Drug substance(s):	Candesartan cilexetil	**SYNOPSIS**	
Edition No.:	1		
Study code:	D2451C00002/Study 328		
Date:	25 March 2009		

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

Study center(s): 18 sites in the United States/Puerto Rico and 20 in Europe enrolled and treated at least 1 subject

Publications: None at the time of writing this report.

Study dates		**Phase of development**
First subject enrolled	04 November 2004	IIIB/Pediatric Programs
Last subject completed	07 August 2008	

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

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

- Change from Day 0 to Day 28 for the dose response relationship of candesartan for the change in trough SBP as a function of dose for each of the 2 body weight panels, separately; for the change in trough diastolic blood pressure (DBP) as a function of dose; and for the mean change in trough SBP and DBP for candesartan for each assigned dose level.
- The mean change in urinary protein/creatinine (P/C) and albumin/creatinine (A/C) ratio for each assigned dose level from baseline to Day 28 and to the end of the 52-week, open-label treatment period.

- Safety as assessed by adverse events (AEs), drug discontinuations due to AEs, serious AEs (SAEs), physical exam findings, growth, and laboratory tests results during the 4-week, double-blind treatment period and the 52-week, open-label treatment period.

- The pharmacokinetics (PK) of candesartan

Study design: 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 ml for those ≥25 kg). Subjects returned weekly during the double-blind period (Day 1 to Day 28) and periodically during the 52-week, open-label treatment period.

Target subject population and sample size: The study population included male and female subjects 1 to <6 years of age with mild to moderate hypertension defined as reproducible mean SBP and/or DBP equal to or exceeding the 95th percentile of the population blood pressure distribution adjusted for height, age and gender, and ≤20 mmHg (systolic) and 10 mmHg (diastolic) above the 95th percentile.

Investigational product and comparator(s): dosage, mode of administration, and batch numbers: Candesartan in doses of 0.05 mg/kg, 0.2 mg/kg, or 0.4 mg/kg was administered once-daily in oral suspension form (the concentration of the suspension was custom prepared for each subject).

Duration of treatment: 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.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics: The primary efficacy outcome measure was the slope by linear regression for the change from baseline in trough SBP at double-blind Week 4 as a function of candesartan dose. Secondary measures of effect included: dose response for each weight stratum for change in trough SBP; dose response for DBP; and treatment effect of each dose relative to baseline in trough SBP and DBP, and median change in urinary protein/creatinine (P/C) ratio and albumin/creatinine (A/C) ratio. Ten subjects were also enrolled in the PK substudy. The PK parameters included the time to maximum plasma concentration (t_{max}), maximum plasma candesartan concentration (C_{max}), terminal elimination half-life ($t_{1/2}$), and AUC.

Safety: AEs served as the primary safety measure.

Statistical methods: The primary efficacy analysis was based on the intent-to-treat (ITT) population and tested the null hypothesis that the slope=0 in a linear regression model with change in trough SBP as the dependent variable and dose pooled across weight panels as the independent variable. For subjects missing a double-blind, Week 4 blood pressure determination, a value was imputed by carrying the last observation forward (LOCF).

Subject population: Although the dose-specific groups were not large (0.05 mg/kg, n=29; 0.2 mg/kg, n=32; and 0.4 mg/kg, n=32) the corresponding treatment groups were relatively balanced with regard to the baseline characteristics. Table S1 shows baseline characteristics for the ITT population all doses pooled.

Table S1 Demographic and baseline characteristics (ITT population, all doses pooled)

Demographic		**N=93**
Sex, n (%)	Female	33 (35.5)
	Male	60 (64.5)
Age, years, (n (%)	1 to <2	16 (17.2)
	2 to <6	77 (82.8)
Race, n (%)	Black	17 (18.3)
	Non-Black	76 (81.7)
Type of hypertension, n(%)	Systolic + diastolic	49 (52.7)
	Diastolic only	20 (21.5)
	Systolic only	21 (22.6)
	None[a]	3 (3.2)
Systolic blood pressure	Mean (SD), mmHg	112 (8.7)
Diastolic blood pressure	Mean (SD), mmHg	70 (8.8)
On antihypertensive therapy prior to study entry	n (%)	39 (41.9)
Source of hypertension, n (%)	Primary	22 (23.7)
	Secondary	71 (76.3)

[a] The sponsor used the same program as the IVRS in constructing the demography tables, but the site used a different calculation for study entry hence some subjects appeared to not have met the criteria. The 'no hypertension group' represents an apparent difference in the site's determination of the 95th percentile (using the charts supplied in the protocol and the program calculation) versus the IVRS program..

Note: Type of hypertension was based on blood pressure at Visit 3 randomization and is defined as diastolic hypertension ≥95th percentile and systolic hypertension ≥95th percentile.

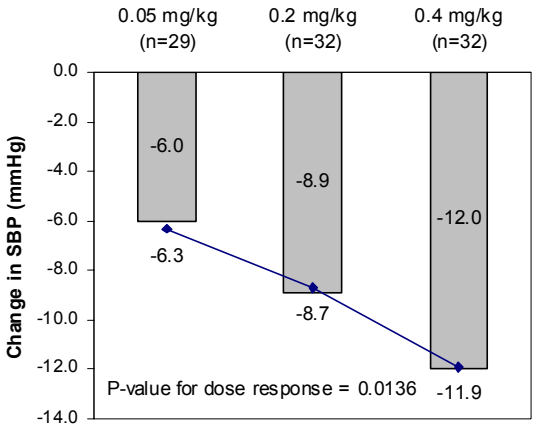
Note: Data for the 'source of hypertension' and 'presence of renal disease' categories were created from a review of the medical history by the study physician.

A total of 69 children (74%) had renal disease at baseline, which included nephrotic 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 (normal range 80 to 125 ml/min). Median urine baseline P/C ratio was 0.3 (range 0.1 to 59.5) and median A/C ratio was 36 mg/g creatinine (range 3 to 5327 mg/g creatinine), normal is 0 to 30 mg/g creatinine.

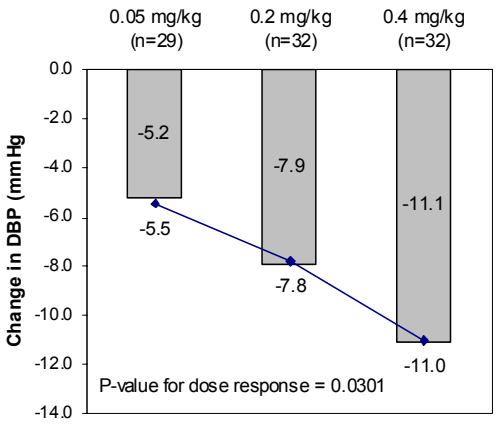
Efficacy and pharmacokinetic results: SBP declined monotonically across the 3 candesartan dose levels by 6 to 12 mmHg, a decline that was significantly related to candesartan dose, Figure S1. Similarly, DBP declined by 5 to 11 mmHg in a significant dose-related fashion, Figure S2.

Figure S1 **Means and dose-response line for changes from baseline to Week 4/LOCF in SBP (ITT population)**



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 S2 **Means and dose-response line for changes from baseline to Week 4/LOCF in DBP (ITT population)**



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.

After 4 weeks of dosing, antihypertensive response rates increased monotonically with increasing dose (28%, 50%, and 66%, respectively) for the 0.05 mg/kg, 0.2 mg/kg, and 0.4 mg/kg dose groups.

Blood pressure reductions were evident across subgroups indicating an antihypertensive effect in Black children, in children with secondary hypertension, children with both diastolic/systolic hypertension, children with renal disease, in both the younger and older children (1 to 2 years vs 2 to 6 years of age), and children in both geographical regions (US/Puerto Rico and Europe).

The antihypertensive effect of candesartan was maintained with long-term dosing and 54% of subjects were 'controlled' (responders) at the end of 1 year of treatment.

With multiple dosing, the plasma candesartan levels were dose related.

The single dose PK substudy indicated that there was no correlation between AUC or C_{max} and age (correlation –0.392, p=0.2627 for AUC and correlation –0.437, p=0.2064 for C_{max}) or body weight (correlation –0.392, p=0.2627 for AUC and correlation -0.437, p=0.2064 for C_{max}) and the. PK profile was similar to that previously described for older children and adults.

Safety results

Overall, administration of candesartan for up to 56 weeks at a mean dose of 0.2 mg/kg was generally well tolerated (2 subjects discontinued because of AEs). The most common AEs included: pyrexia (41%), cough (38%), upper respiratory tract infection (23%), nasopharyngitis (17%), rhinorrhea (15%), and diarrhea (15%). (Most of the subjects with pyrexia had other associated illnesses, eg, pharyngolaryngeal pain, nasal congestion, cough, sinus congestion, upper respiratory infection).

Two subjects were discontinued from the study prematurely due to AEs: 1 child died on Day 200 of treatment from an underlying disorder (chronic glomerulonephritis and progressive renal insufficiency); the other child, who had moderate abdominal pain and fatigue that started on Day 11 of treatment, was discontinued from treatment on Day 37; this child did not enter the open-label period of the study. A total of 14 children had SAEs but these largely reflected the consequence of co-morbid illnesses and none was considered by the investigators to be causally related to study medication.

There were no notable changes in laboratory or other safety measures. Estimated eGFR declined by 5.6 ml/min during the first 4 weeks but was relatively stable thereafter over the 1-year, follow-up period.

The median A/C ratio declined by 38% (25th, 75th percentiles: –61, 25) after 4 weeks treatment with candesartan. The decline appeared dose related and was still evident at Week 56 (median decline 31%; 25th, 75th percentiles –63, 36). In subjects with a baseline A/C ratio >30 mg/g creatinine, the median A/C ratio declined 57% (25th, 75th percentile –72 , –3) after 4 weeks treatment; the decline at Week 56 was 59% (25th, 75th percentiles –85, –26).

There was no change in P/C ratio with candesartan treatment with all subjects considered; there was, however, a 33 median % decline (25th, 75th percentiles: -49, 0) among subjects with a baseline P/C ratio >0.2.

The PK profile of candesartan (suspension formulation) in children 1 to <6 years of age is similar to that in older children and adults (tablet formulation). There is no correlation between C_{max} or AUC and age or body weight.

With multiple dosing, candesartan plasma concentrations are dose related.

In children with albuminuria (A/C ratio >30 mg/g creatinine), candesartan treatment is associated with a reduction in albuminuria which appears to be dose related.

Long-term administration of candesartan for up to 56 weeks in this pediatric hypertensive population was generally well tolerated – the same safety oversight vigilance recommended for hypertensive adults is relevant for hypertensive children.