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 Efficacy and Tolerability of Candesartan Cilexetil in Hypertensive Patients Across Several Aspects of Patient Demographics

Investigator(s): 850 investigators planned, 665 investigators enrolled patients

Study Center(s): 665

Publication (reference):

Bravo E, Wier MR, Neutel JM, et al. Dose response of candesartan cilexetil in essential hypertension: a clinical experience trial. *Am J Hypertens.* 2000;13(4pt2):I128A.

Wier MR, Weber MA, Neutel JM, et al. Effects of candesartan cilexetil as add-on therapy in hypertensive patients uncontrolled on background therapy: a clinical experience trial. *Am J Hypertens.* 2000;13(4pt2):I128-129A.

Neutel JM, Moser M, Wier MR, et al. Effective dose response and tolerability of candesartan cilexetil in isolated systolic hypertension: a clinical experience trial. *Am J Hypertens.* 2000;13(4pt2):I129A.

Neutel JM, Wier MR, Moser M, et al. The effects of candesartan cilexetil in isolated systolic hypertension: a clinical experience trial. *J Clin Hypertens.* 2000; 2:181-186.

Studied Period (years): (date of first enrollment) 24 August 1998 (date of last completed) 23 April 1999	**Phase of development:** IV

Objectives:

To evaluate the tolerability and efficacy of candesartan cilexetil in treated and untreated hypertensive patients across several aspects of patient demographics, and to estimate the additional blood pressure reduction obtained for those patients requiring dose titration from 16 mg to 32 mg. Comparisons were performed across race (black versus nonblack), sex (male versus female), age group (elderly [≥ 65 years] versus non-elderly [< 65 years]), baseline diastolic blood pressure 90 mm Hg to 99 mm Hg (Stage 1) versus 100 mm Hg to 109 mm Hg (Stage 2), and isolated systolic hypertension 140 mm Hg to 179 mm Hg/< 90 mm Hg (Stage 1 and Stage 2).

Methodology:

This was an 8-week, multicenter, open-label, single-arm study in 6,638 patients with uncontrolled essential diastolic and/or systolic hypertension from 665 investigational sites. To be eligible for the study, patients were either taking and tolerating an antihypertensive medication or were not receiving treatment for hypertension. Sitting diastolic blood pressure (DBP) was in the range of 90 mm Hg to 109 mm Hg, inclusive and/or sitting systolic blood pressure (SBP) in the range of 140 mm Hg to 179 mm Hg, inclusive, on the day of enrollment. For all patients with a new diagnosis or undocumented history of hypertension, qualifying blood pressures were exhibited on two consecutive visits (Week -1 and Week 0) prior to inclusion in the study. A Week -1 visit was not required for patients with a documented history of hypertension.

Once eligibility was confirmed, patients were given 16 mg of candesartan cilexetil on the day of qualification (baseline visit). Patients were to return for study visits at Week 2 and Week 4. If the patient's blood pressure remained uncontrolled (DBP ≥ 90 mm Hg and/or SBP ≥ 140 mm Hg) at either visit, the dose of candesartan cilexetil was required to be increased to 32 mg once daily. Reasons for early termination from the study included (but were not limited to): adverse event, insufficient therapeutic response, withdrawal of consents, and lost to follow-up.

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Name of Finished Product: ATACAND®	**Volume:**	
Name of Active Ingredient: candesartan cilexetil	**Page:**	

Number of Patients (Planned and Analyzed):

	Total
Number of Patients Planned for Analysis:	8,500
Number of Patients Enrolled:	6,638
Number of Patients with Baseline Information:	6601
Number of Patients with Post Baseline Safety or Efficacy Information:	6,465
Number of Patients with Post Baseline Efficacy Information:	6,376

Diagnosis and Main Criteria for Inclusion:

- Male, or female without child-bearing potential or using an approved form of birth control.
- 18 years of age or older at the time of the informed consent process.
- Essential hypertension characterized by a mean sitting diastolic blood pressure of 90 mm Hg to 109 mm Hg, inclusive, and/or sitting systolic blood pressure 140 mm Hg to 179 mm Hg, inclusive.
- Currently receiving and tolerating mono- or multiple-hypertension medications or not on current hypertension medication.

Test Product, Dose and Mode of Administration, Batch or Lot Number:

Candesartan cilexetil 16 mg tablets with packaging lot number AM-183, Protocol 205
bulk lot number H1191-01-01-06 (Astra batch number 306)
bulk lot number H1191-01-01-07 (Astra batch number 307)

Duration of Treatment: Eight weeks of open label treatment with candesartan cilexetil

Reference Therapy, Dose and Mode of Administration, Batch or Lot Number: Not Applicable.

Criteria for Evaluation:

Efficacy:

For essential hypertensive patients (baseline diastolic blood pressure 90 mm Hg to 109 mm Hg), the primary measurement of antihypertensive efficacy was the change in trough sitting DBP from the start of open-label treatment to the end of Week 8. For the isolated systolic hypertensive patients (baseline systolic blood pressure 140 mm Hg to 179 mm Hg and baseline diastolic blood pressure < 90 mm Hg), the primary measurement of antihypertensive efficacy was the change in trough sitting SBP from the start of open-label treatment to the end of Week 8. Changes in trough sitting systolic blood pressure in the essential hypertensive patients, changes in trough sitting diastolic blood pressure in the isolated systolic hypertensive patients, and trough standing diastolic and systolic blood pressure in essential and isolated systolic hypertensive patients were also evaluated as were changes in trough sitting and standing heart rate. The proportions of responders and controlled patients based on trough sitting diastolic blood pressure were calculated for the essential hypertensive patients and the proportions of responders and controlled patients based on trough sitting systolic blood pressure were calculated for the isolated systolic hypertensive patients. Additional blood pressure reductions were calculated for patients who required titration of candesartan cilexetil 16 mg to 32 mg to control blood pressure. The efficacy analyses were performed for each of the following subpopulations within the essential hypertensive and isolated systolic hypertensive patient groups: sex, racial categorization (black, nonblack), elderly categorization (age ≥ 65 years, age < 65 years), baseline diastolic blood pressure stage (Stage 1: 90 to 99 mm Hg, Stage 2: 100 mm Hg to 109 mm Hg) in essential hypertensive patients, and baseline systolic blood pressure stage (Stage 1: 140 to 159 mm Hg, Stage 2: 160 to 179 mm Hg) in isolated systolic hypertensive patients. Efficacy was also evaluated by geographic region, weight within sex category, and prior/concomitant antihypertensive medication usage.

Safety:

Safety and tolerability were assessed by the incidence and intensity of adverse events. The safety and tolerability assessments were performed by sex, racial categorization (black, nonblack), elderly categorization (age ≥ 65 years, age < 65 years), baseline diastolic blood pressure stage (Stage 1: 90 to 99 mm Hg, Stage 2: 100 mm Hg to 109 mm Hg), baseline systolic blood pressure stage (Stage 1: 140 to 159 mm Hg, Stage 2: 160 to 179 mm Hg), and type of hypertension (essential or isolated systolic). Safety was also evaluated by geographical region and weight within sex category.

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:	

Statistical Methods:

Essential hypertensive patients and isolated systolic hypertensive patients were analyzed separately. Comparisons of effect in the subpopulations were done using an analysis of covariance for a randomized block design with geographical region as the block, baseline blood pressure as the covariate, and subpopulation parameter as a main effect. The comparison of the primary variable in titrated patients versus non-titrated patients was done using an analysis of covariance for a randomized block design with geographical region as the block, baseline blood pressure as the covariate, and final study drug dose as a main effect. The comparisons of titrated patients versus non-titrated patients in the subpopulations were done using an analysis of covariance for a randomized block design with geographical region as the block, baseline blood pressure as the covariate, and final study drug dose and subpopulation parameter as main effects. The SBP in the titrated and non-titrated groups were compared in the isolated systolic hypertensive patients as described above for the DBP measurements in subpopulations. The proportion of responders in the essential hypertensive patients (sitting trough diastolic blood pressure < 90 mm Hg or a reduction ≥ 10 mm Hg) were analyzed by using the Cochran-Mantel-Haenszel test stratified for geographical region. The proportion of controlled patients (sitting trough diastolic blood pressure < 90 mm Hg) were analyzed using the same method. The proportion of responders in the isolated systolic hypertensive patients (sitting trough systolic blood pressure < 140 mm Hg or a reduction ≥ 10 mm Hg) were analyzed by using the Cochran-Mantel-Haenszel test stratified for geographical region. The proportion of controlled patients (sitting trough systolic blood pressure < 140 mm Hg) were analyzed using the same method. These analyses were carried out based on an intent-to-treat approach with the last observation carried forward. The intent-to-treat approach included data from patients who had baseline measurements and at least one observation while on open-label treatment. The response of patients who discontinued before Week 8 was estimated by using the last available observation on open-label treatment regardless of the reason for discontinuation.

Paired t-tests were used to test the additional blood pressure reductions experienced in patients who required titration of candesartan cilexetil 16 mg to 32 mg in each subpopulation in a post-hoc analysis. This analysis was carried out based on an intent-to-treat approach (not last observation carried forward).

All descriptive efficacy analyses were performed on an intent-to-treat approach (not last observation carried forward).

The safety analyses utilized descriptive statistical techniques to explore the safety of candesartan cilexetil 16 mg to 32 mg across the subpopulations. Adverse events were collected to evaluate safety and tolerability profiles in the subpopulations. All patients who received at least one dose of study medication and had post dose physician contact were included in the analysis of safety.

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Name of Finished Product: ATACAND®	Volume:	
Name of Active Ingredient: candesartan cilexetil	Page:	

SUMMARY

Efficacy Results: Patients with essential hypertension (DBP 90 mm Hg to 109 mm Hg at baseline) were analyzed separately from patients with isolated systolic hypertension (SBP 140 mm Hg to 179 mm Hg and DBP < 90 mm Hg at baseline) and efficacy results are presented separately below. There were 6376 patients who had a baseline efficacy measurement and at least one post-baseline efficacy measurement, 5380 essential hypertensive patients and 995 isolated systolic hypertensive patients (due to missing efficacy information at the baseline visit, one patient could not be categorized as essential or isolated systolic hypertensive). Mean blood pressure results presented below are from the intent-to-treat population (not last observation carried forward), yielding smaller sample sizes.

Patients With Essential Hypertension

In 5,156 patients with essential hypertension, candesartan cilexetil 16 mg to 32 mg used alone or as add-on therapy lowered trough sitting SBP/DBP by 18.0/12.2 mm Hg. Forty-nine percent (2,514 of 5,156) of patients with essential hypertension received candesartan cilexetil as monotherapy and 51% received candesartan cilexetil as add-on therapy to a variety of background antihypertensive medications. In 2,514 patients who were treated with candesartan cilexetil 16 mg to 32 alone, mean changes from baseline in trough sitting SBP/DBP were -18.7/-13.1 mm Hg. The overall response rate (mean change from baseline in DBP of at least 10 mm Hg or DBP < 90 mm Hg) was 77.6% and the control rate (DBP < 90 mm Hg) was 71.4%.

Effective changes from baseline in trough sitting diastolic blood pressure were seen across subgroups [sex, racial categorization (black, nonblack), elderly categorization (age ≥ 65 years, age < 65 years), baseline diastolic blood pressure stage (Stage 1: 90 to 99 mm Hg, Stage 2: 100 mm Hg to 109 mm Hg)] and ranged from -10.7 mm Hg to -15.3 mm Hg. Similarly effective changes from baseline in trough sitting systolic blood pressure were seen across subgroups and ranged from –14.4 mm Hg to –19.9 mm Hg. Responder rates ranged from 71.4% to 81.6% and control rates ranged from 60.0% to 78.1% across subgroups.

Fifty-three percent (2,755 of 5,156) of patients with essential hypertension were uptitrated from candesartan cilexetil 16 mg to 32 mg to control diastolic and systolic blood pressure (DBP < 90 mm Hg and SBP < 140 mm Hg) and remained on candesartan cilexetil 32 mg. In 2,402 patients who received candesartan cilexetil 16 mg at Week 8, the mean changes from baseline in trough sitting SBP/DBP were -20.5/-13.9 mm Hg. In 2,796 patients who were uptitrated to candesartan cilexetil 32 mg (all patients who were uptitrated to candesartan cilexetil 32 mg did not have final treatment group of candesartan cilexetil 32 mg), the mean changes from baseline in trough sitting SBP/DBP were –15.7/-10.7 mm Hg; the additional blood pressure reductions achieved by uptitration were 7.8/5.4 mm Hg. Additional blood pressure reductions ranged from 4.7 mm Hg to 5.9 mm Hg in trough sitting diastolic blood pressure and from 6.8 mm Hg to 9.0 mm Hg in trough sitting systolic blood pressure across subgroups [sex, racial categorization (black, nonblack), elderly categorization (age ≥ 65 years, age < 65 years), baseline diastolic blood pressure stage (Stage 1: 90 to 99 mm Hg, Stage 2: 100 mm Hg to 109 mm Hg)].

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:	

Efficacy Results: (Continued)

Patients With Isolated Systolic Hypertension

In 964 patients with isolated systolic hypertension, candesartan cilexetil 16 mg to 32 mg used alone or as add-on therapy lowered trough sitting SBP/DBP by 16.5/4.5 mm Hg. Thirty-four percent (330 of 964) of patients received candesartan cilexetil as monotherapy and 66% received candesartan cilexetil as add-on therapy to a variety of background antihypertensive regimens. In 330 patients who were treated with candesartan cilexetil 16 mg to 32 mg alone, mean changes from baseline in trough sitting SBP/DBP were –17.0/-4.4 mm Hg. The overall response rate (mean change from baseline in SBP of at least 10 mm Hg or SBP < 140 mm Hg) was 71.8% and the control rate (DBP < 140 mm Hg) was 49.4%.

Effective changes from baseline in trough sitting systolic blood pressure were seen across subgroups [sex, racial categorization (black, nonblack), elderly categorization (age ≥ 65 years, age < 65 years), baseline systolic blood pressure stage (Stage 1: 140 to 159 mm Hg, Stage 2: 160 mm Hg to 179 mm Hg)] and ranged from –12.5 mm Hg to –21.5 mm Hg. Lesser changes from baseline in trough sitting diastolic blood pressure were seen across subgroups and ranged from –3.4 mm Hg to –4.9 mm Hg. Responder rates ranged from 64.4% to 77.5% and control rates ranged from 37.0% to 60.1% across subgroups.

Forty-nine percent (472 of 964) of patients with isolated systolic hypertension were uptitrated from candesartan cilexetil 16 mg to 32 mg to control systolic blood pressure (SBP < 140 mm Hg) and remained on candesartan cilexetil 32 mg. In 492 patients who received candesartan cilexetil 16 mg at Week 8, the mean changes from baseline in trough sitting SBP/DBP were –19.7/-5.5 mm Hg. In 475 patients who were uptitrated to candesartan cilexetil 32 mg (all patients who were uptitrated to candesartan cilexetil 32 mg did not have final treatment group of candesartan cilexetil 32 mg), the mean changes from baseline in trough sitting SBP/DBP were –13.1/-3.5 mm Hg; the additional blood pressure reductions achieved by uptitration were 8.9/3.8 mm Hg. Additional blood pressure reductions ranged from 2.8 mm Hg to 4.1 mm Hg in trough sitting diastolic blood pressure and 5.2 mm Hg to 9.3 mm Hg in trough sitting systolic blood pressure across subgroups [sex, racial categorization (black, nonblack), elderly categorization (age ≥ 65 years, age < 65 years), baseline systolic blood pressure stage (Stage 1: 140 to 159 mm Hg, Stage 2: 160 mm Hg to 179 mm Hg)].

Safety Results:

Overall, 2,461 of 6,465 patients (38.1%) reported at least one treatment emergent adverse event. Of these 2,461 patients, the majority of patients (91.7%) had adverse events which were mild to moderate in intensity. There was a 6.8% patient withdrawal rate from the trial due to an adverse event and 4.8% withdrew due to treatment emergent adverse events. The most frequently reported treatment emergent adverse events were headache (6.3%), dizziness (5.0%) and respiratory infection (4.3%). Orthostatic hypotension was rare (0.6%). There was no dose-related side effect. The number of patients reporting treatment emergent adverse events remained the same or actually decreased on uptitration from candesartan cilexetil 16 mg to 32 mg.

The overall incidence and frequency of the most common adverse events was comparable across subgroups [sex, racial categorization (black, nonblack), elderly categorization (age ≥ 65, age < 65), baseline diastolic blood pressure stage (Stage 1: 90 to 99 mm Hg, Stage 2: 100 mm Hg to 109 mm Hg), region and weight within sex categorization].