AstraZeneca

DRUG PRODUCT		**Synopsis**	(FOR NATIONAL AUTHORITY USE ONLY)
DRUG SUBSTANCE(S)	candesartan cilexetil	REFERRING TO PART	
DOCUMENT NO.	SH-AHM-0016	OF THE DOSSIER	
VERSION NO.	1.0		
STUDY CODE	SH-AHM-0016		
DATE	20 September, 1999		

THE EFFECT DURATION OF CANDESARTAN CILEXETIL (8-16 MG) ONCE DAILY, IN COMPARISON WITH ENALAPRIL (10-20 MG) ONCE DAILY, IN PATIENTS WITH MILD TO MODERATE HYPERTENSION.

COUNTRY CO-ORDINATING INVESTIGATORS SIGNATORY:

STUDY CENTRE(S)

Multicenter study including 12 centers in Spain, 10 centers in The Netherlands, 2 centers in Finland, 16 centers in France and 2 centers in Sweden.

PUBLICATION (REFERENCE)

Not applicable.

STUDY PERIOD

- **DATE OF FIRST PATIENT ENROLLED** November 4, 1997
- **DATE OF LAST PATIENT COMPLETED** February 22, 1999

PHASE OF DEVELOPMENT

Therapeutic confirmatory

OBJECTIVES

The objective of the study was to compare the antihypertensive effect duration of candesartan cilexetil 8-16 mg once daily (o.d.) and enalapril 10-20 mg mg o.d. in patients with mild to moderate hypertension.

STUDY DESIGN

Double-blind, randomised, parallel group design.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Primary hypertension, mean sitting diastolic blood pressure (DBP) 95-114 mmHg and at least 24 hours Ambulatory Blood Pressure Monitoring (ABPM) post dose completed with an awake mean diastolic ambulatory blood pressure (ABP) ≥85 mmHg after 4 weeks of placebo run-in, female or male 20-80 years of age, signed informed consent. Excluded were fertile women, patients with myocardial infarction, coronary by-pass surgery, stroke or transient ischaemic attack within six months prior to study start, angina pectoris requiring more than short-acting nitrates, haemodynamically significant aortic or mitral valve stenosis or atrial fibrillation, cardiac failure requiring treatment, severely impaired liver function or impaired renal function, renal artery stenosis or kidney transplantation.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Candesartan cilexetil 8 mg o.d., tablet, batch number H 1156-02-01, oral administration
Candesartan cilexetil 16 mg o.d., tablet, batch number H 1191-01-01, oral administration

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Comparator drug, dosage and formulation	Batch No.
Enalapril 10 mg o.d., encapsulated tablet	H 0787-03-02
Enalapril 20 mg o.d., encapsulated tablet	H 0780-02-04
Placebo (candesartan cilexetil 8 mg) o.d., tablet	H 1210-02-01
Placebo (candesartan cilexetil 16 mg) o.d., tablet	H 1203-03-01
Placebo (enalapril maleate capsules) o.d., capsule	H 1078-03-02

DURATION OF TREATMENT

Four weeks of single-blind placebo run-in treatment followed by an eight-week double-blind period (4 weeks on candesartan cilexetil 8 mg o.d. or enalapril 10 mg o.d., followed by a further 4 weeks of candesartan cilexetil 16 mg o.d. or enalapril 20 mg o.d., respectively).

MAIN VARIABLE(S):

- **EFFICACY**

  Primary: the change in mean diastolic and systolic ambulatory blood pressure (ABP) 22-24 hours post dose from baseline (visit 3, week 0) to week 8.
  Secondary: the change from baseline in:
  a) mean daytime ABP on the day of the missed dose (6 a.m. to 6 p.m.) to week 8
  b) mean ABP 0-24 hours post dose to week 8
  c) the proportion of responders and patients with blood pressure (BP) control at week 8

- **SAFETY**

Adverse events, laboratory assessments

STATISTICAL METHODS

Statistical inference concerning the difference in reduction in trough diastolic and systolic blood pressure between treatments for both the intention to treat (ITT) and per protocol (PP) data sets was based in results from a Multivariate Analysis of Covariance with factors for center and treatment and baseline values as covariate. All other results were obtained by fitting univariate Analysis of Covariance models with the same model as for the primary outcome. Tests of differences in proportions of responders and controlled patients are based on the Mantel-Haenszel chi square statistic.

PATIENTS

	Cand. cil.	**Enalapril**	**Total**
No. planned	145	145	290
No. randomised and treated	198	197	395
No. analysed for safety	197	197	394
No. analysed for efficacy	196	194	390
Males/Females	123/73	109/85	232/158
Mean age (M/F)	53.7/55.9	54.2/57.7	53.9/56.9
No. completed	187	176	363

SUMMARY

- **EFFICACY RESULTS**

The mean adjusted reduction from baseline to 8 weeks of treatment in mean diastolic ABP 22-24 hours post dose was 8.7 mmHg (95% CI 7.0-10.5) in the candesartan cilexetil group and 5.8 mmHg (95% CI 4.0-7.6) in the enalapril group. When comparing candesartan cilexetil to enalapril, the adjusted mean difference was 3.0 mmHg (95% CI 0.8-5.1), p=0.008. For mean systolic ABP 22-24 hours post dose, the mean adjusted reduction in the candesartan cilexetil group was 13.5 mmHg (95% CI 10.9-16.1) and 9.9 mmHg (95% CI 7.3-12.6) in the enalapril group. The mean adjusted difference between the candesartan cilexetil and the enalapril groups was 3.5 mmHg (95% CI 0.3-6.8), p=0.032. The p-value was 0.031 for the test of the bivariate hypothesis that the reduction in diastolic and systolic blood pressure for the group treated with candesartan cilexetil was greater than the reduction for the group treated with enalapril.

Mean adjusted reduction of diastolic ABP on the day of a missed dose (6 a.m. – 6 p.m.) was 8.0 mmHg (95% CI 6.7-9.3) in the candesartan cilexetil group and 4.5 mmHg (95% CI 3.2-5.9) in the enalapril group. The adjusted mean difference between the two groups was 3.5 mmHg (95% CI 1.8-5.1) with a significantly greater reduction in the candesartan cilexetil group, p<0.001. The mean reduction of systolic ABP on the day of a missed dose was 11.4 mmHg (95% CI 9.3-13.5) in the candesartan cilexetil group and 7.2 mmHg (95% CI 5.1-9.4) in the enalapril group, and the adjusted mean difference 4.2 mmHg (95% CI 1.6-6.8) was statistically significant, p=0.002. Both treatment groups demonstrated similar reductions of mean diastolic and systolic ABP 0-24 h post dose, as well as of mean awake and mean night-time diastolic and systolic ABP.

The results of the PP analysis for the primary efficacy variable, mean adjusted diastolic and systolic ABP 22-24 h post dose, were consistent with the results from the ITT analysis.

- **SAFETY RESULTS**

  Candesartan cilexetil 8-16 mg was well tolerated. The proportion of patients who experienced at least one AE was lower among candesartan cilexetil-treated patients compared to enalapril-treated patients (47% and 56%, respectively). Cough occurred in twice as many patients on enalapril compared to candesartan cilexetil (7.6% and 3.6%, respectively), and in two patients, the treatment with enalapril was stopped due to cough. The proportion of patients in the candesartan cilexetil and enalapril group who experienced serious adverse events (SAE) was 2.5% and 1.5%, respectively and AE leading to discontinuation 2% and 3.6%, respectively. One patient experienced angioedema while on candesartan cilexetil. The analysis of laboratory variables revealed no changes that suggest a clinically significant effect of candesartan cilexetil.

DATE OF THE REPORT

20 September, 1999