comparison of Olmesartan Pharmacokinetics and Blood Pressure Lowering Effects between Adults and Paediatric Patients to Support Dosage Regimen

Question 11- Similar plots for subgroups of interest would be helpful to determine if this overestimation is a general phenomenon or limited to one or more subgroups.

Question 12- Additional model qualification information is necessary to demonstrate the value of using the post-hoc estimates of clearance, volume, etc, e.g. an assessment of the shrinkage of the individual estimates towards the population mean, visual predictive checks for subgroups of interest and individual plots of observed concentrations versus time with the population and individual predicted profiles overlaid.

Relationship between individual post-hoc clearances and weight in final model

Question 13- The post-hoc estimates graph of the central volume of distribution and weight.

Question 14- Plots generated to screen for other covariate relationships, following adjustment of clearance and volume for weight, should be provided.

Question 15- More details are needed regarding the basis of this calculation, particularly regarding the covariate distribution and variability of the simulation data set for the paediatric and adult populations.

Assessor's comment: the response to questions 10, 11, 12, 13, 14 and 15 are captured in final assessment of POP PK in page 88.

Day 85 Comments And Questions Received From The Other MSs:

Other Members of state have commented on the Day 70 report, both supporting the Rapporteur's overall conclusions and recommendations, but have asked the applicant for the following:

Question 16- Regarding the proposed posology, further justification should be provided by the MAH. Indeed, 10mg daily dosage, as proposed in the SPC, is different from the dosages tested in the provided clinical study U301. In fact, patients >20kg and <35kg have received either 2.5 mg or 20mg during periods II and III of the study; patients ≥ 35kg have received 5mg or 40mg during periods II and III. The 10 mg was only used in the first patients group (>20kg and <35kg) during the open period IV.

In the 1 to 5 age group, no definitive conclusion can be drawn based on the provided study, even if reductions in SBP and DBP were observed. Due to difficulties of data interpretation, whether a medical need in undeniable in this target group, results should be further explored before any decision.

We sustain the Rapporteur's RSI.

APPLICANT'S RESPONSE

The doses selected for the study design (an overview is provided in Appendix 9) were based on establishing a dose response curve for olmesartan in the study cohorts during Period II considering the fact that OM efficacy is related to exposure (adjusted for weight) and shows linear pharmacokinetics following single oral doses up to 320 mg, and multiple oral doses of up to 80 mg. For Cohorts A, B, and A+B, a first order linear regression model was used to test if the slope is zero for SeSBP or for SeDBP to assess whether there was a dose response for olmesartan during Period II. Consequently, to demonstrate a degree of therapeutic separation among doses within a weight class based on exposure (>20kg and <35kg; or ≥ 35kg) both minimal and maximal therapeutic doses known to be safe and efficacious, were selected based on known comparative plasma levels to adults (see table 30 below).

Based on the results from a Sankyo Study 866-110, "A Comparative Pharmacokinetics study of CS-866 Tablets in Healthy Adult Male and Female Volunteers," (data on file) the oral clearance of OM is estimated to be 0.07 L/hr/kg. Using this estimate of clearance the table below shows the expected steady-state AUC values for OM across a range of body weight values, with the knowledge that AUC values (or exposure) are correlated with blood pressure lowering efficacy.

Table 30- Body weight dependent variation in the steady-state exposure (AUC) of olmesartan at olmesartan doses of 2.5, 10, 20, 40 and 80 mg, respectively.

Steady-state AUC (ng*hr/mL) values of olmesartan for Different Body Weights and Doses

	Body Weight (kg)						
Dose (mg)	20	30	35	40	50	60	70
2.5	1786	1190	1020	893	714	595	510
10	7143	4762	4082	3571	2857	2381	2041
20	14286	9524	8163	7143	5714	4762	4082
40	28571	19048	16327	14286	11429	9524	8163
80	57143	38095	32653	28571	22857	19048	16327

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Dose selection for the paediatric study using a liquid suspension was based on achieving exposures similar to those doses tested in adults. The effective and safe steady-state AUC for a 70 kg individual administered 40 mg per day would be 8163 ng*hr/mL and for an individual administered 80 mg per day would be 16327 ng*hr/mL. Assuming that paediatric patients have similar oral clearance of OM, e.g. 0.07 L/hr/kg, the estimated effective and safe doses of olmesartan needed to achieve steady-state AUC in this range would be 20 mg QD for patients weighing >20kg and <35kg, and 40 mg QD for patients weighing > 35 kg. This latter AUC value would represent the upper safe bound of plasma exposure since this is the highest dose that was routinely studied in Phase II and Phase III trials with OM. The lowest doses selected for each weight cohort would then represent the minimally effective dose; thus establishing a discernable dose response strategy.

In alignment with the currently approved and available marketed doses of OM (10-40 mg) subjects >20kg and <35kg given a starting dose of 10 mg would be appropriate since AUC levels of 4000-7100 ng*hr/mL would demonstrate a tolerability and efficacy profile similar to 70kg adult on 40mg which has been shown to be a therapeutically effective level for BP lowering. Similarly, patients > 35kg with a starting dose of 20 mg would be expected to show a tolerability and efficacy profile based on AUC levels of 4000-8100 ng*hr/mL, based on the table shown above.

Consequently, a dose-response relationship and exposure-response relationship adjusted by weight is expected to correlate with pharmacodynamic BP lowering effect.

The applicant agrees that in the 1 to 5 age group, no definitive conclusion can be drawn based on the provided study even if reductions in SBP and DBP were observed. Consequently no dosing posology will be requested in the SmPC.

Assessor's comment: There is no doubt that in pursuit of demonstrating dose – response relationship, the applicant has chosen the extreme low (2.5- 5 mg) and high (20-40 mg) doses. And indeed there are very few patients who received 10 mg dose. The applicant claims that there is an overlap in the PK/PD relationship (blood pressure lowering as a function of plasma AUC) for olmesartan between adult and paediatric patients. Thus, doses that achieve similar olmesartan plasma exposure in children as in adults will achieve a similar level of blood pressure lowering. If this assumption becomes acceptable pending on provision of further POP PK data, then in alignment with the currently marketed doses of OM (10-40 mg) subjects >20kg and <35kg given a starting dose of 10 mg would be appropriate since AUC levels of 4000-7100 ng*hr/mL would demonstrate a tolerability and efficacy profile similar to 70kg adult on 20mg which has been shown to be a therapeutically effective level for BP lowering. Similarly, patients > 35kg with a starting dose of 20 mg would be expected to show an efficacy profile based on AUC levels of 4000-8100 ng*hr/mL, based on the table shown above.

However as the PK assessor has mentioned above, given the limited documentation provided by the company, it has not been possible (1) to assess the validity of the model development and qualification and (2) to verify the reliability of the post-hoc estimates of clearance and AUC.

Issue partially resolved.

Question 17- The posology needs to be further justified. The lower dose seems far separated from the higher dose, and no middle dose has been tested. This is not in agreement with the proposed posology. According to the posology all patients should be started with the 10 mg dose, while in the study patients start at 20 or 40 mg depending on their weight.

APPLICANT'S RESPONSE
The response to this question is covered by the response to question 16.

Question 18- There seems to be some dose dependent adverse events, mainly dizziness and headache. This seems to be worrying, mainly with a doubled incidence for the use of higher doses. The dose justification and posology should be further discussed taken these safety issues into account.

APPLICANT'S RESPONSE
During the double-blind period the percentage of subjects experiencing a treatment emergent adverse event (TEAE) within each cohort A (18% black) and B (100% black) was similar for the low dose (2.5 and 5 mg/day) and high dose (20 and 40 mg/day) OM groups (Cohort A: 43.2% and 47.4%, respectively; Cohort B: 34% and 29%, respectively). The majority of TEAEs were

mild or moderate in intensity. However, a greater percentage of subjects in cohort A reported having a least 1 TEAE compared with cohort B. The system organ class - Nervous System Disorders showed the most apparent dose response relationship to TEAE incidence, especially in cohort A where low dose and high dose groups showed an incident level of 9.5% and 24.2%, respectively. In contrast cohort B showed an unremarkable incidence of 5.3% to 9% that was not dose related based on a few number of events. The most frequently occurring TEAEs demonstrating a dose response relationship in cohort A for low dose were headache (7.4%) and dizziness (2.1%). This is in contrast to cohort A high dose group that showed an incidence for headache and dizziness of 14.7% and 9.5%, respectively. Interestingly, cohort B did not show any remarkable differences for low dose or high dose for these TEAEs.

The pharmacodynamic potency of OM may have an effect on the incidence of these dose related TEAEs. Both Black (cohort B) and Non-black subjects demonstrated a dose response BP lowering effect. For Non-black subjects the SeSBP reduction from baseline was -7.8mmHg for low dose and -13.2 mmHg for high dose. In contrast, Black subjects showed reductions of -5.5mmHg for low dose and -10.4 mmHg for high dose. Similarly, for SeDBP, reductions from baseline in Non-Black subjects were -5.3 mmHg and -10.7 mmHg for low dose and high dose, respectively. This contrasts with Black subjects who showed reductions of -4.1 mmHg and -6.7 for low dose and high dose, respectively. Hence, the reduced response to OM in the black population (a low renin population) would account for the reduced incidence of overall TEAEs in Cohort B vs. Cohort A as well as the lack of a dose response relationship for TEAES of headache and dizziness. The pharmacodynamic BP lowering potency and the associated TEAE dose-response relationship in Cohort A is clearly more apparent, in particular for TEAEs of headache and dizziness.

Drug-related TEAEs were events judged by the investigator to be possibly, probably, or definitely related to active therapy. Drug related TEAEs in cohort A included 5 of the 21 reported for headache and 4 of the 11 reported for dizziness. In cohort B only 1 of the 5 reported for headache was drug related. Hence, the significance of the dose response relationship to TEAEs for headache and dizziness is acknowledged; however, the true magnitude of the incident TEAE is uncertain since there is no placebo control for non-specific effects. It should be noted that this is in contrast with data from the adult population in which headache is frequently reported in the placebo controlled group and less when hypertension seems well controlled. The incidence of headache in the adult population in controlled clinical trials is 3% vs. 1% for placebo.

The baseline blood pressure for cohort A and B was 129/77 and 131/79, respectively. A closer inspection of the magnitude of the systolic response to the various doses for those subjects experiencing headache and dizziness showed a change from baseline peak response of -25 mmHg. This one particular subject was 94 kg, received a 40 mg dose and had a final BP of 100/58 mmHg. Similarly, the peak DBP response was -23 mmHg. This one particular subject was 42 kg, received a 40 mg dose and had a final BP of 110/50. For perspective, the 50th percentile for BP and height for the 6-17 year old age group ranges from 96/55 mmHg to118/67 mmHg, respectively. So these BP drops do not seem exaggerated relative to the norm for adolescent BP. In addition, reviewing the TEAEs for headache and dizziness in the context of the magnitude of BP reduction and final BP level at the end of Period II does not show a good correlation with the incidence of these TEAEs (i.e. other subjects have similar BP reductions with no TEAEs reported). Hence, there appears to be a dose response relationship with TEAEs, the magnitude of the response may have an association with the onset of headache and dizziness, but there does not appear to be a strict correlation, as supported by the Black population whose cohort has similar extreme responses in some subjects with a reduced number of incident headache and dizziness events.

The evaluation above attempts to confirm a dose related incidence for certain types of TEAEs such as headache and dizziness. This effect may be dependent upon the pharmacodynamic potency of the drug in terms of total overall exposure and tolerability. There are cases where high exposure levels produce pharmacodynamic BP lowering effects with symptomatic sequelae such as headache or dizziness as shown for cohort A, which contrasts to a presented case where this correlation is not consistent (i.e. Black cohort).

Consequently, the recommended starting does of OM in children from 6-17 years of age is 10 mg once daily so that tolerability to BP reduction is established. In children whose BP is not adequately controlled at this dose, OM can be increased to 20 mg daily as an optimal dose and not exceeded if the child is <35kg. If additional BP reduction is required in children ≥ 35 kg, the OM dose may be increased to a maximum of 40 mg. Slow titration based on BP assessment is therefore imperative, to avoid extreme drug exposure and pronounced pharmacodynamic effects over a short time period, thus establishing a better tolerability profile.

Assessor's comment: The applicant has confirmed a dose related incidence for headache and dizziness, which is attributed to pharmacodynamics potency of the drug in terms of total overall exposure and tolerability, stating the following: *"There are cases where high exposure levels produce pharmacodynamic BP lowering effects with symptomatic sequelae such as headache or dizziness as shown for cohort A, which contrasts to a presented case where this correlation is not consistent (i.e. Black cohort)".*

The proposed dosing will start at a minimal dose with up titration based on need and tolerance. Headache and dizziness are generally common occurrence with all types of antihypertensive therapy, however the fact that the incidence of them doubles on high dose, should be captured in section 4.8 of the SmPC, as follows:

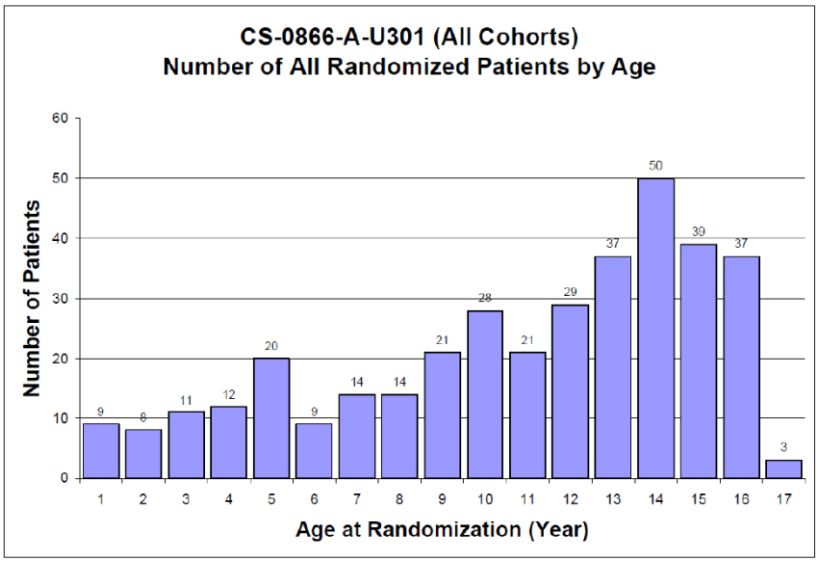
- During the 3 weeks of Double blind study, the incidence of treatment emergent dizziness and headache nearly doubled in children 6-17 years of age in the high olmesartan dose group.

Issue resolved.

Question 19- Although the mean age of around 12 years has been provided it is important to know whether all ages are equally represented. Therefore, the MAH has to provide the data on this, for instance by showing a histogram according to age.

APPLICANT'S RESPONSE

The applicant provides the distribution of patient's age for all cohorts in the figure 27 below.



Assessor comment: The applicant has provided the requested histogram of distribution of patient's age. The age groups are not equally represented, and there is higher representation of adolescents compared to 6-12 year olds. Although this may not be an optimal distribution, but all age groups were represented.

Issue Resolved.

Question 20- As younger patients are more presented with secondary hypertension (mainly due to renal comorbidity) and the older patients have more hypertension because of overweight, the applicant should provide data of efficacy according to etiology.

APPLICANT'S RESPONSE

The applicant provides the requested subgroup analysis for efficacy for patients with and without primary hypertension in the attachment 2 to this response. Changes from baseline in SeSBP and SeDBP were summarized by Status of Primary Hypertension (Yes, No) for Cohort C and by Status of Primary Hypertension (Yes, No) and OM Dose (Low, High) for Cohort A+B at end of Period II.

The table 31, summarizes the changes from baseline in BP by status of primary hypertension (Yes/No) and OM dose group for Cohort A+B and the changes from baseline in BP by status of primary hypertension (Yes/No) for Cohort C.

For Cohort A+B (N=300), there were a total of 224 (74.7% of N) subjects with primary hypertension. Out of the 224 subjects, 111 (49.6%) were in the low dose group (2.5 and 5 mg/day) and 113 (50.4%) in the high dose group (20 and 40 mg/day). For Cohort A+B, there were 76 subjects without primary hypertension. Out of the 76 (25.3% of N) subjects, 39 (51.3%) were in the low dose group and 37 (48.7%) in the high dose group.
For Cohort C (N=59), there were 20 (33.9%) subjects with primary hypertension and 39 (66.1%) without primary hypertension.
As shown in the summary table, for Cohort A+B, the mean changes in BP (mm Hg) at the end of period II LOCF were as follows.

• For subjects with primary hypertension, the mean changes from baseline in SeSBP were -5.29 for low dose and -10.91 for high dose respectively, and the mean changes from baseline in SeDBP were -3.45 for low dose and -7.88 for high dose respectively.

• For subjects without primary hypertension, the mean changes from baseline in SeSBP were -10.44 for low dose and -14.79 for high dose respectively, and the mean changes from baseline in SeDBP were -8.47 for low dose and -11.54 for high dose respectively.

As shown in the summary table, for Cohort C, the mean changes in BP (mmHg) at the end of period II LOCF were as follows.

• For subjects with primary hypertension, the mean change from baseline in SeSBP was -13.4 and the mean change from baseline in SeDBP was -10.05.

• For subjects without primary hypertension, the mean change from baseline in SeSBP was -13.33 and the mean change from baseline in SeDBP was -10.77.

For Cohort A + B it appears that the response for patients without primary hypertension had a greater therapeutic effect than those patients with primary hypertension at both low and high dose levels. Cohort C demonstrated similar therapeutic responses for both those with or without the diagnosis of primary hypertension.

Table 31- Change from baseline in BP (mm Hg) by primary hypertension (yes, no) and OM dose group (low, high) for all intent-to-treat subjects – at end of period 2

COHORT	BP	PRIMARY HYPERTENSION	OM DOSE	N	CORRESPONDING BASELINE					CHANGE FROM BASELINE				
					MEAN	SD	MEDIAN	MIN	MAX	MEAN	SD	MEDIAN	MIN	MAX
A+B	SeSBP	YES	LOW	111	131.5	8.92	131.2	109.3	149.7	-5.29	10.002	-4.67	-29.7	20.7
			HIGH	113	130.7	9.19	130.3	107.2	156.3	-10.91	10.183	-11.00	-41.3	16.7
		NO	LOW	39	127.3	8.93	127.3	112.3	145.3	-10.44	9.787	-10.83	-41.7	8.5
			HIGH	37	127.0	7.78	126.3	113.5	142.8	-14.79	8.170	-14.17	-34.2	2.8
	SeDBP	YES	LOW	111	78.3	8.10	78.8	60.7	97.5	-3.45	8.107	-3.00	-23.8	-18.0
			HIGH	113	76.8	7.77	75.7	57.8	99.7	-7.88	9.134	-7.17	-36.0	34.5
		NO	LOW	39	79.3	9.71	79.0	57.2	101.8	-8.47	8.156	-8.17	-24.7	7.8
			HIGH	37	79.2	7.61	78.8	61.7	98.0	-11.54	9.035	-9.83	-35.7	2.0
C	SeSBP	YES		20	116.4	8.57	112.5	106.0	137.0	-13.40	12.738	-14.50	-39.0	10.0
		NO		39	115.1	10.22	114.0	92.0	150.0	-13.33	10.827	-12.00	-37.0	20.0
	SeDBP	YES		20	73.7	11.15	71.0	58.0	106.0	-10.05	12.849	-7.50	-55.0	5.0
		NO		39	72.3	9.68	72.0	55.0	101.0	-10.77	9.778	-10.00	-33.0	10.0

Assessor's comment: The applicant has provided subgroup analysis of the efficacy for patients with and without primary hypertension.

Cohort C demonstrated similar therapeutic responses both for those with primary or secondary hypertension.

In Cohort A+B (n=300, 6-17 years of age), there were 224 subjects with primary hypertension and 76 subjects with secondary hypertension. For subjects with primary hypertension, the mean changes from baseline in SeSBP were -5.29 for low dose and -10.91 for high dose respectively, and the mean changes from baseline in SeDBP were -3.45 for low dose and -7.88 for high dose respectively. For subjects with secondary hypertension, the mean changes from baseline in SeSBP were -10.44 for low dose and -14.79 for high dose respectively, and the mean changes from baseline in SeDBP were -8.47 for low dose and -11.54 for high dose

respectively.

For Cohort A + B it appears that in patients with secondary hypertension olmesartan had a greater therapeutic effect than those patients with primary hypertension at both low and high dose levels. The applicant is requested to run a statistical analysis to resolve whether this difference is statistically significant, with a view of mentioning it in the section 5.1 of the SmPC.

Issue not resolved.

APPLICANT'S 2ND RESPONSE

The requested statistical analysis is provided in the table hereafter:

The analysis of BP responsiveness in cohorts A + B, comparing primary vs. secondary hypertension for both low dose and high dose OM showed significant differences from this analysis. The response differences between these two cohorts are multifactorial; therefore the MAH will not rationalize the statistical outcome. However, it should be regarded that the sample size for the primary hypertension cohort (n=111 to 113) is approximately 3-fold greater than that of the secondary hypertension group (n=37 to 39). It should be concluded that the therapy is effective in both primary and secondary hypertension, and the responsiveness for both cohorts of subjects is found to be in alignment with adults receiving similar dosages.

Section 5.1 of the SmPC has been revised in order to reflect these results.

Table 32- change from baseline in BP (mm Hg) by primary hypertension (yes, no) and OM dose group (low, high) for all intent-to-treat subjects – at end of period 2

COHORT	BP	PRIMARY HYPERTENSION	OM DOSE	N	CHANGE FROM BASELINE					
					MEAN	SD	MEDIAN	MIN	MAX	P-value*
A+B	SeSBP	YES	LOW	111	-5.29	10.002	-4.67	-29.7	20.7	0.0061
		NO	LOW	39	-10.44	9.787	-10.83	-41.7	8.5	
		YES	HIGH	113	-10.91	10.183	-11.00	-41.3	16.7	0.0368
		NO	HIGH	37	-14.79	8.170	-14.17	-34.2	2.8	
	SeDBP	YES	LOW	111	-3.45	8.107	-3.00	-23.8	**18.0**	0.0011
		NO	LOW	39	-8.47	8.156	-8.17	-24.7	7.8	
		YES	HIGH	113	-7.88	9.134	-7.17	-36.0	34.5	0.0357
		NO	HIGH	37	-11.54	9.035	-9.83	-35.7	2.0	
C	SeSBP	YES		20	-13.40	12.738	-14.50	-39.0	10.0	
		NO		39	-13.33	10.827	-12.00	-37.0	20.0	
	SeDBP	YES		20	-10.05	12.849	-7.50	-55.0	5.0	
		NO		39	-10.77	9.778	-10.00	-33.0	10.0	

Assessor's comment: The applicant has provided the information requested and shown that olmesartan is effective in both primary and secondary hypertension. The proposed text to 5.1*"The treatment was effective both in paediatric patients with primary and secondary hypertension. As observed in adult populations, the blood pressure reductions were smaller in black patients."* is acceptable.

Issue resolved.

List of additional questions proposed by pharmacokinetics assessor

Question 21- The applicant should provide a full study report(s) that documents all aspects of the population PK and PK/PD analyses in support of the dosing recommendations in children. The report should meet current standards for the reporting of population pharmacokinetic analyses and specifically address all unresolved and partially resolved questions, including the following missing elements:

21.a . A description of all models evaluated, the distribution of samples utilised in the analysis, summary statistics and histograms of covariates (see Question #10).

21.b Additional model qualification information, including intermediate analysis steps, visual predictive check and individual plots of observed concentrations versus time with the population and individual predicted profiles overlaid (Questin #12).

21.c Exploratory plots, following adjustment of clearance and volume of distribution for weight, to screen for other covariates (Question #14).

21.d An explanation with justification of the confidence interval for weight normalized clearance ratio between adult and paediatric patients, particularly with regard to the covariate distribution and variability (Question #15).

Pharmacokinetic assessor's comment: The response to question 21 is captured in final assessment of POP PK in page 88.

Question 22- The applicant should discuss the impact of renal dysfunction on the pharmacokinetics and dosing recommendations for Olmesartan in children.

Pharmacokinetic assessor's comment: The applicant's suggestion to address the lack of clinical pharmacokinetic data in renal impaired paediatric subjects by SmPC modification is accepted. The applicant should propose appropriate text.
Issue partially resolved.

Additional Late questions from other member of state
Please note that figures and table numbers relate to PPdAR:

Question 23- <u>Figure 10 of the AR "effect of olmesartan dose on diastolic blood pressure lowering effects in adult and adult + paediatric population".</u>
The applicant should give justification why graph for paediatric population alone was not provided.
For adult is not clear if a statistically significant relationship was observed as no p value was provided. Moreover neither equation, nor p value illustrated the lower figures (adult + paediatric population). The applicant should comment.

APPLICANT'S RESPONSE
The graphs provided in the previous response showed paediatric exposure response overlaps adult population as a trend analysis. The first graphs on the top show adult population exposure response, while the last three graphs on the bottom show paediatric exposure response overlaid on the top of the adult exposure-response curve. Therefore, the bottom graphs showed all of the paediatric data points. Hence, paediatric independent information was not plotted separately.

The p-values were not evaluated partly because these comparisons were exploratory based, derived from historic data from adult clinical studies. The major purpose was trend analysis not equivalence/superiority/inferiority evaluation.

Pharmacokinetic assessor's comment: The explanation provided is acceptable.

Issue resolved.

Question 24 - <u>Figure 11 of the AR</u>
Same general remark as figures 10 is made.
It seems that some mistakes were introduced in two equations of the figures 11 as they included doses instead of AUC
For the graph 8663-301: dDBP = -0.006*<u>dose</u> -7.343
For graph 866-419: dDBP: -0.0005*<u>dose</u> -3.0866
The applicant should comment

APPLICANT'S RESPONSE

The applicant acknowledges the comment and recognises the typographical error; it should read AUC not "dose".

Pharmacokinetic assessor's comment: The error is acknowledged.
Issue resolved.

Question 25- <u>Table 7 of the AR:</u> no statistical test was provided. The applicant should comment. The equation N°1 needs more explanation and detail.

APPLICANT'S RESPONSE
Table 7 of the Assessment Report (Table 1 from Report "Comparison of Olmesartan Pharmacokinetics and Blood Pressure Lowering Effects Between Adults and Paediatric Patients to Support Dosage Regimen: Addendum to Pharmacokinetic and exposure - response analysis for CS0866-A-U102 and CS0866-A-301") is a summary table of the peak and trough blood pressure lowering effects.
As the difference in (1) peak and baseline and (2) peak and predose blood pressures were derived from within subjects and there is no test and control groups to conduct statistical test,

therefore P-values were not evaluated. The major purpose of the analysis was to evaluate the clinical significance in peak blood pressure lowering effects compared to baseline and predose to evaluate the needs for a dosing schedule modification. We found no need to change dosing schedule as the differences in within subjects blood pressure lowering effects between peak and predose level were not considered clinically significant.

For information, the following table was newly generated to describe one-sample t-test to evaluate the statistical significance to the mean differences of 0 shown in Table 33.

Table 33- Post-hoc T-Test comparison for the blood pressure differences between peak (A) and baseline (B) and predose (C):

	ALL	Delta	SD	N	T value	P-value
(A-B)	Diastolic	-8.32	10.48	75	6.875316	1.67728E-09
	Systolic	-6.99	11.32	75	5.34763	9.53025E-07
(A-C)	Diastolic	-2.68	7.77	75	2.987063	0.003818619
	Systolic	-0.59	9.26	75	0.551787	0.582756679

Equation 1 is based on new analysis performed utilizing the applicant's internal report.

Pharmacokinetic assessor's comment: The explanation provided is acceptable.

Issue resolved.

Question 26- Comment from other member of state

We consider that before the approval of an extension of indication in the treatment of hypertension for children and adolescents (6-18 years), the Applicant should commit to submit a consolidated version of a Risk Management Plan (RMP) for olmesartan included the identified risks for the paediatric population. The paediatric exposure in clinical trials and in post marketing use by age group, indication (including off label use), dose, duration of use, gender and ethnicity should be specifically discussed and followed. Moreover as for others ARB II, important risks (hyperkalemia, hypotension) and important potential risks (renal impairment, elevation of liver function values, hypersensitivity including angioedema and serum sickness, hemoglobin/hematocrit decreased) have been identified and should be monitored for olmesartan in the paediatric hypertensive population aged 6 – 18 years.

APPLICANT'S RESPONSE

The applicant confirms that a Risk Management Plan will be issued when a paediatric indication will be included in the SmPC.

Pharmacokinetic assessor's comment: The applicant has agreed to update paediatric information in the risk management plan following the introduction of a new paediatric indication. Adverse events of joint sprain and eye pain and their related preferred terms and/or SOCs, should be monitored in the updated risk management plan, with the view of potential for an idiopathic/paediatric signal.
Issue Resolved.

FINAL ASSESSMENT OF THE POPULATION PK
APPLICANT'S 2ND RESPONSE TO POP PK QUESTIONS

The applicant submitted a number of files and graphical and tabular output to confirm that the population pharmacokinetic model developed by the company adequately describes the pharmacokinetics of olmesartan in the paediatric population. This included:

In response to Question 10:

- Distribution of blood samples (actual number per subject sorted by study, treatment group and visit)
- Summary statistics and histograms of covariates for ALT, AST and serum creatinine and a note regarding the exclusion criteria in Study CS0866-A-U301 (AST or ALT> 2 times the upper limit of the reference range or creatinine clearance < 25 mL/min/1.73m^2).
- A description of the models evaluated.

In response to Question 11:

- Plots comparing Olmesartan pharmacokinetics and blood pressure lowering effects between adults and paediatric patients for subgroups of interest. These plots confirm the overlap of paediatric adult and paediatric PK/PD responses.

In response to Question 12:

- Visual predictive check showing 95% confidence intervals for the simulated data from the population PK model in comparison to the observed data.
- Individual plots of observed concentrations versus time with population and individual predicted profiles overlaid.
- NONMEM control file, output and data as electronic files.

In response to Question 14:

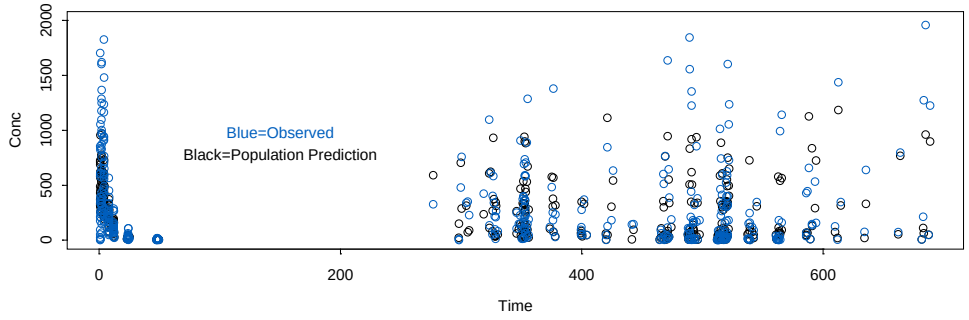
- Exploratory plots of clearance and volume of distribution, following adjustment for weight. The Applicant noted that these were provided in response to this question, but were not used for covariate screening, as the PK behaviour of olmesartan in the adult population was well defined.

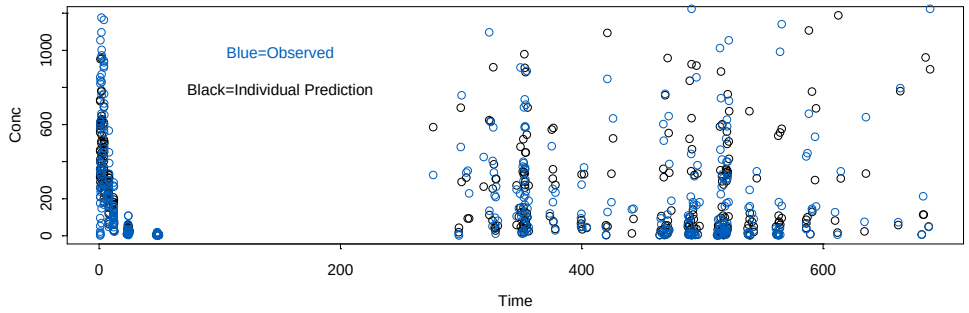
In response to Question 15:

- Data source used for calculation of confidence interval comparing adult and paediatric PK parameters.

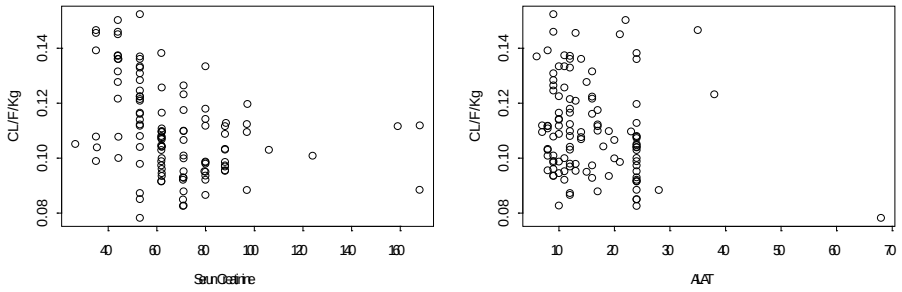
In response to Question 21 (requesting a full study report documenting all aspects of the population PK and PK/PD analyses in support of the dosing recommendations in children):

- References to previous questions that address the points raised, but note that complete study report not available (only abbreviated reports, as previously submitted and supplementary material generated in response to CHMP LoQ).
- Concentration-time profiles of olmesartan medoxomil in paediatrics with observed (blue) and model fitted (population (top) and individual (bottom) in Figure below.





- Plots of total body clearance as a function of body weight, age, serum creatinine and ALAT (not shown); bodyweight normalized total body clearance as a function of body weight, age, serum creatinine (shown below) and ALAT (shown below), central volume of distribution as a function of body weight and age (not shown).



Final assessment of Population PK: Although not reported to the standard expected, on balance, the additional information provided by the applicant has confirmed that the population pharmacokinetic model developed by the company adequately describes the pharmacokinetics of olmesartan in the paediatric population. It is noted in the figure above that weight normalised clearance appears to show a relationship to serum creatinine. This is difficult to interpret without body weight (as serum creatinine is determined by muscle mass and renal function) and it would have been helpful to see this graph versus creatinine clearance. However, as (1) no children with creatinine clearance less than 25 ml/min were included in the study and (2) the applicant proposes a modification to the SmPC to advise caution (see Question 22), this issue is considered resolved.

Issue Resolved.

VII. RAPPORTEUR'S FINAL CONCLUSIONS AND RECOMMENDATION

The submitted data provide a statistically and clinically meaningful dose response for both systolic and diastolic blood pressure reductions with olmesartan in children 6 to 17 years old. The evidence on its efficacy in children of 1-5 years is not robust enough to allow an indication in this age range.

Although not reported to the standard expected, on balance, the additional information provided by the applicant has confirmed that the population pharmacokinetic model developed by the company, adequately describes the pharmacokinetics of olmesartan in the paediatric population. In children 6-17 years old, the proposed starting doses of 10 mg in children $\leq$ 35 Kg, and 20 mg $\geq$ 35 Kg will provide mean exposures similar to that in adults starting dose of 20 mg.

The applicant has provided comparison of the safety data between 338 children and adolescents exposed to olmesartan during 2 clinical trails and a total of 3190 adult patients. The safety profile of olmesartan in the paediatric population generally resembles that of adults; however events of joint sprain and eye pain with all related preferred terms and/or SOCs should be monitored in the updated risk management plan, with the view of a potential paediatric signal. Epistaxis was more frequent in the paediatric population, dizziness and headache nearly doubled at higher dose and this information must be included in the section 4.8 of the SmPC.

RECOMMENDATION

Based on the review of the presented paediatric data on pharmacokinetics, safety and efficacy and the assessment of the response to the list of questions raised by the Rapporteur and other MSs, it is considered that the results of these studies support a positive benefit:risk ratio for children with hypertension older than 6 years of age. The additional information has confirmed that the population pharmacokinetic model used adequately describes the pharmacokinetics of olmesartan in the paediatric population, thus the paediatric dosing used in these studies was sufficient to demonstrate an effect. The evidence of efficacy in the 1-5 years old is not robust enough to support the use of olmesartan in this age group, however the findings in should also be included in the SmPC.

The safety profile of olmesartan generally resembles that of adults, however higher frequency of epistaxis in children compared with adults and higher incidence of dizziness and headache with increasing dose of olmesartan have been noted.

Risk Management Plan:
The applicant has agreed to update paediatric information in the risk management plan when a paediatric indication is included in the SmPC. The following issues have been identified and must be included in the updated RMP:

- Adverse events of joint sprain and eye pain and their related preferred terms and/or SOCs, should be monitored in the updated risk management plan, with the view of potential for an idiopathic/paediatric signal.

- Adverse event of Sprue-like enteropathy has recently been reported in patients taking olmesartan medoxomil. The diarrhoea and abdominal pain were more frequent in children than in adults. Since this AE may occur years after starting treatment and since the negative impact

may be of particular importance for the development of a child, it should be included and monitored in the RMP update, in particular under paediatric heading.

FINAL SmPC TEXT

4.2 Posology and method of administration

Paediatric population

The safety and efficacy of olmesartan in children and adolescents below 18 years has not been established. ~~No data are available~~. **Currently available data are described in section 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.**

Olmesartan medoxomil should not be used in children below 1 years of age because of safety concerns and lack of data in this age group.

4.8 Undesirable effects

Paediatric population:

The safety of olmesartan was monitored in 361 children and adolescents, aged 1-17 years old during 2 clinical trials. Whilst the nature and severity of the adverse events are similar to that of the adults, the frequency of the following is higher in the children:

- Epistaxis is a common adverse event in children (i.e. ≥ 1/100 to < 1/10) that has not been reported in adults.
- During the 3 weeks of double blind study, the incidence of treatment emergent dizziness and headache nearly doubled in children 6-17 years of age in the high olmesartan dose group.

The overall safety profile for olmesartan in paediatric patients does not differ significantly from the safety profile in adults.

5.1 Pharmacodynamic properties

Paediatric population:

The antihypertensive effects of Olmetec in the paediatric population were evaluated in a randomized, double-blind, placebo-controlled study in 302 hypertensive patients aged 6 to 17 years. The study population consisted of an all black cohort of 112 patients and a mixed racial cohort of 190 patients, including 38 blacks. The aetiology of the hypertension was predominantly essential hypertension (87% of the black cohort and 67% of the mixed cohort). Patients who weighed 20 to <35 kg were randomized to 2.5 mg (low dose) or 20 mg (high dose) of Olmetec once daily and patients who weighed ≥35 kg were randomized to 5 mg (low dose) or 40 mg (high dose)of Olmetec once daily. Olmetec significantly reduced both systolic and diastolic blood pressure in a weight-adjusted dose-dependent manner. Olmetec at both low and high doses significantly reduced systolic blood pressure by 6.6 and 11.9 mmHg from the baseline, respectively. This effect was also observed

during the 2 weeks randomized withdrawal phase, whereby both mean systolic and diastolic blood pressures demonstrated a statistically significant rebound in the placebo group compared to olmetec group. The treatment was effective in both, paediatric patients with primary and secondary hypertension. As observed in adult populations, the blood pressure reductions were smaller in black patients.

In the same study, 59 patients aged 1 to 5 years who weighed ≥5 kg received 0.3 mg/kg of Olmetec once daily for three weeks in an open label phase and then were randomized to receiving Olmetec or placebo in a double-blind phase. At the end of the second week of withdrawal, the mean systolic/diastolic blood pressure at trough was 3/3 mmHg lower in the group randomized to Olmetec; this difference in blood pressure was not statistically significant (95% C.I. -2 to 7/-1 to 7).

5.2 Pharmacokinetic properties

Paediatric population:

The pharmacokinetics of olmesartan was studied in paediatric hypertensive patients aged 1 to16 years. The clearance of olmesartan in paediatric patients was similar to that in adult patients when adjusted by the body weight.

There is no pharmacokinetic information available in renally impaired paediatric subjects.

Final PIL text:

4. Possible side effects

Children and adolescents:
In children, side effects are similar to those reported in adults. However, dizziness and headache are seen more often in children, and nose bleeding is a common side effect seen in children only.

VIII. List of Medicinal products and marketing authorisation holders involved

MAH	Product	Strength	Pharmaceutical form
Berlin-Chemie	Laresin	10 mg	film coated tablet
Berlin-Chemie	Laresin	20 mg	film coated tablet
Berlin-Chemie	Laresin	40 mg	film coated tablet
Berlin-Chemie	Santini	10 mg	film coated tablet
Berlin-Chemie	Santini	20 mg	film coated tablet
Berlin-Chemie	Santini	40 mg	film coated tablet
Berlin-Chemie	Tenzar	10 mg	film coated tablet
Berlin-Chemie	Tenzar	20 mg	film coated tablet
Berlin-Chemie	Tenzar	40 mg	film coated tablet
Berlin-Chemie	Votum	10 mg	film coated tablet
Berlin-Chemie	Votum	20 mg	film coated tablet
Berlin-Chemie	Votum	40 mg	film coated tablet
Daiichi Sankyo	Benetor	10 mg	Film-coated tablets
Daiichi Sankyo	Benetor	10 mg	Film-coated tablets
Daiichi Sankyo	Benetor	10 mg	Film-coated tablets
Daiichi Sankyo	Olmes	10 mg	Film-coated tablets
Daiichi Sankyo	Olmes	20 mg	Film-coated tablet
Daiichi Sankyo	Olmes	40 mg	Film-coated tablet
Daiichi Sankyo	Olmetec	10 mg	Film-coated tablet
Daiichi Sankyo	Olmetec	20 mg	Film-coated tablet
Daiichi Sankyo	Olmetec	40 mg	Film-coated tablets
Menarini International Operations Luxembourg S.A	Benetor	10 mg	film coated tablet
Menarini International Operations Luxembourg S.A	Benetor	20 mg	film coated tablet
Menarini International Operations Luxembourg S.A	Benetor	40 mg	film coated tablet
Menarini International Operations Luxembourg S.A	Mesar	10 mg	film coated tablet
Menarini International Operations Luxembourg S.A	Mesar	20 mg	film coated tablet
Menarini International Operations Luxembourg S.A	Mesar	40 mg	film coated tablet
Menarini International Operations Luxembourg S.A	Olpress	10mg	film coated tablet
Menarini International Operations Luxembourg S.A	Olpress	20mg	film coated tablet
Menarini International Operations Luxembourg S.A	Olpress	40mg	film coated tablet
Menarini International Operations Luxembourg S.A	Olsar	10mg	film coated tablet
Menarini International Operations Luxembourg S.A	Olsar	20mg	film coated tablet
Menarini International Operations Luxembourg S.A	Olsar	40mg	film coated tablet
Menarini International Operations Luxembourg S.A	Plaunac	10mg	film coated tablet
Menarini International Operations Luxembourg S.A	Plaunac	20mg	film coated tablet
Menarini International Operations Luxembourg S.A	Plaunac	40mg	film coated tablet
Menarini International Operations Luxembourg S.A.	Alteis	10 mg	film coated tablet
Menarini International Operations Luxembourg S.A.	Alteis	20 mg	film coated tablet
Menarini International Operations Luxembourg S.A.	Alteis	40 mg	film coated tablet
Menarini International Operations Luxembourg S.A.	Belsar	10 mg	film coated tablet
Menarini International Operations Luxembourg S.A.	Belsar	20 mg	film coated tablet
Menarini International Operations Luxembourg S.A.	Belsar	40 mg	film coated tablet
Menarini International Operations Luxembourg S.A.	IXIA	10 mg	film coated tablet
Menarini International Operations Luxembourg S.A.	IXIA	20 mg	film coated tablet
Menarini International Operations Luxembourg S.A.	IXIA	40 mg	film coated tablet
Menarini International Operations Luxembourg S.A.	Mencord	10 mg	film coated tablet
Menarini International Operations Luxembourg S.A.	Mencord	20 mg	film coated tablet
Menarini International Operations Luxembourg S.A.	Mencord	40 mg	film coated tablet
Menarini International Operations Luxembourg S.A.	Olartan	10mg	film coated tablet
Menarini International Operations Luxembourg S.A.	Olartan	20mg	film coated tablet

Menarini International Operations Luxembourg S.A.	Olartan	40mg	film coated tablet
Menarini International Operations Luxembourg S.A.	Olmetec	10 mg	film coated tablet
Menarini International Operations Luxembourg S.A.	Olmetec	20 mg	film coated tablet
Menarini International Operations Luxembourg S.A.	Olmetec	40 mg	film coated tablet
Menarini International Operations Luxembourg S.A.	Omesar	10 mg	film coated tablet
Menarini International Operations Luxembourg S.A.	Omesar	20 mg	film coated tablet
Menarini International Operations Luxembourg S.A.	Omesar	40 mg	film coated tablet
Menarini International Operations Luxembourg S.A.	Revival	10 mg	film coated tablet
Menarini International Operations Luxembourg S.A.	Revival	20 mg	film coated tablet
Menarini International Operations Luxembourg S.A.	Revival	40 mg	film coated tablet
Menarini International Operations Luxembourg S.A.	Sarten	10 mg	film coated tablet
Menarini International Operations Luxembourg S.A.	Sarten	20 mg	film coated tablet
Menarini International Operations Luxembourg S.A.	Sarten	40 mg	film coated tablet
Menarini International Operations Luxembourg S.A.	Tensar	10 mg	film coated tablet
Menarini International Operations Luxembourg S.A.	Tensar	20 mg	film coated tablet
Menarini International Operations Luxembourg S.A.	Tensar	40 mg	film coated tablet
Menarini International Operations Luxembourg S.A.	Tensiol	10 mg	film coated tablet
Menarini International Operations Luxembourg S.A.	Tensiol	20 mg	film coated tablet
Menarini International Operations Luxembourg S.A.	Tensiol	40 mg	film coated tablet
PFIZER	Olmetec	10 mg	Tablet, Film Coated
PFIZER	Olmetec	20 mg	Tablet, Film Coated
PFIZER	Olmetec	40 mg	Tablet, Film Coated
PFIZER	Openvas	10 mg	Tablet, Film Coated
PFIZER	Openvas	20 mg	Tablet, Film Coated
PFIZER	Openvas	40 mg	Tablet, Film Coated
Terapia SA	Olmetec	10 mg	film coated tablet
Terapia SA	Olmetec	20 mg	film coated tablet
Terapia SA	Olmetec	40 mg	film coated tablet