CLINICAL REVIEW

Application Type	NDA 20-838
Submission Number	S-022
Submission Code	SE 1
Reviewer Name	Khin Maung U, MD
Review Completion Date	16-Oct-2004
Established Name	Candesartan Cilexetil
(Proposed) Trade Name	Atacand®
Therapeutic Class	Selective AT_1 subtype angiotensin II receptor antagonist
Applicant	AstraZeneca LP
Priority Designation	P
Formulation	oral
Dosing Regimen	Initial dose 4 mg q.d., up-titrated to a target dose of 32 mg q.d.
Indication	Treatment of heart failure (Labeling claim = Treatment with Atacand® reduces relative risk of death from cardiovascular causes or hospitalization for heart failure, and improves symptoms)
Intended Population	Patients with chronic heart failure (NYHA functional class II – IV)

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Candesartan cilexetil is an angiotensin II type 1 (AT_1)-receptor blocker currently approved in the United States for the treatment of hypertension with an oral starting dose of 16 mg titratable up to 32 mg daily. The CHARM (**C**andesartan cilexetil (candesartan) in **H**eart Failure **A**ssessment of **R**eduction in **M**ortality and Morbidity) Program consists of three pivotal efficacy trials comprising 7,601 patients with NYHA Class II – IV chronic heart failure (CHF) who were randomized to candesartan (titrated from 4 mg or 8 mg once daily to a target dose of 32 mg once daily as tolerated) or matching placebo, and followed for at least 2 (up to 4) years. The analysis of the CHARM Program was divided into (i) patients with depressed left ventricular systolic function (ejection fraction (EF) ≤40%) who were intolerant to angiotensin converting enzyme (ACE) inhibitors (CHARM-Alternative), (ii) patients with depressed left ventricular systolic function (EF ≤40%) receiving an ACE inhibitor (CHARM-Added), and (iii) patients with Preserved left ventricular systolic function (EF >40%) (CHARM-Preserved). This efficacy supplement #022 pertains to CHARM-Added trial which received priority review.

In CHARM-Added (SH-AHS-0006) Study of 2,548 patients with CHF who were receiving an ACE inhibitor, candesartan significantly (P=0.011) reduced the relative risk of time to CV death or CHF hospitalization by14.7% (primary efficacy endpoint). This benefit translates into a reduction of 4.4 events per 100 patients treated for two years; i.e., treating 23 patients with candesartan for two years will prevent one patient from suffering the outcome of CV death or CHF hospitalization. The reduction in CV death was attributed to a reduction in sudden death and CHF death, which are the most common modes of death in patients with CHF. The study was not powered to assess the effect on all-cause mortality.

The benefit of candesartan was evident in the presence of treatment with ACE inhibitors at recommended doses. The mean daily dose of enalapril at baseline was 17 mg, which compares to 16.6 mg in the treatment arm of the **S**tudies **O**f **L**eft **V**entricular **D**ysfunction (SOLVD) and 17 mg in the **Val**sartan **He**art **F**ailure **T**rial (Val-HeFT). This benefit was also evident in patients treated with β-blockers, suggesting that there is no negative interaction between the AT_1-receptor blocker candesartan, ACE-inhibitors and β-blockers as was reported with valsartan in Val-HeFT.

The CHARM Program (Combined SH-AHS-0003, SH-AHS-0006 and SH-AHS-0007 Studies) failed to reach statistical significance for the primary efficacy endpoint of time to all-cause mortality (reduction in relative risk = 8.6%; P= 0.055) in patients with symptomatic CHF; a significant (P= 0.018) reduction in time to all-cause mortality by 11.4% was seen in the sub-population of CHF patients with depressed LV systolic function (secondary efficacy endpoint). This was attributed to a 12.4 -15.6% relative risk reduction in CV death (P= 0.011), subsequently attributed to reductions in relative risks of sudden death (by 15.2 - 19.9%; P=0.013) and CHF death (by 21.7 - 24.2%; P=0.008). The beneficial effects of candesartan were also evident in patients treated with ACE inhibitors, β-blockers or digoxin, unlike that reported in Val-HeFT.

There were no significant safety issues associated with candesartan treatment of CHF other than the expected adverse events (AEs) consistent with the pharmacology of the drug and the health status of patients. Discontinuation or dose reduction of study drug attributed to a decline in renal

function, hypotension or hyperkalemia occurs more frequently with candesartan than placebo.

Based on my review limited to NDA 20-838 Efficacy Supplement # 022 with data on the CHARM-Added (SH-AHS-0006) study and the overall CHARM Program (SH-AHS-0003, -0006, -0007) studies, I recommend this application as for the indication of treatment of heart failure (NYHA class II-IV) with left ventricular systolic dysfunction (ejection fraction ≤40%) in patients who are receiving other heart failure treatments including ACE-inhibitors or β-blockers and for the labeling claim that candesartan reduces the relative risk of time to cardiovascular death or the first occurrence of a hospitalization for heart failure. I suggest that the issues related to (a) the role and dose of AT_1 receptor blockers in the treatment of patients with heart failure (b) the effect on survival of interactions between AT_1 receptor blockers and ACE-inhibitors, β-blockers and digoxin in the treatment of patients with heart failure, be discussed at a Cardio-Renal Drug Advisory Committee Meeting.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

(i) Analyze data from the CHARM-Program studies to determine dose of candesartan and/or ACE-inhibitor and/or β-blockers and/or spironolactone in relation to AEs (hypotension, hyperkalemia, deterioration of renal function) and study drug discontinuation and/or dose reduction. This information should be provided in the labeling as well as communicated to practicing physicians through educational measures.

(ii) Ensure educational activities regarding the importance of starting with the lowest initial dose of candesartan and of increasing the dose gradually while monitoring the heart rate, blood pressure, serum creatinine, and serum potassium.

1.2.2 Required Phase 4 Commitments

Not applicable.

1.2.3 Other Phase 4 Requests

(i) Plan/perform a prospective clinical trial to find the optimal dose combination of ACE-inhibitor (high or low dose) and candesartan (high or low dose) in the treatment of CHF which will provide the most benefit [survival benefit (all-cause death, CV death, sudden death and CHF death) and clinical benefit (reduced hospitalization, improved symptoms, hemodynamics and exercise tolerance)] with the least risk [of AEs such as aggravated heart failure, hypotension, hyperkalemia, and deterioration of renal function].

(ii) Plan/perform a prospective clinical trial of candesartan in treatment of patients (tolerant and intolerant to ACE inhibitors) with high risk of heart failure without structural heart disease or symptoms (i.e. Stage A heart failure) to determine if candesartan will prevent or delay development of structural heart disease (Stage B), symptomatic heart failure (Stage C) or refractory symptoms of heart failure (Stage D).

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Candesartan cilexetil is an angiotensin II type 1 (AT_1)-receptor blocker. It is currently approved in the United States for the treatment of hypertension with the usual oral starting dose of 16 mg titratable up to 32 mg daily. Candesartan is proposed for the reduction of mortality and morbidity and reduction in hospitalization due to heart failure (NYHA Class II-IV) and improvement in the signs and symptoms of heart failure. The proposed starting dose in heart failure is 4 mg daily, being doubled every two weeks as tolerated to a maximum dose of 32 mg daily.

CHARM Program (SH-AHS-0003, SH-AHS-0006 & SH-AHS-0007): The three CHARM Program studies were randomized, double-blind, placebo-controlled, parallel group, multicenter studies conducted at 618 sites in 26 countries. The program was designed to evaluate the effect of candesartan on all-cause mortality and morbidity in three target populations of patients with symptomatic CHF. The 3 pivotal clinical trials under the CHARM Program are:

- CHARM-Alternative (SH-AHS-0003) study in 2,028 patients with CHF who are ACE inhibitor intolerant and have depressed left ventricular systolic function (EF ≤ 40%)
- CHARM-Added (SH-AHS-0006) study of 2,548 patients with CHF who are treated with ACE inhibitors and have depressed left ventricular systolic function (EF ≤ 40%)
- CHARM-Preserved (SH-AHS-0007) study of 3,023 patients with CHF and preserved left ventricular systolic function (EF > 40%)

The three pivotal efficacy trials comprise 7,601 patients (7,599 patients with data) with NYHA Class II – IV CHF of at least 4 weeks duration who were randomized to candesartan or matching placebo, and followed for at least 2 (up to 4) years. The primary endpoint was all-cause mortality (time from randomization to death from any cause) in the overall population (from studies SH-AHS-0003, SH-AHS-0006 and SH-AHS-0007). The secondary endpoint was all-cause mortality in the population of patients with depressed left ventricular systolic function (from studies SH-AHS-0003 and SH-AHS-0006). For all endpoints, the time was calculated from randomization to the first occurrence of one of the components.

CHARM-Added (SH-AHS-0006) Study: This pivotal study was a randomized, double-blind, placebo-controlled, parallel group, multicenter study of 2,548 patients randomized at 473 sites in 25 countries. The aim of the study was to evaluate the effect of candesartan on mortality and morbidity in symptomatic CHF patients with depressed left ventricular systolic function (EF ≤ 40%), and treated with an ACE inhibitor.

Patients were randomized at visit 1 to candesartan or placebo. The starting dose was 4 mg once daily, which was 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. All patients remained in the study until the last randomized patient had been in the study for ≥ 2 years. The median duration of double-blind treatment was 34.8 months, the median time of follow up was 37.7 months, and the longest follow-up time was 47.6 months.

The primary efficacy endpoint was a composite of the time from randomization to (CV) death or the first occurrence of a CHF hospitalization. The secondary efficacy endpoints were (i) a composite of all-cause mortality or CHF hospitalization and (ii) a composite of CV death, CHF hospitalization or non-fatal MI. The time was censored if no event had occurred at the last available time point, closing visit or, at the latest, March 31, 2003.

In addition to the CHARM Program trials, the sponsor submitted data from 24 clinical studies (comprising 4,062 patients with CHF). These include 7 long-term (6 – 12 months) clinical trials of 3,016 patients with CHF (six double-blind studies comprising 2,661 patients, and one open, uncontrolled, study comprising 355 patients) and 17 clinical trials of 1,046 patients with CHF (3 clinical pharmacology studies comprising 262 patients, 11 studies comprising 677 patients under the Japanese study program and 4 investigator-initiated studies comprising 107 patients). Thus, a total of 11,661 patients were studied in clinical trials of candesartan in the treatment of CHF.

1.3.2 Efficacy

The efficacy endpoints in the pivotal clinical trial (CHARM-Added (SH-AHS-0006) Study) and the pooled CHARM Program clinical trials are shown in Table 1.

Table 1 Endpoints in the CHARM-Alternative study (SH-AHS-0003), CHARM-Added study (SH-AHS-0006) and the CHARM Program (Pooled studies SH-AHS-0003, SH-AHS-0006 and SH-AHS-0007)

Endpoints	SH-AHS-0006 (CHARM-Added)	Pooled SH-AHS-0003 + SH-AHS-0006	Pooled SH-AHS-0003 + SH-AHS-0006+ SH-AHS-0007
P°: CV death or CHF hospitalization	**HR =0.853; P=0.011**	HR = 0.816; P<0.001	HR = 0.836; P<0.001
S°: All-cause death or CHF hospitalization	**HR =0.871; P=0.021**	HR = 0.840; P<0.001	HR = 0.862; P<0.001
S°: CV death/CHF hospitalization/non-fatal MI	**HR =0.852; P=0.008**	HR = 0.822; P<0.001	HR = 0.843; P<0.001
All-cause Mortality	HR =0.885; P=0.086 (Covar. adj: P=0.105)	**HR =0.886; P=0.018**	**HR =0.914; P=0.055** (Covar. adj: P=0.032)
All-cause death or all-cause hospitalization	HR =0.961; P=0.387	HR =0.943; P=0.092	HR =0.948; P=0.055
All-cause hospitalization	HR =0.955; P=0.346	HR =0.937; P=0.078	HR =0.948; P=0.064
CHF hospitalization	HR =0.825; P=0.014	HR = 0.76 ; P<0.001	HR = 0.79 ; P<0.001
Non-fatal MI	HR =0.512; P=0.006	HR = 0.--- ; P<0.097	HR = 0.--- ; P<0.267
CV death	HR =0.842; P=0.029	HR =0.844; P=0.005	HR =0.876; P=0.011
CHF death	HR =0.752; P=0.041	HR =0.758; P=0.008	HR =0.783; P=0.008
Sudden death	HR =0.865; P=0.196	HR =0.801; P=0.013	HR =0.848; P=0.037
Death due to MI	HR =0.830; P=0.562	HR =1.327; P=0.185	HR =1.187; P=0.368
Death due to stroke	HR =1.120; P=0.765	HR =0.973; P=0.919	HR =1.001; P=0.996
Death due to other CV cause	HR =0.965; P=0.894	HR =1.007; P=0.972	HR =1.057; P=0.734
Non-CV death	HR =1.112; P=0.529	HR =1.073; P=0.595	HR =1.081; P=0.452

P°: Primary; S°: Secondary; CV= cardiovascular; CHF= chronic heart failure; MI= myocardial infarction; Covar. Adj.= covariate adjustment

CHARM-Added study: In CHF patients with depressed left ventricular systolic function (EF ≤40%) treated with ACE inhibitors, candesartan significantly (P=0.011) reduced the relative risk of CV death or CHF hospitalization by 14.7% (primary efficacy endpoint), and significantly (P=0.021) reduced the relative risk of all-cause mortality or CHF hospitalization by 12.9%, and significantly (P=0.008) reduced the relative risk of CV death or CHF hospitalization or non-fatal MI by 14.8%, (secondary efficacy endpoints) (Table 1).

Other Efficacy Findings: There are significant reductions in the individual components of CHF hospitalization (relative risk reduction = 17.5%, P = 0.014), non-fatal MI (relative risk reduction = 48.8%, P = 0.006), CV death (relative risk reduction = 15.8%, P = 0.029), and CHF death (relative risk reduction = 24.8%, P = 0.041), which appear to contribute to the beneficial effect of candesartan on the corresponding composite primary or secondary endpoint (Table 1).

CHARM-Program studies: Candesartan reduced the relative risk of all-cause mortality by 8.6% in patients with symptomatic CHF in the pooled studies SH-AHS-0003, SH-AHS-0006 and SH-AHS-0007 (primary efficacy endpoint) (Table 1). This was NOT statistically significant (P= 0.055). For the secondary efficacy endpoint, candesartan significantly (P=0.018) reduced the relative risk of all-cause mortality by 11.4% in patients with symptomatic CHF and depressed left ventricular systolic function (EF ≤40%) in the pooled studies SH-AHS-0003 and SH-AHS-0006 (Table 1).

1.3.3 Safety

In the total population of patients with symptomatic CHF, there were no significant safety issues associated with candesartan treatment of CHF other than the expected AEs of aggravated heart failure, hypotension, hyperkalemia and deterioration of renal function typical of the class of drugs and the clinical findings expected for the study populations. In the CHARM Program comparing candesartan (n=3,803) with placebo (n=3,796), 21.0% of candesartan-treated patients discontinued for AEs vs. 16.1% of patients on placebo.

1.3.4 Dosing Regimen and Administration

The initial dose for treating CHF is 4 mg once daily. The dose is doubled at approximately 2 week intervals to a target dose of 32 mg once daily, while monitoring the heart rate, blood pressure, serum creatinine and serum potassium to hold or step down the dose if necessary.

1.3.5 Drug-Drug Interactions

The reductions in the risk of CV death and CHF hospitalization in CHF patients were observed in patients with symptomatic CHF who were receiving ACE-inhibitors, β-blockers or digoxin as part of the conventional treatment for CHF.

1.3.6 Special Populations

Geriatric Patients: Of 7,599 CHF patients in the CHARM Program 4,343 (57 %) were ≥65 years and 1,736 (23 %) were ≥75 years old. The pharmacokinetics of candesartan remained linear in patients with CHF; however, the AUC was almost doubled in CHF patients >65 years old compared to healthy, younger subjects. The incidence of drug discontinuations due to AEs was higher for both candesartan and placebo groups in patients ≥75 years of age (compared with patients <75 years), the most common AEs leading to discontinuation of candesartan vs. placebo being abnormal renal function (7.9% vs. 4.0%), hypotension (5.2% vs. 3.2%) and hyperkalemia (4.2% vs. 0.9%). Thus, greater sensitivity of older individuals with heart failure to candesartan must be considered.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

This submission is an efficacy supplement. Please refer to the original NDA review. The original NDA was submitted on 30-Apr-1997.

2.2 Currently Available Treatment for Indications

Please refer to section 8.1 and section 8.5 of this efficacy supplement review.

2.3 Availability of Proposed Active Ingredient in the United States

Not applicable.

2.4 Important Issues with Pharmacologically Related Products

Not applicable

2.5 Pre-submission Regulatory Activity

Not applicable

2.6 Other Relevant Background Information

Not applicable

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Not applicable

3.2 Animal Pharmacology/Toxicology

Not applicable

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sponsor submitted a total of 27 Phase II/III clinical trials including 3 pivotal clinical trials under the CHARM (Candesartan Cilexetil (Candesartan) In Heart Failure Assessment of Reduction in Mortality and Morbidity) program as follows:

- "Clinical Study (SH-AHS-0003) of Candesartan in Patients With Heart Failure Who Are ACE Inhibitor Intolerant and Have Depressed Left Ventricular Systolic Function (CHARM – Alternative study: 2,028 patients)"
- "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 (CHARM – Added study: 2,548 patients)"
- "Clinical Study (SH-AHS-0007) of Candesartan in Patients With Heart Failure and Preserved Left Ventricular Systolic Function (CHARM – Preserved study: 3,023 patients)"

These three pivotal efficacy trials comprise 7,601 patients (7,599 patients with data) with NYHA Class II – IV chronic heart failure (CHF) of at least 4 weeks duration who were randomized to candesartan (titrated from 4 mg or 8 mg once daily to a target dose of 32 mg once daily as tolerated) or matching placebo, and followed for at least 2 (up to 4) years.

In addition to the 7,599 CHF patients in the CHARM Program clinical trials, the sponsor submitted 24 clinical studies (comprising 4,062 patients with CHF) including:

(a) seven clinical trials of 3,016 patients with CHF

  (i) 5 randomized, double-blind, placebo-controlled clinical trials with duration of 2 to 12 months, comprising a total of 1,893 patients,

  (ii) one randomized, double-blind, active-treatment (enalapril)-controlled study (RESOLVD) comprising 768 patients, and

  (iii) one open, uncontrolled, long-term (6 month) study comprising 355 patients.

(b) seventeen clinical trials of 1,046 patients with CHF

  (i) 3 clinical pharmacology studies comprising 262 patients,

  (ii) 11 clinical studies comprising a total of 677 patients under the Japanese study program (for which FDA granted the sponsor a waiver from providing case report tabulations and case report forms, and 10 studies were pertinent to efficacy), and

  (iii) 4 investigator-initiated clinical studies comprising 107 patients.

Thus, a total of 11,661 patients with CHF were studied in various clinical trials of candesartan in the treatment of CHF.

The sponsor submitted that there are no on-going clinical studies currently conducted under US IND 50,115, with the exception on an investigator-initiated study (BLO K016) in Germany with a planned recruitment of only 40 patients with CHF. Therefore, the sponsor would not prepare/submit a 4-month safety update.

During the course of the review of this NDA Supplement # S-022, we determined that – per FDA policy expressed in the FDA Guidance for Industry "Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees" – this NDA Supplement was inappropriately bundled. On August 12, 2004, the sponsor was informed that the application would be split into three separate supplements as follows:

1. 20-838/S-022: CHARM – Added. Review classification = Priority (P)
2. 20-838/S-024: CHARM – Alternative. Review classification = Standard (S)
3. 20-838/S-025: CHARM – Preserved. Review classification = Standard (S)

This review is for NDA Supplement # S-022 (CHARM – Added. Review classification = Priority (P)).

This application was submitted electronically in CTD format. All materials are located at \\Cdsesub1\n20838\S 022\2004-06-30.

4.2 Tables of Clinical Studies

A listing of the clinical studies in the CHARM Program is given in Table 2 below. Of these 30 clinical trials listed, one is a pooled data analysis (SH-AHS-pooled) and for two studies (BC 605fu and BLO K016) data were not submitted. Thus, there are 27 clinical studies for review.

Table 2 List of Clinical Efficacy Trials

Study #	Type	Total N=	Patients	Duration	Dose	eCTD
Pivotal Clinical Trials						
SH-AHS-0003	R, db, pc, pg, mc	2028	chf, EF≤40%; ACEi intol	≥ 2 yr	Start CC 4 or 8 mg qd, up-titrate to 32 mg qd or highest tolerated dose	5.3.5.1.1
SH-AHS-0006	R, db, pc, pg, mc	2548	chf, EF≤40%; ACEi treated	≥ 2 yr		5.3.5.1.2
SH-AHS-0007	R, db, pc, pg, mc	3025	chf, EF>40%	≥ 2 yr		5.3.5.1.3
SH-AHS-pooled	R, db, pc, pg, mc	7601	chf, all above	≥ 2 yr		5.3.5.1.4
Pharmacology studies						
EC602 (pk,pd)	R, db, pc, mc	57	Symptomatic chf,; PAP ≥ 25 mmHg or PCWP ≥13mmHg	1 day	CC 4, 8 or 16 mg, single oral dose	5.3.3.2.1
EC608 (pk)	r, db, md, co, mc	31	Mild to mod chf	Pt I: 1 day Pt II: 21 d	Pt I: CC 8mg, E 10mg, CC8 + E 10mg Pt II: qd x 7 days, 3 periods	5.3.3.2.2
EC605A(pk)	R, db, pc, pg, mc	174	chf, EF≤40%, PCWP≥ 13mmHg	12 wk	CC 2, 4, 8 or 16 mg qd	5.3.3.2.3
Randomized, placebo-controlled studies with duration up to 12 months						
SH-AHS-0002	R, db, pc, pg, mc	270	chf, EF≤35%; ACEI intol	12 wk	CC 4 or 8 mg qd, up-titrate to 32 mg qd	5.3.5.1.5
EC604	R, db, pc, pg, mc	844	chf, EF≤30-45%	12 wk	CC 4, 8 or 16 mg, bid (pm dose = placebo)	5.3.5.1.6
EC605	R, db, pc, pg, mc	218	chf, EF≤40%, PCWP≥ 13mmHg	12 wk	CC 2, 4, 8 or 16 mg qd	5.3.5.1.7
EC614	R, db, pc, mc	463	chf, EF≤45%; ACEi intol	52 wk	CC 2, 4, 8 or 16 mg qd	5.3.5.1.8
SH-AHS-0008	R, db, pc, mc	98	chf, EF≤40%; ACEi treated	8 wk	CC 2, 4, 8, 16 or 32 mg qd	5.3.5.1.9
Randomized, active treatment-controlled study						
SH-AHS-0001 (RESOLVD)	R, db, pg, mc control = (E)	768	chf, EF≤40%; 6-min walking distance ≤500 m	43 wk	CC 4 or 8 mg qd, up-titrate to 32 mg qd	5.3.5.1.10
Open, Uncontrolled, Long-term Study						
EC610	ol,mc, fuEC604	355	chf, Completion of EC604	>6 mo	CC 8 mg qd, up-titrated to 16 mg qd, PRN	5.3.5.2.1
Other study reports – *Japanese programme*						
CPH102 (pk)	ol	5	chf, ser creatinine ≤2.0mg/dl	9 days	CC 4 qd, day1 and days 3-9. +dig + lasix	5.3.5.4.1
CPH103 (pd)	ol	10	chf, NYHA II-III	12 wk	CC 2, 4, 8 or 12 mg, qd	5.3.5.4.2
CPH104 (pd)	ol	16	chf, NYHA II-III	12 wk	CC 2, 4, 8 or 12 mg qd	5.3.5.4.3
CCT101	db, pc, mc	83	chf, EF≤45%	12 wk	CC 1, 2, 4 or 8 mg qd	5.3.5.4.4
CCT102	db, pc, mc	302	chf, EF≤45%	6 mo	CC 4 mg qd x 2 wk, 8 mg qd x 6 months	5.3.5.4.5
OCT105	db, pc, pg	2	chf, EF≤40%	6 mo	CC 8 mg qd	5.3.5.4.6
OCT102	ol	33	chf; NYHA II_M–III	1 yr	CC 1mg qd, up-titrated to 8 mg qd	5.3.5.4.7
OCT104	ol	126	chf: NYHA II_M–III	52 wks	CC 4mg qd. Up-titrated to 8 mg qd	5.3.5.4.8
OCT106	ol	10	chf, NYHA II	14 wk	CC 2 mg qd x 2 wk, then 8 mg qd x 12 wk	5.3.5.4.9
OCT101	ol	77	chf, NYHA II_M–III	10 wk	CC 0.5 mg qd, up-titrated to 4 mg qd	5.3.5.4.10
CPH101	ol	13	chf, PCWP≥15mmHg or cardiac index ≤2.2L/min/m^2	single dose	CC 1, 2, 4, 8, and 12 mg single oral dose	5.3.5.4.11
Other study reports – *Investigator Initiated*						
SH-AHS-0004	r, pc	33	chf, EF≤35%; ACEi treated	4 wk	CC 8 mg qd x 1 wk, up-titrate to 16 mg qd	5.3.5.4.12
SH-AHS-0005	r, db, pc, co	21	chf, EF≤40%; ACEi intol or not treated	Pt I: 1 hr Pt II: 4 wk	Pt I: CC 8mg single oral dose Pt II: CC 8mg qd x 2wk, up-titrate to 16mg qd	5.3.5.4.13
Hikosaka Publ.	Ol, pc	20	chf, NYHA I-II	4 wk	CC 8 mg qd	5.3.5.4.14
EC605 fu	ol, fu	33	chf, EF≤40%, PCWP≥ 13mmHg Completion of EC605	9 months	CC 16 mg qd	Data not submitted
BLO K016	r, db, pc, mc	40 (og)	chf, EF≤35%; ACEi treated	24 wk	CC 8mg qd x 2wk, up-titrate to 16mg qd	Data not submitted

db = double blind; r = randomized; pc = placebo-controlled; pg = parallel group; co = crossover; mc= multi-center; ol = open-label; md = multi-dose; fu = follow up; (E) = enalapril as active comparator; PRN = where needed; og = ongoing

4.3 Review Strategy

For NDA Supplement #022 (CHARM – Added Study) the sponsor submitted that candesartan incrementally reduces the risk of cardiovascular (CV) mortality or heart failure (CHF) hospitalization when added to an ACE inhibitor containing regimen in CHF patients with left ventricular systolic function. This is reflected in the sponsor's claim made in the "Indications and Usage" section of the package insert: "*ATACAND is indicated for the treatment of heart failure (NYHA class II-IV). 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).*"

With regard to the use of β-blockers, the pharmacodynamics section of the package insert states: "*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.*"

To determine whether the data submitted by the sponsor supports these claims under the CHARM-Added Study program, I will review data in the pivotal trial (SH-AHS-0006) and other clinical trials in which candesartan was added to a CHF treatment regimen containing an ACE inhibitor. These studies are shown in Table 3.

Table 3 Studies of CHF patients treated with ACE inhibitors AND Candesartan or placebo

Study #	Type	Total N=	Patients	Duration	Dose	eCTD
SH-AHS-0006	r, db, pc, pg, mc	2548	chf, EF≤40%; ACEi treated	≥ 2 yr	Start CC 4 or 8 mg qd, up-titrate to 32 mg qd or highest tolerated dose	5.3.5.1.2
SH-AHS-0008	r, db, pc, mc	98	chf, EF≤40%; ACEi treated	8 wk	CC 2, 4, 8, 16 or 32 mg qd	5.3.5.1.9
SH-AHS-0004	r, pc	33	chf, EF≤35%; ACEi treated	4 wk	CC 8 mg qd x 1 wk, up-titrate to 16 mg qd	5.3.5.4.12
EC608 (pk)	r, db, md, co, mc	31	Mild to mod chf	Pt I: 1 day Pt II: 21 d	Pt I: CC 8mg, E 10mg, CC8 + E 10mg Pt II: qd x 7 days, 3 periods	5.3.3.2.2
SH-AHS-0001	r, db, pg, mc control = (E)	768	chf, EF≤40%; 6-min walking distance ≤500 m	43 wk	CC 4 or 8 mg qd, up-titrate to 32 mg qd	5.3.5.1.10
SH-AHS-pooled (2 studies)	r, db, pc, pg, mc	7601	chf, EF≤40%; ACEi intol & ACEi treated	≥ 2 yr	Start CC 4 or 8 mg qd, up-titrate to 32 mg qd or highest tolerated dose	5.3.5.1.4
SH-AHS-pooled (3 studies)	r, db, pc, pg, mc	7601	chf, EF≤40% & EF>40%; ACEi intol & ACEi treated	≥ 2 yr	Start CC 4 or 8 mg qd, up-titrate to 32 mg qd or highest tolerated dose	5.3.5.1.4

In addition, I reviewed medical journal publications of clinical trials of angiotensin II AT_1-receptor blockers (ARBs), including those in which β- blockers are used in combination with ACE inhibitors and ARBs in the treatment of CHF to obtain a broader perspective of the benefits produced by use of candesartan, ACE inhibitors and β-blockers together, and the possible risks (e.g., hypotension, bradycardia, worsening of renal failure) this combination treatment may impose on these relatively sick patients with CHF.

For ease of following my review, a "road map" of conceptual issues I addressed and the reference clinical trials I reviewed and considered are given below:

1. Dose of candesartan and ACE inhibitors used: This is addressed in detail to determine how-well supported the doses used in the pivotal study are as compared to the doses used in other similar clinical trials, and whether a lack of response can be attributed to not having used an adequate dose of ACE inhibitor or candesartan (or ARBs). The following issues are addressed:

   (a) Is it important to use a high (appropriate) dose of candesartan (ARB)?

   This issue is addressed with reference to the following clinical trials in patients with heart failure: (i) ELITE, (ii) ELITE II, (iii) OPTIMAAL, (iv) VALIANT and (v) LIFE

   (b) Is it important to use a high (appropriate) dose of ACE inhibitor?

   - The ACC/AHA guidelines and the ATLAS trial recommended the need for a high enough dose of an ACE inhibitor in the treatment of heart failure.
   - On the other hand, the NETWORK trial and 4 other articles reported no difference in mortality between patients receiving high dose ACE inhibitors and those receiving low dose ACE inhibitors.

2. Does β-blockers produce additive survival benefit when used together with ARBs plus ACEi?

   I have presented in my review a broad perspective of disparate outcomes reported in different clinical trials as follows:

   (i) RESOLVD trial was not powered to detect deaths as endpoints

   (ii) ELITE II trial no significant effect on mortality

   (iii) Val-HeFT trial reported that β-blockers significantly ***increased*** the risk of mortality and morbidity

   (iv) COPERNICUS trial was the only clinical trial (other than the CHARM-Added trial in this NDA) that reported a significant reduction in relative risk of all-cause death

   (v) CHARM-Added trial reported that β-blockers reduced relative risk of CV death or CHF hospitalization when used together with ARB plus ACE inhibitor

3. Does spironolactone produce additive survival benefit when used together with ARB plus ACE inhibitor?

   - In this context, the EPHESUS trial reported achieving a significant reduction in the relative risk of all-cause mortality, and sudden death in acute MI with LVEF ≤ 40%. However, there was no effect on CV death or CV hospitalization.

4. Does digoxin produce additive survival benefit when used together with ARB plus ACE inhibitor?

- The DIGS trial reported that the combination of digoxin plus diuretic plus ACE inhibitor was better than ACE inhibitor alone in having achieved a relative risk reduction in hospitalizations for heart failure, but there was no reduction in overall mortality.
- CHARM-Added showed a significant reduction in the relative risk of CV death or CHF hospitalization when digoxin was used together with ARB plus ACE inhibitor.

Using the new Staging of Heart Failure (ACC/AHA Guidelines), I will address, in the context of this NDA review, the following issues relevant to the role of ARBs and ACE inhibitors in the treatment of heart failure:

1. Are ARBs superior or comparable (non-inferior) to ACE inhibitors?

   ACE inhibitor vs. placebo/diuretic trials:

   Stage A heart failure:

   - HOPE: ramipril reduced combined rate of CV death, MI and strokes
   - EUROPA: perindopril reduced combined CV death, MI and cardiac arrest
   - ANBP: ACEi reduced CV events

   Stage B, C or D heart failure (the following trials are associated with acute myocardial infarction:

   - SAVE: captopril reduced all-cause mortality, CHF hospitalization and recurrent MI
   - AIRE: ramipril reduced deaths and slow progression to heart failure
   - SMILE: zofendopril reduced mortality and incidence of heart failure
   - TRACE: trandolapril reduced all cause mortality, sudden death, progression to advanced heart failure

   ARBs vs. ACE inhibitor trials:

   Stage A heart failure:

   - RENAAL: Losartan delayed first hospitalization for heart failure in diabetics

   Stage B, C or D heart failure:

   - ELITE I: unexpected survival benefit of losartan compared to captopril, not repeated in ELITE II
   - ELITE II: losartan not superior to captopril
   - OPTIMAAL: losartan not equal to captopril; captopril superior for CV mortality
   - VALIANT: all-cause mortality similar in losartan, captopril and losartan plus captopril.

- LIFE: losartan vs. atenolol: losartan reduced composite endpoint of CV mortality, stroke and MI, and also reduced strokes and the incidence of new-onset diabetes
- CHARM-Alternative: candesartan vs. ACE inhibitor in ACE-intolerant patients reduced composite endpoint of CV death or CHF hospitalization

2. Does ARBs have an additive effective on top of ACE inhibitors?

Stage A heart failure:

- No known trials
- Future trials: (i) TRANSCEND in ACE inhibitor intolerant subjects (telmisartan vs. placebo), and (ii) ONTARGET (telmisartan vs. ramipril vs. telmisartan plus ramipril)

Stage B, C or D heart failure:

- Val-HeFT: valsartan added to ACE inhibitor reduced relative risk of composite endpoint of death or CV morbidity, but valsartan plus ACE inhibitor plus β-blockers was associated with worse outcome
- VALIANT: valsartan and captopril equivalent, valsartan plus captopril did not add survival benefit, but increased AEs
- Meta-analysis of 17 trials: no survival difference between ARB and control if ACE inhibitor in background; if no ACE inhibitor in background, the ARB was better than placebo; ARB vs. ACE inhibitor trials show no survival advantage of either; ARB plus ACE inhibitor vs. ACE inhibitor alone show virtually identical mortality
- CHARM-Added: candesartan plus ACE inhibitor better than ACE inhibitor alone – reduced CV death or CHF hospitalization, reduced all-cause death or CHF hospitalization, and reduced CV death or CHF hospitalization or non-fatal MI
- Future trials: (i) TRANSCEND in ACE inhibitor intolerant subjects (telmisartan vs. placebo), and (ii) ONTARGET (telmisartan vs. ramipril vs. telmisartan plus ramipril)

Other perspectives:

(1) Framingham Study did not document any meaningful change in overall death rates from heart failure though ACE inhibitors, B-blockers, spironolactone and ARBs are shown to reduce mortality and morbidity and improve functional status. This lack of survival benefit seen in the general population is attributed to under-use of these agents, and to co-morbid diseases.

(2) There is no consensus regarding the doses of ACE inhibitors (or ARBs) that can be recommended as effective in heart failure.

4.4 Data Quality and Integrity

DSI audits were considered to be not required for this efficacy supplement because:

(1) this submission is an efficacy supplement of a drug with known safety profile,

(2) there are 473 sites in 25 countries in this large, multi-center trial, with no specific site showing a positive response that was driving the outcome of the trial, and

(3) each site enrolled relatively small numbers of patients in this large, double-blind, randomized, clinical trial so that the design of the study would have prevented any investigator bias that could have affected the outcome of the trial.

I reviewed the narratives of deaths and serious adverse events (SAEs) individually to determine the nature of deaths (cardiovascular or otherwise) and, in the case of SAEs, to evaluate the justification for early discontinuation, if any.

4.5 Compliance with Good Clinical Practices

The sponsor certified that they did not use the services of any person in any capacity debarred under section 306 (a) or (b) of the Generic Drug Enforcement Act of 1992.

The reports of foreign clinical trials – particularly those conducted in Japan – contain certification by the monitoring CRO that the clinical trials were conducted in compliance with (ICH GCP) Good Clinical Practice guidelines, and, where GCP audits were performed, documentation that no data integrity problems were found during the audits.

The submission also contains sample copies of informed consent used at each of the sites (with English translations for consent forms used at foreign sites). A review of sample consent forms shows that they contain all of the elements of informed consent as described in 21 CFR 50.25.

4.6 Financial Disclosures

The sponsor submitted certification for a large proportion of investigators that they had no disclosable financial interest.

The sponsor submitted that seven investigators, in the US and abroad, disclosed having received sums greater than $25,000 or "significant payments (e.g., under an Astra Grant)" from the sponsor. These seven investigators (i.e., 4 investigators are from the U.S. (Eric Eichhorn, Alan Gradman, Marc Pfeffer, Roger Hajjar), one (Prof Struthers) from the U.K., one (Helen D. Ekdal) from Canada and one (Julian Vaile) from Australia) are NOT from any site in Germany where, overall for that country, a statistically significant (P=0.011) relative risk reduction (hazard ratio = 0.613, relative risk reduction = 38.7%) was reported. No other country, by itself, reported a statistically significant relative risk reduction for the primary efficacy endpoint. The seven investigators (i) participated in multicenter, randomized, double-blind trials in the CHARM Program where the trial design would have prevented any investigator bias that could have affected the efficacy outcome, and (ii) each enrolled only small number of patients (e.g., 2 to 9 patients) in the CHARM Program randomized double-blind trials that comprise large sample

sizes so that their contribution of such small numbers of patients could not have affected the outcome of the trial.

The sponsor also submitted a list of 71 "principal" investigators and a large number of "sub-investigators" who did not respond to requests for financial disclosure by the sponsor even after the sponsor made 2 or more written requests. The multicenter, randomized, double-blind design of the clinical trials and the fact that each site enrolled only a small number of patients in this large-sized trial are reasons which make this reviewer assume with reasonable assurance that there is little likelihood that any investigator bias would have affected the outcome of the trial.

5 CLINICAL PHARMACOLOGY

Please refer to the Clinical Pharmacology Review by Dr. Bach Nhi Beasley for a more detailed review. My review of clinical pharmacology studies is done to understand the background information related to the labeling claims the sponsor seeks with this pivotal study. Thus, my review discusses only the clinical aspects of these clinical pharmacology studies as they pertain to the pivotal study and their relevance to the primary efficacy endpoints and labeling claims.

The sponsor claims that the pharmacokinetic and pharmacodynamic properties of candesartan (2mg to 32 mg) have been characterized in their previous submission supporting use of candesartan in hypertension. In this efficacy supplement, the sponsor submitted the results of the following three studies (Table 4) in which the pharmacokinetics (PK) and pharmacodynamics (PD) are examined for use of candesartan in patients with chronic heart failure (CHF).

Table 4 List of Clinical pharmacology studies as submitted by the sponsor

Study #	Type	Total N=	Patients	Duration	Dose	eCTD
EC602(pk,pd)	r, db, pc, mc	57	Symptomatic chf; PAP ≥ 25 mmHg or PCWP ≥13mmHg	1 day	CC 4, 8 or 16 mg, single oral dose	5.3.3.2.1
EC608 (pk)	r, db, md, co, mc	31	Mild to mod chf	Pt I: 1 day Pt II: 21 d	Pt I: CC 8mg, E 10mg, CC8 + E 10mg Pt II: qd x 7 days, 3 periods	5.3.3.2.2
EC605A(pk)	r, db, pc, pg, mc	174	chf, EF≤40%, PCWP≥ 13mmHg	12 wk	CC 2, 4, 8 or 16 mg qd	5.3.3.2.3

db = double blind; r = randomized; pc = placebo-controlled; pg = parallel group; co = crossover; mc= multi-center; md = multi-dose

Source documents for Clinical Pharmacology Review: Also, from the perspective of a clinician, I evaluated the following clinical studies (Table 5) on the clinical aspects of clinical pharmacology for this NDA supplement; one study (CPH 102) reported pharmacokinetics and the remaining studies reported hemodynamic, neurohormonal (autonomic) and pharmaco-dynamic effects (e.g., on exercise tolerance) in patients with CHF treated with candesartan.

Table 5 Studies of patients with CHF treated with candesartan or placebo in which changes in hemodynamics, neurohormones changes and/or exercise tolerance were measured

Study #	Type	Total N=	Patients	Duration	Dose	eCTD
EC604	r, db, pc, pg, mc	844	chf, EF≤30-45%	12 wk	CC 4, 8 or 16 mg, bid (pm dose = placebo)	5.3.5.1.6
EC605	r, db, pc, pg, mc	218	chf, EF≤40%, PCWP≥ 13mmHg	12 wk	CC 2, 4, 8 or 16 mg qd	5.3.5.1.7
EC614	r, db, pc, mc	463	chf, EF≤45%; ACEI intol	52 wk	CC 2, 4, 8 or 16 mg qd	5.3.5.1.8
SH-AHS-0001 **RESOLVD**	r, db, pg, mc control = (E)	768	chf, EF≤40%; 6-min walking distance ≤500 m	43 wk	CC 4 or 8 mg qd, up-titrate to 32 mg qd	5.3.5.1.10
EC610	ol,mc, fuEC604	355	chf, Completion of EC604	>6 mo	CC 8 mg qd, up-titrated to 16 mg qd, PRN	5.3.5.2.1
OCT105	db, pc, pg	2	chf, EF≤40%	6 mo	CC 8 mg qd	5.3.5.4.6
OCT106	ol	10	chf, NYHA II	14 wk	CC 2 mg qd x 2 wk, then 8 mg qd x 12 wk	5.3.5.4.9
CPH101	ol	13	chf, PCWP≥15mmHg or cardiac index ≤2.2L/min/m2	single dose	CC 1, 2, 4, 8, and 12 mg single oral dose	5.3.5.4.11
SH-AHS-0004	r, pc	33	chf, EF≤35%; ACEI treated	4 wk	CC 8 mg qd x 1 wk, up-titrate to 16 mg qd	5.3.5.4.12
SH-AHS-0005	r, db, pc, co	21	chf, EF≤40%; ACEI intol or not treated	Pt I: 1 hr Pt II: 4 wk	Pt I: CC 8mg single oral dose Pt II: CC 8mg qd x 2wk, up-titrate to 16mg qd	5.3.5.4.13
Hikosaka Publ.	Ol, pc	20	chf, NYHA I-II	4 wk	CC 8 mg qd	5.3.5.4.14
CPH102 (pk)	ol	5	chf, ser creatinine ≤2.0mg/dl	9 days	CC 4 qd, day1 and days 3-9. +dig + lasix	**5.3.5.4.1**
CPH103 (pd)	ol	10	chf, NYHA II-III	12 wk	CC 2, 4, 8 or 12 mg, qd	**5.3.5.4.2**
CPH104 (pd)	ol	16	chf, NYHA II-III	12 wk	CC 2, 4, 8 or 12 mg qd	5.3.5.4.3

db = double blind; r = randomized; pc = placebo-controlled; pg = parallel group; co = crossover; mc= multi-center; ol = open-label; md = multi-dose; fu = follow up; (E) = enalapril as active comparator; PRN = where needed; og = ongoing

5.1 Pharmacokinetics

The sponsor contends that pharmacokinetics of candesartan in healthy subjects and in special populations including hypertensive patients, elderly patients and patients with renal and hepatic impairment had been submitted in the original NDA submission. For pharmacokinetics of candesartan in patients with chronic heart failure (CHF), the sponsor submitted the results of two clinical pharmacokinetic (PK) studies (EC602 and EC608), and pharmacokinetic data in an efficacy study (EC605). I reviewed also study CPH102, an open-label PK study of candesartan in patients with CHF which was conducted in Japan (Table 6). Summaries of review of each of these studies are given in Appendix PK1 – Appendix PK 4.

Table 6 Clinical studies of pharmacokinetics

Study #	Type	Total N=	Patients	Duration	Dose	Appendix
EC602 (pk,pd)	r, db, pc, mc	57	Symptomatic chf; PAP ≥ 25 mmHg or PCWP ≥13mmHg	1 day	CC 4, 8 or 16 mg, single oral dose	PK 1
EC605A(pk)	r, db, pc, pg, mc	174	chf, EF≤40%, PCWP≥ 13mmHg	12 wk	CC 2, 4, 8 or 16 mg qd	PK 2
EC608 (pk)	r, db, md, co, mc	31	Mild to mod chf	Pt I: 1 day Pt II: 21 d	Pt I: CC 8mg, E 10mg, CC8 + E 10mg Pt II: qd x 7 days, 3 periods	PK 3
CPH102 (pk)	ol	5	chf, ser creatinine ≤2.0mg/dl	9 days	CC 4 qd day1, and days 3-9, +dig + lasix	PK 4

db = double blind; r = randomized; pc = placebo-controlled; pg = parallel group; co = crossover; mc= multi-center; md = multi-dose

Patients with CHF tend to be older, have gastrointestinal and hepatic congestion (due to slower venous blood flow) and decreased glomerular filtration (due to lower filtration pressure). Thus, the pharmacokinetics (PK) of candesartan may be altered in patients with CHF, in whom a larger AUC or a higher C_{max} may be expected.

Two of these PK studies (Study EC602 – Appendix PK 1, and EC605A – Appendix PK 2) determine the PK parameters in relation to the dose of candesartan.

Study EC602 (please see Appendix PK 1) randomized 57 patients with CHF (to candesartan or placebo) in a study primarily intended for pharmacodynamic (PD) measurements, in which PK parameters were also measured. This single-dose PK study showed a dose-related increase in mean AUC_{0-24} and C_{max} of candesartan (Figure 1, Figure 2 and Figure 3).

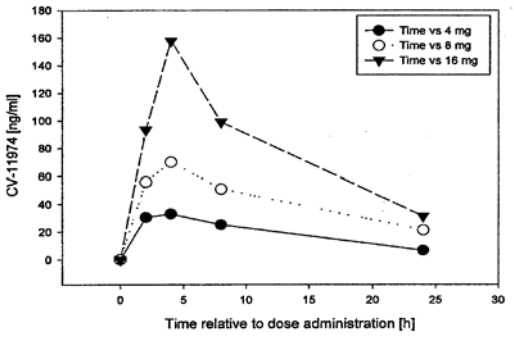


Figure 1 Mean Serum Concentration of CV-11974 (Safety population) – Study EC602

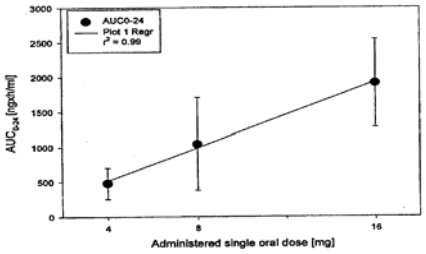


Figure 2 AUC_{0-24} vs. administered dose (Efficacy (ITT) population) – Study EC602

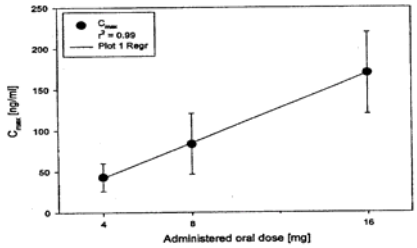
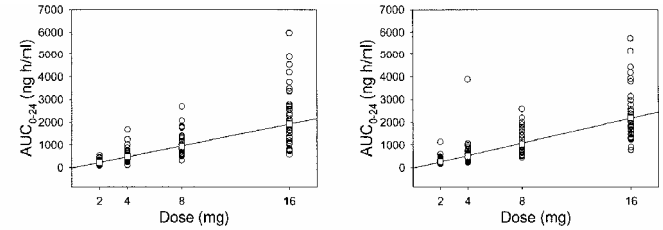


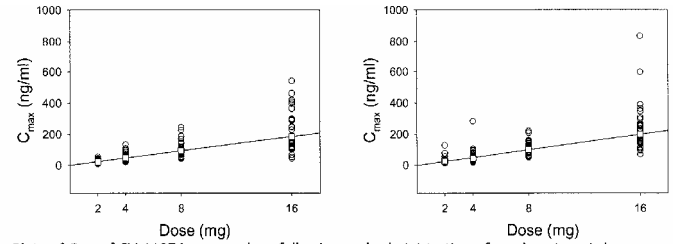
Figure 3 C_{max} vs. administered dose (Efficacy (ITT) population) – Study EC602

In study EC605-A (please see Appendix PK 2), 218 patients with CHF were randomized (44 to placebo and 174 to candesartan), again primarily for PD measurements; PK parameters were also measured for both single dose and multiple-dose (12-week treatment period) situations. Fifteen patients in the candesartan group had missing PK values, so data on 159 patients with evaluable PK data were submitted. For both single-dose and multiple-dose administration of candesartan, dose-proportional increase in AUC_{0-24} and C_{max} of candesartan were reported (Figure 4 and Figure 5). The t_{max} remained constant at around 4 hours after ingestion of oral candesartan in both single dose and multiple-dose situations.



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 4 AUC_{0-24} versus dose on visits 2 (left) and 6 (right) – EC605-A



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 5 C_{max} versus dose on visits 2 (left) and 6 (right) – EC605-A

The results of these two studies, when pooled, also showed dose-related changes in the AUC of candesartan (Figure 6).

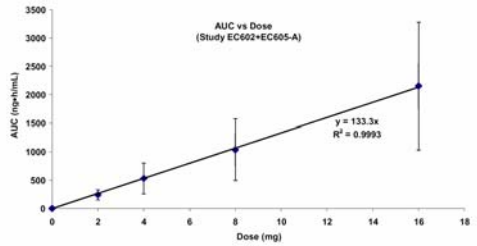


Figure 6 **AUC_{0-24h} (following single doses of candesartan) vs. dose of candesartan cilexetil in patients with CHF (studies EC602 and EC605-A)**

The above support the sponsor's submission that there is no indication that the presence of heart failure had an additional influence on the pharmacokinetics of candesartan.

In two more PK studies drug interactions between candesartan cilexetil and drugs frequently used in the treatment of heart failure, namely ACE-inhibitor enalapril (Study EC608 – Appendix PK 3) and digoxin (Study CPH 102 – Appendix PK 4) were described.

Study EC608 (please Appendix PK 3) was as small study of 31 patients with mild to moderate CHF and varying degrees to renal failure to determine the interaction of candesartan and enalapril on the PK parameters after single dose and at steady state. This study suffered from several protocol deviations, some of which may affect the PK measurements (e.g., 2 patients had their study medication interchanged during different periods of the study, one patient had missing screening laboratory data, etc.).

Notwithstanding these protocol deviations, the study found no interaction between candesartan and enalapril at steady state (apart from a statistically significant increase in AUC_{0-72} of candesartan and enalapril in patients with mild or moderate renal impairment, see Table 7). This study probably provides the rationale for use of candesartan and enalapril in treatment of patients with CHF. In a later communication dated 16-Sep-2004, the sponsor submitted that there are no other studies of the pharmacokinetic interaction of candesartan and enalapril.

Table 7 Study EC608 – 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*

Study CPH102 (please see Appendix PK 4) was a small open-label PK study of 5 patients with CHF in Japan, for evidence of drug interactions with digoxin. Patients with CHF are often on digoxin, and there is a theoretical concern that the metabolite of cilexetil – cyclohexenediol – could have a potential drug interaction with digoxin and produce proarrhythmic effects. This small study showed that digoxin did not produce increased plasma concentrations of candesartan or its metabolites, M-I (active) and M-II (inactive) (Table 8), and their urinary excretions were, respectively, about 2-6 – 4.9% and 0.6 – 3.2% of the dose (Table 9).

Table 8 Study CPH102 – Pharmacokinetic parameters of M-I and M-II after administration of candesartan cilexetil in multiple doses of 4 mg/day in 5 patients with CHF

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 9 Study CPH102 – 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

Conversely, the plasma concentrations of digoxin were not significantly increased in the presence of candesartan (Figure 7). Hence, candesartan cilexetil was considered not to interact with digoxin.

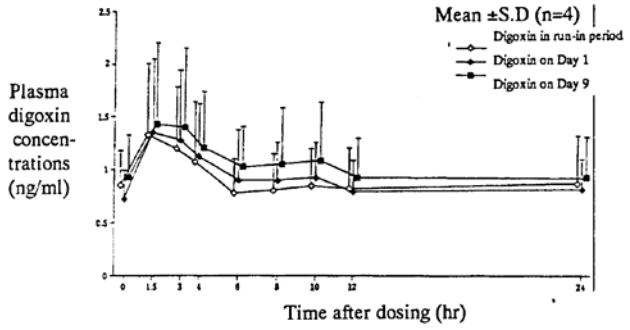


Figure 7 Study CPH102 – Plasma digoxin concentrations

5.2 Pharmacodynamics

The sponsor submitted data from one study (EC602) to be reviewed for pharmacodynamics of candesartan, including data related to hemodynamic and neurohormonal response. The NDA submission contains other clinical studies in which the hemodynamic effects and changes in exercise time, symptoms, neurohormonal response and baroreflex sensitivity following candesartan administration were reported (Table 10, below). Some of these studies are quite large, containing several hundred patients.

I believe that the hemodynamic effects and changes in exercise time, symptoms, neurohormonal response and baroreflex sensitivity reported in these studies are relevant to the understanding of the primary efficacy endpoints in the review of the pivotal study. Also, how these changes support or not support the findings related to the primary endpoints in the pivotal study will have a bearing on the overall consideration of the labeling claims. Thus in this section, I am reporting my review from the perspective of a clinician on the clinical aspects of these pharmacodynamic studies (Reviews of individual pharmacodynamic studies are present in Appendices PD1–PD14).

Table 10 Studies of patients with CHF treated with candesartan or placebo in which hemodynamics, neurohormonal changes and/or exercise tolerance were measured

Study #	Type	Total N=	Patients	Duration	Dose	Appendix
EC602 (pk,pd)	r, db, pc, mc	57	Symptomatic chf; PAP ≥ 25 mmHg or PCWP ≥13mmHg	1 day	CC 4, 8 or 16 mg, single oral dose	PD 1
EC605-A	r, db, pc, pg, mc	218	chf, EF≤40%, PCWP≥ 13mmHg	12 wk	CC 2, 4, 8 or 16 mg qd	PD 2
EC604	r, db, pc, pg, mc	844	chf, EF≤30-45%	12 wk	CC 4, 8 or 16 mg, bid (pm dose = placebo)	PD 3
EC610	ol,mc, fuEC604	355	chf, Completion of EC604	>6 mo	CC 8 mg qd, up-titrated to 16 mg qd, PRN	PD 4
EC614	r, db, pc, mc	463	chf, EF≤45%; ACEI intol	52 wk	CC 2, 4, 8 or 16 mg qd	PD 5
SH-AHS-0001 **(RESOLVD)**	r, db, pg, mc control = (E)	768	chf, EF≤40%; 6-min walking distance ≤500 m	43 wk	CC 4 or 8 mg qd, up-titrate to 32 mg qd	PD 6
OCT105	db, pc, pg	2	chf, EF≤40%	6 mo	CC 8 mg qd	PD 7
OCT106	ol	10	chf, NYHA II	14 wk	CC 2 mg qd x 2 wk, then 8 mg qd x 12 wk	PD 8
CPH101	ol	13	chf, PCWP≥15mmHg or cardiac index ≤2.2L/min/m2	single dose	CC 1, 2, 4, 8, and 12 mg single oral dose	PD 9
CPH103 (pd)	ol	10	chf, NYHA II-III	12 wk	**CC 2, 4, 8 or 12 mg, qd**	**PD 10**
CPH104 (pd)	ol	16	chf, NYHA II-III	12 wk	**CC 2, 4, 8 or 12 mg qd**	**PD 11**
SH-AHS-0004	r, pc	33	chf, EF≤35%; ACEI treated	4 wk	CC 8 mg qd x 1 wk, up-titrate to 16 mg qd	PD 12
SH-AHS-0005	r, db, pc, co	21	chf, EF≤40%; ACEI intol or not treated	Pt I: 1 hr Pt II: 4 wk	Pt I: CC 8mg single oral dose Pt II: CC 8mg qd x 2wk, up-titrate to 16mg qd	PD 13
Hikosaka Publ.	Ol, pc	20	chf, NYHA I-II	4 wk	CC 8 mg qd	PD 14

db = double blind; r = randomized; pc = placebo-controlled; pg = parallel group; co = crossover; mc= multi-center; ol = open-label; md = multi-dose; fu = follow up; (E) = enalapril as active comparator; PRN = where needed

Because there are a large number of studies, I will present my review of these pharmacodynamic studies putting them in groups based on the primary efficacy endpoints that were studied as follows: -

- Studies in which changes in exercise tolerance were measured
- Studies in which changes in hemodynamics were measured
- Studies in which changes in symptoms were measured
- Studies in which changes in neurohormones were measured, and
- Studies in which changes in baroreflex sensitivity were measured.

The pharmacodynamic endpoints are summarized in the following table (Table 11).

Table 11 Studies of patients with CHF treated with candesartan showing the PD endpoints (statistically significant changes, except where mentioned as NS)

Study #	Total N=	Exercise Tolerance	Hemodynamic changes	Symptom changes	Neurohormonal changes	Baroreflex Sensitivity
EC602 (pk,pd)	57	NT	↓$PCWP_{mean}$ and ↓PAP_{mean}	NT	↑Renin(NS), ↑AgII (NS), ↓Aldosterone (NS)	NT
EC605-A	218	NT	↓PCWP, ↓SVR and ↓PAP_{mean}	NT	↑Renin, ↑AgII, ↓Aldosterone, ↓ANF	NT
EC604 (**STRETCH**)	844	↑Bicycle ergometry, ↑walking distance (NS)	↓CTR	↑DFI	No significant change	NT
EC610	355	Bicycle ergometry (NS)	NT	DFI – no change	NT	NT
EC614	463	Bicycle ergometry (NS)	NT	DFI – no change	NT	NT
SH-AHS-0001 **(RESOLVD)**	768	6-min walk test (NS)	Less ↑EDV or ESV, ↑LVEF (NS)	No change in NYHA class / QoL	↑AgII, ↓Aldosterone, ↑Renin (NS), ↓BNP	NT
OCT105	2	Bicycle ergometry (NS)	NT	NT	NT	NT
OCT106	10	↑Treadmill exercise(NS)	↓LVMI, ↑LVEF	NT	↓ANP, ↓BNP	NT
CPH101	13	NT	No sig. Changes in PCWP or PAP	No significant change	↓ANP (NS)	NT
CPH103 (pd)	10	↑Treadmill exercise(NS)	↓LvEDD, ↓LvESD, ↓LvEDV, ↓LvESV, ↑LVEF	No significant change	NT	NT
CPH104 (pd)	16	NT	↓LvEDD, ↓LvESD, ↓LvEDV, ↓LvESV, ↑LVEF	↑Subjective symptom scale and score	↑Renin, ↑AgII, ↓BNP, ↓dopamine, ↓IL-6, ↓TNF, ↓sICAM-1, ↓sVCAM-1	NT
SH-AHS-0004	33	Treadmill exercise test = No change in peak V_{O2} (for oxidative stress)	NT	NT	No change in FR, TBARS	No change in flow-mediated dilatation of brachial artery
SH-AHS-0005	21	NT	↓BP	NT	NT	No consistent change in baroreflex sensitivity
Hikosaka Publ	20	NT	NT	NT	↑Renin, ↑AgII	↓Muscle sympathetic nerve activity ↑Baroreflex sensitivity

NT= not tested; NS= not statistically significant; AgII = angiotensin II; DFI = dyspnea fatigue index, CTR = cardiothoracic ratio; QoL = quality of life assessment; ↑ = significant increase; ↓ = significant decrease.

5.2.1 Studies of patients with CHF treated with candesartan or placebo in which changes in exercise tolerance were measured:

No consistent effect was found in the exercise tolerance tests following treatment with candesartan, probably because different exercise tests were used:

- bicycle ergometry was used in 4 clinical studies (EC604 (STRETCH), EC610, EC614 and OCT105),
- treadmill exercise was used in 3 studies (OCT106, CPH103 and SH-AHS-0004/Ellis), of which SH-AHS-004 measured peak V_{O2} as an indicator of oxidative stress), and
- four studies (EC604 (STRETCH), EC614, SH-AHS-0001 (RESOLVD) and SH-AHS-0002 also used the 6-minute walking test "where a suitable walking space of >20 meters existed."

Of the eight studies (EC604 (STRETCH), EC610, EC614, SH-AHS-0001 (RESOLVD), SH-AHS-0004/Ellis, OCT105, OCT106 and CPH103) in which some form of exercise tolerance test was performed, only one large study (EC604 (STRETCH) with 844

patients) showed a significant increase in the total exercise time with the bicycle ergometer, and this was observed after 3 months' treatment with candesartan in the 16mg-dose group only (compared to placebo); no beneficial effect was observed in the treatment groups receiving candesartan at doses of 4 mg or 8 mg. The sponsor's report contends that there was a dose-related response trend for this exercise tolerance, but in the absence of significant changes, I do not think that this conclusion is valid.

In this same study (EC604 (STRETCH)), the 6-minute walk test performed on a large subset of patients (386 patients total) did not show any significant or consistent increase in the total walking distance in subjects treated with different doses of candesartan. Similarly, no differences were observed in the 6-minute walking distance between either candesartan plus placebo (SH-AHS-0001 (RESOLVD) and EC614), or candesartan plus enalapril (SH-AHS-0002).

In study SH-AHS-0004 (Ellis), a similar and statistically significant improvement in peak V_{O2} was observed in *both* the candesartan and the placebo groups at the end of 1 month.

Thus, none of the pharmacodynamic studies shows any compelling evidence that treatment of CHF patients with candesartan (alone or in combination with enalapril) improves their exercise tolerance or reduces oxidative stress.

5.2.2 Studies of patients with CHF treated with candesartan or placebo in which changes in hemodynamics were measured:

Hemodynamic parameters were measured in 9 pharmacodynamic studies (EC602, EC605-A, EC604 (STRETCH), SH-AHS-0001 (RESOLVD), CPH101, SH-AHS-0005/Vaile publication, and three Japanese studies – OCT106, CPH103 and CPH104).

In three studies (EC602, EC605-A and CPH101), pulmonary capillary wedged pressure (PCWP) and pulmonary arterial pressure (PAP) were measured. PCWP and PAP decreased significantly following treatment with candesartan in studies EC602 and EC605-A (Table 12, Table 13 and Table 14), but not significantly so in study CPH101 (which enrolled only 13 patients).

Table 12 Study EC602: $PCWP_{mean}$ –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	-18.29	-50.38	-44.06
		± 78.40	± 53.85	± 49.25	± 57.49
Peak Change [mmHg]	mean	-6.54	-4.08	-8.44	-8.50
		± 7.39	± 4.14	± 4.26	± 4.30

Table 13 Study EC602: 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

Table 14 Study EC605-A: 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.

The Systemic Vascular Resistance (SVR) was measured in studies EC605 (single and multiple doses) and EC602 (single dose only). The results for study EC605 resembled those for PCWP, being significantly reduced (compared to placebo) at visit 2 (single-dose effect) with Candesartan 8 mg and 16 mg doses, but unchanged for final visit (multiple dose effect).

Left ventricular ejection fraction (LVEF) was measured (using varying methods such as MRI or echocardiography) in four studies: i.e., (SH-AHS-0001 (RESOLVD) and three Japanese studies – OCT106, CPH103 and CPH104). LVEF increased significantly after treatment with candesartan in the three Japanese studies, and LVEF increased though not significantly in study SH-AHS-0001 (RESOLVD).

In a later communication dated 16-Sep-2004, the sponsor submitted data from the original Japanese reports and translated information for the three Japanese studies – OCT106, CPH103 and CPH104. The results from two of these Japanese studies (OCT106 and CPH103) showed a statistically significant increase in LVEF following treatment with candesartan (Table 15 and Table 16).

Table 15 Hemodynamic parameters in study CPH103 (Translated page 118 of Japanese report)

			Patients	mean	SD	min	25%	median	75%	max	t-value	p-value
EF (%)	2 & 4 mg combined	Run-in	8	43.16	11.86	29	33.85	42.4	49	65.8		
		End Treatment	8	47.91	15.41	26	35.65	49.5	56.55	73.9		
		Difference	8	4.75	4.81	-5	2.8	5.6	8.5	9.2	2.792	0.027
	4mg	Run-in	7	44.09	12.5	29	31	44.5	50.5	65.8		
		End Treatment	7	49.43	15.98	26	34	53.1	59.7	73.9		
		Difference	7	5.34	4.87	-5	5	5.6	8.9	9.2	2.902	0.027
	2mg	Run-in	1	36.7		36.7	36.7	36.7	36.7	36.7		
		End Treatment	1	37.3		37.3	37.3	37.3	37.3	37.3		
		Difference	1	0.6		0.6	0.6	0.6	0.6	0.6		

Table 16 Ejection fraction and its % difference at "run-in" and "end-of-treatment"

		EF (%)	
		Run-in	End of Treatment
Patients		9	9
Values	Mean	24.764	34.930
	SD	8.1287	10.6844
	Median	26.100	35.880
	Min	13.66	16.75
	Max	35.39	47.99
Ref: mean in Run-in		N/A	24.764
Difference (%)*	Mean	N/A	47.070
	SD	N/A	48.6428
	Median	N/A	35.603
	Min	N/A	15.18
	Max	N/A	171.98
CI 95% as to Difference		9.681 – 84.4605	
t-test as to Difference		t = 2.9030, p=0.0198	

* (End of treatment value – Run-in value)/Run-in value

Left ventricular volumes and diameters such as LVEDV, LVESV, LVEDD, and LVESD were measured in three pharmacodynamic studies (SH-AHS-0001 (RESOLVD) and two Japanese studies – CPH103 and CPH104).

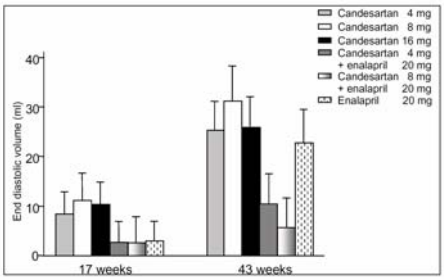


Figure 8 Study SH-AHS-0001 (RESOLVD) – Change in End Diastolic Volume (ml) by different treatments after 17 & 43 weeks.

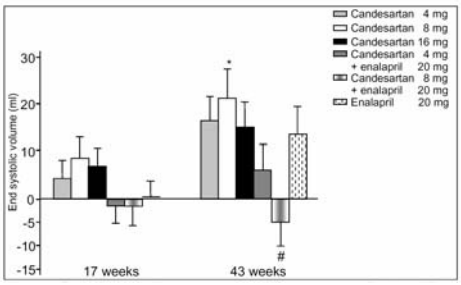


Figure 9 Study SH-AHS-0001 (RESOLVD) – Change in End Systolic Volume (ml) by different treatments after 17 & 43 weeks.

P< 0.01 compared with 0 weeks; # P< 0.01 compared with enalapril

In Study SH-AHS-0001, LVEDV and LVESV were increased to a lesser magnitude with candesartan plus enalapril than with candesartan alone or enalapril alone, and this finding was dose-dependent (Figure 8 and Figure 9). In the two Japanese studies (CPH103 and CPH104), LVDEV, LVESV, LVEDD and LVESD were decreased significantly.

One study (EC604 – STRETCH) that measured cardiothoracic ratios (CTRs) with chest X-rays showed that after treatment with candesartan (compared to placebo), the CTRs were reduced significantly from baseline values (Table 17 and Table 18).

Table 17 Study EC604 – 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 18 Study EC604 – 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

Patients receiving candesartan treatment showed a significant reduction in their blood pressure in one study (SH-AHS-0005/Vaile publication) where blood pressure was an outcome parameter.

Thus, the above findings suggest that patients with CHF who were treated with candesartan showed improvements in their PCWP and PAP. In two Japanese studies, treatment with candesartan was associated with improvements in LVEF. In a large study multicenter (RESOLVD) treatment of CHF patients with candesartan plus enalapril was associated with a reduction of the increase in the left ventricular volumes and diameters; reductions in LV volumes and diameters were also found in Japanese studies. Thus, I think we can conclude that the combination of candesartan and enalapril appears to produce a more beneficial hemodynamic effect than monotherapy with candesartan or enalapril in preventing left ventricular dilatation or remodeling.

5.2.3 Studies of patients with CHF treated with candesartan or placebo in which changes in symptoms were measured:

Cardiovascular symptoms as assessed using dyspnea fatigue index (DFI) scores showed statistically larger (improved symptoms) scores after treatment with candesartan in two studies (EC604 (STRETCH) and CPH104); these improved DFI scores were not dose-related. In two other studies (EC610 and EC614), no change in DFI was found in CHF patients treated with candesartan; two more studies (CPH101 and CPH103) found no changes in subjective symptoms before and after treatment with candesartan.

In the RESOLVD (SH-AHS-0001) study, too, no change in the NYHA class or quality of life was found in the treatment group receiving candesartan.

In the CHARM-Added (SH-AHS-0006) study, there was an improvement in NYHA functional class in candesartan patients compared to placebo patients (P= 0.020, Wilcoxon rank-sum test). In the candesartan group, 548 (43.3%) patients improved 1 or 2 NYHA classes compared to 495 (37.3%) in the placebo group.

CHARM-Alternative (SH-AHS-0003) study provides support to the CHARM-Added (SH-AHS-0006) study and to the sponsor's claim that NYHA functional class was significantly (P=0.0008) better for patients treated long-term with candesartan compared to those treated with placebo.

Thus, the overall finding from the pharmacodynamic studies and the pivotal studies is that treatment of CHF patients with candesartan plus enalapril or candesartan alone or enalapril alone was associated with improvement in cardiovascular symptoms.

5.2.4 Studies of patients with CHF treated with candesartan or placebo in which changes in neurohormones were measured:

In eight pharmacodynamic studies (EC602, EC605-A, EC604, SH-AHS-001, OCT106, CPH101, CPH104 and Hikosaka study), neurohormones were the primary efficacy parameters evaluated before and after treatment of CHF patients with candesartan.

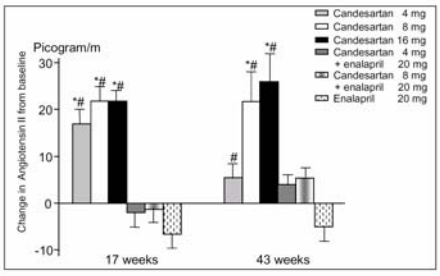


Figure 10 Study SH-AHS-0001 (RESOLVD) – Change in angiotensin II levels after 17 and 43 weeks of treatment with candesartan, candesartan plus enalapril or enalapril

P< 0.01compared with 0 weeks; # P< 0.01 compared with enalapril

A significant increase in angiotensin II and a significant reduction in aldosterone (Figure 10, Figure 11, and Table 19,) were found in two studies (EC605-A and SH-AHS-001), accompanied by a significant increase in renin activity in one of them (EC605-A). There was a statistically significant increase in renin and angiotensin II levels in two more studies (CPH104 and Hikosaka study).

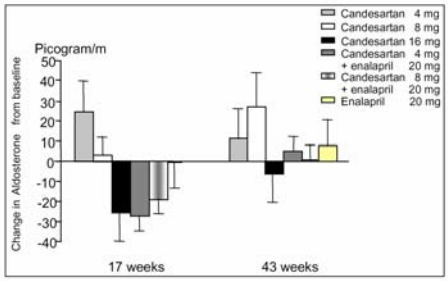


Figure 11 Study SH-AHS-0001 (RESOLVD) – Change in aldosterone levels after 17 and 43 weeks of treatment with candesartan, candesartan plus enalapril or enalapril

P< 0.01compared with 0 weeks; # P< 0.01 compared with enalapril

Table 19 Study EC605-A 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)

An increase in renin levels albeit not statistically significant was found in study SH-AHS-0001 (RESOLVD) and EC602. Study EC602 also showed a non-significant increase in angiotensin and a non-significant decrease in aldosterone. Thus these studies show that in patients with CHF, candesartan treatment was associated with a significant increase in the levels of angiotensin II and renin, and a significant reduction in aldosterone levels.

Atrial natriuretic factor or polypeptide (ANF or ANP – which is an index of atrial load) were reduced significantly in two studies (EC605-A and OCT106) and not significantly in one study (CPH101). (Please also see Table 19, above.)

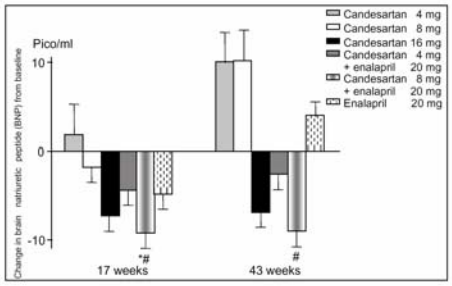


Figure 12 Study SH-AHS-0001 (RESOLVD) – Change in brain natriuretic peptide (BNP) levels after 17 and 43 weeks of treatment with candesartan, candesartan plus enalapril or enalapril
(* P< 0.01compared with 0 weeks; # P< 0.01 compared with enalapril)

Brain natriuretic polypeptide (BNP – which is an index of left ventricular function and myocardial damage) was found reduced significantly in three studies (SH-AHS-0001 (RESOLVD), OCT106 and CPH104). (Please see Figure 12.)

Overall, it appears that treatment of CHF patients with candesartan was associated with an increase in angiotensin II and a reduction in aldosterone levels, and reductions in ANP and BNP levels.

5.2.5 Studies of patients with CHF treated with candesartan or placebo in which changes in baroreflex sensitivity were measured:

Two clinical pharmacology studies evaluated baroreflex sensitivity (using the phenylephrine bolus method).

The Japanese study (Hikosaka study) reported a significant increase in baroreflex sensitivity from baseline in the group treated with candesartan for 4 weeks.

The other (British) study (SH-AHS-0005/Vaile study) reported no consistent effect on baroreflex sensitivity, with a significant increase seen only after chronic candesartan administration (for 4 weeks).

Each of the above studies enrolled only 20 patients; thus, the sample size may not be adequate to make reliable inferences for these studies. Overall, no conclusive inference can be made regarding the effect of candesartan on baroreflex sensitivity based on the results of the submitted studies.

5.3 Exposure-Response Relationships

5.3.1 Total exposure of candesartan

Since its first approval for treatment of hypertension in 1997, the approved once/day doses of 2 to 32 mg candesartan are available in 84 countries. In 1998, the fixed-dose tablets of candesartan and hydrochlorothiazide was first approved; this formulation is now approved in 56 countries. The sponsor submits that the cumulative exposure to candesartan as of October 2003 exceeds 14 million patient-years.

For this NDA submission, the three pivotal (CHARM Program) efficacy trials comprise 7,601 patients (7,599 patients with data) with NYHA Class II – IV heart failure of at least 4 weeks duration who were randomized to candesartan (titrated from 4 mg or 8 mg once daily to a target dose of 32 mg once daily as tolerated) or matching placebo, and followed for at least 2 (up to 4) years. The sponsor estimated that the exposure to the investigational product totaled 18,593 patient-years, and exposure to candesartan 9,222 patient-years.

The median time of follow up for the total population was 37.7 months, and the longest follow-up time was 47.6 months. The median exposure to double-blind treatment was 34.8 months. A total of 5,360 patients (of which 2,659 patients were in the candesartan group) received study medication for 24 months or longer. 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.

In addition to the 7,601 CHF patients in the CHARM Program clinical trials, the sponsor submitted 24 clinical studies (comprising 4,062 patients with CHF) including:

(i) 5 randomized, double-blind, placebo-controlled clinical trials with duration of 2 to 12 months, comprising a total of 1,893 patients,

(ii) one randomized, double-blind, active-treatment (enalapril)-controlled study (RESOLVD) comprising 768 patients, and

(iii) one open, uncontrolled, long-term (6 month) study comprising 355 patients.

(iv) 3 clinical pharmacology studies comprising 262 patients,

(v) 11 clinical studies comprising a total of 677 patients under the Japanese study program (for which FDA granted the sponsor a waiver from providing case report tabulations and case report forms, and 10 studies were pertinent to efficacy), and

(vi) 4 investigator-initiated clinical studies comprising 107 patients.

Thus, a total of 11,661 patients with CHF have been exposed to candesartan in the treatment of CHF in various clinical trials. About one third of these patients were women, and about 15% (1,736) were 75 years or older. About 90% of the population was Caucasian (white) and 326 patients (2.8%) were black. It appears that a representative population of patients with symptomatic CHF has been exposed to candesartan.

5.3.2 Dose Selection

The approved doses of candesartan for treatment of hypertension range from 2 mg to 32 mg once daily. For organ-protective effect (e.g., cardio-protection from remodeling), a higher degree of AT_1-receptor blockade than that required for an anti-hypertensive effect is expected. Thus, higher doses than those optimal for hypertension treatment were thought to be required. The selection of dose of candesartan for treatment of CHF was based on the following studies:

(1) SH-AHS-0001 (RESOLVD) study: In this pilot study of 768 patients with CHF, candesartan 4 mg to 16 mg was found as effective as enalapril 10 mg bid on improving left ventricular function (with or without addition of metoprolol). This study was terminated early because of increased clinical events (deaths) in the treatment groups receiving candesartan and candesartan plus enalapril.

(2) SH-AHS-0002 (SPICE) study: This pilot study of 270 patients with CHF showed that patients intolerant to ACE-inhibitors could be treated for 12 weeks with candesartan 4 mg to 16 mg, with a tolerability similar to placebo.

(3) EC604 study: In this relatively large study of 844 patients with CHF, 4 mg, 8 mg and 16 mg doses of candesartan were given over 12 weeks and, the 16 mg dose was found to improve exercise tolerance (bicycle ergometry only).

(4) SH-AHS-0008 study: In this 8-week study of 98 patients with CHF, candesartan was added to conventional heart failure treatment regimen, starting at 8 mg once daily, titrated at 2-week intervals to doses of 16 mg once daily and to a maximum dose of 32 mg once daily (the highest dose for candesartan in the treatment of essential hypertension approved in the United States). This study showed that the 32 mg dose was generally safe and well-tolerated by these patients with CHF.

In studies conducted prior to the CHARM Program, doses of up to 16 mg once daily were used for treatment of CHF, except in SH-AHS-0008 study which evaluated a target dose of 32 mg once daily. The results of these studies suggested that improvement in the variables tested (left ventricular hemodynamics, neurohormonal changes, exercise tolerance, symptom improvement, etc.) was dose dependent, and maximal at 16 mg dose, and that patients with CHF tolerated the 16 mg dose of candesartan well, and that in the tolerability study (SH-AGS-0008), these CHF patients tolerated the 32 mg dose of candesartan as well. Thus, the target dose of candesartan for the CHARM Program clinical trials was decided as 32 mg once daily.

Also, experience with ACE inhibitors in treatment of heart failure suggests that starting with a low dose is appropriate, and that the dose should then be up-titrated to the target dose.

For this pivotal study SH-AHS-0006 (CHARM-Added trial), a starting dose of 4 or 8 mg candesartan was chosen (at the discretion of the clinical investigator), and this was up-titrated by doubling the dose at intervals of 2 weeks up to a maximum dose of 32 mg once daily or the highest tolerable dose to ensure as complete blockade as possible of AT_1-receptors. The protocol specified monitoring serum potassium and creatinine levels at each dose escalation.

The protocol recommended a starting dose of 4 mg once daily for patients:

- with hypovolemia,
- treated with furosemide >40 mg daily or equivalent,
- with NYHA functional class III-IV,
- with systolic BP ≤110 mmHg,
- with serum creatinine >150μmol/L (1.7 mg/dl),
- who were frail, or
- at the investigator's discretion.

The submission shows that 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). 1,756 (68.9%) patients (candesartan = 857, 67.2%; placebo = 899, 70.7%) received the investigational product for 24 months or more. The mean dose in the candesartan treatment group was 23.5 mg at 6 months.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The sponsor applied for the following indication and labeling under the umbrella of the CHARM Program:
"ATACAND (candesartan cilexetil) is indicated for the treatment of heart failure (NYHA class II-IV). ATACAND (1) reduces the risk of death from cardiovascular causes and (2) improves symptoms in patients with left ventricular systolic dysfunction, and (3) 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 (4) with or without ACE inhibitors, (5) including patients intolerant to ACE inhibitors, and (6) with or without beta-blockers."

For NDA Supplement #022 (CHARM-Added (SH-AHS-0006) Study) under review, the sponsor submitted that candesartan incrementally reduces the risk of cardiovascular mortality or heart failure hospitalization when added to an ACE inhibitor-containing regimen in the treatment of CHF patients with left ventricular systolic function. It also pertains to use of candesartan in the treatment of CHF in patients receiving other heart failure treatments including β-blockers.

With regard to the use of β-blockers, the pharmacodynamics section of the package insert states: "*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.*"

6.1.1 Methods

To determine whether the data submitted by the sponsor supports these claims under the CHARM-Added Study program, I reviewed data in the pivotal trial (SH-AHS-0006) and other relevant clinical trials submitted by the sponsor in which candesartan was added to a CHF treatment regimen containing an ACE inhibitor. These studies are shown in Table 20 below.

Table 20 Studies of CHF patients treated with ACE inhibitors AND Candesartan or placebo

Study #	Type	Total N=	Patients	Duration	Dose	eCTD
SH-AHS-0006	r, db, pc, pg, mc	2548	chf, EF≤40%; ACEi treated	≥ 2 yr	Start CC 4 or 8 mg qd, up-titrate to 32 mg qd or highest tolerated dose	5.3.5.1.2
SH-AHS-0008	r, db, pc, mc	98	chf, EF≤40%; ACEi treated	8 wk	CC 2, 4, 8, 16 or 32 mg qd	5.3.5.1.9
SH-AHS-0004	r, pc	33	chf, EF≤35%; ACEi treated	4 wk	CC 8 mg qd x 1 wk, up-titrate to 16 mg qd	5.3.5.4.12
EC608 (pk)	r, db, md, co, mc	31	Mild to mod chf	Pt I: 1 day Pt II: 21 d	Pt I: CC 8mg, E 10mg, CC8 + E 10mg Pt II: qd x 7 days, 3 periods	5.3.3.2.2
SH-AHS-0001	r, db, pg, mc control = (E)	768	chf, EF≤40%; 6-min walking distance ≤500 m	43 wk	CC 4 or 8 mg qd, up-titrate to 32 mg qd	5.3.5.1.10
SH-AHS-pooled (2 studies)	r, db, pc, pg, mc	7601	chf, EF≤40%; ACEi intol & ACEi treated	≥ 2 yr	Start CC 4 or 8 mg qd, up-titrate to 32 mg qd or highest tolerated dose	5.3.5.1.4
SH-AHS-pooled (3 studies)	r, db, pc, pg, mc	7601	chf, EF≤40% & EF>40%; ACEi intol & ACEi treated	≥ 2 yr	Start CC 4 or 8 mg qd, up-titrate to 32 mg qd or highest tolerated dose	5.3.5.1.4

The sponsor's claim that candesartan incrementally reduces the risk of cardiovascular mortality or heart failure hospitalization when added to an ACE inhibitor containing regimen in CHF

patients with left ventricular systolic dysfunction appears to have scientific basis. It is known that ACE inhibitors only partially block the production of angiotensin II. One or more ACE-independent pathways[1,2] for the synthesis of angiotensin II has been demonstrated, including the "chymase pathway" which produces angiotensin II at the tissue level; about 90% of angiotensin produced in the heart is believed to be produced via this pathway[3,4]. Thus, local production of angiotensin II can occur despite the use of an ACE inhibitor. AT_1-receptor blockers (ARBs), by inhibiting angiotensin II at the AT_1-receptor level, may exert a more complete inhibition of the local adverse effects of angiotensin II. Also, blocking AT_1-receptors causes unopposed stimulation of AT_2-receptors which may produce an additional beneficial effect on cardiac remodeling[5] and vascular epithelial changes. Thus, ACE inhibitors and ARBs such as candesartan may exert different effects at the cardiac and vascular levels, which may be complementary in the treatment of CHF[6].

To address the sponsor's above claim for this pivotal trial, I worked with the statistical reviewer (Dr. Charles Li) to evaluate the reduction in risk of CV mortality or CHF hospitalization (the primary efficacy endpoint) observed when candesartan was used together with the "heart-failure dose" of ACE inhibitors, and when used with low dose ACE inhibitors, in the following sub-populations of patients in study SH-AHS-0006 (Table 21). Dr. Li re-calculated and confirmed the hazard ratios for these populations.

As illustrated in Table 18, I have the following hypothetical factorial analysis:

(1) The effect of candesartan vs. placebo in CHF patients treated with ACE inhibitor (ACEi) *any dose* (sponsor's primary efficacy analysis) is derived from (A+B) vs. (C+D)

(2) The effect of candesartan vs. placebo in CHF patients already on treatment with ACEi *heart failure dose* (i.e., the incremental effect of candesartan added to the effect of *heart failure dose* of ACEi in CHF) is derived from A vs. C

(3) The effect of ACEi at *heart failure dose* vs. *low dose* in CHF patients treated with candesartan (i.e., the incremental effect of *heart failure dose* of ACEi added to the effect of candesartan in CHF, the *low dose* ACEi being, hypothetically, considered as producing no effect) is derived from A vs. B

To show a consistent effect, I think that the incremental effect observed in (2) and that observed in (3) should both be positive and, preferably, statistically significant.

(4) The effect of candesartan vs. placebo in CHF patients treated with ACEi *low dose* (i.e., the effect of candesartan vs. placebo, the *low dose* ACEi being, hypothetically, considered as producing negligible effect) is derived from B vs. D

The relative risk reduction effect observed for this comparison, hypothetically, would be similar that observed in SH-AHS-0003.

(5) The effect of candesartan plus ACEi in *heart failure dose* vs. placebo (*low dose* ACEi being not considered to produce a mortality reduction effect, hypothetically) is derived from A vs. D

This comparison would represent the sum total of candesartan plus ACEi heart failure dose vs. placebo (the *low dose* ACEi being, hypothetically, considered as producing no

effect), and therefore, I would expect this comparison to show the largest relative risk reduction effect.

(6) The effect of ACEi at *heart failure dose* vs. *low dose* in CHF patients treated with placebo is derived from C vs. D. In this case, if the difference is NOT significant, then it is possible that the *low dose* ACEi may be considered as good as the *high dose* ACEi in CHF treatment, or that the sample size is not large enough to show a statistically significant difference.

Table 21 The numbers of patients who received ACE inhibitors at heart failure dose and low dose, who were assigned to candesartan or placebo (Safety Population)

	$ACEi_{HFD}$	**$ACEi_{LD}$**	
Candesartan cilexetil	CC + $ACEi_{HFD}$ **N =643** **Events = 232 (36.1%)** **A**	CC + $ACEi_{LD}$ **N = 633** **Events = 251 (39.7%)** **B**	**A vs. B** Sum effect of CC+$ACEi_{HFD}$ vs. effect of Cc
Placebo	Placebo + $ACEi_{HFD}$ **N = 648** **Events = 275 (42.2%)** **C**	Placebo + $ACEi_{LD}$ **N = 624** **Events = 263 (42.1%)** **D**	**C vs. D** Effect of $ACEi_{HFD}$ vs. Placebo (e.g., VHeFT?)
B vs. C Effect of CC vs. effect of $ACEi_{HFD}$	**A vs. C** Effect of CC+$ACEi_{HFD}$ vs. effect of $ACEi_{HFD}$	**B vs. D** Effect of CC vs. Placebo (e.g., SH-AHS-0003)	**A vs. D** Sum effect of CC+$ACEi_{HFD}$ vs. Placebo

In addition, I reviewed medical journal publications of clinical trials of angiotensin II receptor blockers (ARBs), including those in which β- blockers are used in combination with ACE inhibitors and ARBs in the treatment of CHF to obtain a broader perspective of the benefits produced by use of candesartan, ACE inhibitors and β-blockers together, and the possible risks (e.g., hypotension, bradycardia, worsening of renal failure) this combination treatment may impose on these relatively sick patients with CHF.

N.B. Please refere also to my "road map" of conceptual issues I addressed in my review and the reference clinical trials I reviewed and considered for comparison (with the conduct and findings to the CHARM studies) and discussion; this "road map" is presented under the heading "4.3 Review Strategy" on pages 31-34 of this review.

6.1.2 General Discussion of Endpoints

6.1.2.1 Endpoints for SH-AHS-0006 (CHARM-Added) study

The recently adopted Committee for Proprietary Medicinal Products (CPMP) "Note for guidance on clinical investigations of medicinal products for the treatment of cardiac failure,"[7] recommended that the primary endpoints should include clinical symptoms, cardiovascular mortality and all-cause mortality, that data on morbidity should emphasize disease-specific morbidity (directly related to heart failure), and that use of combined endpoints with mortality and morbidity are appropriate.

For study SH-AHS-0006, the primary efficacy endpoint was a composite of the time from randomization to cardiovascular (CV) mortality or the first occurrence of a CHF hospitalization. The sponsor submitted that this was considered the best measure of clinical efficacy for the purpose of determining whether candesartan treatments reduces cardiovascular mortality and morbidity, since these are the two most frequent and severe events that this population experiences as a result of CHF. For this and other composite time-to-event endpoints, the time was calculated to the first occurrence of one of the components. The time was censored if no event had occurred at last available time point, closing visit or, at the latest, March 31, 2003.

The composite of all-cause mortality or CHF hospitalization was a secondary endpoint, following the emphasis on all-cause mortality by the CPMP. Because of the established role of renin-angiotensin-aldosterone (RAAS) inhibitors in post-myocardial infarction (MI) treatment, non-fatal MI was added to the primary efficacy endpoint, and made into another secondary endpoint as "CV mortality, CHF hospitalization or non-fatal MI."

The protocol specified that all deaths were considered CV unless an unequivocal non-CV cause was established. The CV deaths included sudden deaths, death due to MI, heart failure, stroke, CV investigation/procedure/operation, and other CV causes, presumed CV deaths, and death from unknown causes.

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 (i.e., signs and symptoms of worsening heart failure), and primarily for the treatment of heart failure. Evidence of worsening heart failure must include at least one of the following: increasing dyspnea on exertion, orthopnea, nocturnal dyspnea, increasing peripheral edema, increasing fatigue/decreasing exercise tolerance, renal hypoperfusion (worsening renal function), elevated jugular venous pressure and radiological signs of CHF.

NYHA classification at each scheduled visit: Functional class and symptomatic status were evaluated at each scheduled visit according to the NYHA classification.

6.1.2.1.1 Protocol amendments

The original clinical program protocol was dated 13 November 1998. There were four amendments to the protocol.

The first amendment came into effect before patients were recruited. Another secondary endpoint was added to bring the study into line with European guidelines for studies in heart failure following discussions with regulatory agencies. The change made use of endpoints that were collected but had not been combined in the original protocol. The first amendment did not affect the study procedure, 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. These procedures had been followed for all clinical events occurring before the plan was final. Thus, the same criteria of evaluation of clinical events were applied throughout the study.

The fourth amendment was made one year after the first patient was randomized. The increase in sample size was made 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.

6.1.2.1.2 Changes to planned analyses:

Prior to unblinding of data:

- In amendment 1, the closed test procedure was changed due to an addition to the secondary endpoint. The original closed test procedure was modified to contain three steps with one primary and two secondary endpoints in a hierarchical order.
- In amendment 4, a re-calculation of the power was done 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 for analysis were added 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 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).

6.1.2.1.3 Re-opening of study database

The sponsor submitted that 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 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 22.

Table 22 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

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

The date of 31 March 2003 served as the cutoff date to censor observations to conclude the study and finish data recording. Censoring of observations and/ or imputation of date was implemented in the following situations.

- Patients lost to follow-up/incomplete patient data: Last date known to be alive was used in the analyses;
- Patients who withdrew the consent: Patients alive up to 31 March 2003 were analyzed as being alive 31 March 2003; for dead patients, the death date was estimated by imputation;
- When date of death was unknown, if occurring before 31 March 2003, a death date was estimated by imputation 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.

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.

6.1.2.2 Endpoints for the overall CHARM Program

The primary efficacy endpoint for the 3 CHARM studies was all-cause mortality (time from randomization to death from any cause) in the overall population from studies SH-AHS-0003, SH-AHS-0006 and SH-AHS-0007. The secondary efficacy endpoint was all-cause mortality in the overall population of patients with depressed left ventricular systolic function (from studies SH-AHS-0003 and SH-AHS-0006). The sponsor also pre-specified pooled analysis for the combined endpoint of all-cause mortality or all-cause hospitalization.

For the measure of symptomatic benefit (recommended by the Committee for Proprietary Medicinal Products (CPMP) "Note for guidance on clinical investigations of medicinal products for the treatment of cardiac failure,"[7]), the CHARM program used the improvement in NYHA functional class as the endpoint. Other measures of treatment benefit evaluated included exercise capacity, hemodynamics (LVEF, PCWP, PAP, LVEDV, LVESV, LVEDD, and LVESD), symptoms (dyspnea fatigue index), neurohormonal changes (angiotensin II, renin activity, and aldosterone) and health-related quality of life. All of these endpoints are accepted supportive variables for testing the effect of drugs in the treatment of CHF.

The individual components of each composite endpoint were also examined separately to determine their relative contribution to the composite endpoint findings.

The sponsor submitted that all endpoints were evaluated in a confirmatory analysis based on adjudicated events performed by a blinded critical-events committee, and that in the CHARM studies, every attempt was made to follow up all patients to the trial conclusion regardless of whether or not the patients were still taking study medication. The protocol required follow up of all patients for at least 2 years.

Interim Analysis:

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 all-cause 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 23).

Table 23 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 (Table 23). However, the Committee recommended that the program continue based on the following considerations:-

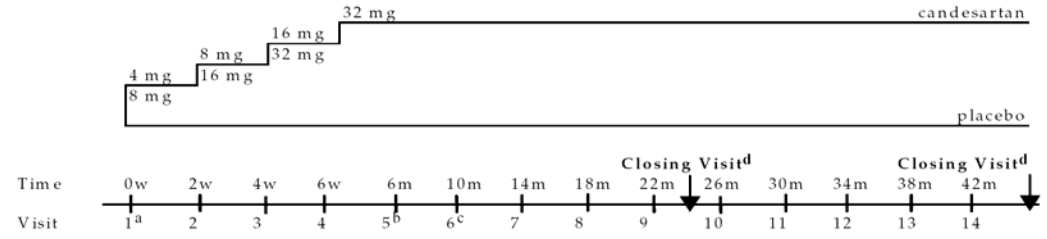
- The treatment difference in mortality was most marked in one study (66 vs100 deaths [P= 0.006 by logrank test], SH-AHS-0003; CHARM-Alternative Study)) and not statistically

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.

6.1.3 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 CHF hospitalization. A total of 2,548 patients were randomized at 473 sites in 25 countries.



[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 13 Study design

Figure 13 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. The median duration of the double-blind treatment was 34.8 months, the median time of follow up was 37.7 months, and the longest follow-up time was 47.6 months.

The sponsor submitted that the design of the CHARM studies is in accordance with the recommendations of the Committee for Proprietary Medicinal Products (CPMP) "Note for guidance on clinical investigations of medicinal products for the treatment of cardiac failure,"[7] and that the study design was discussed with the US FDA in 1998, with the Swedish MPA in 1998 before study initiation, and with the UK MHRA while the studies were in progress.

6.1.4 Efficacy Findings

6.1.4.1 Primary efficacy endpoint: Time from randomization to cardiovascular (CV) death or hospitalization due to CHF

During the follow-up period, a total of 1,021 patients experienced the primary efficacy 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 24).

Table 24 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 (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 (confirmed adjudicated)	Placebo	1272	538	3234.7	166.3	2.5
	Cand. cil.	1276	483	3421.6	141.2	2.7

The relative risk reduction was 14.7% (P=0.011) for the primary outcome of CV death or hospitalization due to CHF, whichever came first, by candesartan treatment (Table 25).

Table 25 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

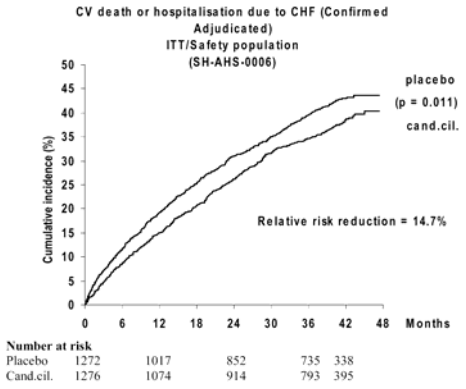


Figure 14 Cumulative incidence (%) of confirmed adjudicated CV death or hospitalization due to CHF over time (ITT/Safety population)

From the Kaplan-Meier plot for the primary efficacy endpoint (Figure 14), the benefit (reduction

in relative risk for the primary outcome of CV death or hospitalization due to CHF, whichever came first) appeared early and was maintained over the course of the study period.

Thus, for the composite primary efficacy endpoint cardiovascular mortality or hospitalization for heart failure, the CHARM-Added (SH-AHS-0006) study showed that candesartan reduced CV mortality or hospitalization for CHF in patients with depressed left ventricular systolic function. This reduction was statistically significant. It also appears that the reduced CV mortality or CHF hospitalization was in addition to that obtained with heart failure doses of ACE inhibitors.

6.1.4.2 Secondary efficacy endpoint

6.1.4.2.1 Time from randomization to all-cause death or hospitalization due to CHF

During the follow-up period, a total of 1,126 patients experienced the secondary efficacy 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 26).

Table 26 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 relative risk for the secondary outcome of all cause death or hospitalization due to CHF, whichever came first, was significantly (P=0.021) reduced by 12.9% by candesartan treatment (Table 26).

Table 27 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

The Kaplan- Meier plot implies that the benefit (reduction in relative risk for the secondary efficacy outcome of all-cause death or CHF hospitalization) of candesartan appeared early and was maintained throughout the study period (Figure 15).

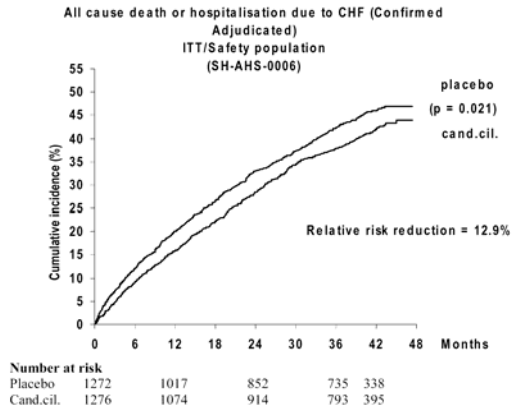


Figure 15 Cumulative incidence (%) of confirmed adjudicated all-cause death or hospitalization due to CHF over time (ITT/Safety population)

6.1.4.2.2 Time from randomization to cardiovascular death, or hospitalization due to CHF or non-fatal MI.

During the follow- up period a total of 1,045 patients experienced the secondary efficacy 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 28).

Table 28 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

The relative risk of CV death or hospitalization due to CHF or non- fatal MI, whichever came first, was significantly (P=0.010) reduced by 14.8% by candesartan (Table 29).

Table 29 Confirmed adjudicated CV death or hospitalization due to CHF or non-fatal MI. Comparison of candesartan vs. 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

The Kaplan- Meier plot implies that the benefit (reduction in relative risk for the secondary efficacy outcome of CV death or CHF hospitalization or non-fatal MI) of candesartan appeared early and was maintained throughout the study period (Figure 16).

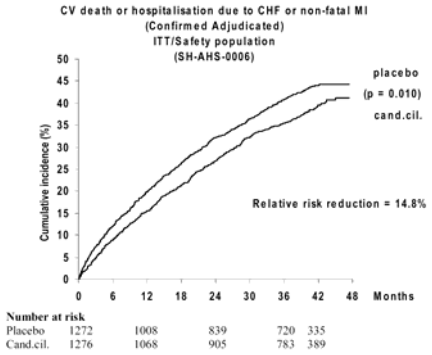


Figure 16 Cumulative incidence (%) of confirmed adjudicated CV death or hospitalization due to CHF or non-fatal MI over time (ITT/Safety population)

6.1.4.3 Components of the primary and secondary variables

The individual components:-

(i) CV death (relative risk reduction 15.8%, P= 0.029),

(ii) hospitalization due to CHF (relative risk reduction 17.5%, P= 0.014),

(iii) all-cause death (relative risk reduction 11.5%, P= 0.086) and

(iv) 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 30 and Table 31).

Table 30 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 31 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

The number and rate of deaths by cause are calculated for each of the component trials of the CHARM Program and the overall CHARM Program and all-cause and cause-specific mortality results[8] are shown in Table 32. There were 1,831 deaths, of which 1,460 were cardiovascular deaths. The three leading causes of death are sudden death (8.5% of patients, or 35% of all deaths), progressive heart failure (6.2% of patients, or 26% of all deaths), and MI (1.5% of patients, 6.1% of all deaths).

Table 32 Number, proportion, and annualized incidence of deaths attributed to different causes in the 3 CHARM Trials and the overall CHARM Program[8] (based on data from Circulation 2004; 110:2180-3)

	CHARM-Alternative		CHARM-Added		CHARM-Preserved		CHARM-Overall		
Cause of Death	Candesartan (n=1013)	Placebo (n=1015)	Candesartan (n=1276)	Placebo (n=1272)	Candesartan (n=1514)	Placebo (n=1508)	Candesartan (n=3803)	Placebo (n=3796)	Hazard Ratio and 95% CI
Sudden death	80 (7.9)	111 (10.9)	150 (11.8)	168 (13.2)	69 (4.6)	65 (4.3)	299 (7.9)	344 (9.1)	0.85 (0.73–0.99)
Incidence rate*	3.0	4.3	3.9	4.5	1.6	1.5	2.7	3.2	*P*=0.036
Progressive HF	70 (6.9)	89 (8.8)	91 (7.1)	117 (9.2)	48 (3.2)	54 (3.6)	209 (5.5)	260 (6.8)	0.78 (0.65–0.94)
Incidence rate*	2.6	3.5	2.4	3.1	1.1	1.2	1.9	2.4	*P*=0.008
MI	34 (3.4)	17 (1.7)	18 (1.4)	21 (1.6)	9 (0.6)	12 (0.8)	61 (1.6)	50 (1.3)	1.19 (0.82–1.73)
Incidence rate*	1.3	0.66	0.47	0.56	0.20	0.27	0.56	0.47	*P*=0.37
Stroke	13 (1.3)	15 (1.5)	15 (1.2)	13 (1.0)	17 (1.1)	16 (1.1)	45 (1.2)	44 (1.2)	1.00 (0.66–1.52)
Incidence rate*	0.49	0.58	0.39	0.35	0.38	0.36	0.41	0.41	*P*=0.99
Procedure related	6 (0.6)	4 (0.4)	10 (0.8)	2 (0.2)	7 (0.5)	6 (0.4)	23 (0.6)	12 (0.3)	1.87 (0.93–3.77)
Incidence rate*	0.23	0.15	0.26	0.05	0.16	0.14	0.21	0.11	*P*=0.073
Other CV	16 (1.6)	16 (1.6)	17 (1.3)	26 (2.0)	18 (1.2)	17 (1.1)	51 (1.3)	59 (1.6)	0.84 (0.58–1.23)
Incidence rate*	0.60	0.62	0.44	0.70	0.41	0.39	0.47	0.55	*P*=0.37
All CV death	219 (21.6)	252 (24.8)	302 (23.7)	347 (27.3)	170 (11.2)	170 (11.3)	691 (18.2)	769 (20.3)	0.88 (0.79–0.97)
Incidence rate*	8.2	9.8	7.9	9.3	3.8	3.9	6.3	7.2	*P*=0.012
Cancer death	25 (2.5)	18 (1.8)	35 (2.7)	19 (1.5) †	26 (1.7)	22 (1.5)	86 (2.3)	59 (1.5)	1.42 (1.02–1.98)
Incidence rate*	0.94	0.70	0.91	0.51	0.59	0.50	0.79	0.55	*P*=0.037
Other non-CV death	21 (2.1)	26 (2.6)	40 (3.1)	46 (3.6)	48 (3.2)	45 (3.0)	109 (2.9)	117 (3.1)	0.91 (0.70–1.18)
Incidence rate*	0.79	1.01	1.04	1.24	1.08	1.03	1.00	1.09	*P*=0.81
All non-CV death	46 (4.5)	44 (4.3)	75 (5.9)	65 (5.1)	74 (4.9)	67 (4.4)	195 (5.1)	176 (4.6)	1.08 (0.88–1.33)
Incidence rate*	1.7	1.7	2.0	1.8	1.7	1.5	1.8	1.7	*P*=0.45
All deaths	265 (26.2)	296 (29.2)	377 (29.6)	412 (32.4)	244 (16.1)	237 (15.7)	886 (23.3)	945 (24.9)	0.91 (0.83–1.00)
Incidence rate*	10.0	11.5	9.8	11.1	5.5	5.4	8.1	8.8	*P*=0.055

*Per 100 person-years.

The reduction in CV death with candesartan (relative risk reduction = 12%, P = 0.012) is largely attributable to a reduction in sudden death (relative risk reduction = 15%, P = 0.036), and progressive heart failure death (relative risk reduction = 22%), P = 0.008). These reductions were observed only in the two left ventricular systolic dysfunction trials (CHARM-Alternative (SH-AHS-0003) and CHARM-Added (SH-AHS-0006)) where patient had LVEF ≤ 40%. The mechanism by which ARBs (candesartan) reduce the incidence of sudden death is not clear (but ACE inhibitors also have been shown to reduce sudden death in patients following acute myocardial infarction[9]). ARBs, like ACE-inhibitors, are potassium sparing, and relative increases in serum potassium may protect these patients from arrhythmias. The overall improvement in hemodynamic status and attenuation of ventricular remodeling[5] may also directly or indirectly decrease the propensity to fatal ventricular arrhythmias[10]. While arrhythmia is the presumed cause in patients who die suddenly, it is also possible that other causes of sudden death such as acute myocardial infarction, pulmonary embolism, aortic dissection and stroke could have been present. In autopsied patients in the Assessment of Treatment with Lisinopril And Survival (ATLAS) trial, myocardial infarction was a frequent

cause of death in autopsied patients who died suddenly[11]. Autopsy data were available in only a few patients in the CHARM trials.

Non-CV death was not affected by treatment. Of 371 non-CV deaths (4.9% of patients, 20.3% of deaths), 145 were cancer-related (1.9% of patients). Death attributed to cancer was more frequent in the candesartan group (HR = 1.42; 95% CI 1.02 to 1.98, P = 0.037).

The efficacy results for the secondary endpoints and the individual components of the endpoints in the CHARM-Added (SH-AHS-0006) study are summarized in Table 33.

Table 33 Endpoints in the CHARM-Added study (SH-AHS-0006)

Endpoints	Hazard Ratio and "P"
P°: CV deaths or CHF hospitalizations	HR =0.853; P=0.011
S°: All-cause deaths or CHF hospitalizations	HR =0.871; P=0.021
S°: CV death/CHF hospitalization/non-fatal MI	HR =0.852; P=0.008
All-cause Mortality	HR =0.885; P=0.086
All-cause deaths or all-cause hospitalizations	HR =0.961; P=0.387
All-cause hospitalizations	HR =0.955; P=0.346
CHF hospitalizations	HR =0.825; P=0.014
Non-fatal MI	HR =0.512; P=0.006
CV deaths	HR =0.842; P=0.029
CHF death	HR =0.752; P=0.041
Sudden death	HR =0.865; P=0.196
Death due to MI	HR =0.830; P=0.562
Death due to stroke	HR =1.120; P=0.765
Death due to other CV cause	HR =0.965; P=0.894
Non-CV death	HR =1.112; P=0.529

Since CHF hospitalization was the component in all three efficacy endpoints (the primary endpoint and the two secondary endpoints) for study SH-AHS-0006 (CHARM-Added), these hospitalizations were further reviewed. There were 2,673 CHF hospitalizations (i.e., the primary reason for hospitalization was reported as cardiovascular as defined by protocol) of which 1,177 were in the candesartan group and 1,496 in the placebo group. Overall, patients in the candesartan group stayed fewer days (a total of 10,061 days) in hospital compared to patients in the placebo group (a total of 12,073 days). This was reflected in candesartan treatment group patients spending fewer days in all levels of medical care:

- intensive care (1,893 days for candesartan group vs. 2,346 days for placebo group),
- intermediate care (2,607 days for candesartan group vs. 3,160 days for placebo group) and
- general medical wards (5,561 days for candesartan group vs. 6,567 days for placebo group).

Table 34 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 34 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

Regarding improvement in symptoms, 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 35).

Table 35 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 36.

Table 36 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%)

6.1.4.4 Overview of Efficacy Findings

The sponsor claimed that candesartan incrementally reduces the risk of cardiovascular mortality or heart failure hospitalization when added to an ACE inhibitor containing regimen in CHF patients with left ventricular systolic dysfunction. To address the sponsor's claim I used the factorial analysis concept for which the hazard ratios of the primary efficacy endpoint (CV deaths or CHF hospitalizations) for patients on heart failure dose and low dose ACE inhibitors which are re-calculated and confirmed (by Dr. Charles Li, statistical reviewer) for the CHARM-Added (SH-AHS-0006) study. The reductions in relative risk for CV deaths or CHF hospitalizations observed for each subgroup are presented in the factorial table below (Table 37).

Table 37 The numbers of patients who received ACE inhibitors at heart failure dose and low dose, who were assigned to candesartan or placebo (Safety Population)

	$ACEi_{HFD}$	**$ACEi_{LD}$**	
Candesartan cilexetil	$CC + ACEi_{HFD}$ **N =643** **Events = 232 (36.1%)** **A**	$CC + ACEi_{LD}$ **N = 633** **Events = 251 (39.7%)** **B**	**A vs. B** Sum effect of $CC+ACEi_{HFD}$ vs. effect of Cc **RRR = 12.6%**
Placebo	$Placebo + ACEi_{HFD}$ **N = 648** **Events = 275 (42.2%)** **C**	$Placebo + ACEi_{LD}$ **N = 624** **Events = 263 (42.1%)** **D**	**C vs. D** Effect of $ACEi_{HFD}$ vs. Placebo **RRR = NA**
B vs. C	**A vs. C** Effect of $CC+ACEi_{HFD}$ vs. effect of $ACEi_{HFD}$ **RRR = 20.6%**	**B vs. D** Effect of CC vs. Placebo (e.g., SH-AHS-0003) **RRR = 8.5%**	**A vs. D** Sum effect of $CC+ACEi_{HFD}$ vs. Placebo **RRR = 20.1%**

N.B. Sponsor's analysis of A+B vs. C+D showed a reduction in relative risk of 14.7%

(1) The effect of candesartan vs. placebo in CHF patients treated with ACE inhibitor (ACEi) *any*

dose (sponsor's primary efficacy analysis) is derived from (A+B) vs. (C+D). This showed a reduction in relative risk of **14.7%** (P<0.011).

(2) The effect of candesartan vs. placebo in CHF patients treated with ACEi *heart failure dose* (i.e., the incremental effect of candesartan added to the effect of *heart failure dose* of ACEi in CHF) is derived from A vs. C. This showed a reduction in relative risk of **20.6%,** which is the largest reduction found for study SH-AHS-0006. This is a statistically significant finding (P=0.010), even for this smaller subgroup of fewer patients (with, therefore, less statistical power). This finding, together with the finding in (1) above, suggests that there is an incremental effect of candesartan added to the effect of ACE inhibitors at *heart failure doses* in the treatment of CHF.

(3) The effect of ACEi at *heart failure dose* vs. ACEi *low dose* in CHF patients treated with candesartan (i.e., the incremental effect of *heart failure dose* of ACEi on top of the effect of candesartan in CHF, the *low dose* ACEi being, hypothetically, considered as producing negligible effect) is derived from A vs. B. This showed a reduction in relative risk of **12.6%,** but the results are not statistically significant (because of the loss of statistical power from the smaller sample size in this subgroup). The results are still in the positive direction, so this is a consistent finding in relation to the findings in (1) and (2) above. This suggests that there is a trend for an incremental effect of *heart failure dose* of ACEi on top of the effect of candesartan in CHF.

Thus, (2) and (3) together suggest that there is a mutually complementary effect when candesartan and *heart failure doses* of ACEi are used together in the treatment of CHF.

(4) The effect of candesartan vs. placebo in CHF patients treated with ACEi *low dose* (i.e., the effect of candesartan vs. placebo, the *low dose* ACEi being, hypothetically, considered as producing negligible effect) is derived from B vs. D. The relative risk reduction for this subgroup is **8.5%** (not statistically significant because of the loss of statistical power from a smaller sample size in this subgroup).

Hypothetically, I would have expected the relative risk reduction effect observed for this subgroup be comparable to that observed in SH-AHS-0003 (where the relative risk reduction is 23.2%). This difference in relative risk reduction in these two studies may be explained partly by loss of statistical power for the subgroup analysis in the SH-AHS-0006 study because of smaller sample size.

(5) The effect of candesartan plus ACEi in *heart failure dose* vs. placebo (*low dose* ACEi being not considered to produce a mortality reduction effect, hypothetically) is derived from A vs. D. The showed a reduction in relative risk of **20.1%**, which is a statistically significant finding (P=0.0127), even for this subgroup of fewer patients (and, therefore, less statistical power).

This comparison represents the sum total of the effect candesartan plus the effect of ACEi *heart failure dose* in Group A vs. placebo in Group D (the *low dose* ACEi being, hypothetically, considered as producing negligible effect). Therefore, I would have expected this comparison to show the largest relative risk reduction effect. There is a statistically significant relative risk reduction effect even for this small subgroup of patients, but slightly smaller than that found in (2) above.

I think that this finding, together with the findings in (1) and (2) above, further supports the inference that there is an incremental beneficial effect when candesartan is added to ACE inhibitors at *heart failure doses* in the treatment of CHF.

(6) The effect of ACEi at *heart failure dose* vs. *low dose* in CHF patients treated with placebo is derived from C vs. D. The hazard ratio is 1.006; no reduction in relative risk is found.

This finding suggests that the CHF patients in the CHARM studies who were on "low doses" of ACE inhibitors might have been at an optimal dosage that they could tolerate; thus they were obtaining a balanced mortality/morbidity benefit without accruing potential adverse effects (hypotension, hyperkalemia, worsening renal function) that could arise from the addition of ARBs to ACE inhibitors. It is also possible that the *low dose* ACEi may be considered as good as the *high dose* ACEi in CHF treatment, but the sample size is not large enough to draw a valid statistical inference. Most randomized trials of ACE inhibitors have reported no difference in mortality between patients receiving high-dose ACE inhibitors and those receiving low-dose ACE inhibitors[12,13,14,15].

I think the findings in (1), (2), (3) and (5) above, which are all positive and consistent, provide credibility to the sponsor's claim that candesartan incrementally reduces the risk of cardiovascular mortality or heart failure hospitalization when added to an ACE inhibitor containing regimen in the treatment of CHF patients with left ventricular systolic dysfunction.

The primary efficacy endpoint findings for the safety population of subjects who received low doses of ACE inhibitors and those who received heart failure doses of ACE inhibitors are shown in Table 38. The primary efficacy endpoint in the CHARM-Alternative (SH-AHS-0003) study is also included in Table 38 for comparison.

Table 38 Comparison of the primary efficacy endpoints for patients treated with candesartan versus those treated with candesartan plus an ACE inhibitor

Primary Efficacy Endpoint	Overall Study AHS-0006	Cc on top of $ACEi_{HFD}$	Cc + $ACEi_{LD}$	Cc in AHS-0003	$ACEi_{HFD}$ on top of Cc	$ACEi_{HFD}$ vs. $ACEi_{LD}$	CC + $ACEi_{HFD}$ vs. $ACEi_{LD}$
CV deaths or CHF hospitalizations:	A+B vs. C+D	A vs. C	B vs. D	~B vs. ~D	A vs. B	C vs. D	A vs. D
Hazard Ratio Relative Risk Reduction P	HR = 0.853; RRR = 14.7% P = 0.011	HR = 0.794 RRR= 20.6% P = 0.010	HR = 0.915 RRR = 8.5% P = 0.314	HR = 0.768 RRR= 23.2% P < 0.001	HR = 0.874 RRR = 12.6% P = NA	HR = 1.006 RRR = NA P = NA	HR = 0.799 RRR= 20.1% P = 0.0127

A, B, C and D = Reference to cells in Table 37; NA = not applicable.

The subgroups of patients for factorial analysis (in Table 38, above) show relatively consistent results for the primary efficacy endpoint of CV deaths or CHF hospitalizations.

6.1.5 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 39 and Table 40, 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 40). 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 39 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 40 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 November 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 November 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 41. 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 42).

The secondary efficacy endpoint of all-cause mortality or CHF hospitalization (Table 43 and Table 44), and for secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI (Table 45 and Table 46) also show similar findings.

Table 41 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 42 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 41.

Table 43 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

<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 = 401
Events = 158 9.4%)
E_1</td><td>$CC_{LD} + ACEi_{HFD}$
N = 99
Events = 49 49.5%)
E_2</td><td>$CC_{00} + ACEi_{HFD}$
N = 143
Events = 56 (39.2%)
E_3</td><td>$CC_{HD} + ACEi_{LD}$
N = 375
Events = 155 (41.3%)
F_1</td><td>$CC_{LD} + ACEi_{LD}$
N = 128
Events = 72 (56.3%)
F_2</td><td>$CC_{00} + ACEi_{LD}$
N = 130
Events = 49 (37.7%)
F_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 44 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 43.

Table 45 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

	$ACEi_{HFD}$			**$ACEi_{LD}$**		
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 = 402** **Events = 150 (37.3%)** **G_1**	$CC_{LD} + ACEi_{HFD}$ **N = 100** **Events = 51 (51.0%)** **G_2**	$CC_{00} + ACEi_{HFD}$ **N = 141** **Events = 40 (28.4%)** **G_3**	$CC_{HD} + ACEi_{LD}$ **N = 373** **Events = 143 (38.3%)** **H_1**	$CC_{LD} + ACEi_{LD}$ **N = 129** **Events = 70 (54.3%)** **H_2**	$CC_{00} + ACEi_{LD}$ **N = 131** **Events = 41 (31.3%)** **H_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 46 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 45.

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.

6.1.6 Efficacy Conclusions

The endpoints (mortality or hospitalizations) in this pivotal clinical trial (CHARM-Added (SH-AHS-0006) Study) and the pooled CHARM Program clinical trials are shown in Table 47.

Table 47 Endpoints in the CHARM-Alternative study (SH-AHS-0003), CHARM-Added study (SH-AHS-0006) and the CHARM Program (Pooled studies SH-AHS-0003, SH-AHS-0006 and SH-AHS-0007)

Endpoints	SH-AHS-0003 (CHARM-Alternative)	SH-AHS-0006 (CHARM-Added)	Pooled SH-AHS-0003 + SH-AHS-0006	Pooled SH-AHS-0003 + SH-AHS-0006+ SH-AHS-0007
P°: CV deaths or CHF hospitalizations	HR =0.768; P<0.001	**HR =0.853; P=0.011**	HR = 0.816; P<0.001	HR = 0.836; P<0.001
S°: All-cause deaths or CHF hospitalizations	HR =0.798; P=0.001	**HR =0.871; P=0.021**	HR = 0.840; P<0.001	HR = 0.862; P<0.001
S°: CV death/CHF hospitalization/non-fatal MI	HR =0.782; P<0.001	**HR =0.852; P=0.008**	HR = 0.822; P<0.001	HR = 0.843; P<0.001
All-cause Mortality	HR =0.872; P=0.105 (Covar. adj: P=0.033)	**HR =0.885; P=0.086 (Covar. adj: P=0.105)**	HR =0.886; P=0.018	HR =0.914; P=0.055 (Covar. adj: P=0.032)
All-cause deaths or all-cause hospitalizations	HR =0.918; P=0.114 (Covar. adj: P=0.028)	**HR =0.961; P=0.387**	HR =0.943; P=0.092	HR =0.948; P=0.055
All-cause hospitalizations	HR =0.913; P=0.107 (Covar. adj: P=0.030)	**HR =0.955; P=0.346**	HR =0.937; P=0.078	HR =0.948; P=0.064
CHF hospitalizations	HR =0.677; P<0.001	**HR =0.825; P=0.014**	HR = 0.76 ; P<0.001	HR = 0.79 ; P<0.001
Non-fatal MI	HR =1.107; P=0.656	**HR =0.512; P=0.006**	HR = 0.--- ; P<0.097	HR = 0.--- ; P<0.267
CV deaths	HR =0.847; P=0.072	**HR =0.842; P=0.029**	HR =0.844; P=0.005	HR =0.876; P=0.011
CHF death	HR =0.766; P=0.095	**HR =0.752; P=0.041**	HR =0.758; P=0.008	HR =0.783; P=0.008
Sudden death	HR =0.704; P=0.017	**HR =0.865; P=0.196**	HR =0.801; P=0.013	HR =0.848; P=0.037
Death due to MI	HR =1.942; P=0.025*	**HR =0.830; P=0.562**	HR =1.327; P=0.185	HR =1.187; P=0.368
Death due to stroke	HR =0.846; P=0.658	**HR =1.120; P=0.765**	HR =0.973; P=0.919	HR =1.001; P=0.996
Death due to other CV cause	HR =1.066; P=0.836	**HR =0.965; P=0.894**	HR =1.007; P=0.972	HR =1.057; P=0.734
Non-CV death	HR =1.014; P=0.948	**HR =1.112; P=0.529**	HR =1.073; P=0.595	HR =1.081; P=0.452

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

CHARM-Added (SH-AHS-0006) Study Primary Efficacy Endpoint: For the composite primary efficacy endpoint cardiovascular mortality or hospitalization for heart failure, the CHARM-Added (SH-AHS-0006) Study showed that candesartan significantly (P=0.011) reduced the

relative risk of CV death or hospitalization for CHF in patients with depressed left ventricular systolic function by 14.7% (Table 33 and Table 47). A factorial analysis of the results (Table 37) suggests that the reduced CV mortality or CHF hospitalization was in addition to that obtained with heart failure doses of ACE inhibitors.

CHARM-Added (SH-AHS-0006) Study Secondary Efficacy Endpoints: For the composite secondary efficacy endpoint all-cause deaths or CHF hospitalizations, the CHARM-Added (SH-AHS-0006) Study showed that candesartan significantly (P=0.021) reduced the relative risk of all-cause deaths or CHF hospitalizations in patients with depressed left ventricular systolic function by 12.9% (Table 33 and Table 47).

For the composite secondary efficacy endpoint CV death or CHF hospitalization or non-fatal MI, the CHARM-Added (SH-AHS-0006) Study showed that candesartan significantly (P=0.008) reduced the relative risk of CV death or CHF hospitalization or non-fatal MI in patients with depressed left ventricular systolic function by 14.8% (Table 33 and Table 47).

CHARM-Added (SH-AHS-0006) Study Other Efficacy Findings: There are significant reductions in the individual components of CHF hospitalizations (relative risk reduction = 17.5%, P = 0.014), non-fatal MI (relative risk reduction = 48.8%, P = 0.006), CV deaths (relative risk reduction = 15.8%, P = 0.029), and CHF deaths (relative risk reduction = 24.8%, P = 0.041), which appear to contribute to the beneficial effect of candesartan on the corresponding composite primary or secondary endpoint (Table 33 and Table 47).

Please note that SH-AHS-0006 (CHARM-Added) Study does **NOT** win on "all-cause mortality" or on "all-cause hospitalization" or on the composite endpoint "all-cause mortality or hospitalization" on its own merit.

6.1.6.2 CHARM Program (SH-AHS-0003, SH-AHS-0006 and SH-AHS-0007 studies)

CHARM Program Primary Efficacy Endpoint Finding: For the primary efficacy endpoint all-cause mortality in the pooled population of patients with symptomatic CHF (pooled studies SH-AHS-0003, SH-AHS-0006 and SH-AHS-0007), the CHARM-Program endpoint analysis showed that candesartan reduced the relative risk of all-cause mortality in patients with symptomatic CHF by 8.6% (Figure 17 and Table 47). This was NOT statistically significant (P=0.055).

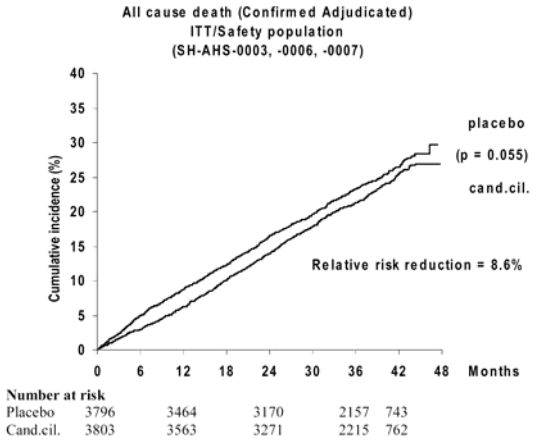


Figure 17 Cumulative incidence (%) of confirmed adjudicated all-cause death in patients with symptomatic CHF over time. ITT/Safety population.

CHARM Program Secondary Efficacy Endpoint Finding: For the secondary efficacy endpoint all-cause mortality in the pooled population of patients with CHF and left ventricular systolic dysfunction (pooled studies SH-AHS-0003 and SH-AHS-0006), the CHARM-Program endpoint analysis showed that candesartan significantly (P=0.018) reduced the relative risk of all-cause mortality in patients with symptomatic CHF and left ventricular systolic dysfunction by 11.4% (Figure 18 and Table 47).

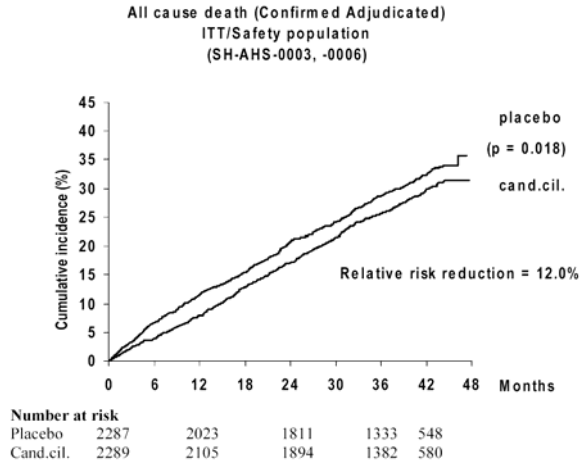


Figure 18 Cumulative incidence (%) of confirmed adjudicated all-cause death in patients with LV systolic dysfunction over time. ITT/Safety population.

CHARM Program – Other Efficacy Endpoint Findings: For the efficacy endpoint all-cause mortality or all cause hospitalization in the pooled population of patients with symptomatic CHF (pooled studies SH-AHS-0003, SH-AHS-0006 and SH-AHS-0007), the CHARM-Program endpoint analysis showed that candesartan reduced the relative risk of all-cause mortality or all cause hospitalization in patients with symptomatic CHF by 5.2% (Table 47). This was NOT statistically significant (P=0.055).

For the efficacy endpoint all-cause death or all-cause hospitalization in the pooled population of patients with CHF and left ventricular systolic dysfunction (pooled studies SH-AHS-0003 and SH-AHS-0006), the CHARM-Program endpoint analysis showed that candesartan reduced the relative risk of all-cause death or all-cause hospitalization in patients with symptomatic CHF and left ventricular systolic dysfunction by 5.7% (Table 47). This was NOT statistically significant (P=0.092).

In the overall CHARM Program, candesartan significantly reduced the relative risk of **all-cause mortality** when only two studies – CHARM-Alternative (SH-AHS-0003) and CHARM-Added (SH-AHS-0006) – are pooled. When the CHARM-Preserved (SH-AHS-0007) study is added to the pooled analysis, the CHARM Program does not significantly reduce the relative risk of all-cause mortality, unless covariate adjustment is allowed (then hazard ratio = 0.904, P = 0.031). Please note also that the CHARM Program does **NOT** win on the composite endpoint "**all-cause mortality or hospitalization**" or on "**all-cause hospitalization**" (regardless of whether 2 or all 3 studies are pooled).

The beneficial effect of candesartan in the CHARM Program was observed in CHF patients with symptomatic CHF (pooled studies SH-AHS-0003, SH-AHS-0006 and SH-AHS-0007) who were receiving ACE-inhibitors, β-blockers or digoxin as part of the conventional treatment for CHF. The beneficial effect of candesartan was observed both for the primary efficacy endpoint of all-cause mortality (Figure 19) and for the composite endpoint of CV death or CHF hospitalization (Figure 20).

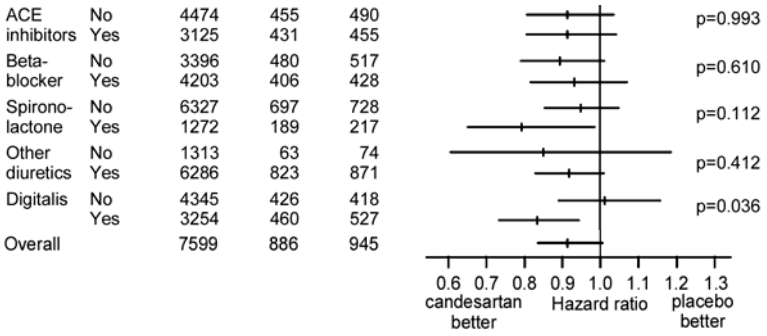


Figure 19 Overall effect of candesartan on all-cause death in subgroups of conventional CHF treatment. Point estimates of hazard ratios given with 95% confidence interval, and P values. ITT/Safety population (SH-AHS-0003, SH-AHS-0006, SH-AHS-0007)

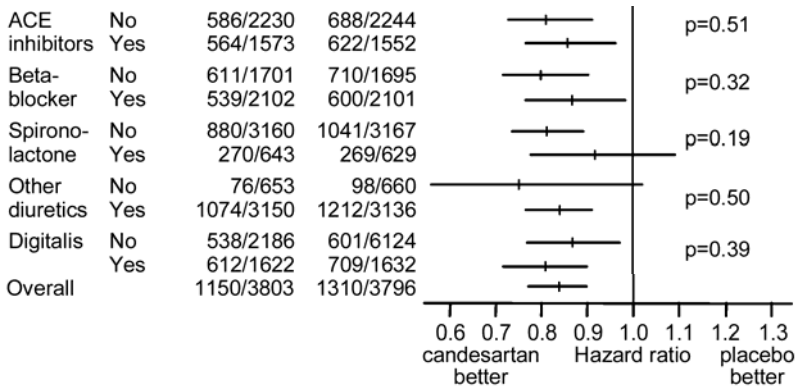


Figure 20 Overall effect of candesartan on CV death or hospitalization in subgroups of conventional CHF treatment. Point estimates of hazard ratios given with 95% confidence interval, and P values. ITT/Safety population (SH-AHS-0003, SH-AHS-0006, SH-AHS-0007).

The beneficial effect of candesartan appears to be complementary to the effects of these drugs used in the conventional treatment of CHF.

In addition to being statistically significant, the magnitude of the reductions in all-cause mortality and CV mortality produced by candesartan in patients already receiving ACE-inhibitors, β-blockers, or digoxin as part of the conventional treatment for CHF reaches a level that is also clinically significant and meaningful.

The following summarizes the efficacy conclusions for CHARM-Added (SH-AHS-0006) study:

- Candesartan significantly reduced the relative risk of CV death or the first occurrence of a CHF hospitalization by 14.7% (P= 0.011). (Primary efficacy endpoint)
- Candesartan significantly reduced the relative risk of all-cause death or the first occurrence of a CHF hospitalization by 12.9% (P= 0.021). (Secondary efficacy endpoint)
- Candesartan significantly reduced the relative risk of CV death or the first occurrence of a CHF hospitalization or a non-fatal myocardial infarction by 14.8% (P=0.008). (Secondary efficacy endpoint)
- The following also met the nominal "P" value for statistical significance based on the results of CHARM-Added (SH-AHS-0006) study:
    - Candesartan reduced the relative risk of CHF hospitalizations.
    - Candesartan reduced the relative risk of non-fatal MIs.
    - Candesartan reduced the relative risk of CV deaths.
    - Candesartan reduced the relative risk of CHF deaths.
    - Candesartan improved NYHA classification from randomization to the LVCF (last-value-carried-forward).
- The following endpoints were not effected by candesartan based on the results of CHARM-Added (SH-AHS-0006) study:

- Candesartan did not reduce all-cause death.
- Candesartan did not reduce all-cause death or the first occurrence of hospitalization.
- Candesartan did not reduce time to the first occurrence of hospitalization.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

I think we would need to evaluate the safety findings reported in the CHARM studies in comparison with that observed with use of AT_1-receptor blockers (ARBs) in patients with congestive heart failure as reported in the medical literature, so that we can make an objective assessment of the nature of the adverse events that can arise in patients who have underlying hyperkalemia, hypotension, chronic or acute on chronic renal dysfunction, and other co-morbid diseases such as diabetes, myocardial infarction, etc. In this way, we may be able to evaluate the risk of use of candesartan versus its benefit in the treatment of chronic heart failure in the context of what is occurring with currently available therapies.

For each of the following subsections (deaths, SAEs, AEs, laboratory findings, etc.) in this review, I will first present the data from the pivotal study CHARM-Added (SH-AHS-0006), followed by data from the overall CHARM-Pooled (SH-AHS-0003, -0006, -0007) studies, findings from exploratory analyses (where performed), and by safety data reported in the medical literature.

From the clinical pharmacology studies and non-CHARM studies, safety data are generally consistent with data from the CHARM-Pooled studies.

7.1.1 Deaths

In this section, deaths are reported as part of the safety review. However, for NDAs of drugs for the treatment of conditions with high likelihood of dying, and also where death is a primary efficacy endpoint, I think that one cannot review deaths for safety as one would in a safety review of a drug for the treatment of hypertension, GERD (where drugs such as cimetidine are known to cause *Torsades des pointes*, and sudden death is an important safety endpoint), etc.

Deaths in CHARM-Added (SH-AHS-0006) Study

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, the death was incompletely documented (vital status only without specified cause of death). However, all deaths were 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. I find that this one death is also not included in the efficacy results (Table 30 and Table 31); however, this only makes the statistical analysis more conservative (and less advantageous for candesartan).

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 (Table 48). 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 48 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.

Deaths in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies

1,834 patients died during the studies, of which 947 (24.9%) were randomized to placebo and 887 (23.3%) randomised to candesartan. For 13 of the patients who died (11 in the subpopulation of patients with depressed LV systolic function), the death was incompletely documented (vital status only without specified cause of death). However, all deaths are included in the tables. Two of the patients in the placebo group and one of the patients in the candesartan group had an SAE with fatal outcome with date of death after the patient's closing visit, thus the deaths of these patients are included in the descriptive safety results but not in the efficacy results.

Table 49 Number (%) of patients with symptomatic CHF 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-0003, -0006, -0007)

Preferred term	Placebo on treatment (N=3796)		Cand. cil. on treatment (N=3803)		Placebo during study (N=3796)		Cand. cil. during study (N=3803)	
	N	(%)	N	(%)	N	(%)	N	(%)
Sudden death	276	(7.3)	231	(6.1)	348	(9.2)	291	(7.7)
Cardiac failure/cardiac failure aggravated[b]	149	(3.9)	79	(2.1)	256	(6.7)	192	(5.0)
Myocardial infarction	35	(0.9)	56	(1.5)	57	(1.5)	77	(2.0)
Pneumonia	25	(0.7)	11	(0.3)	47	(1.2)	30	(0.8)
Cerebrovascular disorder	23	(0.6)	19	(0.5)	39	(1.0)	36	(0.9)
Death	12	(0.3)	11	(0.3)	31	(0.8)	35	(0.9)
Cardiac arrest	16	(0.4)	16	(0.4)	24	(0.6)	27	(0.7)
Sepsis	11	(0.3)	9	(0.2)	26	(0.7)	19	(0.5)
Fibrillation ventricular	19	(0.5)	12	(0.3)	23	(0.6)	17	(0.4)
Cardiomyopathy	9	(0.2)	4	(0.1)	19	(0.5)	14	(0.4)
Pulmonary carcinoma	8	(0.2)	14	(0.4)	12	(0.3)	21	(0.6)
Pulmonary oedema	9	(0.2)	9	(0.2)	17	(0.4)	15	(0.4)
Respiratory insufficiency	7	(0.2)	6	(0.2)	15	(0.4)	15	(0.4)
Accident and/or injury	8	(0.2)	6	(0.2)	15	(0.4)	11	(0.3)
Coronary artery disorder	8	(0.2)	7	(0.2)	11	(0.3)	15	(0.4)
Renal failure acute	5	(0.1)	4	(0.1)	14	(0.4)	12	(0.3)
Renal failure nos	7	(0.2)	1	(<0.1)	14	(0.4)	12	(0.3)
Multiorgan failure	4	(0.1)	4	(0.1)	9	(0.2)	10	(0.3)

[a] The table uses a cut-off of ≥0.3% in the total population during study (N=7599).
[b] Patients having both or all events are counted once only.

The most commonly reported fatal AEs (Table 49) in the placebo and candesartan groups during study were sudden death (348, 9.2% and 291, 7.7% respectively), cardiac failure/cardiac failure aggravated (256, 6.7% and 192, 5.0% respectively) and MI (57, 1.5% and 77, 2.0% respectively).

Exploratory-Analysis: Non-CV death and non-CV hospitalization in CHARM-Added (SH-AHS-0006) Study:

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%).

Exploratory-Analysis: Non-CV death and non-CV hospitalization in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

Analyses of non-CV death and non-CV hospitalizations were specified in the SAP to assure that there were no off-setting adverse events in these areas. There were no significant differences between the candesartan group and the placebo group in non-CV mortality rates (placebo 176; 4.6%; candesartan 195; 5.1%) or non-CV hospitalization rates (placebo 1,469; 38.7%; candesartan 1,521; 40.0%).

Reviewer's Comments with data from the medical literature: In both the CHARM-Added study data and the CHARM-Pooled data, sudden death and death due to aggravated heart failure were the leading causes of death in the candesartan treated group as well as the placebo group (Table 50), being slightly less frequent in the candesartan compared to the placebo group.

Table 50 Comparison of the leading causes of death in the CHARM studies

Study	Candesartan			Placebo		
	All deaths N	Sudden death N (%)*	Aggravated heart failure N (%)*	All deaths N	Sudden death N (%)*	Aggravated heart failure N (%)*
CHARM-Added	377	143 (37.9%)	74 (19.6%)	413	174 (42.1%)	112 (27.1%)
CHARM-Pooled	887	291 (32.8%)	192 (21.6%)	947	348 (36.7%)	256 (27.0%)

* percent of all deaths in the treatment group

In the medical literature, death in heart failure trials is usually an efficacy endpoint, and most articles do not discuss deaths under safety. In the only article that describes death under safety, ELITE[19], the primary efficacy endpoint was renal dysfunction, and a composite of death and/or hospitalization was a secondary endpoint. Of 722 patients with NYHA Class II-IV heart failure enrolled, 65 (18.5%) of the losartan-treated patients died or discontinued treatment compared to 111 (30%) captopril-treated patients ($P<0.001$). In that study, sudden death was the leading cause of death in the captopril-treated group (14 patients, 3.8%) compared to the losartan-treated group (5 patients (1.5%). Progressive heart failure was the cause of death for only 1 patient in each treatment group. The efficacy findings of the ELITE study were not supported by the bigger ELITE II trial[20].

7.1.2 Other Serious Adverse Events

Serious adverse events other than deaths in CHARM-Added (SH-AHS-0006) Study:

The most commonly reported non-fatal SAEs 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%) in the placebo group, and cardiac failure/cardiac failure aggravated (398, 31.2%), angina pectoris/ angina pectoris aggravated (148, 11.6%) and hypotension (143, 11.2%) in the candesartan group (Table 51).

Table 51 Number (%) of patients with the most commonly reported[a] SAEs other than death, sorted by descending frequency. 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.

Serious adverse events other than deaths in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

Non-fatal SAEs were reported in 65.5% (2,487) of the patients in the placebo group during study and in 63.9% (2,432) of the patients in the candesartan group during study.

The most commonly reported non-fatal SAEs during study were cardiac failure/cardiac failure aggravated (1,118, 29.5%), angina pectoris/angina pectoris aggravated (502, 13.2%) and pneumonia (268, 7.1%) in the placebo group, and cardiac failure/cardiac failure aggravated (931, 24.5%), angina pectoris/angina pectoris aggravated (480, 12.6%) and hypotension (318, 8.4%) in the candesartan group (Table 52).

Reviewer's comments with data from the medical literature: Among the top 10 causes of non-fatal SAEs, it is noteworthy that in both the CHARM-Added and CHARM-Pooled studies, nine of these are seen more frequently in the placebo-treated group, and hypotension is the only SAE that is seen more frequently in the Candesartan-treated group (Table 51, and Table 52). In these patients with severe heart failure (and underlying renal disease in many cases) their vascular tone

and renal function depend predominantly on the activity of the RAAS. Treatment with candesartan that inhibits the RAAS would be expected to cause acute hypotension, azotemia, oliguria and, in some instances, renal failure. Symptomatic hypotension is particularly more likely to occur in CHF patients who are volume and salt depleted from use of diuretics. Hypotension is discussed in more detail later under "Adverse events of special interest."

Table 52 Number (%) of patients with symptomatic CHF with the most commonly reported[a] SAEs other than death, sorted by descending frequency. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Preferred term	Placebo on treatment (N=3796)		Cand. cil. on treatment (N=3803)		Placebo during study (N=3796)		Cand. cil. during study (N=3803)	
	N	(%)	N	(%)	N	(%)	N	(%)
Cardiac failure/cardiac failure aggravated[b]	1018	(26.8)	776	(20.4)	1118	(29.5)	931	(24.5)
Angina pectoris/angina pectoris aggravated[b]	457	(12.0)	405	(10.6)	502	(13.2)	480	(12.6)
Hypotension	184	(4.8)	291	(7.7)	212	(5.6)	318	(8.4)
Pneumonia	220	(5.8)	195	(5.1)	268	(7.1)	249	(6.5)
Fibrillation atrial	216	(5.7)	161	(4.2)	246	(6.5)	196	(5.2)
Arrhythmia ventricular	206	(5.4)	159	(4.2)	238	(6.3)	193	(5.1)
Myocardial infarction	185	(4.9)	156	(4.1)	213	(5.6)	181	(4.8)
Cerebrovascular disorder	176	(4.6)	154	(4.0)	202	(5.3)	188	(4.9)
Arrhythmia atrial	175	(4.6)	156	(4.1)	197	(5.2)	187	(4.9)
Coronary artery disorder	163	(4.3)	158	(4.2)	191	(5.0)	189	(5.0)
Chest pain	172	(4.5)	147	(3.9)	196	(5.2)	174	(4.6)
Tachycardia supraventricular	152	(4.0)	129	(3.4)	177	(4.7)	148	(3.9)
Accident and/or injury	106	(2.8)	93	(2.4)	134	(3.5)	115	(3.0)
Syncope	103	(2.7)	112	(2.9)	117	(3.1)	131	(3.4)
Anaemia	84	(2.2)	106	(2.8)	106	(2.8)	140	(3.7)
Tachycardia ventricular/arrhythmia/arrhythmia aggravated[b]	105	(2.8)	94	(2.5)	126	(3.3)	119	(3.1)

a The table uses a cut-off of ≥3.0% in the total population during study (N=7599).

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

7.1.3 Discontinuations and Other Significant Adverse Events

Permanent discontinuations presented descriptively 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. (All patients who died are included in the section on "deaths.") However, if the investigational product was permanently discontinued, the patient still remained in the study and SAEs were reported during the whole study period. Because of the difference in the definitions of permanent discontinuations in the descriptive and exploratory analyses, there were small differences in the number of patients between the two analyses.

7.1.3.1 Overall profile of discontinuations

Discontinuations due to adverse events in CHARM-Added (SH-AHS-0006) Study:

The study medication 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.

Discontinuations due to adverse events in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

The investigational product was permanently discontinued due to AEs in 613 (16.1%) patients in the placebo group and in 799 (21.0%) patients in the candesartan group.

Thus, discontinuation of study medication due to AEs was more frequent in the candesartan group in both the CHARM-Added and CHARM-Pooled studies.

7.1.3.2 Adverse events associated with discontinuations

Discontinuations due to adverse events in CHARM-Added (SH-AHS-0006) Study:

The most common AEs leading to discontinuation of investigational product are presented in Table 53. 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%).

Table 53 Number (%) of patients with the most commonly reported[a] AEs leading to discontinuation of investigational product, sorted by descending frequency. 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.

Discontinuations due to adverse events in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

In this descriptive presentation of data, the most common AEs leading to discontinuation of the investigational product are presented in Table 54. The most commonly reported AEs leading to discontinuation of the investigational product in the placebo group in the total population were cardiac failure/cardiac failure aggravated (186, 4.9%), renal function abnormal/renal dysfunction aggravated (110, 2.9%) and hypotension (76, 2.0%). The most commonly reported AEs leading to discontinuation in the candesartan group were renal function abnormal/renal dysfunction

aggravated (238, 6.3%), cardiac failure/ cardiac failure aggravated (165, 4.3%) and hypotension (155, 4.1%).

Table 54 Number (%) of patients with symptomatic CHF with the most commonly reported[a] AEs leading to discontinuation of the investigational product, sorted by descending frequency. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Preferred term	Placebo on treatment (N=3796)		Cand.cil. on treatment (N=3803)	
	N	(%)	N	(%)
Cardiac failure/cardiac failure aggravated[b]	186	(4.9)	165	(4.3)
Renal function abnormal/renal dysfunction aggravated[b]	110	(2.9)	238	(6.3)
Hypotension	76	(2.0)	155	(4.1)
Hyperkalaemia	22	(0.6)	93	(2.4)
Myocardial infarction	31	(0.8)	26	(0.7)
Cerebrovascular disorder	28	(0.7)	27	(0.7)
Renal failure acute	20	(0.5)	33	(0.9)
Angina pectoris/angina pectoris aggravated[b]	20	(0.5)	30	(0.8)
Dizziness/vertigo	14	(0.4)	32	(0.8)
Pneumonia	22	(0.6)	21	(0.6)
Diarrhoea	10	(0.3)	28	(0.7)
Renal failure nos	13	(0.3)	22	(0.6)

a The table uses a cut-off of ≥0.5% in the total population on treatment (N=7599).
b Patients having both or all events are counted once only.

Reviewer's comment with data from the literature: Worsening heart failure as the leading cause of discontinuation of study drug is not limited to candesartan (or ARBs). In the Assessment of Treatment with Lisinopril And Survival (ATLAS) trial[12], too, worsening heart failure, dizziness, hypotension and worsening renal function were the leading causes AEs requiring withdrawal of study drug which is an ACE-inhibitor (Table 55).

Table 55 AEs in relation to withdrawal of study drug in ATLAS trial[12] (Based on data from Circulation 1999; 100: 2312-8.)

	Patients With Adverse Experience		Patients Requiring Withdrawal of Study Drug	
	Low-Dose (n=1596)	High-Dose (n=1568)	Low-Dose (n=1596)	High-Dose (n=1568)
Worsening heart failure	709 (44)	594 (38)	76 (4.8)	62 (4.0)
Dizziness	193 (12)	297 (19)	0 (0.0)	5 (0.3)
Hypotension	107 (7)	169 (11)	10 (0.6)	13 (0.8)
Worsening renal function	112 (7)	155 (10)	6 (0.4)	5 (0.3)
Cough	211 (13)	166 (11)	14 (0.9)	14 (0.9)
Hyperkalemia	56 (4)	100 (6)	1 (0.1)	6 (0.4)
Hypokalemia	53 (3)	22 (1)	0 (0.0)	0 (0.0)

Values in parentheses indicate percentage.

Exploratory-Analysis: Discontinuation of the investigational product in CHARM-Added (SH-AHS-0006) Study:

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 ($P< 0.001$) and the difference in proportions between treatments of 6.0% ($P< 0.001$) were statistically significant (Table 56, Table 57 and Figure 21).

Table 56 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 57 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

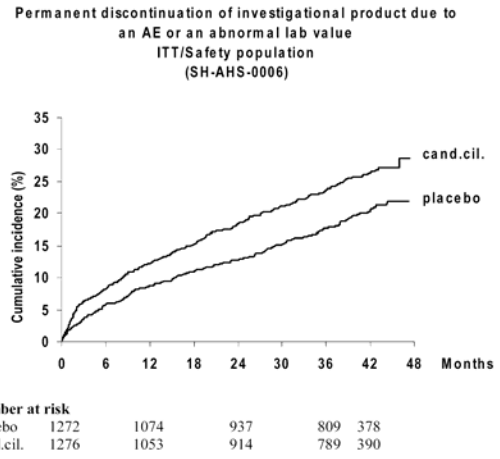


Figure 21 Cumulative incidence (%) of permanent discontinuation of investigational product due to an AE or an abnormal laboratory value. ITT/Safety population

Specific causes of investigational product discontinuation are noted in Table 58. 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 entire study population was characteristic of the relative discontinuation rates across most sub-groups including concomitant medication with ACE-inhibitors, β-blockers and spironolactone.

Table 58 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. 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

Exploratory-Analysis: Discontinuation of the investigational product in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

As specified in the SAP, dose reductions and permanent discontinuations of the investigational product were analyzed both descriptively as a part of the standard safety evaluation and exploratory, using statistical methods.

Because of the difference in the definitions there were small differences in the number of patients between the two analyses. Patients may be included in the descriptive safety analyses but not in the exploratory safety analyses or vice versa. In the placebo treatment group 52 patients were included in the descriptive analysis but not in the exploratory ones and inversely 72 patients were only found in the exploratory analyses. In the candesartan treatment group 71 patients were included in the descriptive analysis only while 70 patients appeared in the exploratory analyses but not in the descriptive results. A patient could have more than one AE, leading to permanent discontinuation of the investigational product, occurring at the same time.

The preferred term "renal function abnormal" used in the descriptive safety analysis and the term "increased creatinine," used in this section refer to 'Abnormal renal function (e.g., creatinine increased)' pre-specified in the CRF.

In this exploratory presentation of data permanent discontinuation of the investigational product due to an AE or abnormal lab value occurred in 633 (16.7%) patients in the placebo group and 798 (21.0%) patients in the candesartan group. Both the difference in time to event (P< 0.001) (Table 59, Table 60and Figure 22) and the difference in proportions between treatments of 4.3% (P< 0.001) (Table 70 and Table 71) were statistically significant.

Table 59 Exploratory safety variables for patients with symptomatic 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-0003, -0006, -0007)

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	3791	969	9355.9	103.6	2.5
	cand.cil.	3788	1135	9177.0	123.7	2.4
Permanent investigational product discontinuation due to an AE or an abnormal lab value	Placebo	3796	633	9937.0	63.7	2.6
	cand.cil.	3803	798	9807.1	81.4	2.6
At least one investigational product discontinuation due to any cause	Placebo	3790	1571	8431.3	186.3	2.2
	cand.cil.	3788	1780	7951.8	223.8	2.1
At least one investigational product discontinuation due to an AE or an abnormal lab value	Placebo	3796	1198	9189.4	130.4	2.4
	cand.cil.	3803	1432	8708.2	164.4	2.3

Table 60 Exploratory safety variables for patients with symptomatic CHF. Comparison of candesartan versus placebo with Logrank test. ITT/Safety population. (SH-AHS-0003, -0006, -0007)

Variable	N	Events cand. cil.	Events placebo	Hazard Ratio	95% CI		p-value
					Lower	Upper	
Permanent investigational product discontinuation due to any cause	7599	1135	969	1.179	1.081	1.285	<0.001
Permanent investigational product discontinuation due to an AE or an abnormal lab value	7599	798	633	1.273	1.147	1.413	<0.001
At least one investigational product discontinuation due to any cause	7599	1780	1571	1.183	1.105	1.267	<0.001
At least one investigational product discontinuation due to an AE or an abnormal lab value	7599	1432	1198	1.249	1.157	1.349	<0.001

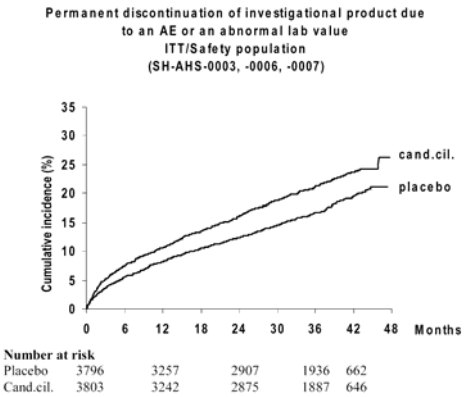


Figure 22 Cumulative incidence (%) of permanent discontinuation of the investigational product due to an AE or an abnormal laboratory value. ITT/Safety population

Specific causes of investigational product discontinuation are shown in Table 61, Table 62, Table 63 and Table 64. Hypotension, hyperkalemia and increased creatinine as causes for the investigational product discontinuation were statistically significantly more frequent for candesartan compared to placebo, being 1.7%, 1.7% and 3.1%, respectively.

Table 61 Exploratory safety variables for patients with symptomatic CHF. The proportions of patients (%) with an event. ITT/Safety population. (SH-AHS-0003, -0006, -0007)

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	3796	969	25.5	24.1	26.9
	cand.cil.	3803	1135	29.8	28.4	31.3
Permanent investigational product discontinuation due to an AE or an abnormal lab value	Placebo	3796	633	16.7	15.5	17.9
	cand.cil.	3803	798	21.0	19.7	22.3
Permanent investigational product discontinuation due to hypotension	Placebo	3796	66	1.7	1.3	2.2
	cand.cil.	3803	132	3.5	2.9	4.1
Permanent investigational product discontinuation due to hyperkalaemia	Placebo	3796	21	0.6	0.3	0.8
	cand.cil.	3803	85	2.2	1.8	2.8
Permanent investigational product discontinuation due to increased creatinine	Placebo	3796	115	3.0	2.5	3.6
	cand.cil.	3803	234	6.2	5.4	7.0
At least one investigational product discontinuation due to any cause	Placebo	3796	1571	41.4	39.8	43.0
	cand.cil.	3803	1780	46.8	45.2	48.4
At least one investigational product discontinuation due to an AE or an abnormal lab value	Placebo	3796	1198	31.6	30.1	33.1
	cand.cil.	3803	1432	37.7	36.1	39.2
At least one investigational product discontinuation due to hypotension	Placebo	3796	127	3.3	2.8	4.0
	cand.cil.	3803	274	7.2	6.4	8.1
At least one investigational product discontinuation due to hyperkalaemia	Placebo	3796	42	1.1	0.8	1.5
	cand.cil.	3803	149	3.9	3.3	4.6
At least one investigational product discontinuation due to Increased creatinine	Placebo	3796	182	4.8	4.1	5.5
	cand.cil.	3803	374	9.8	8.9	10.8
Decreased investigational product dose due to any cause at least once	Placebo	3796	482	12.7	11.7	13.8
	cand.cil.	3803	791	20.8	19.5	22.1
Decreased investigational product dose due to an AE or an abnormal lab value at least once	Placebo	3796	385	10.1	9.2	11.1
	cand.cil.	3803	693	18.2	17.0	19.5

Table 62 Exploratory safety variables for patients with symptomatic CHF. The difference in proportion (%) between treatments. Chi- square test. ITT/ Safety population. (SH-AHS-0003, -0006, -0007)

Variable	Difference in proportion between treatments	95% CI		p-value
	Cand.cil. - Placebo	Lower	Upper	
Permanent investigational product discontinuation due to any cause	4.3	2.3	6.3	<0.001
Permanent investigational product discontinuation due to an AE or an abnormal lab value	4.3	2.6	6.1	<0.001
Permanent investigational product discontinuation due to hypotension	1.7	1.0	2.4	<0.001
Permanent investigational product discontinuation due to hyperkalaemia	1.7	1.2	2.2	<0.001
Permanent investigational product discontinuation due to Increased creatinine	3.1	2.2	4.1	<0.001
At least one investigational product discontinuation due to any cause	5.4	3.2	7.6	<0.001
At least one investigational product discontinuation due to an AE or an abnormal lab value	6.1	4.0	8.2	<0.001
At least one investigational product discontinuation due to hypotension	3.9	2.9	4.9	<0.001
At least one investigational product discontinuation due to hyperkalaemia	2.8	2.1	3.5	<0.001
At least one investigational product discontinuation due to Increased creatinine	5.0	3.9	6.2	<0.001
Decreased investigational product dose due to any cause at least once	8.1	6.4	9.8	<0.001
Decreased investigational product dose due to an AE or an abnormal lab value at least once	8.1	6.5	9.6	<0.001

Table 63 Exploratory safety variables. Comparison of candesartan cilexetil versus placebo with Cox regression test with 33 pre-specified baseline factors as covariates for the total population. ITT/Safety Population. (SH-AHS-0003, -0006, -0007)

Variable	N	Events cand. cil.	Events plac-ebo	Hazard Ratio	95% CI		p-value
					Lower	Upper	
Permanent Investigational product discontinuation due to any cause	7599	1135	969	1.176	1.078	1.283	<0.001
Permanent Investigational product discontinuation due to an AE or an abnormal lab value	7599	798	633	1.272	1.146	1.413	<0.001
At least one Investigational product discontinuation due to any cause	7599	1780	1571	1.188	1.110	1.273	<0.001
At least one Investigational product discontinuation due to an AE or an abnormal lab value	7599	1432	1198	1.255	1.162	1.356	<0.001

Table 64 Exploratory safety variables. Comparison of candesartan cilexetil versus placebo with Cox regression with 33 pre-specified baseline factors as covariates for the subpopulation. ITT/Safety Population. (SH-AHS-0003, -0006)

Variable	N	Events cand. cil.	Events plac-ebo	Hazard Ratio	95% CI		p-value
					Lower	Upper	
Permanent Investigational product discontinuation due to any cause	4576	719	614	1.190	1.068	1.327	0.002
Permanent Investigational product discontinuation due to an AE or an abnormal lab value	4576	528	429	1.251	1.101	1.423	<0.001
At least one Investigational product discontinuation due to any cause	4576	1126	990	1.202	1.103	1.310	<0.001
At least one Investigational product discontinuation due to an AE or an abnormal lab value	4576	937	797	1.243	1.130	1.367	<0.001

Investigational product discontinuation due to an AE or lab abnormality was also examined as an endpoint across the array of subgroups. There was an approximate 1.3 fold excess risk for candesartan discontinuation relative to placebo for the entire study population which was characteristic of the relative discontinuation rates across most subgroups including concomitant medication with ACE-inhibitors, β-blockers and spironolactone.

For patients with a history of diabetes, there was a higher frequency of discontinuation of the investigational product caused by hypotension, hyperkalemia or increased serum creatinine (Table 65 and Table 66), which is an expected finding in these diabetics with possible underlying renal dysfunction and autonomic dysregulation.

Table 65 Discontinuation of investigational product due to hypertension, hyperkalemia and increased creatinine in patients with a history of diabetes for the total population. The proportions of patients (%) with an event. ITT/Safety Population. (SH-AHS-0003, -0006, -0007)

Variable	Treat-ment	N	Number of patients with event	Proportion of patients with event	95% CI	
					Lower	Upper
Permanent Investigational product discontinuation due to Hypotension	placebo	1075	22	2.0	1.3	3.1
	cand.cil.	1088	34	3.1	2.2	4.3
Permanent Investigational product discontinuation due to Hyperkalaemia	placebo	1075	13	1.2	0.6	2.1
	cand.cil.	1088	31	2.8	1.9	4.0
Permanent Investigational product discontinuation due to Increased Creatinine	placebo	1075	57	5.3	4.0	6.8
	cand.cil.	1088	99	9.1	7.5	11.0
At least one Investigational product discontinuation due to Hypotension	placebo	1075	38	3.5	2.5	4.8
	cand.cil.	1088	68	6.3	4.9	7.9
At least one Investigational product discontinuation due to Hyperkalaemia	placebo	1075	23	2.1	1.4	3.2
	cand.cil.	1088	63	5.8	4.5	7.3
At least one Investigational product discontinuation due to Increased Creatinine	placebo	1075	86	8.0	6.4	9.8
	cand.cil.	1088	149	13.7	11.7	15.9

Table 66 Permanent discontinuation of investigational product in patients with a history of diabetes for the total population. The difference in proportion (%) between treatments. Chi square test. ITT/Safety Population (SH-AHS-0003, -0006, -0007)

Variable	Difference in proportion between treatments Cand.cil.-placebo	95% CI		p-value
		Lower	Upper	
Permanent Investigational product discontinuation due to Hypotension	1.1	-0.3	2.4	0.114
Permanent Investigational product discontinuation due to Hyperkalaemia	1.6	0.5	2.8	0.007
Permanent Investigational product discontinuation due to Increased Creatinine	3.8	1.6	6.0	<0.001
At least one Investigational product discontinuation due to Hypotension	2.7	0.9	4.5	0.003
At least one Investigational product discontinuation due to Hyperkalaemia	3.7	2.0	5.3	<0.001
At least one Investigational product discontinuation due to Increased Creatinine	5.7	3.1	8.3	<0.001

Reviewer's comments with data from the medical literature: Adverse events from ARBs in the treatment of patients with CHF appear to lead to more frequent discontinuation of the ARBs (as a class) than placebo. In the Val-HeFT[16] study of valsartan in chronic heart failure, adverse events leading to the discontinuation of the drug occurred in 249 (9.9%) patients receiving valsartan

versus 181 (7.2%) patients receiving placebo (P < 0.001). The adverse events leading to discontinuation and occurring in >1% of the patients in the valsartan and placebo groups included dizziness (1.6% and 0.4% respectively, P < 0.001), hypotension (1.3% and 0.8% respectively, P = 0.124), and renal impairment (1.1% and 0.2% respectively, P < 0.001).

Also, in the VALIANT trial[25] comparing valsartan, captopril or both in MI complicated by heart failure, LV dysfunction or both, adverse events resulting in permanent discontinuation of study treatment are significantly (P<0.05) more frequent in the Valsartan-plus-captopril group compared to the Valsartan-alone or captopril-alone treatment group (Table 67). Also, dose reductions and permanent discontinuations of study drug for hypotension and renal causes were more frequent in the valsartan-plus-captopril and valsartan-alone groups (Table 67).

Table 67 Adverse Events leading to dose reduction or discontinuation of study treatment in VALIANT trial[25] (Based on data from N Engl J Med 2003; 349: 1893-1906.)

Cause	Resulting in Dose Reduction			Resulting in Permanent Discontinuation of Study Treatment		
	Valsartan Group (N=4885)	Valsartan-and-Captopril Group (N=4862)	Captopril Group (N=4879)	Valsartan Group (N=4885)	Valsartan-and-Captopril Group (N=4862)	Captopril Group (N=4879)
	number (percent)					
Hypotension	739 (15.1)*	884 (18.2)*	582 (11.9)	70 (1.4)*	90 (1.9)*	41 (0.8)
Renal causes	239 (4.9)*	232 (4.8)*	148 (3.0)	53 (1.1)	61 (1.3)*	40 (0.8)
Hyperkalemia	62 (1.3)	57 (1.2)	43 (0.9)	7 (0.1)	12 (0.2)	4 (0.1)
Cough	85 (1.7)*	225 (4.6)	245 (5.0)	30 (0.6)*	101 (2.1)	122 (2.5)
Rash	32 (0.7)*	53 (1.1)	61 (1.3)	17 (0.3)*	34 (0.7)	39 (0.8)
Taste disturbance	13 (0.3)*	38 (0.8)	31 (0.6)	9 (0.2)*	16 (0.3)	21 (0.4)
Angioedema	12 (0.2)	22 (0.5)	22 (0.5)	9 (0.2)	12 (0.2)	13 (0.3)
Any of the above events†	1112 (22.8)	1404 (28.9)*	1063 (21.8)	197 (4.0)*	332 (6.8)*	280 (5.7)
Any adverse event	1437 (29.4)	1690 (34.8)*	1388 (28.4)	282 (5.8)*	438 (9.0)*	375 (7.7)
Any reason	2103 (43.1)	2342 (48.2)*	2098 (43.0)	1001 (20.5)	1139 (23.4)*	1055 (21.6)

* The difference from the captopril group is significant at P<0.05.
† The totals of the numbers of patients with each type of event are greater than the numbers given for "any of the above events" because in some patients more than one type of event contributed to the decision to reduce the dose or discontinue study treatment.

Table 68 Adverse events causing discontinuation in the OPTIMAAL trial[22] (Based on data from Lancet 2002; 360: 752-60.)

	Losartan	Captopril	p
Prespecified events of special interest			
Angio-oedema	10 (0·4%)	22 (0·8%)	0·034
Cough	256 (9·3%)	512 (18·7%)	<0·0001
Hypotension	365 (13·3%)	445 (16·3%)	0·002
Skin rash	86 (3·1%)	126 (4·6%)	0·005
Taste disturbance	16 (0·6%)	73 (2·7%)	<0·0001
Congestive heart failure	401 (14·6%)	383 (14·0%)	0·537
Events causing discontinuation*			
Cough	28 (1·0%)	113 (4·1%)	<0·0001
Hypotension	47 (1·7%)	61 (2·2%)	0·17
Skin rash	3 (0·1%)	18 (0·7%)	0·0008
Dizziness	12 (0·4%)	17 (0·6%)	0·36
Taste disturbance	1 (0·0%)	17 (0·6%)	<0·0001
Angio-oedema	4 (0·1%)	14 (0·5%)	0·019

Information on adverse events was collected during the double-blind treatment period and for 14 days afterwards. Within any category of adverse event, patients could be counted only once, but could be represented more than once across multiple categories of adverse event. *Minimum of 14 patients (0·5%) in either treatment group.

However, in the OPTIMAAL trial[22], comparing losartan to captopril on mortality and morbidity in patients with AMI and evidence of heart failure or left ventricular dysfunction, fewer patients on losartan discontinued study medication for any reason (458 patients (17%) on losartan versus 624 (23%) on captopril, HR = 0.70, 95% CI 0.62-0.79, P <0.0001) or for adverse events (202 patients (7%) on losartan versus 387 patients (14%) on captopril; HR = 0.50; 95% CI 0.42-0.59; P < 0.0001), particularly for AEs such as cough, skin rash, taste disturbance and angioedema (Table 68).

Background treatment with ACE-inhibitors may also be the reason for a high frequency of discontinuation. In the SMILE trial[60] (survival from MI long-term evaluation) of zofenopril versus placebo on mortality and morbidity after AMI in Italy, 6.8% of patients in the placebo group and 8.6% of patients in the zofenopril group discontinued treatment permanently; the main reason was symptomatic or severe hypotension.

β-blockers in the treatment of CHF are associated *less* frequently than placebo with permanent discontinuation. In the COPERNICUS Study[37] of carvedilol on survival in severe chronic heart failure, fewer patients in the carvedilol group than in the placebo group required permanent discontinuation of treatment because of adverse events (P=0.02). The Kaplan-Meier analysis (Figure 23) shows that the cumulative discontinuation rates at one year for the total cohort were 18.5% in the placebo group and 14.8% in the carvedilol groups. The discontinuation rates for patients with recent or recurrent cardiac decompensation or severely depressed cardiac function were 24.2% in the placebo group and 17.5% in the carvedilol group.

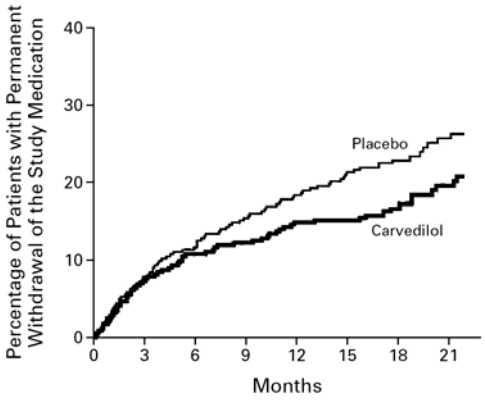


Figure 23 Kaplan–Meier Analysis of the time to permanent withdrawal of the study medication because of adverse reactions or for reasons other than death in placebo and Carvedilol groups in COPERNICUS trial[37]. The risk of withdrawal was 23% lower in the carvedilol group (95% CI: 4% – 38%; P= 0.02). (Based on data from Engl J Med 2001; 344: 1651-8.)

However, when an ARB is compared head-to-head with a β-blocker, as in the LIFE study[23] comparing losartan versus atenolol in patients with hypertension and ECG evidence of LVH, discontinuations as a result of all AEs, drug-related AEs, and SAEs and drug-related SAEs were significantly less in losartan-treated patients than atenolol-treated patients (Figure 24).

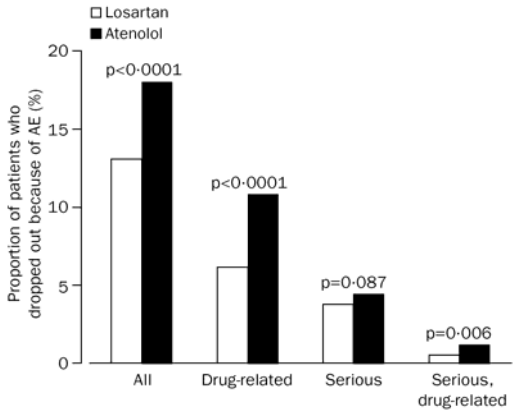


Figure 24 Adverse events resulting in discontinuation of study drug in LIFE study[23] (Based on data from Lancet 2002; 359: 995-1003.)

7.1.3.3 Other significant adverse events (Dose reduction due to adverse events)

The protocol specifies that dose reductions and permanent discontinuations of the investigational product will be analyzed both descriptively as a part of the standard safety evaluation and exploratory evaluation using statistical methods.

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 analysis, 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.

Dose reduction due to adverse events in CHARM-Added (SH-AHS-0006) Study:

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 69.

Table 69 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.

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%).

Dose reduction due to adverse events in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

The dose of the investigational product was reduced due to AEs in 324 (8.5%) patients in the placebo group and in 569 (15.0%) patients in the candesartan group. The most commonly reported AEs leading to dose reduction were hypotension (136, 3.6%), renal function abnormal/renal dysfunction aggravated (0, 1.3%) and dizziness/vertigo (38, 1.0%) in the placebo group, and hypotension (315, 8.3%), renal function abnormal/renal dysfunction aggravated (99, 2.6%) and hyperkalemia (60, 1.6%) in the candesartan group (Table 70).

Table 70 Number (%) of patients with symptomatic CHF with the most commonly reported[a] AEs leading to dose reduction of the investigational product, sorted by descending frequency in the total population on treatment. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Preferred term	Placebo on treatment (N=3796)		Cand. cil. on treatment (N=3803)	
	N	(%)	N	(%)
Hypotension	136	(3.6)	315	(8.3)
Renal function abnormal/renal dysfunction aggravated[b]	50	(1.3)	99	(2.6)
Dizziness/vertigo[b]	38	(1.0)	54	(1.4)
Hyperkalaemia	17	(0.4)	60	(1.6)
Cardiac failure aggravated	29	(0.8)	30	(0.8)
Fatigue	13	(0.3)	24	(0.6)
Nausea	14	(0.4)	15	(0.4)
Dyspnoea/dyspnoea (aggravated)[b]	17	(0.4)	8	(0.2)
Diarrhoea	10	(0.3)	9	(0.2)

a The table uses a cut-off of ≥0.3% in the total population on treatment (N=7599).

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

Exploratory-Analysis: Dose reduction of the investigational product in CHARM-Added (SH-AHS-0006) Study:

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 58). This between-treatment difference in dose reductions for an AE of 8.8% (Table 58) was statistically significant (P< 0.001). As shown in Figure 25 the majority of events occurred during the first 6 to 12 months of treatment with the investigational product.

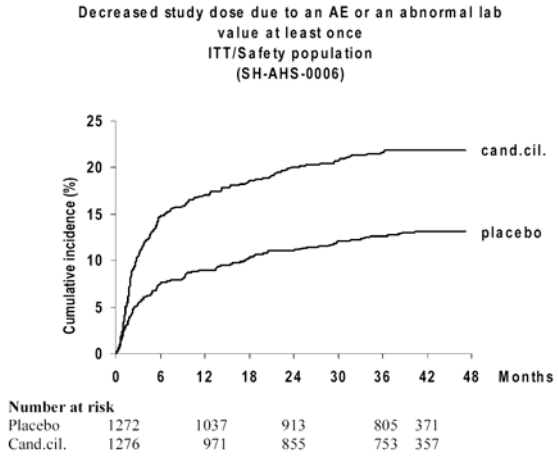


Figure 25 Cumulative incidence (%) of first occurrence of dose decrease of investigational product due to an AE or an abnormal laboratory value. ITT/Safety population

Exploratory-Analysis: Dose reduction of the investigational product in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

A higher frequency of dose reduction is presented in the exploratory safety analysis which is due to the fact that patients experiencing both dose reduction and later permanent discontinuation for the same reason are counted once in each category in the exploratory analysis. In the descriptive safety analysis above these patients are only included in the discontinuation category.

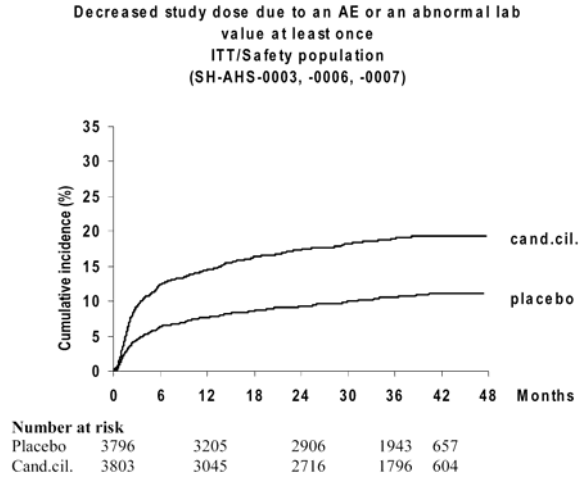


Figure 26 Cumulative incidence (%) of dose reduction of the investigational product due to an AE or an abnormal laboratory value. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Dose reduction of the investigational product due to an AE or abnormal lab value occurred in 385 (10.1%) patients in the placebo group and 693 (18.2%) patients in the candesartan group (Table 61). This between-treatment difference in dose reductions for an AE of 8.1% was statistically significant ($P < 0.001$), (Table 62). As shown in Figure 26, the majority of events occurred during the first 6 to 12 months of treatment with the investigational product.

7.1.4 Common Adverse Events

Adverse events (AEs) collected during the component studies in the total population (SH-AHS-0003, SH-AHS-0006 and SH-AHS-0007) are described depending on whether they were reported during treatment with the investigational product (referred to as "on treatment" in tables) or reported over the entire study period (referred to as "during study"). AEs during study include all AEs reported for each patient, i.e., those reported on treatment as well as any new-onset AEs during the period following discontinuation of the study drug and new-onset SAEs after the patient completed or withdrew from a component study. AEs are organized according to the AAED preferred term level, i.e., AEs of a similar kind share the same preferred term.

7.1.4.1 Appropriateness of adverse event categorization and preferred terms

Categories of adverse events in CHARM-Added (SH-AHS-0006) Study:

AEs were reported by 992 (78.0%) patients randomized to placebo, and by 1,026 (80.4%) patients randomized to candesartan during study. In the placebo group 413 (32.5%) patients had fatal SAEs and 870 (68.4%) patients experienced non-fatal SAEs, compared with the candesartan group where 377 (29.5%) patients had fatal SAEs and 874 (68.5%) patients had non-fatal SAEs. As mentioned in section 7.1.3.2, the investigational product was prematurely discontinued due to AEs for 224 (17.6%) patients in the placebo group and for 310 (24.3%) patients in the candesartan group. The investigational product was reduced in dose due to AEs for 123 (9.7%) patients in the placebo group and for 220 (17.2%) patients in the candesartan group. A summary of adverse events by category is presented in Table 71.

Table 71 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.

Categories of adverse events in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

During study, in the total population AEs were reported by 2,799 (73.7%) patients randomized to placebo, and by 2,841 (74.7%) patients randomized to candesartan. In the placebo group 947 (24.9%) patients had fatal SAEs and 2,487 (65.5%) patients experienced non-fatal SAEs,

compared with the candesartan group where 887 (23.3%) patients had fatal SAEs and 2,432 (63.9%) patients had non-fatal SAEs. The investigational product was prematurely discontinued due to AEs for 613 (16.1%) patients in the placebo group and for 799 (21.0%) patients in the candesartan group. The investigational product was reduced in dose due to AEs for 324 (8.5%) patients in the placebo group and for 569 (15.0%) patients in the candesartan group. A summary of AEs by category in the total population is presented in Table 72, and for CHF patients with depressed LV function is given in Table 73.

Table 72 Number (%) of patients with symptomatic CHF with at least one adverse event in any category, and total numbers of adverse events. ITT/Safety population (SH-AHS-0003, -0006, -0007)

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=3796)		(N=3803)		(N=3796)		(N=3803)	
Any AE	2732	(72.0)	2788	(73.3)	2799	(73.7)	2841	(74.7)
Serious AEs	2562	(67.5)	2410	(63.4)	2698	(71.1)	2624	(69.0)
Serious AEs leading to death	616	(16.2)	504	(13.3)	947	(24.9)	887	(23.3)
Serious AEs not leading to death	2369	(62.4)	2246	(59.1)	2487	(65.5)	2432	(63.9)
Discontinuations of the investigational product due to AEs	613	(16.1)	799	(21.0)	-	-	-	-
Dose reductions of the investigational product due to AEs	324	(8.5)	569	(15.0)	-	-	-	-
	Total number of adverse events							
All AEs[c]	9317		9378		10814		11261	
Serious AEs[c]	8390		7730		9895		9634	

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

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

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

Table 73 Number (%) of patients who had at least one adverse event in any category, and total numbers of adverse events for the subpopulation ITT/Safety population (SH-AHS-0003, -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=2287)		(N=2289)		(N=2287)		(N=2289)	
Any AE	1703	(74.5)	1732	(75.7)	1739	(76.0)	1767	(77.2)
Serious AEs	1605	(70.2)	1506	(65.8)	1688	(73.8)	1651	(72.1)
Serious AEs leading to death	463	(20.2)	375	(16.4)	709	(31.0)	643	(28.1)
Serious AEs not leading to death	1453	(63.5)	1373	(60.0)	1524	(66.6)	1493	(65.2)
Discontinuations of investigational product due to AEs	421	(18,4)	530	(23,2)	-	-	-	-
Dose reductions of investigational product due to AEs	199	(8.7)	377	(16.5)	-	-	-	-
	Total number of adverse events							
All AEs[c]	5875		5928		6885		7123	
Serious AEs[c]	5276		4885		6291		6092	

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

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

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

7.1.4.2 Incidence of common adverse events and common adverse event tables

Most common adverse events in CHARM-Added (SH-AHS-0006) Study**:**

The most commonly reported AEs (Table 74) 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 74 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.

Most common adverse events in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

The most common AEs (Table 75) in the placebo and candesartan groups during study were cardiac failure/cardiac failure aggravated (1,187, 31.3% and 1001, 26.3% respectively), angina pectoris/angina pectoris aggravated (506, 13.3% and 490, 12.9%, respectively), hypotension (399, 10.5% and 736, 19.4% respectively) and renal function abnormal/renal dysfunction aggravated (248, 6.5% and 487, 12.8% respectively).

A similar pattern was seen in the subpopulation of patients with depressed LV systolic function.

Table 75 Number (%) of patients with symptomatic CHF with the most commonly reported[a] AEs, sorted by descending frequency in the total population during study. ITT/ Safety population (SH-AHS-0003, -0006, -0007)

Preferred term	Placebo on treatment (N=3796)		Cand. cil. on treatment (N=3803)		Placebo during study (N=3796)		Cand. cil. during study (N=3803)	
	N	(%)	N	(%)	N	(%)	N	(%)
Cardiac failure/cardiac failure aggravated[b]	1073	(28.3)	831	(21.9)	1187	(31.3)	1001	(26.3)
Hypotension	372	(9.8)	714	(18.8)	399	(10.5)	736	(19.4)
Angina pectoris/angina pectoris aggravated[b]	461	(12.1)	414	(10.9)	506	(13.3)	490	(12.9)
Renal function abnormal/renal dysfunction aggravated[b]	238	(6.3)	474	(12.5)	248	(6.5)	487	(12.8)
Sudden death	282	(7.4)	234	(6.2)	348	(9.2)	291	(7.7)
Pneumonia	243	(6.4)	200	(5.3)	299	(7.9)	261	(6.9)
Myocardial infarction	216	(5.7)	205	(5.4)	257	(6.8)	242	(6.4)
Fibrillation atrial	218	(5.7)	165	(4.3)	249	(6.6)	202	(5.3)
Arrhythmia ventricular	207	(5.5)	159	(4.2)	239	(6.3)	193	(5.1)
Cerebrovascular disorder	189	(5.0)	164	(4.3)	216	(5.7)	203	(5.3)
Coronary artery disorder	170	(4.5)	169	(4.4)	200	(5.3)	205	(5.4)
Chest pain	177	(4.7)	154	(4.0)	202	(5.3)	183	(4.8)
Arrhythmia atrial	175	(4.6)	156	(4.1)	197	(5.2)	187	(4.9)
Hyperkalaemia	78	(2.1)	238	(6.3)	84	(2.2)	242	(6.4)
Tachycardia supraventricular	152	(4.0)	129	(3.4)	177	(4.7)	148	(3.9)
Dizziness/vertigo[b]	107	(2.8)	154	(4.0)	115	(3.0)	168	(4.4)
Accident and/or injury	112	(3.0)	99	(2.6)	143	(3.8)	125	(3.3)
Tachycardia ventricular/arrhythmia/arrhythmia aggravated[b]	110	(2.9)	100	(2.6)	132	(3.5)	128	(3.4)
Syncope	105	(2.8)	121	(3.2)	119	(3.1)	139	(3.7)
Anaemia	87	(2.3)	110	(2.9)	110	(2.9)	145	(3.8)

a This table uses a cut-off of ≥3.0% in the total population during study (N=7599).

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

Reviewer's comments: For both the CHARM-Added and CHARM-Pooled study populations, the three most frequent AEs in the placebo and candesartan groups during study were cardiac failure/cardiac failure aggravated, angina pectoris/angina pectoris aggravated and hypotension. For both study populations, too, cardiac failure/cardiac failure aggravated and angina pectoris/angina pectoris aggravated were more frequent in the placebo group than in the candesartan group, whereas hypotension was more frequently reported in the candesartan group than in the placebo group.

7.1.5 Laboratory Findings

Clinical laboratory results in CHARM-Added (SH-AHS-0006) Study:

Serial laboratory data were collected from patients participating at investigational sites in North America (placebo 477 patients, candesartan 477 patients).

Changes in mean laboratory values were generally small, of minor clinical significance, and occurred primarily in parameters that previously showed changes in studies with inhibitors of the renin-angiotensin-aldosterone system (RAAS), such as creatinine and potassium.

The mean value for creatinine in the placebo group increased 13.64 μmol/L from the baseline value to the "last value carried forward (LVCF)". In the candesartan group, the LCVF increased

19.63 µmol/L. At baseline, 86 (18.5%) of placebo patients had values above the reference range compared with 83 (17.8%) patients in the candesartan group. For the LCVF that were above the upper level of normal, frequency increased in both treatment groups (placebo 140, 30.4%; candesartan 145, 32.4%). For patients who had serial measurements (placebo 447 patients, candesartan 436 patients) baseline serum creatinine was at least doubled in 27 (6.0%) patients in the placebo group, compared with 32 (7.3%) patients in the candesartan group.

For potassium, the mean value for patients treated with placebo increased 0.02 mmol/L from the baseline value to the LVCF compared with 0.12 mmol/L for patients treated with candesartan. During the study, the proportions of patients with values above the reference range increased in the placebo group (14, 3.0% at baseline, 20, 4.4% LVCF) and increased from 21 (4.5%) to 31 (6.9%) in the candesartan group. Potassium levels increased to ≥ 6 mmol/L at any time after randomization in 1.1% (5) of 459 patients valid for evaluation in the placebo group and 2.7% (12) of 447 patients in the candesartan group.

Mean sodium measurements increased 0.10 mmol/L for patients treated with placebo and decreased 0.28 mmol/L for patients in the candesartan group. The AE term hyponatremia was reported for 5 patients treated with placebo compared with 6 patients treated with candesartan.

Minor decreases were seen for mean hemoglobin values for patients treated with placebo (0.30 mmol/L) and candesartan (0.35 mmol/L). The proportion of patients with anemia reported as an AE during treatment with the investigational product was similar for placebo-treated patients (36, 2.8%) compared with candesartan-treated patients (35, 2.7%). One patient (0.2%) in each treatment group had a hemoglobin value below the defined level of abnormality (male ≤ 80 g/L (4.96 mmol/L), female ≤ 70 g/L (4.34 mmol/L)).

Glycohemoglobin A_{1c} levels decreased slightly and no major difference was seen between the placebo (-0.36%) and candesartan groups (-0.38%).

In summary, it appears that the small differences in mean laboratory values (candesartan compared with placebo) and the frequency of outliers are in keeping with the expected findings for treatment with inhibitors of the RAAS.

Clinical laboratory results in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

For the total population, serial laboratory data were collected from patients participating at investigational sites in North America (placebo 1,376 patients, candesartan 1,367 patients).

Changes in mean laboratory values were generally small, of minor clinical significance, and occurred primarily in parameters that previously showed changes in studies with inhibitors of the RAAS, such as creatinine and potassium. As a consequence of the large number of observations, some laboratory variables showed statistically significant between treatment differences, even though the absolute differences were small and may not be clinically significant.

From the results for all clinical laboratory tests in the total population, only clinical important abnormalities in the laboratory tests are presented below.

The number of patients with increase in serum creatinine ≥ 2 times from baseline, and of patients with serum potassium ≥ 6mmol/l after randomization are shown in Table 76 and Table 77 for the total CHARM-Pooled population, and in Table 78 and Table 79 for the subpopulation of CHF patients with LV dysfunction.

Table 76 Number (%) of patients with increase in serum creatinine ≥ 2 x from baseline value. ITT/Safety population (North America) (SH-AHS-0003, -0006,-0007)

Abnormal Laboratory variable	Placebo (N=1279)		Cand.cil. (N=1263)	
	N	%	N	%
Creatinine	47	3.7	82	6.5

Table 77 Number (%) of patients with serum potassium to ≥ 6 mmol/L at any time after randomization. ITT/Safety population (North America) (SH-AHS-0003, -0006,-0007)

Abnormal Laboratory variable	Placebo (N=1310)		Cand.cil. (N=1294)	
	N	%	N	%
Potassium	15	1.1	31	2.4

Table 78 Number (%) of patients with increase in serum creatinine ≥ 2 x from baseline value. ITT/Safety population (North America) (SH- AHS- 0003, -0006)

Abnormal Laboratory variable	Placebo (N=754)		Cand.cil. (N=747)	
	N	%	N	%
Creatinine	32	4.2	49	6.6

Table 79 Number (%) of patients with serum potassium to ≥ 6 mmol/L at any time after randomization. ITT/Safety population (North America) (SH-AHS-0003, -0006)

Abnormal Laboratory variable	Placebo (N=774)		Cand.cil. (N=768)	
	N	%	N	%
Potassium	9	1.2	21	2.7

The mean value for creatinine in the placebo group increased 7.7 µmol/L from the baseline value to the LVCF. In the candesartan group, the mean value increased 17.0 µmol/L. At baseline, 252 (18.8%) of placebo patients had values above the reference range compared with 251 (18.8%) of patients in the candesartan group. For the last values carried forward that were above the upper level of normal, frequency increased in both treatment groups (placebo 358, 27.3%; candesartan 399, 30.8%). For patients who had baseline value and at least one measurement after randomization (placebo 1279 patients, candesartan 1263 patients) baseline serum creatinine was

at least doubled in 47 (3.7%) patients in the placebo group, compared with 82 (6.5%) patients in the candesartan group (Table 76).

For potassium, the mean value for patients treated with placebo increased 0.02 mmol/ L from the baseline value to the LVCF compared with 0.24 mmol/L for patients treated with candesartan. The proportions of patients with values above the reference range increased from 32 (2.4%) to 44 (3.4%) in the placebo group and increased from 38 (2.8%) to 83 (6.4%) in the candesartan group. Potassium levels increased to ≅ 6 mmol/L at any time after randomization in 15 (1.1%) of 1,310 patients valid for evaluation in the placebo group and 31 (2.4%) of 1,294 patients in the candesartan group (Table 77).

AE reports of hypokalemia were rare and occurred more often in the placebo group (placebo 36, 0.9%; candesartan 16, 0.4%).

Mean sodium measurements decreased 0.07 mmol/L for patients treated with placebo and decreased 0.12 mmol/L for patients in the candesartan. The AE term hyponatremia was reported for 13 patients treated with placebo compared with 9 patients treated with candesartan.

Minor decreases were seen for mean hemoglobin values for patients treated with placebo (0.18 mmol/L) and candesartan (0.31 mmol/L). The proportion of patients with anemia reported as an AE on treatment with the investigational product was slightly lower for placebo-treated patients (87, 2.3%) compared with candesartan-treated patients (110, 2.9%). One patient in the placebo treatment group and 4 (0.3%) of 1,290 patients in the candesartan group had a hemoglobin value below the defined level of abnormality (male= 80g/L (4.96 mmol/L), female= 70g/L (4.34 mmol/L)).

Glycohemoglobin A_{1c} levels decreased slightly and no major difference was seen between the placebo (-0.31%) and candesartan groups (-0.32%).

In summary, it appears that the small differences in mean laboratory values (candesartan compared with placebo) and the frequency of critical abnormal values was in keeping with the expected findings for treatment with inhibitors of the RAAS.

Reviewer's comments with data from the medical literature: Clinical trials of ARBs in patients with CHF in the medical literature in general also reported small differences in the mean laboratory values between ARBs and the control drug. In the Losartan Intervention For Endpoint reduction (LIFE) trial[23], no significant differences are found in biochemical variables at the end of the study between losartan and atenolol treatment groups. In OPTIMAAL trial[22], too, the majority of laboratory tests showed minimal differences between losartan and captopril group except for significant (P=0.01) between-group differences detected for serum uric acid (increased by 46.6 μmol/L in losartan group vs. 60.8 μmol/L in captopril group) and serum potassium (increased by 0.19 mmol/L in losartan group vs. 0.22 mmol/L in captopril group).

7.1.6 Vital Signs

For the CHARM Program studies' safety report, vital signs consist of diastolic blood pressure

(DBP), systolic blood pressure (SBP), pulse pressure and heart rate. For physical findings, only the data for body weight are presented.

Vital signs in CHARM-Added (SH-AHS-0006) Study:

Blood pressure declined in both treatment groups. Mean DBP decreased 2.6 mmHg from the baseline value to the LVCF in the placebo group and 3.5 mmHg from the baseline value to the LVCF in the candesartan group. Corresponding values for SBP were 2.5 mmHg for patients treated with placebo and 5.0 mmHg for patients treated with candesartan. The effect on blood pressure in the candesartan group was established during the first 6 months while in the placebo group a trend towards lowering could be seen for a longer time period.

A DBP < 40 mmHg at any time during the study was reported for 32 (2.5%) patient in the placebo group and 42 (3.3%) patients in the candesartan group. 67 (5.3%) patients treated with placebo and 104 (8.2%) patients treated with candesartan had a recorded SBP < 80 mmHg at any time after randomization.

At LVCF mean heart rate was unchanged in patients in the placebo group and 0.3 bpm lower in patients in the candesartan group compared to baseline

In the placebo group, mean body weight decreased by 0.2 kg from baseline to LVCF. In the candesartan population an increase of 0.3 kg was seen.

Vital signs, physical findings and other observations related to safety in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

Changes in vital signs over time in the total population are shown in Figure 27, Figure 28, Figure 29, and Figure 30.

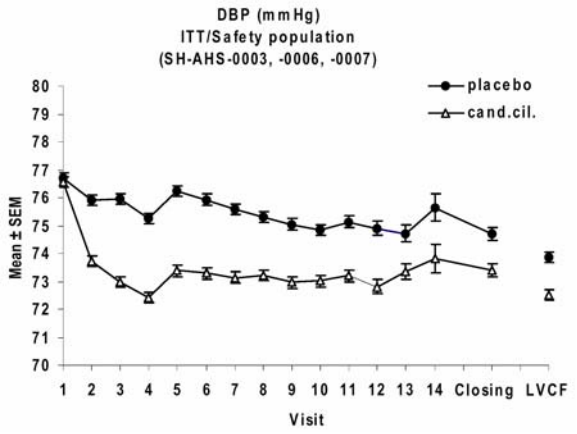


Figure 27 Mean DBP ± SEM (mmHg) by visit for the total population. ITT/Safety population

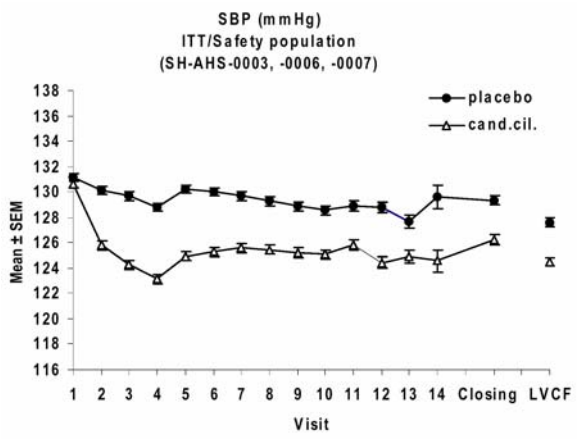


Figure 28 Mean SBP ± SEM (mmHg) by visit for the total population. ITT/Safety population

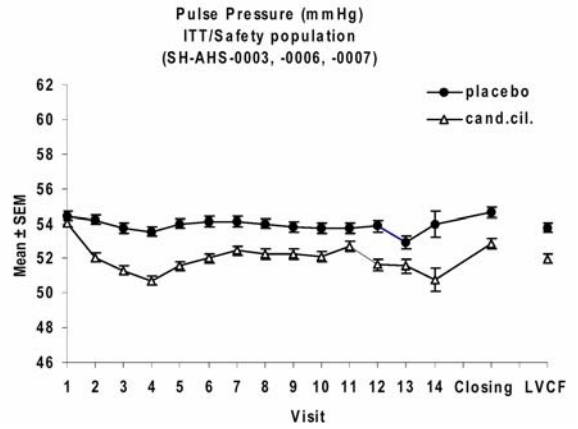


Figure 29 Mean Pulse Pressure ± SEM (mmHg) by visit for the total population. ITT/Safety population

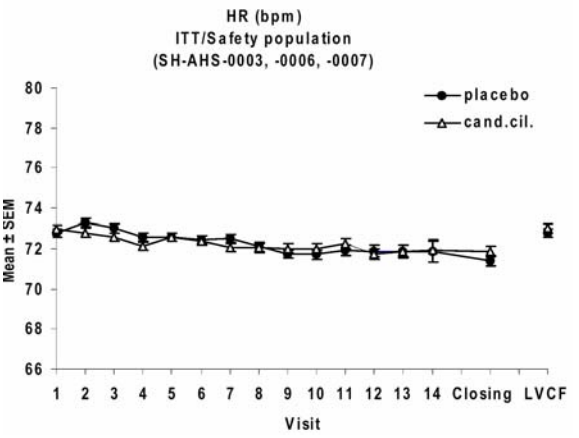


Figure 30 Mean heart rate ± SEM (bpm) by visit for the total population. ITT/Safety population

Changes in vital signs over time in the subpopulation of patients with depressed LV systolic function are shown in Figure 31, Figure 32, Figure 33 and Figure 34.

The number of patients with clinically important changes in vital signs in the total population are shown in (Table 80, Table 81 and Table 82) and the number of patients with clinically important changes in vital signs in the subpopulation of patients with depressed LV systolic function are shown in (Table 83 and Table 84).

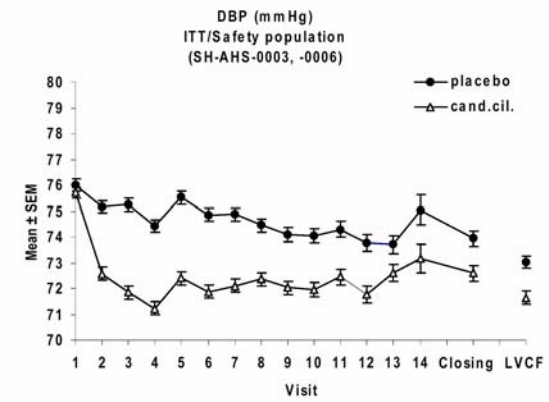


Figure 31 Mean DBP ± SEM (mmHg) by visit for the depressed LV systolic function subpopulation. ITT/Safety population

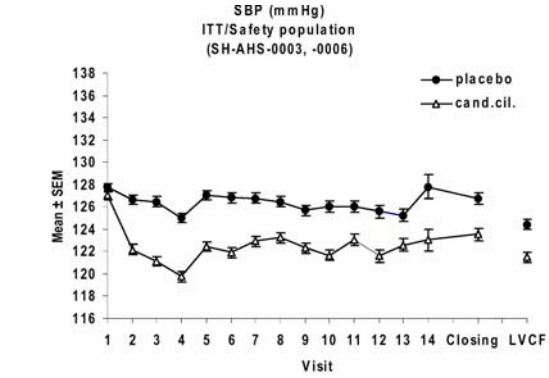


Figure 32 Mean SBP ± SEM (mmHg) by visit for the depressed LV systolic function subpopulation. ITT/Safety population

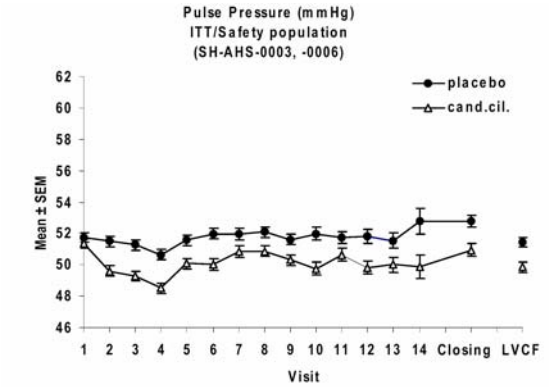


Figure 33 Mean Pulse Pressure ± SEM (mmHg) by visit for the depressed LV systolic function subpopulation. ITT/Safety population

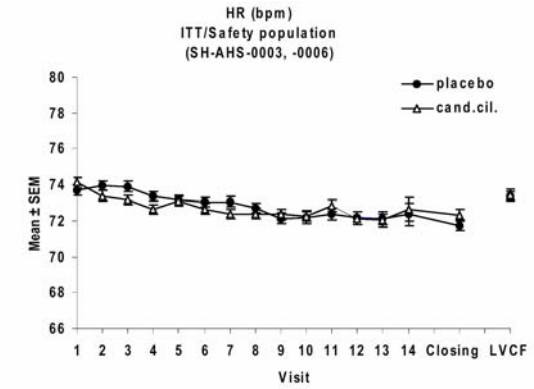


Figure 34 Mean heart rate ± SEM (bpm) by visit for the depressed LV systolic function subpopulation. ITT/Safety population

Table 80 Estimated Means and 95% CI for the change from baseline to LVCF for BP variables with Region as an ANOVA factor for the total population. ITT/Safety Population. (SH-AHS-0003, -0006, -0007)

Variable	Treat-ment	N	Estimated Mean	95% CI	
				Lower	Upper
DBP (mmHg)	placebo	3755	-2.21	-2.66	-1.75
	cand.cil.	3774	-3.66	-4.10	-3.23
SBP (mmHg)	placebo	3756	-2.69	-3.48	-1.89
	cand.cil.	3774	-5.95	-6.70	-5.19
Pulse Pressure (mmHg)	placebo	3755	-0.42	-1.05	0.21
	cand.cil.	3774	-2.22	-2.83	-1.62
Heart rate (bpm)	placebo	3756	0.22	-0.30	0.73
	cand.cil.	3773	0.37	-0.12	0.86

Table 81 Comparison for Change in BP variables with Region as an ANOVA factor for the total population. ITT/Safety Population. (SH-AHS-0003, -0006, -0007)

Variable	Comparison	Estimated Mean	95% CI		p-value
			Lower	Upper	
DBP (mmHg)	cand.cil. - placebo	-1.45	-2.08	-0.82	<0.001
SBP (mmHg)	cand.cil. - placebo	-3.26	-4.35	-2.16	<0.001
Pulse Pressure (mmHg)	cand.cil. - placebo	-1.81	-2.68	-0.93	<0.001
Heart rate (bpm)	cand.cil. - placebo	0.15	-0.56	0.86	0.680

Table 82 Number (%) of patients with decrease in SBP to ≤ 80 mm Hg or DBP to ≤40 mm Hg at any time after randomization for the total population. ITT/safety population. (SH-AHS-0003,-0006, -0007)

Abnormal Vital Sign variable	Placebo (n=3757)		Cand.cil. (n=3774)	
	N	%	N	%
DBP	50	1.3	77	2.0
SBP	109	2.9	201	5.3

Table 83 Number (%) of patients with decrease in SBP to ≤ 80 mm Hg at any time after randomization for the subpopulation. ITT/safety population. (SH-AHS-0003, -0006)

Abnormal Vital Sign variable	Placebo (n=2260)		Cand.cil. (n=2271)	
	N	%	N	%
SBP	87	3.8	158	7.0

Table 84 Number (%) of patients with decrease in DBP to ≤ 40 mm Hg at any time after randomization for the subpopulation. ITT/safety population. (SH-AHS-0003, -0006)

Abnormal Vital Sign variable	Placebo (n=2259)		Cand.cil. (n=2271)	
	N	%	N	%
DBP	37	1.6	58	2.6

Discussion of vital signs, physical findings and other observations related to safety in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

In the total population, blood pressure declined in both treatment groups. Mean DBP decreased 2.9 mmHg from the baseline value to the LVCF in the placebo group and 4.0 mmHg from the baseline value to the LVCF in the candesartan group. Corresponding values for SBP were 3.6 mmHg for patients treated with placebo and 6.1 mmHg for patients treated with candesartan.

The effect on blood pressure in the candesartan group was established during the first 6 months while in the placebo group a trend towards lowering could be seen for a longer time period. Mean heart rate was unchanged during study in both treatment groups. A DBP value less than 40 mmHg at any time during study was reported for 50 (1.4%) patient in the placebo group and 77 (2.0%) patients in the candesartan group. 109 (2.9%) patients treated with placebo and 201 (5.3%) patients treated with candesartan had a recorded SBP value less than 80 mmHg at any time after randomization (Table 82).

In the placebo group, mean body weight decreased by 0.4 kg from baseline to LVCF. In the candesartan population an increase of 0.3 kg was seen.

7.1.7 Overdose Experience

In case reports of overdose (up to 672 mg of candesartan), patient recovery was uneventful. The main manifestation of overdose is symptomatic hypotension and dizziness, which may require placing the patient supine, elevation of legs and, if required, infusion of isotonic saline solution and, sympathomimetic drugs. Candesartan is not removed by hemodialysis.

7.1.8 Postmarketing Experience

The sponsor submits that candesartan has been available in worldwide markets for the treatment of hypertension since 1997. The majority of patients have been treated with 8 to 16 mg dose of candesartan. Since its first approval for treatment of hypertension in 1997, the approved once/day doses of 2 to 32 mg candesartan are available in 84 countries including the United States. In Canada, a 32-mg dose in hypertension was approved in 2002. In 1998, the fixed-dose tablets of candesartan and hydrochlorothiazide was first approved; this formulation is now approved in 56 countries.

During the post marketing period, no unexpected organ-specific toxicity has been reported. Rarely reported reactions include leucopenia, neutropenia, agranulocytosis, hyperkalemia, hyponatremia, increased liver enzymes, abnormal liver function or hepatitis, angioedema, rash, urticaria, pruritus, and renal impairment including renal failure.

7.2 Adequacy of Patient Exposure and Safety Assessments

Please also see section 5.3.1 of the review (Total exposure of candesartan). The sponsor submits that the cumulative exposure to candesartan as of October 2003 exceeds 14 million patient-years.

For this NDA submission, the three pivotal (CHARM Program) efficacy trials comprise 7,601 patients (7,599 patients with data) with NYHA Class II – IV heart failure of at least 4 weeks duration who were randomized to candesartan (titrated from 4 mg or 8 mg once daily to a target dose of 32 mg once daily as tolerated) or matching placebo, and followed for at least 2 (up to 4) years. The sponsor estimated that the exposure to the investigational product totaled 18,593 patient-years, and exposure to candesartan 9,222 patient-years.

In addition to the 7,601 CHF patients in the CHARM Program clinical trials, the sponsor submitted 24 clinical studies (comprising 4,062 patients with CHF) including:

(i) 5 randomized, double-blind, placebo-controlled clinical trials with duration of 2 to 12 months, comprising a total of 1,893 patients,

(ii) one randomized, double-blind, active-treatment (enalapril)-controlled study (RESOLVD) comprising 768 patients, and

(iii) one open, uncontrolled, long-term (6 month) study comprising 355 patients,

(iv) 3 clinical pharmacology studies comprising 262 patients,

(v) 11 clinical studies comprising a total of 677 patients under the Japanese study program (for which FDA granted the sponsor a waiver from providing case report tabulations and case report forms, and 10 studies were pertinent to efficacy), and

(vi) 4 investigator-initiated clinical studies comprising 107 patients.

Thus, a total of 11,661 patients with CHF have been exposed to candesartan in the treatment of CHF in various clinical trials. About one third of these patients were women, and about 15% (1,736) were 75 years or older. About 90% of the population was Caucasian (white) and 326 patients (2.8%) were black. It appears that a representative population of patients with symptomatic CHF has been exposed to candesartan.

7.2.1 Extent of exposure (dose/duration)

The median time of follow up for the total population of the CHARM-Program studies was 37.7 months, and the longest follow-up time was 47.6 months. The median exposure to double-blind treatment was 34.8 months. A total of 5,360 patients (2,659 patients were in the candesartan group) received study medication for ≥ 24 months. 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.

Extent of exposure in CHARM-Added (SH-AHS-0006) Study

A total of 2,548 patients (542 females and 2,006 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. An overview of exposure is presented in Table 85, including data on the number of patients who completed or discontinued the study.

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.

Table 85 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.

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.

Extent of exposure in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies

A total of 2,028 patients were randomized into SH-AHS-0003, 2,548 patients to SH-AHS-0006 and 3,025 patients to SH-AHS 0007. The total ITT/safety population for patients with symptomatic CHF (SH-AHS-0003, SH-AHS-0006 and SH- AHS-0007) comprised 7,599 patients (2,400 females and 5,199 males) and the corresponding figures for SH-AHS-0003 and SH-AHS-0006 are 4,576 (1,188 females and 3,388 males). Two patients were randomized in error and were therefore excluded from the ITT/safety population in SH-AHS-0007 (because no investigational product was dispensed and no data were collected). Patients who received incorrect investigational product during any part of the studies (22 patients in SH-AHS-0007) are

included in the analyses according to the group to which they were randomized. The incorrect investigational product administration lasted for a maximum of 21 days.

An overview of exposure in the total ITT/safety population including the numbers of patients who completed or discontinued the CHARM Program is presented in Table 86. Table 87 presents the exposure and number of patients by time in the component studies.

A total of 5,360 (70.5%) received the investigational product for 24 months or longer, among which 2,659 (69.9%) on candesartan treatment received the investigational product for 24 months or longer.

Table 86 Overview of exposure in patients with symptomatic CHF. ITT/Safety population (SH-AHS-0003, -0006, -0007)

		Placebo (N=3796)		Cand.cil. (N=3803)	
No. (%) of patients evaluable for safety	Male	2582	(68.0)	2617	(68.8)
	Female	1214	(32.0)	1186	(31.2)
Age (years)	<65	1642	(43.3)	1614	(42.4)
	≥65	2154	(56.7)	2189	(57.6)
	<75	2912	(76.7)	2951	(77.6)
	≥75	884	(23.3)	852	(22.4)
Race[a]	Caucasian	3507	(92.4)	3493	(91.8)
	Black	164	(4.3)	162	(4.3)
	Oriental	87	(2.3)	110	(2.9)
	Other	38	(1.0)	38	(1.0)
Exposure by discontinuation due to AE of investigational product and/or study (N and %)	Discontinued investigational product due to AEs	613	(16.1)	799	(21.0)
	Patients who withdrew consent	51	(1.3)	66	(1.7)

[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. See Section 8.3.

Table 87 Exposure and number of patients with symptomatic CHF by time in the component studies. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Period	Time	Placebo	Cand. cil.	Total
From baseline to last visit	>= 0 days	3796	3803	7599
	>= 1 months	3765	3779	7544
	>= 3 months	3707	3738	7445
	>= 6 months	3673	3721	7394
	>= 12 months	3464	3563	7027
	>= 24 months	3170	3271	6441
	>= 36 months	2157	2215	4372
	>= 48 months	0	0	0
	Patient years	10690.3	10938.2	21628.5
	Mean (months)	33.8	34.5	34.2
	Median (months)	37.6	37.9	37.7
	Min/max (months)	0.1/47.4	0.1/47.6	0.1/47.6
From baseline to last day on double-blind investigational product	>= 0 days	3796	3803	7599
	>= 1 months	3653	3660	7313
	>= 3 months	3501	3475	6976
	>= 6 months	3451	3419	6870
	>= 12 months	3105	3071	6176
	>= 24 months	2701	2659	5360
	>= 36 months	1766	1715	3481
	>= 48 months	0	0	0
	Patient years	9371.2	9221.9	18593.1
	Mean (months)	29.6	29.1	29.4
	Median (months)	35.0	34.5	34.8
	Min/max (months)	0.0/47.2	0.0/47.4	0.0/47.4

The median duration of patient follow-up for the total population in the CHARM Program was 37.9 months for patients randomized to candesartan and 37.6 months for patients randomized to placebo (Table 87). The longest follow-up time was 47.6 months.

Corresponding data for the subpopulation of patients with depressed LV systolic function is shown in Table 88 and Table 89.

The median duration of patient follow-up for the two treatment groups in the subpopulation of patients with depressed LV systolic function were 40.2 and 39.9 months respectively (Table 89).

Table 88 Overview of exposure in the ITT/Safety population for the subpopulation. (SH-AHS-0003, -0006)

		Placebo (N=2287)		Cand.cil. (N=2289)	
No. (%) of patients evaluable for	Male	1691	(73.9)	1697	(74.1)
	Female	596	(26.1)	592	(25.9)
Age	<65	1028	(44.9)	1044	(45.6)
	≥65	1259	(55.1)	1245	(54.4)
	<75	1803	(78.8)	1844	(80.6)
	≥75	484	(21.2)	445	(19.4)
Race[a]	Caucasian	2098	(91.7)	2096	(91.6)
	Black	107	(4.7)	93	(4.1)
	Oriental	57	(2.5)	76	(3.3)
	Other	25	(1.1)	24	(1.0)
Exposure by study completion or	Discontinued investigational	421	(18.4)	530	(23.2)
	Discontinued the study[b]	31	(1.4)	43	(1.9)
	Completed the study	2256	(98.6)	2246	(98.1)

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.
b Patients who withdrew consent.

Table 89 Exposure and number of patients for the subpopulation by time in the study. ITT/Safety population. (SH-AHS-0003, -0006)

Period	Time	Placebo	Cand.cil	Total
From Baseline to Last visit	>= 0 days	2287	2289	4576
	>= 1 months	2259	2269	4528
	>= 3 months	2210	2235	4445
	>= 6 months	2185	2223	4408
	>= 12 months	2023	2105	4128
	>= 24 months	1811	1894	3705
	>= 36 months	1333	1382	2715
	>= 48 months	0	0	0
	Patient years	6303.2	6503.9	12807.1
	Mean (months)	33.1	34.1	
	Median (months)	39.9	40.1	
	Min/max (months)	0.1/47.4	0.1/47.6	
From Baseline to last day on double-blind study medication	>= 0 days	2287	2289	4576
	>= 1 months	2181	2191	4372
	>= 3 months	2077	2066	4143
	>= 6 months	2048	2031	4079
	>= 12 months	1813	1798	3611
	>= 24 months	1546	1523	3069
	>= 36 months	1083	1050	2133
	>= 48 months	0	0	0
	Patient years	5513.3	5420.1	10933.4

The median exposure to the investigational product in the total population was 35.0 months in the placebo group and 34.5 months in the candesartan group.

In the total CHARM-Program population, 3,052 (80.3%) patients in the candesartan group started treatment on 4 mg once daily and 751 (19.7%) patients started on 8 mg once daily at randomization (baseline). Among patients still on the investigational product at 6 months (visit 5), (3,233 patients or 88.9% in the candesartan group and 3,301 patients 92.6% in the placebo group), 62.6% of the candesartan patients were treated with the target dose 32 mg once daily. The mean dose in the candesartan group was 24.0 mg at 6 months. At the end of treatment (LVCF) 62.3% of those still treated with candesartan (2,769, 73.1%) received 32 mg of candesartan once daily. The mean candesartan LVCF dose was 23.9 mg.

7.2.2 Literature

The medical literature reviewed (References, section 10) did not reveal reports of unexpected organ-specific toxicity. In this review, I have presented, with tables and figures where necessary, and discussed the information from the medical literature in the context of the data from the CHARM-Added and CHARM-Pooled Studies under each heading in the safety review template.

7.2.3 Additional submissions, including safety update

The sponsor submitted that there are no on-going clinical studies currently conducted under US IND 50,115, with the exception of an investigator-initiated study (BLO K016) in Germany with a planned recruitment of only 40 patients with CHF. Therefore, the sponsor does not plan to prepare/submit a 4-month safety update.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

This section summarizes AEs of special interest relevant to blockade of RAAS in the treatment of CHF by using AT_1-receptor blockers (ARBs) and ACE inhibitors. These AEs of special interest include hypotension, abnormal renal function or worsening of renal function, hyperkalemia, angioedema and myocardial ischemia. In addition, brief descriptions of abnormal hepatic function and neoplasms reported in the safety report are presented.

7.3.1 Hypotensive events

'Hypotension' as an adverse clinical event include a composite of the following AAED preferred terms: 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.

Hypotensive events in CHARM-Added (SH-AHS-0006) Study:

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 90).

Table 90 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 74).

In the candesartan group during treatment, 'hypotension' and 'syncope' were each reported as an AE that led to death in 1 patient. These hypotensive events that led to death were reported in association with other concomitant events such as myocardial infarction and gastroenterocolitis so that the AE is considered unlikely to be related to candesartan.

The investigational product was discontinued for the specific AE term hypotension in 44 (3.5%) placebo patients and 69 (5.4%) candesartan patients (Table 53). Corresponding figures for the exploratory analysis were 40 (3.1%) placebo patients and 58 (4.5%) candesartan patients (Table 58). 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, including diuretics and β-blockers.

Among the patients that discontinued the investigational products due to hypotensive events, a greater proportion had SBP < 100 mmHg at baseline in the candesartan group (placebo 3, 7.5%, candesartan 11, 24.1%).

In patients aged younger than 75 years, discontinuation because of hypotension was reported in 30 (2.9%) of patients in the placebo group and 53 (5.0%) of patients on candesartan.

For patients aged 75 years or older the discontinuation rates were 14 (5.7%) in the placebo group and 16 (7.5%) in the candesartan group.

In the placebo group, permanent discontinuation of the investigational product due to hypotension was reported in 34 (3.4%) males and 10 (3.7%) females. In the candesartan treatment group there were 59 (5.9%) males and 10 (3.7%) females who were permanently discontinued due to hypotension.

In both treatment groups patients discontinued taking the investigational product because of hypotension over the entire study period; however, the candesartan discontinuation rate, shown in the exploratory analysis, was greatest during the first 6 to 12 months of treatment (Figure 35).

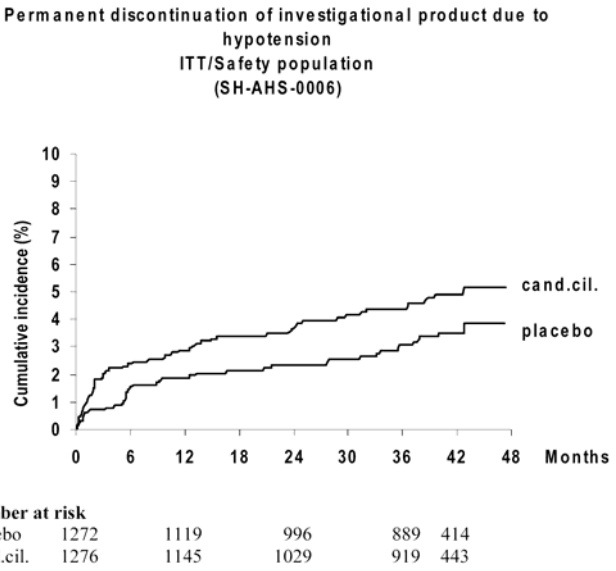


Figure 35 Cumulative incidence (%) of permanent discontinuation of investigational product due to hypotension (Ref. - Table 56). ITT/Safety population

Among the 382 (30.0%) placebo patients and 376 (29.5 %) candesartan patients entering the study with a history of diabetes, investigational product discontinuation for the specific preferred term hypotension was noted for 15 (3.9%) placebo patient and 17 (4.5%) candesartan patients.

Hypotensive events in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

At baseline, there were slightly more patients in the candesartan treatment group with SBP < 100 mmHg (placebo 92, 2.4%; candesartan 126, 3.3%) (North American study population).

AEs suggesting a 'hypotensive' event were reported more frequently in the candesartan group (875, 23.0%) than in the placebo group (519, 13.7%) for patients than on treatment with the investigational product (Table 91).

Table 91 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-0003, -0006, -0007)

Placebo on treatment (N=3796)	Cand. cil. on treatment (N=3803)	Placebo during study (N=3796)	Cand. cil. during study (N=3803)
519 (13.7)	875 (23.0)	560 (14.8)	914 (24.1)

The individual AE term contributing the largest numbers to this composite AE was hypotension, which was reported for 372 (9.8%) patients given placebo and 714 (18.8%) patients given candesartan (Table 92).

Table 92 Number (%) of patients with symptomatic CHF with the most commonly reported[a] AEs, sorted by descending frequency in the total population during study. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Preferred term	Placebo on treatment (N=3796)		Cand. cil. on treatment (N=3803)		Placebo during study (N=3796)		Cand. cil. during study (N=3803)	
	N	(%)	N	(%)	N	(%)	N	(%)
Cardiac failure/cardiac failure aggravated[b]	1073	(28.3)	831	(21.9)	1187	(31.3)	1001	(26.3)
Hypotension	372	(9.8)	714	(18.8)	399	(10.5)	736	(19.4)
Angina pectoris/angina pectoris aggravated[b]	461	(12.1)	414	(10.9)	506	(13.3)	490	(12.9)
Renal function abnormal/renal dysfunction aggravated[b]	238	(6.3)	474	(12.5)	248	(6.5)	487	(12.8)
Sudden death	282	(7.4)	234	(6.2)	348	(9.2)	291	(7.7)
Pneumonia	243	(6.4)	200	(5.3)	299	(7.9)	261	(6.9)
Myocardial infarction	216	(5.7)	205	(5.4)	257	(6.8)	242	(6.4)
Fibrillation atrial	218	(5.7)	165	(4.3)	249	(6.6)	202	(5.3)
Arrhythmia ventricular	207	(5.5)	159	(4.2)	239	(6.3)	193	(5.1)
Cerebrovascular disorder	189	(5.0)	164	(4.3)	216	(5.7)	203	(5.3)
Coronary artery disorder	170	(4.5)	169	(4.4)	200	(5.3)	205	(5.4)
Chest pain	177	(4.7)	154	(4.0)	202	(5.3)	183	(4.8)
Arrhythmia atrial	175	(4.6)	156	(4.1)	197	(5.2)	187	(4.9)
Hyperkalaemia	78	(2.1)	238	(6.3)	84	(2.2)	242	(6.4)
Tachycardia supraventricular	152	(4.0)	129	(3.4)	177	(4.7)	148	(3.9)
Dizziness/vertigo[b]	107	(2.8)	154	(4.0)	115	(3.0)	168	(4.4)
Accident and/or injury	112	(3.0)	99	(2.6)	143	(3.8)	125	(3.3)
Tachycardia ventricular/arrhythmia/arrhythmia aggravated[b]	110	(2.9)	100	(2.6)	132	(3.5)	128	(3.4)
Syncope	105	(2.8)	121	(3.2)	119	(3.1)	139	(3.7)
Anaemia	87	(2.3)	110	(2.9)	110	(2.9)	145	(3.8)

a This table uses a cut-off of ≥3.0% in the total population during study (N=7599).
b Patients having both or all events are counted once only.

A fatal hypotensive event was reported in a comparable proportion of patients in each treatment group (Table 93). In both treatment groups, hypotensive events that led to death were reported in association with other causes of death; notably in the candesartan patients, associated events included electromechanical dissociation, ventricular tachycardia and gastrointestinal bleeding, and were thus assessed by the investigators as unlikely to be related to the investigational product.

Table 93 Number (%) of patients with fatal preferred terms hypotension, hypotension postural, dizziness/ vertigo, syncope, circulatory failure or collapse not otherwise specified (NOS). ITT/ Safety population (SH-AHS-0003, -0006, -0007)

Placebo on treatment (N=3796)	Cand.cil on treatment (N =3803)	Placebo during study (N =3796)	Cand.cil during study (N =3803)
5 (0.1)	6 (0.2)	10 (0.3)	12 (0.3)

As noted in the descriptive analysis for the total population, the investigational product was discontinued for hypotension in 76 (2.0%) placebo patients and 155 (4.1%) candesartan patients (Table 54). Corresponding figures for the exploratory analysis were 66 (1.7%) placebo patients and 132 (3.5%) candesartan patients (Table 61). The higher proportion of permanent discontinuation of the investigational product due to hypotensive events in the candesartan group

could not be explained by higher use of concomitant medication when the event started, including diuretics, β-blockers and ACE-inhibitors. Among the patients that discontinued the investigational product due to hypotensive events, a greater proportion had SBP < 100 mmHg at baseline in the candesartan group (placebo, 7.5%; candesartan, 13.6%).

In patients aged < 75 years, discontinuation because of hypotension was reported in 48 (1.6%) patients in the placebo group and 111 (3.8%) patients on candesartan. For patients aged ≥ 75 years the discontinuation rates were 28 (3.2%) patients in the placebo group and 44 (5.2%) patients in the candesartan group. Permanent discontinuation of the investigational product due to hypotension was reported in 56 (2.2%) males and 20 (1.6%) females in the placebo group, and 107 (4.1%) males and 48 (4.0%) females in the candesartan treatment group.

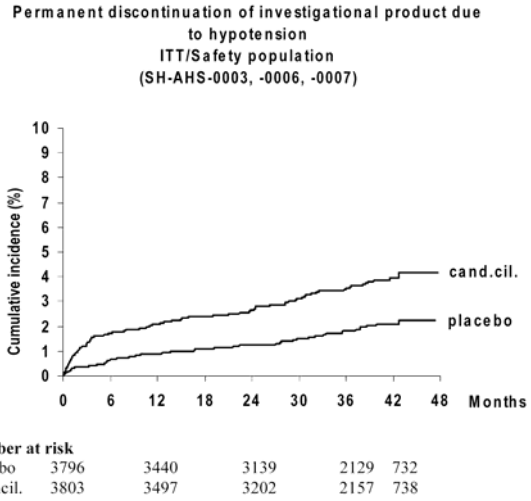


Figure 36 Cumulative incidence (%) of permanent discontinuation of the investigational product due to hypotension. ITT/Safety population

Although patients in both treatment groups discontinued taking the investigational product because of hypotension over the entire study period, the candesartan discontinuation rate shown in the exploratory analysis, was greatest during the first 6 to 12 months of treatment (Figure 36).

Among the 1,075 (28.3%) placebo patients and 1,088 (28.6%) candesartan patients entering the study with a history of diabetes, investigational product discontinuation for hypotension was noted for 22 (2.0%) placebo patients and 34 (3.1%) candesartan patients.

Reviewer's comments with data from the literature: Hypotension is an expected clinical event in this population of patients with chronic heart failure, particularly since they are being treated also with ACE inhibitors, β-blockers, and diuretics all of which may lower the blood pressure. In the VALIANT trial[25], where valsartan with or without captopril were given to high risk patients with radiologic evidence of heart failure, left ventricular systolic dysfunction or both, there was a higher incidence of drug-related adverse events (hypotension and renal dysfunction) in the valsartan-plus-captopril group as well as in the valsartan group.

7.3.2 Abnormal renal function

To summarize abnormal renal function, the following AAED preferred terms were selected and analyzed as a single composite event: renal function, abnormal/renal dysfunction, aggravated; renal failure acute; renal failure, NOS; uremia; non-protein nitrogen, increased; renal failure, aggravated; blood urea nitrogen, increased; increased creatinine, acute pre-renal failure and anuria. For this composite AE, patients with multiple events of any of the selected AE terms were counted only once.

Abnormal renal function in CHARM-Added (SH-AHS-0006) Study:

At baseline, prior to study entry, there were a slightly higher proportion of patients in the candesartan group with serum creatinine ≥ 2.0 mg/ dl at baseline (placebo 20, 4.3%; candesartan 26, 5.6%) (North American study population).

AEs suggesting 'abnormal renal function' occurred in 151 (11.9%) patients in the placebo group and 231 (18.3 %) patients in the candesartan group during study (Table 94).

Table 94 Number (%) of patients with any of the preferred terms renal function abnormal/ renal dysfunction aggravated, renal failure acute, renal failure not otherwise specified (NOS), uremia, non-protein nitrogen increased, renal failure aggravated, blood urea nitrogen increased, acute pre-renal failure or anuria. 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
139 (10.9)	220 (17.3)	151 (11.9)	231 (18.3)

The AE terms that predominately contributed to this composite AE term was renal function abnormal which was reported in 118 (9.3%) of patients given placebo and 195 (15.3%) given candesartan during study. Renal failure, acute (placebo, 38 patients, 3.0%; candesartan, 54 patients, 4.2%) and uremia (placebo, 10 patients, 0.8%; candesartan, 18 patients, 1.4%) were also numerically more frequent in patients given active treatment.

A fatal renal function event was reported for a higher proportion of patients in the placebo group, both 'on treatment' (placebo, 8 patients; candesartan, 2 patients) and 'during study' (placebo, 20 patients; candesartan 15 patients). In both treatment groups, the majority of renal events that led to death were reported in association with other causes of death such as worsening heart failure.

In the descriptive safety analysis (Table 53), on investigational product discontinuation in the overall study population, "renal function abnormal" was the most common reason for permanent discontinuation of the investigational product in both treatment groups (placebo 53, 4.2%; candesartan 105, 8.2%).

In the exploratory analysis, increased creatinine was reported for 52 (4.1%) placebo patients and 100 (7.8%) candesartan patients (Table 58). The higher rate for discontinuation of the investigational product due to 'abnormal renal function' in the candesartan group could not be

explained by higher use of concomitant medication when the event started. Among the patients who discontinued the investigational product due to 'abnormal renal function events', a higher proportion of patients in the placebo group had a serum creatinine level ≥ 2 mg/dL at baseline (placebo 8 (15.4%); candesartan 9 (9.0%)) (North American study population).

In patients aged younger than 75 years, discontinuation because of abnormal renal function was reported in 40 (3.9%) of patients in the placebo group and 82 (7.7%) of patients on candesartan. For patients aged 75 years or older the discontinuation rates were 13 (5.3%) in the placebo group and 23 (10.8%) in the candesartan group.

In the placebo treatment group 43 (4.3%) males and 10 (3.7%) females discontinued due to renal function abnormal. In the candesartan treatment group 82 (8.2%) males and 23 (8.5%) females discontinued due to abnormal renal function.

In the exploratory analysis, patients discontinued study treatment because of 'increased creatinine' over the entire study period, and the rate was greater for candesartan-treated patients (Figure 37).

Among the 382 (30.0%) placebo patients and 376 (29.5 %) candesartan patients entering the study with a history of diabetes, investigational product discontinuation because of increased creatinine was noted for 25 (6.5%) placebo and 42 (11.2%) candesartan patients. Compared to the overall population (placebo 4.1%, candesartan 7.8%) diabetics were slightly more likely to discontinue the investigational product for increased creatinine levels (Table 58).

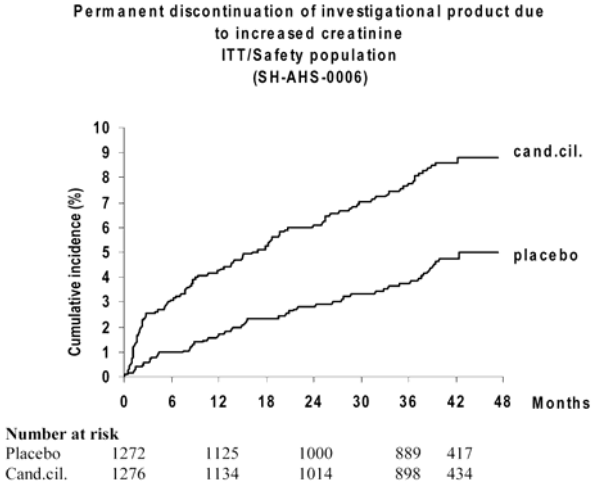


Figure 37 Cumulative incidence (%) of permanent discontinuation of investigational product due to increased creatinine (Ref. - Table 56). ITT/Safety population

Abnormal renal function in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

At baseline, there were more patients in the candesartan group with serum creatinine > 2.0 mg/ dl (placebo 70, 5.2%; candesartan 84, 6.3%) (North American study population).

AEs suggesting 'abnormal renal function' occurred in 349 (9.2%) in the placebo group and 576 (15.1%) patients in the candesartan group during study (Table 95).

Table 95 Number (%) of patients with any of the preferred terms renal function abnormal/renal dysfunction aggravated, renal failure acute, renal failure NOS, uremia, non-protein nitrogen increased, renal failure aggravated, blood urea nitrogen increased, acute pre-renal failure or anuria. ITT/Safety population (SH-AHS-0003, -0006 and -0007)

Placebo on treatment (N=3796)	Cand. cil. on treatment (N=3803)	Placebo during study (N=3796)	Cand. cil. during study (N=3803)
316 (8.3)	546 (14.4)	349 (9.2)	576 (15.1)

The AE terms that predominately contributed to this composite AE term was renal function abnormal which was reported in 247 (6.5%) of patients given placebo and 485 (12.8%) given candesartan during study. Renal failure, acute (placebo, 91 patients, 2.4%; candesartan, 121 patients, 3.2%) and uremia (placebo, 28 patients, 0.7%; candesartan, 43 patients, 1.1%) were also numerically more frequently in patients given active treatment.

Table 96 Number (%) of patients with fatal renal function, abnormal/renal dysfunction, aggravated, renal failure acute, renal failure, NOS, uremia, non-protein nitrogen increased, renal failure aggravated, blood urea nitrogen increased, acute pre-renal failure or anuria. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Placebo on treatment (N=3796)	Cand.cil on treatment (N=3803)	Placebo during study (N=3796)	Cand.cil during study (N=3803)
18 (0.5)	7 (0.2)	41 (1.1)	36 (0.9)

Fatal renal function events 'during study' and 'on treatment' were reported for a higher proportion of patients in the placebo group (Table 96). In both treatment groups, the majority of renal events that led to death were reported in association with other causes of death such as worsening heart failure.

In the descriptive safety analysis, renal function abnormal/renal dysfunction aggravated was the second most common reason for permanent discontinuation of the investigational product (second only to cardiac failure aggravated,) in both treatment groups (placebo 110, 2.9%; candesartan 238, 6.3%) (Table 54). In the exploratory analysis the term increased creatinine was reported for 115 (3.0%) placebo patients and 234 (6.2%) candesartan patients (Table 61). The higher discontinuation rate for 'abnormal renal function' in the candesartan group could not be explained by between-treatment differences in concomitant medications when the event started or baseline serum creatinine levels (North American study population) (Table 97).

Table 97 Permanent discontinuation due to pooled adverse events related to abnormal renal function[a] or hypotensive events[b] or hyperkalemia[c] on treatment with candesartan cilexetil or placebo. Specified concomitant medication at the start of the event. ITT/safety population (SH-AHS-0003, -0006, -0007)[d]

	Placebo Abn renal N=126		Cand cil Abn renal N=266		Placebo Hypotensive N=93		Cand cil Hypotensive N=188		Placebo Hyperkalae N=22		Cand cil Hyperkalae N=93	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Loop diuretics	117	(92.9)	258	(97.0)	83	(89.2)	169	(89.9)	20	(90.9)	84	(90.3)
Potassium - sparing diuretics	59	(46.8)	105	(39.5)	29	(31.2)	80	(42.6)	10	(45.5)	34	(36.6)
Thiazide diuretics	22	(17.5)	52	(19.5)	22	(23.7)	35	(18.6)	3	(13.6)	11	(11.8)
Any β-blocker	72	(57.1)	146	(54.9)	54	(58.1)	93	(49.5)	13	(59.1)	54	(58.1)
Calcium channel blocker	36	(28.6)	67	(25.2)	11	(11.8)	29	(15.4)	1	(4.5)	23	(24.7)
Any ACE-inhibitor	79	(62.7)	141	(53.0)	63	(67.7)	88	(46.8)	18	(81.8)	59	(63.4)

a Preferred terms included in abnormal renal function: Renal function abnormal/renal dysfunction aggravated, renal failure acute, renal failure nos, uraemia, non-protein nitrogen increased, renal failure aggravated, acute pre-renal failure or anuria.
b Preferred terms included in hypotensive events: Hypotension, hypotension postural, dizziness/vertigo, syncope, circulatory failure or collapse not otherwise specified (nos).
c Hyperkalaemia is a single Preferred term.
d Exploratory safety analysis

In patients aged younger than 75 years, discontinuation because renal function abnormal/renal dysfunction aggravated was reported in 75 (2.6%) patients in the placebo group and 171 (5.8%) patients in the candesartan group on treatment with the investigational product. For patients aged 75 years or older the discontinuation rates were 35 (4.0%) patients in the placebo group and 67 (7.9%) patients in the candesartan group. In the placebo group the majority of events were seen in male patients (81, 3.1%) compared to 29 (2.4%) female patients. Corresponding values for the candesartan treatment group were 169 (6.5%) males and 69 (5.8%) females. The majority of patients in both treatment groups were Caucasians.

As shown in the exploratory analysis, patients discontinued study treatment because of 'increased creatinine' over the entire study period, and the rate was greater for candesartan-treated patients (Figure 38).

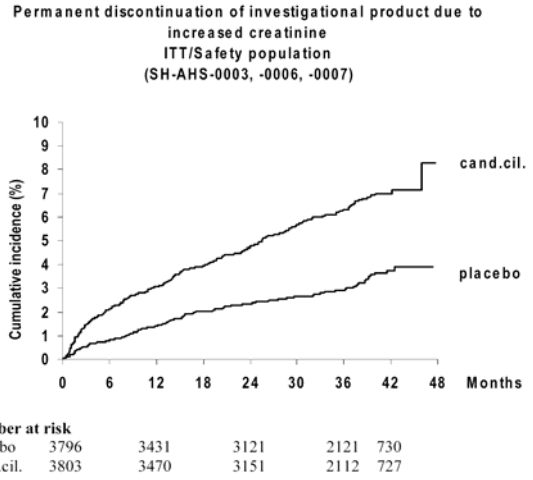


Figure 38 Cumulative incidence (%) of permanent discontinuation of the investigational product due to increased creatinine. ITT/Safety population

Among the 1,075 (28.3%) placebo patients and 1,088 (28.6%) candesartan patients entering the CHARM Program study with a history of diabetes, investigational product discontinuation for increased creatinine was noted for 57 (5.3%) placebo and 99 (9.1%) candesartan patients (Table 65 and Table 66). Compared to the total population (placebo 3.0%, candesartan 6.2%) (Table 61), diabetic patients were slightly more likely to discontinue the investigational product for increased creatinine levels.

Reviewer's comments with data from the literature: The deterioration in renal function tests is an expected clinical event in patients treated with candesartan, particularly so since these patients with CHF have low glomerular filtration rates, hypotension and concomitant treatment with ACE-inhibitors and diuretics, all of which may increase the BUN or serum creatinine. The mean serum creatinine concentration in major clinical trials involving patients with congestive heart failure ranges from 1.2 to 1.4 mg/dL (106 to 124 μmol/L), and one third to one half of patients with congestive heart failure have renal insufficiency[17]. Chronic kidney disease is among the strongest predictors of death in patients with congestive heart failure. It may also predispose these patients to hyperkalemia.

It appears that use of ACE inhibitor and ARBs may be associated with higher levels of serum creatinine. In stage II of the RESOLVD trial[5] where patients with NYHA class II-IV and LVEF <0.40 were treated with candesartan alone, enalapril alone, candesartan plus enalapril, candesartan plus metoprolol, enalapril plus metoprolol, or candesartan plus enalapril plus metoprolol, the cumulative incidence of plasma creatinine concentrations ≥ 50% of baseline and above 106μmol/L was found in 4.8% of patients receiving candesartan or enalapril alone, and 2.4% of patients receiving candesartan plus metoprolol or enalapril plus metoprolol; however, this doubled to 9.3% in patients receiving candesartan *plus* enalapril, and 9.0% in patients receiving candesartan *plus* enalapril plus metoprolol. Although the differences between treatment groups were not significantly different (P=0.34), it is interesting to note that larger proportions of patients who received *both* candesartan *and* enalapril (with or without metoprolol) had elevated plasma creatinine concentrations. In the Val-HeFT trial[16] where valsartan was compared to placebo with all patients receiving standard therapy for heart failure, significantly (P < 0.001) larger increases were found in the valsartan treated group compared to placebo in BUN (5.9 mg/dl in valsartan group vs. 3.3 mg/dl in placebo group) and serum creatinine (15.9μmol/L in valsartan group and 8.8μmol/L with placebo).

7.3.3 Hyperkalemia

Hyperkalemia is reported as observed 'on treatment' rather than 'during study' to present a more clinically meaningful measure of possible relationship to the investigational product.

Hyperkalemia in CHARM-Added (SH-AHS-0006) Study:

At baseline, a slightly higher proportion of patients in the candesartan treatment group had a serum potassium ≥ 5 mmol/L (North American study population).

Hyperkalemia was reported for 44 patients (3.5%) in the placebo group and 121 patients (9.5%) in the candesartan group on treatment with the investigational product Table 74).

Fatal hyperkalemia was reported during the study for 2 patients in the candesartan group and no patient in the placebo group. Patient 155-10493 died of sudden death and hyperkalemia (potassium concentration, 6.2 mmol/ L) after approximately two years of candesartan treatment. Patient 201-12699 had abnormal renal function 20 days after starting treatment with candesartan, and died of sudden death and hyperkalemia (potassium concentration, 6.1 mmol/ L) after 52 days of treatment. Both patients had a concomitant unspecified increase in serum creatinine. These AEs are assessed, respectively, as probably and possibly related to the investigational product.

In Table 53, discontinuation of the investigational product because of hyperkalemia was more frequent with candesartan (placebo 11, 0.9%; candesartan 49, 3.8%). In the exploratory analysis the corresponding numbers were 9 (0.7%) for placebo patients and 44 (3.4%) for candesartan patients (Table 58). The higher rate for hyperkalemia causing discontinuation in the candesartan group could not be explained by higher use of concomitant medication when the event started, including potassium-sparing diuretics. There was no between treatment difference regarding baseline serum potassium levels in patients who discontinued investigational product due to hyperkalemia (North American study population).

In patients < 75 years old, discontinuation because of the AE term hyperkalemia was reported in 8 (0.8%) patients in the placebo group and 31 (2.9%) of patients on candesartan. For patients aged 75 years or older the discontinuation rates were 3 (1.2%) in the placebo group and 18 (8.5%) in the candesartan group.

In the placebo group the majority of events were seen in male patients, in the candesartan group the events were equally distributed between.

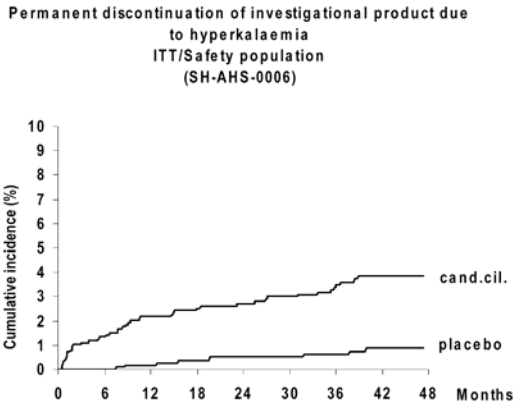


Figure 39 Cumulative incidence (%) of permanent discontinuation of investigational product due to hyperkalemia. ITT/Safety population (Ref. - Table 56).

The discontinuation rate for candesartan-treated patients because of hyperkalemia, presented from exploratory analysis, was greater during the first 6 to 12 months of treatment, but discontinuations still occurred over the entire study period (Figure 39).

Among the 382 (30.0%) placebo patients and 376 (29.5 %) candesartan patients entering the study with a history of diabetes, investigational product discontinuation for the specific preferred term hyperkalemia was noted for 10 (2.6%) placebo and 31 (8.2%) candesartan patients.

Hyperkalemia in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

At baseline, there were more patients in the candesartan treatment group with serum potassium = 5 mmol/L (placebo 125, 9.3%; candesartan 135, 10.1%) (North American study population).

Hyperkalemia was reported for 78 patients (2.1%) in the placebo group and 238 patients (6.3%) in the candesartan group on treatment with the investigational product (Table 75).

Fatal hyperkalemia 'during study' was reported for 2 patients in the candesartan group, and in 1 patient in the placebo group. Both candesartan treated patients were on active treatment in SH-AHS-0006 as described above. The one patient in the placebo group in SH-AHS-0003 was not on treatment with the investigational product and had concomitant renal failure (with an increase in serum creatinine) which could have contributed to the hyperkalemia.

In Table 54, discontinuation of the investigational product because of hyperkalemia occurred more frequently in patients treated with candesartan (placebo 22, 0.6%; candesartan 93, 2.4%). In the exploratory analysis the corresponding numbers were 21 (0.6%) for placebo patients and 85 (2.2%) for candesartan patients (Table 61). The higher rate for hyperkalemia causing discontinuation in the candesartan group could not be explained by between treatment differences in concomitant medications at the start of the event, including potassium – sparing diuretics or baseline serum potassium levels (North American study population) (Table 97).

In patients aged younger than 75 years, discontinuation because of the AE term hyperkalemia was reported in 14 (0.5%) patients in the placebo group and 57 (1.9%) patients on candesartan. For patients aged 75 years or older the discontinuation rates were 8 (0.9%) patients in the placebo group and 36 (4.2%) patients in the candesartan group. In the placebo treatment group 16 (0.6%) males and 6 (0.5%) females discontinued due to hyperkalemia. In the candesartan group the majority of events were seen in male patients (72, 2.8%) compared to female patients (21, 1.8%).

The discontinuation rate for candesartan-treated patients because of hyperkalemia, presented from exploratory analysis, (Figure 40), was somewhat greater during the first 6 to 12 months of treatment, but discontinuations still occurred over the entire study period.

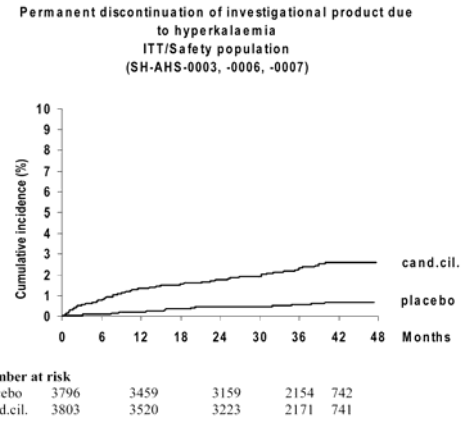


Figure 40 Cumulative incidence (%) of permanent discontinuation of the investigational product due to hyperkalemia. ITT/ Safety population

Among the 1,075 (28.3%) placebo patients and 1,088 (28.6%) candesartan patients entering the CHARM Program with a history of diabetes, investigational product discontinuation for the specific preferred term hyperkalemia was noted for 13 (1.2%) placebo and 31 (2.8%) candesartan patients (Table 65 and Table 66).

Reviewer's comments with data from the medical literature: Hyperkalemia is an expected clinical event in patients treated with candesartan, particularly so since these patients with CHF have hypotension (with poor tissue perfusion and metabolic acidosis) and concomitant treatment with ACE-inhibitors, β-blockers and potassium-sparing diuretics (spironolactone) all of which may increase the serum potassium. Also, one third to one half of patients with congestive heart failure have some degree of renal insufficiency[17] in whom a defect in the renal excretion of potassium further increases the risk of hyperkalemia.

Despite this finding that co-morbid renal insufficiency may cause hyperkalemia, physicians do have to use ACE-inhibitors, ARBs and aldosterone-receptor blockers in the treatment of patients with CHF. This is because chronic kidney disease is among the strongest predictors of death in patients with CHF, and these patients (with CHF and chronic renal failure) happen to be the ones who derive the greatest cardiovascular survival and benefits from these drugs. In the situation where CHF and co-morbid chronic renal failure are present, ACE inhibitors and/or ARBs not only treat the heart failure and reduce the risk of a future cardiovascular event and reduce the risk of death, but they also slow the progression of renal disease[18,23,24,51,52,]. Withholding these drugs on the basis of the level of renal function or fear of causing hyperkalemia will unnecessarily deprive these patients of the cardiovascular benefit and survival benefit that they may obtain from judicious and cautious use of ACE inhibitors and ARBs.

In the OPTIMAAL trial[22], a significant (P=0.01) between-group difference was detected for and serum potassium (increased by 0.19 mmol/l in losartan group vs. 0.22 mmol/L in captopril group), being less with the ARB than with the ACE inhibitor. In the Val-HeFT trial[16] where valsartan was compared to placebo with standard therapy for heart failure, a significantly (P <

0.001) larger increase in potassium was found in the valsartan treated group (increase by 0.12 mmol/L) compared to placebo (decrease by 0.07 mmol/L).

In stage II of the RESOLVD trial[5] where patients with NYHA class II-IV and LVEF <0.40 were treated with candesartan alone, enalapril alone, candesartan plus enalapril, candesartan plus metoprolol, enalapril plus metoprolol, or candesartan plus enalapril plus metoprolol, the cumulative incidence of hyperkalemia defined as any observed plasma potassium concentration > 5.5 mmol/L was observed in 4.0% in patients receiving candesartan or enalapril alone, 2.4% in patients receiving candesartan plus metoprolol or enalapril plus metoprolol, 8.1% for patients receiving candesartan plus enalapril, and 7.9% for patients receiving candesartan plus enalapril plus metoprolol. Although the differences between treatment groups were not significantly different (P=0.3), it is interesting to note that larger proportions of patients who received both candesartan and enalapril (with or without metoprolol) had hyperkalemia.

7.3.4 Angioedema

Angioedema in CHARM-Added (SH-AHS-0006) Study

During the study, two cases of angioedema were reported for patients in the candesartan group. Both patients were Caucasian with concomitant medication with an ACE-inhibitor at the start of the event. One of these patients developed angioedema that required discontinuation of candesartan treatment. For the other patient ACE inhibitor medication was stopped but treatment with candesartan continued.

In the placebo group three patients reported angioedema, in one case leading to discontinuation of the investigational product.

Angioedema in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

During the study 5 cases of angioedema were reported for patients in the candesartan group compared with 3 cases in the placebo treatment group.

All patients in the candesartan treatment group were Caucasian. Three of these patients in the candesartan group had a history of previous angioedema reactions while taking ACE-inhibitors. The remaining two patients in the candesartan group had concomitant medication with an ACE-inhibitor at the start of the event. None of the events was considered life threatening or led to hospitalization. Two patients who developed angioedema required discontinuation of candesartan treatment. For the remaining 3 patients with angioedema, candesartan treatment continued without recurrence of angioedema, and for 1 of these the dose was reduced.

Reviewer's comments with data from the medical literature: Angioedema is an expected clinical event in patients treated with candesartan, particular so since these patients with CHF are receiving concomitant treatment with ACE-inhibitors, and some also had a history of previous angioedema while taking ACE-inhibitors.

The frequency of angioedema as an AE appears to be similar between ARB and ACE-inhibitors.

In the VALIANT trial[25] comparing valsartan, valsartan-plus-captopril and captopril, the proportion of patients with angioedema resulting in discontinuation of the study drug are similar; however, more patients in who received captopril or valsartan-plus-captopril reported angioedema resulting in dose reduction (Table 67).

Also, in the OPTIMAAL study[22] comparing losartan vs. captopril in patients with acute MI and evidence of heart failure or LV dysfunction, angioedema was reported significantly (P=0.034) more frequently (Table 68) in the captopril group (22 patients, 0.8%) compared to the losartan group (10 patients, 0.4%); angioedema was also associated with a significantly higher proportion of discontinuation (Table 68) from study drug treatment (14 patients (0.5%) in captopril group versus 4 patients (0.1%) in losartan group, P=0.019). Thus, it appears that angioedema is generally reported more frequently in patients receiving ACE inhibitors than in those receiving ARBs.

7.3.5 Myocardial ischemia

Myocardial ischemia in CHARM-Pooled (SH-AHS-0003, -0006,-0007) Studies:

'Myocardial ischemia' was evaluated as a composite of the AAED preferred terms: angina pectoris/angina pectoris aggravated, MI and coronary artery disorder. For this composite AE, patients with multiple events including any of the selected AE terms were counted only once.

At baseline prior to enrollment, there were no differences between the treatment groups in the frequencies of patients with previous MI and angina pectoris. Slightly more patients in the candesartan treatment group reported a history of coronary artery bypass grafting (placebo 870, 22.9%; candesartan 921, 24.2%).

The proportions of patients with 'myocardial ischemia' 'on treatment' were approximately equal in the two treatment groups (18.1% in the placebo group and 16.7% in the candesartan group) (Table 98).

Table 98 Number (%) of patients with any of the preferred terms angina pectoris/angina pectoris aggravated, myocardial infarction or coronary artery disorder. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Placebo on treatment (N=3796)	Cand. cil. on treatment (N=3803)	Placebo during study (N=3796)	Cand. cil. during study (N=3803)
688 (18.1)	637 (16.7)	774 (20.4)	755 (19.9)

The AE term accounting for the greatest number of patients in this composite AE was angina pectoris which was more frequently reported in the placebo treatment group (placebo 460, 12.1%; candesartan 405, 10.6%). The AE term MI occurred in 216 (5.7%) patients in the placebo group and in 205 (5.4%) in the candesartan group 'on treatment.'

'Myocardial ischemic' events that were fatal were reported for 70 (1.8%) patients in the placebo group and 97 (2.6%) patients in the candesartan group during study (Table 99).

Table 99 Number (%) of patients with any of the preferred terms angina pectoris/angina pectoris aggravated, myocardial infarction or coronary artery disorder leading to death. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Placebo on treatment (N=3796)	Cand. cil. on treatment (N=3803)	Placebo during study (N=3796)	Cand. cil. during study (N=3803)
44 (1.2)	66 (1.7)	70 (1.8)	97 (2.6)

Most of the fatal 'myocardial ischemic' events 'during study' were attributed to fatal MI (57 patients in the placebo group and 77 in the candesartan group).

7.3.6 Abnormal hepatic function

Abnormal hepatic function in CHARM-Added (SH-AHS-0006) Study:

The most common AE terms suggesting liver dysfunction during treatment were hepatic enzymes increased (placebo 1 patient; candesartan 6 patients) and hepatic function abnormal (placebo 1 patient; candesartan 4 patients). The AE term hepatic failure was reported for 4 patients in the placebo group and 2 patients in the candesartan group.

Abnormal hepatic function in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

The most common AE terms suggesting liver dysfunction were hepatic enzymes, increased NOS and hepatic function, abnormal; which were reported for 7 and 4 patients, respectively, given placebo treatment and 12 and 10 patients, respectively, given candesartan. The AE term hepatic failure was reported for 5 patients in the placebo group and 6 patients in the candesartan group.

In the candesartan group there was one fatal case of hepatic necrosis which the investigator and the sponsor considered related to amiodarone (SH-AHS-0003-373-15108), and one fatal case of cholestatic hepatitis considered related to septic cholangitis (SH-AHS-0003-1476-21109).

Reviewer's comments: There is no signal that candesartan is associated with increased risk of abnormal liver function tests or hepatic failure.

7.3.7 Neoplasms

AEs indicative of neoplasms, whether benign or malignant, were pooled from the SOC (system organ class) 'Neoplasms', plus 3 neoplastic AE terms from other SOCs (Melanoma malignant, Myelomatosis multiple and Pleural mesothelioma).

Neoplasms in CHARM-Added (SH-AHS-0006) Study

In the overall study population, the majority of patients did not have a history of cancer at baseline (placebo 94.1%; candesartan 93.9%).

Neoplasms were reported for 68 patients (5.3%) in the placebo treatment group compared with 90 (7.1%) in the candesartan group. One patient in the placebo group (Site 1532, Patient number 21520) had both Myeloid dysplasia (included in the SOC Neoplasms) and Myelomatosis

multiple. In the total numbers presented above this patient is counted only once. Neoplasms proved fatal for 20 patients (1.6%) in the placebo group and 39 patients (3.0%) in the candesartan group.

The majority of reported neoplasms were malignant. The most common neoplasms during study were pulmonary cancer (placebo, 7 patients; candesartan, 12 patients), prostatic cancer (placebo, 9 patients; candesartan, 7 patients) and colon cancer (placebo 5 patients; candesartan 8 patients), which are quite typical for patients in this age group.

Neoplasms in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies

In the total population slightly more patients in the candesartan treatment group had a history of cancer at baseline (placebo 243, 6.4%, candesartan 270, 7.1%).

Neoplasms were reported for 230 (6.0%) in the placebo group and 244 (6.4%) in the candesartan group. One patient in the placebo group in the component study SH-AHS-0003 (Site 558, Patient number 13436) had Breast neoplasm malignant female and Carcinomatosis (included in the SOC Neoplasms) together with Pleural mesothelioma. One patient in the candesartan group in the component study SH-AHS-0006 (Site 1532, Patient number 21520) had both Myeloid metaplasia (included in the SOC Neoplasms) and Myelomatosis multiple. In the total numbers presented above these patients are counted only once. Neoplasms proved fatal for 59 patients (1.8%) in the placebo group and 84 patients (2.2%) in the candesartan group.

The majority of reported neoplasms were malignant. The most common neoplasm's were prostatic carcinoma (placebo, 27 patients; candesartan, 32 patients), pulmonary carcinoma (placebo, 25 patients; candesartan, 31 patients), colon carcinoma (placebo, 24 patients; candesartan, 26 patients) and breast neoplasm malignant (17 patients in each group). The AE term 'gastrointestinal neoplasm benign' had a higher event rate in the candesartan group during study (placebo, 5; candesartan, 19) whereas 'renal carcinoma' was more frequent in the control group (placebo, 11; candesartan, 5).

7.3.8 Rare Adverse events in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

Rare adverse events reported include:

- pancytopenia (placebo 1 patient; candesartan 3 patients),
- aplastic anemia (candesartan 1 patient),
- anaphylactic shock and anaphylactoid reaction (placebo 1 patient; candesartan 2 patients),
- Stevens- Johnson syndrome (placebo 2 patients),
- rhabdomyolysis (placebo 2 patients; candesartan 3 patients),
- sarcoidosis (candesartan 2 patients), and
- scleroderma (candesartan 1 patient).

In most cases an alternative cause was identified. There was no sufficient evidence to support a causal relationship to the investigational product.

7.4 Is there is relationship between the dose of candesartan and the important adverse events?

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 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

On Nov 12, 2004, I received the sponsor's response containing the information related to the 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.

7.4.1 Relationship of dose of candesartan to permanent study drug discontinuation due to an adverse event or an abnormal laboratory value

In Table 100, no relationship is apparent between the dose of candesartan and the numbers and frequencies of permanent study drug discontinuation due to an adverse event or an abnormal laboratory value.

Table 100 The numbers and frequencies of permanent study drug discontinuation due to an adverse event or an abnormal laboratory value[a] in patients who received high or low dose candesartan plus ACE inhibitors at heart failure dose or low dose– CHARM-Added (SH-AHS-0006) Study

	$ACEi_{HFD}$ (N=643)			**$ACEi_{LD}$ (N=633)**		
Candesartan cilexetil[b]	**CC_{HD} + $ACEi_{HFD}$** N = 426 n = 86 (20.2%)	**CC_{LD} + $ACEi_{HFD}$** N = 138 n = 58 (42.0%)	**CC_{00} + $ACEi_{HFD}$** N = 79 n = 7 (8.9%)	**CC_{HD} + $ACEi_{LD}$** N = 393 n = 75 (19.1%)	**CC_{LD} + $ACEi_{LD}$** N = 162 n = 64 (39.5%)	CC_{00} + $ACEi_{LD}$ N = 78 n = 20 (25.6%)

$ACEi_{HFD}$ = 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] Definition used in exploratory safety analyses; [b] Dose of candesartan preceding the event (or at last visit if no event occurred)
n = number of patients with one or more events (proportion (%) of patients at the dose)

7.4.2 Relationship of dose of candesartan to permanent study drug discontinuation due hypotension

In Table 101, no relationship is apparent between the dose of candesartan and the numbers and frequencies of permanent study drug discontinuation due to hypotension.

Table 101 The numbers and frequencies of permanent study drug discontinuation due to hypotension in patients who received high or low dose candesartan plus ACE inhibitors at heart failure dose or low dose– CHARM-Added (SH-AHS-0006) Study

	$ACEi_{HFD}$ (N=643)			$ACEi_{LD}$ (N=633)		
Candesartan cilexetil[b]	**CC_{HD} + $ACEi_{HFD}$** N = 364 n = 8 (2.2%)	**CC_{LD} + $ACEi_{HFD}$** N = 98 n = 13 (13.3%)	**CC_{00} + $ACEi_{HFD}$** N = 181 n = 1 (0.6%)	**CC_{HD} + $ACEi_{LD}$** N = 342 n = 12 (3.5%)	**CC_{LD} + $ACEi_{LD}$** N = 131 n = 22 (16.8%)	CC_{00} + $ACEi_{LD}$ N = 160 n = 2 (1.3%)

$ACEi_{HFD}$ = 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] Definition used in exploratory safety analyses; [b] Dose of candesartan preceding the event (or at last visit if no event occurred)
n = number of patients with one or more events (proportion (%) of patients at the dose)

7.4.3 Relationship of dose of candesartan to permanent study drug discontinuation due to hyperkalemia

In Table 102, no relationship is apparent between the dose of candesartan and the numbers and frequencies of permanent study drug discontinuation due to hyperkalemia.

Table 102 The numbers and frequencies of permanent study drug discontinuation due to hyperkalemia in patients who received high or low dose candesartan plus ACE inhibitors at heart failure dose or low dose– CHARM-Added (SH-AHS-0006) Study

	$ACEi_{HFD}$ (N=643)			$ACEi_{LD}$ (N=633)		
Candesartan cilexetil[b]	**CC_{HD} + $ACEi_{HFD}$** N = 372 n = 16 (4.3%)	**CC_{LD} + $ACEi_{HFD}$** N = 94 n = 7 (7.5%)	**CC_{00} + $ACEi_{HFD}$** N = 177 n = 1 (0.6%)	**CC_{HD} + $ACEi_{LD}$** N = 342 n = 12 (3.5%)	**CC_{LD} + $ACEi_{LD}$** N = 117 n = 8 (6.8%)	CC_{00} + $ACEi_{LD}$ N = 174 n = 0 (0.0%)

$ACEi_{HFD}$ = 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] Definition used in exploratory safety analyses; [b] Dose of candesartan preceding the event (or at last visit if no event occurred)
n = number of patients with one or more events (proportion (%) of patients at the dose)

7.4.4 Relationship of dose of candesartan to permanent study drug discontinuation due to increased serum creatinine

In Table 103, no relationship is apparent between the dose of candesartan and the numbers and frequencies of permanent study drug discontinuation due to increased serum creatinine.

Table 103 The numbers and frequencies of permanent study drug discontinuation due to increased creatinine in patients who received high or low dose candesartan plus ACE inhibitors at heart failure dose or low dose– CHARM-Added (SH-AHS-0006) Study

	$ACEi_{HFD}$ (N=643)			$ACEi_{LD}$ (N=633)		
Candesartan cilexetil[b]	**CC_{HD} + $ACEi_{HFD}$** N = 385 n = 32 (8.3%)	**CC_{LD} + $ACEi_{HFD}$** N = 105 n = 20 (19.1%)	**CC_{00} + $ACEi_{HFD}$** N = 153 n = 2 (1.3%)	**CC_{HD} + $ACEi_{LD}$** N = 351 n = 25 (7.1%)	**CC_{LD} + $ACEi_{LD}$** N = 127 n = 20 (15.8%)	CC_{00} + $ACEi_{LD}$ N = 155 n = 1 (0.7%)

$ACEi_{HFD}$ = 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] Definition used in exploratory safety analyses; [b] Dose of candesartan preceding the event (or at last visit if no event occurred)
n = number of patients with one or more events (proportion (%) of patients at the dose)

7.4.5 Relationship of dose of candesartan to dose reductions of study drug due to an adverse event or an abnormal laboratory value

In Table 104, no relationship is apparent between the dose of candesartan and the numbers and frequencies of dose reductions of study drug due to an adverse event or an abnormal laboratory value.

Table 104 The numbers and frequencies of dose reductions of study drug due to an adverse event or an abnormal laboratory value[a] in patients who received high or low dose candesartan plus ACE inhibitors at heart failure dose or low dose– CHARM-Added (SH-AHS-0006) Study

	$ACEi_{HFD}$ (N=643)			**$ACEi_{LD}$ (N=633)**		
Candesartan cilexetil[b]	**CC_{HD} + $ACEi_{HFD}$** N = 403 n = 88 (21.8%)	**CC_{LD} + $ACEi_{HFD}$** N = 83 n = 35 (42.2%)	**CC_{00} + $ACEi_{HFD}$** N = 157 n = 1 (0.6%)	**CC_{HD} + $ACEi_{LD}$** N = 380 n = 95 (25.0%)	**CC_{LD} + $ACEi_{LD}$** N = 101 n = 43 (42.6%)	CC_{00} + $ACEi_{LD}$ N = 152 n = 3 (2.0%)

$ACEi_{HFD}$ = 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] Definition used in exploratory safety analyses; [b]Dose of candesartan preceding the event (or at last visit if no event occurred)
n = number of patients with one or more events (proportion (%) of patients at the dose)

7.5 Summary of Safety

7.5.1 Summary of safety for CHARM-Added (SH-AHS-0006) Study:

Adverse events (AEs) were reported for approximately equal proportions of patients in the two treatment groups, both as analyzed during treatment with the investigational product (placebo 979, 77.0%; candesartan 1007, 78.9%) and over the entire study period (placebo 992, 78.0%; candesartan 1026, 80.4%).

Serious adverse events (SAEs) occurred in equal frequency in both treatment groups during study (placebo 75.9%, candesartan 75.9%). Fatal SAEs were less common with candesartan, on treatment with the investigational product (placebo 21.7%; candesartan 16.5%) as well as during the study (placebo 32.5%; candesartan 29.5%). The most common fatal SAEs were CV events and these occurred less frequently in the candesartan treatment group during study (placebo 27.3%; candesartan 23.7%).

24.3% of patients in the candesartan group and 17.6% of the placebo group permanently discontinued treatment with the investigational product due to an AE or an abnormal laboratory finding. 17.2% of the patients receiving candesartan and 9.7% receiving placebo required a reduction in the investigational product dose.

Discontinuations and dose reductions attributed to decline in renal function (placebo 4.2%; candesartan 8.2%), hypotension (placebo 3.5%; candesartan 5.4%) and hyperkalemia (placebo 0.9%; candesartan 3.8%) were more frequent in the candesartan group.

Differences in mean laboratory values (candesartan compared with placebo) were small and in

keeping with expected values for treatment with inhibitors of the renin-angiotensin-aldosterone system, i.e., slightly higher serum potassium and creatinine levels.

Mean blood pressure from baseline to LVCF (SBP and DBP) was lowered in both treatment groups. Mean body weight was slightly decreased in the placebo group and increased in the candesartan group.

The following findings are significantly different between the two treatment groups:

- Candesartan reduced *time* to permanent discontinuation of the investigational product due to any cause ($P < 0.001$).
- Candesartan increased the *number* of permanent discontinuations of the investigational product due to any cause ($P < 0.001$).
- Candesartan reduced *time* to permanent discontinuation of the investigational product due to an AE or an abnormal laboratory value ($P < 0.001$).
- Candesartan increased the *number* of permanent discontinuations of the investigational product due to an AE or an abnormal laboratory value ($P < 0.001$).
- Candesartan increased the *number* of dose reductions due to an AE or an abnormal laboratory value at least once ($P < 0.001$).

Thus, candesartan appears to be safe and well tolerated. Discontinuations and dose reductions attributed to a decline in renal function, hypotension and hyperkalemia occur more frequently with candesartan than placebo. The AE profile of candesartan in heart failure patients is consistent with the pharmacology of the drug and the health status of the patients.

7.5.2 Summary of safety for CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

7.5.2.1 Summary of safety in the total population of patients with symptomatic CHF (SH-AHS-0003, 0006, 0007)

In the total population of patients with symptomatic CHF (SH-AHS-0003, SH-AHS-0006, SH-AHS-0007) AEs were reported for almost equal proportions of patients in the two treatment groups, both during treatment with the investigational drug (placebo 2732, 72.0%; candesartan 2788, 73.3%) and over the entire study period (placebo 2799, 73.7%; candesartan 2841, 74.7%).

SAEs, fatal and non-fatal, occurred less frequently with candesartan than with placebo on treatment (placebo 67.5%; candesartan 63.4%) as well as during the study, whether on or off treatment (placebo 71.1%; candesartan 69.0%). Fatal SAEs were also less common with candesartan (placebo 16.2%; candesartan 13.3%) on treatment as well as during the study (placebo 24.9%; candesartan 23.3%). The most common fatal SAEs were CV events which occurred less frequently in the candesartan treatment group during study (placebo 20.3%; candesartan 18.2%)

16.1% of patients in placebo group and 21.0% in candesartan group permanently discontinued treatment with the investigational product due to an AE or an abnormal laboratory finding.

8.5% of the patients receiving placebo and 15.0% of the patients receiving candesartan required a reduction in the investigational product dose.

Discontinuations and dose reductions attributed to decline in renal function, hypotension and hyperkalemia were more frequent in the candesartan group. Cardiac failure aggravated (placebo 4.9%; candesartan 4.3%), abnormal renal function (placebo 2.9%; candesartan 6.3%), hypotension (placebo 2.0%; candesartan 4.1%) and hyperkalemia (placebo 0.6%; candesartan 2.4%) were the most commonly reported AEs associated with discontinuation of the investigational product.

The differences in mean laboratory values (candesartan compared with placebo), and the frequency of abnormal values were within expected findings for treatment with inhibitors of the RAAS, i.e., slightly higher serum potassium and creatinine levels.

Mean blood pressure from baseline to LVCF (SBP and DBP) was lowered in both treatment groups.

Mean body weight was slightly decreased in the placebo group and increased in the candesartan group.

7.5.2.2 Summary of safety in the population of patients with depressed LV systolic function (SH-AHS 0003, 0006)

The safety findings in the subpopulation of patients with depressed LV systolic function (SHAHS-0003, SH-AHS-0006) were similar to those in the total population, although the absolute AE rate in the patients with depressed LV systolic function were higher than in the total population. Between-treatment differences (candesartan versus placebo) were very similar to those noted for the total population.

AEs were reported for approximately equal numbers of patients in the two treatment groups (placebo 76.0%; candesartan 77.2%), over the entire study period.

SAEs, fatal and non-fatal, occurred less frequently with candesartan treatment (placebo 70.2%; candesartan 65.8%). Fatal SAEs were also less common with candesartan treatment (placebo 20.2%; candesartan 16.4%). The most common fatal SAEs were CV events.

18.4% in the placebo group and 23.2%of the patients in the candesartan group permanently discontinued treatment with the investigational product due to an AE or an abnormal laboratory finding.

Discontinuations and dose reductions attributed to decline in renal function, hypotension and hyperkalemia were more frequent in the candesartan group. Abnormal renal function (placebo, 3.4%; candesartan, 7.4%), hypotension (placebo, 2.5%; candesartan, 5.0%) and hyperkalemia (placebo, 0.6%; candesartan, 3.1%) were the most commonly reported AEs associated with

discontinuation of the investigational product. In the candesartan group the frequency of discontinuation for hyperkalemia relative to placebo was greater in the oldest age groups.

The following findings are significantly different between the two treatment groups:

- Candesartan reduced *time* to permanent discontinuation of investigational product due to any cause ($p < 0.001$).
- Candesartan increased the *number* of investigational product discontinuations due to any cause ($p < 0.001$).
- Candesartan reduced *time* to permanent discontinuation of investigational product due to an AE or an abnormal laboratory value ($p < 0.001$).
- Candesartan increased the *number* of permanent investigational product discontinuations due to an AE or an abnormal laboratory value ($p < 0.001$).
- Candesartan increased the *number* of dose reductions due to any cause ($p < 0.001$).
- Candesartan increased the *number* of dose reductions due to an AE or an abnormal laboratory value ($p < 0.001$).

Thus, candesartan appears to be safe and well tolerated. Discontinuations and dose reductions attributed to a decline in renal function, hypotension and hyperkalemia occur more frequently with candesartan than placebo. The AE profile of candesartan in heart failure patients is consistent with the pharmacology of the drug and the health status of the patients.

Overall conclusions

Candesartan appears to be safe and well tolerated in this population of patients with chronic heart failure. Discontinuations and dose reductions attributed to a decline in renal function, hypotension and hyperkalemia occur more frequently with candesartan than placebo. The AE profile of candesartan in heart failure patients is consistent with the pharmacology of the drug and the health status of the patients.

7.5.3 Pooling Data Across Studies to Estimate and Compare Incidence

The sponsor submitted pooled safety data from all of the CHARM Program studies (SH-AHS-0003, -0006 and -0007). I have presented and discussed the data from this pivotal study (SH-AHS-0006) and the overall CHARM-Pooled data in my safety review above. Safety data from the clinical pharmacology studies and from the non-CHARM studies are generally consistent with data from the CHARM-Pooled studies.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

8.1.1 Dose of Candesartan (or ARB)

An insufficient dose of ARBs used in previous clinical trials may have contributed to the observed lack of beneficial effect of ARBs on mortality. In the ELITE[19] and ELITE II[20] studies, the dose of losartan (50 mg q.d.) was chosen based on the effects of losartan in hypertensive patients, where the antihypertensive dose-response curve to losartan peaks at about 50 mg/day and plateaus at higher doses. This dose may not fully block AT_1 receptors throughout the 24-hour dosing interval.

In a study on human volunteers[21] where each subject was challenged with a pre-determined blood pressure elevating-dose of angiotensin II (to raise radial artery systolic pressure by 20 mmHg) after oral dosing with placebo, losartan 50 mg or losartan 150 mg, only the higher dose of 150 mg losartan was found adequate to produce a maximum inhibition of the pressor response to angiotensin II (Figure 41). Thus, the dose used in ELITE[19] and ELITE II[20] may have been insufficient to substantially block the AT_1 receptor. ELITE II showed no survival advantage of losartan over captopril; the insufficient dose of losartan used may, at least in part, be the reason for this lack of effect.

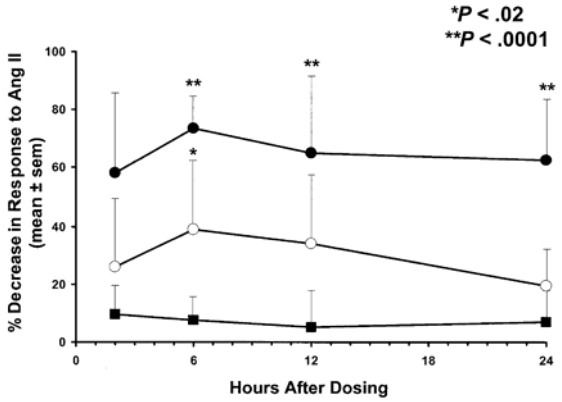


Figure 41 Blockade of the pressor response to intravenous infusions of angiotensin II (Ang II) in normal volunteers after oral administration of placebo (■), losartan 50 mg (○), or losartan 150 mg (●). * P < 0.02, ** P < 0.0001 compared with placebo. (Based on data from J Cardiovasc Pharmacol 2001; 37: 692-6)[21].

Also, in the OPTIMAAL (Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan) trial[22], losartan (at a dose of 50 mg q.d.) was compared to the ACE inhibitor captopril (at a dose of 150 mg/day) in high-risk patients with acute myocardial infarction (Figure 42). The results were in favor of captopril both for all cause mortality (not significant, P = 0.069) and for cardiovascular mortality (P=0.032). In this case, too, an insufficient dose of losartan can be attributed as a reason for the failure to show superiority of losartan over captopril.

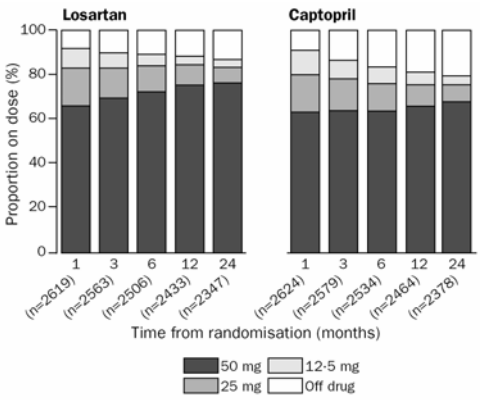


Figure 42 Dose of study drug Losartan was administered once daily and captopril three times daily. (OPTIMAAL Study)[22] (Based on data from Lancet 2002; 360: 752-60.)

In contrast, in two recent clinical trials[23,24] in which the dose of losartan was increased gradually to 100 mg per day in asymptomatic patients with hypertension and ECG evidence of left ventricular hypertrophy, a significant survival benefit among high-risk patients was observed.

In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, 9,193 participants 55-80 years old with essential hypertension and left ventricular hypertrophy ascertained by ECG, were randomly assigned to receive losartan (titrated to 100 mg) or atenolol (titrated to 100 mg) once daily[23]. A significant reduction (by 15%, P = 0.009) in the primary composite endpoint of cardiovascular mortality, stroke and MI was found in the subjects treated with losartan (Figure 43).

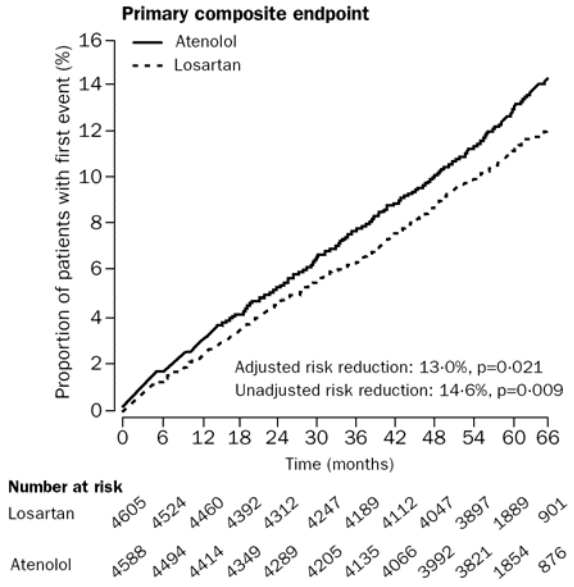


Figure 43 Kaplan Meier curves for primary composite endpoint (LIFE study)[23] (Based on data from Lancet 2002; 359: 995-1003.)

In the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan

(RENAAL) study, 1,513 patients with type II diabetes and nephropathy were randomized to receive losartan (50-100 mg once daily) or placebo, in addition to conventional antihypertensive treatment, for a mean of 3.4 years[24]. The primary outcome was the composite of a doubling of the base-line serum creatinine concentration, end-stage renal disease, or death. Losartan reduced the primary endpoint significantly (relative risk reduction = 16%, P=0.02), and also reduced the incidence of doubling of serum creatinine concentration (relative risk reduction= 25%, P=0.006) and end-stage renal failure (relative risk reduction= 28%; P=0.002), and also reduced the rate of first hospitalization for heart failure (relative risk reduction= 32%, P=0.005) but had no effect on the rate of death (Table 105).

Table 105 Incidence of the primary composite endpoint and its components in RENAAL study[24] (Based on data from N Engl J Med 2001; 345: 861-9.)

End Point	Losartan Group (N=751)		Placebo Group (N=762)		P Value	Risk Reduction
	no. (%)	no./100 patient-yr	no. (%)	no./100 patient-yr		% (95% CI)
Primary composite end point†	327 (43.5)	15.9	359 (47.1)	18.1	0.02	16 (2 to 28)
Doubling of serum creatinine concentration	162 (21.6)	7.9	198 (26.0)	10.0	0.006	25 (8 to 39)
End-stage renal disease	147 (19.6)	6.8	194 (25.5)	9.1	0.002	28 (11 to 42)
Death	158 (21.0)	6.8	155 (20.3)	6.6	0.88	−2 (−27 to 19)
End-stage renal disease or death	255 (34.0)	11.7	300 (39.4)	14.1	0.01	20 (5 to 32)
Doubling of serum creatinine concentration and end-stage renal disease	226 (30.1)	11.0	263 (34.5)	13.2	0.01	21 (5 to 34)

†The primary endpoint was a composite of a doubling of the base-line serum creatinine concentration, end-stage renal disease, or death.

However, when lower doses of ARBs were used, a survival benefit was not found. In a recent trial of valsartan and captopril in myocardial infarction complicated by heart failure and/or left ventricular dysfunction (VALIANT)[25], 14,808 patients were randomized (1:1:1 ratio) to receive either valsartan (titrated to 160 mg b.i.d.), captopril (titrated to 50 mg t.i.d.) or the combination of valsartan (titrated to 80 mg b.i.d.) plus captopril (titrated to 50 mg t.i.d.), beginning 12 hours to 10 days after a myocardial infarction, and followed up to a median of 24.7 months. This study was designed to assess non-inferiority of valsartan relative to captopril. All-cause mortality was 19.9% in the valsartan group, 19.5% in the captopril group and 19.3% in the combination (valsartan-and-captopril) group. The hazard ratio for death in the valsartan group vs. captopril group was 1.00 (97.5% CI: 0.90 to 1.11, P=0.98), and the hazard ratio for death in the valsartan plus captopril group vs. captopril group was 0.98 (97.5% CI: 0.89 to 1.09, P=0.73) (Table 106).

Table 106 Cardiovascular mortality and morbidity in VALIANT trial[25] (Based on data from N Engl J Med 2003; 349: 1893-1906.)

End Point	Valsartan Group (N=4909)	Valsartan-and-Captopril Group (N=4885)	Captopril Group (N=4909)	Valsartan vs. Captopril			Valsartan and Captopril vs. Captopril	
				Hazard Ratio (97.5% CI)	P Value	P Value for Non-inferiority	Hazard Ratio (97.5% CI)	P Value
		number (percent)						
Death from cardiovascular causes	827 (16.8)	827 (16.9)	830 (16.9)	0.98 (0.87–1.09)	0.62	0.001	1.00 (0.89–1.11)	0.95
Death from cardiovascular causes or myocardial infarction	1102 (22.4)	1096 (22.4)	1132 (23.1)	0.95 (0.87–1.05)	0.25	<0.001	0.96 (0.88–1.06)	0.40
Death from cardiovascular causes or heart failure	1326 (27.0)	1331 (27.2)	1335 (27.2)	0.97 (0.90–1.05)	0.51	<0.001	1.00 (0.92–1.09)	0.94
Death from cardiovascular causes, myocardial infarction, or heart failure	1529 (31.1)	1518 (31.1)	1567 (31.9)	0.95 (0.88–1.03)	0.20	<0.001	0.97 (0.89–1.05)	0.37
Death from cardiovascular causes, myocardial infarction, heart failure, resuscitation after cardiac arrest, or stroke	1612 (32.8)	1580 (32.3)	1641 (33.4)	0.96 (0.89–1.04)	0.25	<0.001	0.96 (0.89–1.04)	0.26

The VALIANT study[25] showed that valsartan and captopril were equivalent in terms of overall mortality and in terms of the composite endpoint of fatal and nonfatal cardiovascular events, whereas the combination (valsartan plus captopril) therapy resulted in an increase in adverse events without improving overall survival.

It has been suggested that the lack of beneficial effect of losartan (ELITE[19], ELITE II[20] and OPTIMAAL[22] trials) and valsartan (VALIANT[25] trial) over ACE inhibitors may be due to the fact that a correct (or high enough) dose of the ARB was not used[26].

CHARM-Added (SH-AHS-0006) Study

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.

Primary efficacy endpoint of CV mortality or CHF hospitalization (confirmed, adjudicated):
Please refer to section 6.1.5 (pages 72-77) of this review. 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 41. 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 42).

The secondary efficacy endpoint of all-cause mortality or CHF hospitalization (Table 43 and Table 44), and for secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI (Table 45 and Table 46) also show similar findings.

As discussed earlier, 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) 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.

8.1.2 ACE inhibitor dose

ACC/AHA guidelines recommend ACE inhibitors as the first-line therapy for symptomatic CHF with reduced systolic function and for asymptomatic LV dysfunction[27]. Treatment with ACE inhibitors has been proven to be effective in reducing mortality in CHF[28]. However, in a proportion of patients with congestive heart failure, there are increased plasma angiotensin II levels despite ACE inhibitor therapy resulting in death or decompensated heart failure[29]. While the reasons are not clear, ACE inhibitors block only 13% of the total production of angiotensin II in the human heart due to the existence of ACE-dependent pathways[3]; thus, it is possible that an effective blockade of the RAAS may require larger than standard doses of ACE inhibitor[30]. It is generally thought that to achieve a reduction in mortality in CHF patients, ACE inhibitors must

be used at heart failure doses[31] that have been shown to demonstrate a reduction in mortality and morbidity (Table 107). For the SH-AHS-0006 study, the protocol required that each investigator stated whether the patient was on individualized heart failure dose of ACE inhibitor.

Table 107 Target doses of ACE inhibitors for heart failure used in studies that demonstrate a reduction in mortality and morbidity[31]

ACE inhibitors used in clinical trials in heart failure	Starting dose	Target dose	Clinical Trial	Average dose in study
Captopril	6.25 mg t.i.d.	25 - 50 mg t.i.d.	SAVE	not available
Enalapril	5 mg b.i.d.	10 mg b.i.d.	SOLVD P/T	16-18 mg
Fosinopril	10 mg q.d.	40 mg q.d.	FEST	not available
Lisinopril	2.5 mg q.d.	40 mg q.d.	ATLAS	19 mg
Ramipril	2.5 mg b.i.d.	5 mg b.i.d.	AIRE	not available
Trandalopril	1 mg q.d.	4 mg q.d.	TRACE	not available

The dose of other ACE inhibitors used should be chosen to equate with the above doses.
AIRE = Acute Infarction Ramipril Efficacy; ATLAS = Assessment of Treatment with Lisinopril and Survival; FEST = Fosinopril Efficacy/Safety Trial; SAVE = Survival and Ventricular Enlargement trial; SOLVD P/T = Studies of Left Ventricular Dysfunction (Prevention/Treatment); TRACE = Trandalopril Cardiac Evaluation.

The mean daily dose of enalapril at baseline was 17.0 mg, which compares to 16.6 mg (in those taking drug) in the treatment arm of the Studies Of Left Ventricular Dysfunction (SOLVD)[32] and 17.0 mg in Val-HeFT[16]The mean daily dose of lisinopril was 18.0 mg which is also comparable to the 18.0 mg dose in the treatment arm of Val-HeFT[16]. However, for those on captopril, the main daily dose in the CHARM-Added study was lower (82 mg/day) compared to the dose used (107 mg/day) VALIANT[25] trial. It is possible that in a background of a relatively low dose of an ACE inhibitor (i.e., patients on captopril and patients on low dose ACE inhibitors for reasons of intolerance to higher doses in the CHARM-Added study) there would be more room for improvement with candesartan.

Table 108 shows that for the primary endpoint of CV death or hospitalization due to CHF, there was a statistically significant reduction in relative risk for patients treated with candesartan which was associated with use of ACE inhibitors at baseline (RRR = 14.9%, P=0.010), during the study (RRR = 14.8%, P=0.011), and at the visit preceding the event (RRR = 11.8%, P=0.046). Also, a statistically significant reduction in relative risk the primary endpoint of CV death or hospitalization due to CHF for patients treated with candesartan was associated with use of recommended heart failure dose of ACE inhibitors at baseline (RRR = 20.6%, P=0.010), during the study (RRR = 19.08%, P=0.010), and at the visit preceding the event (RRR = 17.7%, P=0.026).

Table 108 CV death or hospitalization due to CHF (confirmed adjudicated) by use of ACE-inhibitors in study SH-AHS-0006. Comparison of candesartan vs. placebo with Cox regression. ITT/Safety population.

Variable	Group	N	Events cand. cil.	Events plac-ebo	Hazard Ratio	95% CI		p-value
						Lower	Upper	
ACE inhibitors	No	2	0	0				
	Yes	2546	483	538	0.851	0.753	0.963	0.010
ACE inhibitors: Recommended heart failure dose	No	1257	251	263	0.915	0.770	1.088	0.314
	Yes	1291	232	275	0.794	0.666	0.945	0.010
ACE inhibitors during study	No	1	0	0				
	Yes	2547	483	538	0.852	0.753	0.963	0.011
ACE inhibitors during study: Recommended heart failure dose	No	1012	213	208	0.910	0.751	1.101	0.331
	Yes	1535	270	330	0.810	0.689	0.951	0.010
ACE inhibitors at the visit preceding the event	No	1527	0	0				
	Yes	1021	483	538	0.882	0.779	0.998	0.046
ACE inhibitors at the visit preceding the event: Recommended heart failure dose	No	479	233	246	0.947	0.791	1.134	0.556
	Yes	542	250	292	0.823	0.694	0.977	0.026

The reduction in relative risk of cardiovascular death or CHF hospitalization (primary efficacy endpoint) was present in patients taking recommended heart failure dose of ACE inhibitors as shown in Figure 44 below.

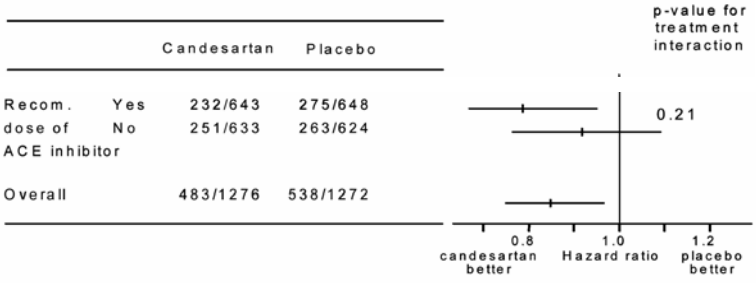


Figure 44 Effect of candesartan compared with placebo on primary outcome in all patients, and patients taking or not taking recommended dose of ACE inhibitors at baseline.

However, I do not think that it is appropriate to just compare the mean daily dose of ACE inhibitors used. As mentioned above, the CHARM-Added (SH-AHS-0006) study consists of CHF patients on "heart-failure doses" of ACE inhibitors and those on "low doses" of ACE inhibitors. One would expect that in a background of a relatively low dose of an ACE-inhibitor, there would be more room for improvement with additional Renin-Angiotensin System (RAS) blockade produced by candesartan. The study's findings contradict this concept (Table 109, below); i.e., candesartan treatment on top of ACE inhibitor treatment was associated with a significant reduction in CV deaths or CHF hospitalizations in the sub-group of CHF patients

receiving high-dose ACE inhibitors (A vs. C in Table 109), and NOT in those receiving low-dose ACE inhibitors (B vs. D in Table 109).

Table 109 Comparison of the primary efficacy endpoints for patients treated with candesartan versus those treated with candesartan plus an ACE inhibitor

Primary Efficacy Endpoint	Overall Study AHS-0006	Cc on top of $ACEi_{HFD}$	Cc + $ACEi_{LD}$	Cc in AHS-0003	$ACEi_{HFD}$ on top of Cc	$ACEi_{HFD}$ vs. $ACEi_{LD}$	CC + $ACEi_{HFD}$ vs. $ACEi_{LD}$
CV deaths or CHF hospitalizations:	A+B vs. C+D	A vs. C	B vs. D	~B vs. ~D	A vs. B	C vs. D	A vs. D
Hazard Ratio Relative Risk Reduction P	HR = 0.853; RRR = 14.7% P = 0.011	HR = 0.794 RRR= 20.6% P = 0.010	HR = 0.915 RRR = 8.5% P = 0.314	HR = 0.768 RRR= 23.2% P < 0.001	HR = 0.874 RRR = 12.6% P = NA	HR = 1.006 RRR = NA P = NA	HR = 0.799 RRR= 20.1% P = 0.0127

A, B, C and D = Reference to cells in Table 37.

This finding in the CHARM-Added study is difficult to explain. The ATLAS (Assessment of Treatment with Lisinopril and Survival)[12] study evaluated the effect of high dose lisinopril (32.5 to 35 mg/day, n = 1,568) versus low dose lisinopril (2.5 to 5 mg/day, n = 1,596) in the treatment of 3,164 patients with CHF (NYHA class III and LVEF ≤ 0.30) with a 39 – 58 months follow-up time. This study showed that all-cause mortality was NOT statistically significant between groups, but high dose lisinopril produced a significant 12% reduction (P=0.002) in the relative risk of the composite endpoint of death or hospitalization for any reason, and significantly (P<0.001) reduced the relative risk for the composite endpoint of all-cause deaths or CHF hospitalizations by 15%, compared with the low-dose regimen (Table 110).

Table 110 Effect of high and low dose lisinopril on major clinical events (ATLAS Study)[12] (Based on data from Circulation 1999; 100: 2312-8.)

	Low-Dose	High-Dose	Hazard Ratio	*P*
All-cause mortality	717 (44.9)	666 (42.5)	0.92 (0.82–1.03)	0.128
Cardiovascular mortality	641 (40.2)	583 (37.2)	0.90 (0.81–1.01)	0.073
All-cause mortality+hospitalization for any reason	1338 (83.8)	1250 (79.7)	0.88 (0.82–0.96)	0.002
All-cause mortality+hospitalization for cardiovascular reason	1182 (74.1)	1115 (71.1)	0.92 (0.84–0.99)	0.036
All-cause mortality+hospitalization for heart failure*	964 (60.4)	864 (55.1)	0.85 (0.78–0.93)	<0.001
Cardiovascular mortality+hospitalization for cardiovascular reason	1161 (72.7)	1088 (69.4)	0.91 (0.84–0.99)	0.027
Fatal and nonfatal myocardial infarction+hospitalization for unstable angina	224 (14.0)	207 (13.2)	0.92 (0.76–1.11)	0.374

Values in parentheses indicate percentage or range. *P* values determined by log-rank test. Hazard ratios represent 95% CI, except for all-cause mortality, shown as 96.1% CI.
*Analysis not specified in protocol before breaking the blind.

In contrast, the NETWORK (Clinical Outcome with Enalapril in Symptomatic Chronic Heart Failure)[33] trial found no differences between high-dose and low-dose treatment groups for any of the endpoints measured among 1,532 patients with NYHA class II (65% of patients) to class III/IV (35% of patients) heart failure randomized to receive enalapril 2.5 mg b.i.d., 5 mg b.i.d. or 10 mg b.i.d., followed up for 24 weeks. It is possible that even maximally recommended doses of ACE inhibitors do not completely prevent ACE-mediated formation of angiotensin II in CHF[34].

In a study of 75 patients with CHF randomized to low- (5 mg daily) and high-dose (40 mg daily) enalapril in a double-blind trial[13], the cardiac dimensions did not change with either high- or low-dose enalapril with the exception of the thickness of the interventricular septum (Table 111).

Table 111 Echocardiographic Characteristics of the CHF Patients Participating in the Low-Dose (5 mg/ day) Versus High-Dose (40 mg/ day) Enalapril Study[13]

		Baseline Mean	End of Study Mean	Change From Baseline (mean [SD])
LV ED (cm)	Low	7.1	7.3	0.1 (0.6)
	High	7.1	6.9	−0.2 (1.1)
LV ES (cm)	Low	6.1	6.1	−0.0 (0.6)
	High	6.2	5.9	−0.1 (0.8)
IVS (cm)	Low	0.98	0.99	−0.01 (0.23)
	High	1.01	0.91	−0.12 (0.25)*
LVPW (cm)	Low	1.01	1.02	0.02 (0.27)
	High	1.02	0.99	−0.08 (0.20)
LV EF (%)	Low	24.4	27.1	3.6 (8.5)
	High	21.0	26.3	3.6 (12.8)

LV ED and LV ES = left ventricular end diastolic and systolic dimensions, respectively; IVS = interventricular septum thickness; LVPW = left ventricular posterior wall thickness; LV EF = left ventricular ejection fraction.
*$p < 0.05$ versus baseline.

The High Enalapril Dose Study Group[14] enrolled 248 patients with advanced CHF who were randomized to receive a maximal tolerated dose of enalapril, up to 20 mg/day in Group 1 (mean dose achieved 17.9 ± 4.3 mg/ day, n=122) and 60 mg/day in Group 2 (mean dose achieved 42 ± 19.3 mg/day, n=126). There were 22 deaths (18.03%) in Group 1, and 23 deaths (18.25%) in Group 2 (hazard ratio = 0.998; confidence interval [CI 0.556 to 1.790, p=0.995) (Figure 45).

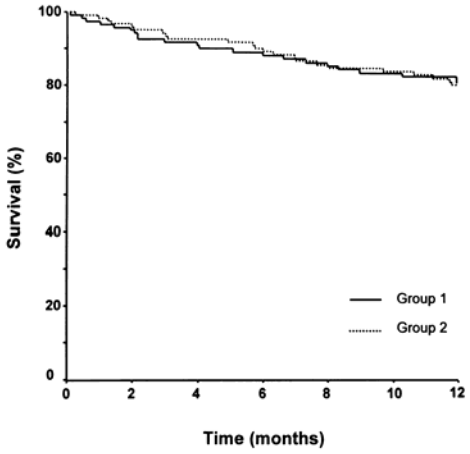


Figure 45 Cumulative mortality in Groups 1 and 2 of High Enalapril Dose Study[14]. (Based on data from (J Am Coll Cardiol 2000; 36: 2090-5.)

No statistically significant differences in survival were observed in subgroup analyses in terms of age, etiology of heart failure, SBP, ejection fraction and HR when using high dose enalapril as a covariant for each subgroup. No difference was found when death and hospital admission were used as a composite end point for statistical analysis (p=0.645, log-rank test) (Figure 46).

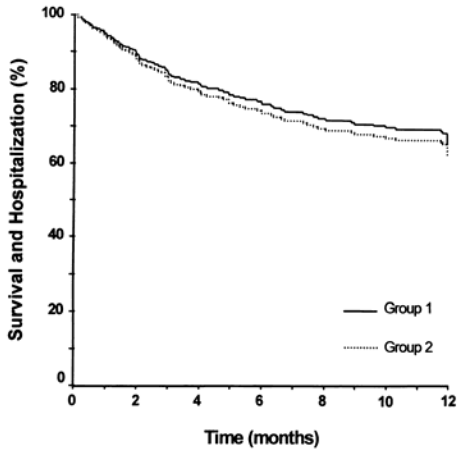


Figure 46 Cumulative incidence of composite end point of mortality and hospital admission in the two treatment groups in High Enalapril Dose Study [14]. (Based on data from (J Am Coll Cardiol 2000; 36: 2090-5.)

The above findings need to be considered in the context of actual clinical practice where the doses of ACE inhibitors used are often less than those demonstrated to be of benefit in clinical trials, mostly because of concern for perceived adverse effects at higher doses. Currently, most physicians are of the opinion that the difference in efficacy between intermediate and high doses of an ACE inhibitor (if any) is likely to be small. The ACC/AHA recommended that patients with CHF should not generally be maintained on very low doses of an ACE inhibitor unless these are the only doses that can be tolerated[27]. Thus, the survival benefit of candesartan that is seen in patients receiving full "heart-failure doses" of ACE inhibitors may not be translated into actual clinical practice in the management of chronic heart failure at the primary care level.

The results in the CHARM-Added (SH-AHS-0006) study suggest that the CHF patients in the CHARM studies who were on "low doses" of ACE inhibitors may have been at an optimal dosage that they could just tolerate, and thus were obtaining a balanced mortality/morbidity benefit without accruing any potential adverse effects that could have arisen from the addition of ARBs to ACE inhibitors in their clinically delicate condition. As discussed above, randomized trials of ACE inhibitors have shown no difference in mortality between patients receiving high-dose ACE inhibitors and those receiving low-dose ACE inhibitors[12,13,14,15].

8.2 Drug-Drug Interactions

In general, patients in the CHARM Program studies were also receiving aggressive heart failure treatment with combinations of diuretics, β-blockers and digitalis as well as individually optimized doses of ACE inhibitors prior to randomization.

CHARM-Added (SH-AHS-0006) Study

At the time of randomization, 99.9% of the patients were on treatment with ACE-inhibitors (as required by the protocol), 56% were on treatment with a β-blocker, 90% with diuretics, 58% with digitalis and 17% were treated with spironolactone, without major differences between treatment groups.

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.

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

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.

CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies

At the time of randomization, the CHF patients in the total CHARM-Pooled population were receiving conventional heart failure treatments including diuretics (6,286, 83%), β-blockers (4,203, 55%), digoxin (3,254, 43%), ACE-inhibitors (3,125, 41%) and spironolactone (1,272, 17%). The most frequently used β-blockers were metoprolol and carvedilol that were taken, respectively, by 26% (1,945 patients) and 13% (980 patients) of the patient population. These two β-blockers accounted for about 70% of the β-blocker use within this patient population.

At the closing visit, there were more patients in the placebo group receiving diuretics (2,195, 77% vs. 2,171, 75%), β-blockers (1,812, 64% vs. 1,765, 61%), digoxin (1,018, 36% vs. 978, 34%), ACE-inhibitors (1,110, 39% vs. 1,051, 36%) and spironolactone (625, 22% vs. 501, 17%).

The efficacy results of the CHARM-Program studies show that the effects on the primary efficacy endpoints (reduction in relative risk of CV death or CHF hospitalization for CHARM-

Added (SH-AHS-0006) and reduction in the relative risk of all-cause mortality for CHARM-Pooled (SH-AHS-0003, -0006, -0007) studies) were present also in patients taking β-blockers or digoxin.

Within the context of my review of this NDA 20-838 Efficacy Supplement #022, I will present and discuss the findings reported in clinical trials in the medical literature in comparison with the results from the CHARM-Added (SH-AHS-0006) trial.

8.2.1 Is there an interaction of candesartan with β-blockers?

β-blockers have been proven to be effective in reducing mortality from heart failure[35,36,37]. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II)[35] in Europe enrolled 2,647 symptomatic patients in New York Heart Association class III or IV, with LVEF ≤ 35%, receiving standard therapy with diuretics and ACE-inhibitors. Patients were assigned bisoprolol 1·25 mg (n= 1,327) or placebo (n= 1,320) daily, the drug being progressively increased to a maximum of 10 mg per day. Patients were followed up for a mean of 1·3 years. Analysis was by intention to treat.

The CIBIS-II study was stopped early, after the second interim analysis, because bisoprolol showed a significant mortality benefit (Table 112). All-cause mortality was significantly lower with bisoprolol than placebo (156 [11·8%] vs. 228 [17·3%] deaths, respectively, with a hazard ratio of 0·66 (95% CI 0·54 – 0·81, P < 0·0001)). There were significantly fewer sudden deaths among patients on bisoprolol than in those on placebo (48 [3·6%] vs. 83 [6·3%] deaths, respectively, with a hazard ratio of 0·56 (95% CI 0·39 – 0·80, P= 0·0011)). Treatment effects were independent of the severity or cause of heart failure.

Table 112 Primary and secondary endpoints and exploratory analyses in CIBIS-II study[35] (Based on data from Lancet 1999; 353: 9-13.)

	Placebo (n=1320)	Bisoprolol (n=1327)	Hazard ratio (95% CI)	p
Primary endpoint				
All-cause mortality	228 (17%)	156 (12%)	0·66 (0·54–0·81)	<0·0001
Secondary endpoints				
All-cause hospital admission	513 (39%)	440 (33%)	0·80 (0·71–0·91)	0·0006
All cardiovascular deaths	161 (12%)	119 (9%)	0·71 (0·56–0·90)	0·0049
Combined endpoint	463 (35)	388 (29%)	0·79 (0·69–0·90)	0·0004
Permanent treatment withdrawals	192 (15%)	194 (15%)	1·00 (0·82–1·22)	0·98
Exploratory analyses				
Sudden death	83 (6%)	48 (4%)	0·56 (0·39–0·80)	0·0011
Pump failure	47 (4%)	36 (3%)	0·74 (0·48–1·14)	0·17
Myocardial infarction	8 (1%)	7 (1%)	0·85 (0·31–2·34)	0·75
Other cardiovascular	23 (2%)	28 (2%)	1·17 (0·67–2·03)	0·58
Non-cardiovascular deaths	18 (1%)	14 (1%)	0·75 (0·37–1·50)	0·41
Unknown cause of death	49 (4%)	23 (2%)	0·45 (0·27–0·74)	0·0012
Hospital admission for worsening heart failure	232 (18%)	159 (12%)	0·64 (0·53–0·79)	0·0001

Numbers refer to patients who presented at least once with given event. For hospital admissions, numbers refer to patients admitted at least once with any cause.

The relatively large Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF)[36] enrolled 3,991 patients with CHF in NYHA class II-IV with EF ≤0.40%, stabilized with optimum standard therapy, in a double-blind randomized controlled study. 1,990 patients were randomly assigned metoprolol CR/XL 12·5 mg (NYHA III–IV) or 25·0 mg once daily (NYHA II), and 2,001 patients were assigned placebo. The target dose was 200 mg once daily and doses were up-titrated over 8 weeks. The primary endpoint was all-cause mortality, analyzed by intention to treat. The MERIT-HF study, too, was stopped by the independent safety committee because all-cause mortality was significantly lower in the metoprolol CR/XL group than in the placebo group (145 [7·2%, per patient-year of follow-up]) vs. 217 deaths [11·0 %], relative risk 0·66 [95% CI 0·53 – 0·81]; p= 0·00009 or adjusted for interim analyses p= 0·0062). There were fewer sudden deaths in the metoprolol CR/XL group than in the placebo group (79 vs. 132, 0·59 [0·45 – 0·78]; p= 0·0002) and fewer deaths from worsening heart failure (30 vs. 58, 0·51 [0·33 – 0·79]; p= 0·0023) (Figure 47).

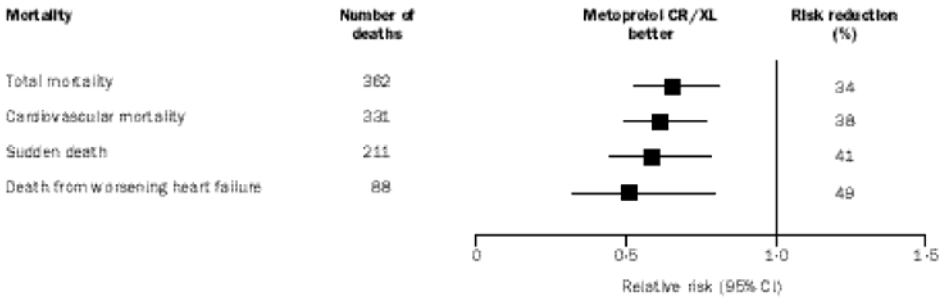


Figure 47 Relative risk (95% CI) for total mortality, cardiovascular mortality, sudden death, and death from worsening heart failure (MERIT-HF study)[36] (Based on data from Lancet 1999; 353: 2001-7.)

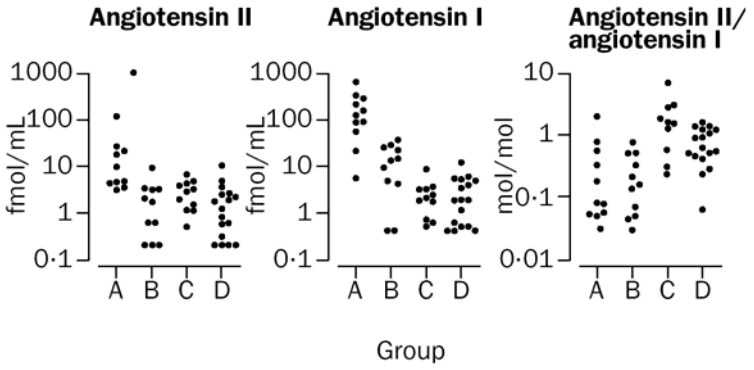


Figure 48 Blood concentrations of angiotensin II and angiotensin I, and angiotensin II/ angiotensin I ratio[29] (Based on data from Lancet 2001; 358: 1609-10.)
Group A= patients with heart failure, receiving ACE inhibitors; Group B= patients with heart failure, receiving ACE inhibitors and β-blockers; Group C= controls; Group D= controls, receiving β-blockers.

β-blockers have been shown to inhibit the activation of the sympathetic nervous system during heart failure and also to reduce renin secretion[38], either of which could result in improved clinical outcome[39]. In a study of two matched groups of patients with NYHA class II-III heart failure receiving maximum tolerated doses of ACE inhibitors, half (11 patients) were randomized to receive β-blockers and the other half (11 patients) did not receive β-blockers[29]. Concentrations

of angiotensin II and angiotensin I (Figure 48) were significantly (P<0.01) higher in the group (Group A) that did not receive β-blockers, whereas patients who received β-blockers (Groups B and D) had low levels of angiotensin II (geometric mean 1·1 [95% CI 0·4 - 2·7] vs. 15·5 [4·6 - 52·6] fmol/mL, 95% CI for difference 3 - 59). Thus, reduction of angiotensin II concentrations by β-blockade might contribute to the therapeutic effects of β-blockade in these CHF patients receiving ACE inhibitors.

In stage II of the RESOLVD (Randomized Evaluation of Strategies for Left Ventricular Dysfunction) Pilot Study, metoprolol CR was added to the treatment of 426 patients with CHF and dilated cardiomyopathy receiving enalapril alone, candesartan alone or both[5,40]. The proportion of patients receiving target doses of ACE inhibitors, candesartan or both was 95% for the group on enalapril alone, 91 % for the group treated with candesartan and 85% for the group treated with enalapril and candesartan. Metoprolol CR did not affect 6-minute walk distance, NYHA functional class or quality of life in any group. However, Figure 49 shows that improvements were seen in LV ejection fraction (increased by 2.4% in the metoprolol CR-treated group, P=0.001), attenuation in the increase in LVEDV (by 6±61 ml, versus 23±65 ml for placebo group, P=0.01) and LVESV (reduced by 2±51ml vs. 19±55 ml for placebo group, P<0.001). There were significantly decreased angiotensin II level (P=0.036) and plasma renin activity (P=0.032), and significantly increased N-terminal atrial natriuretic peptide (ANP) level (P=0.001) and brain natriuretic peptide (BNP) level (P=0.002). There were also fewer deaths in the group receiving metoprolol (3.4%, vs. 8.1 % in the placebo group), but the study was not powered to detect differences in clinical endpoints such as death. This study demonstrated that treatment with candesartan, enalapril *and metoprolol* has a more beneficial effect on cardiac volumes and LVEF than treatment with either enalapril alone, candesartan alone or enalapril and candesartan together without a β-blocker.

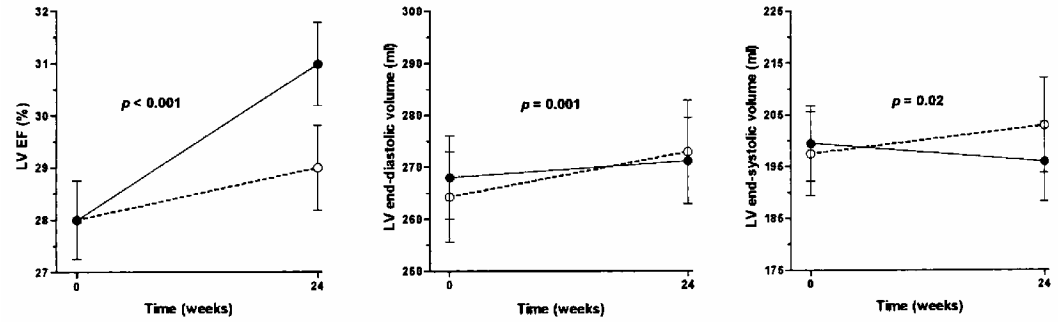
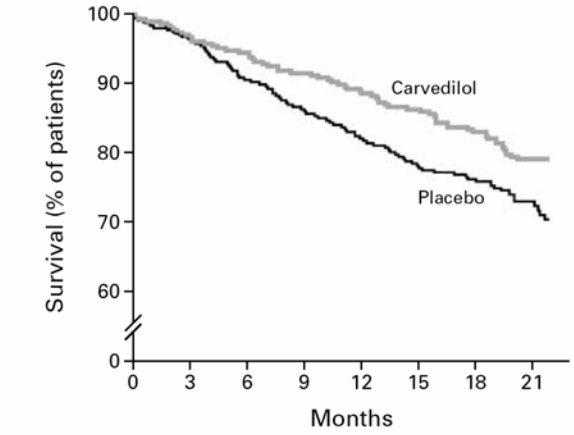


Figure 49 Changes in LVEF and LV volumes in response to metoprolol (●) versus placebo (○) in stage II of the RESOLVD study[40]. Data are mean±SEM. (Based on data from Circulation 2000; 101: 378-84.)

In a later communication dated 16-Sep-2004, the sponsor submitted that there are no other studies on the hemodynamic effects of candesartan in combination with an ACE inhibitor and a β-blocker in patients with heart failure. Also, there are no other reported studies in the medical literature of the hemodynamic effect of this combination treatment in patients with heart failure.

In the COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) Study[37], a total of 2,289 patients with symptomatic heart failure at rest or minimal exertion and with LVEF

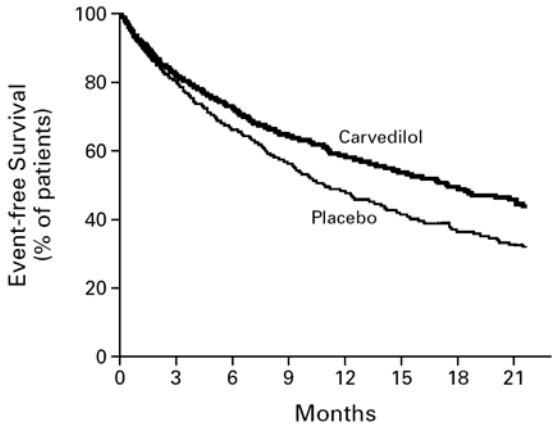
<25% were randomized to receive carvedilol or placebo for a mean period of 10.4 months. They also received conventional heart failure therapy including diuretics, ACE inhibitors or ARBs. There were 190 deaths in the placebo group and 130 deaths in the carvedilol group, reflecting a 35% decrease in the relative risk of death with carvedilol (95% CI 0.19 to 0.48, P = 0.0014, Figure 50). There was also a reduction in the relative risk for the combined endpoint of death or hospitalization by 24% (95% CI 0.13 to 0.33, P<0.001, Figure 51). Thus, addition of carvedilol to conventional therapy for heart failure was beneficial in this group of patients with severe heart failure.



No. of Patients at Risk

Placebo	1133	937	703	580	446	286	183	114
Carvedilol	1156	947	733	620	479	321	208	142

Figure 50 Kaplan-Meier Analysis of Time to Death in Placebo and Carvedilol Groups[37] (Based on data from N Engl J Med 2001; 344: 1651-8.) The 35% lower risk in the carvedilol group was significant: P=0.00013 (unadjusted) and P=0.0014 (adjusted).



No. of Patients at Risk

Placebo	1133	767	513	377	262	154	88	55
Carvedilol	1156	789	559	431	318	208	122	81

Figure 51 Kaplan-Meier Analysis of Time to Death or First Hospitalization for Any Reason in Placebo and Carvedilol Groups[37]. (Based on data from N Engl J Med 2001; 344: 1651-8.)
The 24 percent lower risk in the carvedilol group was significant (P<0.001).

On the other hand, other studies in the medical literature show contradictory findings.

In ELITE II study[20], 3,152 patients with NYHA Class II-IV heart failure and LVEF ≤ 40% were assigned to receive either losartan (50 mg q.d.) or captopril 50 mg t.i.d., and followed up for a median of 1.5 years. Patients were stratified for β-blocker use. The primary and secondary endpoints were all-cause mortality, and sudden death or resuscitated arrest. Median follow-up was 555 days. There were no significant differences in all-cause mortality (11·7 vs. 10·4% average annual mortality rate) or sudden death or resuscitated arrests (9·0 vs. 7·3%) between the losartan and captopril treatment groups (hazard ratios 1·13 [95·7% CI 0·95 – 1·35], p= 0·16 and 1·25 [95% CI 0·98 – 1·60], p= 0·08). No significant interaction was found for concomitant β-blocker use during the study (Figure 52).

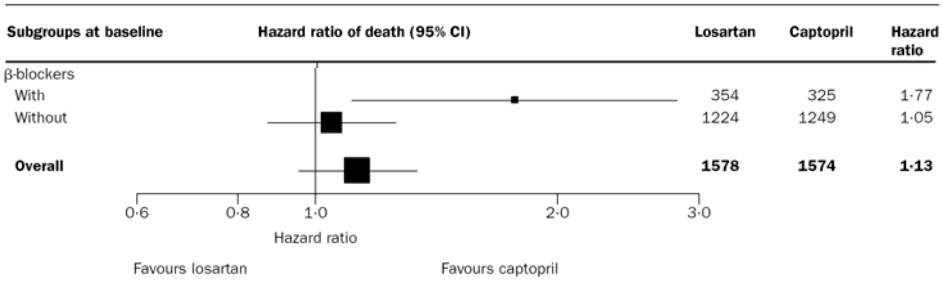


Figure 52 Mortality by subgroup (ELITE II[20]) (Based on data from Lancet 2000; 355: 1582-7.)

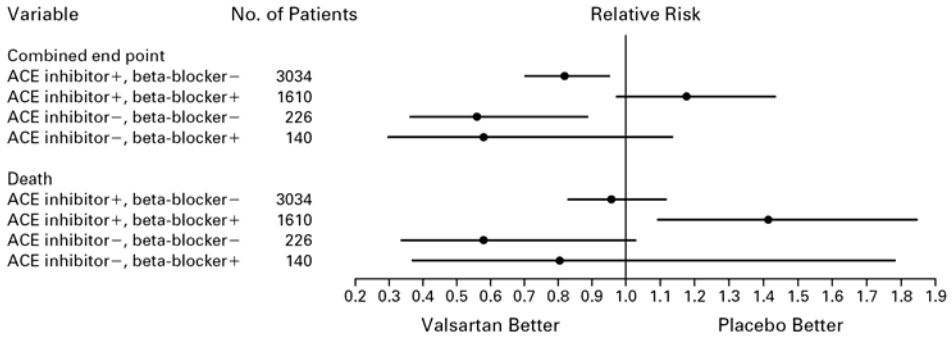


Figure 53 Relative Risks and 95 Percent Confidence Intervals for the Combined End Point (Death from Any Cause, Cardiac Arrest with Resuscitation, Hospitalization for Worsening Heart Failure, or Therapy with Intravenous Inotropes or Vasodilators), According to the Background Therapy at Base Line, in Val-HeFT study[16]. (Based on data from N Engl J Med 2001; 345: 1667-75.)
ACE denotes angiotensin- converting enzyme, + the use of the drug, and – nonuse.

In the Val-HeFT[16,41] study, 5,010 patients with symptomatic CHF (93% already treated with ACE inhibitors) were randomized to receive valsartan (starting dose 40 mg b.i.d., titrated to a target dose of 160 mg b.i.d.) or placebo, and followed for 1.9 years. The study found that patients taking β-blockers at baseline who were randomized to valsartan (36% of all enrolled) did worse than those randomized to placebo; i.e. the former had a 15% ***increased*** risk or morbidity and mortality (P<0.05). The effect of β-blockers are also derived from two sub-groups (Figure 53): (i) in 1,610 patients given triple therapy with ACE inhibitors, β-blockers and

valsartan, there was a significant ***increase*** in mortality (129 vs. 97 deaths, hazard ratio 1.42, 95% CI 1.09-1.85, p = 0.009) compared with 806 patients treated with ACE inhibitors, β-blockers and placebo; and (ii) in 226 patients **not** given ACE inhibitors or β-blockers, there was a 33% reduction in mortality (P=0.012).

These findings in the Val-HeFT[16,41] study could have resulted from the combined treatment of valsartan, an ACE-inhibitor, and a β-blocker causing a reduction in blood pressure of 6 to 7 mmHg in the valsartan group; this drop in BP could have been excessive in patients in whom both the RAS and the β-adrenergic receptors were blocked, leading to ischemic events or worsening of heart failure. This interaction was observed only for the baseline therapy with β-blockers, and did not reflect β-blocker use during the study. The Val-HeFT investigators postulated that extensive blockade of multiple neurohormonal systems in patients with heart failure might be deleterious[42].

One caveat that is unique to the use of β-blockers in heart failure is that they may cause initial worsening before improvement occurs[43]; i.e., initially, β-blockers may worsen symptoms of heart failure, but improvement is seen after long-term therapy. Thus, to avoid deterioration, heart failure patients must first be stabilized on a regimen of digoxin, diuretics and ACE inhibitors and/or ARBs, and β-blockers must be started at low doses and the doses gradually increased over a period of several weeks. Also, data from the ATLAS trial[12], MERIT-HF trial[36] and other β-blocker clinical trials have been computed to show (Table 113) 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 hospitalization to a greater magnitude than increasing the dose of the ACE-inhibitor to a maximally tolerated dose[31,44].

Table 113 Comparative Effects of Two Different Treatment Strategies in Patients Receiving Low Doses of Angiotensin-Converting Enzyme (ACE) Inhibitors (Based on data from Am J Med 2001; 110: 81S-94S)[44]

	Increasing ACE Inhibitor to Maximal Doses	Adding a β Blocker to the ACE Inhibitor
Effect on symptoms	No change	Improved
Effect on risk of death	8% reduction	30%–40% reduction
Effect on risk of death and hospitalization	12% reduction	20%–40% reduction

Data from the ATLAS (Assessment of Treatment with Lisinopril and Survival) trial were used to predict the effect of increasing the dose of the ACE inhibitor from low dose to maximal doses. Data from the MERIT-HF (Metoprolol Controlled Release Randomized Intervention Trial in Heart Failure), PRECISE (Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise), and MOCHA (Multicenter Oral Carvedilol in Heart Failure Assessment) trials were used to predict effect of adding a β-blocker to the regimen of patients already taking low to intermediate doses of an ACE inhibitor.

CHARM-Added (SH-AHS-0006) study

The protocol specified that for patients for whom therapy with a β-blocker or spironolactone was considered, these treatments were initiated and the dose levels stabilized before patients were randomized into the clinical trial to receive candesartan or placebo.

Table 114 CV death or hospitalization due to CHF (confirmed adjudicated) by use of β-blockers in study SH-AHS-0006. Comparison of candesartan vs. placebo with Cox regression. ITT/Safety population.

Variable	Group	N	Events cand. cil.	Events plac-ebo	Hazard Ratio	95% CI		p-value
						Lower	Upper	
Beta-blocker	No	1135	260	264	0.933	0.786	1.107	0.427
	Yes	1413	223	274	0.774	0.649	0.924	0.005
Beta-blocker during study	No	723	186	175	0.948	0.771	1.165	0.609
	Yes	1825	297	363	0.793	0.680	0.924	0.003
Beta-blocker at the visit preceding the event	No	1966	222	217	0.946	0.785	1.141	0.561
	Yes	582	261	321	0.860	0.730	1.014	0.072

Table 114 shows that for the primary endpoint of CV death or CHF hospitalization, there was a statistically significant reduction in relative risk (RRR) for patients treated with candesartan which was associated with use of β-blockers at baseline (RRR =22.6%, P=0.005) or during the study (RRR =20.7%, P=0.003), but not at the visit preceding the event (RRR=14.0%, P=0.072).

The reduction in relative risk of CV death or CHF hospitalization (primary efficacy endpoint) was present in patients taking β-blockers as shown in Figure 54 below.

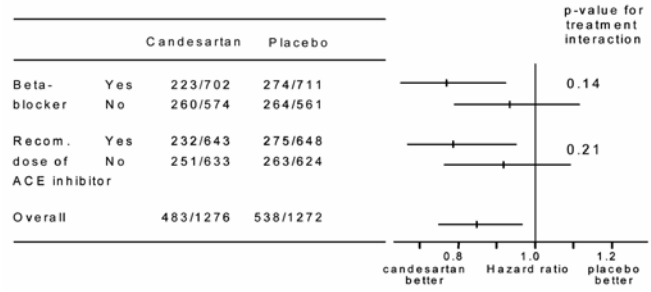


Figure 54 Effect of candesartan compared with placebo on primary outcome in all patients, and patients taking or not taking β-blockers, and/or recommended dose of ACE inhibitors at baseline.

For the component of death in the composite endpoints, there were 175/702 (24.9%) deaths in the candesartan group and 195/711 (27.4%) deaths in the placebo group, with a hazard ratio of 0.88 (95% CI 0.72 to 1.08) in patients treated with a β-blocker at baseline. In patients not treated with a β-blocker at baseline there were 202/574 (35.2%) deaths in the candesartan group and 217/561 (38.7%) deaths in the placebo group, with a hazard ratio of 0.88 (95% CI 0.73 to 1.07). Thus, it appears that candesartan reduced the relative risk of CV death or CHF hospitalization in patients treated with β-blocker in addition to an ACE inhibitor (recommended dose or low dose) at baseline.

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 115 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 116 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 115.

Table 117 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 118 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 117.

Table 119 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 120 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 119.

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 115. 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 116).

The secondary efficacy endpoint of all-cause mortality or CHF hospitalization (Table 117 and Table 118), and for secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI (Table 118 and Table 120) 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) 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).

8.2.2 Is there an interaction of candesartan with spironolactone or aldosterone blockers?

Findings from Clinical Trials in the Medical Literature

Spironolactone has been shown to decrease mortality in NYHA class IV patients with systolic left ventricular dysfunction who were being treated with an ACE inhibitor[45]; this decreased mortality was attributed to a reduction in the rate of death due to progressive heart failure and the rate of sudden death from cardiac causes.

A recent multicenter, randomized, double-blind, placebo-controlled clinical trial (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival (EPHESUS) Study) of eplerenone[46] – an aldosterone blocker that selectively blocks the mineralocorticoid receptor and not the glucocorticoid, progesterone or androgen receptors – involving 6,632 patients with acute

myocardial infarction and left ventricular dysfunction (EF≤40%) and heart failure also supports the above. The EPHESUS study found that eplerenone treatment was associated with reductions in relative risk of all-cause mortality (hazard ratio 0.85, 95% CI 0.75 to 0.96, relative risk reduction 15%, P = 0.008), and cardiovascular death or hospitalization for cardiovascular events (hazard ratio 0.87, 95% CI 0.79 to 0.95, relative risk reduction 13%, P = 0.002). The reduction in cardiovascular mortality (hazard ratio 0.83, 95% CI 0.72 to 0.94, relative risk reduction 15%, P = 0.005), was attributable to a 21% reduction in the rate of sudden death from cardiac causes (hazard ratio 0.79, 95% CI 0.64 to 0.97, relative risk reduction 21%, P = 0.03).

The EPHESUS study also shows that the relative risk for all-cause mortality was significantly (P=0.04) reduced when eplerenone was used together with ACE inhibitors (or ARBs) **and** β-blockers (Figure 55).

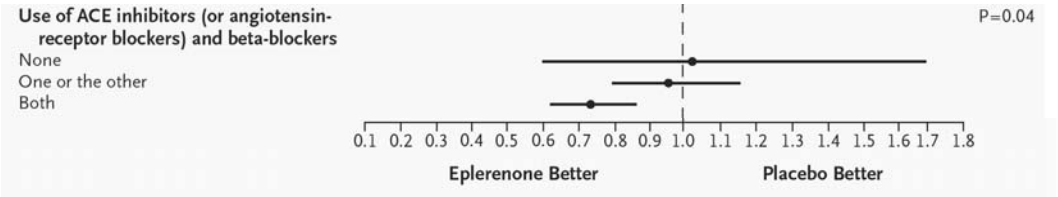


Figure 55 Relative risk of all-cause mortality according to use of and ACE inhibitor (or ARB), a β-blocker or both in EPHESUS study[46] (Based on data from N Engl J Med 2003; 348: 1309-21.)

However, for CV death or hospitalization for CV events, there was no statistically significant reduction in relative risk when eplerenone was used together with an ACE inhibitor or angiotensin receptor blocker (ARB) **and** β-blockers (Figure 56).

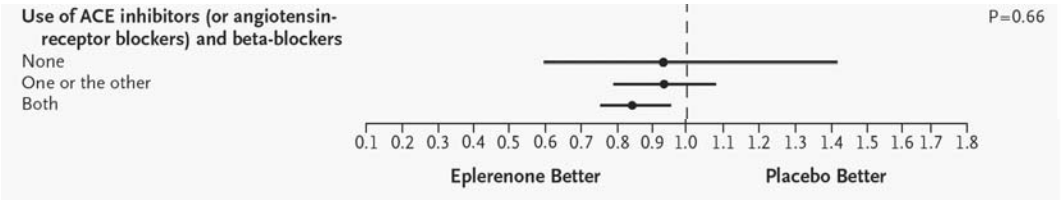


Figure 56 Relative risk of CV death or hospitalization for CV events according to use of an ACE inhibitor (or ARB), a β-blocker or both in EPHESUS study[46] (Based on data from N Engl J Med 2003; 348: 1309-21.)

In addition, eplerenone produces a number of pharmacodynamic effects that may contribute to myocardial protection in patients with acute MI complicated by left ventricular dysfunction, such as preventing ventricular remodeling and collagen formation[47], reducing coronary vascular inflammation and the risk of subsequent development of interstitial fibrosis[48], reducing oxidative stress and improving endothelial dysfunction[49], etc.

CHARM-Added (SH-AHS-0006) Study

The sponsor submitted that for patients for whom therapy with a β-blocker or spironolactone was considered, these treatments were initiated and the dose levels stabilized before patients were randomized into the clinical trial to receive candesartan or placebo.

Table 121 CV death or hospitalization due to CHF (confirmed adjudicated) by use of spironolactone in study SH-AHS-0006. Comparison of candesartan vs. placebo with Cox regression. ITT/Safety population.

Variable	Group	N	Events cand. cil.	Events plac-ebo	Hazard Ratio	95% CI		p-value
						Lower	Upper	
Spironolactone	No	2111	378	441	0.819	0.714	0.940	0.004
	Yes	437	105	97	1.005	0.763	1.325	0.971
Spironolactone during study	No	1572	258	285	0.833	0.704	0.986	0.034
	Yes	976	225	253	0.896	0.749	1.073	0.233
Spironolactone at the visit preceding the event	No	2246	330	389	0.812	0.701	0.940	0.005
	Yes	302	153	149	0.834	0.664	1.048	0.119
ACE inhibitors or beta-blocker or Spironolactone	Yes	2548	483	538	0.853	0.754	0.964	0.011
ACE inhibitors or beta-blocker or Spironolactone during study	Yes	2548	483	538	0.853	0.754	0.964	0.011

Table 121 shows that for the primary endpoint of CV death or hospitalization due to CHF, there was no statistically significant reduction in relative risk for patients treated with candesartan which was associated with use of spironolactone at baseline, during the study or at the visit preceding the event. However, when candesartan use was analyzed in conjunction with use of an ACE inhibitor or β-blockers or spironolactone at baseline or during the study, there was a statistically significant (P=0.011) reduction (by 14.7%) in relative risk of CV death or hospitalization due to CHF.

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

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 122 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** N = 111 n = 49 (44.1%) O_1	**CC_{LD} + SS** N = 57 n = 35 (61.4%) O_2	**CC_{00} + SS** N = 54 n = 21 (38.9%) O_3	**CC_{HD} + NS** N = 662 n = 235 (35.5%) P_1	**CC_{LD} + NS** N = 169 n = 80 (47.3%) P_2	**CC_{00} + NS** N = 223 n = 63 (28.3%) 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 123 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 122.

Table 124 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** N =111 n = 52 (46.9%) Q_1	**CC_{LD} + SS** N = 58 n = 37 (63.8%) Q_2	**CC_{00} + SS** N = 53 n = 22 (41.5%) Q_3	**CC_{HD} + NS** N = 665 n = 261 (39.3%) R_1	**CC_{LD} + NS** N = 169 n = 84 (49.7%) R_2	**CC_{00} + NS** N = 220 n = 83 (37.7%) 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 125 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 124.

Table 126 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 127 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 126.

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 shown in Table 122. 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 patients receiving heart failure doses or low doses of ACE inhibitors (Table 123).

The secondary efficacy endpoint of all-cause mortality or CHF hospitalization (Table 124 and Table 125), and for secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI (Table 126 and Table 127) 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) 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).

8.2.3 Is there an interaction of candesartan with digoxin?

Findings from Clinical Trials in the Medical Literature

The Digitalis Investigation Group (DIG) Study[50] showed that combination therapy (of digoxin, diuretic and ACE inhibitor) was better than ACE inhibitor alone. In the main trial, patients with LVEF ≤ 0.45 were randomly assigned to digoxin (3,397 patients) or placebo (3,403 patients) in addition to diuretics and ACE-inhibitors (median dose of digoxin, 0.25 mg per day; average follow-up, 37 months). In an ancillary trial of patients with LVEF > 0.45, 492 patients were randomly assigned to digoxin and 496 to placebo. In the main trial, mortality was unaffected. There were 1,181 deaths (34.8%) with digoxin and 1,194 deaths (35.1%) with placebo (hazard ratio = 0.99; 95% CI, 0.91 to 1.07; P =0.80) (Table 128).

Table 128 Deaths due to study group and cause in the DIG Study[50] (Based on data from N Engl J Med 1997; 336: 525-33.)

Cause of Death	Digoxin (N=3397)	Placebo (N=3403)	Absolute Difference*	Risk Ratio (95% CI)†	P Value
	no. of patients (%)		%		
All	1181 (34.8)	1194 (35.1)	−0.4	0.99 (0.91–1.07)	0.80
Cardiovascular	1016 (29.9)	1004 (29.5)	0.4	1.01 (0.93–1.10)	0.78
Worsening heart failure‡	394 (11.6)	449 (13.2)	−1.6	0.88 (0.77–1.01)	0.06
Other cardiac§	508 (15.0)	444 (13.0)	1.9	1.14 (1.01–1.30)	
Other vascular¶	50 (1.5)	45 (1.3)	0.1	1.11 (0.74–1.66)	
Unknown	64 (1.9)	66 (1.9)	−0.1	0.97 (0.69–1.37)	
Noncardiac and nonvascular	165 (4.9)	190 (5.6)	−0.7	0.87 (0.71–1.07)	

*Absolute differences were calculated by subtracting the percentage of deaths in the placebo group from the percentage of deaths in the digoxin group (before values were rounded).

†Risk ratios and confidence intervals (CI) were estimated from the Cox proportional-hazards model.

‡This category includes patients who died from worsening heart failure, even if the final event was an arrhythmia.

§This category includes deaths presumed to result from arrhythmia without evidence of worsening heart failure and deaths due to atherosclerotic coronary disease, bradyarrhythmias, low-output states, and cardiac surgery. Although this outcome was not prespecified, P=0.04 for the comparison of study groups with respect to death from other cardiac causes.

¶This category includes deaths due to stroke, embolism, peripheral vascular disease, vascular surgery, and carotid end-arterectomy.

In the digoxin group, there was a trend (not statistically significant) toward a decrease in the risk

of death attributed to worsening heart failure (hazard ratio 0.88; 95% CI, 0.77 to 1.01; P = 0.06) (Figure 57). However, overall mortality was not reduced because an excess of sudden death and ischemic events were observed in patients randomized to digoxin.

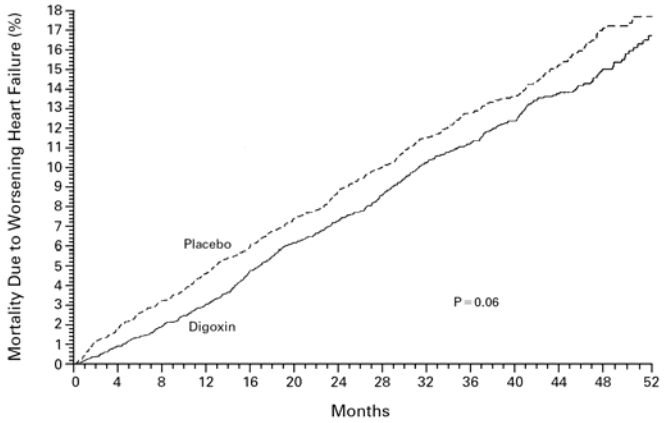


Figure 57 Mortality Due to Worsening Heart Failure in the Digoxin and Placebo Groups[50]. (Based on data from N Engl J Med 1997; 336: 525-33.) The number of patients at risk at each four-month interval is shown below the figure.

Table 129 Patients hospitalized during the DIG study[50], according to study group and reason for hospitalization. (Based on data from N Engl J Med 1997; 336: 525-33.)

Reason for Hospitalization*	Digoxin (N=3397)	Placebo (N=3403)	Absolute Difference†	Risk Ratio (95% CI)‡	P Value
	no. of patients (%)		%		
Cardiovascular	1694 (49.9)	1850 (54.4)	−4.5	0.87 (0.81–0.93)	<0.001
Worsening heart failure	910 (26.8)	1180 (34.7)	−7.9	0.72 (0.66–0.79)	<0.001
Ventricular arrhythmia, cardiac arrest	142 (4.2)	145 (4.3)	−0.1	0.98 (0.78–1.24)	
Supraventricular arrhythmia§	133 (3.9)	152 (4.5)	−0.6	0.87 (0.69–1.10)	
Atrioventricular block, bradyarrhythmia	14 (0.4)	9 (0.3)	0.1	1.56 (0.68–3.61)	
Suspected digoxin toxicity	67 (2.0)	31 (0.9)	1.1	2.17 (1.42–3.32)	<0.001
Myocardial infarction	195 (5.7)	201 (5.9)	−0.2	0.97 (0.79–1.18)	
Unstable angina	399 (11.7)	398 (11.7)	0.1	1.01 (0.87–1.16)	
Stroke	157 (4.6)	164 (4.8)	−0.2	0.95 (0.77–1.19)	
Coronary revascularization¶	83 (2.4)	71 (2.1)	0.4	1.17 (0.85–1.61)	
Cardiac transplantation	25 (0.7)	16 (0.5)	0.3	1.57 (0.84–2.94)	
Other cardiovascular‖	452 (13.3)	381 (11.2)	2.1	1.20 (1.05–1.38)	
Respiratory infection	238 (7.0)	252 (7.4)	−0.4	0.94 (0.79–1.12)	
Other noncardiac and nonvascular	1126 (33.1)	1079 (31.7)	1.4	1.06 (0.98–1.15)	
Unspecified	20 (0.6)	18 (0.5)	0.1	1.11 (0.59–2.10)	
No. of patients hospitalized	2184 (64.3)	2282 (67.1)	−2.8	0.92 (0.87–0.98)	0.006
No. of hospitalizations	6356	6777			

*Data shown include the first hospitalization of each patient for each reason.

†Absolute differences were calculated by subtracting the percentage of patients hospitalized in the placebo group from the percentage of patients hospitalized in the digoxin group (before values were rounded).

‡Risk ratios and confidence intervals (CI) were estimated from a Cox proportional-hazards model that used the first hospitalization of each patient for each reason.

§This category includes atrioventricular block and bradyarrhythmia.

¶This category includes coronary-artery bypass grafting and percutaneous transluminal coronary angioplasty.

‖This category includes embolism, venous thrombosis, peripheral vascular disease, hypertension, other vascular surgery, cardiac catheterization, other types of catheterization, pacemaker implantation, installation of automatic implantable cardiac defibrillator, electrophysiologic testing, transplant-related evaluation, nonspecific chest pain, atherosclerotic heart disease, hypotension, orthostatic hypotension, and valve operation.

There were 6% fewer hospitalizations overall in the digoxin group than in the placebo group, and

fewer patients were hospitalized for worsening heart failure (26.8% vs. 34.7% ; hazard ratio, 0.72; 95% CI, 0.66 to 0.79; P < 0.001) (Table 129). In the ancillary trial, the findings regarding the primary combined outcome of death or hospitalization due to worsening heart failure were consistent with the results of the main trial. Thus, the current concept is that digoxin decreases the need for hospitalization but has not been shown to affect mortality in CHF[50].

CHARM-Added (SH-AHS-0006) Study

The sponsor submitted that patients who were on digitalis glycosides had their dose levels stabilized before they were randomized into the clinical trial to receive candesartan or placebo.

Table 130 CV death or hospitalization due to CHF (confirmed adjudicated) by use of spironolactone in study SH-AHS-0006. Comparison of candesartan vs. placebo with Cox regression. ITT/Safety population.

Variable	Group	N	Events cand. cil.	Events plac-ebo	Hazard Ratio	95% CI		p-value
						Lower	Upper	
Digitalis glycoside	No	1060	172	185	0.873	0.709	1.074	0.200
	Yes	1488	311	353	0.844	0.725	0.983	0.030
Digitalis glycoside during study	No	897	133	134	0.923	0.726	1.173	0.513
	Yes	1651	350	404	0.833	0.722	0.962	0.013
Digitalis glycoside at the visit preceding the event	No	1856	159	170	0.874	0.704	1.085	0.222
	Yes	692	324	368	0.885	0.762	1.029	0.112

Table 130 shows that for the primary endpoint of CV death or hospitalization due to CHF, there was a statistically significant reduction in relative risk for patients treated with candesartan which was associated with use of digitalis glycosides at baseline (RRR = 15.6%, P=0.030) or during the study (RRR = 16.7%, P=0.013), but not at the visit preceding the event (RRR = 11.5%, P=0.112).

8.3 Special Populations

8.3.1 CHF patients with symptomatic hypotension

Patients with heart failure and symptomatic hypotension may require a reduction in the dose of candesartan. In the CHARM program, hypotension was the second most frequently reported adverse event constituting 18.8% of patients on candesartan versus 9.8% of patients on placebo; the incidence of hypotension leading to drug discontinuation in candesartan-treated patients was 4.1% compared with 2.0% in placebo-treated patients.

8.3.2 CHF patients with impaired renal function (creatinine increase)

In heart failure patients with impaired renal function treated with candesartan, increases in serum creatinine may require dose reduction and/or discontinuation of candesartan. In the CHARM program, the incidence of "creatinine increase" was 12.5% in patients treated with candesartan versus 6.3% inpatients treated with placebo; the incidence of "creatinine increase" leading to drug discontinuation in candesartan-treated patients was 6.3% compared with 2.9% in placebo-treated patients.

8.3.3 CHF patients with hyperkalemia

In heart failure patients treated with candesartan, 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; the incidence of hyperkalemia leading to drug discontinuation in candesartan-treated patients was 2.4% compared with 0.6% in placebo-treated patients.

8.3.4 Geriatric patients with CHF

Of the 7,599 patients with heart failure in the 3 trials of the CHARM program, 4,343 (57 %) were ≥ 65 years old and 1,736 (23 %) were ≥ 75 years old. The pharmacokinetics of candesartan remained linear in patients with CHF; however, the AUC was almost doubled in patients > 65 years old compared to healthy, younger patients. In patients ≥ 75 years of age, the incidence of drug discontinuations due to adverse events was higher for those treated with candesartan 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 candesartan than placebo, were abnormal renal function (7.9% vs. 4.0%), hypotension (5.2% vs. 3.2%) and hyperkalemia (4.2% vs. 0.9%). Thus, greater sensitivity of older individuals with heart failure to candesartan must be considered.

8.4 Pediatrics

The sponsor requested a pediatric waiver from assessing the safety and effectiveness of candesartan for the treatment of heart failure in pediatric patients. By letter dated 26-Aug-2004, the division granted a waiver for the requirement of pediatric studies for all age groups for the applications contained in the CHARM program (S-022, S-024, and S-025).

8.5 Literature Review

In the sections presented and discussed above, relevant medical literature is referenced throughout the review so that a broad perspective of the scientific background and current thinking related to clinical issues in the treatment of CHF is brought into consideration, and objective conclusions of the efficacy and safety findings can be made. In this literature review section, I will present recent advances in the treatment of CHF following the ACC/AHA (American College of Cardiology/American Heart Association) Guidelines for the evaluation and management of CHF which defined four stages of heart failure[27].

Instead of the traditional NYHA classification which describes functional limitations the new staging for heart failure is based on its evolution and progression. The stages of heart failure and treatment options for systolic heart failure are shown in Figure 58.

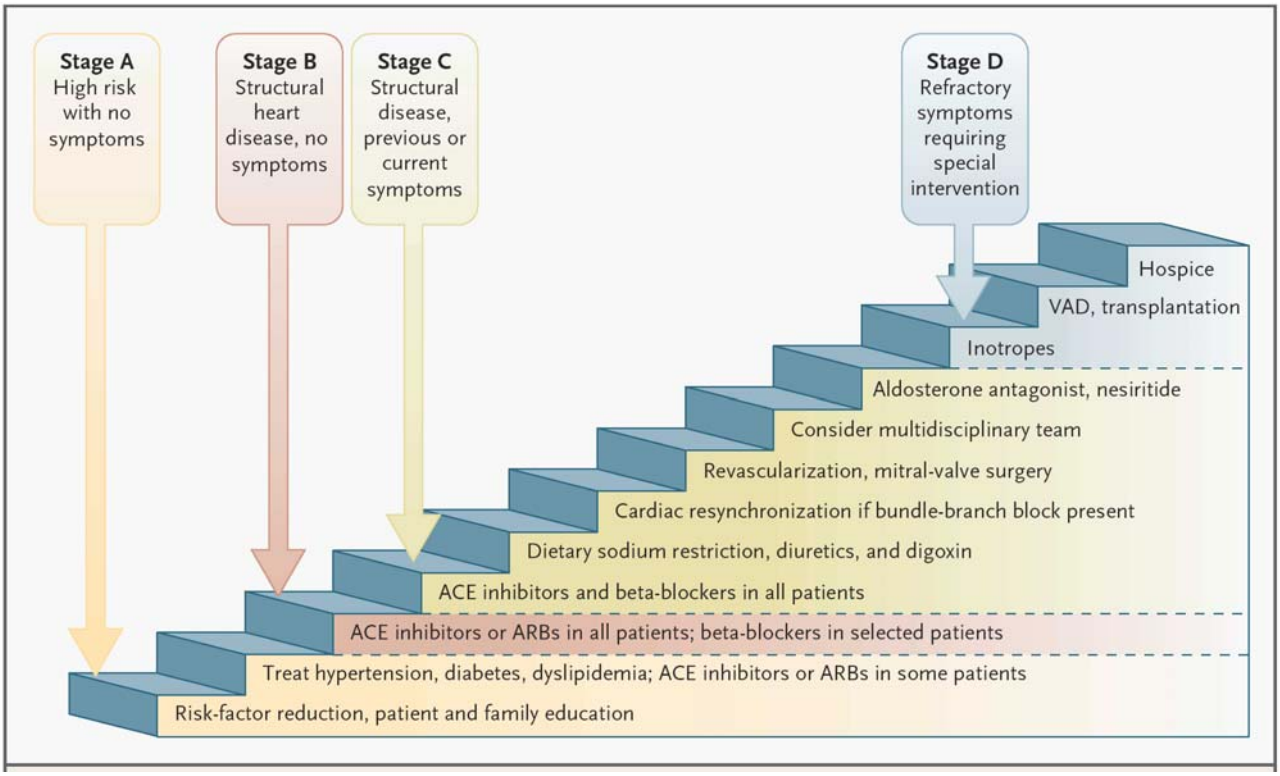


Figure 58 Stages of heart failure and treatment options for systolic heart failure (Based on data from Circulation 2001; 104: 2996-3007)[27]

The states of heart failure may be described as follows:

- Patients with stage A heart failure are at high risk for the development of heart failure but have no apparent structural abnormality of the heart. This group includes patients with hypertension, diabetes, coronary artery disease, previous exposure to cardiotoxic drugs, or a family history of cardiomyopathy.
- Patients with stage B heart failure have a structural abnormality of the heart but have never

had symptoms of heart failure. This group includes patients with left ventricular hypertrophy, previous myocardial infarction, left ventricular systolic dysfunction or valvular heart disease, all of whom would be considered to have NYHA class I symptoms.

- Patients with stage C heart failure have a structural abnormality of the heart and current or previous symptoms of heart failure. Their symptoms may be classified as NYHA class I, II, III or IV.
- Patients with stage D heart failure have end-stage symptoms of heart failure that are refractory to standard treatment (maximal medical therapy), are hospitalized, and require specialized interventions or hospice care. All such patients would be considered to have NYHA class IV symptoms.

In the context of this NDA review and the new staging of heart failure, I will present for consideration in this section of the review the following issues relevant to the role of ACE-inhibitors and ARBs in the treatment of heart failure:

8.5.1 Are angiotensin II-AT_1-receptor blockers (ARBs) comparable to ACE-inhibitors or superior to ACE inhibitors?

This is primarily the issue for the CHARM-Alternative (SH-AHS-0003) study, and this will be addressed in detail later in the review for NDA 20-838 Supplement S-024. The following information in the medical literature is presented to provide a background for the review of this current NDA supplement (CHARM-Added SH-AHS-0006 study).

8.5.1.1 Effect of ACE inhibitors on improving survival in patients with heart failure:

For stage A heart failure, the goal of treatment is to prevent remodeling.

In the Heart Outcomes Prevention Evaluation (HOPE) trial, 9,297 asymptomatic high-risk patients (55 years of age or older) with vascular disease or diabetes plus one other cardiovascular risk factor and who were not known to have a low ejection fraction or heart failure were randomized to receive either ramipril (10 mg once per day orally) or placebo for 5 years[51,52]. The primary outcome was a composite of myocardial infarction, stroke, or death from cardiovascular causes.

A total of 651 patients who were assigned to receive ramipril (14.0%) reached the primary end point, as compared with 826 patients who were assigned to receive placebo (17.8%); thus ramipril reduced the combined rate of CV death, MI and strokes by 22% (relative risk, 0.78; 95% CI, 0.70 to 0.86; P< 0.001). Ramipril also reduced the rates of death from cardiovascular cause, all-cause death, myocardial infarction and stroke (Table 131) in a broad range of high-risk patients who are not known to have a low ejection fraction or heart failure.

Table 131 Incidence of the primary outcome and deaths from any cause in HOPE study[51] (Based on data from N Engl J Med 2000; 342: 145-53)

Outcome	Ramipril Group (N=4645)	Placebo Group (N=4652)	Relative Risk (95% CI)*	z Statistic	P Value†
	no. (%)				
Myocardial infarction, stroke, or death from cardiovascular causes‡	651 (14.0)	826 (17.8)	0.78 (0.70–0.86)	−4.87	<0.001
Death from cardiovascular causes§	282 (6.1)	377 (8.1)	0.74 (0.64–0.87)	−3.78	<0.001
Myocardial infarction§	459 (9.9)	570 (12.3)	0.80 (0.70–0.90)	−3.63	<0.001
Stroke§	156 (3.4)	226 (4.9)	0.68 (0.56–0.84)	−3.69	<0.001
Death from noncardiovascular causes	200 (4.3)	192 (4.1)	1.03 (0.85–1.26)	0.33	0.74
Death from any cause	482 (10.4)	569 (12.2)	0.84 (0.75–0.95)	−2.79	0.005

*CI denotes confidence interval.

†P values were calculated with use of the log-rank test.

‡In the substudy, 34 of 244 patients (13.9 percent) assigned to take a low dose of ramipril (2.5 mg per day) reached the composite end point, as compared with 31 of 244 assigned to take 10 mg of ramipril per day (12.7 percent) and 41 of 244 assigned to placebo (16.8 percent). The inclusion of the data from the low-dose group did not change the overall results (relative risk of the primary outcome, 0.78; 95 percent confidence interval, 0.70 to 0.86).

§All patients with this outcome are included.

In the European Trial on the Reduction of Cardiac Events with Perindopril in Patients with Stable Coronary Artery Disease (EUROPA), 12,218 patients were randomized to receive either perindopril (long acting ACE inhibitor with a terminal half-life of 25-30 h) 8 mg once daily (n=6,110) or placebo (n=6,108)[53]. 65% had previous MI, 50% had coronary artery disease on angiography, and 23% were men with a positive stress test. The mean follow-up was 4.2 years. The primary endpoint was cardiovascular death, myocardial infarction or cardiac arrest. Analysis was by intention to treat. Perindopril reduced the combined frequency of cardiovascular death, MI and cardiac arrest within 4.2 years by 20% (from 603 patients (9.9%) in placebo group to 488 patients (8.0%) in perindopril group (P=0.0003) (Table 132). There was also a non-significant 14% reduction in cardiovascular mortality and a significant 22% reduction in non-fatal MI (P=0.001), and a significant 14% reduction in the composite endpoint of total mortality, non-fatal MI, unstable angina and cardiac arrest (P=0.0009) (Table 132). These benefits were achieved on a background of high usage of aspirin, β-blockers and lipid-lowering agents.

Table 132 Frequency of primary and selected secondary outcomes (EUROPA study)[53] (Based on data from Lancet 2003; 362: 782-8)

	Perindopril (n=6110)	Placebo (n=6108)	Relative risk reduction (95% CI)	p
Cardiovascular mortality, MI, or cardiac arrest	488 (8·0%)	603 (9·9%)	20% (9 to 29)	0·0003
Cardiovascular mortality	215 (3·5%)	249 (4·1%)	14% (–3 to 28)	0·107
Non-fatal MI	295 (4·8%)	378 (6·2%)	22% (10 to 33)	0·001
Cardiac arrest	6 (0·1%)	11 (0·2%)	46% (–47 to 80)	0·22
Total mortality, non-fatal MI, unstable angina, cardiac arrest	904 (14·8%)	1043 (17·1%)	14% (6 to 21)	0·0009
Total mortality	375 (6·1%)	420 (6·9%)	11% (–2 to 23)	0·1

The Second Australian National Blood Pressure Lowering Trial (ANBP2)[54] enrolled 6,083 subjects with hypertension (65 to 84 years of age, receiving health care at 1,594 family practices) in a randomized, open-label study of patients treated with ACE inhibitors vs. those treated with diuretics. Subjects were followed for a median of 4.1 years, and the total numbers of cardiovascular events in the two treatment groups were compared with the use of multivariate proportional-hazards models. There were 695 cardiovascular events or deaths from any cause in the ACE-inhibitor group (56.1 per 1000 patient-years) and 736 cardiovascular events or deaths from any cause in the diuretic group (59.8 per 1000 patient-years; thus, treatment with an ACE inhibitor was associated with a significant reduction in CV events compared with a diuretic-based regimen for the same reduction in blood pressure (the hazard ratio for a cardiovascular event or death with ACE-inhibitor treatment was 0.89 [95% CI, 0.79 to 1.00]; P= 0.05)) (Table 133).

Table 133 Primary endpoints and cause-specific first events in ANBP2 Study[54] (Based on data from N Engl J Med 2003; 348: 583-92)

Event	ACE-Inhibitor Group (N=3044)		Diuretic Group (N=3039)		Hazard Ratio (95% CI)	P Value
	No. of Events	Rate per 1000 Patient-yr	No. of Events	Rate per 1000 Patient-yr		
Primary end points						
All cardiovascular events or death from any cause	695	56.1	736	59.8	0.89 (0.79–1.00)	0.05
First cardiovascular event or death from any cause	490	41.9	529	45.7	0.89 (0.79–1.01)	0.06
Death from any cause	195	15.7	210	17.1	0.90 (0.75–1.09)	0.27
Cause-specific first events						
First cardiovascular event†	394	33.7	429	37.1	0.88 (0.77–1.01)	0.07
Coronary event	173	14.3	195	16.2	0.86 (0.70–1.06)	0.16
Myocardial infarction	58	4.7	82	6.7	0.68 (0.47–0.98)	0.04
Other cardiovascular event	134	11.0	144	11.9	0.90 (0.71–1.14)	0.36
Heart failure	69	5.6	78	6.4	0.85 (0.62–1.18)	0.33
Cerebrovascular event	152	12.5	163	13.6	0.90 (0.73–1.12)	0.35
Stroke	112	9.2	107	8.8	1.02 (0.78–1.33)	0.91

* Hazard ratios are for the event in the group assigned to angiotensin-converting–enzyme (ACE) inhibitors as compared with the diuretic group and are adjusted for age and sex. CI denotes confidence interval.
† Myocardial infarction is a subcategory of coronary events; heart failure is a subcategory of other cardiovascular events; and stroke is a subcategory of cerebrovascular events. Patients were counted once for each type of first cardiovascular event they had, but patients who had more than one type of event were counted only once for the overall category of first cardiovascular event.

Among male subjects, the hazard ratio was 0.83 (95% CI, 0.71 to 0.97; P= 0.02); among female subjects, the hazard ratio was 1.00 (95% CI, 0.83 to 1.21; P= 0.98); the P value for the interaction between sex and treatment-group assignment was 0.15 (Figure 59). This led to the recommendation that initiation of antihypertensive treatment involving ACE inhibitors in older subjects, particularly men, appears to lead to better outcomes than treatment with diuretic agents despite similar reductions of blood pressure.

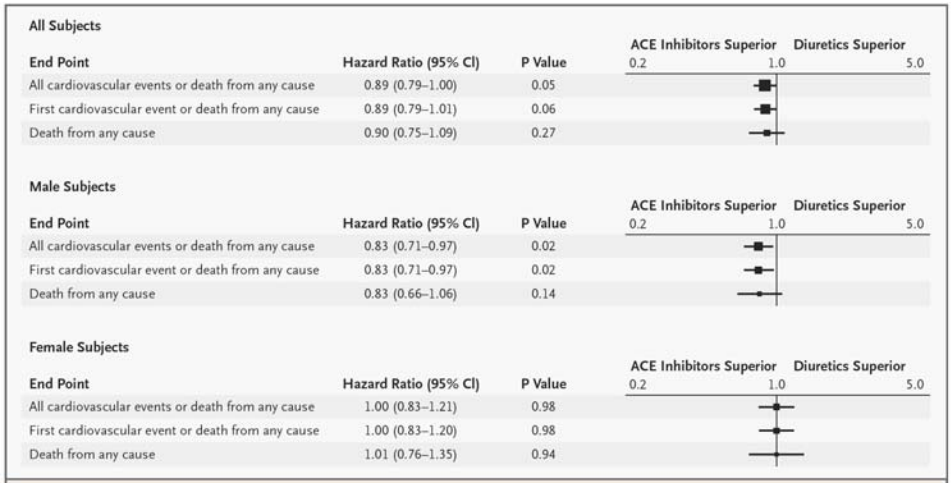


Figure 59 Primary endpoints among all subjects, male subjects and female subjects (ANBP2 Study)[54] (Based on data from N Engl J Med 2003; 348: 583-92). ACE denotes angiotensin-converting enzyme, and CI confidence interval.

For stage B, C or D heart failure, the goal is to improve survival, slow the progression of disease, alleviate symptoms and minimize risk factors. ACE inhibitors decrease the conversion of angiotensin I to angiotensin II, minimizing the multiple pathophysiological effects of angiotensin II, and decrease the degradation of bradykinin. Bradykinin promotes vasodilatation in the vascular endothelium, and cause natriuresis in the kidney. Thus, ACE inhibitors improve survival, reduce the rate of hospitalization, improve symptoms, cardiac performance, neurohormonal levels and reverse remodeling after MI[55]. Recent studies suggest ACE inhibitors may prevent diabetes mellitus, atrial fibrillation and dementia[56,57].

Four major trials provided evidence of the favorable effects of ACE inhibitor treatment after acute myocardial infarction with stage B or stage C heart failure:

(i) The Survival and Ventricular Enlargement (SAVE)[58] trial examined the effect of captopril in 2,231 patients within 3 – 16 days after myocardial infarction, with LVEF ≤40% and without overt heart failure or symptoms of myocardial ischemia. Captopril-treated patients (n=1,115) compared to placebo-treated patients (n=1,116) had a 19% (95% CI 3% - 32%, P=0.019) reduction in the relative risk of all-cause mortality (Figure 60) , 21% (95% CI 5% - 35%, P=0.014) reduction in the relative risk of CV deaths, 37% (95% CI 20% - 50%, P<0.001) reduction in the relative risk of severe heart failure, 22% (95% CI 4% - 37%, P=0.019) reduction in the relative risk of heart failure requiring hospitalization, and a 25% (95% CI 5% - 40%, P=0.015) reduction in the relative risk of recurrent MI (Figure 61). Thus, in patients with asymptomatic LV dysfunction after MI, long-term treatment with captopril was associated with improved survival and reduced morbidity and mortality due to cardiovascular events, and this benefit was seen in patients who received thrombolytic therapy, aspirin or β-blockers.

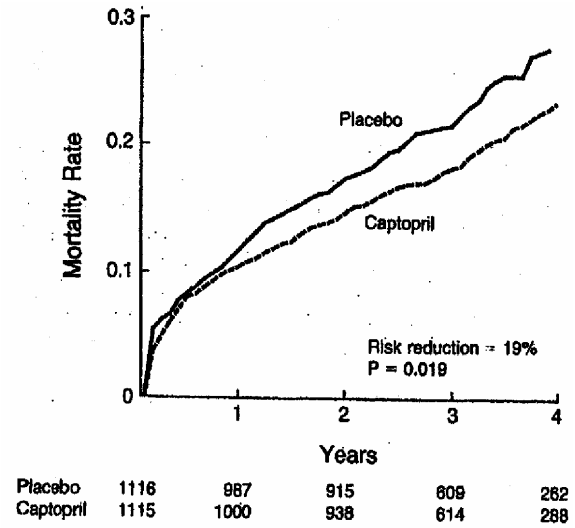


Figure 60 Cumulative mortality from all causes in the study groups in SAVE trial[58] (Based on data from N Engl J Med 1992; 327: 669-77). The number of patients at risk at the beginning of each year is shown at the bottom

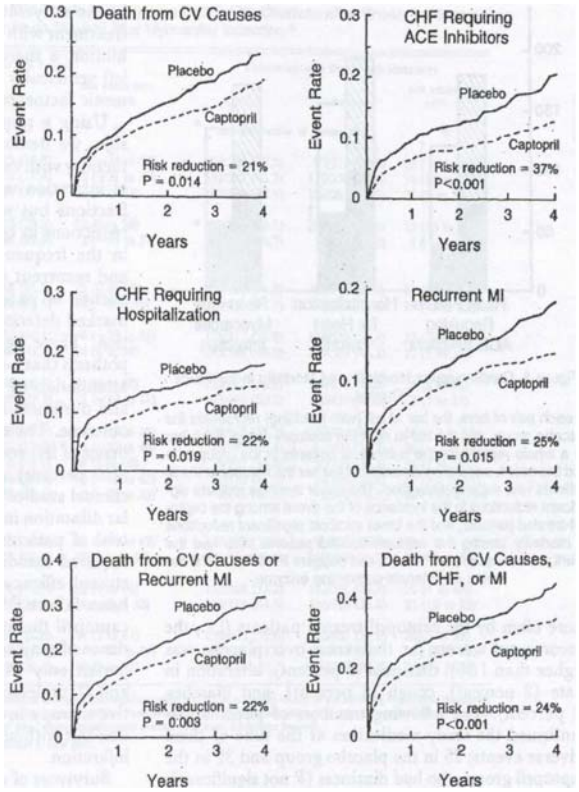


Figure 61 Life tables for cumulative fatal and non-fatal cardiovascular events in SAVE trial[58] (Based on data from N Engl J Med 1992; 327: 669-77). CV denotes cardiovascular, CHF congestive heart failure, MI myocardial infarction. The bottom right panel shows the following events: death from cardiovascular causes, sever heart failure requiring ACE inhibitors or hospitalization, or recurrent myocardial infarction. For all combined analyses, only the time to the first event was used.

(ii) The Acute Infarction Ramipril Efficacy (AIRE)[59] trial enrolled 2,006 patients (in 144 centers in 14 countries) with overt signs of heart failure (except NYHA class IV) after

an acute MI. Patients were randomized to either ramipril (n=1,014) or placebo (n=992) on day 3 to day 10 after AMI, and followed to a minimum of 6 months (average = 15 months). Patients treated with ramipril had a 27% (95%CI 11% - 40%, P=0.02) reduction in the relative risk of all-cause mortality (Figure 62) and a 19% (35% CI 5% - 31%, P=0.008) reduction in the relative risk of progression to the first validated event in a composite outcome of death, severe/resistant heart failure, myocardial infarction or stroke. This study shows that administration of ramipril to patients with clinical evidence of either transient or ongoing heart failure reduced premature death from all causes.

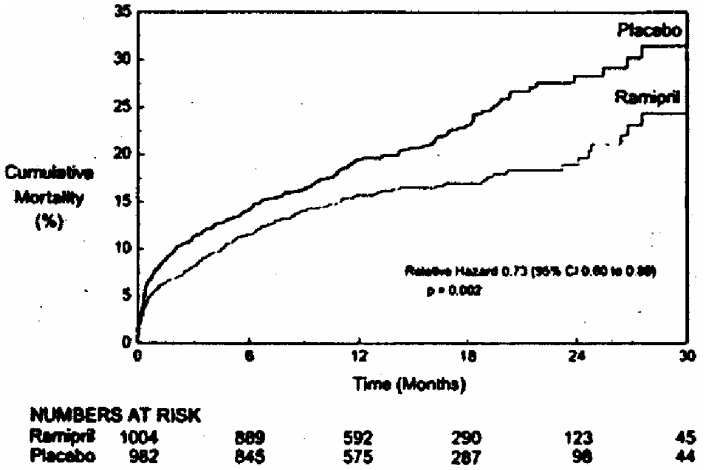


Figure 62 Mortality curves illustrating the primary endpoint of all-cause mortality analyzed by intention-to-treat in AIRE trial[59] (Based on data from Lancet 1993; 342: 821-8). Most patients were followed for <18 months, and the curves have been terminated at 30 months because of the small numbers of patients with prolonged follow-up.

(iii) The Survival of Myocardial Infarction Long-Term Evaluation (SMILE)[60] trial randomized 1,556 patients in Italy within 24 hours after an acute anterior MI to receive zofendopril (n=772) or placebo (n=784) for 6 weeks.

Table 134 Incidence of Severe Congestive Heart Failure or Death as the Combined Primary End Point of the SMILE Study[60] (Based on data from N Engl J Med 1995; 332: 80-5).

Event	Placebo Group (N = 784)	Zofenopril Group (N = 772)	Reduction in Risk (95% CI)*	P Value
	no. of patients (%)		*%*	
Severe congestive heart failure†	32 (4.1)	17 (2.2)	46 (11 to 71)	0.018
Death	51 (6.5)	38 (4.9)	25 (−11 to 60)	0.19
Combined end point	83 (10.6)	55 (7.1)	34 (8 to 54)	0.018

*CI denotes confidence interval.

†At least three of the following had to be present: third heart sound, bilateral pulmonary rales, radiologic evidence of pulmonary congestion, or peripheral edema despite the concomitant administration of digoxin, diuretics, and vasodilators other than ACE inhibitors and necessitating open-label treatment with an ACE inhibitor.

Table 134, Figure 63 and Figure 64 shows that in patients treated with zofendopril, a

34% (95% CI, 8 to 54 percent; P=0.018) reduction in the relative risk of death or severe heart failure was observed at 6 weeks, and a 29% (95% CI, 6% to 51%; P=0.011) reduction in the relative risk of mortality was observed after 1 year.

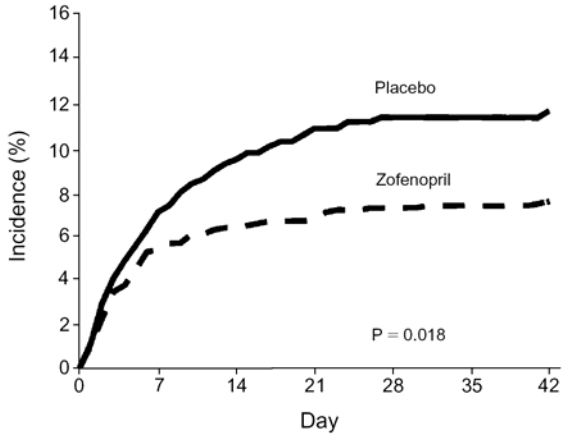


Figure 63 Incidence of Death or Severe Congestive Heart Failure during Six Weeks of Treatment with Zofenopril or Placebo in Patients with Acute Myocardial Infarction (SMILE Study)[60] (Based on data from N Engl J Med 1995; 332: 80-5).

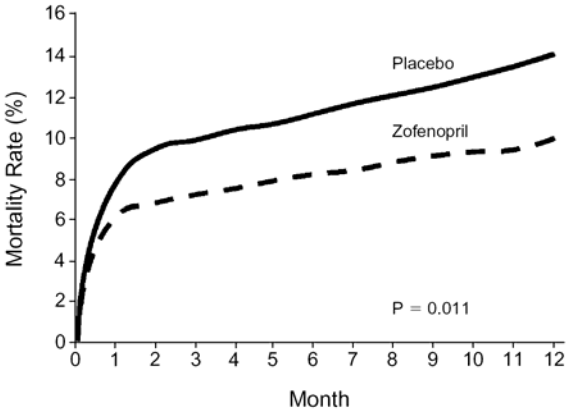
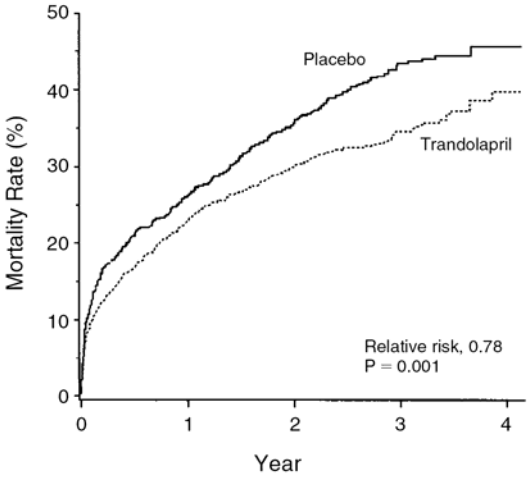


Figure 64 Cumulative Mortality during One Year of Follow- up among Patients with Acute Myocardial Infarction Treated for Six Weeks with Zofenopril or Placebo (SMILE Study)[60] (Based on data from N Engl J Med 1995; 332: 80-5).

(iv) The Danish TRAndolapril Cardiac Evaluation (TRACE)[61] study evaluated the effect of trandolapril on patients with an LVEF ≤0.35 after MI. 6,676 patients with 7001 myocardial infarctions confirmed by enzyme studies were screened. A total of 2,606 patients had echocardiographic evidence of left ventricular systolic dysfunction (LVEF ≤ 35%). On days 3 to 7 after infarction, 1,749 patients were randomly assigned to oral trandolapril (n=876 patients) or placebo (n=873 patients).



No. at Risk					
Trandolapril	876	677	613	319	20
Placebo	873	647	562	280	22

Figure 65 Cumulative Mortality from All Causes among Patients Receiving Trandolapril or Placebo (TRACE Study)[61] (Based on data from N Engl J Med 1955; 333: 1670-6).

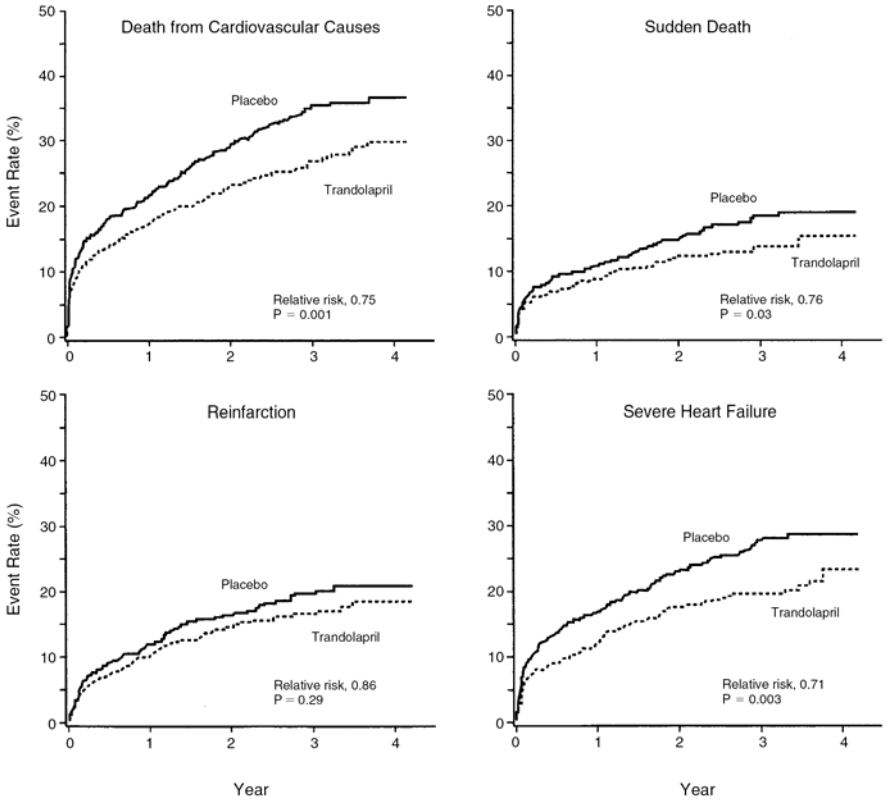


Figure 66 Event Rates for the Secondary End Points of Death from Cardiovascular Causes, Sudden Death, Reinfarction, and Severe or Resistant Heart Failure among Patients Receiving Trandolapril or Placebo (TRACE Study)[61] (Based on data from N Engl J Med 1955; 333: 1670-6).

The duration of follow-up was 24 to 50 months. Patients assigned to treatment with trandolapril had a 22% (hazard ratio 0.78; 95% CI 0.67 to 0.91, P=0.001) reduction in the relative risk of death from all causes (Figure 65), 25% (hazard 0.75; 95% CI 0.63 to 0.89; P=0.001) reduction in the relative risk of death from cardiovascular causes, and 24% (hazard ratio 0.76; 95% CI 0.59 to 0.98; P=0.03) reduction in relative risk of sudden death (Figure 66). The relative risk of progression to advanced heart failure was decreased by 29% (hazard ratio 0.71; 95% CI 0.55 to 0.89; P=0.003) with trandolapril, whereas the drug had no effect on the risk of recurrent MI (Figure 66). The TRACE study shows that long-term treatment with trandolapril in patients with reduced left ventricular function soon after myocardial infarction significantly reduced the relative risk of overall mortality, mortality from cardiovascular causes, sudden death, and the development of severe heart failure[61].

The above information needs to be considered from a clinical practice point of view, particularly in primary care settings where primary care physicians (internists, family practitioners, geriatricians) encounter most patients with Stage A through C heart failure. While ACE inhibitors are recommended for many patients with Stage A heart failure, and also for Stage B, Stage C or Stage D heart failure, there is widespread under-use of ACE inhibitors by physicians as reported in a nation-wide survey of patterns of use of ACE inhibitors in patients with heart failure and left ventricular systolic dysfunction[62].

8.5.1.2 Effect of Angiotensin (AT_1) receptor blockers (ARBs) on improving survival in patients with heart failure:

The ACC/AHA (American College of Cardiology/American Heart Association) Guidelines for the evaluation and management of CHF which defined the four stages of heart failure[27] did not recommend ARBs as first-line therapy for heart failure of any stage, but that they should be used only in patients who cannot tolerate ACE inhibitors because of severe cough or angioedema.

Information from clinical trials of ARBs suggests that ARBs may be as useful as ACE inhibitors.

For stage A heart failure: In the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study, 1,513 patients with type II diabetes and nephropathy were randomized to receive losartan (50-100 mg once daily) or placebo, in addition to conventional antihypertensive treatment, for a mean of 3.4 years[24]. Losartan was found to delay the first hospitalization for heart failure in patients with diabetes mellitus with nephropathy and heart failure (89 (11.9%) patients in the losartan group vs. 127 (16.7%) in the placebo group), for which the relative risk reduction was 32% (P=0.005, Figure 67).

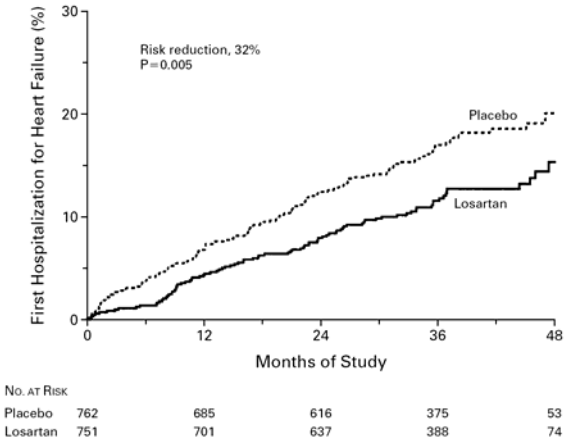


Figure 67 Kaplan-Meier Curves of the Percentage of Patients with a First Hospitalization for Heart Failure in the Losartan and Placebo Groups (RENAAL Study)[24] (Based on data from N Engl J Med 2001;345: 861-9).

For stage B, C or D heart failure: The CHARM-Alternative (SH-AHS-0003) study[63] showed that survival benefits in patients with CHF produced by candesartan (compared to placebo) are in about the same magnitude as that produced by ACE inhibitors described above. In the CHARM-Alternative (SH-AHS-0003) study, 2,028 patients with symptomatic heart failure and LVEF ≤ 40% who were not receiving ACE inhibitors because of previous intolerance were enrolled. Patients were randomly assigned candesartan (target dose 32 mg once daily) or placebo. The sponsor reported a statistically significant 23% reduction (hazard ratio= 0.77; 95% CI 0.67 - 0.89, P = 0.0004) in the relative risk of the composite primary endpoint of cardiovascular death or hospital admission for CHF[63] (Figure 68 and Table 135). This will be reviewed and discussed in detail in my review of the CHARM-Alternative (SH-AHS-0003) study in NDA 20-838 Supplement #024.

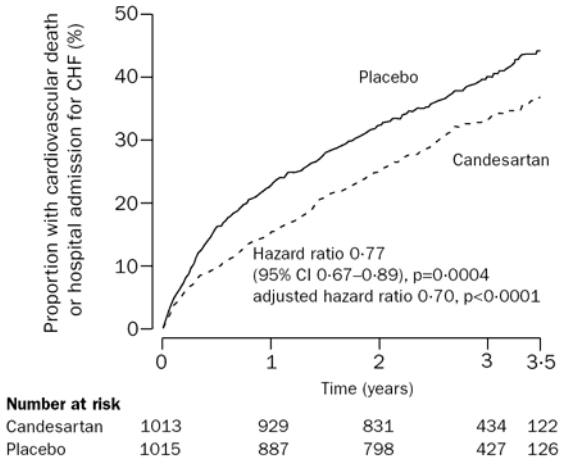


Figure 68 Kaplan-Meier cumulative event curves for primary endpoint (CHARM-Alternative Study)[63] (Based on data from Lancet 2003; 362: 772-6).

Table 135 Primary and secondary endpoints (CHARM-Alternative Study)[63] (Based on data from Lancet 2003; 362: 772-6).

	Candesartan (n=1013)	Placebo (n=1015)	Unadjusted hazard ratio (95% CI)	p	Adjusted hazard ratio (95% CI)*	p
Cardiovascular death or hospital admission for CHF	334 (33·0%)	406 (40·0%)	0·77 (0·67–0·89)	0·0004	0·70 (0·60·0·81)	<0·0001
Cardiovascular death	219 (21·6%)	252 (24·8%)	0·85 (0·71–1·02)	0·072	0·80 (0·66–0·96)	0·02
Hospital admission for CHF	207 (20·4%)	286 (28·2%)	0·68 (0·57–0·81)	<0·0001	0·61 (0·51–0·73)	<0·0001
Cardiovascular death, hospital admission for CHF, MI	353 (34·8%)	420 (41·4%)	0·78 (0·68–0·90)	0·0007	0·72 (0·62–0·83)	<0·0001
Cardiovascular death, hospital admission for CHF, MI, stroke	369 (36·4%)	432 (42·6%)	0·80 (0·69–0·91)	0·001	0·74 (0·64–0·85)	<0·0001
Cardiovascular death, hospital admission for CHF, MI, stroke, coronary revascularisation procedure	396 (39·1%)	456 (44·9%)	0·81 (0·71–0·92)	0·002	0·76 (0·66–0·87)	<0·0001

MI=myocardial infarction. *Covariate-adjusted model for variables shown in table 1.

Table 136 shows the endpoints of the Losartan Intervention for Endpoint reduction (LIFE)[23] study in which 9,193 asymptomatic patients with hypertension and ECG evidence of left ventricular hypertrophy (i.e., stage B heart failure) were randomized to receive losartan or atenolol, and were followed for at least 4 years. Losartan titrated gradually to a dose of 100 mg/day produced a significant reduction (by 13%, P=0.021) in relative risk in the primary composite point of cardiovascular mortality, stroke and MI as well as a decrease (by 25%, P=0.001) in strokes and the incidence of new-onset diabetes (Table 136).

Table 136 Endpoints of LIFE[23] study (Based on data from Lancet 2002; 359: 995-1003).

Endpoint	Losartan (n=4605)		Atenolol (n=4588)		Adjusted hazard ratio (95% CI)†	p	Unadjusted hazard ratio (95% CI)	p
	n	Rate*	n	Rate				
Primary composite endpoint‡	508 (11%)	23·8	588 (13%)	27·9	0·87 (0·77–0·98)	0·021	0·85 (0·76–0·96)	0·009
Cardiovascular mortality	204 (4%)	9·2	234 (5%)	10·6	0·89 (0·73–1·07)	0·206	0·87 (0·72–1·05)	0·136
Stroke	232 (5%)	10·8	309 (7%)	14·5	0·75 (0·63–0·89)	0·001	0·74 (0·63–0·88)	0·0006
Myocardial infarction	198 (4%)	9·2	188 (4%)	8·7	1·07 (0·88–1·31)	0·491	1·05 (0·86–1·28)	0·628
Other prespecified endpoints								
Total mortality	383 (8%)	17·3	431 (9%)	19·6	0·90 (0·78–1·03)	0·128	0·88 (0·77–1·01)	0·077
Admitted to hospital for:								
Angina pectoris	160 (3%)	7·4	141 (3%)	6·6	1·16 (0·92–1·45)	0·212	1·13 (0·90–1·42)	0·284
Heart failure	153 (3%)	7·1	161 (4%)	7·5	0·97 (0·78–1·21)	0·765	0·95 (0·76–1·18)	0·622
Revascularisation	261 (6%)	12·2	284 (6%)	13·3	0·94 (0·79–1·11)	0·441	0·91 (0·77–1·08)	0·292
Resuscitated cardiac arrest	9 (0·2%)	0·4	5 (0·1%)	0·2	1·91 (0·64–5·72)	0·250	1·80 (0·60–5·36)	0·294
New-onset diabetes§	241 (6%)	13·0	319 (8%)	17·4	0·75 (0·63–0·88)	0·001	0·75 (0·63–0·88)	0·001

*Per 1000 patient-years of follow-up. †For degree of left ventricular hypertrophy and Framingham risk score at randomisation. ‡Cardiovascular mortality, stroke, and myocardial infarction (numbers of patients with a first primary event). §In patients without diabetes at randomisation (losartan, n=4019; atenolol, n=3979).

Apart from the CHARM-Alternative study[63] and the LIFE study[23] reviewed above, in the medical literature, most clinical trials comparing ARBs to ACE inhibitors head-to-head have not shown the superiority in beneficial effects of ARBs over ACE inhibitors.

In 1997, the Evaluation of Losartan in the Elderly (ELITE)[19] trial demonstrated an unexpected survival benefit of losartan (50mg.day) compared to captopril (150 mg/day) in 722 elderly patients with CHF (Figure 69). However, mortality was neither a pre-specified primary nor a pre-specified secondary endpoint of ELITE[19].

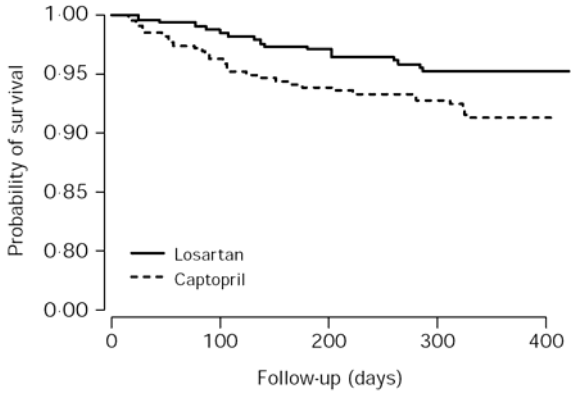


Figure 69 Kaplan-Meier survival curves among patients with CHF in losartan and captopril groups. Patients in losartan group had a 46% lower risk of death than patients in captopril group (p= 0·035). Patients were followed up for 48 weeks (ELITE trial)[19] (Based on data from Lancet 1997; 349: 747-52).

ELITE II[20] was conducted in 3,152 elderly CHF patients with mortality as the primary endpoint. After a mean follow-up of over 500 days, mortality in the captopril group was 15.9%, compared to 17.7% in the losartan group (hazard ratio with captopril 1.13, P = 0.16, Table 137). Thus, ELITE II did not show that losartan was superior to captopril.

Table 137 Endpoint results in ELITE II trial[20] (Based on data from Lancet 2000; 355: 1582-7).

Endpoint	Losartan (n=1578)	Captopril (n=1574)	Hazards ratio (CI)*	p
All-cause mortality (primary endpoint)				
Total mortality	280 (17·7%)	250 (15·9%)	1·13 (0·95–1·35)	0·16
Sudden death	130 (8·2%)	101 (6·4%)	1·30 (1·00–1·69)	
Progressive heart failure	46 (2·9%)	53 (3·4%)	0·88 (0·59–1·30)	
Myocardial infarction	31 (2·0%)	28 (1·8%)	1·11 (0·66–1·85)	
Stroke	18 (1·1%)	11 (0·7%)	1·65 (0·78–3·49)	
Other cardiovascular	5 (0·3%)	6 (0·4%)	0·84 (0·26–2·76)	
Non-cardiovascular	50 (3·2%)	51 (3·2%)	0·99 (0·67–1·47)	
Sudden death or resuscitated cardiac arrest	142 (9·0%)	115 (7·3%)	1·25 (0·98–1·60)	0·08
Combined total mortality or hospital admission for any reason	752 (47·7%)	707 (44·9%)	1·07 (0·97–1·19)	0·18
Hospital admissions				
Any reason	659 (41·8%)	638 (40·5%)	1·04 (0·94–1·16)	0·45
Heart failure	270 (17·1%)	293 (18·6%)	0·92 (0·78–1·08)	0·32

*95·7% CI for total mortality, 95% CI for other endpoints, including components.

In the OPTIMAAL (Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan) trial, losartan (at a dose of 50 mg q.d.) was compared to the ACE inhibitor captopril (at a dose of 150 mg/day) in 5,477 high-risk patients with confirmed acute myocardial infarction and evidence of heart failure or left ventricular dysfunction[22]. The results were in favor of captopril both for all-cause mortality (not significant, P=0.069) and for cardiovascular mortality (P=0.032) (Table 138 and Figure 70).

Table 138 Crude rates and relative risks for pre-specified endpoints in OPTIMAAL Study[22] (Based on data from Lancet 2002; 360: 752-60).

	Losartan (n=2744)	Captopril (n=2733)	Relative risk (95% CI)	p
All-cause mortality	499 (18·2%)	447 (16·4%)	1·13 (0·99–1·28)	0·069
SCD/RCA	239 (8·7%)	203 (7·4%)	1·19 (0·99–1·43)	0·072
Myocardial reinfarction (fatal/ non-fatal)*	384 (14·0%)	379 (13·9%)	1·03 (0·89–1·18)	0·722
Other prespecified endpoints				
MI/total mortality	746 (27·2%)	689 (25·2%)	1·10 (0·99–1·22)	0·085
Cardiovascular death	420 (15·3%)	363 (13·3%)	1·17 (1·01–1·34)	0·032
Stroke (fatal/ non-fatal)	140 (5·1%)	132 (4·8%)	1·07 (0·84–1·36)	0·587
CABG	404 (14·7%)	375 (13·7%)	1·09 (0·95–1·26)	0·228
PTCA	466 (17·0%)	492 (18·0%)	0·94 (0·83–1·07)	0·358
Revascularisation	845 (30·8%)	827 (30·3%)	1·03 (0·93–1·13)	0·620
First all-cause admission	1806 (65·8%)	1774 (64·9%)	1·03 (0·97–1·10)	0·362
First admission for heart failure	306 (11·2%)	265 (9·7%)	1·16 (0·98–1·37)	0·072
Cardiovascular admission	1480 (53·9%)	1421 (52·0%)	1·06 (0·99–1·14)	0·108
Non-cardiovascular admission	885 (32·3%)	905 (33·1%)	0·98 (0·90–1·08)	0·719

SCD=sudden cardiac death; RCA=resuscitated cardiac arrest; MI=myocardial infarction; CABG=coronary-artery bypass grafting; PTCA=percutaneous transluminal coronary angioplasty. *Definite or probable as defined by endpoint classification committee.

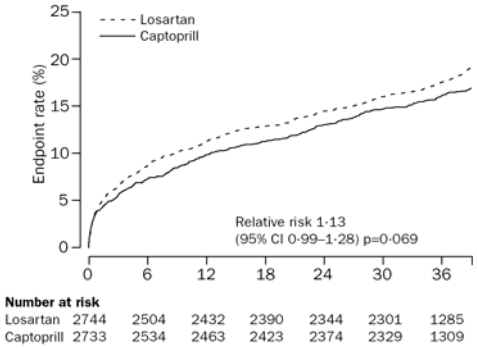


Figure 70 Kaplan- Meier curve for primary endpoint of all-cause mortality. (OPTIMAAL Study)[22] (Based on data from Lancet 2002; 360: 752-60).

The clinical trial of valsartan and captopril in myocardial infarction complicated by heart failure and/or left ventricular dysfunction (VALIANT)[25] was also designed to demonstrate superiority or non-inferiority of valsartan compared to captopril in patients after an acute MI complicated by left ventricular dysfunction and/or heart failure. 14,703 patients were randomized (1:1:1 ratio) to receive either valsartan (titrated to 160 mg b.i.d.), captopril (titrated to 50 mg t.i.d.) or the combination of valsartan (titrated to 80 mg b.i.d.) and captopril (titrated to 50 mg t.i.d.), beginning 12 hours to 10 days after a myocardial infarction, and followed up to a median of 24.7 months. This study was designed to assess non-inferiority of valsartan relative to captopril.

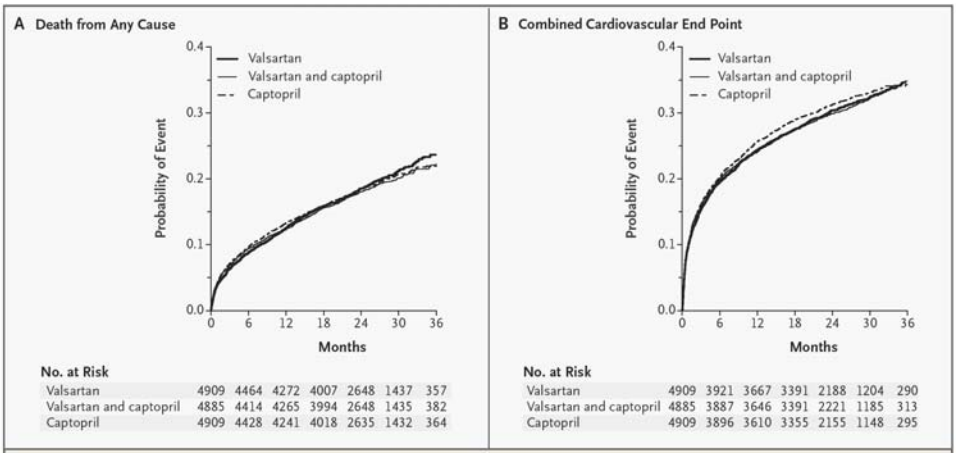


Figure 71 Kaplan-Meier Estimates of the Rate of Death from Any Cause (Panel A) and the Rate of Death from Cardiovascular Causes, Reinfarction, or Hospitalization for Heart Failure (Panel B), According to Treatment Group (VALIANT Study)[25] (Based on data from N Engl J Med 2003; 349; 1893-1906).
For the rate of death from any cause, P= 0.98 for the comparison between the valsartan group and the captopril group and P= 0.73 for the comparison between the valsartan-plus-captopril group and the captopril group; for the rate of death from cardiovascular causes, reinfarction or hospitalization for heart failure, P=0.20 for the comparison between the valsartan group and the captopril group and P= 0.37 for the comparison between the valsartan-plus-captopril group and the captopril group.

All-cause mortality was 19.9% in the valsartan group, 19.5% in the captopril group and 19.3% in the combination (valsartan plus captopril) group. The hazard ratio for death in the valsartan group vs. captopril group was 1.00 (97.5% CI: 0.90 to 1.11, P=0.98), and the hazard ratio for death in the valsartan plus captopril group vs. captopril group was 0.98 (97.5% CI: 0.89 to 1.09, P=0.73) (Figure 71 and Table 139). Valsartan and captopril were equivalent in terms of overall mortality and the composite endpoint of fatal and nonfatal cardiovascular events whereas the combination (valsartan plus captopril) therapy resulted in an increase in adverse events without improving overall survival[25] (Table 139).

Table 139 Cardiovascular Mortality and Morbidity* in VALIANT Study[25] (Based on data from N Engl J Med 2003; 349; 1893-1906).

End Point	Valsartan Group (N=4909)	Valsartan-and-Captopril Group (N=4885)	Captopril Group (N=4909)	Valsartan vs. Captopril			Valsartan and Captopril vs. Captopril	
				Hazard Ratio (97.5% CI)	P Value	P Value for Non-inferiority	Hazard Ratio (97.5% CI)	P Value
		number (percent)						
Death from cardiovascular causes	827 (16.8)	827 (16.9)	830 (16.9)	0.98 (0.87–1.09)	0.62	0.001	1.00 (0.89–1.11)	0.95
Death from cardiovascular causes or myocardial infarction	1102 (22.4)	1096 (22.4)	1132 (23.1)	0.95 (0.87–1.05)	0.25	<0.001	0.96 (0.88–1.06)	0.40
Death from cardiovascular causes or heart failure	1326 (27.0)	1331 (27.2)	1335 (27.2)	0.97 (0.90–1.05)	0.51	<0.001	1.00 (0.92–1.09)	0.94
Death from cardiovascular causes, myocardial infarction, or heart failure	1529 (31.1)	1518 (31.1)	1567 (31.9)	0.95 (0.88–1.03)	0.20	<0.001	0.97 (0.89–1.05)	0.37
Death from cardiovascular causes, myocardial infarction, heart failure, resuscitation after cardiac arrest, or stroke	1612 (32.8)	1580 (32.3)	1641 (33.4)	0.96 (0.89–1.04)	0.25	<0.001	0.96 (0.89–1.04)	0.26

* Heart failure denotes hospitalization for the management of heart failure, and CI confidence interval.

The lack of superiority in beneficial effect of ARBs (losartan and valsartan, above) over ACE inhibitors has been attributed to not using a high enough dose of the ARB[26]. ACE inhibitors such as enalapril (at 20 mg/day) also enhanced the pulmonary diffusion capacity of oxygen after 14 days of treatment[64], whereas losartan 50mg/day was without such effect (Figure 72); this improvement in oxygen diffusion capacity across the alveolar surface is likely to have provided benefit to heart failure patients treated with ACE inhibitors, which was not shared by ARBs.

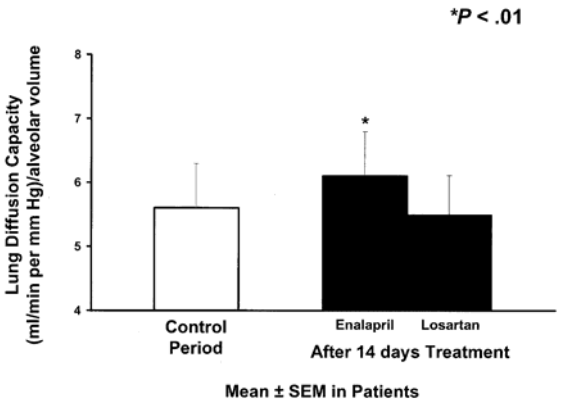


Figure 72 Effect of enalapril or losartan on pulmonary diffusion capacity in heart failure patients[64] (Based on data from J Am Coll Cardiol 2001; 37: 398-406). The bars represent mean±SEM in patients during the control period, after 14 days treatment with enalapril, and after 14 days treatment with losartan. * P < 0.01 compared with control period.

Thus, the findings from reports of clinical trials in the medical literature and the findings from clinical trials in this NDA may lend support to the use of ARBs as an alternative to ACE inhibitors when patients cannot tolerate ACE inhibitors. But there is no consistent evidence that ARBs are superior to ACE inhibitors.

8.5.2 Are the effects of ARBs additive on top of ACE-inhibitors?

That is, can incremental survival benefits be achieved in heart failure by using two inhibitors (ACE-inhibitors and AT_1-receptor blocking agents) of the renin-angiotensin system?
This question arose because it has been suggested that additional survival benefits could not be achieved with ARBs among those already taking proven effective treatments such as ACE inhibitors and β-blockers[65].

For Stage A heart failure: I have not yet found in the medical literature any study where an ACE inhibitor and an ARB are used together in patients who are at high risk for the development of heart failure but have no apparent structural abnormality of the heart (i.e., no studies of use of ACE an inhibitor and an ARB together among patients with hypertension and/or diabetes mellitus, and/or dyslipidemia without an apparent structural abnormality of the heart for the prevention of heart failure).

For Stage B, C or D heart failure: As discussed above, in the Valsartan Heart Failure Trial (Val-HeFT)[16] of 5,010 patients, the addition of valsartan to conventional treatment (including ACE inhibitors in 93% of patients, β-blockers in 35% and spironolactone in 5%) reduced the risk of the composite co-primary outcome of death or cardiovascular morbidity (admission for CHF, ≥ 4 hour intravenous treatment for CHF without admission, or cardiac arrest with resuscitation) by 13.2%. This effect on the composite outcome was explained primarily by a 27.5% reduction in CHF hospital admissions, since valsartan showed no effect on cardiovascular mortality or total mortality.

In a subpopulation of 1,610 (35%) patients treated with both ACE inhibitors and β-blockers at baseline, valsartan was associated with a worse outcome. This finding raised concerns about excessive neuroendocrine inhibition[31,66] and led to guidelines to discourage triple neurohumoral blockade[67,68].

In the Valsartan in Acute Myocardial Infarction Trial (VALIANT)[25], as discussed above, 14,703 patients with myocardial infarction complicated by heart failure and/or left ventricular dysfunction were randomized to receive either valsartan (titrated to 160 mg b.i.d., 4,909 patients), captopril (titrated to 50 mg t.i.d., 4,909 patients) or the combination of valsartan (titrated to 80 mg b.i.d.) and captopril (titrated to 50 mg t.i.d.) (4,885 patients), beginning 12 hours to 10 days after a myocardial infarction, and followed to a median of 24.7 months. All-cause mortality was 19.9% in the valsartan group, 19.5% in the captopril group and 19.3% in the combination (valsartan plus captopril) group. The hazard ratio for death in the valsartan group vs. captopril group was 1.00 (97.5% CI: 0.90 to 1.11, P=0.98), and the hazard ratio for death in the valsartan plus captopril group vs. captopril group was 0.98 (97.5% CI: 0.89 to 1.09, P=0.73) (Figure 71 and Table 139).

In the VALIANT study valsartan and captopril were found to be equivalent in terms of overall mortality and in terms of the composite endpoint of fatal and nonfatal cardiovascular events[25]. The combination (valsartan plus captopril) did not produce any added survival benefit, but resulted in an increase in the rate of adverse events (hypotension, renal

dysfunction and hyperkalemia). It is possible that in the unstable situation after myocardial infarction, the combination of valsartan plus captopril could have lowered the blood pressure too aggressively. On the other hand, this lack of superiority in beneficial effect of losartan over captopril has been attributed to not using a high enough dose of valsartan[26].

In a meta-analysis of 17 randomized, parallel-group, blinded clinical trials of ARBs (five trials had background ACE inhibitor treatment) involving 12,469 patients with NYHA functional class II-IV heart failure, with treatment duration of ≥ 4 weeks, the following all-cause mortality results were reported[69]:

(i) Between the ARB group (n=7,060) and control group (n=5,409), the pooled mortality rate (hazard ratio=0.96; 95% CI:0.75-1.23) was not statistically different (Figure 73).

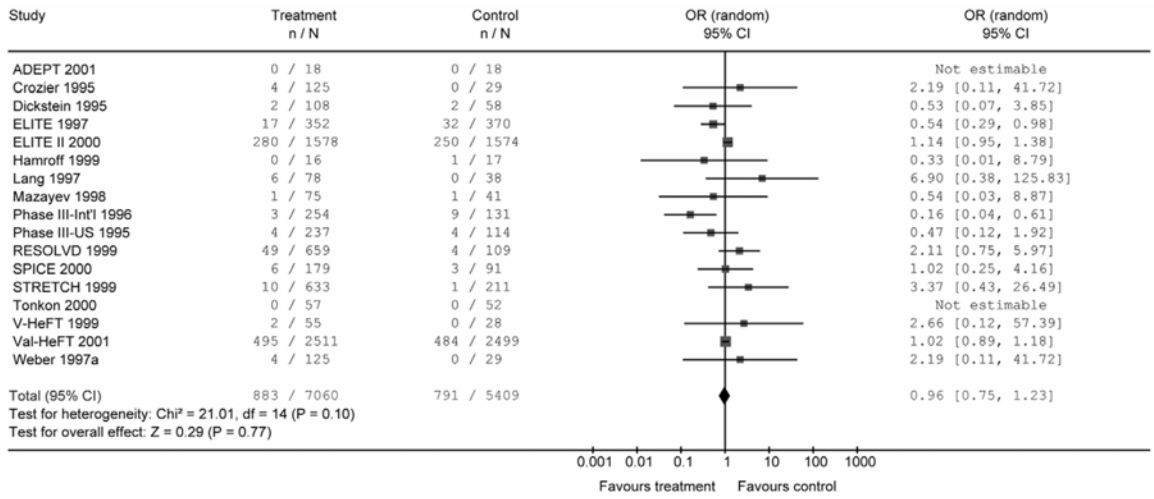


Figure 73 Comparison of angiotensin receptor blockers versus controls on all-cause mortality. (Based on data from J Am Coll Cardiol 2002; 39: 463-70)[69] Controls were either placebo or angiotensin-converting enzyme inhibitor (ACEI). Odds ratios (OR) and the 95% confidence intervals (CI) are shown on a logarithmic scale, with box size proportional to the sample size. The diamond represents the pooled effect.

(ii) Among trials where background ACE inhibitors were not given, the pooled estimate favored ARBs (n=1,628) over placebo (n=631) in improving survival (hazard ratio: 0.68; 95% CI: 0.38 to 1.22) although the sample size was too small to produce statistical significance (Figure 74). The data from the CHARM-Alternative (SH-AHS-0003) study appears to be in conformity with this finding[63].

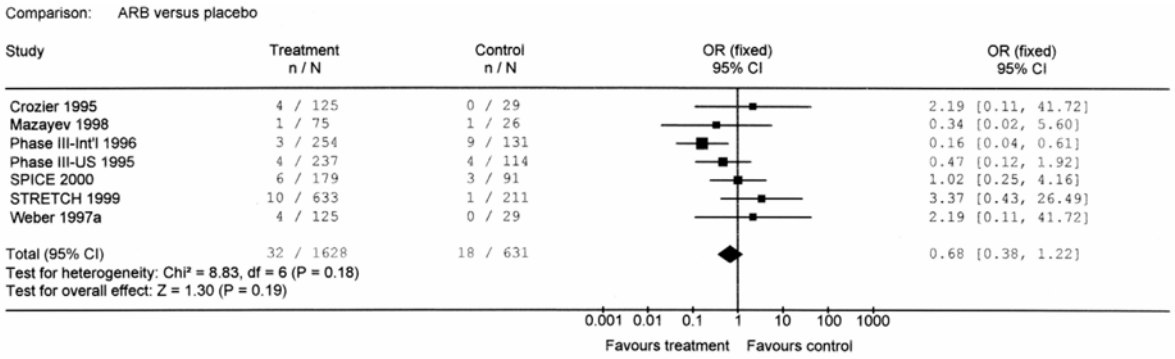


Figure 74 Stratified comparisons of angiotensin receptor blockers (ARB) on all-cause mortality: (Based on data from J Am Coll Cardiol 2002; 39: 463-70)[69]. ARB vs. placebo. Odds ratios (OR) and the 95% confidence intervals (CI) are shown on a logarithmic scale, with box size proportional to the sample size. The diamond represents the pooled effect.

(iii) Among trials that directly compared ARBs (n=2,518) with ACE inhibitors (n=2,164), head-to-head, ARBs were not superior in improving survival (hazard ratio = 1.09; 95% CI 0.92-1.29) (Figure 75).

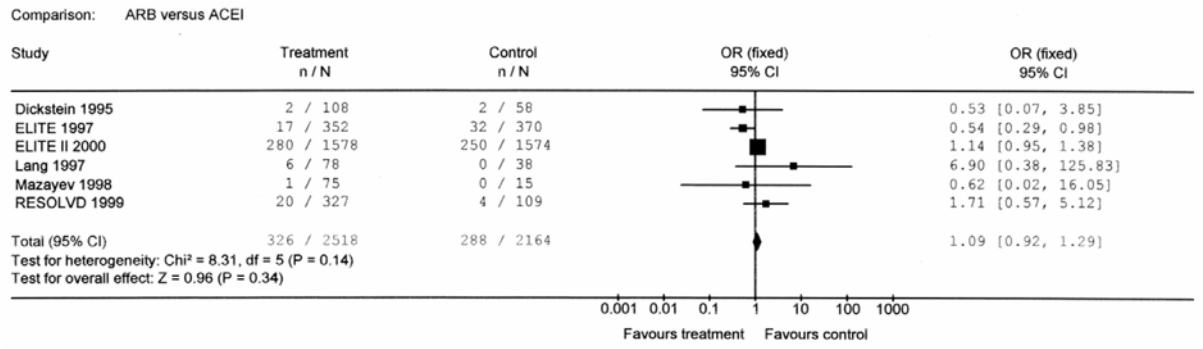


Figure 75 Stratified comparisons of angiotensin receptor blockers (ARB) on all-cause mortality: (Based on data from J Am Coll Cardiol 2002; 39: 463-70)[69]. ARB versus angiotensin-converting enzyme inhibitors (ACEI). Odds ratios (OR) and the 95% confidence intervals (CI) are shown on a logarithmic scale, with box size proportional to the sample size. The diamond represents the pooled effect**.**

(iv) When the combination therapy of ARBs plus ACE inhibitors (n = 2,989) was compared with ACE inhibitors (n = 2,723) alone, the risks of death were virtually identical (hazard ratio = 1.04; 95% CI: 0.91-1.20) (Figure 76). This meta-analysis does not include the data from the CHARM-Added (SH-AHS-0006) study under review, which showed a survival benefit of treatment with candesartan in patients with CHF already taking ACE-inhibitors.

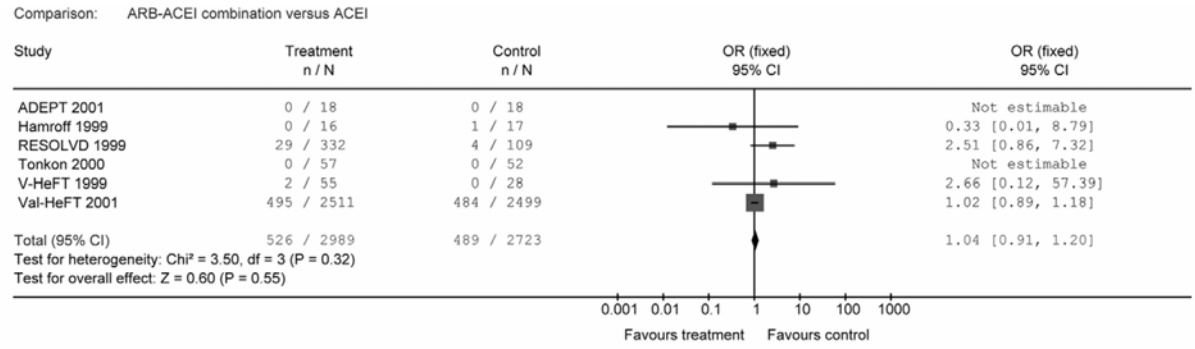


Figure 76 Stratified comparisons of angiotensin receptor blockers (ARB) on all-cause mortality: (Based on data from J Am Coll Cardiol 2002; 39: 463-70)[69]. ARB plus angiotensin-converting enzyme inhibitors (ACEI) combination versus ACEI. Odds ratios (OR) and the 95% confidence intervals (CI) are shown on a logarithmic scale, with box size proportional to the sample size. The diamond represents the pooled effect.

Comparing the survival benefits found in CHARM-Added (SH-AHS-0006) study with other ARB/ACE inhibitor trials in CHF: The CHARM-Added (SH-AHS-0006) study enrolled 2,548 patients with NYHA functional class II-IV CHF and LVEF ≤40% and treated with ACE inhibitors. Patients were randomly assigned candesartan (target dose 32 mg once daily) or placebo. The median follow-up was 41 months. The primary efficacy composite outcome of time to CV death or CHF hospitalization, was reduced significantly by candesartan (by 14.7%, P=0.011). The secondary efficacy outcomes in this (SH-AHS-0006 (CHARM-Added)) study were also reduced consistently by candesartan: "all-cause death or CHF hospitalization" was reduced by 12.9% (P=0.021), and "CV death or CHF hospitalization or non-fatal MI" was reduced by 14.8% (P=0.008). The reductions in these composite efficacy endpoints in CHF patients with LV systolic dysfunction may be attributable to reductions in the individual components of CHF hospitalizations (by 17.5%, P = 0.014), non-fatal MI (by 48.8%, P = 0.006), CV deaths (by 15.8%, P = 0.029), and CHF deaths (by 24.8%, P = 0.041).

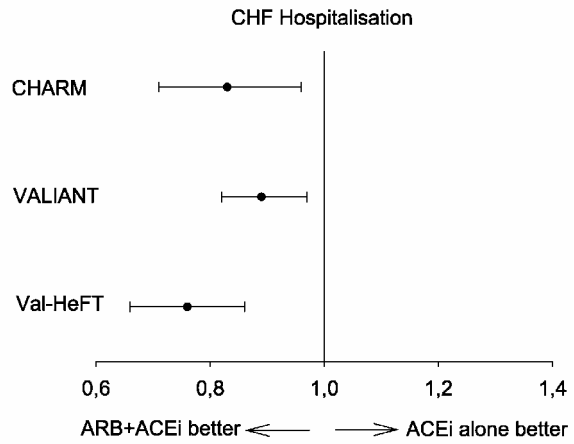


Figure 77 CHF hospitalisation[70] in CHARM-added, VALIANT (added) and Val-HeFT (Based on data from International Journal of Cardiology 2004 (In press; personal communication with Prof A. A. Voors).

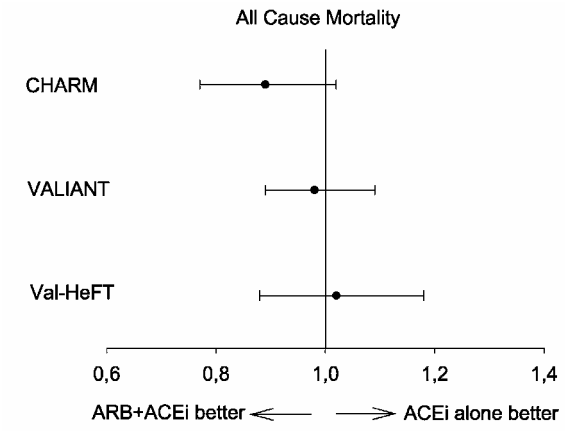


Figure 78 All-cause mortality[70] in CHARM-added, VALIANT (added) and Val-HeFT (Based on data from International Journal of Cardiology 2004 (In press; personal communication with Prof A. A. Voors).

At this point in time, the CHARM-Added study is the ***only*** study which shows that incremental survival benefits are achieved with two inhibitors of the renin-angiotensin system (ACE-inhibitors and AT_1-receptor blocking agents) used together (Figure 77 and Figure 78).

The reasons for this disparity of results between the CHARM-Added (SH-AHS-0006) study and the Val-HeFT and VALIANT trials have been postulated as follows[70]:

1. The VALIANT trial studied patients with acute MI complicated by LV dysfunction, which is very different from established CHF studied in patients in the Val-HeFT and CHARM-Added trials. In the early phase after acute MI during which remodeling occurs, ACE inhibitors might adequately suppress angiotensin II levels and therefore effectively reverse remodeling and contribute to a large extent in improving survival. Thus, the add-on effects of valsartan on captopril in the VALIANT trial will be less than that found with candesartan on ACE-inhibitors in CHARM-Added trial that was not designed to enroll patients with heart failure during the early phase of acute MI.

2. The doses of ACE inhibitors used were lower in CHARM (captopril 82 mg, enalapril 17 mg, lisinopril 18 mg) and Val-HeFT (captopril 82 mg, enalapril 17 mg, lisinopril 18 mg) trials compared to VALIANT (captopril 107 mg) trial. In a background of a relative low dose of an ACE inhibitor, there would be more room for improvement with additional renin-angiotensin-system blockade with ARBs.

   However, the NETWORK (Clinical Outcome with Enalapril in Symptomatic Chronic Heart Failure)[33] trial found no differences between high-dose and low-dose ACE-inhibitor treatment groups for any of the endpoints measured. Also, most randomized trials of ACE inhibitors have shown no difference in mortality between patients receiving high-dose ACE inhibitors and those receiving low-dose ACE inhibitors[12,13,14,15].

3. There could be possible structural differences between losartan, valsartan and candesartan, although there is no large-scale data to support such differences at this time.

4. The proportion of patients in the VALIANT trial that was no longer taking study medication at one year was 16.8% in the captopril group and 19.0% in the combination group. Based on the intent-to-treat analyses, the effects of the combination might be underestimated.

   In the CHARM-Added study, 53.6% of patients treated with candesartan were receiving the target dose of 32 mg once daily at 6 months (visit 5). The mean dose in the candesartan treatment group was 23.5 mg at 6 months. 67.2% of patients in the candesartan treatment group and 70.7% of patients in the placebo group received the investigational product for 24 months or more.

5. The effects of the combination of an ARB and an ACE inhibitor might only be expected in the subgroup of patients with increased concentrations of angiotensin II despite treatment with the ACE inhibitor. On the other hand, it has been suggested that even maximally recommended doses of ACE inhibitors do not completely prevent ACE-mediated formation of angiotensin II in CHF[34].

The above postulations should be viewed in the context of the fact that ACE inhibitors only partially block the production of angiotensin II. One or more ACE-independent pathways[1,2] for the synthesis of angiotensin II has been demonstrated, including the "chymase pathway" which produces angiotensin II at the tissue level, about 90% of angiotensin produced in the heart being believed to be produced via this pathway[3,4]. Thus, local production of angiotensin II can occur despite the use of an ACE inhibitor.

AT_1-receptor blockers, by inhibiting angiotensin II at the AT_1-receptor level, may exert a more complete inhibition of the local adverse effects of angiotensin II. Also, blocking AT_1-receptors causes unopposed stimulation of AT_2-receptors which may produce an additional beneficial effect on cardiac remodeling[5] and vascular epithelial changes.

Thus, hypothetically, ACE inhibitors and AT_1-receptor blockers such as candesartan may exert different effects at the cardiac and vascular levels, which may be complementary in the treatment of CHF[6]. This may explain the incremental clinical benefits observed with two inhibitors of the renin-angiotensin system (ACE-inhibitors and candesartan) in the CHARM-Added (SH-AHS-0006) study.

While a reduction in the relative risk of hospitalization for CHF was found in Val-HeFT and CHARM-Added trials, and a reduction in the relative risk of cardiovascular mortality was demonstrated in CHARM-Added trial, ***no effect on all-cause mortality has been demonstrated*** in any one of these Val-HeFT, VALIANT or CHARM-Added trials (except in the CHARM-Pooled data for CHF patients with depressed left ventricular systolic function, as a secondary efficacy endpoint).

This inconsistency between the results of VALIANT and CHARM/Val-HeFT trials, and the uncertainty concerning the added protective effects of ARBs when used in combination with ACE inhibitors in less high-risk populations with controlled hypertension have led to the development and initiation of two multicenter studies in 40 countries to study the effects of ARBs and ACE when used together in patients with stage A through D heart failure[71]:

(i) The **T**elmisartan **R**andomized **A**ssessme**N**t **S**tudy in a**CE** i**N**tolerant subjects with cardiovascular **D**isease (TRANSCEND). The TRANSCEND study will enroll 6,000 patients (3,000 patients each to be randomized to telmisartan or placebo) with known intolerance ACE inhibitors, and with previous vascular event or diabetes mellitus with target organ damage, but controlled blood pressure and without heart failure.

(ii) The **On**going **T**elmisartan **A**lone and in Combination with **R**amipril **G**lobal **E**ndpoint **T**rial (ONTARGET). The ONTARGET trial plans to enroll 23,400 patients with the same characteristics as TRANSCEND but not ACE intolerant; 7,800 patients each will be randomized to telmisartan or ramipril or telmisartan plus ramipril. Seven sub-studies are embedded in the main trials; they are designed to obtain insights to mechanisms of the effects of the drugs, and to explore the impact of telmisartan on diabetes mellitus, atrial fibrillation, cognitive decline, erectile dysfunction, etc.

8.6 Issues related to the role of angiotensin receptor blockers in patients with heart failure and left ventricular dysfunction

I have summarized the issues related to use of ARBs (and other treatments) in heart failure relevant to the review of this NDA supplement in Table 140.

Table 140 Issues related to the role of angiotensin receptor blockers in patients with heart failure and left ventricular dysfunction

Issue		Evidence from Clinical Trials		
		Stage A	Stage B, C, D	
			CHF	Post-MI
Are ARBs useful in the treatment heart failure (better than placebo)?	Yes		CHARM	
	No		STRETCH, SPICE, Weber	
Are ARBs as useful as ACEi in ACE-intolerant patients with heart failure?	Yes		CHARM-0003	
	No			
Are ARBs as useful as ACEi in the treatment of heart failure?	Yes	LIFE, RENAAL	CHARM-0003, ELITE II, RESOLVD 1999	VALIANT
	No			
Are ARBs superior to ACEi in the treatment of heart failure?	Yes		ELITE I, CHARM-0003	
	No		ELITE II	OPTIMAAL, VALIANT
Are ARBs additive over ACEi for survival in heart failure?	Yes	?RENAAL	Val-HeFT, CHARM-0006	Val-HeFT
	No			VALIANT
Are ARBs additive when used with ACEi and β-blockers in the treatment of heart failure?	Yes		CEBIS-II, MERIT-HF, RESOLVD, CHARM, COPERNICUS,	
	No		ELITE II, Val-HeFT	Val-HeFT
Are ARBs additive when used with ACEi and alsosterone-antagonists in the treatment of heart failure?	Yes		EPHESUS	
	No		?CHARM	
Are ARBs additive when used with ACEi and digoxin in the treatment of heart failure?	Yes		DIG, CHARM	
	No			
Are ARBs additive when used with ACEi, β-blockers, spironolactone and digoxin in the treatment of heart failure?	Yes		CHARM	
	No			
Is dose of ACEi important for the treatment of heart failure?	Yes			
	No		NETWORK, CHARM	
	Dose not addressed		HOPE, EUROPA, ANBP2	SAVE, AIRE, SMILE, TRACE
Is dose of ARB important for the treatment of heart failure?	Yes			VALIANT
	No		?CHARM	
Future studies of ARBs in CHF: (i)telmisartan in ACE intolerant patients		TRANSCEND	TRANSCEND (Stage B)	
(ii) in ACE tolerant patients (telmisartan or ramipril or telmisartan plus ramipril)		ONTARGET	ONTARGET (Stage B)	

8.7 Advisory Committee Meeting

I suggest that the issues related to the role of angiotensin receptor blockers in patients with heart failure and left ventricular dysfunction presented in Table 140 be discussed at the Cardio-Renal Drug Advisory Committee Meeting to be scheduled in February, 2005.

8.8 Postmarketing Risk Management Plan

The sponsor has not submitted a postmarketing risk management plan with the NDA supplement.

8.9 Other Relevant Materials

In the treatment of heart failure, ACE inhibitors, ARBs, β-blockers and spironolactone have contributed to reducing mortality, reducing hospitalizations, and improving functional status. However, large epidemiologic surveys (e.g., Framingham Study still ongoing) have not documented any meaningful change in overall death rates[72]. The reason why the newer and successful therapies failed to result in a meaningful reduction in mortality due to heart failure in the general population may be partly because of structural defects in the heart such as uncorrected valvular disease (aortic stenosis, mitral regurgitation), and partly because many patients have co-morbid diseases such as hypertension, diabetes mellitus, hyperlipidemia, obesity, etc.

A nationwide survey of patients ≥65 years who had survived hospitalization for heart failure with LV systolic dysfunction revealed that ACE inhibitors were widely under prescribed despite evidence of their beneficial effect on survival in patients with heart failure[62]. ACE inhibitors were prescribed to only 68% of this cohort, and 76% received either an ACE inhibitor or an ARB. The underutilization of ACE inhibitors is not completely explained by substitution with ARBs. This finding underscores the importance of measures required to translate clinical trial results into actual clinical practice.

The dose of ACE inhibitors and ARBs for the treatment of heart failure remains to be an issue. Uncertainties regarding use of the optimal dose of ACE inhibitors (as perceived by general practitioners as well as practicing cardiologists) remain an unresolved issue in clinical practice.

For ACE inhibitors, randomized trials have shown that there is no difference in mortality between patients receiving high-doses and those receiving low-doses of ACE inhibitors[12,13,14,15]. (Please also see the discussion in section 8.1.2 of this review.) The CHARM-Added study also shows the same rate of clinical primary efficacy events (CV death or CHF hospitalization) in patients on placebo who received ACE inhibitors at heart failure dose (event rate = 42.4%) or low dose (event rate = 42.1%); similarly for patients on candesartan, the rate of clinical primary efficacy events (CV death or CHF hospitalization) among patients who received ACE inhibitors at heart failure dose (event rate = 36.1%) is about the same as those who received ACE inhibitors at low dose (event rate = 39.7%).

For ARBs, it appears that a survival benefit is found only when higher doses than that for the treatment of hypertension are used. Insufficient dose of ARBs may have contributed to the

observed lack of beneficial effect of ARBs on mortality in ELITE II[20], OPTIMAAL[22], Val-Heft[16] and VALIANT[25] trials. (Please also see section 8.1.1 of this review.) A significant survival benefit in high risk patients was observed when relatively larger doses of ARBs were used in LIFE[23] and RENAAL[24] trials.

I think that only when there is a consensus of opinion about using ACE inhibitors for any type of heart failure regardless of the dose will there be an impetus to facilitate the concept that ACE inhibitors and ARBs are useful and beneficial in the treatment of all stages of heart failure to improve survival and reduce hospitalizations. Further surveys and educational activities in this aspect of heart failure treatment are necessary.

9 OVERALL ASSESSMENT

9.1 Conclusions

CHARM-Added (SH-AHS-0006) Study

In patients with CHF, with 99.9% of them using an ACE-inhibitor, the addition of candesartan significantly (P=0.011) reduced the relative risk of the composite primary efficacy outcome of CV death or CHF hospitalization by14.7%. The effect appeared early and was sustained throughout the duration of the study.

Candesartan treatment also significantly reduced the secondary efficacy outcomes of the relative risks of (i) a composite of all-cause mortality or CHF hospitalization (by 12.9%, P=0.021), and (ii) a composite of CV death or CHF hospitalization or non-fatal myocardial infarction (MI) (by 14.8%; P=0.008). The symptoms of heart failure as evaluated by the NYHA-classification were reduced by candesartan as compared to placebo.

This reduction in CV death and CHF hospitalization observed with candesartan treatment was also evident in those patients being treated with recommended doses of ACE- inhibitors as well as in those treated with β-blockers (56% of patients at baseline), suggesting that there is no negative interaction between the AT_1-receptor blocker candesartan, ACE-inhibitors and β-blocker therapy as was seen with valsartan in Val-HeFT[16].

The sponsor submits that the benefit of candesartan in this study was evident in the presence of background treatment with ACE inhibitors at recommended doses. The mean daily dose of enalapril at baseline was 17 mg, which compares to 16.6 mg (in those taking drug) in the treatment arm of the Studies Of Left Ventricular Dysfunction (SOLVD)[32] and 17 mg in Val-HeFT[16]. The mean daily dose of lisinopril was 18 mg which is also comparable to the 18 mg dose in the treatment arm of Val-HeFT[16]. However, for those on captopril, the main daily dose in the CHARM-Added study was lower (82 mg/day) compared to the dose used (107 mg/day) VALIANT[25] trial. It is possible that in a background of a relatively low dose of an ACE inhibitor (i.e., patients on captopril and patients on low dose ACE inhibitors for reasons of intolerance to higher doses in the CHARM-Added study) there would be more room for improvement with candesartan.

The findings of the CHARM-Added study may also be clinically important. The magnitude of the benefit in reducing cardiovascular death or CHF hospitalization translates into an absolute reduction of 4.4 events per 100 patients treated over a period of two years, which suggests that treating 23 patients for two years with candesartan will prevent one patient from suffering this outcome (of CV death or CHF hospitalization).

The reduction in CV death was attributed primarily to a reduction in sudden deaths and deaths due to heart failure, which are the most common modes of death in patients with CHF. The study was not powered to assess the effect on all-cause mortality.

Dose reduction and discontinuation of investigational product were more common with candesartan than placebo. This was primarily attributable to renal function impairment, hyperkalemia, or hypotension all of which could be expected from inhibitors of the RAAS and the underlying conditions in the CHF population. Monitoring patients for these expected events is therefore necessary in the care of the CHF patient.

More cancer deaths occurred in the candesartan group, but the investigator-reported rate of non-fatal neoplasms was more equal between treatment groups. In the total CHARM population (SH-AHS-0003, SH-AHS-0006, SH-AHS-0007) no significant differences in the incidence of neoplasms were identified.

CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies

In patients with symptomatic heart failure (i.e., the entire CHARM study population) treated with candesartan a statistically borderline 8.6% reduction in the relative risk of all-cause mortality (P= 0.055) was found. This was attributed to a 12.4% reduction in the relative risk of CV deaths (P= 0.011).

In the two studies in patients with depressed LV systolic function (LVEF ≤40% in SH-AHS-0003 and SH-AHS-0006), those treated with candesartan had an 11.4% reduction in the relative risk of all-cause mortality (P=0.018), resulting from a 15.6% reduction in the relative risk of CV deaths (P= 0.005). The all-cause mortality result in the overall (three) study pooled analysis was influenced by the neutral treatment effect in the population with preserved left ventricular systolic function (Study SH-AHS-0007).

The reduction in the relative risk of CV death was attributed primarily to reductions in the relative risks of sudden deaths (by 19.9%; P=0.013) and deaths due to heart failure (by 24.2%; P=0.008), which are the most common modes of death in patients with CHF. Candesartan did not affect non-CV deaths.

There was also a reduction in the relative risk of hospitalization due to heart failure found in each of the component studies of the CHARM Program.

The beneficial effects of candesartan in the CHARM program were not influenced by treatment with ACE-inhibitors, β-blockers or digoxin. This finding, unlike that observed in the Val-HeFT study[16], suggests benefit of use of an AT_1-receptor blocker in patients already receiving β-blockers and ACE-inhibitors.

The most common causes of death for the heart failure patient, sudden death and death due to CHF, were both reduced by candesartan when compared to placebo. The most common cause of non-cardiovascular death was pneumonia in both the candesartan-treated and the placebo-treated groups.

More cancer deaths occurred in the candesartan group but the investigator-reported rate of non-fatal neoplasms was not different between treatment groups.

The incidence of new diabetes was lower in the candesartan group, an effect observed in other large populations treated with either an ACE inhibitor [51,52] or AT_1-receptor blockers[23].

Symptoms of heart failure, as classified by the NYHA-classification, improved more in patients treated with candesartan than in patients treated with placebo (P= 0.004).

Overall, there was no significant safety issue associated with candesartan treatment of CHF other than the expected adverse event findings typical of the class of drugs and the clinical findings expected for the study populations. Discontinuation due to renal dysfunction, hyperkalemia, or hypotension was more common with candesartan than placebo. This distribution of events could be expected from inhibitors of RAAS and the underlying conditions in the CHF population. Monitoring patients for these risks is, therefore, an important consideration in care of the CHF patient.

9.2 Recommendation on Regulatory Action

Candesartan cilexetil is an angiotensin II type 1 (AT_1)-receptor blocker currently approved in the United States for the treatment of hypertension with an oral starting dose of 16 mg titratable up to 32 mg daily. The CHARM (**C**andesartan cilexetil (candesartan) in **H**eart Failure **A**ssessment of **R**eduction in **M**ortality and Morbidity) Program consists of three pivotal efficacy trials comprising 7,601 patients with NYHA Class II – IV chronic heart failure (CHF) who were randomized to candesartan (titrated from 4 mg or 8 mg once daily to a target dose of 32 mg once daily as tolerated) or matching placebo, and followed for at least 2 (up to 4) years. The analysis of the CHARM Program was divided into (i) patients with depressed left ventricular systolic function (ejection fraction (EF) ≤40%) who were intolerant to angiotensin converting enzyme (ACE) inhibitors (CHARM-Alternative), (ii) patients with depressed left ventricular systolic function (EF ≤40%) receiving an ACE inhibitor (CHARM-Added), and (iii) patients with Preserved left ventricular systolic function (EF >40%) (CHARM-Preserved). This efficacy supplement #022 pertains to CHARM-Added trial which received priority review.

In CHARM-Added (SH-AHS-0006) Study of 2,548 patients with CHF who were receiving an ACE inhibitor, candesartan significantly (P=0.011) reduced the relative risk of time to CV death or CHF hospitalization by14.7% (primary efficacy endpoint). This benefit translates into a reduction of 4.4 events per 100 patients treated for two years; i.e., treating 23 patients with candesartan for two years will prevent one patient from suffering the outcome of CV death or CHF hospitalization. The reduction in CV death was attributed to a reduction in sudden death and CHF death, which are the most common modes of death in patients with CHF. The study was not powered to assess the effect on all-cause mortality.

The benefit of candesartan was evident in the presence of treatment with ACE inhibitors at recommended doses. The mean daily dose of enalapril at baseline was 17 mg, which compares to 16.6 mg in the treatment arm of the **S**tudies **O**f **L**eft **V**entricular **D**ysfunction (SOLVD)[32] and 17 mg in the **Val**sartan **He**art **F**ailure **T**rial (Val-HeFT)[16]. This benefit was also evident in patients

treated with β-blockers, suggesting that there is no negative interaction between the AT_1-receptor blocker candesartan, ACE-inhibitors and β-blockers as reported with valsartan in Val-HeFT[16].

The CHARM Program (Combined SH-AHS-0003, SH-AHS-0006 and SH-AHS-0007 Studies) failed to reach statistical significance for the primary efficacy endpoint of time to all-cause mortality (reduction in relative risk = 8.6%; P= 0.055) in patients with symptomatic CHF; a significant (P= 0.018) reduction in time to all-cause mortality by 11.4% was seen in the sub-population of CHF patients with depressed LV systolic function (secondary efficacy endpoint). This was attributed to a 12.4 -15.6% relative risk reduction in CV death (P= 0.011), subsequently attributed to reductions in relative risks of sudden death (by 15.2 - 19.9%; P=0.013) and CHF death (by 21.7 - 24.2%; P=0.008). The beneficial effects of candesartan were also evident in patients treated with ACE inhibitors, β-blockers or digoxin, unlike that reported in Val-HeFT.

There were no significant safety issues associated with candesartan treatment of CHF other than the expected adverse events (AEs) consistent with the pharmacology of the drug and the health status of patients. Discontinuation or dose reduction of study drug attributed to a decline in renal function, hypotension or hyperkalemia occurs more frequently with candesartan than placebo.

Based on my review limited to NDA 20-838 Efficacy Supplement # 022 with data on the CHARM-Added (SH-AHS-0006) study and the overall CHARM Program (SH-AHS-0003, -0006, -0007) studies, I recommend this application as for the indication of treatment of heart failure (NYHA class II-IV) with left ventricular systolic dysfunction (ejection fraction ≤40%) in patients who are receiving other heart failure treatments including ACE-inhibitors or β-blockers, where candesartan has been shown to reduce the relative risk of time to cardiovascular death or the first occurrence of a hospitalization for heart failure. I suggest that the issues related to the role and dose of AT_1 receptor blockers in the treatment of patients with heart failure presented in section 8.6 (Table 140 Issues related to the role of angiotensin receptor blockers in the treatment of patients with heart failure and left ventricular dysfunction) be discussed at a Cardio-Renal Drug Advisory Committee Meeting.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

I suggest the sponsor institute the following risk management activities:

(i) Analyze data from the CHARM-Program studies to determine dose of candesartan and/or ACE-inhibitor and/or β-blockers and/or spironolactone in relation to AEs (hypotension, hyperkalemia, deterioration of renal function) and study drug discontinuation and/or dose reduction. This information should be provided in the labeling as well as communicated to practicing physicians through educational measures.

(ii) Ensure educational activities regarding the importance of starting with the lowest initial dose of candesartan and of increasing the dose gradually while monitoring the heart rate and blood pressure, serum creatinine, and serum potassium.

9.3.2 Phase 4 Requests

(i) Plan/perform a prospective clinical trial of candesartan in treatment of patients (tolerant and intolerant to ACE inhibitors) with high risk of heart failure without structural heart disease or symptoms (i.e. Stage A heart failure) to determine if candesartan will prevent or delay development of structural heart disease (Stage B), symptomatic heart failure (Stage C) or refractory symptoms of heart failure (Stage D).

(ii) Plan/perform a prospective clinical trial (with multiple arms for multiple (e.g., high vs low) doses of candesartan and multiple (recommended heart failure dose vs low) doses of ACE-inhibitors) to find the optimal dose combination of ACE-inhibitor (high or low dose) and candesartan (high or low dose) in the treatment of CHF which will provide the most benefit [survival benefit (all-cause death, CV death, sudden death and CHF death) and clinical benefit (reduced hospitalization, improved symptoms, hemodynamics and exercise tolerance)] with the least risk [of AEs such as aggravated heart failure, hypotension, hyperkalemia, and deterioration of renal function].

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)

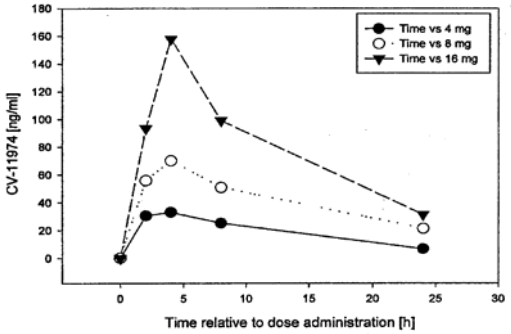


Figure 79 Mean Serum Concentration of CV-11974 (Safety population)

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).

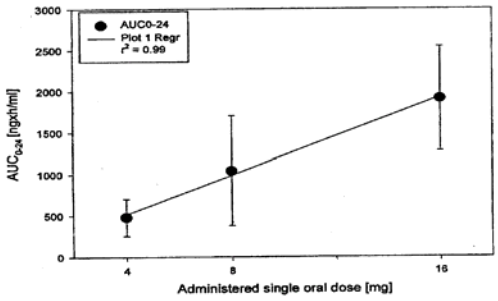


Figure 80 AUC_{0-24} vs. administered dose (Efficacy (ITT) population)

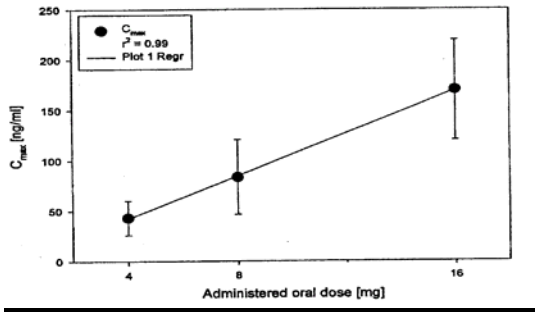


Figure 81 C_{max} vs. administered dose (Efficacy (ITT) population)

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.

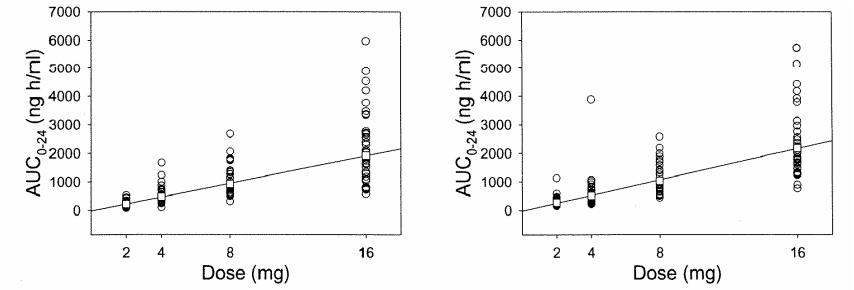
There were 12 (5.5%) major protocol violations: eight (8) patients took prohibited concomitant medications, three (3) patients had PCWP < 13mmHg at visit 2, two (2) patient had PCAP values that were not plausible, and one (1) subject (on 16 mg candesartan) had measurements taken without taking drug.

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)

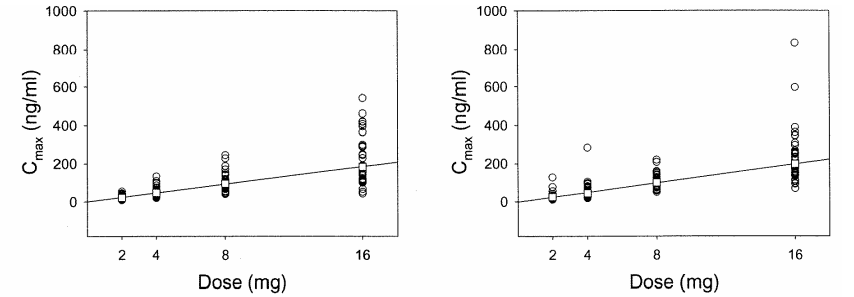
Dose (mg)	Visit 2 C_{max} (ng/ml)	Visit 2 AUC_{0-24} (ng h/ml)	Visit 2 t_{max}* (h)	Visit 6 C_{max} (ng/ml)	Visit 6 AUC_{0-24} (ng h/ml)	Visit 6 t_{max}* (h)
2	21.7 (8.2, 53.9)	225.8 (82.7, 531.1)	4.2 (2.1, 12)	25.2 (10.8, 128)	281.4 (158.8, 1134.7)	4.2 (2.1, 8.3)
4	47.2 (19.1, 133)	477.6 (103, 1669.6)	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)

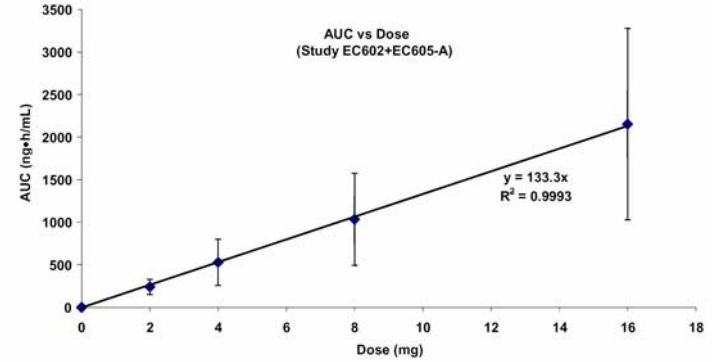


Figure 84 $AUC_{0\text{-}24h}$ (following single doses of candesartan) vs. dose of candesartan cilexetil in patients with CHF (studies 602 and 605-A)

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.

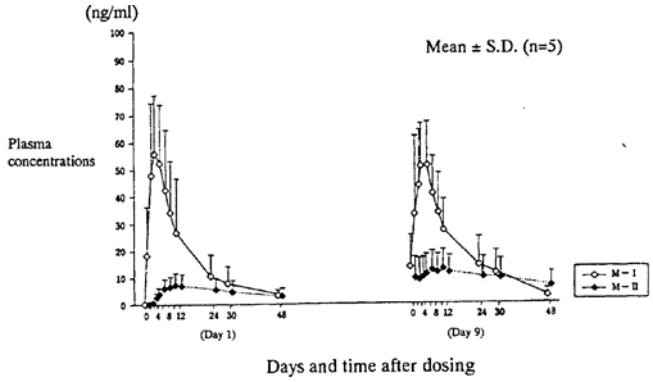


Figure 85 Plasma concentrations of M-I and M-II after administration of candesartan in multiple doses of 4 mg/day in patients with CHF

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

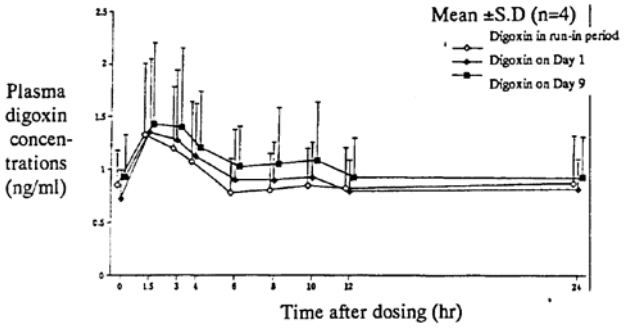


Figure 86 Plasma digoxin concentrations

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).

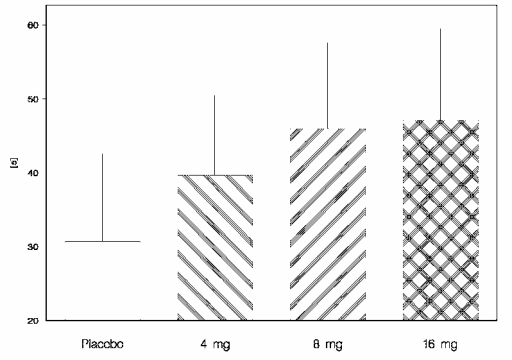


Figure 87 Dose-response relationship for the change in total exercise time[s] between baseline (Visit 5) and last value – Intent-to-treat population (n=807)

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.

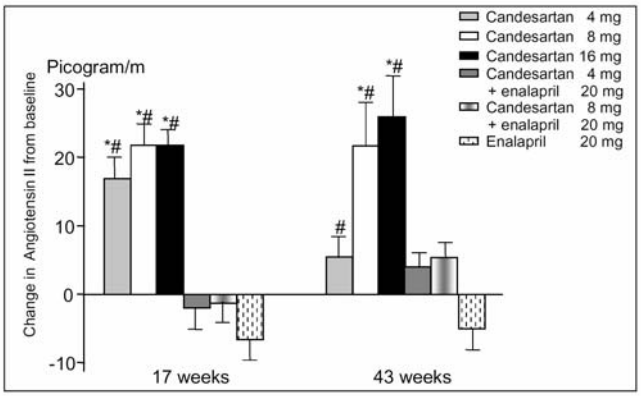


Figure 88 Change in angiotensin II levels after 17 and 43 weeks of treatment with candesartan, candesartan plus enalapril or enalapril
* P< 0.01compared with 0 weeks; # P< 0.01 compared with enalapril

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).

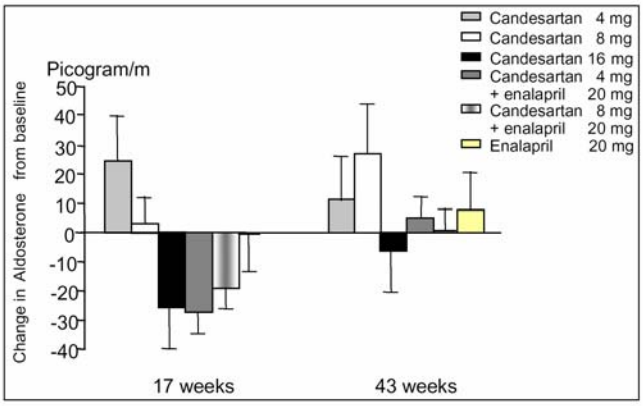


Figure 89 Change in angiotensin II levels after 17 and 43 weeks of treatment with candesartan, candesartan plus enalapril or enalapril
* P< 0.01compared with 0 weeks; # P< 0.01 compared with enalapril

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)

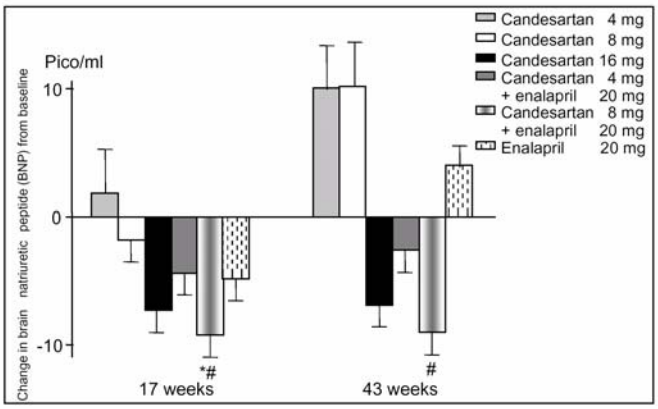


Figure 90 Change in brain natriuretic peptide (BNP) levels after 17 and 43 weeks of treatment with candesartan, candesartan plus enalapril or enalapril
* P< 0.01compared with 0 weeks; # P< 0.01 compared with enalapril

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).

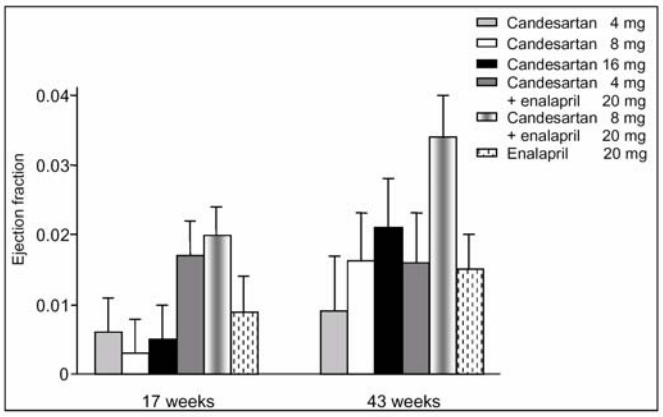


Figure 91 Increase in Ejection Fraction by different treatments after 17 and 43 weeks.

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).

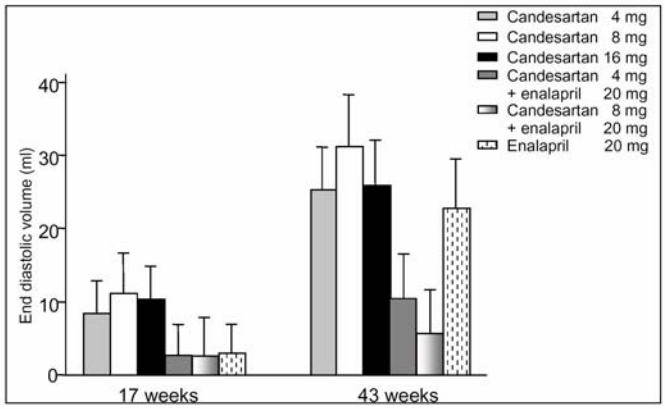


Figure 92 Change in End Diastolic Volume (ml) by different treatments after 17 & 43 weeks.

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.

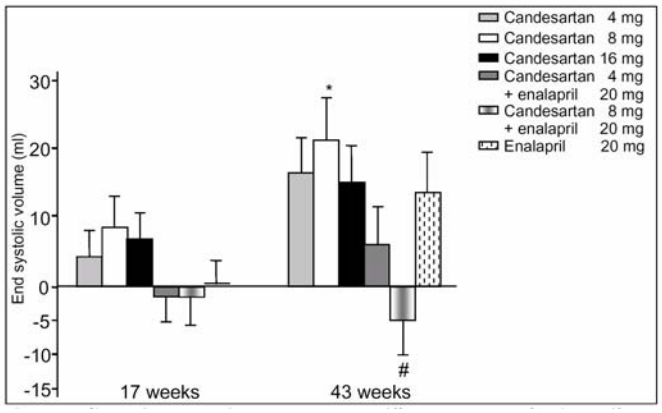


Figure 93 Change in End Systolic Volume (ml) by different treatments after 17 & 43 weeks.
* P< 0.01 compared with 0 weeks; # P< 0.01 compared with enalapril

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).

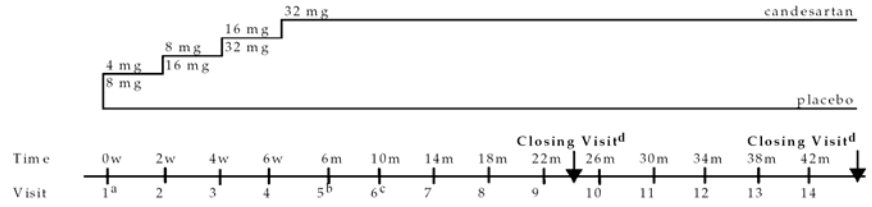
Other objectives: To determine whether candesartan, compared to placebo:

- 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.

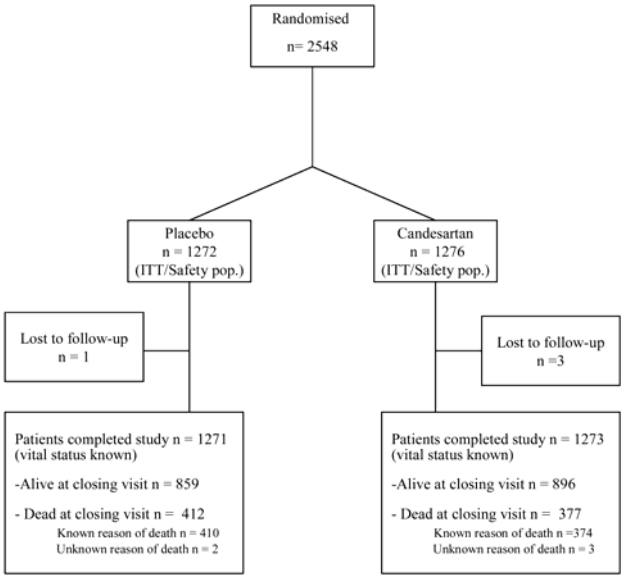


Figure 95 Patient disposition (completion or discontinuation)

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.

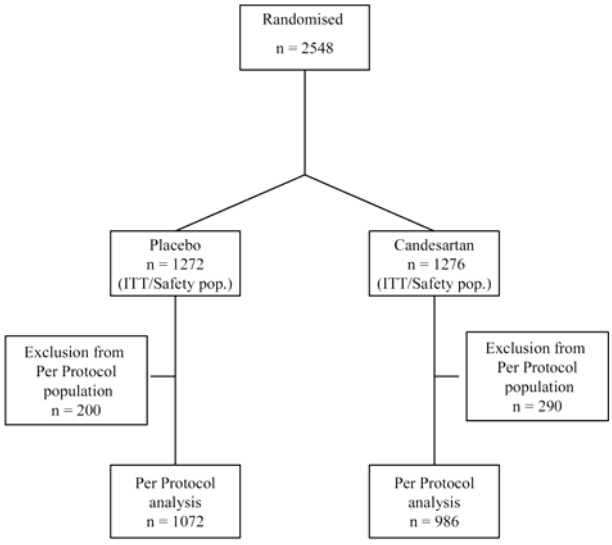


Figure 96 Study populations

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

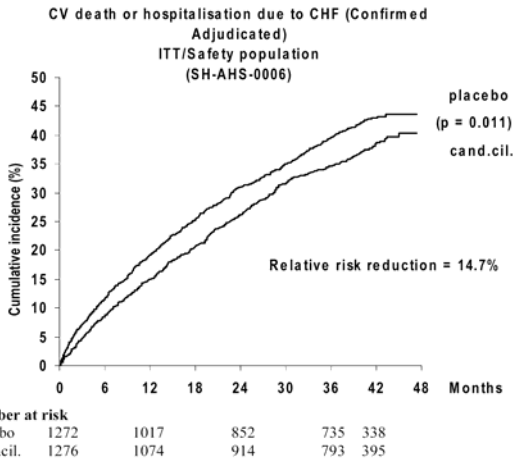


Figure 97 Cumulative incidence (%) of confirmed adjudicated CV death or hospitalization due to CHF over time. ITT/Safety population

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

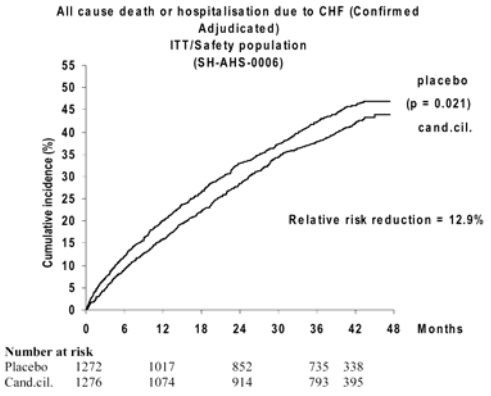


Figure 98 Cumulative incidence (%) of confirmed adjudicated all- cause death or hospitalization due to CHF over time. ITT/Safety population

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

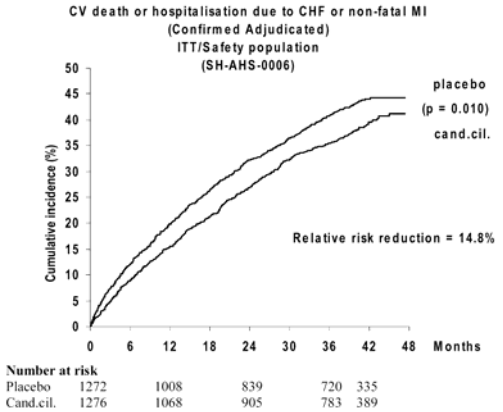


Figure 99 Cumulative incidence (%) of confirmed adjudicated CV death or hospitalization due to CHF or non- fatal MI over time. ITT/Safety population

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).

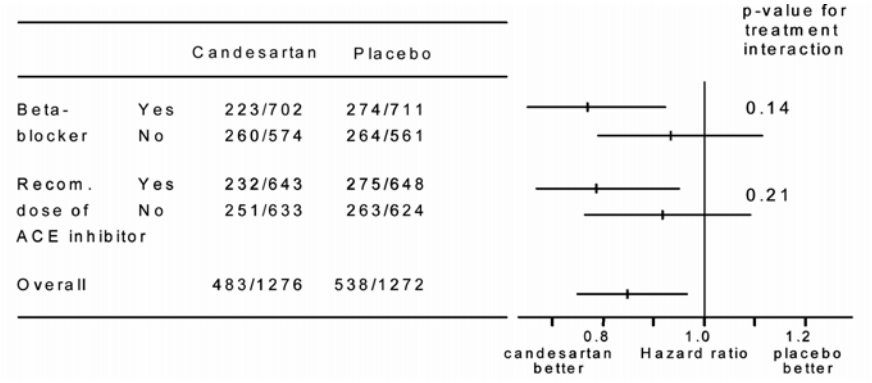


Figure 100 Effect of candesartan compared with placebo on primary outcome in all patients and patients taking or not taking β-blocker and taking or not taking recommended dose of ACE inhibitors at baseline

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

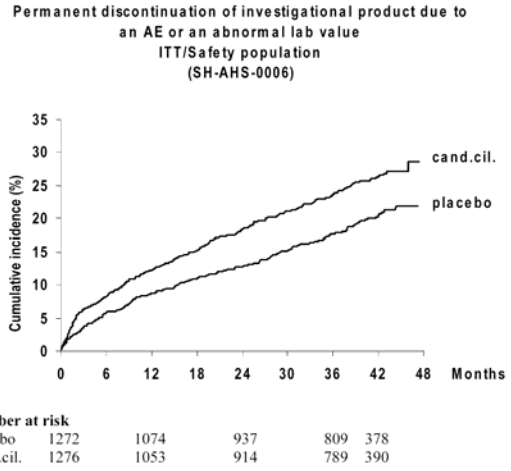


Figure 101 Cumulative incidence (%) of permanent discontinuation of investigational product due to an AE or an abnormal laboratory value. ITT/Safety population

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
	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

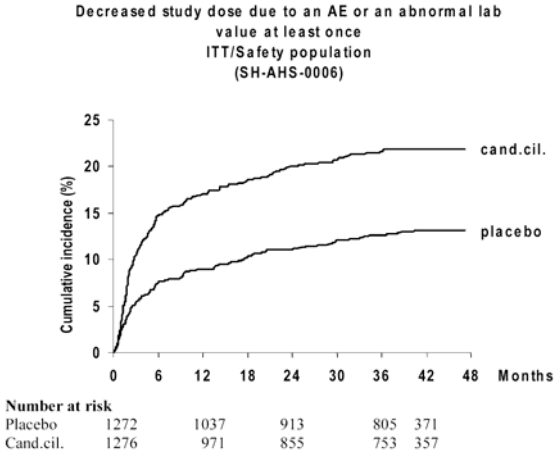


Figure 102 Cumulative incidence (%) of first occurrence of dose decrease of investigational product due to an AE or an abnormal laboratory value. ITT/Safety population

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,

including diuretics and β-blockers.

Among the patients that discontinued the investigational products due to hypotensive events, a greater proportion had SBP < 100 mmHg at baseline in the candesartan group (placebo 3, 7.5%, candesartan 11, 24.1%).

In patients aged younger than 75 years, discontinuation because of the preferred term hypotension was reported in 30 (2.9%) of patients in the placebo group and 53 (5.0%) of patients on candesartan.

For patients aged 75 years or older the discontinuation rates were 14 (5.7%) in the placebo group and 16 (7.5%) in the candesartan group.

In the placebo group, permanent discontinuation of the investigational product due to hypotension was reported in 34 (3.4%) males and 10 (3.7%) females. In the candesartan treatment group there were 59 (5.9%) males and 10 (3.7%) females who were permanently discontinued due to hypotension.

Although over the entire study period patients in both treatment groups discontinued taking the investigational product because of hypotension, the candesartan discontinuation rate, shown in the exploratory analysis, was greatest during the first 6 to 12 months of treatment (Figure 103).

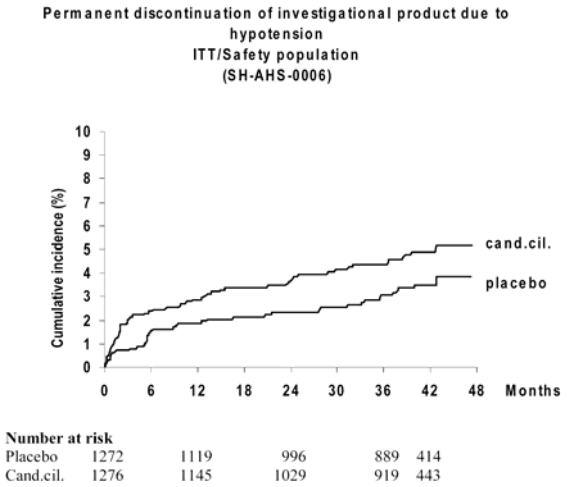


Figure 103 Cumulative incidence (%) of permanent discontinuation of investigational product due to hypotension (Ref. - Table 221). ITT/Safety population

Among the 382 (30.0%) placebo patients and 376 (29.5 %) candesartan patients entering the study with a history of diabetes, investigational product discontinuation for the specific preferred term hypotension was noted for 15 (3.9%) placebo patient and 17 (4.5%) candesartan patients.

Abnormal renal function:

To summarize abnormal renal function, the following AE terms (AAED preferred terms) were

selected and analyzed as a single composite event: renal function, abnormal/ renal dysfunction, aggravated; renal failure acute; renal failure, NOS; uremia; non-protein nitrogen, increased; renal failure, aggravated; blood urea nitrogen, increased; acute pre-renal failure and anuria. For this composite AE, patients with multiple events including any of the selected AE terms were counted only once.

At baseline, prior to study entry, there were a slightly higher proportion of patients in the candesartan group with s-creatinine ≥ 2.0 mg/ dl at baseline (placebo 20, 4.3%; candesartan 26, 5.6%) (North American study population).

AEs suggesting 'abnormal renal function' occurred in 151 (11.9%) patients in the placebo group and 231 (18.3 %) patients in the candesartan group during study (Table 226).

Table 226 Number (%) of patients with any of the preferred terms renal function abnormal/ renal dysfunction aggravated, renal failure acute, renal failure not otherwise specified (NOS), uremia, non-protein nitrogen increased, renal failure aggravated, blood urea nitrogen increased, acute pre-renal failure or anuria. 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
139 (10.9)	220 (17.3)	151 (11.9)	231 (18.3)

The AE terms that predominately contributed to this composite AE term was renal function abnormal which was reported in 118 (9.3%) of patients given placebo and 195 (15.3%) given candesartan during study. Renal failure, acute (placebo, 38 patients, 3.0%; candesartan, 54 patients, 4.2%) and uremia (placebo, 10 patients, 0.8%; candesartan, 18 patients, 1.4%) were also numerically more frequent in patients given active treatment.

A fatal renal function event was reported for a higher proportion of patients in the placebo group, both 'on treatment' (placebo, 8 patients; candesartan, 2 patients) and 'during study' (placebo, 20 patients; candesartan 15 patients). In both treatment groups, the majority of renal events that led to death were reported in association with other causes of death such as worsening heart failure.

The preferred term renal function abnormal used in this descriptive safety analysis correspond 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 CRF.

In the descriptive safety analysis (Table 219), on investigational product discontinuation in the overall study population, the specified AE term renal function abnormal was the most common reason for permanent discontinuation of the investigational product in both treatment groups (placebo 53, 4.2%; candesartan 105, 8.2%).

In the exploratory analysis the term increased creatinine was reported for 52 (4.1%) placebo patients and 100 (7.8%) candesartan patients (Table 223). The higher rate for discontinuation of the investigational product due to 'abnormal renal function' in the candesartan group could not

be explained by higher use of concomitant medication when the event started. Among the patients who discontinued the investigational product due to 'abnormal renal function events', a higher proportion of patients in the placebo group had a serum creatinine level equal to or greater than 2 mg/dL at baseline (placebo 8, 15.4%); candesartan 9 (9.0%) (North American study population).

In patients aged younger than 75 years, discontinuation because of the AE term renal function abnormal was reported in 40 (3.9%) of patients in the placebo group and 82 (7.7%) of patients on candesartan. For patients aged 75 years or older the discontinuation rates were 13 (5.3%) in the placebo group and 23 (10.8%) in the candesartan group.

In the placebo treatment group 43 (4.3%) males and 10 (3.7%) females discontinued due to renal function abnormal. In the candesartan treatment group 82 (8.2%) males and 23 (8.5%) females reported the renal event.

In the exploratory analysis, patients discontinued study treatment because of the term 'increased creatinine' over the entire study period, and the rate was greater for candesartan-treated patients (Figure 104).

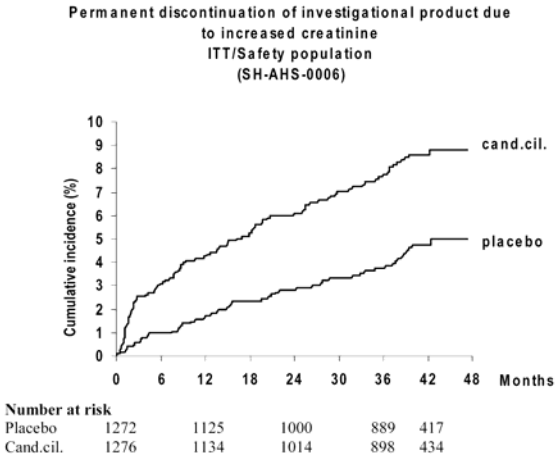


Figure 104 Cumulative incidence (%) of permanent discontinuation of investigational product due to increased creatinine (Ref. - Table 221). ITT/Safety population

Among the 382 (30.0%) placebo patients and 376 (29.5 %) candesartan patients entering the study with a history of diabetes, investigational product discontinuation for the specific term increased creatinine was noted for 25 (6.5%) placebo and 42 (11.2%) candesartan patients. Compared to the overall population (placebo 4.1%, candesartan 7.8%) diabetics were slightly more likely to discontinue the investigational product for increased creatinine levels (Table 223 and Table 224).

Hyperkalemia:

In this section hyperkalemia is discussed 'on treatment' rather than 'during study' as a more clinically meaningful measure of possible relationship to the investigational product.

At baseline, a slightly higher proportion of patients in the candesartan treatment group had a serum potassium ≥ 5 mmol/L (North American study population).

Hyperkalemia was reported for 44 patients (3.5%) in the placebo group and 121 patients (9.5%) in the candesartan group on treatment with the investigational product Table 216).

Fatal hyperkalemia was reported during the study for 2 patients in the candesartan group and no patient in the placebo group. Patient 155-10493 died of sudden death and hyperkalemia (potassium concentration, 6.2 mmol/ L) after approximately two years of candesartan treatment. Patient 201-12699 had abnormal renal function 20 days after starting treatment with candesartan, and died of sudden death and hyperkalemia (potassium concentration, 6.1 mmol/ L) after 52 days of treatment. Both patients had a concomitant unspecified increase in serum creatinine. The Investigators assessed the AEs as probably and possibly, respectively, related to the investigational product.

In Table 219, discontinuation of the investigational product because of hyperkalemia was more frequent with candesartan (placebo 11, 0.9%; candesartan 49, 3.8%). In the exploratory analysis the corresponding numbers were 9 (0.7%) for placebo patients and 44 (3.4%) for candesartan patients (Table 223). The higher rate for hyperkalemia causing discontinuation in the candesartan group could not be explained by higher use of concomitant medication when the event started, including potassium-sparing diuretics. There was no between treatment difference regarding baseline serum potassium levels in patients who discontinued investigational product due to hyperkalemia (North American study population).

In patients < 75 years old, discontinuation because of the AE term hyperkalemia was reported in 8 (0.8%) patients in the placebo group and 31 (2.9%) of patients on candesartan. For patients aged 75 years or older the discontinuation rates were 3 (1.2%) in the placebo group and 18 (8.5%) in the candesartan group.

In the placebo group the majority of events were seen in male patients, in the candesartan group the events were equally distributed between.

The discontinuation rate for candesartan-treated patients because of hyperkalemia, presented from exploratory analysis, was greater during the first 6 to 12 months of treatment, but discontinuations still occurred over the entire study period (Figure 105)

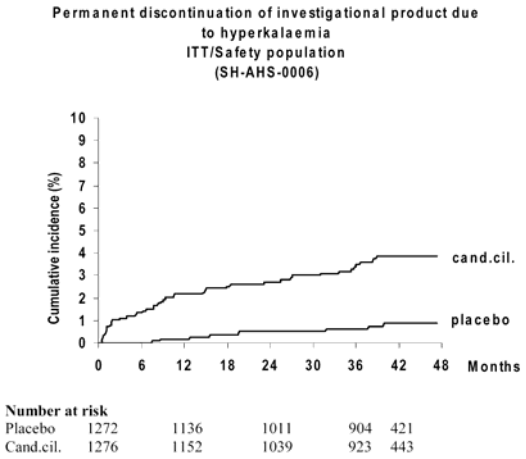


Figure 105 Cumulative incidence (%) of permanent discontinuation of investigational product due to hyperkalemia. ITT/Safety population (Ref. - Table 221).

Among the 382 (30.0%) placebo patients and 376 (29.5 %) candesartan patients entering the study with a history of diabetes, investigational product discontinuation for the specific preferred term hyperkalemia was noted for 10 (2.6%) placebo and 31 (8.2%) candesartan patients.

Abnormal hepatic function:

The most common AE terms suggesting liver dysfunction during treatment were hepatic enzymes increased (placebo 1 patient; candesartan 6 patients) and hepatic function abnormal (placebo 1 patient; candesartan 4 patients). The AE term hepatic failure was reported for 4 patients in the placebo group and 2 patients in the candesartan group.

Neoplasms:

AEs indicative of neoplasms, whether benign or malignant, were pooled from the SOC (System organ class) 'Neoplasms', plus 3 neoplastic AE terms from other SOCs (Melanoma malignant, Myelomatosis multiple and Pleural mesothelioma). Neoplasms were reported for 68 patients (5.3%) in the placebo treatment group compared with 90 (7.1%) in the candesartan group. One patient in the placebo group (Site 1532, Patient number 21520) had both Myeloid dysplasia (included in the SOC Neoplasms) and Myelomatosis multiple. In the total numbers presented above this patient is counted only once. Neoplasms proved fatal for 20 patients (1.6%) in the placebo group and 39 patients (3.0%) in the candesartan group.

In the overall study population, the majority of patients did not have a history of cancer at baseline (placebo 94.1%; candesartan 93.9%).

The majority of reported neoplasms were malignant. The most common neoplasms during study were pulmonary cancer (placebo, 7 patients; candesartan, 12 patients), prostatic cancer (placebo, 9 patients; candesartan, 7 patients) and colon cancer (placebo 5 patients; candesartan 8 patients.

Angioedema:

During study, two cases of angioedema were reported for patients in the candesartan group. Both patients were Caucasian with concomitant medication with an ACE-inhibitor at the start of the event. One of these patients developed angioedema that required discontinuation of candesartan treatment. For the other patient ACE inhibitor medication was stopped but treatment with candesartan continued. In the placebo group three patients reported angioedema, in one case leading to discontinuation of the investigational product.

Discussion of deaths, serious adverse events, discontinuation due to adverse events, and other significant adverse events:

Both CV mortality and overall mortality were lower for patients given candesartan. There were no statistically significant differences between the candesartan group and the placebo group in proportion of patients with non-CV death or non-CV hospitalization.

SAE reports were a common occurrence during the study, an expected finding for a study population with CHF and a long follow-up period. SAEs were reported for more than two thirds of study patients (75.9% in both treatment groups) and most SAEs were CV disorders, reflecting the underlying conditions and risk factors of the study population.

Greater than one fourth of study patients died during the study (placebo 32.5%; candesartan 29.5%), but overall mortality was lower with candesartan treatment (placebo 21.7 %; candesartan, 16.5 %). As expected, most deaths were attributed to CV causes, the most frequent of which were sudden death; cardiac failure/cardiac failure, aggravated; and MI.

Among CV deaths, specific causes such as sudden death and death from heart failure were less common with candesartan treatment. This is an expected finding given that candesartan significantly reduced overall CV death and the most common causes of death in patients with CHF are typically sudden (arrhythmic) death and death from heart failure. Prevention of these causes of CV death is consistent with the survival beneficial effect of candesartan treatment observed in patients with CHF. Death from MI was a less common cause of death in this population (placebo 0.9%; candesartan 1.2%). The overall incidence of MI was 5.7% for placebo and 4.7% for candesartan. The mortality findings in the study population were relatively consistent across subgroups on the basis of age, sex and race. As expected, mortality was higher in older patients.

Also, as expected, some of the most common non-fatal SAEs were cardiovascular (cardiac failure/cardiac failure aggravated; angina pectoris and arrhythmia ventricular), and they generally occurred less frequently in patients in the candesartan group. Pneumonia, also an expected finding in an older population with CHF, was frequently cited with a higher frequency in the placebo treatment group (placebo 7.3%; candesartan 5.7%). 'Renal failure, acute' as a non-fatal SAE was reported for 32 of placebo-treated patients and for 50 of candesartan-treated patients during study.

There was no difference in frequency between treatment groups for AE terms suggesting liver dysfunction.

Of 1,276 candesartan-treated patients in the study, 39 (3.0%) died of cancer; 20 (1.6%) of 1,272 placebo-treated patients also died of cancer. More equal proportions developed a neoplasm during the study (placebo, 5.3%; candesartan, 7.0%). The types of cancer (lung, prostate, colon) were typical for patients in the age group of the study population. In the overall assessment of safety data from the CHARM program (SH-AHS-0003, SH-AHS-0006, SH-AHS-0007), no significant differences in the incidence of malignant neoplasms were identified.

Tolerability of investigational product was not different between patients treated with candesartan and patients treated with placebo. Overall, 71.4% of patients completed participation in the study without discontinuing treatment (74.9% in the placebo and 67.8% in the candesartan groups). Small differences existed between treatment groups for specific causes of investigational product discontinuation.

Discontinuation due to aggravation of cardiac failure was more common in placebo- treated patients (6.4% compared with 5.4% for candesartan-treated patients).

Abnormal renal function, hypotension and hyperkalemia were cited more frequently as reasons for discontinuation with candesartan treatment (8.2% compared with 4.2%, 5.4% compared with 3.5% and 3.8% compared with 0.9%, respectively). Discontinuation of candesartan because of these three reasons was most notable in the first 6 to 12 months of treatment. Hypotension, progressive renal dysfunction and hyperkalemia are well recognized as likely adverse events in patients with CHF, particularly when they are treated with inhibiters of the RAAS.

Safety analyses for subgroups based on sex and race were similar compared to the overall population. As expected, event rates increased with age for both treatment groups. For abnormal renal function and hypotension there were no differences between the treatment groups. In patients aged 75 and younger, discontinuation because of hyperkalemia was reported in 0.8% of patients in the placebo group and 2.9% of patients on candesartan. Corresponding figures for patients aged 75 years or older were 1.2% in the placebo group and 8.5 % in the candesartan group. Generally the frequency of events was higher for males in both treatment groups. The majority of the patients were Caucasians (placebo 92.5%; candesartan 91.7%). Only 4.9% in the placebo group and 5.1% on candesartan treatment were Blacks, among whom a correspondingly smaller number of events was observed. Concomitant medication with ACE-inhibitors, β-blockers and/or spironolactone at the time of the event did not seem to affect the outcome regarding the AEs specifically studied.

For patients with a history of diabetes, the between-treatment difference in frequency of discontinuations caused by increase in creatinine was slightly higher compared to the total population in the study. This is not an unexpected finding in a subpopulation with possible underlying renal dysfunction and autonomic dysregulation.

Study investigators chose to reduce the dose of the investigational product to manage AEs for

17.2% of candesartan-treated patients and 9.7% of placebo-treated patients. In general, AEs cited as prompting investigational product discontinuation were also cited as reasons for dose reductions (hypotension, hyperkalemia and abnormal renal function). However, dose reduction due to aggravated cardiac failure was comparatively rare.

In this study of patients treated with ACE inhibitors, events relatively specific to candesartan (by its being an inhibitor of the RAAS) such as hypotensive events, abnormal renal function and hyperkalemia occurred in the candesartan treatment group.

Clinical laboratory results:

Serial laboratory data were collected from patients participating at investigational sites in North America (placebo 477 patients, candesartan 477 patients).

Changes in mean laboratory values were generally small, of minor clinical significance, and occurred primarily in parameters that previously showed changes in studies with inhibitors of the renin-angiotensin-aldosterone system (RAAS), such as creatinine and potassium.

The mean value for creatinine in the placebo group increased 13.64 μmol/L from the baseline value to the LVCF. In the candesartan group, the value increased 19.63 μmol/L. At baseline, 86 (18.5%) of placebo patients had values above the reference range compared with 83 (17.8%) of patients in the candesartan group. For the last values carried forward that were above the upper level of normal, frequency increased in both treatment groups (placebo 140, 30.4%; candesartan 145, 32.4%). For patients who had serial measurements (placebo 447 patients, candesartan 436 patients) baseline serum creatinine was at least doubled in 27 (6.0%) patients in the placebo group, compared with 32 (7.3%) patients in the candesartan group.

For potassium, the mean value for patients treated with placebo increased 0.02 mmol/L from the baseline value to the LVCF compared with 0.12 mmol/L for patients treated with candesartan. During the study, the proportions of patients with values above the reference range increased in the placebo group (14, 3.0% at baseline, 20, 4.4% LVCF) and increased from 21 (4.5%) to 31 (6.9%) in the candesartan group. Potassium levels increased to ≥ 6 mmol/L at any time after randomization in 1.1% (5) of 459 patients valid for evaluation in the placebo group and 2.7% (12) of 447 patients in the candesartan group.

Mean sodium measurements increased 0.10 mmol/L for patients treated with placebo and decreased 0.28 mmol/L for patients in the candesartan group. The AE term hyponatremia was reported for 5 patients treated with placebo compared with 6 patient treated with candesartan.

Minor decreases were seen for mean hemoglobin values for patients treated with placebo (0.30 mmol/L) and candesartan (0.35 mmol/L). The proportion of patients with anemia reported as an AE during treatment with the investigational product was similar for placebo-treated patients (36, 2.8%) compared with candesartan-treated patients (35, 2.7%). One patient (0.2%) in each treatment group had a hemoglobin value below the defined level of abnormality (male ≤ 80 g/L (4.96 mmol/L), female ≤ 70 g/L (4.34 mmol/L)).

Glycohemoglobin A_{1c} levels decreased slightly and no major difference was seen between the placebo (-0.36%) and candesartan groups (-0.38%).

In summary, both the small differences in mean laboratory values (candesartan compared with placebo) and the frequency of outliers was in keeping with the expected findings for treatment with inhibitors of the renin- angiotensin-aldosterone system, i. e., effects on serum creatinine and potassium levels.

Discussion of vital signs, ECG, physical findings and other observations related to safety:

Vital signs consist of diastolic blood pressure (DBP), systolic blood pressure (SBP), pulse pressure and heart rate. For physical findings, data for body weight are presented.

Blood pressure declined in both treatment groups. Mean DBP decreased 2.6 mmHg from the baseline value to the LVCF in the placebo group and 3.5 mmHg from the baseline value to the LVCF in the candesartan group. Corresponding values for SBP were 2.5 mmHg for patients treated with placebo and 5.0 mmHg for patients treated with candesartan. The effect on blood pressure in the candesartan group was established during the first 6 months while in the placebo group a trend towards lowering could be seen for a longer time period.

A DBP value less than 40 mmHg at any time during the study was reported for 32 (2.5%) patient in the placebo group and 42 (3.3%) patients in the candesartan group. 67 (5.3%) patients treated with placebo and 104 (8.2%) patients treated with candesartan had a recorded SBP value less than 80 mmHg at any time after randomization.

At LVCF mean heart rate was unchanged in patients in the placebo group and 0.3 bpm lower in patients in the candesartan group compared to baseline

In the placebo group, mean body weight decreased by 0.2 kg from baseline to LVCF. In the candesartan population an increase of 0.3 kg was seen.

Is there is relationship between the dose of candesartan and the important adverse events?

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 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

On Nov 12, 2004, I received the sponsor's response containing the information related to the 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.

Relationship of dose of candesartan to permanent study drug discontinuation due to an adverse event or an abnormal laboratory value

In Table 227, no relationship is apparent between the dose of candesartan and the numbers and frequencies of permanent study drug discontinuation due to an adverse event or an abnormal laboratory value.

Table 227 The numbers and frequencies of permanent study drug discontinuation due to an adverse event or an abnormal laboratory value[a] in patients who received high or low dose candesartan plus ACE inhibitors at heart failure dose or low dose– CHARM-Added (SH-AHS-0006) Study

	$ACEi_{HFD}$ (N=643)			**$ACEi_{LD}$ (N=633)**		
Candesartan cilexetil[b]	**CC_{HD} + $ACEi_{HFD}$** N = 426 n = 86 (20.2%)	**CC_{LD} + $ACEi_{HFD}$** N = 138 n = 58 (42.0%)	**CC_{00} + $ACEi_{HFD}$** N = 79 n = 7 (8.9%)	**CC_{HD} + $ACEi_{LD}$** N = 393 n = 75 (19.1%)	**CC_{LD} + $ACEi_{LD}$** N = 162 n = 64 (39.5%)	CC_{00} + $ACEi_{LD}$ N = 78 n = 20 (25.6%)

$ACEi_{HFD}$ = 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] Definition used in exploratory safety analyses; [b]Dose of candesartan preceding the event (or at last visit if no event occurred)
n = number of patients with one or more events (proportion (%) of patients at the dose)

Relationship of dose of candesartan to permanent study drug discontinuation due to hypotension

In Table 228, no relationship is apparent between the dose of candesartan and the numbers and frequencies of permanent study drug discontinuation due to hypotension.

Table 228 The numbers and frequencies of permanent study drug discontinuation due to hypotension[a] in patients who received high or low dose candesartan plus ACE inhibitors at heart failure dose or low dose– CHARM-Added (SH-AHS-0006) Study

	$ACEi_{HFD}$ (N=643)			**$ACEi_{LD}$ (N=633)**		
Candesartan cilexetil[b]	**CC_{HD} + $ACEi_{HFD}$** N = 364 n = 8 (2.2%)	**CC_{LD} + $ACEi_{HFD}$** N = 98 n = 13 (13.3%)	**CC_{00} + $ACEi_{HFD}$** N = 181 n = 1 (0.6%)	**CC_{HD} + $ACEi_{LD}$** N = 342 n = 12 (3.5%)	**CC_{LD} + $ACEi_{LD}$** N = 131 n = 22 (16.8%)	CC_{00} + $ACEi_{LD}$ N = 160 n = 2 (1.3%)

$ACEi_{HFD}$ = 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] Definition used in exploratory safety analyses; [b]Dose of candesartan preceding the event (or at last visit if no event occurred)
n = number of patients with one or more events (proportion (%) of patients at the dose)

Relationship of dose of candesartan to permanent study drug discontinuation due to hyperkalemia

In Table 229, no relationship is apparent between the dose of candesartan and the numbers and frequencies of permanent study drug discontinuation due to hyperkalemia.

Table 229 The numbers and frequencies of permanent study drug discontinuation due to hyperkalemia[a] in patients who received high or low dose candesartan plus ACE inhibitors at heart failure dose or low dose– CHARM-Added (SH-AHS-0006) Study

	$ACEi_{HFD}$ (N=643)			$ACEi_{LD}$ (N=633)		
Candesartan cilexetil[b]	CC_{HD} + $ACEi_{HFD}$	CC_{LD} + $ACEi_{HFD}$	CC_{00} + $ACEi_{HFD}$	CC_{HD} + $ACEi_{LD}$	CC_{LD} + $ACEi_{LD}$	CC_{00} + $ACEi_{LD}$
	N = 372	N = 94	N = 177	N = 342	N = 117	N = 174
	n = 16 (4.3%)	n = 7 (7.5%)	n = 1 (0.6%)	n = 12 (3.5%)	n = 8 (6.8%)	n = 0 (0.0%)

$ACEi_{HFD}$ = 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] Definition used in exploratory safety analyses; [b]Dose of candesartan preceding the event (or at last visit if no event occurred)
n = number of patients with one or more events (proportion (%) of patients at the dose)

Relationship of dose of candesartan to permanent study drug discontinuation due to increased serum creatinine

In Table 230, no relationship is apparent between the dose of candesartan and the numbers and frequencies of permanent study drug discontinuation due to increased serum creatinine.

Table 230 The numbers and frequencies of permanent study drug discontinuation due to increased serum creatinine[a] in patients who received high or low dose candesartan plus ACE inhibitors at heart failure dose or low dose– CHARM-Added (SH-AHS-0006) Study

	$ACEi_{HFD}$ (N=643)			$ACEi_{LD}$ (N=633)		
Candesartan cilexetil[b]	CC_{HD} + $ACEi_{HFD}$	CC_{LD} + $ACEi_{HFD}$	CC_{00} + $ACEi_{HFD}$	CC_{HD} + $ACEi_{LD}$	CC_{LD} + $ACEi_{LD}$	CC_{00} + $ACEi_{LD}$
	N = 385	N = 105	N = 153	N = 351	N = 127	N = 155
	n = 32 (8.3%)	n = 20 (19.1%)	n = 2 (1.3%)	n = 25 (7.1%)	n = 20 (15.8%)	n = 1 (0.7%)

$ACEi_{HFD}$ = 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] Definition used in exploratory safety analyses; [b]Dose of candesartan preceding the event (or at last visit if no event occurred)
n = number of patients with one or more events (proportion (%) of patients at the dose)

Relationship of dose of candesartan to dose reductions of study drug due to an adverse event or an abnormal laboratory value

In Table 231, no relationship is apparent between the dose of candesartan and the numbers and frequencies of dose reductions of study drug due to an adverse event or an abnormal laboratory value.

Table 231 The numbers and frequencies of dose reductions[a] of study drug due to an adverse event or an abnormal laboratory value[a] in patients who received high or low dose candesartan plus ACE inhibitors at heart failure dose or low dose– CHARM-Added (SH-AHS-0006) Study

	$ACEi_{HFD}$ (N=643)			$ACEi_{LD}$ (N=633)		
Candesartan cilexetil[b]	CC_{HD} + $ACEi_{HFD}$	CC_{LD} + $ACEi_{HFD}$	CC_{00} + $ACEi_{HFD}$	CC_{HD} + $ACEi_{LD}$	CC_{LD} + $ACEi_{LD}$	CC_{00} + $ACEi_{LD}$
	N = 403	N = 83	N = 157	N = 380	N = 101	N = 152
	n = 88 (21.8%)	n = 35 (42.2%)	n = 1 (0.6%)	n = 95 (25.0%)	n = 43 (42.6%)	n = 3 (2.0%)

$ACEi_{HFD}$ = 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] Definition used in exploratory safety analyses; [b]Dose of candesartan preceding the event (or at last visit if no event occurred)
n = number of patients with one or more events (proportion (%) of patients at the dose)

Conclusions on safety results:

Candesartan appears to be safe and well tolerated. **Discontinuations and dose reductions attributed to a decline in renal function, hypotension and hyperkalemia occur more frequently with candesartan than placebo.** The AE profile of candesartan in heart failure patients is consistent with the pharmacology of the drug and the health status of the patients.

Standard safety assessments included serious adverse events, serious and non-serious adverse events causing discontinuation of investigational product or dose reduction, clinical laboratory data (North America), vital signs and physical examination. The following were found:

- Serious adverse events occurred in equal frequency in both treatment groups during study (placebo 75.9%, candesartan 75.9%).
- 24.3% of the patients in the candesartan group and 17.6% of the placebo group permanently discontinued treatment with the investigational product due to an AE or an abnormal laboratory finding.
- 17.2% of the patients receiving candesartan and 9.7% receiving placebo required a reduction in the investigational product dose.
- Discontinuations and dose reductions attributed to decline in renal function, hypotension and hyperkalemia were more frequent in the candesartan group.
- Differences in mean laboratory values across the treatment groups were small and in keeping with expectations for inhibitors of the renin-angiotensin-aldosterone system, i.e. increase in creatinine and potassium.
- Mean blood pressure from baseline to LVCF (SBP and DBP) was lowered in both treatment groups. Mean body weight was slightly decreased in the placebo group and increased in the candesartan group.
- Candesartan reduced time to permanent investigational product discontinuation due to any cause (P=< 0.001).
- Candesartan increased the number of investigational product discontinuations due to any cause (P=< 0.001).
- Candesartan reduced time to permanent investigational product discontinuation due to an AE or an abnormal laboratory value (P=< 0.001).
- Candesartan increased the number of permanent investigational product discontinuations due to an AE or an abnormal laboratory value (P=< 0.001).
- Candesartan increased the number of dose reductions due to an AE or an abnormal laboratory value at least once (P=< 0.001).
- Candesartan did not influence time to non-CV death (P= 0.529).
- Candesartan did not increase the number of non-CV deaths (P= 0.395).
- Candesartan did not increase the number of non-CV hospitalizations (P= 0.895).

8.1 Summary of safety

Adverse events (AEs) were reported for approximately equal proportions of patients in the two treatment groups, both as analyzed during treatment with the investigational product (placebo 979, 77.0%; candesartan 1007, 78.9%) and over the entire study period (placebo 992, 78.0%; candesartan 1026, 80.4%).

Serious adverse events (SAEs), fatal and non-fatal, occurred less frequently on treatment with candesartan (placebo 930, 73.1%; candesartan 883, 69.2%) and at equal frequency during the study, whether on or off treatment (placebo 966, 75.9%; candesartan 969, 75.9%).

Fatal SAEs were also less common with candesartan, on treatment with the investigational product (placebo 276, 21.7%; candesartan 210, 16.5%) as well as during the study (placebo 413, 32.5%; candesartan 377, 29.5%). The most common fatal SAEs were CV events and these occurred less frequently in the candesartan treatment group during study (placebo 347, 27.3%; candesartan 302, 23.7%).

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

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

Abnormal renal function (placebo 53, 4.2%; candesartan 105, 8.2%), cardiac failure aggravated (placebo 81, 6.4%; candesartan 69, 5.4%), hypotension (placebo 44, 3.5%; candesartan 69, 5.4%) and hyperkalemia (placebo 11, 0.9%; candesartan 49, 3.8%) were the most commonly reported AE, given as reasons for discontinuing the investigational product.

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

DISCUSSION AND OVERALL CONCLUSIONS

Discussion

In patients with CHF using an ACE inhibitor, the addition of candesartan significantly reduced cardiovascular mortality or hospitalization due to heart failure. The effect appeared early and was sustained throughout the duration of the study. Also the other outcomes included in the confirmatory analysis; all cause mortality or hospitalization due to heart failure as well as cardiovascular mortality or hospitalization due to heart failure or non- fatal myocardial infarction were significantly reduced by candesartan treatment. There were substantial reductions in the individual components of the composite outcomes. Moreover, symptoms of heart failure as

evaluated by the NYHA-classification were reduced by candesartan as compared to placebo.

The reduction in cardiovascular mortality and hospitalization due to heart failure with candesartan treatment was also evident in those patients being treated with recommended doses of ACE-inhibitors as well as in those treated with β-blockers. The finding that treatment with candesartan in combination with β-blockers provided these patients with additional beneficial efficacy is particularly noteworthy, since a large proportion (55% at baseline) of the patients were receiving this lifesaving therapy. A prior subgroup analysis from the Val-HeFT[16] study suggested lack of benefit of an ARB (valsartan) in patients already receiving ACE-inhibitors and β-blockers, but the results of study SH-AHS-0006 suggest that this finding may be specific to the treatments studied in Val-HeFT.

The candesartan treatment benefit observed in the current study is consistent with observations suggesting that blockade of angiotensin II generation is incomplete with chronic ACE inhibitor therapy[1,2,3]. Mechanistic studies show favorable neurohumoral, hemodynamic and left ventricular remodeling effects when an ARB is administered to patients already treated with an ACE inhibitor[6,75]. These potentially beneficial effects are also seen in patients treated with both a β-blocker and an ACE inhibitor. For example, in the RESOLVD pilot study, the greatest left ventricular "reverse-remodeling" was seen with the combination of enalapril, metoprolol and candesartan[5].

When comparing the overall Val-HeFT[16] population (where 93% of the patients were treated with an ACE inhibitor) to the present study, the findings of the two studies can to some extent be considered consistent in that both demonstrated that adding an ARB to conventional therapy reduces hospitalization due to heart failure. However, in Val-HeFT there was no effect on cardiovascular mortality in contrast to the present study with candesartan[16]. Further, in the present study there were statistically significant reductions in cardiovascular mortality as well as in CHF hospitalizations in patients receiving candesartan in addition to ACE-inhibitor and β-blocker suggesting that there is no negative interaction between the ARB (candesartan), ACE-inhibitors and β-blocker therapy as was seen with valsartan in Val-HeFT[16].

The benefit of candesartan in this study was evident even with substantial background treatment with ACE inhibitors at recommended doses. For example, the mean daily dose of enalapril at baseline was 17 mg, which compares to 16.6 mg (in those taking drug) in the treatment arm of the Studies Of Left Ventricular Dysfunction (SOLVD)[32] and 17 mg in Val-HeFT[16]. The present study also shows that this benefit is clinically important. There were consistent and clinically important reductions in both cardiovascular mortality and CHF hospitalizations when patients received candesartan. In addition to prolongation of time to first CHF hospitalization, the number of patients admitted to hospital for CHF and the total numbers of hospital admissions that were primarily for CHF were lower in the candesartan group. Furthermore, the magnitude of the benefit in reducing cardiovascular death or CHF hospitalization translates into an absolute reduction of 4.4 major events per 100 patients treated, which means that one needs to treat 23 patients with candesartan to prevent one patient from suffering this outcome.

There was a statistically significant reduction in cardiovascular mortality attributed primarily to a reduction in sudden deaths and deaths due to heart failure, which are the most common modes of death in patients with CHF. The study was not powered to assess the effect on all cause mortality but since there was no difference in non-cardiovascular deaths, all cause death clearly trended in the direction favoring treatment with candesartan. Although more cancer deaths occurred in the candesartan group, the investigator-reported rate of non-fatal neoplasms was more equal between treatment groups. In the total CHARM population (SH-AHS-003, SH-AHS-0006, SH-AHS-0007) no significant differences in the incidence of neoplasms were identified.

Candesartan in addition to treatment with an ACE-inhibitor, was well tolerated in this study, although dose reduction and discontinuation of investigational product were more common with candesartan than placebo which was primarily attributable to renal function impairment, hyperkalemia, or hypotension. This distribution of events could be expected from the pharmacodynamic profile of inhibitors of the RAAS and the underlying conditions in the CHF population. Monitoring patients for these expected events is already well-established practice for care of the CHF patient.

Overall conclusions

Candesartan reduces mortality and hospitalization due to heart failure and improves symptoms in CHF patients who are receiving an ACE inhibitor. The reduced mortality is attributable to a reduction in cardiovascular deaths. Patients receiving other treatments, including a beta-blocker, also benefit. Candesartan is safe and well tolerated. Discontinuations and dose reductions attributed to a decline in renal function, hypotension and hyperkalemia occur more frequently with candesartan than placebo. The AE profile of candesartan in heart failure patients is consistent with the pharmacology of the drug and the health status of the patients.

10.1.20 Appendix 16 CHARM-Pooled studies

Candesartan cilexetil (candesartan) in heart failure. Assessment of reduction in mortality and morbidity (CHARM) Analysis of two pooled populations of clinical studies SH-AHS-0003, SH-AHS-0006 and SH-AHS–0007

Study program sites: The CHARM program was conducted in 26 countries at a total of 618 sites (Australia 18, Belgium/Luxembourg 18, Canada 72, Czech Republic 12, Denmark 20, Finland 10, France 27, Germany 53, Hungary 10, Iceland 2, Italy 20, Malaysia 3, Netherlands 22, Norway 19, Poland 14, Portugal 17, Russia 10, Singapore 3, South Africa 12, Spain 16, Sweden 18, Switzerland 13, United Kingdom/Ireland 38, and USA 171 sites)

Objectives

Primary objective

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

Secondary objective

To determine whether candesartan, compared to placebo, reduced all- cause mortality in the pooled population of patients with depressed left ventricular (LV) systolic dysfunction (studies SH-AHS-0003 and SH-AHS-0006).

Other objectives

To determine whether candesartan, compared to placebo,

- reduced the combined endpoint of all-cause mortality or all-cause hospitalization in the pooled population of patients with symptomatic chronic heart failure (studies SH-AHS-0003, SH-AHS-0006 and SH-AHS-0007).
- reduced the combined endpoint of all- cause mortality or all-cause hospitalization in the pooled population of patients with depressed LV systolic dysfunction (studies SH-AHS-0003 and SH-AHS-0006).

Component study design

The component studies were randomized, double-blind placebo controlled parallel group multicenter studies. The program was designed to evaluate the influence on mortality and morbidity of candesartan cilexetil (hereafter referred to as candesartan) with a target dose of 32 mg once daily, in three target populations of patients with symptomatic chronic heart failure.

The figure illustrating the component studies is the same as Figure 94 (Appendix 10.1.19 of this review).

Target patient population

Male and female patients, over or equal to 18 years of age, with symptomatic CHF corresponding to New York Heart Association (NYHA) class II-IV and:

- depressed LV systolic function and ejection fraction (EF) < 40% and an intolerance to angiotensin converting enzyme (ACE) inhibitors (study SH-AHS-0003)
- depressed LV systolic function EF< 40% treated with an ACE inhibitor (study SH-AHS-0006)
- preserved LV systolic function EF> 40% (study SH-AHS-0007)

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for enrollment into the CHARM Program studies are similar for all component CHARM-studies except that for enrollment into study SH-AHS-0007, the LVEF must be >40%. The detailed inclusion and exclusion criteria are similar to that described for study SH-AHS-0006 in Appendix 10.1.19

Investigational product

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

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

Duration of CHARM program

The patient recruitment period was 23 months. All patients remained in their respective studies until the last randomized patient had been in the study for two years. Individual time in the study for surviving patients not lost to follow-up could last from 25 to 48 months depending on when the patient was randomized. The median follow-up time for the total population was 37.9 months in the candesartan group and 37.6 months in the placebo group. The median exposure to the investigational product in the total population was 35.0 months in the placebo group and 34.5 months in the candesartan group.

Criteria for evaluation (main variables)

Efficacy

- Primary efficacy endpoint: Time from randomization to all-cause death in patients with symptomatic chronic heart failure.
- Secondary efficacy endpoint: Time from randomization to all-cause death in patients with depressed LV systolic function.

Safety

- Investigational product discontinuation.
- Reduction in dose of investigational product.
- Occurrence of non- cardiovascular death and hospitalization.

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

Patient-reported outcomes

- The patients' global evaluation of change from baseline to the patient's last visit or closing visit using OTE (overall treatment evaluation) in the US and Canadian sites.
- The change in the physical functioning dimension of the disease-specific patient-reported outcomes questionnaire, the Minnesota Living with Heart Failure (LIhFE), from baseline to last/closing visit evaluated in the US and Canadian sites.

Study sample size

With a total of 7200 patients randomized in the pooled population a 16- 20% decrease in the annual placebo incidence rate of all-cause death, assuming an annual placebo rate of 9 to 11%, could be detected with a statistical power of at least 94%. The patients were to be equally distributed between the two treatment groups. The number of randomized patients was 7601; two of the patients were randomized in error (study SH-AHS-0007). These patients received no investigational product and no data were collected; so the actual number of patients was 7599.

Statistical methods

All analyses were made on an intention-to-treat basis.

The time from randomization to an event variable was analyzed with a two-sided Logrank test and for estimation in a Cox proportional hazards model. Kaplan-Meier plots were used to graphically display the time-to-event distributions by treatments.

Secondary analysis was made using a Cox-regression model with pre-specified prognostic factors (baseline covariates).

A Chi-square test was used to test the difference between the proportions of patients with a specific characteristic/outcome.

Changes in the NYHA classification were tested using a Wilcoxon rank-sum test.

For continuous variables, the mean change from baseline to last observed value was tested in an analysis of covariance (ANCOVA) model.

Estimates with 95% confidence intervals (CIs) for each treatment and the difference between the treatments were calculated, as appropriate.

All tests were two-sided. The multiple significance levels were controlled for the primary and secondary objectives using a closed test procedure.

Method of statistical analysis

The primary objective was to determine whether candesartan compared to placebo, reduced all-cause death in the total patient population (SH-AHS-0003, -0006, and -0007), as translated into a

hypothesis problem: time from randomization to the death of any cause. The null hypothesis (H0) was:

H0: The distribution function for the time from randomization to the endpoint when treated with candesartan equals the distribution function for the time from randomization to the endpoint when treated with placebo.

The alternative hypothesis (H1) was:

H1: The distribution functions differ.

The H0 was tested using the two-sided stratified Logrank test for comparing the time from randomization to event distributions. If the P-value was less than 0.0492 (corresponding to a significance level of 0.05 adjusted for six interim analyses performed by the SC) it 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 1,000 patient years. The size of the treatment effect was estimated by means of a Cox proportional hazards model with treatment as the only factor. The hazard ratio, with a 95% CI based on the Wald estimate of the standard error, and corresponding relative risk reduction estimate are reported.

The secondary objective was translated into the null hypothesis:

Time from randomization to the endpoint all-cause death in patients with low LVEF (SH-AHS-0003 and -0006).

The H0 was equality of the distribution functions for the time from randomization to event for candesartan and placebo versus the H1 that they were different.

The null-hypothesis was tested with a stratified Logrank test in exactly the same way as described above for the primary variable. Similarly, the treatment hazards were estimated and the hazard ratios were calculated in a Cox regression model.

If the P-value was less than 0.0492 and if the test for the primary variable was significant at the 0.0492 level, then this test was also considered as a confirmation of a true treatment effect.

This follows from the theory of closed test procedures and will guarantee a multiple α 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 difference in the true distributions.

Protocol amendments

These are similar to that already presented in Appendix 10.1.19 of this review.

Changes to planned analyses

These are similar to that already described in Appendix 10.1.19 of this review.

Re-opening of CHARM program database

The issues are similar to that already described in Appendix 10.1.19 of this review.

CHARM-POOLED STUDY POPULATIONS

In total 7,601 patients were recruited from 618 sites. The first patient was randomized in the CHARM program on 22 March 1999, and the last patient completed on 31 March 2003. All patients, except two who had no investigational product administered and no data available after randomization (study SH-AHS-0007), were analyzed for safety and efficacy. Of the 7,599 patients in the ITT/safety population, 3,803 were randomized to candesartan and 3,796 to placebo (Table 232). Overall, the treatment groups were comparable for demographic characteristics and baseline data.

Baseline characteristics of patients in studies SH-AHS-0003 and SH-AHS-0006 were similar to those in other studies on patients with CHF and reduced left ventricular systolic function, and were considered to be representative of a general population of patients with CHF. Almost a quarter of the patients were older than 75 years and almost a third were females. A large proportion had accompanying atherosclerotic CV disease.

Patients in study SH-AHS-0007 constituted a group that has not been studied in large intervention trials previously, but the characteristics of patients were consistent with the epidemiological studies in patients with CHF and an ejection fraction of more than 40%.

The treatment groups were in general well balanced. However, in the total population there were more patients that had a previous diagnosis of cancer in the candesartan group compared to the placebo group (270; 7.1% vs. 243; 6.4%).

Table 232 Total-pooled patient population and disposition

		Placebo		Cand. cil.		Total	
Population							
N randomised (N planned)		3796	(3600)	3803	(3600)	7599	(7200)
Demographic characteristics							
Sex, N (%)	Male	2582	(68.0)	2617	(68.8)	5199	(68.4)
	Female	1214	(32.0)	1186	(31.2)	2400	(31.6)
Age, mean (SD)	Years	66.0	(11.1)	65.9	(11.0)	66.0	(11.0)
Ethnicity, N (%)	European origin	3458	(91.1)	3412	(89.7)	6870	(90.4)
	Black	164	(4.3)	162	(4.3)	326	(4.3)
	South Asian	34	(0.9)	59	(1.6)	93	(1.2)
	Arab/Middle East	15	(0.4)	22	(0.6)	37	(0.5)
	Oriental	62	(1.6)	71	(1.9)	133	(1.8)
	Malay	25	(0.7)	39	(1.0)	64	(0.8)
	Other	38	(1.0)	38	(1.0)	76	(1.0)
Baseline characteristics							
Ejection fraction, mean (SD)		0.39	(0.15)	0.39	(0.15)	0.39	(0.15)
Diabetes mellitus, N (%)		1075	(28.3)	1088	(28.6	2163	(28.5)
Hypertension, N (%)		2093	(55.1)	2093	(55.0)	4186	(55.1)
Atrial fibrillation, N (%)		1044	(27.5)	1039	(27.3)	2083	(27.4)
Previous myocardial infarction, N (%)		1980	(52.2)	2024	(53.2)	4004	(52.7)
Angina pectoris, N (%)		2178	(57.4)	2174	(57.2)	4352	(57.3)
Stroke, N (%)		330	(8.7)	333	(8.8)	663	(8.7)
NYHA II, N (%)		1686	(44.4)	1730	(45.5)	3416	(45.0)
NYHA III, N (%)		2008	(52.9)	1977	(52.0)	3985	(52.4)
NYHA IV, N (%)		102	(2.7)	96	(2.5)	198	(2.6)
Current smoker, N (%)		549	(14.5)	565	(14.9)	1114	(14.7)
Disposition							
N (%) of patients	Completing the programme	3793	(99.9)	3796	(99.8)	7589	(99.8)
	Lost to follow-up	3	(0.01)	7	(0.02)	10	(0.02)
N analysed for safety (ITT/Safety population[a])		3796		3803		7599	
N analysed for efficacy (ITT/Safety population[a])		3796		3803		7599	

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

In the total population, 3,052 (80.3%) patients in the candesartan group started treatment on 4 mg once daily and 751 (19.7%) patients started on 8 mg once daily. In a total of 5,360 (70.5%) patients, 2,659 (69.9%) who were on candesartan treatment received the investigational product for 24 months or more. Of those patients still on the investigational product at 6 months, (3,233, 88.9% in the candesartan group), 62.6% of the candesartan patients were treated with the target dose 32 mg once daily. The mean dose in the candesartan group was 24.0 mg at 6 months and 23.9 at LVEF.

The countries participating in the program, number of sites and number of patients with symptomatic CHF are shown in Table 233 (studies SH-AHS-0003, -0006 and -0007).

Table 233 Number of sites and randomized patients by country for patients with symptomatic CHF. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Country	No. of sites	No. of patients randomised to placebo	No. of patients randomised to cand. cil.	Total
All	618	3796	3803	7599
Sweden	18	103	89	192
Norway	19	105	112	217
Denmark	20	253	234	487
Finland	10	55	47	102
Iceland	2	38	44	82
Italy	20	78	73	151
Spain	16	64	61	125
Portugal	17	43	50	93
The Netherlands	22	212	207	419
France	27	108	117	225
Czech Republic	12	90	104	194
Poland	14	113	102	215
Hungary	10	101	103	204
Switzerland	13	32	36	68
Belgium/Luxembourg	18	113	136	249
Malaysia	3	54	86	140
Singapore	3	25	37	62
United Kingdom/Ireland	38	138	143	281
Germany	53	425	378	803
Canada	72	475	467	942
USA	171	901	900	1801
Australia	18	108	120	228
South Africa	12	61	58	119
Russia	10	101	99	200

Disposition of patients

The disposition of patients with symptomatic CHF is summarized in Figure 2.

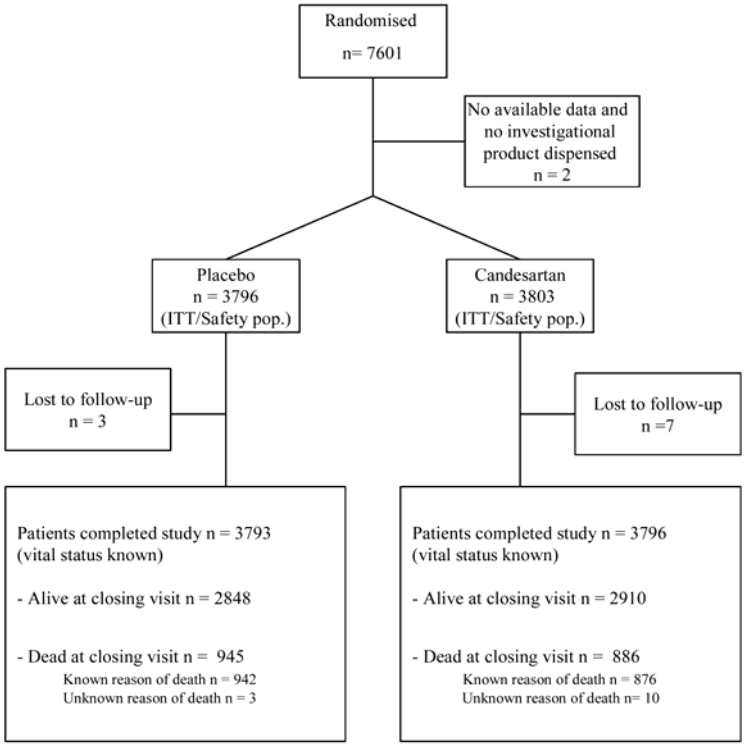


Figure 106 Disposition of patients with symptomatic CHF (completion or discontinuation) (SH-AHS-0003, -0006 and -0007)

Protocol deviations

The numbers of patients with protocol deviations in each treatment group are summarized in Table 234. (N.B. One patient could have more than one protocol deviation throughout the study.)

Table 234 Number of patients with protocol deviations in CHARM-Pooled patient population

	Placebo (N=361)	Cand. cil. (N=341)
Inclusion criteria deviation	103	100
Exclusion criteria deviation	151	120
Patient's consent withdrawn (continued in study or with the investigational product)	0	1
Pregnancy	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	7	15
Wrong investigational product given, wrong bottle and correct investigational product	40	44
Wrong dose of investigational product given (dose<4 or >32mg)	3	9
Incorrect dose of the investigational product given (dose ≠4, 8, 16, 32 mg)	3	1
Pre-randomisation (randomisation date before visit 1)	38	32
Treatment code prematurely broken	14	14
Less than two years in the study (patients lost to follow-up)	1	5

Patient populations analyzed

Two pooled patient populations were analyzed:

- Total population: Patients with symptomatic CHF (ITT/Safety population in studies SH-AHS-0003, -0006 and -0007).
- Subpopulation: Patients with depressed LV systolic dysfunction (ITT/Safety population in studies SH-AHS-0003 and -0006).

Treatment compliance

Compliance was assessed (> 80%, 20- 80% or < 20%) by the treating investigator by estimation of returned tablets and after discussion with the patient. Pill- counts were not done unless required by local regulatory authorities. A listing of estimated individual compliance data is shown in Appendix 12.2.5 for the individual study reports. The vast majority of patients had a compliance of > 80% at all visits.

Concomitant medications

The patients in the total pooled population were receiving conventional heart failure treatments at baseline including diuretics (6,286, 83%), β-blockers (4,203, 55%), digoxin (3,254, 43%), ACE-inhibitor (3,125, 41%) and spironolactone (1,272, 17%). The most frequently used β-blockers were metoprolol and carvedilol that were taken, respectively, by 26% (1,945 patients) and 13% (980 patients) of the patient population. These two β-blockers accounted for about 70% of the β-blocker use within this patient population.

At the closing visit, there were more patients in the placebo group receiving diuretics (2,195, 77% vs. 2,171, 75%), β-blockers (1,812, 64% vs. 1,765, 61%), digoxin (1,018, 36% vs. 978, 34%), ACE-inhibitors (1,110, 39% vs. 1,051, 36%) and spironolactone (625, 22% vs. 501, 17%).

EFFICACY RESULTS

Primary endpoint: Time from randomization to all-cause death in patients with symptomatic CHF

Of the 7,599 patients in the population pooled across the three CHARM component studies a total of 1831 patients died: 886 (23.3%) in the candesartan group and 945 (24.9%) in the placebo group. The HR for the time to death was 0.91 (95% CI 0.83 to 1.00, P= 0.055 unadjusted for interim analyses), which equates to a relative risk reduction of 8.6%. The average annualized death rates were 8.1% and 8.8% respectively (Table 235 and Table 236).

Table 235 Confirmed adjudicated all-cause death in patients with symptomatic CHF. Number of patients with an event by treatment group and events per 1000 years of follow-up. Follow-up time is calculated to event. ITT/Safety population (SH-AHS-0003, -0006, -0007)

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 (confirmed adjudicated)	Placebo	3796	945	10690.3	88.4	2.8
	Cand. cil.	3803	886	10938.2	81.0	2.9

Table 236 Confirmed adjudicated all-cause death in patients with symptomatic CHF. Comparison of candesartan versus placebo with Cox regression. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Variable	N	Events cand. cil.	Events placebo	Hazard Ratio	95% CI		p-value
					Lower	Upper	
All-cause death (confirmed adjudicated)	7599	886	945	0.914	0.834	1.002	0.055

The sponsor submitted that in a pre-specified covariate-adjusted analysis the relative risk reduction for all-cause death with candesartan treatment was 10% (HR= 0.90, 95% CI 0.82 to 0.99, P=0.032).

The Kaplan-Meier plot illustrates the mortality in the two treatment groups over time (Figure 107).

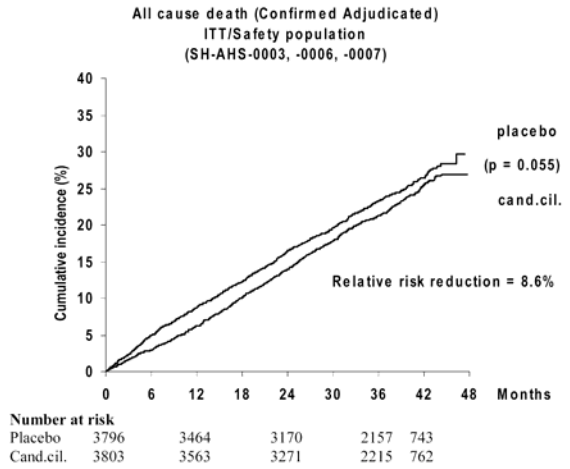


Figure 107 Cumulative incidence (%) of confirmed adjudicated all-cause death in patients with symptomatic CHF over time. ITT/Safety population

Secondary variable: Time from randomization to all-cause death in patients with depressed LV systolic function

Of the 4,576 patients in the population pooled across the two CHARM component studies in patients with depressed systolic LV function a total of 1,350 patients died: 642 (28.0%) in the candesartan group and 708 (30.9%) in the placebo group. The HR for the time to death was 0.88 (95% CI 0.79 to 0.98, P= 0.018), which equates to a relative risk reduction of 12%. The average annualized death rates were 9.9% and 11.2% respectively (Table 237 and Table 238).

Table 237 Confirmed adjudicated all-cause death in patients with depressed LV systolic function. Number of patients with an event by treatment group and events per 1000 years of follow-up. Follow-up time is calculated to event. ITT/Safety population (SH-AHS-0003, -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 (confirmed adjudicated)	Placebo	2287	708	6303.2	112.3	2.8
	Cand. cil.	2289	642	6503.9	98.7	2.8

Table 238 Confirmed adjudicated all-cause death in patients with depressed LV systolic function. Comparison of candesartan versus placebo with Cox regression. ITT/Safety population (SH-AHS-0003,-0006)

Variable	N	Events cand. cil.	Events placebo	Hazard Ratio	95% CI		p-value
					Lower	Upper	
All-cause death (confirmed adjudicated)	4576	642	708	0.880	0.790	0.979	0.018

The Kaplan-Meier plot illustrates the mortality in the two groups over time (Figure 108).

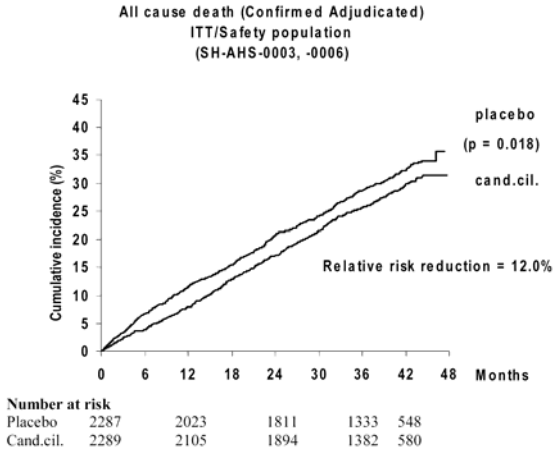


Figure 108 Cumulative incidence (%) of confirmed adjudicated all-cause death in patients with depressed LV systolic function over time. ITT/Safety population

Analysis of components of all-cause death

Patients with symptomatic CHF

The lower mortality in the candesartan group was attributable to a reduction in deaths from cardiovascular causes (HR=0.88, 95% CI 0.79 to 0.97, P=0.012: relative risk reduction 12.4%). There was no apparent difference in non-CV mortality (Figure 109and Table 240). The two most common reasons for CV death were both reduced by treatment with candesartan, sudden death (P=0.037) and death due to CHF (P=0.008) (Table 239 and Table 240).

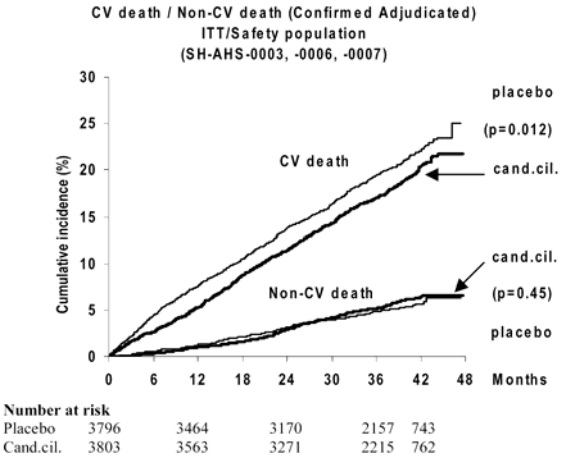


Figure 109 Cumulative incidence (%) of confirmed adjudicated cardiovascular death and non-cardiovascular death patients with symptomatic CHF over time. ITT/Safety population

Table 239 Confirmed adjudicated components of the primary variable. Number of patients with event by treatment group and events per 1000 years of follow-up. Follow-up time is calculated to event. ITT/ Safety population (SH-AHS-0003, -0006, -0007)

Variable	Treatment	N	Events (No of patients)	Total follow-up time (years)	Events / 1000 Follow-up years	Mean follow-up time (years)
CV death	Placebo	3796	769	10690.3	71.9	2.8
	Cand. cil.	3803	691	10938.2	63.2	2.9
Death due to CHF	Placebo	3796	260	10690.3	24.3	2.8
	Cand. cil.	3803	209	10938.2	19.1	2.9
Sudden death	Placebo	3796	344	10690.3	32.2	2.8
	Cand. cil.	3803	299	10938.2	27.3	2.9
Death due to MI	Placebo	3796	50	10690.3	4.7	2.8
	Cand. cil.	3803	61	10938.2	5.6	2.9
Death due to stroke	Placebo	3796	44	10690.3	4.1	2.8
	Cand. cil.	3803	45	10938.2	4.1	2.9
Death due to other CV cause	Placebo	3796	71	10690.3	6.6	2.8
	Cand. cil.	3803	77	10938.2	7.0	2.9
Non-CV death	Placebo	3796	176	10690.3	16.5	2.8
	Cand. cil.	3803	195	10938.2	17.8	2.9

Table 240 Confirmed adjudicated components of primary variable. Comparison of candesartan versus placebo with Cox regression. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Variable	N	Events cand. cil.	Events placebo	Hazard Ratio	95% CI		p-value
					Lower	Upper	
CV death	7599	691	769	0.876	0.790	0.971	0.012[a]
Death due to CHF	7599	209	260	0.783	0.653	0.939	0.008
Sudden death	7599	299	344	0.848	0.726	0.990	0.037[b]
Death due to MI	7599	61	50	1.187	0.817	1.726	0.368
Death due to stroke	7599	45	44	1.001	0.661	1.517	0.996
Death due to other CV cause	7599	77	71	1.057	0.766	1.460	0.734
Non-CV death	7599	195	176	1.081	0.882	1.326	0.452

[a] Logrank test p=0.011
[b] Logrank test p=0.036

Patients with depressed LV systolic function

The lower mortality in the candesartan group was attributable to a reduction in deaths from cardiovascular causes (HR=0.84, 95% CI 0.75 to 0.95, P=0.005: relative risk reduction 15.6%). There was no apparent difference in non- CV mortality. The two most common reasons for CV

death were both reduced by treatment with candesartan, sudden death (P=0.013) and death due to CHF (P=0.008) (Table 241 and Table 242).

Table 241 Confirmed adjudicated components of the primary variable. 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-0003, -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	placebo	2287	599	6303.2	95.0	2.8
	cand.cil.	2289	521	6503.9	80.1	2.8
Death due to CHF	placebo	2287	206	6303.2	32.7	2.8
	cand.cil.	2289	161	6503.9	24.8	2.8
Sudden death	placebo	2287	279	6303.2	44.3	2.8
	cand.cil.	2289	230	6503.9	35.4	2.8
Death due to MI	placebo	2287	38	6303.2	6.0	2.8
	cand.cil.	2289	52	6503.9	8.0	2.8
Death due to stroke	placebo	2287	28	6303.2	4.4	2.8
	cand.cil.	2289	28	6503.9	4.3	2.8
Death due to other CV cause	placebo	2287	48	6303.2	7.6	2.8
	cand.cil.	2289	50	6503.9	7.7	2.8
Non-CV death	placebo	2287	109	6303.2	17.3	2.8
	cand.cil.	2289	121	6503.9	18.6	2.8

Table 242 Confirmed adjudicated components of primary variable. Comparison of candesartan versus placebo with Cox regression. ITT/Safety population (SH-AHS-0003, -0006)

Variable	N	Events cand. cil.	Events placebo	Hazard Ratio	95% CI		p-value
					Lower	Upper	
CV death	4576	521	599	0.844	0.751	0.950	0.005
Death due to CHF	4576	161	206	0.758	0.617	0.932	0.008
Sudden death	4576	230	279	0.801	0.673	0.954	0.013
Death due to MI	4576	52	38	1.327	0.873	2.016	0.185
Death due to stroke	4576	28	28	0.973	0.576	1.643	0.919
Death due to other CV cause	4576	50	48	1.007	0.678	1.497	0.972
Non-CV death	4576	121	109	1.073	0.828	1.390	0.595

NYHA classification of heart failure

Patients with symptomatic CHF

There was an improvement in NYHA functional class in candesartan patients compared to placebo patients (P= 0.004, Wilcoxon rank-sum test) (Table 243).

Table 243 Number of patients and change from baseline to LVEF in NYHA class by treatment in patients with symptomatic CHF. ITT/Safety Population. (SH-AHS-0003, -0006, -0007)

Visit	NYHA class	Placebo	Cand.cil.	Total
Baseline	NYHA II	1686 (44.4%)	1730 (45.5%)	3416 (45.0%)
	NYHA III	2008 (52.9%)	1977 (52.0%)	3985 (52.4%)
	NYHA IV	102 (2.7%)	96 (2.5%)	198 (2.6%)
LVCF	NYHA I	415 (11.0%)	470 (12.4%)	885 (11.7%)
	NYHA II	1881 (49.9%)	1929 (51.0%)	3810 (50.5%)
	NYHA III	1302 (34.6%)	1260 (33.3%)	2562 (33.9%)
	NYHA IV	170 (4.5%)	120 (3.2%)	290 (3.8%)
Change from Baseline to LVCF[a]	NYHA Improved by 3 classes	3 (0.1%)	3 (0.1%)	6 (0.1%)
	NYHA Improved by 2 classes	140 (3.7%)	140 (3.7%)	280 (3.7%)
	NYHA Improved by 1 class	1081 (28.7%)	1196 (31.6%)	2277 (30.2%)
	NYHA Same as baseline	2156 (57.2%)	2100 (55.6%)	4256 (56.4%)
	NYHA Deteriorated by 1 class	368 (9.8%)	319 (8.4%)	687 (9.1%)
	NYHA Deteriorated by 2 classes	20 (0.5%)	21 (0.6%)	41 (0.5%)
	Total	3765	3776	7541

a Wilcoxon rank-sum test, p=0.004

Patients with depressed LV systolic function

There was an improvement in NYHA functional class in candesartan patients compared to placebo patients (P< 0.001, Wilcoxon rank-sum test) (Table 244).

Table 244 Number of patients and change from baseline to LVEF in NYHA class by treatment in patients with depressed LV systolic function. ITT/Safety Population. (SH-AHS-0003, -0006)

Visit	NYHA class	Placebo	Cand.cil.	Total
Baseline	NYHA II	781 (34.1%)	799 (34.9%)	1580 (34.5%)
	NYHA III	1424 (62.3%)	1421 (62.1%)	2845 (62.2%)
	NYHA IV	82 (3.6%)	69 (3.0%)	151 (3.3%)
LVCF	NYHA I	210 (9.3%)	280 (12.3%)	490 (10.8%)
	NYHA II	1069 (47.2%)	1083 (47.7%)	2152 (47.4%)
	NYHA III	860 (38.0%)	821 (36.1%)	1681 (37.0%)
	NYHA IV	127 (5.6%)	88 (3.9%)	215 (4.7%)
Change from Baseline to LVCF[a]	NYHA Improved by 3 classes	2 (0.1%)	3 (0.1%)	5 (0.1%)
	NYHA Improved by 2 classes	98 (4.3%)	108 (4.8%)	206 (4.5%)
	NYHA Improved by 1 class	695 (30.7%)	799 (35.2%)	1494 (32.9%)
	NYHA Same as baseline	1251 (55.2%)	1178 (51.8%)	2429 (53.5%)
	NYHA Deteriorated by 1 class	209 (9.2%)	173 (7.6%)	382 (8.4%)
	NYHA Deteriorated by 2 classes	11 (0.5%)	11 (0.5%)	22 (0.5%)
	Total	2264	2269	4533

a Wilcoxon rank-sum test, p<0.001

Analyses of subgroups

The primary efficacy variable of each of the three component studies was time to CV death or hospitalization due to heart failure. This endpoint indicated a definite benefit with candesartan treatment as assessed in the pooled population of chronic heart failure patients (HR= 0.84, 95% CI 0.77 to 0.91, p< 0.001). The finding was similar across a wide range of subgroups, i.e., there was no apparent indication that the results in any subgroup were notably different from those described for the overall population.

The analyses considered subgroups based on gender, age cohorts, (a substantial number of participating patients were over 75 years of age.), diabetes, concomitant CHF medications and race. The number of black patients randomized in the program was relatively low but there was no indication that the treatment effect was different for Blacks. The beneficial effects of candesartan in the CHARM program were not altered by concomitant treatment with ACE inhibitors, β-blockers, spironolactone, digoxin, aspirin or lipid-lowering therapies (Figure 110).

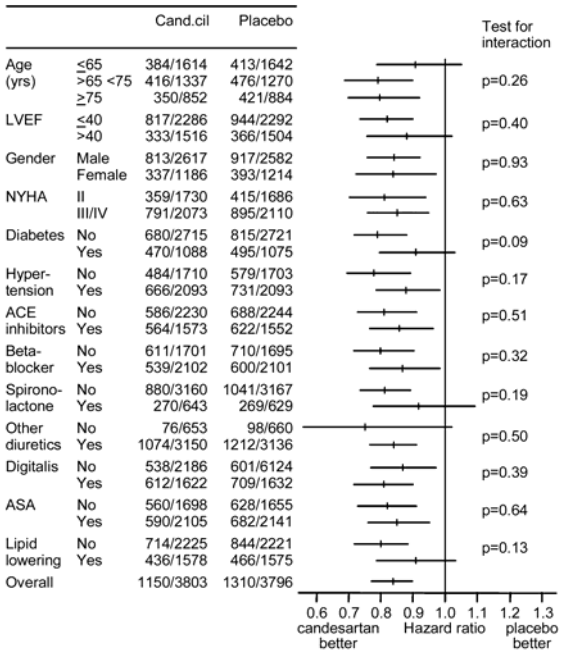


Figure 110 Overall effect of candesartan on cardiovascular death or first admission for CHF in pre-specified subgroups. Point estimates of hazard ratios given with 95 % confidence interval. P-values are for heterogeneity. ITT/ Safety population (SH-AHS-0003, -0006, -0007)

There was no increase in all-cause mortality in any subgroup (Figure 111).

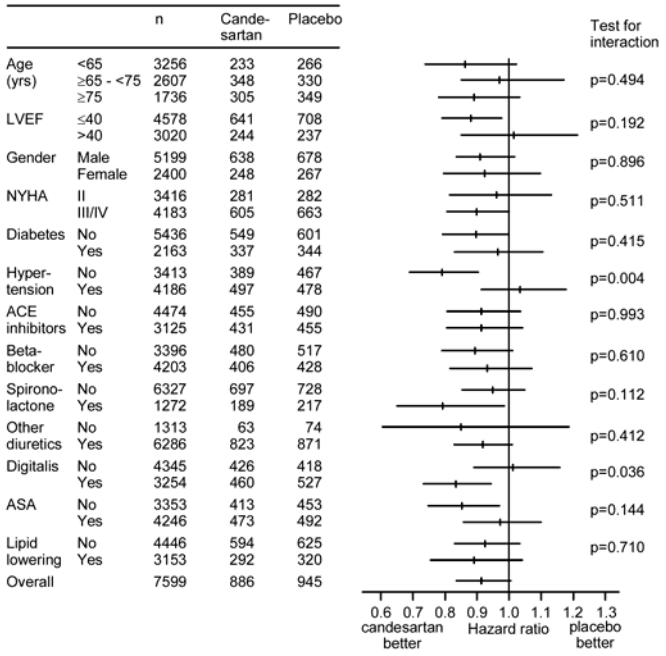


Figure 111 Overall effect of candesartan on all-cause death in pre-specified subgroups. Point estimates of hazard ratios given with 95% confidence interval. P-values are for heterogeneity. ITT/Safety population (SH- AHS-0003, -0006, -0007)

Patient-reported outcome results

Primary Quality of Life variables

Overall treatment evaluation

The patients' global evaluation of treatment effect (OTE) suggests that more patients treated with candesartan rated themselves as improved (Table 245).

Table 245 Frequency of patients by the outcome of the OTE questionnaire at last visit. ITT/Safety population

	Cand. cil.		Placebo	
	n	%	n	%
A very great deal worse	6	0.5	9	0.7
A great deal worse	18	1.4	25	2.0
A good deal worse	26	2.1	33	2.6
Moderately worse	42	3.4	41	3.3
Somewhat worse	21	1.7	19	1.5
A little worse	19	1.5	16	1.3
Almost the same, hardly worse at all	3	0.2	8	0.6
About the same	642	51.4	679	54.4
Almost the same, hardly better at all	16	1.3	16	1.3
A little better	52	4.2	57	4.6
Somewhat better	58	4.6	46	3.7
Moderately better	108	8.6	104	8.3
A good deal better	146	11.7	109	8.7
A great deal better	54	4.3	56	4.5
A very great deal better	38	3.0	30	2.4

Table 246 shows that this difference was significantly in favor of candesartan. In order to estimate the difference between the treatment groups, the OTE items were combined to form an overall 15- point scale, ranging from the worst deterioration (-7) to the highest improvement (+7) with "No change" (0) as the middle score. The overall score was then analyzed using the stratified Wilcoxon- Mann-Whitney test.

Table 246 OTE for patients with symptomatic CHF as assessed by a stratified Wilcoxon-Mann-Whitney test for comparison of the change for the two treatment groups. The data are stratified according to study. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Variable	Treatment	Estimate	Lower 95 % limit	Upper 95 % limit	p-value
Overall treatment effect	Cand. cil.-placebo	0.28	0.04	0.51	0.0167

Change in the physical functioning dimension in LIhFE

Patients in both treatment groups were comparatively little affected at baseline as reflected in the emotional dimension in LIhFE (mean around 8.5 out of 25) and in terms of the total score (mean around 40 out of 105). There was no significant difference between treatment groups in LIhFE emotional dimension or total score.

The physical dimension was slightly more affected (mean around 18.8 out of 45), i.e., a modest impairment. The mean change over time indicates a small improvement in all LIhFE outcomes; however, there was no significant difference between treatment groups in LIhFE physical dimension.

Change in frequency and severity of cough measured by VAS

Cough improved to a small extent during the program with no difference between treatment groups.

CHARM Program overall results

The overall CHARM Program wins on "**all-cause mortality"** when only the two studies involving patients with depressed LV systolic function – CHARM-Alternative (SH-AHS-0003) and CHARM-Added (SH-AHS-0006) – are pooled. When the CHARM-Preserved (SH-AHS-0007) study is added to the pooled analysis, the CHARM Program does not win on "all-cause mortality," unless covariate adjustment is allowed (then hazard ratio = 0.904, P = 0.031). However, this covariate adjustment is not agreed upon by FDA *apriori*.

CHARM Program Primary Efficacy Endpoint Finding: For the primary efficacy endpoint "all-cause mortality in the pooled population of patients with symptomatic CHF (pooled studies SH-AHS-0003, SH-AHS-0006 and SH-AHS-0007)", the CHARM-Program endpoint analysis showed that candesartan reduced (by 8.6%) all-cause mortality in patients with symptomatic CHF (Figure 112 and Table 247). This was NOT statistically significant (P=0.055).

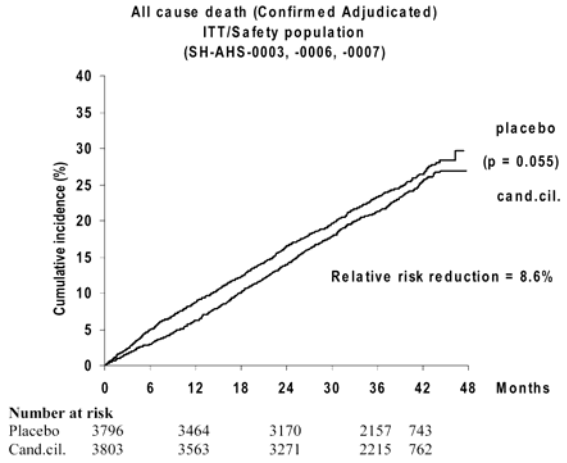


Figure 112 Cumulative incidence (%) of confirmed adjudicated all-cause death in patients with symptomatic CHF over time. ITT/Safety population.

Table 247 Endpoints in the CHARM-Alternative study (SH-AHS-0003), CHARM-Added study (SH-AHS-0006) and the CHARM Program (Pooled studies SH-AHS-0003, SH-AHS-0006 and SH-AHS-0007)

Endpoints	SH-AHS-0003 (CHARM-Alternative)	SH-AHS-0006 (CHARM-Added)	Pooled SH-AHS-0003 + SH-AHS-0006	Pooled SH-AHS-0003 + SH-AHS-0006+ SH-AHS-0007
P°: CV deaths or CHF hospitalizations	HR =0.768; P<0.001	**HR =0.853; P=0.011**	HR = 0.816; P<0.001	HR = 0.836; P<0.001
S°: All-cause deaths or CHF hospitalizations	HR =0.798; P=0.001	**HR =0.871; P=0.021**	HR = 0.840; P<0.001	HR = 0.862; P<0.001
S°: CV death/CHF hospitalization/non-fatal MI	HR =0.782; P<0.001	**HR =0.852; P=0.008**	HR = 0.822; P<0.001	HR = 0.843; P<0.001
All-cause Mortality	HR =0.872; P=0.105 (Covar. adj: P=0.033)	**HR =0.885; P=0.086 (Covar. adj: P=0.105)**	HR =0.886; P=0.018	HR =0.914; P=0.055 (Covar. adj: P=0.032)
All-cause deaths or all-cause hospitalizations	HR =0.918; P=0.114 (Covar. adj: P=0.028)	**HR =0.961; P=0.387**	HR =0.943; P=0.092	HR =0.948; P=0.055
All-cause hospitalizations	HR =0.913; P=0.107 (Covar. adj: P=0.030)	**HR =0.955; P=0.346**	HR =0.937; P=0.078	HR =0.948; P=0.064
CHF hospitalizations	HR =0.677; P<0.001	**HR =0.825; P=0.014**	HR = 0.76 ; P<0.001	HR = 0.79 ; P<0.001
Non-fatal MI	HR =1.107; P=0.656	**HR =0.512; P=0.006**	HR = 0.--- ; P<0.097	HR = 0.--- ; P<0.267
CV deaths	HR =0.847; P=0.072	**HR =0.842; P=0.029**	HR =0.844; P=0.005	HR =0.876; P=0.011
CHF death	HR =0.766; P=0.095	**HR =0.752; P=0.041**	HR =0.758; P=0.008	HR =0.783; P=0.008
Sudden death	HR =0.704; P=0.017	**HR =0.865; P=0.196**	HR =0.801; P=0.013	HR =0.848; P=0.037
Death due to MI	HR =1.942; P=0.025*	**HR =0.830; P=0.562**	HR =1.327; P=0.185	HR =1.187; P=0.368
Death due to stroke	HR =0.846; P=0.658	**HR =1.120; P=0.765**	HR =0.973; P=0.919	HR =1.001; P=0.996
Death due to other CV cause	HR =1.066; P=0.836	**HR =0.965; P=0.894**	HR =1.007; P=0.972	HR =1.057; P=0.734
Non-CV death	HR =1.014; P=0.948	**HR =1.112; P=0.529**	HR =1.073; P=0.595	HR =1.081; P=0.452

CHARM Program Secondary Efficacy Endpoint Finding: For the secondary efficacy endpoint "all-cause mortality in the pooled population of patients with CHF and left ventricular systolic dysfunction (pooled studies SH-AHS-0003 and SH-AHS-0006)", the CHARM-Program endpoint analysis showed that candesartan significantly (P=0.018) reduced (by 11.4%) all-cause mortality in patients with symptomatic CHF and left ventricular systolic dysfunction (Figure 113 and Table 247).

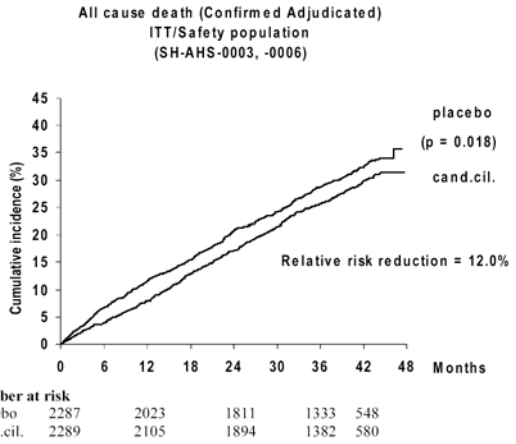


Figure 113 Cumulative incidence (%) of confirmed adjudicated all-cause death in patients with LV systolic dysfunction over time. ITT/Safety population.

CHARM Program – Other Efficacy Endpoint Findings: For the efficacy endpoint "all-cause mortality or all cause hospitalization in the pooled population of patients with symptomatic CHF (pooled studies SH-AHS-0003, SH-AHS-0006 and SH-AHS-0007)", the CHARM-Program endpoint analysis showed that candesartan reduced (by 5.2%) all-cause mortality or all cause hospitalization in patients with symptomatic CHF (Table 247). This was NOT statistically significant (P=0.055).

For the efficacy endpoint "all-cause death or all-cause hospitalization in the pooled population of patients with CHF and left ventricular systolic dysfunction (pooled studies SH-AHS-0003 and SH-AHS-0006)", the CHARM-Program endpoint analysis showed that candesartan reduced (by 5.7%) all-cause death or all-cause hospitalization" in patients with symptomatic CHF and left ventricular systolic dysfunction (Table 247). This was NOT statistically significant (P=0.092).

Please note that the CHARM Program does **NOT** win on the composite endpoint "**all-cause mortality or hospitalization**" or on "**all-cause hospitalization**" (regardless of whether 2 or all 3 studies are pooled).

Summary of efficacy results

Of the 7,599 patients in the population formed by pooling across the three CHARM component studies a total of 1,831 patients died: 886 (23.3%) in the candesartan group and 945 (24.9%) in the placebo group. The HR for the time to death was 0.91 (95% CI 0.83 to 1.00, P= 0.055 unadjusted for interim analyses), which equates to a relative risk reduction of 8.6%. The lower mortality in the candesartan group was attributable to a reduction in deaths from cardiovascular causes (HR=0.88, 95% CI 0.79 to 0.97, P=0.012: relative risk reduction=12.4%).

The sponsor submitted that a pre-specified covariate-adjusted analysis indicated a 10% relative risk reduction for all-cause death with candesartan treatment (HR=0.90, 95% CI 0.82 to 0.99, P=0.032).

In the pooled population of the two studies of patients with depressed LV systolic function (LVEF ≤ 40%) the all-cause mortality relative risk reduction with candesartan was 12% (HR=0.88, 95% CI 0.79 to 0.98, P=0.018). As noted above for the 3-study pooled analysis, the reduction in all cause mortality in the population with depressed LV systolic function was attributable to lower CV mortality (HR=0.88, 95% CI 0.79 to 0.97, P=0.012; relative risk reduction=12%).

During the follow-up period a total of 5,159 patients with symptomatic CHF died or were hospitalized for any reason; 2,554 (67.2%) in the candesartan group and 2,605 (68.6%) in the placebo group The relative risk reduction with candesartan treatment was 5.2% and the HR was 0.95 (95% CI 0.90 to 1.00, P=0.055).

In the population of patients with depressed LV systolic function, 1,608 (70.2%) patients in the candesartan group and 1,641 (71.8%) in the placebo group died or were hospitalized for any

reason. The HR was 0.94 (95% CI 0.88 to 1.01, P=0.092) and the corresponding relative risk reduction was 5.7%

In the total pooled population, 163 patients in the candesartan group and 202 patients in the placebo group developed diabetes during the follow-up period. The relative risk reduction for development of diabetes in patients without a pre-study diagnosis was 22% with candesartan treatment (HR=0.78, 95% CI 0.64 to 0.96, P=0.020).

In the total pooled population, fewer patients in the candesartan group (179, 4.7%) than in the placebo group (216, 5.7%) developed AF (95% CI for difference in proportions 2.0 to 0.0, P=0.054).

For the composite endpoint CV death or hospitalization due to CHF, which was the primary endpoint in the individual studies, the relative risk reduction with candesartan was 16.4% in the total pooled population (HR= 0.84, 95% CI 0.77 to 0.91, P< 0.001) and 18.4% in the population with depressed LV systolic function (HR= 0.82, 95% CI 0.74 to 0.90, P< 0.001).

The relative risk reduction for hospitalization due to CHF was 21% in the pooled population of patients across all studies (HR= 0.79, 95% CI 0.79 to 0.87, P< 0.001) and 24% in patients with depressed LV systolic function (HR= 0.76, 95% CI 0.68 to 0.85, P< 0.001).

Symptoms of heart failure according to NYHA classification improved significantly in patients with symptomatic CHF with candesartan treatment compared to placebo (P= 0.004).

The effect of candesartan with regard to the combined CV mortality CHF hospitalization outcome across sub groups according to age, gender, EF and concomitant CHF medications, was not inconsistent with the effect described for the overall population.

In the total population, the overall treatment evaluation (OTE questionnaire) showed a statistically significant advantage in favor of candesartan over placebo. Health related quality of life was maintained throughout the program with no significant difference between the treatments in any of LIhFE questionnaire outcomes.

SAFETY RESULTS

Deaths

1,834 patients died during the studies, of which 947 (24.9%) were randomized to placebo and 887 (23.3%) randomized to candesartan. For 13 of the patients who died (11 in the subpopulation of patients with depressed LV systolic function), the death was incompletely documented (vital status only without specified cause of death). However, all deaths are included in the tables. Two of the patients in the placebo group and one of the patients in the candesartan group had an SAE with fatal outcome with date of death after the patient's closing visit, thus the deaths of these patients are included in the descriptive safety results but not in the efficacy results.

Table 248 Number (%) of patients with symptomatic CHF 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-0003, -0006, -0007)

Preferred term	Placebo on treatment (N=3796)		Cand. cil. on treatment (N=3803)		Placebo during study (N=3796)		Cand. cil. during study (N=3803)	
	N	(%)	N	(%)	N	(%)	N	(%)
Sudden death	276	(7.3)	231	(6.1)	348	(9.2)	291	(7.7)
Cardiac failure/cardiac failure aggravated[b]	149	(3.9)	79	(2.1)	256	(6.7)	192	(5.0)
Myocardial infarction	35	(0.9)	56	(1.5)	57	(1.5)	77	(2.0)
Pneumonia	25	(0.7)	11	(0.3)	47	(1.2)	30	(0.8)
Cerebrovascular disorder	23	(0.6)	19	(0.5)	39	(1.0)	36	(0.9)
Death	12	(0.3)	11	(0.3)	31	(0.8)	35	(0.9)
Cardiac arrest	16	(0.4)	16	(0.4)	24	(0.6)	27	(0.7)
Sepsis	11	(0.3)	9	(0.2)	26	(0.7)	19	(0.5)
Fibrillation ventricular	19	(0.5)	12	(0.3)	23	(0.6)	17	(0.4)
Cardiomyopathy	9	(0.2)	4	(0.1)	19	(0.5)	14	(0.4)
Pulmonary carcinoma	8	(0.2)	14	(0.4)	12	(0.3)	21	(0.6)
Pulmonary oedema	9	(0.2)	9	(0.2)	17	(0.4)	15	(0.4)
Respiratory insufficiency	7	(0.2)	6	(0.2)	15	(0.4)	15	(0.4)
Accident and/or injury	8	(0.2)	6	(0.2)	15	(0.4)	11	(0.3)
Coronary artery disorder	8	(0.2)	7	(0.2)	11	(0.3)	15	(0.4)
Renal failure acute	5	(0.1)	4	(0.1)	14	(0.4)	12	(0.3)
Renal failure nos	7	(0.2)	1	(<0.1)	14	(0.4)	12	(0.3)
Multiorgan failure	4	(0.1)	4	(0.1)	9	(0.2)	10	(0.3)

[a] The table uses a cut-off of ≥0.3% in the total population during study (N=7599).
[b] Patients having both or all events are counted once only.

The most commonly reported fatal AEs (Table 248) in the placebo and candesartan groups during study were sudden death (348, 9.2% and 291, 7.7% respectively), cardiac failure/cardiac failure aggravated (256, 6.7% and 192, 5.0% respectively) and MI (57, 1.5% and 77, 2.0% respectively).

Exploratory-Analysis: Non-CV death and non-CV hospitalization in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

Analyses of non-CV death and non-CV hospitalizations were specified in the SAP to assure that there were no off-setting adverse events in these areas. There were no significant differences between the candesartan group and the placebo group in non-CV mortality rates (placebo 176; 4.6%; candesartan 195; 5.1%) or non-CV hospitalization rates (placebo 1,469; 38.7%; candesartan 1,521; 40.0%).

Other Serious Adverse Events

Non-fatal SAEs were reported in 65.5% (2,487) of the patients in the placebo group during study and in 63.9% (2,432) of the patients in the candesartan group during study.

The most commonly reported non-fatal SAEs during study were cardiac failure/cardiac failure aggravated (1,118, 29.5%), angina pectoris/angina pectoris aggravated (502, 13.2%) and pneumonia (268, 7.1%) in the placebo group, and cardiac failure/cardiac failure aggravated (931,

24.5%), angina pectoris/angina pectoris aggravated (480, 12.6%) and hypotension (318, 8.4%) in the candesartan group (Table 249).

Table 249 Number (%) of patients with symptomatic CHF with the most commonly reporteda SAEs other than death, sorted by descending frequency in the total population during study. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Preferred term	Placebo on treatment (N=3796)		Cand. cil. on treatment (N=3803)		Placebo during study (N=3796)		Cand. cil. during study (N=3803)	
	N	(%)	N	(%)	N	(%)	N	(%)
Cardiac failure/cardiac failure aggravated[b]	1018	(26.8)	776	(20.4)	1118	(29.5)	931	(24.5)
Angina pectoris/angina pectoris aggravated[b]	457	(12.0)	405	(10.6)	502	(13.2)	480	(12.6)
Hypotension	184	(4.8)	291	(7.7)	212	(5.6)	318	(8.4)
Pneumonia	220	(5.8)	195	(5.1)	268	(7.1)	249	(6.5)
Fibrillation atrial	216	(5.7)	161	(4.2)	246	(6.5)	196	(5.2)
Arrhythmia ventricular	206	(5.4)	159	(4.2)	238	(6.3)	193	(5.1)
Myocardial infarction	185	(4.9)	156	(4.1)	213	(5.6)	181	(4.8)
Cerebrovascular disorder	176	(4.6)	154	(4.0)	202	(5.3)	188	(4.9)
Arrhythmia atrial	175	(4.6)	156	(4.1)	197	(5.2)	187	(4.9)
Coronary artery disorder	163	(4.3)	158	(4.2)	191	(5.0)	189	(5.0)
Chest pain	172	(4.5)	147	(3.9)	196	(5.2)	174	(4.6)
Tachycardia supraventricular	152	(4.0)	129	(3.4)	177	(4.7)	148	(3.9)
Accident and/or injury	106	(2.8)	93	(2.4)	134	(3.5)	115	(3.0)
Syncope	103	(2.7)	112	(2.9)	117	(3.1)	131	(3.4)
Anaemia	84	(2.2)	106	(2.8)	106	(2.8)	140	(3.7)
Tachycardia ventricular/arrhythmia/arrhythmia aggravated[b]	105	(2.8)	94	(2.5)	126	(3.3)	119	(3.1)

a The table uses a cut-off of ≥3.0% in the total population during study (N=7599).

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

Discontinuations and Other Significant Adverse Events

Permanent discontinuations presented descriptively 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. (All patients who died are included in the section on "deaths.") However, if the investigational product was permanently discontinued, the patient still remained in the study and SAEs were reported during the whole study period. Because of the difference in the definitions of permanent discontinuations in the descriptive and exploratory analyses, there were small differences in the number of patients between the two analyses.

Overall profile of discontinuations

Discontinuations due to adverse events in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

The investigational product was permanently discontinued due to AEs in 613 (16.1%) patients in the placebo group and in 799 (21.0%) patients in the candesartan group.

Thus, discontinuation of study medication due to AEs was more frequent in the candesartan

group in the CHARM-Pooled studies.

Adverse events associated with discontinuations

The most common AEs leading to discontinuation of the investigational product (Table 250) in the placebo group in the total population were cardiac failure/cardiac failure aggravated (186, 4.9%), renal function abnormal/renal dysfunction aggravated (110, 2.9%) and hypotension (76, 2.0%). The most commonly reported AEs leading to discontinuation in the candesartan group were renal function abnormal/renal dysfunction aggravated (238, 6.3%), cardiac failure/ cardiac failure aggravated (165, 4.3%) and hypotension (155, 4.1%).

Table 250 Number (%) of patients with symptomatic CHF with the most commonly reporteda AEs leading to discontinuation of the investigational product, sorted by descending frequency in the total population on treatment. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Preferred term	Placebo on treatment (N=3796)		Cand.cil. on treatment (N=3803)	
	N	(%)	N	(%)
Cardiac failure/cardiac failure aggravated[b]	186	(4.9)	165	(4.3)
Renal function abnormal/renal dysfunction aggravated[b]	110	(2.9)	238	(6.3)
Hypotension	76	(2.0)	155	(4.1)
Hyperkalaemia	22	(0.6)	93	(2.4)
Myocardial infarction	31	(0.8)	26	(0.7)
Cerebrovascular disorder	28	(0.7)	27	(0.7)
Renal failure acute	20	(0.5)	33	(0.9)
Angina pectoris/angina pectoris aggravated[b]	20	(0.5)	30	(0.8)
Dizziness/vertigo	14	(0.4)	32	(0.8)
Pneumonia	22	(0.6)	21	(0.6)
Diarrhoea	10	(0.3)	28	(0.7)
Renal failure nos	13	(0.3)	22	(0.6)

[a] The table uses a cut-off of ≥0.5% in the total population on treatment (N=7599).

[b] Patients having both or all events are counted once only.

As specified in the SAP, dose reductions and permanent discontinuations of the investigational product were analyzed both descriptively as a part of the standard safety evaluation and exploratory, using statistical methods.

Because of the difference in the definitions there were small differences in the number of patients between the two analyses. Patients may be included in the descriptive safety analyses but not in the exploratory safety analyses or vice versa. In the placebo treatment group 52 patients were included in the descriptive analysis but not in the exploratory ones and inversely 72 patients were only found in the exploratory analyses. In the candesartan treatment group 71 patients were included in the descriptive analysis only while 70 patients appeared in the exploratory analyses but not in the descriptive results. A patient could have more than one AE, leading to permanent discontinuation of the investigational product, occurring at the same time.

The preferred term “renal function abnormal” used in the descriptive safety analysis and the term “increased creatinine,” used in this section refer to ‘Abnormal renal function (e.g., creatinine increased)’ pre-specified in the CRF.

In this exploratory presentation of data permanent discontinuation of the investigational product due to an AE or abnormal lab value occurred in 633 (16.7%) patients in the placebo group and 798 (21.0%) patients in the candesartan group. Both the difference in time to event (P< 0.001) (Table 251, Table 252 and Figure 114) and the difference in proportions between treatments of 4.3% (P< 0.001) (Table 70 and Table 71) were statistically significant.

Table 251 Exploratory safety variables for patients with symptomatic 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-0003, -0006, -0007)

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	3791	969	9355.9	103.6	2.5
	cand.cil.	3788	1135	9177.0	123.7	2.4
Permanent investigational product discontinuation due to an AE or an abnormal lab value	Placebo	3796	633	9937.0	63.7	2.6
	cand.cil.	3803	798	9807.1	81.4	2.6
At least one investigational product discontinuation due to any cause	Placebo	3790	1571	8431.3	186.3	2.2
	cand.cil.	3788	1780	7951.8	223.8	2.1
At least one investigational product discontinuation due to an AE or an abnormal lab value	Placebo	3796	1198	9189.4	130.4	2.4
	cand.cil.	3803	1432	8708.2	164.4	2.3

Table 252 Exploratory safety variables for patients with symptomatic CHF. Comparison of candesartan versus placebo with Logrank test. ITT/Safety population. (SH-AHS-0003, -0006, -0007)

Variable	N	Events cand. cil.	Events placebo	Hazard Ratio	95% CI		p-value
					Lower	Upper	
Permanent investigational product discontinuation due to any cause	7599	1135	969	1.179	1.081	1.285	<0.001
Permanent investigational product discontinuation due to an AE or an abnormal lab value	7599	798	633	1.273	1.147	1.413	<0.001
At least one investigational product discontinuation due to any cause	7599	1780	1571	1.183	1.105	1.267	<0.001
At least one investigational product discontinuation due to an AE or an abnormal lab value	7599	1432	1198	1.249	1.157	1.349	<0.001

Specific causes of investigational product discontinuation are shown in Table 253, Table 254, Table 255 and Table 256. Hypotension, hyperkalemia and increased creatinine as causes for the investigational product discontinuation were statistically significantly more frequent for candesartan. Absolute differences in these cause-specific discontinuations relative to placebo were 1.7%, 1.7% and 3.1%, respectively.

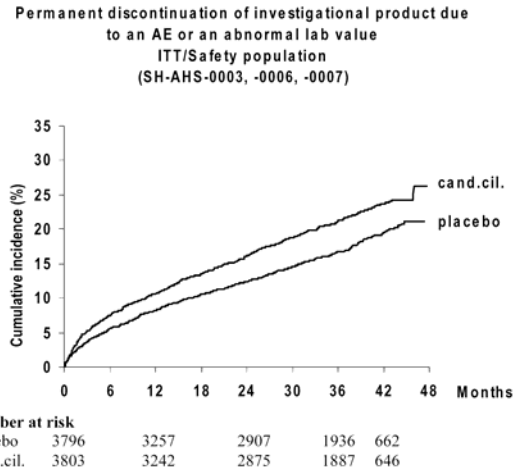


Figure 114 Cumulative incidence (%) of permanent discontinuation of the investigational product due to an AE or an abnormal laboratory value. ITT/Safety population

Table 253 Exploratory safety variables for patients with symptomatic CHF. The proportions of patients (%) with an event. ITT/Safety population. (SH-AHS-0003, -0006, -0007)

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	3796	969	25.5	24.1	26.9
	cand.cil.	3803	1135	29.8	28.4	31.3
Permanent investigational product discontinuation due to an AE or an abnormal lab value	Placebo	3796	633	16.7	15.5	17.9
	cand.cil.	3803	798	21.0	19.7	22.3
Permanent investigational product discontinuation due to hypotension	Placebo	3796	66	1.7	1.3	2.2
	cand.cil.	3803	132	3.5	2.9	4.1
Permanent investigational product discontinuation due to hyperkalaemia	Placebo	3796	21	0.6	0.3	0.8
	cand.cil.	3803	85	2.2	1.8	2.8
Permanent investigational product discontinuation due to increased creatinine	Placebo	3796	115	3.0	2.5	3.6
	cand.cil.	3803	234	6.2	5.4	7.0
At least one investigational product discontinuation due to any cause	Placebo	3796	1571	41.4	39.8	43.0
	cand.cil.	3803	1780	46.8	45.2	48.4
At least one investigational product discontinuation due to an AE or an abnormal lab value	Placebo	3796	1198	31.6	30.1	33.1
	cand.cil.	3803	1432	37.7	36.1	39.2
At least one investigational product discontinuation due to hypotension	Placebo	3796	127	3.3	2.8	4.0
	cand.cil.	3803	274	7.2	6.4	8.1
At least one investigational product discontinuation due to hyperkalaemia	Placebo	3796	42	1.1	0.8	1.5
	cand.cil.	3803	149	3.9	3.3	4.6
At least one investigational product discontinuation due to Increased creatinine	Placebo	3796	182	4.8	4.1	5.5
	cand.cil.	3803	374	9.8	8.9	10.8
Decreased investigational product dose due to any cause at least once	Placebo	3796	482	12.7	11.7	13.8
	cand.cil.	3803	791	20.8	19.5	22.1
Decreased investigational product dose due to an AE or an abnormal lab value at least once	Placebo	3796	385	10.1	9.2	11.1
	cand.cil.	3803	693	18.2	17.0	19.5

Table 254 Exploratory safety variables for patients with symptomatic CHF. The difference in proportion (%) between treatments. Chi-square test. ITT/ Safety population. (SH-AHS-0003, -0006, -0007)

Variable	Difference in proportion between treatments	95% CI		p-value
	Cand.cil. - Placebo	Lower	Upper	
Permanent investigational product discontinuation due to any cause	4.3	2.3	6.3	<0.001
Permanent investigational product discontinuation due to an AE or an abnormal lab value	4.3	2.6	6.1	<0.001
Permanent investigational product discontinuation due to hypotension	1.7	1.0	2.4	<0.001
Permanent investigational product discontinuation due to hyperkalaemia	1.7	1.2	2.2	<0.001
Permanent investigational product discontinuation due to Increased creatinine	3.1	2.2	4.1	<0.001
At least one investigational product discontinuation due to any cause	5.4	3.2	7.6	<0.001
At least one investigational product discontinuation due to an AE or an abnormal lab value	6.1	4.0	8.2	<0.001
At least one investigational product discontinuation due to hypotension	3.9	2.9	4.9	<0.001
At least one investigational product discontinuation due to hyperkalaemia	2.8	2.1	3.5	<0.001
At least one investigational product discontinuation due to Increased creatinine	5.0	3.9	6.2	<0.001
Decreased investigational product dose due to any cause at least once	8.1	6.4	9.8	<0.001
Decreased investigational product dose due to an AE or an abnormal lab value at least once	8.1	6.5	9.6	<0.001

Table 255 Exploratory safety variables. Comparison of candesartan cilexetil versus placebo with Cox regression test with 33 pre-specified baseline factors as covariates for the total population. ITT/Safety Population. (SH-AHS-0003, -0006, -0007)

Variable	N	Events cand. cil.	Events plac-ebo	Hazard Ratio	95% CI		p-value
					Lower	Upper	
Permanent Investigational product discontinuation due to any cause	7599	1135	969	1.176	1.078	1.283	<0.001
Permanent Investigational product discontinuation due to an AE or an abnormal lab value	7599	798	633	1.272	1.146	1.413	<0.001
At least one Investigational product discontinuation due to any cause	7599	1780	1571	1.188	1.110	1.273	<0.001
At least one Investigational product discontinuation due to an AE or an abnormal lab value	7599	1432	1198	1.255	1.162	1.356	<0.001

Table 256 Exploratory safety variables. Comparison of candesartan cilexetil versus placebo with Cox regression with 33 pre-specified baseline factors as covariates for the subpopulation. ITT/Safety Population. (SH-AHS-0003, -0006)

Variable	N	Events cand. cil.	Events plac-ebo	Hazard Ratio	95% CI		p-value
					Lower	Upper	
Permanent Investigational product discontinuation due to any cause	4576	719	614	1.190	1.068	1.327	0.002
Permanent Investigational product discontinuation due to an AE or an abnormal lab value	4576	528	429	1.251	1.101	1.423	<0.001
At least one Investigational product discontinuation due to any cause	4576	1126	990	1.202	1.103	1.310	<0.001
At least one Investigational product discontinuation due to an AE or an abnormal lab value	4576	937	797	1.243	1.130	1.367	<0.001

Investigational product discontinuation due to an AE or lab abnormality was also examined as an endpoint across the array of subgroups. There was an approximate 1.3 fold excess risk for

candesartan discontinuation relative to placebo for the entire study population which was characteristic of the relative discontinuation rates across most subgroups including concomitant medication with ACE-inhibitors, β-blockers and spironolactone.

For patients with a history of diabetes, there was a higher frequency of discontinuation of the investigational product caused by hypotension, hyperkalemia or increased serum creatinine (Table 257 and Table 258), which is an expected finding in these diabetics with possible underlying renal dysfunction and autonomic dysregulation.

Table 257 Discontinuation of investigational product due to hypertension, hyperkalemia and increased creatinine in patients with a history of diabetes for the total population. The proportions of patients (%) with an event. ITT/Safety Population. (SH-AHS-0003, -0006, -0007)

Variable	Treat-ment	N	Number of patients with event	Proportion of patients with event	95% CI	
					Lower	Upper
Permanent Investigational product discontinuation due to Hypotension	placebo	1075	22	2.0	1.3	3.1
	cand.cil.	1088	34	3.1	2.2	4.3
Permanent Investigational product discontinuation due to Hyperkalaemia	placebo	1075	13	1.2	0.6	2.1
	cand.cil.	1088	31	2.8	1.9	4.0
Permanent Investigational product discontinuation due to Increased Creatinine	placebo	1075	57	5.3	4.0	6.8
	cand.cil.	1088	99	9.1	7.5	11.0
At least one Investigational product discontinuation due to Hypotension	placebo	1075	38	3.5	2.5	4.8
	cand.cil.	1088	68	6.3	4.9	7.9
At least one Investigational product discontinuation due to Hyperkalaemia	placebo	1075	23	2.1	1.4	3.2
	cand.cil.	1088	63	5.8	4.5	7.3
At least one Investigational product discontinuation due to Increased Creatinine	placebo	1075	86	8.0	6.4	9.8
	cand.cil.	1088	149	13.7	11.7	15.9

Table 258 Permanent discontinuation of investigational product in patients with a history of diabetes for the total population. The difference in proportion (%) between treatments. Chi square test. ITT/Safety Population (SH-AHS-0003, -0006, -0007)

Variable	Difference in proportion between treatments Cand.cil.-placebo	95% CI		p-value
		Lower	Upper	
Permanent Investigational product discontinuation due to Hypotension	1.1	-0.3	2.4	0.114
Permanent Investigational product discontinuation due to Hyperkalaemia	1.6	0.5	2.8	0.007
Permanent Investigational product discontinuation due to Increased Creatinine	3.8	1.6	6.0	<0.001
At least one Investigational product discontinuation due to Hypotension	2.7	0.9	4.5	0.003
At least one Investigational product discontinuation due to Hyperkalaemia	3.7	2.0	5.3	<0.001
At least one Investigational product discontinuation due to Increased Creatinine	5.7	3.1	8.3	<0.001

Other significant adverse events (Dose reduction due to adverse events)

The protocol specifies that dose reductions and permanent discontinuations of the investigational product will be analyzed both descriptively as a part of the standard safety evaluation and exploratory, using statistical methods.

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 analysis, 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.

The dose of the investigational product was reduced due to AEs in 324 (8.5%) patients in the placebo group and in 569 (15.0%) patients in the candesartan group. The most commonly reported AEs leading to dose reduction were hypotension (136, 3.6%), renal function abnormal/renal dysfunction aggravated (0, 1.3%) and dizziness/vertigo (38, 1.0%) in the placebo group, and hypotension (315, 8.3%), renal function abnormal/renal dysfunction aggravated (99, 2.6%) and hyperkalemia (60, 1.6%) in the candesartan group (Table 259).

Table 259 Number (%) of patients with symptomatic CHF with the most commonly reported[a] AEs leading to dose reduction of the investigational product, sorted by descending frequency in the total population on treatment. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Preferred term	Placebo on treatment (N=3796)		Cand. cil. on treatment (N=3803)	
	N	(%)	N	(%)
Hypotension	136	(3.6)	315	(8.3)
Renal function abnormal/renal dysfunction aggravated[b]	50	(1.3)	99	(2.6)
Dizziness/vertigo[b]	38	(1.0)	54	(1.4)
Hyperkalaemia	17	(0.4)	60	(1.6)
Cardiac failure aggravated	29	(0.8)	30	(0.8)
Fatigue	13	(0.3)	24	(0.6)
Nausea	14	(0.4)	15	(0.4)
Dyspnoea/dyspnoea (aggravated)[b]	17	(0.4)	8	(0.2)
Diarrhoea	10	(0.3)	9	(0.2)

a The table uses a cut-off of ≥0.3% in the total population on treatment (N=7599).

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

Exploratory-Analysis: Dose reduction of the investigational product in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

A higher frequency of dose reduction is presented in the exploratory safety analysis which is due to the fact that patients experiencing both dose reduction and later permanent discontinuation for the same reason are counted once in each category in the exploratory analysis. In the descriptive safety analysis above these patients are only included in the discontinuation category.

Dose reduction of the investigational product due to an AE or abnormal lab value occurred in 385 (10.1%) patients in the placebo group and 693 (18.2%) patients in the candesartan group (Table 253). This between- treatment difference in dose reductions for an AE of 8.1% was statistically significant ($P < 0.001$), (Table 254). As shown in Figure 115, the majority of events occurred during the first 6 to 12 months of treatment with the investigational product.

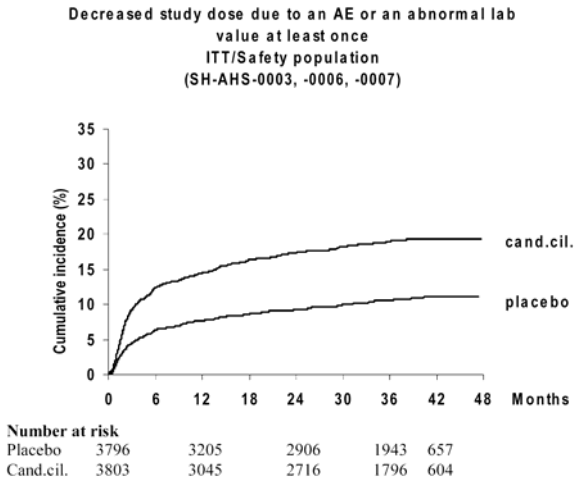


Figure 115 Cumulative incidence (%) of dose reduction of the investigational product due to an AE or an abnormal laboratory value. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Common Adverse Events

Adverse events (AEs) collected during the component studies in the total population (SH-AHS-0003, SH-AHS-0006 and SH-AHS-0007) are described depending on whether they were reported during treatment with the investigational product (referred to as "on treatment" in tables) or reported over the entire study period (referred to as "during study"). AEs during study include all AEs reported for each patient, i.e., those reported on treatment as well as any new-onset AEs during the period following discontinuation of the study drug and new-onset SAEs after the patient completed or withdrew from a component study. AEs are organized according to the AAED preferred term level, i.e., AEs of a similar kind share the same preferred term.

Appropriateness of adverse event categorization and preferred terms

Categories of adverse events in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:
During study, in the total population AEs were reported by 2,799 (73.7%) patients randomized to placebo, and by 2,841 (74.7%) patients randomized to candesartan. In the placebo group 947 (24.9%) patients had fatal SAEs and 2,487 (65.5%) patients experienced non-fatal SAEs, compared with the candesartan group where 887 (23.3%) patients had fatal SAEs and 2,432 (63.9%) patients had non-fatal SAEs. The investigational product was prematurely discontinued due to AEs for 613 (16.1%) patients in the placebo group and for 799 (21.0%) patients in the candesartan group. The investigational product was reduced in dose due to AEs for 324 (8.5%) patients in the placebo group and for 569 (15.0%) patients in the candesartan group. A summary of AEs by category in the total population is presented in Table 260, and for CHF patients with depressed LV function is given in Table 261.

Table 260 Number (%) of patients with symptomatic CHF with at least one adverse event in any category, and total numbers of adverse events. ITT/Safety population (SH-AHS-0003, -0006, -0007)

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=3796)		(N=3803)		(N=3796)		(N=3803)	
Any AE	2732	(72.0)	2788	(73.3)	2799	(73.7)	2841	(74.7)
Serious AEs	2562	(67.5)	2410	(63.4)	2698	(71.1)	2624	(69.0)
Serious AEs leading to death	616	(16.2)	504	(13.3)	947	(24.9)	887	(23.3)
Serious AEs not leading to death	2369	(62.4)	2246	(59.1)	2487	(65.5)	2432	(63.9)
Discontinuations of the investigational product due to AEs	613	(16.1)	799	(21.0)	-	-	-	-
Dose reductions of the investigational product due to AEs	324	(8.5)	569	(15.0)	-	-	-	-
	Total number of adverse events							
All AEs[c]	9317		9378		10814		11261	
Serious AEs[c]	8390		7730		9895		9634	

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

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

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

Table 261 Number (%) of patients who had at least one adverse event in any category, and total numbers of adverse events for the subpopulation ITT/Safety population (SH-AHS-0003, -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=2287)		(N=2289)		(N=2287)		(N=2289)	
Any AE	1703	(74.5)	1732	(75.7)	1739	(76.0)	1767	(77.2)
Serious AEs	1605	(70.2)	1506	(65.8)	1688	(73.8)	1651	(72.1)
Serious AEs leading to death	463	(20.2)	375	(16.4)	709	(31.0)	643	(28.1)
Serious AEs not leading to death	1453	(63.5)	1373	(60.0)	1524	(66.6)	1493	(65.2)
Discontinuations of investigational product due to AEs	421	(18,4)	530	(23,2)	-	-	-	-
Dose reductions of investigational product due to AEs	199	(8.7)	377	(16.5)	-	-	-	-
	Total number of adverse events							
All AEs[c]	5875		5928		6885		7123	
Serious AEs[c]	5276		4885		6291		6092	

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

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

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

Incidence of common adverse events and common adverse event tables

The most common AEs (Table 262) in the placebo and candesartan groups during study were cardiac failure/cardiac failure aggravated (1,187, 31.3% and 1001, 26.3% respectively), angina pectoris/angina pectoris aggravated (506, 13.3% and 490, 12.9%, respectively), hypotension (399, 10.5% and 736, 19.4% respectively) and renal function abnormal/renal dysfunction aggravated (248, 6.5% and 487, 12.8% respectively).

A similar pattern was seen in the subpopulation of patients with depressed LV systolic function.

Table 262 Number (%) of patients with symptomatic CHF with the most commonly reported[a] AEs, sorted by descending frequency. ITT/ Safety population (SH-AHS-0003, -0006, -0007)

Preferred term	Placebo on treatment (N=3796)		Cand. cil. on treatment (N=3803)		Placebo during study (N=3796)		Cand. cil. during study (N=3803)	
	N	(%)	N	(%)	N	(%)	N	(%)
Cardiac failure/cardiac failure aggravated[b]	1073	(28.3)	831	(21.9)	1187	(31.3)	1001	(26.3)
Hypotension	372	(9.8)	714	(18.8)	399	(10.5)	736	(19.4)
Angina pectoris/angina pectoris aggravated[b]	461	(12.1)	414	(10.9)	506	(13.3)	490	(12.9)
Renal function abnormal/renal dysfunction aggravated[b]	238	(6.3)	474	(12.5)	248	(6.5)	487	(12.8)
Sudden death	282	(7.4)	234	(6.2)	348	(9.2)	291	(7.7)
Pneumonia	243	(6.4)	200	(5.3)	299	(7.9)	261	(6.9)
Myocardial infarction	216	(5.7)	205	(5.4)	257	(6.8)	242	(6.4)
Fibrillation atrial	218	(5.7)	165	(4.3)	249	(6.6)	202	(5.3)
Arrhythmia ventricular	207	(5.5)	159	(4.2)	239	(6.3)	193	(5.1)
Cerebrovascular disorder	189	(5.0)	164	(4.3)	216	(5.7)	203	(5.3)
Coronary artery disorder	170	(4.5)	169	(4.4)	200	(5.3)	205	(5.4)
Chest pain	177	(4.7)	154	(4.0)	202	(5.3)	183	(4.8)
Arrhythmia atrial	175	(4.6)	156	(4.1)	197	(5.2)	187	(4.9)
Hyperkalaemia	78	(2.1)	238	(6.3)	84	(2.2)	242	(6.4)
Tachycardia supraventricular	152	(4.0)	129	(3.4)	177	(4.7)	148	(3.9)
Dizziness/vertigo[b]	107	(2.8)	154	(4.0)	115	(3.0)	168	(4.4)
Accident and/or injury	112	(3.0)	99	(2.6)	143	(3.8)	125	(3.3)
Tachycardia ventricular/arrhythmia/arrhythmia aggravated[b]	110	(2.9)	100	(2.6)	132	(3.5)	128	(3.4)
Syncope	105	(2.8)	121	(3.2)	119	(3.1)	139	(3.7)
Anaemia	87	(2.3)	110	(2.9)	110	(2.9)	145	(3.8)

a This table uses a cut-off of ≥3.0% in the total population during study (N=7599).

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

Laboratory Findings

For the total population, serial laboratory data were collected from patients participating at investigational sites in North America (placebo 1,376 patients, candesartan 1,367 patients).

Changes in mean laboratory values were generally small, of minor clinical significance, and occurred primarily in parameters that previously showed changes in studies with inhibitors of the RAAS, such as creatinine and potassium. As a consequence of the large number of observations, some laboratory variables showed statistically significant between treatment differences, even though the absolute differences were small and may not be clinically significant.

From the results for all clinical laboratory tests in the total population, only clinical important abnormalities in the laboratory tests are presented below.

The number of patients with increase in serum creatinine ≥ 2 times from baseline, and of patients with serum potassium ≥ 6mmol/l after randomization are shown in Table 263 and Table 264 for the total CHARM-Pooled population, and in Table 265 and Table 266 for the subpopulation of CHF patients with LV dysfunction.

Table 263 Number (%) of patients with increase in serum creatinine ≥ 2 x from baseline value. ITT/Safety population (North America) (SH-AHS-0003, -0006,-0007)

Abnormal Laboratory variable	Placebo (N=1279)		Cand.cil. (N=1263)	
	N	%	N	%
Creatinine	47	3.7	82	6.5

Table 264 Number (%) of patients with serum potassium to ≥ 6 mmol/L at any time after randomization. ITT/Safety population (North America) (SH-AHS-0003, -0006,-0007)

Abnormal Laboratory variable	Placebo (N=1310)		Cand.cil. (N=1294)	
	N	%	N	%
Potassium	15	1.1	31	2.4

Table 265 Number (%) of patients with increase in serum creatinine ≥ 2 x from baseline value. ITT/Safety population (North America) (SH- AHS- 0003, -0006)

Abnormal Laboratory variable	Placebo (N=754)		Cand.cil. (N=747)	
	N	%	N	%
Creatinine	32	4.2	49	6.6

Table 266 Number (%) of patients with serum potassium to ≥ 6 mmol/L at any time after randomization. ITT/Safety population (North America) (SH-AHS-0003, -0006)

Abnormal Laboratory variable	Placebo (N=774)		Cand.cil. (N=768)	
	N	%	N	%
Potassium	9	1.2	21	2.7

The mean value for creatinine in the placebo group increased 7.7 µmol/L from the baseline value to the LVCF. In the candesartan group, the mean value increased 17.0 µmol/L. At baseline, 252 (18.8%) of placebo patients had values above the reference range compared with 251 (18.8%) of patients in the candesartan group. For the last values carried forward that were above the upper level of normal, frequency increased in both treatment groups (placebo 358, 27.3%; candesartan 399, 30.8%). For patients who had baseline value and at least one measurement after randomization (placebo 1279 patients, candesartan 1263 patients) baseline serum creatinine was at least doubled in 47 (3.7%) patients in the placebo group, compared with 82 (6.5%) patients in the candesartan group (Table 263).

For potassium, the mean value for patients treated with placebo increased 0.02 mmol/ L from the baseline value to the LVCF compared with 0.24 mmol/L for patients treated with candesartan. The proportions of patients with values above the reference range increased from 32 (2.4%) to 44 (3.4%) in the placebo group and increased from 38 (2.8%) to 83 (6.4%) in the candesartan group. Potassium levels increased to = 6 mmol/L at any time after randomization in 15 (1.1%) of 1,310 patients valid for evaluation in the placebo group and 31 (2.4%) of 1,294 patients in the candesartan group (Table 264).

AE reports of hypokalemia were rare and occurred more often in the placebo group (placebo 36, 0.9%; candesartan 16, 0.4%).

Mean sodium measurements decreased 0.07 mmol/L for patients treated with placebo and decreased 0.12 mmol/L for patients in the candesartan. The AE term hyponatremia was reported for 13 patients treated with placebo compared with 9 patients treated with candesartan.

Minor decreases were seen for mean hemoglobin values for patients treated with placebo (0.18 mmol/L) and candesartan (0.31 mmol/L). The proportion of patients with anemia reported as an AE on treatment with the investigational product was slightly lower for placebo-treated patients (87, 2.3%) compared with candesartan-treated patients (110, 2.9%). One patient in the placebo treatment group and 4 (0.3%) of 1,290 patients in the candesartan group had a hemoglobin value below the defined level of abnormality (male = 80 g/L (4.96 mmol/L), female = 70 g/L (4.34 mmol/L)).

Glycohemoglobin A_{1c} levels decreased slightly and no major difference was seen between the placebo (-0.31%) and candesartan groups (-0.32%).

In summary, it appears that the small differences in mean laboratory values (candesartan compared with placebo) and the frequency of critical abnormal values was in keeping with the expected findings for treatment with inhibitors of the RAAS.

Vital Signs

For the CHARM Program studies' safety report, vital signs consist of diastolic blood pressure (DBP), systolic blood pressure (SBP), pulse pressure and heart rate. For physical findings, only the data for body weight are presented.
Changes in vital signs over time in the total population are shown in Figure 116, Figure 117, Figure 118, and Figure 119.

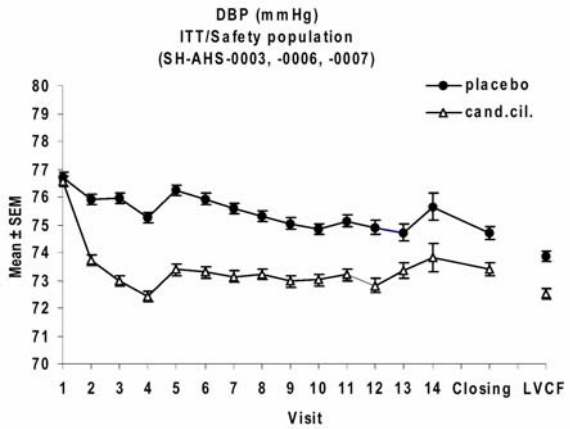


Figure 116 Mean DBP ± SEM (mmHg) by visit for the total population. ITT/Safety population

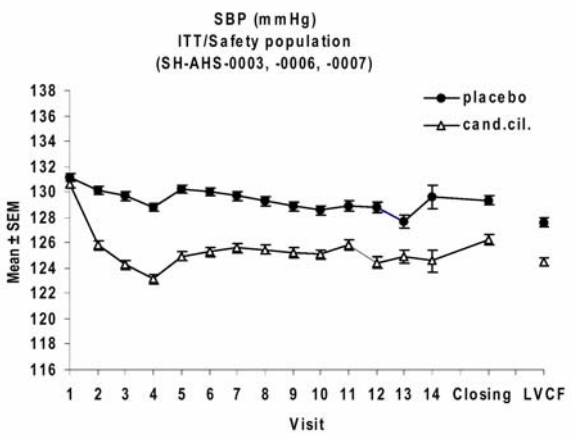


Figure 117 Mean SBP ± SEM (mmHg) by visit for the total population. ITT/Safety population

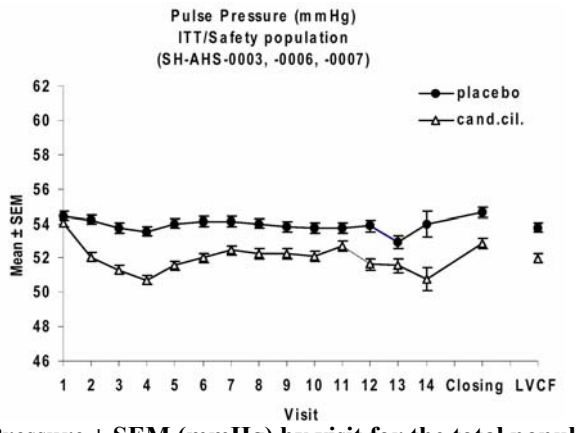


Figure 118 Mean Pulse Pressure ± SEM (mmHg) by visit for the total population. ITT/Safety population

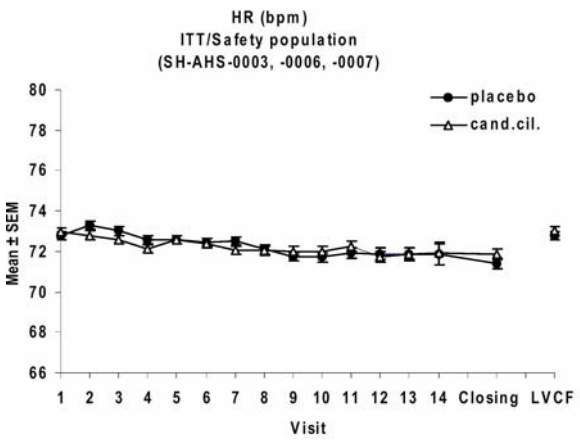


Figure 119 Mean heart rate ± SEM (bpm) by visit for the total population. ITT/Safety population

Changes in vital signs over time in the subpopulation of patients with depressed LV systolic function are shown in Figure 120, Figure 121, Figure 122and Figure 123.

The number of patients with clinically important changes in vital signs in the total population are shown in (Table 267, Table 268 and Table 269) and the number of patients with clinically important changes in vital signs in the subpopulation of patients with depressed LV systolic function are shown in (Table 270 and Table 271).

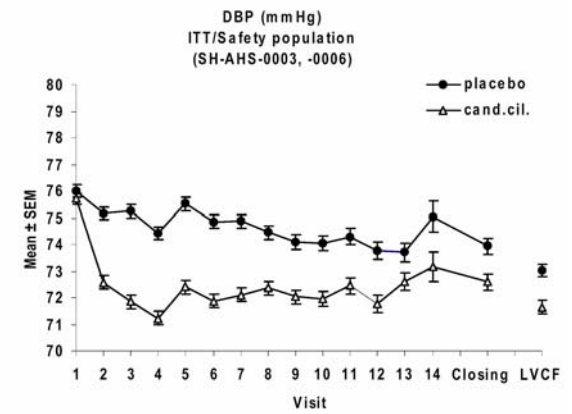


Figure 120 Mean DBP ± SEM (mmHg) by visit for the depressed LV systolic function subpopulation. ITT/Safety population

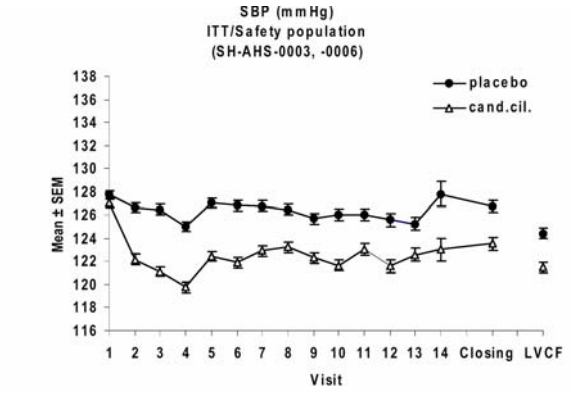


Figure 121 Mean SBP ± SEM (mmHg) by visit for the depressed LV systolic function subpopulation. ITT/Safety population

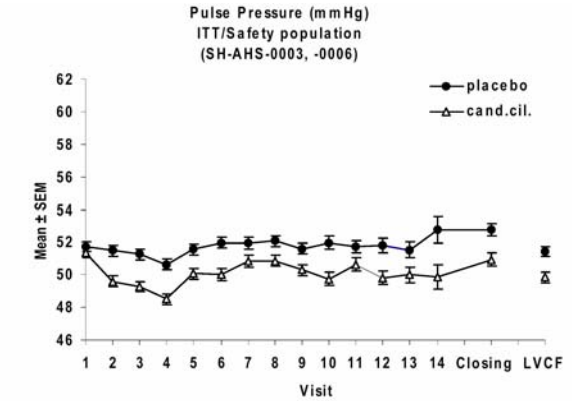


Figure 122 Mean Pulse Pressure ± SEM (mmHg) by visit for the depressed LV systolic function subpopulation. ITT/Safety population

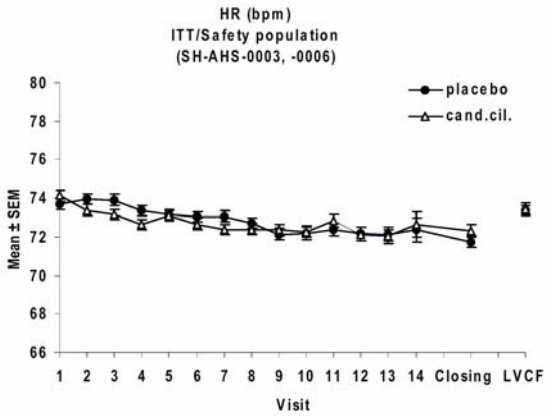


Figure 123 Mean heart rate ± SEM (bpm) by visit for the depressed LV systolic function subpopulation. ITT/Safety population

Table 267 Estimated Means and 95% CI for the change from baseline to LVCF for BP variables with Region as an ANOVA factor for the total population. ITT/Safety Population. (SH-AHS-0003, -0006, -0007)

Variable	Treat-ment	N	Estimated Mean	95% CI	
				Lower	Upper
DBP (mmHg)	placebo	3755	-2.21	-2.66	-1.75
	cand.cil.	3774	-3.66	-4.10	-3.23
SBP (mmHg)	placebo	3756	-2.69	-3.48	-1.89
	cand.cil.	3774	-5.95	-6.70	-5.19
Pulse Pressure (mmHg)	placebo	3755	-0.42	-1.05	0.21
	cand.cil.	3774	-2.22	-2.83	-1.62
Heart rate (bpm)	placebo	3756	0.22	-0.30	0.73
	cand.cil.	3773	0.37	-0.12	0.86

Table 268 Comparison for Change in BP variables with Region as an ANOVA factor for the total population. ITT/Safety Population. (SH-AHS-0003, -0006, -0007)

Variable	Comparison	Estimated Mean	95% CI		p-value
			Lower	Upper	
DBP (mmHg)	cand.cil. - placebo	-1.45	-2.08	-0.82	<0.001
SBP (mmHg)	cand.cil. - placebo	-3.26	-4.35	-2.16	<0.001
Pulse Pressure (mmHg)	cand.cil. - placebo	-1.81	-2.68	-0.93	<0.001
Heart rate (bpm)	cand.cil. - placebo	0.15	-0.56	0.86	0.680

Table 269 Number (%) of patients with decrease in SBP to ≤ 80 mm Hg or DBP to ≤40 mm Hg at any time after randomization for the total population. ITT/safety population. (SH-AHS-0003,-0006, -0007)

Abnormal Vital Sign variable	Placebo (n=3757)		Cand.cil. (n=3774)	
	N	%	N	%
DBP	50	1.3	77	2.0
SBP	109	2.9	201	5.3

Table 270 Number (%) of patients with decrease in SBP to ≤ 80 mm Hg at any time after randomization for the subpopulation. ITT/safety population. (SH-AHS-0003, -0006)

Abnormal Vital Sign variable	Placebo (n=2260)		Cand.cil. (n=2271)	
	N	%	N	%
SBP	87	3.8	158	7.0

Table 271 Number (%) of patients with decrease in DBP to ≤ 40 mm Hg at any time after randomization for the subpopulation. ITT/safety population. (SH-AHS-0003, -0006)

Abnormal Vital Sign variable	Placebo (n=2259)		Cand.cil. (n=2271)	
	N	%	N	%
DBP	37	1.6	58	2.6

Discussion of vital signs, physical findings and other observations related to safety in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

In the total population, blood pressure declined in both treatment groups. Mean DBP decreased 2.9 mmHg from the baseline value to the LVCF in the placebo group and 4.0 mmHg from the baseline value to the LVCF in the candesartan group. Corresponding values for SBP were 3.6 mmHg for patients treated with placebo and 6.1 mmHg for patients treated with candesartan.

The effect on blood pressure in the candesartan group was established during the first 6 months while in the placebo group a trend towards lowering could be seen for a longer time period. Mean heart rate was unchanged during study in both treatment groups. A DBP value less than 40 mmHg at any time during study was reported for 50 (1.4%) patient in the placebo group and 77 (2.0%) patients in the candesartan group. 109 (2.9%) patients treated with placebo and 201 (5.3%) patients treated with candesartan had a recorded SBP value less than 80 mmHg at any time after randomization (Table 269).

In the placebo group, mean body weight decreased by 0.4 kg from baseline to LVCF. In the candesartan population an increase of 0.3 kg was seen.

Overdose Experience

In case reports of overdose (up to 672 mg of candesartan), patient recovery was uneventful. The main manifestation of overdose is symptomatic hypotension and dizziness, which may require placing the patient supine, elevation of legs and, if required, infusion of isotonic saline solution and, sympathomimetic drugs. Candesartan is not removed by hemodialysis.

Post marketing Experience

The sponsor submits that candesartan has been available in worldwide markets for the treatment of hypertension since 1997. The majority of patients have been treated with 8 to 16 mg dose of

candesartan. Since its first approval for treatment of hypertension in 1997, the approved once/day doses of 2 to 32 mg candesartan are available in 84 countries including the United States. In Canada, a 32-mg dose in hypertension was approved in 2002. In 1998, the fixed-dose tablets of candesartan and hydrochlorothiazide was first approved; this formulation is now approved in 56 countries.

During the post marketing period, no unexpected organ-specific toxicity has been reported. Rarely reported reactions include leucopenia, neutropenia, agranulocytosis, hyperkalemia, hyponatremia, increased liver enzymes, abnormal liver function or hepatitis, angioedema, rash, urticaria, pruritus, and renal impairment including renal failure.

Adequacy of Patient Exposure and Safety Assessments

Please also see section 5.3.1 of the review (Total exposure of candesartan). The sponsor submits that the cumulative exposure to candesartan as of October 2003 exceeds 14 million patient-years.

For this NDA submission, the three pivotal (CHARM Program) efficacy trials comprise 7,601 patients (7,599 patients with data) with NYHA Class II – IV heart failure of at least 4 weeks duration who were randomized to candesartan (titrated from 4 mg or 8 mg once daily to a target dose of 32 mg once daily as tolerated) or matching placebo, and followed for at least 2 (up to 4) years. The sponsor estimated that the exposure to the investigational product totaled 18,593 patient-years, and exposure to candesartan 9,222 patient-years.

In addition to the 7,601 CHF patients in the CHARM Program clinical trials, the sponsor submitted 24 clinical studies (comprising 4,062 patients with CHF) including:

(i) 5 randomized, double-blind, placebo-controlled clinical trials with duration of 2 to 12 months, comprising a total of 1,893 patients,

(ii) one randomized, double-blind, active-treatment (enalapril)-controlled study (RESOLVD) comprising 768 patients, and

(iii) one open, uncontrolled, long-term (6 month) study comprising 355 patients,

(iv) 3 clinical pharmacology studies comprising 262 patients,

(v) 11 clinical studies comprising a total of 677 patients under the Japanese study program (for which FDA granted the sponsor a waiver from providing case report tabulations and case report forms, and 10 studies were pertinent to efficacy), and

(vi) 4 investigator-initiated clinical studies comprising 107 patients.

Thus, a total of 11,661 patients with CHF have been exposed to candesartan in the treatment of CHF in various clinical trials. About one third of these patients were women, and about 15% (1,736) were 75 years or older. About 90% of the population was Caucasian (white) and 326 patients (2.8%) were black. It appears that a representative population of patients with symptomatic CHF has been exposed to candesartan.

Extent of exposure (dose/duration)

The median time of follow up for the total population of the CHARM-Program studies was 37.7 months, and the longest follow-up time was 47.6 months. The median exposure to double-blind treatment was 34.8 months. A total of 5,360 patients (2,659 patients were in the candesartan group) received study medication for ≥ 24 months. 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.

A total of 2,028 patients were randomized into SH-AHS-0003, 2,548 patients to SH-AHS-0006 and 3,025 patients to SH-AHS 0007. The total ITT/safety population for patients with symptomatic CHF (SH-AHS-0003, SH-AHS-0006 and SH- AHS-0007) comprised 7,599 patients (2,400 females and 5,199 males) and the corresponding figures for SH-AHS-0003 and SH-AHS-0006 are 4,576 (1,188 females and 3,388 males). Two patients were randomized in error and were therefore excluded from the ITT/safety population in SH-AHS-0007 (because no investigational product was dispensed and no data were collected). Patients who received incorrect investigational product during any part of the studies (22 patients in SH-AHS-0007) are included in the analyses according to the group to which they were randomized. The incorrect investigational product administration lasted for a maximum of 21 days.

An overview of exposure in the total ITT/safety population including the numbers of patients who completed or discontinued the CHARM program is presented in Table 272. Table 273 presents the exposure and number of patients by time in the component studies.

A total of 5,360 (70.5%) received the investigational product for ≥ 24 months, among which 2,659 (69.9%) on candesartan received the investigational product for ≥ 24 months.

Table 272 Overview of exposure in patients with symptomatic CHF. ITT/Safety population (SH-AHS-0003, -0006, -0007)

		Placebo (N=3796)		Cand.cil. (N=3803)	
No. (%) of patients evaluable for safety	Male	2582	(68.0)	2617	(68.8)
	Female	1214	(32.0)	1186	(31.2)
Age (years)	<65	1642	(43.3)	1614	(42.4)
	≥65	2154	(56.7)	2189	(57.6)
	<75	2912	(76.7)	2951	(77.6)
	≥75	884	(23.3)	852	(22.4)
Race[a]	Caucasian	3507	(92.4)	3493	(91.8)
	Black	164	(4.3)	162	(4.3)
	Oriental	87	(2.3)	110	(2.9)
	Other	38	(1.0)	38	(1.0)
Exposure by discontinuation due to AE of investigational product and/or study (N and %)	Discontinued investigational product due to AEs	613	(16.1)	799	(21.0)
	Patients who withdrew consent	51	(1.3)	66	(1.7)

[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. See Section 8.3.

The median duration of patient follow-up for the total population in the CHARM program was 37.9 months for patients randomized to candesartan and 37.6 months for patients randomized to placebo (Table 273). The longest follow-up time was 47.6 months.

Table 273 Exposure and number of patients with symptomatic CHF by time in the component studies. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Period	Time	Placebo	Cand. cil.	Total
From baseline to last visit	>= 0 days	3796	3803	7599
	>= 1 months	3765	3779	7544
	>= 3 months	3707	3738	7445
	>= 6 months	3673	3721	7394
	>= 12 months	3464	3563	7027
	>= 24 months	3170	3271	6441
	>= 36 months	2157	2215	4372
	>= 48 months	0	0	0
	Patient years	10690.3	10938.2	21628.5
	Mean (months)	33.8	34.5	34.2
	Median (months)	37.6	37.9	37.7
	Min/max (months)	0.1/47.4	0.1/47.6	0.1/47.6
From baseline to last day on double-blind investigational product	>= 0 days	3796	3803	7599
	>= 1 months	3653	3660	7313
	>= 3 months	3501	3475	6976
	>= 6 months	3451	3419	6870
	>= 12 months	3105	3071	6176
	>= 24 months	2701	2659	5360
	>= 36 months	1766	1715	3481
	>= 48 months	0	0	0
	Patient years	9371.2	9221.9	18593.1
	Mean (months)	29.6	29.1	29.4
	Median (months)	35.0	34.5	34.8
	Min/max (months)	0.0/47.2	0.0/47.4	0.0/47.4

Corresponding data for the subpopulation of patients with depressed LV systolic function is shown in Table 274 and Table 275.

The median duration of patient follow-up for the two treatment groups in the subpopulation of patients with depressed LV systolic function were 40.2 and 39.9 months respectively (Table 275).

Table 274 Overview of exposure in the ITT/Safety population for the subpopulation. (SH-AHS-0003, -0006)

		Placebo (N=2287)		Cand.cil. (N=2289)	
No. (%) of patients evaluable for	Male	1691	(73.9)	1697	(74.1)
	Female	596	(26.1)	592	(25.9)
Age	<65	1028	(44.9)	1044	(45.6)
	≥65	1259	(55.1)	1245	(54.4)
	<75	1803	(78.8)	1844	(80.6)
	≥75	484	(21.2)	445	(19.4)
Race[a]	Caucasian	2098	(91.7)	2096	(91.6)
	Black	107	(4.7)	93	(4.1)
	Oriental	57	(2.5)	76	(3.3)
	Other	25	(1.1)	24	(1.0)
Exposure by study completion or	Discontinued investigational	421	(18.4)	530	(23.2)
	Discontinued the study[b]	31	(1.4)	43	(1.9)
	Completed the study	2256	(98.6)	2246	(98.1)

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.
b Patients who withdrew consent.

Table 275 Exposure and number of patients for the subpopulation by time in the study. ITT/Safety population. (SH-AHS-0003, -0006)

Period	Time	Placebo	Cand.cil.	Total
From Baseline to Last visit	>= 0 days	2287	2289	4576
	>= 1 months	2259	2269	4528
	>= 3 months	2210	2235	4445
	>= 6 months	2185	2223	4408
	>= 12 months	2023	2105	4128
	>= 24 months	1811	1894	3705
	>= 36 months	1333	1382	2715
	>= 48 months	0	0	0
	Patient years	6303.2	6503.9	12807.1
	Mean (months)	33.1	34.1	
	Median (months)	39.9	40.1	
	Min/max (months)	0.1/47.4	0.1/47.6	
From Baseline to last day on double-blind study medication	>= 0 days	2287	2289	4576
	>= 1 months	2181	2191	4372
	>= 3 months	2077	2066	4143
	>= 6 months	2048	2031	4079
	>= 12 months	1813	1798	3611
	>= 24 months	1546	1523	3069
	>= 36 months	1083	1050	2133
	>= 48 months	0	0	0
	Patient years	5513.3	5420.1	10933.4

The median exposure to the investigational product in the total population was 35.0 months in the placebo group and 34.5 months in the candesartan group.

In the total CHARM-Program population, 3,052 (80.3%) patients in the candesartan group started treatment on 4 mg once daily and 751 (19.7%) patients started on 8 mg once daily at randomization (baseline). Among patients still on the investigational product at 6 months (visit 5), (3,233 patients or 88.9% in the candesartan group and 3,301 patients 92.6% in the placebo group), 62.6% of the candesartan patients were treated with the target dose 32 mg once daily. The mean dose in the candesartan group was 24.0 mg at 6 months. At the end of treatment (LVCF) 62.3% of those still treated with candesartan (2,769, 73.1%) received 32 mg of candesartan once daily. The mean candesartan LVCF dose was 23.9 mg.

Literature

The medical literature reviewed (References, section 10) did not reveal reports of unexpected organ-specific toxicity. In this review, I have presented, with tables and figures where necessary, and discussed the information from the medical literature in the context of the data from the CHARM-Added and CHARM-Pooled Studies under each heading in the safety review template.

Additional submissions, including safety update

The sponsor submitted that there are no on-going clinical studies currently conducted under US IND 50,115, with the exception of an investigator-initiated study (BLO K016) in Germany with a planned recruitment of only 40 patients with CHF. Therefore, the sponsor does not plan to prepare/submit a 4-month safety update.

Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

This section summarizes AEs of special interest relevant to blockade of RAAS in the treatment of CHF by using AT_1-receptor blockers (ARBs) and ACE inhibitors. These AEs of special interest include hypotension, abnormal renal function or worsening of renal function, hyperkalemia, angioedema and myocardial ischemia. In addition, a brief description of abnormal hepatic function and neoplasms reported in the safety report is presented.

Hypotensive events

'Hypotension' as an adverse clinical event include a composite of the following AAED preferred terms: 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 slightly more patients in the candesartan treatment group with SBP < 100 mmHg (placebo 92, 2.4%; candesartan 126, 3.3%) (North American study population).

AEs suggesting a 'hypotensive' event were reported more frequently in the candesartan group (875, 23.0%) than in the placebo group (519, 13.7%) for patients than on treatment with the investigational product (Table 276).

Table 276 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-0003, -0006, -0007)

Placebo on treatment (N=3796)	Cand. cil. on treatment (N=3803)	Placebo during study (N=3796)	Cand. cil. during study (N=3803)
519 (13.7)	875 (23.0)	560 (14.8)	914 (24.1)

The individual AE term contributing the largest numbers to this composite AE was hypotension, which was reported for 372 (9.8%) patients given placebo and 714 (18.8%) patients given candesartan (Table 277).

Table 277 Number (%) of patients with symptomatic CHF with the most commonly reported[a] AEs, sorted by descending frequency in the total population during study. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Preferred term	Placebo on treatment (N=3796)		Cand. cil. on treatment (N=3803)		Placebo during study (N=3796)		Cand. cil. during study (N=3803)	
	N	(%)	N	(%)	N	(%)	N	(%)
Cardiac failure/cardiac failure aggravated[b]	1073	(28.3)	831	(21.9)	1187	(31.3)	1001	(26.3)
Hypotension	372	(9.8)	714	(18.8)	399	(10.5)	736	(19.4)
Angina pectoris/angina pectoris aggravated[b]	461	(12.1)	414	(10.9)	506	(13.3)	490	(12.9)
Renal function abnormal/renal dysfunction aggravated[b]	238	(6.3)	474	(12.5)	248	(6.5)	487	(12.8)
Sudden death	282	(7.4)	234	(6.2)	348	(9.2)	291	(7.7)
Pneumonia	243	(6.4)	200	(5.3)	299	(7.9)	261	(6.9)
Myocardial infarction	216	(5.7)	205	(5.4)	257	(6.8)	242	(6.4)
Fibrillation atrial	218	(5.7)	165	(4.3)	249	(6.6)	202	(5.3)
Arrhythmia ventricular	207	(5.5)	159	(4.2)	239	(6.3)	193	(5.1)
Cerebrovascular disorder	189	(5.0)	164	(4.3)	216	(5.7)	203	(5.3)
Coronary artery disorder	170	(4.5)	169	(4.4)	200	(5.3)	205	(5.4)
Chest pain	177	(4.7)	154	(4.0)	202	(5.3)	183	(4.8)
Arrhythmia atrial	175	(4.6)	156	(4.1)	197	(5.2)	187	(4.9)
Hyperkalaemia	78	(2.1)	238	(6.3)	84	(2.2)	242	(6.4)
Tachycardia supraventricular	152	(4.0)	129	(3.4)	177	(4.7)	148	(3.9)
Dizziness/vertigo[b]	107	(2.8)	154	(4.0)	115	(3.0)	168	(4.4)
Accident and/or injury	112	(3.0)	99	(2.6)	143	(3.8)	125	(3.3)
Tachycardia ventricular/arrhythmia/arrhythmia aggravated[b]	110	(2.9)	100	(2.6)	132	(3.5)	128	(3.4)
Syncope	105	(2.8)	121	(3.2)	119	(3.1)	139	(3.7)
Anaemia	87	(2.3)	110	(2.9)	110	(2.9)	145	(3.8)

a This table uses a cut-off of ≥3.0% in the total population during study (N=7599).

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

A fatal hypotensive event was reported in a comparable proportion of patients in each treatment group (Table 278). In both treatment groups, hypotensive events that led to death were reported in association with other causes of death; notably in the candesartan patients, associated events included electromechanical dissociation, ventricular tachycardia and gastrointestinal bleeding, and were thus assessed by the investigators as unlikely related to the investigational product.

Table 278 Number (%) of patients with fatal preferred terms hypotension, hypotension postural, dizziness/ vertigo, syncope, circulatory failure or collapse not otherwise specified (NOS). ITT/ Safety population (SH-AHS-0003, -0006, -0007)

Placebo on treatment (N=3796)	Cand.cil on treatment (N =3803)	Placebo during study (N =3796)	Cand.cil during study (N =3803)
5 (0.1)	6 (0.2)	10 (0.3)	12 (0.3)

As noted in the descriptive analysis for the total population, the investigational product was discontinued for hypotension in 76 (2.0%) placebo patients and 155 (4.1%) candesartan patients (Table 250). Corresponding figures for the exploratory analysis were 66 (1.7%) placebo patients and 132 (3.5%) candesartan patients (Table 253). The higher proportion of permanent discontinuation of the investigational product due to hypotensive events in the candesartan group could not be explained by higher use of concomitant medication when the event started,

including diuretics, β-blockers and ACE-inhibitors. Among the patients that discontinued the investigational product due to hypotensive events, a greater proportion had SBP < 100 mmHg at baseline in the candesartan group (placebo, 7.5%; candesartan, 13.6%).

In patients aged < 75 years, discontinuation because of hypotension was reported in 48 (1.6%) patients in the placebo group and 111 (3.8%) patients on candesartan. For patients aged ≥ 75 years the discontinuation rates were 28 (3.2%) patients in the placebo group and 44 (5.2%) patients in the candesartan group. Permanent discontinuation of the investigational product due to hypotension was reported in 56 (2.2%) males and 20 (1.6%) females in the placebo group, and 107 (4.1%) males and 48 (4.0%) females in the candesartan treatment group.

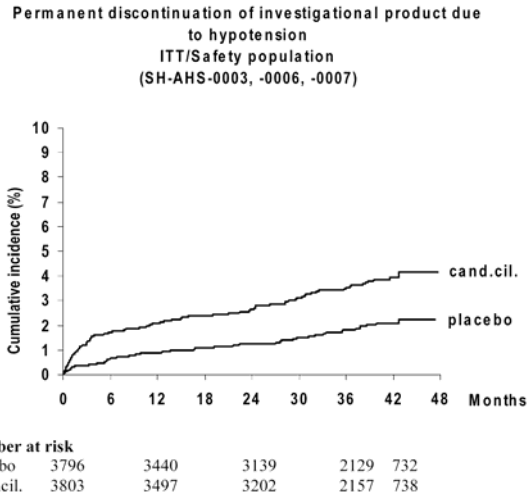


Figure 124 Cumulative incidence (%) of permanent discontinuation of the investigational product due to hypotension. ITT/Safety population

Although patients in both treatment groups discontinued taking the investigational product because of hypotension over the entire study period, the candesartan discontinuation rate shown in the exploratory analysis, was greatest during the first 6 to 12 months of treatment (Figure 124).

Among the 1,075 (28.3%) placebo patients and 1,088 (28.6%) candesartan patients entering the study with a history of diabetes, investigational product discontinuation for hypotension was noted for 22 (2.0%) placebo patients and 34 (3.1%) candesartan patients.

Abnormal renal function

To summarize abnormal renal function, the following AAED preferred terms were selected and analyzed as a single composite event: renal function, abnormal/renal dysfunction, aggravated; renal failure acute; renal failure, NOS; uremia; non-protein nitrogen, increased; renal failure, aggravated; blood urea nitrogen, increased; increased creatinine, acute pre-renal failure and anuria. For this composite AE, patients with multiple events of any of the selected AE terms were counted only once.

At baseline, there were more patients in the candesartan group with serum creatinine > 2.0 mg/ dl (placebo 70, 5.2%; candesartan 84, 6.3%) (North American study population).

AEs suggesting 'abnormal renal function' occurred in 349 (9.2%) in the placebo group and 576 (15.1%) patients in the candesartan group during study (Table 279).

Table 279 Number (%) of patients with any of the preferred terms renal function abnormal/renal dysfunction aggravated, renal failure acute, renal failure NOS, uremia, non-protein nitrogen increased, renal failure aggravated, blood urea nitrogen increased, acute pre-renal failure or anuria. ITT/Safety population (SH-AHS-0003, -0006 and -0007)

Placebo on treatment (N=3796)	Cand. cil. on treatment (N=3803)	Placebo during study (N=3796)	Cand. cil. during study (N=3803)
316 (8.3)	546 (14.4)	349 (9.2)	576 (15.1)

The AE terms that predominately contributed to this composite AE term was renal function abnormal which was reported in 247 (6.5%) of patients given placebo and 485 (12.8%) given candesartan during study. Renal failure, acute (placebo, 91 patients, 2.4%; candesartan, 121 patients, 3.2%) and uremia (placebo, 28 patients, 0.7%; candesartan, 43 patients, 1.1%) were also numerically more frequently in patients given active treatment.

Table 280 Number (%) of patients with fatal renal function, abnormal/renal dysfunction, aggravated, renal failure acute, renal failure, NOS, uremia, non-protein nitrogen increased, renal failure aggravated, blood urea nitrogen increased, acute pre-renal failure or anuria. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Placebo on treatment (N=3796)	Cand.cil on treatment (N=3803)	Placebo during study (N=3796)	Cand.cil during study (N=3803)
18 (0.5)	7 (0.2)	41 (1.1)	36 (0.9)

Fatal renal function events 'during study' and 'on treatment' were reported for a higher proportion of patients in the placebo group (Table 280). In both treatment groups, the majority of renal events that led to death were reported in association with other causes of death such as worsening heart failure.

In the descriptive safety analysis, renal function abnormal/renal dysfunction aggravated was the second most common reason for permanent discontinuation of the investigational product (second only to cardiac failure aggravated,) in both treatment groups (placebo 110, 2.9%; candesartan 238, 6.3%) (Table 250). In the exploratory analysis the term increased creatinine was reported for 115 (3.0%) placebo patients and 234 (6.2%) candesartan patients (Table 253). The higher discontinuation rate for 'abnormal renal function' in the candesartan group could not be explained by between-treatment differences in concomitant medications when the event started or baseline serum creatinine levels (North American study population) (Table 281).

Table 281 Permanent discontinuation due to pooled adverse events related to abnormal renal function[a] or hypotensive events[b] or hyperkalemia[c] on treatment with candesartan cilexetil or placebo. Specified concomitant medication at the start of the event. ITT/safety population (SH-AHS-0003, -0006, -0007)[d]

	Placebo Abn renal N=126		Cand cil Abn renal N=266		Placebo Hypotensive N=93		Cand cil Hypotensive N=188		Placebo Hyperkalae N=22		Cand cil Hyperkalae N=93	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Loop diuretics	117	(92.9)	258	(97.0)	83	(89.2)	169	(89.9)	20	(90.9)	84	(90.3)
Potassium - sparing diuretics	59	(46.8)	105	(39.5)	29	(31.2)	80	(42.6)	10	(45.5)	34	(36.6)
Thiazide diuretics	22	(17.5)	52	(19.5)	22	(23.7)	35	(18.6)	3	(13.6)	11	(11.8)
Any β-blocker	72	(57.1)	146	(54.9)	54	(58.1)	93	(49.5)	13	(59.1)	54	(58.1)
Calcium channel blocker	36	(28.6)	67	(25.2)	11	(11.8)	29	(15.4)	1	(4.5)	23	(24.7)
Any ACE-inhibitor	79	(62.7)	141	(53.0)	63	(67.7)	88	(46.8)	18	(81.8)	59	(63.4)

a Preferred terms included in abnormal renal function: Renal function abnormal/renal dysfunction aggravated, renal failure acute, renal failure nos, uraemia, non-protein nitrogen increased, renal failure aggravated, acute pre-renal failure or anuria.
b Preferred terms included in hypotensive events: Hypotension, hypotension postural, dizziness/vertigo, syncope, circulatory failure or collapse not otherwise specified (nos).
c Hyperkalaemia is a single Preferred term.
d Exploratory safety analysis

In patients aged younger than 75 years, discontinuation because renal function abnormal/renal dysfunction aggravated was reported in 75 (2.6%) patients in the placebo group and 171 (5.8%) patients in the candesartan group on treatment with the investigational product. For patients aged 75 years or older the discontinuation rates were 35 (4.0%) patients in the placebo group and 67 (7.9%) patients in the candesartan group. In the placebo group the majority of events were seen in male patients (81, 3.1%) compared to 29 (2.4%) female patients. Corresponding values for the candesartan treatment group were 169 (6.5%) males and 69 (5.8%) females. The majority of patients in both treatment groups were Caucasians.

As shown in the exploratory analysis, patients discontinued study treatment because of 'increased creatinine' over the entire study period, and the rate was greater for candesartan-treated patients (Figure 125).

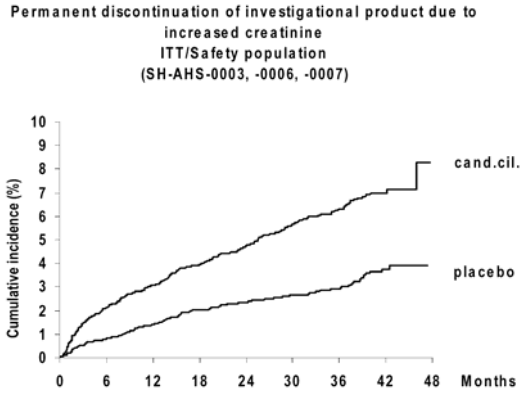


Figure 125 Cumulative incidence (%) of permanent discontinuation of the investigational product due to increased creatinine. ITT/Safety population

Among the 1,075 (28.3%) placebo patients and 1,088 (28.6%) candesartan patients entering the CHARM program study with a history of diabetes, investigational product discontinuation for increased creatinine was noted for 57 (5.3%) placebo and 99 (9.1%) candesartan patients (Table 257 and Table 258). Compared to the total population (placebo 3.0%, candesartan 6.2%) (Table 253), diabetic patients were slightly more likely to discontinue the investigational product for increased creatinine levels.

Hyperkalemia

Hyperkalemia is reported as observed 'on treatment' rather than 'during study' to present a more clinically meaningful measure of possible relationship to the investigational product.

At baseline, there were more patients in the candesartan treatment group with serum potassium = 5 mmol/L (placebo 125, 9.3%; candesartan 135, 10.1%) (North American study population).

Hyperkalemia was reported for 78 patients (2.1%) in the placebo group and 238 patients (6.3%) in the candesartan group on treatment with the investigational product (Table 262).

Fatal hyperkalemia 'during study' was reported for 2 patients in the candesartan group, and in 1 patient in the placebo group. Both candesartan treated patients were on active treatment in SH-AHS-0006 as described above. The one patient in the placebo group in SH-AHS-0003 was not on treatment with the investigational product and had concomitant renal failure (with an increase in serum creatinine) which could have contributed to the hyperkalemia.

In Table 250, discontinuation of the investigational product because of hyperkalemia occurred more frequently in patients treated with candesartan (placebo 22, 0.6%; candesartan 93, 2.4%). In the exploratory analysis the corresponding numbers were 21 (0.6%) for placebo patients and 85 (2.2%) for candesartan patients (Table 253). The higher rate for hyperkalemia causing discontinuation in the candesartan group could not be explained by between treatment differences in concomitant medications at the start of the event, including potassium – sparing diuretics or baseline serum potassium levels (North American study population) (Table 281).

In patients aged younger than 75 years, discontinuation because of the AE term hyperkalemia was reported in 14 (0.5%) patients in the placebo group and 57 (1.9%) patients on candesartan. For patients aged 75 years or older the discontinuation rates were 8 (0.9%) patients in the placebo group and 36 (4.2%) patients in the candesartan group. In the placebo treatment group 16 (0.6%) males and 6 (0.5%) females discontinued due to hyperkalemia. In the candesartan group the majority of events were seen in male patients (72, 2.8%) compared to female patients (21, 1.8%).

The discontinuation rate for candesartan-treated patients because of hyperkalemia, presented from exploratory analysis, (Figure 126), was somewhat greater during the first 6 to 12 months of treatment, but discontinuations still occurred over the entire study period.

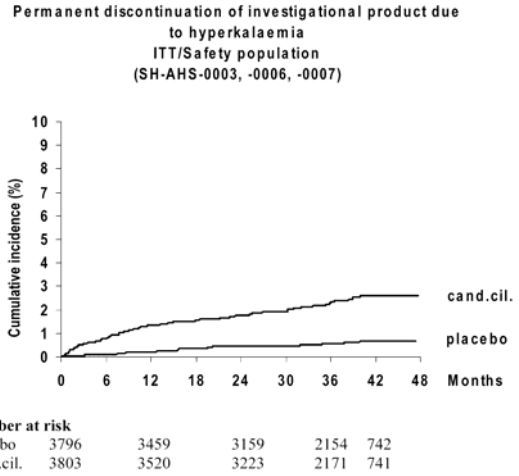


Figure 126 Cumulative incidence (%) of permanent discontinuation of the investigational product due to hyperkalemia. ITT/ Safety population

Among the 1,075 (28.3%) placebo patients and 1,088 (28.6%) candesartan patients entering the CHARM program with a history of diabetes, investigational product discontinuation for the specific preferred term hyperkalemia was noted for 13 (1.2%) placebo and 31 (2.8%) candesartan patients (Table 257 and Table 258).

Angioedema

During study 5 cases of angioedema were reported for patients in the candesartan group compared with 3 cases in the placebo treatment group.

All patients in the candesartan treatment group were Caucasian. Three of these patients in the candesartan group had a history of previous angioedema reactions while taking ACE-inhibitors. The remaining two patients in the candesartan group had concomitant medication with an ACE-inhibitor at the start of the event. None of the events was considered life threatening or led to hospitalization. Two patients who developed angioedema required discontinuation of candesartan treatment. For the remaining 3 patients with angioedema, candesartan treatment continued without recurrence of angioedema, and for 1 of these the dose was reduced.

Myocardial ischemia

'Myocardial ischemia' was evaluated as a composite of the AAED preferred terms: angina pectoris/angina pectoris aggravated, MI and coronary artery disorder. For this composite AE, patients with multiple events including any of the selected AE terms were counted only once.

At baseline prior to enrollment, there were no differences between the treatment groups in the frequencies of patients with previous MI and angina pectoris. Slightly more patients in the candesartan treatment group reported a history of coronary artery bypass grafting (placebo 870, 22.9%; candesartan 921, 24.2%).

The proportions of patients with 'myocardial ischemia' 'on treatment' were approximately equal

in the two groups (18.1% in the placebo vs. 16.7% in the candesartan group) (Table 282).

Table 282 Number (%) of patients with any of the preferred terms angina pectoris/angina pectoris aggravated, myocardial infarction or coronary artery disorder. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Placebo on treatment (N=3796)	Cand. cil. on treatment (N=3803)	Placebo during study (N=3796)	Cand. cil. during study (N=3803)
688 (18.1)	637 (16.7)	774 (20.4)	755 (19.9)

The AE term accounting for the greatest number of patients in this composite AE was angina pectoris which was more frequently reported in the placebo treatment group (placebo 460, 12.1%; candesartan 405, 10.6%). The AE term MI occurred in 216 (5.7%) patients in the placebo group and in 205 (5.4%) in the candesartan group 'on treatment.'

'Myocardial ischemic' events that were fatal were reported for 70 (1.8%) patients in the placebo group and 97 (2.6%) patients in the candesartan group during study (Table 283).

Table 283 Number (%) of patients with any of the preferred terms angina pectoris/angina pectoris aggravated, myocardial infarction or coronary artery disorder leading to death. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Placebo on treatment (N=3796)	Cand. cil. on treatment (N=3803)	Placebo during study (N=3796)	Cand. cil. during study (N=3803)
44 (1.2)	66 (1.7)	70 (1.8)	97 (2.6)

Most of the fatal 'myocardial ischemic' events 'during study' were attributed to fatal MI (57 patients in the placebo group and 77 in the candesartan group).

Abnormal hepatic function

The most common AE terms suggesting liver dysfunction were hepatic enzymes, increased NOS and hepatic function, abnormal; which were reported for 7 and 4 patients, respectively, given placebo treatment and 12 and 10 patients, respectively, given candesartan. The AE term hepatic failure was reported for 5 patients in the placebo group and 6 patients in the candesartan group.

In the candesartan group there was one fatal case of hepatic necrosis which the investigator and the sponsor considered related to amiodarone (SH-AHS-0003-373-15108), and one fatal case of cholestatic hepatitis considered related to septic cholangitis (SH-AHS-0003-1476-21109).

Neoplasms

AEs indicative of neoplasms, whether benign or malignant, were pooled from the SOC (system organ class) 'Neoplasms', plus 3 neoplastic AE terms from other SOCs (Melanoma malignant, Myelomatosis multiple and Pleural mesothelioma).

In the total population slightly more patients in the candesartan treatment group had a history of cancer at baseline (placebo 243, 6.4%, candesartan 270, 7.1%).

Neoplasms were reported for 230 (6.0%) in the placebo group and 244 (6.4%) in the candesartan group. One patient in the placebo group in the component study SH-AHS-0003 (Site 558, Patient number 13436) had Breast neoplasm malignant female and Carcinomatosis (included in the SOC Neoplasms) together with Pleural mesothelioma. One patient in the candesartan group in the component study SH-AHS-0006 (Site 1532, Patient number 21520) had both Myeloid metaplasia (included in the SOC Neoplasms) and Myelomatosis multiple. In the total numbers presented above these patients are counted only once. Neoplasms proved fatal for 59 patients (1.8%) in the placebo group and 84 patients (2.2%) in the candesartan group.

The majority of reported neoplasms were malignant. The most common neoplasm's were prostatic carcinoma (placebo, 27 patients; candesartan, 32 patients), pulmonary carcinoma (placebo, 25 patients; candesartan, 31 patients), colon carcinoma (placebo, 24 patients; candesartan, 26 patients) and breast neoplasm malignant (17 patients in each group). The AE term 'gastrointestinal neoplasm benign' had a higher event rate in the candesartan group during study (placebo, 5; candesartan, 19) whereas 'renal carcinoma' was more frequent in the control group (placebo, 11; candesartan, 5).

Rare Adverse events in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

Rare adverse events reported include:

- pancytopenia (placebo 1 patient; candesartan 3 patients),
- aplastic anemia (candesartan 1 patient),
- anaphylactic shock and anaphylactoid reaction (placebo 1 patient; candesartan 2 patients),
- Stevens- Johnson syndrome (placebo 2 patients),
- rhabdomyolysis (placebo 2 patients; candesartan 3 patients),
- sarcoidosis (candesartan 2 patients), and
- scleroderma (candesartan 1 patient).

In most cases an alternative cause was identified. There was no sufficient evidence to support a causal relationship to the investigational product.

Summary of Safety

Summary of safety for CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies

Summary of safety in the total population of patients with symptomatic CHF (SH-AHS-0003, 0006, 0007)

In the total population of patients with symptomatic CHF (SH-AHS-0003, SH-AHS-0006, SH-AHS-0007) AEs were reported for almost equal proportions of patients in the two treatment groups, both during treatment with the investigational drug (placebo 2732, 72.0%; candesartan 2788, 73.3%) and over the entire study period (placebo 2799, 73.7%; candesartan 2841, 74.7%).

SAEs, fatal and non-fatal, occurred less frequently on treatment with candesartan than with placebo (placebo 67.5%; candesartan 63.4%) as well as during the study, whether on or off treatment (placebo 71.1%; candesartan 69.0%). Fatal SAEs were also less common on treatment with candesartan (placebo 16.2%; candesartan 13.3%) as well as during the study (placebo 24.9%; candesartan 23.3%). The most common fatal SAEs were CV events which occurred less frequently in the candesartan treatment group during study (placebo 20.3%; candesartan 18.2%)

16.1% in the placebo group and 21.0% of the patients in the candesartan group permanently discontinued the investigational product due to an AE or an abnormal laboratory finding.

8.5% of the patients receiving placebo and 15.0% of the patients receiving candesartan required a reduction in the investigational product dose.

Discontinuations and dose reductions attributed to decline in renal function, hypotension and hyperkalemia were more frequent in the candesartan group. Cardiac failure aggravated (placebo 4.9%; candesartan 4.3%), abnormal renal function (placebo 2.9%; candesartan 6.3%), hypotension (placebo 2.0%; candesartan 4.1%) and hyperkalemia (placebo 0.6%; candesartan 2.4%) were the most commonly reported AEs associated with discontinuation of the investigational product.

The differences in mean laboratory values (candesartan compared with placebo), and the frequency of abnormal values were within expected findings for treatment with inhibitors of the RAAS, i.e., slightly higher serum potassium and creatinine levels.

Mean blood pressure from baseline to LVCF (SBP and DBP) was lowered in both treatment groups.

Mean body weight was slightly decreased in the placebo group and increased in the candesartan group.

Summary of safety in the population of patients with depressed LV systolic function (SH-AHS 0003, 0006)

The safety findings in the subpopulation of patients with depressed LV systolic function (SHAHS-0003, SH-AHS-0006) were similar to those in the total population, although the absolute AE rate in the patients with depressed LV systolic function were somewhat higher than in the total population. Between-treatment differences (candesartan versus placebo) were very similar to those noted for the total population.

AEs were reported for approximately equal numbers of patients in the two treatment groups (placebo 76.0%; candesartan 77.2%), over the entire study period.

SAEs, fatal and non-fatal, occurred less frequently with candesartan treatment (placebo 70.2%; candesartan 65.8%). Fatal SAEs were also less common with candesartan treatment (placebo 20.2%; candesartan 16.4%). The most common fatal SAEs were CV events.

18.4% in the placebo group and 23.2%of the patients in the candesartan group permanently discontinued treatment with the investigational product due to an AE or an abnormal laboratory finding.

Discontinuations and dose reductions attributed to decline in renal function, hypotension and hyperkalemia were more frequent in the candesartan group. Abnormal renal function (placebo, 3.4%; candesartan, 7.4%), hypotension (placebo, 2.5%; candesartan, 5.0%) and hyperkalemia (placebo, 0.6%; candesartan, 3.1%) were the most commonly reported AEs associated with discontinuation of the investigational product. In the candesartan group the frequency of discontinuation for hyperkalemia relative to placebo was greater in the oldest age groups.

The following findings are significantly different between the two treatment groups:

- Candesartan reduced *time* to permanent discontinuation of investigational product due to any cause ($p < 0.001$).
- Candesartan increased the *number* of investigational product discontinuations due to any cause ($p < 0.001$).
- Candesartan reduced *time* to permanent discontinuation of investigational product due to an AE or an abnormal laboratory value ($p < 0.001$).
- Candesartan increased the *number* of permanent investigational product discontinuations due to an AE or an abnormal laboratory value ($p < 0.001$).
- Candesartan increased the *number* of dose reductions due to any cause ($p < 0.001$).
- Candesartan increased the *number* of dose reductions due to an AE or an abnormal laboratory value ($p < 0.001$).

Thus, candesartan appears to be safe and well tolerated. Discontinuations and dose reductions attributed to a decline in renal function, hypotension and hyperkalemia occur more frequently with candesartan than placebo. The AE profile of candesartan in heart failure patients is consistent with the pharmacology of the drug and the health status of the patients.

Overall conclusions

Candesartan appears to be safe and well tolerated in this population of patients with chronic heart failure. Discontinuations and dose reductions attributed to a decline in renal function, hypotension and hyperkalemia occur more frequently with candesartan than placebo. The AE profile of candesartan in heart failure patients is consistent with the pharmacology of the drug and the health status of the patients.

10.2 Line-by-Line Labeling Review

NDA 20-838

The prescribing information has been updated to include information for the heart failure supplemental New Drug Application.

Additions are indication by double underlining and deletions are indicated by ~~strikethrough~~.

Reviewer's annotations are in italics, with shaded background, and additions are also wriggly underlined.

XXXXX-XX

ATACAND®
(candesartan cilexetil)
TABLETS

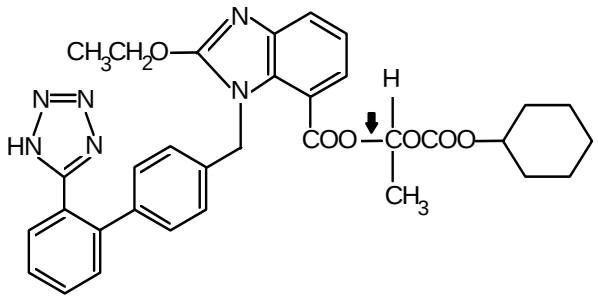
USE IN PREGNANCY-
When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, ATACAND should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

ATACAND® (candesartan cilexetil), a prodrug, is hydrolyzed to candesartan during absorption from the gastrointestinal tract. Candesartan is a selective AT_1 subtype angiotensin II receptor antagonist.

Candesartan cilexetil, a nonpeptide, is chemically described as (±)-1-Hydroxyethyl 2-ethoxy-1-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]-7-benzimidazolecarboxylate, cyclohexyl carbonate (ester).

Its empirical formula is $C_{33}H_{34}N_6O_6$, and its structural formula is



⬇ site of ester hydrolysis.

Candesartan cilexetil is a white to off-white powder with a molecular weight of 610.67. It is practically insoluble in water and sparingly soluble in methanol. Candesartan cilexetil is a racemic mixture containing one chiral center at the cyclohexyloxycarbonyloxy ethyl ester group. Following oral administration, candesartan cilexetil undergoes hydrolysis at the ester link to form the active drug, candesartan, which is achiral.

ATACAND is available for oral use as tablets containing either 4 mg, 8 mg, 16 mg, or 32 mg of candesartan cilexetil and the following inactive ingredients: hydroxypropyl cellulose, polyethylene glycol, lactose, corn starch, carboxymethylcellulose calcium, and magnesium stearate. Ferric oxide (reddish brown) is added to the 8-mg, 16-mg, and 32-mg tablets as a colorant.

CLINICAL PHARMACOLOGY

Mechanism of Action

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Candesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is, therefore, independent of the pathways for angiotensin II synthesis.

There is also an AT_2 receptor found in many tissues, but AT_2 is not known to be associated with cardiovascular homeostasis. Candesartan has much greater affinity (>10,000-fold) for the AT_1 receptor than for the AT_2 receptor.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because candesartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Candesartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of candesartan on blood pressure.

Pharmacokinetics

General

Candesartan cilexetil is rapidly and completely bioactivated by ester hydrolysis during absorption from the gastrointestinal tract to candesartan, a selective AT_1 subtype angiotensin II receptor antagonist. Candesartan is mainly excreted unchanged in urine and feces (via bile). It undergoes minor hepatic metabolism by O-deethylation to an inactive metabolite. The elimination half-life of candesartan is approximately 9 hours. After single and repeated administration, the pharmacokinetics of candesartan are linear for oral doses up to 32 mg of candesartan cilexetil. Candesartan and its inactive metabolite do not accumulate in serum upon repeated once-daily dosing.

Following administration of candesartan cilexetil, the absolute bioavailability of candesartan was estimated to be 15%. After tablet ingestion, the peak serum concentration (C_{max}) is reached after 3 to 4 hours. Food with a high fat content does not affect the bioavailability of candesartan after candesartan cilexetil administration.

Metabolism and Excretion

Total plasma clearance of candesartan is 0.37 mL/min/kg, with a renal clearance of 0.19 mL/min/kg. When candesartan is administered orally, about 26% of the dose is excreted unchanged in urine. Following an oral dose of ^{14}C-labeled

candesartan cilexetil, approximately 33% of radioactivity is recovered in urine and approximately 67% in feces. Following an intravenous dose of ^{14}C-labeled candesartan, approximately 59% of radioactivity is recovered in urine and approximately 36% in feces. Biliary excretion contributes to the elimination of candesartan.

Distribution

The volume of distribution of candesartan is 0.13 L/kg. Candesartan is highly bound to plasma proteins (>99%) and does not penetrate red blood cells. The protein binding is constant at candesartan plasma concentrations well above the range achieved with recommended doses. In rats, it has been demonstrated that candesartan crosses the blood-brain barrier poorly, if at all. It has also been demonstrated in rats that candesartan passes across the placental barrier and is distributed in the fetus.

Special Populations

Pediatric — The pharmacokinetics of candesartan cilexetil have not been investigated in patients <18 years of age.

Geriatric and Gender— The pharmacokinetics of candesartan have been studied in the elderly (≥ 65 years) and in both sexes. The plasma concentration of candesartan was higher in the elderly (C_{max} was approximately 50% higher, and AUC was approximately 80% higher) compared to younger subjects administered the same dose. The pharmacokinetics of candesartan were linear in the elderly, and candesartan and its inactive metabolite did not accumulate in the serum of these subjects upon repeated, once-daily administration. No initial dosage adjustment is necessary. (See DOSAGE AND ADMINISTRATION.) There is no difference in the pharmacokinetics of candesartan between male and female subjects.

Renal Insufficiency— In hypertensive patients with renal insufficiency, serum concentrations of candesartan were elevated. After repeated dosing, the AUC and C_{max} were approximately doubled in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73m^2) compared to patients with normal kidney function. The pharmacokinetics of candesartan in hypertensive patients undergoing hemodialysis are similar to those in hypertensive

patients with severe renal impairment. Candesartan cannot be removed by hemodialysis. No initial dosage adjustment is necessary in patients with renal insufficiency. (See DOSAGE AND ADMINISTRATION.)

Hepatic Insufficiency— The pharmacokinetics of candesartan were compared in patients with mild and moderate hepatic impairment to matched healthy volunteers following a single oral dose of 16 mg candesartan cilexetil. The increase in AUC for candesartan was 30% in patients with mild hepatic impairment (Child-Pugh A) and 145% in patients with moderate hepatic impairment (Child-Pugh B). The increase in C_{max} for candesartan was 56% in patients with mild hepatic impairment and 73% in patients with moderate hepatic impairment. The pharmacokinetics after candesartan cilexetil administration have not been investigated in patients with severe hepatic impairment. No initial dosage adjustment is necessary in patients with mild hepatic impairment. In hypertensive patients with moderate hepatic impairment, consideration should be given to initiation of ATACAND at a lower dose. (See DOSAGE AND ADMINISTRATION.)

Editorial

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. (See DOSAGE AND ADMINISTRATION, Heart Failure).[1]

[1] Module 2, Clinical Summary: Summary of Clinical Pharmacology Studies, 2.7.2.3, Figures 1 and 2, Clinical Study Report EC002, 4.6.1 submitted in original NDA

Studies EC602, EC605-A and EC608 (reviewer's addition)

Drug Interactions

See PRECAUTIONS, Drug Interactions.

Pharmacodynamics

Candesartan inhibits the pressor effects of angiotensin II infusion in a dose-dependent manner. After 1 week of once daily dosing with 8 mg of candesartan cilexetil, the pressor effect was inhibited by approximately 90% at peak with approximately 50% inhibition persisting for 24 hours.

Plasma concentrations of angiotensin I and angiotensin II, and plasma renin activity (PRA), increased in a dose-dependent manner after single and repeated administration of candesartan cilexetil to healthy subjects, hypertensive, and heart failure patients.[2] ACE activity was not altered in healthy subjects after repeated candesartan cilexetil administration. The once-daily administration of up to 16 mg of candesartan cilexetil to healthy subjects did not influence plasma aldosterone concentrations, but a decrease in the plasma concentration of aldosterone was observed when 32 mg of candesartan cilexetil was administered to hypertensive patients. In spite of the effect of candesartan cilexetil on aldosterone secretion, very little effect on serum potassium was observed.

[2] Clinical Study Report EC604, 7.4.1 and Clinical Study Report EC605. 7.4.1.3

In multiple-dose studies with hypertensive patients, there were no clinically significant changes in metabolic function, including serum levels of total cholesterol, triglycerides, glucose, or uric acid. In a 12-week study of 161 patients with non-insulin-dependent (type 2) diabetes mellitus and hypertension, there was no change in the level of HbA_{1c}.

[3]Clinical Study Report EC605, 7.4.1.3 and Clinical Study Report EC604, 7.4.1

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.[3]

Studies: EC602 and 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.[4,5] 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.[6]

[4]McKelvie RS, *Yusuf S, Pericak D,* et al. Circulation 1999; 100: 1056-64.

[5]Clinical study Report SH-AHS-0001,11.4.1.5 *(RESOLVD)*

[6]McKelvie RS, *Rouleau JL, White M,* et al. Eur Heart J 2003; 24:1727-34.

Reviewer's additions are based on data from the same above references.

Clinical Trials

Hypertension

The antihypertensive effects of ATACAND were examined in 14 placebo-controlled trials of 4- to 12-weeks duration, primarily at daily doses of 2 to 32 mg per day in patients with baseline diastolic blood pressures of 95 to 114 mm Hg. Most of the trials were of candesartan cilexetil as a single agent, but it was also studied as add-on to hydrochlorothiazide and

amlodipine. These studies included a total of 2350 patients randomized to one of several doses of candesartan cilexetil and 1027 to placebo. Except for a study in diabetics, all studies showed significant effects, generally dose related, of 2 to 32 mg on trough (24 hour) systolic and diastolic pressures compared to placebo, with doses of 8 to 32 mg giving effects of about 8-12/4-8 mm Hg. There were no exaggerated first-dose effects in these patients. Most of the antihypertensive effect was seen within 2 weeks of initial dosing and the full effect in 4 weeks. With once-daily dosing, blood pressure effect was maintained over 24 hours, with trough to peak ratios of blood pressure effect generally over 80%. Candesartan cilexetil had an additional blood pressure lowering effect when added to hydrochlorothiazide.

The antihypertensive effects of candesartan cilexetil and losartan potassium at their highest recommended doses administered once- daily were compared in two randomized, double-blind trials. In a total of 1268 patients with mild to moderate hypertension who were not receiving other antihypertensive therapy, candesartan cilexetil 32 mg lowered systolic and diastolic blood pressure by 2 to 3 mm Hg on average more than losartan potassium 100 mg, when measured at the time of either peak or trough effect. The antihypertensive effects of twice daily dosing of either candesartan cilexetil or losartan potassium were not studied.

The antihypertensive effect was similar in men and women and in patients older and younger than 65. Candesartan was effective in reducing blood pressure regardless of race, although the effect was somewhat less in blacks (usually a low-renin population). This has been generally true for angiotensin II antagonists and ACE inhibitors.

In long-term studies of up to 1 year, the antihypertensive effectiveness of candesartan cilexetil was maintained, and there was no rebound after abrupt withdrawal.

There were no changes in the heart rate of patients treated with candesartan cilexetil in controlled trials.

Heart Failure

Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity (CHARM) was an international (26

countries including the US) program comprised of 3 independent concurrent double-blind, placebo-controlled trials in which a total of 7601 patients (7599 with data) with NYHA class II - IV heart failure of at least 4 weeks duration, on standard baseline therapy, were randomized to ATACAND (titrated from 4 mg or 8 mg once daily, to a target dose of 32 mg once daily as tolerated) or matching placebo, and followed for at least 2 (up to 4) years. Patients with serum creatinine > 3 mg/dL, serum potassium > 5.5 mg/dL, symptomatic hypotension or known bilateral renal artery stenosis were to be excluded. Baseline characteristics of patients in the 3 CHARM trials are detailed in Table 1.[7]

[7]Module 2, Summary of Clinical Efficacy, 2.7.3.2.1

Table 1. CHARM: Baseline Characteristics[8]

	CHARM-Alternative	CHARM-Added	CHARM-Preserved
Number of patients	2028	2548	3023
Mean age (years)	67	64	67
Female (%)	32	21	40
NYHA class II (%)	48	24	61
III (%)	49	73	38
IV (%)	4	3	2
Mean LVEF (%)	30	28	54
Mean BP (mm Hg)	130/77	125/75	136/78
Medical history (%):			
Myocardial infarction	62	56	44
Hypertension	50	48	64
Diabetes	27	30	28
Atrial fibrillation	25	27	29
Concomitant therapy (%):			
ACE inhibitor	0	100	19
Diuretic	85	90	75
Digitalis	46	58	28
Beta-blocker	55	55	56
Spironolactone	24	17	12

[8]Module 2, Summary of Clinical Efficacy, 2.7.3.1 Table 4

The CHARM – Alternative trial included patients with LVEF ≤40% not receiving an ACE inhibitor due to prior intolerance; the CHARM – Added trial included patients with LVEF ≤40% receiving an ACE inhibitor (96% on an optimum individualized dose); and the CHARM – Preserved trial included patients with LVEF >40%. Most patients were on background diuretic therapy and about 55% on a beta-blocker in all 3 trials.[9]

[9]Module 2, Summary of Clinical Efficacy, 2.7.3.1.1.4 Table 2

The primary endpoint in each of the 3 trials, assessed as time to first event, was cardiovascular (CV) mortality or hospitalization for heart failure (defined as a hospital admission primarily for worsening of chronic heart failure [CHF], requiring intravenous diuretic and an overnight stay).[10] Secondary and other endpoints included other cardiovascular endpoints, as well as effects on NYHA functional class.[11] The initial dose of ATACAND was 4 mg for 80% of patients, the mean daily dose was 24 mg, and 63% of patients were titrated to the target dose of 32 mg once daily.[12] In the CHARM – Alternative trial, the most common reasons for previous ACE inhibitor intolerance (patients could report 1 or more reasons) were cough (n=1455, 72%), hypotension (n=262, 13%), abnormal renal function (n=234, 12%), and angioedema (n=83, 4%).[13]

[10]Module 2, Summary of Clinical Efficacy, 2.7.3.1.1.1

[11]Module 2, Summary of Clinical Efficacy, 2.7.3.1.1.1

[12]Module 2, Summary of Clinical Efficacy, 2.7.3.1.1.3

[13]Module 2, Summary of Clinical Efficacy, 2.7.4.2.1.5 Table 63

CHARM - Alternative Trial

In the CHARM – Alternative trial, the use of ATACAND over a median follow up of 34 months[14] resulted in a 23% (p <0.001) relative risk reduction in the primary endpoint of cardiovascular death or heart failure hospitalization, with each of the components contributing to this effect (Table 2).[15] Risk reductions in deaths attributed to worsening heart failure and sudden deaths both contributed to the effect on cardiovascular death. The use of ATACAND also resulted in a 32% relative risk reduction (hazard ratio 0.68, CI 0.57-0.81, p<0.001)[16] in CHF hospitalizations as a first event, and a reduction in the total number of investigator reported CHF hospitalizations (445 vs. 608, p<0.001).[17] Symptoms of heart failure as assessed by NYHA functional class were also significantly improved in patients treated with ATACAND (p=0.008).[18]

[14]Clinical Study Report SH-AHS-0003, 8.2

[15]Clinical Study Report SH-AHS-0003, 7.1

[16]Clinical Study Report SH-AHS-0003, 7.2.2

[17]Clinical Study Report SH-AHS-0003, 7.2.3.1

[18]Clinical Study Report SH-AHS-0003, 7.2.3.6

[19]Module 2, Summary of Clinical Efficacy, 2.7.3.3.2.1 Table 8 and Figure 4

Table 2. CHARM – Alternative: Primary Endpoint and its Components[19]

Endpoint (time to first event)	ATACAND (n=1013)	Placebo (n=1015)	Hazard Ratio (95% CI)	p-value (logrank)	Relative Risk Reduction
CV death or CHF hospitalization	334	406	0.77 (0.67-0.89)	<0.001	23%
CV death	219	252	0.85 (0.71-1.02)	0.072	15%
CHF hospitalization	207	286	0.68 (0.57-0.81)	<0.001	32%

CHARM - Added Trial

In the CHARM-Added trial, the use of ATACAND over a median follow up of 41 months[20] resulted in a 15% (p = 0.011) relative risk reduction in the primary endpoint of cardiovascular death or heart failure hospitalization with each of the components contributing to this effect (Table 3).[21] Risk reductions in deaths attributed to worsening heart failure and sudden deaths both contributed to the effect on cardiovascular death. This favourable effect in reducing cardiovascular mortality or CHF hospitalization was evident consistently in patients receiving ACE inhibitors at doses recommended for heart failure as well as in patients on lower doses. A beneficial effect on cardiovascular mortality or CHF hospitalization was also evident with concomitant use of an ACE inhibitor, a beta-blocker and ATACAND.[22] The use of ATACAND also resulted in a 17% relative risk reduction (hazard ratio 0.83, CI 0.71-0.97, p=0.014) for CHF hospitalizations as a first event,[23] and a reduction in the total number of investigator reported CHF hospitalizations (607 vs. 836, p=0.002).[24] Symptoms of heart failure as assessed by NYHA functional class were also significantly improved in patients treated with ATACAND (p=0.020).[25]

[20]Clinical Study Report SH-AHS-0006, 8.2

[21]Clinical Study Report SH-AHS-0006, 7.2.1.1

[22]Clinical Study Report SH-AHS-0006, 7.6.3 Figure 11

[23]Clinical Study Report SH-AHS-0006, 7.2.4.1 Table 54

[24] Module 2, Summary of Clinical Efficacy, 2.7.3.3.2.1 Table 10

[25] Module 2, Summary of Clinical Efficacy, 2.7.3.3.2.2 Table 17 and Figure 20

Table 3. CHARM – Added: Primary Endpoint and its Components[26]

Endpoint (time to first event)	ATACAND (n=1276)	Placebo (n=1272)	Hazard Ratio (95% CI)	p-value (logrank)	Relative Risk Reduction
CV death or CHF hospitalization	483	538	0.85 (0.75-0.96)	0.011	15%
CV death	302	347	0.84 (0.72-0.98)	0.029	16%
CHF hospitalization	309	356	0.83 (0.71-0.96)	0.013	17%

[26]Module 2, Summary of Clinical Efficacy, 2.7.3.3.2.1 Table 8 and Figure 5

CHARM: CHF with LV Systolic Dysfunction Trials—Pooled

In a prespecified analysis of the pooled results of the 4576[27] patients from the CHARM-Alternative and CHARM-Added trials (LVEF <40%), over a median follow up of 40 months,[28] ATACAND demonstrated a 12% relative risk reduction in all-cause mortality (hazard ratio 0.88 95% CI 0.79-0.98; p= 0.018).[29] This improvement in survival was attributable to a 16% relative risk reduction in cardiovascular deaths, (hazard ratio 0.84, CI 0.75-0.95, p=0.005). Risk reductions in heart failure deaths (24 %, hazard ratio 0.76, CI 0.62-0.93, p=0.008)[30] and sudden deaths (20%, hazard ratio 0.80, CI 0.67-0.95, p=0.013)[31] both contributed to this effect on cardiovascular death.[32] No effect was seen on cardiovascular deaths due to other causes or on non-cardiovascular deaths. The use of ATACAND also resulted in a 24% relative risk reduction in hospitalizations for heart failure as a first event (hazard ratio 0.76, CI 0.68-0.85, p<0.001),[33] and a reduction in the total number of investigator reported CHF hospitalizations (1052 vs. 1444, p<0.001).[34] Symptoms of heart failure as assessed by NYHA functional class were also improved (p<0.001).[35]

[27]Clinical Study Report SH-AHS-pooled, 6.2 Figure 3

[28]Clinical Study Report SH-AHS-pooled, 8.2

[29]Clinical Study Report SH-AHS-pooled, 7.2.1.2

[30]Clinical Study Report SH-AHS-pooled, 7.2.2 Table 30

[31]Clinical Study Report SH-AHS-pooled, 7.2.2 Table 30

[32]Clinical Study Report SH-AHS-pooled, 7.2.2 Table 30

[33]Clinical Study Report SH-AHS-pooled, 11.2.8.1 Table 134

[34]Module 2, Summary of Clinical Efficacy, 2.7.3.3.2.1 Table 10

[35]Module 2, Summary of Clinical Efficacy, 2.7.3.3.2.2 Table 17 and Figure 23

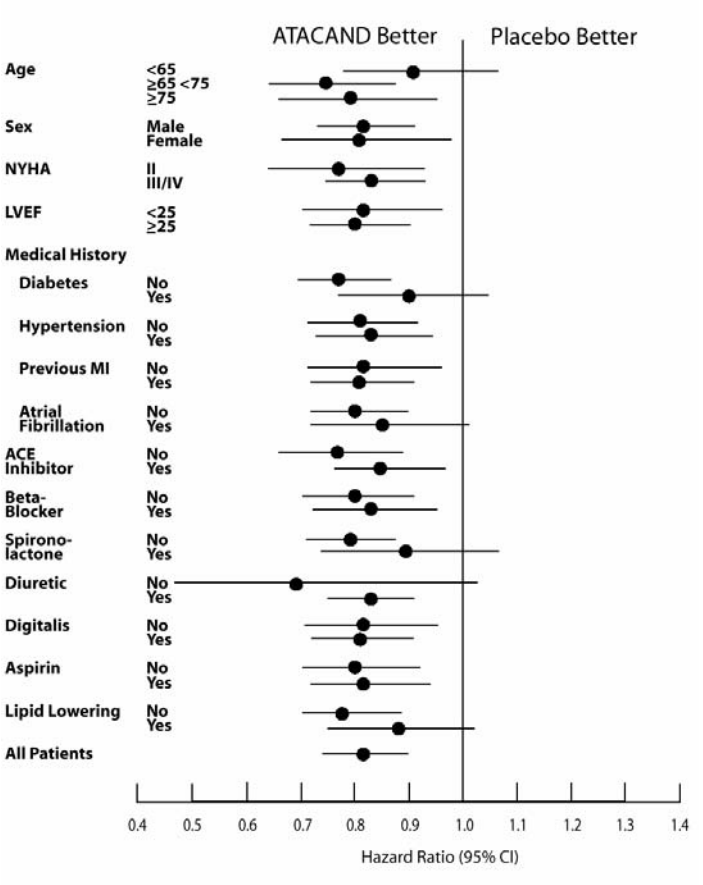
The benefits of ATACAND in reducing CV death or heart failure hospitalization (hazard ratio 0.82, CI 0.74-0.90, p<0.001) were evident in major subgroups and in patients on various combinations of other cardiovascular and heart failure treatments, including ACE inhibitors, beta-blockers, and spironolactone (see Figure 1).[36]

[36]Module 2, Summary of Clinical Efficacy, 2.7.3.3.3 Table 23

[37]Module 2, Summary of Clinical Efficacy, 2.7.3.3.3 Table 23

[38]Clinical Study Report SH-AHS-pooled, 12.1.9.4.126 and 12.1.9.4.172

Figure 1[37,38]



CHARM - Preserved

In the CHARM - Preserved trial, the use of ATACAND over a median follow up of 37 months[39] resulted in an 11% (non-significant, p = 0.118) relative risk reduction in the primary endpoint of cardiovascular death or heart failure hospitalization.[40] Although ATACAND had no apparent effect on cardiovascular mortality, there was a trend in reducing by 15% the relative risk for CHF hospitalizations as a first event (hazard ratio 0.85, CI 0.72-1.01, p=0.072, (Table 4),[41] and a

[39]Clinical Study Report SH-AHS-0007, 8.2

[40]Module 2, Summary of Clinical Efficacy, 2.7.3.3.2.1 Figure 5

[41]Module 2, Summary of Clinical Efficacy, 2.7.3.3.2.1 Table 8

[42]Module 2, Summary of Clinical Efficacy, 2.7.3.3.2.1 Table 10

reduction in total investigator reported heart failure hospitalizations (402 vs. 566, p= 0.013).[42]

Table 4. CHARM–Preserved: Primary Endpoint and its Components:[43]

Endpoint (time to first event)	ATACAND (n=1514)	Placebo (n=1509)	Hazard Ratio (95% CI)	p value (logrank)	Relative Risk Reduction
CV death or CHF hospitalization	333	366	0.89 (0.77-1.03)	0.118	11%
CV death	170	170	0.99 (0.80-1.22)	0.918	1%
CHF hospitalization	241	276	0.85 (0.72-1.01)	0.072	15%

[43]Module 2, Summary of Clinical Efficacy, 2.7.3.3.2.1 Table 8 and Figure 6

CHARM Overall Program—Three Component Trials-Pooled

In a prespecified analysis of the pooled data from the 3 component trials (n=7599),[44] treatment of a broad spectrum of heart failure patients with ATACAND over a median follow up of 38 months[45] resulted in a 9% relative risk reduction[46] (p=0.055) in all-cause death, attributable to a 12% (p = 0.011) relative risk reduction in cardiovascular deaths. No effect was seen on non-cardiovascular deaths.[47]

The beneficial effects of ATACAND on the composite endpoint of cardiovascular death or heart failure hospitalization, the primary endpoint of each of the 3 CHARM trials, were evident across all major subgroups regardless of age, race, sex, ejection fraction, medical history, and concomitant treatments (see Figure 2). The number of black patients in the CHARM program was relatively small (n=326),[48] but the benefits of ATACAND appeared to be consistent with the effects in the Caucasian population, both in the CHARM Overall program and in the component trials.[49]

[44]Clinical Study Report SH-AHS-pooled, 6.1

[45]Clinical Study Report SH-AHS-pooled, 8.2

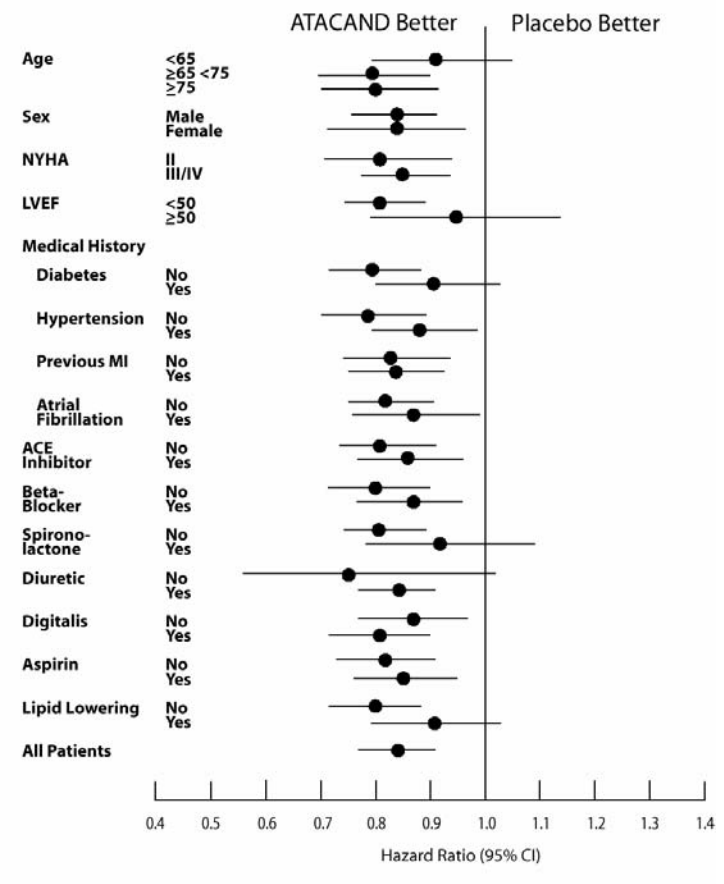
[46]Clinical Study Report SH-AHS-pooled, 7.1

[47]Module 2, Summary of Clinical Efficacy, 2.7.3.3.2.1 Table 11

[48]Clinical Study Report SH-AHS-pooled, 6.5 Table 16

[49]Module 2, Summary of Clinical Efficacy, 2.7.3.3.3 Table 23

Figure 2[50,51]



[50]Module 2, Summary of Clinical Efficacy, 2.7.3.3.3 Table 23

[51]Clinical Study Report SH-AHS-pooled, 6.5 Tables 12.1.9.4.40 and 12.1.9.4.86

INDICATIONS AND USAGE

Hypertension

ATACAND is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

Editorial

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).[52]

Per inclusion and exclusion criteria.

Benefits not found in patients with preserved left ventricular systolic function.

[52]Module 2, Clinical Overview, 2.5.4.3

CONTRAINDICATIONS

ATACAND is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS

Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin- converting enzyme inhibitors. Post-marketing experience has identified reports of fetal and neonatal toxicity in babies born to women treated with ATACAND during pregnancy. When pregnancy is detected, ATACAND should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of ATACAND as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, ATACAND should be discontinued unless it is considered life saving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

Oral doses ≥ 10 mg of candesartan cilexetil/kg/day administered to pregnant rats during late gestation and continued through lactation were associated with reduced survival and an increased incidence of hydronephrosis in the offspring. The 10-mg/kg/day dose in rats is approximately 2.8 times the maximum recommended daily human dose (MRHD) of 32 mg on a mg/m^2 basis (comparison assumes human body weight of 50 kg). Candesartan cilexetil given to pregnant rabbits at an oral dose of 3 mg/kg/day (approximately 1.7 times the MRHD on a mg/m^2 basis) caused maternal toxicity (decreased body weight and death) but, in surviving dams, had no adverse effects on fetal survival, fetal weight, or external, visceral, or skeletal development. No maternal toxicity or adverse effects on fetal development were observed when oral doses up to 1000 mg of candesartan cilexetil/kg/day (approximately 138 times the MRHD on a mg/m^2 basis) were administered to pregnant mice.

Hypotension in Volume-and Salt-Depleted Patients

In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g., those being treated with diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of ATACAND, or the treatment should start under close medical supervision (see DOSAGE AND ADMINISTRATION).

If hypotension occurs, the patients should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment which usually can be continued without difficulty once the blood pressure has stabilized.

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.[53] 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*; the incidence of hypotension leading to drug discontinuation in candesartan-treated patients was 4.1% compared with 2.0% in placebo-treated patients.[54] Monitoring of blood pressure is recommended during dose escalation and periodically thereafter.

[53]Module 2, Summary of Clinical Safety, 2.7.4.4.1 Table 67

Table 22, page 59, of ISS.

[54]Module 2, Summary of Clinical Safety, 2.7.4.2.1.4.1 Table 44

PRECAUTIONS

General

Impaired Hepatic Function— Based on pharmacokinetic data which demonstrate significant increases in candesartan AUC and C_{max} in patients with moderate hepatic impairment, a lower initiating dose should be considered for patients with moderate hepatic impairment. (See DOSAGE AND ADMINISTRATION, and CLINICAL PHARMACOLOGY, Special Populations.)

Impaired Renal Function— As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals treated with ATACAND. In patients whose renal function may depend upon the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe ~~congestive~~ heart failure), treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results may be anticipated in patients treated with ATACAND. (See CLINICAL PHARMACOLOGY, Special Populations.)

Editorial

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen (BUN) have been reported. There has been no long-term use of ATACAND in patients with unilateral or bilateral renal artery stenosis, but similar results may be expected.

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.[55] 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*; 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.[56] 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.

[55]ClinicalStudy Report, SH-AHS-pooled, 11.3.9

Table 22, page 59, of ISS.

[56]Module 2, Summary of Clinical Safety, 2.7.4.2.1.4.1 Table 44

Hyperkalemia

In heart failure patients treated with ATACAND, hyperkalemia may occur,[57] especially when taken concomitantly with ACE inhibitors[58] 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;* the incidence of hyperkalemia leading to drug discontinuation in candesartan-treated patients was 2.4% compared with 0.6% in placebo-treated patients.[59] During treatment with ATACAND in patients with heart failure, monitoring of serum potassium is recommended during dose escalation and periodically thereafter.

Table 22, page 59, of ISS.

[57]Module 2, Summary of Clinical Safety, 2.7.4.2.1.1.1 Table 22

[58]Module 2, Summary of Clinical Safety, 2.7.4.5.2.1 Table 78

[59]Module 2, Summary of Clinical Safety, 2.7.4.2.1.4.1 Table 44

Information for Patients

Pregnancy— Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Drug Interactions

No significant drug interactions have been reported in studies of candesartan cilexetil given with other drugs such as glyburide, nifedipine, digoxin, warfarin, hydrochlorothiazide, and oral contraceptives in healthy volunteers, or given with enalapril to patients with heart failure (NYHA class II and III).[60] Because candesartan is not significantly metabolized by the cytochrome P450 system and at therapeutic concentrations has no effects on P450 enzymes, interactions with drugs that inhibit or are metabolized by those enzymes would not be expected.

[60]Clinical Study Report EC608, 6.7.1 and 8.1

Lithium— Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors, and with some angiotensin II receptor antagonists. An increase in serum lithium concentration has been reported during concomitant administration of lithium with ATACAND, so careful monitoring of serum lithium levels is recommended during concomitant use.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of carcinogenicity when candesartan cilexetil was orally administered to mice and rats for up to 104 weeks at doses up to 100 and 1000 mg/kg/day, respectively. Rats received the drug by gavage, whereas mice received the drug by dietary administration. These (maximally-tolerated) doses of candesartan cilexetil provided systemic exposures to candesartan (AUCs) that were, in mice, approximately 7 times and, in rats, more than 70 times the exposure in man at the maximum recommended daily human dose (32 mg).

Candesartan and its O-deethyl metabolite tested positive for genotoxicity in the *in vitro* Chinese hamster lung (CHL) chromosomal aberration assay. Neither compound tested positive in the Ames microbial mutagenesis assay or the *in vitro* mouse lymphoma cell assay. Candesartan (but not its O-deethyl metabolite) was also evaluated *in vivo* in the mouse micronucleus test and *in vitro* in the Chinese hamster ovary (CHO) gene mutation assay, in both cases with negative results. Candesartan cilexetil was evaluated in the Ames test, the *in vitro* mouse lymphoma cell and rat hepatocyte unscheduled DNA synthesis assays and the *in vivo* mouse micronucleus test, in each case with negative results. Candesartan cilexetil was not evaluated in the CHL chromosomal aberration or CHO gene mutation assay.

Fertility and reproductive performance were not affected in studies with male and female rats given oral doses of up to 300 mg/kg/day (83 times the maximum daily human dose of 32 mg on a body surface area basis).

Pregnancy

Pregnancy Categories C (first trimester) *and D* (second and third trimesters)—See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers

It is not known whether candesartan is excreted in human milk, but candesartan has been shown to be present in rat milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Hypertension

Editorial

Of the total number of subjects in clinical studies of ATACAND, 21% (683/3260) were 65 and over, while 3% (87/3260) were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. In a placebo-controlled trial of about 200 elderly hypertensive patients (ages 65 to 87 years), administration of candesartan cilexetil was well tolerated and lowered blood pressure by about 12/6 mm Hg more than placebo.

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.[61] ~~*In general, there were no notable differences in efficacy or safety between older and younger patients.*~~[62] 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.[63] 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%).[64] 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.

No evidence for this statement.

[61]Module 2, Summary of Clinical Safety, 2.7.4.1.3 Table 6

[62]Module 2, Summary of Clinical Efficacy, 2.7.3.3.3 Table 23

[63]Clinical Study Report SH-AHS-pooled, 11.3.5.3 Table 168

[64]Clinical Study Report SH-AHS-pooled, 11.3.5.3 Table 168

ADVERSE REACTIONS

Editorial

Hypertension

ATACAND has been evaluated for safety in more than 3600 patients/subjects, including more than 3200 patients treated for hypertension. About 600 of these patients were studied for at least 6 months and about 200 for at least 1 year. In general, treatment with ATACAND was well tolerated. The overall incidence of adverse events reported with ATACAND was similar to placebo.

The rate of withdrawals due to adverse events in all trials in patients (7510 total) was 3.3% (i.e., 108 of 3260) of patients treated with candesartan cilexetil as monotherapy and 3.5% (i.e., 39 of 1106) of patients treated with placebo. In placebo-controlled trials, discontinuation of therapy due to clinical adverse events occurred in 2.4% (i.e., 57 of 2350) of patients treated with ATACAND and 3.4% (i.e., 35 of 1027) of patients treated with placebo.

The most common reasons for discontinuation of therapy with ATACAND were headache (0.6%) and dizziness (0.3%).

The adverse events that occurred in placebo-controlled clinical trials in at least 1% of patients treated with ATACAND and at a higher incidence in candesartan cilexetil (n = 2350) than placebo (n = 1027) patients included back pain (3% vs. 2%), dizziness (4% vs. 3%), upper respiratory tract infection (6% vs. 4%), pharyngitis (2% vs. 1%), and rhinitis (2% vs. 1%).

The following adverse events occurred in placebo-controlled clinical trials at a more than 1% rate but at about the same or greater incidence in patients receiving placebo compared to candesartan cilexetil: fatigue, peripheral edema, chest pain, headache, bronchitis, coughing, sinusitis, nausea, abdominal pain, diarrhea, vomiting, arthralgia, and albuminuria.

Other potentially important adverse events that have been reported, whether or not attributed to treatment, with an incidence of 0.5% or greater from the 3260 patients worldwide treated in clinical trials with ATACAND are listed below. It cannot be determined whether these events were causally related to ATACAND. **Body as a Whole:** asthenia, fever; **Central and Peripheral Nervous System:** paresthesia, vertigo; **Gastrointestinal System Disorder:** dyspepsia, gastroenteritis; **Heart Rate and Rhythm Disorders:** tachycardia, palpitation; **Metabolic and Nutritional Disorders:** creatine phosphokinase increased, hyperglycemia, hypertriglyceridemia, hyperuricemia; **Musculoskeletal System Disorders:** myalgia; **Platelet/Bleeding-Clotting Disorders:** epistaxis; **Psychiatric Disorders:** anxiety, depression, somnolence; **Respiratory System Disorders:** dyspnea; **Skin and Appendages Disorders:** rash, sweating increased; **Urinary System Disorders:** hematuria.

Other reported events seen less frequently included angina pectoris, myocardial infarction, and angioedema.

Adverse events occurred at about the same rates in men and women, older and younger patients, and black and non-black patients.

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.[65]

[65]Module 2, Summary of Clinical Safety, 2.7.4.2.1.1.1 Table 21

[66]Module 2, Summary of Clinical Efficacy, 2.7.4.2.1.4.1 Table 44

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%).[66] *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).*

Table 44, page 91, of ISS.

Post-Marketing Experience:

The following have been very rarely reported in post-marketing experience:

Digestive: Abnormal hepatic function and hepatitis.

Hematologic: Neutropenia, leukopenia, and agranulocytosis.

Metabolic and Nutritional Disorders: hyperkalemia, hyponatremia.

Renal: renal impairment, renal failure.

Skin and Appendages Disorders: Pruritus and urticaria.

Editorial

Laboratory Test Findings

Hypertension

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with the administration of ATACAND.

Creatinine, Blood Urea Nitrogen— Minor increases in blood urea nitrogen (BUN) and serum creatinine were observed infrequently.

Hyperuricemia— Hyperuricemia was rarely found (19 or 0.6% of 3260 patients treated with candesartan cilexetil and 5 or 0.5% of 1106 patients treated with placebo).

Hemoglobin and Hematocrit— Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.2 grams/dL and 0.5 volume percent, respectively) were observed in patients treated with ATACAND alone but were rarely of clinical importance. Anemia, leukopenia, and thrombocytopenia were associated with withdrawal of one patient each from clinical trials.

Potassium— A small increase (mean increase of 0.1 mEq/L) was observed in patients treated with ATACAND alone but was rarely of clinical importance. One patient from a congestive heart failure trial was withdrawn for hyperkalemia (serum potassium = 7.5 mEq/L). This patient was also receiving spironolactone.

Liver Function Tests— Elevations of liver enzymes and/or serum bilirubin were observed infrequently. Five patients assigned to candesartan cilexetil in clinical trials were withdrawn because of abnormal liver chemistries. All had elevated transaminases. Two had mildly elevated total bilirubin, but one of these patients was diagnosed with Hepatitis A.

Heart Failure

In the CHARM program, small increases in serum creatinine (mean increase 0.2 mg/dL in candesartan-treated patients and 0.1mg/dL in placebo-treated patients) and serum potassium (mean increase 0.15 mEq/L in candesartan-treated patients and 0.02 mEq/L in placebo-treated patients), and small decreases in hemoglobin (mean decrease 0.5 gm/dL in

candesartan-treated patients and 0.3 gm/dL in placebo-treated patients) and hematocrit (mean decrease 1.6% in candesartan-treated patients and 0.9% in placebo-treated patients) were observed.[67]

[67]Clinical Study Report SH-AHS-pooled, 11.3.9

OVERDOSAGE

No lethality was observed in acute toxicity studies in mice, rats, and dogs given single oral doses of up to 2000 mg/kg of candesartan cilexetil. In mice given single oral doses of the primary metabolite, candesartan, the minimum lethal dose was greater than 1000 mg/kg but less than 2000 mg/kg.

The most likely manifestation of overdosage with ATACAND would be hypotension, dizziness, and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Candesartan cannot be removed by hemodialysis.

Treatment: To obtain up-to-date information about the treatment of overdose, consult your Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*. In managing overdose, consider the possibilities of multiple-drug overdoses, drug-drug interactions, and altered pharmacokinetics in your patient.

DOSAGE AND ADMINISTRATION

Editorial

Hypertension

Dosage must be individualized. Blood pressure response is dose related over the range of 2 to 32 mg. The usual recommended starting dose of ATACAND is 16 mg once daily when it is used as monotherapy in patients who are not volume depleted. ATACAND can be administered once or twice daily with total daily doses ranging from 8 mg to 32 mg. Larger doses do not appear to have a greater effect, and there is relatively little experience with such doses. Most of the antihypertensive effect is present within 2 weeks, and maximal blood pressure reduction is generally obtained within 4 to 6 weeks of treatment with ATACAND.

No initial dosage adjustment is necessary for elderly patients, for patients with mildly impaired renal function, or for patients with mildly impaired hepatic function (see CLINICAL PHARMACOLOGY, Special Populations). In patients with moderate hepatic impairment, consideration should be given to initiation of ATACAND at a lower dose (See CLINICAL PHARMACOLOGY, Special Populations). For patients with possible depletion of intravascular volume (e.g., patients treated with diuretics, particularly those with impaired renal function), ATACAND should be initiated under close medical supervision and consideration should be given to administration of a lower dose (see WARNINGS, Hypotension in Volume- and Salt-Depleted Patients).

ATACAND may be administered with or without food.

If blood pressure is not controlled by ATACAND alone, a diuretic may be added. ATACAND may be administered with other antihypertensive agents.

Heart Failure

The usual 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.[68] ATACAND can be administered with other heart failure treatments including ACE inhibitors, beta-blockers, diuretics, *and/or* digoxin~~, *and/or aldosterone antagonist.*~~[69]

[68]Module 2, Clinical Overview, 2.5.6

[69]Module 2, Clinical Overview, 2.5.5.4.3

No beneficial effect on CV mortality or CHF hospitalization was found with candesartan treatment among CHF patients who were receiving spironolactone (See Figures 1 & 2).

HOW SUPPLIED

No. 3782 — Tablets ATACAND, 4 mg, are white to off-white, circular/biconvex-shaped, non-film-coated tablets, coded ACF on one side and 004 on the other. They are supplied as follows:

NDC 0186-0004-31 unit of use bottles of 30.

No. 3780 — Tablets ATACAND, 8 mg, are light pink, circular/biconvex-shaped, non-film-coated tablets, coded ACG on one side and 008 on the other. They are supplied as follows:

NDC 0186-0008-31 unit of use bottles of 30.

No. 3781 — Tablets ATACAND, 16 mg, are pink, circular/biconvex-shaped, non-film-coated tablets, coded ACH on one side and 016 on the other. They are supplied as follows:

NDC 0186-0016-31 unit of use bottles of 30
NDC 0186-0016-54 unit of use bottles of 90
NDC 0186-0016-28 unit dose packages of 100.

No. 3791 — Tablets ATACAND, 32 mg, are pink, circular/biconvex-shaped, non-film-coated tablets, coded ACL on one side and 032 on the other. They are supplied as follows:

NDC 0186-0032-31 unit of use bottles of 30
NDC 0186-0032-54 unit of use bottles of 90
NDC 0186-0032-28 unit dose packages of 100.

Storage:
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Keep container tightly closed.

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