AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Candesartan cilexetil
Study Code	D2451C0006
Edition Number	1
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An Open-label Extension Study of Candesartan Cilexetil in Hypertensive Pediatric Subjects Ages 1 to <11 Years: A Long-term Study

Study dates: First subject enrolled: 17 September 2007
Last subject last visit: 09 September 2009

Phase of development: IIIB

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study center(s)

There were a total of 13 principal investigators, at 13 study centers, spread over 6 countries: Belgium, France, Italy, Germany, Poland, and the Ukraine.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The primary objective of this study was to describe the long-term clinical experience of candesartan cilexetil in hypertensive children ages 1 to <11 years who have participated in Protocol 328 (D2451C00002), who did not discontinue due to a study-related adverse event, and who have an ongoing clinical indication for treatment with candesartan cilexetil. The primary outcome variable was the measurement of blood pressure response.

Study design

This was an open-label treatment extension of Protocol 328 (D2451C00002), an antecedent dose-ranging trial of candesartan cilexetil liquid formulation that included a 1-year follow-up period. Eligible patients were those who had completed Protocol 328, received study medication at Day 0, and returned every 3 months for follow-up visits and assessments of efficacy and safety, for up to 2 years. Laboratory tests and echocardiograms (ECHOs) were performed annually and at the end of the study or at discontinuation if the last assessment was ≥3 months prior.

Target subject population and sample size

Hypertensive patients ages 1 to <11 years who had participated in Protocol 328, who did not discontinue due to a study-related adverse event, and who had an ongoing clinical indication for treatment with candesartan cilexetil liquid formulation were enrolled in the study.

Investigational product and comparator(s): dosage, mode of administration, and batch numbers

Candesartan cilexetil in doses of approximately 0.05 mg/kg, 0.20 mg/kg, and 0.40 mg/kg was administered once daily in an oral suspension form (the concentration of the suspension was custom-prepared for each patient). Two batches of candesartan cilexetil each for the 4-mg (batch numbers: H1155-02-03-10, H1155-02-03-11) and the 32-mg (batch numbers: H1308-01-03-06 and H1308-01-03-10) concentrations were used in this study. The batch numbers of the suspension vehicles, Ora-Plus® and Ora-Sweet® SF, are included in the Clinical Study Report.

Duration of treatment

The duration of treatment in this study varied based on the time of patient entry into the study. The maximum possible time on treatment was 2 years.

Statistical methods

The clinical experience, consisting of both efficacy and safety measures, was summarized descriptively. The primary efficacy measure was antihypertensive response defined as both systolic blood pressure (SBP) and diastolic blood pressure (DBP) <95th percentile, and response rate was the simple proportion of responders. All patients who took at least 1 dose of study medication and had at least 1 blood pressure measurement were included in the intent-to-treat (ITT) population. Safety evaluations were based upon all patients who took at least 1 dose of study medication.

Subject population

A total of 35 patients from 13 centers in 6 countries were enrolled in the study. All 35 patients were part of the original population of 93 pediatric hypertensive patients who participated in Protocol 328. All 35 patients were included in both the ITT and safety populations. Although the study group in this extension was much smaller than that of the original study (Protocol 328), the predominant characteristics of that population were maintained in this study. Table S1 shows the baseline demographic characteristics for the ITT population.

Table S1 Baseline demographic characteristics for the ITT population

Variable		ITT population (N=35)
Age at first visit, years	2 to <6, n (%)	24 (68.6)
	≥6, n (%)	11 (31.4)
Gender, n (%)	Male	25 (71.4)
	Female	10 (28.6)
Race, n (%)	Caucasian	33 (94.3)
	Oriental	1 (2.9)
	Other	1 (2.9)
Systolic blood pressure, mmHg	Mean (SD)	103.91 (10.84)
Diastolic blood pressure, mmHg	Mean (SD)	62.71 (10.27)
Type of hypertension[a], n (%)	None	1 (2.9)
	Diastolic only	7 (20.0)
	Systolic only	7 (20.0)
	Diastolic + systolic	20 (57.1)
Source of hypertension[a], n (%)	Primary	4 (11.4)
	Secondary	31 (88.6)

[a] Variables carried forward from Protocol 328 (D2451C00002). Source of hypertension and renal disease were created from a review by the study team physician of the Protocol 328 medical history data.

The majority of patients were Caucasian and male, with both systolic and diastolic hypertension of secondary cause, predominantly renal disease. Only European centers were included in the present study and, due to no enrolled Black patients at those centers, there were no Black patients in the current study.

The age range of all patients at entry was 2 to 7 years of age, with a mean of 4.4 years of age. Renal disease was present in 85.7% of the study population. The mean baseline glomerular filtration rate at enrollment was 117.5 mL/min/1.73 m^2 (range: 38, 475 mL/min/1.73 m^2). Eight patients had an estimated glomerular filtration rate <60 mL/min/1.73 m^2 (range: 38, 51 mL/min/1.73 m^2). The body mass index of 20.0% of patients was above the 95th percentile.

The majority of patients (54.3%) received their first dose of study medication within 30 days of the last dose on Protocol 328. There were 16 patients (45.7%) for whom the first dose received on the present study was administered greater than 30 days from the last dose received on Protocol 328. The maximum time for candesartan treatment in this study was 686 days.

With the exception of the absence of Black patients, the patient characteristics in the extension study population closely paralleled those of the overall Protocol 328 population. The characteristics were those of very young children with hypertension; most had renal disease and many had other co-morbid conditions.

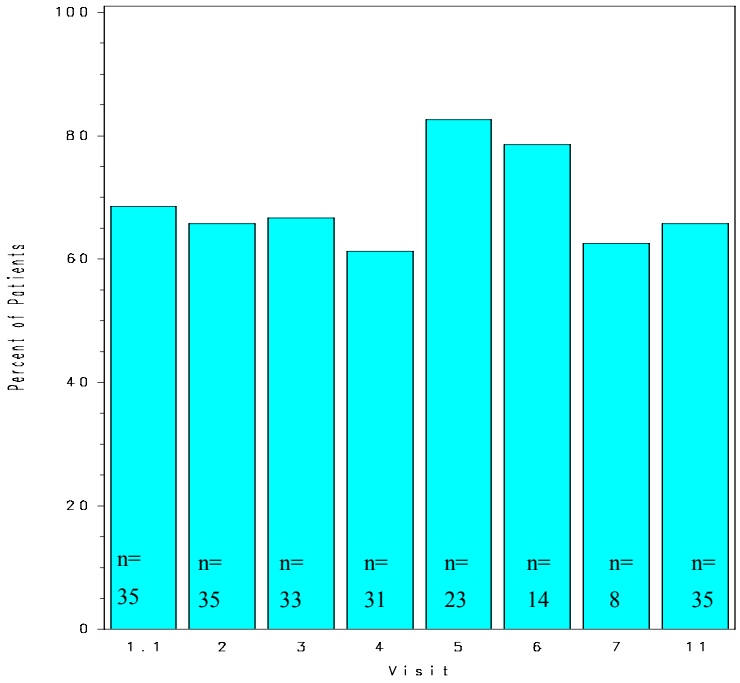
Summary of efficacy results

As expected, given that the patients had been receiving candesartan and in some cases additional antihypertensive medication, most patients entered the study with their hypertension controlled (82.9% with both SBP and DBP <95th percentile), and there was little additional change in blood pressure after enrollment in the present study. Both SBP and DBP values were relatively stable across the study period. At Visit 1.1, the mean SBP was 103.9 mmHg and the mean DBP was 62.7 mmHg. At Visit 11, mean SBP and DBP measurements were 101.1 mmHg and 62.3 mmHg, respectively.

Additionally, there was no notable need for additional antihypertensive medications or dose adjustments in this study. There were 8 patients total who received co-therapy throughout the study, and 7 patients who began the study on co-therapy.

The antihypertensive effect of candesartan was maintained over the study period. At each assessment across the study, greater than 60% of patients were considered ‘controlled’ (responders). The proportion of responders by visit is shown in Figure S1. Note: Blood pressure values were missing for 5 patients at Visit 1.1. This may account for the noticeable difference in proportion of responders between Visit 1 (82.9%) and Visit 1.1 (68.57%).

Figure S1 Percent of responders by visit (ITT population)



ITT Intent-to-treat population; n Number of patients.

The proportions of responders at Visit 1.1 and Visit 11 were 68.6% and 65.8%, respectively.

Summary of safety results

Overall, candesartan administration was generally well tolerated over the study period; only 1 patient discontinued due to an adverse event (lymphedema). The majority of patients remained in the study for 1 year or more, and the prescribed daily dose (mg/kg) of candesartan remained relatively stable across the study. The mean prescribed daily dose was 0.23 mg/kg at Day 0 and 0.24 mg/kg at the end of the study.

The most common adverse events reported over the study were pyrexia (25.7%), pharyngitis (17.1%), rhinitis (17.1%), diarrhea (17.1%), cough (11.4%), and nasopharyngitis (11.4%). The occurrence of pyrexia was coincidental with other reported illness.

There were no deaths in this study. One patient was discontinued from the study due to the serious adverse event of lymphedema. Two other serious adverse events were reported: hyperkalemia and bronchopneumonia. The adverse events described by the patients were typical of those expected as usual childhood illnesses, particularly in this population with co-morbid illnesses, specifically renal disease. There was no apparent trend for unique adverse events to emerge after protracted candesartan exposure time.

Overall, there was no notable change in estimated glomerular filtration rate or other laboratory parameters. There was no notable decline in renal function overall, or among the patients with renal function impairment. However, this study did exclude patients with severe renal impairment. Hyperkalemia, an expected risk when using renin-angiotensin system-inhibiting drugs in patients with renal impairment, was noted in 1 patient; this was considered related to the study drug, successfully identified by monitoring, and appropriately medically managed.

Four patients had ECHO parameters indicating left ventricular hypertrophy on at least 1 visit. None of the patients had a baseline, pre-candesartan ECHO study, but of those values available, there was no notable trend for clinically meaningful effect on cardiac development.

Overall, the safety findings largely reflect the concomitant renal disease in the study population.