9.4 Labeling Review

The following are suggested changes in the applicant's proposed labelling (under the heading mentioned). Deletions are indicated by ~~strikethrough~~ and additions are indicated by double underlining.

(Please refer to Appendix 10.2 for line by line review and annotations.)

(1) Special Populations

Heart Failure— The pharmacokinetics of candesartan were linear in patients with heart failure (NYHA class II and III) after candesartan cilexetil doses of 4, 8, and 16 mg. After repeated dosing, the AUC was approximately doubled in ~~these~~ patients with heart failure ≥ 65 years old compared with healthy, younger subjects (based on studies EC602, EC605-A, EC608). (See DOSAGE AND ADMINISTRATION, Heart Failure).

(2) Pharmacodynamics

In heart failure patients, candesartan cilexetil administration at doses of 8 mg and 16 mg resulted in ~~dose-related~~ significant decreases in systemic vascular resistance and pulmonary capillary wedge pressure (based on studies EC602, EC605).

In heart failure patients, candesartan cilexetil 8 mg in combination with enalapril 20 mg resulted in a ~~dose-related~~ significant decrease in left ventricular end systolic volume compared with enalapril 20 mg alone. Co-administration of metoprolol succinate (extended-release tablets) with candesartan cilexetil plus enalapril resulted in a decrease in left ventricular systolic volume and an increase in left ventricular ejection fraction compared with the combination of candesartan plus enalapril.

(3) INDICATIONS AND USAGE

Heart Failure

ATACAND is indicated for the treatment of heart failure (NYHA class II-IV) with left ventricular systolic dysfunction (ejection fraction (40%). ATACAND reduces the risk of death from cardiovascular causes, ~~and~~ improves symptoms ~~in patients with left ventricular systolic dysfunction,~~ and reduces hospitalizations for heart failure in patients with depressed ~~or preserved~~ left ventricular systolic function. These effects occur in patients receiving other heart failure treatments with or without ACE inhibitors, including patients intolerant to ACE inhibitors, and with or without beta-blockers (see Clinical Trials).

(4) WARNINGS

Hypotension in Heart Failure Patients

Caution should be observed when initiating therapy in patients with heart failure. Patients with heart failure given ATACAND commonly have some reduction in blood pressure.

In patients with symptomatic hypotension this may require temporarily reducing the dose of ATACAND, or diuretic, or both, and/or volume repletion. In the CHARM program, hypotension was the second most frequently reported adverse event (aggravated heart failure was the most frequently reported adverse event), constituting 18.8% of patients on candesartan versus 9.8% of patients on placebo (*based on Table 22, page 59, of ISS*); the incidence of hypotension leading to drug discontinuation in candesartan-treated patients was 4.1% compared with 2.0% in placebo-treated patients. Monitoring of blood pressure is recommended during dose escalation and periodically thereafter.

(5) PRECAUTIONS

General

Impaired Renal Function— As a consequence of inhibiting the renin-angiotensin-aldosterone system, ……..

In heart failure patients treated with ATACAND, increases in serum creatinine may occur. Dosage reduction, and/or discontinuation of the diuretic, and/or ATACAND, and/or volume repletion may be required. In the CHARM program, the incidence of abnormal renal function (e.g., creatinine increase) was 12.5% in patients treated with candesartan versus 6.3% inpatients treated with placebo (*based on Table 22, page 59, of ISS*); the incidence of abnormal renal function (e.g., creatinine increase) leading to drug discontinuation in candesartan-treated patients was 6.3% compared with 2.9% in placebo-treated patients. Evaluation of patients with heart failure should always include assessment of renal function. Monitoring of serum creatinine is recommended during dose escalation and periodically thereafter.

(6) Hyperkalemia

In heart failure patients treated with ATACAND, hyperkalemia may occur, especially when taken concomitantly with ACE inhibitors and potassium-sparing diuretics such as spironolactone. In the CHARM program, the incidence of hyperkalemia was 6.3% in patients treated with candesartan versus 2.1% in patients treated with placebo (*based on Table 22, page 59, of ISS*); the incidence of hyperkalemia leading to drug discontinuation in candesartan-treated patients was 2.4% compared with 0.6% in placebo-treated patients. During treatment with ATACAND in patients with heart failure, monitoring of serum potassium is recommended during dose escalation and periodically thereafter.

(7) Geriatric Use

Heart Failure

Of the 7599 patients with heart failure in the 3 trials of the CHARM program, 4343 (57 %) were age 65 years or older and 1736 (23 %) were 75 years or older. ~~In general, there were no notable differences in efficacy or safety between older and younger patients~~. *(There is no evidence for this statement.)* In patients ≥ 75 years of age, the incidence of drug discontinuations due to adverse events was higher for those treated with ATACAND or placebo compared with patients <75 years of age. In these patients, the most common adverse events leading to drug discontinuation at an incidence of at least 3%, and more

frequent with ATACAND than placebo, were abnormal renal function (7.9% vs. 4.0%), hypotension (5.2% vs. 3.2%) and hyperkalemia (4.2% vs. 0.9%). In addition to monitoring of serum creatinine, potassium, and blood pressure during dose escalation and periodically thereafter, greater sensitivity of some older individuals with heart failure must be considered.

(8) ADVERSE REACTIONS

Heart Failure

The adverse event profile of ATACAND in heart failure patients was consistent with the pharmacology of the drug and the health status of the patients. In the CHARM program, comparing ATACAND in total daily doses up to 32 mg once daily (n=3803) with placebo (n=3796), 21.0% of ATACAND patients discontinued for adverse events vs. 16.1% of placebo patients.

In the CHARM program, adverse events leading to drug discontinuation at an incidence of at least 1% and more frequent with ATACAND than placebo were abnormal renal function (6.3% vs. 2.9%), hypotension (4.1% vs. 2.0%), and hyperkalemia (2.4% vs. 0.6%). Aggravated heart failure was found to lead to study drug discontinuation at an incidence of 4.3% (versus 4.9% with placebo); also, aggravated heart failure was the most frequent adverse event (observed in 21.9% of patients treated with candesartan versus 28.3% of patients treated with placebo). (*Based on Table 44, page 91 of ISS*)

(9) DOSAGE AND ADMINISTRATION

Heart Failure

The initial dose for treating heart failure is 4 mg once daily. The target dose is 32 mg once daily, which is achieved by doubling the dose at approximately 2 week intervals, as tolerated by the patient carefully monitoring the heart rate, blood pressure, serum creatinine and serum potassium to hold or step down the dose if necessary. ATACAND can be administered with other heart failure treatments including ACE inhibitors, beta-blockers, diuretics, and/or digoxin~~, and/or aldosterone antagonist~~. (*No beneficial effect on CV mortality or CHF hospitalization was found with candesartan treatment among CHF patients who were receiving spironolactone – See Figures 1 and 2 in the label.*)

9.5 Comments to Applicant

Please also see section 8.6 (Issues related to the role of angiotensin receptor blockers in patients with heart failure and left ventricular dysfunction), section 9.3 (Recommendations on Postmarketing activities) and section 9.3.1 (Risk Management Activity) above. In addition, the following information is communicated to the sponsor:

(1) In my factorial analysis tables - (Table 38 and Table 37) - candesartan added to high dose ACE inhibitors (643 patients with 232 (36.1%) events) versus candesartan added to low dose ACE inhibitors (633 patients with 251 (39.7%) events) show a relative risk reduction of 12.6%. The sample sizes are too small for the differences to be significant.

Since about 50% of these CHF patients are on 32 mg dose of candesartan, determine from the CHARM-Added study data the proportion of patients receiving low dose (4 or 8 mg) or high dose (16 or 32 mg) candesartan at 6 months or at the time of the event in the each of above two populations of patients (i.e., those receiving high dose ACE inhibitors and those receiving low dose ACE inhibitors).

For each of the four sub-populations of patients identified above (i.e., (i) high dose ACE-inhibitor plus high dose candesartan, (ii) high dose ACE-inhibitor plus low dose candesartan, (iii) low dose ACE-inhibitor plus high dose candesartan, and (iv) low dose ACE-inhibitor plus low dose candesartan), determine the primary and secondary efficacy endpoints.

Analyze data in each of the four sub-population to determine at which doses of ACE-inhibitor and/or candesartan the adverse events of (a) aggravated heart failure, (b) hypotension, (c) hyperkalemia, (d) deterioration of renal function, (e) study drug discontinuation, and (f) reduction in dose of study drug, were most frequently observed.

Make similar sub-group analyses with regard to use of β-blockers and aldosterone antagonists. This will help understand the CHARM Program results better to derive the optimal dose combinations to be recommended for treatment of heart failure.

(2) Use the above information to plan a prospective clinical trial to determine the optimal dose combination of ACE-inhibitor and candesartan that will provide the most benefit (clinical improvement, decrease hospitalization and increased survival) with the least risk (of hypotension, hyperkalemia, deterioration of renal function).

(3) The above comments are made in the context of a concept (not yet proven) that using lower doses of a combination of an ACE-inhibitor, a β-blockers and an angiotensin receptor blocker may improve symptoms and survival and reduce hospitalizations and adverse events to a greater extent than using high doses of once drug such as an ACE inhibitor only. This concept is based on the finding that in patients receiving a low or intermediate dose of an ACE inhibitor, adding a β-blocker may improve symptoms and reduce the risk of death and hospitalizations to a greater extent than increasing the dose of the ACE-inhibitor to a maximally tolerated dose[44] (please see Table 113).

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Appendix PK1 Study EC602

Study of the acute hemodynamic effects of 4mg, 8 mg and 16 mg candesartan cilexetil in patients with impaired left ventricular function (Heart Failure – NYHA Class II/III)

This is a PK/PD study of candesartan, performed as a single- (oral) dose, randomized, double-blind, placebo controlled, Phase II study. It was conducted from May 19 through December 10, 1995. The principal investigator is Prof. Dr. T. Lüscher. All of the study sites are in Germany. The primary objective was to evaluate the dose relationship of placebo vs. candesartan cilexetil (in doses of 4mg, 8mg and 16 mg) in patients with CHF on acute hemodynamic effects (change in mean pulmonary capillary wedge pressure ($PCWP_{mean}$) and pulmonary artery systolic pressure (PAP_{sys}) that were measured via Swann-Ganz catheterization. The secondary efficacy parameters included neurohormonal responses (change in levels of rennin, angiotensin II, aldosterone, adrenalin and noradrenalin at different time points). Blood samples were also taken for pharmacokinetics.

Sixty (60) Caucasian patients 26-77 years old, with CHF (New York Heart Association (NYHA) Class II/III, $PAP_{sys} \geq 25$mmHg and/or PCWP >13mmHg) were consented, 57 were randomized of which one withdrew, and 56 patients completed the study. CHF was due to coronary artery disease (30 patients) cardiomyopathy (24 patients), hypertension (5 patients), valvular disease (1 patient) and unknown (4 patients). Several also had co-morbid illnesses such as diabetes, renal insufficiency, chronic airways obstruction, etc.

There were 6 subjects with major protocol violations (patient 01C received enalapril during the study, patient 17B had NYHA Class I CHF, and four patients (02B, 03B, 05B and 21B) had incompletely recorded PCWP at a majority of time points, and latter three also at baseline.

Patients received a single oral dose of placebo or candesartan 4 mg, 8 mg or 16 mg. The serum concentrations of CV-11974 were determined on day 1, at (0h) pre-dose and at 2h, 4h, 8h and 24h post-dose. $PCWP_{mean}$ and PAP_{mean}, measured via a Swann-Ganz catheter, were used to evaluate the hemodynamic effects of candesartan in patients with CHF.

The serum concentration of CV-11974 was determined by Bio-Pharma using a high performance liquid chromatography (HPLC) method. The following pharmacokinetic parameters were then determined: C_{max}/T_{max} (ng/ml;h), AUC_{0-24} (ng.h/ml), AUMC(ng.h^2/ml), MRT (h)(calculated as AUMC/AUC), K_{el} (h^{-1}) (computed by linear regression over the last concentration data points showing a linear trend as a function of time in semi-log plots), and $T_{½el}$ (h) (calculated as K_{el} /0.693).

Table 141 shows the PK parameters for candesartan in patients with CHF.

Table 141 PK parameters for candesartan

PK parameters for candesartan: All patients with measurements

Parameter	Dose of CC	Geometric mean	IQR (Q3-Q1)
AUC (ng•h/ml)	4mg	430.3	627-290
	8mg	909.7	1186-788
	16mg	1823.4	2368-1447
C_{max} (ng/ml)	4mg	40.0	53.6-31.1
	8mg	74.7	106-57
	16mg	163.2	217-134
$t_{1/2}$ (hours)	4mg	8.1	10.8-6.8
	8mg	10.8	14.5-7.0
	16mg	9.1	9.4-6.5

IQR interquartile range
Data source: Clinical Study Report EC602 Table 131 Appendix IX(VIII)

$t_{max\ (approx)}$	4mg	2-8 hrs
	8mg	2-4 hrs
	16mg	4 hrs

Data source: Clinical Study Report EC602 Table 130 Appendix IX(VIII)

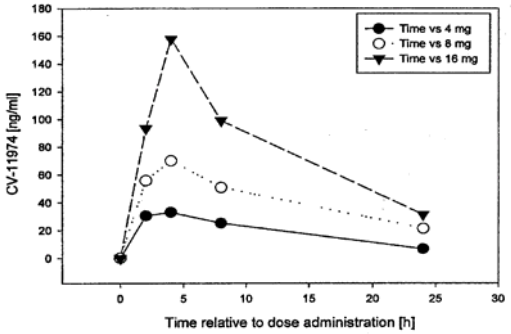


Figure 79 Mean Serum Concentration of CV-11974 (Safety population)

In all patients who received candesartan cilexetil, CV-11974 was detected in the serum samples. Serum samples of all placebo treated patients were free of CV-11974. The highest plasma levels of CV-11974 were measured at 4 h. The mean serum concentrations of CV-11974 are given in Figure 79 (above). The mean AUC_{0-24} and C_{max} values showed a linear correlation to dose (Figure 80 and Figure 81, below).

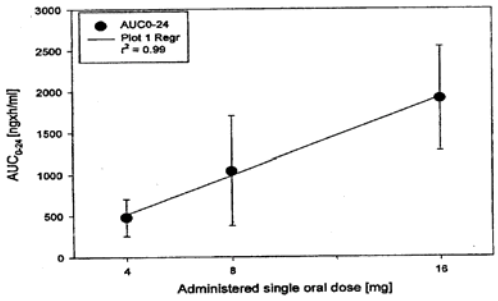


Figure 80 AUC_{0-24} vs. administered dose (Efficacy (ITT) population)

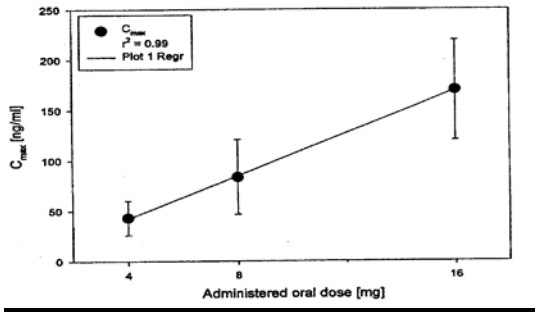


Figure 81 C_{max} vs. administered dose (Efficacy (ITT) population)

10.1.2 Appendix PK2 Study EC605-A (PK component)

Study of the 3- month hemodynamic effects of 2 mg, 4 mg, 8 mg and 16 mg candesartan cilexetil in patients with impaired left ventricular function (Heart failure – NYHA class II/ III). PK Analysis.

This is another PK/PD study performed as a randomized, double blind, placebo- controlled, parallel-group study. The primary objective of the study was determination of the 3- month dose-dependent hemodynamic effects of 2 mg, 4 mg, 8 mg and 16 mg candesartan cilexetil in patients with impaired left ventricular function (Heart failure – NYHA class II/ III). In addition, the pharmacokinetics of candesartan was also evaluated. The study was conducted from February 20, 1997 through January 14, 1999, at 39 centers in Europe and South Africa. The principal investigator is Dr. Vesellin Mitrovic.

218 patients (mean age 56 years, 85% male) with mild to moderate symptomatic CHF (NYHA class II or III, LVEF ≤40%) were randomized; 44 were treated with placebo and 174 patients treated with candesartan. Of 174 patients treated with candesartan, pharmacokinetic analysis for 15 patients had missing PK values at visit 2 or visit 6; thus, 159 patients had evaluable pharmacokinetic profiles at baseline and 138 at final visit.

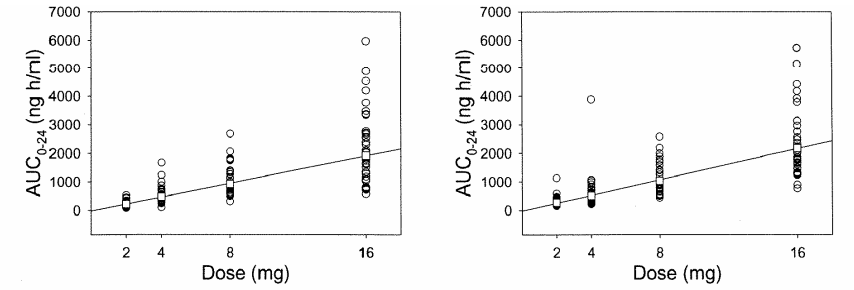
There were 12 (5.5%) major protocol violations: eight (8) patients took prohibited concomitant medications, three (3) patients had PCWP < 13mmHg at visit 2, two (2) patient had PCAP values that were not plausible, and one (1) subject (on 16 mg candesartan) had measurements taken without taking drug.

After a 2- week run- in period, patients were randomized to a 12 week treatment period at doses of candesartan 2 mg, 4 mg, 8 mg or 16 mg. Blood for pharmacokinetics was taken at baseline (visit 2) and the final visit (visit 6, or the early termination visit) pre-dose and at 2, 4, 8, and 24 hours post-dose. The serum levels of CV-11974 (active metabolite of candesartan cilexetil) were determined by Pharma Bio Research International B.V., Zuidlaren, NL. If no pre-dose sample was available at visit 2, the concentration was set to zero at 0 hours. AUC_{0-24}, C_{max} and t_{max} were calculated from the concentration versus time profiles for each evaluable patient.

Table 142 Summary of pharmacokinetic data (geometric mean, min, max)

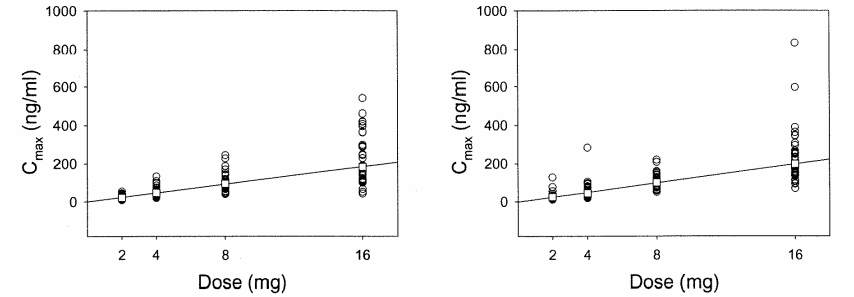
Dose (mg)	Visit 2 C_{max} (ng/ml)	Visit 2 AUC_{0-24} (ng h/ml)	Visit 2 t_{max}* (h)	Visit 6 C_{max} (ng/ml)	Visit 6 AUC_{0-24} (ng h/ml)	Visit 6 t_{max}* (h)
2	21.7 (8.2, 53.9)	225.8 (82.7, 531.1)	4.2 (2.1, 12)	25.2 (10.8, 128)	281.4 (158.8, 1134.7)	4.2 (2.1, 8.3)
4	47.2 (19.1, 133)	477.6 (103, 1669.6)	4.2 (2.3, 12)	44.8 (17.8, 284)	514.7 (223.6, 3882.4)	4.2 (2, 8.4)
8	95.1 (40, 245)	925.2 (312, 2675.1)	4 (2, 8.4)	100.5 (49.6, 220)	1036.2 (448.1, 2578.5)	4.3 (2, 8.4)
16	184 (43, 541)	1923.5 (580.4, 5974.1)	4.3 (2.1, 16.1)	197.5 (68.8, 834)	2180.3 (766.5, 5974.1)	4.2 (2, 12.1)

*Median, (min, max)



Plots of AUC_{0-24} of CV-11974 versus dose following oral administration of candesartan at doses of 2, 4, 8 and 16 mg o.d. Individual subject values (○) and geometric mean values (□).

Figure 82 AUC_{0-24} versus dose on visits 2 (left) and 6 (right)



Plots of C_{max} of CV-11974 versus dose following oral administration of candesartan at doses of 2, 4, 8 and 16 mg o.d. Individual subject values (○) and geometric mean values (□).

Figure 83 C_{max} versus dose on visits 2 (left) and 6 (right)

A summary of key pharmacokinetic data is provided in Table 142, and plots of AUC_{0-24} and C_{max} versus dose are presented in Figure 82 and Figure 83, respectively. At single dosing, candesartan treatment in patients with CHF exhibited dose- proportional increases in AUC_{0-24}, and C_{max}. A similar pattern was observed after multiple dosing for 12 weeks with no large accumulations of candesartan. Independent of dose, t_{max} was approximately 4 hours after single and multiple dosing.

Pooled Pharmacokinetic data (Studies EC602 and EC605-A)

When the pharmacokinetic data are pooled for CHF patients in studies EC602 and EC605-A, the $AUC_{0\text{-}24h}$ vs. dose of candesartan remained linear (Figure 84, below)

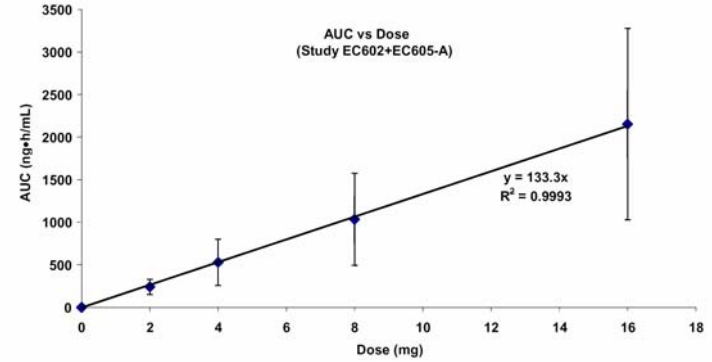


Figure 84 $AUC_{0\text{-}24h}$ (following single doses of candesartan) vs. dose of candesartan cilexetil in patients with CHF (studies 602 and 605-A)

10.1.3 Appendix PK3 Study EC608

A double-blind, multiple-dose, randomized study to evaluate the interaction of 8 mg candesartan cilexetil and 10 mg enalapril after single dosing and as a 3-way crossover at steady state plasma concentration in patient with mild to moderate congestive heart failure (NYHA Class II/III)

This PK study was conducted from February 25, 1997 through February 2, 1998. The principal investigator is Dr. K.M. Eckl. The study sites are in Germany and Poland. The study was performed in two parts after one week of standardization treatment with enalapril 10 mg and HCTZ 25 mg once/day. In the first part (single dosing), patient were randomized to 3 parallel groups receiving candesartan 8 mg alone, candesartan 8 mg plus enalapril 10 mg, or enalapril 10 mg alone. The second part (3 periods of 7 days each) consisted of a randomized, double-blind, crossover, multiple dosing design to evaluate any interaction between candesartan and enalapril.

The primary objective was to evaluate the possible pharmacokinetic interaction of candesartan and enalapril by analyzing candesartan and enalaprilat (active metabolite of enalapril) after single-dose and at steady state. A secondary objective was to obtain safety information on candesartan and assess effect of renal function (and heart failure) on the pharmacokinetics of both drugs. Prohibited concomitant medications were digitalis, β-blockers and Ca-channel blocking agents.

Thirty-one Caucasian patients (mean (SD) age 60.3 (9.9) years), with differing degrees of renal impairment (renal impairment defined as: normal function, $CL_{cr} > 95$ mL/min/1.73m^2; mild renal impairment as 60mL/min/ 1.73m^2 < $CL_{cr} \leq 95$ mL/min/ 1.73m^2; moderately impaired renal function 30 mL/min/ 1.73m$^2 \leq CL_{cr} \leq 60$ mL/min/1.73m^2), with CHF (NYHA Class II/III, Left

ventricular ejection fraction (LVEF) 21-44 (mean (SD) 35.97 (6.35)) were enrolled, one patient discontinued after the first part of the clinical trial, and 30 patients completed the study.

There were several protocol deviations: patients 016, 019, 020 and 021 received enalapril and HCTZ during the standardization period, patients 002 and 003 had their study medication interchanged during Part II, Period 1, patient 017 received captopril and HCTZ on non-kinetic sample days 14-18 and kinetic sample days 20-27, patient 021 was 81 years old, patients 010, 024, 026, 028 and 033 had positive hepatitis B serology, patient 012 was enrolled with missing hematology data at screening, and patient 025 had all laboratory parameters (except serum creatinine) missing at screening.

Candesartan and enalaprilat (active metabolite of enalapril) were analyzed in blood samples in Part I at (0h) pre-dose and at 1h, 2h, 3h, 4h, 6h, 8h, 10h and 12h post-dose on day 1, and at 24h, 48 h and 72 post-dose in the mornings of days 2, 3 and 4 respectively. For Part II, blood samples were collected on Days 13 and 22 for Periods 1 and 2 of Part 2, on Day 31 for Period 3 of Part II. On Days 10, 19 and 28 in Part II, blood was collected over 12 hours (at 1h, 2h, 3h, 4h, 6h, 8h, 10h and 12h post-dose). 24h post-dose samples were collected on Days 11, 20 and 29, and 48h post-dose samples were collected on Days 12, 21 and 30. Blood samples for trough concentrations were taken pre-dose on Days 8, 9 and 10.

The serum concentrations of CV-11974 were determined using an HPLC-fluorescence method. For enalaprilat levels, a radioimmunoassay with a ^{125}I-enalaprilat tracer was used. The following pharmacokinetic parameters were then determined: AUC_{0-72}, $C_{max,}$ $C_{min,}$ $C_{pre,}$ $T_{max,}$ and $t_{½}$. Table 143 shows the PK parameters for candesartan and enalapril in patients with CHF.

Table 143 PK parameters of candesartan and enalaprilat (by ANOVA)

Results of ANOVA candesartan and enalaprilat on PK parameters					
		Single dose		Steady state	
		Ratio coad:mon[1]	90%CI	Ratio coad:mon[1]	90%CI
Candesartan	AUC_{0-72} (ng•h/ml)	1.23	(0.88, 1.73)	1.10	(1.01,1.20)
	C_{max} (ng/ml)	1.17	(0.81,1.70)	1.09	(0.97,1.22)
Enalaprilat	AUC_{0-72} (ng•h/ml)	1.03	(0.80,1.34)	1.10	(1.02,1.18)
	C_{max} (ng/ml)	1.09	(0.79,1.50)	1.10	(1.01,1.19)
Conclusions:		Marginal increases in AUC_{0-72} and C_{max} considered not clinically significant		Point estimates and 90% CI for AUC_{0-72} and C_{max} were contained within the acceptance range of 80-125%	

[1] Geometric mean
Data source: Clinical Study Report EC608 Table 6.3 and Table 6.6

At steady state no evidence of an interaction between candesartan and enalaprilat was found: the geometric means (90% CI) for AUC_{0-72} and C_{max} for co-administration versus candesartan monotherapy were at steady state 1.10 (1.01-1.20) and 1.09 (0.97-1.22), respectively (Table 143). Similarly, the geometric means (90% CI) for AUC_{0-72} and C_{max} for co-administration

versus enalapril monotherapy were at steady state 1.10 (1.02-1.18) and 1.10 (1.01-1 .19), respectively. There were no changes in $t_{½}$.

Compared to patients with normal renal function, after repeated dose monotherapy, statistically significant increases in AUC_{0-72} were observed with candesartan 8 mg (36% and 65%) and enalapril 10 mg (8% and 49%) in patients with mild or moderate renal impairment (Table 144).

Table 144 Summary statistics for candesartan and enalaprilat pharmacokinetic parameters separated by renal groups after repeat dose administration

	Renal Impairment	n	CV-11974 Geom. Mean	p-value	n	Enalaprilat Geom. Mean	p-value
AUC_{0-72}	none	6	954		6	706	
	mild	12	1296	0.03+	12	761	0.02+
	moderate	12	1576		13	1054	
C_{max}	none	6	67.3		6	60.4	
	mild	12	77.1	0.04+	12	65.2	0.09+
	moderate	12	104.6		13	81.6	
$t_{1/2}$	none	6	9.6 *		5	9.4 *	
	mild	12	14.1 *	0.17+	12	7.0 *	0.10+
	moderate	12	13.0 *		11	9.7 *	

** arithmetic mean, n: number of patients; +inter group comparison for groups with differing renal function*

In summary, this interaction study (EC608) of candesartan vs. enalapril showed a tendency towards an increase in AUC_{0-72} and C_{max} for both candesartan and enalapril during concomitant administration, but this increase (95% CI) remained within the accepted range for equivalence (80-125%) during repeated dosing.

10.1.4 Appendix PK4 CPH 102

Pharmacokinetic Evaluation of Candesartan Cilexetil (TCV- 116) in Patients with Chronic Congestive Heart Failure

This open-label, relatively small (5 subjects only) PK study was conducted from September 1994 to March 1996. The principal investigator was Yasuhiro Abo. The study was conducted at Fujita Health University, Banbuntane-Hotokukai Hospital, in Japan. The objective was to examine the effect of candesartan cilexetil on the blood concentrations of digitalis and vice versa in patients with chronic congestive heart failure (CHF). Theoretically, the metabolite of cilexetil – Cyclohexyloxy-carboxyloxy-ethyl – could have a potential drug interaction with digoxin and produce proarrhythmic effects in the canine failing heart (Okunishi H, et al. Pharmacol Res 2002; 46: 301-310).

The subjects were 5 inpatients (mean age 67.6 years, 3 males and 2 females) with CHF (NYHA Stage II (4 patients) or III (one patient)) with serum creatinine value of 2.0 mg/dl or lower. The main underlying diseases were old cardiac infarction, dilated cardiomyopathy, mitral insufficiency, ischemic myocardiopathy, and chronic auricular fibrillation.

Methyldigoxin and furosemide were administered for more than 2 weeks. Various tests including determination of plasma digoxin concentrations and chest X-ray examination were performed during the run-in period of 3 days to confirm that the subjects were eligible. The patients

received 4 mg of candesartan cilexetil once daily after breakfast for 8 days (Day 1 and Days 3 – 9) in addition to methyldigoxin and furosemide. In order to examine the pharmacokinetics for 48 hours after the first dose, administration of candesartan cilexetil was not administered on Day 2. The dosages of methyldigoxin (0.05-0.2mg/day) and furosemide (20-120 mg/day) were kept constant in each patient throughout the study period.

Blood sample collections for plasma concentrations of candesartan cilexetil and its metabolites (M-I and M-II) was conducted before study medication and 1.5, 3, 4, 6, 8, 10, 12, 24, 30 and 48 hours after study medication on Day 1 and Day 9. Urine volumes and urinary concentrations of M-I and M-II were measured on the 0-12 hr, 12-24 hr and 24-48 hr urine fractions after study medication on Days 1 and 9.

Candesartan cilexetil, M-I and M-II were determined by the HPLC method. The plasma digoxin concentrations (before administration and 1.5, 3, 4, 6, 8, 10, 12 and 24 hours after administration) were determined on the first day of the run-in period and Days 1 and 9 of the candesartan cilexetil treatment. Digoxin in plasma was determined by the fluorophotometric immunoassay. 24-hour endogenous creatinine clearance test was conducted on the first day of the run-in period and Day 9 of the candesartan cilexetil treatment.

The plasma concentrations of the active metabolite M-I and the inactive metabolite M-II reached maximum 4- 5 hours and 10 hours after the study medication on Days 1 and 9, respectively, as shown in Figure 85.

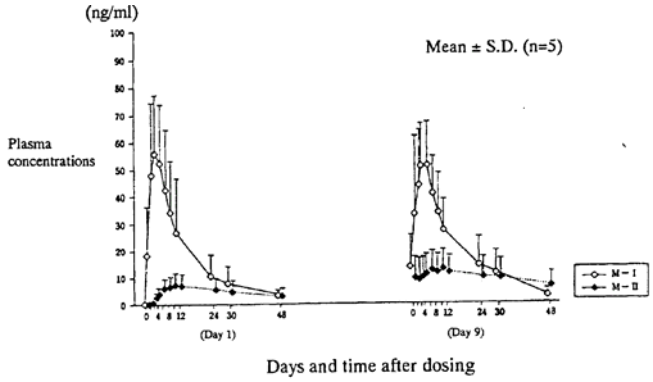


Figure 85 Plasma concentrations of M-I and M-II after administration of candesartan in multiple doses of 4 mg/day in patients with CHF

The pharmacokinetic parameters are shown in the Table 145 below.

The urinary excretions of M-I and M-II in 24 hours after 4 mg were about 4% and 1-2% of dose, respectively. The unchanged compound of candesarta n cilexeti1 was detected in one of the 5 subjects 0 – 12 hours after administration (0.5ng/ml) but not in the other 4 subjects (Table 146).

The plasma digoxin concentrations did not reach the effective concentrations for the maintenance therapy in one subject on the Day of the candesartan treatment (C_{max} 0.4ng/ml). This subject was therefore excluded from the pharmacokinetic analysis. The following Figure 86 shows the plasma digoxin concentrations during the run-in period, on Days 1 and 9 of the candesartan cilexetil treatment.

Table 145 Pharmacokinetic parameters of M-I and M-II after administration of candesartan cilexetil in multiple doses of 4 mg/day in 5 patients with chronic congestive heart failure

Com-pounds	No. of pts.		Pharmacokinetic parameters					
			C_{max} (ng/ml)	T_{max} (h)	AUC_{0-48} (ng,h/ml)	MRT_{0-48} (h)	$t_{1/2}\alpha$	$t_{1/2}\beta$
M-I	5pts.	Day 1	56.7±21.9	3.6±0.6	825±514	12.8±1.2	2.3±0.6(4)	12.0±2.9(4) 10.5(1)
		Day 9	56.8±16.1	4.3±1.9	892±.397	13.5±2.1	3.0±1.9(4)	13.9±5.7(4) 17.6(1)
M-II		Day 1	7.5±4.5	10.0±1.4	223±164	21.2±2.8	-	24.2±14.1
		Day 9	12.5±7.2	7.2±4.6	437±315	20.2±2.6	-	21.0±6.4[2)]

1): 4 patients of M-I were calculated by the 2-compartment model. 1 patient of M-II and M-I was calculated by the 1-compartment model.
2): Calculated by 4 patients.
No. of patients in ( )

Table 146 Urinary excretions of M-I and M-II

Compounds	Cumulative excretion rate in urine (% of each dose)					
	Day 1			Day 9		
	0~12 hour	0~24 hour	0~48 hour	0~12 hour	0~24 hour	0~48 hour
M-I	2.6±1.1	4.1±1.7	4.8±2.1	3.0±2.2	4.2±2.8	4.9±2.9
M-II	0.6±0.9	1.2±1.3	2.3±2.8	1.5±1.7	2.3±2.3	3.2±3.6
Total	3.3±1.4	5.3±2.5	7.1±4.1	4.5±3.7	6.5±4.8	8.1±6.1

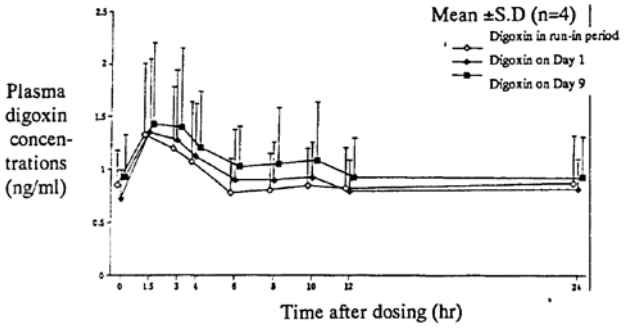


Figure 86 Plasma digoxin concentrations

The 24-hour endogenous creatinine clearance (mean±S.D.) of the 5 subjects was 27.3±13.2 ml/min/1.48m^2 on the first day of the run-in period and 34.2°±3.8 ml/min/1.48 m^2 showing no great difference.

In summary, combined use of candesartan cilexetil with methyldigoxin did not produce any effect on the plasma concentrations of candesartan cilexetil, the active metabolite M-I and the inactive metabolite M-II. Also, there was no accumulation of the plasma concentrations of

candesartan by repeated administration. Hence, candesartan cilexetil was considered not to interact with digoxin.

10.1.5 Appendix PD1 Study EC602:

Study of the acute hemodynamic effects of 4mg, 8 mg and 16 mg candesartan cilexetil in patients with impaired left ventricular function (Heart Failure – NYHA Class II/III)

As mentioned previously, this is a PK/PD study of candesartan, performed as a single- (oral) dose, randomized, double-blind, placebo controlled, Phase II study. It was conducted from May 19 through December 10, 1995. The principal investigator is Prof. Dr. T. Lüscher. All of the study sites are in Germany. The primary objective was to evaluate the dose relationship of placebo vs. candesartan cilexetil (4mg, 8mg and 16 mg) in patients with CHF on acute hemodynamic effects (change in mean pulmonary capillary wedge pressure ($PCWP_{mean}$) and pulmonary artery systolic pressure (PAP_{sys}) measured via Swann-Ganz catheterization. The secondary efficacy parameters were neurohormonal responses (change in levels of rennin, angiotensin II, aldosterone, adrenalin and noradrenalin at different time points).

Sixty (60) Caucasian patients 26-77 years old, with CHF (New York Heart Association (NYHA) Class II/III, PAP_{sys} ≥25mmHg and/or PCWP >13mmHg) were consented, 57 were randomized, one withdrew, and 56 patients completed the study. CHF was due to coronary artery disease (30 patients) cardiomyopathy (24 patients), hypertension (5 patients), valvular disease (1 patient) and unknown (4 patients). Several patients also had co-morbid illnesses such as diabetes, renal insufficiency, chronic airways obstruction, etc.

There were 6 subjects with major protocol violations: one patient (01C) received enalapril during the study, one patient (17B) had NYHA Class I CHF, and four patients (02B, 03B, 05B and 21B) had incompletely recorded PCWP at a majority of time points, and latter three also at baseline (patients 3B, 5B and 21B). In addition, 14 patients were enrolled with a PCWP <13 mmHg or no PCWP (patients 3B, 5B and 21B).

Patients received a single oral dose of placebo or candesartan 4 mg, 8 mg or 16 mg (randomization between candesartan cilexetil and placebo was 3:1); drug intake was allegedly under the supervision of the treating physician. $PCWP_{mean}$ and PAP_{mean}, measured via a Swann-Ganz catheter, were used to evaluate the hemodynamic effects of candesartan in patients with CHF. Blood samples were collected at 0h (pre-dose), 2h, 4h, 8h and 24 h post-dose for determination of aldosterone, angiotensin II, plasma renin activity, catecholamines (adrenaline and noradrenaline), and endothelin-I plasma concentration, cooled on ice, centrifuged (1,500 g for 15 min at 4°C), and the plasma was transferred into labeled polypropylene tubes and stored at –70°C. The hormones were assayed by Bio-Pharma Ltd using radio-immuno-assay (RIA) kits, and endothelin-I plasma concentration was determined at Inselspital Universitätsklinik, Bern, Switzerland, using a RIA.

The changes from baseline for the primary efficacy parameters ($PCWP_{mean}$ and PAP_{mean}) and the secondary efficacy parameters (neurohormonal data) in response to the various doses of candesartan were compared by parametric analysis of covariance, being evaluated by both

AUC_{0-12} analysis and time-point-by-time-point analysis. For the secondary analysis (neurohormones), the values were compared as logarithmic variables.

The $PCWP_{mean}$ and PAP_{mean} decreased in all treatment groups (including placebo) with time, but there was no statistically significant difference ($p>0.05$) between them for all post-dose time points. Also, there was a decrease in $PCWP_{mean}$ and PAP_{mean} and in peak change in $PCWP_{mean}$ and PAP_{mean} in all treatment groups (including placebo) by analysis of AUCs (Table 147 and Table 148) but the differences were not statistically significant.

Table 147 $PCWP_{mean}$ –Mean AUC_{0-12} ±SD (difference to pre-dose [0h], Peak Change±SD (Efficacy (ITT) Population)

			Candesartan cilexetil		
		Placebo	4 mg	8 mg	16 mg
	n	13	12	16	12
AUC [mmHg*h]	mean	-44.10 ± 78.40	-18.29 ± 53.85	-50.38 ± 49.25	-44.06 ± 57.49
Peak Change [mmHg]	mean	-6.54 ± 7.39	-4.08 ± 4.14	-8.44 ± 4.26	-8.50 ± 4.30

There were no statistically significant changes in other hemodynamic parameters: mean arterial blood pressure, systemic vascular resistance, right atrial pressure, heart rate and cardiac output.

Table 148 PAP_{mean} –Mean AUC_{0-12} ±SD (difference to pre-dose [0h], Peak Change±SD (Efficacy (ITT) Population)

			Candesartan cilexetil		
		Placebo	4 mg	8 mg	16 mg
	n	13	12	16	12
AUC [mmHg*h]	mean	-50.92 ± 80.19	-50.98 ± 73.87	-43.38 ± 85.63	-57.13 ± 68.78
Peak Change [mmHg]	mean	-8.54 ± 8.41	-8.00 ± 7.70	-10.63 ± 7.46	-10.13 ± 4.93

The peak change post-dose of the neurohormonal concentrations are shown in Table 149. The plasma renin activity and angiotensin II concentration increased, and the aldosterone serum concentration decreased after administration of candesartan compared to placebo. The concentrations of adrenaline and noradrenaline showed no consistent post-dose changes. There was no statistically significant difference between the treatment groups in the peak changes in neurohormonal levels.

Table 149 Neurohormones – Peak changes of concentration/activity [rennin], post-dose (Efficacy (ITT) Population)

Parameter		Placebo	Candesartan cilexetil 4 mg	8 mg	16 mg
Renin	($ng \cdot ml^{-1} \cdot h^{-1}$)	0.74 ± 0.87 n=11	2.76 ± 1.12 n=11	2.27 ± 1.05 n=15	1.69 ± 1.23 n=12
Angiotensin II	($pg \cdot ml^{-1}$)	0.33 ± 0.36 n=12	1.06 ± 0.81 n=11	0.80 ± 0.57 n=15	0.61 ± 0.61 n=12
Aldosterone	($pg \cdot ml^{-1}$)	-0.72 ± 0.67 n=9	-0.85 ± 0.46 n=9	-1.06 ± 0.73 n=14	-1.30 ± 0.75 n=8
Adrenaline	($pg \cdot ml^{-1}$)	-0.59 ± 0.59 n=10	-0.79 ± 0.71 n=12	-0.62 ± 0.56 n=16	-0.35 ± 0.34 n=12
Noradrenaline	($pg \cdot ml^{-1}$)	-0.44 ± 0.50 n=12	-0.20 ± 0.21 n=12	-0.31 ± 0.34 n=16	-0.38 ± 0.47 n=12

10.1.6 Appendix PD2 Study EC605-A (PD component)

Study of the 3- month hemodynamic effects of 2 mg, 4 mg, 8 mg and 16 mg candesartan cilexetil in patients with impaired left ventricular function (Heart failure – NYHA class II/ III). PD Data Analysis.

This is a PK/PD study performed as a randomized, double blind, placebo-controlled, parallel-group study. The primary objective of the study was determination of the 3- month dose-dependent hemodynamic effects of 2 mg, 4 mg, 8 mg and 16 mg candesartan cilexetil in patients with impaired left ventricular function (Heart failure – NYHA class II/ III). The study was conducted from February 20, 1997 through January 14, 1999, at 39 centers in Europe and South Africa. The principal investigator is Dr. Vesellin Mitrovic.

218 patients (mean age 56 years, 85% male) with mild to moderate symptomatic CHF (NYHA class II or III, LVEF ≤40%) were randomized; 44 were treated with placebo and 174 patients treated with candesartan. Of 174 patients treated with candesartan, pharmacokinetic analysis for 15 patients had missing PK values at visit 2 or visit 6; thus, 159 patients had evaluable pharmacokinetic profiles at baseline and 138 at final visit.

After a 2- week run- in period, patients were randomized to a 12 week treatment period at doses of candesartan 2 mg, 4 mg, 8 mg or 16 mg. The following efficacy variables were assessed: pulmonary capillary wedge pressure (PCWP), systemic vascular resistance (SVR) and cardiac index (CI). The secondary efficacy variables included mean pulmonary artery pressure (PAP), mean arterial blood pressure (MABP), heart rate (HR), mean right atrial pressure (RAP), ejection fraction (EF), symptom scores (three visual analogue scales – "breathlessness", "fatigue" and "ankle swelling"), efficacy score, quality of life (SF- 36 questionnaire) and NYHA classification. The neurohormonal parameters evaluated included plasma renin activity, Angiotensin II, aldosterone, atrial natriuretic factor, epinephrine and norepinephrine. Blood samples for neurohormonal levels were taken at Visit 2 and Visit 6 (or at the "Termination Visit" in the case of premature discontinuation). The blood neurohormonal levels were determined by a central laboratory (Covance Central Laboratory Services S. A., formerly Corning SciCor, Geneva).

There were 12 (5.5%) major protocol violations: eight (8) patients took prohibited concomitant medications, three (3) patients had PCWP < 13mmHg at visit 2, two (2) patient had PCAP values that were not plausible, and one (1) subject (on 16 mg candesartan) had measurements taken without taking drug.

Pulmonary capillary wedge pressure (PCWP)

A regression analysis as well as a one-way ANCOVA (with the last available pre-dosing value at baseline (Visit 2) as covariate for the AUC data and for the values obtained 4 hours after drug administration showed that the reduction of PCWP for the AUC values and for the measurements made 4 hours after dosing were very similar (Table 150). At Visit 2 (single-dose effect), statistically significant differences were obtained with respect to placebo at the p<5% level for candesartan cilexetil 8 mg and 16 mg. At the final visit (repeated-dose effect), the estimated mean differences with respect to placebo were not statistically significant.

Table 150 Pulmonary capillary wedge pressure – One-way ANCOVA

Pairwise comparison against placebo with the last available pre-dosing value of Visit 2 as covariate.
ITT population. *p* values below 0.05 are shown in bold type; those below 0.10 are underlined.

		AUC_{0-8h} (mmHg × h)					4 hours after dosing (mmHg)				
Dosage		a.m.d.	SD	95% CI		*p* value	a.m.d.	SD	95% CI		*p* value
2 mg	Visit 2, single dose	−9.08	5.50	−19.93	1.77	0.100	−1.56	0.88	−3.29	0.16	0.076
	Final visit, multiple dose	4.34	10.97	−17.31	25.98	0.693	0.26	1.43	−2.55	3.08	0.854
4 mg	Visit 2, single dose	−8.74	5.36	−19.31	1.83	0.104	−1.56	0.85	−3.24	0.12	0.069
	Final visit, multiple dose	−13.07	10.50	−33.77	7.64	0.215	−2.15	1.36	−4.84	0.54	0.117
8 mg	Visit 2, single dose	−18.26	5.60	−29.29	−7.23	**0.001**	−3.37	0.89	−5.12	−1.61	**<0.001**
	Final visit, multiple dose	−12.08	10.94	−33.66	9.50	0.271	−2.13	1.42	−4.94	0.67	0.136
16 mg	Visit 2, single dose	−12.24	5.42	−22.92	−1.55	**0.025**	−2.35	0.86	−4.06	−0.65	**0.007**
	Final visit, multiple dose	−19.14	10.79	−40.42	2.14	0.078	−2.54	1.40	−5.30	0.23	0.072

Source: Table IX.3.1.2 and IX.3.1.5.
a.m.d. = adjusted mean difference.

Systemic vascular resistance (SVR)

The results for SVR resembled those for PCWP (Table 151 below). At Visit 2 (single-dose effect), statistically significant differences with respect to placebo were obtained for AUC (candesartan cilexetil 8 mg) and for 4 hours after dosing (candesartan cilexetil 8 mg, 16 mg) in terms of an SVR reduction under active treatment. At the final visit (repeated-dose effect), no statistically significant differences to placebo were found.

Table 151 Systemic vascular resistance – One-way ANCOVA

Pairwise comparison against placebo with the last available pre-dosing value of Visit 2 as covariate. ITT population. *p* values below 0.05 are shown in bold type.

Dosage		AUC_{0-8h} (h × dynes sec / cm^5) a.m.d.	SD	95% CI		*p* value	4 hours after dosing (dynes × sec / cm^5) a.m.d.	SD	95% CI		*p* value
2 mg	Visit 2, single dose	−438	302	−1034	157	0.149	−69	54.6	−176	39	0.208
	Final visit, multiple dose	−247	510	−1252	759	0.629	−21	75.8	−171	128	0.780
4 mg	Visit 2, single dose	−323	300	−915	269	0.283	−80	54.3	−187	27	0.144
	Final visit, multiple dose	163	495	−813	1140	0.742	8	73.6	−137	153	0.915
8 mg	Visit 2, single dose	−800	313	−1418	−183	**0.011**	−139	56.6	−250	−27	**0.015**
	Final visit, multiple dose	−980	516	−1998	39	0.059	−103	76.7	−255	48	0.180
16 mg	Visit 2, single dose	−446	305	−1048	156	0.146	−121	55.2	−230	−12	**0.030**
	Final visit, multiple dose	−314	516	−1333	704	0.543	3	76.2	−148	153	0.971

Source: Table IX.3.2.2 and IX.3.2.5.
a.m.d. = adjusted mean difference.

Cardiac index (CI)

Despite the statistically significant reductions in PCWP and SVR (above), no consistent changes in CI were observed. The mean values of CI fluctuate between 2.6 l/min/m^2 and 3.0 1/min/ m^2 on both assessment days without a time or dose relationship. The regression analysis did not reveal a statistically significant relationship between the results for Cardiac Index and dosage during either visit (Visit 2 or final visit). Also, ANCOVA comparisons on both assessment days showed no significant difference between active treatment and placebo.

Secondary hemodynamic variables

The regression analysis showed a dose-dependent reduction of PAP_{mean} on both assessment days (single- and repeated-dose effect for the AUC values; single-dose effect for the data obtained 4 h after dosing). However, the regression analysis did not reveal a statistically significant treatment effect on either assessment day (Visit 2 or final visit) for mean arterial blood pressure (MABP), heart rate (HR), right atrial pressure (RAP), ejection fraction (EF), NYHA classification or efficacy score at the final visit, and no consistent treatment effect on comparison of the responses to SF-36 Quality of Life questionnaires at baseline and at the final visit.

By one-way ANCOVA, statistically significant treatment differences between candesartan cilexetil and placebo were found (Table 152) for "breathlessness" (16-mg group) and for "tiredness/fatigue" (4-mg and 8-mg groups). There was no significant treatment effect on "swollen ankle".

Table 152 Symptom score – One-way ANCOVA

p values for pairwise comparison with placebo are shown. ITT population.

Candesartan cilexetil dosage:	2 mg	4 mg	8 mg	16 mg
Breathlessness	0.700	0.653	0.632	**0.034**
Tiredness/fatigue	0.438	**0.025**	**0.043**	0.051
Swollen ankles	0.979	0.580	0.316	0.764

Source: Tables IX.3.15.1.2, 3.15.2.2, 3.15.3.2.

Neurohormonal parameters

Table 153 Neurohormonal variables

Figures denote p values for the deviation from zero of the slope of the dose dependence. ITT population

		Visit 2, single dose		Final visit, multiple dose	
		drug effect * trend of regression	*p* value	drug effect * trend of regression	*p* value
Plasma renin activity	AUC_{0-8}	increase	**0.0002**	increase	**0.0007**
	4 hours after dosing	increase	**0.0019**	increase	**0.0312**
Angiotensin II	AUC_{0-8}	increase	**0.0389**	increase	**0.0211**
	4 hours after dosing	increase	0.1522	increase	**0.0325**
Aldosterone	AUC_{0-8}	decrease	0.1640	decrease	**0.0206**
	4 hours after dosing	decrease	**0.0281**	decrease	**0.0352**
Atrial natriuretic factor	AUC_{0-8}	–	0.5578	decrease	**0.0018**
	4 hours after dosing	–	0.5100	decrease	**0.0014**
Epinephrine	AUC_{0-8}	–	0.5612	–	0.8535
	4 hours after dosing	–	0.4571	–	0.7079
Norepinephrine	AUC_{0-8}	–	0.6284	–	0.2323
	4 hours after dosing	–	0.5124	–	0.2763

* Stated only if *p* value <0.2.
Source: Table series IX.3..x.3 and IX.3.x.6 (x = 8–13)

The results of the regression analyses of the neurohormonal variables are summarized in Table 153 (above).

The regression analysis revealed statistically significant increases in mean plasma renin activity and mean blood levels of angiotensin II in a dose-dependent manner at both visit 2 (single-dose effect) and final visit (multiple-dose effect), compared to the placebo group; this was accompanied by a statistically significant dose-dependent decrease in mean blood levels of aldosterone at both visits. This finding suggests that candesartan cilexetil effectively blocked angiotensin II receptors (as evidenced by the fall in aldosterone) with compensatory rises in plasma renin activity and in angiotensin II levels.

The regression analysis also revealed a statistically significant dose-dependent decrease in atrial natriuretic factor (ANF) levels for the final visit (repeated-dose effect). The decreased ANF levels seen after multiple dosing at the end of the study reflect the improvement in left ventricular end diastolic pressures over the treatment period as evidenced by the observation of a significant reduction in PCWP after treatment with candesartan cilexetil.

Mean blood levels of epinephrine and norepinephrine remained largely unchanged and did not follow a consistent pattern.

Overall, the treatment with candesartan cilexetil resulted in sustained, dose-dependent hemodynamic and neurohormonal responses accompanied by symptomatic improvements in the CHF patients. (*Comment: This finding is not replicated in other PD trials, below.)*

10.1.7 Appendix PD3 Study EC604 (STRETCH Study)

Efficacy and Safety of 4 mg, 8 mg & 16 mg Candesartan Cilexetil (TCV–116) in Patients with Impaired Left Ventricular Function (Mild to Moderate Heart Failure – NYHA Class II/ III)

This was a rather large (844 subjects in safety population) PD study to determine whether treatment with different dosages of candesartan cilexetil compared to placebo will improve total exercise time (in seconds) on a bicycle ergometer over a treatment period of 3 months in patients with CHF. The study also intends to determine, as secondary parameters, whether treatment with candesartan cilexetil will improve signs and symptoms of CHF, NYHA functional class, total walking distance (six-minute walk test) or cardiothoracic ratio (chest X-ray), to determine neuroendocrine parameters (adrenaline, noradrenaline, aldosterone, plasma renin activity and angiotensin II), and the drug's safety profile in patients with CHF.

The study was a double- blind, randomized, placebo- controlled, parallel group, multi- centre study. It consisted of 3 study periods: a 2- week wash- out period (for ACE inhibitor pre- treated patients), a 4- week placebo run- in period, and a 12-week double-blind treatment period.

The inclusion and exclusion criteria were similar to those for the CHARM studies. **Patients pre-treated with ACE inhibitors discontinued the intake of this medication.** These patients then entered a 2-week wash-out period before entry into the placebo run- in period. Patients were maintained on optimal background CHF medication including diuretics, nitrates and/or digitalis. Patients who qualified for entry into the double-blind treatment period were randomly assigned to one of four treatment groups: placebo, candesartan cilexetil 4 mg, 8 mg, or 16 mg (ratio: 1:1:1:1). All patients started with a dosage of candesartan cilexetil 4 mg. After one week, patients randomized to the candesartan cilexetil 8 mg and candesartan cilexetil 16 mg groups were titrated up to 8 mg, and after one further week, patients in the candesartan cilexetil 16 mg group were finally titrated up to the 16 mg maintenance dose. For all patients, treatment with nitrates, digitalis, non-potassium sparing diuretics, as well as combinations involving such diuretics, was kept constant from Visit 4 onwards, and was not changed during the study.

The final study protocol was amended once. In Germany, long- acting nitrates are frequently prescribed for the treatment of congestive heart failure in the absence of angina pectoris. Thus, long-acting nitrates were permitted, as long as the dose taken was stable, and the occasional use of short-acting nitrates on demand was allowed. However, nitrates were not permitted to be taken on visit days before exercise testing. Low- dose acetylsalicylic acid (100 mg per day) was also permitted.

Treatment compliance was assessed by counting the number of tablets returned to the investigator by the patient at Visits 3 to 8. A compliance of >75% and <125% was reported in 95.5% of the patients in the safety population.

The principal investigator is Prof G.A.J. Rigger. Eighty-six centers participated: 51 centers in Germany, 34 centers in the Czech Republic, and 1 center in Slovenia. The study was conducted from January 22, 1996 through June 12, 1997. The study enrolled 926 patients in the wash-out/

placebo run-in period (513 patients pre-treated with ACE-inhibitors entered the wash-out phase), 882 in the placebo run-in period; 82 patients discontinued. Thus, 844 patients were randomized (safety population = 844 patients). 55 (6.5%) patients withdrew prematurely. 37 patients who received randomized study medication were not eligible for the intent- to-treat analysis of efficacy because they did not have valid bicycle ergometry data at baseline or post-baseline.

174 patients (20.6%) had at least one important protocol violation, such as taking prohibited concomitant medications, drug intake outside the protocol-specified time window, non-adherence to time schedule for bicycle ergometry, total exercise time during placebo run-in period <2 min or >12 min, non-compliance, ejection fraction >45% at Visit 1, sitting SBP > 160 mmHg or sitting DBP > 95mmHg, symptomatic hypotension, randomized study medication mixed-up, etc.

There were no differences between the treatment groups with respect to gender, age, height, weight, NYHA functional class, ejection fraction, the duration of congestive heart failure, concomitant diseases, and type of prior treatment for CHF. Overall, the mean duration of known congestive heart failure was 3.2 years.

Primary efficacy parameter (total exercise time)

The primary efficacy parameter was total exercise time as determined by bicycle ergometry. At Visits 4, 5, 9, and 11, bicycle ergometries were carried out. The first exercise test was carried out at Visit 4, with the option of three repeated tests including the test at Visit 5. Two consecutive tests had to be 3 days apart from each other. If two consecutive bicycle ergometries between Visit 4 and Visit 5 did not vary more than 15% from each other, the patient's exercise condition was considered stable, thus fulfilling one of the inclusion criteria. Bicycle ergometry was performed at the peak serum concentration of candesartan cilexetil, exactly 3 hours and 45 minutes after the intake of study medication.

Patients bicycled in the upright position and started with a workload of 25 watts. The workload was increased in 25- watt steps every 2 minutes until the patient was unable to continue due to dyspnea and/or fatigue. A 12-lead ECG was recorded during the last 10 seconds of each minute of exercise, and at 1, 3, and 5 minutes after the exercise testing. The total exercise time in seconds was to be documented in the CRF.

The mean total exercise times at baseline were comparable between the treatment groups. At the end of the study (last value), the mean total exercise time had increased by in a dose dependent manner in the candesartan treatment groups (Table 154).

Table 154 Total exercise time[s] (baseline (Visit 5) and last value)) – Intent- to- treat population (n= 807)

		Placebo	Candesartan cilexetil 4 mg	Candesartan cilexetil 8 mg	Candesartan cilexetil 16 mg
		n=201	n=203	n=202	n=201
Baseline (Visit 5)		n=201	n=203	n=202	n=201
	Mean ± SD	419.9 ± 141.8	409.8 ± 135.0	418.8 ± 143.6	419.8 ± 132.3
	Median	420.0	406.0	411.0	420.0
	(min–max)	120 - 840	120 - 720	120 - 720	120 – 720
Last value		n=201	n=203	n=202	n=201
	Mean ± SD	450.7 ± 150.7	449.5 ± 145.1	464.6 ± 164.0	466.9 ± 153.7
	Median	460.0	460.0	480.0	480.0
	(min–max)	120 - 840	120 - 900	120 - 840	120 – 840
Changes baseline to last value		n=201	n=203	n=202	n=201
	Mean ± SD	30.8 ± 83.4	39.7 ± 77.0	45.8 ± 82.5	47.2 ± 87.6
	Median	28.0	30.0	32.5	40.0
	(min–max*)	-258 - 360	-240 - 295	-360 - 300	-230 – 360

*Negative absolute changes indicate a reduction in total exercise time as compared to baseline

Table 155 Total exercise time[s] – Per- protocol population (n= 629)

		Placebo	Candesartan cilexetil 4 mg	Candesartan cilexetil 8 mg	Candesartan cilexetil 16 mg
		n=151	n=167	n=156	n=155
Baseline Visit 5		n=151	n=167	n=156	n=155
	Mean ± SD	422.7 ± 138.6	411.8 ± 136.3	423.8 ± 138.4	419.9 ± 135.8
	Median	415.0	406.0	417.0	420.0
	(min–max)	134 – 720	120 – 720	163 – 720	120 – 720
Visit 11		n =151	n=167	n=156	n=155
	Mean ± SD	454.6 ± 143.2	453.3 ± 146.0	475.7 ± 160.1	473.2 ± 160.5
	Median	463.0	460.0	480.0	480.0
	(min–max)	150 – 840	120 – 900	145 – 840	120 – 840
Changes baseline to Visit 11		n=151	n=167	n=156	n=155
	Mean ± SD	31.9 ± 80.8	41.6 ± 81.7	51.9 ± 73.7	53.3 ± 81.5
	Median	30.0	38.0	37.0	53.0
	(min–max*)	-258 – 359	-240 – 295	-130 – 300	-206 – 360

*Negative absolute changes indicate a reduction in total exercise time as compared to baseline

A more pronounced dose-dependent effect of candesartan cilexetil was seen in the per-protocol population (Table 155), supporting the results for the intent- to-treat population.

An analysis of covariance with the factor treatment and covariate total exercise time at baseline (Visit 5) in Table 156 shows that patients in the candesartan cilexetil 16 mg group had statistically significant increases in total exercise time when compared to placebo (both in the intent- to-treat population and per-protocol population). The increase in total exercise time for patients treated with candesartan cilexetil 4 mg did not show a statistically significant difference when compared to placebo (for both the intent- to- treat population and per- protocol population). The candesartan 8 mg group did not show a consistent result: there was a statistically significant increase in total exercise time compared to placebo in the intent-to-treat population, but not in the per-protocol population.

Table 156 Results of the ANCOVA on change in total exercise time from baseline (Visit 5) to last value

	Intent-to-treat population			Per-protocol population		
	Estimate	95% CI**	p-values*	Estimate	95% CI**	p-values*
Test 1: Candesartan cilexetil 16 mg vs. placebo	16.386	[0.279; 32.507]	0.0463	21.310	[3.641; 39.255]	0.0191
Test 2: Candesartan cilexetil 8 mg vs. placebo	14.934	[-1.093 ; 31.095]	0.0689	20.098	[2.263; 37.820]	0.0268
Test 3: Candesartan cilexetil 4 mg vs. placebo	8.261	[-7.185; 24.963]	0.3135	9.137	[-7.807; 27.169]	0.3055

* F-test, two-sided, α=0.05

** 95% CI: 95% confidence interval for the difference between means (difference between active medication and placebo)

Was there a dose-response?

The study involved three fixed doses of candesartan cilexetil (4 mg, 8 mg and 16 mg) as well as placebo. For the primary efficacy parameter "total exercise time," a dose-response trend was found (Figure 87).

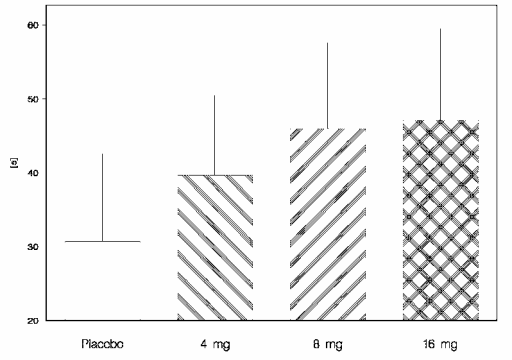


Figure 87 Dose-response relationship for the change in total exercise time[s] between baseline (Visit 5) and last value – Intent-to-treat population (n=807)

Secondary efficacy parameters

Dyspnea Fatigue Index score: In all candesartan treatment groups, the increase from baseline to last value of the dyspnea fatigue index (composite "total focal score" measured using 3 parameters: functional capacity, magnitude of task and pace of task)[73] were statistically larger (by non-parametric ANCOVA) than that in the placebo group, but a dose effect was not observed.

Assessment of dyspnea by the patient: After the bicycle ergometry and after the six- minute walk test, patients assessed their dyspnea on a visual analogue scale after a recovery time of three minutes on a visual analogue scale. An overall pattern of decreasing dyspnea directly after bicycle ergometry over the course of the study was observed which did not show any statistically significant differences between patients in any of the candesartan cilexetil groups and patients in the placebo group.

The six- minute walk test was not carried out in a number of centers due to a lack of facilities; 381 patients (47.2%) of the intent- to-treat population made two assessments (baseline and post-baseline) of their dyspnea after the six- minute walk test (after a recovery time of three minutes).

A decrease of mean dyspnea between baseline and subsequent visits was observed, but this was not statistically significant between patients in any of the candesartan treatment groups and patients in the placebo group.

NYHA functional class: The patients' NYHA functional class was assessed at Visits 1, 5, 9, and 11. Changes in NYHA functional class were classified as 'improved' (decrease in NYHA functional class), 'no change' (identical NYHA functional class) or 'deteriorated' (increase in NYHA functional class). The overall comparison of all active treatment groups to placebo with respect to changes in NYHA functional class from baseline to last value and the corresponding comparisons between each candesartan cilexetil group and placebo showed no statistically significant results.

Total walking distance: Where a suitable walking space of at least 20 meters existed, the six-minute walk test according to Guyatt et al[74] was carried out 3 hours after study drug intake and before the bicycle ergometry. The walk was conducted in an enclosed corridor of known length (not ≤ 15 meters); the patient was instructed to walk from end to end, covering as much distance as they could during the 6 minutes. This distance in meters after six minutes of walking was recorded.

A number of centers did not have the facilities to carry out the six-minute walk test; thus, results on total walking distance were available for less than half of the patients. A total of 386 patients (47.8%) in the intent-to-treat population performed at least one six-minute walk test during the double-blind treatment period. In all treatment groups, the total walking distance during the six-minute walk test increased after baseline (Visit 5) ranging from a mean of 16.0 m in the candesartan cilexetil 16 mg group to 39.3 m in the candesartan cilexetil 4 mg; however, the mean increase in total walking distance in the placebo group was 37.3 m. The comparison of all active treatment groups with the placebo group did not yield statistically significant differences with respect to the total walking distance. It is known that there may be improvement in walking-test scores up to the third walk[2] which is the likely explanation here. Also, encouragement had been shown to have a substantial impact[2] ($P<0.02$) on walking test scores, and it is not mentioned how the administration of the walking-test was standardized.

Cardiothoracic ratio: The cardiothoracic ratio was measured from chest X-rays taken at baseline (Visit 5) and at Visit 11 or at the time of premature discontinuation. Since the treatment groups were compared using a non- parametric ANCOVA, the results reported refer to median values (Table 157). A decrease in the median values for the cardiothoracic ratio was observed in all candesartan cilexetil groups. There was no change in the median value in the placebo group.

Changes in cardiothoracic ratio from baseline to last value in all candesartan cilexetil groups compared to placebo showed statistically significant differences in the intent-to-treat population (Table 158). In the per-protocol population, only the comparisons candesartan cilexetil 16 mg to placebo and candesartan cilexetil 4 mg to placebo were statistically significant.

Table 157 Results of the non- parametric ANCOVA on the change in the cardiothoracic ratio between baseline (Visit 5) and last value – Intent-to-treat population (n= 807)

		Placebo	Candesartan cilexetil 4 mg	Candesartan cilexetil 8 mg	Candesartan cilexetil 16 mg
		n=201	n=203	n=202	n=201
Baseline Visit 5		n=190	n=191	n=194	n=193
	Mean ± SD	0.500 ± 0.073	0.508 ± 0.066	0.501 ± 0.067	0.500 ± 0.066
	Median	0.494	0.509	0.500	0.500
Last Value		n=184	n=186	n=182	n=186
	Mean ± SD	0.498 ± 0.065	0.491 ± 0.060	0.490 ± 0.072	0.484 ± 0.062
	Median	0.494	0.493	0.486	0.485
Changes baseline to last value		n=182	n=184	n=181	n=185
	Mean ± SD*	-0.003 ± 0.050	-0.015 ± 0.053	-0.011 ± 0.042	-0.015 ± 0.050
	Median	0.000	-0.013	-0.006	-0.013

* Negative absolute changes indicate a reduction in cardiothoracic ratio as compared to baseline

Table 158 Results of the non-parametric ANCOVA on the change in the cardiothoracic ratio between baseline (Visit 5) and last value

Comparison	Intent-to-treat population	Per-protocol population
	p-values*	
Test 1: Candesartan cilexetil 16 mg vs. placebo	0.0051	0.0157
Test 2: Candesartan cilexetil 8 mg vs. placebo	0.0408	0.1788
Test 3: Candesartan cilexetil 4 mg vs. placebo	0.0308	0.0307

* F-test on ranked values, two-sided, α=0.05 for each pairwise comparison; all p-values are exploratory in nature

Neuroendocrine parameters

Neuroendocrine parameters (at least one measurement) were determined in a total of 467 patients in the intent-to-treat population and 357 patients in the per-protocol population. However, values from Visits 5 and either Visit 9 or 11, before (trough) and approximately 3.5 hours after drug intake peak), were available in 335 patients (adrenaline at peak) to 394 patients (noradrenaline at trough) in the intent- to- treat population.

Blood samples for determination of the patient's neuroendocrine status (measurement of adrenaline, noradrenaline, aldosterone, angiotensin II, and renin activity) were taken at Visits 5, 9, and 11. At Visits 9 and 11, these samples were drawn before drug intake (at 7: 45) and at C_{max} (before the exercise tests, at 10: 45). Blood levels of neuroendocrine parameters were analyzed by Covance Central Laboratories S. A., Geneva, Switzerland, and serum levels of CV – 11974 by Pharma Bio-Research Laboratories B. V., Zuidlaren, The Netherlands. After 300 patients had completed the study, Takeda Euro R& D Centre GmbH decided to stop collecting further blood samples for neuroendocrine parameters, based on their assumption that this number of patients would be sufficient to make an assessment of the patients' neuroendocrine status.

Adrenaline and noradrenaline serum levels remained essentially unchanged throughout the study. Trough and peak values did not vary. Differences between the treatment groups were not discernible.

Aldosterone serum levels hardly changed over time in the placebo and the candesartan cilexetil 4 mg group; slight decreases from baseline (Visit 5) to Visits 9 and 11 were seen in the two higher dose groups of candesartan. There was no difference between trough and peak values.

In all candesartan cilexetil groups, plasma renin activity and angiotensin II serum levels increased from baseline (Visit 5) to Visits 9 and 11 for both trough and peak values. They remained changed in the placebo group. The increases in plasma renin activity and angiotensin II serum levels tended to be higher with the higher doses of candesartan cilexetil and were more marked for the peak values.

Response rate: Response was defined as an increase in total exercise time from baseline to last value of at least 20%. In the intent to-treat population, the response rates were: 26.9% in the placebo group, 27.1% in the candesartan cilexetil 4 mg group, 30.7% in the candesartan cilexetil 8 mg group, and 31.3% in the candesartan cilexetil 16 mg group. Pairwise comparisons with placebo did not show statistically significant differences. This was also true for the comparison of all active treatment groups versus placebo.

Summary

A statistically significant dose-dependent increase in "total exercise time" by bicycle ergometry (the primary efficacy parameter) was observed for patients treated with candesartan cilexetil 16 mg ($p= 0.0463$, intent- to-treat population) compared to those treated with placebo.

Also, all doses of candesartan cilexetil showed statistically significant improvements on the Dyspnea Fatigue Index score ($p\leq 0.0001$, intent-to-treat population), and a mean decrease in the cardiothoracic ratio.

There were no statistically significant differences between the candesartan-treated group and placebo-treated group in changes in NYHA functional class or total walking distance from baseline (Visit 5) to either Visit 9 or 11 or last visit. Similarly, there were no statistically significant differences between the candesartan-treated group and placebo-treated group in changes in neuroendocrine parameters. The time course of neuroendocrine parameters merely reflected the known pharmacodynamic effects of candesartan cilexetil.

10.1.8 Appendix PD4 Study EC610

Long Term Safety and Efficacy of 8 mg and 16 mg Candesartan Cilexetil (TCV–116) in Patients with Impaired Left Ventricular Function (Mild to Moderate Heart Failure – NYHA Class II/ III). An open, uncontrolled, multicenter follow-up of study EC604

The study was an unblinded, open-label, follow-up of study EC604 performed on 355 out-patients with CHF (NYHA Class II or III) and with impaired left ventricular function. A treatment period of nine months was selected, as this is generally considered an appropriate length of time for obtaining data on long-term safety.

The primary objective was to assess the drug's safety in patients with mild to moderate congestive heart failure treated over a period of 9 months. The secondary objectives were to assess the effects of candesartan cilexetil on exercise tolerance after a treatment period of 9 months, to determine whether treatment with candesartan cilexetil improved signs and symptoms of congestive heart failure and/or keep patients on an improved level, and to assess quality of life during long-term treatment of 9 months with candesartan cilexetil.

The target population consisted of outpatients (male and female) who had completed the preceding study EC604 according to protocol (i.e. Visit 11 and no premature discontinuation), and had mild to moderate CHF (NYHA class II/III). As this was an open uncontro11ed follow-up of study EC604, patients classified as NYHA I also qualified for inclusion in the study. The exclusion criteria were the same as that for study EC 604, plus patients who did not complete the preceding study EC604.

All patients who qualified for entry into the study commenced at a dose of candesartan cilexetil 8 mg. If medically required, the dose was increased to candesartan cilexetil 16 mg at any visit from Visit 2 onwards, and from Visit 3 onwards, the dose was up- or down-titrated.

Concomitant medication was continued during the study, similar to EC604. However, patients were not allowed to take additional medication (including over-the-counter drugs) without informing their physician.

Treatment compliance was assessed by counting the number of tablets returned to the investigator by the patient at Visits 3 to 8. A compliance of > 75% and < 125% was reported in 97.3% of the patients in the ITT-population.

Visit 1 of study EC610 was carried out on the same day as Visit 11 of the preceding study EC604. With the exception of the ejection fraction assessment, blood pressure/heart rate measurements, blood sampling, and Quality of Life assessment, data collected at Visit 11 of study EC604 were used as baseline values (Visit 1) for the present study. All adverse events that were ongoing at the end of the preceding study were documented as concomitant illnesses.

Efficacy assessment

At Visits 1 and 8, total exercise time (bicycle exercise test) was determined by bicycle ergometry: the procedure was essentially similar to that of study EC604. Where a suitable walking space existed, the six-minute walk test according to Guyatt[2] was carried out before the bicycle ergometry (similar to EC604).

At Visits 1, 5, and 8, the patients' signs and symptoms of CHF were rated using the Dyspnea Fatigue Index[1], and the patients' heart failure was assessed according to the NYHA functional classification, and a Quality of Life assessment was conducted using the SF-36 Health Survey.

The ejection fraction was assessed using echocardiography at Visits 1 and 8.

All adverse events reported by patients or observed by the investigator (including clinically relevant abnormal laboratory values and abnormal ECGs) were recorded in the case report form at each visit, regardless of their causal relationship.

In September 1997, the study was terminated prematurely by Takeda Euro R&D Centre GmbH because the required data from long-term, controlled, clinical studies could not be obtained from the present uncontrolled, open study. On 23 March 1998, Takeda Euro R&D Centre GmbH decided to drop the per-protocol population from the statistical analysis defined in the study protocol. Thus, major protocol violations were not defined.

The safety population was defined as all patients enrolled who took at least one dose of study medication. The efficacy analysis included all patients who received at least one dose of study medication and who had a total exercise time (bicycle exercise test) at baseline and at Visit 8.

During the statistical analysis, it became apparent that calculation of response rates had not been deleted from the statistical analysis plan. It was therefore decided *post hoc* (in collaboration with Takeda Euro R&D Centre GmbH) that response rates would not be analyzed and reported.

A total of 355 patients were enrolled in 61 study centers in Germany, the Czech Republic and Slovenia. One patient took no study medication and was excluded from the safety population. Of the 354 patients in the safety population, 282 patients (79.7%) did not complete the 9-month treatment period. For >90% of these patients, this was due to the sponsor's decision to stop the study prematurely. Total exercise time values were not available for two patients at baseline and for 22 patients at Visit 8, leading to their exclusion from the ITT population. Thus, 330 patients were evaluable for the efficacy analysis.

There were 255 male patients (72.0%) and 99 female patients (28.0%). The mean age of the safety population was approximately 62 years (153 patients (43.2%) were over the age of 65). The mean duration of congestive heart failure was 3.3 years. Except for one patient who was Oriental, all patients were Caucasian. The majority of patients (96.9%) were classified as having NYHA class II or III congestive heart failure.

Total exercise time (bicycle exercise test)

Unlike study EC604, in this study EC610, no beneficial increase in total exercise time over the course of the study was observed (Table 159). The sponsor attributed this lack of treatment effect to the premature termination of the study, because the majority of patients performed Visit 8 tests after less than the intended nine months of treatment with study medication.

Table 159 Total exercise time (bicycle exercise test) [s] – ITT population (n=330)

		Mean ± SD	Median	(min – max*)
Baseline (Visit 1)	n = 330	464.4 ± 151.2	465.5	120 – 900
Last value	n = 330	454.2 ± 152.9	446.0	120 – 845
Changes baseline to last value	n = 330	-10.2 ± 79.6	0.0	-350 – 233

*Negative absolute changes indicate a reduction in total exercise time as compared to baseline

Dyspnea Fatigue Index score

Unlike study EC604, there was no change in the mean value of the Dyspnea Fatigue Index score over the course of this study EC610 (Table 160). This lack of treatment effect, too, was attributed by the sponsor to the premature termination of the study earlier than the intended nine months of treatment with study medication.

Table 160 Changes in Dyspnea Fatigue Index score – ITT population (n=330)

		Mean ± SD	Median	(min – max*)
Baseline (Visit 1)	n = 330	7.5 ± 1.7	7.0	3 – 12
Last value	n = 330	7.7 ± 1.8	8.0	3 – 12
Changes baseline to last value	n = 330	0.3 ± 1.4	0.0	-6 – 5

* Negative values indicate a reduction in Dyspnoea Fatigue Index score relative to baseline

Other secondary parameters such as assessment of dyspnea by the patient, KYHA functional class, total walking distance (6-minute walk test), ejection fraction, and Quality of Life assessment did not show any improvement from baseline over the course of the study.

Efficacy Conclusions

Due to premature termination of the study, the sponsor submits that it is not possible to make any interpretation of the efficacy of candesartan in patients with mild to moderate CHF in this study.

10.1.9 Appendix PD5 Study EC614

A Six Month Exercise Tolerance Study of Candesartan Cilexetil with a Further Six Month Follow-Up in Patients with Symptomatic Heart Failure (NYHA Class II/III) Intolerant to Angiotensin Converting Enzyme Inhibitors and not Treated with Angiotensin Converting Enzyme Inhibitors.

This relatively large PD study of 463 patients with CHF was conducted to evaluate the efficacy of candesartan cilexetil in patients with symptomatic congestive heart failure (NYHA class II/ III) who were intolerant to angiotensin converting enzyme inhibitors (ACEi) and not treated with ACEi.

The primary objective at six months was to evaluate the effect of treatment with candesartan cilexetil (up to 16 mg) on exercise tolerance (bicycle exercise test) compared to placebo after a treatment phase of six months in patients intolerant to ACEi and not treated with ACEi. The study initially comprised a six-month double-blind treatment phase, but was amended (Amendment 3 dated May 5, 1998) to continue treatment for a further six-month (resulting in a total of 52- weeks of double- blind treatment) for patients who completed the six- month phase (except those in the Czech Republic).

The secondary objectives were to evaluate to evaluate the effects (at 6 and 12 months) of candesartan on the signs and symptoms of congestive heart failure (dyspnea-fatigue index),

NYHA class, quality of life, the number of hospitalizations due to congestive heart failure, the number of hospitalizations due to all causes, ejection fraction, and cardiothoracic ratio (CTR), and the safety and tolerability profile of candesartan cilexetil in this patient population.

Thus, this study was conducted as a placebo-controlled, parallel-group, randomized study with a single-blind placebo run-in phase of two weeks followed by a 52-week double-blind comparative phase of placebo versus candesartan cilexetil titrated from 4 mg to 8 mg to 16 mg once daily (with the possibility of down- titration if needed). The population studied comprised outpatients with symptomatic congestive heart failure (NYHA class II/ III), impaired left ventricular function (ejection fraction ≤ 45%), intolerance to ACEi therapy and not treated with ACEi, and who were clinically stabilized on optimal background CHF treatment prior to the start of the placebo run- in phase (Visit 1), and who had stable exercise tolerance prior to randomization (Visit 3). Other background CHF therapy (e.g. digoxin, ß- blockers, diuretics, etc., as prescribed) was maintained throughout the trial. The study was conducted from November 1997 through August 1999. The principal investigator is Professor P. Doenecke. This study was conducted in 54 centers in Germany (19), Israel (19), The Czech Republic (3) and Poland (13).

The inclusion and exclusion criteria are generally similar to those in the CHARM protocol SH-AHS-0003.

The procedure for concomitant use of medication was the same as that described for study EC604. Treatment compliance, too, was assessed as in study EC604, with 96.1% of the patients taking ≥ 75% or ≤ 125% of the planned number of capsules (compliant patients).

A total of 558 patients were enrolled in 54 centers. In the candesartan and placebo treatment groups, 34 and 32 patients, respectively, withdrew prematurely, and 92 and 86 patients, respectively, were not included in the second six months of the study. There were no important differences between the treatment groups with respect to the reasons for premature termination during the double-blind randomized phase.

There were 463 patients in the Safety population and 440 patients in the ITT. A total of 32 patients (14 in the placebo group and 18 in the candesartan group) were not included in the "Per-Protocol" (PP) population (n=408) due to at least one major protocol violation (e.g., non-compliance with the bicycle exercise test). Minor protocol deviations were also identified (e.g., patients who were outside of the protocol-defined age range or who had the bicycle exercise test prior to the walk test).

At the screening Visit, the treatment groups were comparable with regard to demography, reason for intolerance to ACEi (cough in >60% in each group), number of patients with concomitant diseases (99.6%), etiology of CHF (coronary heart disease was the most frequent in each treatment group), prior treatment for CHF in the preceding 3 months (85.5% in placebo group and 88.1% in candesartan group), and previous medical history (old myocardial infarction being the most frequently recorded condition (average 59.4%) in the treatment groups).

Efficacy Assessment

Exercise testing (Visits 3, 7, 9): The primary efficacy parameter for this study was exercise tolerance (total bicycle exercise time) assessed by bicycle ergometry (bicycle exercise test). Each patient had to undergo at least 5 exercise tests (Visits 1, 2, 2a (optional), 3, 7, 9). The protocol-specified procedures for the bicycle test were similar to that of study EC604.

Table 161 Total bicycle exercise time (sec) according to NYHA classification (ITT, n=440)

Visit	Exercise time (s)	NYHA II		NYHA III	
		Placebo (n = 172)	Candesartan cilexetil (n = 186)	Placebo (n = 43)	Candesartan cilexetil (n = 39)
Baseline (Visit 3)	n	172	186	43	39
	Mean ± SD	382.3 ± 134.0	379.2 ± 133.8	288.3 ± 95.0	313.7 ± 129.0
	Median	379.0	370.0	270.0	292.0
	Min, Max	156, 720	128, 720	127, 533	152, 660
Last value	n	172	186	43	39
	Mean ± SD	411.4 ± 160.2	408.8 ± 158.5	292.5 ± 93.9	341.3 ± 133.1
	Median	405.0	379.0	277.0	304.0
	Min, Max	82, 900	85, 871	107, 489	121, 594
Change from baseline: to Visit 7*	n	162	182	42	37
	Mean ± SD	20.9 ± 74.6	20.1 ± 55.3	10.0 ± 56.6	22.1 ± 63.7
	Median	9.0	18.5	4.0	17.0
	Min, Max	-149, 288	-235, 282	-120, 142	-128, 195
to Visit 9*	n	156	177	39	33
	Mean ± SD	34.7 ± 82.9	31.7 ± 69.7	4.8 ± 62.7	33.7 ± 60.3
	Median	27.0	26.0	0.0	12.0
	Min, Max	-122, 364	-296, 265	-119, 153	-75, 179
to last value*	n	172	186	43	39
	Mean ± SD	29.1 ± 84.5	29.6 ± 70.7	4.1 ± 60.0	27.6 ± 59.3
	Median	21.0	25.5	-4.0	12.0
	Min, Max	-174, 364	-296, 265	-119, 153	-75, 179

Unlike the findings in study EC604, the mean change in total bicycle exercise time from baseline to last value in the candesartan group was not statistically significantly (p= 0.481) different from that observed in the placebo group (although the sponsor contends that the candesartan treated group had a larger mean change compared to the placebo-treated group [by a placebo-corrected difference of 5.03 seconds!]).

By sub-group analysis (not pre-specified in the protocol) of 43 patients in the placebo group and 39 patients in the candesartan group who were classified as NYHA III at base line, a statistically significant difference (p= 0.044) in the change in bicycle exercise time from baseline to last value (4.1 ± 60.0 s in the placebo group vs. 27.6 ± 59.3 s in the candesartan cilexetil group) was found Table 161). For patients classified NYHA II, no significant difference between the treatment groups was observed in the change in bicycle exercise time from baseline to last value.

Secondary Efficacy Parameters

NYHA classification (Visits 3, 7, 9/ 10, 12, and 15): NYHA functional classification was performed according to the "Criteria Committee of the New York Heart Association" (1994). The assessment of NYHA classification at Visit 3 was taken as the baseline value. The same physician performed the classification throughout the study.

At last value and end-of-study (defined as the last post-baseline value obtained up to Visit 15 [12 month]), less than 7% of patients in both groups had deteriorated compared to baseline; the percentage who had deteriorated was greater in the placebo group at last value and end-of-study

(4.9% and 6.7% respectively) than in the candesartan cilexetil group (3.4% and 3.9% respectively). End- of- study shift table data are presented in Table 162 below.

Table 162 NYHA functional classification - shift table (Safety population; n = 463)

		NYHA classification			
		End-of- study			
At baseline		Class I	Class II	Class III	Class IV Death/CHF drop out
Placebo	Class II	31 (13.8%)	136 (60.4%)	6 (2.7%)	4 (1.8%)
	Class III	1 (0.4%)	14 (6.2%)	28(12.4%)	5 (2.2%)
Candesartan cilexetil	Class II	21 (9.1%)	164 (70.7%)	5 (2.2%)	3 (1.3%)
	Class III	1 (0.4%)	13 (5.6%)	24 (10.3%)	1 (0.4%)

(Appendix IX, Table 3.6.2.3. Cells that indicate no shift are shaded. Percentages were based on the number of non-missing values.)

Other secondary efficacy parameters

There were no statistically significant differences between the treatment groups with respect to the change from baseline in the Six Minute Walk Test, the Total Focal Index of the Dyspnea-Fatigue Index Score, VAS assessments of dyspnea and fatigue, Cardiothoracic ratio, the Ejection Fraction and the Quality of Life Survey.

Summary

In this study, the only statistically significant difference between the treatment groups was the mean change from baseline to last value in the primary efficacy parameter (bicycle exercise time) for the sub-group (not pre-specified in protocol) NYHA Grade III patients, which was significantly greater (p=0.044) in the candesartan cilexetil group (27.6±59.3 sec) than in the placebo group (4.1±60.0 sec). There were no significant differences between the groups with respect to the secondary efficacy parameters.

10.1.10 Appendix PD6 SH-AHS-0001

The RESOLVD (Randomized Evaluation of Strategies for Left Ventricular Dysfunction) Pilot study.

This rather large (N=768) dose-finding pilot trial[75] was intended primarily to determine the efficacy of 3 different dose levels of candesartan, 2 dose levels of candesartan added to enalapril or enalapril in patients with congestive heart failure (CHF) on submaximal exercise capacity and safety and tolerability. The secondary objectives were to determine the effect of the above combinations on neurohormonal parameters, and on QoL (quality of life), NYHA (New York Heart Functional Class) and ventricular volumes and function.

To be eligible for entry into the RESOLVD Pilot Study, patients had to have symptomatic CHF (NYHA II- IV), a 6-minute walking distance of ≤500 m, and a left ventricular ejection fraction (LVEF) < 0.40 obtained by echocardiography, radionuclide ventriculography or conventional angiography.

For consistency, the QOL assessment was always done prior to conducting any other tests. All

neurohormonal tests were done in the morning. Duplicate 6 minute walk tests were done at least 1 day apart.

The study was a randomized double-blind trial with a 6x2 partial factorial design with a two-Stage randomization. The run-in included three 1-week phases: 1) enalapril 2.5 mg b.i.d. plus placebo candesartan; 2) enalapril 2.5 mg b.i.d. plus candesartan 2 mg q.d.; 3) and enalapril 2.5 mg b.i.d. After randomization, in Stage I, the dose was titrated over 4-6 weeks to either candesartan 4, 8 or 16 mg q.d. or enalapril 10 mg b.i.d or candesartan 4 mg + enalapril 10 mg b.i.d or candesartan 8 mg + enalapril 10 mg b.i.d. (i.e., six treatment groups). After 19 weeks eligible patients were randomized in Stage II to receive metoprolol CR/XL up-titrated to 200 mg daily, or placebo and followed for an additional 24 weeks. Patients randomized in Stage II also continued to take the study medications that they were assigned in Stage I. Patients who were not candidates for β-blocker therapy and were not randomized in Stage II continued to take their Stage I study drugs and were followed during the study period.

Patients who were receiving continuous treatment with intravenous inotropic agents and patients with a history of intolerance to ACE-inhibitors or ATII antagonists, were not allowed to enter the study. Otherwise, the use of medication other than the study drugs was not restricted by the protocol and was left to the discretion of the attending physician.

Compliance was monitored by tablet counting at the end of the run-in phase for both Stage I and Stage II. At 18 and 43 weeks, the proportion of patients receiving the allocated target dose was over 80% while the proportion of patients taking more than 80% of the study medication was over 90% for all three groups.

The final evaluation of end points took place at week 43 and 44 after randomization.

The principal investigators are Prof Salim Yusuf and Prof. R.S. McKelvie. Sixty (60) centers in Canada, the United States, Italy and Brazil participated. The study was conducted from January 1996 through July 1997.

The study was prematurely terminated 6 weeks early when the External Safety and Efficacy Monitoring Committee (ESEMC) that were reviewing accumulating data observed on June 12, 1997, the following:

(a) mortality was higher in the treatment groups that contain candesartan: 8.7% with candesartan plus enalapril (4 mg+ 20 mg = 6.1%; 8 mg+ 20 mg = 11.4%), 6.1% with candesartan (4 mg = 6.3%; 8 mg = 6.5%; 16 mg = 5.5%) and 3.7% with enalapril (3 way group comparison p=0.15).

(b) CHF hospitalizations were higher in the treatment groups that contain candesartan: 7.2% with candesartan+ enalapril (4 mg+ 20 mg = 8.5%; 8 mg+ 20 mg = 6.0%), 10.7% with candesartan (4mg = 8.1%; 8 mg = 16.7%; 16 mg = 7.3%), and 3.7% with enalapril (3 way group comparison p= 0.048).

(c) Mortality plus CHF hospitalizations were higher in the treatment groups that contain candesartan: 15.1% for candesartan+ enalapril (4 mg+ 20 mg = 13.9%; 8 mg+ 20 mg = 16.2%), 14.6% for candesartan (4 mg = 13.5%; 8 mg = 18.5%; 16 mg = 11.9%), and 6.4% for enalapril (3 way group comparison p= 0.058).

At that time 695 (90%) patients had completed all visits; for the remaining patients, termination occurred within 10 days. About 9% of patients had a shortened follow-up by a mean of 16 days and 1% did not undergo final assessments.

All protocol deviations found were adjudicated to be minor except in one patient who was randomized after death (the investigator randomized the patient not knowing the patient had died suddenly) and was excluded by the executive committee.

Demographic and other patient characteristics were comparable between the six treatment groups.

Efficacy Assessment

Submaximal Exercise Capacity, 6- minute walk test

Six minute walk tests as described by Guyatt et al[2] were performed in duplicate at least one day apart at baseline, at visit 10 (week 20) and at the end of follow-up (weeks 46 and 47). The distance (6 MWD) and time (SMWT) used for the two tests were recorded as well as any symptoms during the walk.

The 6 MWD at baseline for C was 379 ± 5 m, 386 ± 5 m for C+ E, and 374 ± 8 m for E. There were no significant changes for C (390 ± 6 m), C+ E (358 ± 6 m), or E (387 ± 11 m) over the course of the trial. Nor was there any difference between the six different treatment groups.

Neurohormones

Blood samples were drawn after an overnight fast and 30 minutes of rest in the supine position, centrifuged immediately at 4°C and stored at -80°C until analyzed either in the Canadian Core Laboratory or in the Italian Core Laboratory or at Rigshospitalet in Oslo. Noradrenaline, adrenaline and dopamine were measured by HPLC, angiotensin II, aldosterone and endothelin I were measured by RIA, N-terminal pro-atrial natriuretic peptide (pro-ANP), and brain natriuretic peptide (BNP) were both measured in Oslo, Norway using previously reported techniques, and immunoreactive renin was measured on a subset of patients as described by Morganti et al.

Compared to the group treated with enalapril, the groups treated with candesartan and with candesartan + enalapril showed significantly large increases in angiotensin II levels (Figure 88). Also, a dose effect was observed in the candesartan-treated group with 16 mg candesartan group producing the greatest increase.

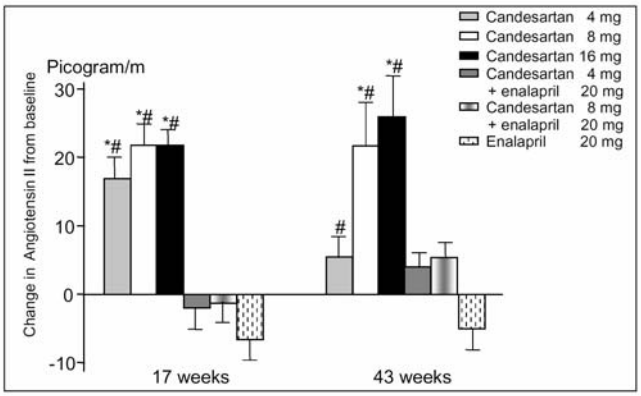


Figure 88 Change in angiotensin II levels after 17 and 43 weeks of treatment with candesartan, candesartan plus enalapril or enalapril
* P< 0.01compared with 0 weeks; # P< 0.01 compared with enalapril

For aldosterone, a decrease at 17 weeks for the treatment group candesartan plus enalapril was significantly (p<0.01) greater than that for enalapril (Figure 89).

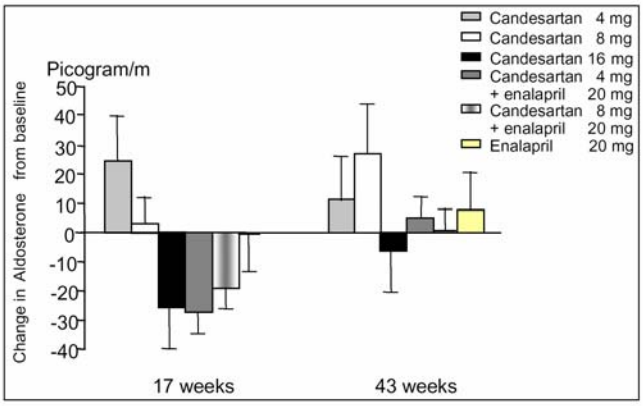


Figure 89 Change in angiotensin II levels after 17 and 43 weeks of treatment with candesartan, candesartan plus enalapril or enalapril
* P< 0.01compared with 0 weeks; # P< 0.01 compared with enalapril

There were progressive decreases in plasma norepinephrine and epinephrine concentrations but no significant between-group differences. N-terminal pro-atrial natriuretic peptide (pro-ANF) concentrations tended to increase mainly in the candesartan only and enalapril only groups between 17 and 43 weeks; the between-group differences were not significant. There was an increase in renin levels, with the candesartan only treatment group showing smallest increase; but the between-group differences were not statistically significant. There were no differences in the changes in endothelin concentrations between the three treatment groups.

Brain natriuretic peptide (BNP) decreased in the treatment group receiving candesartan plus enalapril, and increased in the treatment groups receiving candesartan only or enalapril only (p=0.0002). The greatest difference was observed between the group receiving enalapril only and that receiving candesartan 8 mg plus enalapril (Figure 90)

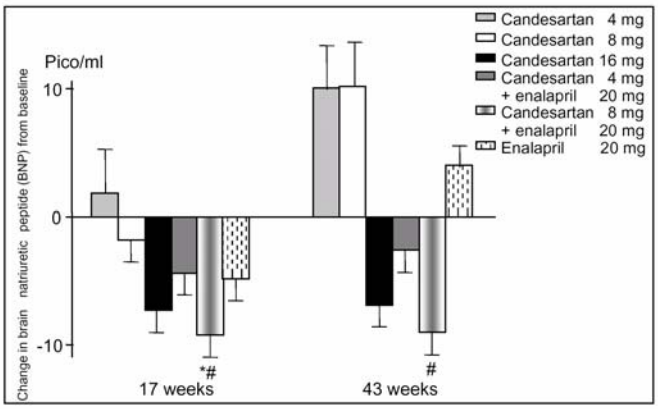


Figure 90 Change in brain natriuretic peptide (BNP) levels after 17 and 43 weeks of treatment with candesartan, candesartan plus enalapril or enalapril
* P< 0.01compared with 0 weeks; # P< 0.01 compared with enalapril

Ventricular function: LVEF (left ventricular ejection fraction), LVESV (left ventricular end systolic volume) and LVEDV (left ventricular end diastolic volume) were measured by ERNA (equilibrium radionuclide angiography) utilizing a standard count- based protocol (10). A core laboratory in Toronto, Canada, was used to determine the LVEF and left ventricular volumes.

There was a dose dependent increase in EF for candesartan plus enalapril group at 43 weeks (Figure 91), but the differences compared to the candesartan and the enalapril groups were not statistically significant (P=NS).

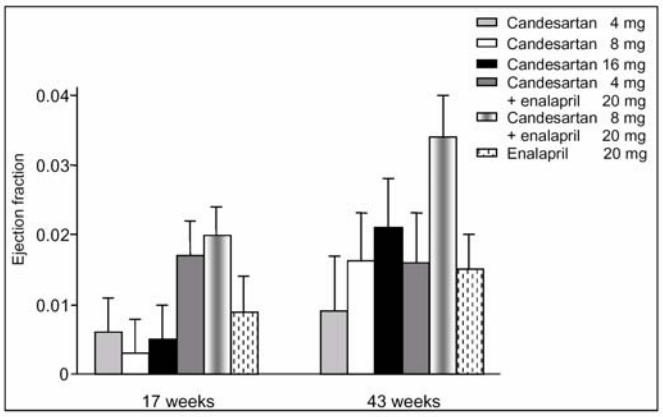


Figure 91 Increase in Ejection Fraction by different treatments after 17 and 43 weeks.

There was a difference among the groups (P< 0.01) in increase in EDV over time (P= 0.0007), with candesartan and enalapril patients showing larger increases (Figure 92). There was no dose-by-time interaction for the 6 groups (P= 0.12).

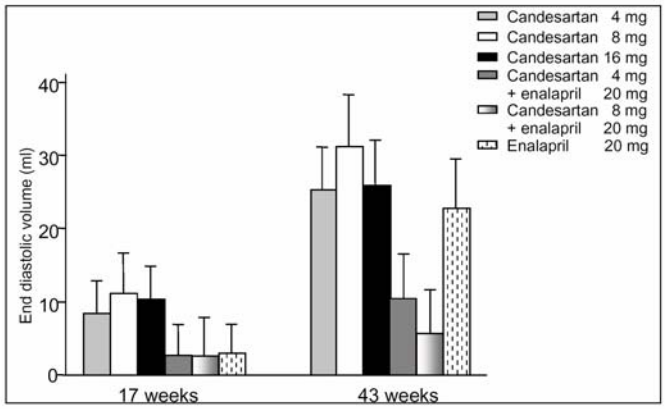


Figure 92 Change in End Diastolic Volume (ml) by different treatments after 17 & 43 weeks.

There was a difference among the groups (P< 0.05) in increase in ESV over time (P= 0.006), with candesartan only and enalapril only patients showing increases (Figure 93). However, patients taking 8 mg of candesartan plus enalapril had a decline (P< 0.01) in ESV at both 17 and 43 weeks, while those 4 mg of candesartan plus enalapril had an intermediate decline at 17 weeks which was not statistically significant.

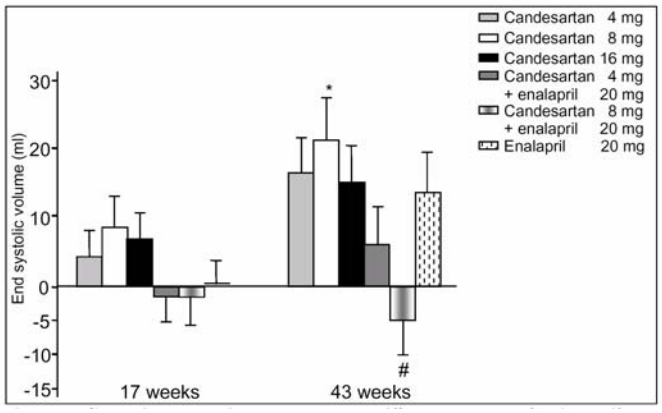


Figure 93 Change in End Systolic Volume (ml) by different treatments after 17 & 43 weeks.
* P< 0.01 compared with 0 weeks; # P< 0.01 compared with enalapril

Blood pressure and heart rate: Seated systolic and diastolic arm blood pressures were measured twice at each visit heart rate was measured once at each visit. Systolic and diastolic blood pressures declined in a similar manner with candesartan or enalapril and more pronounced with candesartan plus enalapril (p< 0.01). There was no increase in resting heart rate.

NYHA functional class: The NYHA functional class scale graded from 1- 4 was used. No significant differences were found at 17 or 43 weeks after randomization.

Quality of life: The Minnesota Living with Heart Failure questionnaire (MLHF) was used to assess quality of life at base- line and at the end of follow- up. There were no significant differences in quality of life at 18 or 43 weeks among the six groups.

Efficacy conclusions:
The RESOLVD pilot study was not powered to evaluate morbidity and mortality. It was prematurely terminated by the ESEMC, due to a trend towards a better outcome in the enalapril group (the number of serious adverse events and deaths were numerically but not statistically significantly higher in patients treated with candesartan plus enalapril or candesartan alone compared to enalapril alone).

The RESOLVD pilot study was designed to compare the effect of the AII antagonist candesartan, with enalapril and their combination on exercise performance, ventricular function, quality of life, neurohormones and tolerability in patients with heart failure. A secondary goal was to identify the optimal dose of candesartan (4, 8 or 16 mg) for a larger outcome study.

In the present study, there was no difference in the walking distance (primary efficacy parameter) between the different treatment regimens at the end of the treatment. No conclusions can be drawn regarding clinical outcome of the different treatments used in this study which was not powered for or intended to study clinical outcomes.

10.1.11 Appendix PD7 Study OCT105

Evaluation of the influence of TCV-116 on exercise tolerability and cardiohemodynamics in patients with chronic heart failure (CHF)

This study was performed in Japan (PI = Hiroshi Kasanuki, The Heart Institute of Japan) as a double-blind, placebo-controlled, parallel-group comparison of candesartan cilexetil (8 mg) vs. placebo on patients with chronic heart failure (CHF: - NYHA class II or III, and EF≤40%).

The objective was to evaluate the influence of candesartan on exercise tolerability (**bicycle ergometer**) and cardiohemodynamics (MRI) in patients with CHF. (Both are primary endpoints.)

After a run-in period of 3-6 weeks (receiving candesartan 8 mg once/day), patients were randomized into the treatment period to receive candesartan 8mg/day or placebo for six months. The study intended to enroll 40 patients (20 in each group).

The study was discontinued after enrolling 2 patients only into the treatment period (N.B. 12 patients gave consent. When the study was discontinued, there were 9 patients in the run-in period, and 1 patient who dropped out during the run-in period).

This study was discontinued along with the premature termination by the Safety Monitoring Board of the Phase III double-blind study (ARCH study) in CHF which was on-going in parallel with this study. No reason was given for the premature termination of either study.

Conclusion: No clinically relevant information was obtained from this study due to early

termination. No serious adverse events were reported. One of the two patients enrolled experienced lumbar pain, and had increased total cholesterol and increased uric acid levels.

10.1.12 Appendix PD8 Study OCT106

Evaluation of the influence of TCV-116 on exercise tolerability and left ventricular function in patients with chronic heart failure

This study was performed in Japan (PI = Tetsuro Shirai, Tokyo Metropolitan Police Hospital) as an open-label study to evaluate the influence of candesartan cilexetil on exercise tolerability (**by treadmill exercise test**) and left ventricular function in patients with chronic heart failure (CHF: - NYHA class II or III, and EF≤45%).

After a run-in period of 2 weeks (during which all previous ACEi or ATII antagonist used was withdrawn and baseline tests were performed), patients were given once daily oral candesartan tablets for 14 weeks (4 mg/day for 2 weeks, 8 mg/day for 12 weeks).

The target number of patients was 13 patients. 12 patients were enrolled. Of them, 2 patients did not enter in the treatment period because the symptoms were aggravated during the run-in period, and one patient discontinued the treatment on Day 14 of treatment because of development of an adverse event (headache). Therefore, the number of patients evaluable for analysis was 9.

Efficacy Results:
1) The exercise time in treadmill exercise test was prolonged by a mean of 1.053 minutes (two-sided 9S% confidence interval: -0.6956 to 2.8023) in the 9 patients, which was not statistically significant (p=0.2023).
2) LVMI value on echocardiogram showed statistically significant (p=0.0164) mean reduction of – 15.402% (two-sided 95% confidence interval: -27.1366 to – 3.6678), compared to that during the run-in period. Also, the EF value showed a statistically significant (p=0.0198) mean increase of 47.070% (two-sided 95% confidence interval: 9.6801 - 84.4605), compared to that during run-in period.
3) Both blood ANP (which is an index of atrial load) and BNP (which is an index of left ventricular function and myocardial damage) concentrations were decreased significantly (ANP: p=0.0207; BNP: p=0.0006).

Safety Results:
1) Headache occurred in 1 patient (10.0%) which disappeared after withdrawal of the study medication. There was one incidence of a "bilateral chronic subdural hematoma" (a serious adverse event).
2) Abnormal alterations of laboratory variables occurred in 7 of the 10 patients (70%) (12 episodes), which included 4 episodes of "K increased", 2 of "BUN increased" and 1 each of "white blood cell count increased", "red blood cell count decreased", "hemoglobin decreased", "hematocrit decreased", "creatinine increased" and "ALT (GPT) increased".

Conclusion: There was a non-significant prolongation of the exercise time in treadmill exercise test together with significant reduction in LVMI and significant increase in EF values on echocardiogram, and significant reduction in blood ANP and BNP concentrations, all of which suggested an improvement in the state of heart failure.

10.1.13 Appendix PD9 Study CPH101

Evaluation of the acute effects of TCV-116 on cardiohemodynamics in patients with chronic heart failure

This study was performed in Japan (PI = Hirofumi Yasue) as a single-dose (2 mg, 4 mg or 8 mg candesartan) open-label study to evaluate the influence of candesartan cilexetil on the cardiohemodynamics and the blood hormone levels in 13 patients with chronic heart failure (CHF: - NYHA class II or III, and PAWP ≥ 15mmHg or CI ≤ 2.2L/min/m^2).

A candesartan cilexetil tablet was orally administered in single doses of 2 mg (4 patients), 4 mg (2 patients) or 8 mg (7 patients). The cardiohemodynamic parameters and the blood hormone concentrations were determined over time before administration and 1, 2, 3, 4, 6, 8, 1Q, 12, 24 and 30 hours after administration of candesartan. The subjective symptoms, physical findings and adverse drug reactions were also recorded.

Cardiohemodynamics measured included pulmonary arterial wedge pressure, pulmonary arterial pressure and right atrial pressure were measured by the Swan-Gantz's catheter method. Also, cardiac outputs, cardiac index, stroke output, stroke output index, total peripheral resistance and pulmonary vascular resistance were measured. Pulse rates were determined from the ECGs. Blood pressures in lying position were measured by MANCHETTE technique.

Blood hormone concentrations measured included atrial natriuretic polypeptide (ANP), brain natriuretic polypeptide (BNP), renin activity, aldosterone, epinephrine, norepinephrine, dopamine and angiotensin conversing enzyme activity.

Efficacy Results:
(1) Of the patients evaluable for cardiohemodynamic parameters (3 patients on 2 mg, 1 patient on 4 mg and 4 patients on 8 mg), no consistent effect was found. Patients on 8 mg candesartan showed a trend (but not statistically significant) towards reduction in the pulmonary arterial wedge pressure and pulmonary arterial pressure. In some patients, reduction in lying blood pressure, pulse rate and peripheral vascular resistance was noted. For other parameters, there was no definite change for any direction.
(2) The level of ANP showed a decreasing trend (but not statistically significant). The levels of BNP and the other hormones did not show any changes.
(3) There was a positive correlation between the change in pulmonary arterial wedge pressure and that in blood ANP concentration.
(4) No changes were found in subjective symptoms, physical findings and ECG findings before and after administration of candesartan.

Safety Results: There were no adverse signs/symptoms or abnormal alterations of laboratory variables that were considered to be attributable to the study medication.

The above results suggest that a single dose of 8 mg candesartan gives rise to lowering of pulmonary arterial wedge pressure and the blood ANP levels though not statistically significant.

10.1.14 Appendix PD10 Study CPH103

Evaluation of the Influence of TCV-116 on Exercise Tolerability in Patients with Chronic Heart Failure

This study was performed in Japan (PI = Shigetake Sasayama Kyoto University Hospital) as an open-label study to evaluate the influence of candesartan on exercise tolerance (**by treadmill exercise test**) in patients with chronic heart failure (CHF) and subjective symptoms. The primary endpoint was Improvement Rating of Exercise Tolerance (IR-ET); the change in exercise tolerability categorized as "improved", "unchanged", "aggravated" or "impossible to be judged."

After a placebo run-in period of 1-4 weeks (and baseline measurements at end of the run-in period), candesartan was administered as one oral table each morning after breakfast to patients with CHF (NYHA class II_M or III) and subjective symptoms. The initial dosage was 2 mg/day titrated up to 12 mg. This was changed since April 21, 1997 to the initial dosage of 4mg/day titrated up to 8 mg. The duration of treatment was 12 weeks.

There were 9 evaluable patients consisting of 7 patients on 4mg/day and 2 patients on 2mg/day. In 3 patients improvement rating was “impossible to be judged” because of short duration of the treatment period. Thus, evaluations were made in 6 (5 on 4mg/day and 1 on 2mg/day).

Efficacy Results:
(1) On IR-ET, exercise tolerance (by treadmill exercise test) was judged “improved” in 2 of the 6 patients. However, no statistically significant change was recognized in maximum loading dose, loading time, maximum oxygen uptake or anaerobic metabolism threshold.
(2) Subjective symptoms were judged “slightly improved” in 4 of the 6 patients.
(3) Clinical symptoms were judged “improved” in 1 of the 6 patients and “slightly improved” in 3 of the 6 patients.
(4) Significant shortenings of left ventricular end-diastolic diameter and end-systolic diameter were recognized at the end of the treatment on echocardiogram. Left ventricular end-diastolic volume and end-systolic volumes were reduced significantly, and shortening rate of left ventricular inside-diameter and ejection fraction (EF) were significantly increased. There were no significant changes in stroke output or cardiac index. (No data submitted for review.)

Conclusion: The above results showed that the treatment of CHF patients with candesartan in dosage of 2- 4mg/day for 12 weeks improved the exercise tolerance in 2 of the 6 patients, but no

significant changes were recognized about the parameters characteristic of exercise tolerability. As the evaluable patients were few and there were no patients who were given 8mg/day (the clinical dose), it was not possible to conduct a pertinent evaluation of the influence of candesartan on exercise tolerability.

Safety Results:
Safety evaluation was made in all the patients who received the study medications (i.e., 7 patients on 4 mg/day and 3 patients on 2mg/day). No significant adverse events related to the study drug were reported. There were 3 episodes of increased BUN/creatinine, and one of these 3 was also associated with increased serum potassium.

10.1.15 Appendix PD11 Study CPH104

Evaluation of the influence of TCV-116 on hormones in patients with chronic heart failure

This study was performed in Japan (PI = Masahiko Kinoshita, Shiga University of Medical Science) as an open-label, dose-titrated (according to symptoms) study to evaluate the influence of candesartan cilexetil on hormones and, where feasible, renal function in patients with chronic heart failure (CHF) and subjective symptoms.

After a placebo run-in period of 2 weeks (and baseline measurements at end of the run-in period), candesartan was administered as one oral table each morning after breakfast to 16 patients with CHF (NYHA class II or III) and subjective symptoms. The initial dosage was 2 mg/day titrated up to 12 mg according to symptoms. The duration of treatment was 12 weeks. The total period of the study was 1 year and 10 months.

Efficacy and clinical pharmacology results:
(i) Blood hormones: Candesartan significantly increased active renin concentration (ARC), angiotensin II (AII), and significantly decreased dopamine (DA), (primary endpoints) brain natriuretic peptide (BNP), intercellular adhesion factor (sICAM-1) & interleukin-6 (IL-6) (secondary endpoints). cGMP/BNP and cGMP/(ANP+BNP) ratios increased significantly although cGMP concentration did not change significantly.
(ii) Cardiohemodynamic parameters: left ventricular end-systolic dimension (LVDs) decreased significantly. As a result, left ventricular end-diastolic volume (LVEDV) significantly decreased, and proportion of fractional shortening of left ventricular inside diameter (%FS), ejection fraction (EF), stroke output volume (SV) significantly increased.
(iii) Specific activity scale and the total score of the subjective symptoms were significantly improved. On Global Improvement Rating of Clinical Symptoms, response was judged "improved" or "markedly improved" in 35.7 % (5/14) of the patients.
(iv) The unchanged compound of candesartan was almost undetectable in blood 3 hours after administration. The active metabolite, M-I, was detected before administration of the last dose, and its concentration became higher 3 hours after administration.
(v) Renal function was not evaluated in the study patients.

Safety results: There were 16 episodes of "mildly" abnormal laboratory variables in 8 patients, including increased GOT/GPT/Al-P/y-GTP, decreased hemoglobin, decreased lymphocyte count, and increased uric acid.

Conclusion: In 16 patients with chronic heart failure treatment with candesartan was associated with an increase in renin and angiotensin II concentrations and a decrease in the concentrations of dopamine, BNP, sICAM-1 and IL-6. As for cardiohemodynamics, LVESV was decreased and % FS, EF, SV were increased. The subjective symptoms, physical findings, severity and specific activity scale appeared to improve on the average over time.

Publication: Naoyoshi Tsutamoto, et al.: Evaluation of the influence of candesartan cilexetil on cardiac function and hormone in patients with chronic heart failure. *Journal of Clinical Therapeutics & Medicines,* 16: 763-776, 2000.

10.1.16 Appendix PD12 Study SH-AHS-0004 (Ellis Study)

Addition of candesartan to angiotensin converting enzyme inhibitor therapy in patients with chronic heart failure does not reduce levels of oxidative stress

This was a British study (published in The European Journal of Heart Failure 2003; 4: 193-199. Corresponding author = Gethin R. Ellis). The investigators investigated whether the addition of AT-R antagonists to ACE inhibitors (ACEi) would reduce oxidative stress and improve endothelial function and exercise tolerance in patients with chronic heart failure (NYHA class II-IV, documented impaired LV systolic function (EF≤ 35%) on stable ACEi therapy).

28 patients were randomized to receive placebo or candesartan. The initial dosage was 8 mg/day titrated up to 16 mg/day after one week depending on blood pressure and renal function. The duration of treatment was one month. The following tests were performed on the first day of the study and repeated following a month of treatment.

Plasma lipid-derived free radicals (FR), thiobarbituric acid reactive substances (TBARS) and neutrophil O_2-generation, markers of oxidative stress, were measure in venous blood. Arterial flow-related endothelial function was assessed as the response of the brachial artery to flow-related shear stress. Exercise capacity was determined by cardiopulmonary exercise testing using a maximal treadmill exercise test (Weber protocol). On-line gas analysis permitted breath-by-breath measurement of expired gas concentrations; peak V_{O2}, exercise time and V_E/V_{CO2} slope were calculated.

Results: Compared with placebo, candesartan had no effect on changes in lipid derived free radicals, TBARS or neutrophil O_2-generating capacity. There was no effect on changes in brachial artery flow-mediated dilatation nor peak V_{O2}.

Conclusion: The addition of candesartan to ACE inhibitor therapy had no effect on oxidative stress and did not improve endothelial function or exercise capacity in patients with CHF.

10.1.17 Appendix PD13 Study SH-AHS-0005 (Vaile study)

Effects of angiotensin II (AT1) receptor blockade on cardiac vagal control in heart failure

This was a British study (published in Clinical Science (2001): 101; 559-566. Lead author =J.C. Vaile). The authors investigated whether the addition of angiotensin II receptor antagonist therapy would have an effect on cardiac autonomic control in patients with heart failure. The study group comprised 21 patients with heart failure [mean (S. E. M.) ejection fraction 33% (1%)], in the absence of angiotensin- converting enzyme (ACE) inhibitor therapy

In a randomized double-blind cross-over study, the effects of candesartan and placebo on baroreflex sensitivity and on heart rate variability at rest, during stress and during 24 h monitoring were studied on 21 patients with stable heart failure (NYHA class not defined; mean (SEM) EF =33% (1%) who were not on current ACEi therapy). The study was performed in a clinical autonomic research laboratory, using the Oxford BRS (baroreflex sensitivity) and heart rate variability (HRV, using a Holter 24 h ECG recording and measuring RR intervals) to determine the autonomic effects of both acute and chronic therapy with candesartan. Acute effects were assessed 4 h after oral candesartan (8 mg/day) and chronic effects after 4 weeks of treatment (dose titrated to 16 mg/day).

Results: In the acute study, candesartan was not different from placebo in its effects on blood pressure or mean RR interval. In the chronic study, candesartan significantly reduced the mean (SEM) blood pressure [placebo, 137(3)/82(3) mmHg; candesartan, 121(4)/75 (2) mmHg; $P < 0.001$), but had no effect on mean RR interval [placebo, 857 (25) ms; candesartan, 857 (21) ms].

Compared with placebo there were no significant effects of acute or chronic candesartan on heart rate variability in the time domain and no consistent effects in the frequency domain. Baroreflex sensitivity assessed by the phenylephrine bolus method was significantly increased after chronic candesartan [placebo, 3.5(0.5)ms/mmHg; candesartan, 4.8(0.7)ms/mmHg; $P<0.05$].

Conclusion: Thus, in contrast to previous results with ACE inhibitors, angiotensin II receptor blockade in heart failure did not increase heart rate variability, and there was no consistent effect on baroreflex sensitivity.

10.1.18 Appendix PD14 Study Hikosaka (Publication)

Candesartan and Arterial Baroreflex Sensitivity and Sympathetic Nerve Activity in Patients with Mild Heart Failure

This was a Japanese study (published in Journal of Cardiovascular Pharmacology (2002): 40; 875-880. Lead author = Makoto Hikosaka). The purpose of this study was to investigate the effects of candesartan on arterial baroreflex sensitivity (BRS) and sympathetic activity in patients with mild heart failure (HF).

Arterial pressure, heart rate, plasma renin activity, plasma angiotensin II and noradrenaline, and muscle sympathetic nerve activity (MSNA) were measured before therapy and after 4 weeks in 20 patients with mild HF (NYHA Class I or II, echocardiographic LVEF 43%±12%). Patients were assigned to a candesartan group (n = 10) or a placebo group (n = 10). Baroreflex sensitivity was assessed by using the phenylephrine bolus method.

Results: Candesartan induced an increase in plasma renin activity and plasma angiotensin II, associated with a reduction in arterial pressure without affecting heart rate. Although plasma noradrenaline was unchanged, MSNA decreased significantly (52±11 bursts/min to 42±9 bursts/min; p < O.OI)) and BRS increased significantly (6.9±3.6 msec/mmHg to 10.2±3.3 msec/mm Hg; p < 0.01) after candesartan. However, there were no significant changes in the measured variables in the placebo group.

Conclusion: These data indicate that candesartan treatment enhanced BRS and reduced sympathetic activity in patients with mild HF. Thus, the inhibitory effect of candesartan on sympathetic activity may, at least in part, contribute to the beneficial effect of angiotensin II receptor blockade in patients with mild HF.

10.1.19 Apendix 15 CHARM-Added (SH-AHS-0006) Trial

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

Study dates

Table 163 shows the chronology of the clinical trials conducted under the CHARM Program.

Table 163 Chronology of the CHARM Program highlights

Original Protocol	November 13, 1998
Amendment #1	December 10, 1998
First Patient randomized	March 22, 1999
Amendment #2	March 31, 1999
Amendment #3	December 21, 1999
Amendment #4	March 7, 2000
Last Patient completed	March 31, 2003
Study Closure	March 31, 2003
Statistical Analysis Plan finalized	April 15, 2003
Database Lock	June 12, 2003
Database Re-Locked	July 4, 2003

Overall Program Title:

"Candesartan Cilexetil (Candesartan) In Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM)"

Individual Study Title:

"Clinical Study (SH-AHS-0003) of Candesartan in Patients With Heart Failure Who Are ACE Inhibitor Intolerant and Have Depressed Left Ventricular Systolic Function"

"Clinical Study (SH-AHS-0006) of Candesartan in Patients With Heart Failure Who Are Treated With ACE Inhibitors and Have Depressed Left Ventricular Systolic Function"

"Clinical Study (SH-AHS-0007) of Candesartan in Patients With Heart Failure and Preserved Left Ventricular Systolic Function"

Objectives of Overall Program (Pooled Analyses):

Primary: To determine whether candesartan, compared to placebo, reduces all cause mortality in the pooled population of patients with symptomatic chronic heart failure (studies SH-AHS-0003, SH-AHS-0006, SH-AHS-0007).

Secondary: To determine whether candesartan, compared to placebo, reduces all-cause mortality in the pooled population of patients with depressed LV function (studies SH-AHS-0003, SH-AHS-0006).

Objectives Specific to Study SH-AHS-0006 (CHARM Added study)

Primary: To determine whether candesartan, compared to placebo, reduces the combined endpoint of cardiovascular (CV) mortality or hospitalization for the management of CHF.

Secondary: To determine whether candesartan, compared to placebo,

- Reduces the combined endpoint of all-cause mortality or hospitalization for the management of CHF
- Reduces the combined endpoint of cardiovascular mortality or hospitalization for the management of CHF or non-fatal myocardial infarction (MI).

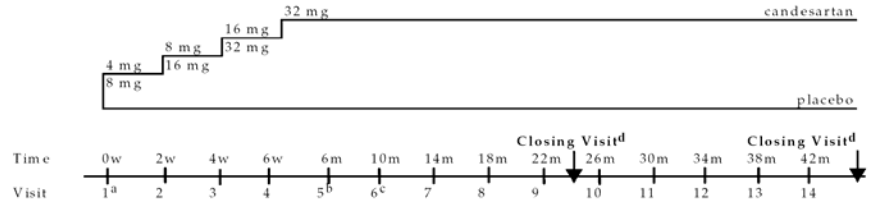
Other objectives: To determine whether candesartan, compared to placebo:

- reduced the combined endpoint of cardiovascular mortality, or hospitalization for the management of CHF or non-fatal MI, or coronary revascularization procedures.
- reduced the combined endpoint of all-cause mortality and all-cause hospitalization.
- reduced all-cause mortality.
- reduced all-cause hospitalization.
- reduced the number of fatal and non-fatal MIs.
- affected functional state and symptoms according to NYHA classification.
- was well tolerated and safe by evaluation of drug discontinuation, dose reduction and non-cardiovascular (CV) death and hospitalization.
- influenced the cost of health care.

Study design:

This was a randomized, double- blind placebo controlled parallel group multicenter study to evaluate the influence of candesartan (4 mg titrated to target dose of 32 mg once daily) on mortality and morbidity in patients with depressed LV systolic function and ejection fraction (EF≤ 40%) and simultaneously treated with an ACE inhibitor. The primary variable for this evaluation was time from randomization to CV mortality or the first occurrence of a hospitalization for CHF. A total of 2548 patients were randomized at 473 sites in 25 countries.

Figure 94 (below) shows the design of the study and the sequence of treatment periods. Randomization was carried out at visit 1. The patients were randomized to candesartan or placebo, and titrated up to 32 mg once daily or to the highest tolerated dose during a 6- week period. Thereafter the patients were scheduled to a visit every 4th month. The information in the CRF for visits 2 to 14 was similar. The recruitment period was 8 months. All patients remained in the study until the last randomized patient had been in the study for at least 2 years. Thus, individual time in the study for surviving patients not lost to follow-up may be 41 to 48 months.



[a] **Titration phase up to 32 mg once daily or highest tolerable dose (visits 1-4):** Time between visits: 2 - 3 weeks.
[b] **Visit 5:** Time from visit 1: 24 weeks ± 4 days.
[c] **Visits 5-14:** Time between visits: 4 calendar months ± 1 week.
[d] **Closing visit:** Conducted during March, 2003

Figure 94 Study design

ACE inhibitor dose

The optimal ACE inhibitor dose was chosen, based on tolerability and clinical information. For each patient enrolled, the investigator had to state whether the patient was on individualized optimal ACE inhibitor dose. The recommended optimal (CHF therapeutic) doses of ACE inhibitor are shown in Table 164.

Table 164 Doses of ACE inhibitors used in studies that demonstrate a reduction in mortality and morbidity

ACE inhibitors used in clinical trials in heart failure	Target dose	Average dose in study
captopril	50 mg t.i.d.	not available
enalapril	10-20 mg b.i.d.	16-18 mg
lisinopril	32.5-35 mg q.d.	19 mg
ramipril	5 mg b.i.d.	not available
trandolapril	4 mg q.d.	not available

The dose of other ACE inhibitors used should be chosen to equate with the above doses.

Therapy with β-blockers or spironolactone:

If therapy with a β-blocker or spironolactone was considered, these treatment were initiated and the dose levels stabilized before patients were randomized into the clinical trial.

Inclusion Criteria (Common to all 3 studies in the CHARM Program)

- Male or female, ≥ 18 years old.
- Symptomatic CHF corresponding to NYHA class II-IV for ≥ 4 weeks before randomization.
- Informed consent. (Obtained before any study specific procedures were carried out).

Criteria specific to CHARM Preserved (SH-AHS-0006)

- Documentation of left ventricular ejection fraction (LVEF) ≤ 40% by contrast ventriculography, radionuclide ventriculography or quantitative echocardiography within the previous 6 months. The most recent measurement was used.
- Patients with NYHA Class II must have been of hospitalized for a cardiac reason in the past 6 months.
- Treatment with a constant dose of an ACE inhibitor at least 30 days before randomization.

Exclusion Criteria (Common to all 3 studies in the CHARM Program)

Any of the following was regarded as a criterion for exclusion:

1. Treatment with an angiotensin II type 1 (AT_1) receptor blocker within 2 weeks before randomization.
2. Known hypersensitivity to AT_1-receptor blocker.
3. Current serum-creatinine ≥ 265 μmol/L (≥ 3 mg/dL). If the patient was in a stable condition the sample could be taken within one month before randomization. For unstable patients a new sample was recommended.
4. Current serum-potassium ≥ 5.5 mmol/L (≥ 5.5 mEq/L) or a history of marked ACE inhibitor induced hyperkalemia resulting in either a serum-potassium ≥ 6.0 mmol/L (≥ 6.0 mEq/L) or a life-threatening adverse event. If the patient was in a stable condition, the sample could be taken within one month before randomization. For unstable patients a new sample was recommended.
5. Known bilateral renal artery stenosis.
6. Current symptomatic hypotension.
7. Persistent systolic or diastolic hypertension (systolic >170 mmHg; diastolic >100 mmHg) despite use of antihypertensive therapy.
8. CHF secondary to any of the following conditions: a) Critical aortic or mitral stenosis b) Non-cardiac disease (e.g., uncorrected thyroid disease) c) Pericardial disease.
9. Stroke, acute myocardial infarction or open-heart surgery within the last 4 weeks before randomization.
10. History of severe obstructive, restrictive or other chronic pulmonary disease.
11. Significant liver disease.
12. The following procedures: a) Planned cardiac surgery expected to be performed within 4 weeks after randomization. b) Previous heart transplants; or heart transplants expected to be performed within the next 6 months
13. Presence of any non-cardiac disease (e.g., cancer) that was likely to significantly shorten life expectancy to <2 years.
14. Pregnant or lactating women or women of childbearing potential who were not protected from pregnancy by an accepted method of contraception, such as the oral contraceptive pill, an intrauterine

device or surgical sterilization (all women of childbearing potential must have a negative pregnancy test before randomization).
15. Any condition that in the opinion of the investigator would jeopardize the evaluation of efficacy or safety or be associated with poor adherence to the protocol.
16. Treatment with any investigational agents within 4 weeks before randomization.

Protocol Amendments:

The protocol amendments to the CHARM program are summarized in Table 165 below. The table below includes the specific date of implementation of each amendment and its relationship to patient recruitment. Particular attention to be paid to Amendment 4 that is highlighted in the table below. The change involved increasing the sample size in the overall CHARM program by 950 patients (15% increase). The increase in sample size affected each component of CHARM differentially. This change occurred more than 15 months after the original protocol was first approved and approximately 12 months after the first patient was randomized.

Table 165 Summary of Protocol Amendments in the CHARM program

Number (date of internal approval)	Key details of amendment (Section of this report affected)	Reason for amendment	Persons who initiated Amendment
Amendment made before the start of patient recruitment			
1 (10 December 1998)	Another secondary objective was added: To determine whether candesartan, compared to placebo, reduced the combined endpoint of all-cause death and hospitalization for the management of CHF. Changes in the primary analysis were made to reflect changes in the secondary endpoint described above.	To meet planned changes in European guidelines for heart failure studies, recommending that "all-cause death" is part of any combined Endpoints.	AstraZeneca Clinical Study Team
Amendments made after the start of patient recruitment			
2 (31 March 1999)	No substantive changes made via this amendment. There were no changes to the primary/secondary endpoints, analysis, inclusion/exclusion criteria that were made	Editorial/Clarification changes	Executive Committee AstraZeneca Clinical Study Team
3 (21 December 1999)	A reference was made to the Clinical Endpoint Committee Manual of Operations (adjudication plan). Inclusion criteria (Section 5.3.1) ACE inhibitors were allowed as concomitant treatment for patients fulfilling the HOPE-study inclusion criteria.	The detailed adjudication plan had not been developed at the time of the original protocol. Publication of the HOPE-study results	Executive Committee

4 (7 March 2000)	The number of randomized patients in the overall CHARM program was increased by 950 patients (6500 to 7450). For CHARM Alternative this increase was 300 patients. For CHARM Added (0006) this was 250 patients. For CHARM Preserved this was 400 patients.	To safeguard statistical power due to lower than expected event rates in blinded data.	Executive Committee

Note: Data in this table adapted from Table 12 of SH-AHS-0007 study report

Statistical Considerations

Please refer to the Statistical Review by Dr. Charles Le for a more detailed discussion.

Primary Analyses (of each component study of CHARM):

The primary variable (time from randomization to a CV event or the first occurrence of a CHF hospitalization) was to be analyzed by a two-sided log rank test. For patients with multiple occurrences of events, the time to first occurrence was to be used. A p-value below 0.05 was to be considered statistically significant.

To meet the secondary objectives in each study a log rank test was to be performed to first compare the incidence curves for the combined endpoint of all cause mortality or CHF hospitalization and then for the combined endpoint of CV mortality, CHF hospitalization or non-fatal MI. A statistically significant difference was to be declared if the p-value was below 0.05.

The primary and secondary endpoints were to be analyzed using a step down procedure in which if and only if the previous analysis was significant at a p value below 0.05, were subsequent analyses of the secondary endpoints were to occur.

Primary Pooled Analyses (CHARM studies pooled):

Data on all cause mortality was to be pooled from all three component studies of the CHARM Program (SH-AHS-0003, SH-AHS-0006, SH-AHS-0007). The primary endpoint of the pooled analysis was to determine if candesartan, compared to placebo, reduces all cause mortality in this patient population. A p-value less than 0.05 for the two-sided log-rank test was to be considered as a confirmation of different incidence curves for the pooled population.

It was estimated that the annual event rate in the overall CHARM program would be approximately 11%. It was anticipated that the event rates in the patient population with a depressed ejection fraction would be higher: 14% and 11.6% for studies SH-AHS-0003 and SH-AHS-0006 respectively. It was anticipated that the annual event rate in the patients with preserved ejection fraction would be 8.3%. It was also anticipated that candesartan arm would reduce the incidence of all cause mortality relative to the placebo by a minimum of 16%. Under

these assumptions the power of the study was greater than 90% (even if one were to assume an even smaller overall event rate of 9%). It was originally expected that 6,500 patients would be required to achieve the endpoint. However, as discussed above in the protocol amendments section, the sample size was increased approximately 1 year after the initiation of the overall CHARM program.

CHARM-Added (SH-AHS-0006) Study Review

The current study is one of three component studies in the CHARM program (SH-AHS-0003, SH-AHS-0006, SH-AHS-0007). This program was designed to investigate the effects of candesartan on mortality and morbidity in patients with CHF.

STUDY OBJECTIVES

Primary objective:

To determine whether candesartan, compared to placebo, reduces the combined endpoint of cardiovascular mortality or hospitalization for the management of CHF.

Secondary objectives:

To determine whether candesartan, compared to placebo:

- reduced the combined endpoint of all-cause mortality or hospitalization for the management of CHF.
- reduced the combined endpoint of cardiovascular mortality or hospitalization 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 cardiovascular mortality, or hospitalization for the management of CHF or non-fatal MI, or coronary revascularization procedures.
- reduced the combined endpoint of all-cause mortality and all-cause hospitalization.
- reduced all-cause mortality.
- reduced all-cause hospitalization.
- reduced the number of fatal and non-fatal MIs.
- affected functional state and symptoms according to NYHA classification.
- was well tolerated and safe by evaluation of drug discontinuation, dose reduction and non- cardiovascular (CV) death and hospitalization.
- influenced the cost of health care.

STUDY PLAN AND PROCEDURES

This was a randomized, double-blind placebo controlled parallel group multicenter study to evaluate the influence of candesartan (4 mg titrated to target dose of 32 mg once daily) on mortality and morbidity in patients with depressed LV systolic function and ejection fraction (EF)< 40% and simultaneously treated with ACE inhibitors. The primary variable for this

evaluation was time from randomization to CV mortality or the first occurrence of a hospitalization for CHF. A total of 2548 patients were randomized at 473 sites in 25 countries.

The patient recruitment period was 8 months. All patients were to remain in the study until the last randomized patient had been in the study for at least two years. 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 randomized. The closing visits were conducted during March 2003.

The Steering and Executive Committees supervised the progress of the study. The LSHTM group conducted the interim analyses and the SC evaluated the data. A Clinical Endpoint Committee (CEC) classified clinical events (CEs).

AstraZeneca, Sweden, manufactured all investigational products, i.e., candesartan 4 and 16 mg tablets and matching placebo.

The investigational products were packed by Quintiles Ltd. in Edinburgh, Scotland and distributed to the investigational sites by Quintiles or its depots around the world.

The QTONE ™ system, an Interactive Voice Response System (IVRS), was used to manage the central randomization, supply and re-supply of investigational product.

There was a shortage of medication during Spring 2002, as expiring stock (1 September and 1 October 2002) was inadvertently marked as available in IVRS. **As a consequence 22 patients took expired drug (**Table 170**)**. However, additional stability testing suggested that the drug was still within specifications

Table 166 Patients on expired drug

Country	Site	Pat no	Bottle no	Expiry date	Days on expired drug
Belgium	757	14209	884899	2002-09-01	3
	794	10304	833959	2002-09-01	16
Canada	1274	20713	779406	2002-09-01	3
Denmark	210	11572	760936	2002-09-01	4
	210	11567	630695	2002-07-01	23
France	509	11450	871612	2002-11-01	3
Germany	1001	11683	755820	2002-10-01	5
	1023	11331	892601	2002-11-01	25
	1025	11604	664369	2002-09-01	1
	1057	11611	829387	2002-11-01	7
	1089	11337	846743	2002-11-01	5
	1092	12146	656493	2000-09-01	7
	1092	12147	600654	2000-11-01	14
	1092	12148	674472	2000-09-01	6
	1092	12149	671219	2000-09-01	7
Poland	610	12715	633330	2000-11-01	28
	612	10391	635203	2001-01-01	44
	612	10400	726284	2001-01-01	44
	614	14743	603808	2001-01-01	51
The Netherlands	450	10273	847111	2002-11-01	10
USA	1507	20600	711775	2002-10-01	13
	1580	21553	859287	2002-11-01	67

Assigning patients to treatment groups: Investigational Products, AstraZeneca R& D Mölndal, Sweden provided a computer generated randomization list (block size = 4) of identifiers to

Quintiles. Using this list Quintiles via the QTONE ™ system assigned each patient a patient number and the patient was randomized to treatment with candesartan or placebo at 1: 1 ratio.

Methods for breaking the blind:

During the study individual treatment codes were available to the investigators or pharmacists at the study site through a 24-hour telephone service by QTONE™ .

The treatment code was only to be broken when the appropriate management of the patient necessitated knowledge of the treatment randomization. Quintiles reported to AstraZeneca any breaking of the treatment code. AstraZeneca retained the right to break the code for serious adverse events that were causally related to treatment and potentially required expedited reporting to regulatory authorities.

Pre-study, concomitant and post-study treatment:

Candesartan was added to optimum conventional CHF treatment. **Baseline therapy with an ACE inhibitor was mandatory.** Before randomization the investigator was asked to optimize therapy for each patient. The investigator chose the optimal ACE inhibitor dose, based on tolerability and clinical information.

Therapy with a β-blocker or spironolactone, if required, was initiated and dose levels stabilized before randomization.

Treatment with non-study AT_1-receptor blockers (ARBs) was avoided. All other medication considered necessary for the patient's safety and well-being could be given at the discretion of the investigator and recorded in the case report forms (CRFs).

Upon completion of the study patients were switched to a low dose of an angiotensin receptor blocker (ARB), beginning the day after the last dose of the CHARM investigational product; this treatment was continued for 2 weeks, after which the decision to up-titrate or to discontinue the ARB.

Primary efficacy variable: The primary efficacy variable was the time from randomization to mortality or the first occurrence of a CHF hospitalization, whichever occurred first.

The secondary efficacy variable: The secondary efficacy variable was all-cause death or hospitalization due to CHF whichever occurred first. The other secondary outcome variable was cardiovascular death or hospitalization due to CHF or non-fatal MI, whichever occurred first.

Endpoints identified by the investigator as possible primary or secondary endpoints required a central adjudication. The process was blinded regarding any information relating to randomization group. All adjudicated endpoints were classified according to pre-specified definitions by the CEC (Clinical Endpoint Committee). Events matching the criteria were classified as 'confirmed adjudicated'.

Definitions:

Cardiovascular death: All deaths were considered CV unless an unequivocal non- CV cause was established. CV deaths include sudden deaths, death due to MI, death due to heart failure, death due to stroke, death due to CV investigation/procedure/operation (procedure-related death), death due to other CV causes (specified), presumed CV deaths and deaths from unknown causes.

First occurrence of CHF hospitalization: A hospitalization was defined as any overnight stay in a hospital (different dates for admission and discharge). A CHF hospitalization was defined as admission to hospital necessitated by heart failure and primarily for the treatment of heart failure. In other words, a patient admitted for this reason demonstrated signs and symptoms of worsening heart failure (see below) and required treatment with intravenous diuretics. Evidence of worsening heart failure had to include at least one of the following items:

- Increasing dyspnea on exertion.
- Orthopnea.
- Nocturnal dyspnea.
- Increasing peripheral edema.
- Increasing fatigue/decreasing exercise tolerance.
- Renal hypoperfusion (i.e. worsening renal function).
- Elevated jugular venous pressure (JVP).
- Radiological signs of CHF.

All-cause death: Death from any cause was considered to be a secondary endpoint. For patients who were lost to follow- up, i.e., without any follow-up data on vital status at the end of the study, the last date known to be alive was used in the analysis.

Myocardial infarction: A diagnosis of MI required at least one of the following conditions:

- Creatine kinase (CK) or creatine kinase muscle-brain (CK-MB) > twice the upper limit of normal.
- CK > 3 times the upper limit of normal immediately following a percutaneous transluminal coronary angioplasty.
- A troponin I or troponin T > 2 times the upper limit of normal in hospitals where CK measurement is not available and ECG demonstrated development of pathological Q-waves and/ or the development or disappearance of localized ST-elevations combined with the development of T-inversion in at least two of the routine standard leads and/ or clinical history consistent with MI.

NYHA Classification of Heart Failure: NYHA classification at each scheduled visit Functional class and symptomatic status were evaluated at each scheduled visit according to the NYHA classification, as follows:

NYHA Class I	No limitation: Ordinary physical exercise does not cause undue fatigue, dyspnea or palpitations.
NYHA Class II	Slight limitation of physical activity: Comfortable at rest but ordinary activity results in fatigue, palpitations, dyspnea.
NYHA Class III	Marked limitation of physical activity: Comfortable at rest but less than ordinary activity results in symptoms.
NYHA Class IV	Unable to carry out any physical activity without discomfort: Symptoms of CHF are present even at rest with increased discomfort with any physical activity.

Coronary revascularization procedures: Coronary revascularization procedures included coronary artery bypass grafting and percutaneous transluminal coronary interventions with or without stents.

Patient- Reported Outcomes measurements and variables: Data on patient-reported outcomes measurements and variables were collected in each study in the CHARM program. The results are presented in the pooled report of the study program.

Health Economics measurements and variables. For assessment of economic impact of candesartan in treatment of heart failure the study included variables to capture resource utilization. Since cost and cost- effectiveness analyses are based partly on the resource utilization and partly on data (primarily unit cost) from other sources such analyses are extrapolations from the findings of this study.

Number of hospitalizations: A hospitalization was defined as any overnight stay in a hospital (different dates for admission and discharge). For each hospitalization the investigator indicated the primary reason for hospitalization. For hospitalizations where the primary reason was not a CV- related one only the fact that a hospitalization occurred is used as a marker of resource utilization.

Resource utilization data for patients hospitalized with a cardiovascular diagnosis: For hospitalizations where the primary reason was CV-related, further data was collected on length of stay by type of ward. Three categories of ward were used, general, intermediate and intensive. The following definitions were used to guide the categorization of each level of care.

- Intensive care: Highest level of observation and intervention available (e.g., Intensive Care Unit, Coronary-Care Unit).
- Intermediate care: Level of intervention less than in Intensive Care but more than general nursing. Includes cardiac monitoring (e.g., Step Down Care, Telemetry, Coronary Step Down Care).
- General care: Care consists of general nursing observation. No cardiac monitoring.

The reporting of CV procedures included coronary artery bypass grafting, percutaneous transluminal coronary intervention without stent, percutaneous transluminal coronary intervention with stent, implantation of cardioverter defibrillator, implantation of pacemaker,

ventricular assist device, heart transplantation, cardiac catheterization including angiography, other cardiac surgery for heart failure, and other CV procedure/ operation.

Adverse events

(a) Definitions
An adverse event (AE) was any unintended and unfavorable sign (e.g. an abnormal laboratory finding), symptom or disease temporally associated with the use of a pharmaceutical product, whether or not considered causally related to the product. A serious adverse event (SAE) was an AE that at any dose:

- resulted in death
- was life-threatening ("Life-threatening" meant that the patient was at immediate risk of death from the AE as it occurred. "Life-threatening" did not mean that had an AE occurred in a more severe form, it might have caused death)
- required in-patient hospitalization or prolongation of existing hospitalization (Outpatient treatment in an emergency room was not in itself a SAE, although the reasons for it might have been (e.g., bronchospasm, laryngeal edema). Hospital admissions and/ or surgical operations planned before or during a study were not considered adverse events if the illness or disease existed before the patient was randomized in the study, provided that it did not deteriorate in an unexpected way during the study)
- resulted in persistent or significant disability/ incapacity, or
- was a congenital anomaly/birth defect

A permanent discontinuation was defined as patients who discontinued treatment with the investigational product permanently, were alive > 5 days after treatment with the investigational product and were not on the investigational product at the closing visit.

AEs considered as 'Other major events during hospitalization' were also collected in the CRF. In the safety analysis these AEs are treated as serious AEs although information on seriousness was not collected.

Pregnancy in itself was not regarded as an AE unless there was a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) was to be followed up and documented even if the patient was discontinued from the study. All reports of congenital abnormalities, birth defects and spontaneous miscarriages were to be recorded as SAEs. Elective abortions without complications were not to be considered as AEs.

Serious adverse events reporting:

The investigator had to inform the CoC within one working day from the time- point when the investigator received information of any SAE/clinical event (CE) that occurred in the course of the study. The CoC was to also receive a completed SAE Form/CE form within 14 calendar days. All SAEs/CEs had to be reported to the CoC, whether or not considered causally related to

the investigational product.

The investigator was required to assess the causal relationship to the investigational products for each SAE as "probable", "possible", or "unlikely".

SAEs/CEs were classified as reported by the investigator, independent of the adjudication of clinical endpoints by the CEC, and were not harmonized with endpoints with regards to classification. All SAE reports were reviewed by the SC who was responsible for monitoring safety in the study and for reporting to AstraZeneca if any events raised safety concerns.

Laboratory safety measurements and variables: Laboratory assessments were made at sites in Canada and USA. The measurements were done at visit 1, 4, 7, 10, 13 and/ or at closing visit, depending on how many visits the patient had. Laboratory assessment made at an extra visit was only included in the analysis if it was a last value carried forward (LVCF).

During evaluation of data, levels for clinically important abnormalities in hematology (hemoglobin) and clinical chemistry (creatinine and potassium) were defined as: Hemoglobin ≤ 80 g/ L (4.96 mmol/ L) for males, ≤ 70 g/ L (4.34 mmol/ L)] for females; creatinine ≥ 2 x baseline value; and potassium ≥ 6 mmol/ L.

Quest Diagnostics was to call the investigator if values reached a predefined limit for the following measurements: creatinine, ASAT, ALAT, alkaline phosphates, hematocrit and hemoglobin.

Laboratory tests were done at local hospital laboratories at the discretion of the investigators when deemed necessary. The investigator was to check creatinine and potassium approximately 2 weeks after each increase in dose.

Urine collected in North America and a subset of European countries was also analyzed for microalbuminuria at a central laboratory.

Other safety measurements and variables: Body weight, heart rate and blood pressure were measured during the study. Changes in heart rate and blood pressure recorded during the course of the study, which caused investigational product discontinuation or dose reduction were considered as AEs.

Clinically important abnormalities in systolic blood pressure (SBP) and diastolic blood pressure (DBP) were defined as: SBP ≤ 80 mmHg and DBP ≤ 40 mmHg.

Quality Assurance:

The sponsor undertook a GCP audit program to ensure compliance with its procedures and to assess the adequacy or its quality control measures. Audits, by a Global Quality Assurance group operating independently of the study monitors and in accordance with documented policies and procedures, were directed towards all aspects of the clinical study process and its associated

documentation.

Monitoring:

The sponsor's monitors regularly visited with the investigational sites to confirm that the facilities remained acceptable, that the investigational teams were adhering to the protocol, that data were being accurately recorded in the CRF and faxed to the CoC, and to provide information and support to the investigator. Source data verification (SDV) was also done. The monitors ensured that drug accountability was carried out. The monitors also assisted the CoC in study issues by checking that relevant photocopies of medical records/ hospital notes were sent to the CEC and the Co-coordinating site as soon as additional information had been requested.

Data management:

The data were entered into an electronic database using DataFax, a direct fax- to- computer data capture system, which was used for data transmission, data entry validation and query handling. Complete CRFs and SAE reports were sent by fax from the investigational sites directly to a computer at the CoC at AstraZeneca R& D Mölndal, Sweden. Handwritten data were manually entered and other information from the CRFs was checked against the fax pages at the CoC. Data were then transferred from DataFax to a Statistical Analysis System (SAS) study database. The sponsor's single patient output listing application (SPOLA) system was used regularly to run quality checks on the study database. Data Clarification Forms (DCFs) were generated and referred to the investigator for clarification. Answered DCFs or corrected CRF pages were faxed to DataFax and the database was updated with the correct validated data. The study database was used for data listings and status reports throughout the study.

The endpoint adjudication process done by the CEC, was handled electronically through the Clinical Endpoint Management System (CEMS). There were predefined CRF pages required for adjudication of each event type. Validated CRF pages for endpoint candidates were collected within the system and sent electronically to the CEC via CEMS. The CEC reviewers adjudicated the endpoints through forms available electronically in CEMS. The adjudication forms were dependent on event type. A QC of the CECs adjudication was carried out to ensure that the reviews were consistent between reviewers and for the same reviewer.

The sponsor submitted that all data editing, data coding and data validation, including logical checks between records in the database were done on blinded data. Before database lock was declared, QC checks on the data were completed and error rates reported, and all decisions on the ability to evaluate of the data from each individual patient were made and documented.

The randomization code was broken after declaration of database lock.

Statistical evaluation:

The statistical analyses were made by the Bio statistics group at AstraZeneca R& D Mölndal, Sweden. The software used was SAS ® Version 8.2.

The analyses included the following SAS ® procedures: LIFETEST (method = KM) for the Log rank test; PROC PHREG with the Wald statistic for estimates and confidence intervals (CIs) for hazard ratios (HR); PROC FREQ (chi sq binomial risk diff) in the analyses of proportions; PROC NPAR1WAY (Wilcoxon) for the analyses of frequency of events and the change in NYHA classes; and PROC MIXED for change from baseline variables. In the analyses of prognostic and other explanatory factors, PROC PHREG (selection = stepwise) was used for time to event variables, PROC LOGISTIC (selection = stepwise) for dichotomous outcome variables, and PROC REG (selection = stepwise, slstay = 0.05) for multivariate regression analyses.

- All tests were two-sided and statistical significance was concluded if the p-value was below 0.05, unless otherwise specified.
- All CIs had a confidence level of 95%.
- All p-values and confidence levels were presented as nominal without any adjustment for multiple comparisons.
- All analyses for the primary and secondary objectives were based on the confirmed adjudicated events.
- If an event could be concluded to have occurred in a specific time interval but no date was recorded, the midpoint of the interval was used as the date of occurrence.
- The LVCF principle was used when data was missing after some visit, e.g., for DBP, SBP, HR and NYHA class.
- For composite endpoints, time to event was defined as the time to the first occurrence of any of the components.
- The following definitions apply throughout this report:
    - Relative risk reduction: (1- hazard ratio) x 100%
    - Cumulative incidence function: (1-Kaplan-Meier survival estimates at time 't') x 100% (Note, these figures are generally referred to as Kaplan-Meier curves in the text in this report.)
    - Estimated hazard rate: Total number of events/1000 patient years.
    - Annualized incidence rates: Total number of events/100 patient years.
    - Follow- up time: The time a patient is at risk for an event, i.e., the time until death, the event, or last known to be alive.

Censoring of observations and imputation of dates for deaths:

Data collection from patients in the study was finished during the planned common closing visit period, 3 March to 31 March 2003.

SAEs and Endpoints were reported up to each patient's individual closing visit date. However, a few patients came to the visit prior to or after the closing visit period.

Four patients were lost to follow up at the closing visit for various reasons.

Endpoints occurring after 31 March 2003 but before the closing visit if the visit for some reason took place after March 31 were not included in the statistical analysis.

A few patients came to their last visit during January and February 2003. This visit date concluded the recording of endpoints for these patients. To conclude the study and finish data recording, the date of 31 March 2003 served to censor observations. Censoring of observations and/ or imputation of date was implemented in the following situations.

Conventional procedures for handling missing values were used throughout and specified prior to unblinding. The rule for handling missing dates was to impute the date midway between two known dates. For example, if an event was known only to have occurred in a certain month, the 15th of that month was used. If only the last date was known, the LVCF principle was used. **All deaths with an unknown cause (4 candesartan and 7 placebo) were considered as CV deaths as stated in the study protocol.** This approach is conservative if the beneficial effect of candesartan over placebo, as hypothesized, is realized primarily in CV-related events.

When month of death was unknown, if occurring before 31 March, a death date was estimated by imputation using the following rule: The death date was allocated to a date exactly between the date of withdrawal of consent (alternatively last date known to be alive) and 31 March 2003. **In the present study there was only one patient for whom the date of death was unknown i.e., the procedure of imputation was only applied in one case.**

Primary and secondary efficacy endpoints included in the confirmatory analyses were adjudicated and verified by the CEC according their Manual of Operations

Safety population: The safety population is identical to the ITT population.

Per Protocol (PP) population: A PP analysis was made for the primary endpoint. The PP population included patients who were on the investigational product at the time of a confirmed adjudicated event or were on the investigational product at the closing visit for patients completing the study without a confirmed, adjudicated event. Patients taking non-study AT1-receptor blocker (ARB) were excluded from the PP analysis.

Protocol deviations were determined prior to unblinding and are listed together with the corresponding patient numbers.

Method of statistical analysis: The primary efficacy endpoint whether candesartan, compared to placebo, reduced the combined endpoint of CV death or hospitalization for the management of CHF, as translated into a hypothesis problem: time from randomization to the combined endpoint CV death or CHF hospitalization, whichever occurs first.

The null hypothesis (H0) was:
H0: The distribution function for the time from randomization to the combined endpoint when treated with candesartan equals the distribution function for the time from randomization to the combined endpoint when treated with placebo.

The alternative hypothesis (H1) was:
H1: The distribution functions differ.

The null hypothesis was tested using the two- sided Log rank test for comparing the time from randomization to event distributions. **A p-value in this test less than 0.05 was considered as a confirmation that there was a true difference between the two distributions.**

In addition, estimates of the treatment hazards were calculated as the number of events per 1000 patient years. The size of treatment effect was estimated by means of a Cox proportional hazards model with treatment as the only factor. The hazard ratio, with a 95% confidence interval based on the Wald estimate of standard error, and corresponding relative risk reduction estimate are reported.

The two secondary efficacy endpoints were translated into null hypotheses about:

Time from randomization to the combined endpoint all-cause death or CHF hospitalization.

Time from randomization to the combined endpoint CV death or, CHF hospitalization or, non-fatal MI, respectively.

The null hypothesis was equality of the distribution functions for the time from randomization to the combined event for candesartan and placebo versus the alternative hypothesis that they were different.

The null-hypotheses were tested with a Log rank test in the same way as described above for the primary efficacy endpoint, and the treatment hazards were estimated and the hazard ratios were calculated in a Cox regression model.

If the p-value for the first of these tests was less than 0.05 and if the test for the primary variable was significant at the 0.05 level, then this test was also considered as a confirmation of a true treatment effect. Similarly, if this occurred and the second p- value was also less than 0.05, then the second combined event distributions were also concluded to be confirmed to be different. **This follows from the theory of closed test procedures and will guarantee a multiple alpha level of 0.05 (**Bauer, 1991).

The Kaplan-Meier estimated time from randomization to event distribution was plotted for each treatment. This graph was used to interpret the likely differences in the true distributions.

Determination of sample size:

In the original study protocol the sample size was calculated as **2,300** patients based on a two-sided Log rank test for the primary variable time from randomization to CV death or a hospitalization due to CHF, whichever occurred first. **The significance level was set to 0.05.**

The study protocol allowed for the possibility of lower event rates (based on overall event rates in blinded data) than assumed in the initial sample size assumptions and permitted additional patients and/or longer follow- up time if required so as to preserve statistical power. Accordingly, the sample size for the study was adjusted in a protocol amendment (# 4 of 4-

March-2000), for a total of **2,550** patients in the study.

Interim analyses:

The protocol specified that the Safety Committee formally compared the treatment groups in the CHARM Program trials with regard to all-cause death. While the total mortality in the three CHARM trials combined was the emphasis, the data from the treatment groups were compared at approximately 6-months intervals with a logrank test, stratified by study. In order to stop the trials for benefit in the overall population, the stopping rule required P<0.0001 for analyses performed within 18 months of the first patient randomized, and P<0.001 for all subsequent analyses. If the test for heterogeneity between trials indicated a differential benefit of candesartan across the individual trials, consideration was to be given to continuing randomization or follow- up for those trials in which findings were less pronounced. In order to stop for safety, should candesartan exhibit greater mortality, the same general principles applied except that the plan required p< 0.001 for analyses performed within 18 months of the first patient randomized and p< 0.01 for any subsequent analysis. In addition, the logrank test for a treatment difference in mortality was performed separately for each trial at each interim analysis. Stopping a single trial for benefit required (1) the same boundary values as for the overall analysis, and (2) statistical evidence of heterogeneity between trials of sufficient strength to justify termination of the trial. The results of 6 interim analyses are summarized in (Table 167).

Table 167 Interim results for CHARM-Pooled

Interim report number	Date of database delivery	Total deaths	Hazard ratio (95% CI)			Nominal p-value	Early stopping criterion
	09 Aug '99	12					
1	27 Mar '00	199	0.63	(0.49,	0.80)[a]	0.00069	0.0001
2	27 Jul '00	331	0.66	(0.53,	0.82)	0.00020	0.0001
3	01 Mar '01	599	0.76	(0.64,	0.89)	0.00064[b]	0.001
4	09 Aug '01	861	0.80	(0.70,	0.91)	0.00103	0.001
5	22 Feb '02	1187	0.86	(0.77,	0.96)	0.00851	0.001
6	01 Aug '02	1438	0.88	(0.79,	0.98)	0.01472	0.001
Final	31 Mar '03	1831	0.91	(0.83,	1.00)	0.055	0.0492

[a]Data taken from source other than CHARM Interim Reports (personal communication).
[b]Boundary crossed for efficacy.
N.B. First patient randomized was 22 March 1999. The initial meeting of the SC was on 22 August 1999 where no formal analyses were performed due to the small number of events observed.

The stopping boundary for efficacy was crossed at the third interim analysis. However, the Committee recommended that the program continue based on the following considerations:-

- The treatment difference in mortality was most marked in one study (66 vs100 deaths [p= 0.006 by logrank test], SH-AHS-0003; CHARM-Alternative Study)) and not statistically significant in the other two (140 vs. 168 deaths [p= 0.070], SH-AHS-0006 (CHARM-Added) study; and, 54 vs. 71 deaths [p= 0.136], SH-AHS-0007 (CHARM-Preserved) Study).
- At that point in time, data on the primary study endpoint, CV death or hospitalization, were incomplete with many such endpoints awaiting adjudication, thus making it difficult to reliably assess the totality of evidence for efficacy.

Data and safety monitoring committees

Safety Committee (SC): The SC functioned independently of all other individuals and bodies associated with the conduct of the CHARM program, including the investigators, the Steering Committee and the program sponsor.

The SC was charged with the following responsibilities:

- To monitor patient safety in the study.
- To monitor efficacy at interim analyses of results.

The SC received safety data on a monthly basis and was responsible for reviewing the safety data continually during the program. A monthly letter was sent from the SC to the CHARM program chairmen and to the sponsor, stating that they had reviewed the data and whether there were any safety concerns or not. Interim efficacy analyses were made every six months. The SC reviewed relevant data and had to make a recommendation to the Steering Committee and the sponsor as to stopping the study for benefit or for harm.

Clinical study protocol amendments and other changes in the conduct of the study:

The original clinical program protocol was dated 13 November 1998.

There were four amendments to the protocol.

The first amendment was made to improve the scientific quality of the study, and came into effect before any patients were recruited. The addition of another secondary objective brought the study into line with forthcoming European guidelines for studies in heart failure as discussed with regulatory agencies. The change made use of endpoints that were collected but had not been combined in the original protocol. Consequently the first amendment did not affect the study procedure as such, only the analysis of the result.

Three further amendments were made after the start of patient recruitment.

The second amendment was made twelve days after the first patient had been included. The changed text reflects that time points for urine sampling were changed and that neutropenia was recognized as an ACE inhibitor-related AE not related to anaphylaxis or angioedema.

The third amendment was made nine months after the first patient was randomized, after the detailed adjudication plan had been developed. The plan describes the procedures for adjudication of clinical endpoints by the Endpoint Committee (CE). These procedures had been followed for all CEs occurring before the plan was final. Thus, the same criteria of evaluation of CEs were applied throughout the study.

The fourth amendment was made one year after the first patient was randomized. The increase in sample size was intended to safeguard the statistical power of the study due to a lower than expected event rate in blinded data.

In addition, there were a total of 21 local amendments (Canada 1, Czech Republic 1, Finland 1, France 6, Germany 1, Ireland 1, the Netherlands 2, Portugal 1, South Africa 1, Spain 3, Sweden 2 and USA 1) to meet planned changes in European guidelines for heart failure studies, recommending that "all-cause death" is part of any combined endpoints. None of these affected the design or analysis of the study. No other changes to the conduct of the study were made.

The amendments were approved by IRBs and Medical Agencies as appropriate, prior to implementation.

Changes to planned analyses:

Prior to unblinding of data:

- In amendment, the closed test procedure was changed due to an addition to the secondary objective. The original closed test procedure was modified to contain three steps with one primary and two secondary variables in a hierarchical order.
- In amendment 4 **a re-calculation of the power was done due to a decision to increase the sample sizes in the two other component studies in the CHARM program (SH-AHS-0003 and SH-AHS-0007).**
- Several efficacy and safety variables were added for analyses to those described in the study protocol, and were finalized before database lock was declared.
- Additional analyses were made for the time to event variables adjusting for 33 pre-specified covariates used in the interim analyses. This was decided before un-blinding the study and is included as a part of the analysis plan for the manuscripts approved by the Executive Committee.
- Analyses in subgroups were made even if the p- value for the interaction treatment by subgroup was greater than 0.1. The interaction p-values were calculated in a regression model for each subgroup separately.
- The non-CV death component, cancer death was included as a separate analysis.
- The planned calculation of medians and percentiles for the cumulative incidence curves were not performed.

After unblinding of data:

- Analyses of CHF as the primary reason for hospitalization were also made.
- An additional analysis for NYHA class was made where class III and IV constituted one class.
- Analyses of hospitalizations due to non-CV cause as a primary reason were added.
- An analysis of time to event variables comparing US versus non- US was performed.
- The variables 'number of days alive' and 'number of days alive out of hospital' were not analyzed since the results would be obvious (P= 1.0 and P= the P-value for the variable

'number of days out of hospital' respectively).

Re-opening of study database:

Shortly before the Clean File meeting and Database Lock on 12 June 2003, death reports and other CRF-pages for patients classified as 'withdrew consent' were removed from the database.

However, based on a recommendation from the Executive Committee the data were re-entered and database was revised to include these data and database lock was declared on July 4, 2003. The cases re-entered into the study database were adjudicated by the endpoint committee as done for all other cases.

In three cases the death reports sent in were crossed out by the investigator with a comment that the information should not be entered into the database. In these cases the information in the reports was not used and it was decided by the Study Team that the date of death was to be estimated by imputation. The number of patients with events added or reclassified in the study database is shown in Table 168.

Table 168 Number of patients with events added (+) or subtracted (-) due to reclassification at the re- opening of the database.

Event	Treatment		Comments
	Placebo	Cand.cil.	
Confirmed, adjudicated CV deaths	+4	+8	12 death reports were added.
Non adjudicated deaths	-6	-8	Due to the new death reports the number of Non adjudicated deaths decreased, due to re-adjudication to CV death
Confirmed, adjudicated non-CV deaths	+2	0	Two of the 12 deaths was reclassified as Non-CV death
Confirmed, adjudicated CHF hospitalisations	0	+1	One CHF hospitalisations was agreed after adjudication
Non-fatal MI	0	+1	One Non-fatal MI was added
Other SAE:s	0	0	No difference

STUDY PATIENTS

In total 2,548 patients were recruited from 473 sites. The first patient was randomized in the study on 22 March 1999, and the last patient completed the study on 31 March 2003. Of the 2548 patients recruited, 1276 were randomized to candesartan and 1272 to placebo. All 2548 patients were analyzed for safety and efficacy. Overall, the treatment groups were comparable for demographic characteristics and baseline data.

Disposition: The disposition of study patients is summarized in Figure 95.

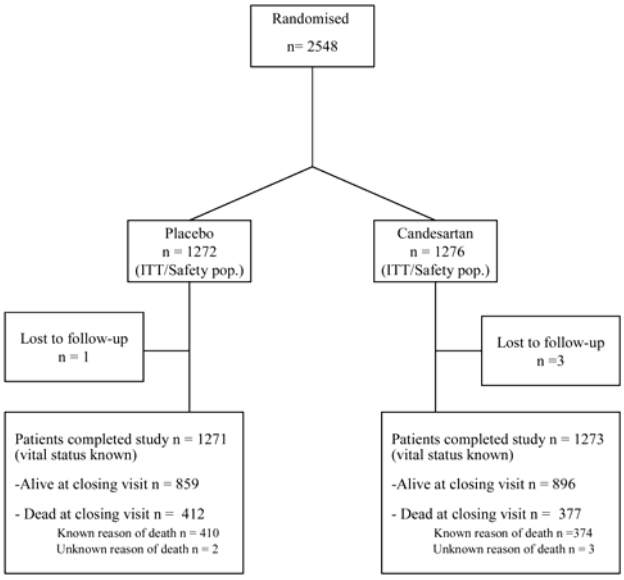


Figure 95 Patient disposition (completion or discontinuation)

Table 169 Number of patients with protocol deviations

	Placebo (N=123)	Cand. cil. (N=119)
Inclusion criteria deviation	29	31
Exclusion criteria deviation	52	44
Patient's consent withdrawn (continued in study or with investigational product)	0	0
Patient pregnant	1	0
Investigational product given without randomisation	0	0
Investigational product never given	0	0
Wrong investigational product given, wrong bottle and wrong investigational product	4	2
Wrong investigational product given, wrong bottle and correct investigational product	17	19
Wrong dose of investigational product given (dose <4 or >32 mg)	0	5
Incorrect dose of investigational product given (dose ≠4, 8, 16, 32 mg)	1	1
Pre-randomisation (randomisation date before visit 1)	11	9
Treatment code prematurely broken	6	6
Less than two years in the study (lost to follow-up)	1	2

Protocol deviations: The number of patients with protocol deviations in each treatment group are summarized in Table 169. (N.B. One patient could have more than one protocol deviation through out the study.)

Patient populations analyzed:

All analyses were based on the ITT/ Safety population, which was defined before the treatment code was broken. The ITT/ Safety population included all randomized patients.

PP analyses were performed only for the primary variable. The PP population included patients who were on investigational product at the time of a confirmed adjudicated event or were on the

investigational product at the closing visit for patients completing the study without a confirmed, adjudicated event. Patients taking non-study ARBs were excluded from the PP analyses. All decisions on the inclusion or exclusion of patients from the PP efficacy analysis population were made while the data were still blinded. The reasons for exclusion from the PP population are given in Table 170. (One patient could be listed for more than one reason in this table.)

Table 170 Reasons for exclusion from PP population and number of patients excluded

Reason for exclusion[a]	Placebo	Cand. cil.
No investigational product at the confirmed, adjudicated CV-death or hospitalisation for the management of CHF, whichever occurred first	87	124
Open label AT_1-receptor blocker taken at any time point before the confirmed, adjudicated CV-death or hospitalisation for the management of CHF, whichever occurred first	3	5
No investigational product at closing visit – patients without confirmed, adjudicated CV-death or hospitalisation for the management of CHF	93	152
Open label AT_1-receptor blocker taken at any time point during the study - patients without confirmed, adjudicated CV-death or hospitalisation for the management of CHF	38	26

[a] Please note that one patient may have more than one reason for exclusion from the PP population. For the total number of patients excluded from PP population see Figure 3.

The study populations analyzed, and the number of patients in each population, are summarized in Figure 96.

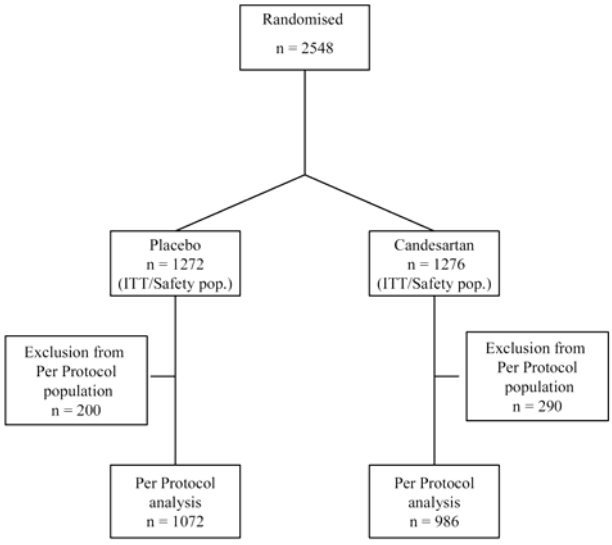


Figure 96 Study populations

Demographic and other patient characteristics:

The baseline characteristics were balanced between the treatment groups. 96.9% of patients were in NYHA functional class II- III (24.1% in class II and 72.8% in class III). Baseline characteristics were representative of a population of patients with chronic heart failure and depressed LV systolic function.

Treatment compliance:

Compliance was assessed (> 80%, 20- 80% or < 20%) by estimation of returned tablets and after discussion with the patient. Pill- counts were not done unless required by local regulatory authorities. The majority of patients had a compliance of > 80% at all visits with no apparent difference between treatment groups.

Use of concomitant medication at randomization:

In general, patients were also receiving aggressive heart failure treatment with combinations of diuretics, β-blockers and digitalis as well as individually optimized doses of ACE inhibitors.

At randomization, 56% of the patients were treated with a β-blocker, 90% with diuretics, 58% with digitalis and 17% were treated with spironolactone without major differences between treatment groups.

ACE inhibitors were used by 99.9% of the patients at randomization. Enalapril, lisinopril, captopril and ramipril were the most commonly used ACE inhibitors, together accounting for 74% of all ACE inhibitors used. In the candesartan group, the mean daily doses of these ACE inhibitors were 16.8, 17.7, 82.2 and 6.8 mg, respectively, and in the placebo group, 17.2, 17.7, 82.7 and 7.3 mg, respectively. Slightly more than 50% of the patients received the recommended ACE inhibitor dose for treatment of heart failure.

The mean daily doses of the two most commonly used β-blockers were for metoprolol 88.8 mg in the candesartan group and 84.1 mg in the placebo group, and for carvedilol 28.6 and 27.5 mg, respectively.

Use of concomitant medications after randomization:

The use of some concomitant medications were more common in the placebo group than in the candesartan group at the closing visit [β-blockers in 586 patients (67.8%) vs. 577 patients (64.3%), spironolactone in 216 patients (25.0%) vs. 182 patients (20.3%) and ACE inhibitors in 727 patients (84.1%) vs. 709 patients (79.0%)].

The proportion of patients using β-blockers and spironolactone increased during the study period while the proportional usage of ACE inhibitors decreased.

EFFICACY RESULTS

Primary efficacy endpoint: Time from randomization to cardiovascular death or hospitalization due to CHF

During the follow-up period, 1,021 patients experienced the primary outcome of CV death or hospitalization due to CHF, 483 (37.9%) in the candesartan group and 538 (42.3%) in the placebo group. The average annualized events rates were 14.1% and 16.6% respectively (Table 171).

The Kaplan- Meier plot implies that the benefit of candesartan appeared early and was maintained throughout the study period. The relative risk reduction was 14.7% for the primary outcome of CV death or hospitalization due to CHF, whichever came first, by candesartan treatment (Table 172 and Figure 97).

The treatment effect of candesartan was similar across geographical regions (test for interaction; P= 0.203).

Table 171 Confirmed adjudicated CV death or hospitalization due to CHF. Number of patients with at least one event by treatment group and events per 1000 years of follow- up. Follow- up time is calculated to first event. ITT/Safety population (H-AHS-0006)

Variable	Treatment	N	Events (No of patients)	Total follow-up time (years)	Events / 1000 follow-up years	Mean follow-up time (years)
CV death or hospitalisation due to CHF (confirmed adjudicated)	Placebo	1272	538	3234.7	166.3	2.5
	Cand. cil.	1276	483	3421.6	141.2	2.7

Table 172 Confirmed adjudicated CV death or hospitalization due to CHF. 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
					Lower	Upper	
CV death or hospitalisation due to CHF (confirmed adjudicated)	2548	483	538	0.853	0.754	0.964	0.011

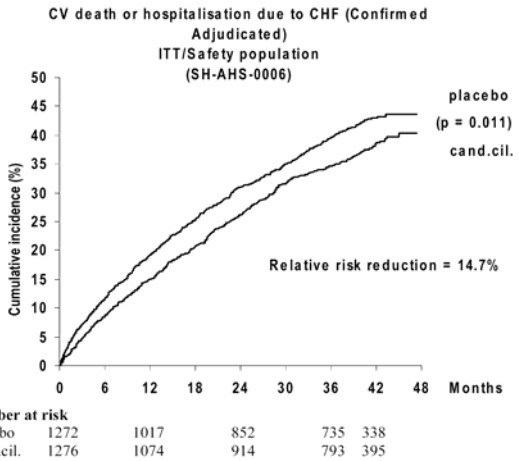


Figure 97 Cumulative incidence (%) of confirmed adjudicated CV death or hospitalization due to CHF over time. ITT/Safety population

Secondary variable: Time from randomization to all-cause death or hospitalization due to CHF

During the follow-up period, 1,126 patients experienced the secondary outcome of all cause

death or hospitalization due to CHF, 539 (42.2%) in the candesartan group and 587 (46.1%) in the placebo group. The average annualized events rates were 15.8% and 18.2%, respectively (Table 173).

Table 173 Confirmed adjudicated all-cause death or hospitalization due to CHF. Number of patients with at least one event by treatment group and events per 1000 years of follow-up. Follow- up time is calculated to first event. ITT/Safety population (SH-AHS-0006)

Variable	Treatment	N	Events (No of patients)	Total follow-up time (years)	Events / 1000 follow-up years	Mean follow-up time (years)
All-cause death or hospitalisation due to CHF (confirmed adjudicated)	Placebo	1272	587	3234.7	181.5	2.5
	Cand. cil.	1276	539	3421.6	157.5	2.7

The Kaplan- Meier plot implies that the benefit of candesartan appeared early and was maintained throughout the study period. The relative risk for the secondary outcome of all cause death or hospitalization due to CHF, whichever came first, was significantly reduced by 12.9% by candesartan treatment (Table 174 and Figure 98).

The treatment effect of candesartan was similar across geographical regions (test for interaction; P= 0.273).

Table 174 Confirmed adjudicated all- cause death or hospitalization due to CHF. 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
					Lower	Upper	
All-cause death or hospitalisation due to CHF (confirmed adjudicated)	2548	539	587	0.871	0.775	0.980	0.021

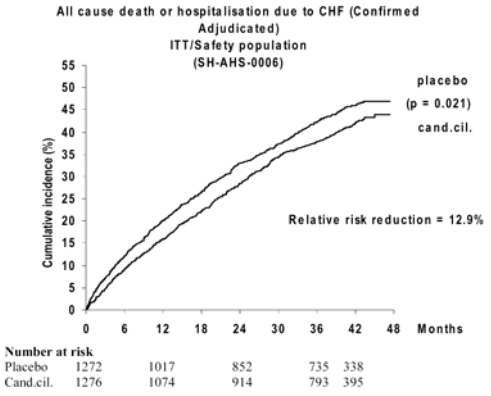


Figure 98 Cumulative incidence (%) of confirmed adjudicated all- cause death or hospitalization due to CHF over time. ITT/Safety population

Secondary variable: Time from randomization to cardiovascular death, or hospitalization due to CHF or non- fatal MI

During the follow-up period, 1,045 patients experienced the secondary outcome of CV death or

hospitalization due to CHF or non- fatal MI, 495 (38.8%) in the candesartan group and 550 (43.2%) in the placebo group. The average annualized events rates were 14.6% and 17.2%, respectively (Table 175).

The Kaplan-Meier plot implies that the benefit of candesartan appeared early and was maintained throughout the study period. The relative risk for the secondary outcome of CV death or hospitalization due to CHF or non-fatal MI, whichever came first, was significantly reduced by 14.8% by candesartan treatment (Table 176 and Figure 99).

Table 175 Confirmed adjudicated CV death or hospitalization due to CHF or nonfatal MI. Number of patients with at least one event by treatment group and events per 1000 years of follow-up. Follow- up time is calculated to first event. ITT/Safety population (SH-AHS-0006)

Variable	Treatment	N	Events (No of patients)	Total follow-up time (years)	Events / 1000 follow-up years	Mean follow-up time (years)
CV death or hospitalisation due to CHF or non-fatal MI (confirmed adjudicated)	Placebo	1272	550	3197.2	172.0	2.5
	Cand. cil.	1276	495	3394.2	145.8	2.7

Table 176 Confirmed adjudicated CV death or hospitalization due to CHF or nonfatal MI. 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
					Lower	Upper	
CV death or hospitalisation due to CHF or non-fatal MI (confirmed adjudicated)	2548	495	550	0.852	0.755	0.962	0.010

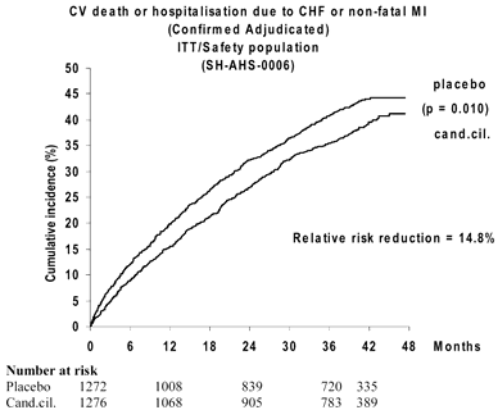


Figure 99 Cumulative incidence (%) of confirmed adjudicated CV death or hospitalization due to CHF or non- fatal MI over time. ITT/Safety population

The treatment effect of candesartan was similar across geographical regions (test for interaction; P= 0.334).

Is there a dose response of the dose of candesartan (plus heart failure dose or low dose of ACE-inhibitors) on the primary and secondary efficacy outcomes?

The submission shows that 1,756 (68.9%) patients (candesartan = 857, 67.2%; placebo = 899, 70.7%) received the investigational product for 24 months or more. A total of 1,096 (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. 53.6% of patients treated with candesartan were receiving the target dose of 32 mg once daily at 6 months (visit 5). Also, the sponsor stated that from the 6-month visit onwards, >50% of patients still receiving candesartan were on a dose of 32 mg/day. The mean dose in the candesartan treatment group was 23.5 mg at 6 months.

In Table 177 and Table 178, the proportions of patients who developed the primary efficacy endpoint events appear to be less in the candesartan-treated groups than the placebo-treated groups, particularly at the lower doses of 4 mg and 8 mg candesartan where the relative risk reduction with candesartan vs placebo was significant (Table 178). However, the results in the table do not take into consideration whether patients were receiving heart failure doses or low doses of ACE-inhibitors.

Table 177 CV death or CHF hospitalization by subgroup: dose of study drug, (events per 1000 years of follow-up), Study SH-AHS-0006

Variable	Group	Treatment	N	Events (number of patients)	Total follow-up time (years)	Events/1000 follow-up years	Mean follow-up time (years)
Dose of study drug (at the visit preceding the event) (at last visit if no event)	4 mg	Placebo	78	57	108.0	527.9	1.4
		Candesartan	127	71	285.1	249.0	2.2
	8 mg	Placebo	89	57	158.8	358.9	1.8
		Candesartan	99	44	247.8	177.6	2.5
	16 mg	Placebo	151	69	349.1	197.6	2.3
		Candesartan	185	75	469.8	159.6	2.5
	32 mg	Placebo	776	295	2123.8	138.9	2.7
		Candesartan	588	209	1629.0	128.3	2.8
	No study drug	Placebo	178	60	494.9	121.2	2.8
		Candesartan	277	84	789.9	106.3	2.9

Table 178 CV death or CHF hospitalization by subgroup: dose of study drug (Cox regression), Study SH-AHS-0006

Variable	Group	N	Events candesartan	Events placebo	Hazard ratio	95% CI	p-value
Dose of study drug (at the visit preceding the event) (at last visit if no event)	4 mg	205	71	57	0.534	0.376, 0.758	<0.001
	8 mg	188	44	57	0.533	0.359, 0.791	0.002
	16 mg	336	75	69	0.823	0.593, 1.141	0.243
	32 mg	1364	209	295	0.927	0.776, 1.106	0.399
	No study drug	455	84	60	0.872	0.626, 1.214	0.418

Following a Telecon with the sponsor on Nov 2, 2004, I requested the sponsor to provide information on the CHARM-Added (SH-AHS-0006) Study regarding the proportion of patients receiving low dose (4 or 8 mg) or high dose (16 or 32 mg) candesartan *at the time of the event* or *at the last visit (if no event occurred)* in the each of the sub-populations of patients receiving

high dose ACE inhibitors and those receiving low dose ACE inhibitors in relation to the primary and secondary efficacy endpoints.

On Nov 12, 2004, I received the sponsor's response containing the information related to the primary and principal secondary efficacy endpoints, and adverse event endpoints according to dose level of candesartan. These analyses consider dose level of candesartan consistent with the sub-group analyses presented in the submission. For the dose analyses, high candesartan dose is defined as 16 mg or 32 mg and low dose candesartan as 4 mg or 8 mg. Dose level was determined as described in the submission as a patient's last dose (if the patient had no event), or, if the patient had an event, as the last dose prior to the event. The category "no-study drug" was used to classify patients who were not on study drug at the visit prior to the event or not on study drug at the last visit if they had no event.

CHF Patients who received high or low dose candesartan plus ACE inhibitors at heart failure dose or low dose

Primary efficacy endpoint of CV mortality or CHF hospitalization (confirmed, adjudicated): The proportion of patients who reached the primary efficacy endpoint while on high or low dose candesartan plus ACE inhibitors at heart failure dose or low are given in Table 179. It appears that there is a relative dose response, the event rates being significantly ($P<0.001$) lower in the high dose (16 and 32 mg) candesartan groups compared to the low dose (4 and 8 mg) candesartan groups for both groups of patients receiving heart failure doses and low doses of ACE inhibitors (Table 180).

The secondary efficacy endpoint of all-cause mortality or CHF hospitalization (Table 181 and Table 182), and for secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI (Table 183 and Table 184) also show similar findings.

Table 179 The numbers and event rates (primary efficacy endpoint of CV mortality or CHF hospitalization, confirmed, adjudicated) of patients who received high or low dose candesartan plus ACE inhibitors at heart failure dose or low dose – CHARM-Added (SH-AHS-0006) Study

	$ACEi_{HFD}$			**$ACEi_{LD}$**		
Candesartan cilexetil[a]	$CC + ACEi_{HFD}$ **N =643** **Events = 232 (36.1%)** **A**			**$CC + ACEi_{LD}$** N = 633 Events = 251 (39.7%) B		
	$CC_{HD} + ACEi_{HFD}$ **N = 401** **Events = 144 (35.9%)** **A_1**	$CC_{LD} + ACEi_{HFD}$ **N = 98** **Events = 46 (46.9%)** **A_2**	$CC_{00} + ACEi_{HFD}$ **N = 144** **Events = 42 (29.2%)** **A_3**	$CC_{HD} + ACEi_{LD}$ **N = 372** **Events = 140 (37.6%)** **B_1**	$CC_{LD} + ACEi_{LD}$ **N = 128** **Events = 69 (53.9%)** **B_2**	$CC_{00} + ACEi_{LD}$ **N = 133** **Events = 42 (31.6%)** B_3
Placebo	**Placebo + $ACEi_{HFD}$** N = 648 Events = 275 (42.2%) C			**Placebo + $ACEi_{LD}$** N = 624 Events = 263 (42.1%) D		

$ACEi_{HFD}$ = ACE inhibitor at heart failure dose; $ACEi_{LD}$ = ACE inhibitor at lower than heart failure dose;
CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC_{00} =Not on candesartan at event or last visit
[a] Dose of study drug preceding the event (or at last visit if no event occurred)

Table 180 Comparison of the effect of high or low dose candesartan plus ACE inhibitor at heart failure dose or low dose on the primary endpoint of time to CV mortality or CHF hospitalization (confirmed, adjudicated) using Cox Regression[a] – CHARM-Added (SH-AHS-0006) Study

Comparison	Relative risk reduction	Hazard ratio	95% confidence interval	P-value (Wald)
$(A_1 + B_1)$ vs $(A_2 + B_2)$	36.9	0.631	(0.508, 0.784)	< 0.001
A_1 vs B_1	--	0.934	(0.740, 1.179)	0.567
A_1 vs A_2	30.4	0.696	(0.499, 0.970)	0.032
A_1 vs B_2	44.6	0.554	(0.416, 0.739)	<0.001
B_1 vs A_2	25.8	0.742	(0.532, 1.036)	0.079
B_1 vs B_2	40.4	0.596	(0.446, 0.795)	< 0.001
A_2 vs B_2	--	0.799	(0.550, 1.160)	0.239

[a] Note: P=0.473 for test for interaction between high/low dose candesartan and baseline covariate (cells A_1, B_1, A_2 and B_2 only)
Cells A_1, B_1, A_2 and B_2 = Reference to cells in Table 179.

Table 181 The numbers and event rates (secondary efficacy endpoint of all-cause mortality or CHF hospitalization, confirmed, adjudicated) of patients who received high or low dose candesartan plus ACE inhibitors at heart failure dose or low dose– CHARM-Added (SH-AHS-0006) Study

	$ACEi_{HFD}$			**$ACEi_{LD}$**		
Candesartan cilexetil[a]	$CC + ACEi_{HFD}$ **N =643** **Events = 232 (36.1%)** **A**			**$CC + ACEi_{LD}$** N = 633 Events = 251 (39.7%) B		
	$CC_{HD} + ACEi_{HFD}$ **N = 401** **Events = 158 9.4%)** **E_1**	$CC_{LD} + ACEi_{HFD}$ **N = 99** **Events = 49 49.5%)** **E_2**	$CC_{00} + ACEi_{HFD}$ **N = 143** **Events = 56 (39.2%)** **E_3**	$CC_{HD} + ACEi_{LD}$ **N = 375** **Events = 155 (41.3%)** **F_1**	$CC_{LD} + ACEi_{LD}$ **N = 128** **Events = 72 (56.3%)** **F_2**	$CC_{00} + ACEi_{LD}$ **N = 130** **Events = 49 (37.7%)** F_3
Placebo	**Placebo + $ACEi_{HFD}$** N = 648 Events = 275 (42.2%) C			**Placebo + $ACEi_{LD}$** N = 624 Events = 263 (42.1%) D		

$ACEi_{HFD}$ = ACE inhibitor at heart failure dose; $ACEi_{LD}$ = ACE inhibitor at lower than heart failure dose;
CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC_{00} =Not on candesartan at event or last visit
[a] Dose of study drug preceding the event (or at last visit if no event occurred)

Table 182 Comparison of the effect of high or low dose candesartan plus ACE inhibitor at heart failure dose or low dose on the secondary efficacy endpoint of all-cause mortality or CHF hospitalization (confirmed, adjudicated) using Cox Regression[a] – CHARM-Added (SH-AHS-0006) Study

Comparison	Relative risk reduction	Hazard ratio	95% confidence interval	P-value (Wald)
$(E_1 + F_1)$ vs $(E_2 + F_2)$	34.0	0.660	(0.535, 0.810)	< 0.001
E_1 vs F_1	--	0.930	(0.745, 1.161)	0.521
E_1 vs E_2	28.0	0.720	(0.522, 0.992)	0.044
E_1 vs F_2	41.8	0.582	(0.440, 0.769)	<0.001
F_1 vs E_2	22.8	0.772	(0.560, 1.065)	0.115
F_1 vs F_2	37.2	0.628	(0.475, 0.830)	0.001
E_2 vs F_2	--	0.810	(0.563, 1.165)	0.255

[a] Note: P=0.512 for test for interaction between high/low dose candesartan and baseline covariate (cells E_1, F_1, E_2 and F_2 only)
Cells E_1, F_1, E_2 and F_2 = Reference to cells in Table 181.

Table 183 The numbers and event rates (secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI, confirmed, adjudicated) of patients who received high or low dose candesartan plus ACE inhibitors at heart failure dose or low dose– CHARM-Added (SH-AHS-0006) Study

<table>
<tr><th></th><th colspan="3">$ACEi_{HFD}$</th><th colspan="3">$ACEi_{LD}$</th></tr>
<tr><td rowspan="2">Candesartan cilexetil[a]</td><td colspan="3">$CC + ACEi_{HFD}$
N =643
Events = 232 (36.1%)
A</td><td colspan="3">$CC + ACEi_{LD}$
N = 633
Events = 251 (39.7%)
B</td></tr>
<tr><td>$CC_{HD} + ACEi_{HFD}$
N = 402
Events = 150 (37.3%)
G_1</td><td>$CC_{LD} + ACEi_{HFD}$
N = 100
Events = 51 (51.0%)
G_2</td><td>$CC_{00} + ACEi_{HFD}$
N = 141
Events = 40 (28.4%)
G_3</td><td>$CC_{HD} + ACEi_{LD}$
N = 373
Events = 143 (38.3%)
H_1</td><td>$CC_{LD} + ACEi_{LD}$
N = 129
Events = 70 (54.3%)
H_2</td><td>$CC_{00} + ACEi_{LD}$
N = 131
Events = 41 (31.3%)
H_3</td></tr>
<tr><td>Placebo</td><td colspan="3">Placebo + $ACEi_{HFD}$
N = 648
Events = 275 (42.2%)
C</td><td colspan="3">Placebo + $ACEi_{LD}$
N = 624
Events = 263 (42.1%)
D</td></tr>
</table>

$ACEi_{HFD}$ = ACE inhibitor at heart failure dose; $ACEi_{LD}$ = ACE inhibitor at lower than heart failure dose;
CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC_{00} =Not on candesartan at event or last visit
[a] Dose of study drug preceding the event (or at last visit if no event occurred)

Table 184 Comparison of the effect of high or low dose candesartan plus ACE inhibitor at heart failure dose or low dose on the secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI (confirmed, adjudicated) using Cox Regression[a] – CHARM-Added (SH-AHS-0006) Study

Comparison	Relative risk reduction	Hazard ratio	95% confidence interval	P-value (Wald)
$(G_1 + H_1)$ vs $(G_2 + H_2)$	37.7	0.632	(0.504, 0.770)	< 0.001
G_1 vs H_1	--	0.959	(0.763, 1.206)	0.720
G_1 vs G_2	34.8	0.652	(0.475, 0.896)	0.008
G_1 vs H_2	42.0	0.580	(0.437, 0.770)	<0.001
H_1 vs G_2	32.1	0.679	(0.493, 0.934)	0.018
H_1 vs H_2	39.4	0.606	(0.455, 0.807)	< 0.001
G_2 vs H_2	--	0.887	(0.619, 1.273)	0.517

[a] Note: P=0.719 for test for interaction between high/low dose candesartan and baseline covariate (cells G_1, H_1, G_2 and H_2 only)
Cells G_1, H_1, G_2 and H_2 = Reference to cells in Table 183.

However, there are many caveats to these findings:

(i) The findings are restricted to patients in the candesartan treatment group, i.e., they cannot be analyzed with corresponding placebo groups.

(ii) Such "within treatment group" analyses are subject to confounding, which limits the ability to interpret findings.

(iii) Dose level comparisons may not be valid because in the CHARM studies, patients were not randomized to dose level.

(iv) The observation time will differ by dose level, particularly because the protocol-specified dose escalation treatment regimen means that after the first dose level, the experience at subsequent dose levels is conditional on the experience at the prior dose levels. For example, a patient hospitalized for CHF in the first 2 weeks would be assigned to the 4

mg dose level and is removed from the risk set. The patient is now no longer at equal risk for hospitalization at any other dose level. Furthermore, this same patient could complete the study at a higher dose and appear in the candesartan high-dose group for the endpoint of discontinuation for an adverse event.

(v) Please note that for the primary and secondary endpoints, the group with the least events is that receiving NO candesartan at the visit preceding the event or at the last visit if no event occurred.

(vi) With regard to other heart failure treatments at baseline, there was no randomization to any treatment including ACE inhibitors at recommended dose vs less than heart failure recommended dose.

Components of primary and secondary variables

The individual components CV death (relative risk reduction 15.8%, P= 0.029), hospitalization 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. (Table 185 and Table 186).

Table 185 Components of primary and secondary variables. Number of patients with at least one event by treatment group and events per 1000 years of follow-up. Follow-up time is calculated to first event. ITT/Safety population (SH-AHS-0006)

Variable	Treatment	N	Events (No of patients)	Total follow-up time (years)	Events / 1000 follow-up years	Mean follow-up time (years)
CV death (confirmed adjudicated)	Placebo	1272	347	3720.8	93.3	2.9
	Cand. cil.	1276	302	3845.8	78.5	3.0
Hospitalisation due to CHF (confirmed adjudicated)	Placebo	1272	356	3234.7	110.1	2.5
	Cand. cil.	1276	309	3421.6	90.3	2.7
All-cause death (confirmed adjudicated)	Placebo	1272	412	3720.8	110.7	2.9
	Cand. cil.	1276	377	3845.8	98.0	3.0
Non-fatal MI (confirmed adjudicated)	Placebo	1272	49	3654.2	13.4	2.9
	Cand. cil.	1276	26	3804.8	6.8	3.0

Table 186 Components of 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
					Lower	Upper	
CV death (confirmed adjudicated)	2548	302	347	0.842	0.722	0.983	0.029
Hospitalisation due to CHF (confirmed adjudicated)	2548	309	356	0.825	0.709	0.961	0.014
All-cause death (confirmed adjudicated)	2548	377	412	0.885	0.770	1.018	0.086
Non-fatal MI (confirmed adjudicated)	2548	26	49	0.512	0.318	0.823	0.006

Time from randomization to all-cause hospitalization:

During the follow-up period, 852 (66.8%) patients in the candesartan group and 858 (67.5%) patients in the placebo group were hospitalized due to any cause. The average annualized events rates were 37.1% and 39.2% respectively (Table 187). The findings were not significant (P= 0.346) (Table 188).

Table 187 Confirmed adjudicated all- cause hospitalization. Number of patients with at least one event by treatment group and events per 1000 years of follow-up. Follow-up time is calculated to first event. ITT/Safety population (SH-AHS-0006)

Variable	Treatment	N	Events (No of patients)	Total follow-up time (years)	Events / 1000 follow-up years	Mean follow-up time (years)
All-cause hospitalisation	Placebo	1272	858	2190.7	391.6	1.7
	Cand. cil.	1276	852	2296.0	371.1	1.8

Table 188 Confirmed adjudicated all-cause hospitalization. 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
					Lower	Upper	
All-cause hospitalisation	2548	852	858	0.955	0.869	1.050	0.346

Number of patients with fatal or non-fatal MI:

There were significantly fewer patients with fatal or non-fatal MI in the candesartan group (44, 3.4%) than in the placebo group (69, 5.4%) (Table 189 and Table 190).

Table 189 The proportion of patients (%) with confirmed adjudicated fatal or nonfatal MI. ITT/Safety population (SH-AHS-0006)

Variable	Treatment	N	Number of patients with event	Proportion of patients with event	95% CI	
					Lower	Upper
Fatal or non-fatal MI (confirmed adjudicated)	Placebo	1272	69	5.4	4.2	6.8
	Cand. cil.	1276	44	3.4	2.5	4.6

Table 190 The difference in proportion (%) of patients with confirmed adjudicated fatal or non- fatal MI between treatments. Chi-square test. ITT/Safety population (SH-AHS-0006)

Variable	Difference in proportion between treatments	95% CI		p-value
	Cand.cil-placebo	Lower	Upper	
Fatal or non-fatal MI (confirmed adjudicated)	-2.0	-3.6	-0.4	0.015

NYHA classification of heart failure:

There was an improvement in NYHA functional class in candesartan patients compared to placebo patients (P= 0.020, Wilcoxon rank-sum test). 548 (43.3%) patients in the candesartan group improved 1 or 2 NYHA classes compared to 495 (37.3%) in the placebo group (Table 191).

Table 191 Number of patients and change from baseline to LVCF in NYHA class by treatment. ITT/Safety population (SH-AHS-0006)

Visit	NYHA class	Placebo	Cand. cil.	Total
Baseline	NYHA II	302 (23.7%)	312 (24.5%)	614 (24.1%)
	NYHA III	925 (72.7%)	931 (73.0%)	1856 (72.8%)
	NYHA IV	45 (3.5%)	33 (2.6%)	78 (3.1%)
	Total	1272	1276	2548
LVCF	NYHA I	115 (9.1%)	136 (10.7%)	251 (9.9%)
	NYHA II	548 (43.4%)	590 (46.6%)	1138 (45.0%)
	NYHA III	523 (41.4%)	489 (38.6%)	1012 (40.0%)
	NYHA IV	76 (6.0%)	51 (4.0%)	127 (5.0%)
	Total	1262	1266	2528
Change from baseline to LVCF[a]	NYHA improved by 3 classes	2 (0.2%)	1 (0.1%)	3 (0.1%)
	NYHA improved by 2 classes	65 (5.2%)	68 (5.4%)	133 (5.3%)
	NYHA improved by 1 class	430 (34.1%)	480 (37.9%)	910 (36.0%)
	NYHA same as baseline	654 (51.8%)	634 (50.1%)	1288 (50.9%)
	NYHA deteriorated by 1 class	103 (8.2%)	80 (6.3%)	183 (7.2%)
	NYHA deteriorated by 2 classes	8 (0.6%)	3 (0.2%)	11 (0.4%)
	Total	1262	1266	2528

[a] Wilcoxon rank-sum test, p=0.020

The shift in NYHA functional class from baseline to last known class is presented in Table 192.

Table 192 NYHA class shift table by treatment. ITT/Safety Population. (SH-AHS-0006)

Change in NYHA class from baseline to LVCF	Number of patients	
	Placebo	Cand.cil.
from II to Unknown	2 (0.2%)	1 (0.1%)
from II to I	56 (4.4%)	74 (5.8%)
from II to II	183 (14.4%)	194 (15.2%)
from II to III	53 (4.2%)	40 (3.1%)
from II to IV	8 (0.6%)	3 (0.2%)
from III to Unknown	8 (0.6%)	9 (0.7%)
from III to I	57 (4.5%)	61 (4.8%)
from III to II	357 (28.1%)	389 (30.5%)
from III to III	453 (35.6%)	432 (33.9%)
from III to IV	50 (3.9%)	40 (3.1%)
from IV to I	2 (0.2%)	1 (0.1%)
from IV to II	8 (0.6%)	7 (0.5%)
from IV to III	17 (1.3%)	17 (1.3%)
from IV to IV	18 (1.4%)	8 (0.6%)

Time from randomization to diagnosed onset of diabetes:

Analyses include only patients without a pre-study diagnosis of diabetes. An equal number of patients in both treatment groups had a diagnosed onset of diabetes during the follow- p period (candesartan 72, 8.0%, placebo 72 8.1%, HR 0.98, 95% CI 0.70 to 1.35, P= 0.88) (Table 193 and Table 194).

Table 193 Diagnosed onset of diabetes. Number of patients with an event by treatment group and events per 1000 years of follow-up. Follow-up time is calculated to first event. ITT/Safety population (SH-AHS-0006)

Variable	Treatment	N	Events (No of patients)	Total follow-up time (years)	Events / 1000 follow-up years	Mean follow-up time (years)
Diagnosed onset of diabetes	Placebo	890	72	2583.4	27.9	2.9
	Cand. cil.	900	72	2645.5	27.2	2.9

Table 194 Diagnosed onset of diabetes. 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
					Lower	Upper	
Diagnosed onset of diabetes	1790	72	72	0.975	0.703	1.351	0.878

Number of patients who developed atrial fibrillation:

Table 195 Development of atrial fibrillation. The proportions of patients (%) with an event. ITT/ Safety population (SH-AHS-0006)

Variable	Treatment	N	Number of patients with event	Proportion of patients with event	95% CI	
					Lower	Upper
Development of atrial fibrillation	Placebo	1272	84	6.6	5.3	8.1
	Cand. cil.	1276	73	5.7	4.5	7.1

Slightly fewer patients in the candesartan group than in the placebo group developed atrial fibrillation (candesartan 73, 5.7%, placebo 84, 6.6%, P= 0.354) during the follow-up period (Table 195 and Table 196).

Table 196 Development of atrial fibrillation. The difference in proportion (%) between treatments. Chi-square test. ITT/Safety population (SH-AHS-0006)

Variable	Difference in proportion between treatments	95% CI		p-value
	Cand.cil-placebo	Lower	Upper	
Development of atrial fibrillation	-0.9	-2.7	1.0	0.354

Deaths:

Death due to MI and non-CV deaths were not affected by candesartan. **There was however more deaths due to cancer in the candesartan group (35 cases vs. 19, P=0.044) (**Table 197 **&** Table 198**).**

Table 197 Number of deaths due to cancer by treatment group and events per 1000 years of follow-up. Follow-up time is calculated to first event. ITT/ Safety population (SH-AHS-0006)

Variable	Treatment	N	Events (No of pati-ents)	Total follow-up time (years)	Events / 1000 follow-up years	Mean follow-up time (years)
Death due to cancer (confirmed adjudicated)	Placebo	1272	19	3720.8	5.1	2.9
	Cand. cil.	1276	35	3845.8	9.1	3.0

Table 198 Deaths due to cancer. 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
					Lower	Upper	
Death due to cancer (confirmed adjudicated)	2548	35	19	1.777	1.017	3.107	0.044[a]

Frequency of hospitalizations:

The effects on hospitalizations for various reasons are presented in Table 199 and Table 200. The number of patients hospitalized for CHF as well as the total numbers of hospital admissions primarily for CHF were reduced by treatment with candesartan.

Table 199 Total number of clinical events by variable and treatment. ITT/ Safety population (SH-AHS-0006)

Variable	Treatment	N	Number of patients with events	Total number of events	Total number of follow-up years	Mean (number of events / follow-up year) by patients	Events / 1000 follow-up years
Coronary revascularisation procedure	Placebo	1272	75	98	3720.8	0.02	26.3
	Cand. cil.	1276	69	86	3845.8	0.02	22.4
All-cause hospitalisation	Placebo	1272	858	2798	3720.8	1.09	752.0
	Cand. cil.	1276	852	2462	3846.2	0.87	640.1
Non-fatal stroke	Placebo	1272	30	37	3720.8	0.01	9.9
	Cand. cil.	1276	38	45	3845.8	0.02	11.7
Non-fatal MI	Placebo	1272	71	124	3720.8	0.05	33.3
	Cand. cil.	1276	52	90	3845.8	0.04	23.4
Hospitalisation due to CHF	Placebo	1272	437	976	3720.8	0.44	262.3
	Cand. cil.	1276	381	736	3845.8	0.33	191.4
Hospitalisation due to CHF (primary reason only)	Placebo	1272	382	836	3720.8	0.39	224.7
	Cand.cil.	1276	323	607	3845.8	0.27	157.8
Number of days alive in hospital	Placebo	1272	801	24436	3720.8	8.37	6567
	Cand. cil.	1276	804	21979	3845.8	7.08	5715

Table 200 Difference between treatments by variable. Wilcoxon rank-sum test. ITT/Safety population (SH-AHS-0006)

Variable	Mean (number of events / follow-up year) by pat.		p-value
	Placebo	Cand. cil.	
Coronary revascularisation procedure	0.02	0.02	0.583
All-cause hospitalisation	1.09	0.87	0.023
Non-fatal stroke	0.01	0.02	0.337
Non-fatal MI	0.05	0.04	0.079
Hospitalisation due to CHF	0.44	0.33	0.002
Hospitalisation due to CHF (primary reason only)	0.39	0.27	0.002
Number of days alive in hospital	8.37	7.08	0.260

Analyses of subgroups:

The treatment effects observed in subgroups in this study generally parallel the findings in the overall population of study SH- AHS- 0006 and paralleled the subgroup analysis in the pooled analysis of the three component studies in the CHARM program (SH-AHS-pooled). The beneficial effects of candesartan in reducing CV death and hospitalization due to heart failure

was generally consistent across important patient subgroups including sex, age, race, region, CHF etiology, baseline NYHA class, baseline LVEF and concomitant medications.

Analyses based on geographic region did not indicate regional heterogeneity for the primary efficacy variable, CV death or heart failure hospitalization (P= 0.203 for the interaction treatment by all regions and P= 0.115 for the interaction treatment by US/non-US).

Within the US, the country contributing the largest number of patients, the HR for the primary efficacy variable was 1.019 (95% CI 0.798-1.303, P=0.877). This finding is not consistent with the US specific results in SH-AHS-0003 in which the treatment effect was in the direction favoring candesartan (HR 0.811, 95% CI 0.605 -1.087, P= 0.162). Taken together, studies SH-AHS-0003 and SH-AHS-0006 (pooled analysis) also demonstrated a treatment effect in the direction favoring candesartan for the US patients (HR 0.928, 95% CI 0.769 -1.119, P= 0.433).

Resource utilization data for patients hospitalized with a CV diagnosis: number of hospitalizations, length of stay, level of hospital care and any major CV procedures performed

Table 201 summarizes the number of hospitalizations and overall length of stay for hospitalized patients where the primary reason for the hospitalization was stated by the investigator as cardiovascular.

Table 201 Total number and total duration (days) of hospitalizations and percentage of time on each unit of care subdivided with respect to treatment and primary reason for hospitalization. ITT/Safety population (SH-AHS-0006)

		Hospitalizations		Intensive care		Intermediate care		General care		All	
Primary reason[a]	Treatment	N	%	Days	%	Days	%	Days	%	Days	%
Worsening CHF	Placebo	731	27.3	1126	16.8	1583	23.7	3982	59.5	6691	100
	Cand.cil.	529	19.8	708	14.0	1036	20.5	3311	65.5	5055	100
Myocardial infarction	Placebo	63	2.4	242	48.3	126	25.1	133	26.5	501	100
	Cand.cil.	31	1.2	200	60.8	34	10.3	95	28.9	329	100
Unstable angina	Placebo	174	6.5	345	29.0	296	24.9	548	46.1	1189	100
	Cand.cil.	134	5.0	242	17.9	643	47.6	465	34.4	1350	100
Stroke	Placebo	26	1.0	109	38.4	47	16.5	128	45.1	284	100
	Cand.cil.	24	0.9	101	26.9	117	31.1	158	42.0	376	100
TIA	Placebo	4	0.1	0	0.0	3	13.6	19	86.4	22	100
	Cand.cil.	11	0.4	1	1.6	17	27.9	43	70.5	61	100
Hypotension	Placebo	16	0.6	20	20.0	8	8.0	72	72.0	100	100
	Cand.cil.	43	1.6	15	4.7	47	14.7	257	80.6	319	100
Atrial tachyarrhythmia	Placebo	49	1.8	25	7.0	65	18.2	267	74.8	357	100
	Cand.cil.	55	2.1	62	18.4	109	32.3	166	49.3	337	100
Ventricular arrhythmia	Placebo	77	2.9	177	28.0	343	54.3	112	17.7	632	100
	Cand.cil.	59	2.2	107	24.8	167	38.7	157	36.4	431	100
Pulmonary embolism	Placebo	9	0.3	0	0.0	39	66.1	20	33.9	59	100
	Cand.cil.	4	0.1	0	0.0	6	19.4	25	80.6	31	100
Other CV event	Placebo	347	13.0	302	13.5	650	29.0	1286	57.5	2238	100
	Cand.cil.	287	10.7	457	25.8	431	24.3	884	49.9	1772	100
All CV events	Placebo	1496	56.0	2346	19.4	3160	26.2	6567	54.4	12073	100
	Cand.cil.	1177	44.0	1893	18.8	2607	25.9	5561	55.3	10061	100

[a] As stated by investigator

Information on length of stay by type of ward was recorded for 2,673 hospitalizations (1,177 in the candesartan group, 1,496 in the placebo group) where the primary reason for hospitalization was reported as cardiovascular. Patients in the candesartan group spent fewer days in hospital (10,061 days) than patients in the placebo group (12,073 days). The candesartan patients spent

fewer days in hospital no matter the level of care (Table 201).

Drug-drug and drug-disease interactions:

The effects were similar in different age groups, in males and females, diabetics and non-diabetics, and in patients with or without a diagnosis of hypertension.

Candesartan reduced the risk of cardiovascular death or CHF hospitalization in all predefined subgroups and there was no evidence of heterogeneity of treatment effect (Pooled CHARM program report). The effects were similar in different age groups, in males and females, diabetics and non-diabetics, and in patients with or without a diagnosis of hypertension.

Effects on the primary outcome were present also in patients taking beta-blocker or digoxin. In particular, candesartan reduced this risk in patients treated with a β-blocker, in addition to an ACE inhibitor at baseline (Figure 100). In patients treated with a β-blocker at baseline, there were 175/702 (24.9%) deaths in the candesartan group and 195/711 (27.4%) deaths in the placebo group, HR 0.88 (0.72, 1.08). The numbers of deaths in patients not taking a β-blocker at baseline were 202/574 (35.2%) in the candesartan group and 217/561 (38.7%) in the placebo group, HR 0.88 (0.73, 1.07).

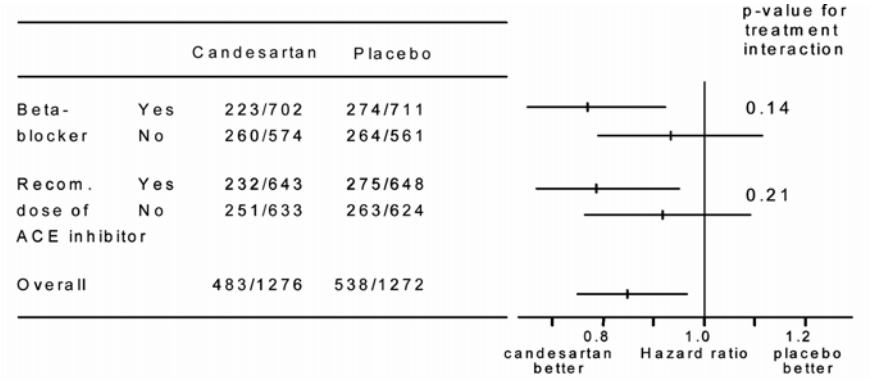


Figure 100 Effect of candesartan compared with placebo on primary outcome in all patients and patients taking or not taking β-blocker and taking or not taking recommended dose of ACE inhibitors at baseline

For the primary outcome, candesartan was as effective in patients taking a recommended dose of ACE inhibitor as in those taking lower doses (Figure 100).

Relationship of dose of candesartan to use or non-use of β-blockers in the treatment of CHF

Following a Telecon with the sponsor on Nov 2, 2004, I requested the sponsor to provide information on the CHARM-Added (SH-AHS-0006) Study regarding the proportion of patients receiving low dose (4 or 8 mg) or high dose (16 or 32 mg) candesartan *at the time of the event* or *at the last visit (if no event occurred)* in the each of the sub-populations of patients receiving or not receiving β-blockers at baseline.

On Nov 12, 2004, I received the sponsor's response containing the information related to the primary and principal secondary efficacy endpoints. These analyses consider dose level of candesartan consistent with the sub-group analyses presented in the submission. For the dose analyses, high candesartan dose is defined as 16 mg or 32 mg and low dose candesartan as 4 mg or 8 mg. Dose level was determined as described in the submission as a patient's last dose (if the patient had no event), or, if the patient had an event, as the last dose prior to the event. The category "no-study drug" was used to classify patients who were not on study drug at the visit prior to the event or not on study drug at the last visit if they had no event.

Table 202 The numbers and event rates (primary efficacy endpoint of CV mortality or CHF hospitalization, confirmed, adjudicated) of patients who did or did not receive β-blockers at baseline – CHARM-Added (SH-AHS-0006) Study

	Receiving β-blocker at baseline			Not on β-blocker at baseline		
Candesartan cilexetil[b]	**CC_{HD} + BB** N = 445 n = 146 (32.8%) I_1	**CC_{LD} + BB** N = 104 n = 41 (39.4%) I_2	**CC_{00} + BB** N = 153 n = 36 (23.5%) I_3	**CC_{HD} + NB** N = 328 n = 138 (42.1%) J_1	**CC_{LD} + NB** N = 122 n = 74 (60.7%) J_2	**CC_{00} + NB** N = 124 n = 48 (38.7%) J_3

BB = receiving β-blocker at baseline; NB = not receiving β-blocker at baseline
CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC_{00} =Not on candesartan at event or last visit
[b] Dose of study drug preceding the event (or at last visit if no event occurred)

Table 203 Comparison of the effect of high or low dose candesartan on CHF patients who did or did not receive β-blockers at baseline on the primary endpoint of time to CV mortality or CHF hospitalization (confirmed, adjudicated) using Cox Regression[a] – CHARM-Added (SH-AHS-0006) Study

Comparison	Relative risk reduction	Hazard ratio	95% confidence interval	P-value (Wald)
$(I_1 + J_1)$ vs $(I_2 + J_2)$	36.9	0.631	(0.508, 0.784)	< 0.001
I_1 vs J_1	--	0.723	(0.573, 0.912)	0.006
I_1 vs I_2	19.0	0.810	(0.573, 1.145)	0.233
I_1 vs J_2	59.8	0.402	(0.303, 0.531)	<0.001
J_1 vs I_2	--	1.122	(0.791, 1.590)	0.519
J_1 vs J_2	44.2	0.558	(0.421, 0.741)	< 0.001
I_2 vs J_2	--	0.500	(0.341, 0.732)	< 0.001

[a] Note: P=0.092 for test for interaction between high/low dose candesartan and baseline covariate (cells I_1, J_1, I_2 and J_2 only)
Cells I_1, J_1, I_2 and J_2 = Reference to cells in Table 202.

Table 204 The numbers and event rates (secondary efficacy endpoint of all-cause mortality or CHF hospitalization, confirmed, adjudicated) of patients who did or did not receive β-blockers at baseline – CHARM-Added (SH-AHS-0006) Study

	Receiving β-blocker at baseline			Not on β-blocker at baseline		
Candesartan cilexetil[b]	**CC_{HD} + BB** N = 447 n = 164 (36.7%) K_1	**CC_{LD} + BB** N = 105 n = 44 (41.9%) K_2	**CC_{00} + BB** N = 150 n = 44 (29.3%) K_3	**CC_{HD} + NB** N = 375 n = 155 (45.3%) L_1	**CC_{LD} + NB** N = 122 n = 77 (63.1%) L_2	**CC_{00} + NB** N = 123 n = 61 (49.6%) L_3

BB = receiving β-blocker at baseline; NB = not receiving β-blocker at baseline
CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC_{00} =Not on candesartan at event or last visit
[b] Dose of study drug preceding the event (or at last visit if no event occurred)

Table 205 Comparison of the effect of high or low dose candesartan plus on CHF patients who did or did not receive β-blockers at baseline on the secondary efficacy endpoint of all-cause mortality or CHF hospitalization (confirmed, adjudicated) using Cox Regression[a] – CHARM-Added (SH-AHS-0006) Study

Comparison	Relative risk reduction	Hazard ratio	95% confidence interval	P-value (Wald)
$(K_1 + L_1)$ vs $(K_2 + L_2)$	34.0	0.660	(0.535, 0.810)	< 0.001
K_1 vs L_1	--	0.749	(0.600, 0.936)	0.011
K_1 vs K_2	15.0	0.850	(0.610, 1.186)	0.340
K_1 vs L_2	57.0	0.430	(0.328, 0.564	<0.001
L_1 vs K_2	--	1.133	(0.810, 1.587)	0.465
L_1 vs L_2	42.4	0.576	(0.437, 0.759)	<0.001
K_2 vs L_2	--	0.512	(0.353, 0.743)	<0.001

[a] Note: P=0.070 for test for interaction between high/low dose candesartan and baseline covariate (cells K_1, L_1, K_2 and L_2 only)
Cells K_1, L_1, K_2 and L_2 = Reference to cells in Table 204

Table 206 The numbers and event rates (secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI, confirmed, adjudicated) of patients who did or did not receive β-blockers at baseline – CHARM-Added (SH-AHS-0006) Study

	Receiving β-blocker at baseline			Not on β-blocker at baseline		
Candesartan cilexetil[b]	**CC_{HD} + BB** N = 445 n = 149 (33.5%) M_1	**CC_{LD} + BB** N = 107 n = 45 (42.1%) M_2	**CC_{00} + BB** N = 150 n = 34 (22.7%) M_3	**CC_{HD} + NB** N = 330 n = 144 (43.6%) N_1	**CC_{LD} + NB** N = 122 n = 76 (62.3%) N_2	**CC_{00} + NB** N = 122 n = 47 (38.5%) N_3

BB = receiving β-blocker at baseline; NB = not receiving β-blocker at baseline
CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC_{00} =Not on candesartan at event or last visit
[b] Dose of study drug preceding the event (or at last visit if no event occurred)

Table 207 Comparison of the effect of high or low dose candesartan on CHF patients who did or did not receive β-blockers at baseline on the secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI (confirmed, adjudicated) using Cox Regression[a] – CHARM-Added (SH-AHS-0006) Study

Comparison	Relative risk reduction	Hazard ratio	95% confidence interval	P-value (Wald)
$(M_1 + N_1)$ vs $(M_2 + N_2)$	37.7	0.632	(0.504, 0.770)	< 0.001
M_1 vs N_1	--	0.707	(0.562, 0.889)	0.003
M_1 vs M_2	23.4	0.766	(0.549, 1.070)	0.118
M_1 vs N_2	60.3	0.397	(0.301, 0.523)	<0.001
N_1vs M_2	--	1.085	(0.777, 1.517)	0.631
N_1 vs N_2	43.8	0.562	(0.426, 0.743)	< 0.001
M_2 vs N_2	--	0.520	(0.359, 0.752)	<0.001

[a] Note: P=0.719 for test for interaction between high/low dose candesartan and baseline covariate (cells M_1, N_1, M_2 and N_2 only)
Cells M_1, N_1, M_2 and N_2 = Reference to cells in Table 206

Primary efficacy endpoint of CV mortality or CHF hospitalization (confirmed, adjudicated): The proportion of patients who reached the primary efficacy endpoint while on high or low dose candesartan with or without concomitant β-blockers at baseline are given in Table 202. It appears that there is a relative dose response, the event rates being significantly (P<0.001) lower in the high dose (16 and 32 mg) candesartan groups compared to the low dose (4 and 8 mg) candesartan groups for both groups of patients receiving heart failure doses and low doses of ACE inhibitors (Table 203).

The secondary efficacy endpoint of all-cause mortality or CHF hospitalization (Table 204 and Table 205), and for secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI (Table 206 and Table 207) also show similar findings.

However, there are many caveats to these findings:

(i) The findings are restricted to patients in the candesartan treatment group, i.e., they cannot be analyzed with corresponding placebo groups.

(ii) Such "within treatment group" analyses are subject to confounding, which limits the ability to interpret findings.

(iii) Dose level comparisons may not be valid because in the CHARM studies, patients were not randomized to dose level.

(iv) The observation time will differ by dose level, particularly because the protocol-specified dose escalation treatment regimen means that after the first dose level, the experience at subsequent dose levels is conditional on the experience at the prior dose levels. For example, a patient hospitalized for CHF in the first 2 weeks would be assigned to the 4 mg dose level and is removed from the risk set. The patient is now no longer at equal risk for hospitalization at any other dose level. Furthermore, this same patient could complete the study at a higher dose and appear in the candesartan high-dose group for the endpoint of discontinuation for an adverse event.

(v) Please note that for the primary and secondary endpoints, the group with the least events is that receiving NO candesartan at the visit preceding the event or at the last visit if no event occurred.

(vi) With regard to other heart failure treatments at baseline, there was no randomization to any treatment including β-blockers (Yes/ No).

Relationship of dose of candesartan to the primary and secondary efficacy endpoints in patients receiving or not receiving spironolactone

Following a Telecon with the sponsor on Nov 2, 2004, I requested the sponsor to provide information on the CHARM-Added (SH-AHS-0006) Study regarding the proportion of patients receiving low dose (4 or 8 mg) or high dose (16 or 32 mg) candesartan *at the time of the event* or *at the last visit (if no event occurred)* in the each of the sub-populations of patients receiving or not receiving aldosterone antagonists at baseline.

On Nov 12, 2004, I received the sponsor's response containing the information related to the primary and principal secondary efficacy endpoints. These analyses consider dose level of candesartan consistent with the sub-group analyses presented in the submission. For the dose analyses, high candesartan dose is defined as 16 mg or 32 mg and low dose candesartan as 4 mg or 8 mg. Dose level was determined as described in the submission as a patient's last dose (if the patient had no event), or, if the patient had an event, as the last dose prior to the event. The category "no-study drug" was used to classify patients who were not on study drug at the visit prior to the event or not on study drug at the last visit if they had no event.

Table 208 The numbers and event rates (primary efficacy endpoint of CV mortality or CHF hospitalization, confirmed, adjudicated) of patients who did or did not receive spironolactone at baseline – CHARM-Added (SH-AHS-0006) Study

	Receiving spironolactone at baseline			Not on spironolactone at baseline		
Candesartan cilexetil[b]	**CC_{HD} + SS**	**CC_{LD} + SS**	**CC_{00} + SS**	**CC_{HD} + NS**	**CC_{LD} + NS**	**CC_{00} + NS**
	N = 111	N = 57	N = 54	N = 662	N = 169	N = 223
	n = 49 (44.1%)	n = 35 (61.4%)	n = 21 (38.9%)	n = 235 (35.5%)	n = 80 (47.3%)	n = 63 (28.3%)
	O_1	O_2	O_3	P_1	P_2	P_3

SS = receiving spironolactone at baseline; NS = not receiving spironolactone at baseline
CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC_{00} =Not on candesartan at event or last visit
[b] Dose of study drug preceding the event (or at last visit if no event occurred)

Table 209 Comparison of the effect of high or low dose candesartan on CHF patients who did or did not receive spironolactone at baseline on the primary endpoint of time to CV mortality or CHF hospitalization (confirmed, adjudicated) using Cox Regression[a] – CHARM-Added (SH-AHS-0006) Study

Comparison	Relative risk reduction	Hazard ratio	95% confidence interval	P-value (Wald)
(O_1 + P_1) vs (O_2 + P_2)	36.9	0.631	(0.508, 0.784)	< 0.001
O_1 vs P_1	--	1.321	(0.971, 1.798)	0.076
O_1 vs O_2	38.1	0.619	(0.401, 0.955)	0.030
O_1 vs P_2	11.4	0.886	(0.620, 1.264)	0.504
P_1 vs O_2	54.2	0.458	(0.321, 1.653)	< 0.001
P_1 vs P_2	33.1	0.669	(0.519, 0.862)	0.002
O_2 vs P_2	--	1.442	(0.969, 2.146)	0.071

[a] Note: P=0.708 for test for interaction between high/low dose candesartan and baseline covariate (cells O_1, P_1, O_2 and P_2 only)
Cells O_1, P_1, O_2 and P_2 = Reference to cells in Table 208

Table 210 The numbers and event rates (secondary efficacy endpoint of all-cause mortality or CHF hospitalization, confirmed, adjudicated) of patients who did or did not receive spironolactone at baseline – CHARM-Added (SH-AHS-0006) Study

	Receiving spironolactone at baseline			Not on spironolactone at baseline		
Candesartan cilexetil[b]	**CC_{HD} + SS**	**CC_{LD} + SS**	**CC_{00} + SS**	**CC_{HD} + NS**	**CC_{LD} + NS**	**CC_{00} + NS**
	N =111	N = 58	N = 53	N = 665	N = 169	N = 220
	n = 52 (46.9%)	n = 37 (63.8%)	n = 22 (41.5%)	n = 261 (39.3%)	n = 84 (49.7%)	n = 83 (37.7%)
	Q_1	Q_2	Q_3	R_1	R_2	R_3

SS = receiving spironolactone at baseline; NS = not receiving spironolactone at baseline
CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC_{00} =Not on candesartan at event or last visit
[b] Dose of study drug preceding the event (or at last visit if no event occurred)

Table 211 Comparison of the effect of high or low dose candesartan plus on CHF patients who did or did not receive spironolactone at baseline on the secondary efficacy endpoint of all-cause mortality or CHF hospitalization (confirmed, adjudicated) using Cox Regression[a] – CHARM-Added (SH-AHS-0006) Study

Comparison	Relative risk reduction	Hazard ratio	95% confidence interval	P-value (Wald)
(Q_1 + R_1) vs (Q_2 + R_2)	34.0	0.660	(0.535, 0.810)	< 0.001
Q_1 vs R_1	--	1.268	(0.942, 1.708)	0.118
Q_1 vs Q_2	37.3	0.627	(0.411, 0.956)	0.030
Q_1 vs R_2	10.4	0.896	(0.634, 1.267	0.535
R_1 vs Q_2	51.6	0.484	(0.343, 0.683)	<0.001
R_1 vs R_2	29.5	0.705	(0.551, 0.901)	0.005
Q_2 vs R_2	--	1.435	(0.975, 2.114)	0.067

[a] Note: P=0.586 for test for interaction between high/low dose candesartan and baseline covariate (cells Q_1, R_1, Q_2 and R_2 only)
Cells Q_1, R_1, Q_2 and R_2 = Reference to cells in Table 210

Table 212 The numbers and event rates (secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI, confirmed, adjudicated) of patients who did or did not receive spironolactone at baseline – CHARM-Added (SH-AHS-0006) Study

	Receiving spironolactone at baseline			Not on spironolactone at baseline		
Candesartan cilexetil[b]	**CC_{HD} + SS** N = 112 n = 50 (44.6%) S_1	**CC_{LD} + SS** N = 57 n = 36 (63.2%) S_2	**CC_{00} + SS** N = 53 n = 20 (37.7%) S_3	**CC_{HD} + NS** N = 663 n = 243 (36.7%) T_1	**CC_{LD} + NS** N = 172 n = 85 (49.4%) T_2	**CC_{00} + NS** N = 219 n = 61 (27.9%) T_3

SS = receiving spironolactone at baseline; NS = not receiving spironolactone at baseline
CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC_{00} =Not on candesartan at event or last visit
[b] Dose of study drug preceding the event (or at last visit if no event occurred)

Table 213 Comparison of the effect of high or low dose candesartan on CHF patients who did or did not receive spironolactone at baseline on the secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI (confirmed, adjudicated) using Cox Regression[a] – CHARM-Added (SH-AHS-0006) Study

Comparison	Relative risk reduction	Hazard ratio	95% confidence interval	P-value (Wald)
$(S_1 + T_1)$ vs $(S_2 + T_2)$	37.7	0.632	(0.504, 0.770)	< 0.001
S_1 vs T_1	--	1.293	(0.954, 1.753)	0.098
S_1 vs S_2	39.0	0.610	(0.397, 0.937)	0.024
S_1 vs T_2	15.0	0.850	(0.600, 1.206)	0.364
T_1vs S_2	53.9	1.461	(0.325, 0.655)	<0.001
T_1 vs T_2	34.4	0.656	(0.513, 0.840)	< 0.001
S_2 vs T_2	--	1.409	(0.954, 2.082)	0.085

[a] Note: P=0.719 for test for interaction between high/low dose candesartan and baseline covariate (cells M_1, N_1, M_2 and N_2 only)
Cells M_1, N_1, M_2 and N_2 = Reference to cells in Table 212.

CHF Patients who received high or low dose candesartan with or without spironolactone at baseline

Primary efficacy endpoint of CV mortality or CHF hospitalization (confirmed, adjudicated): The proportion of patients who reached the primary efficacy endpoint while on high or low dose candesartan with or without spironolactone are given in Table 208. It appears that there is a relative dose response, the event rates being significantly (P<0.001) lower in the high dose (16 and 32 mg) candesartan groups compared to the low dose (4 and 8 mg) candesartan groups for both groups of patients receiving heart failure doses and low doses of ACE inhibitors (Table 209).

The secondary efficacy endpoint of all-cause mortality or CHF hospitalization (Table 210 and

Table 211), and for secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI (Table 212 and Table 213) also show similar findings.

However, there are many caveats to these findings:

(i) The findings are restricted to patients in the candesartan treatment group, i.e., they cannot be analyzed with corresponding placebo groups.

(ii) Such "within treatment group" analyses are subject to confounding, which limits the ability to interpret findings.

(iii) Dose level comparisons may not be valid because in the CHARM studies, patients were not randomized to dose level.

(iv) The observation time will differ by dose level, particularly because the protocol-specified dose escalation treatment regimen means that after the first dose level, the experience at subsequent dose levels is conditional on the experience at the prior dose levels. For example, a patient hospitalized for CHF in the first 2 weeks would be assigned to the 4 mg dose level and is removed from the risk set. The patient is now no longer at equal risk for hospitalization at any other dose level. Furthermore, this same patient could complete the study at a higher dose and appear in the candesartan high-dose group for the endpoint of discontinuation for an adverse event.

(v) Please note that for the primary and secondary endpoints, the group with the least events is that receiving NO candesartan at the visit preceding the event or at the last visit if no event occurred.

(vi) With regard to other heart failure treatments at baseline, there was no randomization to any treatment including spironolactone (Yes/No).

Conclusions:

Candesartan significantly reduced all-cause death or the first occurrence of a CHF hospitalization (P= 0.021).

Candesartan significantly reduced cardiovascular death or the first occurrence of a CHF hospitalization or non- fatal myocardial infarction (P= 0.010).

Candesartan significantly reduced cardiovascular death or the first occurrence of a CHF hospitalization or a non- fatal myocardial infarction or a coronary revascularization procedure (P= 0.008).

Candesartan significantly reduced the number of fatal and non-fatal MIs (P= 0.012).

Candesartan significantly improved NYHA classification from randomization to the LVCF (P= 0.020).

Candesartan was not shown to reduce all-cause death or the first occurrence of hospitalization (P= 0.387).

Candesartan did not reduce all-cause death (P= 0.086).

Candesartan was not shown to reduce time to the first occurrence of hospitalization (P= 0.346).

Summary of Efficacy Results:

Candesartan treatment significantly reduced cardiovascular death or hospitalization due to CHF (HR 0.85, 95% CI 0.75- 0.96, P= 0.011). This corresponds to a relative risk reduction of 14.7%. The effect appeared early and was sustained throughout the study period. The two secondary efficacy outcomes included in the confirmatory analysis were also significantly reduced by treatment with candesartan. The relative risk reduction for all-cause death or hospitalization due

to CHF was 12.9% (HR 0.87, 95% CI 0.78- 0.98, P= 0.021), and for CV death or hospitalization due to CHF or non-fatal MI 14.8% (HR 0.85, 95% CI 0.76- 0.96, P= 0.010).

The individual components CV death (relative risk reduction 15.8%, P= 0.029), hospitalization 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) 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

Extent of exposure

A total of 2,548 patients (542 females and 2006 males) were randomized into the study, all of who were included in the ITT/ Safety population. Patients who received incorrect investigational product during any part of the study (6 patients) are included in the analyses according to the group to which they were randomized. Duration of treatment was defined as the time from the first to the last day of treatment, regardless of temporary discontinuations of the investigational product. The last day of treatment was either the day the patient completed or withdrew from the study or died, or, if the investigational product was discontinued prematurely, the date for the permanent discontinuation. An overview of exposure is presented in Table 214, including data on the number of patients who completed or discontinued the study.

Table 214 Overview of exposure. ITT/Safety population (SH-AHS-0006)

		Placebo (N=1272)		Cand. cil. (N=1276)	
No. (%) of patients evaluable for safety	Male	1000	(78.6)	1006	(78.8)
	Female	272	(21.4)	270	(21.2)
Age	<65	636	(50.0)	632	(49.5)
	≥65	636	(50.0)	644	(50.5)
	<75	1027	(80.7)	1064	(83.4)
	≥75	245	(19.3)	212	(16.6)
Race[a]	Caucasian	1176	(92.5)	1170	(91.7)
	Black	62	(4.9)	65	(5.1)
	Oriental	20	(1.6)	33	(2.6)
	Other	14	(1.1)	8	(0.6)
Exposure by discontinuation of investigational product due to AE and/or discontinuation of study (N and %)	Discontinued investigational product due to AEs	224	(17.6)	310	(24.3)
	Patients who withdrew consent	15	(1.2)	25	(2.0)

[a]Race is presented according to the four race groups Caucasian (including European origin, South Asian and Arab/ Middle East), Black, Oriental (including Oriental and Malay) and Other.

The median duration of patient follow-up in the study was 41.1 months for patients randomized to candesartan and 40.9 months for patients randomized to placebo. 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.

A total of 1,096 (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 at randomization (baseline). A total of 1,756 (68.9%) patients (candesartan 857, 67.2%; placebo 899, 70.7%) received the investigational product for 24 months or more. 5 3.6% 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. At the end of treatment (LVCF) 41.2% (8.4% of those still treated with candesartan) received 32 mg candesartan once daily. The mean candesartan LVCF dose was 23.1 mg.

Adverse events

Permanent discontinuations are defined as patients who discontinued treatment with the investigational product permanently, were alive > 5 days after treatment discontinuation and were not on the investigational product at the closing visit. However, if the investigational product was permanently discontinued, the patient still remained in the study and SAEs were reported during the whole study period.

In the descriptive analyses, patients who had a reduction of the dose of the investigational product and later permanently discontinued the investigational product for the same reason were counted only in the category of discontinuation; whereas, for the exploratory analyze, these patients were counted as having a reduction of the dose of the investigational product as well as

having discontinued treatment with the investigational product. As a result of this difference, the rates of dose reductions were higher in the exploratory safety analyses.

Categories of adverse events

AEs were reported by 78.0% (992) of the patients randomized to placebo, and by 80.4% (1,026) of the patients randomized to candesartan during study. In the placebo group 32.5% (413) of the patients had fatal SAEs and 68.4% (870) of the patients experienced non- fatal SAEs, compared with the candesartan group where 29.5% (377) of the patients had fatal SAEs and 68.5% (874) of the patients had non-fatal SAEs. The investigational product was prematurely discontinued due to AEs for 17.6% (224) of the patients in the placebo group and for 24.3% (310) of the patients in the candesartan group. The investigational product was reduced in dose due to AEs for 9.7% (123) of the patients in the placebo group and for 17.2% (220) of the patients in the candesartan group. A summary of adverse events by category is presented in Table 215.

Table 215 Number (%) of patients who had 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		Cand. cil. on treatment		Placebo during study[b]		Cand. cil. during study[b]	
	(N=1272)		(N=1276)		(N=1272)		(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.

Most common adverse events**:**

The most commonly reported AEs (Table 216) in the placebo group during study were cardiac failure/cardiac failure aggravated (472, 37.1%), hypotension (184, 14.5%), and sudden death (174, 13.7%). The most commonly reported AEs in the candesartan group during study were cardiac failure/cardiac failure aggravated (421, 33.0%), hypotension (296, 23.2%), and renal function abnormal/renal dysfunction aggravated (196, 15.4%).

Table 216 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 (N=1272)		Cand. cil. on treatment (N=1276)		Placebo during study (N=1272)		Cand. cil. during study (N=1276)	
	N	(%)	N	(%)	N	(%)	N	(%)
Cardiac failure/cardiac failure aggravated[b]	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[b]	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[b]	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)
Fibrillation atrial	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[b]	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[b]	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[b]	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 Patients having both AEs are counted once only.

Deaths:

790 patients died during study, of which 413 (32.5%) patients were randomized to placebo and 377 (29.5%) to candesartan. For 6 of the patients who died (Site – Patient number: 206-12114, 1863-14910, 1411-20937, 1420-21541, 1510-21309, 1510-21311), the death was incompletely documented (vital status only without specified cause of death). However all deaths are included in the analysis. One of the patients in the placebo group had an SAE with fatal outcome with date of death after the patient's closing visit. Thus, the death of this patient is included in the descriptive safety results, but not in the exploratory results.

The most common fatal SAEs are presented in Table 217. The most common fatal AE in both treatment groups during study was sudden death, reported in 174 (13.7%) patients in the placebo group and in 143 (11.2%) patients in the candesartan group. Cardiac failure/cardiac failure aggravated was the second most common fatal AE in the placebo and candesartan group (112, 8.8% and 74, 5.8%, respectively).

Table 217 Number (%) of patients with the most commonly reported[a] AEs leading to death, sorted by descending frequency in the total population during study. ITT/ Safety population (SH-AHS-0006)

Preferred term	Placebo on treatment (N=1272)		Cand. cil. on treatment (N=1276)		Placebo during study (N=1272)		Cand. cil. during study (N=1276)	
	N	(%)	N	(%)	N	(%)	N	(%)
Sudden death	139	(10.9)	113	(8.9)	174	(13.7)	143	(11.2)
Cardiac failure/cardiac failure aggravated[b]	61	(4.8)	28	(2.2)	112	(8.8)	74	(5.8)
Myocardial infarction	12	(0.9)	15	(1.2)	20	(1.6)	21	(1.6)
Death	5	(0.4)	7	(0.5)	13	(1.0)	19	(1.5)
Pneumonia	11	(0.9)	3	(0.2)	19	(1.5)	10	(0.8)
Cardiac arrest	8	(0.6)	8	(0.6)	13	(1.0)	13	(1.0)
Fibrillation ventricular	14	(1.1)	6	(0.5)	16	(1.3)	9	(0.7)
Cerebrovascular disorder	7	(0.6)	8	(0.6)	11	(0.9)	12	(0.9)
Sepsis	6	(0.5)	5	(0.4)	10	(0.8)	11	(0.9)
Cardiomyopathy	3	(0.2)	2	(0.2)	8	(0.6)	8	(0.6)
Pulmonary carcinoma	4	(0.3)	5	(0.4)	5	(0.4)	10	(0.8)
Pulmonary oedema	4	(0.3)	3	(0.2)	8	(0.6)	6	(0.5)
Renal failure nos	3	(0.2)	0		8	(0.6)	4	(0.3)
Accident and/or injury	3	(0.2)	3	(0.2)	5	(0.4)	5	(0.4)
Renal failure acute	3	(0.2)	2	(0.2)	5	(0.4)	5	(0.4)
Multiorgan failure	0		1	(0.1)	4	(0.3)	4	(0.3)
Colon carcinoma	0		1	(0.1)	0		7	(0.5)
Coronary artery disorder	2	(0.2)	1	(0.1)	2	(0.2)	5	(0.4)
Renal function abnormal	2	(0.2)	0		5	(0.4)	2	(0.2)

a This table uses a cut-off of at ≥0.3% in the total population during study (N=2548).

b Patients having both AEs are counted once only.

Serious adverse events other than deaths:

Table 218 Number (%) of patients with the most commonly reported[a] SAEs other than death, sorted by descending frequency in the total population during study. ITT/Safety population (SH-AHS-0006)

Preferred term	Placebo on treatment (N=1272)		Cand.cil. on treatment (N=1276)		Placebo during study (N=1272)		Cand.cil. during study (N=1276)	
	N	(%)	N	(%)	N	(%)	N	(%)
Cardiac failure/cardiac failure aggravated[b]	418	(32.9)	333	(26.1)	450	(35.4)	398	(31.2)
Angina pectoris/angina pectoris aggravated[b]	152	(11.9)	126	(9.9)	168	(13.2)	148	(11.6)
Hypotension	91	(7.2)	133	(10.4)	102	(8.0)	143	(11.2)
Arrhythmia ventricular	106	(8.3)	78	(6.1)	120	(9.4)	88	(6.9)
Pneumonia	77	(6.1)	55	(4.3)	93	(7.3)	73	(5.7)
Arrhythmia atrial	61	(4.8)	59	(4.6)	71	(5.6)	67	(5.3)
Fibrillation atrial	67	(5.3)	52	(4.1)	71	(5.6)	65	(5.1)
Tachycardia ventricular/ arrhythmia/arrhythmia aggravated[b]	61	(4.8)	51	(4.0)	66	(5.2)	62	(4.9)
Myocardial infarction	61	(4.8)	47	(3.7)	70	(5.5)	52	(4.1)
Chest pain	62	(4.9)	45	(3.5)	68	(5.3)	53	(4.2)
Cerebrovascular disorder	43	(3.4)	51	(4.0)	53	(4.2)	63	(4.9)
Coronary artery disorder	39	(3.1)	55	(4.3)	47	(3.7)	68	(5.3)
Tachycardia supraventricular	46	(3.6)	47	(3.7)	50	(3.9)	54	(4.2)
Syncope	44	(3.5)	44	(3.4)	48	(3.8)	55	(4.3)
Cardiomyopathy	34	(2.7)	32	(2.5)	42	(3.3)	47	(3.7)
Renal function abnormal/renal dysfunction aggravated[b]	31	(2.4)	45	(3.5)	36	(2.8)	53	(4.2)
Pulmonary oedema	37	(2.9)	35	(2.7)	41	(3.2)	42	(3.3)
Anaemia	34	(2.7)	32	(2.5)	40	(3.1)	42	(3.3)
Renal failure acute	24	(1.9)	42	(3.3)	32	(2.5)	50	(3.9)
Accident and/or injury	30	(2.4)	31	(2.4)	39	(3.1)	39	(3.1)
Dehydration	18	(1.4)	39	(3.1)	22	(1.7)	54	(4.2)
Diabetes mellitus/diabetes mellitus aggravated[b]	39	(3.1)	29	(2.3)	40	(3.1)	36	(2.8)

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

b Patients having both or all AEs are counted once only.

Non-fatal SAE during study were reported in 870 (68.4%) patients in the placebo group and in 874 (68.5%) patients in the candesartan group during study. The most common non-fatal SAEs are presented in Table 218.

The most commonly reported non-fatal SAEs in the placebo group during study were cardiac failure/cardiac failure aggravated (450, 35.4%) followed by angina pectoris/angina pectoris aggravated (168, 13.2%) and arrhythmia ventricular (120, 9.4%). The most commonly reported non-fatal SAEs in the candesartan group during study were cardiac failure/cardiac failure aggravated (398, 31.2%), angina pectoris/ angina pectoris aggravated (148, 11.6%) and hypotension (143, 11.2%).

Discontinuations due to adverse events:

The investigational product was permanently discontinued due to AEs in 224 (17.6%) patients in the placebo group and in 310 (24.3%) patients in the candesartan group. The most common AEs leading to discontinuation of investigational product are presented in Table 219. A patient could have more than one AE, leading to permanent discontinuation of the investigational product, occurring at the same time.

The most commonly reported AEs leading to discontinuation of the investigational product in the placebo group were cardiac failure/cardiac failure aggravated (81, 6.4%), renal function abnormal (53, 4.2%), and hypotension (44, 3.5%). In the candesartan group the most commonly reported AEs leading to discontinuation were renal function abnormal 105, (8.2%), hypotension and cardiac failure/ cardiac failure aggravated (69, 5.4% for both) and hyperkalemia (49, 3.8%).

The preferred term 'renal function abnormal' used in this descriptive safety analysis corresponds to the term increased creatinine used in the exploratory safety analyses. Both terms refer to 'Abnormal renal function, e.g. creatinine increased' pre-specified in the study data collection instrument (CRF).

Table 219 Number (%) of patients with the most commonly reported[a] AEs leading to discontinuation of investigational product, sorted by descending frequency in the total population on treatment. ITT/Safety population (SH-AHS-0006)

Preferred term	Placebo on treatment (N=1272)		Cande.cil. on treatment (N=1276)	
	N	(%)	N	(%)
Renal function abnormal	53	(4.2)	105	(8.2)
Cardiac failure/cardiac failure aggravated[b]	81	(6.4)	69	(5.4)
Hypotension	44	(3.5)	69	(5.4)
Hyperkalaemia	11	(0.9)	49	(3.8)
Renal failure acute	14	(1.1)	15	(1.2)
Cerebrovascular disorder	7	(0.6)	9	(0.7)
Diarrhoea	5	(0.4)	11	(0.9)
Myocardial infarction	8	(0.6)	8	(0.6)
Angina pectoris	7	(0.6)	8	(0.6)
Dizziness	7	(0.6)	7	(0.5)
Pneumonia	5	(0.4)	8	(0.6)
Dehydration	5	(0.4)	7	(0.5)
Pulmonary oedema	5	(0.4)	7	(0.5)

a This table uses a cut-off of ≥0.5% in total population during study (N=2548).

b Patients having both AEs are counted once only.

Dose reduction due to adverse events:

The investigational product was reduced in dose due to AEs in 123 (9.7%) patients in the placebo group and in 220 (17.2%) patients in the candesartan group. The most common AEs leading to dose reduction of the investigational product are presented in Table 220.

The most commonly reported AEs leading to dose reduction in the placebo group were hypotension (57, 4.5%), renal function abnormal/ renal dysfunction aggravated (23, 1.8%) and dizziness/vertigo (11, 0.9%). The most commonly reported AEs leading to dose reduction in the candesartan group were hypotension (124, 9.7%), renal function abnormal/ renal dysfunction aggravated (37, 2.9%) and hyperkalemia (32, 2.5%).

Table 220 Number (%) of patients with the most commonly reported[a] AEs leading to dose reduction of investigational product, sorted by descending frequency in the total population on treatment. ITT/Safety population (SH-AHS-0006)

Preferred term	Placebo on treatment (N=1272)		Cand. cil. on treatment (N=1276)	
	N	(%)	N	(%)
Hypotension	57	(4.5)	124	(9.7)
Renal function abnormal/renal dysfunction aggravated[b]	23	(1.8)	37	(2.9)
Hyperkalaemia	6	(0.5)	32	(2.5)
Dizziness/vertigo[b]	11	(0.9)	15	(1.2)
Cardiac failure aggravated	9	(0.7)	7	(0.5)
Fatigue	6	(0.5)	7	(0.5)
Nausea	6	(0.5)	5	(0.4)
Headache	3	(0.2)	4	(0.3)

a The table uses a cut-off of ≥0.3% in the total population on treatment (N=2548).

b Patients having both AEs are counted once only.

Exploratory safety variables

Discontinuation of investigational product:

In this exploratory presentation of data, the permanent discontinuation of the investigational product due to an AE or abnormal lab value occurred in 233 (18.3%) patients in the placebo group and 310 (24.3%) patients in the candesartan group. Both the difference in time to event ($P< 0.001$), (Table 221, Table 222 and Figure 101) and the difference in proportions between treatments of 6.0% ($P< 0.001$) were statistically significant.

Table 221 Permanent discontinuation and at least one discontinuation of investigational product due to any cause, an AE or an abnormal laboratory value. Number of patients with at least one event by treatment group and events per 1000 years of follow-up. Follow-up time is calculated to first event. ITT/Safety population (SH-AHS-0006)

Variable	Treatment	N	Events (No of patients)	Total follow-up time (years)	Events / 1000 follow-up years	Mean follow-up time (years)
Permanent investigational product discontinuation due to any cause	Placebo	1271	319	3327.9	95.9	2.6
	Cand. cil.	1276	411	3201.1	128.4	2.5
Permanent investigational product discontinuation due to an AE or an abnormal lab value	Placebo	1272	233	3460.6	67.3	2.7
	Cand. cil.	1276	310	3380.5	91.7	2.6
At least one investigational product discontinuation due to any cause	Placebo	1271	534	2999.7	178.0	2.4
	Cand. cil.	1276	637	2766.2	230.3	2.2
At least one investigational product discontinuation due to an AE or an abnormal lab value	Placebo	1272	442	3186.0	138.7	2.5
	Cand. cil.	1276	538	2976.7	180.7	2.3

Table 222 Permanent discontinuation and at least one discontinuation of investigational product due to any cause, an AE or an abnormal laboratory value. 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
					Lower	Upper	
Permanent investigational product discontinuation due to any cause	2548	411	319	1.336	1.154	1.547	<0.001
Permanent investigational product discontinuation due to an AE or an abnormal lab value	2548	310	233	1.357	1.145	1.609	<0.001
At least one investigational product discontinuation due to any cause	2548	637	534	1.281	1.142	1.437	<0.001
At least one investigational product discontinuation due to an AE or an abnormal lab value	2548	538	442	1.292	1.139	1.465	<0.001

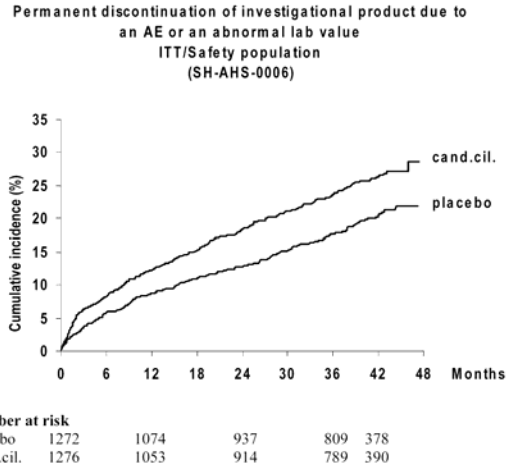


Figure 101 Cumulative incidence (%) of permanent discontinuation of investigational product due to an AE or an abnormal laboratory value. ITT/Safety population

Specific causes of investigational product discontinuation are noted in Table 223 and Table 224. Hyperkalemia and increased creatinine as causes for investigational product discontinuation were statistically significantly more frequent for candesartan; absolute differences in these cause-specific discontinuations relative to placebo were 2.7% and 3.7%, respectively (p< 0.001). For hypotension the absolute difference of 1.4% was not statistically significant (P= 0.066).

The approximate 1.3 to 1.4 fold excess risk for candesartan discontinuation relative to placebo for the study population was characteristic of the relative discontinuation rates across most sub-groups including concomitant medication with ACE-inhibitors, β-blockers and spironolactone.

Dose reduction of the investigational product:

Dose reduction of the investigational product due to an AE or abnormal lab value occurred in 153 (12.0%) patients in the placebo group and 265 (20.8%) patients in the candesartan group (Table 223). This between- treatment difference in dose reductions for an AE of 8.7% was statistically significant (P< 0.001), (Table 224). As shown in Figure 102 the majority of events occurred during the first 6 to 12 months of treatment with the investigational product.

Table 223 Permanent discontinuation, at least one discontinuation and decreased dose of investigational product due to any cause, an AE, an abnormal laboratory value, hypotension, hyperkalemia or increased creatinine. The proportions of patients (%) with an event. ITT/Safety population (SH-AHS-0006)

Variable	Treatment	N	Number of patients with event	Proportion of patients with event	95% CI	
					Lower	Upper
Permanent investigational product discontinuation due to any cause	Placebo	1272	319	25.1	22.7	27.6
	Cand. cil.	1276	411	32.2	29.7	34.9
Permanent investigational product discontinuation due to an AE or an abnormal lab value	Placebo	1272	233	18.3	16.2	20.6
	Cand. cil.	1276	310	24.3	22.0	26.7
Permanent investigational product discontinuation due to hypotension	Placebo	1272	40	3.1	2.3	4.3
	Cand. cil.	1276	58	4.5	3.5	5.8
Permanent investigational product discontinuation due to hyperkalaemia	Placebo	1272	9	0.7	0.3	1.3
	Cand. cil.	1276	44	3.4	2.5	4.6
Permanent investigational product discontinuation due to increased creatinine	Placebo	1272	52	4.1	3.1	5.3
	Cand. cil.	1276	100	7.8	6.4	9.4
At least one investigational product discontinuation due to any cause	Placebo	1272	534	42.0	39.3	44.7
	Cand. cil.	1276	637	49.9	47.1	52.7
At least one investigational product discontinuation due to an AE or an abnormal lab value	Placebo	1272	442	34.7	32.1	37.4
	Cand. cil.	1276	538	42.2	39.4	44.9
At least one investigational product discontinuation due to hypotension	Placebo	1272	67	5.3	4.1	6.6
	Cand. cil.	1276	111	8.7	7.2	10.4
At least one investigational product discontinuation due to hyperkalaemia	Placebo	1272	23	1.8	1.1	2.7
	Cand. cil.	1276	73	5.7	4.5	7.1
At least one investigational product discontinuation due to increased creatinine	Placebo	1272	86	6.8	5.4	8.3
	Cand. cil.	1276	152	11.9	10.2	13.8
Decreased investigational product dose due to any cause at least once	Placebo	1272	184	14.5	12.6	16.5
	Cand. cil.	1276	294	23.0	20.8	25.5
Decreased investigational product dose due to an AE or an abnormal lab value at least once	Placebo	1272	153	12.0	10.3	13.9
	Cand. cil.	1276	265	20.8	18.6	23.1

Table 224 Permanent discontinuation, at least one discontinuation and decreased dose of investigational product due to any cause, an AE, an abnormal laboratory value, hypotension, hyperkalemia or increased creatinine. The difference in proportion (%) between treatments. Chi-square test. ITT/Safety population (SH-AHS-0006)

Variable	Treatment	N	Number of patients with event	Proportion of patients with event	95% CI	
					Lower	Upper
Permanent investigational product discontinuation due to any cause	Placebo	1272	319	25.1	22.7	27.6
	Cand. cil.	1276	411	32.2	29.7	34.9
Permanent investigational product discontinuation due to an AE or an abnormal lab value	Placebo	1272	233	18.3	16.2	20.6
	Cand. cil.	1276	310	24.3	22.0	26.7
Permanent investigational product discontinuation due to hypotension	Placebo	1272	40	3.1	2.3	4.3
	Cand. cil.	1276	58	4.5	3.5	5.8
Permanent investigational product discontinuation due to hyperkalaemia	Placebo	1272	9	0.7	0.3	1.3
	Cand. cil.	1276	44	3.4	2.5	4.6
Permanent investigational product discontinuation due to increased creatinine	Placebo	1272	52	4.1	3.1	5.3
	Cand. cil.	1276	100	7.8	6.4	9.4
At least one investigational product discontinuation due to any cause	Placebo	1272	534	42.0	39.3	44.7
	Cand. cil.	1276	637	49.9	47.1	52.7
At least one investigational product discontinuation due to an AE or an abnormal lab value	Placebo	1272	442	34.7	32.1	37.4
	Cand. cil.	1276	538	42.2	39.4	44.9
At least one investigational product discontinuation due to hypotension	Placebo	1272	67	5.3	4.1	6.6
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At least one investigational product discontinuation due to hyperkalaemia	Placebo	1272	23	1.8	1.1	2.7
	Cand. cil.	1276	73	5.7	4.5	7.1
At least one investigational product discontinuation due to increased creatinine	Placebo	1272	86	6.8	5.4	8.3
	Cand. cil.	1276	152	11.9	10.2	13.8
Decreased investigational product dose due to any cause at least once	Placebo	1272	184	14.5	12.6	16.5
	Cand. cil.	1276	294	23.0	20.8	25.5
Decreased investigational product dose due to an AE or an abnormal lab value at least once	Placebo	1272	153	12.0	10.3	13.9
	Cand. cil.	1276	265	20.8	18.6	23.1

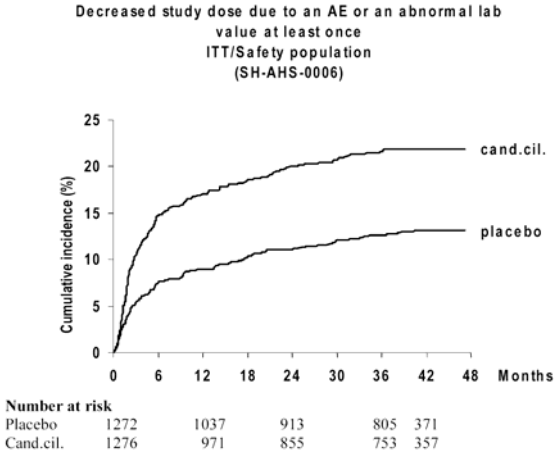

Figure 102 Cumulative incidence (%) of first occurrence of dose decrease of investigational product due to an AE or an abnormal laboratory value. ITT/Safety population

Non-CV death and non-CV hospitalization:

There were no significant differences between the candesartan group and the placebo group in the proportion of patients with non-CV mortality rates (placebo 65, 5.1%; candesartan 75, 5.9%) or non-CV hospitalization rates (placebo 544, 42.8%; candesartan 549, 43.0%).

Adverse events of special interest: This section summarizes AEs relevant to treatment of CHF, AT_1-receptor blockers (ARBs) and ACE inhibitors.

Hypotensive events:

To more completely evaluate 'hypotension' as an adverse CE, the following AE terms (AAED preferred terms) were selected and analyzed as a composite AE: hypotension; hypotension, postural; dizziness/vertigo; syncope; circulatory failure; and collapse, not otherwise specified (NOS). For this composite AE, patients with multiple events including any of the selected AE terms were counted only once.

At baseline, there were a slightly higher proportion of patients in the candesartan group with SBP < 100 mmHg (placebo 54, 4.2%; candesartan 77, 6.0%). AEs suggesting a hypotensive event were reported more frequently for patients in the candesartan group (26.8%) than the placebo group (17.5%) during treatment with the investigational product (Table 225).

Table 225 Number (%) of patients with any of the preferred terms hypotension, hypotension postural, dizziness/vertigo, syncope, circulatory failure or collapse not otherwise specified (NOS). ITT/Safety population (SH-AHS-0006)

Placebo on treatment	Cand. cil. on treatment	Placebo during study	Cand. cil. during study
N=1272	N=1276	N=1272	N=1276
223 (17.5)	342 (26.8)	236 (18.6)	358 (28.1)

The individual AE term contributing the largest numbers to this composite AE was hypotension, which was reported for 176 (13.8%) of patients given placebo and 288 (22.6%) of patients given candesartan (Table 216).

In the candesartan group during treatment, 'hypotension' and 'syncope' were each reported as an AE that led to death in 1 patient. Hypotensive events that led to death were reported in association with other concomitant events such as myocardial infarction and gastroenterocolitis. In the candesartan treated patients, the fatal events were assessed by the investigators as unlikely related to the investigational product.

The investigational product was discontinued for the specific AE term hypotension in 44 (3.5%) placebo patients and 69 (5.4%) candesartan patients (Table 217). Corresponding figures for the exploratory analysis were 40 (3.1%) placebo patients and 58 (4.5%) candesartan patients (Table 223). The higher proportion of hypotensive events leading to discontinuation in the candesartan group could not be explained by higher use of concomitant medication when the event started,