U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	20-838
Drug Name:	Candesartan cilexetil
Indication(s):	reduce blood pressure in pediatric patients
Applicant:	AstraZeneca
Date(s):	April 23, 2009
Review Priority:	Standard
Biometrics Division:	Biometrics I (HFD-710)
Statistical Reviewer:	John Lawrence
Concurring Reviewers:	Jim Hung
Medical Division:	Division of Cardiovascular and Renal Products (HFD-110)
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Keywords: pediatric studies

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The sponsor conducted two dose ranging studies in pediatric subjects. One study in children less than 6 years old showed a dose response among the three doses studied. A second study in children age 6 to 17 failed to show a dose response among the three doses studied using the pre-specified primary analysis.

1.2 Brief Overview of Clinical Studies

One study (328) enrolled 93 subjects less than 6 years old. Subjects were randomized to low, middle, or high dose regimen of candesartan with actual dose based on body weight (0.05, 0.2, or 0.4 mg/kg). The primary endpoint was change in systolic blood pressure after 4 weeks of treatment. This study did not have the required percentage of black patients according to the Written Request letter.

One study (261A) enrolled 240 subjects between 6 and 17 years old. Subjects were randomized to placebo, or to a low dose, medium dose, or high dose of candesartan. For subjects under 50 kg in body weight, the doses were 2, 8, and 16 mg per day, for subjects 50 kg or greater, the doses were 4, 16, and 32 mg per day. The primary endpoint was change in sitting systolic blood pressure after 4 weeks of treatment. The primary analysis was based on the slope of the dose response relationship for the non-placebo groups.

1.3 Statistical Issues and Findings

The first study (328) showed a difference between the three dose regimens using the per-specified primary analysis (p=0.014).

The second study failed to show a difference between the three doses using the pre-specified primary analysis (p=0.1). An exploratory analysis in the second study showed that all three doses were different from placebo.

2. INTRODUCTION

2.1 Overview- Study 328

Study 328 was a multicenter, dose-ranging study of candesartan in hypertensive pediatric subjects ages 1 to <6 years. It employed a double-blind, randomized, dose-ranging design

followed by a 52-week, open-label treatment experience evaluation. Subjects underwent a screening evaluation, then a 1-week, single-blind, placebo run-in period, after which eligible subjects received ½ the dose until Day 7. If tolerated, dose was increased to full dose: 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), liquid formulation, in a 1:1:1 ratio. The study drug concentration was adjusted to correspond to a fixed dose volume (5 ml for subjects <25 kg and 10 m for those ≥25 kg). Subjects returned weekly during the double-blind period (Day 1 to Day 28).

The primary objective of the study was to determine if candesartan induced a dose-related reduction in blood pressure in the double-blind phase of the study. The primary efficacy measure was SBP determined at 'trough' (24 hours post-dosing) and the measure of effect was change from baseline to Week 4. Missing data was imputed by last observation carried forward. More than 90% of patients in each group completed the study.

The total number of subjects were randomized was 93 (out of 118 enrolled). According to the study report: "The candesartan pediatric hypertension clinical trial program has examined children from 1 to <17 years of age. The sample size estimates for the program took into account criteria outlined in a FDA modification to the written request to assure that studies were adequately powered to detect a meaningful antihypertensive effect, (see FDA Written Request, Module 1). The sample size for this study was chosen to assure that 25% of the efficacy evaluable subjects participating in the overall program were between 1 and <6 years of age." About the only thing I can agree with in that statement is the first and last sentence, indeed the two studies examined subjects from 1 to less than 17 years of age and about 25% of the total number of subjects in the two studies were between 1 and less than 6 years old. The middle sentence is vague, not describing exactly how the sample size was chosen, but even this vague description is different from what was in the written request letter. For example, the letter did not say to find a sample size, then split up that sample size into two studies which would be analyzed independently. Moreover, even the total sample size for the two studies combined is far short of what was required to achieve 90% to detect a clinically meaningful effect as defined in the letter.

The summary of the baseline demographics appears in Table 1. Of note, the percentage of Black subjects was only 18%, which did not fall within the range required by the written request (at least 35%).

Table 1 Summary of demographics and other baseline data (Study 328).

Demographic characteristics		Candesartan treatment			
		0.05 mg/kg N=29 n (%)	0.2 mg/kg N=32 n (%)	0.4 mg/kg N=32 n (%)	Total N=93 n (%)
Sex (n, % of subjects)	Female	11 (37.9)	10 (31.3)	12 (37.5)	33 (35.5)
	Male	18 (62.1)	22 (68.8)	20 (62.5)	60 (64.5)
Age at screening (years)	1 to <2	6 (20.7)	5 (15.6)	5 (15.6)	16 (17.2)
	2 to <6	23 (79.3)	27 (84.4)	27 (84.4)	77 (82.8)
	Mean (SD)	3.0 (1.3)	3.3 (1.4)	3.0 (1.4)	3.1 (1.4)
	Range	1 to 5	1 to 5	1 to 5	1 to 5
	Median	3.0	4.0	3.0	3.0
Race (n, % of subjects)	Caucasian	20 (69.0)	25 (78.1)	26 (81.3)	71 (76.3)
	Black	6 (20.7)	5 (15.6)	6 (18.8)	17 (18.3)
	Oriental	1 (3.4)	1 (3.1)	0	2 (2.2)
	Other	2 (6.9)	1 (3.1)	0	3 (3.2)
Baseline characteristics					
Weight at randomization (kg)	10 to <25	25 (86.2)	27 (84.4)	29 (90.6)	81 (87.1)
	25 to 40 kg	4 (13.8)	5 (15.6)	3 (9.4)	12 (12.9)
	Mean (SD)	17.5 (6.5)	18.0 (6.2)	17.0 (6.3)	17.5 (6.3)
	Range	10 - 38	11 - 34	11 - 39	10 - 39
	Median	15.8	16.8	15.7	16.0
BMI percentile at screen	<95%	17 (58.6)	17 (53.1)	22 (68.8)	56 (60.2)
	≥95%	6 (20.7)	10 (31.3)	5 (15.6)	21 (22.6)
	Unknown	6 (20.7)	5 (15.6)	5 (15.6)	16 (17.2)

Source: p 56 of Study Report.

The primary analysis was conducted using a linear regression model. The response (dependent) variable was the change from baseline to the end of the double-blind treatment period in trough SBP, and the independent variables were dose ratio (1:4:8, representing the low, middle, and high dose groups) and weight group (0 or 1 representing the 2 weight panels) as a blocking factor. If the coefficient for the dose ratio term was significantly different from zero at a significance level of 0.050, then a dose response relationship was concluded. The regression model takes the following form: change from baseline=$\alpha + \beta*(\text{dose ratio}) + \tau*(\text{weight group}) + \varepsilon$, where α, β, and τ are coefficients to be derived in the model and ε is the error term. In order to retrieve a single-point estimate for each of the 3 dose ratios, a value had to be applied to the weight group parameter. The weight group parameter identifies those subjects in the lower (assigned a value of 0) and higher (assigned a value of 1) weight panels. To represent the

study population, the proportion of subjects in the upper weight group (0.129) was entered into the regression equation. Each of the 3 dose ratio estimates was calculated by entering the dose ratio value into the equation.

Secondary endpoints included the dose response 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. No adjustment was made for these secondary analyses to control the familywise error rate.

2.2 Overview- Study 261A

Study 261A was a multicenter, placebo-controlled dose-ranging study of candesartan in hypertensive pediatric subjects ages 6 to <17 years. It employed a double-blind, randomized, dose-ranging design followed by a 52-week, open-label treatment experience evaluation. Subjects underwent a screening evaluation, then a 1-week, single-blind, placebo run-in period. The study included 2 dosing panels based on subject weight:
Panel 1: Subjects <50 kg were allocated (1:2:2:2) to placebo or candesartan cilexetil 2 mg, 8 mg ,or 16 mg
Panel 2: Subjects ≥50 kg were allocated (1:2:2:2) to placebo or candesartan cilexetil 4 mg, 16 mg, or 32 mg

The primary study objective was to characterize the dose relationship of candesartan cilexetil (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. Missing data was imputed by last observation carried forward. About 95% of patients in each group completed the study.

The total number of subjects were randomized was 240 (out of 301 enrolled). According to the study report: "The study sample size was initially based on an assumed 8 mmHg reduction in SiSBP for the highest candesartan cilexetil treatment group when compared to the lowest candesartan cilexetil group. This assumption led to a sample size of 176 subjects completing Study 261A to provide 84% power to reject a null hypotheses of regression of slope =0 assuming that the standard deviation of the predictor variable (dose) was 10.1, the standard deviation of the residuals was 12, and using a t-test with an α 0.05 with a 2-sided significance level. If a 20% dropout rate was assumed, then approximately 210 randomized subjects were required. The target sample size was subsequently increased based on additional (negative interpretability) criteria specified in a re-issued written request from the FDA 8 January 2003 (see details in Section 5.8). These criteria define an interpretable study in the event that neither a dose response nor a difference for active doses vs. placebo was found. A blinded interim analysis of Study 261A, as suggested in the written request from the FDA, showed an approximate 9 mmHg standard deviation for the reduction in SiSBP for all treatment groups. Using a more conservative projection of 10 mmHg for the final standard deviation for the

261A completed study, the total number of subjects needed to satisfy the negative interpretability criteria was calculated to be 320 subjects for the Studies 261A and 328 combined." Again, the letter did not say to find a sample size, then split up that sample size into two studies which would be analyzed independently. Moreover, even the total sample size for the two studies combined is far short of what was required to achieve 90% to detect a clinically meaningful effect as defined in the letter. This study was initially planned to achieve 84% power assuming an 8 mmHg difference between the high dose and low dose- it was never designed to have 90% power for a difference of 3 mmHg- not at the beginning, nor after the interim analysis, nor even by combining both studies together.

The summary of the baseline demographics appears in Table 2.

The primary efficacy measure was the placebo-corrected change from baseline to the end of treatment in SiSBP. The primary efficacy analysis was based on the slope of linear regression for the placebo-corrected change from baseline to DB Week 4 in trough SiSBP as a function of non-zero dose. SiDBP and standing BP served as secondary efficacy measures. The protocol specified a primary analysis based on the slope of change from baseline to DB Week 4/LOCF in trough SiSBP as a function of non-zero dose as determined by a multiple linear regression, which included 2 weight panels. 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. The independent variables for the regression models involved body weight panel as a blocking factor and dose ratio (1/4/8).

Table 2 Summary of demographics and other baseline data (261A).

Demographic or baseline characteristic		Treatment group				
		Placebo	2/4 mg	8/16 mg	16/32 mg	Total
		N=35	N=69	N=68	N=68	N=240
Demographic characteristics						
Age, years: n (%)	<12	11 (31.4)	18 (26.1)	21 (30.9)	20 (29.4)	70 (29.2)
	≥12	24 (68.6)	51 (73.9)	47 (69.1)	48 (70.6)	170 (70.8)
Age, years	Mean (SD)	13.0 (2.8)	13.2 (2.3)	12.8 (2.8)	12.7 (2.8)	12.9 (2.6)
	Range	6 to 16	6 to 16	6 to 17	6 to 16	6 to 17
Sex, n (%)	Male	26 (74.3)	52 (75.4)	48 (70.6)	44 (64.7)	170 (70.8)
	Female	9 (25.7)	17 (24.6)	20 (29.4)	24 (35.3)	70 (29.2)
Race n (%)	Caucasian	14 (40.0)	32 (46.4)	30 (44.1)	32 (47.1)	108 (45.0)
	Black	17 (48.6)	32 (46.4)	32 (47.1)	32 (47.1)	113 (47.1)
	Other	4 (11.4)	5 (7.2)	6 (8.8)	4 (5.9)	19 (7.9)
Baseline characteristics						
Group by Tanner Score	<3	14 (40.0)	18 (26.1)	27 (39.7)	23 (33.8)	82 (34.2)
	≥3	21 (60.0)	51 (73.9)	41 (60.3)	45 (66.2)	158 (65.8)
Weight at screen (kg)	<50	5 (14.3)	8 (11.6)	10 (14.7)	8 (11.8)	31 (12.9)
	≥50	30 (85.7)	61 (88.4)	58 (85.3)	60 (88.2)	209 (87.1)
Weight at screen (kg)	Mean (SD)	82 (28)	85 (33)	74 (25)	85 (30)	81 (29)
	Range	28 to 146	23 to 171	21 to 158	22 to 156	21 to 171
BMI percentile at screen	<95	11 (31.4)	25 (36.2)	23 (33.8)	16 (23.5)	75 (31.3)
	≥95	24 (68.6)	44 (63.8)	45 (66.2)	52 (76.5)	165 (68.8)
BMI at screen, kg/m^2	Mean (SD)	30 (8)	31 (10)	28 (7)	32 (9)	30 (9)
	Range	16 to 48	16 to 55	13 to 43	15 to 59	13 to 59

Source: pp 59-60 of Study Report.

Secondary efficacy variables, which included the placebo-corrected change from baseline to the end of treatment in SiDBP, standing SBP and DBP, and sitting pulse pressure were analyzed using the same multiple-linear regression model as described for the primary variable in Section 5.7.4.1. To supplement the analyses, a multiple linear regression was also performed with treatment and race as factors. The slope of change from baseline to DB Week 4/LOCF in trough SiSBP as a function of dose was also determined for each of the 2 weight panels separately with a simple linear regression. Secondary analyses for the primary and secondary efficacy variables also included comparisons of each of the 3 active treatment groups and all active treatment groups pooled relative to placebo by linear contrasts in an analysis of covariance (ANCOVA) model, with treatment group as a factor and the baseline value as a covariate. The differences of the treatment least square means, together with one-sided nominal p-values and 95% CI are provided and no adjustments for multiplicity were made for these analyses. The individual least square

means and 95% CI are also provided. For the SiSBP and SiDBP, the least square mean of the active treatments pooled was calculated. While the ANCOVA analysis was planned in the protocol, the study was not powered to show significant differences between an individual active treatment group and placebo. No adjustment was made for these secondary analyses to control the familywise error rate.

2.3 Data Sources

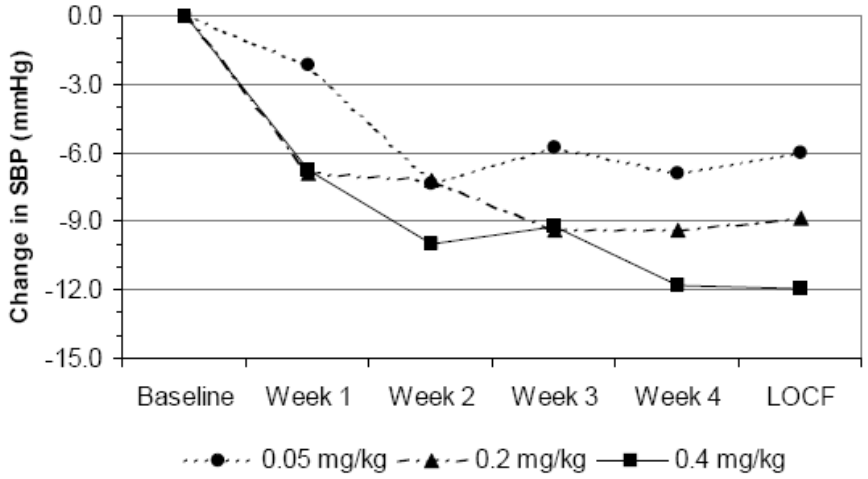
Electronic study reports and data sets (\\CDSESUB1\EVSPROD\NDA020838)

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy- Study 328

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 (see Figure 1 and Table 3), a decline that was significantly related to the candesartan dose (p=0.0136). Similarly, DBP declined by 5 to 11 mmHg in a significant dose-related fashion (p=0.0301).

Figure 1 Changes in SBP at each week (Study 328)



Source: page 65 of Study Report

Table 3 Analysis of primary endpoint SBP (change at Week 4/LOCF) and secondary endpoint DBP (Study 328).

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

DF degrees of freedom; ITT intention-to-treat; LOCF last observation carried forward; SBP Systolic blood pressure; DBP Diastolic blood pressure; SE Standard error.

Linear regression equation: (Change from baseline)=α + β*(dose ratio) + τ*(weight group) where dose ratio is 1, 4, or 8 and weight group is 0 or 1.

Source: Study Report, p 67 and confirmed by the FDA reviewer.

I would have liked to see all pairwise comparisons of the three doses following the global test. These three tests of all pairwise comparisons can be done without correction for multiple comparisons under a closed test procedure (when there are exactly three groups). Then, I could see if any dose is significantly better than any other. When I do that in this case, I found that only the high dose is significantly different than the low dose. No other pairwise comparison is significant.

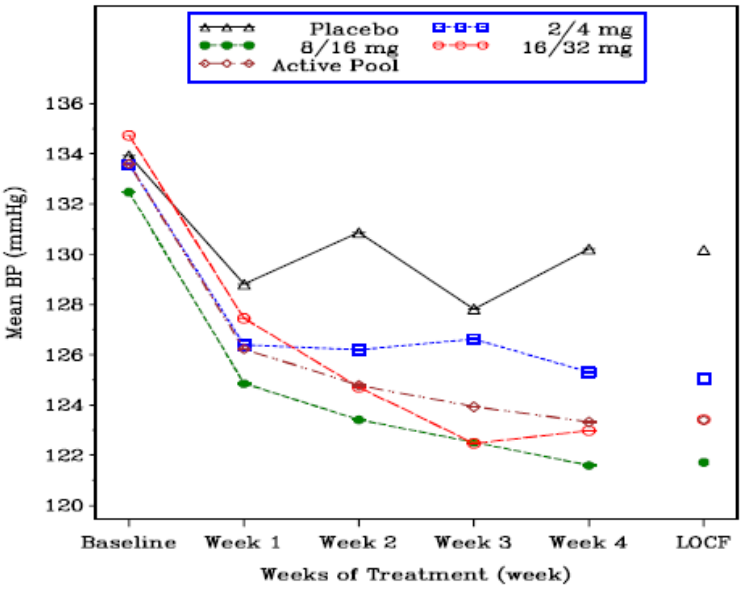
3.2 Evaluation of Efficacy- Study 261A

"In hypertensive children 6 to <17 years of age, the reduction from baseline in SiSBP with candesartan cilexetil administered for 4 weeks was not dose related (over the range of doses studied: 2/4 mg, 4/8 mg, and 16/32 mg in children weighing <50 kg/≥50 kg (p=0.0973)" [from p. 65 of Study Report]. Also, see Figure 2 and Table 4 for the plot of the changes in blood pressure over time by group and the summary statistics for the primary efficacy analysis.

As an exploratory analysis, I also fit a linear regression model similar to that used in the primary analysis. However, I did not include weight in the model, but I included the placebo group (treating it as a dose of 0 mg). I fit two straight line regression (one including the placebo data and one not including placebo) and also a quadratic curve (including placebo) as a function of dose level (see Figure 3 and Table 5). The figure shows that neither straight line does a good job of modeling the data; in particular, neither line comes close to the observed mean in the placebo group. Also, the quadratic model fits better, but has a U-shape that I would not expect for this data since I would expect the actual change in SiSBP to be monotonically decreasing as a function of dose in the range studied, unless for some reasons patients in the high dose group did not take full dose or

there are high dropout rate in that dose group. To me, this indicates that none of these models makes sense for this data if we want to include the placebo data (using the dose levels 0, 1, 4, and 8) for this study. This modeling exercise also taught us that statistical inference based on modeling can be risky in confirmatory trials. If the question is whether there is a difference among the three doses, the pre-specified model is adequate to answer that question and the red line in the figure (the linear regression line not including the placebo data) fits the data from the 3 doses fairly well, it was also the pre-specified primary analysis model (except I did not adjust for weight strata in this analysis). The only "problem" with it is that it fails to show a difference between the 3 doses. But, that doesn't mean the model is wrong- a plausible explanation for that is that there is no difference between the doses or that the sample size was too small to detect the difference.

Figure 2 Changes in SBP at each week (Study 261A)



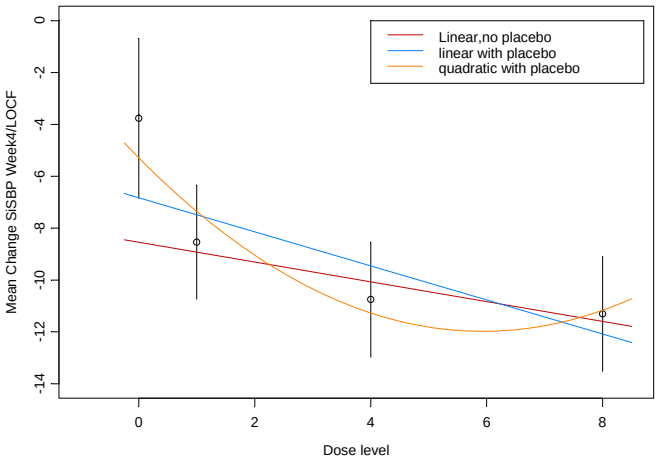
Source: Study Report, p 67.

Table 4 Analysis of primary endpoint SBP (change at Week 4/LOCF) and secondary endpoint DBP (study 261A).

		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.
Source: Study Report, p 69 and confirmed by the FDA reviewer.

Figure 3 Changes in SBP by dose level and three fitted regression models (with dose level as independent variable, not including weight) (Study 261A)



Circles are unadjusted means, vertical lines represented confidence limits for unadjusted means.
Source: FDA exploratory analysis.

Table 5 Exploratory analysis of SBP (change at Week 4/LOCF)- linear and quadratic regression models including placebo (dose levels 0, 1, 4, 8)[†] (study 261A).

Parameter	Estimate	Standard Error	p-value
Response as a linear function of dose			
Intercept	-6.832	0.947	<0.001
Dose	-0.656	0.198	0.001
Response as a quadratic function of dose			
Intercept	-5.293	1.204	<0.001
Dose	-2.254	0.804	0.006
$Dose^2$	0.190	0.093	0.042

[†]Regression model with response equal to change in SBP at Week 4/LOCF and independent variable dose level (0=placebo, 1=low dose group, 4=middle, 8=high)
Source: FDA reviewer.

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 also not significantly different from 0 (p=0.3708, see Table 4). In a secondary analysis, Candesartan cilexetil administered for 4 weeks (at doses of 2/4 mg, 8/16 mg, and 16/32 mg) effectively lowered SiSBP (post-hoc 2-sided $p \leq 0.0074$, each candesartan cilexetil dose vs placebo, see Table 6).

Table 6 Secondary analysis of SBP (change at Week 4/LOCF) and DBP, pairwise comparison to placebo (study 261A). [NB: these are one-sided p-values and confidence limits at the bottom four rows and are also not adjusted for multiple comparisons]

	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.

Source: Study Report, p 70

3.3 Evaluation of Safety

See clinical review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The results for the primary endpoint for Study 328 in subgroups defined by gender, race and age appear in Table 7. There seems to be consistent effect across these subgroups in this study. The results for the primary endpoint for Study 261A in subgroups defined by gender, race and age appear in Table 8. There is a suggestion of a 2-3 mmHg difference between Blacks and non-Blacks in this study for each dose. Otherwise, there does not appear to be much difference in response by gender or age group in this study.

Table 7 Results for change in BP in demographic subgroups (Study 328, all doses pooled)

		Mean change from baseline to Week 4/LOCF (mmHg)		
		n	**SBP**	**DBP**
Sex	Male	60	–8.9	–8.5
	Female	33	–9.3	–7.5
Weight	10 to <25 kg	81	–9.8	–8.9
	25 to ≤40 kg	12	–3.8	–3.0
Age group (years)	1 to <2	16	–9.8	–7.2
	≥2 to <6	77	–8.9	–8.4
Race	Black	17	–10.2	–6.7
	Non-Black	76	–8.8	–8.5

Source: p 71 Study Report

Table 8 Results for primary endpoint (proportion of responders) in demographic subgroups (261A)

			Candesartan Treatment Groups				
	Gender		Placebo (N=35)	2/4 mg (N=69)	8/16 mg (N=68)	16/32 mg (N=68)	Active Pooled (N=205)
Changes in Systolic BP	Male	N	26	52	48	44	144
		Mean	-4.1	-8.1	-9.4	-10.2	-9.2
		SD	8.8	7.7	8.4	11.3	9.2
		Minimum	-21.7	-23.3	-28.3	-40.7	-40.7
		Median	-2.7	-7.7	-7.7	-12.3	-8.0
		Maximum	12.7	14.7	4.7	19.0	19.0
	Female	N	9	17	20	24	61
		Mean	-2.9	-9.8	-14.1	-13.3	-12.6
		SD	3.5	8.7	11.5	9.5	10.0
		Minimum	-8.0	-21.3	-34.7	-28.0	-34.7
		Median	-2.0	-10.7	-15.3	-12.0	-12.0
		Maximum	2.0	14.7	10.0	7.3	14.7

Table 8 (continued)

	Black or Non-black		Placebo (N=35)	2/4 mg (N=69)	8/16 mg (N=68)	16/32 mg (N=68)	Active Pooled (N=205)
			Candesartan Treatment Groups				
Changes in Systolic BP	Black	N	17	32	32	32	96
		Mean	-3.8	-7.1	-9.4	-9.1	-8.6
		SD	8.7	8.9	8.6	9.9	9.1
		Minimum	-20.7	-21.3	-26.7	-27.3	-27.3
		Median	-2.0	-7.7	-7.2	-11.0	-8.3
		Maximum	10.7	14.7	4.0	19.0	19.0
	Non-Black	N	18	37	36	36	109
		Mean	-3.7	-9.8	-11.9	-13.3	-11.6
		SD	7.0	6.9	10.4	11.3	9.7
		Minimum	-21.7	-23.3	-34.7	-40.7	-40.7
		Median	-2.7	-9.3	-11.2	-13.0	-11.0
		Maximum	12.7	6.7	10.0	13.3	13.3

	Group by Age (years)		Placebo (N=35)	2/4 mg (N=69)	8/16 mg (N=68)	16/32 mg (N=68)	Active Pooled (N=205)
			Candesartan Treatment Groups				
Changes in Systolic BP	<12	N	11	18	21	20	59
		Mean	0.0	-6.7	-9.4	-12.3	-9.6
		SD	5.5	8.5	7.6	8.6	8.4
		Minimum	-7.0	-19.0	-21.0	-26.3	-26.3
		Median	-0.7	-8.3	-10.7	-12.3	-9.3
		Maximum	10.7	14.7	4.0	2.0	14.7
	>=12	N	24	51	47	48	146
		Mean	-5.5	-9.2	-11.3	-10.9	-10.4
		SD	8.2	7.8	10.4	11.6	10.0
		Minimum	-21.7	-23.3	-34.7	-40.7	-40.7
		Median	-4.3	-9.3	-10.0	-12.0	-9.7
		Maximum	12.7	14.7	10.0	19.0	19.0

Source:Study Report pp 312, 313, and 315

4.2 Other Special/Subgroup Populations

NA

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Study 328, in children less than 6 years old showed a dose response among the three doses studied. When I looked at the pairwise comparisons, I only saw a significant difference between the high dose and low dose. I think the pairwise comparisons should always be done after finding a dose response, which is simply a test of the global null hypothesis. In the case of exactly three groups, no adjustment is needed to these pairwise comparisons following a significant global test. The second study, 261A, in children age 6 to 17 failed to show a dose response among the three doses studied using the pre-specified primary analysis.

5.2 Conclusions and Recommendations

The sponsor did not conduct a study in pediatric subjects that met the terms of the written request letter. Study 328 was successful on the primary analysis, but did not meet the other terms of the letter. I recommend the sponsor to follow the terms of the letter. Moreover, I would recommend all sponsors to think about all the chances they want to have of winning and then create an analysis plan that controls the error rate for all those chances. In this case, the sponsor could have claimed a significant effect for one or more doses compared to placebo if they had planned six analyses and used, for example a Bonferroni correction for these six analyses: a) high dose vs. low dose b) high dose vs. middle dose c) middle dose vs. low dose d,e,f) pairwise comparison of each dose vs. placebo. These six analyses are all permitted by the letter (the first 3 fall under the category of "look for a dose response"). Clearly, something better than a Bonferroni correction would be possible, but what's not desirable is to spend all the α on a single test and then argue post hoc that if only I had chosen some other analysis, I would have won, so can't I just pretend that I did choose that other one? (there is nothing wrong with the first part of that, but something seriously wrong with the rest).

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 20838	SUPPL 31	ASTRAZENECA PHARMACEUTICALS LP	ATACAND

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/s/

JOHN P LAWRENCE
08/20/2009

HSIEN MING J J HUNG
08/20/2009