2.0 SYNOPSIS

Name of Company: AstraZeneca LP	**Individual Study Table Referring to Item of the Submission**	**(For National Authority Use only)**
Name of Finished Product: ATACAND®	**Volume:**	
Name of Active Ingredient: candesartan cilexetil	**Page:**	

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):	**Phase of development:**
10 August 1999 04 February 2000	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 8 week, multicenter, randomized, Double-blind, forced-titration, parallel design study.

Number of Patients (Planned and Analyzed):
Number of Patients Enrolled into Placebo Run-In: 921

	CC Group	Losartan Group
Number of Patients Planned for Analysis:	367	367
Number of Patients Analyzed:		
Randomized:	332	323
Safety Population:	332	322
Efficacy Intent-to-treat:	332	322
Efficacy per Protocol:	312	289

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 Weeks 8.

Duration of Treatment:
8 weeks

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Reference Therapy, Dose and Mode of Administration, Batch or Lot Number: N/A

Criteria for Evaluation:

Efficacy:

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 randomization as the covariate. Trough to peak ratios for both treatment regimens were also evaluated.

Safety:

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 and heart rate 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 fitted as fixed effects in the model. Centers with few patients were pooled. Least squares means and treatment difference 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 descriptively 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

EFFICACY RESULTS:

This study demonstrated that candesartan cilexetil initiated at 16 mg qd and forced titrated at 2 weeks to 32 mg qd was superior to losartan 50 mg qd forced titrated to 100 mg qd at 2 weeks in reducing trough sitting diastolic blood pressure at 8 weeks ($p = 0.023$). The reduction in trough sitting diastolic blood pressure produced by candesartan cilexetil was 10.9 mm Hg, and the reduction produced by losartan was 8.7 mm Hg. There was a significant difference in the reduction from baseline in trough sitting systolic blood pressure at Week 8 (13.3 mm Hg vs 9.8 mm Hg in candesartan cilexetil and losartan respectively, ($p = 0.0007$). The candesartan cilexetil regimen also produced more effective blood pressure reductions as compared to the losartan regimen at Week 8 and at the 48 hour post last dose. This includes sitting diastolic and systolic blood pressure measured 24 ± 3 hours and 6 ± 2.5 hours after dosing (peak effect, analyses performed only at Week 8) and 48 hours post last dose. The blood pressure control rates at Week 8 were 56% in the candesartan cilexetil group and 46.9% in the losartan group. The trough to peak ratios for candesartan cilexetil and losartan (0.958 and 0.877, respectively demonstrated the persistence of blood pressure lowering effects of both regimens for a full 24 hours with once daily dosing. The effect of the candesartan cilexetil regimen on trough sitting heart rate was small, and similar to that of the losartan regimen.

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 46.4% for candesartan cilexetil and 45.7% for losartan with the most commonly occurring adverse events being back pain, dizziness, headache, pharyngitis, respiratory infection, rhinitis, and sinusitis. The percentages of patients prematurely discontinuing from the study were 4.5% for candesartan cilexetil and 6.2% for losartan, including 6 (1.8%) vs 5 (1.6%) for adverse events, and 0.6% vs 1.6% for lack of efficacy, on candesartan cilexetil and losartan respectively. Four patients (0.6%) experienced adverse events that were considered serious but not related to study medication 3(0.9%) vs 1 (0.3%), on candesartan and losartan, respectively. There were no differences in changes from baseline in laboratory measurements of serum chemistry, hematology, and urinalysis within and between treatment groups.

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