AstraZeneca

Drug product	Atacand®	**SYNOPSIS**	
Drug substance	Candesartan cilexetil		
Document No.	SH-AHS-0007		
Edition No.	Final		
Study code	SH-AHS-0007		
Date	23 February 2004		

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

Study of candesartan in patients with heart failure and preserved left ventricular systolic function (CHARM Preserved)

International Co-ordinating investigator

Study site

This study was conducted in 26 countries at a total of 514 sites (Australia 17, Belgium 12, Canada 60, Czech Republic 11, Denmark 19, Finland 9, France 19, Germany 37, Hungary 9, Iceland 2, Italy 18, Luxembourg 1, Malaysia 3, Netherlands 21, Norway 18, Poland 14, Portugal 13, Russia 10, Singapore 3, South Africa 9, Spain 14, Sweden 15, Switzerland 8, United Kingdom/Ireland 29 and USA 143 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 mortality or hospitalisation for the management of chronic heart failure.

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

- reduced the combined endpoint of all-cause mortality or hospitalisation for the management of chronic heart failure.
- reduced the combined endpoint of cardiovascular mortality or hospitalisation for the management of chronic heart failure or non-fatal myocardial infarction.

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

- reduced the combined endpoint of cardiovascular mortality, or hospitalisation for the management of chronic heart failure or non-fatal myocardial infarction, or coronary revascularisation procedures.
- reduced the combined endpoint of all-cause mortality and all-cause hospitalisation.
- reduced all-cause mortality.
- reduced all-cause hospitalisation.
- reduced the number of fatal and non-fatal myocardial infarctions.
- affected functional state and symptoms according to New York Heart Association (NYHA) classification.
- was well tolerated and safe by evaluation of drug discontinuation, decrease in dose and non-cardiovascular mortality and hospitalisation.
- 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 heart failure and preserved left ventricular (LV) systolic function and ejection fraction (EF) >40%.

Target patient population and sample size

Male and female patients, over or equal to18 years of age, with symptomatic chronic heart failure (CHF) corresponding to NYHA class II-IV and with preserved left ventricular systolic function EF>40% treated or not treated with an angiotensin converting enzyme (ACE) inhibitor.

A total of 2900 patients were estimated to be randomised in order to detect a 16-20% decrease in the annual placebo incidence rate of cardiovascular (CV) death or hospitalisation for heart failure, assuming an annual placebo rate of 13 to 14%, at a statistical power of at least 70%. The patients were to be equally distributed between the two treatment groups. The number of randomised patients was 3025; two of the patients were randomised by mistake. The patients got no investigational product and no data were collected, so the actual number of patients was 3023.

Investigational product: 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 cilexetil 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 cilexetil 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 cilexetil 4 mg were: H 1242-01-01-02, -03, -04, -05, -06, -07, -08 and 09. The batch numbers for placebo candesartan cilexetil 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 CHARM programme for two years. The patient recruitment period was 16 months. Individual time in the study for surviving patients not lost to follow-up could last from 32 to 48 months depending on when the patient was randomised. The median follow-up time was 36.6 months in the candesartan group and 36.5 months in the placebo group. The median duration of exposure of the investigational product was 35.4 months in the placebo group and 35.0 months in the candesartan group

Criteria for evaluation (main variables)

Efficacy

- Primary variable in the confirmatory analysis: Time from randomisation to cardiovascular death or to hospitalisation due to a CHF, whichever occurred first.
- Secondary variables in the confirmatory analysis:
  - Time from randomisation to all-cause death or to hospitalisation due to CHF, whichever occurred first.
  - Time from randomisation to cardiovascular death or to hospitalisation due to chronic heart failure, or a non-fatal MT, whichever occurred first.

Safety

- Investigational product discontinuation.
- Reduction in dose of investigational product.
- Occurrence of non-cardiovascular death and hospitalisation.
- Standard safety assessments including adverse event reports, clinical laboratory data (North America), vital signs and physical examination.

Health economics

- Resource utilisation data for all patients: Number of hospitalisations.
- For patients hospitalised with a cardiovascular diagnosis: Length of hospital stay, level of hospital care and any major cardiovascular 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 levels were controlled for the primary and secondary objectives using a closed test procedure.

Patient population

The patients were mainly in NYHA functional class II or III. Baseline characteristics were representative of a population of patients with CHF and preserved LV systolic function. The two treatment groups were generally well-balanced with respect to baseline characteristics but several factors associated with a poorer outcome, such as previous myocardial infarction, stroke and smoking, were more common in the candesartan group. Such imbalances can be accounted for in covariate adjusted analyses.

A total of 1132 (74.8%) patients in the candesartan group started treatment on 4 mg once daily and 382 (25.2%) patients started on 8 mg once daily. A total of 2291 (75.8%) patients (candesartan 1136, 75.0%; placebo 1155, 76.5%) received the investigational product for 24 months or more. 59.6% of the candesartan patients (66.8% 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 25.0 mg at 6 months and 24.9 mg at the end of trial (last value carried forward).

Table S1 Patient population and disposition

		Placebo		Cand. cil.		Total	
Population							
N randomised (N planned)		1509	(1450)	1514	(1450)	3023[a]	(2900)
Demographic characteristics							
Sex, N (%)	Male	891	(59.0)	920	(60.8)	1811	(59.9)
	Female	618	(41.0)	594	(39.2)	1212	(40.1)
Age, mean (SD)	Years	67.1	(11.1)	67.2	(11.1)	67.2	(11.1)
Ethnicity, N (%)	European origin	1393	(92.3)	1374	(90.8)	2767	(91.5)
	Black	57	(3.8)	69	(4.7)	126	(4.2)
	South Asian	11	(0.7)	18	(1.2)	29	(1.0)
	Arab/Middle East	5	(0.3)	5	(0.3)	10	(0.3)
	Oriental	22	(1.5)	20	(1.3)	42	(1.4)
	Malay	8	(0.5)	14	(0.9)	22	(0.7)
	Other	13	(0.9)	14	(0.9)	27	(0.9)
Baseline characteristics							
Ejection fraction, mean (SD)		0.54	(0.09)	0.54	(0.09)	0.54	(0.09)
Diabetes mellitus, N (%)		423	(28.0)	434	(28.7)	857	(28.4)
Hypertension, N (%)		959	(63.6)	984	(65.0)	1943	(64.3)
Atrial fibrillation, N (%)		442	(29.3)	439	(29.0)	881	(29.1)
Previous MI, N (%)		659	(43.7)	681	(45.0)	1340	(44.3)
Angina pectoris, N (%)		902	(59.8)	915	(60.4)	1817	(60.1)
Stroke, N (%)		128	(8.5)	140	(9.2)	268	(8.9)
NYHA II, N (%)		905	(60.0)	931	(61.5)	1836	(60.7)
NYHA III, N (%)		584	(38.7)	556	(36.7)	1140	(37.7)
NYHA IV, N (%)		20	(1.3)	27	(1.8)	47	(1.6)
Current smoker, N (%)		187	(12.4)	222	(14.7)	409	(13.5)
Disposition							

		Placebo		Cand. cil.		Total	
N (%) of patients	Completing the study	1508	(99.9)	1512	(99.9)	3020	(99.9)
	Lost to follow-up	1	(0.01)	2	(0.01)	3	(0.01)
N analysed for safety (ITT/Safety population[b])			1509		1514		3023
N analysed for efficacy (ITT/Safety population[b])			1509		1514		3023
N analysed for efficacy (PP population)			1258		1204		2462

[a] The number of randomised patients was 3025; two of the patients were randomised by mistake. The patients got no investigational product and no data were collected, so the actual number of patients was 3023.

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

Efficacy results

Candesartan treatment non-significantly reduced cardiovascular death or hospitalisation due to CHF. This corresponds to a relative risk reduction of 11.2%. In a pre-specified covariate-adjusted analysis the hazard radio (HR) was 0.86 (95% CI 0.74 to 1.00; p=0.051). Similar results were obtained in the additional pre-specified analyses utilising the investigator-reported outcomes. According to these assessments, the relative risk reduction for cardiovascular death or hospitalisation due to CHF was 13.1% (HR 0.87, 95% CI 0.75 to 1.00; p=0.051).

The other two outcomes included in the confirmatory analysis were also non-significantly reduced by treatment with candesartan. The relative risk reduction for all-cause death or hospitalisation due to CHF was 8.3% and for CV death or hospitalisation due to CHF or non-fatal myocardial infraction (MI) 10.5%.

Table S2 Summary of efficacy results, primary and secondary variables. Comparison of candesartan versus placebo with Cox regression. ITT/Safety population (SH-AHS-0007)

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)	3023	333	366	0.888	0.766	1.031	0.118 (0.051)*
All-cause death or hospitalisation due to CHF (confirmed adjudicated)	3023	386	411	0.917	0.798	1.054	0.221 (0.108)*
CV death or hospitalisation due to CHF or non-fatal MI (confirmed adjudicated)	3023	365	399	0.895	0.777	1.032	0.126 (0.051)*

[a] Logrank test

* covariate adjusted p-value

There was no effect on the individual component of CV death (placebo, n=170; candesartan, n=170). Altogether, there were a total of 244 deaths in the control group and 237 deaths in the candesartan group due to any cause.

There was an apparent reduction in time to first hospitalisation due to CHF (relative risk reduction 14.7%, p=0.072) and non-fatal MIs (relative risk reduction 22.9%, p=0.171) during candesartan treatment.

The total number of hospitalisations due to CHF was lower in the candesartan group than in the placebo group (510 vs. 692; p=0.022).

Symptoms of heart failure according to NYHA classification were not improved by candesartan as compared to placebo (p=0.875).

There was a significant 40% reduction in the number of individuals diagnosed to have new diabetes in the candesartan group (47 vs. 77, HR 0.60; 95% CI of 0.41 to 0.86, p=0.005).

Similar number of patients in the two treatment groups developed atrial fibrillation during the follow-up period (candesartan 57, 3.8% and placebo 62, 4.1%, p=0.627).

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 1029, 68.2%; candesartan 1056, 69.7%) and over the entire study period (placebo 1060, 70.2%; candesartan 1074, 70.9%).

Serious adverse events (SAEs), fatal and non-fatal, occurred less frequently on treatment with candesartan (placebo 957, 63.4%; candesartan 904, 59.7%) as well as during the study, whether on or off treatment (placebo 1010, 66.9%; candesartan 973, 64.3%). Fatal SAEs were also less common with candesartan, on treatment with the investigational product (placebo 153, 10.1%; candesartan 129, 8.5%) but during the study the rates were 238 (15.8%) in placebo group and 244 (16.1%) in candesartan group. The most common fatal SAEs were cardiovascular events and these occurred at equal frequency in both treatment groups during study (placebo 170, 11.3%; candesartan 170, 11.2%).

A total of 461 (15.2%) of the patients permanently discontinued taking the investigational product because of an adverse event (AE) or abnormal laboratory value (placebo 192, 12.7%; candesartan 269, 17.8%).

Study investigators chose to reduce the investigational product dose because of an AE for 125 (8.3%) of patients taking placebo and 192 (12.7)% taking candesartan.

Abnormal renal function (placebo 32, 2.1%; candesartan 68, 4.5%), cardiac failure aggravated (placebo 33, 2.2%; candesartan 43, 2.8%), hypotension (placebo 18, 1.2%; candesartan 40,

2.6%) and hyperkalaemia (placebo 8, 0.5%; candesartan 23, 1.5%) were the most commonly reported AE, given as reasons for discontinuing the investigational product.

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-0007)

Category of adverse event	N (%) of patients who had an adverse event in each category[a]							
	Placebo on treatment[d] (N=1509)		Cand. cil. on treatment[d] (N=1514)		Placebo during study[b,e] (N=1509)		Cand. cil. during study[b,e] (N=1514)	
Any AE	1029	(68.2)	1056	(69.7)	1060	(70.2)	1074	(70.9)
Serious AEs	957	(63.4)	904	(59.7)	1010	(66.9)	973	(64.3)
Serious AEs leading to death	153	(10.1)	129	(8.5)	238	(15.8)	244	(16.1)
Serious AEs not leading to death	916	(60.7)	873	(57.7)	963	(63.8)	939	(62.0)
Discontinuations of investigational product due to AEs	192	(12.7)	269	(17.8)	-	-	-	-
Dose reductions of investigational product due to AEs	125	(8.3)	192	(12.7)	-	-	-	-
	Total number of adverse events							
All AEs[c]	3442		3450		3929		4138	
Serious AEs[c]	3114		2845		3604		3542	

[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-0007)

Preferred term	Placebo on treatment[b] (N=1509)		Cand. cil. on treatment[b] (N=1514)		Placebo during study[c] (N=1509)		Cand. cil. during study[c] (N=1514)	
	N	(%)	N	(%)	N	(%)	N	(%)
Cardiac failure/cardiac failure aggravated	321	(21.3)	247	(16.3)	356	(23.6)	300	(19.8)

Preferred term	Placebo on treatment[b] (N=1509)		Cand. cil. on treatment[b] (N=1514)		Placebo during study[c] (N=1509)		Cand. cil. during study[c] (N=1514)	
	N	(%)	N	(%)	N	(%)	N	(%)
Angina pectoris/angina pectoris aggravated	198	(13.1)	182	(12.0)	217	(14.4)	213	(14.1)
Hypotension	120	(8.0)	236	(15.6)	125	(8.3)	247	(16.3)
Renal function abnormal/renal dysfunction aggravated	74	(4.9)	146	(9.6)	79	(5.2)	150	(9.9)
Pneumonia	91	(6.0)	78	(5.2)	116	(7.7)	102	(6.7)
Atrial fibrillation	103	(6.8)	79	(5.2)	119	(7.9)	93	(6.1)
Myocardial infarction	85	(5.6)	74	(4.9)	101	(6.7)	87	(5.7)
Coronary artery disorder	89	(5.9)	73	(4.8)	102	(6.8)	83	(5.5)
Cerebrovascular disorder	86	(5.7)	68	(4.5)	97	(6.4)	82	(5.4)
Chest pain	71	(4.7)	72	(4.8)	81	(5.4)	82	(5.4)
Tachycardia supraventricular	76	(5.0)	55	(3.6)	88	(5.8)	60	(4.0)
Arrhythmia atrial	73	(4.8)	53	(3.5)	82	(5.4)	64	(4.2)
Sudden death	57	(3.8)	55	(3.6)	68	(4.5)	68	(4.5)
Accident and/or injury	49	(3.2)	46	(3.0)	63	(4.2)	59	(3.9)
Dizziness/vertigo	51	(3.4)	62	(4.1)	52	(3.4)	66	(4.4)
Anaemia	35	(2.3)	46	(3.0)	47	(3.1)	63	(4.2)
Dyspnoea/dyspnoea (aggravated)	48	(3.2)	39	(2.6)	51	(3.4)	46	(3.0)

[a] This table uses a cut-off ≥3.0% in the total population during study (N=3023).

[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 2371 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 (1118) during the study period than the placebo-treated patients (1253) as well as a shorter length of stay (9166 vs. 10471 days).

Date of the report

23 February 2004