		SYNOPSIS	
Drug substance(s):	Candesartan cilexetil		
Study code:	D2451C00261 (Protocol 261A)		
Date:	16 May 2007		

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

Study centre(s): This study was initiated at 50 centers in the United States and 8 centers in Europe.
Publications: No publications at the time of the writing of this report.

Study dates		**Phase of development**
First subject enrolled	03 September 2003	Therapeutic use (IV)
Last subject completed	21 November 2005	

Objectives: 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.
Secondary key objectives included: the slope for the change from Baseline to DB Week 4 in trough SiSBP for each of the 2 body weight panels separately; the slope of change from Baseline to Week 4 in trough sitting diastolic blood pressure (SiDBP), trough standing DBP and standing SBP, trough sitting pulse pressure; mean change from baseline to DB Week 4 in SiSBP, SiDBP, pulse pressure, and standing SBP and DPB relative to placebo for each dose group and for all dose groups pooled; safety as assessed by adverse events (AEs), AEs which necessitated study drug discontinuation, serious AEs, heart rate, electrocardiographic findings, physical exam findings, and laboratory tests results. Sub-study objectives considered effects on metabolic parameters, including insulin sensitivity.
Study design: This randomized, DB, placebo-controlled study determined the antihypertensive dose ranging effects across 3 dose levels of candesartan cilexetil (low, medium, or high) following 4-weeks of DB treatment in hypertensive pediatric subjects 6 to less than17 years of age. Following a screening evaluation, subjects underwent a 1-week, single-blind, placebo run-in after which, those that were randomization eligible, were

allocated to receive 1 of 3 doses levels of candesartan cilexetil or placebo. 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

Target subject population and sample size: Male or female subjects aged 6 to <17 years with a mean SiSBP and/or SiDBP ≥95th percentile of height-adjusted, age and gender BP distributions and ≤20 mmHg (systolic) and/or ≤10 mmHg (diastolic) above the 95th percentile. Assuming a 10 mmHg standard deviation for the reduction in SiSBP for all candesartan cilexetil treatment groups pooled as compared to placebo, the study sample size calculations estimated a need for 270 enrolled subjects to ensure 238 randomized evaluable subjects.

Investigational product and comparator(s): dosage, mode of administration and batch numbers: Candesartan cilexetil was administered once-daily in oral tablet form: batch numbers for each dose were: 2 mg tablet (H 1181-01-01-06, H 1181-01-01-07), 4 mg tablet (H 1155-02-01-17, H 1155-02-01-18, H 1155-02-01-19), 8 mg tablet (H 1156-02-01-27, H 1156-02-01-28), and 16 mg tablet (H 1191-01-01-30, H 1191-01-01-32, H 1191-01-01-33). Placebo tablets, manufactured and packaged to match each strength of candesartan cilexetil and administered once-daily, served as the comparator: batch numbers for each placebo matching dose were: 2 mg tablet (H 1157-01-01-11, H 1157-01-01-12), 4 mg tablet (H 1242-01-01-09, H 1242-01-01-11), 8 mg tablet (H 1210-02-01-17), and 16 mg (H 1203-03-01-25, H 1203-03-01-26).

Duration of treatment: The study included a 1-week, single blind placebo run-in, and a 4-week, DB treatment period. At the end of the DB period, eligible subjects had the option to enter a 1-year open-label treatment study (Protocol 261B).

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics: The primary efficacy variable was 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. A single trough plasma candesartan level was collected at DB Week 4 to validate study drug exposure.

Safety: Reported AEs served as the primary safety measure.

Statistical methods: 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 primary efficacy measure was the placebo-corrected change from baseline to the end of treatment in SiSBP. The low (2/4 mg), medium (8/16 mg), and high (16/32 mg) doses were pooled and assigned values corresponding to relative dose, 1:4:8. The independent variables for the regression models involved body weight panel as a blocking factor and dose ratio (1/4/8). Because of the small sample sizes in the lower weight panel (n=25 on active treatment), the analysis of the primary variable was also performed without weight panel in the model. Changes in BPs relative to placebo were also analyzed in ANCOVA models with baseline BP as the covariate with nominal p-values (both 1-sided and 2-sided) reported without corrections for multiple comparisons.

Safety evaluations included reported AEs, heart rate, physical examinations, and ECG findings, premature discontinuations, and clinical laboratory test results. Microalbumin and creatinine urine concentrations and their ratios were also determined.

Subject population: The study randomized 240 subjects (205 candesartan cilexetil and 35 placebo). Seventy-one percent of the children were ≥12 years of age, 71% were male, 87% weighed ≥50 kg at screening, and 69% were ≥95 percentile for BMI. There were approximately equal proportions of subjects who were Black (47%) vs non-Black (53%). About a third were pre-adolescents (Tanner Score of <3). The majority of subjects (64%) were discovered to be hypertensive within the prior 1 year; 52% had isolated systolic hypertension and 35% had systolic plus diastolic hypertension. Most subjects (78%) were also naive to pharmacologic hypertensive therapy.

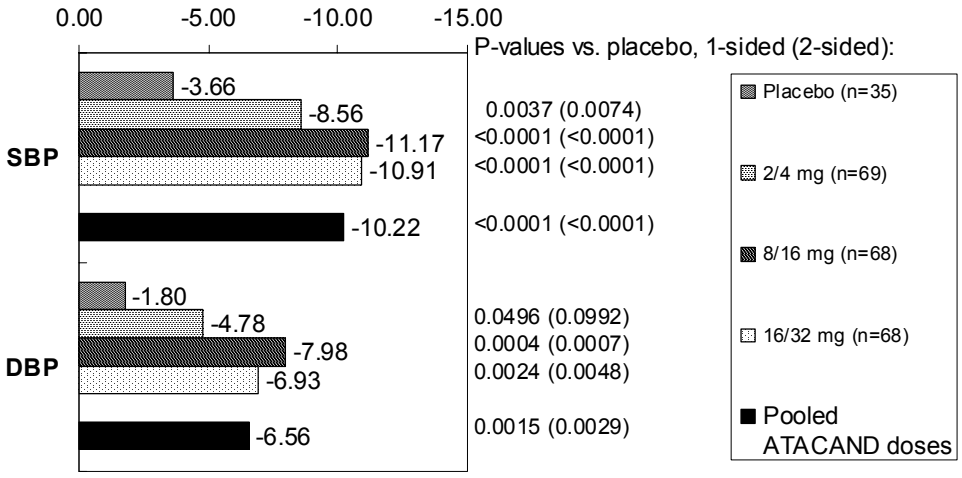
Efficacy and pharmacokinetic results: The reduction in SiSBP with candesartan cilexetil was not dose related, with dose expressed as a dose ratio (p=0.0973); similarly the reduction in SiDBP with candesartan cilexetil was not dose related (p=0.3708). Over the range of candesartan cilexetil doses studied, least square mean SiSBP/SiDBP decreases ranged from 8.6/4.8 mmHg to 11.2/8.0 mmHg; the decline with placebo was 3.7/1.8 mmHg (Table S1). Candesartan cilexetil, at the doses studied, did effectively lower SiSBP (1-sided p ≤0.0037, post-hoc 2-sided p≤0.0074, each candesartan cilexetil dose vs placebo) and SiDBP (1-sided p<0.0500 each candesartan cilexetil dose vs placebo, post-hoc 2-sided p=non-significant for low dose and p<0.0050 medium and high doses vs placebo), Figure S1.

BP reductions with candesartan cilexetil across subgroups of age, sexual maturity, weight, gender, type of hypertension (systolic hypertension, diastolic hypertension, or both), and whether or not previously treated were consistent with findings in the overall population, although Blacks had somewhat lesser BP reductions than non-Blacks.

Table S1 Mean Week 4/LOCF SiSBP and SiDBP and least square mean change from baseline (ITT population)

	SBP			DBP		
Treatment group	**Week 4 Mean (SD)**	**Least square mean change**	**95% CI**	**Week 4 Mean (SD)**	**Least square mean change**	**95% CI**
Placebo, N=35	130.2 (10.1)	–3.65944	–6.5731, –0.7458	76.3 (11.2)	–1.80137	–4.6838. 1.0810
Candesartan cilexetil, 2/4 mg, N=69	125.0 (9.9)	–8.56178	–10.6368, –6.4868	74.3 (8.4)	–4.77879	–6.8336, –2.7239
Candesartan cilexetil, 8/16 mg, N=68	121.7 (10.5)	–11.1714	–13.2670, –9.0758	70.3 (10.6)	–7.9797	–10.0472, –5.9122
Candesartan cilexetil ,16/32 mg, N=68	123.4 (10.8)	–10.91424	–13.0091, –8.8194	71.7 (9.3)	–6.92544	–8.9916, –4.8592
Candesartan cilexetil, active pooled, N=205	**123.4 (10.5)**	**–10.2168**	**–11.4207, –9.0129**	**72.1 (9.6)**	**–6.5613**	**–7.7515, –5.3712**

Figure S1 **Least square mean changes from baseline to Week 4/LOCF in SiSBP and SiDBP, by treatment group**



Safety results: The safety population included all 240 randomized subjects. The median duration of treatment was 28 days (range 5 to 36 days). There were no deaths; 1 subject (4 mg candesartan cilexetil) had a serious AE (anaphylactic reaction to raspberries). Three candesartan cilexetil subjects discontinued the study due to nonserious AEs: moderate hypotension, 32 mg candesartan cilexetil; compound wrist fracture, 16 mg candesartan cilexetil; and mild worsening of dizziness, 16 mg candesartan cilexetil. One placebo-treated subject discontinued because of moderate hypertension and headache.
The proportion of subjects reporting AEs was generally similar across the treatment groups (50% to 63%). The most common AEs occurring at a rate of ≥3% with candesartan cilexetil (all doses pooled) and more frequently with candesartan cilexetil than with placebo were: headache (16.1% vs 8.6%), dizziness (6.8 % vs 5.7%), pharyngolaryngeal pain, 'sore throat' (4.9% vs 0%), and upper respiratory infection (4.9% vs 2.9%).