OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	20-838/S031
Submission Date	April 27, 2009
Brand Name	Atacand $^®$
Generic Name	Candesartan cilexetil
Sponsor	AstraZeneca
Submission Type	Pediatric supplement
Therapeutic Class	Angiotensin II receptor blocker (ARB)
Marketed Formulation (Strength)	Oral tablet (4, 8, 16 and 32 mg)
Indication & Dosing Regimen (Approved in Adults)	Hypertension, 16 mg tablet QD (starting) Heart failure, 4 mg tablet QD (starting)
Intended Population	Pediatric hypertensive patients 1 to < 17 years of age
Proposed Indication	Hypertension

Proposed Dosing Regimen	1 to < 6 years old:
	   0.2 mg/kg oral suspension QD (starting)
	 6 to < 17 years old:
	   <50 kg: 4-8 mg tablet QD (starting)
	   >50 kg: 8-16 mg tablet QD (starting)

OCP Division	Division of Clinical Pharmacology I
OND Division	Division of Cardiovascular and Renal Products
OCP Reviewer	Islam R. Younis, Ph.D.
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1 EXECUTIVE SUMMARY

Candesartan cilexetil (Atacand®), an angiotensin receptor blocking (ARB) agent, is approved in the United States for the treatment of hypertension and heart-failure in adults. The current submission (NDA 20-838 SE5 # 031) is a pediatric supplement submission for the treatment of hypertension in response to a pediatric written request originally issued in 1999.

The sponsor submitted four studies for this pediatric clinical development program:

- A relative bioavailability study of the age-appropriated oral suspension to the marketed tablet (Study D2451C00005) and

- Two 4-week dose-ranging safety and efficacy studies with a 1-year open label clinical follow-up were conducted in hypertensive pediatric subjects :

  - Children 6 to <17 years of age were studied before the younger children and candesartan was administered as a tablet formulation in 2 studies (Study D2451C00261 (261A) and 1-year clinical follow-up Study D2451C00001 (261B))

  - Children 1 to <6 years of age were then evaluated in a third study (D2451C00002 (328)) which employed a candesartan liquid suspension formulation

  - A single dose pharmacokinetics sub-study for each age group was performed as part of the long term safety and efficacy studies

Based on the results of these studies, the sponsor is proposing that candesartan coupled with a favorable safety profile is effective in lowering blood pressure in hypertensive children 1 to < 17 years of age.

The following are the major findings:

1. The pharmacokinetics of candesartan is comparable across pediatrics and adults.

2. The change in trough SBP/DBP from baseline was similar between two age groups (6-12/5.2-11.1 mmHg for 1 to <6 years and 8.6-11.2/4.8-8 mmHg for 6 to <17 years).

3. Candesartan effectiveness in 6 to <17 years group was established using key supportive analysis and identifying key deficiency in the primary analysis.

4. Based upon the blood pressure response and the pharmacokinetics, the proposed dosing regimen was found to be appropriate.

5. The blood pressure response to candesartan was similar between children with and without renal disease.

1.1 RECOMMENDATIONS

Based on the clinical pharmacology and biopharmaceutics information provided in the current submission (NDA 20-838/S031), Division of Clinical Pharmacology I and Division of Pharmacometrics recommend the submission to be approved, provided that the sponsor and the agency come to an

agreement regarding the labeling language.

1.2   PHASE IV COMMITMENTS

None.

1.3   CLINICAL PHARMACOLOGY SUMMARY

This pediatric clinical pharmacology program describes the antihypertensive effects of candesartan in hypertensive children aged 1 to <17 years, in terms of dose relationship and describes the single-dose pharmacokinetics of candesartan in the same population. The study population was consistent with the clinical hypertension population of this age range in terms of sex, obesity, and etiology components.

An age-appropriate oral suspension formulation was prepared extemporaneously for children who cannot swallow tablets. A relative bioavailability study was conducted to compare the systemic exposure of candesartan following the administration of candesartan pediatric oral suspension and tablets. 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.

The selection of doses attempted to mimic the candesartan doses established for adult hypertensive subjects by adjusting for weight. Across the studies, the pharmacokinetics of candesartan is comparable across subgroups of age, weight, and gender and the profile supports once daily dosing.

Over the range of candesartan doses studied, the magnitude of the responses in blood pressure reduction was similar among children aged 1 to <6 years (6-12/5.2-11.1 mmHg in trough SBP/DBP reduction) and children aged 6 to <17 years (8.6-11.2/4.8-8 mmHg in trough SBP/DBP reduction). Candesartan once daily lowers blood pressure in a dose related fashion in children aged 1 to <6 years. A similar relationship was shown for pediatrics aged 6 to <17 years when a placebo-anchored dose-response analysis was performed. The exposure-response relationship for SBP reduction based on the observed trough concentration was consistent in pediatrics aged 1 to <17 years.

Based upon the blood pressure response and the pharmacokinetics, the dose ranges studied (0.05 mg/kg, 0.20 mg/kg, and 0.40 mg/kg in children 1 to <6 years of age, and 2, 8 and 16 mg in children 6 to <17 years of age and weigh <50 kg, and 4, 16, and 32 mg in children 6 to <17 years of age and weigh ≥50 kg) are considered to be clinically relevant. The following dosing recommendations from the sponsor are acceptable.

Table 1. The dosing recommendation in the proposed labeling

	Starting Dose	Dose Range
Adult Hypertension (2.1)	16 mg tablet once daily	8 - 32 mg tablet total daily dose
Pediatric Hypertension (1 to < 6 years) (2.2)	0.20 mg/kg oral suspension once daily	0.05 - 0.4 mg/kg oral suspension once daily
Pediatric Hypertension (6 to < 17 years) (2.2)	< 50 kg 4 – 8 mg tablet once daily ≥ 50 kg 8 – 16 mg tablet once daily	< 50 kg 4 – 16 mg tablet once daily ≥ 50 kg 4 – 32 mg tablet once daily

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09/21/2009
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Cc: NDA-20838/S031, HFD 110, HFD-860 (Liu, Younis, Mehta, Uppoor)

Clinical Pharmacology Briefing: 09/16/2009

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2 QUESTION BASED REVIEW

An abbreviated version of the QBR is used for this review since key QBR elements have been addressed previously.

2.1 GENERAL ATTRIBUTES OF THE DRUG

Candesartan cilexetil (Atacand®), an angiotensin receptor blocking (ARB) agent, was approved in the United States for the treatment of hypertension and heart-failure in adults. Conventional ATACAND tablets of five strengths (2, 4, 8, 16 and 32 mg) were developed previously. For clinical studies in the pediatric population, an age appropriate oral suspension was made extemporaneously, by crushing candesartan cilexetil tablets in a mix of 2 commercially available vehicles (Ora-Plus and Ora-Sweet, premix available as Ora-Blend). The proposed starting doses are: 0.2 mg/kg oral suspension, once daily for 1 to <6 years old hypertensive children; 4-8 mg tablet, once daily for 6 to <17 years old hypertensive children less than 50 kg; 8-16 mg tablet, once daily for 6 to <17 years old hypertensive children greater than 50 kg.

2.2 GENERAL CLINICAL PHARMACOLOGY

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

The sponsor submitted four studies for this pediatric clinical development program:

- A relative bioavailability study of the age-appropriated oral suspension to the marketed tablet (Study D2451C00005) and

- Two 4-week dose-ranging efficacy studies with a 1-year open label clinical follow-up were conducted in hypertensive pediatric subjects :

  - Children 6 to <17 years of age were studied before the younger children and candesartan was administered as a tablet formulation in 2 studies (Study D2451C00261 (261A) and clinical follow-up Study D2451C00001 (261B)

  - Children 1 to <6 years of age were then evaluated in a third study (D2451C00002 (328) which employed a candesartan liquid suspension formulation

  - A single dose pharmacokinetics sub-study for each age group was performed as part of the long term studies

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

In Study 328, the primary efficacy variable (measure of effect) was the change in trough SBP from baseline to the end of Week 4/LOCF, double-blind treatment period. The secondary response variable was the change in trough DBP from baseline to the end of Week 4/LOCF, double-blind treatment period.

In Study 261A, the primary efficacy variable was the <u>placebo-corrected change from baseline</u> in trough SiSBP (sitting SBP) to the end of Week 4/LOCF, double-blind treatment period. The secondary response variables included change in trough SiDBP, trough standing SBP and DBP, and trough sitting pulse pressure.

Based on previous clinical experience in adults, a 4-week treatment period assured that a nearly full antihypertensive effect would be observed for each dose level without an excessive exposure of placebo subjects to potentially elevated blood pressures. Evaluation of the trough effect would help to determine whether the antihypertensive effect of candesartan was well maintained during each dosing interval.

Trough blood pressure was defined as 24 hours (±4 hours) after receiving the last dose of the study medication except at double-blind Week 4 when it was 24 ± 2 hours. If the trough recording was outside of this specified window, a repeat visit was required. 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 pre-specified primary efficacy endpoint was the slope of linear regression for the change in trough systolic blood pressure (SBP) from baseline at Week4/LOCF as a function of candesartan dose for Study 328 (age 1 to < 6 years old). The primary efficacy endpoint was the slope of linear regression for the change in trough sitting systolic blood pressure (SiSBP) from placebo at Week4/LOCF as a function of candesartan dose for Study 261A (age 6 to < 17 years old).

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Candesartan was identified and measured in pediatrics using a validated reversed-phase liquid chromatography and mass spectrometric method. Refer to Section 2.6 for further details regarding analytical methodology and performance.

2.2.4 Exposure-response

The exposure-response relationship was identified for blood pressure reduction after four weeks of the candesartan treatment. No relationship could be identified between exposure and toxicity.

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

In both Study 261A and Study 328, the antihypertensive effects were apparent within about 1 to 2 week of initiating candesartan treatment and a full effect was seen by Week 4. Following treatment with candesartan for 4 weeks, the trend of BP reduction with candesartan dose was observed (Figure 1 and Figure 2).

Figure 1. Mean changes in SiSBP/SiDBP from baseline over time (ITT population in Study 261A)
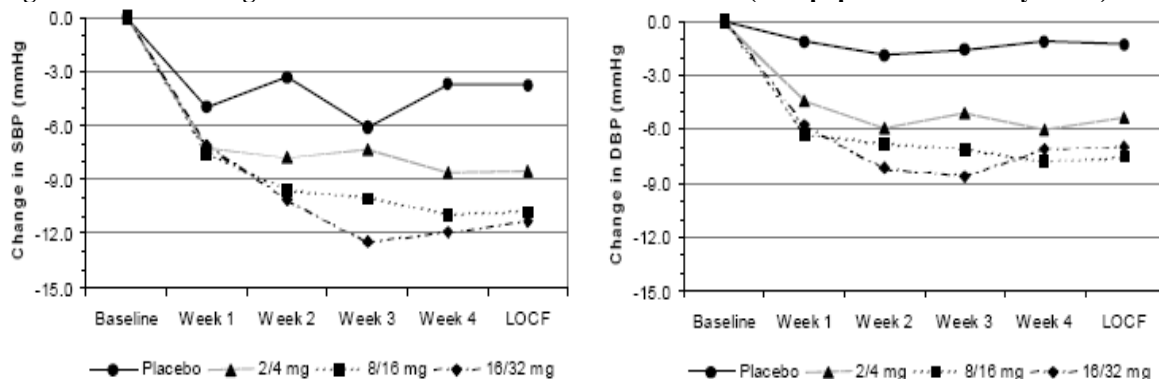
Figure 2. Mean changes in SBP/DBP from baseline over time (ITT population in Study 328)
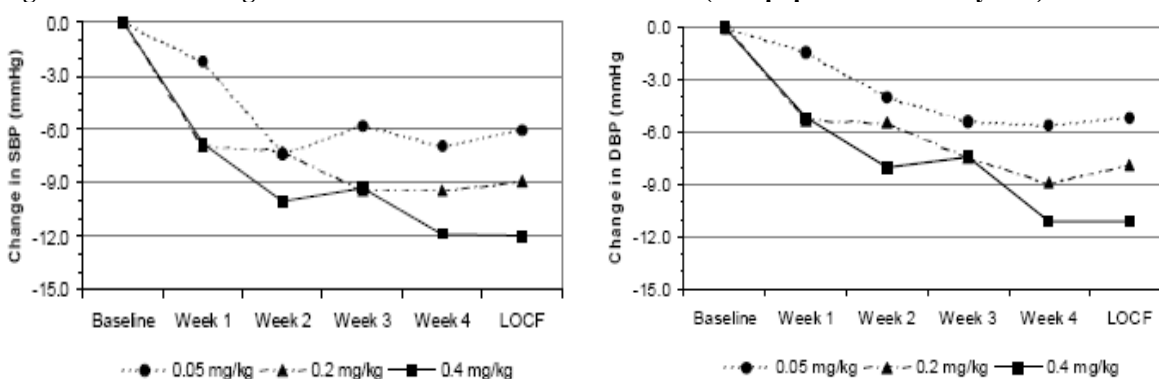
The dose-response for blood pressure reduction was well established in Study 328 (1 to <6 years of age). SBP declined monotonically across the 3 candesartan dose levels by 6 to 12 mmHg. The BP reduction from baseline was significantly related to candesartan dose (the slope for dose ratio (1:4:8) was: −0.80 with p=0.0136). Similarly, DBP declined by 5 to 11 mmHg in a significant dose-related fashion (the slope for dose ratio (1:4:8) was: −0.79 with p=0.0301) (Figure 3).

Figure 3. Means and dose-response line for changes from baseline to Week 4/LOCF in SBP/DBP (ITT population in Study 328)
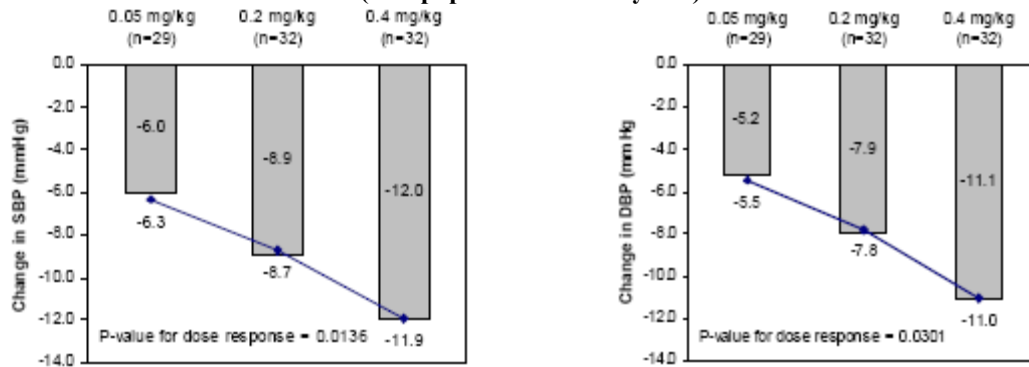
Note: Numbers inside the bars are the raw means. The connected dots and the values that are provided below the dots represent the dose-response line assuming the weight effect is proportional to the number of subjects in the upper weight panel.

The sponsor's primary analysis failed (p-value=0.0973) to show a dose-related blood pressure reduction of candesartan from placebo in Study 261A (6 to <17 years of age). However, with the placebo anchored method (placebo dose=0), the slope for reduction in SiSBP from baseline was significant with p-value 0.0009. Similar results were also shown in the regression for reduction in sitting diastolic blood pressure (SiDBP) with p-value 0.0096 (Figure 4).

Figure 4. Mean changes from baseline in SiSBP (left) and SiDBP (right) at Week 4/LOCF in Study 261A with placebo anchored dose-response regression line
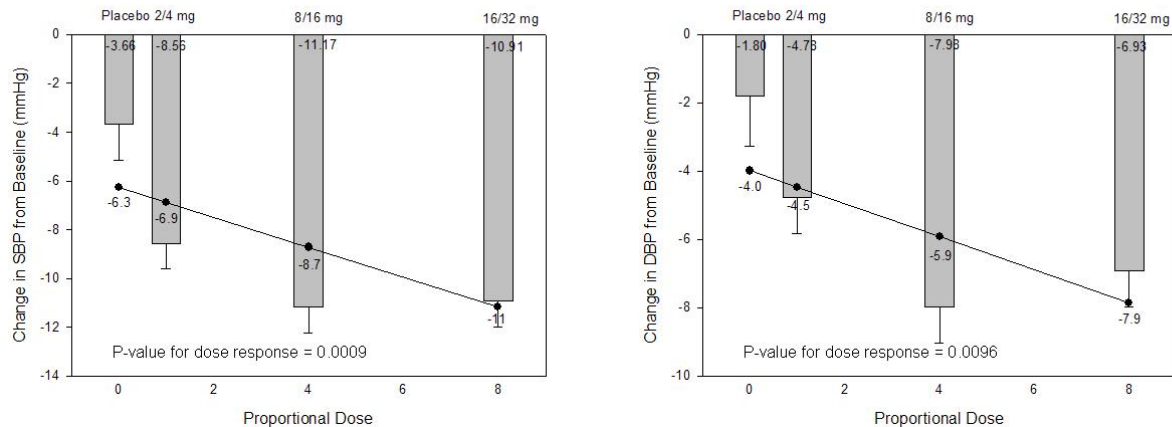
Note: Numbers inside the bars are the least square means. The connected dots and the values that are provided below the dots represent the dose-response line accounting for the effect of the upper body weight panel and mean baseline blood pressure.

The analyses from the pharmacometric reviewer suggest that the concentration-response relationship of candesartan is consistent across the entire studied pediatrics and adults. By pooling the exposure-response data in Study 328 and Study 261A, a simple linear regression model based on the observed trough concentrations of active arms clearly showed a significant exposure-response correlation for SiSBP reduction from baseline (p=0.0025) (Figure 5).

Figure 5. Pooled exposure-response for changes in SBP from baseline to the last treatment (based on the observed trough concentrations of active arms)
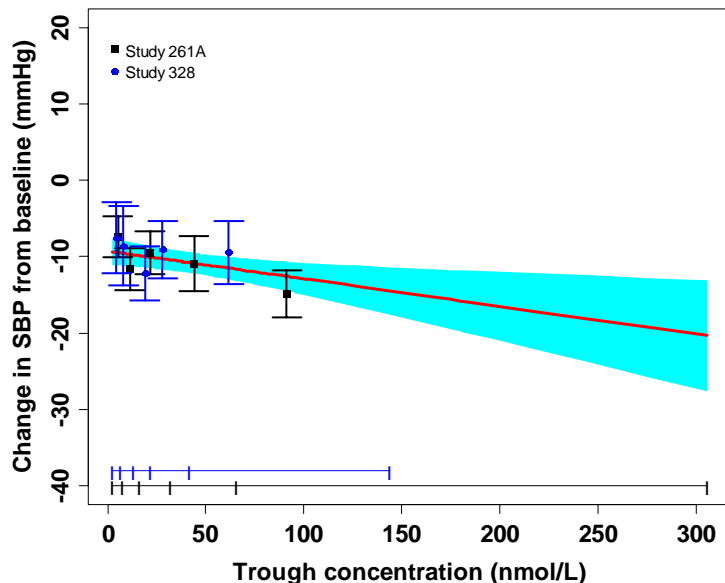
Note: Solid symbols and bars represent the mean and 95% confidence interval of SBP reduction from baseline for each concentration quantile. The concentration range is denoted by the horizontal line. The black color represents data from Study 261A and the blue color represents data from Study 328. The solid red line represents the mean linear regression prediction based on the pooled studies. The shaded area represents the 95% confidence interval.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

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. The safety/tolerability profile of candesartan as treatment of hypertension in pediatrics is consistent with the experience of treating adults.

2.2.4.3 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The dose and dosing regimen proposed by the sponsor in pediatrics is consistent with the known relationship between dose-concentration-response in adults. As shown in Table 2, the proposed dose ranges produce the similar blood pressure reduction in hypertensive pediatric subjects 1 to < 17 years of age and adults. The pharmacokinetics of candesartan is also comparable across pediatrics and adults. In adults, the starting dose, 16 mg QD (tablet), produces maximum reduction in blood pressure. From the clinical studies in pediatrics, 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. Because candesartan is well tolerated across the studied pediatric and adult population, the similar maximum effect dose selection strategy in hypertensive children 6 to <17 years of age as in adults is reasonable. 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. This dose regimen was supported in the long term clinical follow-up. 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. Using the exposure –response analysis, we expected the 4/8 mg starting dose in children 6 to <17 years old would produce similar blood pressure reduction (9 mmHg in trough SBP) as the 0.2 mg/kg starting dose did (8.7/7.8 mmHg in trough SBP/DBP) in children 1 to <6 years old. Using this conservative starting dose in pediatrics (especially for younger children) is also acceptable.

The efficacy data in this pediatric clinical program were all collected at the trough time point of the once a day dose regimen and have proved that the antihypertensive effect of candesartan was well preserved. In the original review for the treatment of hypertension in adults, there is an inconclusive study that suggested there may be some benefit with BID vs. QD in some patients for 16 mg total daily dose. We think it is an option for pediatrics to change the dose regimen from QD in proposed dose range labeling to total daily as in adults.

Table 2. Comparison of blood pressure reduction at the proposed doses in pediatric and adult populations

	Starting Dose	Trough SBP/DBP Reduction from Baseline (mmHg)	Dose Range	Trough SBP/DBP Reduction from Baseline (mmHg)
Adult Hypertension	16 mg tablet QD	14.1/9.3[a]	8-32 mg tablet total daily	10.5-14.5/6.9-10.9[b]
Pediatric Hypertension (6 to < 17 years)	4/8 - 8/16 mg tablet QD for <50 or >50 kg	9[c]-11.2/8	4/4 - 16/32 mg tablet QD for <50 or >50 kg	8.6-11.2/4.8-8
Pediatric Hypertension (1 to < 6 years)	0.20 mg/kg oral suspension QD	8.7/7.8	0.05-0.4 mg/kg oral suspension QD	6-12/5.2-11.1

[a]   The data is from the meta-analysis of the original ATACAND medical review, June 4th, 1998.

[b]   These data were derived from the candesartan labeling statement: "on trough (24 hour) systolic and diastolic pressures compared to placebo, with doses of 8 to 32 mg giving effects of about 8-12/4-8 mm Hg." The 2.5/2.9 mmHg reduction in SBP/DBP on placebo was used (based the meta-analysis reported in the original ATACAND medical review, June 4th, 1998). The placebo response in adults is comparable to the placebo effect of 3.7/1.8 mmHg in Study 261A.

[c]   The value is estimated from the exposure-response linear regression model for trough SBP reduction from baseline as a function trough concentration.

2.2.5   What are the pharmacokinetic characteristics of candesartan in hypertensive children 1 to < 17 years of age

Table 3 and Table 4 displays the pharmacokinetic parameters of candesartan in children 1- <6

and 6- <17 years of age following a single oral dose once-daily.

Table 3. Pharmacokinetic parameters of candesartan in children 1- <6 years of age following a single 0.2 mg/kg once-daily

	$AUC_{0-\infty}$ (nM*h)	AUC_{0-28} (nM*h)	C_{max} (nM)	t_{max} (h)	$t_{1/2}$* (h)
N	10	10	10	10	10
Mean	1781	1711	250.8	3.3	5.8
SD	611	582	61.3	1.0	1.4
CV%	34.3	34.0	24.4	31.8	23.4

*$t_{1/2}$ is not a terminal half-life

Table 4. The pharmacokinetic parameters of candesartan in children 6- <17 years of age following a single 16 once-daily dose

		$AUC_{0-\infty}$ (nM*h)	AUC_{0-25} (nM*h)	C_{max} (nM)	T_{max} (h)	$t_{1/2}$ (h)
6 to <12 years	N	12	11	12	12	11
	Mean	2727.6	2462.5	333.9	4.3	6.7
	SD	1270.8	1099.7	180.0	2.1	1.3
	CV%	46.6	44.7	53.9	47.9	18.9
12 to <17 years	N	10	9	10	10	9
	Mean	3059.9	2951.2	396.9	4.3	5.7
	SD	1091.0	1041.8	212.0	1.5	1.3
	CV%	35.7	35.3	53.4	35.4	22.6

2.3   INTRINSIC FACTORS

2.3.1   Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.1.1   Pediatric patients

Pharmacokinetics, efficacy and safety of candesartan have been established in hypertensive subjects 1 to <17 years of age. The PK profile of candesartan was generally comparable among pediatrics and adults. The degree of blood pressure reduction across the entire studied pediatrics and adults is similar (Table 2). Because candesartan is well tolerated across the studied pediatric and adult population, the near maximum-effect starting dose selection strategy in pediatrics as in adults is reasonable. The dosage regimen adjustments are based upon the dose-response relationships in different populations.

2.3.1.2   Renal Impairment

No specific study has been conducted in pediatrics with renal impairment. Because of the similarity in PK, efficacy, and safety profile of candesartan between adults and pediatrics, the similar profile is expected between pediatrics with renal impairment and adults with renal impairment. In study 328, a total of 69 children (74%) had renal disease at baseline, which included nephritic syndrome, congenital cystic renal diseases, dysplastic disorders, hemolytic uremic syndrome, and others. 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 (< 80 mL/min). Based on the proportional dose normalized trough concentration, candesartan exposure in subjects with renal disease is about 70% higher than exposure in subjects without renal disease. Reduction in SBP in subjects with renal disease is not significantly different from reduction in subjects without renal disease (see pharmacometric review). Therefore, no dose adjustment is necessary in hypertensive pediatrics with renal disease. This is consistent with the recommendation in adults that no initial dosage adjustment is necessary for patients with mildly impaired renal function.

2.4   EXTRINSIC FACTORS

Not applicable.

2.5   GENERAL BIOPHARMACEUTICS

2.5.1   What is the relative bioavailability of candesartan suspension compared to candesartan tablets?

There was no statistically significant difference in candesartan $AUC_{0-\infty}$ systemic exposure between the tablet and the suspension. On the other hand, the candesartan suspension and tablet are not equivalent in terms of C_{max}, since the upper bound of the 90% CI is more than 125% (Table 5). However, the efficacy and safety results were consistent across the formulations and study groups. Considering the proposed starting dose is producing the near maximum effect at trough concentration and the drug is well-tolerated, the difference in C_{max} between suspension and tablet should not be clinically relevant.

Table 5. The relative bioavailability of candesartan suspension to candesartan tablets in adult healthy volunteers

Parameter	N	Geometric Mean (%CV) Suspension (S)	N	Tablet (T)	Ratio S/T	90% CI Lower	Upper
$AUC_{0-\infty}$ (nM*h)	22	7086.8 (27.4)	22	6559.0 (34.7)	108	100	116
C_{max} (nM)	22	643.1 (28.3)	22	522.6 (43.8)	122	109	136

2.6   ANALYTICAL SECTION

2.6.1   How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

A brief summary of the different bioanalytical methods used is shown in Table 6. Accepted validation indicates that accuracy and precision of the quality control samples met the FDA guidance "Bioanalytical Method Validation" recommendations. Acceptability of quality control sample performance during unknown plasma sample analysis is also indicated in Table 6.

Table 6. Summary of the bioanalytical methods used in the clinical studies

Rport #	Type	Analyte(s)	Matrix	Calibration Range	Validation	Study Sample Performance
D2451C00002 (Study 328) D2451C00001 (261B)	LC-MS/MS	Candesartan	Plasma	2 – 1000 nM	Acceptable	Acceptable
D2451C00005	HPLC-Fluorescence	Candesartan	Plasma	1 – 300 nM	Acceptable	Acceptable

2.6.2   For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Total drug was measured for all moieties.

3   DETAILED LABELING RECOMMENDATIONS

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in <u>underline blue font</u>. At the time of this review, labeling negotiation is ongoing.

DOSAGE AND ADMINISTRATION
Pediatric Hypertension 1 to < 17 Years of age

(b) (4)

CLINICAL PHARMACOLOGY
Pharmacokinetics
Pediatrics

(b) (4)

CLINICAL STUDIES
Hypertension
Pediatrics

(b) (4)

APPENDIX (PHARMACOMETRICS REVIEW)

# OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 KEY REVIEW QUESTIONS

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

1.1.1 Do available data support effectiveness of candesartan in the studied pediatric population?

Yes, the sponsor's data provide evidence to support effectiveness of candesartan for the treatment of hypertension in pediatric subjects 1 to < 17 years of age. The pre-specified primary efficacy endpoint was the slope of linear regression for the change in trough systolic blood pressure (SBP) from baseline at Week4/LOCF as a function of candesartan dose for Study 328 (age 1 to < 6 years old). The primary efficacy endpoint was the slope of linear regression for the change in trough sitting systolic blood pressure (SiSBP) from placebo at Week4/LOCF as a function of candesartan dose for Study 261A (age 6 to < 17 years old). Study 328 successfully showed a significant (p-value=0.0136) dose-response relationship according to the primary analysis. Study 261A (age 6 to < 17 years old) failed (p-value=0.0973) to show a significant dose-response relationship according to the primary analysis. However, there were multiple pieces of evidence supporting effectiveness of candesartan in 6 to < 17 years old hypertensive children. With the placebo anchored method (placebo dose=0), the slope for reduction in SiSBP was significant with p-value 0.0009. Similar results were also shown in the regression for reduction in sitting diastolic blood pressure (SiDBP) with p-value 0.0096 (Figure 6 and Table 7). Additional supporting evidence was discussed in the sponsor's and reviewer's analysis sections. Therefore, data support effectiveness of candesartan for the treatment of hypertension in pediatric subjects 1 to < 17 years.

Figure 6. Mean changes from baseline in SiSBP (left) and SiDBP (right) at Week 4/LOCF in Study 261A with placebo anchored dose-response regression line
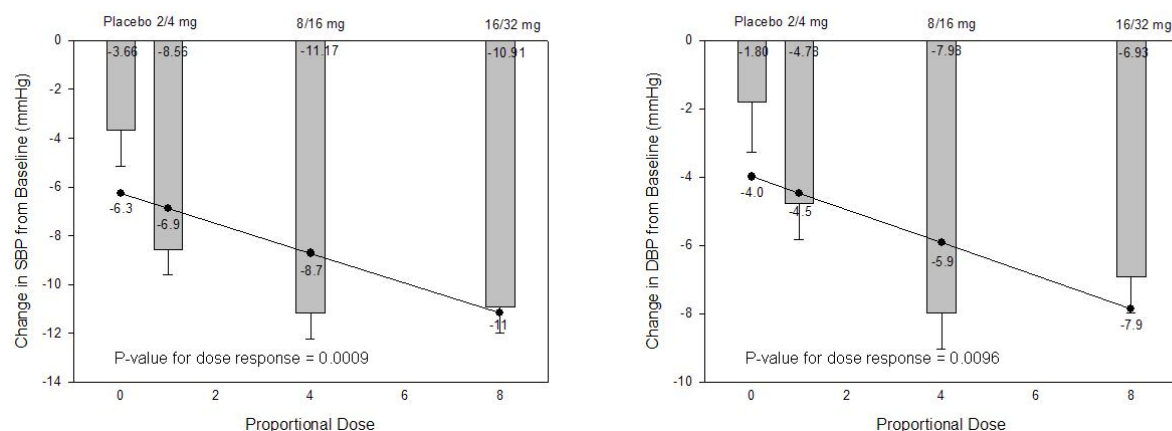
Note: Numbers inside the bars are the least square means. The connected dots and the values that are provided below the dots represent the dose-response line accounting for the effect of the upper body weight panel and mean baseline blood pressure.

Table 7. Dose-response regression for change from baseline in SiSBP and SiDBP at Week 4/LOCF (placebo anchored regression model for Study 261A: $\Delta BP=\beta 0+ \beta 1*dose+ \beta 2*weight\_group+ \beta 3*BP\_Baseline$)

Model variable	SBP DF	Estimate (SE)	p-value	DBP DF	Estimate (SE)	p-value
Intercept ($\beta 0$)	1	-6.2504 (0.9070)	<.0001	1	-3.9863 (0.9121)	<.0001
Coefficient for dose ($\beta 1$)	1	-0.6153 (0.1837)	0.0009	1	-0.4826 (0.1847)	0.0096
Coefficient for weight group ($\beta 2$)*	1	-5.8682 (1.7578)	0.001	1	-0.7508 (1.7113)	0.6613
Coefficient for BP Baseline ($\beta 3$)**	1	-0.4021 (0.0667)	<.0001	1	-0.5255 (0.0591)	<.0001

* Weight was set as a class variable: 1 for weight < 50 kg, and 0 for weight > 50 kg.

** For the regression, the blood pressure baseline values were centered at the sample mean.

1.1.2 Is the dosing recommendation in the proposed labeling statements acceptable?

Yes. As shown in Table 8, the proposed dose ranges produce the similar blood pressure reduction in hypertensive pediatric subjects 1 to < 17 years of age and adults. The pharmacokinetics of candesartan is also comparable across pediatrics and adults. In adults, the starting dose, 16 mg QD (tablet), produces maximum reduction in blood pressure. From the clinical studies in pediatrics, 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. Because candesartan is well tolerated across the studied pediatric and adult population, the similar maximum effect dose selection strategy in hypertensive children 6 to <17 years of age as in adults is reasonable. 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. This dose regimen was supported in the long term clinical follow-up. 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. Using the exposure–response analysis, we expected the 4/8 mg starting dose in children 6 to <17 years old would produce similar blood pressure reduction (9 mmHg in trough SBP) as the 0.2 mg/kg starting dose did (8.7/7.8 mmHg in trough SBP/DBP) in children 1 to <6 years old. Using this conservative starting dose in pediatrics (especially for younger children) is also acceptable.

Table 8. Comparison of blood pressure reduction at the proposed doses in pediatric and adult populations

	Starting Dose	Trough SBP/DBP Reduction from Baseline (mmHg)	Dose Range	Trough SBP/DBP Reduction from Baseline (mmHg)
Adult Hypertension	16 mg tablet QD	14.1/9.3[a]	8-32 mg tablet total daily	10.5-14.5/6.9-10.9[b]
Pediatric Hypertension (6 to < 17 years)	4/8 - 8/16 mg tablet QD for <50 or >50 kg	9[c]-11.2/8	4/4 - 16/32 mg tablet QD for <50 or >50 kg	8.6-11.2/4.8-8
Pediatric Hypertension (1 to < 6 years)	0.20 mg/kg oral suspension QD	8.7/7.8	0.05-0.4 mg/kg oral suspension QD	6-12/5.2-11.1

[a] The data is from the meta-analysis of the original ATACAND medical review, June 4th, 1998.
[b] These data were derived from the candesartan labeling statement: "on trough (24 hour) systolic and diastolic pressures compared to placebo, with doses of 8 to 32 mg giving effects of about 8-12/4-8 mm Hg." The 2.5/2.9 mmHg reduction in SBP/DBP on placebo was used (based the meta-analysis reported in the original ATACAND medical review, June 4th, 1998). The placebo response in adults is comparable to the placebo effect of 3.7/1.8 mmHg in Study 261A.
[c] The value is estimated from the exposure-response linear regression model for trough SBP reduction from baseline as a function trough concentration.

1.1.3   Is there a need to adjust candesartan dose in pediatrics with renal disease?

No. In study 328, a total of 69 children (74%) had renal disease at baseline, which included nephritic syndrome, congenital cystic renal diseases, dysplastic disorders, hemolytic uremic syndrome, and others. 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 (< 80 mL/min). Based on the proportional dose normalized trough concentration, candesartan exposure in subjects with renal disease is about 70% higher than exposure in subjects without renal disease. Reduction in SBP in subjects with renal disease is not significantly different from reduction in subjects without renal disease (see pharmacometric review). Therefore, no dose adjustment is necessary in hypertensive pediatrics with renal disease. This is consistent with the recommendation in adults that no initial dosage adjustment is necessary for patients with mildly impaired renal function.

Figure 7. Mean changes in SBP from baseline at Week 4/LOCF (with or without renal disease in Study 328)
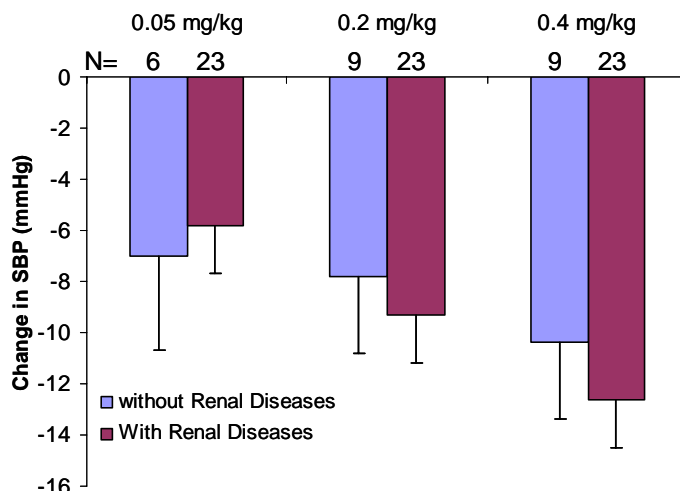
Table 9. Dose-response regression for change in SBP from baseline at Week 4/LOCF (treating renal disease as a covariate in Study 328)

Model variable	SBP DF	Estimate (SE)	p-value
Intercept (β_0)	1	-6.0914 (1.6753)	0.0005
Coefficient for dose (β_1)	1	-0.8323 (0.3063)	0.0079
Coefficient for BP Renal Disease (β_2)*	1	2.8294 (2.0561)	0.1722
Coefficient for BP Baseline (β_3)**	1	-0.3755 (0.1036)	0.0005

* Renal Disease was set as a class variable: 1 for without renal disease, and 0 for with renal disease.
** For the regression, the blood pressure baseline values were centered at the sample mean.

1.2 RECOMMENDATIONS

Based on dose-response and supporting set of analyses, approval of candesartan in pediatric population (1-<16 years) is recommended.

2 PERTINENT REGULATORY BACKGROUND

Candesartan, an angiotensin receptor blocking (ARB) agent, was approved for marketing in the United States in 1998 for once-daily treatment of hypertension in adults. It was also approved for the treatment of heart failure in adults in 2005. Conventional tablets of five strengths (2, 4, 8, 16 and 32 mg) have been developed previously. In this current application, the sponsor seeks approval for the treatment of hypertension in pediatrics 1 year and older. The sponsor submitted four studies which include a relative

bioavailability study of the age-appropriated oral suspension to the marketed tablet (D24551C00005), an efficacy and safety study (Study 328) in 1 to <6 years old hypertensive children (D2451C00002), a 4-week dose-ranging efficacy and safety study (Study 261A) in 6 to <17 years old hypertensive children, and a 1-year efficacy and safety study (Study 261B) in 6 to <17 years old hypertensive children. The biopharmaceutic study and Study 328 support the proposed indication in 1 to <6 years old children. Study 261A failed to achieve a significant dose-response relation according to the primary end point. However, effectiveness of Candesartan over placebo in 6 to <17 years old children was supported by multiple evidence.

3   RESULTS OF SPONSOR'S ANALYSIS

Effectiveness of Candesartan in Study 328

Study 328 was a 4 week randomized, parallel double-blind dose-ranging study followed by a 52-week, open label clinical experience evaluation. To determine the dose ranging effects of Candesartan, 3 dose levels (0.05, 0.2 and 0.4 mg/kg once daily) were studied. The study included 2 weight panels (10 to <25 kg or 25 to 40 kg). The primary efficacy endpoint was the slope of linear regression for the change in trough SBP from baseline to Week4/LOCF as a function of candesartan dose. Also, dose-response relation for change in DBP from baseline to Week4/LOCF and treatment effect of each dose over time relative to baseline in trough SBP and DBP were assessed.

The study results suggest effectiveness of candesartan in hypertensive pediatric subjects 1 to <6 years of age. SBP declined monotonically across the 3 candesartan dose levels by 6 to 12 mmHg, a decline that was significantly related to candesartan dose (the slope for dose ratio (1:4:8) was: –0.80 with p=0.0136). Similarly, DBP declined by 5 to 11 mmHg in a significant dose-related fashion (the slope for dose ratio (1:4:8) was: –0.79 with p=0.0301) (Figure 8). Moreover, the antihypertensive effect of candesartan was clearly supported by the response-time course (Figure 9).

Figure 8. Means and dose-response line for changes from baseline to Week 4/LOCF in SBP/DBP (ITT population in Study 328)
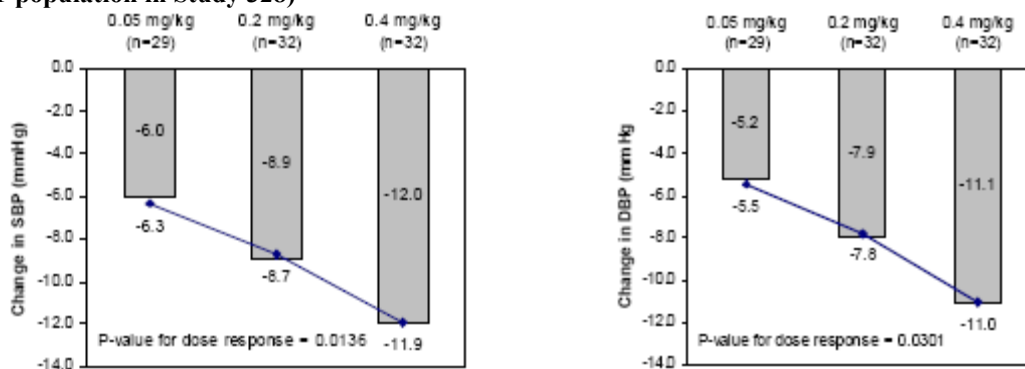
Note: Numbers inside the bars are the raw means. The connected dots and the values that are provided below the dots represent the dose-response line assuming the weight effect is proportional to the number of subjects in the upper weight panel.

Figure 9. Mean changes in SBP/DBP from baseline over time (ITT population in Study 328)
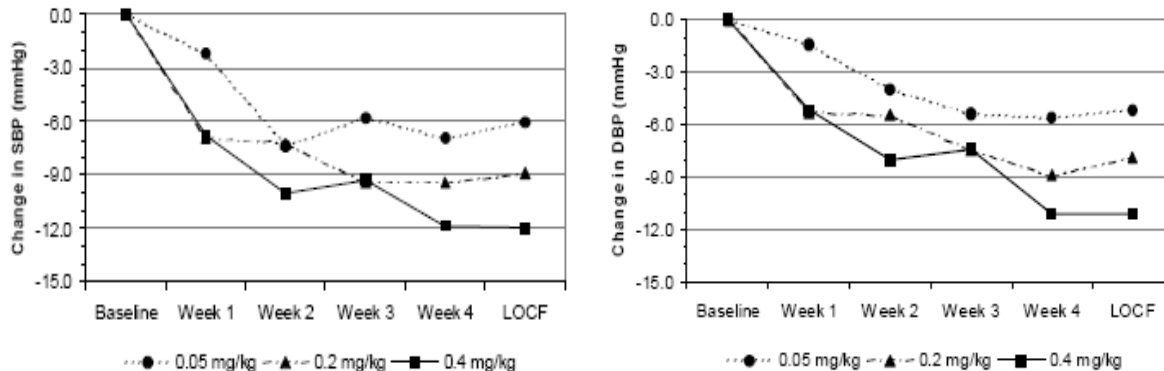
Reviewer's comments: The sponsor's regression model did not include the blood pressure baseline as a covariate whose effect is highly significant (p<0.0001). With the blood pressure baseline as a covariate, the slopes for the change in trough SBP/DBP as a function of candesartan dose ratio are still significant (slope for SBP=-0.72 with p=0.0141 and slope for DBP=-0.76 with p=0.0055). Therefore, effectiveness and dose-response of candesartan for the treatment of hypertension in the 1 to <6 years of age children is acceptable.

In Study 328, subjects receiving antihypertensive medications other than the classes of ARB or an ACEI (eg, diuretics, calcium channel blockers, or beta-blockers; not ARBs or ACEIs) and whose blood pressure values met inclusion/exclusion criteria could participate in the study while continuing their current antihypertensive medication without change in doses and dose regimens during the 4-week, period of the study. Therefore, if there are BP changes from baseline for those subjects, it is likely due to the candesartan antihypertensive effect. 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 can not reject the null hypothesis that the subjects receiving concomitant antihypertensive medications were randomly distributed among the different candesartan dose groups (p-value = 0.0887). Recognizing that there are problems associated with drawing conclusions from this type of analysis, we further tested the dose-response relationship of candesartan in population without any concomitant antihypertensive medication. Without the subjects under concomitant anti-hypertensive medications, the slope for SBP reduction versus dose is -1.114 with p-value 0.0053, which is more significant than the original analysis in the ITT population (slope= -0.80259 with p-value 0.0136 for the entire sample set as the sponsor reported). Therefore, it confirms that the observed BP reduction of candesartan in Study 328 is not a result of concomitant antihypertensive medications.

Effectiveness of Candesartan in Study 261A

Study 261A was a 4 week randomized, parallel placebo controlled double-blind dose-ranging study. To determine the dose effects of candesartan, a placebo control and 3 dose levels (2/4, 8/16 and 16/32 mg once daily) were studied. The study included 2 weight panels (<50 kg or ≥50 kg). The primary efficacy endpoint was the slope of linear regression for the change in trough sitting SBP from placebo to Week4/LOCF as a function of candesartan dose. Also, dose response for the change in trough sitting DBP from placebo to Week4/LOCF, changes of each dose treatment in BPs from baseline comparing to placebo, and treatment effect of each dose over time relative to baseline in trough SiSBP and SiDBP were evaluated.

The primary analysis failed to reject the null hypothesis that the slope for the change in trough SiSBP from placebo as a function of dose ratio (1:4:8) is 0 (slope for SiSBP=-0.3814 with p=0.0973). Similarly the change in SiDBP from placebo was not significantly dose related either (slope for SiDBP=-0.2128 with p=0.3708) (Figure 10). However, the antihypertensive effect of candesartan was clearly supported by the direct comparison of candesartan to placebo (Figure 11) and the response-time course (Figure 12).

Figure 10. Means and dose-response line for changes from baseline to Week 4/LOCF in SiSBP/SiDBP (ITT population in Study 261A)
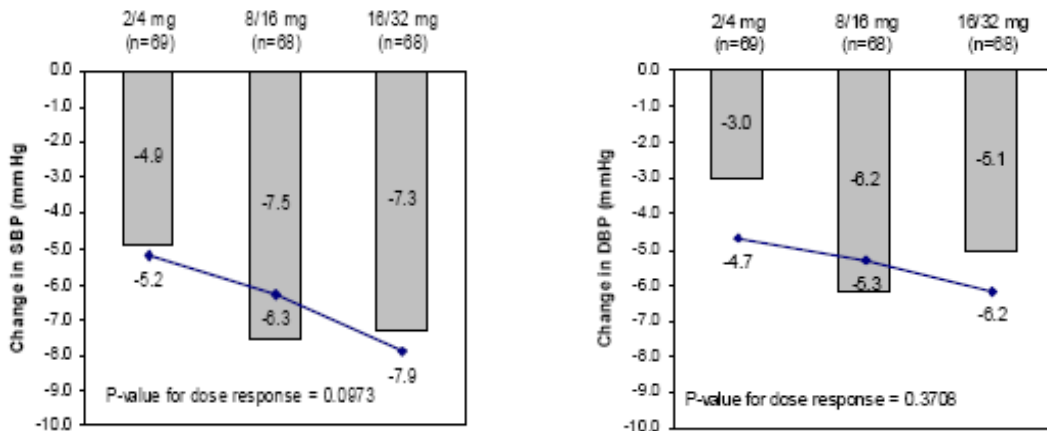
Note: Numbers inside the bars are the placebo subtracted <u>raw means</u> (*reviewer's comment: the number should be least square mean*). The connected dot and the values that are provided below the dots represent the dose-response line assuming the weight effect is proportional to the number of subjects in the upper weight panel.

Figure 11. Least square mean changes from baseline in SiSBP and SiDBP relative to placebo in Study 261A (ANCOVA and pair-wise contrasts without corrections for multiple comparisons)
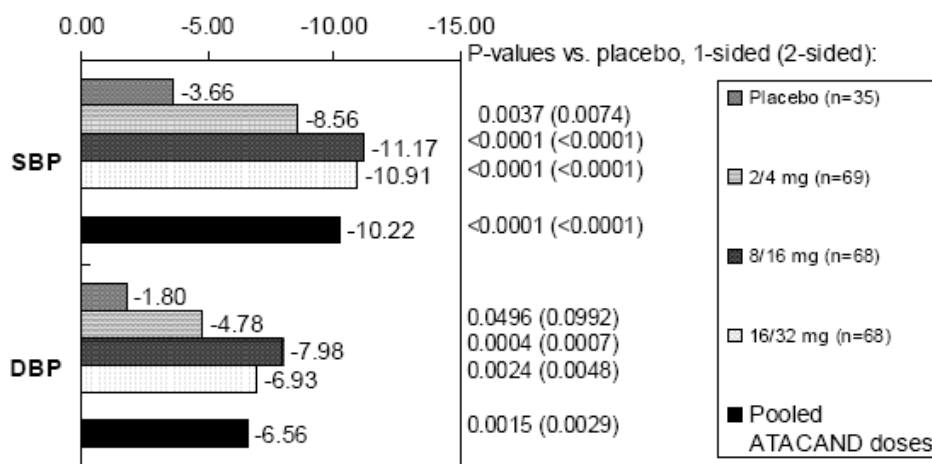
Figure 12. Mean changes in SiSBP/SiDBP from baseline over time (ITT population in Study 261A)
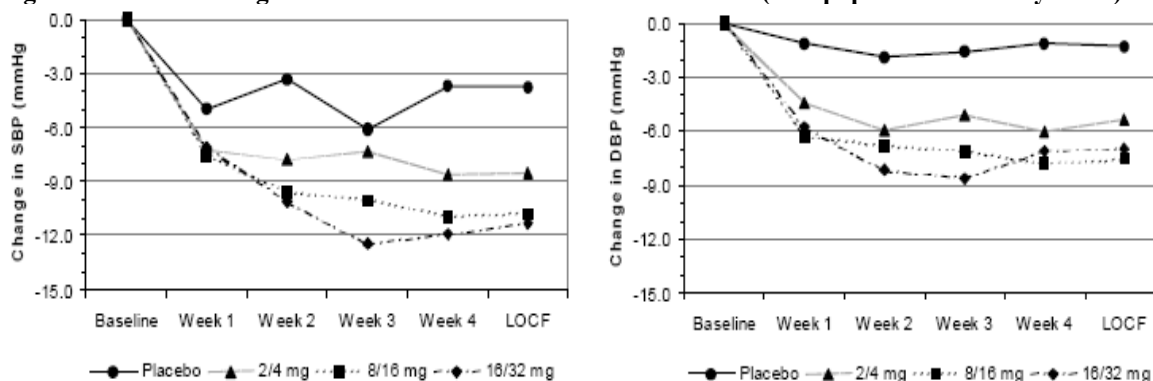
Reviewer's comments: The sponsor's primary analysis mainly focused on the test of dose-related effect. It ignored the information from the placebo arm obtained in the same study. Per the WR statement on trial design, the primary analysis should include all patients with data on randomized treatment. The sponsor's secondary analyses are informative in supporting the effectiveness of candesartan for the treatment of hypertension in the 6 to <17 years of age children. Additional analyses were conducted and the results are shown in the reviewer's analysis section.

Effectiveness of Candesartan in Pooled Studies

The fact that candesartan induced blood pressure reduction of a similar magnitude in both Study 328 and Study 261A is notable given the existence of the apparent between study differences (such as, the different proportion of subjects with secondary hypertension, the different proportion of subjects who had systolic hypertension versus diastolic hypertension, and the greater level of obesity in the older versus younger children). This similar degree of the blood pressure lowering effect across these two somewhat heterogenous study populations suggests that candesartan has a relatively predictable antihypertensive effect across the entire pediatric age range. In the combined analysis of children 1 to <17 years of age, candesartan induced a statistically significant dose related decrease in both SBP and DBP (slope for SBP=-0.51 with p=0.0065 and slope for DBP=-0.39 with p=0.0493) (Figure 13).

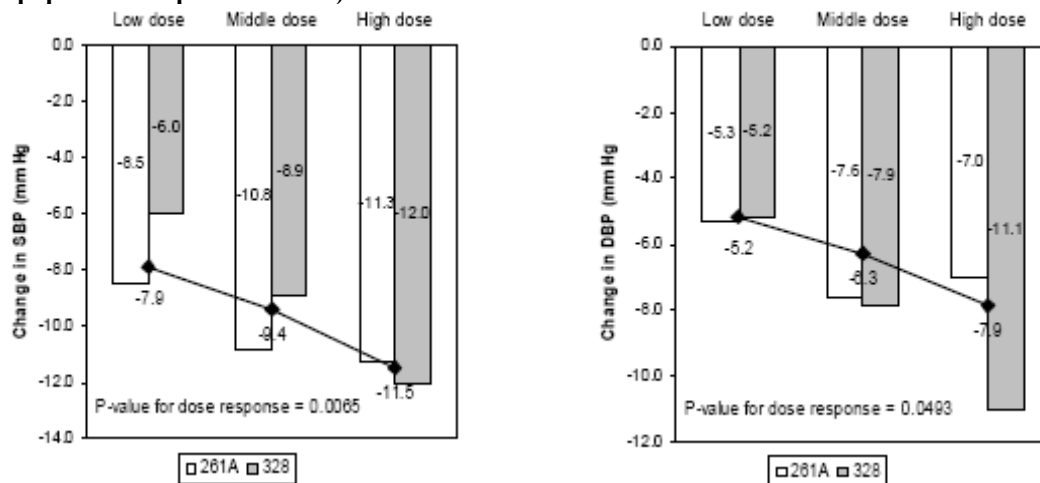**Figure 13. Means and dose-response line for changes from baseline to Week 4/LOCF in SBP/DBP (ITT population in pooled studies)**

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.

Reviewer's comments: the sponsor's analysis is informative. The degree of blood pressure reduction of candesartan across the entire studied pediatric population (1 to < 17 years of age) is similar. The combined analyses are informative in supporting the effectiveness of candesartan for the treatment of hypertension in pediatrics, but the model assumption of the same slope in the two different studies may misleading. Additional comparisons were conducted and the results are shown in the reviewer's analysis section.

4   REVIEWER'S ANALYSIS

4.1   INTRODUCTION

In Study 261A, the primary analysis failed to illustrate dose-related effectiveness of candesartan. The sponsor's primary analysis was found to be inadequate in evaluating candesartan effectiveness because it ignored the information from placebo obtained in the same study. This was especially important due to near maximal effects on two highest dose groups leading to shallow dose-response relationship. Per the WR statement on trial design, the primary analysis should include all patients with data on randomized treatment. The sponsor's secondary analyses and pooled studies are informative in supporting the effectiveness of candesartan for the treatment of hypertension in pediatric subjects 6 to <17 years of age. The following is the summary of additional analyses conducted to assess effectiveness of candesartan, the dosing recommendation proposed by the sponsor, and the impact of renal disease on the efficacy of candesartan in pediatrics.

4.2   OBJECTIVES

Analysis objectives are:

1. to assess effectiveness of candesartan for the treatment of hypertension in pediatric subjects 1 to < 17 years of age

2. to assess the dosing recommendation in the proposed labeling statements

3. to assess the effect of renal disease on the efficacy of candesartan

4.3 METHODS

4.3.1 Data Sets

Data sets used are summarized in Table 10.

Table 10. Analysis Data Sets

Study Number	Name	Link to EDR
d2451c00002 (Study 328)	vitol000.xpt	\\cdsesub1\evsprod\NDA020838\0003\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hypertension\5351-stud-rep-contr\d2451c00002\crt\datasets\vitol000.xpt
d2451c00002 (Study 328)	pk000.xpt	\\cdsesub1\evsprod\NDA020838\0003\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hypertension\5351-stud-rep-contr\d2451c00002\crt\datasets\pk000.xpt
d2451c00261 (Study 261A)	vit000.xpt	\\cdsesub1\evsprod\NDA020838\0003\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hypertension\5351-stud-rep-contr\d2451c00261\crt\datasets\vit000.xpt
d2451c00261 (Study 261A)	pk000.xpt	\\cdsesub1\evsprod\NDA020838\0003\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hypertension\5351-stud-rep-contr\d2451c00261\crt\datasets\pk000.xpt

4.3.2 Software

SAS 9.2 was used for the analysis.

4.3.3 Models and Results

Effectiveness of Candesartan in Pediatrics

Study 261A was a parallel placebo controlled double-blind dose-ranging study. Placebo anchored method (placebo dose=0) was deemed to be more suitable in evaluating drug effectiveness. The linear model may not be a good model to describe the dose-response relationship since the dose-range covered is too wide. However, the main purpose of this analysis is to test drug effectiveness. A significant slope will automatically prove the drug effect. Moreover, the randomization for each treatment group was preserved. The new analysis takes advantage of information from placebo, so the mean squared error estimate will be more accurate. With this analysis, the slope for reduction in SiSBP is significant with p-value 0.0009. Similar results were also shown in the regression for reduction in SiDBP with p-value 0.0096 (Figure 6 and Table 7). Therefore, these analyses clearly confirmed the effectiveness of candesartan for the treatment of hypertension in pediatric subjects 6 to <17 years of age.

The similar degree of blood pressure reduction of candesartan across the entire studied pediatric subjects 1 to 17 years of age was notable (Figure 13). Further, the potential reasons for a significant dose-response relationship in Study 328 but a non-significant relationship in Study 261 for an identical analysis method were explored.

- Study 328 used body weight based doses as compared to fixed doses in 261A. Because body weight has been shown to correlated (negatively) with Cmax and AUC estimates in Study 261A, the fixed dosing method is likely to introduce larger noise in the exposure-response relationship than dosing by body weight (e.g., in mg/kg) as in Study 328. In Study 261A, the weight based dosing method is likely to be more powerful in revealing the dose-related effect due to a wider dose range that will be achieved. A simple linear regression model with candesartan active dose

expressed in mg/kg showed a significant dose-response correlation for SiSBP (p=0.0032) and SiDBP (p=0.0347) in Study 261A (Table 11). This, in some degree, confirmed the dose-related drug-response relationship. More directly, the exposure-response based on the observed trough concentrations of active arms clearly showed a significant correlation for SiSBP reduction from baseline (the slope was: –0.03570 with p=0.0101).

- The selected doses in Study 261A are more likely to produce a relatively flat slope for the dose-response relationship than in Study 328. Comparing the drug exposures between these two studies (Figure 14), it shows that the exposures of candesartan in Study 261A are higher than in Study 328, especially for the medium (8/16 mg) and high dose (16/32 mg) groups. Since the medium dose already achieved the similar exposure of the adult 16 mg dose (related to maximum effect in adults), the dose selection already implied a relatively flat slope in Study 261A.

- The high dose group in Study 328 exhibited similar candesartan exposure as the medium dose group in Study 261A as well as the 16 mg dose in adults (Figure 14), and they all achieved the similar maximum effect as in adults (Table 8). This observation suggests that the concentration-response relationship of candesartan is consistent across the entire studied pediatrics and adults. By pooling the exposure-response data in Study 328 and Study 261A, a simple linear regression model based on the observed trough concentrations of active arms clearly showed a significant exposure-response correlation for SiSBP reduction from baseline (the slope was: –0.03767 with p=0.0025) (Figure 15), and the slope of the regression line in the pooled studies was similar as the slope in the individual studies. This confirms the effectiveness of candesartan across the entire studied pediatrics and provides an alternative approach for the dosing recommendation.

Table 11. Dose-response regression for change in SiSBP and SiDBP from baseline at Week 4/LOCF as a function of active arm dose (the dose is expressed in mg/kg, Study 261A)

Model variable	SBP DF	Estimate (SE)	p-value	DBP DF	Estimate (SE)	p-value
Intercept ($\beta 0$)	1	-7.6312 (1.0610)	<.0001	1	-4.8234 (1.0009)	<.0001
Coefficient for dose ($\beta 1$)	1	-11.8766 (3.9807)	0.0032	1	-7.9708 (0.0347)	0.0347
Coefficient for BP Baseline ($\beta 2$)	1	-0.3934 (0.0719)	<.0001	1	-0.5206 (0.0608)	<.0001

* For the regression, the baseline value was centered at the sample mean.

Figure 14. Comparison of the trough concentrations between Study 328 and Study 261A
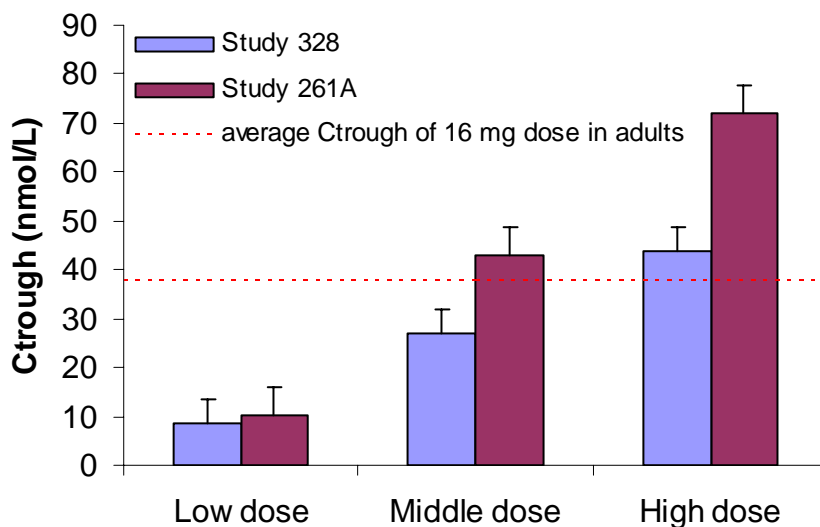
Figure 15. Pooled exposure-response for changes in SBP from baseline to the last treatment (based on the observed trough concentrations of active arms)
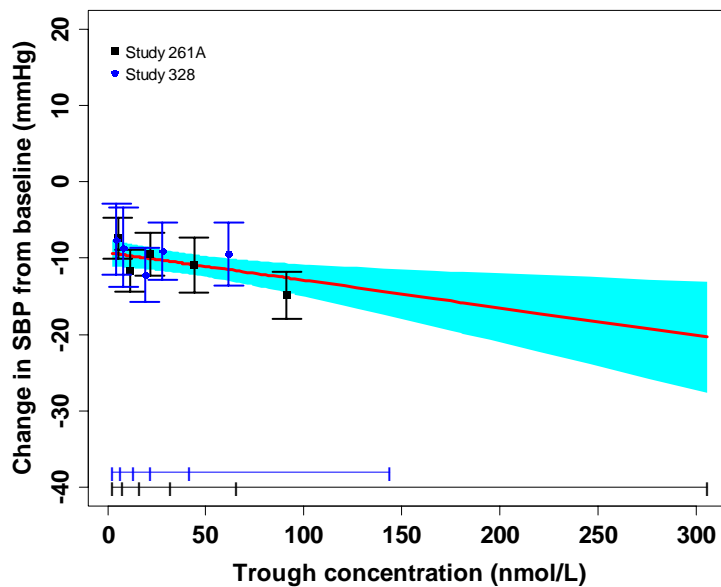
Note: Solid symbols and bars represent the mean and 95% confidence interval of SBP reduction from baseline for each observed concentration quantile. The concentration range is denoted by the horizontal line. The black color represents data from Study 261A and the blue color represents data from Study 328. The solid red line represents the mean linear regression prediction based on the pooled studies. The shaded area represents the 95% confidence interval.

Dosing Recommendation of Candesartan in Pediatrics

As shown in Table 8, the proposed dose ranges produce the similar blood pressure reduction in

hypertensive pediatric subjects 1 to < 17 years of age and adults. The pharmacokinetics of candesartan is also comparable across pediatrics and adults. In adults, the starting dose, 16 mg QD (tablet), produces maximum reduction in blood pressure. From the clinical studies in pediatrics, 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. Because candesartan is well tolerated across the studied pediatric and adult population, the similar maximum effect dose selection strategy in hypertensive children 6 to <17 years of age as in adults is reasonable. 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. This dose regimen was supported in the long term clinical follow-up. 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. Using the exposure –response analysis, we expected the 4/8 mg starting dose in children 6 to <17 years old would produce similar blood pressure reduction (9 mmHg in trough SBP) as the 0.2 mg/kg starting dose did (8.7/7.8 mmHg in trough SBP/DBP) in children 1 to <6 years old. Using this conservative starting dose in pediatrics (especially for younger children) is also acceptable.

The efficacy data in this pediatric clinical program were all collected at the trough time point of the once a day dose regimen and have proved that the antihypertensive effect of candesartan was well preserved. In the original review for the treatment of hypertension in adults, there is an inconclusive study that suggested there may be some benefit with BID vs. QD in some patients for 16 mg total daily dose. We think it is an option for pediatrics to change the dose regimen from QD in proposed dose range labeling to total daily as in adults.

Impact of Renal Disease on Candesartan in Pediatrics

In study 328, a total of 69 children (74%) had renal disease at baseline, which included nephritic syndrome, congenital cystic renal diseases, dysplastic disorders, hemolytic uremic syndrome, and others. 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 (< 80 mL/min). Based on the proportional dose normalized trough concentration, candesartan exposure in subjects with renal disease is about 70% higher than exposure in subjects without renal disease (Figure 16). Reduction in SBP in subjects with renal disease is not different from reduction in subjects without renal disease (Figure 7 and Table 9). Therefore, no dose adjustment is necessary in hypertensive children with renal disease. This is consistent with the recommendation in adults that no initial dosage adjustment is necessary for patients with mildly impaired renal function.

Figure 16. Comparison of the proportional dose normalized trough concentration between subjects with or without renal disease (Study 328)
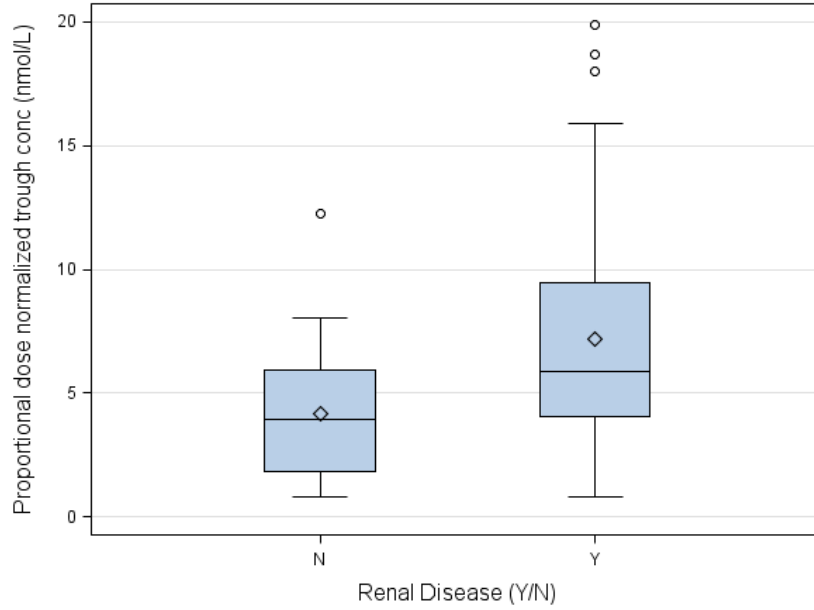
5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
261A_test.sas	Efficacy Analysis for Study 261A	\Candesartan_NDA020838_JL\ER Analyses
combined_test.sas	Efficacy Analysis for Study 328 and Study 261A	\Candesartan_NDA020838_JL\ER Analyses

APPENDIX (CLINICAL PHARMACOLOGY REVIEW)

OFFICE OF CLINICAL PHARMACOLOGY:
CLINICAL PHARMACOLOGY REVIEW

Report #	D2451C00005
Investigator	Kenneth C. Lasseter, MD
Study Site	SFBCI Clinical Pharmacology Associates
	11190 Biscayne Road, Miami, Florida 33181
Study Period	April 2004- May 2004

Title

A randomized, open label, 2-way crossover study comparing the bioavailability of the 32 mg commercial formulation of candesartan cilexetil given in tablet form to an oral suspension in healthy subjects

Objectives

The primary objective is to determine the relative bioavailability of 32 mg candesartan tablets and 32 mg candesartan suspension.

Study Design

This was an open-label, randomized, 2-period, 2-way crossover study in healthy subjects. During each treatment period blood sampling was performed over three days followed by a seven day washout period between treatments. Twenty four subjects participated in the study.

Study Drug

Test Drug: 32 mg of candesartan cilexetil given as a single oral dose in a 20 mL suspension. The suspension was prepared on site using 32 mg candesartan tablets (Lot # N5834). 1 tablet was crushed with mortar and pestle and then mixed with 10 ml of Ora-Sweet SF™ and 10 ml of Ora-Plus™ to create a 20 mL suspension.

Reference Drugs: A 32 mg candesartan cilexetil tablet (Lot # N5834) was given as a single oral dose. Tablets were taken orally with 240 mL of water.

Pharmacokinetic Blood Sampling

Venous blood samples were collected at pre-dose and at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, and 48 hours post-dose

Assay Method

A validated HPLC method with fluorescence detection was used for the quantification of candesartan in plasma. During the analysis of the study unknown plasma samples, the calibration range was 1.0 – 300

nM with LLOQ of 1.0 nM (%CV $\leq$ 7.1, %RE: -4.3 – 5.5). The precision of the quality control samples was $\leq$ 6.5 and the accuracy was -3.8 - -1.0.

Pharmacokinetics Data Analysis

Candesartan primary PK measures (AUC, C_{max}, and t_{max}) were calculated by standard non-compartmental methods of analysis

Statistical Method

A mixed-effect analysis of variance (ANOVA) model on log transformed parameters was used to compare the pharmacokinetic parameters of candesartan for each treatment period. Two-sided 90% confidence intervals (CI) for the intra-subject test to reference ratio (as estimated by the ratio of the geometric means) of each of $AUC_{0-\infty}$ and C_{max} were calculated.

Results

Twenty two subjects (6 males and 16 females) completed the study with mean age of 31 ± 7 years. Two subjects were withdrawn from the study; one for an adverse event [hepatic enzyme increased], and one for a positive urine drug screen.

There was no statistically significant difference in candesartan $AUC_{0-\infty}$ systemic exposure between the tablet and the suspension. On the other hand, the candesartan suspension and showed a 22% higher C_{max}, (90% CI: 109 – 136%), as shown in the table below:

Parameter	N	Geometric Mean (%CV) Candesartan Suspension (S)	N	Candesartan Tablet (T)	Ratio S/T	90% CI Lower	Upper
$AUC_{0-\infty}$ (nM h)	22	7086.8 (27.4)	22	6559.0 (34.7)	108	100	116
C_{max} (nM)	22	643.1 (28.3)	22	522.6 (43.8)	122	109	136

Safety

No death or any other serious adverse events occurred during this study.

Conclusions

Candesartan suspension is bioequivalent to candesartan tablet in terms of AUC. The C_{max} following the administration of candesartan suspension is 22% higher compared to that   following administration of candesartan tablet.

Comments

There is no difference in the adverse events among both age groups, 1 < 6 using the suspension and 6 <17 using the tablets, so the significance difference in C_{max} is not of a concern.

Report #	D2451C00002(Study 328)
Investigator	Franz Schaefer, MD
Study Site	Center for Pediatrics and Adolescent Medicine
	Im Neuenheimer Feld 430, 68120 Heidelberg, Germany
Study Period	11/04/2004 – 08/27/2008

Title

A dose-ranging, safety and pharmacokinetics study of candesartan cilexetil in hypertensive pediatric subjects 1 to less than 6 years of age: A 4-week, multicenter, randomized, double-blind study with a 1-year open-label, follow-up period

Objectives

One of the study objectives is the determination of the pharmacokinetics of candesartan in children 1 < 6 years of age.

Study Design

This is a double-blind, randomized, multicenter, dose-ranging study of candesartan in hypertensive pediatric subjects ages 1 to <6 years. The study included a 1-week, single-blind, placebo run-in and a 4-week, double-blind treatment period followed by a 1-year, open-label treatment period. Subjects were allocated to receive 1 of 3 dose levels of candesartan (0.05 mg/kg, 0.2 mg/kg, or 0.4 mg/kg),

For the PK sub-study, a single 0.2 mg/kg dose was administered. Subjects participated in the serial PK study either at study entry prior to the double-blind period of the study or at any point during the open-label extension period but only after discontinuing study drug for at least 48 hours.

Study Drug

Candesartan oral suspension was prepared using candesartan tablets (4 mg and 32 mg). Ora-Sweet SF and Ora-Plus® 50/50 %weight was used as the suspension vehicle. Regional central pharmacies manufactured the following concentrations of candesartan: 0.1, 0.2, 0.4, 0.6, 0.8, 1, 1.2, 1.4, 1.6, 1.8, and, 2.0 mg/ml, the batch volume was either 5 mL or 10 mL.

Pharmacokinetic Blood Sampling

Venous blood samples were collected at pre-dose and at 0.5, 1, 1.5, 3, 5, 8, 24, and 28 hours post-dose

Pharmacodynamic Measurement

Blood pressure was measured by an auscultatory method at pre-dose and at 0.5, 1, 1.5, 3, 5, 8, 24, and 28 hours post-dose
Assay Method

A validated LC-MS/MS method was used for the quantification of candesartan in plasma. During the analysis of the study unknown plasma samples, the calibration range was 2.0 – 1000 nM with LLOQ of 2.0 nM (%CV ≤ 7.5, %RE: -4.2 – 10.0). The precision of the quality control samples was ≤ 5.2 and the accuracy was 2.3 - -9.5.

Pharmacokinetics Data Analysis

Candesartan primary PK measures (AUC, C_{max}, t_{max}, and $t_{1/2}$) were calculated by standard non-compartmental methods of analysis

Results

Ten subjects (5 males and 5 females) completed the PK substudy, 1 were 1 - < 2 years old and 9 were 2- < 6 years old, mean age was 3.1 years (range 1 – 4). All the subjects weigh between 10 and < 25 Kg, 6 were Caucasian and 4 were Black.

Figure 1 shows candesartan plasma concentration-time profile for all subjects. The PK measures of candesartan in all subjects are displayed in the table below; note that $t_{1/2}$ is not a terminal half-life

|	$AUC_{0-\infty}$ (nM h)	AUC_{0-28} (nM h)	C_{max} (nM)	t_{max} (h)	$t_{1/2}$ (h)
N	10	10	10	10	10
Mean	1781	1711	250.8	3.3	5.8
(SD)	(611)	(582)	(61.3)	(1.0)	(1.4)
CV%	34.3	34.0	24.4	31.8	23.4

Figure 1 shows the time course of candesartan on systolic blood pressure. On average candesartan appears to have a concentration dependent decrease in systolic blood pressure. The effect is totally diminished at 10 hours post dose.

Comments

1. Based on Figure 1 twice-daily dosing seems to be more appropriate to sustain the effect of candesartan on systolic blood pressure. However, the systolic blood pressure is not correlated to candesartan concentration as shown in Figure 2.
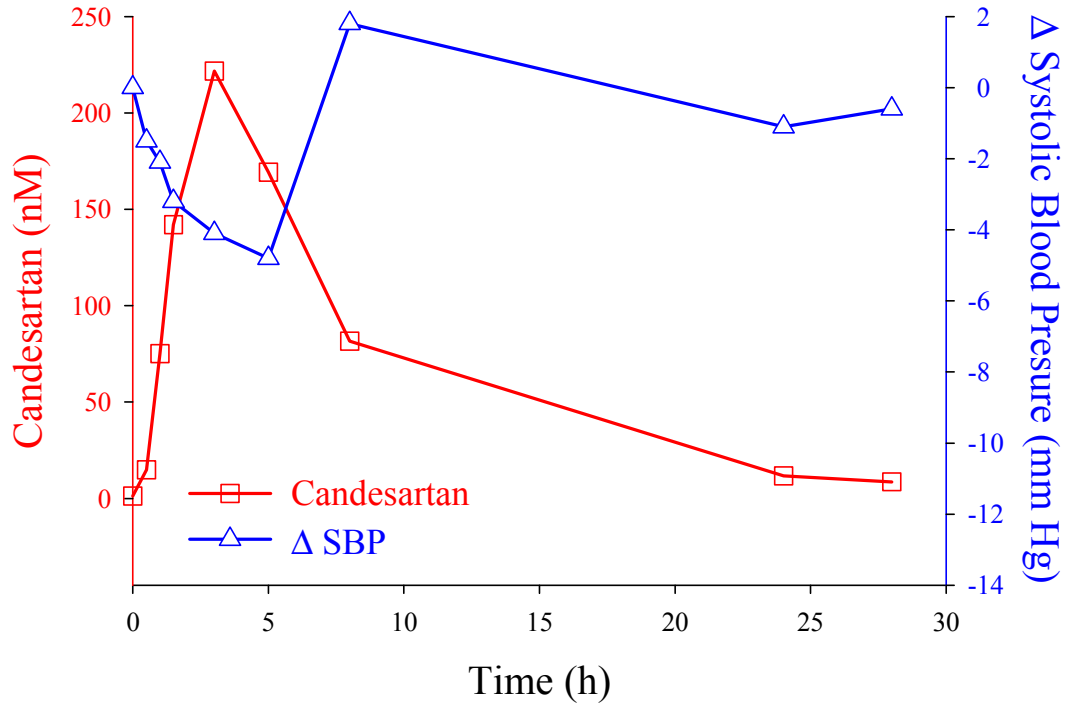
Figure 1. Time course effect of candesartan on systolic blood pressure, following the administration of 0.2 mg/Kg dose in children 1 - <6 years old. Each point represents the mean (n = 10) .
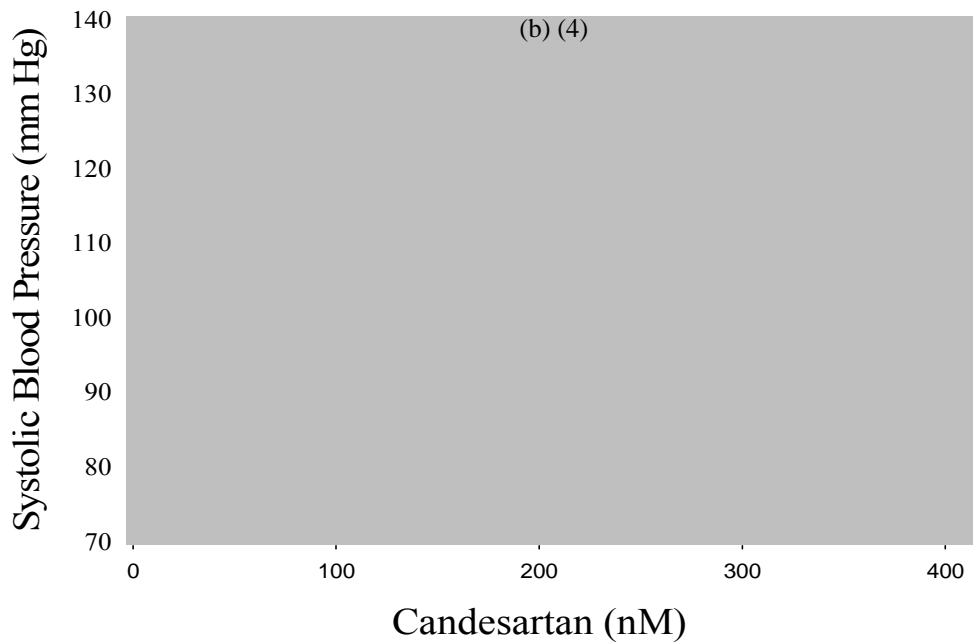
Figure 2. Scatter plot of systolic blood pressure vs. candesartan plasma concentration, solid line represents linear regression line while dashed lines represents the 95% confidence interval.

Report #	D2451C00001(261B)
Investigator	Howard Trachtman MD
Study Site	27 sites in the United States and 7 in Europe enrolled and treated at least 1 subject
	PK substudy was performed at selected sites in the united states
Study Period	10/10/2004 – 11/22/2006

Title

A multicenter, multinational, open-label study of the efficacy, safety, and pharmacokinetics of candesartan cilexetil in hypertensive pediatric subjects 6 to <17 years of age

Objectives

One of the study objectives is the determination of the pharmacokinetics of candesartan in children 6 < 17 years of age.

Study Design

This is an open-label, uncontrolled, 52-week study. Suggested starting doses for children <50 kg was 4 mg once-daily and for children >50 kg, 8 mg once-daily. Investigators were allowed to adjust the candesartan dose between 4 mg and 32 mg once-daily.

For the PK sub-study, a single 16 mg dose was administered; thereafter; the subjects began (or resumed) treatment. The minimum permissible body weight for the PK sub-study was 25 kg (a maximum dose equaling 0.64 mg/kg) to assure that the 16 mg dose was appropriate for all PK study participants on a mg/kg basis. Per protocol the substudy could be done at any time during the 52 weeks study period.

Pharmacokinetic Blood Sampling

Venous blood samples were collected at pre-dose and at 1, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours post-dose

Assay Method

A validated LC-MS/MS method was used for the quantification of candesartan in plasma. During the analysis of the study unknown plasma samples, the calibration range was 2.0 – 1000 nM with LLOQ of 2.0 nM (%CV ≤ 7.5, %RE: -4.2 – 10.0). The precision of the quality control samples was ≤ 5.2 and the accuracy was 2.3 - -9.5

Pharmacokinetics Data Analysis

Candesartan primary PK measures (AUC, C_{max}, t_{max}, and $t_{1/2}$) were calculated by standard non-compartmental methods of analysis

Pharmacodynamic Measurement

Blood pressure was measured by an auscultatory method at pre-dose and at 1, 2, 4, 8, and 12 hours post-dose

Results

Twenty two subjects (14 males and 8 females) completed the PK substudy, 12 were 6 - < 12 years old and 10 were 12- 6 - < 17 years old. Eleven of the subjects were preadolescents (Tanner Stage <3) and most were overweight (19 with BMI ≥95th percentile). All but 1 subject weighed ≥50 kg.

Per sponsor, body weight correlated (negatively) with C_{max} (r^2 = -0.557, p = 0.0108) and AUC (r^2 = -0.528, p = 0.0116).

The PK measures of candesartan in all subjects are displayed in the table below. Younger children (6 < 12 years) have slightly lower systemic exposure than older childrens (Age 12 - < 17).

		$AUC_{0-\infty}$ (nM h/)	AUC last (nM h)	C_{max} (nM)	T_{max} (h)	$t_{1/2}$ (h)
6 to <12 years	N	12	11	12	12	11
	Mean (SD)	2727.6 (1270.8)	2462.5 (1099.7)	333.9 (180.0)	4.3 (2.1)	6.7 (1.3)
	CV%	46.6	44.7	53.9	47.9	18.9
12 to <17 years	N	10	9	10	10	9
	Mean (SD)	3059.9 (1091.0)	2951.2 (1041.8)	396.9 (212.0)	4.3 (1.5)	5.7 (1.3)
	CV%	35.7	35.3	53.4	35.4	22.6

Figures 1 and 2 shows the time course of candesartan on systolic blood pressure. On average candesartan appears to have a concentration dependent decrease in systolic blood pressure and the effect is sustained up to 12 hours.
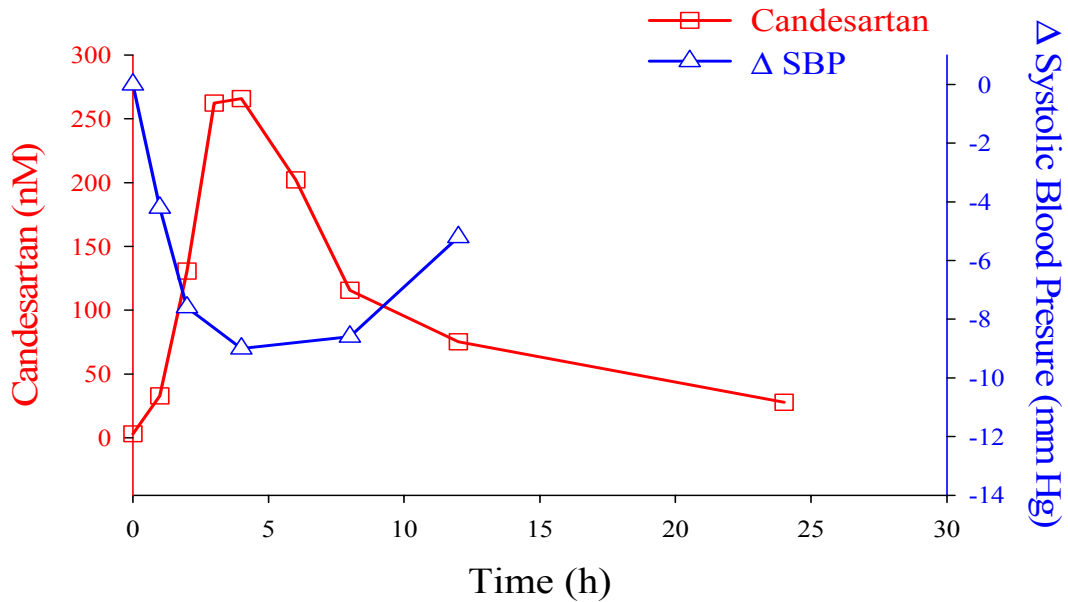
Figure 1. Time course effect of candesartan on systolic blood pressure, following the administration of 16 mg dose in children 6 - <12 years old. Each point represents the mean (n = 9) .
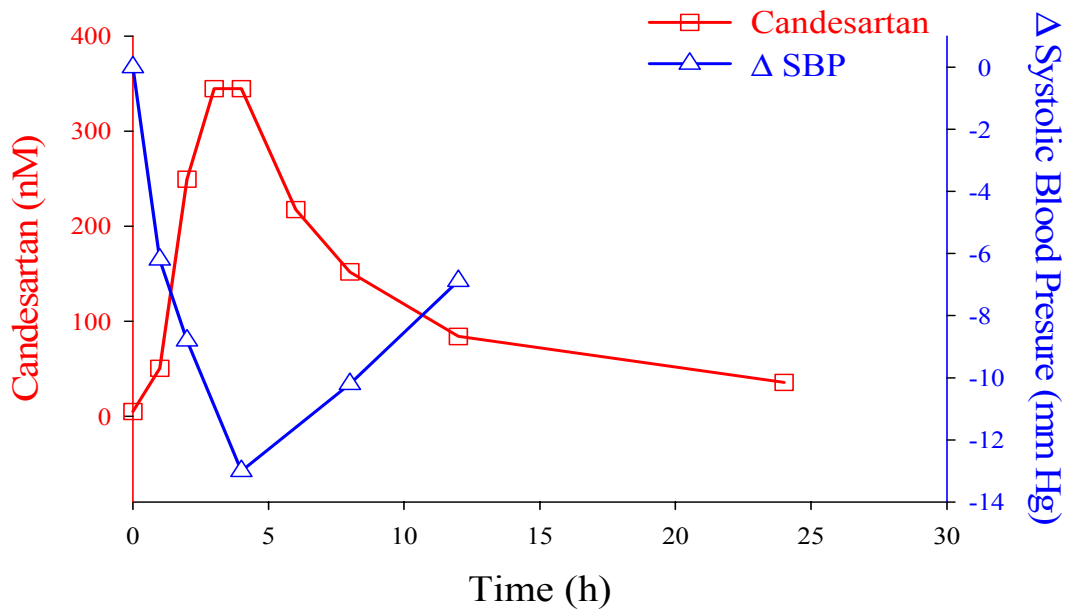
Figure 2. Time course effect of candesartan on systolic blood pressure, following the administration of 16 mg dose in children 12 - <17 years old. Each point represents the mean (n = 9)
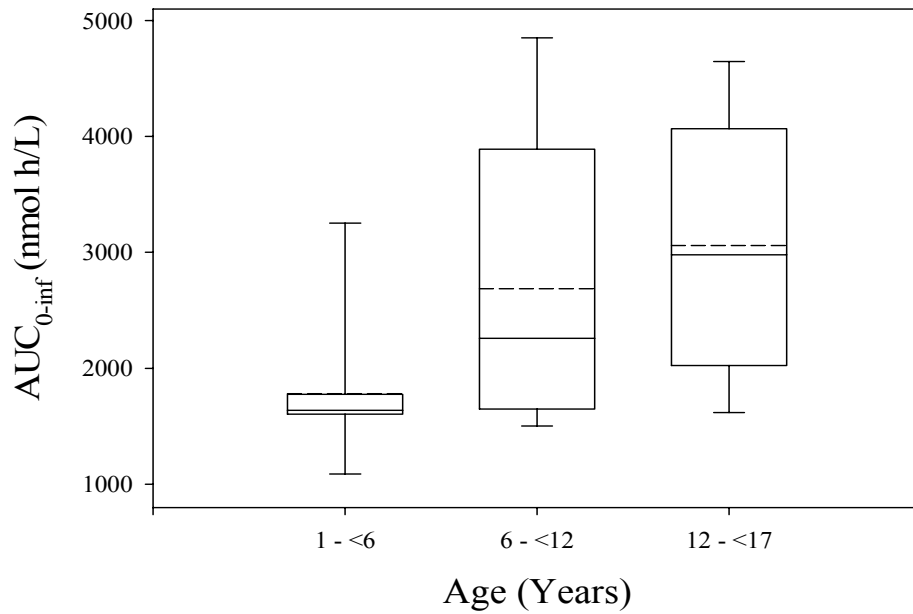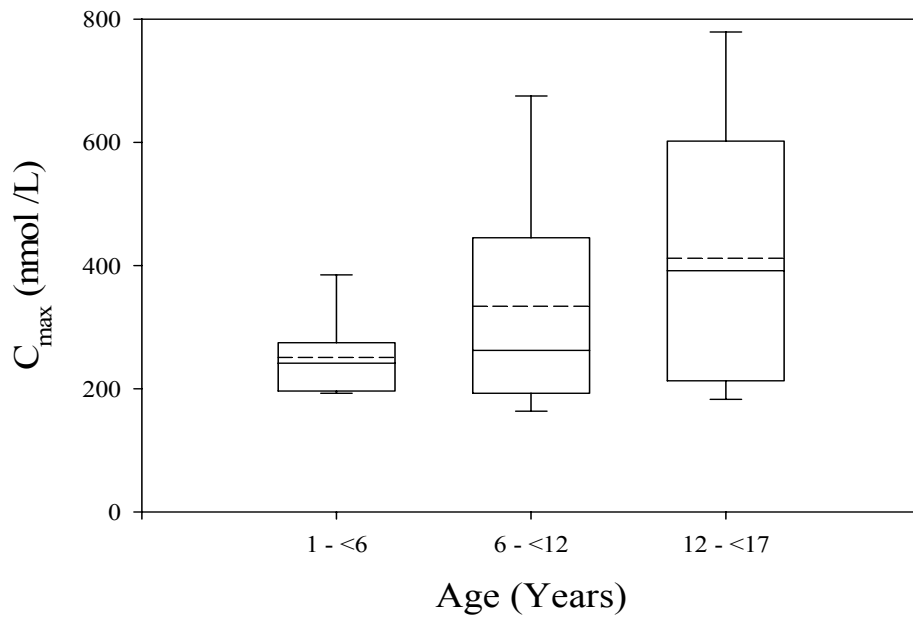**Comments:**

The systemic exposure of candesartan in children 6 to <17 years of age comparable to that in younger

children as shown in Figures 3 and 4.

Figure 3. Candesartan $AUC_{0-\infty}$ comparison among the different children age groups, dash line represent mean

Figure 4. Candesartan C_{max} comparison among the different children age groups, dash line represent mean

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

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