Public Assessment Report for paediatric studies submitted in accordance with Articles 45 & 46 of Regulation (EC) No1901/2006, as amended

Candesartan Cilexetil

Atacand, Amias, Blopress

UK/W/023/pdWS/002

AstraZeneca

Rapporteur:	UK
Start of the procedure (day 0):	27 September 2011
Date of this report:	20 December 2011
Deadline for Rapporteur's preliminary paediatric assessment report (PPdAR) (day 70):	20 December 2011
Deadline for CMS's comments (day 85):	15 January 2011
Date re-start procedure (day 90):	12 March 2013
Deadline for CMS's comments (day 115):	2 April 2013
Finalisation procedure (day 120):	25 April 2013

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Atacand, Amias, Blopress
INN (or common name) of the active substance(s):	Candesartan Cilexetil
MAH (s):	AstraZeneca & Takeda Ltd
Pharmaco-therapeutic group (ATC Code):	C09CA06
Pharmaceutical form(s) and strength(s):	4, 8, 16, 32 mg tablets Extemporaneous oral solution

I. EXECUTIVE SUMMARY

This is an assessment of data for candesartan cilexetil. The applicant submitted one paediatric study completed before January 2007, in accordance with Article 45 and four paediatric studies completed after January 2007 in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use. The UK is Rapporteur for this procedure.

Candesartan cilexetil is a selective (AT1) angiotensin II receptor blocking agent available as a cilexetil salt tablet 'prodrug' that is hydrolyzed to the active candesartan upon absorption from the gastrointestinal tract. It was first approved for the treatment of hypertension in adults in 1997 through a mutual recognition procedure (MRP), with UK as the reference member state (RMS).

The applicant carried out an extensive paediatric program that includes 4 clinical studies of candesartan in children with hypertension: an efficacy and safety 4 weeks base study in children 6 to <17 years old, followed by a 1-year open-label extension and a single dose PK study; an efficacy and safety 4 weeks base study in children 1 to <6 years old, followed by a 1-year open-label extension and a single dose PK study. The applicant also submitted one bioavailability study, 7 juvenile/neonatal toxicological studies in dogs and rats, a brief clinical overview, and a 5 year PSUR covering the period of (April 2006 – April 2011).

These studies have been conducted in response to a written request for paediatric data from the US Food and Drug Administration (FDA) Paediatric Exclusivity list in March 1999. In the US, assessment of these studies resulted in a paediatric indication for hypertension in children aged 1 -18 years of age. This program was further modified based on scientific advice from the Committee for Medicinal Products for Human Use (CHMP) (27 July 2006, EMEA/H/SA/740/1/2006/III).

The applicant seeks indication for hypertension in children 1-18 years of age and has proposed SmPC changes in sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8, 5.1, 5.2, 5.3 and 6.6.

Following the first round of preliminary assessment, comments and additional requests for information were received from the other MSs were put to the Applicant in January 2012. A number of issues remained partially resolved in particular on posology and safety. Hence a second round of questions ensued (September 2012). Comments were received from three Member States, whom all agreed with the Rapporteur's conclusions and recommendations. This report includes the assessment of the data, the applicant's response to both rounds of questions raised (pages 89-127) for the finalization of the procedure.

In conclusion, in the submitted studies, efficacy was demonstrated in lowering both systolic and diastolic blood pressure in children 6 - <17 years old, but in the 1 to <6 year olds the efficacy is unclear, due to lack of placebo comparison. Other major issues concerning bioequivalence, PK and safety were clarified and added to the SmPC accordingly.

Provisional Summary of outcome

☒ New indication: 4.1, 4.2, 4.3, 4.4, 4.5, 4.8, 5.1, 5.2, 5.3

II. RECOMMENDATION (FINAL)

Based on the review of the presented paediatric data on pharmacokinetics, safety, efficacy and toxicology of candesartan and the assessment of the response to two rounds of questions raised by the Rapporteur and other MSs, it is considered that the results of these studies support the indication for treatment of hypertension in children 6 < 17 years of age, in the section 4.1 with dose recommendation in section 4.2 at a lower maximum dose than originally proposed by the MAH. The additional information provided failed to clarify the effect of weight on exposure/response in the lower age group as no clearance data was available. Together with the lack of a placebo arm, the evidence of efficacy and the PK data in 1<6 years old are not considered robust enough to support an indication in the younger age group. However the summary of the findings should be included in sections 5.1 and 5.2 of the SmPC.

The safety profile of candesartan generally resembles that of adults, but nearly all adverse events are more frequent in children. Sinus arrhythmia in children and the higher frequency of AEs must be captured in the section 4.8 of the SmPC. The ligament / joint related AEs must be included and kept under review in the updated risk management plan. Similarly the non-clinical findings of reduction in body and heart weight from juvenile animal studies must be captured in section 5.3 of SmPC and kept under review in the updated risk management plan.

The MAH is requested to submit appropriate variation within 60 days of finalization of this procedure.

PROPOSED SmPC & PIL CHANGES
The following changes to the SmPC were proposed by the applicant. The Rapporteur's / Member of State suggested text is in *Italic* and strike through:

SmPC

4.1 Therapeutic indications

- Treatment of hypertension in children and adolescents aged 6 to <18 years.

4.2 Posology and method of administration

Paediatric Population

Children and adolescents aged 6 to <18 years:
The recommended starting dose is 4 mg once daily.

- For patients weighing < 50 kg: In ~~some~~ patients whose blood pressure is not adequately controlled, the dose can be increased to a maximum of 8 mg once daily.

- For patients weighing ≥ 50 kg: In ~~some~~ patients whose blood pressure is not adequately controlled, the dose can be increased to 8 mg once daily and then to 16 mg once daily if needed *(see section 5.1)*. ~~In exceptional cases, the dose can be adjusted to a maximum of 32 mg once daily, at the discretion of the treating physician.~~

Doses above 32 mg have not been studied in paediatric patients.

Most of the antihypertensive effect is attained within 4 weeks.

For children with possible intravascular volume depletion (e.g., patients treated with diuretics, particularly those with impaired renal function), Atacand treatment should be initiated under close medical supervision and a lower starting dose than the general starting dose above should be considered (see section 4.4).

Atacand has not been studied in children with glomerular filtration rate less than 30 ml/min/1.73m^2 (see section 4.4).

Black paediatric patients
The antihypertensive effect of candesartan is less pronounced in black patients than in non-black patients. ~~Consequently, uptitration of Atacand and concomitant therapy may be more frequently needed for blood pressure control in black patients than in non-black patients~~ (see section 5.1).

Children aged below 1 year to <6 years

- The safety and efficacy in children aged 1 to <6 years of age has not been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made. ~~Candesartan should not be used in children aged 1 to <6 years of age.~~

- Atacand is contraindicated in children aged below 1 year (see section 4.3).

Posology in Heart Failure

Paediatric Population
The safety and efficacy of Atacand in children aged between birth and 18 years have not been established in the treatment of heart failure. No data are available.

4.3 Contraindications

Children aged below 1 year (see section 5.3).

4.4 Special warnings and precautions for use

Use in paediatric patients, *including patients* with renal impairment
Atacand has not been studied in children with a glomerular filtration rate less than 30 ml/min/1.73m^2 (see section 4.2).

For children with possible intravascular volume depletion (e.g. patients treated with diuretics, particularly those with impaired renal function), Atacand treatment should be initiated under close medical supervision and a lower starting dose should be considered (see section 4.2).

In post-menarche patients the possibility of pregnancy should be evaluated on a regular basis. Appropriate information should be given and/or action taken to prevent the risk of exposure during pregnancy (see sections 4.3 and 4.6)

4.5 Interaction with other medicinal products and other forms of interaction

Paediatric population

Interaction studies have only been performed in adults.

4.8 Undesirable effects

The frequencies used in the tables throughout section 4.8 are: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000).

Paediatric population

The safety of candesartan cilexetil was monitored in 255 hypertensive children and adolescents, aged 6 to <18 years old, during a 4 week clinical efficacy study and a 1 year open label study (see section 5.1). *In nearly all different system organ classes, the frequency of adverse events in children are within common/uncommon range.* Whilst the nature and severity of the adverse events are similar to *those in* ~~that of the~~ adults *(see the table above)*, the frequency of *all adverse events* ~~the following, all which are considered common childhood diseases or symptoms, compared to what has been reported in adults~~ *are higher in* ~~*the*~~ *children and adolescent, particularly in:*

- Headache, dizziness and upper respiratory tract infection, *are* "very common" (ie, ≥1/10) *in children and common (≥ 1/100 to < 1/10) in adults.*
- Cough is "very common" (ie, > 1/10) in children and very rare (<1/10,000) in adults.
- Rash is "common" (ie, ≥1/100 to <1/10) in children and "very rare" (<1/10,000) in adults.
- *Hyperkalemia, hyponatraemia and abnormal liver function are uncommon (≥ 1/1,000 to < 1/100) in children and very rare (< 1/10,000) in adults.*
- Sinus arrhythmia, Nasopharyngitis, pyrexia *are* "common" (ie, ≥1/100 to <1/10) and *oropharyngeal pain is "very common" (ie, ≥1/10) in children; but none are reported in adults.* However these are temporary and widespread childhood illnesses.

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

5.1 Pharmacodynamic properties

Paediatric population - hypertension

The antihypertensive effects of candesartan were evaluated in hypertensive children aged 1 to <6 years and 6 to <17 years in two randomised, double-blind multicentre, 4 week dose ranging studies.

In children aged 1 to <6 years, 93 patients, 74% of whom had renal disease, were randomised to receive an oral dose of candesartan cilexetil suspension 0.05, 0.20 or 0.40 mg/kg once daily. The primary method of analysis was slope of the change in systolic blood pressure (SBP) as a function of dose. SBP and diastolic blood pressure (DBP) decreased 6.0/5.2 to 12.0/11.1 mmHg from baseline across the three doses of candesartan cilexetil. However, since there was no placebo group, the true magnitude of blood pressure effect remains uncertain which makes a conclusive assessment of benefit-risk balance difficult in this age group.

In children aged 6 to <17 years, 240 patients were randomised to receive either placebo or low, medium, or high doses of candesartan cilexetil in a ratio of 1: 2: 2: 2. For children who weighed < 50 kg, the doses of candesartan cilexetil were 2, 8, or 16 mg once daily. In children who weighed > 50 kg, the candesartan cilexetil doses were 4, 16 or 32 mg once daily. *Candesartan at pooled doses reduced SiSBP by 10.2~~2~~ mmHg (P< 0.0001) and SiDBP (P=0.0029) by 6.~~5~~6 mmHg, from the base line. In the placebo group, there was also a reduction of 3.~~6~~6~~6~~7 mmHg in SiSBP (p=0.0074) and 1.80 mmHg for SiDBP (p=0.0992) from the baseline. Despite the large placebo effect, all individual candesartan doses (and all doses pooled) were significantly superior to placebo. Maximum response in reduction of blood pressure in children below and above 50 kg was reached at 8mg and 16 mg doses, respectively and the effect plateaued after that point.*

Of those enrolled, 47% were black patients and 29% were female; mean age +/- SD was 12.9 +/- 2.6 years. ~~The placebo subtracted effect at trough for sitting systolic blood pressure/sitting diastolic blood pressure for the different doses were from 4.9/3.0 to 7.5/6.2 mmHg.~~ In children aged 6 to < 17 years there was a trend for a lesser effect on blood pressure in black patients compared to non-black patients.

~~The safety and tolerability of candesartan cilexetil in hypertensive children aged 6 to 18 years was *further* studied in children aged 6 to <17 years in the randomised, placebo controlled, double-blind, 4 week dose ranging study presented above, and in a 1-year, open-label, follow-up study, during which some children turned 18 years of age. In general the safety profile of candesartan treatment in hypertensive children is consistent with the experience of treating adults. with the exception of headache, dizziness, cough, upper respiratory tract infection, oropharyngeal pain (frequencies very common), nasopharyngitis, pyrexia and rash (frequencies common), all which are considered common childhood diseases or symptoms. Sinus arrhythmia that is generally recognised as a benign physiologic phenomenon in children, was also reported in these paediatric studies. In other respects the safety profile of candesartan cilexetil was similar in children compared to adults *Whilst the nature and severity of the adverse events are similar to that of the adults, the frequency of all adverse events in all different system organ classes, are higher in the children and adolescents* (see section 4.8).~~

5.2 Pharmacokinetic properties

Paediatric population
The Pharmacokinetic properties of candesartan were evaluated in hypertensive children aged 1 to <6 years and 6 to <17 years in two single dose PK studies.

In children aged 1 to <6 years, 10 children weighting 10 to <25 kg received a single dose of 0.2 mg/kg, oral suspension. There was no correlation between Cmax and AUC with age or weight. No clearance data has been collected; therefore the possibility of a correlation between clearance and weight/age in this population is unknown.

In children aged 6 to <17 years, 22 children received a single dose of 16 mg tablet. ~~Half the subjects were below and half were above 12 years of age.~~ There was no correlation between Cmax and AUC with age. However weight seems to significantly correlate with Cmax (p=0.012) and AUC (p=0.011). No clearance data, has been collected, therefore the possibility of a correlation between clearance and weight/age in this population is unknown.

Children >6 years of age had exposure similar to adults given the same dose.

~~The pharmacokinetics (C_{max} and AUC) of candesartan cilexetil were not modified by age, sex or body weight. The dose-ranging studies of candesartan cilexetil revealed a dose related increase in plasma candesartan concentrations.~~

The pharmacokinetics of candesartan cilexetil have not been investigated in paediatric patients <1 year of age.

5.3 Preclinical safety data

In preclinical studies in normotensive neonatal and juvenile rats, candesartan caused a reduction in body weight and heart weight. As in adult animals, these effects are considered to result from the pharmacological action of candesartan. At the lowest dose of 10 mg/kg exposure to candesartan was between 12 and 78 times the levels found in children aged 1 to <6 who received candesartan cilexetil at a dose of 0.2 mg/kg and 7 to 54 times those found in children aged 6 to <17 who received candesartan cilexetil at a dose of 16 mg. As a no observed effect level was not identified in these studies, the safety margin for the effects on heart weight and the clinical relevance of the finding is unknown.

The renin-angiotensin-aldosterone system plays a critical role in kidney development in utero. Renin-angiotensin-aldosterone system blockade has been shown to lead to abnormal kidney development in very young mice. Administering drugs that act directly on the renin-angiotensin-aldosterone system can alter normal renal development. Therefore, children aged less than 1 year ~~must~~ *should* not receive Atacand (see section 4.3).

PIL

1. What Atacand is and what it is used for

The name of your medicine is Atacand. The active ingredient is candesartan cilexetil. This belongs to a group of medicines called angiotensin II receptor antagonists. It works by making your blood vessels relax and widen. This helps to lower your blood pressure. It also makes it easier for your heart to pump blood to all parts of your body.

This is medicine is used for:
- treating high blood pressure (hypertension) in adult patients and in children and adolescents aged 6 to <18 years.
- treating adult heart failure patients with reduced heart muscle function, in addition to Angiotensin Converting Enzyme (ACE) inhibitors or when ACE inhibitors cannot be used (ACE inhibitors are a group of medicines used to treat heart failure).

2. What you need to know before you take Atacand

- if the patient is a child under 1 year of age.

Warnings and precautions
Children and adolescents
Atacand has been studied in children. For more information, talk to your doctor. Atacand must not be given to children under 1 year of age due to the potential risk to the developing kidneys.

3. How to take Atacand
Use in children and adolescents with high blood pressure:

Children 6 to <18 years of age:
The recommended starting dose is 4 mg once daily.
For patients weighing < 50 kg: In some patients whose blood pressure is not adequately controlled, your doctor may decide the dose needs to be increased to a maximum of 8 mg once daily.

For patients weighing ≥ 50 kg: In some patients whose blood pressure is not adequately controlled, your doctor may decide the dose needs to be increased to 8 mg once daily and to 16 mg once daily. ~~In exceptional cases and if judged necessary by your doctor, the dose can be adjusted to a maximum of 32 mg once daily.~~

4. Possible side effects

In children treated for high blood pressure, *side effects appear* to *be similar* to those seen in adults, *but they happen more often*. Sore throat is a very common side effect in children but not reported in adults and runny nose, fever and increased heart rate are common in children but not reported in adults.

III. INTRODUCTION

On 26th of September 2011, AstraZeneca and its licensing partner Takeda Global Research & Development centre (Europe) Ltd submitted one paediatric study for candesartan completed before January 2007, in accordance with Article 45 and four paediatric studies completed after January 2007 in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

In adults in the EU, candesartan tablets are authorised for the treatment of hypertension and heart failure. In the current submission the applicant has requested a paediatric indication for children aged 1-18 years old.

The applicant carried out an extensive paediatric program that includes 4 clinical studies of candesartan in children with hypertension: an efficacy and safety 4 weeks base study in children 6 to <17 years old, followed by a 1-year open-label extension and a single dose PK study; an efficacy and safety 4 weeks base study in children 1 to <6 years old, followed by a 1-year open-label extension and a single dose PK study. The applicant also submitted one bioavailability study, 7 juvenile/neonatal toxicological studies in dogs and rats, a brief clinical overview, and a 5 year PSUR covering the period of (April 2006 – April 2011).

These studies have been conducted in response to a written request for paediatric data from the US Food and Drug Administration (FDA) Paediatric Exclusivity list in March 1999. The program was further modified based on scientific advice from the Committee for Medicinal Products for Human Use (CHMP) (27 July 2006, EMEA/H/SA/740/1/2006/III) these included:

• A request for an extended follow-up for 2 years in younger children
• A request for echocardiographic assessments.

The program of studies was carried out in the US/Puerto Rico and 26 sites in 10 European countries.

In the US, assessment of these studies resulted in a paediatric indication for hypertension in children aged 1 year and above. In addition, the US labelling includes information regarding the extemporaneous formulation.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do influence the benefit risk for candesartan and that there is a request for consequential regulatory action. The applicant proposes indication for hypertension in children 1-17 years of age and has proposed SmPC changes in sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8, 4.9, 5.1, 5.2, 5.3 and 6.6.

In addition, the following documentation has been included as per the procedural guidance:

- A line listing

- An annex including SPC wording of sections 4.1 and 4.2 related to the paediatric use of the medicinal product, but no related PL wording

Product characteristics

Candesartan is an angiotensin receptor blocker (ARB) that selectively inhibits the AT1 receptor by binding tightly to and dissociating slowly from the receptor site. It is administered orally as candesartan cilexetil, which is hydrolyzed to candesartan upon absorption from the gastrointestinal tract and, in hypertensive adults, candesartan lowers blood pressure in a dose-related fashion over a range of 2 mg to 32 mg administered once daily. Accordingly, the MAH's paediatric development program sought to evaluate candesartan as an antihypertensive pharmacologic treatment for hypertensive children from the age of 1 year through adolescence.

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.

The choice of antihypertensive agents available for treating children is more limited than that for adults, in part, because antihypertensives commonly used in adults may carry additional concerns when used in children. These include: diuretic-related changes in lipid and glucose metabolism, nifedipine-related acute neurologic symptoms, and propranolol effects on mental concentration, and athletic performance. Acceptable drug classes for use in children include

ACE inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, calcium channel blockers, and diuretics. At present in UK, valsartan, losartan and amlodipine have paediatric indication in 4.1 and captopril and enalapril, have paediatric posology in 4.2.

IV. SCIENTIFIC DISCUSSION

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

Pharmaceutical Development
Candesartan cilexetil is a white to off-white, non-hygroscopic crystalline powder with almost no odour or taste. It is practically insoluble in water (<1 µg/mL at 20°C, pH 1 to 8). Candesartan cilexetil is not sensitive to temperature, heat and moisture.

The extemporaneous oral suspension consists of ground candesartan cilexetil tablets dispersed in a 50/50% v/v blend of Ora-Sweet SF and Ora-Plus, which is available as a premix OBSF. The applicant has stated that any concentration within the range of 0.1 mg/mL to 2.0 mg/mL can be prepared, in any suitable batch size.

The Pharmaceutical Development document provided by the applicant details formulation development work undertaken using crushed tablet material together with the commercially available suspension vehicle. The suspension vehicle is supplied in the form of commercially available Ora-Blend Sugar-Free (OBSF), or alternatively Ora-Sweet Sugar Free (OSSF) and Ora-Plus (OP).

The applicant has provided a table detailing the qualitative composition of the OBSF. The product contains a paraben preservative system which appears effective from data provided and meets Ph. Eur. 5.1.3 requirements (P.2.5 Tables 4-9). Whilst there is an Acceptable Daily Intake (ADI) for methylparaben of 10mg/kg/day, no ADI for propylparaben has been agreed. In July 2006, the European Parliament agreed to withdraw the preservative propylparaben (propyl-parahydroxybenzoate) from food products based on advice from the EFSA. The withdrawal was based on the EC Scientific Committee for Food (SCF) being unable to recommend an ADI for propylparaben because of the lack of a clear NOAEL from non-clinical study data. Subsequently, applicants who apply for a Marketing Authorisation for products including propylparaben are asked to justify its inclusion given its withdrawal from food products. This position is likely continue until data has been generated which enable the derivation of an ADI. Methyl and ethyl paraben preservatives have been assigned an ADI of 10mg/kg/day by the European Food Standards Authority (EFSA).

Quality assessor's comment:
The applicant is asked to discuss and justify the inclusion of propylparaben in its liquid formulation.
Given the stability of the active substance, with respect to temperature, heat and moisture, it is not clear why a crushed tablet product should be the source of the candesartan cilexetil used to prepare the liquid suspension as opposed to active substance. A more straightforward and desirable formulation would be a fixed quantity of active substance as dry powder/granule presented in an extemporaneous dispensing pack for reconstitution with a suitable amount of OBSF suspension vehicle. A reconstitution pack would be particularly desirable as it would remove the issue of separate availability of the appropriate suspension vehicle and provide an appropriate volume of vehicle, thereby reducing preparation errors. This method of dry powder for reconstitution, using a packaged and supplied suspending vehicle, has already proven successful for other ARBs licensed for use in patient populations who require a liquid formulation. Given the clear advantages outlined above, the applicant is asked to discuss the possibility of providing a powder/solvent reconstitution pack for candesartan cilexetil.

Stability

Stability studies were conducted with candesartan cilexetil oral suspension 0.1 mg/mL and 2.0 mg/mL, filled in amber polyethylene terephthalate (PET) bottles fitted with a child resistant closure, indicate that the formulation has sufficient chemical and physical stability for its intended use when stored up to 100 days at 5°C/ambient humidity or at 25°C/60% RH (P.8 Stability for Drug Product). The prepared suspension can be stored below 25°C and used within 100 days from preparation. Photostability, in-use, low temperature testing (-20°C) and high temperature testing (50°C) has also been performed. Acceptance criteria for organic impurities were derived from the candesartan tablet specifications. All stability batches met the acceptance criteria set by the tablets. Stability data submitted support the 30 day open-bottle shelf-life proposed, though product must be shaken well before use to ensure homogeneity. No development or stability data has been presented for the extemporaneous product in amber glass bottles, probably because the commercial Ora-products are available in plastic primary packaging materials rather than amber glass.

Quality assessor's comment:

The assessor agrees that the formal stability data and supportive stability data support a shelf-life of 100 days for candesartan cilexetil oral suspensions within the range of 0.1 mg/mL to 2.0 mg/mL when stored below 25°C. Opened amber PET bottles should be used within 30 days.

However the container closure system (description-and-composition.pdf) describes the primary pack as '*typically… an amber polyethylene terephthalate bottle of appropriate size…*' The applicant should clarify and describe any development work that has been carried out in amber glass (or other glass variants) with the proposed extemporaneous formulation. If no data is available, container closure information should specifically restrict the primary product packaging to PET materials only.

Bioequivalence study (D2451C00005)

The bioequivalence study D2451C00005 has been submitted in support of a candesartan extemporaneous oral solution for patients unable to swallow solid oral dosage forms. The primary objective of the study was to determine the relative bioavailability (F_{rel}) or the commercial tablet and the extemporaneously prepared suspension by comparing $AUC_{(0-\infty)}$. Secondary objectives were the pharmacokinetics of candesartan: C_{max}, t_{max}, and $t_{1/2}$. All test subjects were fasted.

It is noteworthy that the extemporaneous suspension was submitted as a paediatric sNDA to FDA in April 2009, including a label describing the extemporaneous preparation of a tablet based suspension. The sNDA was approved in US October 2009.

Table 1- Pharmacokinetic parameters from study D2451C00005 (n=22)

		t_{max} (h)	C_{max} (nmol/L)	$t_{1/2}$ (h)	AUC_{0-t} (nmol·h/L)	AUC (nmol·h/L)
Suspension	Mean	NA	667.0	NA	6974.5	7322.8
	Min	2.0	379.0	6.5	3564.2	3697.8
	Median	3.00	651.50	12.0	7308.45	7610.39
	Max	5.00	1050.00	16.56	9802.06	10627.49
	CV%	NA	28.339	NA	26.711	27.358
	Geometric mean	NA	643.1	NA	6760.3	7086.8
Tablet	Mean	NA	565.5	NA	6447.4	6903.7
	Min	2.0	236.0	6.4	2616.4	2683.0
	Median	3.53	585.50	11.1	6057.15	6262.43
	Max	6.00	989.00	22.29	11340.40	11903.83
	CV%	NA	43.782	NA	33.811	34.653
	Geometric mean	NA	522.6	NA	6136.2	6559.0

AUC = area under the plasma concentration curve, C_{max} = observed maximum plasma drug concentration, CV = coefficient of variance, NA = not applicable, $t_{1/2}$ = terminal elimination half-life, t_{max} = time to reach C_{max}

Note: The PK parameters for both the suspension and the tablet formulation are based on 22 subjects. Data derived from Section 11.2, Table 11.2.1.1, Clinical Study Report D2451C00005.

Figure 1- Geometric mean plasma concentrations of candesartan

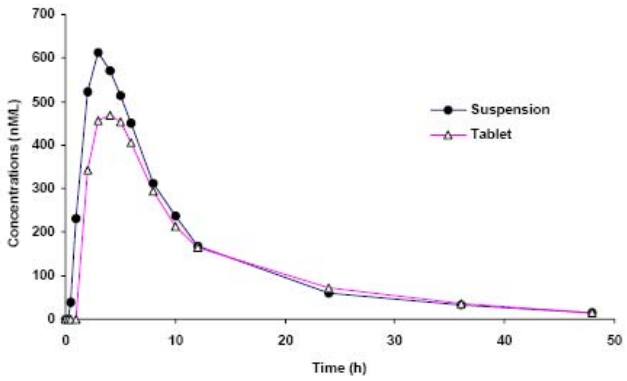


Table 1 shows the pharmacokinetic parameters for the suspension and the tablet formulation. The t_{max} and $t_{½}$ estimates for the suspension were comparable to those of the tablet: median values were 3.0 hours and 3.5 hours for t_{max}, respectively, and 12.0 hours and 11.1 hours for $t_{½}$, respectively.

The 90% CI on the ratio of the mean AUC estimates for the suspension and the tablet was (0.86, 1.00), which is within the accepted boundary of 0.80-1.25 for establishing bioequivalence. In addition the two concentration-time curves are reassuringly similar between the two formulations, which is to be expected given that the liquid is effectively a modified, extemporaneously manipulated version of the solid oral dosage formulation.

However the 90% CI on the ratio of the mean C_{max} estimates for the tablet and suspension was (0.74, 0.91), which fell below the accepted boundary of 0.80-1.25 for establishing bioequivalence. The above values at the 90% CI are defined in the current bioequivalence guidelines and remain consistent with the guidelines that were available when the bioequivalence study was performed (CPMP/EWP/QWP/1401/98 - 14 Dec 2000).

Quality assessor's comment:
No explanation for the higher C_{max} for the liquid has been provided by the applicant and no indication is given as to whether there are any clinical consequences. Given that the suspension is derived from the reference tablet, the discrepancy in extent of absorption between the tablets and suspension may simply be due to disintegration of the tablet structure and a return to an uncompressed granular mix that is more readily penetrated by suspension vehicle and, subsequently, gastrointestinal fluids. However the discrepancy has not been discussed and wider acceptance intervals were not prospectively defined.

The applicant should discuss the discrepancies in C_{max}, particularly with respect to any clinical significant differences seen, if any.

The applicant states that 'the pharmacokinetic profiles established that the suspension was suitable for once daily treatment and that no 'formulation-based' dosage adjustment was needed.' Given the higher C_{max} the no dose adjustment statement should be further explained.

Both formulations were well tolerated and treatment-related adverse events were comparable between formulations.

The extent of candesartan exposure was essentially the same for both formulations: relative bioavailability 93% (tablet vs. suspension). The results of the study also showed that time to maximum plasma concentration (t_{max}) and terminal half-life ($t_{1/2}$) estimates for the candesartan suspension were comparable, but not equivalent, to those of the candesartan tablet.

Overall quality conclusion
The formal stability data and supporting development data supports a shelf life of 100 days for candesartan cilexetil oral suspension in Ora-Blend vehicle within the range of 0.1 mg/mL to 2.0 mg/mL when stored below 25°C. The applicant's proposed restriction on using opened bottles within 30 days is acceptable. It is accepted that bioavailability of extemporaneous products can be unpredictable. Some of the unpredictability could be removed by providing candesartan cilexetil active substance and a suspension vehicle for reconstruction. A powder-for-reconstitution pack would remove much of the variability inherent in extemporaneously preparing a suspension using crushed tablet material. Manipulation of existing formulations should always be a last resort where alternative formulations are not available. Given that a powder-for-reconstitution ARB product is already commercially available, a crushed tablet formulation would undoubtedly be an inferior presentation; the applicant should discuss whether a straightforward candesartan cilexetil powder-for-reconstitution product could be made available.

A formulation obtained from a crushed solid dosage form may not be bioequivalent with the same dose form when swallowed whole, even when prepared in a standardised commercial vehicle. Bioequivalence (study D2451C00005) was not proven with respect to C_{max}. Wider acceptance limits may have been accepted if appropriately and prospectively justified, but justification and discussion were not provided. Given that candesartan cilexetil is a prodrug, the applicant should discuss whether the higher liquid formulation C_{max} has any clinical significance. There are some other outstanding issues regarding alternative primary packaging materials (other than PET). More importantly, specifically in relation to the proposed patient population, the question of the use of propylparaben in a paediatric formulation requires justification.

IV.2 Non-clinical aspects

The applicant has submitted 7 neonatal/juvenile animal study reports to support the paediatric indication of Atacand (Candesartan Cilexetil) in the treatment of hypertension in children and adolescents (aged 1-18 years):

- **C-42-01979**: Single dose oral toxicokinetic study in neonatal rats.
- **C-42-01980**: Range finding study for the effects of TCV-116 on heart development in neonatal Crl:CD(SD) rats by 7-day oral administration
- **TCV-116-10158**: A study on the effects of candesartan on heart development and toxicokinetics in neonatal rats.
- **TCV - 116-10021**: 1 week oral dose range findings study in juvenile rats.
- **TCV-116-10162**: 5 week oral dose-range finding study in juvenile rats.
- **TCV-116-10169**: 13 week oral repeat dose study in juvenile rats - effect on heart development and toxicokinetics.
- **SR02173-01**: Single ascending oral dosing of candesartan cilexetil in juvenile beagle dogs.

The angiotensin II type 1 (AT_1) receptor antagonist candesartan cilexetil has been licensed for the following indications in adults: monotherapy, at doses up to 32mg, and as a fixed dose combination product at doses, up to 32 mg candesartan and 25 mg hydrochlorothiazide in adults and is thus supported by a package of adult non-clinical efficacy and safety studies. A summary of the main findings of these studies is included in section 4.4 for information.

The applicant has submitted the 6 non-clinical overviews/expert reports prepared in support of the adult indications for information.

- Heywood, R 1996: Expert Report on the Pharmaco-toxicological Documentation. Candesartan Cilexetil. 12 September 1996;
- Heywood, R 1997: Expert Report on the Pharmaco-Toxicological Documentation. Candesartan Cilexetil/Hydrochlorothiazide. 25 November 1997;
- Heywood, R 1999: Expert Report on the Pharmaco-toxicological Documentation. Candesartan Cilexetil/Hydrochlorothiazide. 17 February 1999;
- Säfholm, C 2002: Nonclinical Statement: Candesartan Cilexetil: Preclinical toxicology data to support 32mg/day in man 13 June 2002;
- Säfholm, C 2004: Nonclinical Overview: Candesartan Cilexetil in the treatment of Chronic heart failure. 19 January 2004
- James, R 2008: Nonclinical overview as part of the submission for candesartan cilexetil/hydrochlorothiazide 32/12.5mg and 32/25 mg doses. 21 May 2008.

GLP aspects

Half of the neonatal and juvenile toxicity/toxicokinetic studies submitted for evaluation were not conducted in compliance with Good Laboratory Practice (GLP). The GLP status of each study has been noted in the description of the studies.

Non-clinical studies

The following juvenile toxicity/toxicokinetic studies have been conducted to: (a) investigate potential age-related differences in sensitivity to adverse effects previously identified in adult non-clinical studies, (b) identify novel toxicities and/or (c) identify effects on developmental

parameters relevant to the indicated paediatric patient population of 1-18 years following treatment with the angiotensin II type 1 (AT_1) receptor antagonist candesartan cilexetil.

Table 2- Approximate human developmental age of the animals used in the studies

	Neonatal rat PND 0 to13	Juvenile rat PND 7 to 105	Juvenile dog PND 42/49 (6-7 weeks or 1.5 - 2 months old)
Human	Birth to 12 months	1 month to adulthood	18-24 months

The studies were provided by AstraZeneca and Takeda Global Research & Development Centre (Europe) Ltd as agreed for this work sharing procedure.

Table 3- Juvenile/Neonatal toxicity/toxicokinetic studies conducted with candesartan cilexetil

Study type/reference	Species/age at study start	Route	Treatment	Duration treatment	GLP status
Juvenile toxicity/SR 02173-01	Beagle dog/ 6-7 weeks	Oral gavage	Candesartan cilexetil 0, 20, 100, 300 mg/kg/day	Single dose	GLP
Juvenile toxicity/TCV -116-10021	SD Rat/7 days	Oral gavage	Candesartan cilexetil 0, 100, 1000 mg/kg/day	7 days with 1 week recovery	Non-GLP
Juvenile toxicity/TCV -116-10162	SD Rat/7 days	Oral gavage	Candesartan cilexetil 0, 10, 100 mg/kg/day	5 weeks	Non-GLP
Juvenile toxicity/TCV-116-10169	SD Rat/7 days	Oral gavage	Candesartan cilexetil 0, 10, 100 mg/kg/day	13 weeks	GLP
Neonatal/C-42-01980	SD Rat/0 or 7 days	Oral gavage	Candesartan cilexetil 0, 3, 30, 100 mg/kg/day Enalapril 30mg/kg/day	7 days (postnatal days 0-6 or 7-13) with or without 9- or 8-week recovery for 30 and 100 mg/kg group	Non-GLP
Neonatal/TCV-116-10158	SD Rat/0 or 7 days	Oral gavage	Candesartan cilexetil 0, 100 mg/kg/day	7 days (postnatal days 0-6 or 7-13)	GLP
Neonatal toxicokinetics/C-42-01979	SD Rat/0 or 7 days	Oral gavage	Candesartan cilexetil 30, 100 mg/kg/day	Single dose	Non-GLP

Concerns regarding potential effects on heart growth in children

The publication of two reviews in the open literature has raised concerns regarding potential adverse effects on the somatic heart growth of the intended paediatric population. The non-clinical and clinical study findings cited in these reviews showed that inhibitors of the renin-angiotensin-aldosterone system (RAAS) were able to suppress the growth of the heart through inhibition of hypertrophy, the physiological mechanism of cardiac growth in children beyond the age of 6 months.

In order to investigate the significance of these findings the neonatal and juvenile toxicity studies have been designed to include an examination of effects on heart growth.

STUDIES IN NEONATAL ANIMALS - Rats

C-42-01979: Single dose oral toxicokinetic study in neonatal rats

Description: Systemic exposure of candesartan cilexetil was quantified in neonatal rats following a single oral dose and compared to values recorded in adult rats and hypertensive children in this non-GLP study.
Method: Groups of neonatal Crl:CD(SD) rats aged 0 day old (30 pups/sex/group) or 7 day old (15 pups/sex/group were) rats were administered a single dose of either **30 or 100mg/kg** candesartan cilexetil orally by gavage.

Results: The mean plasma concentrations of candesartan achieved are shown in table 3. The applicant stated that the $AUC_{0\text{-}24h}$ values of the 100mg/kg pups on postnatal days 0 (162133 ng.h/mL) and 7 (166662 ng.h/mL) was 2.2 times higher than the $AUC_{0\text{-}24h}$ of adult rats (6 weeks old F344/Jcl rats) at the same dose and is approximately 150 times higher than that in a 6-12 years old hypertensive patient receiving 16 mg candesartan cilexetil. The increased AUCs in the neonatal rats relative to adult values was due to the higher Tmax values attained in the young rats (4.0 to 24.0 hours) compared to those observed in the 6 week old rats following a dose of 30 and 100mg/kg candesartan cilexetil (0.5 hours). See table 4.

Table 4- Pharmacokinetic parameters in neonatal rats following single dose administration

Group	Dose (mg/kg)	Tmax (h)	Cmax (ng/mL)	$AUC_{0\text{-}24h}$ (ng·h/mL)
		Male:Female	Male:Female	Male:Female
Day 0	30	24:24	4340:7689	60740:92169
Day 7	30	24:24	8318:7223	129946:120336
Day 0	100	24:24	18890:8640	215477:108788
Day 7	100	24:24	11860:7343	177987:155336

Source: Report C-42-01 979 Tale 1
Cmax: Maximum observed concentration
Tmax: Time to reach Cmax

Non-clinical assessor's comments
As neonatal rats are not age/developmentally equivalent to the 6-12 year old hypertensive patients, comparison of the exposure profiles between the two is not considered acceptable. The applicant will be requested to provide exposure data for 1 to <6 years olds and to calculate the margin of exposures for this age group.

C-42-01980: Range finding study for the effects of TCV-116 on heart development in neonatal Crl:CD(SD) rats by 7-day oral administration

Description: Non-GLP range finding study investigating the potential effects of candesartan cilexetil on heart development in neonatal rats.

Method: Groups of neonatal Crl:CD(SD) rats (5/sex/dose) were administered 0, (0.5% methylcellulose solution) 3, 30 and 100 mg/kg/day candesartan cilexetil on either PND 0 to 6 or PND 7 to 13. The ACE inhibitor Enalapril (30mg/kg/day) was included as a positive control. Additional groups were included for interim sacrifices at PND 7, 14 or 10 weeks of age (recovery group). Parameters evaluated during the treatment and recovery phase included mortality, clinical signs and bodyweights, heart and kidney weights and histopathology examination of these tissues. The immunohistochemical techniques proliferating cell nuclear antigen (PCNA)

and terminal dUTP nick end-labelling (TUNEL) was used to evaluate proliferating activity of the cardiomyocytes and apoptosis respectively in 3 regions of the heart, left ventricle, right ventricle and interventricular septum in the 100mg/kg candesartan and 30mg/kg enalapril groups.

Result:

Subgroup A (PND 0 to 6):

- **Increased bodyweights** at 30 (males) and 100mg/kg/day (statistically significant) and in the positive control group (enalapril).
- The **absolute heart weight** reduced only at 3 mg/kg/day candesartan and thus non-dose related. No other groups were affected therefore the **heart weight relative to bodyweight was reduced** at all doses tested.

Subgroup B (PND 7 to 13):

- **Increased bodyweights** at 30 and 100mg/kg/day (statistically significant) candesartan cilexetil but **reduced** in the enalapril PND 7-14 group due to inadequate nursing of the pups.
- **Absolute heart weight** was not affected leading to a **reduced heart weight relative to bodyweight** at all doses tested (female only at 100mg/kg/day).
- Effects in the **recovery groups** was adverse **renal pathology** at 30 and 100mg/kg/day – (atrophy of the papilla, cysts, dilatation of the pelvis, renal tubule dilatation, mononuclear cell infiltration and tubular basophilia) and hyaline casts at 100mg/kg, which had not been observed in the main test groups indicating a delayed effect.

Both subgroups

- No effect on the apoptotic rate.
- A statistically significant increase in the **number of PCNA positive cardiomyocytes, PCNA negative cardiomyocytes** and/or total cardiomyocytes were observed in some regions of the heart in the PND 0 to 6 and PND 7 to 13 100mg/kg candesartan group however this was not considered to be treatment related due to the absence of an effect on the PCNA positive ratio. No increases in mortality or abnormal clinical signs were observed.

Table 5- Heart weight relative to final bodyweight

	% of final bodyweight Subgroup A - PND **0-6**		**% of final bodyweight** Subgroup B - PND **7-13**	
	Female	**Male**	**Female**	**Male**
Control	**0.80**	**0.83**	**0.54**	**0.54**
3	0.68	0.63	0.45	0.46
30	0.64	0.70	0.48	0.47
100	0.68	0.73	0.47	0.50

Significantly different from control; *:p≤0.05

Non-clinical Assessor's comments

This was a non-GLP dose-range finding study with a small number of animals used for the evaluation; therefore only limited conclusions can be drawn from the findings.

Heart weight

The reduction in relative heart weights in subgroups A and B was due to the increased bodyweight with no change in the absolute heart weight. The applicant did not consider this to be a toxicologically significant finding however it might represent an uncoupling of heart growth from total body growth in this study. There was no evidence of apoptosis in the study, and there was no clear change in the rate of myocardial cell proliferation, which is consistent with the absence of effect on absolute heart weight. The positive control did not affect the proliferative myocardial cell numbers, which is in contrast to the findings of an earlier study (Choi et al, 2002) that showed a 23% reduction in the number of cardiomyocytes, high mortality, decreased body weight gain (by 14.6%) and decreased heart weight by 18% in neonatal Sprague-Dawley rats

administered 30mg/kg/day enalapril on postnatal days 0-6. The applicant could not explain the reason for these contrasting findings.

Body weight
The increased bodyweights contrast the reduction in bodyweights observed in most of the studies conducted with candesartan (i.e. reduced body weights) and other inhibitors of the renin-angiotensin system. As food consumption data was not recorded the cause of this effect is unknown.

Renal toxicity
Given the known effects of candesartan on renal development the reported histopathological findings in the recovery groups are considered to be treatment-related. The appearance of this effect in the recovery animals – 10 weeks after dosing indicated a long term irreversible effect, which is consistent with the known effects of inhibitors of the renin-angiotensin-aldosterone system (RAAS) on renal development in neonatal rats.

TCV-116-10158: A study on the effects of candesartan on heart development and toxicokinetics in neonatal rats

Description: GLP study investigating the potential effects of candesartan cilexetil on the heart of neonatal rats and characterising the toxicokinetic profile of candesartan.
Method: 100mg/kg Candesartan cilexetil was administered orally by gavage to 2 subgroups of 10 neonatal male and female Crl:CD(SD) rats once daily during postnatal days (PND) 0 to 6 (subgroup A) or PND 7-13 (subgroup B). Toxicokinetic analysis of candesartan cilexetil, candesartan and the M-II metabolite was performed (Subgroup A: control n=15 pups/sex; 100mg/kg n= 81 pups/sex Subgroup B: control n=9 pups/sex; 100mg/kg n=48 pups/sex). Proliferating activity and apoptosis of cardiomyocytes was assessed by proliferating cell nuclear antigen *(PCNA) staining and *(TUNEL) staining respectively. Heart and kidney weights were measured. Organ to final bodyweight ratios were calculated.

Result:
Subgroup A
- Reduced mean **body weights** and **bodyweight gain** in males* and females resulting in final body weights of **16.6% and 9.5% lower**, respectively, compared to concurrent controls.
- Statistically significant reduction in the **absolute heart weight** in males [20%*] and females [18.0%*] ; and reduced **heart weights relative to final bodyweights** in males [4.7%] and females [11.4%] (not significantly different from the controls)
- Reduced cardiac myocyte proliferation in females (but not males) considered to be related to the reduced heart weight in the female pups.
- No change in myocardial cell apoptotic rates.

Subgroup B
- Statistically significant reduction in the number and percentage of PCNA-positive cells in each of the 3 sub regions and the 3 sub regions combined compared to controls (left ventricle, right ventricle and interventricular septum) in the female rats.

Table 6- Subgroup A bodyweight and organ weight changes

Text Table 1. Toxicologically Relevant Final Body Weight And Organ Weight Changes

Parameter	Direction and magnitude of change	Dosage level (mg/kg/day)	Sex	Cohort
Final Body Weight	↓ 16.6%	100	M	Subgroup A
(PND7)	↓ 9.5%	100	F	Subgroup A
Heart				
Absolute	↓ 20.0%	100*	M	Subgroup A
Relative to body wt.	↓ 4.7%	100	M	Subgroup A
Absolute	↓ 18.0%	100*	F	Subgroup A
Relative to body wt.	↓ 11.4%	100	F	Subgroup A

* = Significantly different from the control group at 0.05 using a two-sample t-test

The Cmax and AUC values were generally comparable between males and females and at all time points. The time to reach Cmax (Tmax) occurred at 24 hours on PND 0 and 7 and at 4 hours on PND 6 and 13. The tabulated results are in Toxicokinetic section in pages 25 - 29.

The MAH concluded that there were no treatment-related effects in the study.

Non-clinical assessor's comments

This study was designed to evaluate the potential effects of candesartan on heart growth in young neonatal animals therefore the duration of dosing was confined to the period of expected rapid heart growth. The sample size (n=10/sex/group) is acceptable for a mechanistic investigation.

Body weight

The younger pups (PND 0 to 6) appeared to be more sensitive to the toxicological effects of candesartan compared to the PND 7 to14 group as evidenced by the significant reduction in bodyweights and bodyweight gain throughout the treatment period in this group. There was also an age related reduction in the time to reach Cmax.

Heart weight

For the females in the PND 0 to 6 group the % reduction in the absolute heart weight was higher than could be accounted for by the effect on bodyweight. The study author conceded that this was a direct effect of treatment and suggested a relationship to the lower cell proliferation values (PCNA), which is plausible. In this study there appears to be an age-related difference in susceptibility to effects on heart weight judging by the reductions observed in the pups aged PND 0 to 6 (equivalent to a newborn baby), compared to a lack of effect in pups aged PND 7 to 13. The significance of this is unclear because a clear reduction in myocardial cell proliferation was evident in females in subgroup B. Overall the applicant's conclusion that there were no treatment-related effects in the study is not supported by the findings.

It should be noted that the pups in the PND 0 to 6 groups were dosed from PND 4 to 6 due to the technical limitations of gavage dosing pups aged from PND 0 to 3. This is considered acceptable. Effects on heart growth was observed in the treated animals and the toxicokinetic data confirmed exposure therefore it is unlikely that the reduced duration of exposure had a negative impact on the outcome of the study.

CONCLUSION ON NEONATAL STUDIES

Overall the neonatal studies showed a treatment related reduction in female heart weight that appears to be due to a reduction in the proliferation of the myocardial cells. There were no clear effects in the male pups, however, as discussed later in this report reduced heart weight (and bodyweights) was observed in both male and female pups treated from PND 7 to 13 in the 1 week juvenile rat study (***TCV - 116-10021***) therefore this finding does not appear to be restricted to females and the early postnatal period (PND 0 to 6). In rats the proliferative activity of the cardiomyocytes is at its highest in the first week after birth and decreases to a level of almost zero by 3 weeks of age so adverse effects on heart growth, as observed in these studies is a concern. The age range of the affected pups is equivalent to neonates/infants aged from birth to approximately 1 year.

With regards to effects on bodyweight, the definitive study showed a significant reduction in bodyweights and bodyweight gain in the younger pups (PND 0 to 6 males and females reduced by 16.6% and 13.4% respectively, relative to controls) compared to the older pups. As indicated above, reduced bodyweight gain was observed during the recovery period of pups that had been dosed between PND 7 to 13 in the 1 week juvenile toxicity study (***TCV - 116-10021***); therefore this finding does not appear to be restricted to the early postnatal period (PND 0 to 6).

The applicant has not provided clinical exposure data for the 1>6 year old patients and has based their safety margin calculations on data from 6-12 year olds alone even though the proposed paediatric patient population is 1-18 year olds. The applicant will be asked to provide the clinical pharmacokinetic data and the safety margins for the effects identified in these studies.

STUDIES IN JUVENILE ANIMALS - Rats

TCV - 116-10021: 1 week oral dose range findings study in juvenile rats

Description: A preliminary non-GLP study was designed to evaluate doses for the preliminary 5 week toxicity study (TCV-116-10162),
Method: Groups of 7 day old Crl:CD(SD) juvenile rats (n=6/sex/dose) were administered either 0 (0.5% methylcellulose solution), 100 or 1000 mg/kg/day candesartan cilexetil orally by gavage for 7 days followed by a 1 week recovery period. Parameters evaluated included mortality, clinical signs, bodyweights, heart and kidney weights and gross morphology.

Results: The results of the study showed a treatment related reduction in **absolute and relative heart weights**, relative **kidney weights** and **hydronephrosis** in the 100 and 1000/mg/kg group. **Body weight gain** was suppressed during the recovery period.

Non-clinical assessor's comments
Treatment related reductions in relative and absolute heart weight and suppressed bodyweight gains following a week long recovery period were observed in these 7 day old rats.

TCV-116-10162: ***5 week oral dose-range finding study in juvenile rats***

Description: Preliminary non-GLP study conducted to evaluate doses for the definitive 13 week juvenile toxicity study (TCV-116-10169).
Method: groups of 7 day old Crl:CD(SD) juvenile rats (n=6/sex/dose) were administered either 0 (0.5% methylcellulose solution), 10 or 100 mg/kg/day candesartan cilexetil orally by gavage for 5 weeks. Parameters evaluated included mortality, clinical signs, bodyweights, haematology,

blood chemistry, organ weights, gross pathology of all organs and histopathological examination of the heart and kidneys. Blood samples were collected for toxicokinetic evaluation after the 1st and 35th dose.

Results:

- Decreased **bodyweight gain** at 10 and 100mg/kg/day (both sexes)
- Decreases in erythrocyte counts, hematocrit values and haemoglobin concentration observed in both sexes. Females also had increased platelet and reticulocyte counts at 10 and 100mg/kg/day
- **Effects on blood chemistry parameters** at 10 and 100mg/kg/day: Increased urea nitrogen, decreased total protein and albumin (both sexes). These findings have previously been observed in adult rats. Decreased calcium, potassium, increased total cholesterol observed in males. However potassium levels were increased in previous studies in adult F344 rats and in Wistar pups exposed during lactation. The reasons for these contrasting effects were unclear.
- **Renal toxicity** at 10 and 100mg/kg - pale kidneys and dilatation of the renal pelvis and increased absolute and relative kidney weight, a non-dose related dilatation of the renal pelvis, nephropathy and oedematous papillae considered to be related to hydronephrosis. Tubular basophilia in the kidney in most of the animals in the control group. The frequency in the treated groups was decreased and this was considered to be toxicologically significant. Hypertrophy of the juxtaglomerular cells and tunica media of the arterioles were noted and have previously been observed in adult rats.
- Decreased **absolute and relative heart weights** at 100mg/kg. No adverse histopathology in the cardiac tissue.
- Survival was unaffected.
- Toxicokinetic evaluation showed a less than dose proportional increase in AUC and Cmax values after the 1st and 35th dose indicating that enzyme induction may have occurred.

Table 7- $AUC_{0\text{-}24h}$ of candesartan cilexetil from the 5 week juvenile rat study

Age	**Daily Dose (mg/kg/day)** N= 6/sex/dose	**Animal $AUC_{0\text{-}24h}$ (ng•h/mL)**			**Animal: Human XXX Exposure**
		Male	**Female**	**Total**	**Multiple**
PND 7 (1st)	10	443	337	390	0.36 x
PND 42 (35th)	10	1	20	11	0.01 x
PND 7 (1st)	100	893	1258	1073	0.98 x
PND 42 (35th)	100	16	33	24.5	0.02 x

Paediatric clinical AUC =1094 ng•h/ml

Non-clinical assessor's comments

Treatment related reductions in relative and absolute heart weight and bodyweight gain was observed at clinically relevant doses (Candesartan cilexetil $AUC_{0\text{-}24}$) in this study. The effects on the kidney and haematological parameters are consistent with findings previously reported in adult mice, rats, dogs and monkeys treated with candesartan.

TCV-116-10169: 13 week oral repeat dose study in juvenile rats - effect on heart development and toxicokinetics

Description: Study designed to evaluate the effects of candesartan cilexetil on cardiomyocyte development in juvenile animals and to assess toxicokinetic parameters.
Method: Groups of 12 juvenile Crl:CD(SD) male and female rats were administered 0, 10 and 100 mg/kg/day orally by gavage once daily from postnatal days 7 to 97. Satellite groups (6/sex for controls and 24/sex in each drug treatment group) were added for toxicokinetic evaluation of the pro-drug candesartan cilexetil, candesartan (metabolite M-I) and metabolite M-II. In life observations included physical examinations, body weights, food consumption, physical development (vaginal patency and balanopreputial separation), haematology, serum chemistry and mortality. Selected organs, including the heart and kidney, were weighed for all survivors and tissues examined microscopically for animals in the control and 100 mg/kg/day groups. The kidneys of all animals were examined microscopically.

Results:

- **Body weight gain** reduced (females only) at 10 and 100mg/kg/day groups resulting in low body weights from PND 21 onwards.
- Food consumption unaffected.
- Reduced **absolute and relative heart weight** (both sexes) at 10 and 100 mg/kg/day (statistically significant). No reported findings in histopathology examination of the heart tissue.
- **Renal toxicity** at 10 and 100mg/kg/day - dose–related increase in mean urea nitrogen and increased creatinine (males only), dilated renal pelvis, increased absolute and relative kidney weights, nephropathy and dilated renal pelvis, dilated renal papillary ducts, renal papillary oedema, and lymphocyte infiltrate which was considered to be a toxic effect. Hypertrophy of the juxtaglomerular cells and tunica media of the arterioles had also been noted in adult rats and not considered to be toxic lesions because of pharmacology-related changes.
- Increase in absolute and relative **adrenal gland** weights at 10 and 100mg/kg/day.
- All other parameters (e.g. haematology, physical development etc) were unaffected.
- The tabulated results are in Toxicokinetic section in pages 25 - 29.

As adverse effects were observed at all doses tested a no-observed-adverse-effect-level (NOAEL) was not identified.

Non-clinical assessor's comments
Reductions in absolute and relative heart weights and female bodyweights were observed at all doses tested, therefore a safety margin cannot be determined for these effects. Food consumption was not affected; therefore the cause of the reduced bodyweight is unclear. The relevance of these findings to the patient population cannot be ruled out. The effects in the kidney which occurred at all doses tested is consistent with the known effect of inhibition of the angiotensin II type I receptor on renal development in young rats. In humans the functional maturation of the kidneys completes at around the age of 1. This product is intended for a patient population aged from 1 to 18, therefore this effect will only be relevant to infants whose renal development has been delayed beyond the age of 1. The MAH has proposed to add the study findings to the SPC and it is recommended that it should also be included in the risk management plan.

Dog

SR02173-01: Single ascending oral dosing of candesartan cilexetil in juvenile beagle dogs

Description: In a GLP study designed to investigate potential effects of single ascending doses of candesartan cilexetil on clinical parameters and histopathology in juvenile beagle dogs, **Method:** Juvenile beagle dogs (3/sex) were administered either control (tap water), or candesartan cilexetil orally by gavage at doses of 20, 100 and 300 mg/kg. The doses selected were the same as doses used in previous safety and toxicokinetic studies conducted in adult dogs which would enable the identification of age-related differences in response. On day 0 of dosing, dogs received 20mg/kg candesartan cilexetil or control 3 to 4.5 hours after feeding. The dogs were then rested for 3 days and dosed with 100mg/kg on day 4. The dose was escalated to 300mg/kg after another 3 day break on day 8. The animals were followed up for 14 days after the final dose and sacrificed. Parameters evaluated included clinical observations (daily), body weight, haematology and clinical chemistry (24 hour post-dose and at termination), urinalysis, organ weights, gross pathology and histopathology of the kidneys, heart, and any gross lesions. Blood samples were collected for toxicokinetic evaluation at pre-treatment, 1 and 24 hours after 20 and 100 mg/kg were administered, and at 1,2,4,8 and 24 hours after the 300mg/kg dose.

Results: There was no treatment related effects on all parameters evaluated. The mean plasma concentrations of candesartan achieved are shown in table 5.

Table 8- Plasma concentrations of candesartan in juvenile Beagle dogs

Dose (mg/kg)	n	Day	C_{1hr}±SD (nmol/l)	AUC ±SD (µmol·h/L)	C_{max}±SD (nmol/L)
20	6	0	489 ± 421 [a]	nc	nc
100	6	4	1600 ± 310 [a]	nc	nc
300	6	8	nc	15.7 ± 10.0	4070 ± 1130

[a] = mean plasma concentration 1 hour after dosing
AUC: Area under the concentration-time curve
Cmax: maximum observed concentration
nc: not calculated

Non-clinical assessor's comments
This was the only study conducted in a juvenile dog. No treatment related effects on heart growth or any other developmental parameter was reported, however this was a single dose study therefore effects arising from longer term exposures, which is relevant to the proposed paediatric population, was not modelled in this study.

CONCLUSION ON JUVENILE STUDIES

The age-range of the juvenile animals used in the studies are equivalent to a 1 month old through to adulthood. A reduction in heart weight, body weights/bodyweight gain and renal toxicity was a consistent finding in the juvenile rats treated from PND 7 (same initial age of the subgroup B animals in the neonatal studies) up to 1, 5 or 13 weeks. The lowest dose associated with these effects was 10mg/kg in the 13 week juvenile rat study (plasma candesartan AUC_{0-24h} PND 7 = 33115 ng•h/ml and PND 97 = 13902 ng•h/ml). A NOAEL was not identified in this study, therefore a safety margin cannot be determined. The clinical AUC value achieved in 6 to 12 year old hypertensive patients (n=22) following a 16 mg dose of candesartan cilexetil is 1094 ng•h/ml, which is 12-30 fold lower than exposures at the lowest-observed-adverse-effect dose (LOAEL) of 10mg/kg measured in the 13 week study. Effects in the 5 week study occurred at clinically relevant doses. Exposure data for children aged from 1 to <6 years have not been provided therefore the applicant will be requested to submit this information.

The duration of exposure in the juvenile dog study was insufficient for investigating the effects of candesartan. Information on other juvenile animals has not been provided, therefore a conclusion on whether the effects induced by candesartan are rodent specific or not, cannot be determined from the available dataset. Data from the open literature, albeit indirect, do provide some evidence of a non-rodent specific effect. For example reduced heart weights have been observed in neonatal pigs treated with the ACE inhibitor enalapril, which appeared to be mediated via its inhibitory effects on angiotensin II, not through its effects on bradykinin. It is likely that these common effects induced by inhibitors of the renin-angiotensin system in young pigs and rodents are mediated via a common mechanism. The nephrotoxic potential of drugs that pharmacologically modify the renin-angiotensin-aldosterone system on the developing kidney in humans and animals (rat) is well understood and was replicated in the studies performed with candesartan cilexetil in juvenile (and neonatal rats). These effects were the result of exposure during the period of kidney development in the neonatal and juvenile rats. Kidney development is expected to have reached completion in the age-range of the proposed paediatric population and thus should not pose a risk to the patient population unless there are sub-populations with developmental delays. The effects on blood chemistry observed in the 5 week study was not observed at the same doses (10 and 100 mg/kg) in the 13 week study, however this might be due to the higher plasma concentration of candesartan (M-I) achieved in the 5 week study compared to the equivalent dose in the 13 week study.

TOXICOKINETICS

The tabulated results of the toxicokinetic evaluation, including paediatric clinical and adult non-clinical pharmacokinetic data is presented below.

Neonatal Rats

The plasma $AUC_{0\text{-}24h}$ for candesartan in neonatal rat pups given a single oral dose of 100/mg/kg was approximately 2.2 times greater than when the same dose was administered to adult rats. The rate and extent of achieved systemic exposure was not sex-dependant and did not change appreciably after repeated dosing of 100mg/kg over 7 days irrespective of whether the dosing commenced on PND 0 or PND 7.

Neonatal Rats

Table 9- Pharmacokinetic parameters in neonatal rats following single dose administration

Group	Dose (mg/kg)	Tmax (h)	Cmax (ng/mL)	$AUC_{0\text{-}24h}$ (ng·h/mL)
		Male:Female	Male:Female	Male:Female
Day 0	30	24:24	4340:7689	60740:92169
Day 7	30	24:24	8318:7223	129946:120336
Day 0	100	24:24	18890:8640	215477:108788
Day 7	100	24:24	11860:7343	177987:155336

Source: Report C-42-01 979 Tale 1
Cmax: Maximum observed concentration
Tmax: Time to reach Cmax

Table 10- Toxicokinetic parameters of candesartan in neonatal rats following 1 week administration (PND0-6 and PND 7-14**)**

Group/time point	Parameter	Male:Female	Total
Subgroup A (100 mg/kg/day)			
PND 0	AUC_{0-24h} (ng·h/mL)	141372:120750	131061
	Cmax (ng/mL)	11690:10105	10898
	Tmax (h)	24:24	24
PND 6	AUC_{0-24h} (ng·h/mL)	293363:346322	319843
	Cmax (ng/mL)	15321:16015	15668
	Tmax (h)	4:4	6
Subgroup B (100 mg/kg/day)			
PND 7	AUC_{0-24h} (ng·h/mL)	105091:105282	105187
	Cmax (ng/mL)	7328:7629	7478
	Tmax (h)	24:24	24
PND 13	AUC_{0-24h} (ng·hr/mL)	394024:404261	399143
	Cmax (ng/mL)	19592:22111	20600
	Tmax (h)	4:4	4

Source: Report TCV-116-10158 Tables 3,4

Juvenile Rats

The systemic exposure achieved following a single oral dose of 100mg/kg candesartan was approximately 200-fold higher than reported for hypertensive patients aged 6 to12 years treated with candesartan cilexetil at 16 mg (). However the rate and extent of systemic exposure achieved following repeated oral dosing of juvenile rats for either 5 or 13 weeks is substantially lower than after a single oral dose. The MAH stated that the magnitude of exposure was at the minimum 35- to 40-fold higher than reported for patients clinically, however as stated previously the AUC at the LOAEL for effects on heart weight, renal effects and haematological effects in the 13 week study for candesartan cilexetil was 12-30 fold higher than the clinical AUC (1094 ng•h/ml) measured in paediatric patients given a clinically relevant dose.

Juvenile Rats

Table 11- Toxicokinetic parameters of candesartan cilexetil and candesartan in juvenile rats during treatment for 5 weeks.

Analyte	Parameter	Day	Candesartan cilexetil 10 mg/kg/day	Candesartan cilexetil 100 mg/kg/day
			Male:Female	Male:Female
Candesartan cilexetil	Tmax (h)	1st	2.0:2.0	2.0:2.0
		35th	1.3:8.7	2.0:2.0
	Cmax (ng/mL)	1st	63.6:61.6	196.6:283.2
		36th	0.2:3.7	4.6:11.7
	AUC_{0-24h} (ng·h/mL)	1st	443:337	893:1258
		35th	1:20	16:33
	AUC_{0-48h} (ng·h/mL)	1st	503:462	1075:1423
Candesartan	Tmax (h)	1st	24.0:24.0	8.0:8.0
		35th	2.7:2.0	2.0:2.0
	Cmax (ng/mL)	1st	2708:4044	10773:11929
		35th	1066:1152	7360:6105
	AUC_{0-24h} (ng·h/mL)	1st	51373:65816	208342:228777
		35th	9932:7513	48838:31309
	AUC_{0-48h} (ng·h/mL)	1st	101797:132848	391738:424401

Table 12- Toxicokinetic parameters for candesartan cilexetil in juvenile rats during treatment for 13 weeks

Dosage level (mg/kg/day):		Male		Female		Total	
		10	100	10	100	10	100
Candesartan cilexetil							
T_{max} (h)	PND 7	0.5	1.0	1.0	1.0	1.0	1.0
	PND 97	2.0	4.0	2.0	2.0	2.0	4.0
C_{max} (ng/mL)	PND 7	77	141	86	102	52	121
	PND 97	4	24	7	11	5	17
AUC_{0-24h} (ng·h/mL)	PND 7	137[a]	990[a]	139[a]	400[a]	138[b]	695[b]
	PND 97	24[a]	118[a]	15[a]	78[a]	20[b]	98[b]
Candesartan (M-I)							
T_{max} (h)	PND 7	24.0	8.0	24.0	8.0	24.0	8.0
	PND 97	2.0	4.0	2.0	2.0	2.0	2.0
C_{max} (ng/mL)	PND 7	2469	10843	1789	6565	2129	8704
	PND 97	1581	7346	2435	7586	2008	6666
AUC_{0-24h} (ng·h/mL)	PND 7	35789[a]	180520[a]	30441[a]	107702[a]	33115[b]	144111[b]
	PND 97	12301[a]	47552[a]	15503[a]	45648[a]	13902[b]	46600[b]
M-II							
T_{max} (h)	PND 7	24.0	8.0	24.0	8.0	24.0	8.0
	PND 97	4.0	4.0	1.0	2.0	2.0	0.5
C_{max} (ng/mL)	PND 7	32	191	23	84	27	137
	PND 97	7	47	10	42	7	42
AUC_{0-24h} (ng·h/mL)	PND 7	534[a]	2771[a]	430[a]	1441[a]	482[b]	2106[b]
	PND 97	31[a]	326[a]	48[a]	269[a]	40[b]	298[b]

Juvenile Dogs

Table 13- Plasma concentrations of candesartan in juvenile beagle dogs

Dose (mg/kg)	N	Day	$C_{1 hr}$±SD	AUC±SD (μmol·h/L)	C_{max}±SD (nmol/L)
20	6	0	489±421[a]	nc	nc
100	6	4	1600±310[a]	nc	nc
300	6	8	nc	15.7±10.0	4070±1130

a= mean plasma concentration 1 hour after dosing.
nc. Not calculated
Source Report SR 01273-01 section 18.8

Clinical

Pharmacokinetics of candesartan cilexetil in paediatric hypertensive patients of 6-17 years of age. (2008) Teng R., Sugg J., Mcmenamin B., Hainer JW. Global Clinical development, AstraZeneca LP, Wilmington, DE.

Teng et al conducted a clinical pharmacokinetic study in 22 paediatric hypertensive patients aged 6-12 years of age (6-12 [n=11] or 12-17 [n=11] years of age). A single oral dose of candesartan cilexetil (16mg tablet) was administered to the patients and serial blood samples were collected for plasma determination of candesartan concentrations and calculation of pharmacokinetic parameters. The pharmacokinetic profiles following dosing were broadly comparable among the younger and older subjects although there was large inter-subject variability. There was no correlation between the C_{max} or AUC_{0-24h} and age, over the age ranges studied. Bodyweight correlated (negatively) with C_{max}, and AUC estimates but there was considerable variability and the strength of the association was relatively weak (correlation coefficients was -0.528 and -0.557, respectively). There were no gender related differences in the pharmacokinetic parameters. The pharmacokinetic estimates were concluded to be similar to the values measured in healthy adults.

Table 14- Clinical Pharmacokinetics of **candesartan cilexetil** in 6-17 year old paediatric hypertensive patients

Age of paediatric patients	C_{max} (nM/L)	AUC_{0-24h} (nM•hr/L)
6-12	297	2265
12-17	349	2780

Ref. Teng et al 2008

Adult non-clinical pharmacokinetic data

- After oral administration in rats and dogs candesartan cilexetil was absorbed and hydrolysed almost completely to candesartan with an oral bioavailability of approximately 20% in fasted animals. In both species, increase in plasma levels was dose proportional. After repeated dosing, area under the concentration-time curves (AUCs) of candesartan at the no-observed-adverse-effect levels in rats (10 mg/kg) and dogs (20 mg/kg) were 6 to 7 μg·h/mL and 0.82 to 1.82 μg·h/mL respectively. The corresponding value in humans was 1.2 μg·h/mL at a dose of 16 mg/day.

- Candesartan cilexetil and its metabolites were not retained in the tissues. Studies in rats demonstrated that candesartan passed the placental barrier and was distributed to the foetus. Plasma protein binding of ^{14}C was >99% and >96% in rats and dogs respectively and erythrocyte distribution of ^{14}C was <2.2%.

- Candesartan cilexetil is metabolised to candesartan (M-I) by enzymatic hydrolysis of the ester moiety and further conjugated to its carboxylic glucuronide (M-I-AG) and tetrazole-N-glucuronide (M-I-NG). These metabolites have been identified in rats and dogs. A further metabolite, M-II, has been identified in rat faeces. In human liver microsomes candesartan undergoes cytochrome P-450 (CYP) mediated metabolism to M-II.

- The majority of the administered oral dose was eliminated within 72 hours with more than 95% appearing in the rat faeces. In bile duct cannulated rats biliary excretion was extensive (34%) (Heywood R 1997).

- The inhibitory effects of candesartan on CYP activities were investigated using human liver microsomes. Candesartan showed no substantial effects on CYP activities even at the highest concentration examined (100 μmol/L).

SUMMARY OF ADULT NON-CLINICAL STUDIES

The juvenile toxicity data supplements the existing pharmaco-toxicological data currently supporting the European marketing authorisations of candesartan cilexetil as a monotherapy, at doses up to 32mg, and as a fixed dose combination product at doses, up to 32 mg candesartan and 25 mg hydrochlorothiazide in adults. These include studies of single and repeat dose toxicity, genotoxicity, carcinogenicity and reproductive and developmental toxicity

The main findings of these studies were the following:

- The toxicological target of candesartan cilexetil was the kidney and red blood cell parameters in mice, rats, dogs and monkeys at high administered doses. Effects on the kidney characterised as regeneration, dilatation, and basophilia in tubules; increased plasma concentrations of urea nitrogen and creatinine, was considered to be the result of alterations of renal perfusion due to the drug's hypotensive actions
- A peri-postnatal study showed an increase in hydronephrosis at all doses tested in 30% to 100% of the F1 progeny of Jcl:Wistar rats treated with 10, 50 and 300mg/kg from day 15 of

gestation to day 21 of lactation. Mechanistic studies indicated the sensitive period for hydronephrosis was lactation days 0 to 13 and the cause was related to increased urine volume accompanied by renal histopathological change and low aldosterone secretion.

- In the repeat dose toxicity studies findings **relevant to effects on the heart** were as follows:

  Rats
  Statistically significant decreases in heart weight has been observed in adult rats (Fischer 344/Jcl aged 6 weeks at the start of treatment) treated with ≥3 mg/kg/day candesartan cilexetil for 4 weeks, and in rats treated with ≥300mg/kg/day for 13 weeks. In a longer term study reduction in heart weight was observed after 26 weeks treatment at doses as low as 1mg/kg/day in females and 10mg/kg/day (both sexes). A mechanistic study showed saline supplementation suppressed the candesartan induced reduction of heart weight.

  Mice
  Candesartan also induced a statistically significant reduction in heart weight in mice (B6C3F1 strain aged 5 weeks at study onset) at ≥10mg/kg/day in a 13 week study and in a 4 week dietary study at concentrations of 0.5% and 5% candesartan cilexetil.

  Dogs
  In beagle dogs candesartan had no effect on heart weight in 2 studies at doses up to 300mg/kg following a 4 and 52 week treatment period. In a separate study doses up to 100mg/kg/day administered for 6 months also had no effect on heart weight of adult dogs. Conversely a third study in dogs treated with candesartan cilexetil 20, 100 and 300 mg/kg/day for 4 weeks showed a statistically significant reduction in heart weights at 100mg/kg/day. No further information has been provided on effects at the other doses tested however in the absence of this it is assumed that effects on heart weight was not observed at 300 mg/kg/day and consequently the effect observed at 100mg/kg is not dose-related.

Discussion on non clinical aspects and conclusion

General findings

With the exception of the effects discussed below there was no novel toxicities identified in the neonatal/juvenile studies that differs from findings previously reported in adults. The target organs of toxicity were red blood cell parameters and the kidneys. The toxicokinetic data showed that neonatal rats attained a 2.2 fold higher systemic exposure compared to adults following the administration of an equivalent dose (100mg/kg) and this was due to a longer Tmax indicating a potential age-related difference in GI absorption rates. The applicant did not discuss this finding so will be requested to address this. Adverse effects have been observed in adult rats at doses as low as 1mg/kg (e.g. reduced heart weight) therefore there is no evidence of neonatal and juvenile rats having an increased sensitivity to these common effects.

Effects on developmental parameters

Renal Development
Impaired renal development was observed in the neonatal and juvenile toxicity studies which was consistent with the findings of earlier studies (pre-postnatal studies) in this age group, and is an expected finding given the essential role of angiotensin II and its downstream effectors on the anatomical and functional development of the kidneys. The age range of the intended paediatric population is 1-18 and renal development is considered to be completed around the age of 1 in humans therefore these findings are not considered to be relevant to the intended paediatric population, unless there are sub-populations where renal development might progress beyond the age of 1. The applicant proposes to add these findings to the SPC which is acceptable.

Body weight

The reduced bodyweights and bodyweight gain in the neonatal and juvenile rat studies was a reproducible finding. The non-clinical overview and the study reports did not discuss the cause of these effects on bodyweight. Impaired nutrition does not appear to be a factor because food consumption, where measured, was not affected. Water consumption and urinary output was also not recorded. Studies in the open literature have reported reduced bodyweights in animals treated with inhibitors of the renin-angiotensin system (e.g. prolonged reduction in bodyweight [10 weeks+] induced by a 20 day treatment of neonatal male Wister Kyoto rats with enalapril which occurred in the absence of an effect on food consumption, and in the presence of increased urine production and water intake [Friberg et al 1994]). One study by Bosc et al (2000) with normal rats (from PND 21 to 6 months) treated with enalapril, suggested that metabolic alterations was the likely cause of the reduced body weight gain in these animals, because food consumption was also unaffected in this study. The reduced bodyweight gain in the present studies did not delay the onset of sexual maturation. Other indices of growth (e.g. growth velocity per unit time, tibial length) were not evaluated in these studies. The study by Bosc et al (2000) did show that growth (as measured by tail length) was not impaired by the reduced body weight gain. There was no evidence of an effect on other developmental parameters relevant to the age range of the proposed paediatric population. It is not possible to estimate the safety margin for bodyweights because a NOAEL was not identified and the clinical exposures for patients aged 1 - <6 have not been provided. The margin of exposure for effects on bodyweight at the LOAEL for 6- 12 year old patients is 12-30 fold.

Heart Growth

Concerns regarding the potential for candesartan to suppress the growth of the heart in a child that has not completed its somatic growth was raised by the publication of 2 reviews (Grenier *et al* 2000 and Lipshultz *et al* 2002), which showed that inhibitors of the renin-angiotensin system could cause a reduction in heart weight through inhibition of hypertrophy, the physiological mechanism of heart growth in children aged 6 months and above. These reviews cited the results of 3 studies, the first of which showed a reduction in the rapid growth of the ventricle of newborn piglets treated with enalapril over the first 2 weeks of postnatal life (Beinlich *et al* 1996); the second showing a pharmacologically induced regression of pressure-overload cardiac hypertrophy in aortic banded rats (Wambolt *et al* 1997); and the third showing regression of left ventricular hypertrophy in a study of the efficacy and safety of enalapril monotherapy for significant essential hypertension in adolescents (aged 12 to 18 years) (Cichocka *et al* 1995). Reduced heart weight has been observed following long and short term exposures in adult rats and mice, so is not an age-specific effect. The MAH stated that a mechanistic study in rats showed saline supplementation suppressed the candesartan induced reduction of heart weight in the adult rats, but provided no further details.

The latest studies conducted in juvenile and neonatal aged rats showed, in most cases, a treatment related reduction in the absolute and relative mean heart weights following long and short term exposures to candesartan in animals that are of an equivalent developmental age of the intended paediatric population. This was a direct effect of treatment and not secondary to effects on body weight. In general the non-clinical findings were not associated with adverse histopathology results and did not appear to be clinically significant judging by the lack of effect on survival and general condition of the animals in the longer term studies. Nevertheless a reduction in heart weight in an actively growing child is an undesirable effect therefore (1) the absence of a NOAEL in the 13 week repeat dose toxicity study, ***TCV-116-10169,*** (with a LOAEL 12 fold higher than clinical exposures) and (2) effects occurring at clinically relevant doses in the 5 week study is a cause for concern. In terms of the mechanism it is to be expected that a reduction in the haemodynamic load (through reduced peripheral vascular resistance) would be associated with a reduction in the size of the heart, and it is likely to be a factor. Regression of

ventricular hypertrophy, when present, is obviously an intended pharmacological effect. However the potential to suppress the growth of healthy (as opposed to hypertrophied) tissue in children still undergoing somatic growth is a concern and the available non-clinical data from young healthy animals undergoing active phases of growth demonstrates this effect. The clinical relevance is also supported by the findings of a study in adolescents (Cichocka et al 1995) which demonstrated through, echocardiographic examination, a significant decrease in the interventricular septum thickness, following 6 months of therapy.

Investigations into the mechanism of the reduced heart growth in the neonatal studies showed that a treatment related suppression of myocardial cell proliferation played a part in the reduced heart weight observed in the female neonatal pups. This would be consistent with findings in studies (conducted with enalapril) in neonatal pigs that indicate that angiotensin II might play a role in the regulation of cardiac growth through induction of cardiomyocyte proliferation (e.g. Beinlich et al 1991). Angiotensin II is also known to stimulate growth factors, (e.g. transforming growth factor B [TGF-B]), that regulate endothelial, cardiomyocyte and fibroblast growth, development and function. The results of the study by Beinlich *et al* 1996 showed that the effects on heart weight observed with ACE inhibitors were not mediated by increases in the levels of bradykinin associated with the use of these products but more likely via an inhibition of angiotensin II, which is supported by the results of the present juvenile and neonatal studies conducted with candesartan. The MAH did not investigate effects on myocyte size/volume. A study has shown that cellular proliferation plays a substantially lesser role than cellular hypertrophy (associated with increases in protein synthesis and ribosome formation) in the rapid physiological growth of the heart during the first 2 weeks of neonatal life in pigs. This study showed the mass of the left ventricular free wall (LVFW) of neonatal pigs increasing by 333% during the first 2 weeks of life (the right ventricular free wall increased by 75%). Piglets treated with enalapril during these first 2 weeks had a 24% reduction in their LVFW mass which was caused by a reduction in myocyte volume (cited in Beinlich *et al* 1996). Decreased cellular proliferation rate (or increased apoptosis) did not play a substantial role.

Overall there is evidence to show that candesartan can suppress the growth of the heart, but the lack of evidence from a non-rodent species means that it is unclear whether the effect is potentially relevant to man, and if it is, then whether the suppression in heart weight will be clinically significant. As the MAH has not provided evidence to rule out a potential effect in babies/children undergoing somatic growth, these findings should be added to the SPC and included in the risk management plan for future monitoring.

Proposed Candesartan Cilexetil SmPC

For the paediatric indication the applicant proposes to amend section 5.3 of the SmPC for Cilexetil Candesartan with text highlighted in bold font in Table 15:

Table 15- Proposed SmPC wording for preclinical safety data (bold font)

SPC 5.3 Preclinical safety data: Candesartan cilexetil
There was no evidence of abnormal systemic or target organ toxicity at clinically relevant doses. In preclinical safety studies candesartan had effects on the kidneys and on red cell parameters at high doses in mice, rats, dogs and monkeys. Candesartan caused a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit). Effects on the kidneys (such as interstitial nephritis, tubular distension, basophilic tubules; increased plasma concentrations of urea and creatinine) were induced by candesartan which could be secondary to the hypotensive effect leading to alterations of renal perfusion. Furthermore, candesartan induced hyperplasia/hypertrophy of the juxtaglomerular cells. These changes were considered to be caused by the pharmacological action of candesartan. For therapeutic

SPC 5.3 Preclinical safety data: Candesartan cilexetil
doses of candesartan in humans, the hyperplasia/hypertrophy of the renal juxtaglomerular cells does not seem to have any relevance. Foetotoxicity has been observed in late pregnancy (see section 4.6). Data from in vitro and in vivo mutagenicity testing indicates that candesartan will not exert mutagenic or clastogenic activities under conditions of clinical use. There was no evidence of carcinogenicity. **The renin-angiotensin-aldosterone system plays a critical role in kidney development. Renin-angiotensin-aldosterone system blockade has been shown to lead to abnormal kidney development in very young mice. Administering drugs that act directly on the rennin-angiotensin-aldosterone system can alter normal renal development. Therefore, children aged less than 1 year must not receive Atacand (see section 4.3).**

The applicant has not proposed to add information on the effects on heart weight and bodyweight observed in the neonatal and juvenile rats. A safety margin could not be calculated for these effects in the 5 and 13 week juvenile rat studies, therefore the relevance to a patient population undergoing somatic growth cannot be ruled out. The applicant will be requested to add information on the effects on heart weight and body weights to the SmPC; and to include these and the renal effects in the Risk management plan (RMP) for future monitoring.

Human to animal comparisons of developmental periods

Table 16- Age comparisons across species

Species	Neonate	Infant	Child	Adolescent
Rat (week)	0–1	1–3	3–9	9+
Dog (month)	0–0.75	0.75–1.5	1.5–5	5+
Primate (year)	0–0.05	0.05–0.5	0.5–3	3+
Man (year)	0–0.1	0.1–2	2–12	12+

Ref: Baldrick 2010

IV.3 Clinical aspects

IV.3.1. Introduction

The MAH submitted reports for:

- D2451C00005: Bioequivalence study

- Clinical study 261A: A Dose-Ranging and Safety Study of Candesartan Cilexetil in Hypertensive Paediatric Subjects 6 to <17 Years of Age: A 4-Week, Multinational, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel- Group Study

- Clinical study 261B: A Multicenter, Multinational, Open-Label Study of the Efficacy, Safety, and Pharmacokinetics of Candesartan Cilexetil in Hypertensive Paediatric Subjects 6 to <17 Years of Age

- Clinical Study 328 - A Dose-ranging, Safety and Pharmacokinetics Study of Candesartan Cilexetil in Hypertensive Paediatric Subjects 1 to Less Than 6 Years of Age: A 4-week, Multicenter, Randomized, Double-Blind Study

- Clinical Study D2451C00006- an Open-label Extension Study of Candesartan Cilexetil in Hypertensive Paediatric Subjects Ages 1 to <11 Years: A Long-term Study, which also included results from CHMP paediatric committee scientific advice on:
• A request for an extended follow-up for 2 years in younger children
• A request for echocardiographic assessments.

IV. 3. 2. Clinical studies

IV. 3. 2. 1 Clinical study 261A: A Dose-Ranging and Safety Study of Candesartan Cilexetil in Hypertensive Paediatric Subjects 6 to <17 Years of Age: A 4-Week, Multinational, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel- Group Study

➢ Description

This was a randomised, double-blind, parallel group, placebo-controlled study to determine the antihypertensive dose-ranging effects across three dose levels of candesartan following four weeks of treatment in hypertensive paediatric patients 6 - < 17 years of age. Following a single blind placebo run-in period of approximately one week, eligible patients were randomised to one of three dose levels, (low, medium or high), of oral candesartan tablets or matching placebo. All patients had a plasma candesartan level collected at the end of the 4-week study.

➢ Methods

- Objective(s)

Primary objective:
The slope of multiple-linear regression for the change from baseline to DB Week 4 in trough SiSBP as a function of non-zero dose for paediatric subjects 6 to less than 17 years of age with hypertension based on the ITT population.

Secondary objectives:
- The slope for the change from Baseline to DB Week 4 in trough SiSBP as a function of non-zero dose for each of the 2 body weight panels separately

- Slope of change from baseline to DB Week 4 for
  Trough SiDBP
  Trough StDBP and trough StSBP
  Trough sitting pulse pressure, which was determined by subtracting trough sitting (mean) DBP from trough sitting (mean) SBP

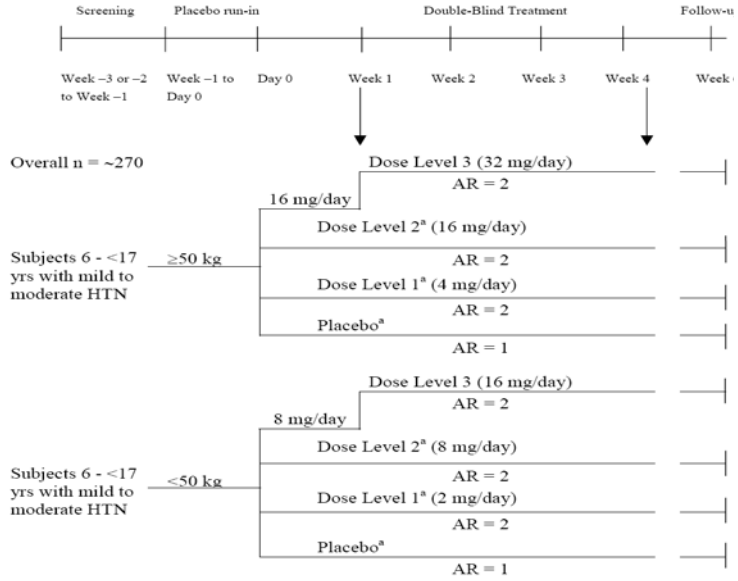
- Mean change from baseline to DB Week 4 in trough SiSBP, trough SiDBP, trough StSBP, trough StDBP and pulse pressure
- Urinary microalbumin/creatinine ratio was an additional descriptive measure
- The mean change from baseline to DB Week 4 in the QUICKI value

- Summary of the metabolic profiling results at baseline, including the prevalence of insulin resistance and hyperlipidemia.
- Safety as assessed by AEs, AEs which necessitated study drug discontinuation, SAEs, heart rate, electrocardiographic findings, physical exam findings, and laboratory tests.

- Study design

One to 2-weeks following a screening evaluation, subjects underwent a 1-week, single-blind, placebo run-in after which those that were randomization eligible were allocated to receive 1 of 3 doses levels of candesartan or placebo. The 3 dose levels were: low, medium, and high (2 or 4 mg/d, 8 or 16 mg/d, and 16 or 32 mg/d, respectively), for the <50 kg and ≥50 kg weight panels. The doses selected represented a 1:4:8 dose ratio within each weight panel. At least 3 dose levels were required to test the primary hypothesis of a linear dose response. Figure 2 shows the design of the study and the sequence of treatment periods.

Figure 2- Protocol 261A study design



BP was measured by an ausculatory method and with a mercury sphygmomanometer. At each visit, BP was measured at least 6 times (minimum of 3 times in each position of sitting and standing).

There were no pharmacokinetic measures planned for the study. A single plasma candesartan level was collected at DB Week 4, 24 ± 2 hours following the last study drug dose to serve as a potential measure to validate study drug exposure.

- Study population /Sample size

The number from Study 261A was planned to be 238 randomized subjects. Allowing for drop outs, 270 enrolled subjects were planned in order to obtain 238 randomized, evaluable subjects. It was planned that Study 261 include at least 33 % of Tanner Stage <3. In addition inclusion of Black subjects (between 35% to 60%) as was also specified in the written request.

- Treatments

The study included two dose level panels based on weight; within each panel patients were stratified according to whether or not they were black. The panels were as follows:

Panel 1: subjects <50 kg allocated to 2 mg, 8 mg or 16 mg or placebo once daily in 2:2:2:1 ratio stratified as Black or non-Black;

Panel 2: subjects ≥50 kg allocated to 4 mg, 16 mg or 32 mg or placebo once daily in 2:2:2:1 ratio stratified as Black or non-Black;

Doses were referred to as low, medium and high based on body weight in each panel.
This study was conducted in 50 centres in the United States and 8 centres in Europe.

Antihypertensive medications including diuretics, beta-blockers, ACEIs, etc, were not permitted from at least 1-week prior to the beginning of the placebo run-in to the DB Week 4 visit.

Statistical assessor's comments:
The overall design of the study is accepted.

- Statistical Methods

The protocol was amended four times including an increase in the sample size at the request of FDA. Two blinded interim assessments of variability were conducted to estimate the sample size required to power the study at ≥ 90% to detect a clinically meaningful benefit of 3mmHg reduction in BP.

No major changes in the analysis strategy and methods were made in the statistical analysis plan (SAP) compared to those defined in the protocol. The SAP was finalised before database lock; however some changes were made after the SAP had been finalised but before the unblinding of treatment codes. Some additional changes were made after unblinding the study data to include additional analyses and to modify the definition of subgroups by age.

Three analysis populations were defined including the following two populations for analysis of efficacy:

- intent-to-treat (ITT) population: all randomised patients who took at least one dose of study medication with both a baseline and at least one post-baseline blood pressure measurement;
- per-protocol (PP) population: a subset of the ITT population made up of those patients without a pre-specified major violation or deviation of the protocol.

The ITT was the primary population for efficacy analysis with analyses of the PP population performed as a robustness check of the ITT analysis for the primary objective.

The primary efficacy variable was the placebo-corrected change from baseline to the end of treatment in SiSBP where the placebo correction was made by subtracting the mean change from baseline for the placebo group from the individual subject changes in the other treatment groups. The primary endpoint (outcome variable) was the slope by linear regression as a function of non-zero candesartan dose, pooled across weight groups with low dose as 2 mg/4 mg, medium dose as 8 mg/16 mg and high dose 16 mg/32 mg for low/high weight groups respectively. The change from baseline of trough SiSBP was the dependent variable. The independent variables for the regression models involved body weight panel as a blocking factor (0 or 1 depending on body weight panel, <50 kg or ≥ 50 kg) and dose ratio (1, 4 or 8 depending on low, medium or high dose). Centre and centre-by-treatment interaction were not considered

in the primary analysis. As only 25 patients were included in the lower weight panel, the analysis of the primary variable was also performed without weight panel in the model.

The slope of the dose response was estimated together with the 95% confidence interval. The result of the two-sided Student t-test of the null hypothesis of zero slope was presented.

Similar analyses were conducted for each of the weight panels separately.

Secondary efficacy variables included mean change from baseline in SiSBP relative to placebo for each dose group and for all dose groups pooled. The treatment difference was estimated using an analysis of covariance (ANCOVA) model which include treatment and centre as effects with baseline blood pressure as a covariate. One-sided tests with nominal p-values were planned. However after unblinding it was decided to present two-sided results to be consistent with the usual convention. No adjustments for multiplicity were made in these analyses. This analysis was also conducted for each weight panel.

If a blood pressure measurement was missing for any reason the last observation was carried forward to Week 4 (LOCF). If no non-zero post-baseline value was available the value was treated as missing.

In addition response rates were summarized according to a predefinition of a responder as having both systolic and diastolic BP less than the 95th percentile at Week 4. If either or both of the measurements were missing, the patient was considered to be a non-responder. The 95% confidence intervals were calculated using the normal approximation to the binomial distribution.

Initially the sample size was based on an assumed 8 mmHg reduction in SiSBP for the highest candesartan group compared to the lowest group. This lead to a sample size of 176 patients required to complete Study 261A to provide 84% power to reject a null hypothesis of a zero regression slope using a t-test with a two-sided 5% significance level. Allowing for a 20% drop-out rate, 210 randomised subjects were required. The final sample size assessment using the blinded pooled interim analysis for assessing variability of blood pressure measurements was performed when approximately 50% of patients had completed the double blind treatment period. Therefore the sample size was increased to 238 patients required from Study 261A. Although the secondary analysis using ANCOVA to compare individual doses with placebo was planned in the protocol, no attempt was made to power the study for this analysis.

Statistical assessor's comments:
Although the definition of the ITT population is not standard, all randomised patients were included in the population as required.
The placebo correction of the primary variable was made by subtracting the mean change from baseline for the placebo group from the individual subject changes in the other treatment groups. The Applicant is asked to justify this method.
The randomisation of patients in each weight panel has been stratified by race (Black and non-Black). However race has not been used as an independent variable in the regression model or as a covariate in the ANCOVA model as required by the guideline on the adjustment for baseline covariates (CPMP/EWP/2863/99). This should be discussed by the Applicant and, where appropriate, the analyses should be repeated with adjustment for race.
The ANCOVA analysis of change from baseline in trough SiSBP has not included any adjustment for testing multiple doses. However as all three doses have achieved statistically significant improvement compared to placebo with small p-values it is considered that any method of adjustment for multiplicity (for example, Bonferroni correction or a hierarchical testing scheme) is unlikely to change the findings.

The chosen method for handling missing data is LOCF without any additional methods used to provide sensitivity analyses to investigate the robustness of the results as discuss in the current guideline on handling missing data (EMA/CPMP/EWP/1776/99 Rev.1). However, as less than 5% of the randomised patients failed to complete the study this is not considered to be an important issue.

Results

- Recruitment/ Number analysed

Subjects were diagnosed and untreated or previously diagnosed and currently treated with a mean SiSBP and/or SiDBP ≥95th percentile and ≤20 mmHg (systolic) and/or 10 mmHg (diastolic) above the 95th percentile at randomization based on height-adjusted charts for age and gender. About a third were pre-adolescents (Tanner Score of <3). The majority of subjects (64%) were discovered to be hypertensive within the prior 1 year; 52% had isolated systolic hypertension and 35% had systolic plus diastolic hypertension. Most subjects (78%) were also naive to pharmacologic hypertensive therapy.

Of 240 patients randomised, all were included in the ITT population and almost 89% were included in the PP population. Approximately equal percentages of children were black (47%) versus non-Black (53%). Over 87% were at least 50 kg and the majority (71%) were 12 years or over.

Statistical assessor's comments:
It is noted that less than 30% of the patients were under 12 years and, probably related to this, only 13% of the children were below 50 kg. The Applicant is asked to discuss this also in relation to the two racial subgroups.

- Baseline data

The demographic and key baseline characteristics of the 205 subjects who received active treatment and the 35 who received placebo are summarized in the tables 17 & 18 below:

Table 17- baseline data for ITT population

Demographic or baseline characteristic		Treatment group				
		Placebo	2/4 mg	8/16 mg	16/32 mg	Total
		N=35	N=69	N=68	N=68	N=240
Demographic characteristics						
Age, years: n (%)	<12	11 (31.4)	18 (26.1)	21 (30.9)	20 (29.4)	70 (29.2)
	≥12	24 (68.6)	51 (73.9)	47 (69.1)	48 (70.6)	170 (70.8)
Age, years	Mean (SD)	13.0 (2.8)	13.2 (2.3)	12.8 (2.8)	12.7 (2.8)	12.9 (2.6)
	Range	6 to 16	6 to 16	6 to 17	6 to 16	6 to 17
Sex, n (%)	Male	26 (74.3)	52 (75.4)	48 (70.6)	44 (64.7)	170 (70.8)
	Female	9 (25.7)	17 (24.6)	20 (29.4)	24 (35.3)	70 (29.2)
Race n (%)	Caucasian	14 (40.0)	32 (46.4)	30 (44.1)	32 (47.1)	108 (45.0)
	Black	17 (48.6)	32 (46.4)	32 (47.1)	32 (47.1)	113 (47.1)
	Other	4 (11.4)	5 (7.2)	6 (8.8)	4 (5.9)	19 (7.9)
Baseline characteristics						
Group by Tanner Score	<3	14 (40.0)	18 (26.1)	27 (39.7)	23 (33.8)	82 (34.2)
	≥3	21 (60.0)	51 (73.9)	41 (60.3)	45 (66.2)	158 (65.8)
Weight at screen (kg)	<50	5 (14.3)	8 (11.6)	10 (14.7)	8 (11.8)	31 (12.9)
	≥50	30 (85.7)	61 (88.4)	58 (85.3)	60 (88.2)	209 (87.1)
Weight at screen (kg)	Mean (SD)	82 (28)	85 (33)	74 (25)	85 (30)	81 (29)
	Range	28 to 146	23 to 171	21 to 158	22 to 156	21 to 171
BMI percentile at screen	<95	11 (31.4)	25 (36.2)	23 (33.8)	16 (23.5)	75 (31.3)
	≥95	24 (68.6)	44 (63.8)	45 (66.2)	52 (76.5)	165 (68.8)
BMI at screen, kg/m^2	Mean (SD)	30 (8)	31 (10)	28 (7)	32 (9)	30 (9)
	Range	16 to 48	16 to 55	13 to 43	15 to 59	13 to 59
Height at screen, cm	Mean (SD)	164 (15)	163 (14)	162 (15)	162 (16)	163 (15)
	Range	133 to 191	111 to 192	125 to 196	115 to 188	111 to 196
Duration of hypertension, yrs	<1	27 (77.1)	40 (58.0)	48 (70.6)	39 (57.4)	154 (64.2)
	1 to <2	4 (11.4)	12 (17.4)	6 (8.8)	13 (19.1)	35 (14.6)
	2 to <3	1 (2.9)	8 (11.6)	7 (10.3)	7 (10.3)	23 (9.6)
	3 to <4	2 (5.7)	7 (10.1)	4 (5.9)	1 (1.5)	14 (5.8)
	4 to <5	0	0	1 (1.5)	3 (4.4)	4 (1.7)
	≥5	1 (2.9)	2 (2.9)	2 (2.9)	5 (7.4)	10 (4.2)
Type of hypertension[a]	None	2 (5.7)	7 (10.1)	3 (4.4)	2 (2.9)	14 (5.8)
	DBP only	3 (8.6)	5 (7.2)	4 (5.9)	4 (5.9)	16 (6.7)
	SBP only	21 (60.0)	31 (44.9)	37 (54.4)	36 (52.9)	125 (52.1)
	SBP + DBP	9 (25.7)	26 (37.7)	24 (35.3)	26 (38.2)	85 (35.4)
Previously treated hypertension	No	32 (91.4)	52 (75.4)	55 (80.9)	47 (69.1)	186 (77.5)
	Yes	3 (8.6)	17 (24.6)	13 (19.1)	21 (30.9)	54 (22.5)

Table 18- Blood pressure at baseline (ITT population)

Baseline		Placebo N=35	2/4 mg N=69	8/16 mg N=68	16/32 mg N=68	Total N=240
SiSBP	Mean (SD)	134 (10)	134 (9)	133 (9)	135 (9)	134 (9)
	Range	119 to 151	109 to 156	110 to 152	111 to 155	109 to 156
SiDBP	Mean (SD)	78 (10)	80 (9)	78 (10)	79 (10)	79 (10)
	Range	53 to 96	58 to 111	42 to 91	52 to 98	42 to 111
StSBP	Mean (SD)	134 (10)	131 (9)	132 (8)	134 (9)	133 (9)
	Range	117 to 152	108 to 150	109 to 151	103 to 155	103 to 155
StDBP	Mean (SD)	80 (9)	81 (10)	79 (11)	80 (11)	80 (10)
	Range	62 to 95	55 to 116	43 to 97	49 to 107	43 to 116

Assessor's comment: The age range in this study is 6 to <17 years olds with mean age of 12.9

years, mean body weight of 81 kg and mean BMI of 30 kg/m2. 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. 31 (13%) children were in the lower and 209 (87 %) in the higher weight strata.

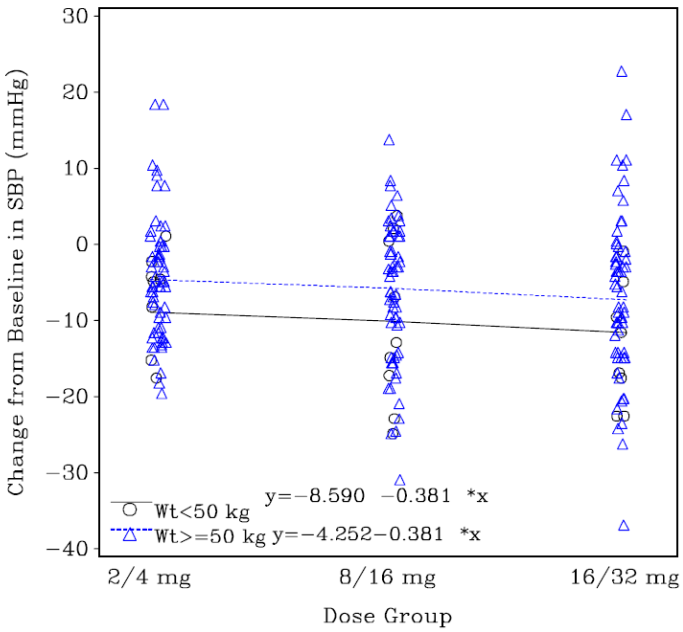
The majority of subjects (52%) had systolic hypertension only or both systolic and diastolic hypertension (35.4%). Approximately 80% of subjects had been diagnosed with hypertension within the preceding 2 years, and 78% were naive to antihypertensive pharmacologic therapy.

- Efficacy results

Primary end point

The primary study efficacy measure was trough SiSBP and the measure of effect was the placebo-corrected change from baseline to DB Week 4/LOCF. The regression model for this primary analysis included weight panel as a blocking factor and dose expressed as a ratio (1:4:8), and found that the dose-effect was not significant (p=0.0973, 95 % CI for slope –0.8329, 0.07), figure 3, and table 19 below:

Figure 3- Regression Line and Scatter plot for Changes fromBaseline to Week 4/LOCF in Sitting SBP vs. Dose and Weight groups



Neither was the dose effect statistically significant in a model that excluded weight panel as a blocking factor, nor was it statistically significant within each of the individual weight panels weight group <50 kg and weight group ≥50 kg.

Table 19- Dose response for placebo-corrected change from baseline to Week 4/LOCF for SiSBP and SiDBP (ITT population)

	SiSBP			SiDBP		
	DF	Estimate (SE)	p-value	DF	Estimate (SE)	p-value
Model						
Intercept	1	–8.5904 (2.1256)	0.0001	1	–5.9303 (2.2023)	0.0077
Dose group	1	–0.3814 (0.2289)	0.0973	1	–0.2128 (0.2372)	0.3708
Weight group	1	4.3376 (2.0079)	0.0319	1	1.6634 (2.0804)	0.4249

Note: Placebo is not included in the model. The individual values for subjects in the active dose groups have been adjusted by subtracting the mean placebo change from baseline. Dose group (1, 4, 8) and weight group (0, 1) are the independent variables in the model. Weight group 0 =<50 kg and weight group 1 = ≥50 kg.
Note: The 95% CI for the slope for SiSBP was –0.8329, 0.0700.
DF degrees of freedom. ITT intention-to-treat. LOCF last observation carried forward. SiSBP Sitting systolic blood

A simple linear regression model with candesartan dose expressed in mg/kg showed a significant dose response for SiSBP (p=0.0193) (Table 20 below).

Table 20- Regression on mg/kg Dose for Placebo-Corrected Change from Baseline to Week 4/LOCF for Sitting SBP Intention-to-Treat Patients

Trough Sitting SBP	DF	Estimate	Standard Error	P-value	95% Confidence Interval
Model Parameter					
Intercept	1	-4.2581	1.1316	0.0002	
mg/kg Dose	1	-9.9973	4.2394	0.0193	-18.3562,-1.6384
Model Statistics					
Mean square error	203	88.8758			
F statistic for model		5.5610			
F p-value		0.0193			
R square		0.0267			

The regression model did, however, indicate a statistically significant dose response when the analysis was conducted with the PP population (p=0.0469) for SiSBP (table 21 below).

Table 21- Dose Response for Placebo-Corrected Change from Baseline to Week 4 for Sitting SBP Per-Protocol Patients

Trough Sitting SBP	DF	Estimate	Standard Error	P-value	95% Confidence Interval
Model Parameter					
Intercept	1	-8.8002	2.2375	0.0001	
Dose Group	1	-0.4749	0.2374	0.0469	-0.9433,-0.0066
Weight Group	1	4.3758	2.0954	0.0382	
Predicted Values					
Low =1 wtgrp = 0		-9.2751	2.1344		-13.4867,-5.0635
Low =1 wtgrp = 1		-4.8993	1.0913		-7.0527,-2.7459
Medium =4 wtgrp = 0		-10.6998	1.9697		-14.5864,-6.8133
Medium =4 wtgrp = 1		-6.3240	0.7320		-7.7683,-4.8797
High =8 wtgrp = 0		-12.5995	2.1344		-16.8111,-8.3879
High =8 wtgrp = 1		-8.2237	1.1134		-10.4206,-6.0267
Model Statistics					
Mean square error	181	85.0434			
F statistic for model		4.2114			
F p-value		0.0163			
R square		0.0445			

Other noteworthy study efficacy findings are based on the ITT population for the change in BP from baseline to the Week 4/LOCF value. For 9 subjects, a Week 4 value was imputed by carrying forward the last observation (LOCF). Over the range of candesartan doses studied, SiSBP/SiDBP declined by 8.5/5.3 mmHg to 11.3/7.0 mm Hg; the decline with placebo was 3.8/1.3 mmHg from baseline to Week 4/LOCF, table 22 below.

Table 22- Mean Week 4/LOCF and mean change from baseline to Week 4/LOCF in SiSBP and SiDBP (ITT population)

	SBP		DBP	
Treatment group	Week 4 Mean (SD)	Mean (SD) change from baseline	Week 4 Mean (SD)	Mean (SD) change from baseline
Placebo, N=35	130.2 (10.1)	–3.8 (7.8)	76.3 (11.2)	–1.3 (11.5)
Candesartan, 2/4 mg, N=69	125.0 (9.9)	–8.5 (8.0)	74.3 (8.4)	–5.3 (9.1)
Candesartan cilexetil, 8/16 mg, N=68	121.7 (10.5)	–10.8 (9.6)	70.3 (10.6)	–7.6 (10.2)
Candesartan cilexetil,16/32 mg, N=68	123.4 (10.8)	–11.3 (10.8)	71.7 (9.3)	–7.0 (9.9)
Candesartan cilexetil, active pooled, N=205	123.4 (10.5)	–10.2 (9.5)	72.1 (9.6)	–6.6 (9.7)

Assessor's comment: The primary efficacy endpoint of establishing a significant dose-response slope for reduction of trough SiSBP from the base line was not achieved. In the ITT population the slope of the dose response across the 3 dose levels low, medium, and high was not different from 0, when dose was expressed as a dose ratio. Neither was the dose effect statistically significant in a model that excluded weight panel as a blocking factor, nor was it statistically significant within each of the individual weight panels.

A significant dose effect for SiSBP was seen when the dose was expressed relative to body weight in mg/kg (P=0.0193) and a marginal significance (p=0.0469) when the analysis was restricted to the PP population.

Over the range of candesartan doses studied, SiSBP/SiDBP declined by 8.5/5.3 mmHg to 11.3/7.0 mm Hg; the decline with placebo was 3.8/1.3 mmHg from baseline.

The magnitude of placebo effect is rather large SiSBP/SiDBP; 3.8/1.3 mmHg. This is not surprising as the children in this age group are highly susceptible to the 'white coat' phenomena. The greater prevalence of "white coat" hypertension in the paediatric population is well described in the literature. Different studies have shown that depending on measurement methods, time of the day, rest/activity status from 5% to 62% children may display elevated blood pressure in the clinic setting but not at home (Sorof & Portman 2000). The placebo 3.8 mmHg reduction in SiSBP may explain why the analysis of results was placebo corrected.

Statistical assessor's comments:
As no statistically significant dose-response relationship was found for both analyses of the ITT population the marginal significance of the analysis of the PP population is not convincing.

Secondary end points

For the secondary efficacy measure SiDBP, the slope for change from baseline to Week 4/LOCF across the 3 active dose groups (ITT population) was similarly not significantly different from 0 (p=0.3708), Table ---16 mixed table above. The 95% CI for the slope for SiDBP was –0.6805, 0.2550. The dose effect also was not significant in the PP analysis (p=0.2519).

Results from a simple linear regression model with candesartan dose expressed in mg/kg for SiDBP were consistent with a statistically non-significant slope (p=0.1296).

Assessor's comment: This lack of statistical significance in reducing SiDBP is not surprising as

less than half (42%) of patients had elevated diastolic blood pressure at the baseline. In children the prevalence of elevated systolic blood pressure is naturally greater than that of diastolic blood pressure.

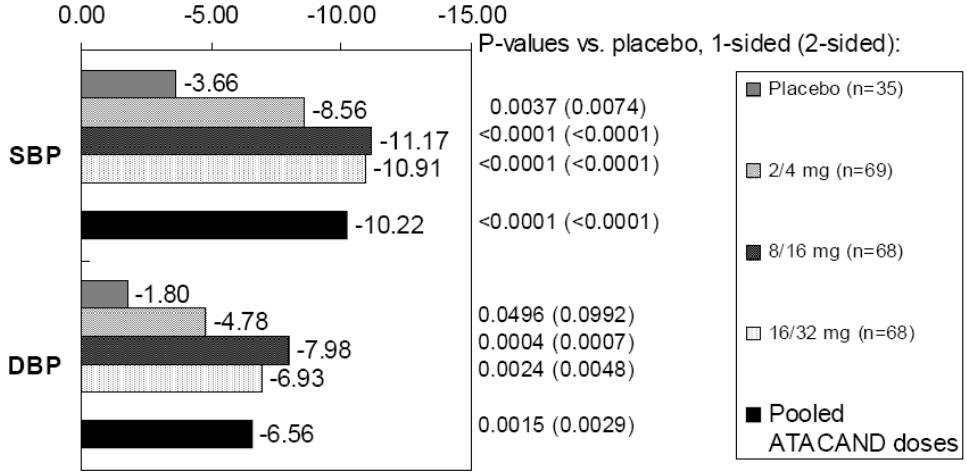
Secondary efficacy analyses also included contrasts of the active treatments (individually and pooled) and placebo at Week 4/LOCF in ANCOVA models with baseline BP as the covariate, with 1-sided tests and nominal p-values without multiplicity corrections. In these analyses each candesartan dose level as well as the pooled doses proved superior to placebo for the change in SiSBP ($p<0.01$ for each comparison) and for SiDBP ($p<0.05$ for each comparison). The pair-wise contrasts were repeated (post-hoc) specifying 2-sided tests. Under this condition, all individual candesartan doses (and all doses pooled) proved significantly superior to placebo for change in SiSBP and all but the low dose proved statistically superior to placebo for change in SiDBP, table 23; Figure 4.

Table 23- Pairwise comparisons for change from baseline to Week 4/LOCF for SiSBP and SiDBP; 2-sided p-values and 95% confidence interval (ITT population)

	SiSBP (N=240)			SiDBP (N=240)		
Change from baseline	**Least square mean**	**p-value**	**95% CI**	**Least square mean**	**p-value**	**95% CI**
Low vs placebo	–4.9023	0.0074	–8.4794, –1.3253	–2.9774	0.0992	–6.5214, 0.5666
Medium vs placebo	–7.5120	<0.0001	–11.1025, –3.9214	–6.1783	0.0007	–9.7231, –2.6336
High vs placebo	–7.2548	<0.0001	–10.8419, –3.6677	–5.1241	0.0048	–8.6709, –1.5772
All candesartan cilexetil groups pooled vs placebo	–6.5564	<0.0001	–9.7090, –3.4037	–4.7599	0.0029	–7.8792, –1.6407

Note: ANCOVA model for SiSBP includes treatment effects with baseline SiSBP as covariate. ANCOVA model for SiDBP includes treatment effects with baseline SiDBP as covariate. For the linear contrasts, the p-value and 95% confidence interval are 2-sided test.

Figure 4- Least square mean changes from baseline to Week 4/LOCF in SiSBP and SiDBP, by treatment group



Assessor's comment: Both sitting systolic and diastolic BP were significantly reduced from the baseline within the dosing groups. Candesartan at pooled doses reduced SiSBP by 10.22 mmHg ($P< 0.0001$) and SiDBP ($P=0.0029$) by 6.56 mmHg, from the baseline. This reduction was highly significant and is clinically meaningful.

In the placebo group, there was also a reduction of 3.66 mmHg in SiSBP (p=0.0074) and 1.80 mmHg for SiDBP (p=0.0992) from the baseline. Despite the large placebo effect, the post hoc analysis of the pair-wise contrasts showed that, all individual candesartan doses (and all doses pooled) were significantly superior to placebo for change in SiSBP and all but the low dose proved statistically superior to placebo for change in SiDBP. This statistical superiority in the candesartan group is also clinically advantageous compared to placebo.

Maximum response in reduction of both SiSBP (11.7 mmHg) and SiDBP (7.98 mmHg) was reached at the medium dose 8/16 mg and the effect seemed to plateau after that point.

Statistical assessor's comments:
All three doses of candesartan demonstrated a statistically significant improvement compared to placebo in terms of SiSBP. However for SiDBP the lower dose failed to achieve significance. Although not formally tested there may be a difference in effect between the low and medium doses but no meaningful difference between the medium and high doses suggesting that they are on a flat section of the dose-response curve.

Responder analyses

Treatment response was defined as SBP and DBP less than the 95% percentile at Week 4. The results are presented in the table below.

Table 24- Number and proportion of responders (ITT population)

Treatment group	N	Number of responders	Proportion of responders	95% CI	2-sided Fisher's Exact Test vs placebo
Placebo	35	11	0.314	0.1605, 0.468	
Candesartan cilexetil 2/4 mg	69	37	0.536	0.4186, 0.653	0.0386
Candesartan cilexetil 8/16 mg	68	42	0.618	0.5021, 0.733	0.0040
Candesartan cilexetil 16/32 mg	68	44	0.647	0.5335, 0.760	0.0017
All candesartan cilexetil groups pooled	205	123	0.600	0.5329, 0.667	0.0028

Note: A Responder was defined as any subject whose SiSBP and SiDBP was less than the 95th percentile at Week 4. Subjects without a value at Week 4 were considered nonresponders. P-values were generated in post-hoc analysis.
CI Confidence interval. ITT Intention to treat.

Statistical assessor's comments:
The proportion of responders was statistically significantly greater than placebo for each dose. Although the response rate for the medium dose was greater than for the low dose (62% compared to 54%), there was little difference between the rates for the medium and high doses (62% and 65% respectively). This supports the findings of the ANCOVA for the pairwise comparisons of each dose with placebo.

Other secondary variables (StSBP, StDBP, pulse pressure)

The secondary efficacy measures StSBP and StDBP were generally consistent with the sitting position. However for StSBP, the dose effect (expressed as dose ratio) was statistically

significant; for pairwise comparisons. The dose effect for StDBP was not statistically significant but all doses individually and pooled were significantly superior to placebo.

Analyses of sitting pulse pressure, dose effect, pairwise individually and pooled, were not statistically significant.

Subgroup analyses

Weight
While the change in SiSBP appeared somewhat greater for the <50 kg group than for the ≥50 kg weight group (placebo-corrected reductions of 12.4 vs 5.6 mmHg, active doses pooled). However, there were only 25 patients in the <50 kg group and the test for treatment by weight interactions for SiSBP was not powered enough to determine significance.

The same trend was not apparent for SiDBP (placebo-corrected reductions of 5.2 vs 5.4 mmHg).

Race
In all, 113 of the randomized patients were Black and 127 were non-Black. While candesartan lowered BP in both racial groups, the reduction with candesartan in Blacks was somewhat less than non-Blacks. The test for race by treatment interaction in an ANCOVA model for SiSBP was not significant (p=0.4007).

Other subgroups
Children with Tanner stage <3 tended to have somewhat lesser BP reductions with candesartan than children stage ≥3 but the difference was not statistically significant (p=0.1901). For other subgroups (sex, age [<12 vs ≥12], BMI [<95th vs ≥95th percentile], systolic hypertension vs diastolic vs both, and whether the subject was previously treated for hypertension), there were no consistent subgroup-specific trends that were apparent for changes in both SiSBP and SiDBP.

Assessor's comment: The sub group analysis of blood pressure in standing position was generally consistent with the results of sitting position. For StSBP, the dose effect was statistically significant; for pair wise comparisons, medium dose, high dose, and all doses pooled were statistically significant compared to placebo. The dose effect for StDBP was not statistically significant but all doses individually and pooled were significantly superior to placebo. Sitting pulse pressure was not effected by candesartan.

The reduction in SiSBP was greater in the lower weight strata (12.4 mmHg, <50 kg) than for the higher weight strata (5.6 mmHg, ≥50 kg). However, there were only 25 patients in the <50 kg group and the test for treatment by weight interactions for SiSBP was not powered enough to determine significance. This effect was not seen in SiDBP. Further investigation of the effect across different subgroups by weight should be carried out.

Pharmacokinetic results

Plasma samples were collected for candesartan level determinations at Week 4 (24 ±2 hours following the last study drug dose). Plasma concentration data from a total of 173 patients were included in the analysis.

Although there was substantial variability in the observed candesartan plasma concentrations, mean trough values increased with increases in dose, table 25. Trough values observed at doses of 8 mg to 32 mg were also similar to those obtained previously in adults.

Table 25- Summary of trough candesartan concentrations

		<50 kg Candesartan cilexetil treatment			≥50 kg Candesartan cilexetil treatment		
		2 mg N=8	8 mg N=9	16 mg N=8	4 mg N=59	16 mg N=57	32 mg N=58
Candesartan concentrations included in analysis		8	7	8	51	49	50
Candesartan concentrations not recorded, not trough, or below LOQ		0	2	0	8	8	8
Candesartan concentration, nmol/L	Mean (SD)	8.6 (3.8)	22.8 (25.5)	59.9 (54.4)	10.6 (10.7)	41.1 (46.1)	73.4 (62.8)
	Range	4.5 to 15.1	0 to 68.7	12.4 to 180.0	0 to 59.0	0 to 246.0	0 to 306.0
	Median	7.2	11.6	39.2	7.2	29.5	62.5

LOQ Limits of quantitation.

Assessor's comment: This is not a comprehensive PK study, it is only one parameter of through concentration being measured in this age group of 6 to <17 year olds.

- Safety results

Of the 240 randomized subjects, all were included in the safety analyses, the median duration of treatment was 28 days.

Adverse events

The most common AEs were headache, dizziness, cough, pharyngolaryngeal pain, and upper respiratory tract infection – events that would be expected for a general paediatric population, Table 26.

Table 26- Number (%) of subjects with adverse events in descending frequency by active pooled group and occurring with an incidence of at least 1.5% (safety analysis set)

	Number (%) of subjects who had an adverse event in each category[a]				
	Placebo N=35	2/4 mg N=69	8/16 mg N=68	16/32 mg N=68	Active pooled N=205
Number (%) of subjects with at least 1 AE	22 (62.9)	36 (52.2)	35 (51.5)	34 (50.0)	105 (51.2)
Headache	3 (8.6)	12 (17.4)	10 (14.7)	11 (16.2)	33 (16.1)
Dizziness	2 (5.7)	2 (2.9)	6 (8.8)	6 (8.8)	14 (6.8)
Cough	3 (8.6)	3 (4.3)	4 (5.9)	5 (7.4)	12 (5.9)
Pharyngolaryngeal pain	0	3 (4.3)	2 (2.9)	5 (7.4)	10 (4.9)
Upper respiratory tract infection	1 (2.9)	2 (2.9)	4 (5.9)	4 (5.9)	10 (4.9)
Sinus arrhythmia	0	1 (1.4)	3 (4.4)	2 (2.9)	6 (2.9)
Abdominal pain upper	0	1 (1.4)	3 (4.4)	1 (1.5)	5 (2.4)
Fatigue	0	1 (1.4)	1 (1.5)	2 (2.9)	4 (2.0)
Vomiting	0	1 (1.4)	2 (2.9)	1 (1.5)	4 (2.0)
Nasal congestion	3 (8.6)	1 (1.4)	2 (2.9)	0	3 (1.5)
Nasopharyngitis	0	2 (2.9)	1 (1.5)	0	3 (1.5)
Rhinitis	1 (2.9)	0	2 (2.9)	1 (1.5)	3 (1.5)
Sinusitis	0	1 (1.4)	0	2 (2.9)	3 (1.5)

No deaths were reported. A 14 year old black girl had anaphylactic reaction to raspberries on Day 24 of treatment. She had medical history of many allergies and was on a whole host of other concomitant medications.

Three candesartan treated subjects were discontinued due to non-serious AEs: hypotension (n=1), compound fracture of the left radius and ulna, and fracture with dorsal displacement (n=1), and worsening of dizziness (n=1). One placebo-treated subject discontinued because of hypertension and headache.

Assessor's comments: The incidence of AEs was slightly higher in the medium-dose group, but it is of little consequence as there was no evidence for a dose relationship in either the frequency or nature of adverse events.

One child had anaphylactic reaction to raspberries, whilst on candesartan; however she had medical history of many allergies and other concomitant medications. There were 3 discontinuations due to hypotension, compound fracture and worsening of dizziness. Whilst compound fracture is probably unrelated to candesartan use, hypotension and dizziness are well described adverse event of all ARBs.

Metabolic substudy

Table 27 shows that in the metabolic substudy changes from baseline to final visit were generally comparable across the treatment groups except for insulin level where the placebo treated subjects had a moderately greater decrease than the active treatment groups but the placebo group had a higher baseline insulin value.

Table 27- Descriptive statistics for baseline and Week 4, metabolic substudy

Parameter (units)		Candesartan cilexetil treatment				
		Placebo	2/4 mg	8/16 mg	16/32 mg	Active pooled
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Insulin	Baseline	n=3 28.0 (27.1)	n=9 21.1 (7.5)	n=6 18.2 (14.6)	n=8 17.4 (8.9)	n=23 19.0 (9.8)
	Δ	–9.3 (22.4)	2.0 (9.3)	5.0 (16.3)	1.4 (4.8)	2.6 (10.1)
Fasting glucose[a] (g/dl)	Baseline	n=9 84.2 (9.3)	n=26 88.1 (5.2)	n=26 86.2 (8.8)	n=27 86.0 (7.6)	n=79 86.8 (7.3)
	Δ	–1.6 (7.8)	5.3 (20.8)	0.9 (9.9)	3.5 (10.3)	3.2 (14.4)
C-reactive protein	Baseline	n=3 4.7 (2.7)	n=9 5.5 (7.3)	n=7 4.0 (3.9)	n=8 5.5 (7.4)	n=24 5.1 (6.3)
	Δ	1.5 (5.8)	–1.3 (4.5)	2.5 (9.5)	1.7 (12.1)	0.8 (8.8)
Homocystein	Baseline	n=3 5.8 (2.4)	n=9 5.8 (1.6)	n=6 4.5 (1.4)	n=8 5.3 (1.5)	n=23 5.3 (1.5)
	Δ	0.6 (0.2)	–0.5 (0.9)	0.3 (0.4)	0.5 (1.2)	0.1 (1.0)
Uric acid, (mg/dl)	Baseline	n=4 5.7 (2.3)	n=9 6.1 (0.8)	n=7 5.2 (1.6)	n=8 5.1 (1.1)	n=24 5.5 (1.2)
	Δ	–0.1 (0.5)	–0.6 (0.8)	–0.0 (1.0)	0.3 (1.9)	–0.1 (1.3)
HbA1C, (meq/L)	Baseline	n=3 5.3 (0.6)	n=8 5.1 (0.6)	n=6 5.2 (0.5)	n=8 5.4 (0.3)	n=22 5.3 (0.4)
	Δ	0.0 (0.1)	0.1 (0.2)	0.1 (0.2)	0.0 (0.3)	0.1 (0.2)
QUICKI	Baseline	n=3 0.14 (0.02)	n=8 0.13 (0.01)	n=5 0.14 (0.02)	n=8 0.14 (0.1)	n=21 0.14 (0.01)
	Δ	0.0 (0.01)	–0.0 (0.01)	0.0 (0.00)	–0.0 (0.01)	–0.0 (0.01)

Δ = Change from baseline to final visit.

The trial also collected metabolic parameters on a subset of study subjects but the number of subjects who elected to participate was fewer than expected, many of the values could not be confirmed as fasting values and no apparent treatment related trends were apparent.

Assessor's comment: The number of patients was too small to highlight any metabolic advantage or disadvantage of candesartan. The applicant's position that no treatment related trends were apparent is acceptable.

Urinalysis

No subjects had notably high proteinuria the highest urine total protein value was 38 mg/dl at Week 4 for 1 subject (baseline was 16 mg/dl; normal range 0 to 15 mg/dl). Table 28 presents descriptive statistics for baseline and Week 4 microalbumin/creatinine ratio.

Table 28- Descriptive statistics for baseline and Week 4 microalbumin/creatinine ratio (safety population)

			Placebo	2/4 mg	8/16 mg	16/32 mg	Active pooled
			N=35	N=69	N=68	N=68	N=205
A/C ratio (mg/g creat)	Baseline	N	22	51	41	45	137
		Mean (SD)	12.6 (30.3)	16.5 (42.0)	21.1 (94.0)	31.2 (78.1)	22.7 (72.5)
		Range	1 to 139	1 to 226	1 to 605	1 to 411	1 to 605
		Median	3.0	3.0	3.0	5.0	3.0
	Δ from baseline	N	22	51	41	45	137
		Mean (SD)	4.8 (20.9)	11.4 (44.7)	26.2 (174.2)	–8.1 (74.9)	9.4 (108.0)
		Range	–13 to 96	–38 to 233	–36 to 1113	–242 to 322	–242 to 1113
		Median	0.0	0.0	1.0	0.0	0.0

A/C = Albumin/creatinine ratio.
Δ = Change from baseline.

Assessor's comment: Although candesartan seems to reduce AC ratio at 32 mg dose, but this effect has not been quantified. The number of patients participated was too small to highlight any reno-protective effect of candesartan.

The adverse event presentation in its current format is unacceptable. There is no comprehensive table of adverse events with the SOC and preferred terms, the results are scattered amongst tables and texts under many different headings of: Most common adverse events, Other significant adverse events, Clinical laboratory evaluation, Cardiac evaluation. At present format the data is difficult to assess. The applicant is requested to fully reformat the Adverse event section of the Safety results and provide a comprehensive table containing all adverse events.

The results of Metabolic sub-study and Urinalysis are acceptable in the current format.

IV. 3. 2. 2. Clinical study 261B: A Multicenter, Multinational, Open-Label Study of the Efficacy, Safety, and Pharmacokinetics of Candesartan Cilexetil in Hypertensive Paediatric Subjects 6 to <17 Years of Age

- **Description**

This open-label, uncontrolled study describes a 1-year clinical experience with candesartan as treatment for hypertensive paediatric subjects ages 6 to less than 17 years. Other objectives included: change in growth, change in neurocognition, determination of the pharmacokinetics of candesartan, and a description of safety.

- **Methods**

  - Objective(s)

Objectives were not specified as primary and secondary objectives. Objectives of the study are described below.

- to describe candesartan antihypertensive effects in terms of achieved blood pressure and hypertension control rates and the relationship between subject characteristics and antihypertensive efficacy, and between antihypertensive therapy (candesartan dose and add-on treatments) and efficacy over a 1 year treatment period in hypertensive children ages 6 to <17 years.

- determine the pharmacokinetics of candesartan in hypertensive paediatric subjects ages 6 to <17 years (US only)

- describe growth in terms of height and weight in the study population

- describe change in neurocognition over a 1 year interval as assessed by the Full Scaled IQ score in a subset of study subjects (US only)

- describe safety including adverse events and adverse events necessitating study drug discontinuation including dose level and dose duration relationships and growth over a 1 year period in hypertensive children age 6 to <17 years.

- Study design

The study is 1-year open-label, uncontrolled, clinical experience in pediatric subjects ages 6 to less than 17 years. Most subjects had previously participated in the 4 weeks candesartan dose ranging study (261A). Eligible subjects began open-label candesartan with a starting dose of 4 mg once daily for children <50 kg and of 8 mg once daily for children ≥50 kg. During the study, the dose was adjusted between 4 and 32 mg once-daily. If the subject's BP was not controlled with candesartan 32 mg or the maximum tolerated dose, add other antihypertensive were given.

At selected sites in the United States, anytime during the study, up to 16 subjects were identified to participate in the single-dose pharmacokinetic (PK) substudy. Half of these subjects were between the ages of 6 to less than 12 years and half aged 12 to less than 17 years with a minimum weight requirement (25 kg). In addition, selected sites in the United States participated in a neurocognitive (IQ testing) substudy which targeted the enrolment of approximately 24 subjects.

Assessor's comment: It is not clear whether treatment with the candesartan in the open label phase started immediately or with a time lapse from the end of the 4 weeks double blind phase. The applicant should clarify this.

- Study population /Sample size

The inclusion criteria for non-participants of Study 261A were: diagnosed and untreated hypertension or diagnosed and treated, but off antihypertensive treatment for at least 2 days with a mean SiSBP and/or SiDBP ≥95th percentile and ≤20 mmHg (systolic) and/or 10 (diastolic) mmHg above the 95th percentile based on height adjusted charts for age and gender.

Females of childbearing potential (post-menarche) were required to have a negative urine pregnancy test and to adhere to a pregnancy prevention method. Subjects with diabetes, valvular heart disease, significant arrhythmia, Nephrotic syndrome bilateral renal artery stenosis, coarctation of the aorta, pheochromocytoma, hyperthyroidism, Cushing's syndrome and Glomerular filtration rate <50 ml/min were excluded.

In the PK portion of the trial half of the subjects were between 6 to <12 years of age and half between 12 to <17 years of age.

- Treatments

Patients began on a starting dose of 4 mg once daily for children <50 kg and of 8 mg once daily for children ≥50 kg in oral tablet form. During the study, investigators adjust the dose as necessary (between 4 mg and 32 mg), choosing from 4 mg, 8 mg, 16 mg or 32 mg. If the subject's BP was not controlled with candesartan 32 mg or the maximum tolerated dose, the investigator was permitted to add other antihypertensive medication. The adult recommended initial dose and usual maintenance dose of candesartan in Europe is 8 mg.

The majority of subjects (73%) took concurrent medications during the study, including paracetamol 16.3%, ibuprofen 6.0% and naproxen sodium 1.3%, and hydrochlorothiazide 4.7%.

Twenty-two subjects took ‘add-on’ antihypertensive including beta blockers, hydrochlorothiazide, and ACEI agents.

For the PK study, a single 16 mg dose was administered; thereafter; the subjects began (or resumed) treatment.

- Statistical Methods

This open-label, uncontrolled study required no formal statistical hypotheses testing. It includes descriptive measures of effect and safety.

- PK study

The single-dose (16 mg) PK study, included candesartan pharmacokinetics parameters of: maximum plasma concentration (Cmax), the time (Tmax) of the first occurrence of Cmax, area under the concentration-time curve (AUC), and terminal phase half-life (t1/2).

Half the subjects were between ages 6 and <12 years and half between ages 12 and <17 years. To assure that the 16 mg dose was appropriate for all PK study participants on a mg/kg basis, a minimum weight of 25 kg, ie, a maximum dose equaling 0.64 mg/kg, were set. The PK substudy targeted 16 subjects. Subjects could enter the PK substudy prior to dosing in Study 261B or at any time during their participation in the study, provided that candesartan treatment was withheld for 48 hours.

Blood samples were drawn for drug concentration measurements after the subjects received a single (16 mg) candesartan dose. The following PK parameters were summarized:

- t1/2, which was calculated as 0.693/Kel
- AUC, which was calculated by the linear trapezoidal method with extrapolation to infinity
- Cmax, which was obtained directly from the experimental data
- tmax, which was defined as the time of the first occurrence of Cmax.

Assessor’s comment: The applicant should explain why clearance is not included in the analysis.

Neurocognitive measures

Neurocognitive function was assessed at the beginning and end of the study using the Full Scale IQ (FSIQ), as determined by the Wechsler Intelligence Scale for Children version 4 (WISC IV). The change in Full Scale IQ (FSIQ) from Visit 1 to the end of the study (52 weeks) served as the neurocognitive measure of effect. A 10-point decline in the FSIQ Scores was considered of potential clinical significance. The neurocognitive measures were summarized as follows:

- Descriptive statistics and 95% CI for the continuous change in FSIQ from the beginning to the end of the study for all subjects and by age group
- Number, proportion, and 95% CI for the proportion of subjects with a >10 point decline in FSIQ score and ≤10 point decline in FSIQ score from the beginning to the end of the study

Results

- Recruitment/ Number analysed

A total of 213 subjects how completed the randomized, double blind 4 weeks efficacy study 261A, carried on in to the open label phase, study 261B. In addition, 24 subjects enrolled directly into 261B. Of the 237 subjects who enrolled, 39 (16.5%) discontinued the study.

About half of the subjects had isolated systolic and about one-third had systolic / diastolic hypertension. Although co-morbid renal / urologic conditions were noted for some subjects, most of the study subjects likely had 'primary' or 'essential' hypertension rather than hypertension secondary to underlying renal, endocrinologic or congential disorders.

Sixteen percent of subjects (37 subjects) were less than 80% compliant and 84% (196 subjects) were considered compliant.

- Baseline data

Demographic and key baseline characteristics of study subjects are summarized in table 29 below.

Table 29- Demographic characteristics, ITT population

Demographic or baseline characteristic, N=233		n (%)
Age, years	<12 years	68 (29.2)
	≥12 years	165 (70.8)
	Mean (range)	12.9 (6 to 17)
Sex, n (%)	Male	166 (71.2)
	Female	67 (28.8)
Race, n (%)	Caucasian	111 (47.6)
	Black	102 (43.8)
	Other	20 (8.6)
Tanner stage, n (%)	<3	75 (32.2)
	≥3	140 (60.1)
	Unknown	18 (7.7)
Weight at Visit 1, n(%)	<50 kg	34 (14.6)
	≥50 kg	199 (85.4)
	Mean (range), kg	80.0 (20 to 179)
BMI percentile at Visit 1, n (%)	<95%	77 (33.0)
	≥95%	156 (67.0)
	Mean (range), kg/m·2)	29.6 (13.9 to 58.3)
Duration of hypertension, n (%)	<1 year	151 (64.8)
	1 to <2 years	32 (13.7)
	2 to <3 years	25 (10.7)
	3 to <4 years	12 (5.2)
	≥ 4 years	13 (5.6)
Type of hypertension, n (%)	None	9 (3.9)
	Diastolic only	14 (6.0)
	Systolic only	122 (52.4)
	Diastolic and systolic	88 (37.8)
Randomized groups in 261A	2/4 mg	62 (26.6)
	8/16 mg	61 (26.2)
	16/32 mg	62 (26.6)
	Placebo	27 (11.6)
	Not randomized in 261A	21 (9.0)

A total of 233 subjects were in the ITT population. Most (71%) of the subjects were ≥12 years of age and there were more males (71%) than females. With regard to race, an approximately

equal proportion were Caucasian or Black (48% and 44%, respectively). About one-third of the subjects were pre-adolescent (Tanner Stage <3). Two-thirds of subjects had a BMI ≥95th percentile and 65% had a known history of hypertension for less than 1 year. About half had isolated systolic and about one-third systolic/diastolic hypertension.

Assessor's comment: The baseline characteristics are very similar to those of the pivotal study in children 6 to <17 years old, as most patients randomized for the 4 weeks double blind phase, carried on to the open label extension. There was an additional 21 subjects naive to the study.

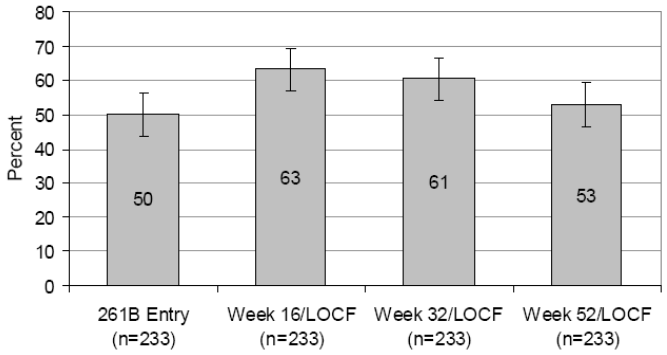
The average age in this study is 12.9 years with mean body weight of 80 kg and BMI of 29.6 kg/m2. As with the pivotal efficacy study, the majority of children in this age group have adult weight or are obese. Approximately equal numbers were pre-vs post adolescent (Tanner stage <3 vs ≥3), and about equal proportions were black and white.

The majority of subjects (52%) had systolic hypertension only or both systolic and diastolic hypertension (37.8%). A minority of subjects had underlying or related disorders such as renal / genito-urinary disorder and the majority appeared to have 'essential' primary hypertension.

- Efficacy results

After open-label treatment with candesartan, at Week 52/LOCF, more than half (53%) of the subjects were considered responders to treatment (both SBP and DBP <95th percentile).

Figure 5- Response rates at selected times with 95% confidence intervals, ITT/LOCF population



Achieved blood pressure

Blood pressure results in Study 261B were examined in 3 ways:

- for all subjects who were randomized in Study 261A and treated in Study 261B (candesartan + placebo subjects, N=212)
- separately for subjects who were randomized to double-blind active treatment with candesartan (N=185) or were randomized to placebo (N=27) in Study 261A
- For those subjects without prior randomization in Study 261A (N=21).

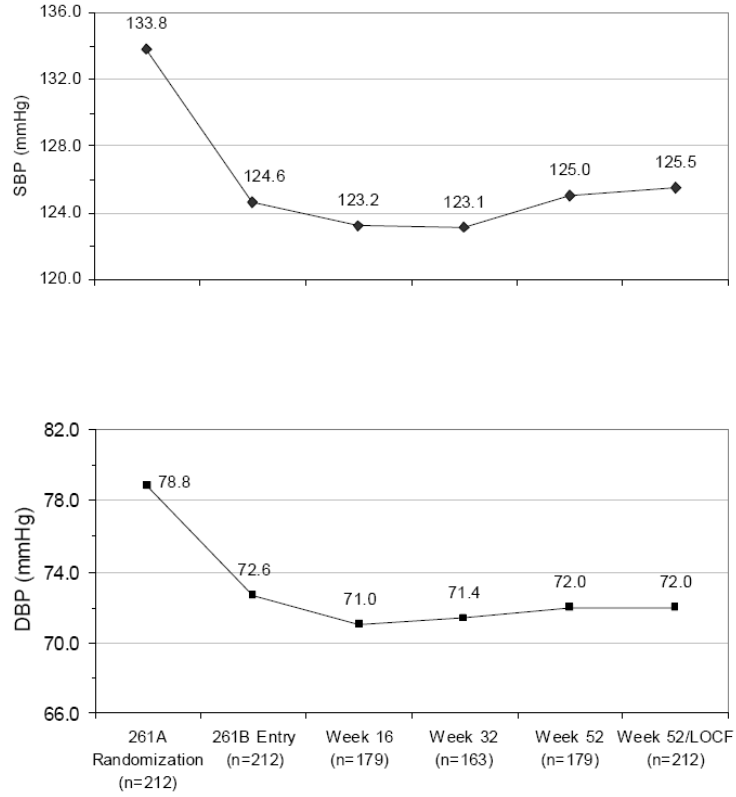
Achieved SiSBP and SiDBP over time for all subjects who were randomized in Study 261A and treated in Study 261B is shown in table 30.

Table 30- Descriptive statistics for SiSBP and SiDBP over time for all subjects who entered 261B after being randomized in 261A, ITT population

Time	N	Mean SiSBP/SiDBP mmHg (range mmHg)	Mean change in SiSBP/SiDBP from randomization in 261A (range mmHg)
261A randomization	212	134/79 (109 to 156/42 to 111)	
Entry to 261B	212	125/73 (91 to 149/43 to 99)	–9.2/–6.1 (–41 to 15/–40 to 37)
Week 16	179	123/71 (81 to 155/50 to 99)	–10.6/–7.7 (–39 to 23/–40 to 38)
Week 32	163	123/71 (87 to 159/50 to 105)	–10.9/–7.6 (–45 to 10/–35 to 26)
Week 52	179	125/72 (101 to 154/38 to 99)	–8.5/–6.9 (–33 to 24/–36 to 20)
Week 52/LOCF	212	126/72 (101 to 159/38 to 105)	–8.3/–6.7 (–33 to 24/–36 to 20)

Figure 6 presents mean SiSBP and SiDBP over time for all subjects who entered Study 261B after being randomized in 261A.

Figure 6- Mean SiSBP and SiDBP over time for subjects who entered 261B after being randomized in 261A, ITT population



A total of 27 subjects, who received only placebo treatment while in Study 261A, enrolled in Study 261B. For these placebo subjects, small changes in BP were noted at the end of double blind placebo treatment; however, following initiation of candesartan treatment in Study 261B, BP decreases from baseline over time ranged from 6.3 to 11.9 mmHg for SBP and 4.8 to 8.4 mmHg for DBP.

Assessor's comment: In the long term, open label arm of the candesartan study in the 6 to <17 years old, it appears that the SiSBD/SiDPB remain lowered by 9-11 / 6-7 mmHg at the end of the 52-week study. No statistical analysis has been performed and descriptive method of presenting data is employed, wholly relaying on the responders rate.

Responders by different subgroups

The proportion of subjects who were responders stratified by age and sex was similar. For subjects weighing less than 50 kg, the response rate was higher (68%) compared to subjects weighing ≥50 kg (50%). It is difficult to interpret this finding since the number of subjects in the lower weight group was small (n=34), and the confidence intervals for response for the 2 weight groups overlap. Most subjects received the 8 mg or 16 mg dose of candesartan and the response rates at these doses were 54% and 59%, respectively. Of note, there was a similar trend with respect to BMI – the response rate was slightly lower in subjects with a BMI ≥95th percentile (51% vs. 57%).

Stratified by race, the proportion of responders was higher for Caucasians (61%) than for Blacks (43%). An examination of baseline and dosing characteristics amongst Black and non-Black subjects failed to identify any alternative reasons (weight, dose, etc) for the observed race difference in response to treatment

Assessor comment: The fact that Caucasian children are more responsive to candesartan than Black children, ties in well with the lower response to ARBs and ACE inhibitors observed in the Black adults too.

But it is of great importance to clarify whether weight affects the response, as it can alter the dose recommendation. Therefore the applicant is requested to provide further analysis (question 8).

- PK results

<u>End-of-study plasma concentration data: all subjects</u>

Trough plasma candesartan concentrations were obtained 24 hours after the last dose of study medication, 172 subjects (74%) had trough candesartan concentrations above the limit of quantification, and 35 (15%) had concentrations at or below the limits of quantification.

The mean (SD) trough concentration was 39.6 (61) nmol/L, with a range from 0 to 424 nmol/L. These ranges were generally comparable to those obtained previously in adults, and children ages 6 to <17 years (Study 261A). Table 31 shows trough candesartan concentration by final dose and suggests a dose/concentration relationship.

Table 31- Trough candesartan concentration (nMol/L) by final dose, all subjects

Final daily candesartan dose in mg	N	Mean (SD)	Min, max
4 mg	27	29 (38)	0, 143
8 mg	64	36 (73)	0, 424
16 mg	49	36 (43)	0, 245
24 mg	3	57 (61)	7, 124
32 mg	48	61 (74)	0, 379
Other dose	12	20 (30)	0, 108

Assessor's comment: Trough concentrations of candesartan appeared to increase with dose, but not in a dose-proportional manner. It is not clear if the data were normally distributed or not, however there was a tendency of stepwise increase in candesartan exposure with increasing dose.

Pharmacokinetic single dose study

A substudy of subjects (N=22) had pharmacokinetics of candesartan assessed based on 24-hour plasma concentration data following a single candesartan dose of 16 mg. Half the subjects were between ages 6 and <12 years and half between ages 12 and <17 years. To assure that the 16 mg dose was appropriate for all PK study participants on a mg/kg basis, a minimum weight of 25 kg, ie, a maximum dose equalling 0.64 mg/kg, were set. The PK substudy targeted 16 subjects. Subjects could enter the PK substudy prior to dosing in Study 261B or at any time during their participation in the study, provided that candesartan treatment was withheld for 48 hours. Figure 7 shows plasma concentrations by age for subjects in the pharmacokinetic substudy.

Figure 7- Mean (SD) plasma concentrations by age, pharmacokinetic substudy

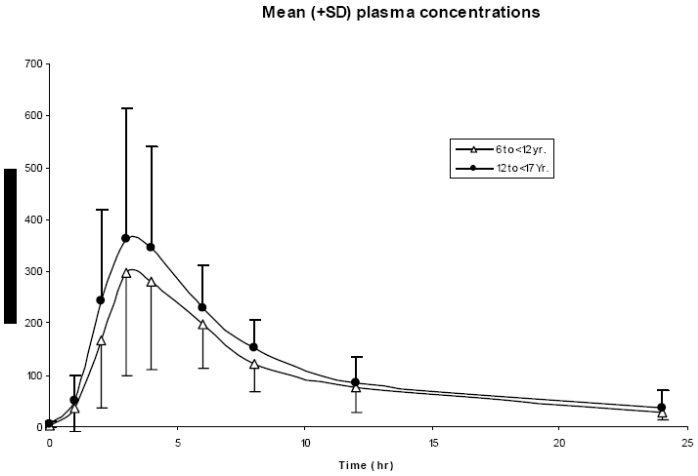


Table 32 summarizes PK parameters. The PK profile of candesartan following a 16 mg dose was generally comparable (large inter-subject variabilities) among younger and older children. Over the age ranges studied, no correlation between Cmax or AUC and age was observed (297 nMol/L and 2265 nMol.hr/L in subjects of 6 to <12 years of age, respectively, compared with 349 nMol/L and 2780 nMol.hr/L in subjects of 12 to <17 years of age, respectively).

Table 32- Summary of pharmacokinetic parameters by age, pharmacokinetic substudy

		AUC (nMol*h/L)	AUC last (nMol*h/L)	C_{max} (nMol/L)	T_{max} (hour)	$T_{1/2}$ (hour)
6 to <12 years	N	12	11	12	12	11
	Mean (SD)	2727.6 (1270.8)	2462.5 (1099.7)	333.9 (180.0)	4.3 (2.1)	6.7 (1.3)
	Min, max	1498.0, 5005.7	1379.6, 4336.6	155.0, 683.0	3.0, 9.9	4.6, 8.3
	CV%	46.6	44.7	53.9	47.9	18.9
	Geometric mean	2486.9	2265.1	297.1	4.0	6.5
12 to <17 years	N	10	9	10	10	9
	Mean (SD)	3059.9 (1091.0)	2951.2 (1041.8)	396.9 (212.0)	4.3 (1.5)	5.7 (1.3)
	Min, max	1618.6, 4646.9	1548.0, 4491.8	183.0, 779.0	3.0, 8.0	2.9, 7.5
	CV%	35.7	35.3	53.4	35.4	22.6
	Geometric mean	2883.1	2780.4	349.3	4.2	5.5

No differences were noted in PK parameter estimates (Cmax, AUC, t1/2, and Tmax) between males and females.

Body weight correlated (negatively) with Cmax and AUC estimates but there was considerable variability and the strength of the association was relatively weak (correlation coefficient was –0.528 and –0.557, respectively).

Table 33- Pearson's correlations of age and weight with pharmacokinetic parameters Pharmacokinetic Sub-study Patients

	Statistic	AUC (nmol*hr/L)	Cmax (nmol/L)	Tmax (hr)	T 1/2 (hr)
Age (years)	n	20	22	22	20
	Correlation	-0.098	0.072	-0.120	-0.458
	P-value	0.6824	0.7509	0.5945	0.0424
Weight at Baseline (kg)	n	20	22	22	20
	Correlation	-0.557	-0.528	0.187	-0.035
	P-value	0.0108	0.0116	0.4056	0.8829

Assessor's comment: This a single dose (16 mg) candesartan PK study in 22 children, half the subjects were below 12 years old and half above.

Subjects entered the PK evaluation prior to dosing in study 261B or at any time during their participation in the study, provided that candesartan treatment was withheld for 48 hours. The applicant must clarify, whether 2 days wash out period is adequate to fully eliminate all residual candesartan.

There is no correlation between Cmax and AUC with age. However weight seems to significantly correlate with Cmax (p=0.012) and AUC (p=0.011). No clearance data, has been collected/ presented, therefore the possibility of a correlation between clearance and weight in this population can not be assessed.

In conclusion this PK study is very sparse and inconclusive, the 48 hr washout period may not be adequate for elimination of all residual candesartan, there is no clearance data, the correlation between Cmax and AUC and weight to assess reasonable basis for dosing based on body weight (mg/kg) is also unclear.

- Safety results

Candesartan was taken for up to 52 weeks in doses ranging from 4- 32 mg. The mean duration of treatment was 343 days and the median duration was 365 days (range: 5 to 451 days).

Adverse events

A summary of AEs in each category of AE is presented in table 34. A total of 174 (74%) subjects had an AE. Few subjects had SAEs (6%) or were withdrawn from the study for an AE (2.1%).

Table 34- Number (%) of subjects who had an adverse event in any category (safety population)

Category of adverse event	Number (%) of subjects who had an adverse event[a]
Subjects with any adverse events	174 (74)
Subjects with non-fatal serious adverse events	14 (6.0)
Subjects with fatal serious adverse events	0
Subjects who discontinued the study due to an adverse event	5 (2.1)
Subjects who discontinued treatment due to an adverse event	6 (2.6)
Number of adverse events	625
Number of non-fatal serious adverse events	18
Number of adverse events leading to treatment discontinuation	8

Most common adverse events
The most frequently reported AEs involved the following SOCs:

- Infections and Infestations (43.4%) of which upper respiratory tract infection (19.6%)
- Nervous System Disorders (31.1%) of which headache (20.0%)
- Respiratory, Thoracic, and Mediastinal Disorders (28.1%) of which cough (9.8%)

The most common AEs were headache, upper respiratory tract infection, dizziness, cough, and pharyngolaryngeal pain – events that would generally be expected for a general pediatric population. Most of the subjects with pyrexia reported as an AE had other associated illnesses (eg, pharyngolaryngeal pain, nasal congestion, cough, sinus congestion, upper respiratory infection).

A total of 174 subjects (74%) had AEs reported and most were mild in intensity. A total of 27 subjects (11.5%) had AEs that investigators considered drug related, the most common being dizziness (3%), headache (2.1%), hypotension (1.3%), and orthostatic hypotension (1.3%).

Assessor's comments: This is a long-term study of candesartan in 207 children and adolescents for approximately 343 days. The type of reported adverse events is similar to the results of the 4 weeks period in the same ITT population. However as the use of candesartan went on, the frequency of these events increased (namely upper respiratory tract infection (19.6%), headache (20.0%) and cough (9.8%).

No subject died and five subjects were discontinued from the study prematurely due to an AE: mild dizziness (1 event), mild WBC decreased (2 events), mild nephropathy (1 event), and severe renal failure chronic (1 event).

There were 9 reports of joint sprain, which might be a signal for an idiosyncratic adverse event in

children.

Urinalysis: Albumin/creatinine ratio

The mean (SD) albumin/creatinine ratio was 24.6 (109.9) mg/g (range 1 to 1139 mg/g) at Visit 1. The mean change at Visit 9 was 47.3 mg/g (range –195 to 6485 mg/g). 23 subjects had albumin/creatinine (A/C) ratios above 30 mg/g at Visit 1 and/or at post Visit 1 from Study 261B.

Assessor's comment: Twenty-three subjects had micro-albuminuria (A:C ratio >30 mg/g) at some point either in Study 261A or Study 261B. However there was considerable variability in mean change of albumin/creatinine (47.3 mg/g, range –195 to 6485 mg/g) at 52 weeks. The applicant's position is acceptable; that there is no consistent trend for the micro-albuminuria to either improve or to progress is acceptable.

Growth measures; Body weight, height and Z-scores

Mean body weight increased by 5.9 kg at Week 52 relative to study entry. An increase in mean body weight over a year in growing children is not unexpected.

Mean height increased 3.7 cm at Week 52; however, height relative to height-specific distribution data (mean Z-score) remained relatively constant. Although, on average, BMI increased slightly over the 1-year study (29.7 to 30.4 kg/m2), there was a slight decrease in mean Z-score.

Neurocognitive measures

Table 35 shows the number (%) of subjects with a >10 or a ≤10-point decline in Full Scale WISC-IV IQ score. Within the sample of 33 subjects, 24 subjects obtained Full Scale IQ scores within 10 points of their original score at the 52 weeks assessment.

Table 35- Subjects Full Scale WISC-IV IQ score stratified by 10-point differences, neurocognitive substudy subjects

	Change in Full Scale IQ from Visit 1 to Week 52	n (%)	95% CI
All substudy subjects	Total N	33	
	>10 point decline	3 (9.1)	0.0, 18.9
	≤10 point decline	30 (90.9)	81.1, 100.0
Subjects <12 years of age	Total N	12	
	>10 point decline	2 (16.7)	0.0, 37.8
	≤10 point decline	10 (83.3)	62.3, 100.0
Subjects ≥12 years of age	Total N	21	
	>10 point decline	1 (4.8)	0.0, 13.9
	≤10 point decline	20 (95.2)	86.1, 100

Assessor's comment: There were no outstanding changes in body weight, height and BMI considering the expected growth for the ITT population. There was also no notable change in neurocognitive function as assessed by IQ testing in a subset of the subjects.

Similar to the safety section of the pivotal 4 weeks study in the 6 to >17, the adverse event presentation in its current format is unacceptable. There is no comprehensive table of adverse event with the SOC and preferred terms, the results are scattered amongst tables and texts, under many different headings. The applicant is requested to fully reformat the adverse event section of the safety results and provide a comprehensive table containing all adverse events including other significant adverse events, haematology, clinical chemistry, renal/hepatic

function, cardiac/vascular function etc.

The results of Urinalysis, growth and Neurocognitive measures and are acceptable in the current format.

IV. 3. 2. 3. Clinical Study 328 - A Dose-ranging, Safety and Pharmacokinetics Study of Candesartan Cilexetil in Hypertensive Pediatric Subjects 1 to Less Than 6 Years of Age: A 4-week, Multicenter, Randomized, Double-Blind Study

- **Description**

This was a randomised, double-blind, parallel group, study to determine the antihypertensive dose-ranging effects across three dose levels of candesartan following four weeks of treatment in hypertensive paediatric patients 1 - < 6 years of age. Following a single blind placebo run-in period of approximately one week, eligible patients were randomised to one of three doses levels, (low, medium or high), of oral candesartan suspension. The 4-week, double-blind treatment period was followed by a 52–week, open-label clinical experience evaluation (study D2451C00006). A PK sub-study was also included.

- **Methods**

- Objective(s)

The primary objective of this study was to characterize the dose response relationship of candesartan once-daily in hypertensive paediatric subjects (1 to <6 years of age) by evaluation of the slope of the linear regression for the change in trough systolic blood pressure (SBP) from baseline (Day 0) to the end of the 4-week, double-blind treatment period (Day 28) as a function of dose.

The secondary objectives were to further evaluate the antihypertensive effects and the safety of candesartan by determining:

- Change from Day 0 to Day 28 for the dose response relationship of candesartan for the change in trough SBP as a function of dose for each of the 2 body weight panels, separately; for the change in trough diastolic blood pressure (DBP) as a function of dose; and for the mean change in trough SBP and DBP for candesartan for each assigned dose level.

- The mean change in urinary protein/creatinine (P/C) and albumin/creatinine (A/C) ratio for each assigned dose level from baseline to Day 28 and to the end of the 52- week, open-label treatment period.

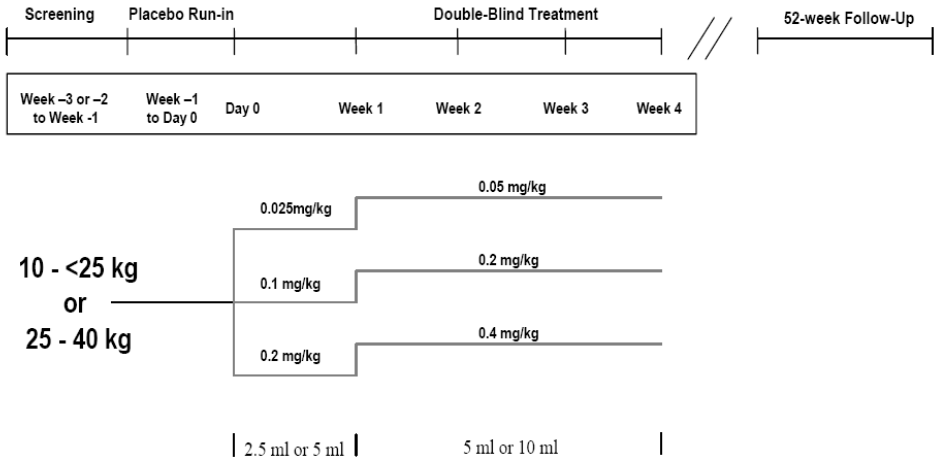
- Safety as assessed by adverse events (AEs), drug discontinuations due to AEs, serious AEs (SAEs), physical exam findings, growth, and laboratory tests results during the 4-week, double-blind treatment period.

- The pharmacokinetics (PK) of candesartan

- Study design

One to 2 weeks following a screening evaluation, subjects underwent a 1-week, single-blind, placebo run-in period during which subjects in Weight Panel 1 (10 to <25 kg) received 2.5 ml of study medication (placebo), and subjects in Weight Panel 2 (25 to ≤40 kg) received 5 ml of study medication (placebo). Subjects, were randomly allocated to receive 1 of 3 dose levels (0.05 mg/kg, 0.2 mg/kg, and 0.4 mg/kg, ie, a ratio of 1:4:8.) of candesartan during the double-blind, dose-response period.

Figure 8- Study design



The subjects had a one week single blind placebo run-in period to reduce the variability in the baseline blood pressure measurements and to stabilize any concurrent antihypertensive medications. There were no placebo group, to avoid harm in this very young and potentially more seriously hypertensive population.

Subjects receiving an ARB or an ACEI were included only after a 2-week, washout period. Subjects receiving other classes of antihypertensive medications (eg, diuretics, calcium channel blockers, or beta-blockers) were allowed in the study with the doses and dose regimens remained unchanged during the 4-week, double-blind period of the study.

Assessor's comment: There was no placebo arm and concurrent antihypertensive medications were allowed.

- Study population /Sample size

Children age 1 to <6 years SBP and/or DBP ≥95th percentile and ≤20 mmHg (systolic) and/or 10 mmHg (diastolic) above the 95th percentile at screening and at randomization based on height-adjusted charts for age and gender. Subjects with estimated glomerular filtration rate (eGFR) <30 ml/min/1.73m2 for non-transplant and <40 ml/min/1.73 m2 after transplant were excluded.

Of the 93 subjects entering the double-blind period, 86 completed; 85 entered the long-term, follow-up period, and 81 completed the entire study (study D2451C00006).

Assessor's comment: Only 35 patients completed the long term open label arm (study D2451C00006).

- Treatments

The 3 target dose levels of candesartan were 0.05 mg/kg, 0.2 mg/kg, and 0.4 mg/kg, ie, a ratio of 1:4:8. These doses were approximately comparable on a mg/kg basis to doses studied in children ages 6 to <17 years of age. The volume of study dose was standardized within each weight panel. Several suspension concentrations (range 0.1 to 1.8 mg/ml) were used to allow the fixed dosing volume of 5 ml per dose in the 10 to <25 kg weight panel and 10 ml per dose in the 25 to ≤40 kg weight panel. "Actual" doses in mg/kg were clustered around the "target" dose in mg/kg to achieve the 3 dose groups.

The study included two dose level panels based on weight. The panels were as follows:

Panel 1: subjects weighing 10 to <25 kg allocated to 0.05 mg/kg, 0.20 mg/kg or 0.40 mg/kg once daily in 1:1:1 ratio (5 ml/dose);

Panel 2: subjects weighing 25 to <40 kg allocated to 0.05 mg/kg, 0.20 mg/kg or 0.40 mg/kg once daily in 1:1:1 ratio (10 ml/dose).

The primary efficacy objective was to characterise the dose-response relationship of candesartan in once-daily oral suspension doses in hypertensive paediatric patients aged 1 - < 6 years by evaluation of the slope of the linear regression for the change from baseline to Week 4 in trough systolic blood pressure (SBP) as a function of dose.

This study was conducted in 18 centres in the United States and Puerto Rica and 20 centres in Europe.

Statistical assessor's comments:
The overall design of the study is accepted. However in view of the placebo effect seen in the study in older patients (Study 261A) where 31% of patients responded to placebo, the inclusion of a placebo arm would have been helpful.

- Statistical Methods

The protocol was amended three times with no important changes to the statistical methods. No major changes in the analysis strategy and methods were made in the statistical analysis plan (SAP) compared to those defined in the protocol. The SAP was finalised before database lock with only minor corrections after the study was unblinded.

In general the statistical methods were similar to those planned for Study 261A with appropriate allowance for the lack of a placebo arm in this study. The linear regression analysis was defined as for the earlier trial. As it was not possible to compare to a placebo group, changes from baseline to the end of the double-blind period were examined within each treatment group. ANCOVA models for changes in SiSBP and SiDBP included factors for weight panel and treatment group with the baseline blood pressure as the covariate. Least squares means for treatment effects were calculated with 95% confidence interval. However p-values were not reported.

The sample size estimates for the paediatric hypertension clinical trial programme took into account criteria outlined in an FDA modification to assure that studies were adequately powered. Therefore the sample size for this study was chosen to ensure that 25% of the efficacy evaluable subjects participating in the overall program were aged 1 - < 6 years.

Statistical assessor's comments:
As no placebo arm was included in this study, the dose-response was investigated without any placebo correction to the change from baseline in the primary efficacy variable. As a placebo response was seen in the study in older children, this is a concern and the Applicant should discuss the possible impact of the lack of placebo. In general the statistical methods are acceptable, with the same comment concerning the use of LOCF to handle missing data. Although the sample size was apparently not formally estimated for this study alone, the number of patients randomised was adequate to establish statistical significance for the primary endpoint as well as other secondary endpoints.

- PK measurements

Random PK samples were collected from all subjects at the end of the double-blind period. In addition, a subset of subjects (10 subjects) went in the serial PK study. Subjects participated in the serial PK study either at study entry prior to the double-blind period of the study or at any point during the open-label extension period but only after discontinuing study drug for at least 48 hours.

On the morning of dosing in the serial PK study (Day 1), 45 minutes to 1 hour after completion of the morning meal, subjects received a single dose of candesartan, 0.2 mg/kg, oral suspension once daily. Pulse and blood pressure measurements were carried out prior to PK sample collections. Subjects were not to eat for the first 2 hours after dosing.

The following PK parameters were summarized: the time to maximum plasma concentration (tmax), maximum plasma concentration (Cmax), terminal elimination half-life (t1/2), and AUC for candesartan.

- t1/2, which was calculated as 0.693/Kel
- AUC, calculated by the linear trapezoidal method with extrapolation to infinity
- AUCt, area under plasma concentration-time curve (AUC) from zero to time t, where t is the last time-point with the quantifiable concentration
- Cmax, which was obtained directly from the experimental data
- tmax, which was defined as the time of the first occurrence of Cmax

Assessor's comment: The applicant should explain why clearance is not included in the analysis.

Results

- Recruitment/ Number analysed

95.7% of subjects reported at least 1 medical condition. The most common of these included hypertension (n=33), chronic renal failure (n=18), congenital cystic kidney disease (n=17), asthma (n=12) and renal dysplasia (n=12). Nearly half of the subjects had elevations in both systolic and diastolic blood pressure, while about a quarter had either lone systolic or lone diastolic elevations. About three-fourths of the subjects had hypertension that was judged to be 'secondary', principally because of coexisting renal disease.

Most of the subjects were Caucasians (n=71); however, 17 were Black. Over half of the subjects had a BMI less than the 95th percentile. Most subjects (87%) were in the lower weight stratum (10 to <25 kg.).

- Baseline data

Demographic and key baseline characteristics of study subjects by treatment group are summarized in table 36 below. At baseline, most subjects were ≥2 to <6 years of age (16 subjects were 1 to <2 years) and about two-thirds were males.

Table 36- Demographic and baseline characteristics by treatment group (ITT population)

		Candesartan treatment			
Demographic characteristics		**0.05 mg/kg N=29 n (%)**	**0.2 mg/kg N=32 n (%)**	**0.4 mg/kg N=32 n (%)**	**Total N=93 n (%)**
Sex (n, % of subjects)	Female	11 (37.9)	10 (31.3)	12 (37.5)	33 (35.5)
	Male	18 (62.1)	22 (68.8)	20 (62.5)	60 (64.5)
Age at screening (years)	1 to <2	6 (20.7)	5 (15.6)	5 (15.6)	16 (17.2)
	2 to <6	23 (79.3)	27 (84.4)	27 (84.4)	77 (82.8)
	Mean (SD)	3.0 (1.3)	3.3 (1.4)	3.0 (1.4)	3.1 (1.4)
	Range	1 to 5	1 to 5	1 to 5	1 to 5
	Median	3.0	4.0	3.0	3.0
Race (n, % of subjects)	Caucasian	20 (69.0)	25 (78.1)	26 (81.3)	71 (76.3)
	Black	6 (20.7)	5 (15.6)	6 (18.8)	17 (18.3)
	Oriental	1 (3.4)	1 (3.1)	0	2 (2.2)
	Other	2 (6.9)	1 (3.1)	0	3 (3.2)
Baseline characteristics					
Weight at randomization (kg)	10 to <25	25 (86.2)	27 (84.4)	29 (90.6)	81 (87.1)
	25 to 40 kg	4 (13.8)	5 (15.6)	3 (9.4)	12 (12.9)
	Mean (SD)	17.5 (6.5)	18.0 (6.2)	17.0 (6.3)	17.5 (6.3)
	Range	10 - 38	11 - 34	11 - 39	10 - 39
	Median	15.8	16.8	15.7	16.0
BMI percentile at screen	<95%	17 (58.6)	17 (53.1)	22 (68.8)	56 (60.2)
	≥95%	6 (20.7)	10 (31.3)	5 (15.6)	21 (22.6)
	Unknown	6 (20.7)	5 (15.6)	5 (15.6)	16 (17.2)
BMI at screen (kg/m^2)	Mean (SD)	17.9 (3.3)	18.4 (4.3)	17.5 (3.3)	17.9 (3.6)
	Range	14 to 28	15 to 36	14 to 30	14 to 36
	Median	17.3	17.2	16.4	17.1
Height at randomization (cm)	Mean (SD)	97.6 (12.6)	98.0 (11.4)	97.3 (12.2)	97.6 (11.9)
	Range	74 to 129	76 to 116	78 to 123	74 to 129
	Median	96.2	98.8	95.3	97.0
Type of hypertension[a]	None	2 (6.9)	0	1 (3.1)	3 (3.2)
	Diastolic only	7 (24.1)	7 (21.9)	6 (18.8)	20 (21.5)
	Systolic only	6 (20.7)	7 (21.9)	8 (25.0)	21 (22.6)
	Systolic + diastolic	14 (48.3)	18 (56.3)	17 (53.1)	49 (52.7)
Source of hypertension (n, % of subjects)	Primary	6 (20.7)	7 (21.9)	9 (28.1)	22 (23.7)
	Secondary	23 (79.3)	25 (78.1)	23 (71.9)	71 (76.3)
Presence of renal disease	No	6 (20.7)	9 (28.1)	9 (28.1)	24 (25.8)
	Yes	23 (79.3)	23 (71.9)	23 (71.9)	69 (74.2)

Table 37- Mean and SD for baseline blood pressure (ITT population)

		Candesartan treatment							
Parameter, units	**Time**	**n**	**0.05 mg/kg**	**n**	**0.2 mg/kg**	**n**	**0.4 mg/kg**	**n**	**Total**
SBP, mmHg	Baseline	29	111 (9.2)	32	114 (8.0)	32	112 (8.9)	93	112 (8.7)
DBP, mmHg	Baseline	29	69 (8.9)	32	71 (9.6)	32	70 (9.6)	93	70 (8.8)

Assessor's comment: The average age in this study in 1 to 5 years olds is 3.1 years; only 16 children (17%) were under 2 years old. Over half of the subjects had a BMI less than the 95th percentile. Most subjects (87%) were in the lower weight stratum (10 to <25 kg).

74% of the subjects had secondary hypertension due to coexisting renal disease, which is expected in this age group.

A total of 99 children received a randomisation number although 6 did not receive study drug. Therefore the 93 patients who received double-blind medication were designated as the randomised population. Of these, 86 (92.5%) patients completed the 4-week double-blind period with only 7 patients discontinuing prematurely. The PP population consisted of 79 patients with 14 children excluded with protocol deviations.

Of the 93 patients who received double-blind treatment only 12 (13%) were in the higher weight stratum.

Statistical assessor's comments:
Unfortunately only 13% of the children were in the higher weight stratum. This is similar to the study in older children where the lower weight stratum contained only 13% of the patients randomised in the study.

- Efficacy results

Primary end point

Systolic blood pressure declined from baseline to Week 4 by 6 to 12 mmHg over the 3 dose levels (0.05 mg/kg, 0.2 mg/kg, and 0.4 mg/kg), a decline that was both monotonic and significantly dose related (p=0.0136) (tables 38 & 39). There was a similar, monotonic, significantly dose related decline in DBP of 5.2 to 11.1 mmHg (p=0.0301).

Table 38- Mean Week 4/LOCF and mean change from baseline to Week 4/LOCF in SBP and DBP (ITT population)

		SBP, mmHg			DBP, mmHg	
Treatment group	**n**	**Week 4/LOCF Mean (SD)**	**Mean (SD) change from baseline**	**n**	**Week 4/LOCF Mean (SD)**	**Mean (SD) change from baseline**
Candesartan, 0.05 mg/kg,	29	105 (9.8)	–6.0 (9.4)	29	64 (7.5)	–5.2 (6.7)
Candesartan, 0.2 mg/kg	32	105 (10.2)	–8.9 (9.2)	32	63 (9.0)	–7.9 (12.9)
Candesartan, 0.4 mg/kg	32	100 (10.5)	–12.0 (8.3)	32	59 (6.6)	–11.1 (9.2)
Candesartan pooled	93	103 (10.4)	–9.1 (9.2)	93	62 (8.0)	–8.2 (10.2)

The dose-effect from baseline to Week 4/LOCF was significant for the ITT population (Table ---). The slope for dose ratio (1:4:8) was:

- SBP: –0.80 (CI –1.436, – 0.1692; p=0.0136)
- DBP: –0.79 (CI –1.5066, – 0.0781; p=0.0301)

The coefficient for the weight group p-value was 0.0386. However, very few subjects were in the higher weight stratum (n=12).

Table 39- Dose-response regression for change from baseline to Week 4/LOCF for SBP and DBP (ITT population)

	SBP			DBP		
	DF	Estimate (SE)	p-value	DF	Estimate (SE)	p-value
Model						
Intercept (α)	1	–6.2270 (1.7345)	0.0005	1	–5.3637 (1.9558)	0.0074
Coefficient for dose (β)	1	–0.8026 (0.3188)	0.0136	1	–0.7923 (0.3595)	0.0301
Coefficient for weight group (τ)	1	5.6874 (2.7098)	0.0386	1	5.5053 (3.0555)	0.0749

Figures 9 & 10 show mean change from baseline to Week 4/LOCF in SBP and DBP, respectively, for the ITT population. Candesartan exhibited a significant dose response for changes from baseline to Week 4/LOCF in both SBP and DBP.

Figure 9- Means and dose-response line for changes from baseline to Week 4/LOCF in SBP (ITT population)

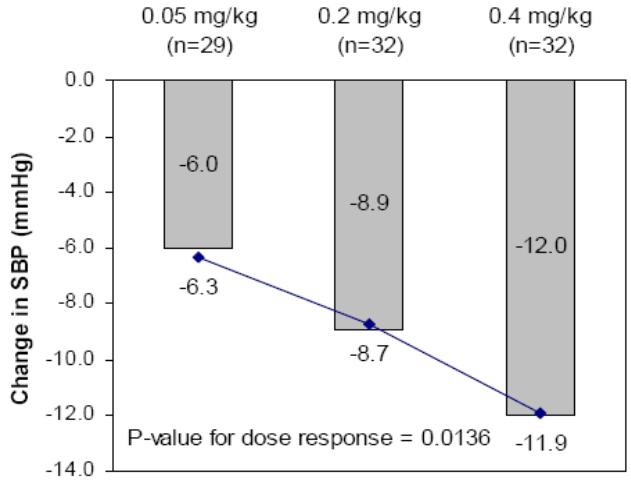
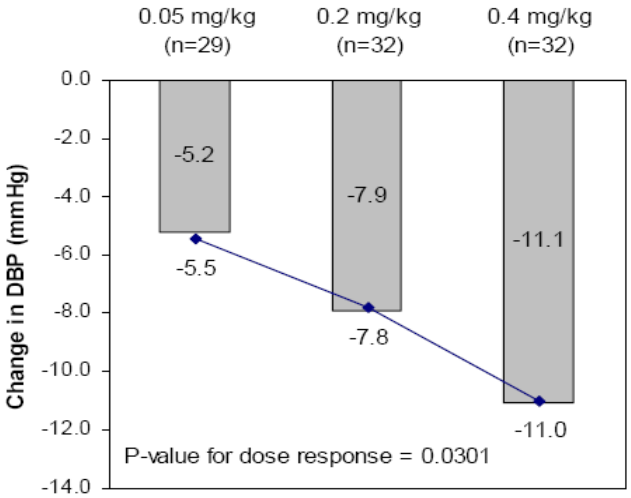


Figure 10- Means and dose-response line for changes from baseline to Week 4/LOCF in DBP (ITT population)



In the PP analyses both SBP and DBP also declined with candesartan but in this smaller (N=79) analysis set the slope for dose effect was not statistically significant (p=0.0644 for SBP; p=0.0622 for DBP).

Assessor's comment: A statistically significant candesartan dose response was observed for SBP (p=0.0136) and DBP (p=0.0301) in the ITT population.

The mean changes in SBP/DBP from the study baseline to the end of 4 weeks were 6.0/5.2 mm Hg, 8.9/7.9 mmHg and 12.0/8.2 mm Hg for low, medium and high OM doses, respectively.

The low, medium and high doses of candesartan were effective in reducing both SBP and DBP. This efficacy is also of clinical importance as the SBP and DBP were reduced in the range of 6-12 mmHg and 5.2 -11 mmHg respectively, in this age group. However lack of placebo comparator in a population prone to 'white coat phenomena' makes the interpretation of this out come difficult.

Secondary end points

The dose response relationship of candesartan for change in SBP as a function of dose for each body weight panel was analysed. There was a decline in SBP and DBP with dose within both weight strata albeit 1 that was not statistically significant in the heavier weight group. There were only 12 children in the higher weight stratum of 25 to ≤40 kg (81 children were in the weight stratum 10 to <25 kg).

A summary of findings is provided below:

10 to <25 kg weight strata
Dose response for change from baseline to Week 4/LOCF for SBP and DBP was significant for the weight group 10 to <25 kg. The slope for dose ratio (1:4:8) was:

- SBP: –0.80 (CI –1.4904, –0.1071, p=0.0242)
- DBP: –0.81 (CI –1.5861, –0.0331, p=0.0412)

25 to ≤40 kg weight strata

Dose response for change from baseline to Week 4/LOCF for SBP and DBP was not significant for the weight group 25 to <40 kg. The slope for dose ratio (1:4:8) was:

- SBP: –0.83 (CI –2.5663, 0.8996, p=0.3091)
- DBP: –0.65 (CI –2.7107, 1.4012, p=0.4942)

Statistical assessor's comments:
A significant dose response has been established by the demonstration of the slope of the regression line being statistically significantly different to zero in terms of the primary variable. This is supported by a similar dose response in the corresponding change from baseline in SiDBP. As the majority of children were in the lower weight panel it is not surprising that this result was repeated in the analysis of this subgroup. However although there were only 12 patients in the higher weight group and therefore statistical significance was not achieved due to lack of power, the estimated slope for this subgroup (0.83) was similar in size to that for the lower weight subgroup (0.80). It was not possible to apply a placebo-correction to the change from baseline in the primary variable before the analysis was conducted. Also due to the lack of a placebo arm, no pairwise comparisons with placebo are available. Although it is only possible to speculate what effect a placebo arm might have had on the interpretation of the results the Applicant should discuss the possible impact of a lack of placebo comparator.

Sub-group analyses

Ten subgroups were analyzed for changes from baseline to Week 4/LOCF, table 40 below.

Table 40- Change from baseline to Week 4/LOCF in SBP and DBP by subgroup, all doses pooled (ITT population)

		Mean change from baseline to Week 4/LOCF (mmHg)		
		n	SBP	DBP
Sex	Male	60	–8.9	–8.5
	Female	33	–9.3	–7.5
Weight	10 to <25 kg	81	–9.8	–8.9
	25 to ≤40 kg	12	–3.8	–3.0
Age group (years)	1 to <2	16	–9.8	–7.2
	≥2 to <6	77	–8.9	–8.4
Race	Black	17	–10.2	–6.7
	Non-Black	76	–8.8	–8.5
Body Mass Index	<95th percentile	56	–9.8	–8.9
	≥95th percentile	21	–6.6	–7.0
	Unknown	16	–9.8	–7.2
Type of hypertension	None	3	2.4	–3.9
	Diastolic only	20	–3.8	–4.5
	Systolic only	21	–6.5	–2.5

	Diastolic and systolic	49	–13.0	–12.4
Previously treated with an antihypertensive medication	No	54	–10.2	–8.7
	Yes	39	–7.5	–7.4
Hypertension	Primary	22	–8.0	–6.8
	Secondary	71	–9.4	–8.6
Renal disease	No	24	–8.6	–7.5
	Yes	69	–9.2	–8.4
Region	Europe	48	–9.5	–9.7
	US/Puerto Rico	45	–8.6	–6.6

Assessor's comment: The result of all subgroups examined imply that candesartan is effective independent of age, gender, race, primary versus secondary hypertension, antecedent treatment for hypertension, and geographic region.

Of all the 10 subgroups analysed, weight seems to be the only one that has an inverse relation ship with response. The effect of candesartan in lowering both SBP and DBP in the lower weight strata (10 to<25 Kg) is nearly triple than in higher weight strata (25 <40 kg), but due to small number of patients in the heavier weight strata, the significance of this can not be determined. Similar ambiguity with the effect of weight on the response was seen in the older age group (6 to <17 year, study 621A).

There seems to be a difference in candesartan response in different weight group that is somehow masked by low number of children in 25 to >50 Kg weight band.

Responder analysis

Treatment response was defined as SBP and DBP less than the 95% percentile based on height-adjusted charts for age and gender at Week 4. The results are presented in the table below.

Table 41- Number and proportion of responders during the double-blind treatment period (ITT population)

Treatment group	N	Number of responders	Proportion of responders (%)	95% CI
Candesartan cilexetil 0.05 mg/kg	29	8	27.6	11.32 to 43.85
Candesartan cilexetil 0.2 mg/kg	32	16	50.0	32.68 to 67.32
Candesartan cilexetil 0.4 mg/kg	32	21	65.6	49.17 to 82.08
All candesartan groups pooled	93	45	48.4	38.23 to 58.54

CI Confidence interval.

Statistical assessor's comments:
Although the response rates for the medium and high doses were at least 50% for the low dose the percentage of responders was less than 30%. Unfortunately no comparison with placebo is possible and this is a matter of concern as in Study 261A in the older children the response to placebo was slightly over 30%.

Pooled analysis of efficacy data

Data from Study 261A conducted in 6 to <17 year old children were pooled with data from Study 328 (children aged 1 to <6 years) to assess dose response for changes in blood pressure across the full age range examined in the paediatric programme. The blood pressure measurements were not placebo-corrected as there was no placebo arm in the study in younger children. Terms in the analysis model included dose ratio, study, by dose-ratio interaction and weight panel nested within study. If the interaction term was found to be not significant at the 10% level it was removed and the dose response was determined from the reduced model.

Statistical assessor's comments:
As the studies have been conducted in different age groups and with different forms of treatment (tablets for older children and a suspension for the younger group), the value of the pooled analysis is limited.

Pharmacokinetic results

Of the 93 subjects in the ITT population, 5 subjects in the 10 to <25 kg weight group and 2 subjects in the 25 to ≤40 kg weight group had no samples collected. Table 42 describes the candesartan concentrations for 86 subjects who had detectable candesartan plasma concentrations. The mean candesartan concentrations increased in a dose related manner within both the 10 to <25 kg and the 25 to ≤40 kg weight groups.

Although there were few subjects in the heavier weight stratum, the candesartan concentrations across the dose groups were comparable to those in the lower weight stratum in the corresponding mg/kg dose groups except for the 0.2 mg/kg group, where the Candesartan concentration was relatively lower in the heavier weight stratum.

Table 42- Random trough candesartan concentration (nMol/L) (All subjects)

			nMol/L		
Suspension, weight group	**Daily candesartan dose**	**N**	**Mean (SD)**	**Median**	**Min, max**
5 ml, 10 to <25 kg	0.05 mg/kg	24	7.0 (8.4)	4.9	0, 40.3
	0.2 mg/kg	25	25.0 (18.4)	21.5	0, 79.6
	0.4 mg/kg	27	37.1 (40.3)	22.6	0, 144.0
	Total	76	23.6 (29.0)	14.2	0, 144.0
10 ml, 25 to ≤40 kg	0.05 mg/kg	3	8.4 (4.3)	7.8	4.5, 13.0
	0.2 mg/kg	4	12.6 (13.2)	11.3	0, 27.9
	0.4 mg/kg	3	45.4 (23.2)	52.6	19.5, 64.1
	Total	10	21.2 (21.0)	16.2	0, 64.1

Assessor's comment: Similar to the findings of the older age group children 6 to <17 years old (Study 621B), thorough concentrations of candesartan appeared to increase with dose, but not in a dose-proportional manner. It is not clear if the data were normally distributed or not, however there was a tendency of stepwise increase in candesartan exposure with increasing dose.

Pharmacokinetic single dose study

Ten subjects participated in a substudy to assess the pharmacokinetics of Candesartan following oral administration of a 0.2 mg/kg single dose of the candesartan suspension. The mean age of the subjects was 3.1 years, most were in the age range of 2 to <6 years, and all of the subjects were in the weight group of 10 to <25 kg. Other baseline characteristics were consistent with the characteristics of the overall study population.

Subjects participated in the serial PK study either at study entry prior to the double-blind period of the study or at any point during the open-label extension period but only after discontinuing study drug for at least 48 hours. Table 43 presents a summary of PK parameters. Tmax and t1/2 were similar to that observed in adolescent hypertensive subjects and young healthy adults administered a tablet formulation.

Cmax and AUC values were consistent with the ranges in adolescent hypertensive subjects and young healthy adults, see Study D2451C00261 and Study D2451C00005, respectively.

Table 43- Summary of pharmacokinetic parameters (Pharmacokinetic substudy)

	AUC (nMol*h/L)	AUC_{last} (nMol*h/L)	C_{max} (nMol/L)	t_{max} (hour)	$t_{1/2}$[a] (hour)
N	10	10	10	10	10
Mean (SD)	1781 (611)	1711 (582)	250.8 (61.3)	3.3 (1.0)	5.8 (1.4)
Min, max	1031, 3411	1005, 3266	193, 394	1.5, 5.1	4.4, 8.3
CV%	34.3	34.0	24.4	31.8	23.4
Geometric mean	1708.9	1642.2	244.9	3.1	5.6

The effects of age and body weight on the PK parameters were also examined. No correlation between Cmax or AUC and age (correlation –0.392, p=0.2627 for AUC and –0.437, p=0.2064 for Cmax) or body weight (correlation –0.369, p=0.2943 for AUC and –0.512, p=0.1303 for Cmax) was observed table 44 below.

Table 44- Pearson's Correlation of Age and Weight with Pharmacokinetic Parameters Pharmacokinetic Sub-Study Patients

	Statistic	AUC (nmol*hr/L)	Cmax (nmol/L)	Tmax (hr)	T 1/2 (hr)
Age(years)	n	10	10	10	10
	Correlation	-0.392	-0.437	0.107	0.317
	P-value	0.2627	0.2064	0.7678	0.3717
Weight at Baseline(kg)	n	10	10	10	10
	Correlation	-0.369	-0.512	-0.098	-0.261
	P-value	0.2943	0.1303	0.7879	0.4669

Pharmacodynamic results

Table 43 shows that mean tmax (time to Cmax) occurred at 3.2 hours (range 1.5 to 5.1 hours). For both SBP and DBP, the greatest change in blood pressure from hour 0 occurred at 5 hours post-dosing (-4.8 mmHg for both SBP and DBP). As shown in table 45, at trough, (24 hours post-dosing), there was a -1.1 mmHg change from hour 0 for SBP and a –2.3 mmHg change from hour 0 for DBP implying that even with single dose administration there is residual antihypertensive activity to 24 hours.

Table 45- Mean blood pressure following a single dose of candesartan oral suspension 0.2 mg/kg body weight (Study 328)

			Observed blood pressure		Change from hour 0	
Blood pressure parameter	**Time (hours)**	**N**	**Mean (SD), mmHg**	**Min, max mmHg**	**Mean (SD) mmHg**	**Min, max mmHg**
SBP, mmHg	0	10	107.7 (10.8)	86, 120	0.0 (0.0)	0, 0
	0.5	10	106.2 (9.2)	93, 118	-1.5 (8.3)	-23, 7
	1	10	105.6 (11.9)	82, 125	-2.1 (7.7)	-11, 14
	1.5	10	104.5 (13.9)	81, 127	-3.2 (11.5)	-21, 15
	3	10	103.6 (7.9)	91, 114	-4.1 (11.8)	-27, 8
	5	10	102.9 (8.5)	84, 114	-4.8 (13.2)	-26, 13
	8	10	109.5 (10.3)	96, 129	1.8 (14.2)	-18, 22
	24	10	106.6 (14.6)	82, 137	-1.1 (12.8)	-21, 25
	28	10	107.1 (9.7)	89, 118	-0.6 (8.4)	-13, 9
DBP, mmHg	0	10	66.2 (12.9)	46, 85	0.0 (0.0)	0, 0
	0.5	10	66.5 (8.9)	53, 78	0.3 (11.6)	-11, 21
	1	10	65.9 (9.7)	49, 78	-0.3 (10.5)	-24, 13
	1.5	10	64.4 (15.4)	44, 96	-1.8 (9.9)	-13, 16
	3	10	61.8 (10.1)	44, 77	-4.4 (12.4)	-27, 10
	5	10	61.4 (10.1)	48, 73	-4.8 (15.1)	-28, 27
	8	10	63.9 (8.5)	53, 76	-2.3 (9.2)	-18, 15
	24	10	63.9 (12.7)	44, 87	-2.3 (8.0)	-12, 10
	28	10	63.0 (8.7)	51, 80	-3.2 (12.1)	-21, 22

Assessor's comment: This a single dose (0.2 mg/kg, suspension) candesartan PK study in 10 children, 2 to <6 years old, weighting 10 to <25 kg.

Subjects entered the PK evaluation prior to dosing in study 238 or at any time during the open-label extension period, provided that candesartan treatment was withheld for 48 hours. The applicant must clarify, whether 2 days wash out period is adequate to fully eliminate all residual candesartan.

There is no correlation between Cmax and AUC with age or weight. Same as the PK measurements of the 261B study in older children (6 to<17 years) no clearance data, have been collected/ presented, therefore the possibility of a correlation between clearance and weight/age in this population can not be assessed.

Similar to the PK study of the older children 6 to <17 years of age, this PK study is also sparse and inconclusive. The sample size is very small (n=10), there is no clearance data, the 48 hr washout period may not be adequate for elimination of all residual candesartan and similar to outcomes of PK study in the older children (261B), proper dose may not be deducted from the results of these PK parameters.

- Safety results

All 93 randomized subjects are included in the safety population. A total of 95% of subjects who participated in the open-label period completed greater than 360 days of treatment. The median dose received at Week 4 was 3.1 mg. Median daily doses increased slightly over time and by Week 56/LOCF the median dose was 3.8 mg (mean 3.94 mg).

Adverse events

Table 46- Number (%) of subjects with the most commonly reported adverse events, sorted by decreasing order of frequency in the total group (Safety population)

Preferred term	Candesartan: 4-week double-blind period n (%)			Candesartan: Open-label period n (%)	Total over all periods n (%)
	0.05 mg/kg N=29	0.2 mg/kg N=32	0.4 mg/kg N=32	All dose levels N=85	All dose levels N=93
Number of subjects with at least 1 AE	19 (65.5)	20 (62.5)	19 (59.4)	78 (91.8)	83 (89.2)
Pyrexia	4 (13.8)	5 (15.6)	4 (12.5)	32 (37.6)	38 (40.9)
Cough	2 (6.9)	2 (6.3)	4 (12.5)	32 (37.6)	35 (37.6)
Upper respiratory tract infection	2 (6.9	5 (15.6)	3 (9.4)	15 (17.6)	21 (22.6)
Nasopharyngitis	1 (3.4)	1 (3.1)	1 (3.1)	15 (17.6)	16 (17.2)
Rhinorrhea	3 (10.3)	2 (6.3)	2 (6.3)	12 (14.1)	14 (15.1)
Diarrhea	2 (6.9)	3 (9.4)	0	12 (14.1)	14 (15.1)
Otitis media	0	2 (6.3)	0	13 (15.3)	13 (14.0)
Vomiting	2 (6.9)	0	0	11 (12.9)	12 (12.9)
Urinary tract infection	0	0	2 (6.3)	10 (11.8)	12 (12.9)
Bronchitis	1 (3.4)	0	0	9 (10.6)	9 (9.7)
Conjunctivitis	0	0	1 (3.1)	7 (8.2)	8 (8.6)
Headache	1 (3.4)	3 (9.4)	0	5 (5.9)	8 (8.6)
Pharyngitis	2 (6.9)	0	1 (3.1)	6 (7.1)	8 (8.6)
Rhinitis	2 (6.9)	0	2 (6.3)	7 (8.2)	8 (8.6)
Fatigue	3 (10.3)	1 (3.1)	1 (3.1)	3 (3.5)	7 (7.5)
Abdominal pain upper	1 (3.4)	1 (3.1)	0	5 (5.9)	6 (6.5)
Gastroenteritis	0	0	0	6 (7.1)	6 (6.5)
Contusion	1 (3.4)	0	0	4 (4.7)	5 (5.4)
Nasal congestion	0	0	0	5 (5.9)	5 (5.4)

Deaths, serious adverse events, discontinuation of study drug

One subject died. A child with nephrotic syndrome initially appeared to tolerate the study drug. There was evidence of decline in renal function with time and the child died after 200 days in the study. An autopsy indicated that the child had glomerulonephritis. Upon review of the case, the study safety committee concluded that the child succumbed to chronic renal failure consequent to glomerulonephritis.

Serious adverse events

A total of 14 children had non-fatal SAEs. The investigators considered none as being drug related and none led to treatment discontinuation. The most common non-fatal SAEs were urinary tract infection and pyrexia, which would be expected for very young children many of whom had renal diseases. One subject discontinued treatment after the double-blind period because of AEs of abdominal pain and fatigue. A total of 5 subjects temporarily stopped study drug for 1 to 3 days because of concurrent illnesses.

Assessor's comment: The safety aspects of both periods, the 4 weeks double blind and the long term (1 year) open label are presented together in this section. 81 (95.3%) completed >360

days of treatment at the average dose of 3.94 mg. Similar types of common AEs were observed in the double-blind period as in the open-label period of the study, however the frequency of the AEs was higher during the open-label period.

Over the 1-year study period, most (89%) of the subjects experienced at least 1 AE. There were no apparent acute hypotensive responses, orthostatic hypotension, hyperkalemia and angioedema or convulsions in this younger 1 to <6 years age group. The most common AEs are pyrexia, cough and upper respiratory infections. Interestingly the occurrence of headache is reduced with prolong use of candesartan.

Similar to the older age group (6 to <17 years), AEs associated with candesartan seem not be dose-related.

One subject died of underlying chronic glomerulonephritis during the open-label period. One subject discontinued the study due to nausea, abdominal pain and fatigue. 5 subjects temporarily (1-3 days) discontinued treatment due to pyrexia, diarrhoea, oral herpes, urinary tract infection and increased potassium.

Albumin/creatinine ratio and protein/creatinine ratio

As the distributions of the A/C and P/C ratios were quit disparate, the median value were considered as the most appropriate measure of central tendency and the percent change based on median values the most relevant assessment of a treatment effect. Table 47 presents descriptive statistics for change from baseline to Week 4 and Visit 56 in urinalysis tests. Median values are presented because of the very wide distribution of values.

In the open-label population (Week 56 data), at Baseline 34 subjects had P/C ratios of ≤0.2 and values remained low throughout the study: median change from baseline to Week 56 was 0.0 (range –0.1 to 0.2). In the open-label population (Week 56 data), at Baseline 32 subjects had P/C ratios >0.2 and the median value decreased by Week 56: median change from baseline to Week 56 was –0.2 (range –5.1 to 0.80).

Because some children had underlying renal disease prior to the study and some children had no renal disease, interpreting mean changes from baseline can be difficult.

Table 47- Descriptive statistics for change from baseline to Week 4 and Week 56 in urinalysis tests (Safety population)

Test	Units	N	Baseline median (range)	Median change (range): Baseline to Week 4	N	Baseline, median (range)	Median change (range): Baseline to Week 56
Albumin	mg/L	58	11.5 (3 to 977)	–2 (–739 to 2598)	54	9.5 (3 to 977)	–1 (–896 to 178)
Albumin/ creatinine ratio	mg/g creat	57	36 (3 to 5327)	–4 (–4438 to 30039)	53	29 (3 to 5327)	–6 (–4927 to 452)
Creatinine	mg/dl	78	36 (9 to 208)	6.0 (–106 to 139)	69	36 (12 to 208)	8.0 (–164 to 134)
Total protein	mg/dl	80	13.5 (2 to 1190)	0.5 (–403 to 10714)	68	14.0 (2 to 713)	0.0 (–103 to 29)
Protein/creatinine ratio	mg/dl/ mg/dl	78	0.3 (0.1 to 60)	0.0 (–4.4 to 262)	66	0.2 (0.1 to 22)	0.0 (–5.1 to 0.8)
Baseline protein/creatinine ratio ≤0.2	mg/dl/ mg/dl	38	0.2 (0.1 to 0.2)	0.0 (–0.1 to 0.2)	34	0.2 (0.1 to 0.2)	0.0 (–0.1 to 0.2)
Baseline protein/creatinine ratio >0.2	mg/dl/ mg/dl	40	0.5 (0.3 to 59.5)	–0.1 (–4.4 to 262.2)	32	0.5 (0.3 to 21.6)	–0.2 (–5.1 to 0.8)

The median A/C ratio declined by 38% after 4 weeks treatment with candesartan. The decline appeared dose related and was still evident at Week 56 (median decline 31%). In subjects with a baseline A/C ratio >30 mg/g creatinine, the median A/C ratio declined 57%. In subjects with baseline P/C ratios >2, reductions were not dose related but similar reductions were observed at Week 4 and Week 56.

Assessor's comment: Whilst protein/creatinine ratio remained mostly unchanged, the children with albuminuria (A/C ratio >30 mg/g creatinine) appeared to have an actual decline in the level of albuminuria with candesartan at 56 weeks. Most inhibitors of angiotensin II system, (both ACE and ARBs) display certain improvement in renal function at the start of the treatment, but this effect gradually wears off. In this study, the variability in mean change of albumin/creatinine and relatively short (1 year) duration of the study makes it impossible to comment on candesartan effect on renal function.

Weight & Height

As might be expected for these young hypertensive children, many with renal disease, there was little weight gain over the course of a year, mean body weight increased by 3.3 kg at Week 56 relative to study entry. Overall, however, the children were slightly above average weight for their age and remained so over the 1-year study period. No change in BMI was observed over the course of a year. The children did grow over the course of the study; mean body height increased by 8.8 cm at Week 56 relative to study entry.

Assessor's comment: Similar to the findings on the growth measurements in the older age group (6 to <17 years), there were no outstanding changes in body weight, height and BMI considering the expected growth in this population.

Similar to the safety section of the pivotal 4 weeks and one year long term studies in the 6 to <17, the adverse events presentation in its current format is unacceptable. There is no comprehensive table of adverse events with the SOC and preferred terms, the results are scattered amongst tables and texts, under many different headings. The applicant is requested to fully reformat the adverse event section of the safety results and provide a comprehensive

table containing all adverse events including; most common adverse events, other significant adverse events, haematology, clinical chemistry, routine urinalysis, renal/hepatic function, cardiac/vascular function etc.

The results of A/C, P/C ratio and growth measures and are acceptable in the current format.

IV. 3. 2. 4. Clinical Study D2451C00006- An Open-label Extension Study of Candesartan Cilexetil in Hypertensive Paediatric Subjects Ages 1 to <11 Years: A Long-term Study

- **Description**

This is a 1-year open-label, follow-up extension of the dose ranging, safety, and pharmacokinetic study (328A) of candesartan in hypertensive paediatric subjects aged 1 to less than 6 years and is comprised of a 4-week, DB treatment period.

- **Methods**

  - Objective(s)

The primary objective of this study was to describe the long-term clinical experience of candesartan in hypertensive children ages 1 to <11 years who had participated in Protocol 328 without discontinuation due to a study drug-related AE, and who had an ongoing clinical indication for treatment with candesartan.

  - Study design

This was an open-label treatment extension of Protocol 328. Eligible study patients received study medication on Day 0 and returned every 3 months for a follow-up visit, extra visits were permitted at the investigator's discretion. To align closely with study 328; doses of 0.05 mg/kg, 0.2 mg/kg, and 0.4 mg/kg were administered, once daily, in oral suspension form in the open-label phase as well. The starting dose in the current study was 0.20 mg/kg once daily.

An electrocardiogram (ECHO) was performed at study entry and then annually during the course of this study. In addition, an ECHO was performed at the end of study or at premature discontinuation unless the procedure was done within the preceding 3 months.

  - Study population /Sample size

Analysis groups included an ITT (N=35) and safety population (N=35), age 1 to <11 years and weight ≥10 kg and ≤40 kg. No patients were excluded from the ITT or safety population. The individual patient's duration of treatment varied based on the calendar time of entry into the study. The majority of patients (n=24) were treated for 1 to 2 years. There were only 2 patients

treated for 6 months or less. Similar to study 328, subjects with estimated glomerular filtration rate (eGFR) <30 ml/min/1.73m2 for non-transplant and <40 ml/min/1.73 m2 after transplant were excluded.

- Treatments

This study employed candesartan in approximately 0.05-mg/kg, 0.2-mg/kg, and 0.4-mg/kg doses administered in oral suspension form. The recommended starting dose was 0.20 mg/kg once daily. Candesartan dose adjustments were permitted, but doses were not to exceed 0.4 mg/kg/day. Investigators determined the appropriate dose on a visit-by-visit basis depending on the patient's clinical and blood pressure response. The addition of other antihypertensive medications was permitted, with the exception of other ARBs.

A central pharmacy prepared study medication and managed the distribution of study medication to the investigative sites. Dose adjustments occurred by adjustment of dose volume, or by adjusting the suspension concentrations by the central pharmacy. All investigational products were kept in a secure place under appropriate storage conditions at room temperature (up to 25°C or 79°F). The shelf life of the suspension was 5 months.

- Statistical Methods

Descriptive statistics (mean, standard deviation [SD], minimum, median, and maximum) along with 95% confidence intervals are provided for efficacy and some safety variables.

The LV mass index standard difference scores (Z-scores) were derived as described by Foster et al 2008. Relative wall thickness was derived as the sum of the posterior wall thickness and septal wall thickness divided by end diastolic LV diameter. No formal statistical analyses of the echocardiographic data were conducted.

Results

- Recruitment/ Number analysed

Analysis groups included an ITT (N=35) and safety population (N=35). The majority of patients (n=24) were treated for 1 to 2 years. There were only 2 patients treated for 6 months or less.

The time of enrolment from Protocol 328 to the present study was measured as time from last dose on Protocol 328 to first dose in the present study. For the majority of patients (54.3%; manual calculation), time from last dose to the first dose of study drug on this study was less than 30 days. Six (17.1%) patients received their first dose within 1 day, 1 patient (2.9%) within 2 to 10 days, 12 patients (34.3%) between 11 and 30 days, and 16 patients (45.7%) at greater than 30 days.

Assessor's comment: With exception of the 6 patients that started the next day after the last dose of study 328, all other patients went through a 10 to more that 30 days wash out period. The applicant must clarify this point.

- Baseline data

The demographic and key baseline characteristics of study patients are summarized in table 48 below.

Table 48- Patient Demography

		(N=35)
Age at First Visit (yr)	2 to <6 years	24 (68.6%)
	>=6 years	11 (31.4%)
Age at Last Visit (yr)	2 to <6 years	17 (48.6%)
	>=6 years	18 (51.4%)
Gender	Female	10 (28.6%)
	Male	25 (71.4%)
Race	Caucasian	33 (94.3%)
	Oriental	1 (2.9%)
	Other	1 (2.9%)
Body Mass Index Percentile	<95%	27 (77.1%)
	>=95%	7 (20.0%)
	Unknown	1 (2.9%)
SBP>=95th Percentile	No	28 (80.0%)
	Yes	7 (20.0%)
DBP>=95th Percentile	No	25 (71.4%)
	Yes	10 (28.6%)
SBP and DBP>=95th Percentile	No	29 (82.9%)
	Yes	6 (17.1%)
Type of Hypertension*	None	1 (2.9%)
	Diastolic Only	7 (20.0%)
	Systolic Only	7 (20.0%)
	Diastolic & Systolic	20 (57.1%)
Source of Hypertension*	Primary	4 (11.4%)
	Secondary	31 (88.6%)
Presence of Renal Disease*	No	5 (14.3%)

The majority of patients (77.1%) were below the 95th percentile for BMI. Over half of the patients (57.1%) had an initial diagnosis of hypertension based on elevations of both SBP and DBP upon entry into Protocol 328, and for the majority of patients (88.6%), were assumed to have 'secondary' hypertension, primarily due to underlying renal disease. Renal disease was present in 85.7% of patients. Eight patients had renal function impairment (eGFR 30 to <60 mL/min/1.73 m2).

Assessor's comment: The population tested in this extension phase is rather different to the one in the pivotal efficacy study 238 in children 1< 6 years. In the open label part of the study, 35 children were 2-7 years old with an average age of 4.4 years, from European or Ukraine centres only.

Similar to the pivotal efficacy study, the majority of patients (77.1%) were below the 95th percentile for BMI and had secondary hypertension due to coexisting renal disease. Eight patients had renal function impairment (eGFR 30 to <60 mL/min/1.73 m2).

- Efficacy results

Given that the patients had been receiving candesartan, and in some cases, additional antihypertensive medications, there was little additional change in blood pressure after enrolment in the present study. The SBP was stable across the study period. SBP mean changes from baseline ranged from -9.88 to -0.8 mmHg across the study.

Primary variable blood pressure response
An antihypertensive effect was maintained across the study period following continuation of treatment with candesartan. Both SBP and DBP values remained relatively stable from Visits 1.1 to Visit 11.

The means changes for both SBP and DBP were relatively small over the course of the study, supporting the continued antihypertensive effect of candesartan in this patient population. Mean changes in SBP were decreases ranging between 9.88 mmHg (n=8) and 0.18 mmHg. At the final visit, the mean change in SBP from Day 0 was -2.86 mmHg.

For DBP, the mean changes ranged from decreases of 4.50 mmHg to increases of 0.03 mmHg, over the study period. At the final visit, the mean change from Day 0 was a decrease of 0.43 mmHg.

Responder Analysis
The response rates across the study were consistent with the relatively stable values for SBP and DBP across visits. The proportion of responders by visit is summarized in table 49.

Table 49- Number and proportion of responders over the study period (ITT population)

Visit	N	Number of responders	Proportion of responders (%)	95% CI lower, upper limit
Visit 1.1 (Day 0)	35	24	68.57	53.19, 83.95
Visit 2 (Month 3)	35	23	65.71	49.99, 81.44
Visit 3 (Month 6)	33	22	66.67	50.58, 82.75
Visit 4 (Month 9)	31	19	61.29	44.14, 78.44
Visit 5 (Month 12)	23	19	82.61	67.12, 98.10
Visit 6 (Month 15)	14	11	78.57	57.08, 100.00
Visit 7 (Month 18)	8	5	62.50	28.95, 96.05
Visit 11 (Final visit)	35	23	65.71	49.99, 84.44

Note: No patient data were collected on Visits 8, 9, and 10. A responder is defined as a patient whose systolic and diastolic blood pressures are less than the 95th percentile at a specific time point. Percentiles are sex-, age-, and height-adjusted, and are re-assessed according to the most data on or prior to the visit.

Across the study visits, at least 60% of patients were considered controlled (responders) at each visit. At the final visit, 65.71% of patients met the criteria of both SBP and DBP less than the 95th percentile.

Assessor's comment: The mean SBP/DBP at the end of the study was 101/62 mmHg, compared to entry blood pressures of 104 and 63 mmHg.

Long-term dosing with candesartan maintained the antihypertensive effect in more than 60% of patients across the study period. At the end of the study period, 65.7% remained responders.

However this is a small study in 35 patients, majority of which went through a 10 to more that 30 days wash out period and the results are presented in descriptive rather than statistically analysed. Although long term studies in this young population are welcomed, but the value of this study in terms of establishing long term efficacy of candesartan is not substantial.

- Safety results

35 patients enrolled in this study are included in the safety population. The mean time on treatment for all patients was 444 days at the mean dose in mg/kg of 0.24 mg/kg of candesartan.

Adverse events

Table 50 presents the most common AEs occurring in at least 3 patients, presented by preferred term in descending frequency.

Table 50- Number (%) of adverse events by system organ class (safety population)

Preferred term	Safety patients, N (%)
Number of patients with at least 1 AE	28 (80.0)
Pyrexia	9 (25.7)
Pharyngitis	6 (17.1)
Rhinitis	6 (17.1)
Diarrhea	6 (17.1)
Cough	4 (11.4)
Nasopharyngitis	4 (11.4)
Bronchitis	3 (8.6)
Upper respiratory tract infection	3 (8.6)
Varicella	3 (8.6)
Nausea	3 (8.6)
Vomiting	3 (8.6)
Enuresis	3 (8.6)
Urinary tract infection	2 (5.7)

No AEs with fatal outcome were reported in this study. One patient permanently discontinued the study due to the SAE of lymphedema. A 6-year-old boy, with a medical history significant for hypertension, iron deficiency, mild psychomotor development delay, pectus excavatum, and lymphedema left foot.

Clinical laboratory evaluation

Hematology

No patient had an abnormal hematology value noted.

Clinical chemistry
There was a common finding among the study patients of low serum bicarbonate level, consistent with the metabolic acidosis that can accompany the renal diseases in the population. The lowest recorded bicarbonate value was 13 meq/L in Patient E0401002, a patient who also had renal impairment.

In all, there were 7 patients with an eGFR <50 mL/min/1.73 m2, but there was no apparent trend for a persistent decline in eGFR for these patients. The lowest reported eGFR was 34 mL/min/1.73m2.

For 2 patients, eGFR decreased by approximately 10 mL/min/1.73 m2 or more over the course of the study (Patients E0401002 and E0704002). However, overall, there was no persistent trend for decline in eGFR for the study population

Urinalysis
As expected for the study population with underlying proteinuric renal disease as documented by elevated urine albumin/creatinine ratios in Protocol 328, many patients had urinalyses notable for the presence of albumin. A few patients also had cellular elements.
For those patients with high leukocyte esterase values or white blood cells in urine, the majority of elevations were reported at Visit 1. None of these patients reported an AE. One patient had a medical history that included pyelonephritis.

Assessor's comment: This is a long term open label extension in 35 patients aged 2 to 7 years old receiving 0.24 mg/kg of candesartan for 444 days. This study has been carried out in compliance with CHMP scientific advice.

Similar types of common AEs were observed in the older children group: pyrexia (25.7%), pharyngitis (17.1%), rhinitis (17.1%), diarrhoea (17.1%) and cough (11.4%).

There were no deaths; one patient permanently discontinued the study due to the serious lymphedema. Two children had serious hyperkalemia, and bronchopneumonia.

Five patients had creatinine levels increased by 30% across the study. There were 7 patients with eGFR values noted as <50 mg/mL on at least 1 assessment; with no apparent trend for persistent decline in any of these patients.

The applicant's position that "overall, AEs and clinical abnormalities reported in this study are consistent with what would be expected for the study population with underlying renal disease, or typical childhood illnesses" is acceptable.

Vital signs
There was a trend for heart rate to be decreased across the study. At Visit 1, the mean heart rate was 100.26 bpm, compared to 94.14 bpm at Visit 11. These findings are consistent with the expectation of the decline in heart rate with age in children.

<u>Echocardiogram</u>
Of the 35 patients in the safety population, 33 had ECHOs performed on the present study. The LV mass index was chosen as the parameter of interest in this study to reflect the likelihood of

LV cardiac hypertrophy in children with hypertension. None of the patients had a baseline, pre-candesartan ECHO study and, as expected for this kind of study. Hence for assessment of LV cardiac hypertrophy, the LV mass index value of ≥51 g/m2.7 was used as the reference value, and patients with values greater than this were classified as having LV hypertrophy.

In the 31 patients with more than 1 ECHO performed, there was no consistent trend with regard to change in the LV mass index: 17 appeared to have a decrease in LV mass index, 12 had an increase, and 2 remained the same. There was no notable trend for a clinically meaningful change in measures of cardiac size/mass.

Weight, Height & BMI

Over the course of the study, mean body weight increased 3.1 kg on average. Overall, there was no notable change in relative weight across the study as determined by Z-score. The average height of the study patients was similar to the reference population, with very little change across the study period. There was very little change in BMI observed over the course of the study.

Assessor's comment: None of the patients had a baseline, pre-candesartan ECHO study, as expected for this kind of study. Hence for assessment of LV cardiac hypertrophy, the LV mass index value of ≥51 g/m2.7 was used as the reference value, and patients with values greater than this were classified as having LV hypertrophy.

In the 31 patients with more than 1 ECHO performed, there was no consistent trend with regard to change in the LV mass index: 17 appeared to have a decrease in LV mass index, 12 had an increase, and 2 remained the same. There was no apparent trend for any clinically notable reductions in cardiac mass or size.

Left ventricular hypertrophy is often associated with progression of hypertension and heart failure eventually. The applicant must clarify whether the lack of reduction in LV mass is due to candesartan being ineffective and whether the 12 children with increased LV mass are the same as no responders.

Similar to the findings on the growth measurement in the older age group (6 to <17 years), there were no outstanding changes in body weight, height and BMI considering the expected growth in this population.

PSUR: Periodic safety updates Report; Period 29 April 2006 to 28 April 2011

This report refers to candesartan cilexetil and the fixed-dose combination product of candesartan cilexetil + hydrochlorothiazide. It integrates the safety information presented in 8 PSURs covering the 5 year period. The number of patients exposed to candesartan during this PSUR period can be estimated to be approximately 6.9 million and the cumulative exposure can be estimated to be approximately 44.7 million patient-years.

Overall during the period covered by this report, 488 case reports met the criteria for inclusion. Serious case reports of rhabdomyolysis, thrombocytopenia, pancreatitis, vasculitis and unlisted hepatobiliary disorders which have all been kept under close surveillance were reported. The applicant concluded that the overall evaluation of each ADR indicates that there is no evidence

of change in the characteristics of the ADRs, in terms of seriousness, severity, outcome, or population at risk for adverse reaction. The applicant further states that no evidence was obtained to indicate an increased risk of any adverse drug reactions in elderly patients, children, or those with impaired organ function.

Overall, this PSUR does not present severe, unexpected events which would signal, based on their frequency or general characterization, a new risk with candesartan in paediatric population.

IV.3.3. Discussion on clinical aspects and conclusion

Efficacy
The study population was consistent with the characteristics established for children with hypertension: more common among males, strongly associated with obesity and usually "primary" or "essential" in aetiology in the age group 6 to <17 years, and mainly secondary to renal disease in the age group 1 to <6 years.

In the older children group (6 to <17 years), the slope of the dose response across the 3 dose levels low, medium, and high was not different from 0. Although the primary efficacy endpoint was not achieved, there is other evidence supporting effectiveness of candesartan. Both sitting systolic and diastolic BP were significantly reduced from the baseline within the dosing groups. Candesartan at pooled doses reduced SiSBP by 10.22 mmHg (P< 0.0001) and SiDBP (P=0.0029) by 6.56 mmHg, from the baseline. This reduction was highly significant and is clinically meaningful. Furthermore, analysis of the pair-wise contrasts showed that, all individual candesartan doses proved significantly superior to placebo for change in SiSBP and all but the low dose proved statistically superior to placebo for change in SiDBP. This statistical superiority in the candesartan group is also clinically advantageous compared to placebo.

The magnitude of the placebo effect was rather large, with a reduction of SiSBP/SiDBP; 3.8/1.3 mmHg, which is not surprising as the children in this age group are highly susceptible to the 'white coat' phenomena.

The maximum response in reduction of both SiSBP (11.7 mmHg) and SiDBP (7.98 mmHg) was detected at the medium dose 8/16 mg and the effect seemed to plateau after that point. After that point there was no beneficial result from increasing dose to 16/32 mg.

In the younger children group (1 to <6 years), statistically significant candesartan dose response was observed for both SBP (p=0.0136) and DBP (p=0.0301). This significance is also of clinical importance as the SBP and DBP were reduced in the range of 6-12 mmHg and 5.2-11 mmHg respectively, in this age group. But lack of a placebo arm, in a population prone to white coat phenomenon, makes the efficacy results difficult to interpret.

The effect of candesartan in lowering both SBP and DBP in 10 to<25 kg children is nearly triple than in 25 <40 kg weight strata in the younger age group (1 to <6 years). Similarly the effect of candesartan in lowering SBP in <50 kg children is nearly double than in >50 kg weight strata (6

to <17 years). There seems to be a difference in candesartan response in different weight groups that is somehow masked by low number of children in 25 to <50 kg weight band (n=12, study 328 and n=25 study 621A). The effect of weight on response is of great importance for proposing the dose regimen in children, therefore the applicant is requested to provide further analysis using an ANCOVA model for four subgroups of patients divided by weight.

The 1 year, open label arm of the candesartan study in the 6 to <17 years old showed that the SiSBD/SiDPB remain lowered by 9-11 / 6-7 mmHg at the end of the 52-week study. Similarly in younger age group of 2-7 years the mean SBP/DBP remained low at the end of one year. Long-term dosing with candesartan maintained the antihypertensive effect in 60- 66% of patients of both age groups.

PK/PD

2 single dose PK studies were carried out in children 6 to <17 (n=22) and 2-6 (n=10) years old. Both studies are very sparse in the PK parameters evaluated and are inconclusive. There is no clearance data and the 48 hr washout period may not be adequate for elimination of all residual candesartan. There seems to be a correlation between Cmax, AUC and weight in the older age group. In the younger children the sample size of 10 patients is too small, to establish whether a correlation exists between Cmax, AUC and weight. In addition, there are no data regarding more than one dose. Therefore, it is not possible to assess a reasonable basis for dosing based on body weight (mg/kg), or otherwise.

Furthermore in the efficacy data the maximum response in reduction of both SiSBP (11.7 mmHg) and SiDBP (7.98 mmHg) was detected at the medium dose 8/16 mg and the effect seemed to plateau after that point. The correct dosage regimen cannot be deducted from the results of these PK parameters; the applicant is therefore requested to justify the paediatric dose recommendation.

In order to compare adult and children exposure and to substantiate the applicant's claim that the candesartan pharmacokinetic profile in children is comparable to that previously reported for adults, the applicant should provide a summary data of all available PK parameters for adult and each Paediatric age group.

Safety

Safety aspects of candesartan were recorded in 207 patients 6 to <17 years old and 81 patients 1to <6 year old for a period of 4 weeks to a year. At this point of the procedure (Day 70) it is not possible to draw any safety conclusion as the presentation adverse events is unacceptable. In all 4 studies, there is no comprehensive table of adverse events with the SOC and preferred terms, the results are scattered amongst tables and texts under many different headings. Thus the safety conclusions will be made after assessment of the applicant's response.

Furthermore the frequency of occurrence of AEs in children must be compared to the frequency of occurrence in adults in accordance with SmPC guidelines of September 2009. The applicant is requested to provide a tabulated summary of pooled AEs data of both paediatric age groups from all 4 studies with available data in adults.

There were 9 reports of joint sprain in older children (6 to <17 years), which might be a signal for an idiosyncratic adverse event in children.

In the 31 younger (2 – 7 years) patients in which more than 1 ECHO performed, no apparent trend for any clinically notable reductions in cardiac mass or size was documented.

Statistical Conclusion

Study 261A in the older age group failed to demonstrate a significant dose response in terms of the slope of the fitted regression line over the three doses (low, medium and high). However the secondary analysis of the pairwise contrasts of each dose compared to placebo demonstrated a statistically significant improvement in reduction in sitting systolic blood pressure for all three doses and in sitting diastolic blood pressure for the medium and high doses. Although formal testing with pre-specified adjustment for multiplicity was not conducted, the findings would suggest that although the medium and high doses were probably more effective than the low dose, there was no meaningful difference between them. It should be noted that there were certain deficiencies in this study in the relatively small percentage of children under 12 years (30%) and also the limited population in the group weighing less than 50 kg (n=25). Furthermore it is unclear why the statistical models used in the analysis did not include any adjustment for race although it was a stratification factor and this, too, should be investigated to confirm the findings for the full population.

Unfortunately the study in the younger children (Study 328) did not include a placebo arm and therefore it was not possible to compare each dose with placebo. This is a concern as the responder analysis of Study 261A indicated a 30% response rate to placebo. In this study a dose-response in terms of the slope of the regression line fitted to the change from baseline in SiSBP was significantly different from zero. This was supported by the corresponding dose response in diastolic blood pressure. Although the limited patient numbers in the higher weight stratum and the consequent lack of statistical power resulted in failure to achieve significance, the estimated slope for the two subgroups were similar suggesting that the dose-response could be almost the same for both weight strata. However it was not possible to apply a placebo-correction to the data before the analysis of dose-response was carried out. Therefore there is some concern over the impact on the interpretation of the results without reference to a placebo comparator.

Quality conclusion

The formal stability data and supporting development data supports a shelf life of 100 days for candesartan cilexetil oral suspension in Ora-Blend vehicle within the range of 0.1 mg/mL to 2.0 mg/mL when stored below 25°C. The applicant's proposed restriction on using opened bottles within 30 days is acceptable. It is accepted that bioavailability of extemporaneous products can be unpredictable. Some of the unpredictability could be removed by providing candesartan cilexetil active substance and a suspension vehicle for reconstruction. A powder-for-reconstitution pack would remove much of the variability inherent in extemporaneously preparing a suspension using crushed tablet material. Manipulation of existing formulations should always be a last resort where alternative formulations are not available. Given that a powder-for-reconstitution ARB product is already commercially available, a crushed tablet formulation would undoubtedly be an inferior presentation; the applicant should discuss whether a straightforward candesartan cilexetil powder-for-reconstitution product could be made available.

A formulation obtained from a crushed solid dosage form may not be bioequivalent with the same dose form when swallowed whole, even when prepared in a standardised commercial vehicle. Bioequivalence (study D2451C00005) was not proven with respect to C_{max}. Wider acceptance limits may have been accepted if appropriately and prospectively justified, but justification and discussion were not provided. Given that candesartan cilexetil is a prodrug, the applicant should discuss whether the higher liquid formulation C_{max} has any clinical significance. There are some other outstanding issues regarding alternative primary packaging materials (other than PET). More importantly, specifically in relation to the proposed patient population, the question of the use of propylparaben in a paediatric formulation requires justification.

Toxicological Conclusion

The neonatal and juvenile toxicity study results indicate that candesartan cilexetil causes a treatment related reduction in bodyweights/bodyweight gain, weight of the heart and renal toxicity. However there is insufficient data on clinical exposures for the age range of 1- 6 years to enable a calculation of the safety margin therefore the relevance of these findings to the intended paediatric population cannot be ruled out. The MAH has not proposed to add information regarding the effects on bodyweight and heart weight to the SPC.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION (DRAFT)

➢ Overall conclusion (Draft)

In the submitted studies, efficacy was demonstrated in lowering both systolic and diastolic blood pressure in children 6 - <17 years of age, but in the 1 to <6 years the efficacy is unclear, due to lack of placebo comparison. In addition, there are major issues concerning, bioequivalence, PK and safety that need further clarification.

The proposed text for the SmPC will be reviewed after the applicant's response to this assessment, since further information has been requested which may alter the proposed text.

➢ Recommendation (Draft)

The data submitted by the applicant demonstrate the efficacy of candesartan in lowering systolic and diastolic blood pressure in children 6 to <17 years of age. In the 1 to <6 years, the lack of a placebo arm, although allowance for concurrent medication, makes results difficult to interpret. The bioavailability needs further justification and discussion to establish the claim of bioequivalence. In addition, the PK data provided in both age groups are sparse and inconclusive; and the safety analysis needs reformatting.

The issues on bioavailability, dose recommendation and safety must be resolved before a paediatric indication and other changes in the SmPC can be considered.

Based on the data submitted, the MAH should provide clarification of the following issues:

Quality Points

1- The applicant is asked to discuss and justify the inclusion of propylparaben in its liquid formulation.

2- The applicant should discuss the discrepancies in C_{max}. They state that 'the pharmacokinetic profiles established that the suspension was suitable for once daily treatment and that no 'formulation-based' dosage adjustment was needed.' Given the higher C_{max} the no dose adjustment statement should be explained.

3 - The applicant should clarify and describe any development work that has been carried out in amber glass (or other glass variants) with the proposed extemporaneous formulation. If no data is available, container closure information should specifically restrict the primary product packaging to PET materials only.

4 - The applicant should discuss the development of a powder-for-reconstitution product, containing separate candesartan cilexetil powder and suspension vehicle for reconstitution.

Toxicological Points

5- The applicant is requested to provide the relevant clinical exposure data needed to calculate safety margins with a view to adding the information on heart weights and bodyweights to the section 5.3 of the SmPC.

6- The applicant is requested to further discuss the results of the mechanistic study which showed saline supplementation suppressed the candesartan induced reduction of heart weight in rats.

Statistical Points
Study 261A

7-The placebo correction of the primary variable was made by subtracting the mean change from baseline for the placebo group from the individual subject changes in the other treatment groups. The Applicant is asked to justify this method.

8- Race has not been used as an independent variable in the regression model or as a covariate in the ANCOVA model as required by the guideline on the adjustment for baseline covariates (CPMP/EWP/2863/99). This should be discussed by the Applicant and, where appropriate, the analyses for both the slope of the regression line and the pairwise comparisons should be repeated with adjustment for race. In addition the estimated treatment differences together with the 95% confidence intervals should be presented for the pairwise comparisons of each dose with placebo using the ANCOVA model for the subgroups by race.

9- Less than 30% of the patients were under 12 years and, probably related to this, only 13% of the children were below 50 kg. The Applicant is asked to discuss this also in relation to the two racial subgroups. Additional information concerning the distribution of age of the children should be provided to confirm that the age range has been adequately represented in the population studied. Furthermore the Applicant should conduct an analysis using an ANCOVA model for four subgroups of patients divided by weight using the quartiles and median as limits so that approximately a quarter of the ITT population is included in each subgroup. It is understood that these subgroups will not be powered for statistical significance and may be unbalanced between treatment groups. However estimated treatment differences and the associated 95% confidence intervals should be provided for the pairwise comparisons of each dose with placebo in order to investigate possible lack of consistency of effect across the weight range of patients included in the study.

Study 328

10- As no placebo arm was included in this study the dose-response was investigated without any placebo correction to the change from baseline in the primary efficacy variable. As a placebo response was seen in the study in older children this is a concern and the Applicant should discuss the possible impact of the lack of placebo with reference to the findings of Study 261A.

Efficacy, PK & Safety Points

Clinical study 261A

11- The reported maximum response in reduction of both SiSBP (11.7 mmHg) and SiDBP (7.98 mmHg) was detected at the medium dose 8/16 mg, and the effect seemed to plateau after that point. The applicant should comment on this point.

12- The applicant is requested to fully reformat the adverse event section of the safety results and provide a comprehensive table containing all AEs including other significant adverse events, haematology, clinical chemistry, renal/hepatic function, cardiac/vascular function etc.

Clinical study 261B

13- The applicant should clarify: whether treatment with the candesartan in the open label phase started immediately, or with a time lapse from the end of the 4 weeks double blind phase.

14- For the single dose PK study, the applicant must justify, whether a wash out period of 2 days is adequate to fully eliminate all residual candesartan.

15- If clearance data has been collected during single dose PK study, it should be provided to clarify the possibility of a relation between clearance and weight/age in this population.

16- The applicant should comment on the possibility of joint sprain reported in 9 patients, being a signal for an idiosyncratic adverse event in children.

17- The applicant is requested to fully reformat the adverse event section of the safety results and provide a comprehensive table containing all adverse events including other significant adverse events, haematology, clinical chemistry, renal/hepatic function, cardiac/vascular function etc.

Clinical Study D2451C00006

18- The applicant should comment on the reason for most patients undergoing a 10 to more that 30 days wash out period.

19- For the single dose PK study, the applicant must clarify, whether a wash out period of 2 days is adequate to fully eliminate all residual candesartan.

20- If clearance data has been collected during single dose PK study, it should be provided to clarify the possibility of a relation between clearance and weight/age in this population.

21- The applicant must clarify whether the lack of reduction in LV mass is due to candesartan being ineffective and whether the 12 children with increased LV mass are the same as no responders.

General Points

22- In order to compare adult and children exposure and to substantiate the applicant's claim that the candesartan pharmacokinetic profile in children is comparable to that previously reported for adults, the applicant should provide a summary data of all available PK parameters for adult and each paediatric age group.

23- The applicant is requested to provide a summary table of frequency of adverse events in children (pooled both age groups, across 4 studies) and the available adult data.

24- In the view of a probable paediatric indication, the applicant is requested to submit a consolidated version of Risk Management Plan (RMP) for candesartan including 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 ARBs, important risks (hyperkalemia, hypotension) and important potential risks (renal impairment, haemoglobin/ hematocrit decreased, rhabdomyolysis, thrombocytopenia, pancreatitis, vasculitis and unlisted hepatobiliary disorders) have been identified and should be monitored for candesartan in the paediatric hypertensive population aged 1 to <17 years. The RMP update should also include toxicological information on the effects of candesartan on heart weight, body weights and the renal effects for future monitoring.

Additional questions by other MSs

25- In order to support recommendations of use in paediatric population, the applicant should attempt to derive specific PK information in different sub-groups, specially, in children under 2 years and children aged 2 to 4 years. Therefore, the available data should be re-analysed accordingly and the outcome of such analysis should be submitted and commented.

26- The applicant should discuss the relevance of candesartan plasma trough levels (collected in the clinical studies) for the estimation of the systemic exposure as candesartan exhibits a relatively short half-life with minimal accumulation when administered once daily.

27- Given the limited/absent myocardial cell proliferation observed in the juvenile toxicity studies, long-term studies with very extensive timelines focussing on myocardial development are needed.

VI. ASSESSMENT OF RESPONSE TO QUESTIONS

Following the first round of preliminary assessment comments and additional requests for information were received from the other MS, a first round of questions was put to the Applicant. After assessment of the applicant's response a number of issues have remained partially resolved in particular on posology and safety. Hence second round of questions ensued, comments were received from three MSs, they all agreed with the Rapporteur's conclusions and recommendations. The following is applicants responses to all questions raised in both rounds:

Quality Points

1- The applicant is asked to discuss and justify the inclusion of propylparaben in its liquid formulation.

MAH first Response: The MAH acknowledges that the regulatory environment regarding parabens, specifically regarding propylparaben, has changed since the candesartan cilexetil oral suspension was designed and that propylparaben has since been excluded from the group Acceptable Daily Intake for parabens (10 mg/kg body weight), because of the lack of a clear NO(A)EL.

The Ora-Blend SF (or 50/50% blend of Ora-Sweet SF and Ora-Plus) is developed and provided by Paddock Laboratories. The Ora-Blend SF is not designed specifically for candesartan cilexetil, but designed to be a universal aid in transforming tablets into a liquid formulation, and it is sold as a commercial product off-the-shelf.

The Ora-Blend SF contains mainly methylparaben (0.029%) and potassium sorbate as microbiological preservatives, but also a small amount of propylparaben (0.004%). Propylparaben and methylparaben often have synergistic effects when used in combination, which makes it possible to decrease the total concentration of parabens with the addition of a small amount of propylparaben.

As per the proposed SmPC, the candesartan cilexetil oral suspension is designed for paediatric patients aged 1-<6 years who cannot swallow tablets. The maximum dose of candesartan cilexetil for this patient group is 0.4 mg/kg body weight. For a typical suspension concentration of 1 mg/mL candesartan cilexetil this equates to a weight adjusted maximum daily intake of 0.12 mg/kg bodyweight for methylparaben and 0.016 mg/kg bodyweight for propylparaben. The maximum daily intake of propylparaben and methylparaben are illustrated in Table 51 for patients of varying body weights in the target age group based on a typical suspension concentration of 1 mg/mL candesartan cilexetil. It is the MAH's opinion that the maximum total daily intake of parabens, and the daily intake of propylparaben specifically, from the formulation is very low.

Table 51- Maximum daily intake of parabens, based on maximum dose of candesartan cilexetil (0.4 mg/kg body weight) and a typical candesartan cilexetil oral suspension concentration of 1 mg/mL

Body weight	Maximum dose of candesartan cilexetil	Volume of candesartan cilexetil oral suspension, 1 mg/mL	Maximum daily intake (weight adjusted)		Maximum daily intake	
			Methyl-paraben	Propyl-paraben	Methyl-paraben	Propyl-paraben
5 kg	2 mg	2 mL	0.12 mg/kg body weight	0.016 mg/kg body weight	0.6 mg	0.08 mg
10 kg	4 mg	4 mL	0.12 mg/kg body weight	0.016 mg/kg body weight	1.2 mg	0.16 mg
20 kg	8 mg	8 mL	0.12 mg/kg body weight	0.016 mg/kg body weight	2.4 mg	0.32 mg
30 kg	12 mg	12 mL	0.12 mg/kg body weight	0.016 mg/kg body weight	3.6 mg	0.48 mg
40 kg	16 mg	16 mL	0.12 mg/kg body weight	0.016 mg/kg body weight	4.8 mg	0.64 mg

Quality Assessor's comment: The main constituent of the preservative system for

the vehicle Ora-Blend SF is methylparaben (0.029%) with a small amount of propylparaben (0.004%). Propylparaben and methylparaben often have synergistic effects when used in combination and therefore the addition of a small amount of propylparaben allows the total concentration of parabens to be reduced in the product.

The MAH acknowledges that the regulatory environment regarding parabens has changed since the initial development of the suspension.

A tabulation has been provided showing that a child weighing 40 Kg would received a total daily intake of approx 5.5mg total parabens, which is below the 10mg/Kg ADI (acceptable daily intake) established for methyl and ethyl parabens and their sodium salts, as food additives, by the EFSA. The maximum intake of propylparaben would be 0.64mg per day. The EFSA could not assign an ADI to propylparaben due to research demonstrating that this substance had effects on sperm production in juvenile rats, at a relatively low dose. The EFSA did however state that the presence of propylparaben in the diet is limited and unlikely to present a risk to consumers. The MAH is of the opinion that the maximum total daily intake of propyl paraben and specifically, the total intake of the combined parabens is very low from the formulation.

Due to the proposed indication the medication would be administered chronically and therefore removal of propylparaben would be preferable. However, it is acknowledged that the total daily dose of propylparaben is low and the use of Ora-Blend SF as a vehicle for reconstitution could be accepted as an interim measure while a paediatric specific formulation is developed.

Issue partially resolved.

MAH Second Response: The applicant acknowledges the Health Authority's requirement for the development of an age-appropriate formulation, if an indication in children less than 6 years of age is pursued. In view of the applicant's acceptance of restricting the indication to children above 6 years of age and the suitability of the available tablet formulations for this paediatric population, the applicant has removed all information on the extemporaneously compounded suspension from the Product Information. The applicant furthermore confirms that there are no plans to perform any further development work in relation to a formulation for paediatric use.

Quality Assessor's comment: The applicant's response is acceptable.

Issue resolved.

2- The applicant should discuss the discrepancies in C_{max}. They state that 'the pharmacokinetic profiles established that the suspension was suitable for once daily treatment and that no 'formulation-based' dosage adjustment was needed.' Given the higher C_{max} the no dose adjustment statement should be explained.

MAH Response: Pharmacokinetics, efficacy and safety of candesartan cilexetil have been established in hypertensive subjects 1 to < 17 years of age. The pharmacokinetic profile of

candesartan cilexetil was generally comparable among children and adults. The degree of blood pressure reduction across the entire studied paediatric population and adults is similar. Because candesartan cilexetil is well tolerated across the studied paediatric and adult population, the near maximum-effect dose selection strategy in paediatrics, as in adults, is reasonable. The candesartan cilexetil suspension and tablet are not equivalent in terms of Cmax. However, the efficacy and safety results were consistent across the formulations and study groups.

Considering that the proposed starting dose is producing the near maximum effect at trough concentration and that the drug is well tolerated, the difference in Cmax between the suspension and tablet is not considered to be clinically relevant. One might note, for example, that the peak decline in blood pressure in the single dose PK studies did not suggest an excessive effect with the candesartan cilexetil suspension. The blood pressure decline was 4.8 / 4.8 mmHg at hour 5 in the younger patients (1-<6 years) receiving the suspension (Study 328); 11/9.9 mmHg at hour 4 in the older children (6-<17 years) receiving the tablet (Study 261B) Data derived from Table 11.2.6.1, Section 11, (Study 328), and Tables from Study 261B and study 328 provided as Appendix A. It is not expected that patients will frequently interchange the liquid and solid formulations.

Rather it is expected that the suspension formulation will be used in the younger children and that they will switch to the solid formulation as they get older. Theoretic formulation-specific pharmacodynamic differences are addressed in the dosing and administration text in the proposed SmPC. Doses are expected to be individualized and adjusted according to blood pressure response, whether following a dose adjustment or a change in formulation.

In summary, Study D2451C00005 was a relative bioavailability study conducted in adult, healthy (normotensive) volunteers. The study sought to assist with the pre-trial planning of Study 328 (younger children) as to the appropriate dose and dosing interval for the extemporaneously prepared candesartan cilexetil formulation. As the extent of absorption (AUC values) for the tablet and suspension formulations proved very similar and as there was a residual plasma drug concentration at trough (24 hours) for both formulations, Study D2451C00005 supported the plan to evaluate the suspension in the clinical studies of children 1-6 years of age and to do so without modification of the dosing interval or the weightadjusted doses.

The higher Cmax with the suspension in Study D2451C00005 was noted and was not unexpected. The magnitude of the higher Cmax value was not, however, judged to be an undue safety concern given that there had not been a strong relationship between candesartan cilexetil dose and adverse events, such as a first dose hypotension, in either hypertensive adults or in older children. In conclusion, the clinical and PK study findings proved consistent with the pre-trial assumptions, ie, the suspension was effective and well-tolerated given the doses selected and the once daily dosing regimen.

Quality Assessor's comment: The MAH considers that the difference in C_{max} between the tablet and the suspension is not clinically relevant.
The higher C_{max} of the suspension was noted by the MAH and was not unexpected. The magnitude of the higher C_{max} value was not considered to present a safety concern given that there is not a strong relationship between candesartan cilexitil dose and adverse events, such as first dose hypotension.

It is not expected that patients will frequently interchange between the solid and liquid formulations. It is anticipated that the suspension formulation will be used in younger children who would then switch to the solid dose formulation as they get older and are able to take tablets. Doses are expected to be individualised and adjusted

according to blood pressure response, whether following a dose adjustment or a change in the formulation.

Issue resolved.

3 - The applicant should clarify and describe any development work that has been carried out in amber glass (or other glass variants) with the proposed extemporaneous formulation. If no data is available, container closure information should specifically restrict the primary product packaging to PET materials only.

MAH Response: No data is available with other primary pack materials. The MAH accepts to restrict container closure information to PET as primary packaging material, which is consistent with the terminology used within Section 6.6 of the proposed SmPC.

Quality Assessor's comment: The applicant has confirmed that there are no available data with other primary pack materials and that the container will be restricted to PET. An updated SmPC Section 6.6 has been provided.

Issue resolved.

4 - The applicant should discuss the development of a powder-for-reconstitution product, containing separate candesartan cilexetil powder and suspension vehicle for reconstitution.

MAH Response: The MAH considers the proposed suspension formulation to be a suitable and age-appropriate alternative formulation for paediatric patients aged 1-<6 years who cannot swallow tablets.

The suspension is of well-documented quality and it is also easy to prepare for a registered or qualified pharmacist. The MAH has shown evidence that the formulation and it's preparation is robust, eg the stability is satisfactory for a reasonable time and the same dissolution profiles are achieved irrespective of the grinding time applied (0 to 5 minutes). Typically, a concentration of 1 mg/ml is suitable for the prescribed dose. However, the proposed suspension formulation also provides for flexibility in concentration with respect to dose volume, ie dose volume can be reduced for higher doses while still enabling a reasonable dose volume to facilitate handling and dosing in practice for lower doses.

This is also the formulation which was used in the paediatric clinical programme. It was decided to progress with the tablet as source of active, to ensure reaching bioequivalence with the clinical formulation.

The suspension formulation has been approved in the US, since 2009, and recently also in Switzerland. The MAH considers the proposed suspension formulation to be suitable and age-appropriate and therefore has no plans to perform any further development work in relation to a formulation for paediatric use.

Quality Assessor's comment: The MAH considers that the extemporaneously prepared suspension formulation is a suitable product and an age appropriate alternative formulation for paediatric patients aged 1 to 6 years who may have difficulty swallowing tablets. The preparation of the suspension from crushed tablets is considered something that could easily be undertaken by a qualified pharmacist.

As an indication in children less than 6 years of age is not recommended the applicant does not need to develop an age-appropriate formulation, either a liquid formulation or a kit for preparation of a suspension.

Issue resolved.

Toxicological Points

5- The applicant is requested to provide the relevant clinical exposure data needed to calculate safety margins with a view to adding the information on heart weights and bodyweights to the section 5.3 of the SmPC.

MAH First Response (Summary)

- The exposure to candesartan in children aged 1 to <6 years was evaluated in clinical study D2451C00002/328. A sub-study enrolled 10 subjects for pharmacokinetic profiling based on candesartan plasma concentration data collected over a 28-hour period following a single dose of 0.2 mg/kg candesartan cilexetil oral suspension. The mean age of the subjects was 3.1 years, most were in the age range of 2 to <6 years, and all of the subjects were in the weight group of 10 to <25 kg. The geometric mean area under the curve (AUC) 0-24h value for candesartan (i.e the active metabolite of candesartan cilexetil) was 1709 nMol.h/L(752 ng.h/mL).
- The pharmacokinetics of candesartan were also evaluated in children aged 6 to <12 (n=12) and 12 to <17 (n=10) in clinical study D2451C00001(261B). In this study hypertensive subjects received 16 mg candesartan cilexetil and pharmacokinetics were assessed based on 24 hour plasma concentrations after a single dose. The geometric mean AUC0-24h values in the age groups 6 to <12 and 12 to <17 were 2486.9 nMol.h/L (**1094 ng.h/mL**) and 2883.1 nMol.h/L (**1269 ng.h/mL**) respectively.
- Exposure multiples in each neonatal and juvenile rat study, based on the clinical AUC for candesartan in children aged 1 to <6 years are shown in Table 53, Exposure multiples in each juvenile rat study, based on the clinical AUC for candesartan in children aged 6 to < 12 years and 12 to < 17 years are shown in Table 51.
- The recalculated margins of exposures show that the effects on heart growth occur at non-clinically relevant exposures.

Table 52- Calculated exposure multiples of candesartan: neonatal and juvenile rat/child aged 1 to <6 years (n=10)

Study	Group	Dose (mg/kg)	$AUC_{0\text{-}24h}$ (ng·h/mL)	Exposure Multiple Rat/child
				Aged 1 to <6 (Mean[a] AUC 752 ng.h/ml)*
C-42-01979 Neonatal Rat Single Dose (Table 1, p 8)	PND 0 PND 7 PND 0 PND 7	30 30 100 100	76455 125141 162133 166662	101.67 166.41 215.60 221.63
TCV-116-10158 Neonatal Rat Heart Development (Text tables 3,4 page 37)	Subgroup A (PND 0-6) PND 0 PND 6 Subgroup B (PND 7-13) PND 7 PND 13	 100 100 100 100	 131061 319843 105187 399143	 174.28 425.32 139.88 530.78
TCV-116-10162 Juvenile Rat 5 Week Toxicity Study (Table 10 ,p 32)	Ist Day 35th Day Ist Day 35th Day	10 10 100 100	58595 8722 218560 40074	77.92 11.60 290.64 53.29
TCV-116-10169 Juvenile Rat 13 Week Toxicity Study (Text Table 5)	PND 7 PND 97 PND 7 PND 97	10 10 100 100	33115 13902 144111 46600	44.04 18.49 191.64 61.97

* Clinical Report 328 Table 29. Candesartan Cilexetil dose = 0.2mg/kg

[a] Geometric mean AUC0-24h.

For calculation of exposure multiples the human AUC values were converted from nMol.h/L to ng.hr/mL based on the following: Molecular weight of candesartan cilexetil is 440 thus AUC in nMol*h/L x 440 ÷ 1000 = AUC in ng*h/mL

Table 53- Calculated exposure multiples of candesartan:juvenile rat/child aged 6 to<12 years**(n=12) and 12 to <17 years**(n=10)

Study	Group	Dose (mg/kg)	$AUC_{0\text{-}24h}$ (ng·h/mL)	Exposure Multiple Rat/child	
				Aged 6 to <12 (Mean[a] AUC 1094ng.h/ml)**	Aged 12 to <17 Mean[a] AUC 1269ng.h/ml)**
TCV-116-10162 Juvenile Rat 5 Week Toxicity Study (Table 10 ,p 32)	Ist Day 35th Day Ist Day 35th Day	10 10 100 100	58595 8722 218560 40074	53.56 7.97 199.78 36.63	46.17 6.87 172.23 31.58
TCV-116-10169 Juvenile Rat 13 Week Toxicity Study (Text Table 5)	PND 7 PND 97 PND 7 PND 97	10 10 100 100	33115 13902 144111 46600	30.27 12.71 131.73 42.60	26.10 10.96 113.56 36.72

** Clinical report 261B Table 23. Candesartan Cilexetil dose = 16 mg

[a] Geometric mean $AUC_{0\text{-}24h}$

For calculation of exposure multiples the human AUC values were converted from nMol.h/L to ng.hr/mL based on the following: Molecular weight of candesartan cilexetil is 440 thus AUC in nMol*h/L x 440 ÷ 1000 = AUC in ng*h/mL

- In consideration of the fact that effects on heart and body weights only occurred at exposure levels sufficiently in excess of the human paediatric exposure, the applicant does not consider that addition of the information on the neonatal/juvenile toxicity studies adds to the information needed by the prescriber of candesartan cilexetil. However the applicant has proposed addition of the following wording for Section 5.3 of the Summary of Product Characteristics (SmPC), for consideration by the Agency:

Proposed text for SmPC 5.3

In preclinical studies in normotensive neonatal and juvenile rats candesartan caused a reduction in body weight and heart weight. As in adult animals, these effects are considered to result from the pharmacological action of candesartan. At the lowest dose of 10 mg/kg exposure to candesartan was between 12 and 78 times the levels found in children aged 1 to <6 who received candesartan cilexetil at a dose of 0.2 mg/kg and 7 to 54 times those found in children aged 6 to <17 who received candesartan cilexetil at a dose of 16 mg.

If the Agency considers the suggested additional wording will be valuable for the prescriber, the applicant will add this to the proposed SmPC, which was submitted as part of this application, before completion of this Worksharing procedure.

Toxicological assessor's comments

The applicant states that the AUC values quoted for candesartan cilexetil in the previous non-clinical overview were in fact the values of the main metabolite candesartan and not the parent compound, therefore the margin of exposure between the effect dose and the maximum recommended dose are higher than previously estimated.

For children aged 1-6 years the lowest margin of exposures between effects on heart weight in a juvenile tox study (10mg/kg/day = Candesartan cilexetil: Study TCV- 116-10162 Juvenile rat 5 week toxicity study) and the maximum clinical dose of 0.2mg/kg candesartan cilexetil (mean AUC 752 ng.h/ml) is 11.60 fold. For 6 to 12 and 12 to 17 year olds the lowest margin of exposure between the effect dose and the clinical dose is 7.97 fold and 6.87 fold respectively. A safety margin cannot be calculated because a NOEL was not identified and hence the threshold for this effect is unknown. For these reasons the proposed amendment of section 5.3 of the SmPC with information reflecting the reported effects on heart growth is necessary and welcomed. The proposed SmPC text is acceptable however the applicant will need to amend the text to clearly state that a safety margin for the effects on heart weight is unknown.

Issue partially resolved

MAH Second Response: The MAH agrees to amend the proposed SmPC text to include the statement on heart weight as requested by the Rapporteur. The following revised text is proposed for inclusion in Section 5.3 of the SmPC:

5.3 Preclinical safety data

There was no evidence of abnormal systemic or target organ toxicity at clinically relevant doses. In preclinical safety studies candesartan had effects on the kidneys and on red cell parameters at high doses in mice, rats, dogs and monkeys. Candesartan caused a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit). Effects on the kidneys (such as interstitial nephritis, tubular distension, basophilic tubules; increased plasma concentrations of urea and creatinine) were induced by candesartan which could be secondary to the hypotensive effect leading to alterations of renal perfusion. Furthermore, candesartan induced hyperplasia/hypertrophy of the juxtaglomerular cells. These changes were considered to be caused by the pharmacological action of candesartan. For therapeutic doses of candesartan in humans, the hyperplasia/hypertrophy of the renal juxtaglomerular cells does not seem to have any relevance.

In preclinical studies in normotensive neonatal and juvenile rats, candesartan caused a reduction in body weight and heart weight. As in adult animals, these effects are considered to result from the pharmacological action of candesartan. At the lowest dose of 10 mg/kg exposure to candesartan was between 12 and 78 times the levels found in children aged 1 to <6 who received candesartan cilexetil at a dose of 0.2 mg/kg and 7 to 54 times those found in children aged 6 to <17 who received candesartan cilexetil at a dose of 16 mg. As a no observed effect level was not identified in these studies, the safety margin for the effects on heart weight and the clinical relevance of the finding is unknown.

Foetotoxicity has been observed in late pregnancy (see section 4.6). Data from *in vitro* and *in vivo* mutagenicity testing indicates that candesartan will not exert mutagenic or clastogenic activities under conditions of clinical use. There was no evidence of carcinogenicity. The renin-angiotensin-aldosterone system plays a critical role in kidney development *in utero*.

Renin-angiotensin-aldosterone system blockade has been shown to lead to abnormal kidney development in very young mice. Administering drugs that act directly on the reninangiotensin-aldosterone system can alter normal renal development. Therefore, children aged less than 1 year must not receive Atacand (see section 4.3).

Quality Assessor's comment: The proposed SmPC text is in line with Rapporteur's recommendations.

Issue resolved.

6- The applicant is requested to further discuss the results of the mechanistic study which showed saline supplementation suppressed the candesartan induced reduction of heart weight in rats.

MAH Response (Summary)

- During the non-clinical development of candesartan cilexetil a mechanistic study was conducted to confirm that changes observed in toxicity studies in rats treated with candesartan cilexetil and the active metabolite candesartan (increases in plasma urea nitrogen, slight decreases in erythrocyte counts and heart weights) were a result of the pharmacodynamic activity of the molecule (Report C-42-79). These same changes had previously been reported in rats treated with the ACE inhibitors captopril (Imai et al 1981) and enalapril (Bagdon et al 1985).
- In study C-42-79, groups of 5 male, 5 female F344/Jcl rats aged 6 weeks at start of treatment received candesartan cilexetil 0 or 300 mg/kg/day orally for 2 weeks with or without saline (0.9%) supplementation of the drinking water.
- decreases in body weight gain, food consumption, urine osmolality, creatinine clearance, erythrocytes, haematocrit, haemoglobin concentration and heart weight and increases in plasma urea nitrogen, urine output and water intake were observed in rats treated with candesartan cilexetil 300 mg/kg/day **without** saline supplementation but not in rats treated with candesartan cilexetil 300 mg/kg/day **plus** saline supplementation with the exception of increased urine output and water intake.
- Overall the saline supplementation suppresses the activity of the renin-angiotensin system resulting in decreased sensitivity of angiotensin II receptors to the action of an angiotensin II receptor antagonist. The results of the mechanistic study with candesartan cilexetil concur with observations in the published literature indicating that the heart weight reductions were induced by exaggerated pharmacological activity of candesartan cilexetil.

Toxicological assessor's comment
It is agreed that the effect of candesartan on heart growth is due to excessive pharmacological action.

Issue resolved.

Statistical Points
Study 261A

7-The placebo correction of the primary variable was made by subtracting the mean change from baseline for the placebo group from the individual subject changes in the other treatment groups. The Applicant is asked to justify this method.
MAH Response: In Study 261A, the primary efficacy measure was trough sitting systolic blood pressure (SiSBP) and the measure of effect was the placebo-corrected change from baseline to Week 4 (last observation carried forward [LOCF] analysis); the placebo-corrected value was determined by subtracting the mean change from baseline in the placebo group from the individual subject changes in the candesartan treatment groups. The placebo adjusted analyses were pre-planned and consistent with the protocol objective to determine the dose response for the 'non-zero' doses. The placebo correction still allows for an unbiased test of the antihypertensive effect in the linear dose response analysis. Specifically, the estimated regression coefficient for the slope and its standard error, after subtracting the placebo average from each individual observation, will be unbiased and identical to an analysis of the raw observations. Thus, the evaluation of the primary objective will be unaffected by the subtraction of the placebo average. Note that this is consistent with the CPMP/EWP guidance which indicates that when the baseline is included as a covariate in the model, the estimated treatment effects are identical for both 'change from baseline' and the 'raw outcome' analyses (CPMP/EWP/2863/99).

Adjustment for the 'placebo effect' as estimated by a concurrent placebo control, when available, may be preferred by some regulatory agencies because such analyses tend to give a better estimate of the 'true drug effect'. Accordingly, it is customary for product labels to describe the results of clinical trials in terms of the placebo corrected reductions in blood pressure.

With regard to the magnitude of the 'placebo effect' observed in Study 261A, it should be noted that the mean decline of 3.66/1.80 mmHg in the placebo group is consistent with the 5.0/3.0 mmHg, median decline with placebo in a pooled analysis of other hypertensive studies in children of similar age (Smith et al 2008). One might also note that in a study of metoprolol succinate reported by Batisky et al 2007, which was of similar design to Study 261A and was conducted at many of the same US centres, the placebo group's blood pressure declined by 1.9/2.1 mmHg (Batisky et al 2007). In both the Batisky study and in Study 261A, blood pressure declines for all treatments were most evident at the first (1 week) postrandomization visit; however, the placebo group's blood pressures tended to remain about the same thereafter while those in the active treatment group tended to continue to decline to the Week 4, end-of-study visit (See Figure 12, Figure 13, and Figure 14). The 'placebo adjustment' of the treatment effect was being done in order to correct for any possible regression towards the mean or placebo effect.

Figure 12- Mean SiSBP by week and LOCF, by treatment group (Study 261A)

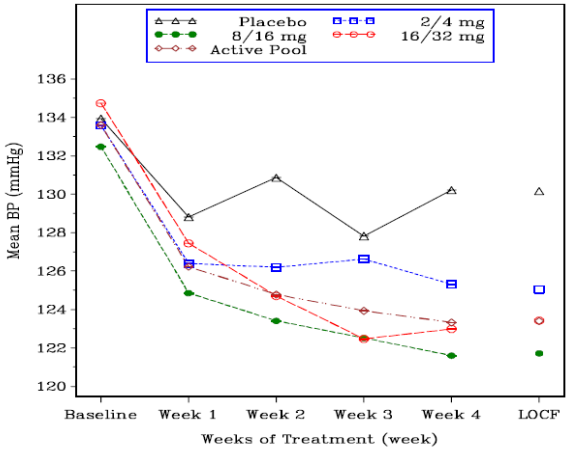


Figure 13- Mean SiDBP by week and LOCF. by treatment group (Study 261A)

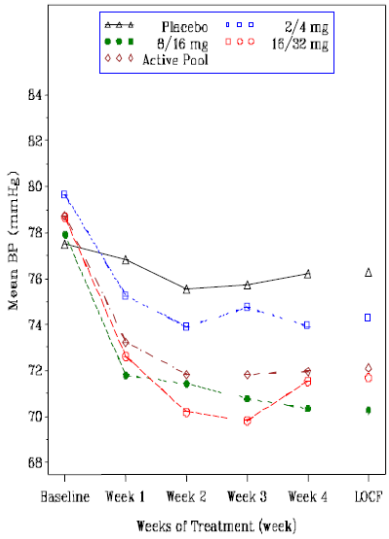
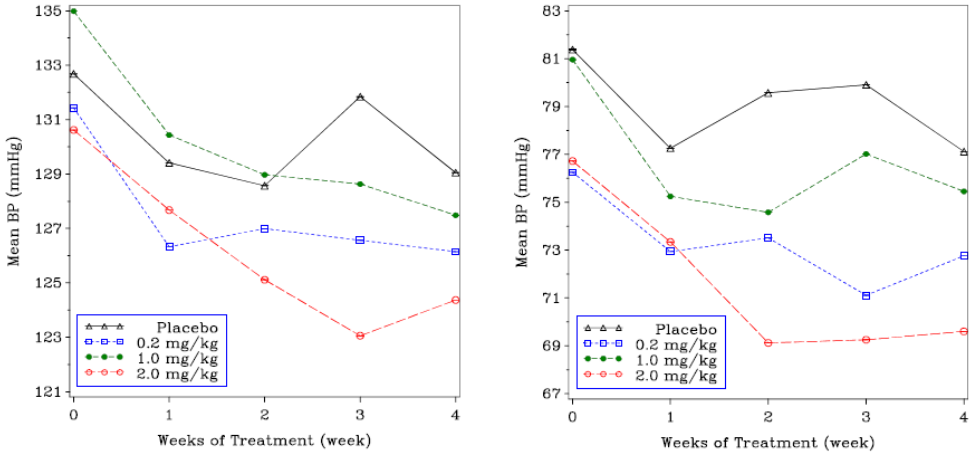


Figure 14- Mean changes over time for SiSBP and SiDBP (ITT population) (Study 307A)



While the 'white coat hypertension' phenomenon has been noted, particularly in older children and adolescents, much of the emphasis has been within the context of establishing the initial diagnosis of hypertension (Lurbe et al 2009, The Fourth Report 2005). The protocols for Study

261A (older children) and Study 328 (younger children) specified the entry of children with confirmed, established hypertension. Furthermore, the 'white coat' phenomenon may be less evident in the very young child with secondary and often more severe hypertension (Swinford and Portman 2004).

See also MAH Response to 2.1.2.1MHRA comment 10.

Statistical Assessor's comment: It should be noted that statistical methods are not necessarily appropriate simply because they are pre-planned and in line with the protocol. Furthermore although it is customary to present the results of clinical trials in terms of improvement over and above the placebo effect this is normally using the estimated treatment difference between the product and placebo provided by the appropriate analysis model. Therefore these arguments for using this subtraction method for adjusting for the placebo are not accepted. However as the MAH has provided their justification, the point may be consider to be resolved.

Issue resolved.

8- Race has not been used as an independent variable in the regression model or as a covariate in the ANCOVA model as required by the guideline on the adjustment for baseline covariates (CPMP/EWP/2863/99). This should be discussed by the Applicant and, where appropriate, the analyses for both the slope of the regression line and the pairwise comparisons should be repeated with adjustment for race. In addition the estimated treatment differences together with the 95% confidence intervals should be presented for the pairwise comparisons of each dose with placebo using the ANCOVA model for the subgroups by race.

MAH Response: The candesartan paediatric program was originally constructed in accordance with the FDA written request (1999), which specified that 40% (later revised to 35%) to 60% of the overall program population (older + younger children) be of Black race (FDA Written request).

Consistent with 'Points To Consider on Adjustment for Baseline Covariates' (CPMP/EWP/2863/99), race (Black vs. non-Black) was prospectively identified as an influential covariate. Accordingly, the potential confounding effect of race was addressed by a stratified randomization. This stratified randomization process was successful in producing treatment groups well-balanced as to race; in Study 261A, Black subjects accounted for 46.4% to 48.6% of the subjects across the treatment groups.

Race was not considered *a priori* as a potential covariate in the ANCOVA model, as this would have been viewed as being redundant to the stratified randomization.

We acknowledge the recommendation in CPMP/EWP/2863/99 to also include stratification variables as adjustment covariates and the requested reanalyses are included below:

The dose response linear regression analysis for SiSBP (primary analysis) and for SiDBP with race (Black vs non- Black) as a covariate (ITT Population) testing slope = 0, is presented in Table 54 and Table 55.

Table 54- Estimated slope for change in SiSBP by dose, covariates include weight and race (Black and non-Black): Study 261A

Race	Estimate	Std Error	Lower 95% CI	Upper 95% CI	Pr > |t|
Black	-0.1188	0.2643	-0.6399	0.4023	0.6535
Non-black	-0.6158	0.2572	-1.1229	-0.1087	0.0176
Total	-0.3839	0.2272	-0.8320	0.06410	0.0926

Table 55- Estimated slope for change in SiDBP by dose, covariates include weight and race (Black and non-Black): Study 261A

Race	Estimate	Std Error	Lower 95% CI	Upper 95% CI	Pr > |t|
Black	-0.0049	0.2749	-0.5469	0.5370	0.9857
Non-black	-0.3982	0.2675	-0.9257	0.1292	0.1381
Total	-0.2139	0.2374	-0.6819	0	0.3685

Pair-wise comparison of each active dose and of all doses pooled vs placebo by ANCOVA with race and weight group as covariates (ITT population) testing equivalence of means in change from baseline in SiSDP and SiDBP is shown in Table 56 and Table 57, respectively.

Table 56- Pair-wise comparisons of each candesartan dose group and all doses pooled vs placebo for change in SiSBP. Covariates include weight group and race (Black vs. Non Black): Study 261A

Group	Estimate	Std Error	Lower 95% CI	Upper 95% CI	Pr > |t|
2/4 vs Placebo	-4.7982	1.9055	-8.5524	-1.0440	0.0125
8/16 vs Placebo	-6.9800	1.9095	-10.7421	-3.2179	0.0003
16/32 vs Placebo	-7.5727	1.9100	-11.3357	-3.8097	<0.0001
All doses vs placebo	-6.4503	1.6792	-9.7586	-3.1420	0.0002

Table 57- Pair-wise comparisons of each candesartan dose group and all doses pooled vs placebo for change in SiDBP. Covariates include weight group and race (Black vs. Non Black): Study 261A

Group	Estimate	Std Error	Lower 95% CI	Upper 95% CI	Pr > |t|
2/4 vs Placebo	-4.1080	2.0823	-8.2104	-0.0056	0.0497
8/16 vs Placebo	-6.3835	2.0866	-10.4944	-2.2725	0.0025
16/32 vs Placebo	-5.7435	2.0872	-9.8555	-1.6314	0.0064
All doses vs placebo	-5.4116	1.8350	-9.0268	-1.7965	0.0035

Treatment difference of each active dose and of all doses pooled vs placebo as determined by ANCOVA by sub-groups of race (Black vs non-Black) (ITT Population) is shown in Table 58 (for SiSBP) and Table 59 for (SiDBP).

Table 58- Pair-wise comparisons of each candesartan dose group and all doses pooled vs placebo for change in SiSBP by race. Covariates include weight group and race

Group	Estimate	Std Error	Lower 95% CI	Upper 95% CI	Pr > |t|
Black					
2/4 vs Placebo	-3.4629	2.7674	-8.9155	1.9897	0.2121
8/16 vs Placebo	-5.8066	2. 7674	-11.2592	-0.3541	0.0370
16/32 vs Placebo	-5.4629	2. 7674	-10.9155	-0.0103	0.0496
All doses vs placebo	-4.9108	2.4268	-9.6924	-0.1293	0.0442
Non- Black					
2/4 vs Placebo	-6.0547	2.6481	-11.2722	-0.8372	0.0231
8/16 vs Placebo	-8.0946	2.6606	-13.3367	-2.8525	0.0026
16/32 vs Placebo	-9.5185	2.6601	-14.7597	-4.2774	0.0004
All doses vs placebo	-7.8893	2.3445	-12.5087	-3.2699	0.0009

Table 59- Pair-wise comparisons of each candesartan dose group and all doses pooled vs placebo for change in SiDBP by race. Covariates include weight group and race

Group	Estimate	Std Error	Lower 95% CI	Upper 95% CI	Pr > |t|
Black					
2/4 vs Placebo	-4.0363	3.0161	-9.9789	1.9063	0.1821
8/16 vs Placebo	-4.7238	3.0161	-10.6664	1.2188	0.1187
16/32 vs Placebo	-3.2446	3.0161	-9.1872	2.6980	0.2832
All doses vs placebo	-4.0016	2.6449	-9.2128	1.2097	0.1317
Non- Black					
2/4 vs Placebo	-4.2616	2.8861	-9.9480	1.4248	0.1411
8/16 vs Placebo	-7.9237	2.8997	-13.6369	-2.2105	0.0068
16/32 vs Placebo	-8.0278	2.8992	-13.7399	-2.3156	0.0061
All doses vs placebo	-6.7377	2.5552	-11.7722	-1.7032	0.0089

MAH interprets these new analyses as follows:

- The inclusion of race as a covariate does not modify the conclusion of the dose response analyses, ie, the non-zero dose response is not statistically significant.

- The pair-wise comparisons with race included as a covariate indicate a nominally significant effect relative to placebo for each individual candesartan dose and for all doses pooled for both SiSBP and SiDBP. As opposed to the original analysis that did not include race as a covariate, the reductions in SiSBP are monotonic (- 4.8, - 7.0 – 7.6 mmHg).

- The candesartan effects relative to placebo are clinically meaningful for both Black subjects and non-Black subjects although the magnitude of the blood pressure reductions tends to be less in Black subjects than non-Black subjects. This is consistent with findings in adults as noted in the current SmPC. SBP effects relative to placebo are also nominally significant for both Black subjects and non- Black subjects with the single exception of the low dose among Black subjects.

As noted in the Study 261A CSR, a race by blood pressure interaction analysis was not statistically significant (p=0.4007; see Section 7.2.4.2 of the CSR for Study 261A)

As a point of information, it was necessary to include European sites in Study 328 in order to meet patient enrolment targets. Accordingly, there were proportionally fewer Black subjects in Study 328 (18.3%, n= 17) than in Study 261A (47.1% %, n= 113). Taken together, however, the 39 % of Black subjects in the overall program was sufficient to meet the FDA race quota requirement.

Statistical assessor's comment:
The MAH suggests that stratification by race in the randomisation made it unnecessary to include race as a factor in the ANCOVA model but this is not accepted. However the analysis requested adjusting for race has been conducted. The estimated slopes presented in Tables 54 and 55 of the response are clearly different for black and non-black patients for both systolic and diastolic blood pressure. However when all patients are included in the analysis adjusted for race, the findings of the dose response analysis remain unchanged from those of the original analysis. Furthermore the analyses using the adjusted model of the pairwise contrasts show little change in the estimates for both systolic and diastolic blood pressure especially for the medium and high doses. The MAH states that when the populations of black and non-black patients are analysed separately there is a greater effect in the non-black patients although a clinically meaningful improvement is found in both subgroups which is consistent with findings in racial subgroups of adult patients. Finally it should be noted that a non-significant interaction terms for race by blood pressure is not evidence of a lack of difference between the two groups as this may be due to insufficient power. In conclusion it is recognised by the MAH that there are differences in size of effects between non-black and black patients and as for adults, this should be noted in the SmPC.

Issue resolved.

9- Less than 30% of the patients were under 12 years and, probably related to this, only 13% of the children were below 50 kg. The Applicant is asked to discuss this also in relation to the two racial subgroups. Additional information concerning the distribution of age of the children should be provided to confirm that the age range has been adequately represented in the population studied. Furthermore the Applicant should conduct an analysis using an ANCOVA model for four subgroups of patients divided by weight using the quartiles and median as limits so that approximately a quarter of the ITT population is included in each subgroup. It is understood that these subgroups will not be powered for statistical significance and may be unbalanced between treatment groups. However estimated treatment differences and the associated 95% confidence intervals should be provided for the pairwise comparisons of each dose with placebo in order to investigate possible lack of consistency of effect across the weight range of patients included in the study.

MAH First Response: The FDA written request specified challenging overall program requirements with regard to the proportions of patients by age groups (1-2 years, 2-6, 6 to 12 and 12 to 17 years) along with overall requirements that half be below age 12, as well as the proportions of patients by sexual maturity (Tanner stage) categories. To comply with these directives as well as with the Black race quota requirement, it was necessary to carefully manage enrolment into each study.

Given that a separate trial would be evaluating children 1-6 years of age, Study 261A necessarily limited the number of patients permitted to enrol who were less than 12 years of age so as to not violate the overall program (Study 261A + Study 328) age group/sexual maturity

requirements. As a consequence, there were few patients less than 12 years of age in Study 261A and few patients in the <50 kg weight group. As previously noted randomization was stratified for race within dose/weight groups, however the <50 kg dose group was relatively small.

As requested by the Rapporteur, the weight group by race by treatment group distributions for patients <50 kg appear in Table 60.

Table 60- Study 261A - Descriptive statistics of baseline characteristics by race, weight ≤ 50 kg

Variable		Weight ≤ 50 kg, black				Weight ≤ 50 kg, non-black			
		Placebo N=2	2 mg N=2	4 mg N=2	8 mg N=2	Placebo N=3	2 mg N=6	4 mg N=7	8 mg N=6
Age, years n(%)	< 12	2 (1)		1 (1)	2 (1)	2 (1)	6 (1)	5 (1)	5 (1)
	≥ 12		2 (1)	1 (1)		1 (0)		2 (0)	1 (0)
Age ,years	Mean (SD)	6.5 (0.71)	14.0 (0.00)	12.0 (7.07)	9.5 (2.12)	12.0 (3.61)	9.3 (2.07)	11.1 (2.85)	8.7 (2.88)
Sex	Male	2 (1)	1 (1)		1 (1)	2 (1)	4 (1)	4 (1)	3 (1)
	Female		1 (1)	2 (1)	1 (1)	1 (0)	2 (0)	3 (0)	3 (1)
Tanner Score	< 3	2 (1)		1 (1)	2 (1)	2 (1)	6 (1)	6 (1)	6 (1)
	≥ 3		2 (1)	1 (1)		1 (0)		1 (0)	
Weight, kg	Mean (SD)	42 (7.6)	45 (4.0)	32 (16.2)	44 (0.8)	40 (11.3)	36 (9.8)	41 (5.8)	34 (10.8)
Height, cm	Mean (SD)	138 (6)	158 (7)	141 (23)	139 (12)	152 (18)	136 (13)	147 (14)	134 (18)
BMI, kg/m^2	Mean (SD)	22 (2.3)	18 (0.1)	15 (3.2)	23 (3.7)	17 (2.6)	19 (2.7)	19 (3.0)	19 (3.9)
Duration of hypertension, years	Mean (SD)	0.8 (0.78)	0.5 (0.71)	0.2 (0.07)	0.2 (0.07)	0.4 (0.32)	0.8 (1.23)	0.6 (0.82)	3.5 (3.82)
Type of hypertension	None						1 (0)		
	DBP only			1 (1)				1 (0)	
	SBP only		1 (1)		1 (1)		2 (0)	2 (0)	
	DBP + SBP	2 (1)	1 (1)	1 (1)	1 (1)	3 (1)	3 (1)	4 (1)	6 (1)
Previous treated hypertension	No	1 (1)	2 (1)	1 (1)	2 (1)	3 (1)	5 (1)	4 (1)	3 (1)
	Yes	1 (1)		1 (1)			1 (0)	3 (0)	3 (1)

In the <50 kg weight group, 8 of the 30 (27%) patients were black and 22 (73%) were non-black. This compares to 108/240 (45%) blacks and 132/240 (55%) non-blacks in the overall 261A Study population. Mean weights for blacks vs non-blacks were approximately the same within each dose group.

With regard to an age-representative study population, Studies 261A and Study 328, taken together, provided data for children 1-18 years and did so in-line with the requirements of the FDA written request, ie, 16 patients 1-2 years of age, 77 of ages 2-6, 70 ages 6 to 12 and 170 ages 12 to 17 (Table 61 and Table 62).

Table 61- Number of patients by age group Randomized in Study 261A

Demographic or baseline characteristic		Treatment group				
		Placebo N=35	2/4 mg N=69	8/16 mg N=68	16/32 mg N=68	Total N=240
Demographic characteristics						
Age, years: n (%)	6 to <12	11 (31.4)	18 (26.1)	21 (30.9)	20 (29.4)	70 (29.2)
	≥12	24 (68.6)	51 (73.9)	47 (69.1)	48 (70.6)	170 (70.8)

Table 62- Number of patients by age group Randomized in Study 328

Demographic characteristics		Candesartan treatment			
		0.05 mg/kg N=29 n (%)	0.2 mg/kg N=32 n (%)	0.4 mg/kg N=32 n (%)	Total N=93 n (%)
Age at screening (years)	1 to <2	6 (20.7)	5 (15.6)	5 (15.6)	16 (17.2)
	2 to <6	23 (79.3)	27 (84.4)	27 (84.4)	77 (82.8)

An additional 21 patients, ages 6 to 17 years, were enrolled directly into Study 261B.

As requested, the estimated mean differences and 95% CI for decline in SiSBP and SiDBP for pair-wise comparisons of each dose vs placebo by weight quartiles as determined by an ANCOVA model appear in Table 63 and Table 64. The interpretation of these data should take into account that there was a dose adjustment by weight group (<50 kg vs ≥50 kg).

Table 63- Pair-wise comparisons of each active dose group vs placebo for each weight group; weight group as covariate, testing equivalence of means in change in SiSBP from baseline Study 261A

LABEL	Estimate	Std Error	Lower CI	Upper CI	Pr > |t|
≤Q1: 2mg vs placebo	-7.6722	4.7295	-16.9931	1.6486	0.1062
≤Q1: 4mg vs placebo	-7.6444	5.0966	-17.6889	2.4000	0.1351
≤Q1: 8mg vs placebo	-11.0704	4.6006	-20.1372	-2.0035	0.0169
≤Q1: 16mg vs placebo	-20.9754	7.9490	-36.6413	-5.3095	0.0089
≤Q1: 32mg vs placebo	-10.3032	4.8902	-19.9408	-0.6656	0.0363
Q1<W≤median: 4mg vs placebo	-5.3167	4.0864	-13.3701	2.7368	0.1946
Q1<W≤median: 16mg vs placebo	-3.7778	4.1448	-11.9464	4.3909	0.3631
Q1<W≤median: 32mg vs placebo	-5.5111	4.2593	-13.9054	2.8831	0.1971
median<W≤Q3: 4mg vs placebo	-5.4444	3.7988	-12.9311	2.0422	0.1532
median<W≤Q3: 16mg vs placebo	-10.4980	3.7083	-17.8064	-3.1896	0.0051
median<W≤Q3: 32mg vs placebo	-9.4926	3.6700	-16.7254	-2.2598	0.0103
Q3<W: 4mg vs placebo	-0.8833	3.6039	-7.9858	6.2192	0.8066
Q3<W: 16mg vs placebo	-3.4667	4.1614	-11.6679	4.7346	0.4057
Q3<W: 32mg vs placebo	-3.3000	3.6039	-10.4025	3.8025	0.3608

Q1=61.7 kg, median=76.05 kg, Q3=98.1 kg, W=weight at baseline; CI = 95% Confidence interval
N=60 per quartile

Table 64- Pair-wise comparisons of each active dose group vs placebo for each weight group; weight group as covariate, testing equivalence of means in change in SiDBP from baseline Study 261A

LABEL	Estimate	Std Error	Lower CI	Upper CI	Pr > |t|
≤Q1: 2mg vs placebo	-1.4917	5.1857	-11.7116	8.7283	0.7739
≤Q1: 4mg vs placebo	-3.3111	5.5882	-14.3245	7.7022	0.5541
≤Q1: 8mg vs placebo	-4.5519	5.0443	-14.4933	5.3896	0.3678
≤Q1: 16mg vs placebo	-13.7274	8.7158	-30.9045	3.4497	0.1167
≤Q1: 32mg vs placebo	-2.0810	5.3619	-12.6482	8.4863	0.6983
Q1<W≤median: 4mg vs placebo	-6.2738	4.4806	-15.1041	2.5565	0.1629
Q1<W≤median: 16mg vs placebo	-9.4497	4.5446	-18.4063	-0.4931	0.0387
Q1<W≤median: 32mg vs placebo	-7.3460	4.6702	-16.5500	1.8579	0.1172
median<W≤Q3: 4mg vs placebo	-2.8333	4.1652	-11.0422	5.3755	0.4971
median<W≤Q3: 16mg vs placebo	-3.0098	4.0660	-11.0232	5.0036	0.4600
median<W≤Q3: 32mg vs placebo	-2.6667	4.0240	-10.5972	5.2638	0.5082
Q3<W: 4mg vs placebo	-5.1333	3.9515	-12.9209	2.6543	0.1953
Q3<W: 16mg vs placebo	-6.2333	4.5628	-15.2257	2.7590	0.1733
Q3<W: 32mg vs placebo	-7.7500	3.9515	-15.5376	0.03761	0.0511

Q1=61.7 kg, median=76.05 kg, Q3=98.1 kg, W=weight at baseline; CI = 95% Confidence interval
N=60 per quartile

As, expected some of the weight quartile groups are small with wide confidence intervals and, nominal significance is apparent for only a few of the contrasts. All point estimates, however, are directionally in favour of a blood pressure reduction with candesartan.

In general, comparisons of dose-specific point estimates in Table 62 and Table 63 across weight quartiles imply a somewhat greater blood pressure reduction in the lower weight quartiles. This finding supports the MAH's dosing recommendation of a lower range of doses for children weighing less than 50 kg. As noted in the 261A CSR, the dose response analysis with dose expressed in mg/kg, indicates a significant dose response (p=0.0193 for SiSBP).

The MAH's proposed dosing recommendation for adjustment by weight group (<50 kg vs ≥50 kg) also takes into account pragmatic considerations, ie, the tablet strengths are available for each of the recommended doses (4, 8, 16 and 32 mg); they are small and palatable for children.

Statistical assessor's comment:
It is understood from the clinical study report that 240 children were randomised into Study 261A and that all were included in the ITT population. However the information provided in Table 60 includes only a small number of those children who weighed 50 kg or less. It would have been useful to have the same information concerning the other children included in this table in order to make comparisons. In Table 63 the estimate decrease in systolic blood pressure compared to placebo for the lowest quartile of patients is 21 mmHg for the 16 mg dose which seems particularly high especially as the effect for the 32 mg dose is half that size. This should be investigated. Unfortunately the numbers of patients included in each analysis have not been provided in the table. Therefore it is considered that this issue requires further investigation.

Issue partially resolved.

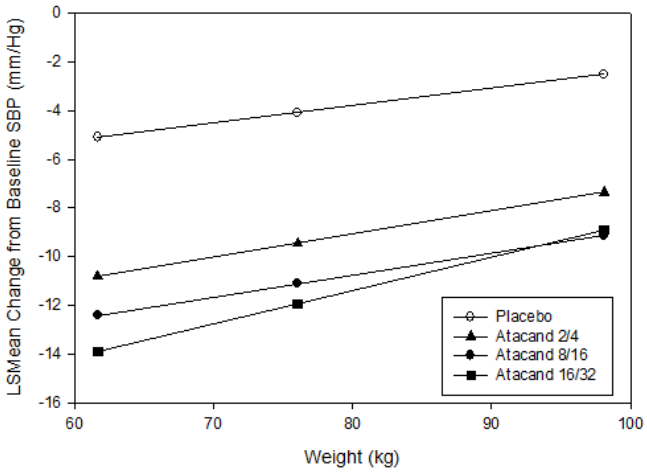
Assessor's comments
From clinical point of view the answer provided dose not address the question. In the PK analysis of study 621A, weight seems to significantly correlated with Cmax (p=0.012) and AUC (p=0.011). But no clearance data were collected and in the absence of which, it is not possible to rule out the effect of weight on the response. The applicant has acknowledged that comparisons of dose-specific point estimates imply a somewhat greater blood pressure reduction in the lower weight quartiles. Question 9 was meant to clarify and tease out any possible relation between weight and response. That is of great importance for a more accurate dose recommendation in the lower age/weight group. As it stands the question is still remains unclear and the influence of weight on exposure/response particularly in the younger children (1-6 years) is ambiguous.

Issue unresolved.

MAH Second Response (summary):

An additional analysis was performed using candesartan 2/4, 8/16, 16/32 and placebo, similar to the clinical study report methodology. It is important to note that age, dose (per the protocol), body weight, baseline blood pressure that is known to increase with both age and weight, and the magnitude of the blood pressure responses are all correlated, which may make the effect of weight difficult to clearly describe. The analysis of covariance model included terms for treatment, weight, treatment-by-weight interaction and baseline systolic blood pressure. Figure 15 plots the average treatment response at the quartiles for weight.

Figure 15- Study 261A: LSMean Change from baseline to Week 4/LOCF in Sitting SBP by Weight (ITT population)



All active treatments show larger SBP decreases compared to placebo, and in general show larger responses with increasing candesartan dose. All treatment groups, including placebo, show decreased magnitude of SBP changes as weight increases. Regression slopes are generally parallel for placebo, candesartan 2/4, and candesartan 8/16, while candesartan 16/32 shows relative decrease in blood pressure lowering effect at the highest weight ranges.

Overall, a similar response pattern is seen in both candesartan and placebo across weight. The MAH considers that this, in conjunction with the agreed restriction to age from 6 to <18 years, alleviates concerns for the smallest children for which an indication is no longer sought.

Assessor's comments: The question still remains unclear and the influence of weight on exposure/response particularly in the younger children (1-6 years) is ambiguous. However since the applicant has agreed to age restriction and no longer seeks indication in the younger age group (1-6 years), this question is no longer an issue.

Issue resolved.

Study 328

10- As no placebo arm was included in this study the dose-response was investigated without any placebo correction to the change from baseline in the primary efficacy variable. As a placebo response was seen in the study in older children this is a concern and the Applicant should discuss the possible impact of the lack of placebo with reference to the findings of Study 261A.

MAH First Response: The absence of a concurrent placebo control arm in Study 328 would not be expected to alter the study primary analysis interpretation, ie, there is a statistically significant dose-related reduction in both SBP and DBP.

While the absence of a placebo group does prohibit the quantification of the 'true drug effect', given the assumption that the 'placebo effect' is the same across the dose groups, the summary effect of the doses should remain unbiased and interpretable.

While the value of including a placebo control in paediatric studies is appreciated, the challenge of including placebo in studies of children with significant diseases has been widely discussed (Smith et al 2008, FDA Written request). Not unexpectedly, the sponsors faced adamant opposition to the inclusion of a placebo control group in Study 328, both by potential study investigators and by national competent authorities. The FDA written request acknowledges the challenge of a placebo control group and accepts that a demonstration of a significant positive dose response across a range of active doses is an interpretable finding (FDA Written request).

The considerations presented in response to MHRA comment 7 suggest that much of the 'placebo effect' in Study 261A could be explained by the regression to the mean phenomenon. Since, the treatment groups in Study 328 were formed by random assignment, one could assume that, given reasonable sample sizes, the regression to the mean would manifest equally across all treatment groups and to an extent approximating that seen with placebo had one been included in the study.

While a 'white coat' effect could well have been operative in Study 328, an interpretable treatment effect is still possible as has been illustrated by a paediatric ramapril antihypertensive study reported from the ESCAPE trial group. In this study investigators employed both casual office blood pressure (CBP) assessment and ambulatory blood pressure monitoring (ABPM), in part to determine the variability introduced by the 'white coat effect'. While the variability was less in the ABPM group, the treatment effect (magnitude of blood pressure decline) was essentially the same for both assessment methods (Gimpel et al 2009).

A conclusion of significant antihypertensive activity in Study 328 is further supported by the composite dose response analysis with the study in the older children in Study 261A. This pre-specified (composite) analysis took into account the FDA written request to conduct a study across the entire paediatric age range. The division of the program into 2 studies was to accommodate practical considerations, eg, the time required for development of the age-appropriate suspension formulation. While the possibility of a 'by-study' interaction was acknowledged given differences in the epidemiology of hypertension in the younger vs older children, such an interaction was not apparent. Hence, the composite analysis is interpretable and confirms a statistically significant candesartan antihypertensive dose response in children 1 to 17 years of age (P <0.0065 for SBP).

***Statistical assessor's comment**:*
The explanation that a placebo-controlled study would be difficult to conduct is accepted. However, as discussed by the MAH in the response to Point 7, it is normal practice to present the results in the SmPC in terms of improvement compared to placebo and for the lower age group this is not possible. Although it is agreed that it is possible to identify that there is an effect in young children it is therefore very difficult to quantify this. However it is not accepted that a 'composite analysis' presumably a pooled analysis - is acceptable as the two studies are very different.

Issue partially resolved.

MAH Second Response: As an indication is not recommended in the younger children (1 to <6 years of age) and the MAH accepts this, no further response is considered warranted.

Assessor's comments: The question of lack of placebo arm in the younger children (1-6 years) remains an important short coming of this study. However since the applicant has agreed to the age restriction and no longer seeks indication in the younger age group (1-6 years), this question is no longer an issue.

Issue resolved.

<u>Efficacy, PK & Safety Points</u>
Clinical study 261A

11- The reported maximum response in reduction of both SiSBP (11.7 mmHg) and SiDBP (7.98 mmHg) was detected at the medium dose 8/16 mg, and the effect seemed to plateau after that point. The applicant should comment on this point.

MAH First Response: As noted, the reduction in blood pressure in Study 261A was not strictly monotonic across doses levels. It should be noted that the study was not powered to discriminate between doses. Perhaps the dose range was not sufficiently broad. The challenge of studying a wide range of doses in paediatric studies given the limitations imposed by formulations, attainable doses and study sizes has been recognized. In fact, the inability to include a sufficient number of doses has been offered as an explanation for the 'failure' of many paediatric studies (Benjamin et al 2008). As the absolute difference in blood pressure lowering between the mid and high dose is <1 mmHg for SBP, little practical consequence would be

expected, particularly given the expectation that treating physicians will adjust doses based on blood pressure response.
As noted in the response to MHRA comment 8 and shown in Table 65, once race is included in the analysis model, the decline in SBP becomes monotonic with increasing dose.

Table 65- Pair-wise comparisons of each candesartan dose group and all doses pooled vs placebo for change in SiSBP. Covariates include weight group and race (Black vs. Non Black): Study 261A

Group	Estimate	Std Error	Lower 95% CI	Upper 95% CI	Pr > |t|
2/4 vs Placebo	-4.7982	1.9055	-8.5524	-1.0440	0.0125
8/16 vs Placebo	-6.9800	1.9095	-10.7421	-3.2179	0.0003
16/32 vs Placebo	-7.5727	1.9100	-11.3357	-3.8097	<0.0001
All doses vs placebo	-6.4503	1.6792	-9.7586	-3.1420	0.0002

Assessor's comment: The question does not relate to discrimination between doses or insufficient dose range. The question is to address the proposed dosing regimen and considering 8/16 mg as the maximum dose in this population. In agreement with the applicant's statement that *"as the absolute difference in blood pressure lowering between the mid and high dose is <1 mmHg for SBP, little practical consequence would be expected, …"* and the fact that the dose response curve plateaus at 8/16 mg, we recommend maximum dose of 8 mg for patients weighing < 50 kg and 16 mg for children weighing ≥ 50 kg 16 mg in the 6-17 years old group.

Issue partially resolved.

Assessor's comment: The MAH accepts the maximum dosing in children ages 6 to <18 year of age weighing less than 50 kg. In children over 50 kg of weight the applicant points out to the recognized and well documented current epidemy of childhood obesity in most industrialized countries and the need to achieve a clinically meaningful blood pressure reduction in heavier adolescents. In the pivotal efficacy study presented here, the 68 children/adolescents in the 16/32 mg dose, had a mean body weight of 85 ±30 kg & BMI of 32 ± 9 kg/m2. Although the majority of children in this age group have adult weight or are obese, the 32 mg dose failed to reduce blood pressure any further than 16 mg.

Therefore based on the ***evidence*** provided, the maximum dose recommendation in section 4.2 of the SmPC in children over 50 kg should remain 16 mg.

Issue resolved.

12- The applicant is requested to fully reformat the adverse event section of the safety results and provide a comprehensive table containing all AEs including other significant

adverse events, haematology, clinical chemistry, renal/hepatic function, cardiac/vascular function etc.

MAH First Response (summary): A new table addressing the current request to show the AEs per dose of candesartan and placebo is included in this response. For presentation of total numbers of AEs in the candesartan group please refer to Table A10 of the previous response.

The new table shows AEs of the pooled 4 paediatric studies based on the candesartan dose per kg bodyweight. The pooling of data by dose was done in the following way in accordance with the individual study design:

For studies 261A and 328 part A, individual doses were chosen as the randomized dose per kg bodyweight. For studies 261B and 328 part B, and D2451C00006 individual doses were chosen as the maximum dose per kg bodyweight.

Each patient was counted only once in the denominator (N) of each treatment group. However, patients with changes in dose level between studies and parts of the same study may occur in more than one treatment/dose group. In other words, a patient who changed dose during the study may be counted in more than one treatment/dose group.

Assessor's response: The applicant has presented an inclusive pooled table of AEs in the 4 studies. The table is large and only extracts of it will be discussed below.

In children 1-17 years old, during all 4 clinical studies 78% of candesartan group experienced one or more AE compared with 63% in the placebo group.

There were higher number of AEs including upper respiratory infection (n=84), nasopharyngitis (n=33), cough (n=78), oropharyngeal pain, headache (n=89), dizziness (n=38), pyrexia (n=71), rash (n=10) but they are all common childhood occurrences and are labelled in the SmPC. However all these AEs occur more frequently in children compared with adult, which must be captured in the section 4.8 on the SmPC (see response to question 23).

There were 10 incidences of sinus arrhythmia, which is not documented in the SmPC for adults. While Sinus arrhythmia in childhood is considered common and temporary, in children with hypertension, it may be indicative of further cardiac complications and should be added to section 4.8 under the paediatric heading.

There were 10 incidences of ligament sprain and 3 joint injuries, 2 cases of joint effusion, 2 cases of joint swelling, one case of ligament rapture and one case of tendonitis that may point to an idiopathic effect of candesartan on connective tissue in children (see response to question 16).

The majority of haematology, serum chemistry, and urinalysis findings are recognized and documented Laboratory adverse events related to candesartan in adults.

Issue partially resolved.

MAH Second Response: The MAH acknowledge the assessor's comment above regarding the AEs occurring more frequently in children. A separate paragraph on the paediatric population is

added in section 4.8 of the SmPC, including observations on sinus arrhythmia. However, the MAH cannot find any evidence that this recognised physiologic phenomenon indicates heart disease.

Assessor's comments: The applicant response is acceptable.

Issue resolved.

Clinical study 261B

13- The applicant should clarify: whether treatment with the candesartan in the open label phase started immediately, or with a time lapse from the end of the 4 weeks double blind phase.

MAH Response: In Study 261A, consenting patients graduated directly to Study 261B; there was no protocol directive for a washout period. Study 261B did allow for the direct enrolment of a limited number of patients (n=21) that had not participated in Study 261A. Accordingly, blood pressure results for Study 261B were provided for three individual cohorts: patients who had received candesartan during Study 261A, those who received placebo in Study 261A and those who entered directly into Study 261B.

Assessor's comment: The clarification is acceptable.

Issue resolved.

14- For the single dose PK study, the applicant must justify, whether a wash out period of 2 days is adequate to fully eliminate all residual candesartan.

MAH Response: A minimum washout period was judged necessary to minimize the interruption of the active treatment of the children's hypertension. A washout of 2 days (48 hours) represents approximately 5 candesartan half lives. Candesartan level in the PK study at time 0 (pre-dosing) was 4.5 nM/L (range LOQ-20.3 nM/L) (<LOQ in 9 of the 22 subjects) and this compared to a mean Cmax value of 356 nM/L (range 155-683 nM/L) and a mean 24 hr value of 36.2 nM/L (range 9.0-123 nM/L) indicating no important residual candesartan carry-over. Accordingly, the PK study fairly represents single dose PK parameters.

Assessor's comment: The explanation provided is acceptable.

Issue resolved.

15- If clearance data has been collected during single dose PK study, it should be provided to clarify the possibility of a relation between clearance and weight/age in this population.

MAH Response: Clearance data were not collected in this single dose pharmacokinetic study.

Assessor's comment: Without clearance data it is not possible to know whether the kinetics of

candesartan are weight/ age dependent or not.

Issue resolved, although clearance data would have been helpful.

16- The applicant should comment on the possibility of joint sprain reported in 9 patients, being a signal for an idiosyncratic adverse event in children.

MAH First Response: A review of the 9 subjects with reported joint sprain(s) revealed that the reported affected joint varied in location between the patients. The reported adverse events were the following: 3 left ankle sprains, 4 right ankle sprains, 1 left knee sprain, 1 left third finger sprain, 1 right wrist sprain, and 1 left foot sprain which suggests inconsistent mechanisms of injury. Data regarding blood pressure values for these subjects did not indicate instances of hypotension, and therefore injury due to hypotensive episodes can likely be ruled out. Detailed narratives surrounding the event in each subject were not reported, though in one case injury was reported to occur while playing basketball. According to Soprano 2005, approximately 7% of organized sports participants age 5 to 24 in the US visited the emergency department annually. The most common types of injuries were reported as sprains, contusions, and fractures, with each accounting for 20% to 30% of the injuries. These findings are consistent with the 4% of subjects in Study 261B who reported joint sprain.
Furthermore, the mean BMI in this patient group was 29.6 kg/m² with most of the subjects at the ≥95 percentile, meeting criteria for an overweight or obese population. A case controlled study conducted by Zonfrillo et al 2008 demonstrated that such a population may be at increased risk of ankle injury, which may have been a contributing factor to the sprains seen in the study group. Therefore, while causality is difficult to assess, association with candesartan cilexetil use seems remote and is more in line with injuries commonly seen in this particular population.

Assessor's comment: The applicant presented a review of the 9 subjects with reported joint sprain(s), clarifying that the affected joint varied in location between the patients with inconsistent mechanisms of injury. Furthermore blood pressure values for these subjects did not indicate instances of hypotension, and therefore injury due to hypotensive episodes can be ruled out.

From the pooled table of all AEs in response to questions 12 &17, 3 further cases of joint injury, 2 cases of joint effusion, 2 cases of joint swelling, one case of ligament rapture and one case of tendonitis have also emerged in children treated with candesartan. Although it may very well be due to higher play/sport activity level of children, it is plausible that candesartan may have an idiopathic effect on connective tissue during growth but not in adulthood.

Therefore events of joint sprain/injury, and 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.

MAH Second Response: The MAH acknowledges that joint sprain/injury, were reported in numbers as concluded by the Assessor within the Paediatric population 1-18 years of age. All AEs were reported in the population of 6 years and above. Although the information of the cases is limited, there is no indication of a relationship between the events and candesartan treatment. In agreement with the Assessor, the higher incidence of joint sprain/injury found in children compared to adults might very well be due to a higher activity level in children which is also

supported in the literature. Eg, ankle sprains, reported by 9 of the 12 candesartan patients reporting joint sprain/injury, have an approximately three-fold higher incidence in adolescents than the general population (Waterman et al 2010). An age of 10 to 19 years old is associated with higher rates of ankle sprain

In summary, the 12 cases reported lack a consistent pattern of reported AE location. No indication of a relationship between the events and candesartan treatment has been revealed and a plausible mechanism between candesartan and the effect on joints is unknown. In contrary, a higher incidence of joint sprain/injuries might be expected in this age group compared to adults.

For the reasons mentioned above, the MAH respectfully disagrees with the Assessor that joint sprain/injury is warranted as a potential important risk within the EU-RMP. Instead, the MAH suggests a periodic review of the preferred terms “Ligament Sprain” and “Sprain Injury” (MedDRA version 15.1) to be reported in the next scheduled PSUR, due for submission in accordance with the published EU Reference Dates and frequencies for PBRERs.

Assessor’s comment: The applicant points out that joint sprains/injuries, have an approximately three-fold higher incidence in adolescents than the general population (Waterman et al 2010). Furthermore no indication of a relationship between the events and candesartan treatment has been revealed and a plausible mechanism between candesartan and the effect on joints is not known. It is concluded that it should not be included in the RMP, but only reported in the next scheduled PSUR.

However in the Rapporteur’s opinion, as already described before, the ***lack of*** a plausible mechanism between candesartan and the effect on joints, consistent pattern of joint/ligament injury location, or drug induced hypotension, points to a possible idiopathic paediatric signal. Furthermore PSURs are not adequate tools for flagging and following up signals in a very small population such as hypertensive children. Therefore the Rapporteur’s position on the inclusion of events of joint (sprain/injury, and related preferred terms and/or SOCs), with the view of potential idiopathic paediatric signal in the RMP, remains unchanged.

Issue resolved.

17- The applicant is requested to fully reformat the adverse event section of the safety results and provide a comprehensive table containing all adverse events including other significant adverse events, haematology, clinical chemistry, renal/hepatic function, cardiac/vascular function etc.

See the response and the assessor’s comment to question 12.

Clinical Study D2451C00006

18- The applicant should comment on the reason for most patients undergoing a 10 to more that 30 days wash out period.

MAH Response: The study D2451C00006 protocol did not mandate a ‘washout’ following Study 328. As participation in the study was elective for both patients and investigators, this translated

into a ‘decision-making’ delay to entry for some patients. In addition, some patients had completed Study 328 before study D2451C00006 could be initiated at all sites. The study did allow patients to forgo repeat laboratory testing if they enrolled within 30 days following the Study 328 final visit. The responsibility for managing the patient’s blood pressure upon concluding participation in any of the paediatric studies was the investigators’ and this provision would have applied to any ‘lapse’ between participation in Study 328 and D2451C00006.

Assessor’s comment: The explanation provided is acceptable.

Issue resolved.

19- For the single dose PK study, the applicant must clarify, whether a wash out period of 2 days is adequate to fully eliminate all residual candesartan.

MAH Response: A minimum washout period was judged necessary to minimize the interruption of the active treatment of the children’s hypertension. A washout of 2 days (48 hours) represents approximately 5 candesartan half lives. Candesartan level in the PK study at time 0 (pre-dosing) was 1.3nM/L (range LOQ-5.9 nM/L) (<LOQ in 7 of the 10 subjects) and this compared to a mean Cmax value of 252 nM/L (range 193-394 nM/L) and a mean 24 hr value of 11.7 nM/L (range 4.6-28.6 nM/L) indicating no important residual candesartan carry over. Accordingly, the PK study fairly represents single dose PK parameters.

Assessor’s comment: Similar to the response given to question 14 on the study 261B, the explanation provided is acceptable.

Issue resolved.

20- If clearance data has been collected during single dose PK study, it should be provided to clarify the possibility of a relation between clearance and weight/age in this population.

MAH Response: Clearance data were not collected in this single dose pharmacokinetic study.

Assessor’s comment: Similar to the response given to question 15 on the study 261B, without clearance data it is not possible to know whether the kinetics of candesartan are weight/ age dependent or not.

Issue resolved, although clearance data would have been helpful.

21- The applicant must clarify whether the lack of reduction in LV mass is due to candesartan being ineffective and whether the 12 children with increased LV mass are the same as no responders.

MAH Response: The ECHO-cardiographic assessments were added to Study D2451C00006, after study initiation, at the request of the PDCO to address the question as to whether candesartan could impair cardiac development. The left ventricular mass index (LVMI) was selected as the measure of effect. As approximately equal numbers of patients had an increase

(n=12) as had a decrease (n=17) in standard deviation scores relative to a normal population, the findings were interpreted as showing no directional trend in cardiac mass. In addition, for those patients with more than one ECHO, there was no directional change in LVMI. Only 4 patients had a LVMI exceeding 51 g/m*2.7, a published criterion for left ventricular hypertrophy on at least one echocardiogram. In one of these patients LVMI appeared to decrease and in the other 3 patients LVMI appeared to increase. In an attempt to illustrate any relationship between hypertension control and left ventricular mass we have replicated table 26 from the CSR but with the addition of the fraction of visits at which the patient's blood pressure was controlled. (<=95th percentile for both SBP and DBP).

By inspection, the data in the reformatted table do not imply a consistent relationship between blood pressure control and LVMI. Furthermore, for those 12 patients whose LVMI increased, their absolute scores were not notably increased.

Assessor's comment: In an attempt to illustrate a potential relationship between hypertension control and left ventricular mass the applicant has replicated the table from the CSR but with the addition of the fraction of visits at which the patient's blood pressure was controlled. The data do not imply a consistent relationship between blood pressure control and LVMI.

Issue Resolved.

General Points

22- In order to compare adult and children exposure and to substantiate the applicant's claim that the candesartan pharmacokinetic profile in children is comparable to that previously reported for adults, the applicant should provide a summary data of all available PK parameters for adult and each paediatric age group.

MAH Response: The requested summary data are presented in Table 66.
All studies in healthy subjects and those in hepatic impairment were single dose studies whereas the studies in renal impairment were multiple dose studies.
Although there is some variation in pharmacokinetic parameters in children compared to adults (Table 65) the magnitude of the differences are less than seen within sub-populations of adults for which the SmPC does not recommend any dosage adjustment. For example, Cmax and AUC of candesartan are approximately 50% to 80% higher in subjects >65 years compared to younger subjects but no dosage adjustment is deemed necessary. Similarly, Cmax and AUC are approximately 50% higher in patients with severe renal impairment compared to healthy subjects and again no dosage adjustment is necessary. The MAH therefore considers that adjustments for age based on PK considerations are not necessary; the age specific dosing recommendations as put forward in the labelling and which are supported by the clinical studies are appropriate; and any dose adjustments need only be based on pharmacodynamics (blood pressures) response.

Table 66- Pharmacokinetics of candesartan in children compared to adult healthy volunteers by age range

Population	Age (yrs)	Dose (mg)	N	C_{max} (µg/L)	T_{max} (h)	AUC (µg.h/L)	$T_{½}$ (h)
Hypertensive Children	1 to <6	0.2/Kg	10	61	3.2	427	5.7[a]
	6 to <12	16	12	80	4.3	655	6.7
	12 to <17	16	10	95	4.3	734	5.7
Healthy volunteers	19 to 40	4[1]	18	28	3.8	250	9.2
	65 to 78	4[1]	14	42	4.3	NR	9.2
	19 to 40	8[1]	17	55	4.3	550	9.1
	19 to 40	8[2]	18	87	3.3	642	9.1
	65 to 78	8[1]	14	84	4.1	NR	NR
	65 to 78	8[2]	12	81	5.0	NR	NR
	19 to 40	12[1]	12	64	3.8	850	12.1
	65 to 78	12[1]	12	110	4.8	NR	11.7
	19 to 40	16[1]	12	108	3.6	1100	9.1
	65 to 78	16[1]	12	184	4.8	NR	12.3
	18 to 59	32[3]	53	263	4.0	3253	10.2
Renal impairment							
Normal to mild	26 to 49	8[4]	8	55	3.8	485	6.7
Moderate	44 to 62	8[4]	7	96	3.8	1026	8.0
Severe	48 to 60	8[4]	8	79	4.3	1359	12.0
On dialysis	38 to 75	8[5]	8	87	3.5	1025	7.3
	44 to 78	16[6]	9	244	3.3	2767	NR
Hepatic impairment							
NR	NR	4[7]	8	58	4.1	657	9.1
Mild to Moderate	32 to 71	12[8]	12	109	2.7	1107	12.0
Mild to Moderate	48 to 67	16[9]	12	156	4.4	2021	9.6

Assessor's comment: Tmax values of 3-4 hrs seem to be similar across all ages and different doses. All the other parameters presented are dose dependent and are only comparable at 16 mg which was tested in children 6-17 years old and adults 19-40 years old. At the 16 mg dose, the half life of candesartan is shorter in children (5.7-6.7hrs) compared with 9.1 hrs in adults, the Cmax (80-108 µg/L) and the AUC (550 -1100 µg.h/L) values are similar across all ages. On the whole the applicant's claim that the candesartan pharmacokinetic profile in children is comparable to that previously reported for adults is acceptable.

As there were no clearance measurements in either paediatric age groups it is not possible to know if the kinetics of candesartan are weight/ age dependent or not. However in the pivotal efficacy study there is exposure –response relationship starting from 4/8 mg to 8/16 mg dose and the effect seemed to plateau after that point. Therefore in the 6-17 years old age group the proposed starting dose of 4 mg is acceptable. The maintenance dose should be adjusted individually based on blood pressure control, however the maximum should be 8/16 mg rather that 16/32mg.

Issue resolved.

23- The applicant is requested to provide a summary table of frequency of adverse events in children (pooled both age groups, across 4 studies) and the available adult data.

MAH response: Table 67 presents AEs that have been reported for both paediatric and adults, with a reported frequency of >1 (>0.2%) reported AE in the paediatric population and >3 (>0.1%) reported AEs in the adult population to ensure all very common, common and uncommon frequencies were captured. The difference in cut off numbers (for adults and paediatrics) is due to the lower number of subjects in the paediatric pool.

Of note, the paediatric studies were not large enough to reach an adverse event rate of smaller frequency than 'Uncommon'. In other words, even a single adverse event, reported for only one subject, would be considered 'uncommon' rather than 'rare' or 'very rare'. This limitation must be carefully considered when comparing and interpreting the AE data presented.

The frequencies used in the table are: very common (1/10), common (1/100 to <1/10), uncommon (1/1,000 to <1/100), rare (1/10,000 to <1/1,000) and very rare (<1/10,000). Text in italics is imported from the SmPC, which is based on adult data.

Table 67- Frequencies of ADRs/AEs in paediatric pooled studies and those stated in the SmPC based on adults data

System organ class (SOC) MedDRA preferred term (PT)	Pool of paediatric studies		Frequency term SmPC
	%	Frequency term	
Infections and infestations			
Respiratory infection			*Common*
Upper respiratory tract infection*	14.8	Very common	
Respiratory tract infection*	0.5	Uncommon	
Respiratory tract infection viral*	0.5	Uncommon	
Blood and lymphatic system disorders			
Leukopenia	-		*Very rare*
Neutropenia	-		*Very rare*
Agranulocytosis	-		*Very rare*
Metabolism and nutrition disorders			
Hyperkalaemia	0.4	Uncommon	*Very rare*
Hyponatraemia	0.2	Uncommon	*Very rare*
Nervous system disorders			
Dizziness	6.7	Common	*Common*
Vertigo	-		*Common*
Headache	15.7	Very common	*Common*
Respiratory, thoracic and mediastinal disorders			
Cough	13.7	Very common	*Very rare*
Gastrointestinal disorders			
Nausea	2.1	Common	*Very rare*
Hepatobiliary disorders			
Increased liver enzymes	-		*Very rare*
Abnormal hepatic function	-		*Very rare*
Hepatitis	-		*Very rare*
Liver function test abnormal*	0.2	Uncommon	*Very rare*
Skin and subcutaneous tissue disorders			
Angioedema	-		*Very rare*
Rash	1.8	Common	*Very rare*
Urticaria	0.2	Uncommon	*Very rare*
Pruritus	0.4	Uncommon	*Very rare*
Musculoskeletal and connective tissue disorders			
Back pain	1.5	Common	*Very rare*
Arthralgia	0.7	Uncommon	*Very rare*
Myalgia	0.7	Uncommon	*Very rare*
Renal and urinary disorders			
Renal impairment, including renal failure in susceptible patients	-		*Very rare*
Renal failure*	0.2	Uncommon	
Renal failure chronic*	0.2	Uncommon	

Assessor's comment: The MAH has provided a summary table of safety data, pooled from all children and adolescents exposed to candesartan during the 4 clinical trials and a total of adult patients in all studies during the clinical development program.

In all different system organ classes and MedDRA preferred terms presented, the frequency of adverse events in children is within the common/uncommon range, whilst they are considred "very rare" for adults as captured in the current SmPC.

Many of these adverse events are also childhood diseases or occurrences and are expected to be documented in children more often than in adults. However, the higher frequencies of certain AEs in children are of particular concern, either because of the class effects of ARBS (hyperkalemia, hyponatraemia, rash, liver function abnormal) and/or impact on learning (headache, cough) and the prescriber should be aware of it. Therefore hyperkalemia, hyponatraemia, headache, cough, rash and liver function abnormal must be captured individually in the section 4.8 of the SmPC, under paediatric heading.

In the assessor's opinion to avoid clustering section 4.8 of the SmPC with too much detailed information it is best to summarize all the other differences of frequencies between all system organ classes as a general point between adults and children, in one paragraph.

The applicant is requested to propose new SmPC wording under paediatric population heading of section 4.8, in accordance with the EMA SmPC guidelines of September 2009.

Issue partially resolved.

MAH Second Response: The MAH acknowledge that a separate paragraph on the paediatric population is added in section 4.8 of the SmPC. Please refer to updated QRD, SmPC section 4.8. All adverse events, except hyperkalaemia, hyponatraemia and abnormal hepatic function, mentioned in the question above are addressed in question 12. Please refer to Question 12.

The terms hyperkalaemia, hyponatraemia and abnormal hepatic function are already listed within section 4.8, why the MAH considers these are sufficiently presented for prescribers and do not need to be repeated under the paediatric paragraph within section 4.8.

Assessor's comment: Hyperkalemia, hyponatraemia, liver function abnormal are labelled in the SmPC, however it is the higher **frequency** of them in children that must be captured under paediatric population heading in accordance with the EMA SmPC guidelines of September 2009. See the Rapporteur's suggested text of the SmPC.

24- In the view of a probable paediatric indication, the applicant is requested to submit a consolidated version of Risk Management Plan (RMP) for candesartan including 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 ARBs, important risks (hyperkalemia, hypotension) and important potential risks (renal impairment, haemoglobin/ hematocrit decreased, rhabdomyolysis, thrombocytopenia, pancreatitis, vasculitis and unlisted hepatobiliary disorders) have been identified and should be monitored for candesartan in the paediatric hypertensive population aged 1 to <17 years. The RMP update should also include toxicological information on the effects of candesartan on heart weight, body weights and the renal effects for future monitoring.

MAH Response: To date, no EU Patient Risk Management Plan (EU RMP) for candesartan cilexetil has been submitted or approved. However, the MAH confirms that an EU RMP will be prepared if warranted, depending on the outcome of the ongoing consultations with the MHRA and the EMA Pharmacovigilance Working Party regarding the actions to be taken to minimise the inappropriate use of Angiotensin II receptor blockers during pregnancy, as well as the outcome from the ongoing candesartan cilexetil Paediatric Worksharing procedure (UK/H/023/PdWS/002). As both of these ongoing assessments are expected to be completed during the first half of 2012, the MAH suggests that a candesartan cilexetil EU RMP, if warranted (ie, if a paediatric indication is granted), should be submitted as a separate Type II variation after completion of these procedures.

The points included in the question above concerning specific areas relating to the paediatric population that should be specifically discussed and followed as well as important risks and potential risks that are suggested for monitoring in the paediatric population will be considered in the preparation of the RMP, if required.

Assessor's comment: The response is satisfactory.

Issue resolved.

Additional questions by other MSs

25- In order to support recommendations of use in paediatric population, the applicant should attempt to derive specific PK information in different sub-groups, specially, in children under 2 years and children aged 2 to 4 years. Therefore, the available data should be re-analysed accordingly and the outcome of such analysis should be submitted and commented.

MAH Response: There were only 10 children in this PK study and only 1 less than 2 years of age. Thus, the MHA considers that analyses based on sub-groups by age will be challenging to interpret.

Assessor's comment: The applicant points out that there was only 1 child under 2 years of age and can not run an analysis on the age subgroup.

Issue resolved, although additional data would have been helpful.

26- The applicant should discuss the relevance of candesartan plasma trough levels (collected in the clinical studies) for the estimation of the systemic exposure as

candesartan exhibits a relatively short half-life with minimal accumulation when administered once daily.

MAH Response: Plasma candesartan concentrations at trough (24 hrs post dosing) after multiple dosing once daily in clinical studies are dose related (Table 67 and Table 68). Dose in turn is related to the antihypertensive effect determined at 'trough' and the antihypertensive effect with once daily dosing is attained without an undue peak: trough variability in blood pressure Table 70.
Of the 199 subjects with plasma samples in Study 261A, 26 had plasma candesartan concentrations that were below the limits of quantitation (LOQ), were not trough, or were not recorded, Table 67. Therefore, plasma concentration data from a total of 173 patients were included in the analysis. Although there was substantial variability in the observed candesartan plasma concentrations, mean trough values increased with increases in dose, Table 68. The dose related plasma candesartan concentrations were apparent within each weight stratum. Trough values observed at doses of 8 mg to 32 mg were also similar to those obtained previously in adults.

Table 68 Summary of trough candesartan concentrations, all subjects aged 6 to <17 years included at Week 4 (Study 261A)

		<50 kg weight group Candesartan			≥50 kg weight group Candesartan		
		2 mg N=8	8 mg N=9	16 mg N=8	4 mg N=59	16 mg N=57	32 mg N=58
Candesartan concentrations included in analysis		8	7	8	51	49	50
Candesartan concentrations not recorded, not trough, or <LOQ		0	2	0	8	8	8
Candesartan concentration, nmol/L	Mean (SD)	8.6 (3.8)	22.8 (25.5)	59.9 (54.4)	10.6 (10.7)	41.1 (46.1)	73.4 (62.8)
	Range	4.5 to 15.1	0 to 68.7	12.4 to 180.0	0 to 59.0	0 to 246.0	0 to 306.0
	Median	7.2	11.6	39.2	7.2	29.5	62.5

LOQ Limits of quantitation. SD Standard deviation.

Of the 93 subjects in the ITT population in Study 328, 5 subjects in the 10 to <25 kg weight group and 2 subjects in the 25 to ≤40 kg weight group had no samples collected.

Table 69 describes the candesartan concentrations for 86 subjects who had detectable candesartan plasma concentrations. The mean trough candesartan concentrations increased in a dose related manner.
By weight group (10 to <25 kg and 25 to 40 mg/kg), trough concentrations also increased in a dose related manner.

Table 69- Random trough candesartan concentration (all subjects, Study 328)

		Candesartan concentration, nMol/L		
Daily candesartan dose	N	Mean (SD)	Median	Min, max
0.05 mg/kg	27	7.2 (8.0)	5.2	0, 40.3
0.2 mg/kg	29	23.3 (18.1)	21.5	0, 79.6
0.4 mg/kg	30	38.0 (38.7)	24.6	0, 144.0
Total	86	23.3 (28.2)	14.2	0, 144.0

Note: Concentrations reported as <2 or < 4 nmol/L are included in the summary statistics as 0 nmol/L.

Table 70 shows trough candesartan concentration by final dose from Study 261B and suggests a dose/concentration relationship.

Table 70- Trough candesartan concentration (nMol/L) by final dose, (all subjects, Study 261B)

Final daily candesartan dose in mg	N	Mean (SD)	Min, max
4 mg	27	29 (38)	0, 143
8 mg	64	36 (73)	0, 424
16 mg	49	36 (43)	0, 245
24 mg	3	57 (61)	7, 124
32 mg	48	61 (74)	0, 379
Other dose	12	20 (30)	0, 108

Note: Data from 4 subjects were inadvertently not included in this table because their samples were collected early due to premature discontinuation.

In the candesartan paediatric hypertension studies, the principal determination for blood pressure change was at 24-hours postdose ('trough'), to provide a conservative estimate of the antihypertensive effect. Blood pressures were also taken 6 hours post dose ('peak') in Study 261B, Table 71.

Table 71- Mean blood pressure at peak and trough (Study 261B)

		Systolic blood pressure		Diastolic blood pressure	
Time	N	Mean (SD)	Min, max	Mean (SD)	Min, max
Peak[a]	192	117.7 (10.2)	82.7, 160.7	69.3 (9.0)	32.0, 86.7
Trough[b]	192	122.5 (10.8)	79.3, 154.7	73.4 (9.2)	40.7, 97.3

[a] 6 hours (± 2 hours) post dosing.
[b] 24 hours (± 4 hours) post dosing.

A sustained antihypertensive effect with once daily dosing with candesartan is consistent with its tight binding to and slow dissociation from the AT1 receptor (Morsing 1999). As a consequence, pharmacodynamic effects (blood pressure lowering) persist in the face of declining plasma levels (Lacourciere and Asmer 1999).

Assessor's comment: The applicant has provided blood pressure measurements for both Peak at 6 hrs post dose and Through at 24 hrs post dose. Although there is a slight rebound in blood pressure, the antihypertensive effect of candesartan on both Systolic and Diastolic blood pressure is maintained 24 hrs post dose. Therefore the applicant's argument that the pharmacodynamics effects (blood pressure lowering) of candesartan persist in the face of declining plasma levels, is acceptable.

Issue resolved

27- Given the limited/absent myocardial cell proliferation observed in the juvenile toxicity studies, long-term studies with very extensive timelines focussing on myocardial development are needed.

MAH First Response:
Any interpretation of the animal findings in the neonatal and juvenile toxicity studies with candesartan cilexetil must take into account the known pharmacological effects of compounds of this class on the renal system and the sequelae for other systems including the heart. As already noted, exaggerated pharmacological effects consisting of haematological changes, renal effects and reductions in heart weight, the latter unaccompanied by histopathologic changes, were observed following administration of high doses of candesartan cilexetil in repeat dose studies in

adult rodents, dogs and monkeys. The same findings have been observed in animal studies with other ARBs and ACE inhibitors and are acknowledged class effects (Bagdon et al 1985, Imai et al 1981, Cozaar SmPC, Micardis SmPC, Olmetec SmPC).

The rat has been confirmed as a suitable species for the safety evaluation of candesartan cilexitil as the organ effects, based on exaggerated pharmacology, observed in other ARBs and ACE inhibitors have been well characterised. Effects on heart weight have been considered secondary to the known effects of ACE inhibitors on sympathetic nervous system activity and peripheral resistance. Effects on myocyte proliferation were observed in studies in rat neonates at an age (<14 days) when this is the predominant mechanism for increase in heart mass, and are considered not to be representative of humans over the age of 4 months where any increase is due to hypertrophy of cardiac myocytes (Linzbach 1950, Linzbach 1952, and Hort 1953, all cited in Hew and Keller 2003). Moreover the exposure multiples in the neonatal studies in which effects occurred were >100 to >500-fold those observed in children aged 1 to <6 years.

It difficult to substantiate the supposition that agents that inhibit the rennin-angiotensin-aldosterone system (RAAS) may have adverse cardiac effects in the growing child. Rather, these agents appear to have favourable effects when administered in the face of pathologic conditions such as hypertension and heart failure.

The data support the premise that reduction in body weight and in heart weight is a class effect observed for all ACE inhibitors in adult rats, which is also expressed in neonatal and juvenile animals and does not, therefore, represent a unique toxicity.

The effects observed in neonates and juveniles at high multiples of the anticipated human dose (see response to Comment 5) do not indicate any novel toxicities or increased sensitivity. The use of non-rodents for juvenile toxicity studies is limited and there is a paucity of background data on relative heart development in minipigs and dogs (Carleer and Karres 2011).

In view of the large safety margins the applicant considers, therefore that further juvenile studies in a non-rodent species are unlikely to provide further safety information which would substantially contribute to the risk assessment of candesartan cilexitil for the intended patient population of children aged 1 year and above.

Toxicological assessor's comments:

The applicant has provided a comprehensive discussion of the published literature which (a) focussed on interspecies differences in PK parameters and (b) included a critique of the published literature (e.g. highlighting apparent deficiencies in the conduct and/or reporting of some of the published studies).

The effects on bodyweight and heart weights appear to be a pharmacodynamic effect. It is not an age-related effect as suppression of cardiac hypertrophy has also been observed in adult studies however the potential consequences (i.e. effects on somatic heart growth) is only relevant to the paediatric population.

It is fully accepted that regression of hypertrophy induced by hypertension, heart failure or other pathological conditions, where present, would be a desirable effect. However the concern regarding the suppression of heart growth is focussed on the section of the paediatric population that do not have a pathologically induced cardiac hypertrophy and/or do not have a significant risk of developing this during phases of somatic growth. A review by Hew and Keller showed that

in humans the greatest increase in absolute heart weight occurs during the first postnatal year. The heart doubles its weight by 6 months of age and triples by 1 year (Smith, 1928; Rakusan, 1980). After the early postnatal phase the increase in heart weight is proportional to body weight resulting in a constant relative cardiac weight throughout the first half of life. During the early postnatal period increase in cardiac mass is by cell proliferation. However from the age of 4 months onwards the increase in heart mass is by hypertrophy of the cardiac myocytes which is relevant to the intended paediatric population. As candesartan is capable of suppressing cardiac hypertrophy it is not possible to rule out a potential effect on heart growth if sufficient and continuous exposures are achieved.

Human Heart Weight and Heart Weight as Percent of Body Weight[a]

	Mean heart weight (g)		% Body weight	
Age (years)	Male	Female	Male	Female
Birth to 1 year	45	35	0.62	0.55
2–4	69	55.5	0.43	0.37
5–7	87.7	94	0.35	0.37
8–12	149	120	0.44	0.42
13–17	225	180	0.43	0.38
18–21	308	245	0.42	0.42

[a]Smith, 1928.

With regards to the reduction in heart weights observed in the neonatal and juvenile studies, it is likely that the effects on heart weight were due to the very high non-clinically relevant exposures recorded at the earlier stages of these studies as compared to the levels recorded at the end. The decline in plasma concentrations observed between the beginning and end of these studies were a reflection of the metabolic processes maturing during the course of the treatment period. The lowest margins of exposure (based on AUC values) measured for 0 to 6, 6 to 12 and 12 to 17 year olds, 11.60 fold, 7.97 fold and 6.87 respectively, were based on values recorded at the end of the juvenile rat 5 week toxicity study. This was approximately 7 fold lower than the values recorded at the beginning of the study.

Nevertheless a risk to patients cannot be ruled out as a safety margin cannot be calculated due to the failure to identify a no observed effect level (NOEL). It is thus necessary to communicate these findings to patients and prescribers in the SPC. As the relevance and risk is still unclear the benefit/risk is not considered altered by these findings and that should also be communicated.

With regards to the need to conduct a study to assess the long term effects of sustained suppression of cardiac hypertrophy it is agreed that the presence of a margin of exposure of ≥7 fold, and the likelihood that the effects on heart weight were due to the higher exposures attained at the beginning of the juvenile studies, negates the need for such an extensive study. The applicant has proposed to add information to the SPC which is considered acceptable. The applicant will however need to add these findings to the risk management plan and investigate any signal that arises in the future.

Issue partially resolved

MAH Second Response: The MAH accepts the Assessor's comment for additional wording in the non-clinical section of the SmPC. Please refer to separately attached QRD, SmPC section 5.3.

Furthermore, the MAH accepts to include information regarding non-clinical findings into the European Risk Management Plan, that will be prepared and submitted after submission of this response document.

Assessor's comment: The response is satisfactory.

Issue resolved.

VII. FINAL RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

Overall conclusion

In the submitted studies, efficacy was demonstrated in lowering both systolic and diastolic blood pressure in children 6 - <17 years of age, but it has not been robustly documented in children 1 to <6 years, due to lack of placebo comparison and insufficient PK data. Other major issues concerning, bioequivalence, PK and safety have been clarified. The bioequivalence issue has become redundant as indication in 1 to <6 years age group was not granted and liquid formulation for children under 6 will not be required. Safety issues were also clarified and the applicant agreed to change the SmPC and update the RMP, accordingly.

Due to limited PK data in the 1<6 years old children, it is recommended that the applicant considers further follow up measures in acquiring this information.

Recommendation (Final)

Based on the review of the presented paediatric data on pharmacokinetics, safety, efficacy and toxicology of candesartan and the assessment of the response to two rounds of questions raised by the Rapporteur and other MSs, it is considered that the results of these studies support the indication for treatment of hypertension in children 6 < 17 years of age, in the section 4.1 with dose recommendation in section 4.2 at a lower maximum dose than originally proposed by the MAH. The additional information provided failed to clarify the effect of weight on exposure/response in the lower age group as no clearance data was available. Together with the lack of a placebo arm, the evidence of efficacy and the PK data in 1<6 years old are not considered robust enough to support an indication in the younger age group. However the summary of the findings should be included in sections 5.1 and 5.2 of the SmPC.

The safety profile of candesartan generally resembles that of adults, but nearly all adverse events are more frequent in children. Sinus arrhythmia in children and the higher frequency of AEs must be captured in the section 4.8 of the SmPC. The ligament / joint related AEs must be included and kept under review in the updated risk management plan. Similarly the non-clinical findings of reduction in body and heart weight from juvenile animal studies must be captured in section 5.3 of SmPC and kept under review in the updated risk management plan.

The MAH is requested to submit appropriate variation within 60 days of finalization of this procedure.

VIII. LIST OF MEDICINCAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

Takeda UK Ltd:

Amias	2mg	Tablets	Candesartan cilexetil
Amias	4mg	Tablets	Candesartan cilexetil
Amias	8mg	Tablets	Candesartan cilexetil
Amias	16mg	Tablets	Candesartan cilexetil
Amias	32mg	Tablets	Candesartan cilexetil

AstraZeneca:

Atacand	4mg	Tablets	Candesartan cilexetil
Atacand	8mg	Tablets	Candesartan cilexetil
Atacand	16mg	Tablets	Candesartan cilexetil
Atacand	32mg	Tablets	Candesartan cilexetil

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