AstraZeneca

DRUG PRODUCT	Atacand	**Synopsis**	(FOR NATIONAL AUTHORITY USE ONLY)
DRUG SUBSTANCE(S)	Candesartan cilexetil	REFERRING TO PART	
DOCUMENT NO.	1	OF THE DOSSIER	
VERSION NO.	1		
STUDY CODE	SH-AHM-0011		
DATE	31 October, 2002		

Study on cognition and prognosis in elderly (SCOPE)

INVESTIGATORS

STUDY CENTRES

Multicentre study with randomised patients at a total number of 527 centres (Belgium 55, Canada 7, Finland 10, France 133, Germany 58, Hungary 13, Israel 16, the Netherlands 76, Norway 41, Poland 14, Portugal 10, Spain 29, Sweden 25, the United Kingdom (UK) 30 and the United States of America (USA) 10).

PUBLICATIONS (REFERENCES)

Ten abstracts have been presented, here attached in Appendix 16.1.11. The following manuscripts have been published:

1. Degl' Innocenti A et al. Cognitive function and health-related quality of life in elderly patients with hypertension - Baseline data from the Study on Cognition and Prognosis in the Elderly (SCOPE). Blood Pressure 2002;11:157-165.

2. Hansson L et al. Study on Cognition and Prognosis in the Elderly (SCOPE): Randomisation characteristics. Blood Pressure 2000;9(2-3):146-151.

3. Hansson L et al. A. Study on Cognition and Prognosis in the Elderly (SCOPE). Blood Pressure 1999;8(3):177-183.

STUDY PERIOD

- **DATE OF FIRST PATIENT RANDOMISED** March 1997
- **DATE OF LAST PATIENT COMPLETED** March 2002

PHASE OF DEVELOPMENT

Therapeutic confirmatory

OBJECTIVES

Primary objective

The primary objective of the study was to assess the effect of candesartan cilexetil (candesartan) on major cardiovascular (CV) events (CV death, non-fatal myocardial infarction and non-fatal stroke) in elderly patients with mild hypertension.

Secondary objectives

Secondary objectives were to assess the effect of candesartan on:

- Cognitive function as measured by the Mini Mental State Examination (MMSE)
- Dementia
- Total mortality
- CV mortality
- Fatal and non-fatal myocardial infarction (MI)
- Fatal and non-fatal stroke
- Hospitalisation
- Discontinuation of study drug
- Impaired renal function (a doubling of S-creatinine values as compared with baseline)
- New-onset diabetes
- Quality of Life (QoL)
- Health Economics (HE)

STUDY DESIGN

Double-blind, randomised, placebo-controlled and parallel groups. The double-blind treatment was started with candesartan 8 mg once daily (o.d.), in the morning, or corresponding placebo. The dose was doubled to 2 tablets o.d. if systolic blood pressure (SBP) >160 mmHg (or decrease in SBP <10 mmHg since randomisation) or diastolic blood pressure (DBP) >85 mmHg. If a SBP $\geq$160 mmHg or a DBP $\geq$90 mmHg was observed during the study, in spite of 2 tablets o.d. of the study drug, open-label additional antihypertensive treatment was recommended.

The patients were seen at scheduled check-up visits at which data on clinical events (CE), adverse events (AE), laboratory variables, blood pressure (BP), heart rate (HR), physical examination, MMSE, QoL and HE were recorded. All CV events, deaths and dementia events were classified by an independent clinical event committee.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Main inclusion criteria: Male or female, aged 70-89 years, with or without antihypertensive treatment and a SBP 160-179 mmHg and/or DBP 90-99 mmHg and MMSE score 24 or above. Antihypertensive treatment was standardized to hydrochlorothiazide (HCT) 12.5 mg o.d. Main exclusion criteria: Need of antihypertensive treatment other than HCT, stroke or MI within 6 months prior to randomisation, decompensated congestive heart failure, other serious concomitant diseases considered by the investigator to affect survival during the next 3-4 years, obvious dementia, conditions which preclude MMSE, vitamin B_{12} deficiency, hypothyroidism, severe brain disorder that may have interfered with cognitive function and certain mental disorders.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Candesartan cilexetil 8 mg. Batch No.: H 1156-02-01-04, H 1156-02-01-05, H 1156-02-01-07, H 1156-02-01-09, H 1156-02-01-10, H 1156-02-01-14, H 1156-02-01-15, H 1156-02-01-16, H 1156-02-01-17, H 1156-02-01-20, H 1156-02-01-21, H 1156-02-01-22, H 1156-02-01-23, H 1156-02-01-25 and H 1156-02-01-26. One (1) to 2 tablets o.d., oral administration.

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Placebo. Identical to the candesartan 8 mg tablet. Batch No.: H 1210-02-01-01, H 1210-02-01-02, H 1210-02-01-03, H 1210-02-01-05, H 1210-02-01-08, H 1210-02-01-09, H 1210-02-01-10, H 1210-02-01-11, H 1210-02-01-12, H 1210-02-01-13, H 1210-02-01-14 and H 1210-02-01-15. One (1) to 2 tablets, o.d., oral administration.

Additional product: HCT 12.5 mg. Batch No.: H 0425-07-01-03, H 0425-07-01-04, H 0425-07-01-05, H 0425-07-01-06, H 0425-07-01-07, H 0425-07-01-08, H 0425-07-01-10 and H 0425-07-01-11. Tablets, o.d., oral administration.

DURATION OF TREATMENT

The double-blind period lasted for up to 5 years. The mean follow-up time was 3.7 years.

MAIN VARIABLE(S):

- **EFFICACY**

The primary efficacy variable was the time to a first major CV event, calculated from the time of randomisation to the event.

- **SAFETY**

AEs and laboratory assessments.

STATISTICAL METHODS

The analysis was conducted according to the intention to treat (ITT) principles. Variables of the type "time to an event" were analysed by a log-rank test. Number of patients with an event

were analysed by Chi-square test. Time-interval events were analysed by a Mantel-Haenszel test. Change from randomisation variables were analysed in an Analysis of Covariance (ANCOVA) model. Prognostic and explanatory factors were analysed using a Cox regression model.

PATIENTS

	Cand. cil.	Placebo	Total
No. analysed for efficacy (ITT)	2 477	2 460	4 937
No. analysed for safety	2 477	2 460	4 937
Males/Females	872/1605	881/1579	1753/3184
Mean age (years)	76.4	76.4	76.4
Age ≥80	526 (21.2%)	529 (21.5%)	1 055
SBP/DBP (mmHg)	166.0/90.3	166.5/90.4	166.2/90.3
MMSE (score)	28.5	28.5	28.5

The total number of patients randomised was 4 964. However, all 13 patients at 1 centre were excluded prior to code breaking because of quality concerns on individual patient data and 14 patients were excluded because no study drugs were ever dispensed.

Summary

- **EFFICACY RESULTS**

The vast majority of patients in the control group, 84%, received active antihypertensive treatment, and only 16% were treated with placebo only. As a consequence, mean supine BP was lowered effectively in both treatment groups; in the candesartan group from 166.0/90.3 mmHg to 145.2/79.9 mmHg and in the control group from 166.5/90.4 mmHg to 148.5/81.6 mmHg ($p<0.001$ for all). The average difference in adjusted BP reduction between the treatment groups was 3.2/1.6 mm Hg ($p<0.001$ for both). Therefore, the SCOPE study must be regarded as a comparison between two actively treated groups (with and without candesartan, respectively) and not as a placebo-controlled study.

The primary endpoint, a first major CV event (CV death, non-fatal MI or non-fatal stroke) occurred in 242 patients in the candesartan group (26.7 events per 1 000 patient-years) and in 268 patients (30.0 events per 1 000 patient-years) in the control group, a risk reduction of 10.9% (95% CI –6.0 to 25.1, p=0.19).

Non-fatal stroke occurred in 68 patients in the candesartan group (7.4 events per 1000 patient-years) and in 93 patients (10.3 events per 1 000 patient-years) in the control group, a risk reduction of 27.8% (95% CI 1.3 to 47.2, p=0.04). All stroke occurred in 89 patients (9.7 events per 1 000 patient-years) in the candesartan group and in 115 patients (12.8 events per 1 000 patient-years) in the control group, a risk reduction of 23.6% (95% CI –0.7 to 42.1, p=0.056).

There were no statistically significant differences between the two groups as regards fatal, non-fatal or total MI, fatal stroke, CV mortality or total mortality.

A *post hoc* analysis in patients without open-label add-on antihypertensive treatment after randomisation (reflecting the intention to conduct a placebo controlled study) showed a greater difference in BP between the treatment groups (4.7/2.6 mmHg) and corresponding greater risk reductions in the candesartan group. For example, the risk reduction was 32% (p=0.012) for major CV events, 29% (p=0.050) for CV mortality and 27% (p=0.018) for total mortality. This suggests that the widespread use of antihypertensive add-on therapy was responsible for the smaller BP difference in the main ITT analysis and that this smaller BP difference translated into the smaller risk reduction in CV events.

Cognitive function was generally well maintained in both treatment groups, and there was no difference between treatments. The mean MMSE score fell from 28.5 to 28.0 in the candesartan group and from 28.5 to 27.9 in the control group (mean difference in adjusted change 0.15, 95% CI –0.08 to 0.38, p=0.20). In a *post hoc* analysis in patients with MMSE score 24-28 at baseline (to avoid a "ceiling" effect), the reduction in MMSE during the study was significantly less in the candesartan group than in the control group (mean difference in adjusted change 0.49, 95% CI 0.02 to 0.97, p=0.04).

The proportion of patients who discontinued the study drug was lower in the candesartan group, 29.6%, than in the control group, 32.6% (p=0.02). New-onset diabetes mellitus was reported in 4.3% and 5.3% of the patients in the candesartan and control groups, respectively (p=0.09). There were no significant differences between the treatment groups in the proportion of patients being hospitalised (candesartan 34.4%, control 36.1%) or having impaired renal function, i.e. a doubling of S-creatinine in comparison with baseline (candesartan 0.8%, control 0.6%).

Health-related QoL was generally good at baseline in both the candesartan group and the control group. It also appeared well maintained during follow-up, with no marked differences between the groups. Some health-related QoL results indicated an advantage of candesartan-based treatment compared with control treatment (PGWB Anxiety and Positive well-being, SSA-P Cardiac symptoms, and EuroQoL Thermometer and TTO Tariff).

- SAFETY RESULTS

Candesartan 8-16 mg o.d (alone, in addition to HCT 12.5 mg and/or in combination with other antihypertensive agents) was generally safe and well tolerated during long-term treatment in this population of elderly patients with mild hypertension, including a large proportion of females and a substantial number of patients above the age of 80 at randomisation.

Overall, similar proportions of patients in the candesartan group and in the control group experienced non-serious or serious AEs. Slightly fewer patients randomised to candesartan

discontinued the double-blind study drug as a result of an AE (15.3% for candesartan compared to 17.2% for placebo). The most frequently observed AEs in patients receiving candesartan were dizziness/vertigo, accident/injury and back pain, which was similar to the pattern seen in the control group. For individual AEs, back pain was slightly more common in the candesartan group (19.2% versus 17.1%), while headache was reported more frequently in the control group (7.9% in the candesartan group versus 10.6% in the control group).

Gender or very high age (≥80 years at enrolment) had no apparent effects on the AE profile of candesartan in comparison with placebo.

As could be expected, 'hypotension' or 'hypotension postural' were reported as AE in somewhat more patients in the candesartan group than in the placebo group (1.4% and 0.9% in the candesartan group versus 0.7% and 0.4% in the control group). These events, however, only occasionally led to discontinuation of double-blind study drug. Four patients only discontinued candesartan due to 'hypotension' and 3 patients due to 'postural hypotension'. In the control group, 5 patients discontinued placebo due to hypotension and 1 patient due to postural hypotension.

As regards laboratory AEs, hyperkalemia or hyponatremia were reported in 1.0% and 1.3%, respectively, in the candesartan group, which was somewhat higher than in the control group (0.5% for both AEs). Hypokalemia was more common in the control group (0.5% in the candesartan group versus 1.2% in the control group). These events caused discontinuation of double-blind study drug in a low number of patients only. Hyperkalemia, hyponatremia and hypokalemia caused discontinuation of study drug in 4 patients, 5 patients and 1 patient, respectively, in the candesartan group versus 3 patients, 0 patient and 1 patient in the control group.

Renal function variables (mean S-creatinine and S-urea) increased in both treatment groups, and slightly more in the candesartan group. (9.6 µmol/L and 0.8 mmol/L, respectively, in the candesartan group versus 5.3 µmol/L and 0.3 mmol/L in the control group).

Mean haemoglobin decreased in both treatment groups and slightly more in the candesartan group (5.1 g/L in the candesartan group and 2.5 g/L in the control group), consistent with previous experience with ACE-I and AT_1-receptor blockers.

DATE OF THE REPORT

31 October 2002