AstraZeneca

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| Drug product | Atacand® | **SYNOPSIS** | |
| Drug substance | Candesartan cilexetil | | |
| Document No. | SH-AHS-0003 | | |
| Edition No. | Final | | |
| Study code | SH-AHS-0003 | | |
| Date | 15 January 2004 | | |

**Candesartan cilexetil (candesartan) in heart failure assessment of reduction in mortality and morbidity (CHARM)**

**Clinical study of candesartan in patients with heart failure who are ACE inhibitor intolerant and have depressed left ventricular systolic function** (CHARM Alternative)

**International Co-ordinating investigator**

**Study sites**

This study was conducted in 25 countries at a total of 484 sites (Australia 16, Belgium 14, Canada 51, Czech Republic 12, Denmark 18, Finland 7, France 18, Germany 33, Hungary 10, Iceland 2, Ireland 1, Italy 17, Malaysia 3, Netherlands 21, Norway 17, Poland 14, Portugal 13, Russia 10, Singapore 3, South Africa 8, Spain 15, Sweden 14, Switzerland 7, United Kingdom 29 and USA 131 sites).

**Publications**

The publications are presented in Appendix 12.1.11.

| **Study dates** | | **Phase of development** |
| --- | --- | --- |
| First patient randomised | 22 March 1999 | Therapeutic confirmatory (Phase III) |
| Last patient completed | 31 March 2003 | |

**Objectives**

Primary objective:
To determine whether candesartan, compared to placebo, reduced the combined endpoint of cardiovascular (CV) mortality or hospitalisation for the management of chronic heart failure (CHF).

Secondary objectives:
To determine whether candesartan, compared to placebo:

1. reduced the combined endpoint of all-cause mortality or hospitalisation for the management of CHF.

2. reduced the combined endpoint of CV mortality or hospitalisation for the management of CHF or non-fatal myocardial infarction (MI).

Other objectives:
To determine whether candesartan, compared to placebo:

3. reduced the combined endpoint of CV mortality, or hospitalisation for the management of CHF, or non-fatal MI, or coronary revascularisation procedures.

4. reduced the combined endpoint of all-cause mortality and all-cause hospitalisation.

5. reduced all-cause mortality.

6. reduced all-cause hospitalisation.

7. reduced the number of fatal and non-fatal MIs.

8. affected functional state and symptoms according to New York Heart Association (NYHA) classification.

9. was well tolerated and safe by evaluation of drug discontinuation, decrease in dose and non-CV mortality and hospitalisation.

10. influenced the cost of health care.

## Study design

This was a randomised, double-blind placebo controlled parallel group multicenter study to evaluate the influence of candesartan cilexetil (hereafter referred to as candesartan) with a target dose of 32 mg once daily on mortality and morbidity in patients with depressed left ventricular (LV) systolic function and ejection fraction (EF)≤40% and an intolerance to angiotensin converting enzyme (ACE) inhibitors.

## Target patient population and sample size

Male and female patients, over or equal to18 years of age, with symptomatic CHF corresponding to NYHA class II-IV and with depressed LV systolic function and intolerance to ACE inhibitors.

A total of 2000 patients were estimated to be randomised in order to detect a 16-20% decrease in the annual placebo incidence rate of CV death or hospitalisation for heart failure, assuming an annual placebo rate of 20 to 24%, at a statistical power of at least 80%. The patients were to be equally distributed between the two treatment groups. The actual number of randomised patients was 2028.

## Investigational products: dosage, mode of administration and batch numbers

The active treatment group received candesartan (Atacand®) tablets 4 mg (white) or 16 mg (pink) once daily. A starting dose of 4 mg or 8 mg once daily, was up-titrated by doubling the dose at 2 week intervals to a maximum of 32 mg or the highest tolerated level. Tablets were to be swallowed with water in the morning. The batch numbers for candesartan 4 mg used in the study programme were: H 1155-02-01-07, -09, -10, -11, -12, -13, -14, and –16. The batch numbers for candesartan 16 mg were: H 1191-01-01-06, -12, -13, -14, -15, -16, -17, -18, -19, -20, -21, -22, -24, -25 and 28.

The comparator group received placebo tablets identical to the active tablets, with the exception of the active ingredient. The batch numbers for placebo candesartan 4 mg were: H 1242-01-01-02, -03, -04, -05, -06, -07, -08 and 09. The batch numbers for placebo candesartan 16 mg were: H 1203-03-01-05, -07, -08, -09, -10, -11, -12, -13, -14, -15, -16, -17, -21, -22 and 23.

## Duration in study

All patients remained in the study until the last randomised patient had been in the study for two years. Individual time in the study for surviving patients not lost to follow-up could last from 25 to 48 months depending on when a patient was randomised. The median follow-up time was 33.8 months in the candesartan group and 33.6 months in the placebo group. The median duration of exposure of the investigational product was 29.5 months in the placebo group and 29.4 months in the candesartan group. The patient recruitment period was 23 months.

**Criteria for evaluation (main variables)**

Efficacy

11. Primary variable in the confirmatory analysis: Time from randomisation to CV death or to hospitalisation due to symptomatic CHF, whichever occurred first.

12. Secondary variables in the confirmatory analysis:

1. Time from randomisation to all-cause death or to hospitalisation due to symptomatic CHF whichever occurred first.

2. Time from randomisation to CV death or to hospitalisation due to symptomatic CHF, or a non-fatal MI, whichever occurred first.

Safety

3. Investigational product discontinuation.

4. Reduction in dose of investigational product.

5. Occurrence of non-CV death and hospitalisation.

6. Standard safety assessments including adverse event reports, clinical laboratory data (North America) vital signs and physical examination.

Health economics

7. Resource utilisation data for all patients: Number of hospitalisations.

8. For patients hospitalised with CV diagnosis: Length of hospital stay, level of hospital care and any major CV procedures carried out.

**Statistical methods**

All analyses were made on an intention-to-treat basis. The time from randomisation to an event variable was analysed with a two-sided Logrank test and for estimation in a Cox proportional hazards model. Kaplan-Meier plots were used to graphically display the time-to-event distributions by treatments. Secondary analysis was made using a Cox-regression model with pre-specified prognostic factors (baseline covariates). A Chi-square test was used to test the difference between the proportions of patients with a specific characteristic/outcome. Changes in the NYHA classification were tested using a Wilcoxon rank-sum test. For continuous variables, the mean change from baseline to last observed value was tested in an analysis of covariance (ANCOVA) model. Estimates with 95% confidence intervals (CIs) for each treatment and the difference between the treatments were calculated, as appropriate. All tests were two-sided. The multiple significance level was controlled for the primary and secondary objectives using a closed test procedure.

## Patient population

The patients were in NYHA functional class II-IV. Baseline characteristics were representative of a population of patients with CHF and depressed LV systolic function. The two treatment groups were well balanced with respect to baseline characteristics. The patient population was clinically considered intolerant to an ACE inhibitor but treated with beta-blockers in 55% and spironolactone in 24%.

A total of 824 (81.3%) patients in the candesartan group started treatment on 4 mg once daily and 189 (18.7%) patients started on 8 mg once daily. A total of 1313 (64.7%) patients (candesartan 666, 65.8%; placebo 647, 63.7%) received the investigational product for 24 months or more. 52.2% of the candesartan patients (58.9% of those still receiving the investigational product) were treated with the target dose 32 mg once daily at 6 months (visit 5). The mean dose in the candesartan group was 23.2 mg at 6 months and 23.1 at LVCF.

Cough was the most common reason for ACE intolerance in both treatment groups. It was more common in the placebo group than in the candesartan group (751, 74.0% vs 704, 69.5%). ACE intolerance due to hypotension or renal dysfunction was more common in the candesartan group (143, 14.1% vs 119, 11.7% and 134, 13.3% vs 100, 9.9% respectively)

**Table S1 Patient population and disposition**

| | | Placebo | | Cand. cil. | | Total | |
|---|---|---|---|---|---|---|---|
| **Population** | | | | | | | |
| N randomised (N planned) | | 1015 | (1000) | 1013 | (1000) | 2028 | (2000) |
| **Demographic characteristics** | | | | | | | |
| Sex, N (%) | Male | 691 | (68.1) | 691 | (68.2) | 1382 | (68.1) |
| | Female | 324 | (31.9) | 322 | (31.8) | 646 | (31.9) |
| Age, mean (SD) | Years | 66.8 | (10.5) | 66.3 | (11.0) | 66.6 | (10.7) |
| Ethnicity, N (%) | European origin | 901 | (88.8) | 895 | (88.4) | 1796 | (88.6) |
| | Black | 45 | (4.4) | 28 | (2.8) | 73 | (3.6) |
| | South Asian | 15 | (1.5) | 22 | (2.2) | 37 | (1.8) |
| | Arab/Middle East | 6 | (0.6) | 9 | (0.9) | 15 | (0.7) |
| | Oriental | 27 | (2.7) | 29 | (2.9) | 56 | (2.8) |
| | Malay | 10 | (1.0) | 14 | (1.4) | 24 | (1.2) |
| | Other | 11 | (1.1) | 16 | (1.6) | 27 | (1.3) |
| **Baseline characteristics** | | | | | | | |
| Ejection fraction, mean (SD) | | 0.30 | (0.07) | 0.30 | (0.08) | 0.30 | (0.07) |
| Diabetes mellitus, N (%) | | 270 | (26.6) | 278 | (27.4) | 548 | (27.0) |
| Hypertension, N (%) | | 515 | (50.7) | 500 | (49.4) | 1015 | (50.0) |

| | | Placebo | | Cand. cil. | | Total | |
|---|---|---|---|---|---|---|---|
| Atrial fibrillation, N (%) | | 261 | (25.7) | 254 | (25.1) | 515 | (25.4) |
| Previous MI, N (%) | | 618 | (60.9) | 629 | (62.1) | 1247 | (61.5) |
| Angina pectoris, N (%) | | 592 | (58.3) | 593 | (58.5) | 1185 | (58.4) |
| Stroke, N (%) | | 90 | (8.9) | 85 | (8.4) | 175 | (8.6) |
| NYHA II, N (%) | | 479 | (47.2) | 487 | (48.1) | 966 | (47.6) |
| NYHA III, N (%) | | 499 | (49.2) | 490 | (48.4) | 989 | (48.8) |
| NYHA IV, N (%) | | 37 | (3.6) | 36 | (3.6) | 73 | (3.6) |
| Current smoker, N (%) | | 127 | (12.5) | 149 | (14.7) | 276 | (13.8) |
| **Disposition** | | | | | | | |
| N (%) of patients | Completing the study | 1014 | (99.9) | 1011 | (99.8) | 2025 | (99.9) |
| | Lost to follow-up | 1 | (0.1) | 2 | (0.2) | 3 | (0.1) |
| N analysed for safety (ITT/Safety population[a]) | | 1015 | | 1013 | | 2028 | |
| N analysed for efficacy (ITT/Safety population[a]) | | 1015 | | 1013 | | 2028 | |
| N analysed for efficacy (PP population) | | 795 | | 745 | | 1540 | |

a Safety and ITT population was defined as all randomised patients. ITT Intention to treat; N Number

## Efficacy results

Candesartan treatment significantly reduced cardiovascular death or hospitalisation due to CHF. This corresponds to a relative risk reduction of 23.2%. The effect appeared early and was sustained throughout the study period. The other two outcomes included in the confirmatory analysis were also significantly reduced by treatment with candesartan. The relative risk reduction for all-cause death or hospitalisation due to CHF was 20.2% and for CV death or hospitalisation due to CHF or non-fatal myocardial infarction was 21.8%.

**Table S2 Summary of efficacy results, primary and secondary variables. Comparison of candesartan versus placebo with Cox regression. ITT/Safety population (SH-AHS-0003)**

| Variable | N | Events cand. cil. | Events placebo | Hazard Ratio | 95% CI | | p-value[a] |
|---|---|---|---|---|---|---|---|
| | | | | | Lower | Upper | |
| CV death or hospitalisation due to CHF (confirmed adjudicated) | 2028 | 334 | 406 | 0.768 | 0.665 | 0.888 | <0.001 |

| Variable | N | Events cand. cil. | Events placebo | Hazard Ratio | 95% CI | | p-value[a] |
|---|---|---|---|---|---|---|---|
| | | | | | Lower | Upper | |
| All-cause death or hospitalisation due to CHF (confirmed adjudicated) | 2028 | 371 | 433 | 0.798 | 0.695 | 0.917 | 0.001 |
| CV death or hospitalisation due to CHF or non-fatal MI (confirmed adjudicated) | 2028 | 353 | 420 | 0.782 | 0.679 | 0.901 | <0.001 |

[a] Logrank test

The individual components CV death (relative risk reduction 15%, p=0.072), hospitalisation due to CHF (relative risk reduction 32%, p<0.001) and all-cause death (relative risk reduction 13%, p=0.105) all contributed to the benefit of candesartan as described by the respective composite endpoints. However, there was no reduction in non-fatal MI.

Symptoms of heart failure according to NYHA classification improved significantly during candesartan treatment compared to placebo (p= 0.008).

The incidence of diagnosed onset of diabetes mellitus during the follow-up period was numerically reduced by candesartan (HR 0.79, 95% CI 0.53 to1.18, p=0.254).

Fewer patients in the candesartan group (49, 4.8%) than in the placebo group (70, 6.9%) developed atrial fibrillation (95% CI –4.1 to 0.0, p=0.048).

**Safety results**

Adverse events (AEs) were reported for approximately equal proportions of patients in the two treatment groups, both as analysed during treatment with the investigational product (placebo 724, 71.3%; candesartan 725, 71.6%) and over the entire study period (placebo 747, 73.6%; candesartan 741, 73.1%)

Serious adverse events (SAEs), fatal and non-fatal, occurred less frequently with candesartan treatment (placebo 675, 66.5%; candesartan 623, 61.5%) as well as during the study, whether on or off treatment (placebo 722, 71.1%; candesartan 682, 67.3%). Fatal SAEs were also less common on treatment with candesartan (placebo 187, 18.4%; candesartan 165, 16.3%) as well as during the study (placebo 296, 29.2%; candesartan 266, 26.3%). The most common fatal SAEs were cardiovascular events which were included in the CV death endpoint (confirmed adjudicated) and these occurred less frequently in the candesartan treatment group during study (placebo 252, 24.8%; candesartan 219, 21.6%).

A total of 417 (20.6%) of the patients permanently discontinued taking the investigational product because of an AE or abnormal laboratory value (placebo 197, 19.4%; candesartan 220, 21.7%).

Study investigators chose to reduce the investigational product dose because of an AE in 76 patients (7.5%) taking placebo and 157 patients (15.5%) taking candesartan.

Apart from cardiac failure aggravated, abnormal renal function (placebo 25, 2.5%; candesartan 65, 6.4%), hypotension (placebo 14, 1.4%; candesartan 46, 4.5%) and hyperkalaemia (placebo 3, 0.3%; candesartan 21, 2.1%) were the most commonly-reported AEs given as reasons for discontinuing the investigational product.

Cough (the most common reason for patients not taking an ACE-inhibitor due to drug intolerance) led to discontinuation in only a few patients in each treatment group. Also most patients with ACE-inhibitor intolerance for other reasons at study entry, including hypotension, renal dysfunction and angioedema, were able to tolerate candesartan treatment. Angioedema, specifically, occurred in none of the placebo patients and in 3 patients in the candesartan group. One of 39 candesartan patients with a history of angioedema when taking an ACE-inhibitor permanently discontinued candesartan because of angioedema.

Differences in mean laboratory values (candesartan compared with placebo) were small and in keeping with expected values for treatment with inhibitors of the renin-angiotensin-aldosterone system, ie, slightly higher serum potassium and creatinine levels.

**Table S3 Number (%) of patients with at least one adverse event in any category, and total numbers of adverse events. ITT/Safety population (SH-AHS-0003)**

| Category of adverse events | N (%) of patients who had an adverse event in each category[a] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Placebo on treatment[d] (N=1015) | | Cand. cil. on treatment[d] (N=1013) | | Placebo during study[b,e] (N=1015) | | Cand. cil. during study[b,e] N=1013) | |
| Any AEs | 724 | (71.3) | 725 | (71.6) | 747 | (73.6) | 741 | (73.1) |
| Serious AEs | 675 | (66.5) | 623 | (61.5) | 722 | (71.1) | 682 | (67.3) |
| Serious AEs leading to death | 187 | (18.4) | 165 | (16.3) | 296 | (29.2) | 266 | (26.3) |
| Serious AEs not leading to death | 611 | (60.2) | 571 | (56.4) | 654 | (64.4) | 619 | (61.1) |
| Discontinuations of investigational product due to AEs | 197 | (19.4) | 220 | (21.7) | - | - | - | - |
| Dose reductions of investigational product due to AEs | 76 | (7.5) | 157 | (15.5) | - | - | - | - |
| | Total number of adverse events | | | | | | | |
| Any AEs[c] | 2302 | | 2402 | | 2780 | | 2894 | |
| Serious AEs[c] | 2069 | | 1956 | | 2546 | | 2453 | |

a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

b Only one occurrence of an event during the study period is counted

c Events are counted by preferred term, ie, for patients with multiple events falling under the same preferred term, only one occurrence of the event is counted.

d On treatment = on treatment with investigational product.

e During study = total study period, irrespective of treatment with investigational product or not.

**Table S4 Number (%) of patients with the most commonly reported[a] AEs, sorted by descending frequency in the total population during study. ITT/Safety population (SH-AHS-0003)**

| Preferred term | Placebo on treatment[b] (N=1015) | | Cand. cil. on treatment[b] (N=1013) | | Placebo during study[c] (N=1015) | | Cand. cil. during study[c] (N=1013) | |
|---|---|---|---|---|---|---|---|---|
| | N | (%) | N | (%) | N | (%) | N | (%) |
| Cardiac failure/cardiac failure aggravated | 317 | (31.2) | 234 | (23.1) | 359 | (35.4) | 280 | (27.6) |
| Hypotension | 76 | (7.5) | 190 | (18.8) | 90 | (8.9) | 193 | (19.1) |
| Angina pectoris/angina pectoris aggravated | 110 | (10.8) | 105 | (10.4) | 120 | (11.8) | 127 | (12.5) |
| Renal function abnormal/renal dysfunction aggravated | 49 | (4.8) | 136 | (13.4) | 50 | (4.9) | 141 | (13.9) |

| Preferred term | Placebo on treatment[b] (N=1015) | | Cand. cil. on treatment[b] (N=1013) | | Placebo during study[c] (N=1015) | | Cand. cil. during study[c] (N=1013) | |
|---|---|---|---|---|---|---|---|---|
| | N | (%) | N | (%) | N | (%) | N | (%) |
| Sudden death | 85 | (8.4) | 65 | (6.4) | 106 | (10.4) | 80 | (7.9) |
| Pneumonia | 64 | (6.3) | 65 | (6.4) | 75 | (7.4) | 83 | (8.2) |
| Myocardial infarction | 58 | (5.7) | 71 | (7.0) | 68 | (6.7) | 85 | (8.4) |
| Arrhythmia ventricular | 64 | (6.3) | 58 | (5.7) | 79 | (7.8) | 73 | (7.2) |
| Cerebrovascular disorder | 55 | (5.4) | 41 | (4.0) | 61 | (6.0) | 52 | (5.1) |
| Arrhythmia atrial | 41 | (4.0) | 44 | (4.3) | 44 | (4.3) | 56 | (5.5) |
| Fibrillation atrial | 46 | (4.5) | 34 | (3.4) | 57 | (5.6) | 43 | (4.2) |
| Chest pain | 42 | (4.1) | 37 | (3.7) | 50 | (4.9) | 47 | (4.6) |
| Coronary artery disorder | 39 | (3.8) | 38 | (3.8) | 48 | (4.7) | 49 | (4.8) |
| Tachycardia ventricular/arrhythmia | 31 | (3.1) | 28 | (2.8) | 44 | (4.3) | 39 | (3.8) |
| Cardiomyopathy | 29 | (2.9) | 25 | (2.5) | 40 | (3.9) | 37 | (3.7) |
| Tachycardia supraventricular | 30 | (3.0) | 27 | (2.7) | 39 | (3.8) | 34 | (3.4) |
| Hyperkalaemia | 16 | (1.6) | 54 | (5.3) | 18 | (1.8) | 54 | (5.3) |
| Dizziness/vertigo | 21 | (2.1) | 43 | (4.2) | 23 | (2.3) | 45 | (4.4) |
| Dyspnoea/dyspnoea (aggravated) | 39 | (3.8) | 17 | (1.7) | 43 | (4.2) | 22 | (2.2) |
| Syncope | 28 | (2.8) | 26 | (2.6) | 35 | (3.4) | 30 | (3.0) |

a This table uses a cut-off of ≥3.0% in total population during study (N=2028).

b On treatment = on treatment with investigational product.

c During study = total study period, irrespective of treatment with investigational product or not.

## Health economics results

For CV-related hospitalisations (in total 1882 hospitalisations) data were collected on the length of stay according to type of ward (intensive, intermediate or general). The patients treated with candesartan had fewer CV-related hospitalisations (879) during the study period than the placebo-treated patients (1003) as well as a shorter length of stay (6973 vs 9216 days). The relative distribution of the length of stay by type of ward showed a higher use of intensive care wards in the candesartan group (candesartan 25.0% vs placebo 15.7% of days) compared to the use of intermediate care wards (candesartan 25.8% vs placebo 28.8% of days) and general care wards (candesartan 49.2% vs placebo 55.6% of days).

**Date of the report**

15 January 2004