

2.0 SYNOPSIS

Name of Company: AstraZeneca LP	Individual Study Table Referring to Item of the Submission Volume: Page:	(For National Authority Use only)
Name of Finished Product: ATACAND®		
Name of Active Ingredient: Candesartan cilexetil		
Title of Study: Evaluation of the Antihypertensive Efficacy of Candesartan Cilexetil in Comparison to Losartan: A Multicenter, Double-blind, Randomized, Parallel-group, Forced-titration Study		
Investigator(s): Multicenter Trial		
Study Center(s): 72 sites enrolled patients in this trial		
Publication (reference):		
Studied Period (years): First patient in: 17 August 1999 Last patient out: 18 February 2000	Phase of development: Phase IIIb	
Objectives: To assess the difference in antihypertensive efficacy between the treatment regimens (candesartan cilexetil and losartan) at Double-blind Week 8.		
Methodology: This was an eight-week, multicenter, randomized, double-blind, forced-titration, and parallel design study.		
Number of Patients (Planned and Analyzed): Number of Patients Enrolled into Placebo Run-In: 926		
	<u>CC Group</u>	<u>Losartan Group</u>
Number of Patients Planned for Analysis:	367	367
Number of Patients Analyzed:		
Randomized:	309	304
Safety Population	307	304
Efficacy Intent-to-treat:	307	303
ITT/ LOCF	306	303
Efficacy per Protocol (# evaluable)	276	277
Diagnosis and Main Criteria for Inclusion: Males and females (without childbearing potential) 18 to 80 years of age with mean sitting diastolic blood pressure of 95 mm Hg to 114 mm Hg were included in this study.		
Test Product, Dose and Mode of Administration, Batch or Lot Number: Candesartan cilexetil 16 mg tablets (bulk lot number H1191-01-01-11) with matching placebo (bulk lot number H1203-03-01-10) Losartan 50 mg over-encapsulated tablets (bulk lot number 99A002) with matching placebo (bulk lot number 99A003) One tablet and one capsule taken orally once daily. At Double-blind Week 2, patients up-titrated to two tablets and two capsules daily through Double-blind Week 8.		
Duration of Treatment: Eight weeks		

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Reference Therapy, Dose and Mode of Administration, Batch or Lot Number: N/A		
Criteria for Evaluation:		
<u>Efficacy:</u>		
The primary endpoint was mean change in trough sitting diastolic blood pressure from the end of the placebo run-in period (randomization) to the Double-blind Week 8 evaluation. Mean changes in trough sitting systolic blood pressure, peak sitting diastolic and systolic blood pressures, and sitting diastolic and systolic blood pressures at 48 hours post dosing were also measured. These mean changes from baseline were analyzed using analysis of covariance with the baseline measurements as the covariate. Trough to peak ratios for both treatment regimens were also evaluated.		
<u>Safety:</u>		
Safety was determined by the incidence and severity of adverse events. All such adverse events (whether clinical or laboratory) were analyzed to evaluate differences between the treatment regimens.		
Statistical Methods:		
The changes from Baseline to Double-blind Week 8 in the blood pressure measurements were analyzed using analysis of covariance for the intent-to-treat last observation carried forward population with baseline fitted as the covariate and treatment, center, and treatment by center interaction fitted as fixed effects in the model. Centers with few patients were pooled. Least squares means and treatment difference least squares means were calculated along with their 95% confidence intervals. P-values were obtained for the treatment comparison. For non-normally distributed variables, analysis of variance on the ranks of the observations using the Kruskal-Wallis test was performed.		
The proportion of responders (patients with trough sitting diastolic blood pressure < 90 mm Hg at the end of the study or a reduction from baseline to the end of the study of at least 10 mm Hg) and patients controlled (patients with trough sitting diastolic blood pressure < 90 mm Hg at the end of the study) were calculated for each treatment group. Trough to peak ratios for change in diastolic blood pressure were calculated for each treatment group as well.		
Adverse event and laboratory data were collected to evaluate and descriptively compare safety and tolerability profiles between the two treatment groups. All patients who received at least one dose of double-blind medication were included in the analysis of safety for this phase of the study. Laboratory measurements were summarized according to predefined limits of change, and mean changes from baseline were also evaluated.		

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SUMMARY		
<p>EFFICACY RESULTS: This study demonstrated that candesartan cilexetil initiated at 16 mg qd and forced titrated at two weeks to 32 mg qd was superior to losartan 50 mg qd forced titrated to 100 mg qd at two weeks in reducing trough sitting diastolic blood pressure at eight weeks (p = 0.0411). The reduction in trough sitting diastolic blood pressure produced by candesartan cilexetil was 10.5 mm Hg, and the reduction produced by losartan was 9.1 mm Hg. There was significant difference in the reduction from baseline in trough sitting systolic blood pressure at Week 8 (13.4 mm Hg vs 10.1 mm Hg in candesartan cilexetil and losartan, respectively, p-value = 0.0050). The candesartan cilexetil regimen also produced more effective blood pressure reductions as compared to the losartan regimen at the Week 8 and at the 48 hour follow-up visits. This includes the sitting diastolic and systolic blood pressure measured 6 ± 2.5 hours after dosing (peak effect, analyses performed only at Week 8) and 48-hour post last dose. The blood pressure control rates at Week 8 were 49% in the candesartan cilexetil group and 44.6% in the losartan group. The trough to peak ratios for candesartan cilexetil and losartan (0.855 and 0.915, respectively) demonstrated the persistence of blood pressure lowering effects of both regimens for a full 24 hours with once daily dosing.</p> <p>SAFETY RESULTS: Candesartan cilexetil and losartan were safe and well-tolerated when used in the treatment of hypertension. The incidence of treatment emergent adverse events was 45.6% for candesartan cilexetil and 44.7% for losartan with the most commonly occurring adverse events being dizziness, headache, respiratory infection, rhinitis, sinusitis, and fatigue. The percentages of patients prematurely discontinuing from the study were 12.7% for candesartan cilexetil and 12.2% for losartan, including 9 (2.9%) vs 6 (2.0%) for adverse events, and 2.6% vs 4.3% for lack of efficacy, on candesartan and losartan respectively. Four patients (0.7%) experienced adverse events that were considered serious, 2 (0.7%) vs 2 (0.7%), on candesartan cilexetil and losartan, respectively. Three of the four patients discontinued from the study, 2 patients were on candesartan cilexetil and 1 patient was on losartan. There were no clinically meaningful changes from baseline in laboratory measurements of serum chemistry, hematology, and urinalysis within and between treatment groups, and there were no apparent changes in the physical examination data.</p>		
Date of the Report: 16 October 2000		
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