CLINICAL REVIEW

Application Type	Supplemental NDA
Application Number(s)	20838
Priority or Standard	Priority
Submit Date(s)	April 23, 2009
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PDUFA Goal Date	October 23, 2009
Division / Office	DCRP/HFD 110
Reviewer Name(s)	Suchitra Balakrishnan, MD, PhD
Review Completion Date	10/1/09
Established Name	Candesartan Cilexitil
(Proposed) Trade Name	ATACAND
Therapeutic Class	Angiotensin II (AT_1subtype) receptor antagonist
Applicant	Astra Zeneca
Formulation(s)	Pediatric tablet, oral suspension
Dosing Regimen	0.05-0.4 mg/kg PO QD or 2-32 mg/kg PO QD.
Indication(s)	Treatment of hypertension
Intended Population(s)	1-17 yrs

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of candesartan for the treatment of hypertension in the pediatric population. The sponsor's proposed dosing recommendation is as outlined below and appears acceptable.

- Starting dose of 0.2 mg/kg oral suspension once daily with a dose range of 0.05-0.4mg/kg in children 1-6 yrs of age
- Children 6 < 17 yrs: Starting dose of 4-8 mg once daily, range 4-16 mg once daily if < 50 kg; starting dose of 8-16 mg, range 4-32mg if over 50 kg.

The once daily dosing *in adults* is supported by the PK-PD data including over 50% inhibition of the effect of Angiotensin II at 24 hrs (see Clinical pharmacology Section 4.4.1 and 4.4.2 and Section 6). Since it is unknown if these effects are similar in children, a twice daily dosing interval may be considered before switching to a higher once-daily dose. This is further supported by the pediatric pharmacokinetic data demonstrating an over tenfold decline in Cmax-Cmin concentrations over a 24-hr interval and the dose-related side effects of hypotension and syncope noted in the pediatric efficacy and safety studies.

1.2 Risk Benefit Assessment

Based on review of studies 328 and 261 and post-marketing data available regarding candesartan use in adult and pediatric populations, candesartan appears to have a favorable risk-benefit profile. There was a single case of toxic nephropathy in a 14 yr old black female in Study 261 which was difficult to interpret (see Section 7.3.2). The renal biopsy report was focal degenerative tubular changes, thought to be drug related. This case was confounded by a concomitant medication, tiagabine and possible other causes for the degenerative changes (hemodynamic, infectious, metabolic). However, relationship to candesartan although not likely, cannot be excluded. Excluding this event, there does not appear to be any other unexpected adverse events in children compared to adults

1.3 Recommendations for Post-market Risk Evaluation and Mitigation Strategies (REMS)

(b) (4)

These concerns are addressed in the label. I don't think a formal REMS is required.

1.4 Recommendations for Post-market Requirements and Commitments

NA

2 Introduction and Regulatory Background

2.1 Product Information

Candesartan Cilexetil (ATACAND) is an angiotensin II (AT_1 sub-type) receptor antagonist, approved for the treatment of hypertension and congestive heart failure in adults. The sponsor (Astra Zeneca) is seeking approval for the treatment of pediatric hypertension.

2.2 Tables of Currently Available Treatments for Proposed Indications

Approved or previously studied angiotensin converting enzyme inhibitors (ACEI's) and angiotensin receptor blockers (ARBs) for the treatment of pediatric hypertension include Benazapril, Captopril, Enalapril, Fosinopril, Lisinopril, Quinapril, Irbesartan and Losartan. Please refer to the NHLBI fourth report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents for additional details.

2.3 Availability of Proposed Active Ingredient in the United States

Candesartan is approved in adults for the treatment of hypertension and heart failure (NYHA class II-IV) in patients with left ventricular systolic dysfunction (ejection fraction < 40%) to reduce cardiovascular death and to reduce heart failure hospitalizations. Candesartan is also indicated as an add-on treatment for these outcomes when used with an angiotensin converting enzyme (ACE) inhibitor. Off-label use is generally consistent with indications for other ACEI or ARBs and includes cerebrovascular accident (CVA) prophylaxis, diabetic nephropathy, left ventricular hypertrophy (LVH) due to essential hypertension, proteinuria in chronic glomerulo-nephritis, migraine prophylaxis, restenosis of coronary artery prophylaxis and renal transplant recipients.

2.4 Important Safety Issues with Consideration to Related Drugs

ACEI and ARBs are not indicated for children under one year of age and in pregnancy due to the association of congenital renal/ urinary tract anomalies and oligohydramnios with antenatal use in the second and third trimesters of pregnancy. Oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation and hypoplastic lung development.

Other expected safety issues include hypotension in volume and/or salt depleted patients, oliguria and/or progressive azotemia and (rarely) acute renal failure in patients whose renal function may depend upon the activity of the renin-angiotensin aldosterone system (e.g., patients with severe heart failure, patients with unilateral or bilateral renal artery stenosis). Hyperkalemia may occur, especially when taken concomitantly with ACE inhibitors and potassium-sparing diuretics such as spironolactone.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

A Pediatric Written request (WR) was originally issued by the agency in March 15, 1999. There have been several amendments to the written request and to the protocols for Studies 261A, 261B and 328. The final version of the WR was issued on Jan 30, 2007. Pediatric Exclusivity was granted on July 22, 2009.

2.6 Other Relevant Background Information

NA

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Based on review of case report forms (CRF), datasets, protocols and study reports, the sponsor's submission appears adequate. The format of the reports meets the requirements of the WR.

3.2 Compliance with Good Clinical Practices

According to the sponsor, all studies were conducted in full compliance with Good Clinical practice. This reviewer saw no evidence to the contrary.

3.3 Financial Disclosures

The sponsor certified that they have not entered into any financial arrangement with the listed clinical investigators (for Studies 261A, 261B and 328) that could affect the outcome of the study. They also certified that each listed clinical investigator was required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in Astra Zeneca and there were no investigators who had any interests to disclose. The sponsor further certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (CMC)

CMC review by Dr. Julia Pinto and Dr. James Vidra dated 9/2/09, recommended approval of this supplement. The primary supplement has the preparation and stability data of an extemporaneous formulation of candesartan to be used in pediatric patients, 1-6 yrs of age. The Candesartan oral suspension is prepared by dispersing the Atacand® tablet (4mg, 8mg 16mg or 32mg) in an Ora-Blend Sugar Free vehicle or Ora- Sweet® Sugar Free/Oraplus blend. The appropriate number of tablets in any combination of strengths can be used to achieve a concentration of 0.1mg/ml to 2mg/ml. There were no changes to the approved drug substance used in the Candesartan tablets. All data is referenced to the original NDA.

The Ora-Blend® SF, used in the pediatric formulation, is referenced to DMF 14443. This DMF is adequate per Dr. Don Klein (CMC Review # 3, November 21, 2008). There are no additional updates to this DMF, since 2008. The drug product suspension can be stored up to 100 days at ambient temperatures and shaken well before each use to ensure adequate dispersion of the drug particles The CMC reviewer determined that there were no issues regarding batch to batch homogeneity, assay, dissolution profiles or stability up to a 100 days at ambient temperatures of the suspension. More rapid dissolution of the suspension was noted, compared to the tablet. The sponsor reports a relative bioavailability of 93% (tablet vs. suspension) with no requirement for formulation-based dosage adjustment.

4.2 Clinical Microbiology

The product quality microbiologist found no issues of concern and recommended approval.

4.3 Preclinical Pharmacology/Toxicology

No pediatric animal studies were permitted.

4.4 Clinical Pharmacology

Relevant findings from the pharmacometrics and clinical pharmacology reviews regarding efficacy and pharmacokinetics of candesartan in the pediatric trials conducted by the sponsor will be discussed in the efficacy sections (Section 6).

4.4.1 Mechanism of Action

ATACAND (candesartan cilexetil), a prodrug, is hydrolyzed to candesartan during absorption from the gastrointestinal tract. Candesartan is a selective AT_1 subtype angiotensin II receptor antagonist. Candesartan blocks the vasoconstrictor and aldosterone-secreting effects of

angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland.

4.4.2 Pharmacodynamics

The AT_1 receptor is a G-protein coupled receptor that, when activated, stimulates the phosphoinositide signaling system and ultimately results in an elevation of intracellular free calcium concentrations. It is unknown whether G-protein coupled signaling (expression, activities or regulation of G-protein signaling) varies with age.

Candesartan has demonstrated specific binding to the AT1 receptor in a monophasic and concentration- dependent manner with an inhibition constant (Ki) of 0.64 nmol/L in rabbit aorta, thereby completely blocking the binding of angiotensin II to the receptor. When compared with other angiotensin II receptor antagonists, candesartan was a more potent inhibitor of angiotensin II binding to human AT1 receptors expressed in COS-7 cells than EXP-3174 (the active metabolite of losartan), eprosartan, irbesartan and valsartan [Easthope SE and Jarvis B., Drugs 2002; 62 (8)]. The same authors report that the maximum effects of single 4 to 16mg oral doses of candesartan cilexetil were seen 6 to 9 hours after administration and the effect persisted more than 24 hours, probably as a result of the slow rate of dissociation from the receptor. They state that receptor binding studies *in vitro* indicate that candesartan can dissociate from and re-associate with the receptor and this may explain why the effects of candesartan can be observed *in vivo* after plasma concentrations have diminished. Candesartan inhibits the pressor effects of angiotensin II infusion in a dose-dependent manner in adults. After 1 week of once daily dosing with 8 mg of candesartan cilexetil, the pressor effect was inhibited by approximately 90% at peak with approximately 50% inhibition persisting for 24 hours. In children, the Cmax/Cmin concentrations over a 24-hr interval decline by over ten fold, in the PK sub-studies conducted with Studies 261 and 328 submitted by the sponsor.

4.4.3 Pharmacokinetics

In adults, candesartan cilexetil is rapidly and completely bioactivated by ester hydrolysis during absorption from the gastrointestinal tract to candesartan. It is mainly excreted unchanged in urine and feces (via bile). It undergoes minor hepatic metabolism by O-deethylation to an inactive metabolite. The elimination half-life of candesartan is approximately 9 hours. After single and repeated administration, the pharmacokinetics of candesartan is linear for oral doses up to 32 mg of candesartan cilexetil. Candesartan and its inactive metabolite do not accumulate in serum upon repeated once-daily dosing.

Following administration of candesartan cilexetil, the absolute bioavailability of candesartan was estimated to be 15%. After tablet ingestion, the peak serum concentration (Cmax) is reached after 3 to 4 hours. The volume of distribution of candesartan is 0.13 L/kg. Candesartan is highly bound to plasma proteins (>99%) and does not penetrate red blood cells.

Food with a high fat content does not affect the bioavailability of candesartan after candesartan cilexetil administration. Dose adjustment is recommended for patients with moderate hepatic impairment or volume depletion with renal impairment.

4.5 Biometrics

Dr. John Lawrence, the statistical reviewer inferred that based on the results of Study 328 in children less than 6 years old, candesartan showed a dose response on SBP and DBP among the three doses studied. However when he looked at the pair wise comparisons of the three doses, there was a significant difference between the high dose and low dose. No other paired wise comparison was significant.

With regard to the second study, 261A in children aged 6 to 17, candesartan failed to show a dose response among the three doses studied using the pre-specified primary analysis. Dr. Lawrence fitted a linear regression model similar to that used in the primary analysis without including weight but including the placebo group (treating it as a dose of 0 mg). He fit two straight line regressions (one including the placebo data and one not including placebo) and also a quadratic curve (including placebo) as a function of dose level. None of these models were appropriate if we want to include the placebo data (using the dose levels 0, 1, 4, and 8) for this study. If the question is whether there is a difference among the three doses, the sponsor's pre-specified model is adequate to answer that question and the linear regression line not including the placebo data fits the data from the 3 doses fairly well. Dr. Lawrence states that a plausible explanation for failing to show a difference between the 3 doses is that there is no difference between the doses or that the sample size was too small to detect the difference.

Reviewer's Comments: It is not unexpected for the linear regression line to be away from the placebo mean and expected that the quadratic curve would fit better. Curvilinear shape to the curve to fit the placebo dose can be expected if the doses used to generate were close to maximal drug effect.

5 Sources of Clinical Data

The major source of clinical data was the submission by the sponsor. In addition, the reviewer conducted a PubMed search of the medical literature and an MGPS Data mining analysis of the AERs database for AEs related to candesartan use in children 1-17 yrs of age.

5.1 Tables of Studies/Clinical Trials

The candesartan pediatric clinical development program consisted of the following studies

Study identifier	Study objective	Study design	Test product	Number of subjects	Diagnosis of subjects	Duration of treatment
D2451C00261 (Study 261A)	Characterize the dose relationship of candesartan in once-daily, oral doses, in hypertensive pediatric subjects (6 to <17 years) receiving treatment for 4-weeks by evaluation of the slope of linear regression for the change from baseline to double-blind (DB) Week 4 in trough sitting systolic blood pressure (SiSBP) as a function of non-zero dose	Randomized, DB, placebo-controlled Parallel group 1-week, single-blind, placebo run-in 4 week DB treatment	Candesartan : 2 mg, 8 mg, or 16 mg oral tablet for subjects weighing <50 kg Candesartan 4 mg, 16 mg, or 32 mg oral tablet for subjects weighing ≥50 kg) Placebo In a 2:2:2:1 ratio.	240 ITT population	Hypertension A mean SiSBP and/or SiDBP ≥95th percentile of height-adjusted, age and gender blood pressure distributions and ≤20 mmHg (systolic) and ≤10 mmHg (diastolic) above the 95th percentile.	4 week
D2451C00001 (Study 261B)	Describe candesartan antihypertensive effects in terms of achieved BP 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.	Open-label, uncontrolled, 52-week study. Pharmacokinetic (PK) assessments were carried out in a subset of subjects. Neurocognitive (Full Scale IQ test, WISC IV) measurements were done in a subset of study participants in the US	Suggested starting doses for children <50 kg was 4 mg of candesartan once-daily and for children ≥50 kg, 8 mg once-daily. Investigators could adjust the candesartan dose (between 4 mg and 32 mg. If hypertension was not controlled at 32 mg daily or at the maximum tolerated dose, supplemental antihypertensive medication was permitted.	233 ITT population 212 had participated in Study 261A and 21 entered directly into Study 261B	Hypertension A mean SiSBP and/or SiDBP ≥95th percentile of height-adjusted, age and gender blood pressure distributions and ≤20 mmHg (systolic) and ≤10 mmHg (diastolic) above the 95th percentile.	1 year open label
D2451C00002 (Study 328)	Characterize the dose response relationship of candesartan (once-daily) in hypertensive pediatric subjects (1 to <6 years of age) by evaluation of the slope of the linear regression for the change in trough SiSBP from baseline (Day 0) to the end of the 4-week DB treatment period (Day 28) as a function of dose.	1-week single-blind, placebo run-in 4 week, DB, randomized, dose ranging study of candesartan Followed by a 52-week, open-label treatment period.	Candesartan: (0.05 mg/kg, or 0.20 mg /kg, or 0.40 mg /kg) liquid formulation In a 1:1:1 ratio.	93 ITT population	Hypertension A mean SiSBP and/or SiDBP ≥95th percentile and ≤20 mmHg (systolic) and 10 mmHg (diastolic) above the 95th percentile blood pressure distributions adjusted for height, age, and gender.	4 weeks DB 1 year open label

DB Double blind. PK Pharmacokinetic. SiSBP Sitting systolic blood pressure. SiDBP Sitting Diastolic blood pressure.

Clinical Pharmacology Studies:

Type of study	Study identifier	Key objective of the study	Study design and type of control	Test products, Dosage regimen, Route of administration	No. of randomized subjects Gender (M/F)	Study population	Duration of treatment period	Study status and type of report
Reports of Biopharmaceutic studies								
Bioequivalence study	D2451C0005	To determine the relative bioavailability (Frel) of candesartan comparing candesartan given in tablet form with an oral suspension by assessment of the area under the plasma concentration-time curve (AUC).	Open-label, randomized, 2-period, 2-way crossover study in healthy subjects	A single, oral 32 mg tablet of candesartan A single, oral 32 mg suspension of candesartan	N=24 (7/17)	Healthy adult subjects	Two single doses	Complete, full
Clinical pharmacology studies								
Pharmacokinetic substudy	Study D2451C00001 (Study 261B)	Single-dose pharmacokinetic substudy in children 6 to<17 years of age	To assure that the 16 mg dose was appropriate for all substudy participants on a mg/kg basis, there was a minimum weight criteria of 25 kg, ie, a maximum dose equaling 0.64 mg/kg.	A single, oral 16 mg tablet of candesartan	N=22 (14/8)	Hypertensive children	A single dose	Complete, full
Pharmacokinetic substudy	Study D2451C00002 (Study 328)	Single-dose pharmacokinetic substudy in children 1 to <6 year of age	Open label Subjects received a single dose of oral suspension of candesartan based on body weight.	A single 0.2 mg/kg oral suspension of candesartan	N=10 (5/5)	Hypertensive children	A single dose	Complete, full

(Source: tabular listing of all Clinical studies submitted by the Sponsor)

5.2 Review Strategy

This reviewer primarily used study protocols, study reports, data summaries, tables and electronic datasets of studies 261A, 261B and 328 in conducting this review.

5.3 Discussion of Individual Studies/Clinical Trials

The two dose ranging, multi-center trials in hypertensive pediatric patients were Study 328 (age 1-6 yrs) and 261A (age 6-17 yrs). Safety data was collected in 261A, 261B which was a one year, open-label study following 261A and for a 1-year open-label, follow-up period in Study 328. Infants under 1 yr were not included per FDA correspondence dated November 15, 2002 regarding administration of ARBs to infants less than 1 yr of age.

Study 261A was a randomized, parallel, double blind, placebo controlled study to determine the anti-hypertensive dose ranging effects across 3 dose levels of candesartan (2/4, 8/16 and 16/32 mg once daily) following 4 weeks of DB treatment in hypertensive pediatric subjects 6-17 yrs of age (WR trial design A). The study included 2 weight panels with subjects less than 50 kg receiving the lower dose within each dose level.
Study 328 was a randomized, parallel double-blind study in hypertensive subjects 1-6 yrs of age to determine the dose ranging effects of candesartan across 3 dose levels (0.05, 0.2 and 0.4 mg/kg) following WR trial design B.

Subjects for 261A were excluded from enrollment if they were unable to be weaned off previous anti-hypertensive medication (diuretics, beta-blockers, ACE inhibitors, etc) for 6-weeks. Subjects on anti-hypertensive medications other than ACEI and ARBs were allowed to participate in 328 if BP values met inclusion criteria.

The primary efficacy variable was the change in trough SBP in 328 and trough sitting SBP (SiSBP) in 261A from baseline to the end of the 4-week, DB treatment period. The slope to the dose response relationship as a function of non-zero dose was measured.

Efficacy and safety results were analyzed separately and by pooling both studies. Laboratory results were not pooled. These are discussed in the following sections (6 and 7)
Due to differences in hypertension etiology (primarily due to renal disease or other specific causes), higher incidence of obesity/possibly metabolic syndrome in the older age group, concomitant anti-hypertensive treatment in the double–blind phase and formulation issues in children under six years of age compared to older children, this reviewer feels it is appropriate to analyze these studies separately and pooled to assess efficacy and safety. It seems reasonable to pool subjects from both studies to satisfy the race (35-60% black) and age (50% pre-pubertal and under 12 yrs of age, 25% infants to pre-school age) criteria of the written request.

6 Review of Efficacy

Efficacy Summary

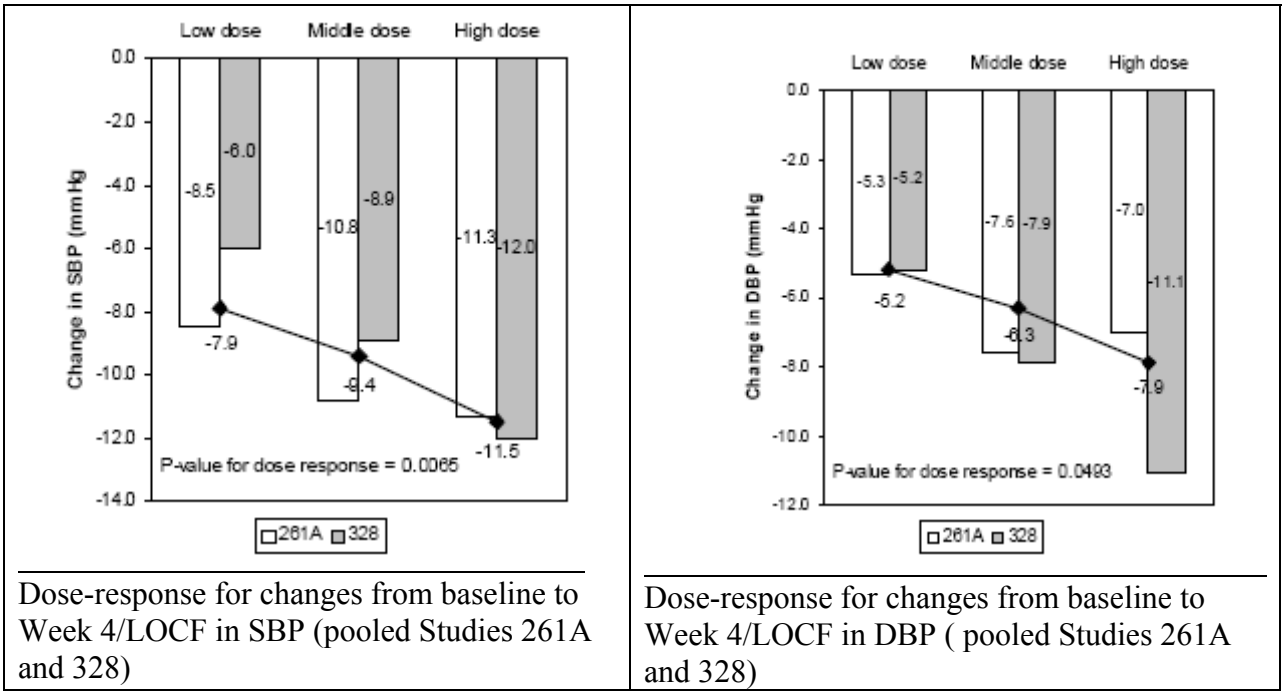
Candesartan is effective for the treatment of hypertension in children 1-17 yrs of age and lowered BP in a dose-related fashion. The antihypertensive effect is usually present within 1 to 2 weeks of initiating treatment and a full effect is generally obtained within 4 weeks of treatment. There are no differential effects with regard to age, gender, level of sexual maturity, primary versus secondary hypertension, and race, although there is a somewhat lesser reduction in Black children over six years of age.

Based on the meta-analysis reported in the original candesartan medical review a 16 mg dose in adults produced a trough SBP/DBP reduction from baseline of 14.1/9.3 mm Hg. Based on the OCP review, 8/16 mg tablet QD (for body weight <50 or ≥50 kg respectively) in children 6 to <17 years old produced similar candesartan exposure-response as the 16 mg QD starting dose in adults. Therefore, choosing 8/16 mg tablet QD for body weight <50 or ≥50 kg respectively in children 6 to <17 years old as a starting dose is consistent with adults. The exposure at 0.2 mg/kg in children 1 to <6 years old was about 40% lower than the exposure at 16 mg in children 6 to < 17 years old, but was similar as the exposure at 4 or 8 mg (weight < 50 kg or weight > 50 kg respectively) in children 6 to <17 years old. Hence the sponsor's proposed starting dose is acceptable. The once daily dosing in adults is supported by the PK-PD data including over 50% inhibition of the effect of Angiotensin II at 24 hrs (see Clinical pharmacology Section 4.4.1 and 4.4.2 and Section 6). Since it is unknown if these effects are similar in children and adults, a twice daily dosing interval may be considered before switching to a higher dose.

Pooled Analyses

In the combined Study 261A and Study 328 4-week, dose-response analysis, change from baseline to Week 4 in blood pressure served as the dependent variable and dose ratio (1:4:8), study (0 or 1), weight group (0 or 1), and study by weight group interaction were included as independent variables. The placebo group was not included. In Study 328, low, medium and high doses were 0.05 mg/kg, 0.20 mg/kg, and 0.40 mg/kg, respectively; in Study 261A, they were 2/4 mg, 8/16 mg, and 16/32 mg , respectively, for subjects <50 kg ≥50 kg . The study variable was 0 for Study 328 and 1 for Study 261A. The weight variable was 0 for the lower weight group and 1 for the higher weight group. The analysis considered all 93 ITT subjects from Study 328, and 205 candesartan ITT subjects from Study 261A. The analysis examined the dose ratio by study interaction, which was found to be not significant (p=0.2976 for SBP and p=0.1776 for DBP) and the variable, study, was removed from the model. In this combined analysis of children 1 to <17 years of age, candesartan induced a statistically significant dose related decrease in both SBP and DBP. Per the pharmacometric opinion, this analyses is informative but the model assumption of the same slope in the two different studies may be misleading.

Figure 1: Dose-response for changes from baseline to Week 4/LOCF in SBP and DBP



Dose-response for changes from baseline to Week 4/LOCF in SBP (pooled Studies 261A and 328)

Dose-response for changes from baseline to Week 4/LOCF in DBP (pooled Studies 261A and 328)

Note: Numbers inside the bars are the raw means. The connected dots, and the values that are provided below the dots, represent the dose-response line assuming the study and weight effects are proportional to the number of subjects in Study 261A and the upper weight panel, respectively.

Source figures 11 and 12 from the Summary of clinical Efficacy, pg 34 & 35

Individual analyses:

Study 328

Study 328 was successful for its pre-specified primary end point and is interpretable. Systolic blood pressure (SBP), the primary efficacy variable, declined monotonically across the three candesartan dose levels (0.05 mg/kg, 0.2 mg/kg, and 0.4 mg/kg) by 6 to 12 mmHg (see Figure 4), a decline that was significantly related to the candesartan dose (p=0.0136). Similarly, diastolic blood pressure (DBP) declined by 5 to 11 mmHg in a significant dose-related fashion (p=0.0301). As indicated by the biometrics reviewer, on pair-wise comparisons of the three doses following the global test, there was a significant difference between the high dose and low dose. No other paired wise comparison was significant. However, the pharmacometrics reviewers noted that average C_{trough} concentrations following a 16 mg dose in adults (39 nmol/L) were reached only with the 0.4 mg/kg dose.

Since about 20% of the subjects were on concomitant medications, I requested the pharmacometrics reviewer to conduct additional analyses. The number of subjects receiving concomitant antihypertensive medications was 2 (7%), 8 (25%), and 9 (28%) for the low dose, middle dose and high dose candesartan group, respectively. With the frequency chi-square test, we cannot reject the null hypothesis that the subjects receiving concomitant antihypertensive medications were randomly distributed among the different candesartan dose groups (p-value = 0.0887).

However, when those subjects with concomitant anti-hypertensive medications were excluded, the slope of the regression line is -1.114 with p-value 0.0053, compared to slope= -0.80259 with p-value 0.0136 for the entire sample as reported by the sponsor, indicating that the observed BP reduction of candesartan in Study 328 is not a result of concomitant antihypertensive medications.

Study 261A
Over the range of candesartan cilexetil doses studied, sitting systolic blood pressure (SiSBP declined by 8.5 to11.3 mmHg and sitting diastolic blood pressure (SiDBP) declined by 5.3-7 mm Hg; the decline with placebo was 3.8/1.3 mmHg from baseline to Week 4/LOCF (see Table 5). Per sponsor's analysis, Study 261A failed for its primary end-point. The slope for change in systolic blood pressure using placebo corrected regression was not significant (see Table 6). However, analysis by placebo anchored regression by the pharmacometrics reviewer shows a significant slope for the change in SiSBP (p=0.001).

Pharmacokinetic results
A relative bioavailability study was conducted to compare the systemic exposure of candesartan following the administration of candesartan pediatric oral suspension and tablets. Per the OCP review, Candesartan $AUC_{0-\infty}$ was equivalent for both formulations with relative bioavailability 108% (suspension vs. tablet), but the C_{max}, value of suspension was 22% higher with the upper bound of the 90% CI of the ratio between suspension and tablet more than 125%. The clinical data in hypertensive children aged 1 to <6 years were generated using the to be marketed oral suspension formulation.

Following multiple dose administration of candesartan cilexetil, there was a dose related increase in plasma candesartan concentrations across the different dose levels. PK profile was comparable among children and adults and consistent across subgroups of age, weight and gender.

Candesartan exposure in subjects with renal disease is higher compared to exposure in subjects without renal disease. However, reduction in SBP in subjects with renal disease is not significantly different from reduction in subjects without renal diseases. Therefore, no dose adjustment is necessary in hypertensive children with renal diseases.

6.1 Indication

Treatment of hypertension in children from one to < 17 years of age.

6.1.1 Methods

Study 328 (see Figure 2)
This randomized, double-blind study determined the antihypertensive dose ranging effects of candesartan across 3 dose levels following 4 weeks of double-blind treatment in hypertensive subjects 1 to <6 years of age. The 4-week, double-blind treatment period was followed by a 52–week, open-label clinical experience evaluation. A PK sub-study was also included. One to two 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, who were deemed eligible to participate in the study were randomly allocated to receive 1 of 3 dose levels of candesartan during the double-blind, dose-response period

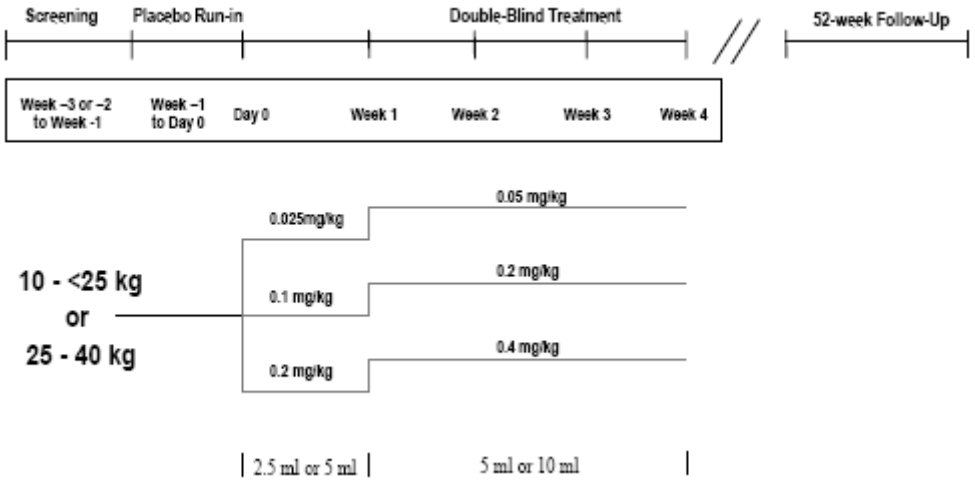
Panel 1: Subjects weighing 10 to <25 kg were allocated 1:1:1 to candesartan 0.05 mg/kg, 0.2 mg/kg, or 0.4 mg/kg once-daily in oral suspension form (5 ml/dose).
Panel 2: Subjects weighing 25 to ≤40 kg were allocated 1:1:1 to candesartan 0.05 mg/kg, 0.2 mg/kg, or 0.4 mg/kg once-daily in oral suspension form (10 ml/dose)

Male or female subjects aged 1 to <6 years with a mean SiSBP and/or SiDBP ≥95th percentile of height-adjusted, age and gender blood pressure distributions and ≤20 mmHg (systolic) and ≤10 mmHg (diastolic) above the 95th percentile based on height-adjusted charts for age and gender were enrolled.

The primary measurement for evaluating antihypertensive efficacy was trough SBP. At each visit, blood pressures were measured 3 times, at least 1 minute apart. Acceptable values were to vary by no more than 7 mmHg between the highest and the lowest readings. The blood pressure determination at each visit represented the mean of the 3 values.

The primary efficacy analysis was based on the intent-to-treat (ITT) population and tested the null hypothesis that the slope=0 in a linear regression model with change in trough SBP as the dependent variable and dose pooled across weight panels as the independent variable. For subjects missing a double-blind, Week 4 blood pressure determination, a value was imputed by carrying the last observation forward (LOCF). Dose response was also examined within each weight panel separately where changes from baseline in trough SBP were analyzed using simple linear regression with dose ratio as the independent variable. The dose-response analyses were repeated for the secondary blood pressure variable, change from baseline to the end of the double-blind period in trough DBP. Changes from baseline to the end of the double-blind period were examined within each treatment group. ANCOVA models for changes in SBP and DBP had factors for weight panel and treatment group along with a covariate for baseline blood pressure.

Figure 2: Study design for 328



Source Figure 1 in the CSR for Study 328, pg-26

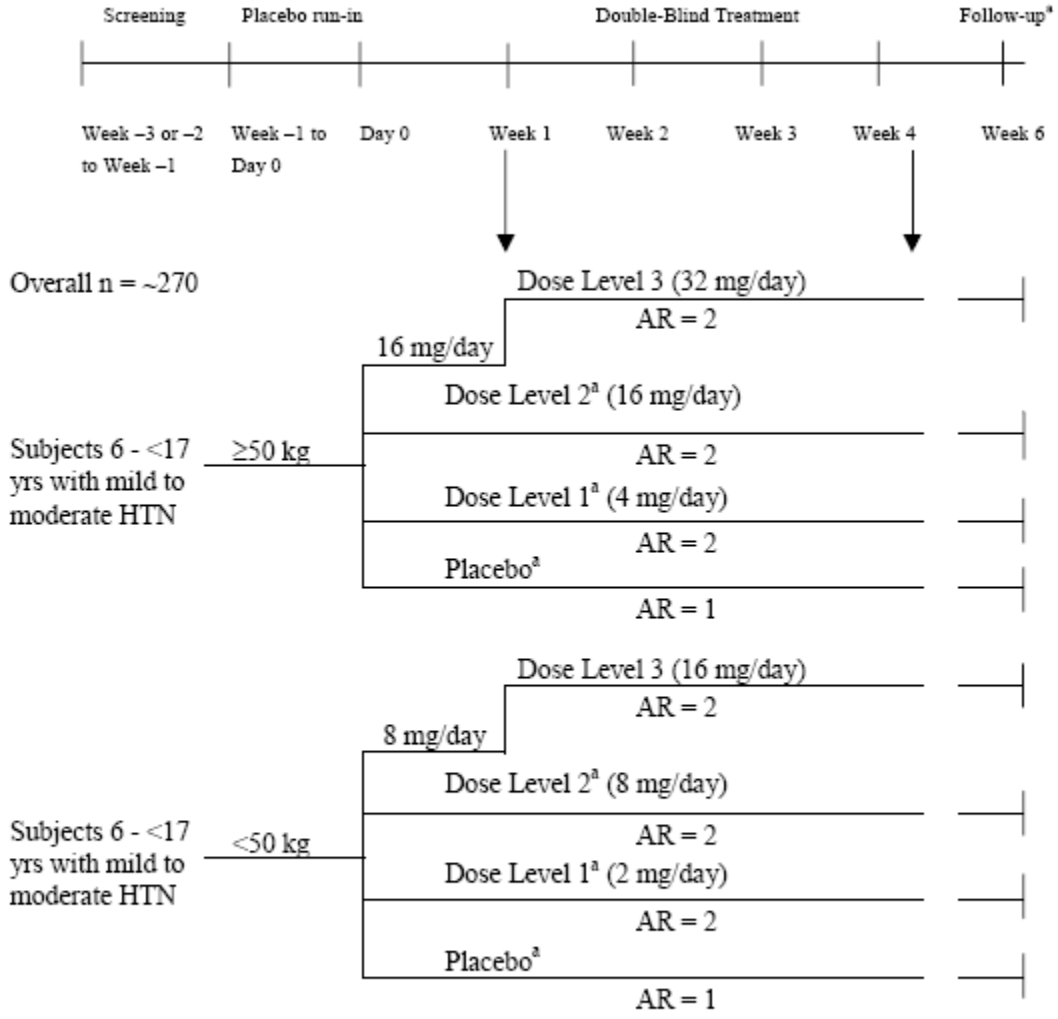
Study 261A (see Figure 3)

This randomized, double blind, placebo-controlled study determined the antihypertensive dose ranging effects across 3 dose levels of candesartan following 4-weeks of double blind treatment. Following a screening evaluation, subjects underwent a 1-week, single-blind, placebo run-in after which, those deemed randomization eligible, were allocated to receive placebo or 1 of 3 doses of candesartan: 2 mg, 8 mg, or 16 mg for subjects with a body weight <50 kg, or 4 mg, 16 mg, or 32 mg for subjects with a body weight ≥50 kg, 1:2:2:2 ratio (also presented as low dose 2/4 mg, medium dose 8/16 mg, and high dose 16/32 mg).

Male or female subjects aged 6 to <17 years with a mean SiSBP and/or SiDBP ≥95th percentile of height-adjusted, age and gender blood pressure distributions and ≤20 mmHg (systolic) and ≤10 mmHg (diastolic) above the 95th percentile were enrolled.

The primary efficacy measure was the placebo-corrected change from baseline to the end of treatment in SiSBP. The low (2/4 mg), medium (8/16 mg), and high (16/32 mg) doses were pooled and assigned values corresponding to relative dose, 1:4:8 in a multiple linear regression model which included the 2 weight panels as blocking factors. Changes in blood pressure relative to placebo were also analyzed in ANCOVA models with baseline blood pressure as the covariate with nominal p-values (both 1-sided and 2-sided) reported without corrections for multiple comparisons.

Figure 3:**Protocol 261A study design**



[a] Subjects have simulated dose increase at Week 1
AR Allocation ratio.
HTN Hypertension.

Source: Sponsor's Figure 1 in the CSR for 261A, Page 21

6.1.2 Demographics

Key demographic features are summarized below in Table 1. Within Study 261, the demographic characteristics between the double blind and open-label portions were quite similar, an expected finding given that of the 233 subjects in the open label period, most (212 subjects) had also participated in the antecedent double blind Study 261A. Only 21 subjects enrolled in Study 261B, without having participated in Study 261A.

Across the studies, there were more males than females, and the majority of subjects were Caucasian although close to half (47 %) were Black in Study 261. The actual number of Black children who participated in both studies was 39%.

In older children, the most common type of hypertension was systolic whereas in younger children the majority had both systolic and diastolic hypertension.

Subjects were excluded from 261A if they had a history of renal transplant, GFR < 50 ml/min based on the Schwartz formula or had insulin-dependent diabetes mellitus (IDDM). In contrast, subjects in Study 328 were excluded only for an estimated glomerular filtration rate (eGFR) <30 ml/min/1.73m^2 for non-transplant subjects based on the Schwartz Formula and <40 ml/min/1.73 m^2 for transplant patients; subjects with a renal transplant < 6 months prior to study entry, and unstable IDDM were excluded.

More of the younger children (42%) had a history of receiving antihypertensive medication up to the time of entry into the study compared to 23% in Study 261. In Study 328 subjects receiving an angiotensin receptor blocker or an angiotensin converting enzyme inhibitor were eligible if they undergo withdrawal of the antihypertensive medication over a 2-week washout period and subsequently meet BP inclusion/exclusion criteria. Other classes of antihypertensive medication were permitted. By contrast, in older children (Study 261A) there was a placebo run-in period and the protocol required a 1-week washout of *any* antecedent antihypertensive treatment.

During the 4-week double-blind treatment period in Study 261A, none of the subjects received concomitant antihypertensive medication; during the long-term extension, 9% of subjects took concomitant antihypertensive medication (the most common concomitant medications included thiazides [5.6% of subjects], beta blocking agents, selective[1.3%] and beta blocking agents, selective and thiazides [1.3%]). In Study 328, during the 4-week double blind period, 20.4% of subjects continued to receive an antihypertensive medication at the dose they were receiving at baseline in addition to study drug (the most common concomitant antihypertensive agents were dihydropyridine derivatives [14.0%], beta blocking agents selective [5.4%], and thiazides plain [2.2%],]). During long-term treatment, 16% of subjects received a supplemental antihypertensive agent (the concomitant antihypertensive agents included dihydropyridine derivatives [9.5%], beta blocking agents, selective [1.2%], thiazides, plain [2.4%], aldosterone [1.2%], and beta blocking agents nonselective [1.2%]).

Other differences between the older (Study 261) and younger (Study 328) subjects relate to the higher proportion of presumed primary hypertension, and *the greater level of obesity (69% versus 23%, respectively, with BMI ≥ 95th percentile)*.

In Study 261, 4 children had baseline creatinine values outside of the specific normal range listed for their test result. Approximately 27 children had cardiovascular abnormalities; the most common finding was left ventricular hypertrophy (14 subjects). Twenty-two subjects had a medical or surgical history of a renal or urinary tract abnormality.

In Study 328, most of the subjects (n=69, 74%) had renal diseases, predominately chronic renal failure (n=18), congenital cystic disease (n=17), renal dysplasia (n=12), hydronephrosis (n=9), vesicoureteric reflux (n=9), and nephrotic syndrome (n=5). Consistent with the medical histories, the most common surgical procedures included a history of nephrectomy (n=8), vesicoureteral reflux surgery (n=6), and cystostomy (n=5). Baseline mean serum estimated glomerular filtration rate (eGFR) was 121.3 ml/min (baseline range 37 to 462 ml/min) and 22 children had below normal eGFR at baseline (normal range 80 to 125 ml/min). Median urine baseline P/C ratio was 0.3 (range 0.1 to 59.5) and median A/C ratio was 36 mg/g creatinine (range 3 to 5327 mg/g creatinine), normal is 0 to 30 mg/g creatinine.

Table 1:Demographics for children 6 to <17 years and children 1 to < 6 years of age Safety population Studies 261 and 328)

Demographic or baseline characteristic		Placebo	Candesartan treatment				
		Study 261A short term N=35	Study 261A short-term N=205	Study 261B long-term N=235	Study 328 short term N=93	Study 328 long term N=85	Active pooled studies 261A, 261B, 328 N=348
Demographic characteristics							
Age, years: n (%)	1 to <2	NA	NA	NA	16 (17.2)	16 (18.8)	16 (4.6)
	2 to <6	NA	NA	NA	77 (82.8)	69 (81.2)	77 (22.1)
	6 to <12	11 (31.4)	59 (28.8)	69 (29.4)	NA	NA	76 (21.8)
	≥12 to <17	24 (68.6)	146 (71.2)	166 (70.6)	NA	NA	179 (51.4)
Age, years	Mean (SD)	13.0 (2.8)	12.9 (2.6)	12.9 (2.7)	3.1 (1.4)	3.1 (1.4)	10.2 (4.9)
	Range	6 to 16	6 to 17	6 to 17	1 to 5	1 to 5	1 to 17
Sex, n (%)	Male	26 (74.3)	144 (70.2)	168 (71.5)	60 (64.5)	55 (64.7)	241 (69.3)
	Female	9 (25.7)	61 (29.8)	67 (28.5)	33 (35.5)	30 (35.3)	107 (30.7)
Race n (%)	Caucasian	14 (40.0)	94 (45.9)	112 (47.7)	71 (76.3)	66 (77.6)	192 (55.2)
	Black	17 (48.6)	96 (46.8)	102 (43.4)	17 (18.3)	15 (17.6)	130 (37.4)
	Oriental	0	0	0	2 (2.2)	1 (1.2)	2 (0.6)
	Other	4 (11.4)	15 (7.3)	21 (8.9)	3 (3.2)	3 (3.5)	24 (6.9)
Baseline characteristics							
Group by Tanner Score,	Not done	NA	NA	19 (8.1)	93 (100)	85 (100)	112 (32.2)
n (%)	<3	14 (40.0)	68 (33.2)	76 (32.3)	NA	NA	80 (23.0)
	≥3	21 (60.0)	137 (66.8)	140 (59.6)	NA	NA	156 (44.8)
Weight at screen (kg)	10 to <25 kg	0	4 (2.0)	4 (1.7)	81 (87.1)	75 (88.2)	86 (24.7)
	25 to <40 kg	2 (5.7)	6 (2.9)	12 (5.1)	12 (12.9)	10 (11.8)	22 (6.3)
	40 to <50	3 (8.6)	16 (7.8)	18 (7.7)	NA	NA	20 (5.7)
	≥50	30 (85.7)	179 (87.3)	201 (85.5)	NA	NA	220 (63.2)
Weight at screen (kg)	Mean (SD)	82 (28)	81(30)	80 (30)	18 (6)	17 (6)	64 (38)
	Range	28 to 146	21 to 171	20 to 179	10 to 39	10 to 39	10 to 171

Demographic or baseline characteristic		Placebo	Candesartan treatment				
		Study 261A short term N=35	Study 261A short-term N=205	Study 261B long-term N=235	Study 328 short term N=93	Study 328 long term N=85	Active pooled studies 261A, 261B, 328 N=348
Height at screen, cm	Mean (SD)	164 (15)	163 (15)	163 (15)	98 (12)	97 (12)	145 (32)
	Range	133 to 191	111 to 196	111 to 194	74 to 129	74 to 123	74 to 196
BMI percentile at screen	<95	11 (31.4)	64 (31.2)	77 (32.8)	56 (60.2)	50 (58.8)	135 (38.8)
n (%)	≥95	24 (68.6)	141 (68.8)	158 (67.2)	21 (22.6)	19 (22.4)	197 (56.6)
	Unknown	0	0	0	16 (17.2)	16 (18.8)	16 (4.6)
BMI at screen, kg/m^2	Mean (SD)	30 (8)	30 (9)	30 (9)	18 (4)	18 (4)	27 (9)
	Range	16 to 48	13 to 59	14 to 58	14 to 36	14 to 36	13 to 59
Duration of hypertension, years	<1	27 (77.1)	127 (62.0)	153 (65.1)	NC	NC	165 (47.4)
	1 to <2	4 (11.4)	31 (15.1)	32 (13.6)	NC	NC	37 (10.6)
	2 to <3	1 (2.9)	22 (10.7)	25 (10.6)	NC	NC	25 (7.2)
	3 to <4	2 (5.7)	12 (5.9)	12 (5.1)	NC	NC	13 (3.7)
	4 to <5	0	4 (2.0)	5 (2.1)	NC	NC	5 (1.4)
	≥5	1 (2.9)	9 (4.4)	8 (3.4)	NC	NC	10 (2.9)
Type of hypertension n (%)	Not available	2 (5.7)	12 (5.9)	9 (3.8)	3 (3.2)	2 (2.4)	17 (4.9)
	DBP only	3 (8.6)	13 (6.3)	15 (6.4)	20 (21.5)	19 (22.4)	35 (10.1)
	SBP only	21 (60.0)	104 (50.7)	123 (52.3)	21 (22.6)	20 (23.5)	153 (44.0)
	SBP + DBP	9 (25.7)	76 (37.1)	88 (37.4)	49 (52.7)	44 (51.8)	143 (41.1)
Primary hypertension	n (%)	ND	ND	ND	22 (23.7)	21 (24.7)	22 (6.3)
Secondary hypertension	n (%)	ND	ND	ND	71 (76.3)	64 (75.3)	71 (20.4)
Previously treated hypertension, n (%)	No	32 (91.4)	154 (75.1)	NC	NC	NC	154 (44.3)
	Yes	3 (8.6)	51 (24.9)	NC	NC	NC	51 (14.7)

Note: The Tanner Score was only done in Study 261.
NC Not collected. NA Not applicable. ND Not determined. BMI Body mass Index. SBP Systolic blood pressure. DBP diastolic blood pressure.
Data derived from Table 6.1 in Section 6.

(Source: Sponsor's Table 9, pg17-18, Summary of Clinical Safety)

6.1.3 Subject Disposition

Study 328

A total of 118 children were enrolled in this study; 99 were allocated a randomization number, and 93 were randomized and dispensed study drug double-blind medication since six subjects were found to be ineligible to enter the double blind period. Of the 25 enrolled children who were not randomized and dispensed medication, the most common reasons for discontinuation were eligibility criteria not fulfilled (16 subjects) and not willing to continue (4 subjects). 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.

Table 2: Subject disposition (All randomized subjects), study 328

	Candesartan treatment			Total
	0.05 mg/kg N=29	0.2 mg/kg N=32	0.4 mg/kg N=32	All dose levels N=93
Subjects randomized and dispensed double-blind medication	29 (100)	32 (100)	32 (100)	93 (100)
Subjects completed 4-week, double-blind period	27 (93.1)	29 (90.6)	30 (93.8)	86 (92.5)
Subjects discontinued from study, double-blind period	2 (6.9)	3 (9.4)	2 (6.3)	7 (7.5)
Eligibility criteria not fulfilled	2 (6.9)	0	0	2
Condition under investigation (improved/recovered)	0	1 (3.1)	0	1 (1.1)
Lack of therapeutic response	0	1 3.1)	0	1 1.1)
Development of specific discontinuation criteria	0	0	1 (3.1)	1 (1.1)
Subject not willing to continue in study	0	1 (3.1)	0	1 (1.1)
Subject lost to follow-up	0	0	1 (3.1)	1 (1.1)
Subjects completed double-blind but discontinued prior to open-label	1 (3.4)	0	0	1 (1.1)
Adverse event	1 (3.4)	0	0	1 (1.1)
Subjects completed open-label treatment period	25 (86.2)	28 (87.5)	28 (87.5)	81 (87.1)
Subjects discontinued from study, open-label period	1 (3.4)	1 (3.1)	2 (6.3)	4 (4.3)
Adverse event	0	0	1 (3.1)	1 (1.1)
Subject not willing to continue in study	1 (3.4)	0	0	1 (1.1)
Subject lost to follow-up	0	1	0	1 (1.1)
Other	0	0	1 (3.1)	1 (1.1)

Data derived from Table 11.1.2, Section 11.1.

Source: Table 9 from the CSR for study 328, pg 54

Study 261A

Of the 301 enrolled subjects, a total of 240 subjects were randomized of whom 229 (95.4%) completed the study. The primary reasons that subjects discontinued the study were because the eligibility criteria were not fulfilled or the subject had an AE.

Table 3: Patients Randomized, Discontinued and Completed Study, All Randomized Patients, Study 261A

	Candesartan Treatment Groups									
	Placebo (N=35)		2/4 mg (N=69)		8/16 mg (N=68)		16/32 mg (N=68)		Active Pooled (N=205)		Total (N=240)	
Patients Randomized	35	(100.0%)	69	(100.0%)	68	(100.0%)	68	(100.0%)	205	(100.0%)	240	(100.0%)
Patients Completed	34	(97.1%)	66	(95.7%)	64	(94.1%)	65	(95.6%)	195	(95.1%)	229	(95.4%)
Patients Discontinued from Study	1	(2.9%)	3	(4.3%)	4	(5.9%)	3	(4.4%)	10	(4.9%)	11	(4.6%)
..Eligibility Criteria Not Fulfilled	0		2	(2.9%)	0		1	(1.5%)	3	(1.5%)	3	(1.3%)
..Adverse Event	0		0		2	(2.9%)	1	(1.5%)	3	(1.5%)	3	(1.3%)
..Lack of Therapeutic Response	1	(2.9%)	0		0		1	(1.5%)	1	(0.5%)	2	(0.8%)
..Subject not Willing to Continue in Study	0		1	(1.4%)	0		0		1	(0.5%)	1	(0.4%)
..Subject Lost to Follow	0		0		1	(1.5%)	0		1	(0.5%)	1	(0.4%)
..Other	0		0		1	(1.5%)	0		1	(0.5%)	1	(0.4%)

Note: Percentages of patient is determined from number of patient randomized.
/csre/prod/atacand/261a/sp/output/tlf/t110102.lst term201.sas 08JUN2006:13:53 pettersd

Source: Table 11.1.2 in the CSR for 261A, pg 114

Study 261B

Of the 237 subjects who enrolled, 39 (16.5%) discontinued the study. Reasons for discontinuations were primarily for subjects who were lost to follow-up or 'Other' reasons (most commonly for non-compliance with study requirements).

Table 4: Subject disposition for 261B

	Number (%)
All subjects enrolled	237
Randomized in 261A, enrolled in B	213 (89.9)
Enrolled in 261B only	24 (10.1) [includes 4 screen failures from 261A]
Subjects who took at least 1 dose of study medication	235 (99.2)
Subjects who had entry and end of study IQ scores	33
Subjects in the pharmacokinetic substudy	22
Subjects completed study	198 (83.5)
Subjects discontinued	39 (16.5)
Eligibility criteria not met[a]	3 (1.3)
Adverse event	5 (2.1)
Lack of therapeutic response	1 (0.4)
Not willing to continue study	9 (3.8)
Lost to follow-up	11 (4.6)
Other[b]	10 (4.2)

[a] Subject E0022001 had normal BP, Subject E0040007 had left ventricular hypertrophy, E0011021 had an elevated ALT at entry.
[b] Other included: noncompliant with study requirements (6), surgical procedure (1), dizziness (1), withdrew consent (1), family moved (1).
Data derived from Tables 11.1.1 and 11.1.2, Section 11.

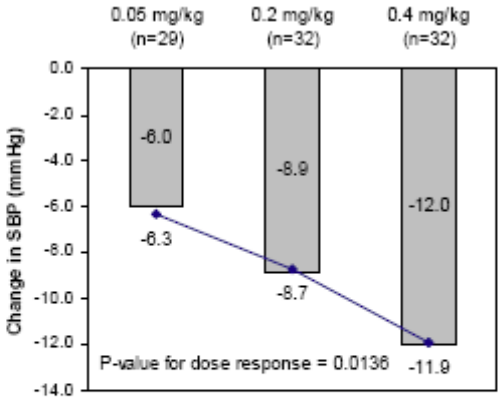
Source: table 9, CSR for 261B

6.1.4 Analysis of Primary Endpoint(s)

Study 328

Study 328 was successful for its pre-specified primary end point and is interpretable. Systolic blood pressure, the primary efficacy variable, declined monotonically across the three candesartan dose levels (0.05 mg/kg, 0.2 mg/kg, and 0.4 mg/kg) by 6 to 12 mmHg, a decline that was significantly related to the candesartan dose (p=0.0136). As indicated by the biometrics reviewer, on pair wise comparisons of the three doses following the global test, there was a significant difference between the high dose and low dose. No other paired wise comparison was significant. However, the pharmacometrics reviewers have noted that average Ctrough concentrations following a 16 mg dose in adults (39 nmol/L) were reached only with the 0.4 mg/kg dose which may explain the lack of a significant difference between the middle and low dose.

Figure 4: Means and dose-response line for changes from baseline to Week 4/LOCF in SBP (ITT population), Study 328



Note: Numbers inside the bars are the raw means. The connected dots, and the values that are provided below the dots, represent the dose-response line assuming the weight effect is proportional to the number of subjects in the upper weight panel.
Data derived from Table 11.2.2.3 and Table 11.2.2.6.

Source: sponsor's Figure 4, pg 68 in the CSR for Study 328.

Study 261A

Over the range of candesartan cilexetil doses studied, SiSBP declined by 8.5 to 11.3 mmHg to and SiDBP declined from 5.3 to 7.0 mm Hg; the decline with placebo was 3.8/1.3 mmHg from baseline to Week 4/LOCF (Table 5). Per sponsor's analysis, Study 261A failed for its primary end-point. The slope for change in systolic blood pressure using placebo corrected regression was not significant(Table 6). However, analysis by placebo anchored regression by the pharmacometrics reviewer shows a significant slope for the change in siSBP (p=0.0009). Similarly, a simple linear regression model with candesartan cilexetil dose expressed in mg/kg showed a significant dose response for SiSBP (p=0.0032) and SiDBP (p=0.0347). Similarly the slope for change in siSBP was also significant with pooled regression analysis of candesartan trough concentrations (p= 0.0025). It is to be noted that although the Ki is reported to be

0.64nmol/L, the LOQ was 2nmol/L which resulted in missing Ctrough values from several subjects. A more sensitive assay would have possibly given more significant results.

In the opinion of the clinical and clinical pharmacology reviewer's the sponsor's analysis was inappropriate since the placebo effect was excluded. The primary question to be addressed is "does the drug work?". To answer this question, placebo comparison as part of the analysis is the most appropriate analysis. A subordinate analysis is whether any dose is superior. Moreover, per the WR statement on trial design the primary analysis should include all patients with data on randomized treatment. ANCOVA analysis and paired-wise contrasts comparing all doses of candesartan to placebo were also significant (Table 7).

Table 5: Mean Week 4/LOCF and mean change from baseline to Week 4/LOCF in SiSBP and SiDBP (ITT population), Study 261A

	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)

Derived from Tables 11.2.2.1, 11.2.2.3, 11.2.3.1, and 11.2.3.3.

Source: Table 15, page 66, CSR for 261A

Table 6: Dose response for placebo-corrected change from baseline to Week 4/LOCF for SiSBP and SiDBP (ITT population), Study 261A. [Model-multiple linear regression, primary efficacy variable- the slope of placebo-corrected change in BP from baseline to DB Week 4/LOCF, independent variables -body weight panel as a blocking factor (0/1 depending on body weight panel, <50 kg, ≥50 kg) and dose ratio (1/4/8, depending on low, medium, or high dose].

	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 pressure. SiDBP Sitting diastolic blood pressure. SE Standard error.
Data derived from Table 11.2.2.6 and 11.2.3.6, Section 11.2.

Source: Table 16 pg 69 in the CSR for 261A

6.1.5 Analysis of Secondary Endpoints(s)

Study 328
Similar to SBP, monotonic, significantly dose related decline in DBP of 5.2 to 11.1 mmHg (p=0.0301).

The dose response relationship of candesartan for change in SBP as a function of dose for each body weight panel was a specified secondary objective of the study. However, only 12 children were in the higher weight stratum of 25 to ≤40 kg (81 children were in the weight stratum 10 to <25 kg). So the small number of subjects could account for the lack of significance of dose response (see below). The analyses of secondary end-point was mainly exploratory since there was no pre-specified α allocation

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)

Study 261A

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) However, the slope for change from baseline was significant (p=0.0096) in the clinical pharmacology reviewers analysis using placebo-anchored regression.

The protocol-specified 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 (Table 7). In these analyses each candesartan cilexetil 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 sponsor repeated the pair-wise contrasts 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. However, as indicated in the statistical review, there was no adjustment for multiple comparisons.

Table 7: Treatment group effects and pair wise comparisons for change from baseline to Week 4/LOCF for SiSBP and SiDBP; 1-sided p-values and 95% confidence interval (ITT population)- Study 261A

	SiSBP (N=240)			SiDBP (N=240)		
Change from baseline	**Least square mean**	**p-value**	**95% CI**	**Least square mean**	**p-value**	**95% CI**
Placebo	−3.65944	0.0141	−6.5731, −0.7458	−1.80137	0.2195	−4.6838, 1.0810
Candesartan cilexetil						
Low dose	−8.56178	<0.0001	−10.6368, −6.4868	−4.77879	<0.0001	−6.8336, −2.7239
Medium dose	−11.1714	<0.0001	−13.2670, −9.0758	−7.9797	<0.0001	−10.0472, −5.9122
High dose	−10.91424	<0.0001	−13.0091, −8.8194	−6.92544	<0.0001	−8.9916, −4.8592
All active	−10.2168	<0.0001	−11.4207, −9.0129	−6.5613	<0.0001	−7.7515, −5.3712
Low vs placebo	−4.9023	0.0037	, −1.9040	−2.9774	0.0496	, −0.0068
Medium vs placebo	−7.5120	<0.0001	, −4.5023	−6.1783	0.0004	, −3.2071
High vs placebo	−7.2548	<0.0001	, −4.2481	−5.1241	0.0024	, −2.1511
All candesartan cilexetil groups pooled vs placebo	−6.5564	<0.0001	, −3.9138	−4.7599	0.0015	, −2.1454

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 1-sided test.
CI Confidence interval SiDBP Sitting diastolic blood pressure. SiSBP Sitting systolic blood pressure.
ITT Intention to treat. LOCF Last observation carried forward.
Derived from Tables 11.2.2.8 and 11.2.3.8, Section 11.2.

(Source: Table 17 in the CSR for 261 A)

6.1.6 Other Endpoints

Study 261A

The sponsor's analyses for standing systolic blood pressure (StSBP), StDBP to Week4/LOCF were similar to their findings for SiSBP and SiDBP. For StSBP (using the same placebo corrected linear regression analyses) the dose effect (expressed as dose ratio) was statistically significant for pair wise comparisons but not for StDBP. The ANCOVA model declared that the medium dose, high dose, and all doses pooled were statistically significant compared to placebo for both StDBP and StSBP.

6.1.7 Subpopulations

Study 328
Ten subgroups were analyzed for changes from baseline to Week 4/LOCF. Overall the sponsor reported a treatment effect (decline in blood pressures; all doses pooled) across all subgroups examined implying that candesartan would be effective independent of age, gender, race, weight, BMI, systolic vs. diastolic hypertension, primary versus secondary hypertension, antecedent treatment for hypertension, renal disease and geographic region. There was no apparent dose level by subgroup interactions.
Since the number of subjects in each center for this study were small (8 subjects each in the largest centers) a center effect was unlikely.

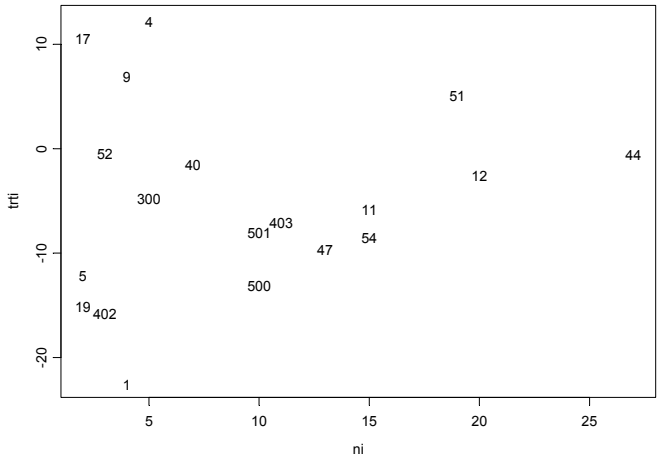
Study 261A
Formal statistical tests of interaction were done only for change in SiSBP by the sponsor. These were done by including the subgroup by treatment interaction term in ANCOVA models. While the change in SiSBP appeared somewhat greater for the <50 kg group than for the ≥50 kg weight group (placebo-corrected reductions of 12.4 vs. 5.6 mmHg, active doses pooled), this same trend was not apparent for SiDBP (placebo corrected reductions of 5.2 vs. 5.4 mm Hg). Of note, there were only 25 patients in the <50 kg group and the test for treatment by weight interactions for SiSBP was not significant.

Consistent with the literature regarding response in Blacks to ACEI's and ARB's, the reduction with candesartan cilexetil of both SiSBP and SiDBP in Blacks was somewhat less than non-Blacks. Placebo-corrected reduction in SiSBP (all active doses pooled) was 4.8 vs. 7.9 mmHg for Blacks compared to non-Blacks; placebo-corrected reductions in SiDBP were 3.9 vs. 6.7 mmHg, respectively. However, the test for race by treatment interaction in an ANCOVA model for SiSBP was not significant.

Formal tests for treatment interactions for sex, age [<12 vs. ≥ 12], Tanner Stage, and type of hypertension were all non-significant.

The sponsor reports that only 3 centers in Study 261A (12, 44, and 51) had more than 15 randomized subjects, with a maximum of 27 subjects, making it difficult to assess potential center effects. The biometrics reviewer constructed the funnel plot shown below. As seen below, there were no unexpected findings, with increased variability in response in centers with smaller number of subjects.

Figure 5 Biometrics' Reviewer's funnel plot for treatment response by study center (Study 261A)



Center numbers for each center with at-least one patient randomized to placebo or drug are plotted on the graph; y-co-ordinate- corresponding treatment response (change in SiSBP); x-co-ordinate- corresponding sample size.

Study 261B

Only descriptive statistics are reported for this study with no formal hypothesis testing. The sponsor reported response rates. A responder is defined as a subject who has a SiSBP and SiDBP less than the 95th percentile based on height-adjusted charts for age and sex. The sponsor reports that the proportion of responders (response rate) was independent of age and sex. Response rates stratified by weight and by race did, however, suggest differences: subjects weighing less than 50 kg (n=34) had a higher response rate than subjects weighing ≥50 kg (n=199), 68% vs. 50%, respectively. Similar to Study 261A, 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. Caucasians had a higher response rate than Blacks, 61% vs. 43%, respectively.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendation

Discussed in section 1.1 and efficacy summary. Comparability of exposures to adult dose-response based on clinical pharmacology review.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Study 328

The sponsor reports that relative to baseline (prior to double-blind dosing), blood pressure declines continued into the open-label period as witnessed by the first assessment at Week 20 (see Table 8). The mean daily dose in mg/kg was 0.20 at Week 4 and Week 56. While the anti-hypertensive effect appears to have been maintained, this is difficult to confirm, since other

therapies were allowed for up to 16 % of subjects and there is no control group. A randomized withdrawal study would be required to confirm this finding.

Table 8: Mean and mean change from baseline over time in SBP and DBP for the open-label period (Open-label population) SBP, Study 328

		SBP		DBP	
Week	N	Mean (SD)	Mean (SD) change from baseline	Mean (SD)	Mean (SD) change from baseline
Baseline	93	112 (8.7)		70 (8.8)	
Week 20	80	103 (9.9)	–8.1 (9.0)	63 (8.9)	–6.9 (10.1)
Week 36	76	102 (9.0)	–9.1 (9.2)	62 (9.2)	–7.9 (10.5)
Week 56	76	102 (10.3)	–8.7 (9.9)	62 (7.8)	–7.5 (9.7)
Week 56/LOCF	85	102 (9.7)	–9.3 (9.2)	63 (8.4)	–7.1 (9.7)

DBP Diastolic blood pressure; LOCF Last observation carried forward; N Number of subjects; SBP Systolic blood pressure; SD Standard deviation.
Note: At each time point, the n's reflect the number of subjects with a baseline observation and a post-baseline observation within the defined day range for that time point.
Data derived from Tables 11.2.2.1, 11.2.2.3, 11.2.3.1, and 11.2.3.3.

Source: Table 25 from the CSR for study 328, pg-74

Study 261B

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). After completing the double-blind study (Study 261A, N=212 {placebo and candesartan treated subjects]), mean SiSBP/SiDBP was 125/73 mmHg at entry to Study 261B. At the final visit (Week 52/LOCF) of Study 261B, mean BP had been maintained for these subjects (SiSBP/SiDBP was 126/72 mmHg). For candesartan treated subjects, after completing the double-blind study (Study 261A, N=185), mean BP was 124/72 mmHg at entry to Study 261B. At the final visit (Week 52/LOCF) of Study 261B, mean BP was maintained for these subjects (125/72 mmHg).

Among the subgroup of 27 subjects who entered Study 261B having received only placebo in the antecedent 261A study (about a 6-week placebo experience), 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 (Table 9)

Reviewer's Comments: It might be preferable to interpret response in terms of change in BP from baseline. Based on results from the table below, the hypotensive effect appears to be maintained but again, similar to study 328, 9% of subjects were on other therapies and there was no control group.

Table 9: Descriptive statistics for SiSBP and SiDBP over time for subjects who received placebo or candesartan in Study 261A, ITT population

Time	N	Mean SiSBP/SiDBP mmHg (range mmHg)	Mean change in SiSBP/SiDBP from randomization in 261A (range mmHg)
Placebo group from Study 261A			
261A randomization (baseline)	27	133.4/77.8 (119 to 151/61 to 96)	
Entry to 261B	27	130.4/75.5 (107 to 149/54 to 93)	–3.0/–2.3 (–21 to 11/–19 to 23)
Week 16	25	120.1/68.1 (98 to 137/51 to 90)	–11.9/–8.4 (–39 to 7/–37 to 11)
Week 32	23	124.6/72.3 (109 to 159/51 to 105)	–9.0/–5.8 (–31 to 8/–23 to 12)
Week 52	22	126.0/71.8 (107 to 151/38 to 99)	–7.2/–5.7 (–29 to 9/–36 to 20)
Week 52/LOCF	27	127.2/73.0 (111 to 159/38 to 105)	–6.3/–4.8 (–29 to 9/–36 to 20)
Pooled candesartan cilexetil treatment groups from Study 261A			
261A randomization (baseline)	185	133.9/78.9 (109 to 156/42 to 111)	
Entry to 261B	185	123.7/72.2 (91 to 149/43 to 99)	–10.1/–6.7 (–41 to 15/–40 to 37)
Week 16	154	123.7/71.5 (81 to 155/50 to 99)	–10.4/–7.6 (–33 to 23/–40 to 38)
Week 32	140	122.8/71.2 (87 to 148/50 to 95)	–11.2/–7.9 (–45 to 10/–35 to 26)
Week 52	157	124.9/72.0 (101 to 154/51 to 93)	–8.7/–7.1 (–33 to 24/–34 to 13)
Week 52/LOCF	185	125.2/71.9 (101 to 154/41 to 99)	–8.6/–7.0 (–33 to 24/–34 to 12)

Derived from Tables 11.2.2.3 and 11.2.3.3, Section 11.

Source: Table 17, pg 62 in the CSR for Study 261B

6.1.10 Additional Efficacy Issues/Analyses
NA

7 Review of Safety

Safety Summary

Overall, treatment with candesartan at daily doses of 0.05 mg/kg to 0.4 mg/kg in children 1 to <6 years of age and doses of 2 mg to 32 mg in children 6 to <17 years of age was well tolerated.

- One death occurred in study 328 due to progression of chronic glomerulonephritis and renal failure.

- A 14 yr old discontinued from Study 261B due to "toxic nephropathy" where relationship to candesartan cannot be excluded
- Ten of 348 children (2.9%) aged 1 to <17years of age discontinued candesartan because of adverse events (AEs) (hypotension (n=1 subject), compound fracture of radius and ulna (n=1), dizziness (n=2), abdominal pain and nausea and fatigue (n=1), nephropathy toxic (n=1), renal failure and hyperkalemia (n=1), white blood cell decreased (n=2), and glomerulonephritis (n=1, this child died of this underlying disease).
- As reported in adults with congestive heart failure or hypertension with volume depletion, hypotension/orthostatic hypotension and elevations in serum creatinine was clearly dose dependent in susceptible subjects. There was no clear evidence for dose-dependant hyperkalemia.
- The common AEs for children receiving candesartan largely reflect the manifestations of co-morbid illnesses or childhood illnesses to which the subjects were susceptible. The AEs were typically mild to moderate in intensity.
- There was a small decline in renal function following short-term (4 weeks) treatment with candesartan [estimated glomerular filtration rate (eGFR) declined by 5.6 ml/min at 4weeks in study 328). It is unclear how reliable this estimation is since a few subjects had baseline eGFR's greater than 200 (up to 462 ml/minute in one subject) which seems unusual in this population with predominantly secondary hypertension. This did not appear to be progressive with long-term treatment.
- Urinary albumin/creatinine (A/C) ratio declined with candesartan treatment, primarily among subjects with a baseline value >30 mg/g creatinine, and the decline appeared to be dose related in younger children and in older children similar trends were observed when the A/C ratio was >30 mg/g creatinine (although the numbers were too small to come to any definitive conclusion). There is no withdrawal data available. This is likely a renal hemodynamic effect rather than renal parenchymal improvement.
- Laboratory test findings including infrequent elevations in liver enzymes and small decreases in hemoglobin and hematocrit were similar to the adult clinical trial experience.
- Candesartan had no apparent adverse effect on growth based on height and weight Z scores reported at the end of one year and had no adverse effect on neurocognitive function in school age children. Information submitted regarding head circumference in children under 36 months of age is inconclusive

7.1 Methods

The main source of information for the safety analysis was the three clinical studies in the sponsor's submission in addition to a PUBMED literature search and data mining of AERS. The current PI for candesartan was used as a reference for expected AEs. In addition, the sponsor submitted the results of a literature search, a physician survey of pediatric nephrologists and unpublished data submitted to the Astra Zeneca internal AE database (SAPPHIRE).

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

- Study 328 including one year open-label extension phase
- Study 261A
- Study 261B (open label extension study of 261A)

7.1.2 Categorization of Adverse Events

For both studies 261 and 328, adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 11.1).
A SAE was an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), and at any dose of the investigational product or placebo, that fulfilled one or more of the following criteria

- resulted in death
- was immediately life-threatening
- required subject hospitalization or prolongation of existing hospitalization
- resulted in persistent or significant disability or incapacity
- was a congenital abnormality or birth defect
- was an important medical event that may have jeopardized the subject or may have required medical intervention to prevent one of the outcomes listed above

Significant AEs of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the subject from study treatment, were classified as other adverse events (OAEs).

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

The sponsor presented a pooled analyses of adverse events in any category, common adverse events, SAEs and AEs of special interest in both clinical studies (see Table 10 and Table 11). There were some apparent differences in the AE patterns between the younger and older children. In general, most of the AEs were consistent with respiratory symptoms/infections (upper respiratory tract infection, cough, oropharyngeal pain, nasopharyngitis, nasal congestion, rhinorrhea, and pharyngitis) along with a febrile illness (pyrexia). As expected, bronchitis, otitis media and pyrexia were more common in the younger (<6 years of age) children (Study 328). In the absence of a placebo group it is difficult to assess if this is the age-related background rate of these illnesses or drug-related. The younger children, most of whom had renal disease, were also more prone to develop urinary tract infections and to experience gastrointestinal complaints (diarrhea/vomiting). Headache and dizziness complaints were more common in the older children. However the data should be interpreted in terms of duration of exposure (see reviewers addendum below sponsor's Table 10). For example based on patient weeks of exposure, the incidence of headache would be similar in the treatment and placebo groups. The small number of subjects in the placebo group also makes the data difficult to interpret.

Four subjects had hypotension (one subject discontinued due to this AE) and 3 had orthostatic hypotension reported from Studies 261Aand B; investigators considered all of these AEs to be

drug related. Three subjects had syncope and 1 subject had convulsion reported as AEs reported in Study 261; none led to study discontinuation. In study 328, syncope was reported for 1 subject (0.4 mg/kg candesartan) and the investigator considered this AE as possibly drug-related.

Four subjects experienced hypersensitivity reported as mild and related to environmental allergies, one subject experienced an anaphylactic reaction with respiratory compromise reported as due to raspberries, which did not lead to study drug discontinuation. Subjects reported papular, pustular, erythematous and pruritic rash but these did not lead to subject discontinuation.

SAEs and discontinuations due to AEs are discussed with the individual studies and laboratory data was not pooled. Since the etiology of hypertension, incidence of underlying renal disease (also see section 7.2.1), the normal range of laboratory values, ability to perceive and communicate AEs, the expected background diseases or AEs and the use of other anti-hypertensive medications was different in the two age-groups; the primary medical reviewer is of the opinion that safety signals should be analyzed separately.

Table 10: Number (%) of subjects with adverse events in descending frequency by active pooled group and occurring with an incidence of at least 3.0% in the active pooled column (Safety population)

	Placebo	Candesartan treatment				
Adverse event preferred term	Study 261A short term	Study 261A short term	Study 261B long term	Study 328 short term	Study 328 long term	Active pooled 261A, 261B, 328
	N=35 n(%)	N=205 n (%)	N=235 n (%)	N=93 n (%)	N=85 n (%)	N=348 n (%)
Number of subjects with an AE	22 (62.9)	105 (51.2)	174 (74.0)	58 (62.4)	78 (91.8)	276 (79.3)
Upper respiratory tract infection	1 (2.9)	10 (4.9)	46 (19.6)	10 (10.8)	15 (17.6)	73 (21.0)
Headache	3 (8.6)	33 (16.1)	47 (20.0)	4 (4.3)	5 (5.9)	70 (20.1)
Cough	3 (8.6)	12 (5.9)	23 (9.8)	8 (8.6)	32 (37.6)	68 (19.5)
Pyrexia	1 (2.9)	2 (1.0)	15 (6.4)	13 (14.0)	32 (37.6)	55 (15.8)
Dizziness	2 (5.7)	14 (6.8)	24 (10.2)	0	0	34 (9.8)
Oropharyngeal pain	0	10 (4.9)	23 (9.8)	1 (1.1)	3 (3.5)	34 (9.8)
Nasopharyngitis	0	3 (1.5)	7 (3.0)	3 (3.2)	15 (17.6)	25 (7.2)
Diarrhea	1 (2.9)	2 (1.0)	9 (3.8)	5 (5.4)	12 (14.1)	24 (6.9)
Vomiting	0	4 (2.0)	7 (3.0)	2 (2.2)	11 (12.9)	22 (6.3)
Nasal congestion	3 (8.6)	3 (1.5)	14 (6.0)	0	5 (5.9)	21 (6.0)
Rhinorrhea	0	2 (1.0)	4 (1.7)	7 (7.5)	12 (14.1)	20 (5.7)
Fatigue	0	4 (2.0)	10 (4.3)	5 (5.4)	3 (3.5)	19 (5.5)
Urinary tract infection	0	1 (0.5)	4 (1.7)	2 (2.2)	10 (11.8)	17 (4.9)
Gastroenteritis	0	2 (1.0)	9 (3.8)	0	6 (7.1)	16 (4.6)
Pharyngitis	2 (5.7)	2 (1.0)	8 (3.4)	3 (3.2)	6 (7.1)	16 (4.6)
Abdominal pain upper	0	5 (2.4)	5 (2.1)	2 (2.2)	5 (5.9)	15 (4.3)
Bronchitis	0	2 (1.0)	4 (1.7)	1 (1.1)	9 (10.6)	15 (4.3)
Otitis media	0	1 (0.5)	1 (0.4)	2 (2.2)	13 (15.3)	15 (4.3)
Rhinitis	1 (2.9)	3 (1.5)	5 (2.1)	4 (4.3)	7 (8.2)	14 (4.0)
Sinus congestion	1 (2.9)	1 (0.5)	13 (5.5)	0	0	14 (4.0)
Sinusitis	0	3 (1.5)	11 (4.7)	0	1 (1.2)	14 (4.0)
Asthma	0	2 (1.0)	7 (3.0)	2 (2.2)	2 (2.4)	11 (3.2)

N Total number of subjects. n Number of subjects with an AE.
Derived from Tables 6.2 and 6.3 in Section 6.

Source: Sponsor's Table 5, Summary of clinical safety, pg 22

Approximate Exposure (Patient	Placebo Study 261A	Short-term-261A	Long term-261B	Short term-328	Long term 328
Weeks)	*88*	*820*	*12,220*	*372*	*4420*

Table 11: Adverse events of special interest by study and intensity (Safety population)

	Placebo	Candesartan treatment Number of subjects (intensity)				
Preferred term	Study 261	Study 261A, short term	Study 261B long term	Study 328 short term	Study 328 long term	Active pooled: Studies 261A, 261B, 328 N=348 n (%)
	N=35	N=205	N=235	N=93	N=85	
Rash	0	1 (mild)	5 (4 mild, 1 moderate)	0	3 (all mild)	9 (2.6)
Rash papular	1 (mild)	0	0	0	0	0
Rash pustular	0	0	0	1 (mild)	0	1 (0.3)
Rash erythematous	0	0	1 (severe)	1 (mild)	0	2 (0.6)
Pruritus	1 (mild)	0	2 (all mild)	0	0	2 (0.6)
Hypotension	0	2 (all moderate)	3 (1 mild, 2 moderate)	0	0	4 (1.1)
Orthostatic hypotension	0	1 (mild)	3 (all mild)	0	0	3 (0.9)
Hypersensitivity	0	1 (mild)	4 (all mild)	0	0	4 (1.1)
Drug hypersensitivity (vancomycin)	0	0	0	0	1 (moderate)	1 (0.3)
Anaphylactic reaction	0	1 (moderate)	0	0	0	1 (0.3)
Convulsion	0	0	1 (severe)	0	0	1 (0.3)
Syncope	0	1 (moderate)*	1 (severe)	1 (moderate)	0	3 (0.9)
Syncope vasovagal	0	0	1 mild	0	0	1 (0.3)

* Site changed the verbatim term to 'near syncopal episode'; the preferred term is 'presyncope'. This was changed by the site after the Study 261A database was locked. This child had concurrent cough, sore throat, and dizziness.
Note: An AE can continue into the next study or period.
Derived from Table 25 in CSR 261A, Table 31 in CSR 261B, and Table 38 in CSR 328, see Module 5.

Source Sponsors Table 7 from the Summary of Clinical safety, pg-28

7.2 Adequacy of Safety Assessments

The safety database for 1-5 yr old patients is relatively small but acceptable, considering the patient population. The duration of exposure appears adequate in both studies. Except for additional information that is requested for the subjects discussed in the safety summary and relevant sections, the assessments for studies 261A and B appear adequate to exclude a large safety signal.

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

Refer to Section 6.1.2 for subject demographics.

7.2.2 Explorations for Dose Response

Exposure: Study 328

Table 12: Descriptive statistics for time (days) on double-blind treatment, open label treatment, and total treatment (safety population and open-label population).

Categort		Candesartan double-blind treatment group				Candesartan
		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 (%)	Open-label N=85 n (%)
Double-blind treatment	N	29	32	32	93	85
	Mean (SD)	27.2 (5.9)	27.0 (5.5)	27.5 (3.6)	27.2 (4.3)	28.4 (1.4)
	Min, max	7, 36	6, 35	13, 33	6, 36	26, 35
	Median	28.0	28.0	28.0	28.0	28.0
Open-label treatment	N	26	28	30	84	84
	Mean (SD)	368.0 (21.7)	370.7 (15.4)	357.7 (51.8)	365.2 (34.4)	365.2 (34.5)
	Min, max	306, 439	349, 427	124, 410	124, 439	124, 439
	Median	364.0	366.5	369.0	366.0	366.0
Total treatment	N	29	32	32	93	85
	Mean (SD)	357.1 (119.5)	351.3 (129.5)	362.9 (104.2)	357.1 (102.0)	389.4 (52.3)
	Min, max	7, 466	6, 455	13, 438	6, 466	29, 466
	Median	392.0	394.0	397.5	394.0	394.0

N Total number of subjects in each treatment group. n Number of subjects in each category.
Note: Total treatment includes subjects who discontinued during the double-blind period, which affects the mean durations and results in smaller mean values than in the open-label period. Median values may be more informative.
Data derived from Table 11.1.24, Section 11.1.

Source: Table 32, CSR for Study 328, pg-85

Exposure: Study 261 A& B

An overview of exposure (duration of treatment and doses received) for Study 261A &261B is presented in Table 13 and Table 14)

In study 261B 76% were treated for a year, mean duration of treatment was 343 days. 64% of all subjects started candesartan treatment at the 8 mg dose. By Week 52/LOCF, approximately equal proportions of subjects were taking an 8 mg, 16 mg, or 32 mg dose (29%, 24% and 23%, respectively).

Table 13 Overview of study treatment –Study 261 A

		Treatment group					
		Placebo N=35	2/4 mg N=69	8/16 mg N=68	16/32 mg N=68	Active pooled N=205	Total N=240
Days on treatment	1 to 7	1 (2.9)	1 (1.4)	1 (1.5)	0	2 (1.0)	3 (1.3)
	8 to 14	0	1 (1.4)	2 (2.9)	1 (1.5)	4 (2.0)	4 (1.7)
	15 to 21	0	0	1 (1.5)	1 (1.5)	2 (1.0)	2 (0.8)
	22 to 28	18 (51.4)	51 (73.9)	45 (66.2)	45 (66.2)	141 (68.8)	159 (66.3)
	>28	16 (45.7)	16 (23.2)	19 (27.9)	21 (30.9)	56 (27.3)	72 (30.0)
	Mean (SD)	28.3 (4.4)	27.6 (3.9)	27.1 (4.3)	27.8 (3.1)	27.5 (3.8)	27.6 (3.9)
	Median	28.0	28.0	28.0	28.0	28.0	28.0
	Range	5 to 36	7 to 35	5 to 34	10 to 35	5 to 35	5 to 36

Data derived from Tables 11.1.16 and 11.1.17, Section 11.1.

Source: Table 22, pg 78 in the CSR for Study 261A

Table 14: Subject by duration of treatment, ITT population, Study 261B

Duration of treatment	N=233 n (%)
1 to 30 days	4 (1.7)
31 to 120 days	10 (4.3)
121 to 240 days	12 (5.2)
241 to 360 days	29 (12.4)
>360 days	178 (76.4)

Derived from Table 11.1.11, Section 11.

Source: table 25, pg 72, CSR for Study 261B

7.2.3 Special Animal and/or In Vitro Testing

NA

7.2.4 Routine Clinical Testing

In study 261B, subject E0003008 had an ALT result of 146 IU/L and an AST result of 103 IU/L on Day 387, no f/u information was available. This was requested from the sponsor and reviewed. The subject was evaluated for renal colic 2yrs later and LFT's were normal in this visit. Similarly a few other subjects with elevated ALTs (around 1.5X ULN) did not have follow-up data. Excluding these cases the routine clinical testing done by the sponsor appears adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

NA

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

See sections 7.1.3 and 7.3.4 for discussion of AEs of special interest

7.3 Major Safety Results

7.3.1 Deaths

Study 328
One child (3yr old female) died in the study due to progressive renal failure secondary to chronic glomerulonephritis on Day 200 of the study (0.42 mg/kg candesartan). She had been ill since birth with recurrent viral infections and developed a severe nephrotic syndrome. Eventually the nephrotic syndrome stabilized with steroid and immunosuppressive therapy. The presumptive diagnosis was focal segmental glomerulonephritis (no renal biopsy results are available). This child had progressive chronic renal insufficiency as evidenced by increases in serum creatinine (Day 8=0.6 mg/dl; Day 29=1.1 mg/dl [normal range 0.2 to 0.5 mg/dl]) and decreases in GFR (eGFR Day 8=82 ml/min; Day 29=46 ml/min [normal range 80 to 125 ml/min]). The child became increasingly ill over several days and had dark diarrheal stools. Disseminated intravascular coagulation (severe coagulopathy) was suspected. The investigator encouraged the family to bring the child in for medical care (documented as information over phone in CRF). However, the child died at home on Day 200 (1 day before the planned medical visit). Autopsy results showed chronic bilateral glomerulonephritis complicated by lung edema, anasarca, and renal insufficiency. Also brain edema and dystrophic changes of liver, kidneys, and myocardium were present. Based on review of the data the sponsor's conclusion appears reasonable.

261A&B
There were no deaths reported

7.3.2 Nonfatal Serious Adverse Events

Study 328
A total of 14 children had non-fatal SAEs, none led to treatment discontinuation (Table 15). The most common non-fatal SAEs were urinary tract infection and pyrexia. On review of the narratives, all the subjects with SAEs required hospitalizations. There was one case each of pyelonephritis and nephrotic syndrome. The subject with nephrotic syndrome had a prior history of nephrotic syndrome and experienced a relapse. One subject was hospitalized with severe respiratory distress requiring intubation and assisted ventilation due to parainfluenza pneumonia. There were two other cases of pneumonia and bronchiolitis. One subject experienced a drug hypersensitivity reaction due to vancomycin. The sponsor's conclusion regarding SAEs being unrelated to study drug appears reasonable.

Table 15: Number and percent of subjects who had non-fatal serious adverse events by preferred term in descending frequency, Study 328

Preferred term	4-week double-blind[a]			Open-label period[a]	Pooled[a] 4-week and open-label period
	0.05 mg/kg N=29 n (%)	0.2 mg/kg N=32 n (%)	0.4 mg/kg N=32 n (%)	All dose levels N=85 n (%)	All dose levels N=93 n (%)
Number of subjects with at least 1 SAE	1 (3.4)	0	1 (3.1)	14 (16.5)	15 (16.1)
Urinary tract infection	0	0	1 (3.1)	3 (3.5)	4 (4.3)
Pyrexia	0	0	0	2 (2.4)	2 (2.2)
Bronchiolitis	0	0	0	1 (1.2)	1 (1.1)
Catheter site hematoma	1 (3.4)	0	0	1 (1.2)	1 (1.1)
Catheter site necrosis	0	0	0	1 (1.2)	1 (1.1)
Drug hypersensitivity	0	0	0	1 (1.2)	1 (1.1)
External ear cellulites	0	0	0	1 (1.2)	1 (1.1)
Glomerulonephritis, chronic	0	0	0	1 (1.2)	1 (1.1)
Lymphadenitis	0	0	0	1 (1.2)	1 (1.1)
Nephrotic syndrome	0	0	0	1 (1.2)	1 (1.1)
Pneumonia	0	0	0	1 (1.2)	1 (1.1)
Pneumonia parainfluenza viral	0	0	0	1 (1.2)	1 (1.1)
Post procedural hemorrhage	0	0	0	1 (1.2)	1 (1.1)
Pyelonephritis	0	0	0	1 (1.2)	1 (1.1)
Upper respiratory tract infection	0	0	0	1 (1.2)	1 (1.1)
Vena cava thrombosis	0	0	0	1 (1.2)	1 (1.1)

[a] Subjects with multiple AEs in the same category are counted only once in that category. Subjects with AEs in more than 1 category are counted once in each of those categories.
AE Adverse event; N Total number of subjects at each dose; n Number of subjects with an AE; SAE Serious adverse event.
Data derived from Table 11.3.4.1.

Source: table 36, CSR for Study 328, pg-90

261A
A 14 yr old black female (003-7020) experienced a non-fatal SAE of anaphylactic reaction on Day 24 of treatment. This subject received placebo run-for 5 days, and was randomized to 4 mg candesartan cilexetil from 8 April 2004 to 02 May 2004. She had an acute onset of facial itching, rash, swelling, and dyspnea. Medical history included allergies (eggs, pollen, grass, raspberries), asthma, eczema and mild left ventricular hypertrophy. Concomitant medications recorded at screening (24 March 2004) included Depo-Provera, lisinopril, albuterol, elidel, and triamcinolone topical. On Day 24 ((b) (6)), the subject was taken to the emergency room because of an anaphylactic reaction and was treated with Epi-pen twice, oral benadryl, prednisone 60 mg orally, and famotidine 20 mg. On review of the CRF, treatment was stopped on May 3 2004, however on review of the datasets, the subject did continue in Study 261B. The investigator's conclusion that the event was unrelated to study drug appears reasonable.

261B
14 subjects had non-fatal SAEs . Two subjects discontinued due to these events-they are discussed below. The other SAEs which appear unrelated to study drug are coarctation of the aorta, appendicitis/congestive heart failure (one day post-appendectomy due to fluid overload)

tibial fracture, anxiety/asthma, ovarian cyst, slipped femoral epiphysis, dehydration/hyponatremia, ligament rupture, asthma and wrist fracture/displacement.

Subject E0001/002 was a 14-year-old black female. In addition to hypertension she had diagnoses of attention deficit disorder and bipolar disorder: concomitant medications included Strattera (atomoxetine hydrochloride) and Gabitril (tiagabine hydrochloride), respectively. At entry into Study 261A the subject was noted to have trace proteinuria (6 mg/L) and a serum creatinine value of 0.9 mg/dl. She completed Study 261A and progressed into Study 261B but was referred to a nephrologist for evaluation of hypertension and proteinuria. She received 4mg of study drug in 261A and a maximum dose of 8mg in 261B. An observation plan was recommended. This was followed by a renal biopsy which showed focal degenerative tubular changes, findings which were interpreted as consistent with toxic / medication effects. Accordingly, all medications were discontinued. On follow-up, urinary microalbumin was <3 mg/L (microalbumin:creatinine ratio <2mg/g). The sponsor reported no association to study drug. On review of the CRF, patient had the AE listed as tubular necrosis. Study drug was dispensed starting Dec 4, 2003 and was discontinued on April 20, 2004. Baseline microalbumin and albumin/creatinine ratios are unavailable. The nephrology consultation and renal biopsy reports were requested from the sponsor and reviewed. Although confounded by the concomitant medications, relationship of nephrotoxicity to study drug cannot be excluded. Tiagabine does have renal failure listed in the PI under other AEs observed during the clinical trials as an infrequent event (1/100 to 1/1000 patients). Atomoxetine has no nephrotoxicity reported in the PI.

Subject E0011/004 was a 15-year-old white male. In addition to hypertension, this subject had a history of chronic renal insufficiency since February 2004. The subject had undergone renal biopsy (date unknown), which revealed focal sclerosis. This subject entered Study 261A in April 2004. After completing the 4-week DB portion of the study, he started the open-label extension study in May 2004. On Day 81 of the study (29 July 2004), this subject started mycophenolate to slow the progression of the renal disease. Over the following week, he developed nausea, vomiting, diarrhea, and light-headedness; on 9 August 2004 the investigator had the subject stop mycophenolate and there was prompt resolution of symptoms. The subject's renal function continued to decline however and the study drug was discontinued on 7 September 2004. The subject started peritoneal dialysis on 15 October 2004 and a renal transplant was planned. At entry to Study 261A (2 April 2004), Subject E0011/004 had evidence of renal disease as reflected in abnormal baseline laboratory abnormalities: potassium 6.4 meq/L, BUN 23 mg/dl, creatinine 2.2 mg/dl, and A/C ratio 193mg/g. After completing double-blind treatment (May 10) with 32 mg candesartan, these values were 5.2 meq/L, 22 mg/dl, 2.1 mg/dl, and 158 mg/g, respectively. On 13 July 2004, his A/C ratio was 6643 mg/g; his dose of candesartan was increased from 8 mg to 16 mg on 7 June and again increased to 32 mg on 13 July 2004. He continued to receive the 32 mg dose until he was discontinued from the study, at which time his potassium was 4.4 meq/L, BUN 59 mg/d, and creatinine 6.7 mg/dl.. The sponsor's conclusion that this SAE was due to progression of chronic renal failure and unrelated to study drug appears reasonable.

Subject E0003/008, a 14 yr old female with no prior history of seizures was admitted to emergency room after slumping against a friend while in school and reporting vision narrowing and getting dark in addition to numbness and weakness in her extremities. Episode lasted approximately 1 to 1.5 minutes. Subject was not treated for the suspected seizure and was discharged home the same day. Based on the history the diagnosis is compatible with seizure disorder. The event occurred on day 378 and the subject continued treatment.

Subject E 0004/004, a 9yr old male was hospitalized on Day 157 for a 30 second syncopal episode while shopping with mother. Physician attributed the event to dehydration; subject had been in camp all day. Subject continued treatment in the study.

7.3.3 Dropouts and/or Discontinuations

Study 328
Subject E0401004 was a 5-year-old boy who had moderate abdominal pain and fatigue, and mild nausea that started on Day 11 of treatment. He was receiving candesartan 0.05 mg/kg. This child had no relevant medical history and there were no relevant concomitant medications. The nausea stopped on Day 14, but abdominal pain and fatigue were ongoing. The investigator discontinued this subject on Day 37 and considered the AEs related to study medication. On review of the CRF additional complaints included diarrhoea, URI; eGFR remained at 118ml/min and LFTs were normal. Patient's bicarbonate decreased to 17 from 19 meq/L. The etiology for the patient's symptoms remains unclear but is clearly confounded by a possible viral illness.

One subject had an abnormal potassium value reported as an AE. Subject E0034002 (2-year old, Black, male) had potassium increased (mild) reported as an AE on Day 14 of treatment (baseline value was 4.4 meq/L (normal range 3.5 to 5.5 meq/L). On Days 7 and 14 the potassium values were 5.0 and 6.1 meq/L, respectively. No assessments or laboratory data are available after Day 14. Treatment was reported as 'temporarily stopped' due to this AE and then the subject was lost to follow-up. This child had a medical history of renal dysplasia, hydronephrosis and urologic surgery. The sponsor reported this as an AE under clinical laboratory evaluation.

Study 261A
Three candesartan cilexetil-treated subjects were discontinued due to non-serious AEs: hypotension related to study drug (n=1, candesartan 32 mg), compound fracture of the left radius and ulna unrelated to study drug (n=1), and worsening of dizziness which was reported as study drug unrelated because the subject had a history of the same (n=1, 16 mg candesartan). However on review of the narrative, this appears possibly related to study drug since the subject experienced a worsening of the same. One placebo-treated subject discontinued because of hypertension and headache.

Study 261B
A total of five subjects had AEs that led to discontinuation. They are discussed below

Table 16: Adverse events leading to study discontinuation by preferred term in descending frequency, Study 261B

Preferred term	N=235 n (%)
Number of subjects with at least 1 AE leading to study discontinuation	5 (2.1)
White blood cell count decreased	2 (0.9)
Dizziness	1 (0.4)
Hyperkalemia	1 (0.4)
Nephropathy toxic	1 (0.4)
Renal failure	1 (0.4)
Renal failure chronic	1 (0.4)

Note: A subject is counted once and only once in a preferred term. A subject may have more than 1 adverse event leading to discontinuation.
Derived from Table 11.3.5.1.1, Section 11.

Source: Table 30 in the CSR for 261B, pg 81.

Subjects who discontinued due to chronic renal failure/hyperkalemia and toxic nephropathy have already been discussed earlier under SAEs.
Two subjects discontinued due to the AE of WBC count decreased after being on study drug for 336 days and 187 days respectively. For subject E0047011, a 15 yr old black male, the WBC counts (ANC) were between 2.9 (1.35), and 3.0 (1.41) x 10^3/UL on Visits 1 and 9, respectively and similar to screening values. The sponsor's conclusion of no causal relationship to study drug appears reasonable. However for subject E0047009 the WBC counts were 4.0-4.7X10^3/UL at screening and during study 261A . This subject received placebo during the entire double blind period of Study 261A. She entered Study 261B and had the following WBC counts (absolute neutrophil counts): 4.1 (2.43), 3.4 (1.86), 3.4 (1.51), and 3.7 (1.81) x 10^3/UL, on Visits 1, 5, 6, and 9, respectively. Other hematologic results (RBC counts, hemoglobin, and platelet counts) were normal throughout the study. Hence this event although mild appears causally related to study drug.
Subject E0047012, a 14 yr old black male on 4 mg candesartan was discontinued from treatment due to worsening of dizziness on Day 4. The AE resolved in 3 days and was causally related to study drug. The baseline BP was 124/83 mmHg. Blood pressure values during active treatment were not recorded. The investigator discontinued the subject from the study on 31 January 2006 (Day 169); 3 BP values done on Day 169 while receiving no BP treatment were 128/70, 130/68, and 126/72 mmHg.

7.3.4 Significant Adverse Events

Also refer to Section 7.1.3 for pooled discussion of these events. As expected, especially in volume depleted states, hypotension, orthostatic hypotension and syncope were observed AEs and appeared to be dose dependent.

Study 328

One subject on the 0.4 mg/kg dose of candesartan experienced syncope that was judged to be possibly drug related.

Study 261A

There were two cases of **hypotension** in subjects on *high and mid-dose* candesartan, one case of **orthostatic hypotension** on *mid-dose candesartan* and one case of **syncope/near syncopal episod**e in one subject on *high-dose* candesartan.

Study 261B

There were three events of **hypotension**: Subject E0015001 on candesartan 16 mg, Subject E0019001 on 4 mg candesartan, Subject E0500008 on candesartan 8 mg. On review of the narratives, as expected a drug-related effect is evident. The subjects on 8 and 16 mg candesartan continued on the study at a reduced dose (up to 2mg on day 332 for subject E0500008).

There were three subjects who had **orthostatic hypotension:** Subject E0300002 on candesartan 32 mg, Subject E0300003 on candesartan 8 mg, Subject E0011007, on candesartan 8 mg. On review of the narratives all the events were drug related as proposed by the sponsor. The dose was not reduced for the subjects on 8mg candesartan but was reduced from 32mg to 8mg for subject E0300002.

Subject E0004004, a 9 yr old Caucasian, male, on candesartan 8 mg experienced **syncope** (severe) on Day 157 of treatment. The sponsor reported the event as not study drug related but the dose was lowered to 4 mg. Similarly subject E0003012 a 12 yr old male on candesartan 16mg experienced syncope on day 59 reported as vasovagal but had a dose reduction to 8mg. Clearly there was an association to study drug with a dose related effect in both these cases.

Subject E0003008 experienced **convulsion** (severe) on Day 378 of treatment: see SAE narrative).

Because of the recognized association between RAS inhibitors and a risk for angioedema, the AEs reported were searched by the sponsor and there were no reports of angioedema. None of the cases of hypersensitivity was considered related to study drug. A number of miscellaneous rashes were reported (also discussed in section 7.1.3)

7.3.5 Submission Specific Primary Safety Concerns

Based on review of the clinical trial data there do not appear to be any unexpected AEs compared to adults

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Refer to Section 7.1.3

7.4.2 Laboratory Findings

Study 328

Mean changes from baseline in hematology were small (see

Figure 6. Scatter plots for baseline vs. visit 7 and visit 15 values done by this reviewer).

During this 56-week study 4 subjects had findings consistent with iron deficiency anemia and anemia of chronic disease based on review of the narratives (1 of these subjects also had a RBC abnormality reported), and 1 subject had WBC count increased up to 29.3X 10^3/UL on Day 441 of treatment which resolved on day 447. This child had nephrotic syndrome. Few subjects shifted from normal WBC and platelet count to values above or below the normal range at the end of week 4 and week 56.

Mean change in clinical chemistry values were small. Mean estimated GFR declined by 5.8 ml/minute at week 4 and by 6.8 ml/minute at week 56 compared to baseline per sponsors analyses. It is unclear how reliable this estimation is since a few subjects had baseline eGFR's greater than 200(up to 462 ml/minute in one subject) which seems unusual in this population with predominantly secondary hypertension. Median values are not reported. Three subjects had large declines in eGFR (Subject E0034002 had a change in eGFR from 91 ml/min at baseline to 25 ml/min on Day 7 and then an increase to 57 ml/min on an unknown date, Subject E0801002 had a change from 82 ml/min at baseline to 46 ml/min on Day 29 [no follow-up was done]), and Subject E704003 had a decline of 60 ml/min then improved to near baseline values of approximately 87 ml/min.

Seven subjects had creatinine values that were >30% increase from baseline, the post-baseline values for these subjects ranged from 0.3 to 1.1 mg/dl. Subject E0801002 who died due to chronic glomerulonephritis has been discussed earlier. Two subjects had nephrotic syndrome reported as AEs. On review of the sponsor's report both had a history of nephrotic syndrome with normal eGFRs and creatinine throughout the study. Association to study drug appears unlikely.

The subject who discontinued due to hyperkalemia has been discussed earlier under Section 7.3.3.

As also noted in the scatter plots and Table 17 below, total of 23 subjects who had normal bicarbonate levels at baseline shifted to below normal values. 45 subjects were below normal at baseline, and 35 of these subjects stayed below normal levels at Week 4. At the end of week 56, a total of 26 subjects who had normal bicarbonate levels at baseline shifted to below normal. 43 subjects were below normal at baseline, and 34 of these subjects stayed below normal levels. The significance of this finding is unclear since there is confounding due to progression of renal disease in this population.

Table 17: Sponsor's shift tables for changes in Serum HCO3 from Visit 1, Study 328

Chemistry Parameter (units)	Treatment Group	Visit 1:	At Visit 7: Below n(%)	Within n(%)	Above n(%)	TOTAL n(%)
Bicarbonate, Standard (MEQ/L)	0.05mg/kg	Below	11 (91.7%)	1 (8.3%)		12 (26.7%)
		Within	8 (53.3%)	7 (46.7%)		15 (36.6%)
	0.20mg/kg	Below	11 (73.3%)	4 (26.7%)		15 (33.3%)
		Within	9 (64.3%)	5 (35.7%)		14 (34.1%)
	0.40mg/kg	Below	13 (72.2%)	5 (27.8%)		18 (40.0%)
		Within	6 (50.0%)	6 (50.0%)		12 (29.3%)
	Total	Below	35 (77.8%)	10 (22.2%)		45 (100.0%)
		Within	23 (56.1%)	18 (43.9%)		41 (100.0%)

Source: Table 11.3.7.1.11
Shifts from Visit 1 to Visit 7 according to Reference Ranges for Chemistry, CSR for Study 328

Chemistry Parameter (units)	Visit 1:	At Visit 15: Below n(%)	Within n(%)	Above n(%)	TOTAL n(%)
Bicarbonate, Standard (MEQ/L)	Below	34 (79.1%)	9 (20.9%)		43 (51.2%)
	Within	26 (63.4%)	15 (36.6%)		41 (48.8%)
	Total	60 (71.4%)	24 (28.6%)		84 (100.0%)

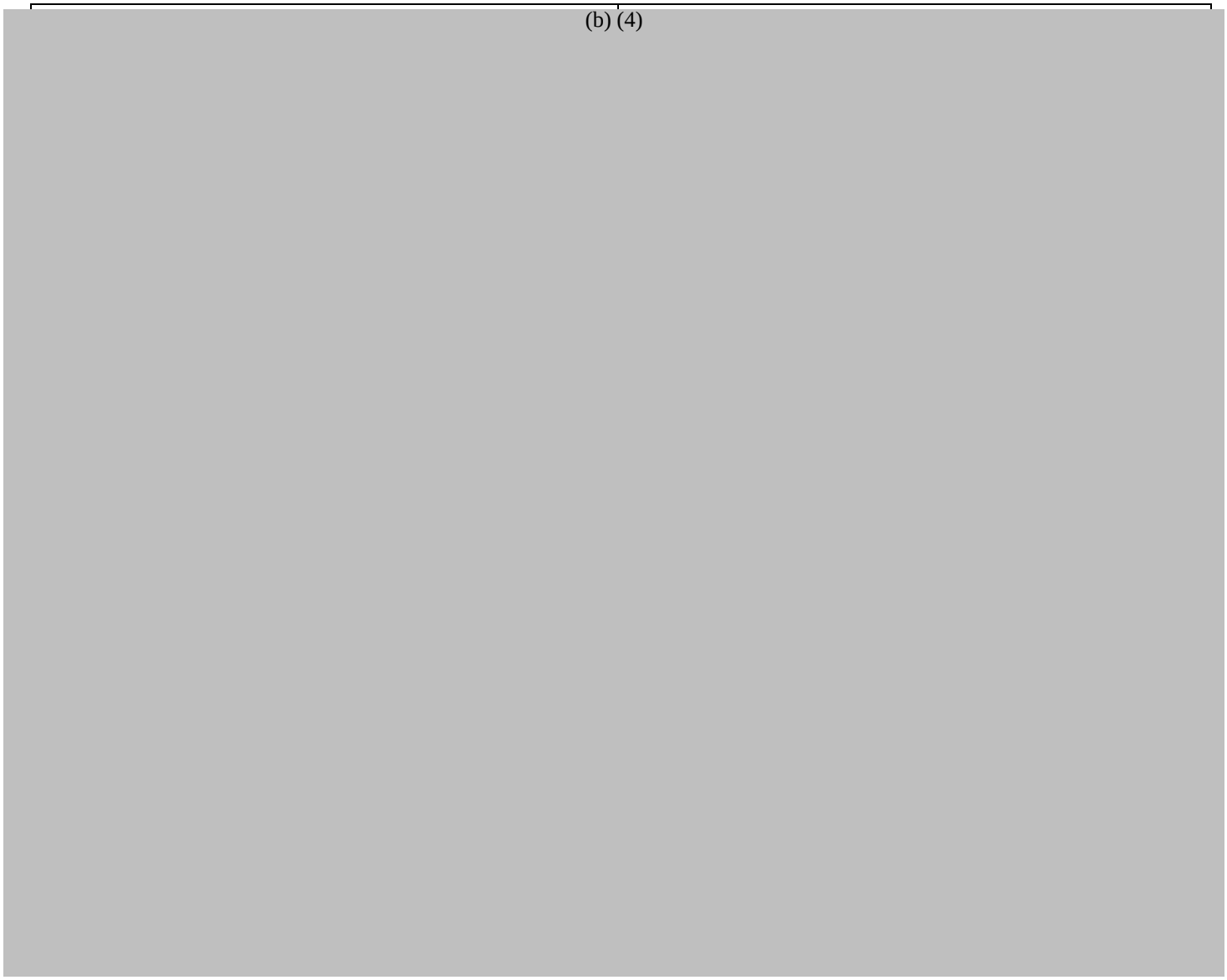
Table 11.3.7.1.12
Shifts from Visit 1 to Visit 15 (Week 56) according to Reference Ranges for Chemistry, CSR for Study 328

Subject E0039008 (1-year-old, male, race was reported as 'other') had mild metabolic acidosis (HCO3-16 meq/L) reported as an AE on Day 28 and the acidosis lasted until Day 392. This child's medical history included a lung disorder, gastro esophageal reflux disease, meconium peritonitis, and bowel reconstruction (possibly due to necrotizing enteritis), history of prematurity and maternal drug abuse. This case seems likely related to the child's co-morbidities.

As seen in the scatter plots below one subject had an ALT of 196 at visit 7 which declined later. Increased alkaline phosphatase (mild) was reported for Subject E0014005 (1-year-old, Caucasian, male), that started on Day 399 of treatment (alkaline phosphatase was 1120 IU/L, normal range 110 to 510 IU/L, all other liver enzymes were normal) and this AE resolved on Day 511. Subject E0102002 had an elevate sodium of 165 meq/L at visit 7 which declined to 145 meq/L by visit 15

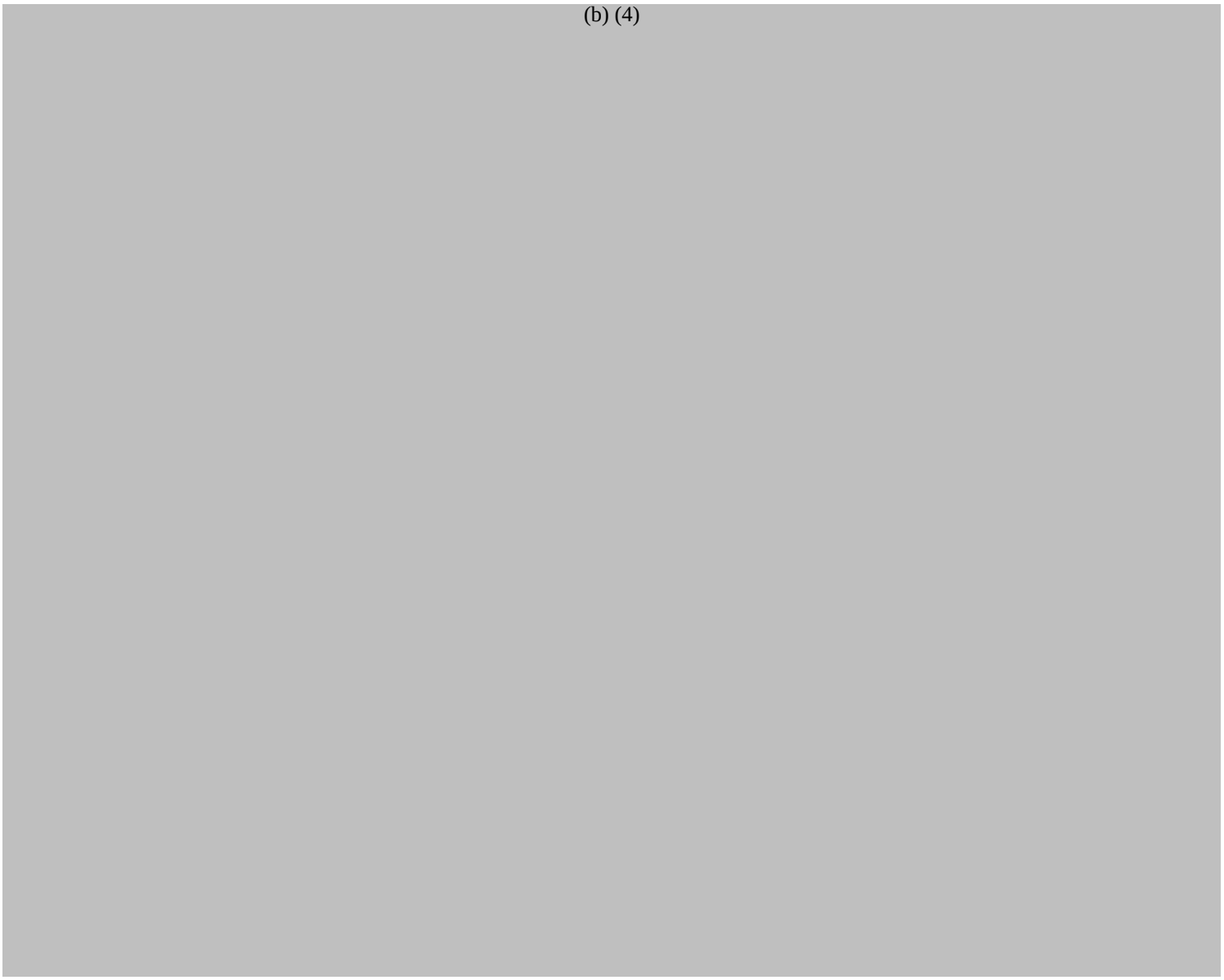
Figure 6: Reviewer's scatter plots of lab values for study 328 for visit 7 and 15 vs. baseline, 1 outlier with alkaline phophatase over 3000 U at visit 1 excluded, GFR- 1outlier with eGFR 462 at baseline excluded

(b) (4)

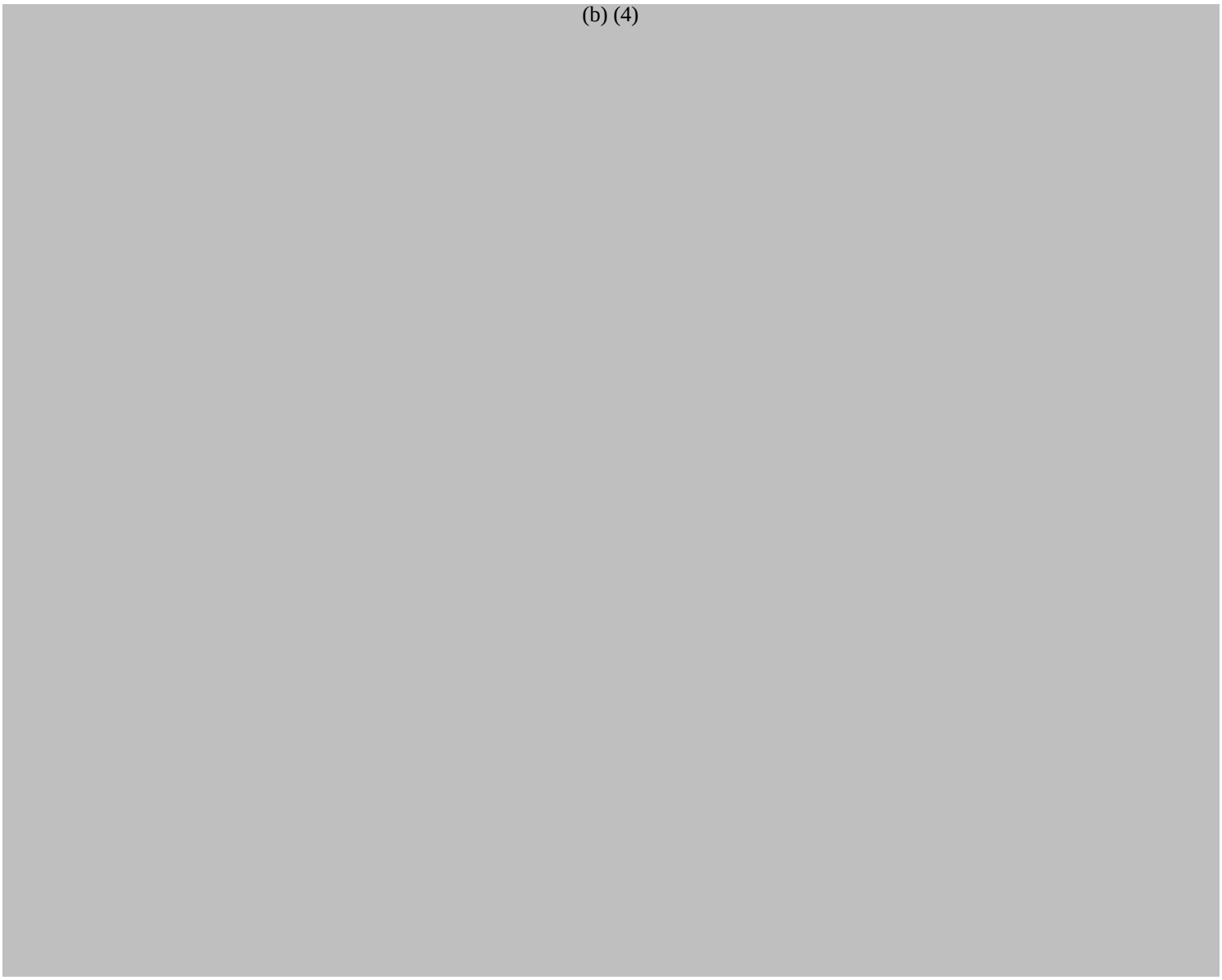


(b) (4)

(b) (4)



(b) (4)



(b) (4)

(b) (4)

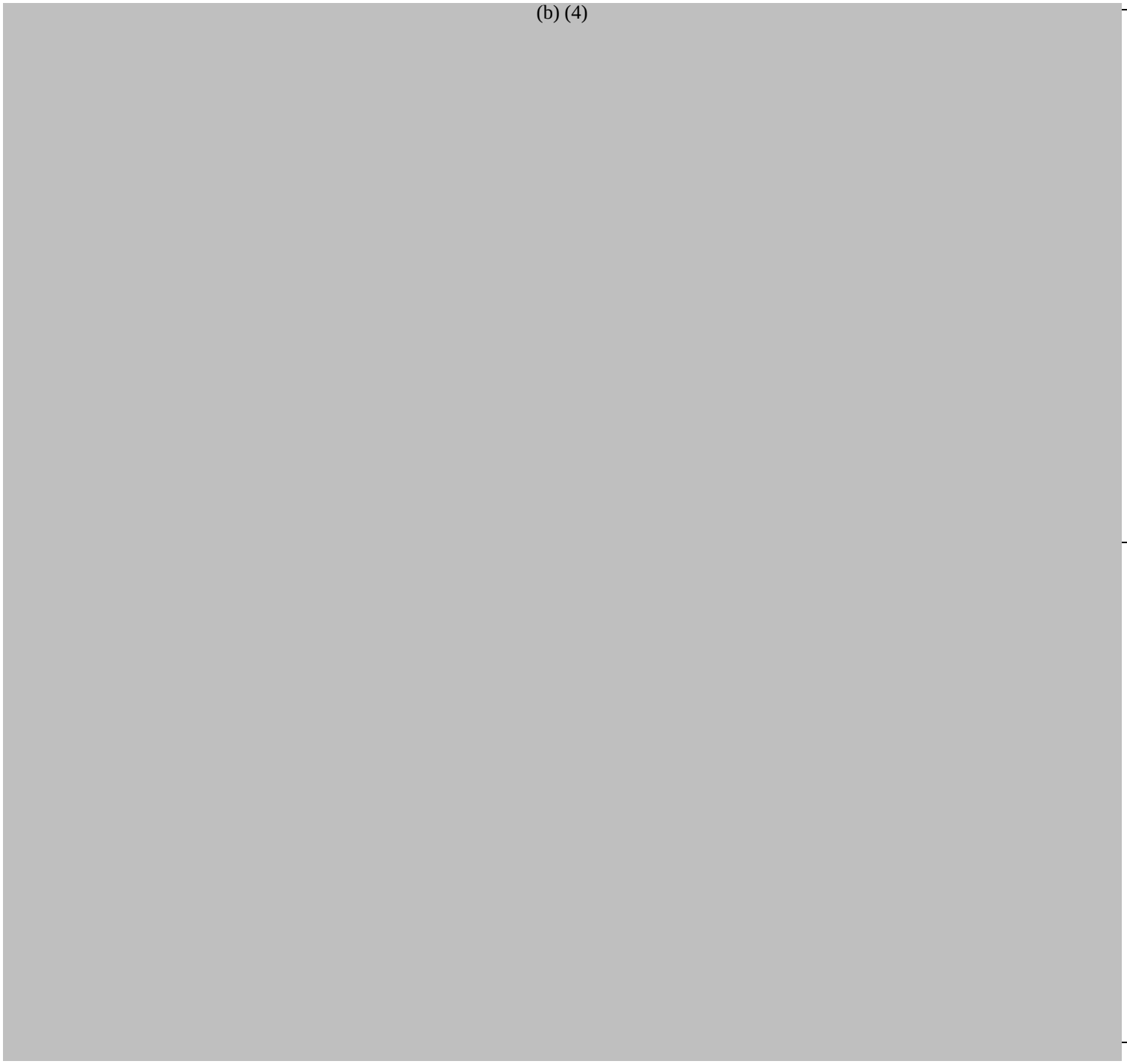
261A

Mean changes from baseline in hematology, clinical chemistry and values were small and comparable across all treatment groups. While more than 30% increase from baseline creatinine occurred in 3 subjects, they did not appear to be dose related (two of these subjects were on candesartan 4 mg). While some individual subjects had a increase in serum potassium from baseline and 3 subjects had an elevated serum potassium that normalized, overall there were no definitive trends or dose related effects.

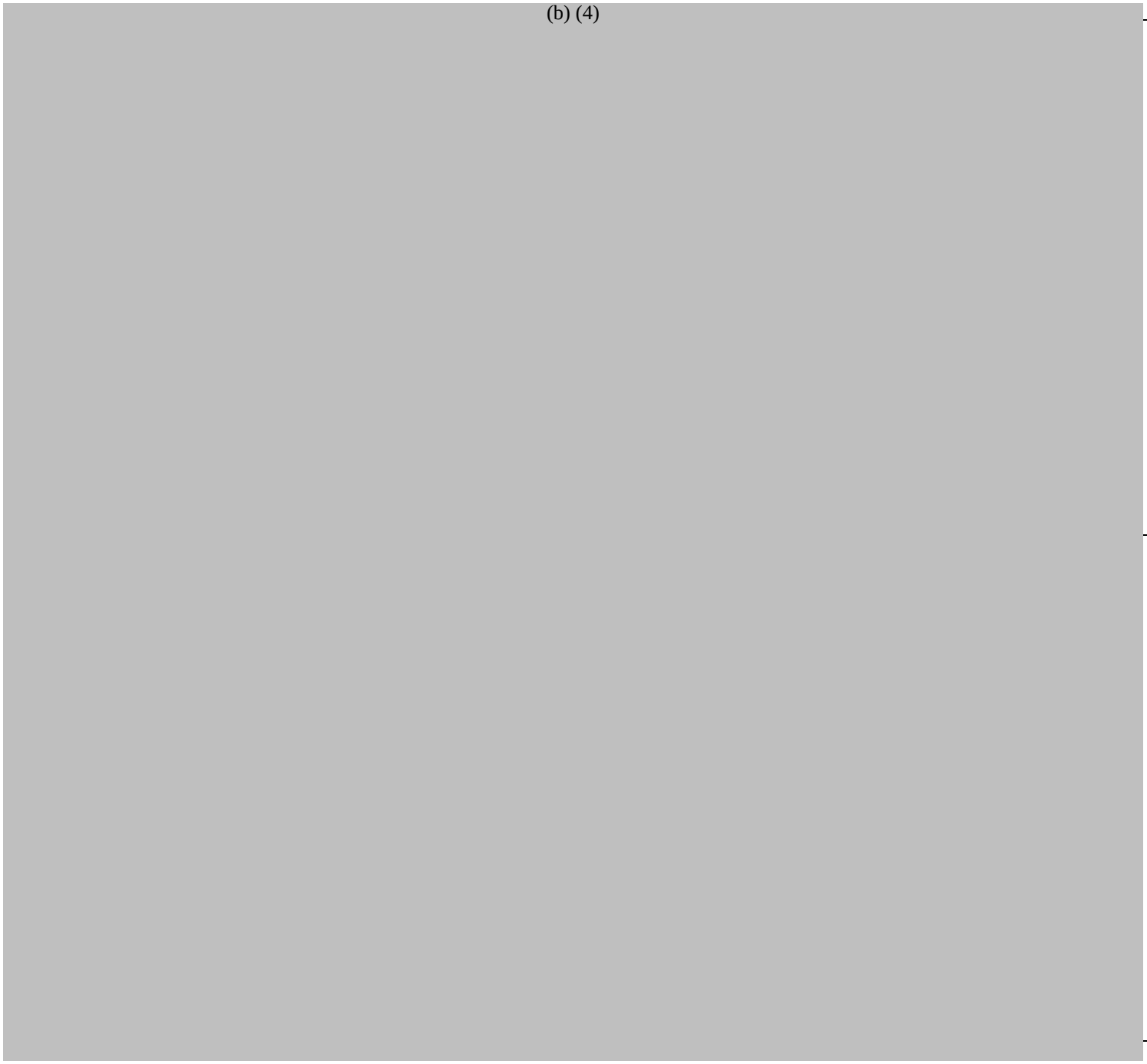
261B

Figure 7 Sponsor's scatter plots for baseline to week 52 values from the Clinical study report for 261B

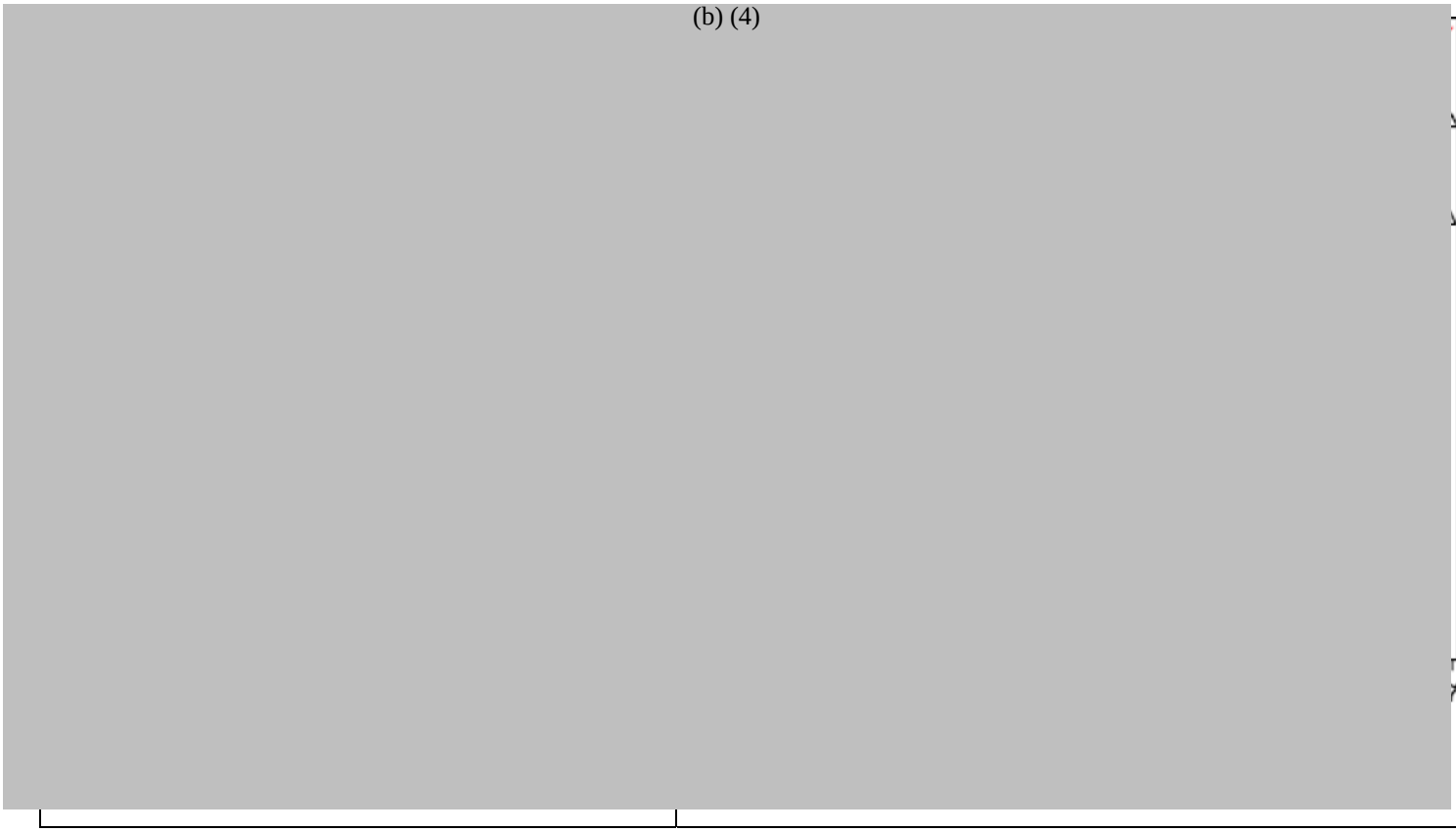
(b) (4)



(b) (4)



(b) (4)



Scatter plots for sponsor's lab results comparing baseline to visit 9 data are shown above and relevant individual findings are discussed below.
Mean changes from baseline in hematology values were small, Six subjects had AEs reported that were associated with a hematology laboratory abnormality . Four had anemia and two had decreased white blood cell counts(discussed earlier). Subject E0011004 had anemia reported on Day 65 of treatment (hemoglobin 9.7 g/dl). The Visit 1 value was 11.3 g/dl. The anemia was ongoing at the Final Visit, Day 121 (9.1 g/dl). The anemia was mild in intensity. This subject also had progressive chronic renal failure and was withdrawn from the study (discussed earlier).

Mean changes from Visit 1 to Week 52 for clinical chemistry parameters were small except for alkaline phosphatase, where the mean change was –39.6 IU/L (range: –208 to 134 IU/L) which is possibly reflective of the population studied and their change in pubertal stages over the year.

For potassium, two subjects shifted from within the normal reference range at baseline to above the reference range. Subject E0011004 had progressive chronic renal failure, Subject E0004003 (potassium results of 6.0 and 5.8 meq/l) had a normal creatinine on review of the datasets and was on candesartan 16mg.

The sponsor reported that a total of 24 subjects had changes in creatinine results that were greater than 30% increased from Visit 1. Among these the sponsor reported a 75-190% change in 7 subjects.

- Subject E0011004 (8 mg, 16 mg, and 32 mg doses) had a Visit 1 creatinine value of 2.1 mg/dl and a Visit 9 value of 6.1 mg/dl (190% change). This subject had renal failure described in the SAE section.
- Subject E0300001 (4 mg dose, maximum of 16 mg per datasets) had a Visit 1 creatinine value of 2.2 mg/dl and a Visit 9 value of 5.4 mg/dl (145% change). This subject had chronic renal insufficiency due to nefronoftisis (congenital cystic kidney disease) and continued in the study.
- The remaining five subjects with no known pre-existing renal disease had a baseline creatinine from 0.2-0.5mg/dl and a 75-150% change (maximum post-baseline value was 0.9 mg/dl). Three of these subjects received a maximum dose of 16 mg candesartan. The remaining two subjects received a dose of 8mg and 32 mg respectively. In adults with volume depletion and congestive heart failure, reversible elevations in serum creatinine and hyperkalemia can be expected to occur post-treatment with candesartan in susceptible subjects. While two of the subjects with a large changes in creatinine in the long-term study had underlying renal disease, we cannot definitively conclude that the elevations in creatinine were candesartan related in the remaining five subjects since the maximum value was 0.9 mg/dL and were within normal range in this group of children 6-14 yrs of age.

Nine subjects had ALT (normal range 5 to 45 IU/L) and/or AST (normal range 15 to 45 IU/L) results greater than 1.5 times the upper limit of normal (see table below). Subject E0011010 (6-year-old, Caucasian, female) had ALT increased reported as an AE at the final visit (Day 366) even though less than 1.5 X ULN. At Visit 1 the ALT result was 30 IU/L and at Days 170 and 366 the values were 61 IU/L and 54 IU/L, respectively. She had been receiving candesartan 16 mg dose from Day 226 through Day 365. No other information is reported. Subject E0003008 had an ALT result of 146 IU/L and an AST result of 103 IU/L on Day 387, the sponsor submitted additional information regarding this subject, she had normal LFTs on an evaluation for renal colic 2 yrs later.

Table 18: Subjects with abnormal ALT or AST results, Study 261B

Subject ID	Analyte	baseline	Maximum value	Follow-up value
E0003008	ALT	normal	146 IU/L	normal
E0003008	AST	normal	103 IU/L	normal
E0011021	ALT	68 IU/L (visit 1)	Not available	Not available
E0042003	ALT	69 IU/L	80 IU/L (day171)	66 IU/L (last visit)
E0044007	ALT	80IU/L	76IU/L (day 391)	Not available
E0044034	ALT	normal	90IU/L (day 225) 81IU/L (day 366)	Not available
E0044034	AST	normal	74IU/L (Day366)	Not available
E0500001	ALT	76 IU/L	81IU/l (day179)	61 IU/L (day372)
E0017002	AST	96 IU/L	normal	normal
E0053003	AST	normal	81IU/L (visit 9)	Not available
E0300001	AST	normal	72 IU/L (day174)	17IU/L (day 230)

Although the information is confounded since four subjects had elevated ALT at baseline, the absence of all f/u labs and relevant clinical information makes it difficult to come to a conclusion regarding ALT or liver injury trends. Subject E0011021 had a history of fatty liver/hepatic steatosis on ultrasound and E0044007 had a history of elevated liver enzymes. In addition, on review of the datasets seven subjects had elevated total bilirubin values above the reference range but their ALTs were normal. One subject, E0047010 had a baseline total bilirubin of 1.1mg/dl with values of 1.9 and 2.0 on visit 5 and 9 respectively.

7.4.3 Vital Signs

261A

There were no notable differences between treatment groups in mean baseline or mean change from baseline in sitting pulse or ECG parameters or in the frequency of new or aggravated physical examination findings. Effects on sitting pulse are shown below, standing HR was not reported.

Table 19 Mean baseline values and mean changes from baseline in sitting pulse over time (safety population), Study 261A

Sitting pulse (bpm)	Placebo N=35		2/4 mg N=69		8/16 mg N=68		16/32 mg N=68		Active pooled N=205	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Baseline	35	79.3 (10.6)	69	78.5 (11.8)	68	80.9 (13.1)	68	80.2 (9.6)	205	79.9 (11.6)
Change from baseline										
Week 1	34	−0.4 (8.1)	69	0.7 (10.0)	67	1.2 (8.9)	66	0.8 (7.5)	202	0.9 (8.8)
Week 2	32	−1.1 (9.2)	65	1.2 (10.6)	64	−0.7 (8.5)	65	0.1 (9.5)	194	0.2 (9.5)
Week 3	34	1.3 (8.9)	67	0.2 (9.5)	59	−1.0 (9.5)	65	0.0 (10.7)	191	−0.2 (9.9)
Week 4	34	−0.6 (9.1)	67	−0.1 (11.9)	64	−1.8 (9.1)	65	−1.7 (9.5)	196	−1.2 (10.2)
LOCF	35	−0.7 (9.0)	69	0.1 (11.8)	68	−2.1 (9.2)	68	−1.6 (9.5)	205	−1.2 (10.2)

Derived from Tables 11.3.8.1 and 11.3.8.3.

7.4.3 Electrocardiograms (ECGs)

328
Heart rate increased 2 bpm from study entry to Week 4 (there were no notable dose-related differences) and decreased by 8.8 bpm from study entry to Week 56. There was no consistent effect on ECG intervals, small decreases during the first 4 weeks with no notable dose-related effects and slight prolongations at Week 56, consistent with the slower heart rate. These visits had a window of ± 2 days and timing of ECGs relative to dosing is not pre-specified.

Per protocol subjects were to have echocardiograms between Visit 7-15. If an ECHO was performed within the last 3 months it did not have need to be repeated at study completion/discontinuation. Only seven subjects had echocardiograms for which additional information has been requested for interpretation of results.
261A
ECG parameters were generally similar between the two groups with no significant change from baseline.
No end-of study ECG was planned for 261B

7.4.5 Special Safety Studies/Clinical Trials

Already discussed.

7.4.6 Immunogenicity

NA

7.5 Other Safety Explorations

Metabolic sub-study-261A

In the sub-group of patients that participated in the metabolic sub-study (Table 19), no treatment related trends were noted, but the number of subjects who participated was very small to draw any definitive conclusions. It would have been more clinically meaningful to obtain this information from the long-term study (261-B).

Table 20: Descriptive statistics for baseline and Week 4, metabolic sub-study

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* (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, (nsq/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)

* Most study visits were conducted after school; thus it was unlikely that a subject fasted for the blood tests. Thus, after 10 Feb 2004, fasting glucose was changed to nonfasting glucose. Because of this change there are inconsistencies in reference ranges. Also, information regarding the fasting state is considered not reliable.
Δ = Change from baseline to final visit.
Derived from Table 11.3.7.1.4.

Source: Table 26 from the CSR for 261A, pg 87

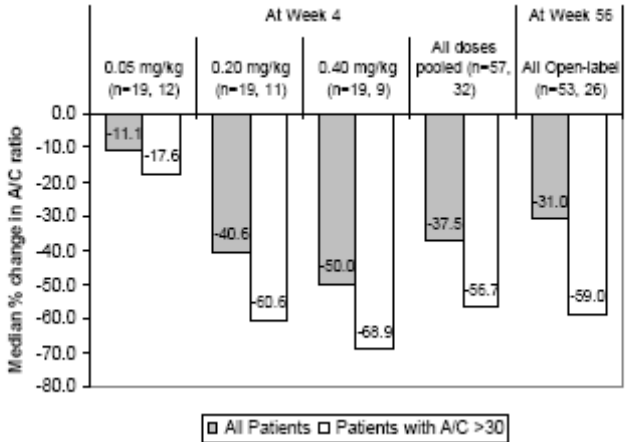
Albumin/creatinine ratio in Study 261B and 328

Per protocol Urinary protein, creatinine and albumin concentrations were determined on freshly voided urine specimens collected at Day 0 (Visit 3), at the end of the double-blind treatment period (Visit 7), and at the end of the study (Visit 15). First in AM sample is not specified. The results are summarized below.

Study 328

The sponsor reported that while there was considerable within subject variability in ratios, there was a trend for subjects with significant proteinuria and/or albuminuria to have a decline in the P/C and AC ratios over the course of the study (Figure 8)

Figure 8:Median percent changes from baseline in albumin/creatinine (A/C) ratio (Safety patients, Study 328)



Note: the first value in the parenthesis for n denotes all subjects and the second value denotes subjects with an A/C ration >30 mg/g creatinine.
Derived from Table 11.3.7.1.5.2 and Table 11.3.7.1.6.2 in Study 328, Module 5.

Source: Figure 1 from the Summary of Clinical safety, pg-41

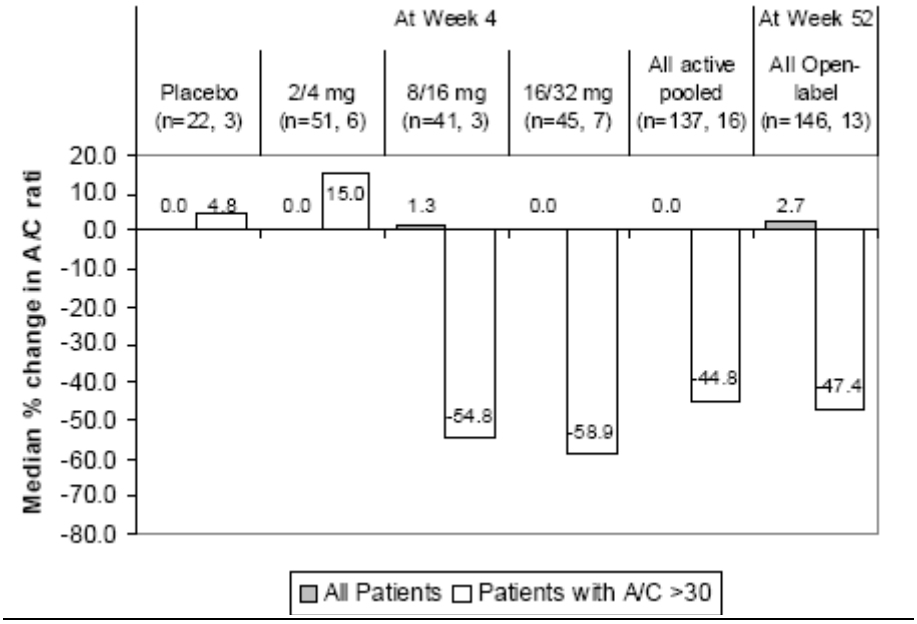
Study 261B

For all subjects, there was considerable variability in the values and there was no consistent trend for the micro-albuminuria to either improve or to progress (see Figure 9). A trend for a decline in the albumin/creatinine ratio was seen for subjects with an A/C ratio greater than 30mg/gm creatinine.

23 subjects had albumin/creatinine (A/C) ratios above 30 mg/g at Visit 1 and/or at post Visit 1 from Study 261B and thus had baseline values available following a wash out period from other antihypertensive medications. Ten of the subjects had abnormal A/C ratios at baseline and 6 improved at the post Visit 1 visit. The highest value for A/C ratio (6485 mg/g) was for Subject E0011/004 who had a SAE of renal failure. Subject E0011001 had A/C ratios of 1139 and 1131 at Visits 1 and 9, respectively. This subject had no history of renal disease and no AEs associated with renal disease. Five of the subjects (011-5003, 011-8030, 034-7049, 300-6007, and 300-6015), who were in Study 261A and continued into 261B, had baseline medical/surgical histories associated with the kidneys or urinary tract.

Reviewer's Comments: It is reasonable to conclude that the albuminuria did not worsen in subjects with baseline abnormalities but a true beneficial effect on the renal parenchyma vs. a renal hemodynamic response can only be confirmed by a washout study with comparison to a placebo group.

Figure 9: Median percent changes from baseline in albumin/creatinine (A/C) ratio (Safety patients, Studies 261A and 261B)



Note: the first value in the parenthesis for n denotes all subjects and the second value denotes subjects with an A/C ration >30 mg/g creatinine.
Derived from Table 6.13 and 6.14 in Section 6.

Source: Figure 2 from the Summary of Clinical Safety, pg-42

7.5.1 Dose Dependency for Adverse Events

As reported in adults with congestive heart failure or hypertension with volume depletion, hypotension/orthostatic hypotension and elevations in serum creatinine was clearly dose dependent in susceptible subjects. There was no clear evidence for dose-dependent hyperkalemia in study 261B since the cases were confounded

7.5.2 Time Dependency for Adverse Events

No conclusions could be made regarding time-dependency since information about time of events relative to dosing (i.e. whether event occurred around Tmax~ 4hrs) is unavailable.

7.5.3 Drug-Demographic Interactions

While there was a trend for reduced response in blacks, there were no such effects observed for AEs.

7.5.4 Drug-Disease Interactions

Already discussed under section 7.5.1

7.5.5 Drug-Drug Interactions

NA

7.6 Additional Safety Evaluations

NA

7.6.1 Human Carcinogenicity

NA

7.6.2 Human Reproduction and Pregnancy Data

NA- see PI

7.6.3 Pediatrics and Assessment of Effects on Growth

Study 328
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 notable change in Z-score). The average height of the study subjects was slightly less than the average for a corresponding reference population at baseline (negative Z-score) and at Week 56 little change was observed. 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.

Table 21 Descriptive statistics for weight and weight Z-score (Open-label population), Study 328

	N	Mean (SD), min to max	Change from baseline to Week 56 Mean (SD), min, max
Weight (kg)			
Baseline	85	16.9 (5.7), 10.2 to 39.0	
Week 56	81	20.4 (6.8), 12.1 to 48.0	3.3 (1.8), 0.7 to 12.1
Weight Z-score			
Baseline	85	0.4 (1.6), –4.2 to 4.0	
Week 56	81	0.6 (1.5), –3.9 to 3.9	0.1 (0.5), –1.0 to 2.2

SD Standard deviation.
Note: The Z-score represents normalized data relative to the mean weight for children of the same age according to NHANES growth data collected by the CDC. A Z-score of zero is equivalent to the mean weight.
Negative Z-scores reflect weights below the mean, and positive Z-scores reflect weights above the mean.
Data derived from Table 11.3.8.1.5.

Table 22 :**Descriptive statistics for height and height Z-score (Open-label population), Study 328**

	N	Mean (SD), min to max	Change from baseline to Week 56 Mean (SD), min, max
Height (cm)			
Baseline	85	97.0 (11.6), 74.1 to 123.0	
Week 56	82	106.0 (10.8), 83.0 to 128.0	8.8 (3.2), –0.7 to 18.1
Height Z-score			
Baseline	85	–0.1 (1.4), –5.3 to 2.8	
Week 56	82	0.0 (1.4), –5.7 to 2.6	0.1 (0.7), –1.9 to 2.6

SD Standard deviation.
Note: The Z-score represents normalized data relative to the mean height for children of the same age according to NHANES growth data collected by the CDC. A Z-score of zero is equivalent to the mean height.
Negative Z-scores reflect heights below the mean, and positive Z-scores reflect heights above the mean.
Data derived from Table 11.3.8.1.6.

Source table 48 and 49, from the CSR for Study 328, pg 116

Head circumference: Although 16 children in the study were 1-2 years of age and head circumference data can be collected in subjects <36 months of age, only six children had head circumference measured at Baseline or at Week 56. Among these 6 children, only 1 child had head circumference measured at both Baseline and Week 56: the mean change in head circumference for this child was 2.4 cm. Hence this information is inconclusive.

Study 261 B

Mean body weight increased by 5.9 kg at Week 52 relative to study entry. Weight matched to age-specific distribution data as reflected by the mean Z-score implies that there was no appreciable change in relative weight. Mean height increased 3.7 cm at Week 52; however, height relative to height-specific distribution data (mean Z-score) remained relatively constant.

Table 23: Descriptive statistics for weight and weight Z-score, safety population, study 261B

	N	Mean (SD), min, max	Change from Visit 1 Mean (SD), min, max
Weight (kg)			
Visit 1	235	80.4 (29.9), 20.0, 179.0	
Visit 9 (Week 52)	217	85.8 (31.6), 23.6, 208.9	5.9 (7.2), –22.5, 29.9
Weight Z-score			
Visit 1	235	1.94 (1.3), –3.2, 4.4	
Visit 9 (Week 52)	217	1.90 (1.3), –2.9, 4.4	–0.01 (0.31), –1.02, 1.21

Note: The Z-score represents normalized data relative to the mean weight for children of the same age according to NHANES growth data collected by the CDC. A Z-score of zero is equivalent to the mean weight. Negative Z-scores reflect weights below the mean, and positive Z-scores reflect weights above the mean.
Derived from Table 11.3.8.2, Section 11.

Source: Table 35, pg 95, CSR for Study 261 B

Table 24: Descriptive statistics for height and height Z-score, safety population, study 261B

	N	Mean (SD), min, max	Change from Visit 1 Mean (SD), min, max
Height (cm)			
Visit 1	235	162.6 (15.2), 111.0, 193.5	
Visit 9 (Week 52)	216	166.6 (13.8), 121.0, 199.0	3.7 (3.3), –3.0, 15.5
Height Z-score			
Visit 1	235	0.68 (1.2), –2.8, 3.5	
Visit 9 (Week 52)	216	0.63 (1.1), –3.0, 3.4	–0.05 (0.35), –0.95, 1.70

Note: The Z-score represents normalized data relative to the mean height for children of the same age according to NHANES growth data collected by the CDC. A Z-score of zero is equivalent to the mean height. Negative Z-scores reflect heights below the mean, and positive Z-scores reflect heights above the mean.
Derived from Table 11.3.8.3, Section 11.

Source Table 36, pg 96, CSR for 261B

Neurocognitive measures: Thirty-three subjects had baseline and end of treatment IQ scores assessed. On Day 1, the mean daily dose for subjects in the neurocognitive sub study was 8.6 mg daily. At Week 52, the mean daily dose was 17.2 mg daily. At baseline, the group as a whole showed a mean Full Scale IQ value of 95.0, the Scale Scores ranged from 93.9 to 99.4. At the 52 weeks assessment, very little change in Full Scale or Scale Scores was evident. For the group as a whole, the Full Scale mean change was + 2.6.
Stratified by age, baseline scores for subjects <12 years of age and those ≥12 years were comparable, with mean Full Scale IQ at 97.7 (SD 15.8) for those subjects <12 years and Full Scale IQ at 93.4 (SD 10.7) for subjects ≥12 years. At the 52 weeks assessment, for those <12 years, mean change was + 0.8 (SD 8.1), and for those ≥12 years, mean change was + 3.6 (SD 5.3), three subjects showed declines in Full Scale IQ of 10 points or more.

Table 25: Descriptive statistics for Visit 1 and changes from Visit 1 to Visit 9 (Week 52) in IQ test, neurocognitive sub-study subjects, Study 261B

			Visit 1	Change from Visit 1 to Week 52/LOCF	
	IQ assessment	n	Mean (SD), min, max	Mean (SD), min, max	95% CI
All substudy subjects	Full Scale IQ	33	95.0 (12.7) 75, 133	2.6 (6.5) –11, 12	0.3, 4.9
	Verbal comprehension	33	95.5 (12.5) 79, 140	2.2 (6.1) –11, 15	0.1, 4.4
	Perceptual processing	33	95.8 (11.2) 75, 131	2.0 (6.8) –12 to 15	–0.4, 4.4
	Working memory	33	99.4 (17.1) 62, 150	3.2 (12.2) –22, 32	–1.1, 7.5
	Processing speed	33	93.9 (13.5) 70, 121	0.7 (9.0) –21, 23	–2.4, 3.9

Derived from Table 11.3.8.11, Section 11.

Source: Table 39, pg 98, CSR for 261B

Accurate interpretation of these test results or the explanation of the sponsor's consultant regarding the 3 subjects with > 10 point decline in Full Scale WISC-IV IQ scores is beyond the scope and expertise of this reviewer. The sponsor has satisfied the WR requirements. Possibly more objective measures like school performance in larger number of subjects would have been useful.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

As expected with adults based on review of available data. The most likely manifestation of over dosage with candesartan would be hypotension, dizziness, and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. Candesartan cannot be removed by hemodialysis.

7.7 Additional Submissions / Safety Issues

NA

8 Postmarket Experience

There is no consult pending from OSE. The DRISK staff determined that since there are no patient package inserts or medication guides a DRISK review was not required.

The sponsor submitted two periodic safety update reports (PSURs) for candesartan cilexetil and the combination product with hydrochlorothiazide for 2007-2008 and 2008-2009. The sponsor reports continued surveillance of rhabdomyolysis, thrombocytopenia, pancreatitis, anaphylaxis, vasculitis, hepatobiliary disorders, bone marrow failure and toxic epidermal necrosis and

concluded that the current company core data sheets adequately reflect the safety profile of the mono and fixed-combination products.

Dr. Ana Szarfman (medical officer, DCRP) conducted an MGPS data-mining analyses of the AERS database for approved ARBs along with a few ACEI and other drugs. She looked for drug-event combinations where signal scores (EBGM values) were greater than one. The details of the run were as follows:

> "Dimension: 2 Selection Criteria: Generic name(Aliskiren, Amlodipine, Atenolol, Benazepril, Candesartan, Captopril, Eprosartan, Irbesartan, Losartan, Olmesartan, Telmisartan, Valsartan), Subset: (All) Where: EBGM > 1.0
>
> SELECT * FROM OutputData_1174 WHERE (DIM=2 AND EBGM>1.0 AND ((P1='D' AND ITEM1 IN ('Aliskiren','Amlodipine','Atenolol','Benazepril','Candesartan','Captopril','Eprosartan','Irbesartan','Losartan','Olmesartan','Telmisartan','Valsartan') AND P2='E'
>
> Details of the run:
> ID: 1174
> Type: MGPS
> Name: Generic By Age (S)
> Description: Generic; Suspect drugs only; Subset by Age; Minimum count=1; Standard strata (Age, FDA Year, Gender); includes PRR and ROR; includes hierarchy information information
> Project: CBAERS Standard Runs
> Configuration: CBAERS BestRep (S)
> Configuration Description: CBAERS data; best representative cases; suspect drugs only; with duplicate removal
> As Of Date: 08/28/2009 00:00:00
> Item Variables: Generic name, PT
> Stratification Variables: Standard strata
> Subsets: Variable: Age for Subsets
> Cumulative: No
> Labels: 00-01, 02-05, 06-11, 12-16, 17-20, 21-30, 31-40, 41-50, 51-60, 61-70, 71+, Unknown
>
> Highest Dimension: 2
> Minimum Count: 1
> Calculate PRR: Yes
> Calculate ROR: Yes
> Base Counts on Cases: Yes
> Use "All Drugs" Comparator: No
> Apply Yates Correction: Yes
> Stratify PRR and ROR: No
> Fill in Hierarchy Values: Yes
> Exclude Single Itemtypes: Yes
> Fit Separate Distributions: Yes
> Save Intermediate Files: No
> Created By: Empirica Signal Administrator
> Created On: 09/07/2009 18:15:35 EDT
> User: Ana Szarfman
> Source Database: Source Data: CBAERS data from Extract provided by CBER as of 08/28/2009 00:00:00 loaded on 2009-09-03 07:06:55.0 "

This reviewer looked at candesartan signal scores for adverse event associations *other* than those already reported in clinical trials and post-marketing [i.e. congenital renal/ urinary tract anomalies , oligohydramnios, fetal limb contractures, craniofacial deformation and hypoplastic lung development with antenatal use in the second and third trimesters of pregnancy; hypotension in volume and/or salt depleted patients, oliguria and/or progressive azotemia and (rarely) acute renal failure in patients whose renal function may depend upon the activity of the renin-angiotensin aldosterone system (e.g., patients with severe heart failure, patients with unilateral or bilateral renal artery stenosis) and Hyperkalemia were excluded]. Signal scores where the lower bound of the signal score (EB-05 value was greater than two, implying twice the expected background rate) were reviewed and a drill-down of the cases was done. The following associations were noted with candesartan in *adults*:

- Interstitial Lung disease and bronchiolitis obliterans with organizing pneumonia (BOOP)
- Nephrogenic DI
- Intravascular hemolysis
- Hepatic atrophy
- Hyperproteinemia
- Acute pancreatitis
- Supraventricular arrhythmias
- Sick sinus syndrome
- Cerebral infarction
- Toxic skin eruption (mainly pruritis and various other rashes on review of the cases, no toxic epidermal necrolysis)

On review of all the individual cases there were several repetitions in the AERS reports and confounding due to co-morbidities and concomitant medications. The association that may need further exploration in adults (not reported in children) is interstitial lung disease (ILD). There were patients with no previous lung disease who developed CT-scan confirmed ILD (interstitial opacities and honey- combing) after treatment with candesartan. Some cases improved after withdrawal, but often more than one agent was withdrawn and there was no re-challenge data available. As stated earlier these data alone do not indicate causation and further exploration of this association may be required.
In summary, in children the reported AEs are consistent with events reported in clinical trials, the literature and the current candesartan package insert.

9 Appendices

9.1 Literature Review/References

The sponsor reports conducting a literature search of an internal database (Pl@net) and several external databases: EMBASE, Ovid MEDLINE(R]) Ovid MEDLINE(R, Current Contents, BIOSIS Previews, International Pharmaceutical abstracts [IPAB], In-Process & Other Non-Indexed Citations to identify published reports of candesartan use for hypertension in pediatric subjects. The search terms were Atacand, candesartan cilexetil, safety, tolerability, pediatrics, children, adolescents, hypertension, high blood pressure, antihypertensive, systolic blood pressure, and diastolic blood pressure. The dates specified were from 1996 to August 2008. Unpublished safety information was solicited from physicians electronically with international membership comprised of pediatric nephrologists, pediatric cardiologists, and pediatric hypertension specialists accounting to over 1,700 members of various organizations. There were 12 case reports, including 8 SAEs, from the physician safety survey of pediatric candesartan usage. Four physicians reported AEs for children ranging from 6 to 16 years of age, which included 8 girls and 4 boys. On review of these reports the candesartan prescription rate by these physicians compared to other anti-hypertensives is unknown.

The AstraZeneca in-house safety database (SAPPHIRE) was searched for all spontaneous and solicited reports of candesartan use in pediatric subject's ≤17 years of age, using a cut-off date of 31 December 2008. The search yielded a total of 38 case reports . All case reports were reviewed and the findings from these reports are consistent with the candesartan safety profile as described in product labeling.

This reviewer searched PubMed using search terms " candesartan, pediatric", "Candesartan, children" and "candesartan, adolescent". No new safety issues other than those already reported were noted.

9.2 Labeling Recommendations

The sponsor's revisions to the proposed PI regarding use in pediatric hypertension were reviewed. I recommend the following:

- Dosage and administration (section 2.2)- under pediatric hypertension include "The once daily dosing *in adults* is supported by the PK-PD data including over 50% inhibition of the effect of Angiotensin II at 24 hrs (see Clinical pharmacology Section 4.4.1 and 4.4.2 and Section 6). Since it is unknown if these effects are similar in children, a twice daily dosing interval may be considered before switching to a higher once-daily dose. This is further supported by the pediatric pharmacokinetic data demonstrating an over tenfold decline in Cmax-Cmin concentrations over a 24-hr interval and the dose-related side effects of hypotension and syncope noted in the pediatric efficacy and safety studies

- Adverse reactions (section 6.1) under pediatric hypertension include "there was one case of toxic nephropathy in a 14 yr old black female who was discontinued from the open label extension study. Relationship to candesartan could not be excluded. Laboratory test findings including infrequent elevations in serum creatinine, potassium, liver enzymes and small decreases in hemoglobin and hematocrit were similar to the adult clinical trial experience "
- Clinical studies (section 14.1, Pediatric)- to include after "An antihypertensive effect was maintained with long-term use (one year)". *However, this information is inconclusive without a randomized withdrawal study because 16% of subjects in Study 1 and 9% of subjects in Study 2 took supplemental anti-hypertensive medications."*

9.3 Advisory Committee Meeting

No advisory committee meeting is planned for this submission.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20838	SUPPL-31	ASTRAZENECA PHARMACEUTICALS LP	ATACAND

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/s/

SUCHITRA M BALAKRISHNAN
10/02/2009