AstraZeneca

Drug substance(s):	Candesartan cilexetil	**SYNOPSIS**	
Study code:	D2451C00001 (261B)		
Date:	29 August 2007		

A Multicenter, Multinational, Open-Label Study of the Efficacy, Safety, and Pharmacokinetics of Candesartan Cilexetil in Hypertensive Paediatric Subjects 6 to <17 Years of Age

Study center(s): 27 sites in the United States and 7 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	10 October 2003	IIIB Pediatric Program
Last subject completed	22 November 2006	

Objectives: To describe candesartan cilexetil antihypertensive effects in terms of achieved blood pressure (BP) and hypertension control rates and the relationship between subject characteristics and antihypertensive efficacy, and between antihypertensive therapy (candesartan cilexetil dose and add-on treatments) and efficacy over a 1 year treatment period in hypertensive children ages 6 to <17 years. Other objectives included: change in growth, change in neurocognition, determination of the pharmacokinetics of candesartan, and a description of safety.
Study design: Open-label, uncontrolled, 52-week study. Suggested starting doses for children <50 kg was 4 mg of candesartan cilexetil (hereafter referred to as candesartan) once-daily and for children >50 kg, 8 mg once-daily. Investigators adjusted the candesartan dose (between 4 mg and 32 mg). If hypertension was not controlled at 32 mg once-daily or the maximum tolerated dose, the investigator added supplemental antihypertensive medication as required to manage the subject's hypertension. Pharmacokinetic (PK) assessments were carried out in 22 subjects, with half in each of the 2 age groups (6 to <12 years of age and 12 to <17 years of age). Neurocognitive (Full Scale IQ test) measurements were done in a subset of study participants in the US.
Target subject population and sample size: Hypertensive children 6 to <17 years of age. Study 261B required no formal sample size determination. Approximately 238 subjects were expected to enroll. A sample size of 16 subjects was expected to provide adequate information on the PK profile of candesartan and 24 subjects was considered adequate to detect a 10-point decline in FSIQ score (alpha = 0.05, power = 80%, one-sided test) assuming

a mean FSIQ score of 100 with a SD of 15.

Investigational product and comparator(s): dosage, mode of administration and batch numbers: Open-label candesartan in oral tablet forms of 4 mg, and 16 mg (doses for this study were 4 mg, 8 mg, 16 mg, and 32 mg). Subjects receiving the 8 mg or 32 mg dose were instructed to ingest 2 tablets of 4 mg or 16 mg, respectively. Batch numbers for the 4 mg tablets were H 1155-02-01-17, H 1155-02-01-18, H 1155-02-01-19, and H 1155-02-01-20 and batch numbers for the 16 mg tablets were H 1191-01-01-30, H 1191-01-01-32, and H 1191-01-01-33. Tablets were manufactured by AstraZeneca Tablet Production, Sweden.

Duration of treatment: 52 weeks

Criteria for evaluation (main variables): BP response rate: defined as both sitting systolic BP (SiSBP) and sitting diastolic BP (SiDBP) less than the 95th percentile based on height-adjusted charts for age and gender.

Efficacy and pharmacokinetics: BP response rates were considered the most clinically meaningful assessment of efficacy. Response rates were based on the proportion meeting the definition (described above) at selected timepoints. Additional efficacy measures were achieved SiSBP and SiDBP at selected timepoints. The PK parameters, maximum plasma concentration (C_{max}), area under the curve (AUC), time to maximum plasma concentration (t_{max}), and half-life ($t_{½}$) were determined based on plasma candesartan levels.

Safety: Reports of AEs (including serious AEs and discontinuations) and laboratory data. Given that study subjects were of school age, a neurocognitive (Full Scale IQ test) assessment was also included in a subset of study participants in the US. In addition, growth (height and weight) was measured over the course of the study in all subjects.

Statistical methods: This open-label, uncontrolled study required no formal statistical hypotheses testing but includes descriptive measures of effect and safety.

Subject population: A total of 237 subjects were enrolled and 233 were in the intention-to-treat (ITT) population. Four subjects were excluded from the ITT population because 2 did not take any study drug and 2 had no post-Visit 1 BP values. A total of 198 (83.5%) subjects completed the study. The most common reason for discontinuation was lost to follow-up (n=11).

Subjects were mostly male (71%), older than 12 years of age (71%), and Caucasian (48%) (44% of subjects were Black). The mean age of all subjects was 12.9 years, and 60% of subjects had a Tanner Stage of ≥3. The mean body mass index (BMI) at Visit 1 was 29.6 kg/m^2 and 67% of subjects were overweight (BMI ≥95th percentile adjusted for age and gender). Approximately 79% of subjects had been diagnosed with hypertension for less than 2 years prior to study entry; 52% of subjects entered with isolated systolic hypertension and 38% had both systolic and diastolic hypertension. Among subjects who had been randomized in Protocol 261A and entered Study 261B (n=212), SiSBP/SiDBP averaged 125/73 mmHg upon entry in the 52-week study.

Efficacy and pharmacokinetic results: A responder was defined as a subject having a SiSBP and SiDBP less than the 95th percentile based on height-adjusted charts for age and sex. Among the subjects in this 52-week study, at Weeks 16/LOCF, 32/LOCF, and 52/LOCF approximately 63%, 61%, and 53% of subjects were responders.

SiSBP/SiDBP were reduced from baseline of Study 261A by an average of–9/–6 mmHg upon entry into the 52-week study. Achieved SiSBP and SiDBP over time for all subjects who were treated in Study 261B (and had been randomized in Study 261A) is shown in Table S1. Reductions from baseline in SiSBP/SiDBP were observed during open-label treatment with candesartan at all timepoints over the 52-week study.

Table S1 Descriptive statistics for SiSBP and SiDBP over time for all subjects who entered 261B after being randomized in 261A, ITT population

Time	N	Mean SiSBP/SiDBP mmHg (range mmHg)	Mean change in SiSBP/SiDBP from randomization in 261A (range mmHg)
261A randomization (baseline)	212	134/79 (109 to 156/42 to 111)	
Entry to 261B	212	125/73 (91 to 149/43 to 99)	–9/–6 (–41 to 15/–40 to 37)
Week 16	179	123/71 (81 to 155/50 to 99)	–11/–8 (–39 to 23/–40 to 38)
Week 32	163	123/71 (87 to 159/50 to 105)	–11/–8 (–45 to 10/–35 to 26)
Week 52	179	125/72 (101 to 154/38 to 99)	–9/–7 (–33 to 24/–36 to 20)
Week 52/LOCF	212	126/72 (101 to 159/38 to 105)	–8/–7 (–33 to 24/–36 to 20)

For 21 ITT subjects who entered into Study 261B directly without a washout from antecedent blood pressure treatment and were never randomized into Study 261A, the baseline SBP/DBP values were 134/78 mmHg. Mean SBP/DBP values decreased to 119/68 mmHg at Week 52.

Stratified by age and sex, the proportions of subjects who were responders were similar (ranged: from 51% to 54%). For subjects weighing <50 kg, the response rate was higher (68%, n=34) compared to subjects weighing ≥50 kg (50%, n=199). Most subjects received the 8 mg or 16 mg dose of candesartan and the response rates at these doses were 54% and 59%, respectively. Stratified by race, the proportion of responders was higher for Caucasians (61%) than for Blacks (43%). A comparison of Black and non-Black subjects failed to identify any alternative reasons for this race difference in response to treatment.

The PK profile of candesartan following a 16 mg dose was generally comparable (large inter-subject variabilities) among younger and older children. Over the age ranges studied, no correlation between C_{max} or AUC and age was observed. Body weight correlated (negatively) with C_{max} and AUC estimates but there was considerable variability and the strength of the association was relatively weak. No differences were noted in PK parameter estimates (C_{max}, AUC, $t_{1/2}$, and T_{max}) between males and females.

Safety results: The mean duration of treatment was 345 days and the median duration was 265 days (range 5 to 451 days). At Week 52/LOCF, 29%, 24%, and 23% of subjects received

candesartan at the 8 mg, 16 mg, or 32 mg dose, respectively. Fifty-five percent (n=127) of subjects had their dose up-titrated at least once. Few subjects (n=34) required down titration of study medication during the study.

Long-term administration of candesartan was generally well tolerated in this pediatric population. Seventy-four percent (n=174) of subjects had an adverse event (AE) reported and 6% (n=14) had non-fatal serious AEs (SAEs). The investigators considered none of the SAEs as causally related to study medication; 2 of these subjects discontinued the study because one subject had a SAE of 'toxic nephropathy' and another had 'chronic renal failure'. No subject died. The vast majority of events were mild to moderate in intensity. The most common individual AEs reported were headache (20.0%), upper respiratory tract infection (19.6%), dizziness (10.2%), cough (9.8%), pharyngolaryngeal pain (9.8%), and pyrexia (6.4%). Most of the subjects with pyrexia reported as an AE had other associated illnesses (eg, pharyngolaryngeal pain, nasal congestion, cough, sinus congestion, upper respiratory infection).

Among the subgroups (gender, age, race, Tanner stage, BMI percentile, maximum dose, and final mg/kg dose), there were some differences in the percentages of subjects experiencing AEs in each of these subgroups; however, most of the differences were small. Overall, there were no patterns pointing to specific subpopulations that appeared particularly susceptible to AEs or to a dose level that was associated with a greater AE rate, except for subjects receiving the 32 mg dose where a higher proportion of subjects had AEs, specifically headache, reported.

Treatment with candesartan for up to 52 weeks was associated with few clinically significant changes in clinical laboratory tests, pulse, or physical examination results. Findings were consistent with the known effects of candesartan treatment in adults or simply reflected the expectations for the study population and the recognized co-morbid conditions.

Based on weight, height, and BMI Z-scores, candesartan had no apparent effect on the normal growth of pediatric and adolescent subjects in this study. Overall, among the 33 children in the substudy of cognitive function, subjects receiving candesartan did not show evidence of declines in cognitive functioning.