AstraZeneca

Drug product	Atacand®	**SYNOPSIS**	
Drug substance	Candesartan cilexetil		
Document No.	SH-AHS-0006		
Edition No.	Final		
Study code	SH-AHS-0006		
Date	17 February 2004		

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

Study of candesartan in patients with heart failure who are treated with ACE inhibitors and have depressed left ventricular systolic function (CHARM Added)

International Co-ordinating investigator

Study sites

This study was conducted in 25 countries at a total of 473 sites (Australia 18, Belgium 14, Canada 53, Czech Republic 12, Denmark 19, Finland 6, France 25, Germany 47, Hungary 9, Iceland 2, Italy 6, Malaysia 3, Netherlands 20, Norway 18, Poland 13, Portugal 8, Russia 4, Singapore 3, South Africa 10, Spain 6, Sweden 16, Switzerland 9, United Kingdom/Ireland 29 and USA 123 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, reduces 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:

- reduces the combined endpoint of all-cause mortality or hospitalisation for the management of chronic heart failure.
- reduces 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:

- reduced the combined endpoint of CV mortality, or hospitalisation for the management of CHF or non-fatal MI, 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 MIs.
- 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-CV 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 depressed left ventricular (LV) systolic function and ejection fraction (EF) $\leq$40% treated with an angiotensin converting enzyme (ACE) inhibitor.

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 treated with ACE inhibitors.

A total of 2550 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 16 to 18%, at a statistical power of at least 85%. The patients were to be equally distributed between the two treatment groups. The actual number of randomised patients was 2548.

Investigational product: dosage, mode of administration and batch numbers

The active treatment group received candesartan cilexetil (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 8 months. Individual time in the study for surviving patients not lost to follow-up could last from 41 to 48 months depending on when a patient was randomised. The median follow-up time was 41.1 months in the candesartan group and 40.9 months in the placebo group. The median duration of exposure of the investigational product was 40.4 months in the placebo group and 40.3 months in the candesartan group.

Criteria for evaluation (main variables)

<u>Efficacy</u>

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

– Time from randomisation to all-cause death or to hospitalisation due to chronic heart failure, whichever occurred first.

– Time from randomisation to cardiovascular death or to hospitalisation due to chronic heart failure, or a non-fatal myocardial infarction, whichever occurred first.

Safety

- Investigational product discontinuation.
- Reduction in dose of investigational product.
- Occurrence of non-CV 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 in NYHA functional class II-IV. Baseline characteristics were representative of a population of patients with chronic heart failure and depressed LV systolic function and were well balanced between the treatment groups. In general, patients were also receiving

aggressive heart failure treatment with combinations of diuretics, beta-blockers and digitalis as well as individually optimised doses of ACE inhibitors.

A total of 1096 (85.9%) patients in the candesartan group started treatment on 4 mg once daily and 180 (14.1%) patients started on 8 mg once daily. A total of 1756 (68.9%) patients (candesartan 857, 67.2%; placebo 899, 70.7%) received the investigational product for 24 months or more. 53.6% of the candesartan patients (60.5% 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 23.5 mg at 6 months and 23.1 mg at last value carried forward.

Table S1 Patient population and disposition

		Placebo		Cand. cil.		Total	
Population							
N randomised (N planned)		1272	(1275)	1276	(1275)	2548	(2550)
Demographic characteristics							
Sex, N (%)	Male	1000	(78.6)	1006	(78.8)	2006	(78.7)
	Female	272	(21.4)	270	(21.2)	542	(21.3)
Age mean (SD)	Years	64.1	(11.3)	64.0	(10.7)	64.1	(11.0)
Ethnicity, N (%)	European origin	1164	(91.5)	1143	(89.6)	2307	(90.5)
	Black	62	(4.9)	65	(5.1)	127	(5.0)
	South Asian	8	(0.6)	19	(1.5)	27	(1.1)
	Arab/Middle East	4	(0.3)	8	(0.6)	12	(0.5)
	Oriental	13	(1.0)	22	(1.7)	35	(1.4)
	Malay	7	(0.6)	11	(0.9)	18	(0.7)
	Other	14	(1.1)	8	(0.6)	22	(0.9)
Baseline characteristics							
Ejection fraction, mean (SD)		0.28	(0.07)	0.28	(0.08)	0.28	(0.07)
Diabetes mellitus, N (%)		382	(30.0)	376	(29.5)	758	(29.7)
Hypertension, N (%)		619	(48.7)	609	(47.7)	1228	(48.2)
Atrial fibrillation, N (%)		341	(26.8)	346	(27.1)	687	(27.0)
Previous MI, N (%)		703	(55.3)	714	(56.0)	1417	(55.6)
Angina pectoris, N (%)		684	(53.8)	666	(52.2)	1350	(53.0)
Stroke, N (%)		112	(8.8)	108	(8.5)	220	(8.6)
NYHA II, N (%)		302	(23.7)	312	(24.5)	614	(24.1)
NYHA III, N (%)		925	(72.7)	931	(73.0)	1856	(72.8)
NYHA IV, N (%)		45	(3.5)	33	(2.6)	78	(3.1)
Current smoker, N (%)		235	(18.5)	194	(15.2)	429	(16.8)
Disposition							
N (%) of patients	Completing the study	1271	(99.9)	1273	(99.8)	2544	(99.8)
	Lost to follow-up	1		3		4	
N analysed for safety (ITT/Safety population[a])			1272		1276		2548
N analysed for efficacy (ITT/Safety population[a])			1272		1276		2548
N analysed for efficacy (PP population)			1072		986		2058

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 14.7%. 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 12.8% and for CV death or hospitalisation due to CHF or non-fatal MI 14.8%.

Table S2 Summary of efficacy results, primary and secondary variables. Comparison of candesartan versus placebo with Cox regression. ITT/Safety population (SH-AHS-0006)

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)	2548	483	538	0.853	0.754	0.964	0.011
All-cause death or hospitalisation due to CHF (confirmed adjudicated)	2548	539	587	0.871	0.775	0.980	0.021
CV death or hospitalisation due to CHF or non-fatal MI (confirmed adjudicated)	2548	495	550	0.852	0.755	0.962	0.010

[a] Logrank test

The individual components CV death (relative risk reduction 15.8%, p=0.029), hospitalisation due to CHF (relative risk reduction 17.5%, p=0.014), all-cause death (relative risk reduction 11.5%, p=0.086) and non-fatal MI (relative risk reduction 48.8%, p=0.006) all contributed to the benefit of candesartan as described by the respective composite endpoints.

Symptoms of heart failure according to NYHA classification improved significantly during candesartan treatment (p=0.020).

An equal number of patients in both treatment groups had a diagnosed onset of diabetes during the follow-up period (candesartan 72, 8.0%, placebo 72 8.1%, HR 0.98, 95% CI 0.70 to 1.35, p=0.88).

Slightly fewer patients in the candesartan group than in the placebo group developed atrial fibrillation) during the follow-up period (candesartan 73, 5.7%, placebo 84, 6.6%, p=0.354).

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 979, 77.0%; candesartan 1007, 78.9%) and over the entire study period (placebo 992, 78.0%; candesartan 1026, 80.4%).

Serious adverse events (SAEs), fatal and non-fatal, occurred less frequently on treatment with candesartan (placebo 930, 73.1%; candesartan 883, 69.2%) and at equal frequency during the study, whether on or off treatment (placebo 966, 75.9%; candesartan 969, 75.9%). Fatal SAEs were also less common with candesartan, on treatment with the investigational product (placebo 276, 21.7%; candesartan 210, 16.5%) as well as during the study (placebo 413, 32.5%; candesartan 377, 29.5%). The most common fatal SAEs were cardiovascular events

and these occurred less frequently in the candesartan treatment group during study (placebo 347, 27.3%; candesartan 302, 23.7%).

A total of 534 (21.0%) of the patients permanently discontinued taking the investigational product because of an adverse event (AE) or abnormal laboratory value (placebo 224, 17.6%; candesartan 310, 24.3%).

Study investigators chose to reduce the investigational product dose because of an AE for 123 (9.7%) of patients taking placebo and 220 (17.2)% taking candesartan.

Abnormal renal function (placebo 53, 4.2%; candesartan 105, 8.2%), cardiac failure aggravated (placebo 81, 6.4%; candesartan 69, 5.4%), hypotension (placebo 44, 3.5%; candesartan 69, 5.4%) and hyperkalaemia (placebo 11, 0.9%; candesartan 49, 3.8%) 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, i.e. 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-0006)

Category of adverse event	N (%) of patients who had an adverse event in each category[a]							
	Placebo on treatment[d] (N=1272)		Cand. cil. on treatment[d] (N=1276)		Placebo during study[b,e] (N=1272)		Cand. cil. during study[b,e] (N=1276)	
Any AE	979	(77.0)	1007	(78.9)	992	(78.0)	1026	(80.4)
Serious AEs	930	(73.1)	883	(69.2)	966	(75.9)	969	(75.9)
Serious AEs leading to death	276	(21.7)	210	(16.5)	413	(32.5)	377	(29.5)
Serious AEs not leading to death	842	(66.2)	802	(62.9)	870	(68.4)	874	(68.5)
Discontinuations of investigational product due to AEs	224	(17.6)	310	(24.3)	-	-	-	-
Dose reductions of investigational product due to AEs	123	(9.7)	220	(17.2)	-	-	-	-
	Total number of adverse events							
All AEs[c]	3573		3526		4105		4229	
Serious AEs[c]	3207		2929		3745		3639	

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, i.e. 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-0006)

Preferred term	Placebo on treatment[b] (N=1272)		Cand. cil. on treatment[b] (N=1276)		Placebo during study[c] (N=1272)		Cand. cil. during study[c] (N=1276)	
	N	(%)	N	(%)	N	(%)	N	(%)
Cardiac failure/cardiac failure aggravated	435	(34.2)	350	(27.4)	472	(37.1)	421	(33.0)
Hypotension	176	(13.8)	288	(22.6)	184	(14.5)	296	(23.2)
Angina pectoris/angina pectoris aggravated	153	(12.0)	127	(10.0)	169	(13.3)	150	(11.8)
Sudden death	140	(11.0)	114	(8.9)	174	(13.7)	143	(11.2)
Renal function abnormal/renal dysfunction aggravated	115	(9.0)	192	(15.0)	119	(9.4)	196	(15.4)
Arrhythmia ventricular	107	(8.4)	78	(6.1)	121	(9.5)	88	(6.9)
Pneumonia	88	(6.9)	57	(4.5)	108	(8.5)	76	(6.0)
Hyperkalaemia	44	(3.5)	121	(9.5)	46	(3.6)	123	(9.6)
Myocardial infarction	73	(5.7)	60	(4.7)	88	(6.9)	70	(5.5)

Preferred term	Placebo on treatment[b] (N=1272)		Cand. cil. on treatment[b] (N=1276)		Placebo during study[c] (N=1272)		Cand. cil. during study[c] (N=1276)	
	N	(%)	N	(%)	N	(%)	N	(%)
Atrial fibrillation	69	(5.4)	52	(4.1)	73	(5.7)	66	(5.2)
Arrhythmia atrial	61	(4.8)	59	(4.6)	71	(5.6)	67	(5.3)
Tachycardia ventricular/arrhythmia/ arrhythmia aggravated	63	(5.0)	52	(4.1)	68	(5.3)	65	(5.1)
Cerebrovascular disorder	48	(3.8)	55	(4.3)	58	(4.6)	69	(5.4)
Chest pain	64	(5.0)	45	(3.5)	71	(5.6)	54	(4.2)
Coronary artery disorder	42	(3.3)	58	(4.5)	50	(3.9)	73	(5.7)
Syncope	45	(3.5)	49	(3.8)	49	(3.9)	59	(4.6)
Tachycardia supraventricular	46	(3.6)	47	(3.7)	50	(3.9)	54	(4.2)
Cardiomyopathy	38	(3.0)	33	(2.6)	48	(3.8)	51	(4.0)
Dizziness/vertigo	35	(2.8)	49	(3.8)	40	(3.1)	57	(4.5)
Pulmonary oedema	41	(3.2)	39	(3.1)	47	(3.7)	48	(3.8)
Renal failure acute	29	(2.3)	45	(3.5)	38	(3.0)	54	(4.2)
Anaemia	36	(2.8)	35	(2.7)	43	(3.4)	46	(3.6)
Accident and/or injury	32	(2.5)	34	(2.7)	43	(3.4)	44	(3.4)
Diabetes mellitus/diabetes mellitus aggravated	41	(3.2)	30	(2.4)	42	(3.3)	37	(2.9)
Dehydration	18	(1.4)	40	(3.1)	22	(1.7)	55	(4.3)

a This table uses a cut-off of ≥3.0% in the total population during study (N=2548).

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 2673 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 (1177) during the study period than the placebo-treated patients (1496) as well as a shorter length of stay (10061 vs. 12073 days).

Date of the report

17 February 2004