CLINICAL REVIEW

Application Type	NDA 20-838
Submission Number	S-024
Submission Code	SE 1
Reviewer Name	Khin Maung U, MD
Review Completion Date	10-Dec-2004
Established Name	Candesartan Cilexetil
(Proposed) Trade Name	Atacand®
Therapeutic Class	Selective AT_1 subtype angiotensin II receptor antagonist
Applicant	AstraZeneca LP
Priority Designation	S
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)

For the following sections, please refer to my review of NDA 20-838 efficacy supplement SE 1 #022 for CHARM-Added (SH-AHS-0006) study.

Section 5 Clinical Pharmacology

Section 9. 4 Labeling Review

Section 10.1 Review of Individual Study Reports

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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 (LV) systolic function (ejection fraction (EF) ≤40%) who were intolerant to angiotensin converting enzyme (ACE) inhibitors (CHARM-Alternative), (ii) patients with depressed LV systolic function (EF ≤40%) receiving an ACE inhibitor (CHARM-Added), and (iii) patients with preserved LV systolic function (EF >40%) (CHARM-Preserved). This review pertains to efficacy supplement #024 (CHARM-Alternative trial).

In CHARM-Alternative (SH-AHS-0003) Study of 2,028 patients with CHF and depressed LV systolic function who were intolerant to ACE inhibitors, candesartan significantly (P<0.001) reduced the relative risk of time to CV death or CHF hospitalization by 23.2% (primary efficacy endpoint). This benefit translates into a reduction of 7 major events per 100 patients with CHF and depressed LV systolic function who were intolerant to ACE inhibitors treated with candesartan for two years; i.e., treating 14 patients with CHF and depressed LV systolic function who were intolerant to ACE inhibitors with candesartan for two years will prevent one patient from suffering the outcome of CV death or CHF hospitalization. This beneficial effect may be attributed to a reduction in sudden death, the most commonly reported fatal adverse event in both treatment groups. 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 β-blockers and digoxin.

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 # 024 with data on the CHARM-Alternative (SH-AHS-0003) 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 depressed left ventricular systolic function (ejection fraction ≤40%) in patients who are intolerant to ACE-inhibitors, and receiving other heart failure treatments including β-blockers and digoxin, 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 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 the doses 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 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 (e.g., for high dose and low dose candesartan, and placebo) to determine the effect of candesartan (high or low dose) in the treatment of CHF in patients who are intolerant to ACE-inhibitors in order to 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].

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 indication of treatment of heart

failure (NYHA Class II-IV) to reduce the risk of death from cardiovascular causes and reduce hospitalizations for 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 LV 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 LV systolic function (EF ≤ 40%)
- CHARM-Preserved (SH-AHS-0007) study of 3,023 patients with CHF and preserved LV 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-Alternative (SH-AHS-0003) Study: This pivotal study was a randomized, double-blind, placebo-controlled, parallel group, multicenter study of 2,028 patients (646 females, 1,382 males) randomized at 484 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 LV systolic function (EF ≤ 40%), and intolerant to ACE inhibitors.

Patients were randomized at visit 1 to candesartan or placebo. The starting dose was 4 mg once daily, titrated up to 32 mg once daily or to the highest tolerated dose during a 6-week period. Thereafter, 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. 1,313 (64.7%) patients (candesartan 666, 65.8%; placebo 647, 63.7%) received the investigational product for 24 months or more. 824 (81.3%) patients in the candesartan group started treatment on 4 mg once daily and 189 (18.7%) patients started on 8 mg once daily at randomization (baseline). 52.2% of the candesartan patients were treated with the target dose of 32 mg once daily at 6 months (visit 5). The mean dose in the candesartan group was 23.2 mg at 6 months. At the end of treatment 44.1% (60.3% of those still treated with candesartan) received 32 mg candesartan once daily.

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 the time from randomization to all-cause mortality or CHF hospitalization and (ii) a composite of the time from randomization to 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 for the treatment of CHF.

1.3.2 Efficacy

The efficacy endpoints in the pivotal clinical trial (CHARM-Alternative (SH-AHS-0003) Study) and the pooled CHARM Program clinical trials are shown in Table 1.

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

Endpoints	SH-AHS-0003 (CHARM-Alternative)	Pooled SH-AHS-0003 + SH-AHS-0006	Pooled SH-AHS-0003 + SH-AHS-0006+ SH-AHS-0007
P°: CV death or CHF hospitalization	**HR =0.768; P<0.001**	HR = 0.816; P<0.001	HR = 0.836; P<0.001
S°: All-cause death or CHF hospitalization	**HR =0.798; P=0.001**	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 = 0.822; P<0.001	HR = 0.843; P<0.001
All-cause Mortality	**HR =0.918; P=0.114 (Covar. adj: P=0.028)**	**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 =0.872; P=0.105 (Covar. adj: P=0.033)**	HR =0.943; P=0.092	HR =0.948; P=0.055
All-cause hospitalization	**HR =0.913; P=0.107 (Covar. adj: P=0.030)**	HR =0.937; P=0.078	HR =0.948; P=0.064
CHF hospitalization	**HR =0.677; P<0.001**	HR = 0.759; P<0.001	HR = 0.787 ; P<0.001
Non-fatal MI	**HR =1.107; P=0.656**	HR = 0.763; P<0.098	HR =0.766; P=0.032
CV death	**HR =0.847; P=0.072**	HR =0.844; P=0.005	HR =0.876; P=0.012
CHF death	**HR =0.766; P=0.095**	HR =0.758; P=0.008	HR =0.783; P=0.008
Sudden death	**HR =0.704; P=0.017**	HR =0.801; P=0.013	HR =0.848; P=0.037
Death due to MI	**HR =1.942; P=0.025***	HR =1.327; P=0.185	HR =1.187; P=0.368
Death due to stroke	**HR =0.846; P=0.658**	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 =1.007; P=0.972	HR =1.057; P=0.734
Non-CV death	**HR =1.014; P=0.948**	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-Alternative (SH-AHS-0003) study: In CHF patients with depressed LV systolic function (EF ≤40%) intolerant to ACE inhibitors, candesartan significantly (P<0.001) reduced the relative risk of CV death or CHF hospitalization by 23.2% (primary efficacy endpoint), and significantly (P=0.001) reduced the relative risk of all-cause mortality or CHF hospitalization by 20.2%, and significantly (P<0.001) reduced the relative risk of CV death or CHF hospitalization or non-fatal MI by 21.8%, (secondary efficacy endpoints) (Table 1).

Other Efficacy Findings: There are significant reductions in the individual components of CHF hospitalization (relative risk reduction = 32.2%, P < 0.001), and sudden death (relative risk reduction = 29.6%, P = 0.017), which appear to contribute to the beneficial effect of candesartan on the corresponding composite primary or secondary endpoint (Table 1). There was a significant increase in death due to MI (P=0.025) by 1.942 times (Table 1).

CHARM-Program studies: Candesartan reduced the relative risk of all-cause mortality by 8.6% (NOT statistically significant; P= 0.055) in patients with symptomatic CHF in the pooled studies SH-AHS-0003, SH-AHS-0006 and SH-AHS-0007 (primary efficacy endpoint) (Table 1). 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 LV 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 in the CHARM Program comparing candesartan (n=3,803) with placebo (n=3,796), 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, which were expected for this class of drugs and the disease present in the study population.

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 in the CHARM Program were observed in patients with symptomatic CHF who were receiving ACE-inhibitors, β-blockers or digoxin as part of the conventional treatment for CHF. In the CHARM-Alternative Study, too, a decrease in CV deaths or CHF hospitalization were observed in patients with CHF intolerant to ACE inhibitors who were receiving β-blockers and/or digoxin.

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 (Rationale, dosing regimen and administration) and section 8.5 (Literature review) 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 the initial NDA Efficacy 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 pertains to NDA Supplement # S-024 (CHARM – Alternative. Review classification = Standard (S)).

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 28 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 (SPICE)	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 (STRETCH)	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 #024 (CHARM – Alternative Study) the sponsor submitted that candesartan reduces the risk of cardiovascular (CV) mortality or heart failure (CHF) hospitalization in CHF patients with left ventricular systolic function who are Angiotensin Converting Enzyme (ACE) inhibitor intolerant. 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).*"

To determine whether the data submitted by the sponsor supports these claims under the CHARM-Alternative program, I will review data in the pivotal trial (SH-AHS-0003) and other clinical trials in which candesartan was added to a CHF treatment regimen in patients who are intolerant to ACE inhibitors. These studies are shown in Table 3.

Table 3 Studies of CHF patients intolerant to ACE inhibitors who are treated Candesartan or placebo

Study #	Type	Total N=	Patients	Duration	Dose	eCTD
SH-AHS-0003 (pivotal study)	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-0002 (SPICE)	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
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-0005	r, db, pc, co	21	chf, EF≤40%; ACEi 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
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, spironolactone or digoxin are used in combination with ARBs in the treatment of CHF in ACE inhibitor intolerant patients to obtain a broader perspective of the benefits produced by use of candesartan and these drugs together, and the possible risks the 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. Prevalence of intolerance to ACE-inhibitors in patients with heart failure
   Data based on a registry of CHF patients and a nationwide survey.
2. Other situations where patients with CHF may be candidates for treatment with ARBs
   Patients who undergo "ACE-escape", and those with DD genotype of the ACE gene.

3. Is candesartan tolerated by patients with CHF who are intolerant to ACE inhibitors?
   Based on the SPICE (SH-AHS-0002) study.

4. Are all ARBs equal in their clinical effects?
   Comparison of 6 ARBs approved in the U.S. for PK and PD characteristics.

5. Do ARBs need to be used at high doses for treatment of heart failure?
   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

6. Selection of dose of candesartan for the CHARM program.
   Based on (i) SH-AHS-0001 (RESOLVD), and (ii) SH-AHS-0002 (SPICE) studies.

7. Relationship between dose of candesartan and the primary and secondary efficacy outcomes.
   Based on new data sponsor submitted in response to my request in November 2004.

8. Do β-blockers produce additive survival benefit when used together with ARBs?
   Disparate outcomes are 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 use of β-blockers together with an ARB (valsartan) and an ACE inhibitors 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 by use of β-blockers in patients with CHF receiving ARBs or ACE inhibitors
   (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

9. Does spironolactone produce additive survival benefit when used together with ARB?
   The EPHESUS trial reported a significant reduction in the relative risk of all-cause mortality, and sudden death in acute MI with LVEF ≤ 40%, but no effect on CV death or CV hospitalization. The CHARM-Alternative (as well as the CHARM-Added) study did not show additive survival benefit when spironolactone was used together with candesartan

10 Does digoxin produce additive survival benefit when used together with ARB?
   - 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-Alternative as well as the 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 for CHARM-Added trial).

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?

ARBs vs. ACE inhibitor or placebo:

Stage A heart failure:

- RENAAL: Losartan (compared to placebo) 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. placebo in ACE-intolerant patients reduced composite endpoint of CV death or CHF hospitalization
- Future trials: (i) TRANSCEND in ACE inhibitor intolerant subjects (telmisartan vs. placebo), and (ii) ONTARGET (telmisartan vs. ramipril vs. telmisartan plus ramipril)

4.4 Data Quality and Integrity

Audits by the Division of Scientific Investigations (DSI) 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 484 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) 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 are distributed across world regions as follows:

- four investigators are from the U.S. (Eric Eichhorn, Alan Gradman, Marc Pfeffer, Roger Hajjar),
- one (Prof Struthers) is from the U.K.,
- one (Helen D. Ekdal) is from Canada, and
- one (Julian Vaile) is from Australia.

These investigator are NOT from any site in South Africa (total enrolled patients = 48) where, overall for that country, a statistically significant (P=0.028) relative risk reduction (hazard ratio = 0.369, relative risk reduction = 63.1%) was reported. However, five of these investigators are from the US and Canada combined (as the North America region) where a total of 677 subjects were enrolled and a statistically significant (P=0.048) relative risk reduction (hazard ratio = 0.786, relative risk reduction = 21.4%) 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 affect the efficacy outcome, and (ii) each enrolled only small number of 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 my review of clinical pharmacology (pharmacokinetic (PK) and pharmacodynamic (PD)) studies (Chapter 5, pages 37-53) in my clinical review for efficacy supplement SE 1 #022 of NDA 20-838 {CHARM-Added (SH-AHS-0006) study} in which I discussed, from the perspective of a clinician, 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.

Briefly, the PK studies showed no indication that the presence of heart failure had an additional influence on the PK of candesartan. No interaction was found between candesartan and enalapril at steady state, providing the rationale for use of candesartan and ACE-inhibitors together in patients who are tolerant to ACE inhibitors. Also, candesartan did not interact with digoxin.

The PD studies that measured exercise tolerance (using bicycle ergometry, treadmill exercise or the 6-minute walking test) did not show any consistent effect.

In PD studies that measured hemodynamics, reductions in pulmonary capillary wedged pressure (PCWP) and pulmonary arterial pressure (PAP) and improvements in left ventricular ejection fraction (LVEF) were found.

Regarding cardiovascular symptoms, PD studies including the RESOLVD (SH-AHS-0001) study did not find any change in symptoms; however, this pivotal study (CHARM-Alternative SH-AHS-0003) under review and the CHARM-Added (SH-AHS-0006) study found significant improvements in NYHA functional class.

In eight PD studies where neurohormones were the primary efficacy endpoints, significant increases in angiotensin II and renin activity, and a significant reduction in aldosterone were found, as expected, together with significant reductions in atrial natriuretic factor or polypeptide (ANF or ANP – which is an index of atrial load) and brain natriuretic polypeptide (BNP – which is an index of left ventricular function and myocardial damage).

Two small PD studies of candesartan on baroreflex sensitivity did not show any consistent effect of candesartan.

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 #024 (CHARM-Alternative (SH-AHS-0003) Study) under review, the sponsor submitted that candesartan reduces the relative risk of cardiovascular mortality or heart failure hospitalization when added to in the treatment of CHF patients with depressed left ventricular systolic function who are intolerant to ACE inhibitors. 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-Alternative Study program, I reviewed data in the pivotal trial (SH-AHS-0003) 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 4 below.

Table 4 Studies of CHF patients intolerant to ACE inhibitors who are treated with Candesartan or placebo

Study #	Type	Total N=	Patients	Duration	Dose	eCTD
SH-AHS-0003 (pivotal study)	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-0002 (SPICE pilot study)	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
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-0005	r, db, pc, co	21	chf, EF≤40%; ACEi 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
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 reduces the risk of cardiovascular mortality or heart failure hospitalization when added to the standard treatment of CHF patients with depressed left ventricular (LV) systolic function who are ACE-inhibitor intolerant appears to have scientific as well as clinical basis. ACE inhibitors have been shown to be effective in reducing mortality in heart failure[1]. The benefit of ACE inhibitors is believed to result from inhibition of the production of angiotensin II and, to a lesser extent, from a decrease in the breakdown of bradykinin resulting in higher levels of bradykinin.[2] This increase in bradykinin with use of ACE inhibitors may contribute to the adverse effects of ACE inhibitors such as cough and angioedema. Angiotensin II receptor antagonists differ from ACE-inhibitors in that they block the effect of angiotensin II at the AT1 receptor, thus blocking the effects of angiotensin II produced through both ACE-dependent and ACE-independent pathways.

A nationwide survey of patterns of use of ACE inhibitors in patients ≥65 years old who had survived hospitalization for heart failure with left ventricular systolic dysfunction revealed that ACE inhibitors were prescribed to only 68% of this cohort[3]. At least 20% of patients with heart failure do not take ACE inhibitors[4], in part because of intolerance. Estimates of the incidence of intolerance of ACE inhibitors among patients with heart failure range from 5% to 10%[5,6,7]. A registry of almost 10,000 patients with depressed LV systolic function showed that 10% of these patients had a history of intolerance to ACE inhibitors, and 6% were both intolerant to ACE inhibitors and were candidates for angiotensin II AT_1-receptor blockers (ARBs)[8]. While this is a small percentage, in the United States alone there are an estimated 2 million persons with heart failure[9]; thus, 120,000 such patients become candidates for treatment with ARBs.

The Study of Patients Intolerant to Converting Enzyme Inhibitors (SPICE)[10] showed that patients with CHF and LVEF <35% who are intolerant to ACE inhibitors tolerated candesartan (4 mg once/day, titrated to 16 mg once/day) similar to those who tolerated placebo (84% vs. 87%) However, the mortality and all-cause hospitalization were not significantly different between the candesartan and placebo groups in this relatively small pilot study of 270 patients. The finding that direct inhibition of the effect of angiotensin is tolerated by patients in heart failure with a history of intolerance to ACE inhibitors[5] suggest that intolerance to ACE inhibitors is primarily mediated through effects other than those of angiotensin. 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[11] and vascular epithelial changes. The findings of thi SPICE study provide the rationale that ARBs such as candesartan may be useful in the treatment of CHF with depressed LV systolic function in patients who are intolerant to ACE inhibitors.

In addition to the pivotal study (CHARM-Alternative, SH-AHS-0003) data, I reviewed medical journal publications of clinical trials of ARBs, including those in which β-blockers, aldosterone antagonists and digoxin 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 or spironolactone or digoxin 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 refer 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 26 to 28 of this review.

6.1.2 General Discussion of Endpoints

6.1.2.1 Endpoints for SH-AHS-0003 (CHARM-Alternative) 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,"[12] 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 the CHARM-alternative (SH-AHS-0003) study, 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: NYHA Functional class and symptomatic status were evaluated at each scheduled visit.

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 two 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 5.

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).

Table 5 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	+2	+4	Seven death reports were added. As a result six patients with CV-deaths were re-classified based on this new information.
Non adjudicated deaths	-2	-5	Due to the new death reports the number of non-adjudicated deaths decreased, they were re-adjudication to CV death.
Confirmed, adjudicated non-CV-deaths	0	+1	One of the seven deaths was re-classified as non-CV death.
Confirmed, adjudicated CHF-hospitalisations	0	+1	One CHF hospitalisations was agreed after adjudication.
Non-fatal MI	0	0	No difference.
Other SAE:s	0	+1	Six SAE-reports were added, but only one patient was re-classified as "other SAE".

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 LV 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"[12]), 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-Program 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 6).

Table 6 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 6). 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

The CHARM-Alternative (SH-AHS-0003) study 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 intolerant to ACE inhibitors. The primary variable for this evaluation was time from randomization to CV mortality or the first occurrence of a CHF hospitalization. A total of 2,028 patients were randomized at 484 sites in 25 countries.

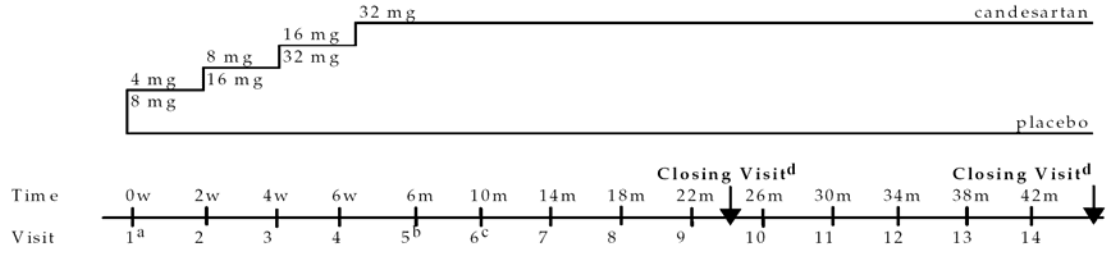
In this patient population, the most common reason for ACE inhibitor intolerance was cough, being more common in the placebo group than in the candesartan group (751, 74.0% vs. 704, 69.5%). ACE intolerance due to hypotension or renal dysfunction was more common in the candesartan group (143, 14.1% vs. 119, 11.7%, and 134, 13.3% vs. 100, 9.9% respectively) (Table 7).

Table 7 Reasons for ACE inhibitor intolerance at randomization. ITT/Safety Population (SH-AHS-0003)

Reason for ACE inhibitor intolerance at randomisation[a]	Treatment	
	Placebo (N=1015)	Cand. cil. (N=1013)
	Number of intolerant patients at randomisation, N (%)	Number of intolerant patients at randomisation, N (%)
Cough	751 (74.0)	704 (69.5)
Hypotension	119 (11.7)	143 (14.1)
Renal dysfunction	100 (9.9)	134 (13.3)
Angioedema	44 (4.3)	39 (3.8)
Other[b]	109 (10.7)	101 (10.0)

[a] A patient may have more than one reason for intolerance
[b] Includes any AE, lab value, or unknown reason.

Figure 1 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 23 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 25 to 48 months. The median duration of the double-blind treatment was 33.8 months, the median time of follow up was 33.8 months in the candesartan group, and 33.6 months in the placebo group. The median duration of exposure of the investigational product was 29.5 months in the placebo group and 29.4 months in the candesartan group.



[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 1 Study design

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,"[12] 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, 740 patients experienced the primary outcome of CV death or hospitalization due to CHF, 334 (33.0%) treated with candesartan and 406 (40.0%) treated with placebo. The average annualized events rates were 13.8% and 18.2%, respectively (Table 8). The relative risk for the primary outcome of CV death or hospitalization due to CHF, whichever came first, was significantly (P<0.001) reduced by 23.2% by candesartan treatment (Table 9).

Table 8 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-0003)

Variable	Treat-ment	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	1015	406	2229.2	182.1	2.2
	Cand. cil.	1013	334	2418.9	138.1	2.4

Table 9 Confirmed adjudicated CV death or hospitalization due to CHF. Comparison of candesartan versus placebo with Cox regression. ITT/Safety population (SH-AHS-0003)

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

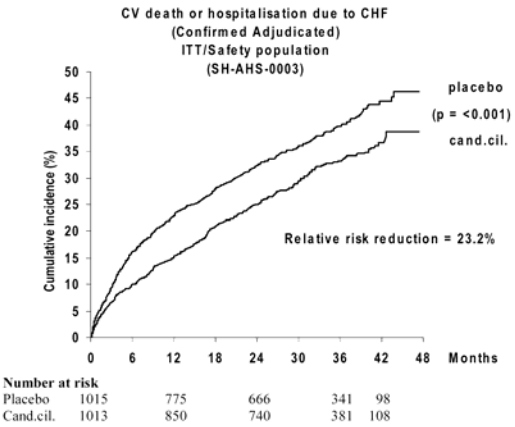


Figure 2 Cumulative incidence (%) of confirmed adjudicated CV death or hospitalization due to CHF over time. ITT/Safety population

The Kaplan-Meier plot implies that the benefit of candesartan appeared early and was maintained throughout the study period. (Figure 2).

The treatment effect of candesartan was similar across geographical regions (test for interaction; P= 0.972).

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, 804 patients experienced the secondary outcome of all-cause death or hospitalization due to CHF, 371 (36.6%) treated with candesartan and 433 (42.7%) with placebo. The average annualized events rates were 15.3% and 19.4%, respectively (Table 10). The relative risk for the secondary outcome of all-cause death or hospitalization due to CHF, whichever came first, was significantly (P=0.001) reduced by 20.2% by candesartan treatment (Table 11).

Table 10 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-0003)

Variable	Treat-ment	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	1015	433	2229.2	194.2	2.2
	Cand. cil.	1013	371	2418.9	153.4	2.4

Table 11 Confirmed adjudicated all- cause death or hospitalization due to CHF. Comparison of candesartan versus placebo with Cox regression. ITT/Safety population (SH-AHS-0003)

Variable	N	Events cand. cil.	Events placebo	Hazard Ratio	95% CI		p-value
					Lower	Upper	
All-cause death or hospitalisation due to CHF (confirmed adjudicated)	2028	371	433	0.798	0.695	0.917	0.001

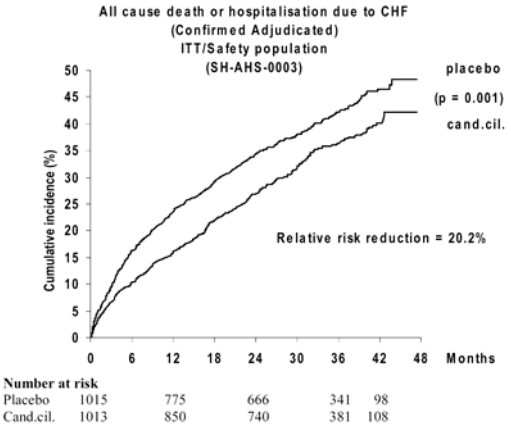


Figure 3 Cumulative incidence (%) of confirmed adjudicated all- cause death or hospitalization due to CHF over time. ITT/Safety population

The Kaplan-Meier plot implies that the benefit of candesartan appeared early and was maintained throughout the study period. (Figure 3).

The treatment effect of candesartan was similar across geographical regions (test for interaction; P= 0.721).

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, 773 patients experienced the secondary outcome of CV death or hospitalization due to CHF or non-fatal MI, 353 (34.8%) treated with candesartan and 420 (41.4%) treated with placebo. The average annualized events rates were 14.8% and 19.1%, respectively (Table 12). 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 21.8% by candesartan treatment (Table 13).

Table 12 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-0003)

Variable	Treat-ment	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	1015	420	2196.4	191.2	2.2
	Cand. cil.	1013	353	2389.2	147.8	2.4

Table 13 Confirmed adjudicated CV death or hospitalization due to CHF or non-fatal MI. Comparison of candesartan versus placebo with Cox regression. ITT/Safety population (SH-AHS-0003)

Variable	N	Events cand. cil.	Events placebo	Hazard Ratio	95% CI		p-value
					Lower	Upper	
CV death or hospitalisation due to CHF or non-fatal MI (confirmed adjudicated)	2028	353	420	0.782	0.679	0.901	<0.001

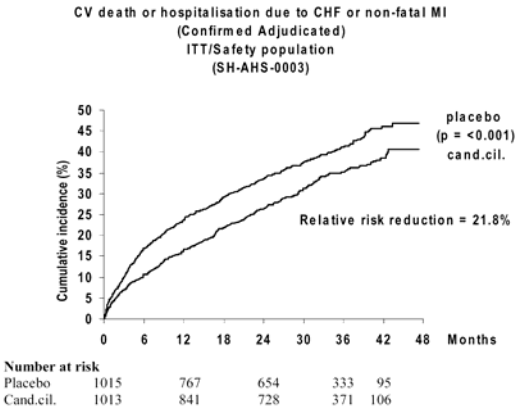


Figure 4 Cumulative incidence (%) of confirmed adjudicated CV death or hospitalization due to CHF or non- fatal MI over time. ITT/Safety population

The Kaplan-Meier plot implies that the benefit of candesartan appeared early and was maintained throughout the study period. (Figure 4).

The treatment effect of candesartan was similar across geographical regions (test for interaction; P= 0.983).

6.1.4.3 Components of the primary and secondary variables

The individual components:

(i) CV death (relative risk reduction 15%, P= 0.072),

(ii) hospitalization due to CHF (relative risk reduction 32%, P< 0.001), and

(iii) all-cause death (relative risk reduction 13%, P= 0.105),

all contributed to the benefit of candesartan as described by the respective composite endpoints. There was no reduction in non-fatal MI (Table 14 and Table 15).

Table 14 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-0003)

Variable	Treatment	N	Events (No of pati-ents)	Total follow-up time (years)	Events/ 1000 follow-up years	Mean follow-up time (years)
CV death (confirmed adjudicated)	Placebo	1015	252	2582.4	97.6	2.5
	Cand. cil.	1013	219	2658.1	82.4	2.6
Hospitalisation due to CHF (confirmed adjudicated)	Placebo	1015	286	2229.2	128.3	2.2
	Cand. cil.	1013	207	2418.9	85.6	2.4
All-cause death (confirmed adjudicated)	Placebo	1015	296	2582.4	114.6	2.5
	Cand. cil.	1013	265	2658.1	99.7	2.6
Non-fatal MI (confirmed adjudicated)	Placebo	1015	36	2534.5	14.2	2.5
	Cand.cil.	1013	41	2619.5	15.7	2.6

Table 15 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)	2028	219	252	0.847	0.707	1.015	0.072
Hospitalisation due to CHF (confirmed adjudicated)	2028	207	286	0.677	0.566	0.810	<0.001
All-cause death (confirmed adjudicated)	2028	265	296	0.872	0.739	1.029	0.105[a]
Non-fatal MI (confirmed adjudicated)	2028	41	36	1.107	0.708	1.733	0.656 [b]

[a] Logrank test p=0.104
[b] Logrank test p=0.655

Time from randomization to all-cause death:

Time from randomization to all-cause death is a component of a secondary variable, and is presented in Table 14 and Table 15 (relative risk reduction 13%, P= 0.105).

Time from randomization to all-cause hospitalization:

During the follow-up period, 610 (60.2%) patients in the candesartan group and 643 (63.3%) patients in the placebo group were hospitalized due to any cause. The average annualized events rates were 36.3% and 40.0% respectively (Table 16). The relative risk of all-cause hospitalization was non-significantly (P= 0.107) reduced by candesartan treatment (Table 17).

Table 16 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-0003)

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	1015	643	1606.2	400.3	1.6
	Cand. cil.	1013	610	1681.6	362.7	1.7

Table 17 Confirmed adjudicated all-cause hospitalization. Comparison of candesartan versus placebo with Cox regression. ITT/Safety population (SH-AHS-0003)

Variable	N	Events cand. cil.	Events placebo	Hazard Ratio	95% CI		p-value
					Lower	Upper	
All-cause hospitalisation	2028	610	643	0.913	0.817	1.020	0.107

Number of patients with fatal or non-fatal MI:

There were significantly fewer patients with fatal or non-fatal MI in the placebo group (48,4.7%) than in the candesartan group (75, 7.4%) (Table 18 and Table 19).

Table 18 The proportion of patients (%) with confirmed adjudicated fatal or nonfatal MI. ITT/Safety population (SH-AHS-0003)

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	1015	48	4.7	3.5	6.2
	Cand. cil.	1013	75	7.4	5.9	9.2

Table 19 The difference in proportion (%) of patients with confirmed adjudicated fatal or non- fatal MI between treatments. Chi-square test. ITT/Safety population (SH-AHS-0003)

Variable	Difference in proportion between treatments	95% CI		p-value
	Cand.cil-placebo	Lower	Upper	
Fatal or non-fatal MI (confirmed adjudicated)	2.7	0.6	4.7	0.012

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[13] are shown in Table 20. 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).

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 LV systolic dysfunction trials (CHARM-Alternative (SH-AHS-0003) and CHARM-Added (SH-AHS-0006)) where patient had LVEF ≤ 40%.

Table 20 Number, proportion, and annualized incidence of deaths attributed to different causes in the 3 CHARM Trials and the overall CHARM Program[13] (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 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[14]). 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[11] may also directly or indirectly decrease the propensity to fatal ventricular arrhythmias[15]. 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[16]. 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-Alternative (SH-AHS-0003) study are summarized in Table 21. Of interest is the finding that the relative risk of death due to MI is significantly (P=0.025) increased by 1.942 times among patients receiving candesartan (Table 21).

Table 21 Endpoints in the CHARM-Added study (SH-AHS-0006)

Endpoints	Hazard Ratio and "P"
P°: CV deaths or CHF hospitalizations	HR =0.768; P<0.001
S°: All-cause deaths or CHF hospitalizations	HR =0.798; P=0.001
S°: CV death/CHF hospitalization/non-fatal MI	HR =0.782; P<0.001
All-cause Mortality	HR =0.918; P=0.114 (Covar. adj: P=0.028)
All-cause deaths or all-cause hospitalizations	HR =0.872; P=0.105 (Covar. adj: P=0.033)
All-cause hospitalizations	HR =0.913; P=0.107 (Covar. adj: P=0.030)
CHF hospitalizations	HR =0.677; P<0.001
Non-fatal MI	HR =1.107; P=0.656
CV deaths	HR =0.847; P=0.072
CHF death	HR =0.766; P=0.095
Sudden death	HR =0.704; P=0.017
Death due to MI	HR =1.942; P=0.025*
Death due to stroke	HR =0.846; P=0.658
Death due to other CV cause	HR =1.066; P=0.836
Non-CV death	HR =1.014; P=0.948

Since CHF hospitalization was the component in all three efficacy endpoints (the primary endpoint and the two secondary endpoints) for study SH-AHS-0003 (CHARM-Alternative), these hospitalizations were further reviewed.

Table 22 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-0003)

		Hospitalisations		Intensive care		Intermediate care		General care		All	
Primary reason[a]	Treatment	N	%	Days	%	Days	%	Days	%	Days	%
Worsening CHF	Placebo	523	27.8	572	11.7	1267	26.0	3041	62.3	4880	100
	Cand.cil.	392	20.8	773	21.3	981	27.0	1873	51.6	3627	100
Myocardial infarction	Placebo	48	2.6	176	38.2	151	32.8	134	29.1	461	100
	Cand.cil.	49	2.6	257	51.8	98	19.8	141	28.4	496	100
Unstable angina	Placebo	93	4.9	122	11.8	571	55.2	341	33.0	1034	100
	Cand.cil.	120	6.4	217	29.8	205	28.1	307	42.1	729	100
Stroke	Placebo	17	0.9	44	33.3	22	16.7	66	50.0	132	100
	Cand.cil.	18	1.0	8	3.7	32	14.7	177	81.6	217	100
TIA	Placebo	13	0.7	9	8.3	26	23.9	74	67.9	109	100
	Cand.cil.	9	0.5	0	0.0	5	7.8	59	92.2	64	100
Hypotension	Placebo	8	0.4	9	11.8	5	6.6	62	81.6	76	100
	Cand.cil.	20	1.1	19	12.0	65	41.1	74	46.8	158	100
Atrial tachyarrhythmia	Placebo	37	2.0	38	6.8	62	11.2	456	82.0	556	100
	Cand.cil.	42	2.2	50	25.3	41	20.7	107	54.0	198	100
Ventricular arrhythmia	Placebo	48	2.6	152	36.5	135	32.4	130	31.2	417	100
	Cand.cil.	41	2.2	138	37.3	116	31.4	116	31.4	370	100
Pulmonary embolism	Placebo	6	0.3	0	0.0	15	22.7	51	77.3	66	100
	Cand.cil.	5	0.3	10	22.7	22	50.0	12	27.3	44	100
Other CV event	Placebo	210	11.2	322	21.7	398	26.8	765	51.5	1485	100
	Cand.cil.	183	9.7	269	25.1	235	22.0	566	52.9	1070	100
All CV events	Placebo	1003	53.3	1444	15.7	2652	28.8	5120	55.6	9216	100
	Cand.cil.	879	46.7	1741	25.0	1800	25.8	3432	49.2	6973	100

[a] As stated by investigator

Table 22 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. 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.

Information on length of stay by type of ward was recorded for 1,882 hospitalizations (879 in the

candesartan group, 1,003 in the placebo group) where the primary reason for hospitalization was reported as cardiovascular. Patients in the candesartan group spent fewer days in hospital (6,973 days) than patients in the placebo group (9,216 days). (Table 22).

When hospitalized, the candesartan patients spent proportionally *more* days in more resource intensive care than the placebo patients (intensive care 25.0 vs. 15.7% of days, intermediate care 25.8 vs. 28.8% of days and general care 49.2 vs. 55.6% of days). (Table 22)

Reviewer's comment: This is different than the finding in my review of the CHARM-Added (SH-AHA-0006) study (Please see item 6.1.4.3, page 68 of my review of NDA 20-838 Efficacy Supplement #022). The CHARM-Added (SH-AHS-0006) study showed that 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), with the candesartan-treated group spending fewer days than the placebo-treated group in higher levels of medical care (intensive care 18.8% vs. 19.4% of days, intermediate care 25.9% vs. 26.2% of days) but not general care (55.3% vs. 54.4% of days).

Regarding improvement in symptoms, there was an improvement in NYHA functional class in candesartan patients compared to placebo patients (P= 0.008, Wilcoxon rank-sum test). 359 (35.7%) patients in the candesartan group improved 1 or 2 NYHA classes compared to 298 (29.7%) in the placebo group (Table 23).

Table 23 Number of patients and change from baseline to LVCF in NYHA class by treatment. ITT/Safety population (SH-AHS-0003)

Visit	NYHA class	Placebo	Cand. cil.	Total
Baseline	NYHA II	479 (47.2%)	487 (48.1%)	966 (47.6%)
	NYHA III	499 (49.2%)	490 (48.4%)	989 (48.8%)
	NYHA IV	37 (3.6%)	36 (3.6%)	73 (3.6%)
	Total	1015	1013	2028
LVCF	NYHA I	95 (9.5%)	144 (14.3%)	239 (11.9%)
	NYHA II	521 (51.9%)	493 (49.0%)	1014 (50.4%)
	NYHA III	337 (33.6%)	332 (33.0%)	669 (33.3%)
	NYHA IV	51 (5.1%)	37 (3.7%)	88 (4.4%)
	Total	1004	1006	2010
Change from baseline to LVCF[a]	NYHA improved by 3 classes	0	2 (0.2%)	2 (0.1%)
	NYHA improved by 2 classes	33 (3.3%)	40 (4.0%)	73 (3.6%)
	NYHA improved by 1 class	265 (26.4%)	319 (31.7%)	584 (29.1%)
	NYHA same as baseline	597 (59.5%)	544 (54.1%)	1141 (56.8%)
	NYHA deteriorated by 1 class	106 (10.6%)	93 (9.2%)	199 (9.9%)
	NYHA deteriorated by 2 classes	3 (0.3%)	8 (0.8%)	11 (0.5%)
	Total	1004	1006	2010

[a] Wilcoxon rank-sum test, p=0.008

The shift in NYHA functional class from baseline to last known class is presented in Table 24.

Table 24 NYHA class shift table by treatment. ITT/Safety Population. (SH-AHS-0003)

Change in NYHA class from baseline to LVCF	Number of patients (%)	
	Placebo (N=1015)	Cand.cil. (N=1013)
from II to Unknown	4 (0.4%)	4 (0.4%)
from II to I	71 (7.0%)	112 (11.1%)
from II to II	328 (32.3%)	294 (29.0%)
from II to III	73 (7.2%)	69 (6.8%)
from II to IV	3 (0.3%)	8 (0.8%)
from III to Unknown	4 (0.4%)	2 (0.2%)
from III to I	24 (2.4%)	30 (3.0%)
from III to II	184 (18.1%)	189 (18.7%)
from III to III	254 (25.0%)	245 (24.2%)
from III to IV	33 (3.3%)	24 (2.4%)
from IV to Unknown	3 (0.3%)	1 (0.1%)
from IV to I	0	2 (0.2%)
from IV to II	9 (0.9%)	10 (1.0%)
from IV to III	10 (1.0%)	18 (1.8%)
from IV to IV	15 (1.5%)	5 (0.5%)

6.1.5 Is there a relationship between the dose of candesartan and the primary and secondary efficacy outcomes?

1,313 (64.7%) patients (candesartan 666, 65.8%; placebo 647, 63.7%) received the investigational product for 24 months or more. A total of 824 (81.3%) patients in the candesartan group started treatment on 4 mg once daily and 189 (18.7%) patients started on 8 mg once daily at randomization (baseline). 52.2% of the candesartan patients (58.9% of those still receiving the investigational product) were treated with the target dose 32 mg once daily at 6 months (visit 5). The mean dose in the candesartan group was 23.2 mg at 6 months. At the end of treatment (LVCF) 44.1% (60.3% of those still treated with candesartan) received 32 mg candesartan once daily. The mean candesartan LVCF dose was 23.1 mg.

In Table 25 and Table 26, 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 at the higher doses of 16 mg and 32 mg candesartan where the relative risk reduction with candesartan vs. placebo was significant (P<0.001) (Table 26).

Table 25 CV death or CHF hospitalization by subgroup: dose of study drug, (events per 1000 years of follow-up), Study SH-AHS-0003

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	68	45	71.7	627.8	1.1
		Candesartan	116	70	199.8	350.3	1.7
	8 mg	Placebo	62	41	79.3	516.7	1.3
		Candesartan	97	48	179.6	267.2	1.9
	16 mg	Placebo	117	71	190.8	372.0	1.6
		Candesartan	120	50	260.1	192.2	2.2
	32 mg	Placebo	603	199	1461.7	136.1	2.4
		Candesartan	475	111	1257.1	88.3	2.6
	No study drug	Placebo	164	49	425.6	115.1	2.6
		Candesartan	205	55	522.1	105.3	2.5

Table 26 CV death or CHF hospitalization by subgroup: dose of study drug (Cox regression), Study SH-AHS-0003

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	184	70	45	0.668	0.458, 0.974	0.036
	8 mg	159	48	41	0.568	0.374, 0.863	0.008
	16 mg	237	50	71	0.542	0.377, 0.779	<0.001
	32 mg	1078	111	199	0.650	0.515, 0.820	<0.001
	No study drug	369	55	49	0.918	0.624, 1.349	0.661

Following a Telecon on November 18, 2004, I requested the sponsor to provide information on the CHARM-Alternative (SH-AHS-0003) 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 relation to the primary and secondary efficacy endpoints.

On November 24 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, I used the definition for high candesartan dose 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): The proportion of patients who reached the primary efficacy endpoint while on high or low dose candesartan are given in Table 27. There appears to be a 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 (cells A1 vs. A2 in Table 28); however, patients receiving placebo also exhibited the same dose response! (cells B1 vs. B2 in Table 28).

The secondary efficacy endpoint of all-cause mortality or CHF hospitalization (Table 29 and Table 30), and for secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI (Table 31 and Table 32) also show similar findings.

Table 27 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 – CHARM-Alternative (SH-AHS-0003) Study

Candesartan	**N = 1013** **Events = 334 (33.0%)**		
			A
	CC_{HD} n = 595 events = 161 (27.1%)	CC_{LD} n = 213 events = 118 (55.4%)	CC_{00} n = 205 events = 55 (26.8%)
	A1	**A2**	**A3**
Placebo	**N = 1015** **Events = 406 (40.0%)**		
			B
	P_{HD} n = 720 events = 270 (37.5%)	P_{LD} n = 130 events = 86 (66.2%)	P_{00} n = 165 events = 50 (30.3%)
	B1	**B2**	**B3**

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 28 Comparison of the effect of high or low dose candesartan on the primary endpoint of time to CV mortality or CHF hospitalization (confirmed, adjudicated) using Cox Regression– CHARM-Alternative (SH-AHS-0003) Study

Comparison	Relative risk reduction (%)	Hazard ratio	95% confidence interval	p-value (Wald)
A vs B	23.2	0.768	(0.665, 0.888)	<0.001
A_1 vs B	40.7	0.593	(0.494, 0.712)	<0.001
A_1 vs A_2	64.5	0.355	(0.280, 0.451)	<0.001
A_2 vs B	-	1.652	(1.346, 2.028)	<0.001
A_1 vs B_1	34.5	0.655	(0.539, 0.796)	<0.001
A_2 vs B_2	37.6	0.624	(0.472, 0.825)	<0.001

Cells A, B, A_1, B_1, A_2 and B_2 = Reference to cells in Table 27.

Table 29 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 – CHARM-Alternative (SH-AHS-0003) Study

Candesartan	**N = 1013** **Events = 371 (36.6%)**		
			A
	CC_{HD} n = 597 events = 180 (30.2%)	CC_{LD} n = 213 events = 124 (58.2%)	CC_{00} n = 203 events = 67 (33.0%)
	A1	**A2**	**A3**
Placebo	**N = 1015** **Events = 433 (42.7%)**		
			B
	P_{HD} n = 721 events = 282 (39.1%)	P_{LD} n = 131 events = 94 (71.8%)	P_{00} n = 163 events = 57 (35.0%)
	B1	**B2**	**B3**

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 30 Comparison of the effect of high or low dose candesartan on the secondary efficacy endpoint of all-cause mortality or CHF hospitalization (confirmed, adjudicated) using Cox Regression[a] – CHARM-Alternative (SH-AHS-0003) Study

Comparison	Relative risk reduction (%)	Hazard ratio	95% confidence interval	p-value (Wald)
A vs B	20.2	0.798	(0.695, 0.917)	0.001
A_1 vs B	38.2	0.618	(0.519, 0.735)	<0.001
A_1 vs A_2	62.7	0.373	(0.297, 0.470)	<0.001
A_2 vs B	-	1.631	(1.336, 1.992)	<0.001
A_1 vs B_1	30.2	0.698	(0.579, 0.841)	<0.001
A_2 vs B_2	40.1	0.599	(0.458, 0.784)	<0.001

Cells A, B, A_1, B_1, A_2 and B_2 = Reference to cells in Table 29.

Table 31 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 – CHARM-Alternative (SH-AHS-0003) Study

Candesartan	**N = 1013** **Events = 353 (34.9%)**		**A**
	CC_{HD} n = 599 events = 176 (29.4%)	CC_{LD} n = 215 events = 121 (56.3%)	CC_{00} n = 199 events = 56 (28.1%)
	A1	**A2**	**A3**
Placebo	**N = 1015** **Events = 420 (41.4%)**		**B**
	P_{HD} n = 720 events = 279 (38.8%)	P_{LD} n = 134 events = 91 (67.9%)	P_{00} n = 161 events = 50 (31.1%)
	B1	**B2**	**B3**

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 32 Comparison of the effect of high or low dose candesartan on the secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI (confirmed, adjudicated) using Cox Regression[a] – CHARM-Alternative (SH-AHS-0003) Study

Comparison	Relative risk reduction (%)	Hazard ratio	95% confidence interval	p-value (Wald)
A vs B	21.8	0.782	(0.679, 0.901)	<0.001
A_1 vs B	37.9	0.621	(0.521, 0.741)	<0.001
A_1 vs A_2	62.1	0.379	(0.301, 0.478)	<0.001
A_2 vs B	-	1.620	(1.323, 1.983)	<0.001
A_1 vs B_1	30.9	0.691	(0.572, 0.834)	<0.001
A_2 vs B_2	39.5	0.605	(0.460, 0.795)	<0.001

Cells A, B, A_1, B_1, A_2 and B_2 = Reference to cells in Table 31.

However, there are many caveats to these findings:

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

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

(iii) 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.

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

Please also see more detailed discussion under Section 8 (Additional Clinical Issues) in Sub-section 8.1.7 (Inference on the finding of a relationship between the dose of candesartan and the primary and secondary efficacy outcomes in CHARM-Alternative (SH-AHS-0003) study: pages 123-125) of this review.

6.1.6 Efficacy Conclusions

The endpoints (mortality or hospitalizations) in this pivotal clinical trial (CHARM-Alternative (SH-AHS-0003) Study) and the pooled CHARM Program clinical trials are shown in Table 33.

Table 33 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 = 0.759; P<0.001	HR = 0.787; P<0.001
Non-fatal MI	**HR =1.107; P=0.656**	HR =0.512; P=0.006	HR = 0.763; P<0.098	HR =0.766; P=0.032
CV deaths	**HR =0.847; P=0.072**	HR =0.842; P=0.029	HR =0.844; P=0.005	HR =0.876; P=0.012
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-Alternative (SH-AHS-000) Study

CHARM-Alternative (SH-AHS-0003) Study Primary Efficacy Endpoint: For the composite primary efficacy endpoint cardiovascular mortality or hospitalization for heart failure, the CHARM-Alternative (SH-AHS-0003) Study showed that candesartan significantly (P<0.001) reduced the relative risk of CV death or hospitalization for CHF in patients with depressed left ventricular systolic function by 23.2% (Table 21 and Table 33).

CHARM-Alternative (SH-AHS-0003) Study Secondary Efficacy Endpoints: For the composite secondary efficacy endpoint all-cause deaths or CHF hospitalizations, the CHARM-Alternative (SH-AHS-0003) Study showed that candesartan significantly (P=0.001) reduced the relative risk of all-cause deaths or CHF hospitalizations in patients with depressed left ventricular systolic function by 20.2% (Table 21 and Table 33).

For the composite secondary efficacy endpoint CV death or CHF hospitalization or non-fatal MI, the CHARM-Alternative (SH-AHS-0003) Study showed that candesartan significantly (P<0.001) reduced the relative risk of CV death or CHF hospitalization or non-fatal MI in patients with depressed left ventricular systolic function by 21.8% (Table 21 and Table 33).

CHARM-Alternative (SH-AHS-0003) Study Other Efficacy Findings: There are significant reductions in the individual components of CHF hospitalizations (relative risk reduction = 32.3%%, P< 0.001), and sudden death (relative risk reduction = 29.6%, P = 0.017), which appear to contribute to the beneficial effect of candesartan on the corresponding composite primary or secondary endpoint (Table 21 and Table 33). There was a significant increase in deaths due to MI (P = 0.025) by 1.942 times (Table 21 and Table 33).

Please note that SH-AHS-0003 (CHARM-Alternative) 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 5 and Table 33). This was NOT statistically significant (P=0.055).

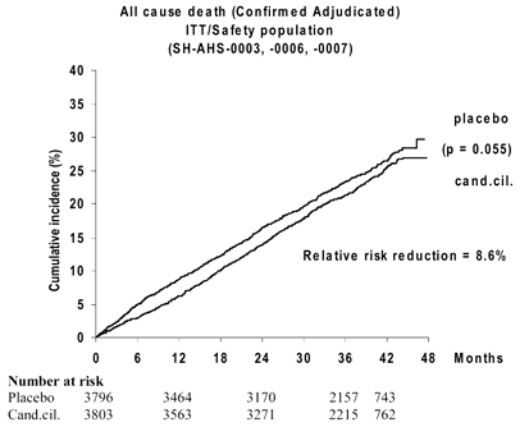


Figure 5 Cumulative incidence (%) of confirmed adjudicated all-cause death in patients with symptomatic CHF over time. ITT/Safety population.

CHARM Program Secondary Efficacy Endpoint Finding: For the secondary efficacy endpoint all-cause mortality in the pooled population of patients with CHF and depressed LV systolic function (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 depressed LV systolic function by 11.4% (Figure 6 and Table 33).

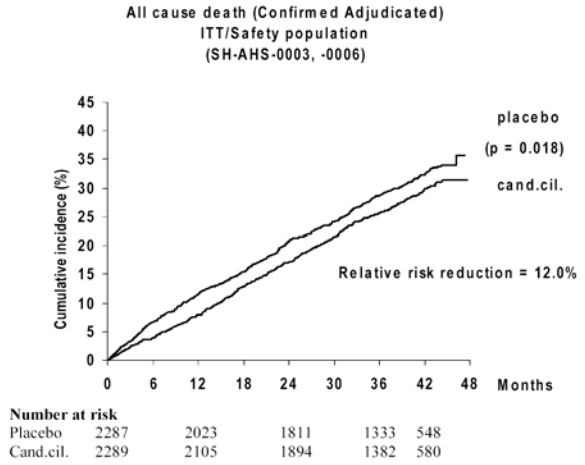


Figure 6 Cumulative incidence (%) of confirmed adjudicated all-cause death in patients with LV systolic dysfunction over time. ITT/Safety population.

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 33). 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 depressed LV systolic function (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 depressed LV systolic function by 5.7% (Table 33). 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 following summarizes the efficacy conclusions for CHARM-Alternative (SH-AHS-0003) study:

- Candesartan significantly reduced the relative risk of CV death or the first occurrence of a CHF hospitalization by 23.2% (P< 0.001). (Primary efficacy endpoint)
- Candesartan significantly reduced the relative risk of all-cause death or the first occurrence of a CHF hospitalization by 20.2% (P= 0.001). (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 21.8% (P<0.001). (Secondary efficacy endpoint)
- The following also met the nominal "P" value for statistical significance based on the results of CHARM-Alternative (SH-AHS-0003) study:
    - Candesartan reduced the relative risk of CHF hospitalization.
    - Candesartan reduced the relative risk of sudden death.
    - 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.
    - Candesartan did not reduce the number of fatal and non-fatal MIs. Candesartan appeared to have increased the relative risk of death from MI.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

I evaluated 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 an objective assessment could be made regarding the nature of the adverse events that could arise in patients who had underlying hyperkalemia, hypotension, chronic or acute on chronic renal dysfunction, and other co-morbid diseases such as diabetes, myocardial infarction, etc.

In each of the following subsections (deaths, SAEs, AEs, laboratory findings, etc.) in this review, I will first present the data from the CHARM-Alternative (SH-AHS-0003) study, 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.

Safety data in the clinical pharmacology studies and non-CHARM studies are generally consistent with data from the CHARM-Pooled studies.

7.1.1 Deaths

In this section, I will present deaths as part of the safety review following the existing clinical review template. 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-Alternative (SH-AHS-0003) Study

562 patients died during the CHARM-Alternative (SH-AHS-0003) study, of whom 296 (29.2%) were randomized to placebo and 266 (26.3%) randomized to candesartan. For 5 of the patients who died (Site-Patient number: 201-13446, 653-12566, 1006-10801, 1406-22827, 1531-20373), 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 candesartan 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 commonly reported fatal AE in both treatment groups during study was sudden death, reported for 10.4% (106) of the patients in the placebo group and for 7.9% (80) in the candesartan group (Table 34). Cardiac failure/ cardiac failure aggravated was the second most common fatal AE, reported for 9.0% (91) of the patients in the placebo group and for 7.6% (77) in the candesartan group, respectively.

Table 34 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-0003)

Preferred term	Placebo on treatment (N=1015)		Cand. cil. on treatment (N=1013)		Placebo during study (N=1015)		Cand. cil. during study (N=1013)	
	N	(%)	N	(%)	N	(%)	N	(%)
Sudden death	81	(8.0)	64	(6.3)	106	(10.4)	80	(7.9)
Cardiac failure/cardiac failure aggravated[b]	52	(5.1)	37	(3.7)	91	(9.0)	77	(7.6)
Myocardial infarction	10	(1.0)	29	(2.9)	17	(1.7)	38	(3.8)
Cerebrovascular disorder	9	(0.9)	7	(0.7)	14	(1.4)	13	(1.3)
Cardiac arrest	6	(0.6)	7	(0.7)	9	(0.9)	9	(0.9)
Death	3	(0.3)	2	(0.2)	7	(0.7)	9	(0.9)
Pneumonia	3	(0.3)	2	(0.2)	9	(0.9)	6	(0.6)
Fibrillation ventricular	5	(0.5)	4	(0.4)	7	(0.7)	6	(0.6)
Cardiomyopathy	2	(0.2)	1	(0.1)	6	(0.6)	5	(0.5)
Coronary artery disorder	1	(0.1)	3	(0.3)	4	(0.4)	7	(0.7)
Respiratory insufficiency	2	(0.2)	3	(0.3)	5	(0.5)	6	(0.6)
Sepsis	3	(0.3)	2	(0.2)	7	(0.7)	2	(0.2)
Pulmonary carcinoma	2	(0.2)	5	(0.5)	2	(0.2)	6	(0.6)
Tachycardia ventricular/arrhythmia[b]	1	(0.1)	3	(0.3)	3	(0.3)	4	(0.4)
Accident and/or injury	1	(0.1)	2	(0.2)	4	(0.4)	2	(0.2)
Pulmonary oedema	2	(0.2)	2	(0.2)	3	(0.3)	3	(0.3)

[a] This table uses a cut-off of ≥0.3% in total population during study (N=2028).
[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%) 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 35 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 35) 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 44, 4.3%; candesartan 46, 4.5%) or non-CV hospitalization rates (placebo 353, 34.8%; candesartan 362, 35.7%).

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-Alternative 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 36), being slightly less frequent in the candesartan compared to the placebo group.

Table 36 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-Alternative	266	80 (7.9%)	77 (7.6%)	296	106 (10.4%)	91 (9.0%)
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[35], 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%) 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[36].

7.1.2 Other Serious Adverse Events

Serious adverse events other than deaths in CHARM-Alternative (SH-AHS-0003) Study:

Non-fatal SAEs were reported in 64.4% (654) of the patients in the placebo group during study and in 61.1% (619) of the patients in the candesartan group during study. The most commonly reported non-fatal SAEs in the placebo group during study (as shown in Table 37) were cardiac failure/cardiac failure aggravated (334, 33.0%), angina pectoris/angina pectoris aggravated (120, 12.0%) and arrhythmia ventricular (79, 7.8%). The most commonly reported non-fatal SAEs in the candesartan group during study were cardiac failure/cardiac failure aggravated (251, 25.0%), angina pectoris/angina pectoris aggravated (122, 12.0%) and hypotension (88, 8.7%).

Table 37 Number (%) of patients with the most commonly reported[a] SAEs other than death, sorted by descending frequency. ITT/Safety population (SH-AHS-0003)

Preferred term	Placebo on treatment (N=1015)		Cand. cil. on treatment (N=1013)		Placebo during study (N=1015)		Cand. cil. during study (N=1013)	
	N	(%)	N	(%)	N	(%)	N	(%)
Cardiac failure/cardiac failure aggravated[b]	297	(29.3)	209	(20.6)	334	(32.9)	251	(24.8)
Angina pectoris/angina pectoris aggravated[b]	110	(10.8)	100	(9.9)	120	(11.8)	122	(12.0)
Arrhythmia ventricular	64	(6.3)	58	(5.7)	79	(7.8)	73	(7.2)
Pneumonia	62	(6.1)	64	(6.3)	71	(7.0)	81	(8.0)
Hypotension	39	(3.8)	84	(8.3)	51	(5.0)	88	(8.7)
Myocardial infarction	50	(4.9)	46	(4.5)	57	(5.6)	56	(5.5)
Cerebrovascular disorder	50	(4.9)	38	(3.8)	56	(5.5)	46	(4.5)
Arrhythmia atrial	41	(4.0)	44	(4.3)	44	(4.3)	56	(5.5)
Fibrillation atrial	46	(4.5)	32	(3.2)	57	(5.6)	41	(4.0)
Chest pain	41	(4.0)	36	(3.6)	49	(4.8)	45	(4.4)
Coronary artery disorder	39	(3.8)	34	(3.4)	46	(4.5)	42	(4.1)
Tachycardia ventricular/arrhythmia[b]	30	(3.0)	24	(2.4)	42	(4.1)	35	(3.5)
Tachycardia supraventricular	30	(3.0)	27	(2.7)	39	(3.8)	34	(3.4)
Cardiomyopathy	27	(2.7)	24	(2.4)	35	(3.4)	33	(3.3)
Syncope	27	(2.7)	25	(2.5)	34	(3.3)	29	(2.9)

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

b Patients having both 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 38).

Table 38 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.

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-Alternative and CHARM-Pooled studies, six of these are seen more frequently in the placebo-treated group, and hypotension is the only SAE in both study populations that is seen more frequently in the Candesartan-treated group (Table 37, and Table 38). 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."

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-Alternative(SH-AHS-0003) Study:

The study medication was permanently discontinued due to AEs in 197 (19.4%) patients in the placebo group and in 220 (21.7%) 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-Alternative (SH-AHS-0003) Study:

The most common AEs leading to discontinuation of investigational product are presented in Table 39. 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 in the placebo group were cardiac failure/cardiac failure aggravated (72, 7.1%), renal function abnormal/renal dysfunction aggravated (25, 2.5%) and hypotension (14, 1.4%). In the candesartan group the most commonly reported AEs leading to discontinuation were renal function abnormal/renal dysfunction aggravated (65, 6.4%), cardiac failure/cardiac failure aggravated (53, 5.2%) and hypotension (46, 4.5%).

Table 39 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-0003)

Preferred term	Placebo on treatment (N=1015)		Cand. cil. on treatment (N=1013)	
	N	(%)	N	(%)
Cardiac failure/cardiac failure aggravated[b]	72	(7.1)	53	(5.2)
Renal function abnormal/renal dysfunction aggravated[b]	25	(2.5)	65	(6.4)
Hypotension	14	(1.4)	46	(4.5)
Hyperkalaemia	3	(0.3)	21	(2.1)
Myocardial infarction	10	(1.0)	12	(1.2)
Angina pectoris/angina pectoris aggravated[b]	6	(0.6)	10	(1.0)
Pneumonia	9	(0.9)	7	(0.7)
Cerebrovascular disorder	10	(1.0)	4	(0.4)
Dizziness/vertigo[b]	3	(0.3)	11	(1.1)
Coronary artery disorder	7	(0.7)	5	(0.5)
Cardiomyopathy	6	(0.6)	5	(0.5)
Dyspnoea/dyspnoea (aggravated)[b]	8	(0.8)	3	(0.3)
Renal failure acute	3	(0.3)	8	(0.8)
Tachycardia ventricular	7	(0.7)	4	(0.4)
Headache	4	(0.4)	6	(0.6)

a This table uses a cut-off of ≥0.5% in total population on treatment (N=2028).

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 40. 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 40 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[17], 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 41).

Table 41 AEs in relation to withdrawal of study drug in ATLAS trial[17] (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-Alternative (SH-AHS-0003) Study:

In this exploratory presentation of data, the permanent discontinuation of the investigational product due to an AE or abnormal lab value occurred in 196 (19.3%) patients in the placebo group and 218 (21.5%) patients in the candesartan group. Neither the difference in time to event (P=0.332) nor the difference in proportions between treatments of 2.2% (P=0.217) were statistically significant (Table 42, Table 43 and Figure 7).

Table 42 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-0003)

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	1013	295	2176.1	135.6	2.1
	Cand. cil.	1011	308	2212.9	139.2	2.2
Permanent investigational product discontinuation due to an AE or an abnormal lab value	Placebo	1015	196	2350.3	83.4	2.3
	Cand. cil.	1013	218	2379.8	91.6	2.3
At least one investigational product discontinuation due to any cause	Placebo	1013	456	1973.3	231.1	1.9
	Cand. cil.	1011	489	1933.0	253.0	1.9
At least one investigational product discontinuation due to an AE or an abnormal lab value	Placebo	1015	355	2177.6	163.0	2.1
	Cand. cil.	1013	399	2115.1	188.6	2.1

Table 43 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-0003)

Variable	N	Events cand. cil.	Events placebo	Hazard Ratio	95% CI		p-value
					Lower	Upper	
Permanent investigational product discontinuation due to any cause	2028	308	295	1.028	0.876	1.207	0.735
Permanent investigational product discontinuation due to an AE or an abnormal lab value	2028	218	196	1.100	0.907	1.334	0.332
At least one investigational product discontinuation due to any cause	2028	489	456	1.090	0.959	1.239	0.187
At least one investigational product discontinuation due to an AE or an abnormal lab value	2028	399	355	1.151	0.997	1.328	0.054

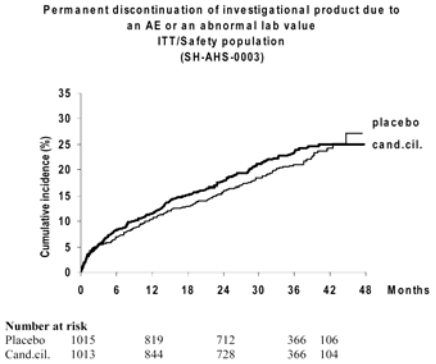


Figure 7 Cumulative incidence (%) of permanent discontinuation of investigational product due to an AE or an abnormal laboratory value. ITT/Safety population

Specific causes of investigational product discontinuation are noted in Table 44 and Table 45. Hypotension, 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 2.8%, 1.6% and 3.5%, respectively.

The approximate 1.1 fold excess risk for candesartan discontinuation relative to placebo for the entire study population was characteristic of the relative discontinuation rates across most subgroups. The approximate 1.5 fold higher risk of candesartan than placebo discontinuation among patients receiving spironolactone at baseline (placebo 47 patients, candesartan 75 patients) was statistically significant (P= 0.022). Also, the approximate 1.3 fold higher risk for candesartan discontinuation among patients receiving spironolactone at the visit prior to investigational product discontinuation (placebo 74 patients, candesartan 90 patients) was statistically significant (P= 0.003). However, the 1.1 fold excess risk for candesartan discontinuation for patients having spironolactone recorded as a concomitant medication 'during study' was not significant (P= 0.422).

Table 44 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-0003)

Variable	Treatment	N	Number of patients with events	Proportion of patients with event	95% CI	
					Lower	Upper
Permanent investigational product discontinuation due to any cause	Placebo Cand. cil.	1015 1013	295 308	29.1 30.4	26.3 27.6	32.0 33.3
Permanent investigational product discontinuation due to an AE or an abnormal lab value	Placebo Cand. cil.	1015 1013	196 218	19.3 21.5	16.9 19.0	21.9 24.2
Permanent investigational product discontinuation due to hypotension	Placebo Cand. cil.	1015 1013	9 37	0.9 3.7	0.4 2.6	1.7 5.0
Permanent investigational product discontinuation due to hyperkalaemia	Placebo Cand. cil.	1015 1013	3 19	0.3 1.9	0.1 1.1	0.9 2.9
Permanent investigational product discontinuation due to increased creatinine	Placebo Cand. cil.	1015 1013	27 62	2.7 6.1	1.8 4.7	3.8 7.8
At least one investigational product discontinuation due to any cause	Placebo Cand. cil.	1015 1013	456 489	44.9 48.3	41.8 45.2	48.0 51.4
At least one investigational product discontinuation due to an AE or an abnormal lab value	Placebo Cand. cil.	1015 1013	355 399	35.0 39.4	32.0 36.4	38.0 42.5
At least one investigational product discontinuation due to hypotension	Placebo Cand. cil.	1015 1013	23 72	2.3 7.1	1.4 5.6	3.4 8.9
At least one investigational product discontinuation due to hyperkalaemia	Placebo Cand. cil.	1015 1013	9 37	0.9 3.7	0.4 2.6	1.7 5.0
At least one investigational product discontinuation due to increased creatinine	Placebo Cand. cil.	1015 1013	37 102	3.6 10.1	2.6 8.3	5.0 12.1
Decreased investigational product dose due to any cause at least once	Placebo Cand. cil.	1015 1013	106 201	10.4 19.8	8.6 17.4	12.5 22.4
Decreased investigational product dose due to an AE or an abnormal lab value at least once	Placebo Cand. cil.	1015 1013	89 182	8.8 18.0	7.1 15.6	10.7 20.5

Table 45 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-0003)

Variable	Difference in proportion between treatments	95% CI		p-value
	Cand.cil. - placebo	Lower	Upper	
Permanent investigational product discontinuation due to any cause	1.3	-2.6	5.3	0.509
Permanent investigational product discontinuation due to an AE or an abnormal lab value	2.2	-1.3	5.7	0.217
Permanent investigational product discontinuation due to hypotension	2.8	1.5	4.1	<0.001
Permanent investigational product discontinuation due to hyperkalaemia	1.6	0.7	2.5	<0.001
Permanent investigational product discontinuation due to increased creatinine	3.5	1.7	5.2	<0.001
At least one investigational product discontinuation due to any cause	3.3	-1.0	7.7	0.131
At least one investigational product discontinuation due to an AE or an abnormal lab value	4.4	0.2	8.6	0.040
At least one investigational product discontinuation due to hypotension	4.8	3.0	6.7	<0.001
At least one investigational product discontinuation due to hyperkalaemia	2.8	1.5	4.1	<0.001
At least one investigational product discontinuation due to increased creatinine	6.4	4.2	8.6	<0.001
Decreased investigational product dose due to any cause at least once	9.4	6.3	12.5	<0.001
Decreased investigational product dose due to an AE or an abnormal lab value at least once	9.2	6.3	12.1	<0.001

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.

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 46, Table 47and Figure 8) and the difference in proportions between treatments of 4.3% ($P< 0.001$) (Table 48 and Table 49) were statistically significant.

Table 46 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 47 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

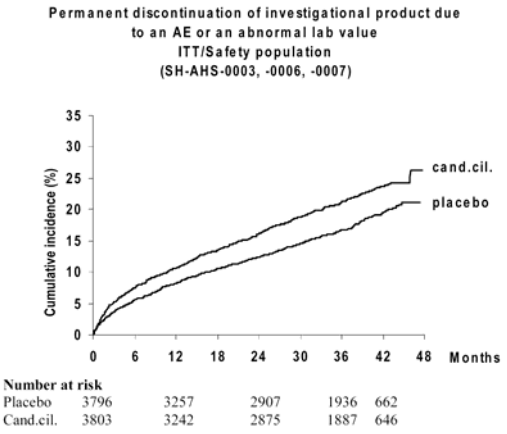


Figure 8 Cumulative incidence (%) of permanent discontinuation of the investigational product due to an AE or an abnormal laboratory value. ITT/Safety population

Specific causes of investigational product discontinuation are shown in Table 48, Table 49, Table 50 and Table 51. 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 48 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 49 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 50 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 51 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 52 and Table 53), which is an expected finding in these diabetics with possible underlying renal dysfunction and autonomic dysregulation.

Table 52 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 53 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[18] 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[39] 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 54). 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 54).

Table 54 Adverse Events leading to dose reduction or discontinuation of study treatment in VALIANT trial[39] (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.

However, in the OPTIMAAL trial[38], 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 55).

Table 55 Adverse events causing discontinuation in the OPTIMAAL trial[38] (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.

Background treatment with ACE-inhibitors may also be the reason for a high frequency of discontinuation. In the SMILE trial[19] (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[45] 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 9) 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.

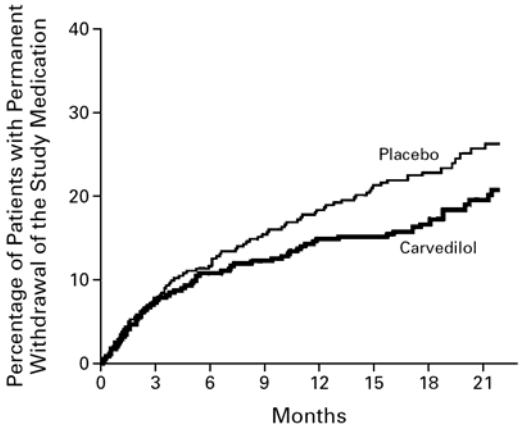


Figure 9 Kaplan–Meier Analysis of the time to permanent withdrawal of the study medication because of adverse reactions or for reasons other than death in placebo and Carvedilol groups in COPERNICUS trial[45]. The risk of withdrawal was 23% lower in the carvedilol group (95% CI: 4% – 38%; P= 0.02). (Based 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[41] 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 10).

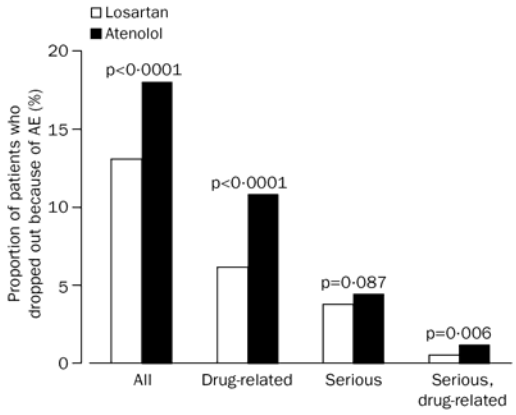


Figure 10 Adverse events resulting in discontinuation of study drug in LIFE study[41] (Based on data from Lancet 2002; 359: 995-1003.)

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-Alternative (SH-AHS-0003) Study:

The investigational product was reduced in dose due to AEs in 76 (7.5%) patients in the placebo group and in 157 (15.5%) patients in the candesartan group. The most common AEs leading to dose reduction of the investigational product are presented in Table 56.

Table 56 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-0003)

Preferred term	Placebo on treatment (N=1015)		Cand. cil. on treatment (N=1013)	
	N	(%)	N	(%)
Hypotension	27	(2.7)	85	(8.4)
Renal function abnormal	10	(1.0)	32	(3.2)
Dizziness/vertigo[b]	6	(0.6)	23	(2.3)
Cardiac failure aggravated	7	(0.7)	13	(1.3)
Hyperkalaemia	6	(0.6)	12	(1.2)
Dyspnoea	7	(0.7)	1	(0.1)
Abdominal pain	3	(0.3)	4	(0.4)
Fatigue	2	(0.2)	5	(0.5)
Nausea	3	(0.3)	4	(0.4)
Angina pectoris/angina pectoris aggravated[b]	2	(0.2)	4	(0.4)
Diarrhoea	3	(0.3)	3	(0.3)

[a] The table uses a cut-off of ≥0.3% in total population on treatment (N=2028).

[b] Patients having both AEs are counted once only.

The most commonly reported AEs leading to dose reduction in the placebo group were hypotension (27, 2.7%), renal function abnormal (10, 1.0%) and cardiac failure aggravated and dyspnea (7, 0.7%). The most commonly reported AEs leading to dose reduction in the candesartan group were hypotension (85, 8.4%), renal function abnormal (32, 3.2%) and dizziness/vertigo (23, 2.3%).

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 57).

Table 57 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-Alternative(SH-AHS-0003) Study:

Dose reduction of the investigational product due to an AE or abnormal lab value occurred in 89 (8.8%) patients in the placebo group and 182 (18.0%) patients in the candesartan group (Table 44). This between-treatment difference in dose reductions for an AE of 8.8% (Table 44) was statistically significant (P< 0.001). As shown in Figure 11 the majority of events occurred during the first 6 to 12 months of treatment with the investigational product.

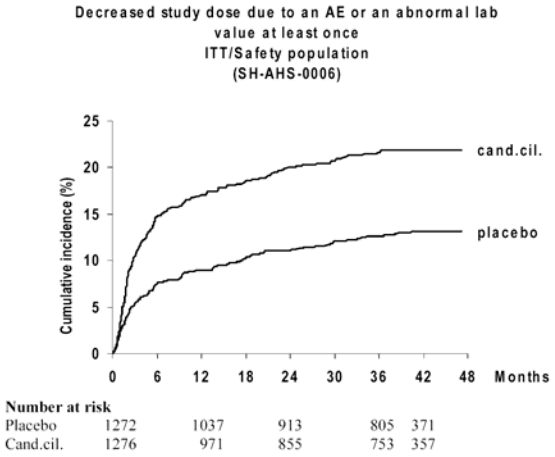


Figure 11 Cumulative incidence (%) of first occurrence of dose decrease of investigational product due to an AE or an abnormal laboratory value. ITT/Safety population

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.

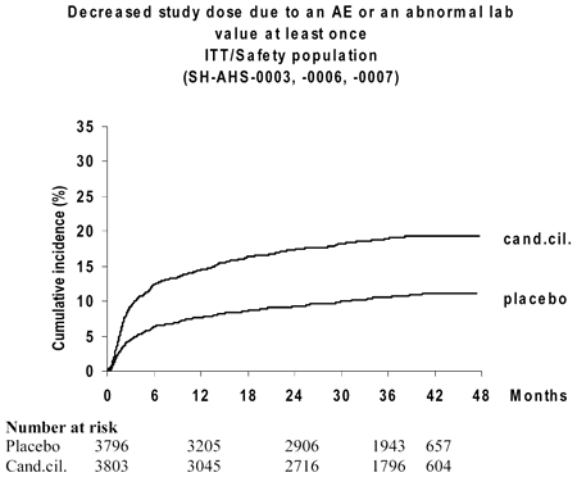


Figure 12 Cumulative incidence (%) of dose reduction of the investigational product due to an AE or an abnormal laboratory value. ITT/Safety population (SH-AHS-0003, -0006, -0007)

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 48). This between-treatment difference in dose reductions for an AE of 8.1% was statistically significant ($P < 0.001$), (Table 49). As shown in Figure 12, 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 CHARM-Program 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") or reported over the entire study period (referred to as "during study"). AEs during the 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 by 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-Alternative (SH-AHS-0003) Study:

AEs were reported by 73.6% (747) of the patients randomized to placebo, and by 73.1% (741) of the patients randomized to candesartan during study. In the placebo group 29.2% (296) of the patients had fatal SAEs and 64.4% (654) of the patients experienced non-fatal SAEs, compared with the candesartan group where 26.3% (266) of the patients had fatal SAEs and 61.1% (619) of the patients had non-fatal SAEs. The investigational product was prematurely discontinued due to AEs for 19.4% (197) of the patients in the placebo group and for 21.7% (220) of the patients in the candesartan group. The investigational product was reduced in dose due to AEs for 76 (7.5%) patients in the placebo group and for 157 (15.5%) patients in the candesartan group. A summary of adverse events by category is presented in Table 58.

Table 58 Number (%) of patients who had at least one adverse event in any category, and total numbers of adverse events. ITT/Safety population (SH-AHS-0003)

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

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

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

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

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 59, and for CHF patients with depressed LV function is given in Table 60.

Table 59 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 60 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-Alternative (SH-AHS-0003) Study**:**

The most commonly reported AEs (Table 61) in the placebo group during study were cardiac failure/cardiac failure aggravated (359, 35.4%), angina pectoris/ angina pectoris aggravated (120,

11.8%), sudden death (106, 10.4%) and renal function abnormal/ renal dysfunction aggravated (50, 4.9%). The most commonly reported AEs in the candesartan group during study were cardiac failure/cardiac failure aggravated (280, 27.6%), hypotension (193, 19.1%) and renal function abnormal/ renal dysfunction aggravated (141, 13.9%).

Table 61 Number (%) of patients with the most commonly reported[a] AEs, sorted by descending frequency in the total population during study. ITT/Safety population (SH-AHS-0003)

Preferred term	Placebo on treatment (N=1015)		Cand. cil. on treatment (N=1013)		Placebo during study (N=1015)		Cand. cil. during study (N=1013)	
	N	(%)	N	(%)	N	(%)	N	(%)
Cardiac failure/cardiac failure aggravated[b]	317	(31.2)	234	(23.1)	359	(35.4)	280	(27.6)
Hypotension	76	(7.5)	190	(18.8)	90	(8.9)	193	(19.1)
Angina pectoris/angina pectoris aggravated[b]	110	(10.8)	105	(10.4)	120	(11.8)	127	(12.5)
Renal function abnormal/renal dysfunction aggravated[b]	49	(4.8)	136	(13.4)	50	(4.9)	141	(13.9)
Sudden death	85	(8.4)	65	(6.4)	106	(10.4)	80	(7.9)
Pneumonia	64	(6.3)	65	(6.4)	75	(7.4)	83	(8.2)
Myocardial infarction	58	(5.7)	71	(7.0)	68	(6.7)	85	(8.4)
Arrhythmia ventricular	64	(6.3)	58	(5.7)	79	(7.8)	73	(7.2)
Cerebrovascular disorder	55	(5.4)	41	(4.0)	61	(6.0)	52	(5.1)
Arrhythmia atrial	41	(4.0)	44	(4.3)	44	(4.3)	56	(5.5)
Fibrillation atrial	46	(4.5)	34	(3.4)	57	(5.6)	43	(4.2)
Chest pain	42	(4.1)	37	(3.7)	50	(4.9)	47	(4.6)
Coronary artery disorder	39	(3.8)	38	(3.8)	48	(4.7)	49	(4.8)
Tachycardia ventricular/arrhythmia[b]	31	(3.1)	28	(2.8)	44	(4.3)	39	(3.8)
Cardiomyopathy	29	(2.9)	25	(2.5)	40	(3.9)	37	(3.7)
Tachycardia supraventricular	30	(3.0)	27	(2.7)	39	(3.8)	34	(3.4)
Hyperkalaemia	16	(1.6)	54	(5.3)	18	(1.8)	54	(5.3)
Dizziness/vertigo[b]	21	(2.1)	43	(4.2)	23	(2.3)	45	(4.4)
Dyspnoea/dyspnoea (aggravated)[b]	39	(3.8)	17	(1.7)	43	(4.2)	22	(2.2)
Syncope	28	(2.8)	26	(2.6)	35	(3.4)	30	(3.0)

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

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 62) 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 62 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-Alternative 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 the CHARM-Pooled population, 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. In the CHARM-Alternative study population, cardiac failure/cardiac failure aggravated was more frequent in the placebo group than in the candesartan group, whereas hypotension and angina pectoris/angina pectoris aggravated were more frequently reported in the candesartan group than in the placebo group.

7.1.5 Laboratory Findings

Clinical laboratory results in CHARM-Alternative (SH-AHS-0003) Study:

Serial laboratory data were collected from patients participating at investigational sites in North America (placebo 334 patients, candesartan 326 patients).

Changes in mean laboratory values from baseline values to the last value carried forward (LVCF) 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, such as creatinine and potassium.

The mean value for creatinine in the placebo group decreased 4.73 µmol/L from the baseline value to the LVCF (two extreme values were present at baseline but not at LVCF explaining the decrease). In the candesartan group, the value increased 17.9 µmol/L. At baseline, 75 (22.4%) of placebo patients had values above the reference range compared with 78 (23.9%) 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 94, 29.8%; candesartan 120, 37.3%).m For patients who had serial measurements (placebo 307 patients, candesartan 311 patients) baseline serum creatinine was at least doubled in 5 (1.6%) patients in the placebo group, compared with 17 (5.4%) 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 0.24 mmol/L for patients treated with candesartan. During the study, the proportions of patients with values above the reference range remained approximately the same in the placebo group (6, 1.8% at baseline, 7, 2.2% LVCF) and increased from 7 (2.1%) to 22 (6.8%) in the candesartan group. Potassium levels increased to ≥ 6 mmol/ L at any time after randomization in 1.3% (4) of 315 patients valid for evaluation in the placebo group and 2.8% (9) of 321 patients in the candesartan group.

Mean sodium measurements increased 0.03 mmol/L for patients treated with placebo and decreased 0.39 mmol/L for patients in the candesartan group. The AE term hyponatremia was reported for four patients (Site – Patient number: 358 – 10453, 455 – 16036, 943 – 14360, 1515 – 20840) treated with placebo compared with one patient (Site 1480, Patient number 23729) treated with candesartan.

Minor decreases were seen for mean hemoglobin values for patients treated with placebo (0.13 mmol/L) and candesartan (0.24 mmol/ L). The proportion of patients with anemia reported as an AE during treatment with the investigational product was slightly lower for placebo-treated patients (16, 1.6%) compared with candesartan-treated patients (29, 2.9%). No patients in the placebo treatment group and 1 (0.3%) of 320 patients valid for evaluation 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 (-0.39%) and candesartan groups (-0.25%).

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 63 and Table 64 for the total CHARM-Pooled population, and in Table 65 and Table 66 for the subpopulation of CHF patients with LV dysfunction.

Table 63 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 64 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 65 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 66 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 63).

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 64).

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[41], no significant differences are found in biochemical variables at the end of the study between losartan and atenolol treatment groups. In OPTIMAAL trial[38], 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-Alternative (SH-AHS-0003) Study:

At LVCF mean heart rate was 0.7 bpm lower in patients in the placebo group and 1.8 bpm lower in patients in the candesartan group compared to baseline.

Blood pressure declined in both treatment groups. Mean DBP decreased 3.5 mmHg from the baseline value to the LVCF in the placebo group and 4.8 mmHg from the baseline value to the LVCF in the candesartan group. Corresponding values for SBP were 4.4 mmHg for patients treated with placebo and 6.5 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 5 (0.5%) patient in the placebo group and 16 (1.6%) patients in the candesartan group. 20 (2.0%) patients treated with placebo and 54 (5.4%) patients treated with candesartan had a recorded SBP value less than 80 mmHg at any time after randomization.

In the placebo group, mean body weight decreased by 0.5 kg from baseline to LVCF. In the candesartan population an increase of 0.7 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 13, Figure 14, Figure 15, and Figure 16.

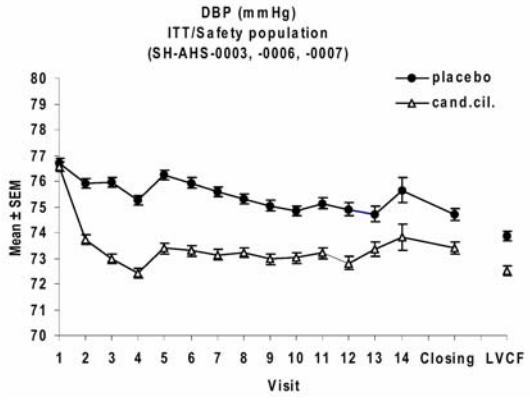


Figure 13 Mean DBP ± SEM (mmHg) by visit for the total population. ITT/Safety population

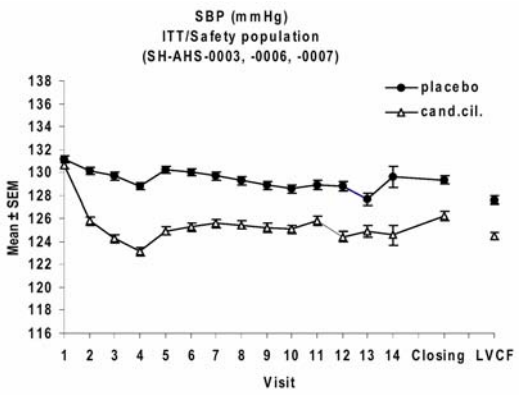


Figure 14 Mean SBP ± SEM (mmHg) by visit for the total population. ITT/Safety population

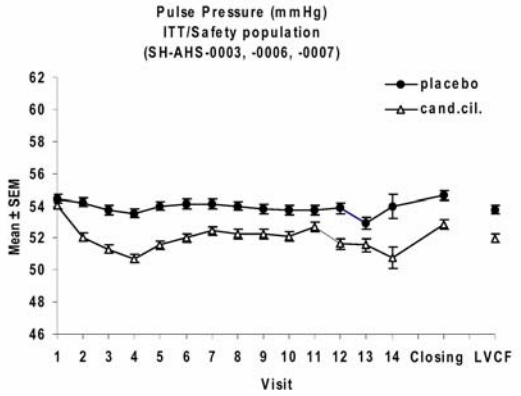


Figure 15 Mean Pulse Pressure ± SEM (mmHg) by visit for the total population. ITT/Safety population

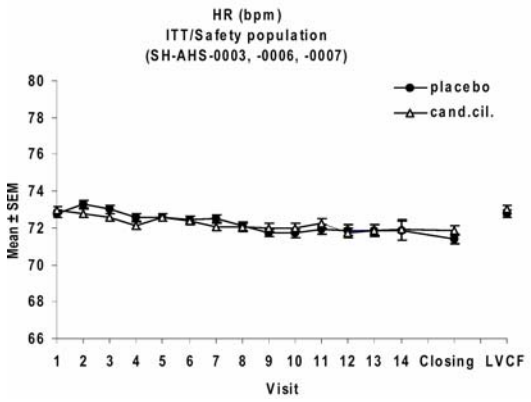


Figure 16 Mean heart rate ± SEM (bpm) by visit for the total population. ITT/Safety population

Changes in vital signs over time in the subpopulation of patients with depressed LV systolic function are shown in Figure 17, Figure 18, Figure 19 and Figure 20.

The number of patients with clinically important changes in vital signs in the total population are shown in (Table 67, Table 68 and Table 69) 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 70 and Table 71).

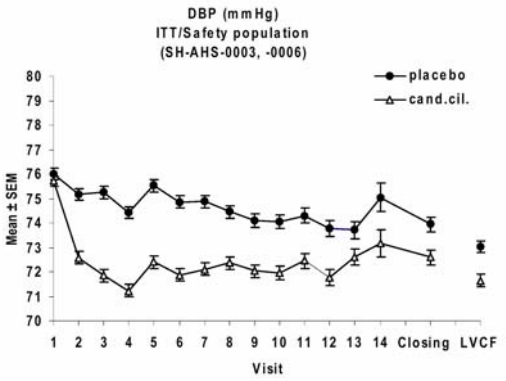


Figure 17 Mean DBP ± SEM (mmHg) by visit for the depressed LV systolic function subpopulation. ITT/Safety population

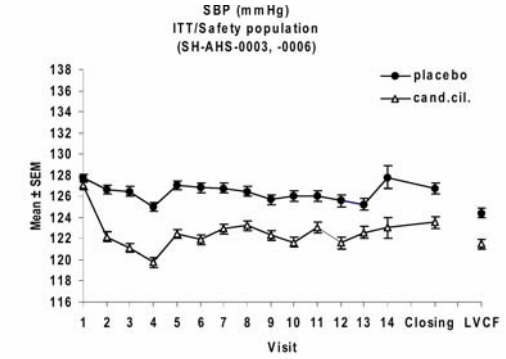


Figure 18 Mean SBP ± SEM (mmHg) by visit for the depressed LV systolic function subpopulation. ITT/Safety population

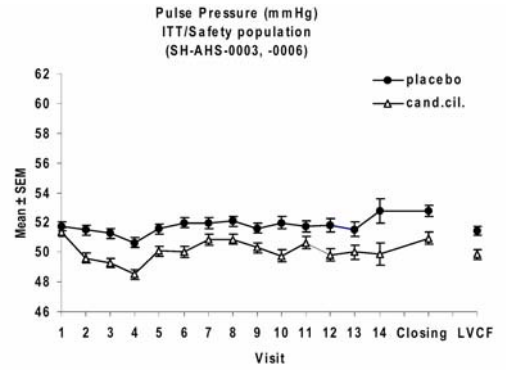


Figure 19 Mean Pulse Pressure ± SEM (mmHg) by visit for the depressed LV systolic function subpopulation. ITT/Safety population

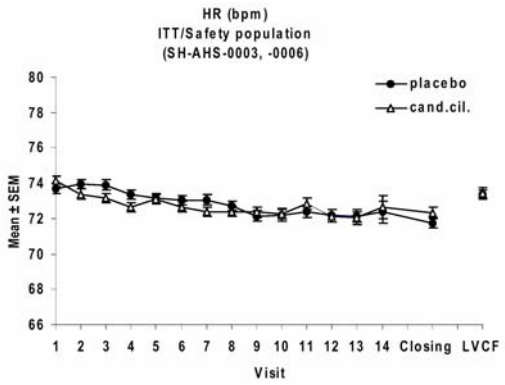


Figure 20 Mean heart rate ± SEM (bpm) by visit for the depressed LV systolic function subpopulation. ITT/Safety population

Table 67 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 68 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 69 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 70 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 71 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 69).

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

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-Alternative (SH-AHS-0003) Study

A total of 2,028 patients (646 females and 1,382 males) were randomized into the study; all were included in the ITT/safety population. Patients who received incorrect investigational product

during any part of the study (7 patients) were 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 is presented in Table 72, including data on the number of patients who completed or discontinued the study.

Table 72 Overview of exposure. ITT/Safety population (SH-AHS-0003)

		Placebo (N=1015)		Cand. cil. (N=1013)	
No. (%) of patients evaluable for safety	Male	691	(68.1)	691	(68.2)
	Female	324	(31.9)	322	(31.8)
Age	<65	392	(38.6)	412	(40.7)
	≥65	623	(61.4)	601	(59.3)
	<75	776	(76.5)	780	(77.0)
	≥75	239	(23.5)	233	(23.0)
Race[a]	Caucasian	922	(90.8)	926	(91.4)
	Black	45	(4.4)	28	(2.8)
	Oriental	37	(3.6)	43	(4.2)
	Other	11	(1.1)	16	(1.6)
Exposure by discontinuation due to AE of investigational product and/or study (N and %)	Discontinued investigational product due to AEs	197	(19.4)	220	(21.7)
	Patients who withdrew consent	16	(1.6)	18	(1.8)

[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 33.8 months for patients randomized to candesartan and 33.6 months for patients randomized to placebo. The median duration of exposure of the investigational product was 29.5 months in the placebo group and 29.4 months in the candesartan group.

A total of 824 (81.3%) patients in the candesartan group started treatment on 4 mg once daily and 189 (18.7%) patients started on 8 mg once daily at randomization (baseline). A total of 1,313 (64.7%) patients (candesartan 666, 65.8%; placebo 647, 63.7%) received the investigational product for 24 months or more. 52.2% of the candesartan patients (58.9% of those still receiving the investigational product) were treated with the target dose 32 mg once daily at 6 months (visit 5). The mean dose in the candesartan group was 23.2 mg at 6 months. At the end of treatment (LVCF) 44.1% (60.3% 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 73. Table 74 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 73 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 74 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 74). 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 75 and Table 76.

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 76).

Table 75 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 76 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 (Section 10 (References) of this review) did not reveal reports of unexpected organ-specific toxicity. In this review, I have presented and discussed under each heading of the safety review template the data in the medical literature, with tables and figures where necessary, within the context of the CHARM-Alternative and CHARM-Program Studies.

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, slightly more of the study patients randomized to candesartan cited hypotension as their reason for ACE inhibitor intolerance (placebo 119, 11.7%; candesartan 143, 14.1%). Also, there was a slightly higher proportion of patients in the candesartan group with SBP < 100 mmHg (placebo 22, 2.2%; candesartan 31, 3.1%) (North American study population). AEs suggesting a ' hypotensive' event were reported less frequently for patients in the placebo group (116, 11.4%) than the candesartan group (228, 22.5%) on treatment with the investigational product (Table 77).

Table 77 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)

Placebo on treatment N=1015	Cand. cil. on treatment N=1013	Placebo during study N=1015	Cand. cil. during study N=1013
116 (11.4)	228 (22.5)	137 (13.5)	233 (23.0)

The individual AE term contributing the largest numbers to this composite AE was hypotension, which was reported for 76 (7.5%) of patients given placebo and 190 (18.8%) of patients given candesartan (Table 61).

Of the patients in the composite 'hypotensive' group, fatal events were reported in the same number of patients in each treatment group (3 in the candesartan group, 3 in the placebo group). In both treatment groups, hypotensive events that led to death were reported in association with other causes of death such as cardiac arrest or failure, ventricular tachycardia and respiratory failure. In the candesartan treated patients, the fatal events occurred well after the titration phase and were assessed by the investigators as related to the investigational product.

The investigational product was discontinued for the specific AE term hypotension in 14 (1.4%) placebo patients and 46 (4.5%) candesartan patients (Table 39). Corresponding figures for the exploratory analysis were 9 (0.9%) placebo patients and 37 (3.7%) candesartan patients (Table 44). The higher proportion of hypotensive events leading to discontinuation in the candesartan group could not be explained by between treatment differences in baseline blood pressure or concomitant medications when the event started, including diuretics and β-blockers As noted above, more candesartan patients had a history of hypotension on an ACE inhibitor.

In patients aged younger than 75 years, discontinuation because of the preferred term hypotension was reported in 11 (1.4%) of patients in the placebo group and 32 (4.1%) of patients on candesartan. For patients aged ≥75 years the discontinuation rates were 3 (1.3%) in the placebo group and 14 (6.3%) in the candesartan group.

In the placebo group, permanent discontinuation of the investigational product due to hypotension was reported in 11 (1.6%) males and 3 (0.9%) females. In the candesartan treatment group there were 34 (4.9%) males and 12 (3.7%) females who were permanently discontinued due to hypotension). The majority of patients were Caucasians.

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 21).

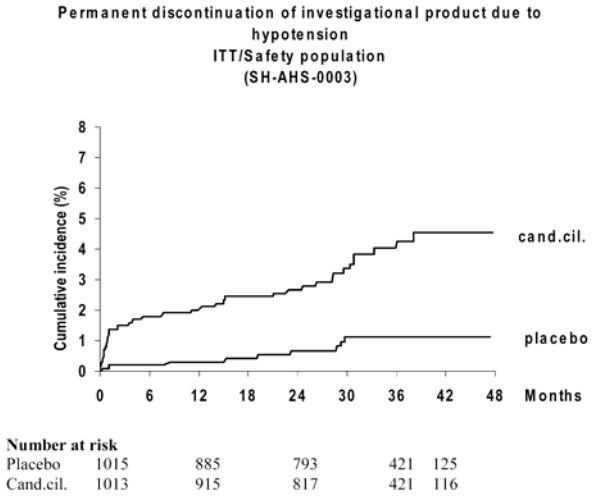


Figure 21 Cumulative incidence (%) of permanent discontinuation of investigational product due to hypotension (Ref. - Table 42). ITT/Safety population

Among the 270 (26.6%) placebo patients and 278 (27.4 %) candesartan patients entering the study with a history of diabetes, investigational product discontinuation for the specific preferred term hypotension was noted for 1 (0.4%) placebo patient and 11 (4.0%) 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 78).

Table 78 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 79).

Table 79 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 80). 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 80 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 40). Corresponding figures for the exploratory analysis were 66 (1.7%) placebo patients and 132 (3.5%) candesartan patients (Table 48). 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.

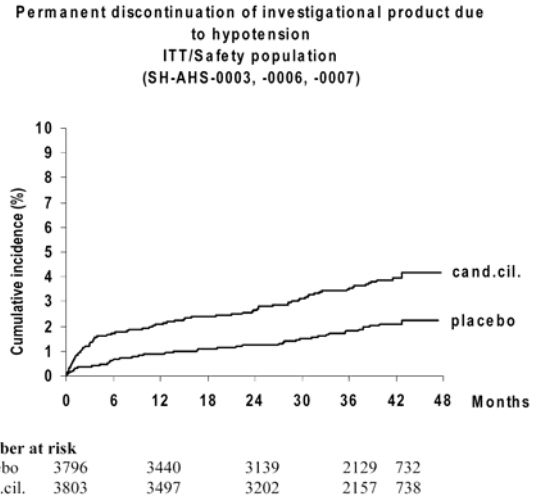


Figure 22 Cumulative incidence (%) of permanent discontinuation of the investigational product due to hypotension. ITT/Safety population

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 22).

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[39], 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-Alternative (SH-AHS-0003) Study:

At baseline, prior to study entry, more patients randomized to candesartan (placebo 100, 9.8 %; candesartan 134, 12.8 %) cited 'renal dysfunction' as the reason for ACE-inhibitor intolerance. Also, there were a slightly higher proportion of patients in the candesartan group with serum creatinine > 2.0 mg/dl at baseline placebo 26, 7.8%; candesartan 30, 9.2%)(North American study population).

AEs suggesting 'abnormal renal function' occurred in 82 (8.1%) in the placebo group and 163 (16.1 %) patients in the candesartan group during study (Table 81).

Table 81 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-0003)

Placebo on treatment N=1015	Cand. cil. on treatment N=1013	Placebo during study N=1015	Cand. cil. during study N=1013
74 (7.3)	157 (15.5)	82 (8.1)	163 (16.1)

The AE terms that predominately contributed to this composite AE term was renal function abnormal which was reported in 50 (4.9%) of patients given placebo and 141 (13.9%) given candesartan during study. Renal failure, acute (placebo, 19 patients, 1.9%; candesartan, 31 patients, 3.1%) and uremia (placebo, 7 patients, 0.7%; candesartan, 14 patients, 1.4%) were also numerically more frequent in patients given active treatment.

Among the patients with 'abnormal renal function', similar numbers in both treatment group had an event, which proved a fatal renal function event 'during study' (8 in the candesartan group, 9 in the placebo group). 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 or respiratory failure.

In the descriptive safety analysis (Table 39), on investigational product discontinuation in the overall study population, the specified AE term renal function abnormal/renal dysfunction aggravated was, second to aggravation of cardiac failure, the most common reason for permanent discontinuation of the investigational product in both treatment groups (placebo 25, 2.5%; candesartan 65, 6.4%). (Table 44).

In the exploratory analysis the term increased creatinine was reported for 27 (2.7%) placebo patients and 62 (6.1%) candesartan patients (Table 44). The higher rate for discontinuation of the investigational product due to '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). As noted above, more candesartan than placebo patients gave a history of ACE inhibitor intolerance because of abnormal renal function.

In patients aged younger than 75 years, discontinuation because of the AE term renal function abnormal/renal dysfunction aggravated was reported in 20 (2.6%) of patients in the placebo group and 44 (5.6%) of patients on candesartan. For patients aged 75 years or older the discontinuation rates were 5 (2.1%) in the placebo group and 21 (9.4%) in the candesartan group.

In the placebo group the majority of events were seen in male patients (24, 3.5%) compared to only one female. In the candesartan treatment group 47 (6.8%) males and 18 (5.6%) females reported the renal event. The vast majority of patients in both treatment groups were Caucasians.

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 23).

Among the 270 (26.6 %) placebo patients and 278 (27.4 %) candesartan patients entering the study with a history of diabetes, investigational product discontinuation for the specific term increased creatinine was noted for 12 (4.4%) placebo and 25 (9.0%) candesartan patients. Compared to the overall population (placebo 2.7%, candesartan 6.1%) diabetics were slightly more likely to discontinue the investigational product for increased creatinine levels (Table 44).

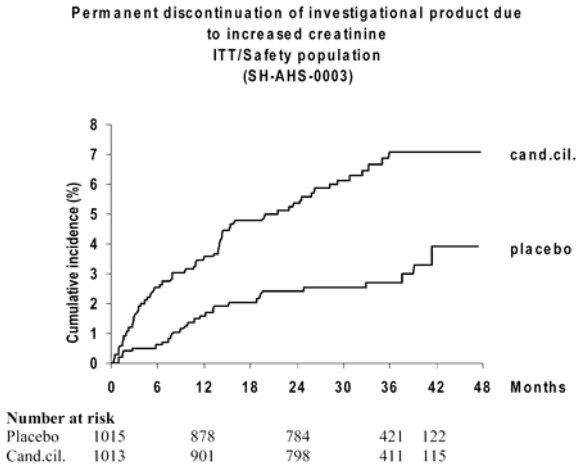


Figure 23 Cumulative incidence (%) of permanent discontinuation of investigational product due to increased creatinine (Ref. - Table 42). ITT/Safety population

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 82).

Table 82 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 83 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 83). 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 40). In the exploratory analysis the term increased creatinine was reported for 115 (3.0%) placebo patients and 234 (6.2%) candesartan patients (Table 48). 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 84).

Table 84 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 24).

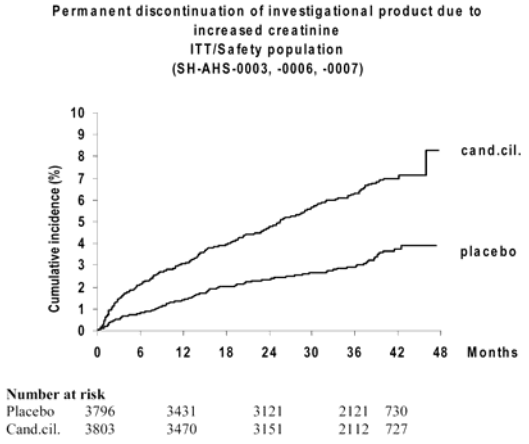


Figure 24 Cumulative incidence (%) of permanent discontinuation of the investigational product due to increased creatinine. ITT/Safety population

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 52 and Table 53). Compared to the total population (placebo 3.0%, candesartan 6.2%) (Table 48), 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[20]. 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 inhibitors and/or ARBs may be associated with higher levels of serum creatinine. In stage II of the RESOLVD trial[11] 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[18] 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-Alternative (SH-AHS-0003) Study:

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

Hyperkalemia was reported for 16 patients (1.6%) in the placebo group and 54 patients (5.3%) in

the candesartan group on treatment with the investigational product (Table 61).

Fatal hyperkalemia 'on treatment' was not reported for any patients in the candesartan group or the placebo group.

In Table 39, discontinuation of the investigational product because of hyperkalemia was predominately limited to patients treated with candesartan (placebo 3, 0.3%; candesartan 21, 2.1%). In the exploratory analysis the corresponding numbers were 3 (0.3%) for placebo patients and 19 (1.9%) for candesartan patients (Table 44). 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).

In patients < 75 years old, discontinuation because of the AE term hyperkalemia was reported in 2 (0.3%) patients in the placebo group and 11 (1.4%) of patients on candesartan. For patients aged 75 years or older the discontinuation rates were 1 (0.4%) in the placebo group and 10 (4.5%) in the candesartan group.

In the placebo group there was a low frequency of events for both genders, in the candesartan treatment group the majority of events were seen in male patients (17, 2.5%) compared to females (4, 1.2%). The vast majority of patients in both treatment groups were Caucasians.

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 25).

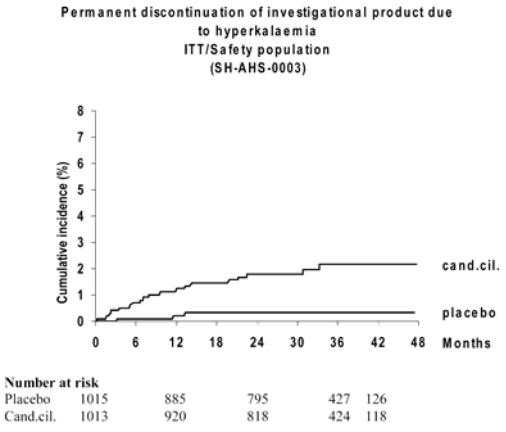


Figure 25 Cumulative incidence (%) of permanent discontinuation of investigational product due to hyperkalemia. ITT/Safety population (Ref. - Table 42).

Among the 270 (26.6 %) placebo patients and 278 (27.4 %) candesartan patients entering the study with a history of diabetes, investigational product discontinuation for the specific preferred term hyperkalemia was noted for 3 (1.1%) placebo and 5 (1.8%) 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 62).

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 40, 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 48). 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 84).

In patients aged < 75 years old, discontinuation because of hyperkalemia was reported in 14 (0.5%) patients in the placebo group and 57 (1.9%) patients on candesartan. For patients aged ≥ 75 years, the discontinuation rates due to hyperkalemia 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%).

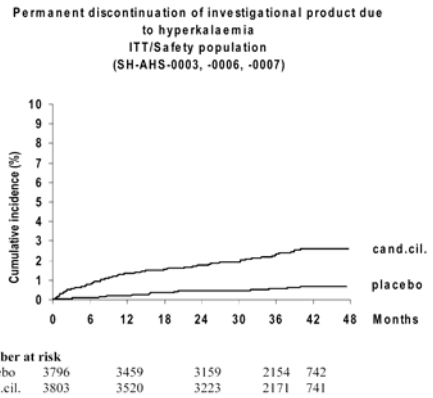


Figure 26 Cumulative incidence (%) of permanent discontinuation of the investigational product due to hyperkalemia. ITT/ Safety population

The discontinuation rate for candesartan-treated patients because of hyperkalemia (Figure 26), presented from exploratory analysis, was somewhat greater during the first 6 to 12 months of treatment, but discontinuations still occurred over the entire study period.

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 52 and Table 53).

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[20] 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[21,41,42]. 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[38], 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[18] 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[11] 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 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.

Myocardial ischemia in CHARM-Alternative (SH-AHS-0003) Study:

At baseline, prior to randomization into the study there were no major 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 bypass grafting (placebo 244, 24.0 %; candesartan 269, 26.5 %).

The proportions of patients with 'myocardial ischemia' 'on treatment' were approximately equal between the placebo treatment group (16.4%) and the candesartan group (18.0%) (Table 87).

Table 85 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)

Placebo on treatment N=1015	Cand. cil. on treatment N=1013	Placebo during study N=1015	Cand. cil. during study N=1013
166 (16.4)	182 (18.0)	190 (18.7)	217 (21.4)

The AE term accounting for the greatest number of patients in this composite AE was angina pectoris which was also reported for essentially equal proportions of patients in the two groups (placebo 109, 10.7%; candesartan 105, 10.4%). The AE term MI occurred in 58 (5.7%) patients in the placebo group and in 71 (7.0%) in the candesartan group 'on treatment.'

The risk of 'myocardial ischemic' events during candesartan therapy could not be explained by concomitant medication at the start of the event. AEs related to hypotension, reported at the same time as angina pectoris or MI, were more frequent in the candesartan group (angina pectoris 9 patients, MI 7 patients) than in the placebo group (angina pectoris 2 patients, MI 0 patients). For coronary artery disorder there was no difference.

'Myocardial ischemic' events that were fatal were reported for 21 (2.1%) patients in the placebo group and 48 (4.7%) patients in the candesartan group during study (Table 86).

Table 86 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)

Placebo on treatment N=1015	Cand. cil. on treatment N=1013	Placebo during study N=1015	Cand. cil. during study N=1013
11 (1.1)	35 (3.5)	21 (2.1)	48 (4.7)

Most of the fatal 'myocardial ischemic' events 'during study' were attributed to fatal MI (17 patients in the placebo group and 38 in the candesartan group). For patients treated with candesartan in CHARM-Alternative study, the hazard ratio for fatal MI was 1.942 (P=0.025).

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

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%, placebo group vs. 16.7% candesartan group) (Table 87).

Table 87 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 88).

Table 88 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).

7.3.5 Angioedema

Angioedema in CHARM-Alternative (SH-AHS-0003) Study

During study, three cases of angioedema were reported for patients in the candesartan group. All 3 patients were Caucasian with a history of previous angioedema reactions while taking ACE-inhibitors. None of the three events was considered life threatening or led to hospitalization.

Thirty-nine patients in the candesartan group had a history of ACE-inhibitor intolerance due to angioedema. One of these patients developed angioedema that required discontinuation of

candesartan treatment. For the two remaining patients with angioedema, candesartan treatment continued without recurrence, and for one of these the dose was reduced. For two patients, the reaction occurred one month after randomization, and for the third patient the angioedema occurred more than a year after administration of the first dose of candesartan.

Of 44 patients in the placebo group who had a history of angioedema, none discontinued investigational product because of angioedema.

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, particularly 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[39] 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 54).

Also, in the OPTIMAAL study[38] 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 55) 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 55) 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.

7.3.6 Abnormal hepatic function

Abnormal hepatic function in CHARM-Alternative (SH-AHS-0003) Study:

The most common AE terms suggesting liver dysfunction during treatment were hepatic

enzymes increased (placebo 4 patients; candesartan 2 patients) and hepatic function abnormal (placebo 3 patients; candesartan 3 patients). The AE term hepatic failure was reported for 1 patient in the placebo group and 2 patients in the candesartan group.

In the candesartan group there was one fatal case of hepatic necrosis considered related to amiodarone (Site 373, Patient number 15108), and one fatal case of cholestatic hepatitis considered related to septic cholangitis (Site 1476, Patient number 21109; this patient is not included in the listings of AEs of special interest).

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-Alternative (SH-AHS-0003) Study

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 59 patients (5.8%) in each treatment group. One patient in the placebo group (Site 558, Patient number 13436) had breast neoplasm, malignant, female and carcinomatosis together with pleural mesothelioma. In the total numbers presented above this patient is counted only once. Neoplasms proved fatal for 18 patients (1.8%) in the placebo group and 23 patients (2.3%) in the candesartan group.

In the overall study population, the majority of patients did not have a history of cancer at baseline (placebo 92.9%; candesartan 93.9%).

The majority of reported neoplasms were malignant. The most common neoplasms during study were pulmonary cancer (placebo, 3 patients; candesartan, 10 patients), colon cancer (6 patients in each group), prostatic cancer (placebo, 3 patients; candesartan, 8 patients) and breast neoplasm

malignant female (placebo 4 patients; candesartan 5 patients).

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).

Permanent discontinuation and dose reduction of investigational product according to reason for ACE-inhibitor intolerance

Reasons for ACE-inhibitor intolerance, as noted at study entry, were not common reoccurrences as causes for permanent discontinuation or dose reduction of the investigational product (Table 89 and Table 90).

Table 89 Reasons for permanent discontinuation of investigational product compared to reason for ACE inhibitor intolerance at baseline. ITT/Safety Population (SH-AHS-0003)

	Treatment			
	Placebo (N=1015)		Cand. cil. (N=1013)	
Reason for ACE inhibitor intolerance at baseline	Number of patients, who were intolerant at baseline	Number of patients (%), who permanently discontinued treatment with investigational product	Number of patients, who were intolerant at baseline	Number of patients (%), who permanently discontinued treatment with investigational product
Cough	751	4 (<1.0)	704	2 (<1.0)
Hypotension	119	5 (4.2)	143	13 (9.0)
Renal dysfunction[a]	100	12 (12.0)	134	31 (23.0)
Angioedema	44	0 (0)	39	1 (2.6)
Other[b]	109	9 (8.3)	101	8 (7.9)
Any reason	1015	295 (29.1)	1013	308 (30.4)

a Reason for ACE-inhibitor intolerance was defined as renal dysfunction. Reason for permanent discontinuation of investigational product included was defined as abnormal renal function.
b Includes any adverse event, lab value, or unknown reason.

Table 90 Reasons for the first dose reduction of investigational product compared to reason for ACE- inhibitor intolerance at baseline. ITT/Safety Population (SH-AHS-0003)

	Treatment			
	Placebo (N=1015)		Cand. cil. (N=1013)	
Reason for ACE inhibitor intolerance at baseline	Number of patients, who were intolerant at baseline	Number of patients (%), who had at least one dose reduction of investigational product	Number of patients, who were intolerant at baseline	Number of patients (%), who had at least one dose reduction of investigational product
Cough	751	3 (<1.0)	704	4 (<1.0)
Hypotension	119	6 (5.0)	143	25 (17.4)
Renal dysfunction[a]	100	3 (3.0)	134	22 (16.4)
Angioedema	44	0 (0)	39	1 (2.6)
Other[b]	109	1 (<1.0)	101	17 (16.8)
Any reason	1015	106 (10.4)	1013	201 (19.8)

a Reason for ACE-inhibitor intolerance was defined as renal dysfunction. Reason for permanent discontinuation of investigational product was defined as abnormal renal function.
b Includes any adverse event, lab value, or unknown reason.

Cough was the most frequently cited reason for ACE-inhibitor intolerance at baseline (73.9% of placebo-treated patients; 69.5% of candesartan-treated patients) but was associated with a discontinuation rate < 1% in both groups for a recurring event during study. Of patients with a history of symptomatic hypotension as a reason for ACE-inhibitor intolerance, 4.2% in the placebo group and 9.0% in the candesartan group discontinued because of hypotension. Renal dysfunction as a recurrent event was reported for 12.0% of patients in the placebo group compared with 23.0% in the candesartan group.

Regarding dose reductions, the rate for cough was < 1% in both treatment groups for a recurring event during study. In the candesartan group, compared to discontinuation, it was more common to have a dose reduction for recurring hypotension, while it was more common to permanently discontinue candesartan treatment if abnormal renal function was the recurring event.

7.3.9 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 on November 18, 2004, I requested the sponsor to provide information on the CHARM-Alternative (SH-AHS-0003) 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 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 November 24, 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, I used the definition for high candesartan dose 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 91, 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 91 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 – CHARM-Alternative (SH-AHS-0003) Study

Candesartan	**N = 1013** **Events = 218 (21.5%)**		
			A
	CC_{HD} n = 626 events = 97 (15.5%)	CC_{LD} n = 260 events = 100 (38.5%)	CC_{00} n = 127 events = 21 (16.5%)
	A1	**A2**	**A3**
Placebo	**N = 1015** **Events = 196 (19.3%)**		
			B
	P_{HD} n = 748 events = 124 (16.6%)	P_{LD} n = 140 events = 60 (42.9%)	P_{00} n = 127 events = 12 (9.5%)
	B1	**B2**	**B3**

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

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

In Table 92, no relationship is apparent between the dose of candesartan and the numbers and frequencies of permanent study drug discontinuation due to hypotension.

Table 92 The numbers and frequencies of permanent study drug discontinuation due to hypotension[a] in patients who received high or low dose candesartan – CHARM-Alternative (SH-AHS-0003) Study

Candesartan	**N = 1013** **Events = 37 (3.7%)**		
			A
	CC_{HD} n = 556 events = 9 (1.6%)	CC_{LD} n = 207 events = 24 (11.6%)	CC_{00} n = 250 events = 4 (1.6%)
	A1	**A2**	**A3**
Placebo	**N = 1015** **Events = 9 (0.9%)**		
			B
	P_{HD} n = 666 events = 5 (0.8%)	P_{LD} n = 102 events = 4 (3.9%)	P_{00} n = 247 events = 0 (0.0%)
	B1	**B2**	**B3**

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

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

In Table 93, no relationship is apparent between the dose of candesartan and the numbers and frequencies of permanent study drug discontinuation due to hyperkalemia.

Table 93 The numbers and frequencies of permanent study drug discontinuation due to hyperkalemia[a] in patients who received high or low dose candesartan – CHARM-Alternative (SH-AHS-0003) Study

Candesartan	**N = 1013** **Events = 19 (1.9%)**		
			A
	CC_{HD} n = 557 events = 10 (1.8%)	CC_{LD} n = 192 events = 8 (4.2%)	CC_{00} n = 264 events = 1 (0.4%)
	A1	**A2**	**A3**
Placebo	**N = 1015** **Events = 3 (0.3%)**		
			B
	P_{HD} n = 665 events = 3 (0.5%)	P_{LD} n = 98 events = 0 (0.0%)	P_{00} n = 252 events = 0 (0.0%)
	B1	**B2**	**B3**

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

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

In Table 94, 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 94 The numbers and frequencies of permanent study drug discontinuation due to increased creatinine[a] in patients who received high or low dose candesartan – CHARM-Alternative (SH-AHS-0003) Study

Candesartan	**N = 1013** **Events = 62 (6.1%)**		
			A
	CC_{HD} n = 578 events = 32 (5.5%)	CC_{LD} n = 209 events = 26 (12.4%)	CC_{00} n = 226 events = 4 (1.8%)
	A1	**A2**	**A3**
Placebo	**N = 1015** **Events = 27 (2.7%)**		
			B
	P_{HD} n = 675 events = 16 (2.4%)	P_{LD} n = 106 events = 9 (8.5%)	P_{00} n = 234 events = 2 (0.9%)
	B1	**B2**	**B3**

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

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 95, 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 95 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 – CHARM-Alternative (SH-AHS-0003) Study

Candesartan	**N = 1013** **Events = 182 (18.0%)**		
			A
	CC_{HD} n = 621 events = 120 (19.3%)	CC_{LD} n = 171 events = 60 (35.1%)	CC_{00} n = 221 events = 2 (0.9%)
	A1	**A2**	**A3**
Placebo	**N = 1015** **Events = 89 (8.8%)**		
			B
	P_{HD} n = 693 events = 64 (9.2%)	P_{LD} n = 97 events = 25 (25.8%)	P_{00} n = 225 events = 0 (0.0%)
	B1	**B2**	**B3**

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

7.5 Summary of Safety

7.5.1 Summary of safety for CHARM-Alternative (SH-AHS-0003) 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 724, 71.3%; candesartan 725, 71.6%) and over the entire study period (placebo 747, 73.6%; candesartan 741, 73.1%).

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

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

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

Apart from cardiac failure aggravated (placebo 72, 7.1%; candesartan 53, 5.2%), abnormal renal function (placebo 25, 2.5%; candesartan 65, 6.4%), hypotension (placebo 14, 1.4%; candesartan 46, 4.5%) and hyperkalemia (placebo 3, 0.3%; candesartan 21, 2.1%) were the most commonly reported AE, given as reasons for discontinuing the investigational product.

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

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

The following findings are noted between the two treatment groups:

- Candesartan did not influence *time* to permanent discontinuation of the investigational product due to any cause (P =0.735).
- Candesartan did not increase the *number* of permanent discontinuations of the investigational product due to any cause (P =0.509).
- Candesartan did not influence *time* to permanent discontinuation of the investigational product due to an AE or an abnormal laboratory value (P =0.332).
- Candesartan did not increase the *number* of permanent discontinuations of the investigational product due to an AE or an abnormal laboratory value (P =0.217).
- 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=0.948).
- Candesartan did not increase the *number* of non-CV deaths (P=0.822)
- Candesartan did not increase the *number* of non-CV hospitalizations (P=0.652).

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% of patients in the placebo group and 23.2% of 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 CHARM Program studies (SH-AHS-0003, -0006 and -0007). I have presented and discussed the pivotal CHARM-Alternative (SH-AHS-000) study data 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 Rationale, Dosing Regimen and Administration

8.1.1 Prevalence of intolerance to ACE-inhibitors and candidates for treatment with ARBs

Estimates of the incidence of intolerance of ACE inhibitors among patients with heart failure range from 5% to 10%[5,6,7]. A registry of almost 10,000 patients with depressed LV systolic function also showed that 10% of these patients had a history of intolerance to ACE inhibitors[8].

A nationwide survey of patterns of use of ACE inhibitors in patients ≥65 years old who had survived hospitalization for heart failure with left ventricular systolic dysfunction revealed that ACE inhibitors were prescribed to only 68% of this cohort[3]. At least 20% of patients with heart failure do not take ACE inhibitors[4], in part because of intolerance. Similarly, of the 10% of the 10,000 patients with depressed LV systolic function who had a history of intolerance to ACE inhibitors, 6% were found to be both intolerant to ACE inhibitors and candidates for angiotensin II AT_1-receptor blockers (ARBs)[8]. While this is a small percentage, in the United States alone there are an estimated 2 million persons with heart failure[9]; this translates into 120,000 such CHF patients with depressed LV systolic function and intolerance to ACE inhibitors becoming candidates for treatment with ARBs.

8.1.2 Other situations where patients with CHF may be candidates for treatment with ARBs

Patients on ACE-inhibitors may undergo "ACE-escape," in which a gradual elevation of serum angiotensin II and aldosterone levels occurs despite ongoing RAAS inhibition with ACE-inhibitors[22,23]. "ACE-escape" is considered to portend a worse prognosis from CHF[24]. These patients may be candidates to be treated with ARBs which may prevent "ACE-escape"[25,26] because ARBs produce specific angiotensin II blockade via AT_1 receptors and preserve (theoretical) benefits derived from unopposed AT_2 receptor agonism (which is believed to counter the AT_1 response and lead to anti-proliferative, anti-growth and vasodilatory effects[27,28]).

The genetic heterogeneity of the ACE gene may influence the effectiveness of ACE inhibitors. A polymorphism in intron 16 of the ACE gene may cause two alleles (I= insertion; D= deletion) to differ on the presence or absence of a 287 pair-based insertion[29]. The ACE DD genotype, which forms about one-third of the general population, is associated with higher ACE activity[30], and with poor survival for patients with congestive heart failure[31]. In a study of 479 patients with systolic dysfunction (LVEF 0.25±0.08) who were genotyped for the ACE D/I polymorphism[32] and followed to the endpoint of death or cardiac transplantation, 227 patients received ACE inhibitor at "low doses" (≤50% of target dose), 201 patients received "high (standard) dose," and 51 patients received ARBs. The ACE-D allele was associated with an increased risk of events (P=0.026), particularly in the low-dose group (2-year event-free survival percentage: II/ID/DD = 79/66/59, P = 0.032). In the high dose group, this impact was not found (2-year event-free survival percentage: II/ID/DD = 77/70/71, P=0.64). These CHF patients who are not able to tolerate standard doses of ACE inhibitors and are at increased risk of mortality from HF, particularly those with the DD genotype, are potential candidates for ARB treatment.

8.1.3 Can ARBs be tolerated by patients with CHF who are intolerant to ACE inhibitors?

The Study of Patients Intolerant to Converting Enzyme Inhibitors (SPICE)[10] showed that patients with CHF and LVEF <35% who are intolerant to ACE inhibitors were able to tolerate candesartan (4 mg once/day, titrated to 16 mg once/day) similar to those who tolerated placebo (84% vs. 87%); however, the mortality and all-cause hospitalization were not significantly different between the candesartan and placebo groups in this relatively small pilot study of 270 patients. This finding that direct inhibition of the effect of angiotensin is tolerated by patients with a history of intolerance to ACE inhibitors suggests that intolerance to ACE inhibitors is primarily mediated through effects other than those of angiotensin.

ARBs differ from ACE-inhibitors in that they block the effect of angiotensin II at the AT_1 receptor, thus blocking the effects of angiotensin II produced through both ACE-dependent and ACE-independent pathways. Therefore, ARBs may exert a more complete inhibition of the local 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[11] and vascular epithelial changes. Thus, ARBs may be useful in the treatment of CHF with left ventricular dysfunction in patients who are intolerant to ACE inhibitors.

8.1.4 Are all ARBs equal in their clinical effects?

The PK and PD characteristics of ARBs approved in the United States[33] are shown in Table 96.

Table 96 Pharmacokinetic and Pharmacodynamic properties of AT_1 receptor antagonists[33]. (Based on data from Lancet 2000; 355:637-45.)

Drug	In-vitro AT_1-receptor affinity*	Bioavailability (%)	Food effect	Active metabolite	Half-life (h)	Protein binding (%)	Daily dosage (mg)
Losartan (EXP 3174)	IC_{50}:20 nmol/L	33	No	Yes	2 (6–9)	98·7 (99·8)	50–100
Valsartan	IC_{50}:2·7 nmol/L	25	Yes (−40%)	No	9	95	80–320
Irbesartan	IC_{50}:1·3 nmol/L	70	No	No	11–15	90†	150–300
Candesartan cilexetil							
TCV 116		—	No	Yes	3·5–4	—	4–16 (32)
CV11974	K_i:0·6 nmol/L	42			3–11	99·5	
Telmisartan	K_i:3·7 nmol/L	43	No	No	24	>99	40–80
Eprosartan	IC_{50}:1·4–3·9 nmol/L	15	No	No	5–7	98	400–800

*IC_{50}=concentration displacing specifically 50% of the binding of angiotensin II; K_i=inhibition constant.
†Some studies suggest that irbesartan has a greater protein binding (>95%).

The pharmacokinetic and pharmacodynamic differences among ARBs may be clinically relevant. For example, candesartan and valsartan are dose-dependent inhibitors of the AT_1 receptor, with respective receptor affinities approximately 80 and 100 times that of losartan[33]. Valsartan's bioavailability drops if it is taken with food. Losartan is a relatively weaker AT_1 receptor blocker than either valsartan or candesartan, but its active metabolite (EXP3174) is 10-20 times more potent than losartan and is capable of an insurmountable receptor blockade. All six drugs lower BP more effectively than placebo without affecting heart rate, and do so regardless of sex, age or race. However, in a meta-analysis of 43 ranxomised placebo-controlled trials of ARBs in blood pressure studies[34], valsartan 160 mg is superior to losartan 100 mg daily, candesartan at doses of 8 mg and 16 mg daily is superior to losartan at 50 mg and 100 mg daily, and telmisartan 40 mg and 80 mg for 6 weeks reduced 24 hour ambulatory BP significantly more

than losartan 50 mg. While these results suggest differences in efficacy related to control of blood pressure, whether these differences are clinically relevant in terms of morbidity and mortality in patients with CHF remains to be seen.

8.1.5 Do ARBs need to be used at high doses for the treatment of heart failure with depressed LV systolic function?

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[35] and ELITE II[36] 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 of human volunteers[37] who were given oral doses of placebo, losartan 50 mg or losartan 150 mg, and were subsequently challenged with a pre-determined blood pressure elevating-dose of angiotensin II (to raise radial artery systolic pressure by 20 mmHg), only the higher dose of 150 mg losartan was found adequate to produce a maximum inhibition of the pressor response to angiotensin II (Figure 27). Thus, the dose of 50 mg once/day of losartan used in ELITE[35] and ELITE II[36] 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, in part, be the reason for this lack of effect.

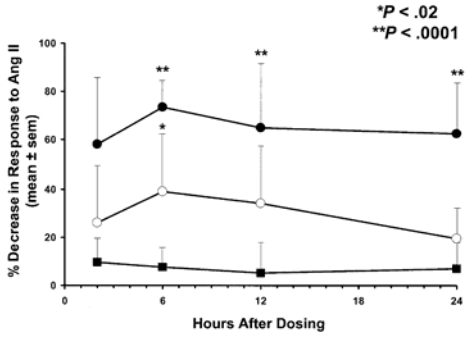


Figure 27 Blockade of the pressor response to intravenous infusions of angiotensin II (Ang II) in normal volunteers after oral administration of placebo (■), losartan 50 mg (○), or losartan 150 mg (●). * P < 0.02, ** P < 0.0001 compared with placebo. (Based on data from J Cardiovasc Pharmacol 2001; 37: 692-6)[37].

In the OPTIMAAL (Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan) trial[38], losartan (50 mg q.d.) was compared to captopril (150 mg/day) in high-risk patients with acute myocardial infarction (Figure 28). 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 may, in part, be a reason for the lack of effect of losartan.

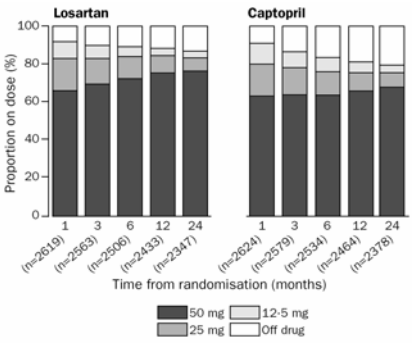


Figure 28 Dose of study drug Losartan was administered once daily and captopril three times daily. (OPTIMAAL Study)[38] (Based on data from Lancet 2002; 360: 752-60.)

In a recent trial of valsartan and captopril in myocardial infarction complicated by heart failure and/or left ventricular dysfunction (VALIANT)[39], 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 97).

Table 97 Cardiovascular mortality and morbidity in VALIANT trial[39] (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[39] 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.

The lack of beneficial effect of losartan (ELITE[35], ELITE II[36] and OPTIMAAL[38] trials) and valsartan (VALIANT[39] trial) over ACE inhibitors may be due to the fact that a correct (or high enough) dose of the ARB was not used[40].

In contrast, in two recent clinical trials[41,42] 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[41]. A significant reduction in relative risk (by 15%, P = 0.009) of the primary composite endpoint of cardiovascular mortality, stroke and MI was found in the subjects treated with losartan (Figure 29).

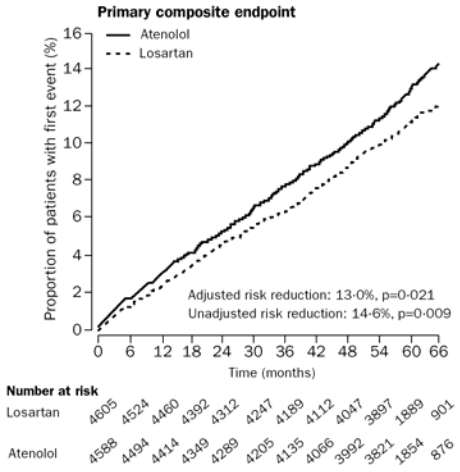


Figure 29 Kaplan Meier curves for primary composite endpoint (LIFE study)[41] (Based on data from Lancet 2002; 359: 995-1003.)

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[42]. 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 98).

Table 98 Incidence of the primary composite endpoint and its components in RENAAL study[42] (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.

The above findings suggest that for ARBs to demonstrate a beneficial survival effect in the treatment of patients with heart failure, ARBs must be used at high enough doses that will fully block AT_1 receptors throughout the dosing interval.

8.1.6 Selection of dose of candesartan for the CHARM Program studies

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 sponsor's view of the results of these studies was 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, that patients with CHF tolerated the 16 mg dose of candesartan well, and that in the tolerability study (SH-AHS-0008), these CHF patients tolerated the 32 mg dose of candesartan as well. Based on this finding, the sponsor decided the target dose of candesartan for the CHARM Program clinical trials 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-0003 (CHARM-Alternative 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 tolerated 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 (CHARM-Alternative, SH-AHS-0003, study) shows that 824 (81.3%) patients in the candesartan group started treatment on 4 mg once daily and 189 (18.7%) patients started on 8 mg once daily at randomization (baseline). 1,313 (64.7%) patients (candesartan 666, 65.8%; placebo 647, 63.7%) received the investigational product for 24 months or more. 52.2% of the candesartan patients (58.9% of those still receiving the investigational product) were treated with the target dose 32 mg once daily at 6 months (visit 5). The mean dose in the candesartan group was 23.2 mg at 6 months. At the end of treatment (LVCF) 44.1% (60.3% of those still treated with candesartan) received 32 mg candesartan once daily. The mean candesartan LVCF dose was 23.1 mg.

8.1.7 Inference on the finding of a relationship between the dose of candesartan and the primary and secondary efficacy outcomes in CHARM-Alternative (SH-AHS-0003) study

Please refer to section 6.1.5 (Is there a relationship between the dose of candesartan and the primary and secondary efficacy outcomes: Pages 49 – 52) of this review for the tables of data submitted by the sponsor on November 24, 2004 in response to my request to provide information on the CHARM-Alternative (SH-AHS-0003) 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 relation to the primary and secondary efficacy endpoints.

For the composite primary efficacy endpoint of CV death or CHF hospitalization, a dose related response was observed with 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 (cells A1 vs. A2 in Table 27 and Table 28); however, patients receiving placebo also exhibited the same dose response! (cells B1 vs. B2 in Table 27 and Table 28).

The secondary efficacy endpoint of all-cause mortality or CHF hospitalization (Table 29 and Table 30), and for secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI (Table 31 and Table 32) also show similar findings.

As discussed earlier, there are many caveats to these findings:

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

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

(iii) 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.

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

My interpretation of the data provided by the sponsor in Table 27 through Table 32 (in section 6.1.5) is as follows.

(i) Patient sub-populations by severity of CHF (presumed): Patients in cells A3 (not receiving candesartan prior to event) and B3 (not receiving "double-blind" placebo (perceived by the clinical investigator and the patient as candesartan) prior to event) were, I think, "the most sick" patients who, for some reason (hypotension, hyperkalemia, deterioration in renal function) could not tolerate candesartan for an unknown period of time prior to the primary or secondary efficacy event. Patients in cells A2 (receiving 4 mg or 8 mg candesartan prior to event) and B2 (receiving "double-blind" placebo (perceived by the clinical investigator and the patient as 4 mg or 8 mg candesartan) prior to event) were "moderately sick" patients who could not tolerate the higher doses of candesartan. Patients in cells A1 (receiving 16 mg or 32 mg candesartan prior to event) and B1 (receiving "double-blind" placebo (perceived by the clinical investigator and the

patient as 16 mg or 32 mg candesartan) prior to event) were "the least sick" patients who tolerated the higher doses of candesartan.

(ii) Effect of no drug – internal consistency: Patients in both treatment groups A3 and B3 were not receiving any investigational drug (candesartan or placebo) and had the same (albeit presumed) severity of CHF. Thus, the events rates in treatment groups A3 and B3 are expected to be similar. The event rates in treatment groups A3 and B3 for the primary and secondary efficacy endpoints are, indeed, similar (Table 27 through Table 32), suggesting internal consistency, and providing some confidence to the logic and integrity of the data.

(iii) Effect of candesartan (1): Comparing the event rates in A2 to B2 allowed the comparison of events in the same population of patients with similar severity of CHF ("moderately sick" patients). A statistically significant reduction in the event rates between A2 vs. B2 for the primary and secondary efficacy endpoints suggests a true difference in this sub-population of moderately sick patients with CHF.

(iv) Effect of candesartan (2): Comparing the event rates in A1 to B1 allow the comparison of event rates in same population of patients with similar degree of CHF ("the least sick" group of patients). A statistically significant reduction in the event rates between A1 vs. B1 for the primary and secondary efficacy endpoints suggests a true difference among patients with the same severity of CHF.

(v) Effect of candesartan (3): The effect of candesartan in the "least sick" and "moderately sick" sub-populations of patients appears to be about the same (for the primary endpoint, a reduction in the relative risk by 34.5% (A1 vs. B1) or 37.6% (A2 vs. B2). This suggests a consistent effect of candesartan for the primary (and also for the secondary) efficacy endpoints.

(vi) Effect of disease: Comparison of the event rates in cells B1 vs. B2 (patients receiving placebo) also shows that the event rates are significantly ($P<0.001$) lower in the "high dose" group compared to the "low dose" group (Table 27 through Table 32). Since neither group (B1 or B2) was receiving candesartan, this finding is clearly due to the severity of CHF.

(vii) Effect of disease severity (or) effect of dose of candesartan? Comparison of cells A1 vs. A2 shows that the event rates are significantly ($P<0.001$) lower in the high dose (16 and 32 mg, A1) candesartan groups compared to the low dose (4 and 8 mg, A2) candesartan groups (Table 27 through Table 32), giving the appearance of a dose-related response. I think that the lower event rate in the "high dose" candesartan group is mainly due to the fact that subjects in cell A1 are "the least sick" of the study population; conversely, the higher event rate in the "low dose" candesartan group is due to the fact that subjects in cell A2 are relatively less sick patients. Thus, rather than a "dose-related" response for candesartan regarding the primary and secondary efficacy endpoints as the data in Table 27 through Table 32 appear to suggest, I think the differences observed between the "high dose" and "low dose" candesartan groups are attributable to the severity of CHF.

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-Alternative (SH-AHS-0003) Study

At the time of randomization, 1,106 (55%) patients were on treatment with a β-blocker, 1,733 (86%) patients were treated with diuretics, 924 (46%) patients with digitalis and 483 (24%) patients were treated with spironolactone, without major differences between treatment groups. Metoprolol and carvedilol were the two most commonly used β-blockers. Four patients were using ACE-inhibitors at randomization.

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 480 patients (67%) vs. 476 patients (64%), respectively, spironolactone in 209 patients (29%) vs. 183 patients (25%) respectively, and any diuretics 572 patients (79%) vs. 566 patients (76%), respectively].

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 compared to the candesartan treatment group, respectively, 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 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 30) and for the composite endpoint of CV death or CHF hospitalization (Figure 31).

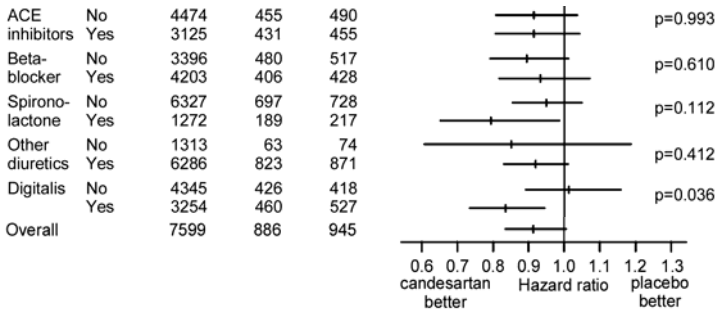


Figure 30 Overall effect of candesartan on all-cause death in subgroups of conventional CHF treatment. Point estimates of hazard ratios given with 95% confidence interval, and P values. ITT/Safety population (SH-AHS-0003, SH-AHS-0006, SH-AHS-0007)

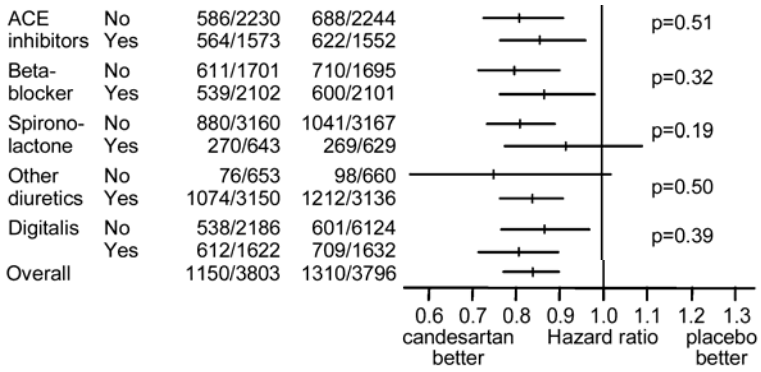


Figure 31 Overall effect of candesartan on CV death or hospitalization in subgroups of conventional CHF treatment. Point estimates of hazard ratios given with 95% confidence interval, and P values. ITT/Safety population (SH-AHS-0003, SH-AHS-0006, SH-AHS-0007).

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

Within the context of my review of this NDA 20-838 Efficacy Supplement #024, I will present and discuss, in the following sections, the findings reported in clinical trials in the medical literature in comparison with the results from the CHARM-Alternative (SH-AHS-0003) 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[43,44,45]. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II)[43] 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.

Table 99 Primary and secondary endpoints and exploratory analyses in CIBIS-II study[43] (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 CIBIS-II study was stopped early, after the second interim analysis, because bisoprolol showed a significant mortality benefit (Table 99). 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.

The relatively large Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF)[44] 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 32).

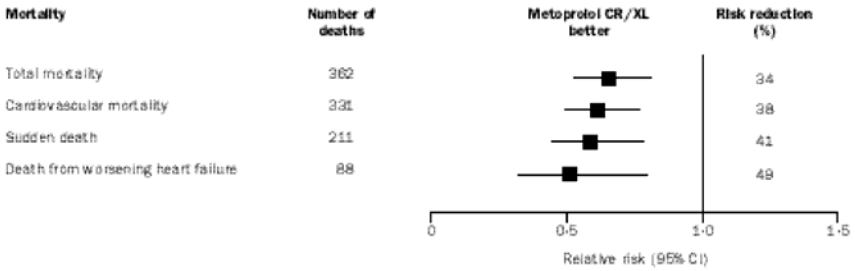


Figure 32 Relative risk (95% CI) for total mortality, cardiovascular mortality, sudden death, and death from worsening heart failure (MERIT-HF study)[44] (Based on data from Lancet 1999; 353: 2001-7.)

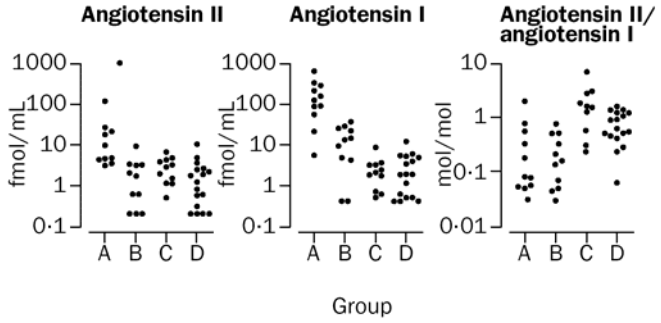


Figure 33 Blood concentrations of angiotensin II and angiotensin I, and angiotensin II/ angiotensin I ratio[48] (Based on data from Lancet 2001; 358: 1609-10.)
Group A= patients with heart failure, receiving ACE inhibitors; Group B= patients with heart failure, receiving ACE inhibitors and β-blockers; 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[46], either of which could result in improved clinical outcome[47]. 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[48]. Concentrations of angiotensin II and angiotensin I (Figure 33) 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[11,49]. 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 34 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.

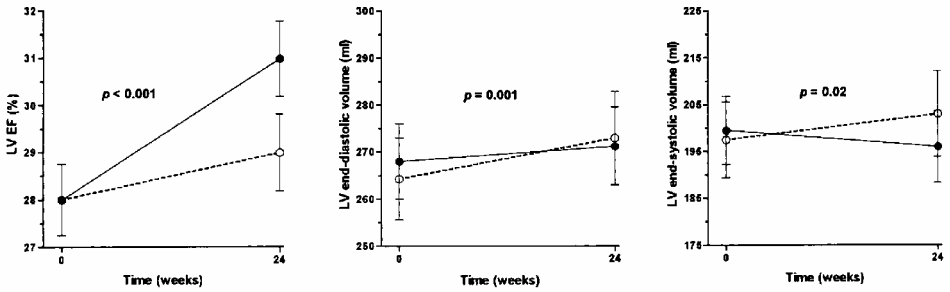


Figure 34 Changes in LVEF and LV volumes in response to metoprolol (●) versus placebo (○) in stage II of the RESOLVD study[49]. Data are mean±SEM. (Based on data from Circulation 2000; 101: 378-84.)

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[45], 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 35). 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 36). Thus, addition of carvedilol to conventional therapy for heart failure was beneficial in this group of patients with severe heart failure.

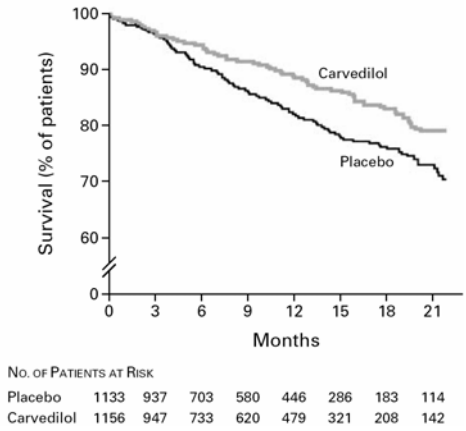


Figure 35 Kaplan-Meier Analysis of Time to Death in Placebo and Carvedilol Groups[45] (Based on data from N Engl J Med 2001; 344: 1651-8.) The 35% lower risk in the carvedilol group was significant: P=0.00013 (unadjusted) and P=0.0014 (adjusted).

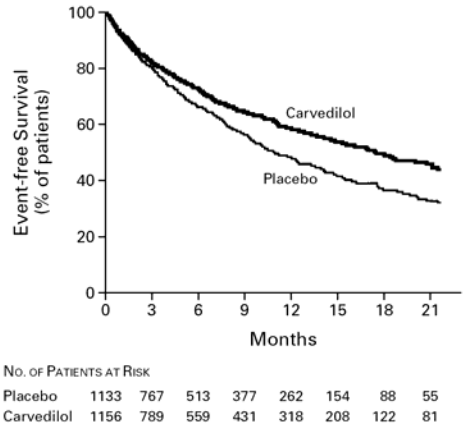


Figure 36 Kaplan-Meier Analysis of Time to Death or First Hospitalization for Any Reason in Placebo and Carvedilol Groups[45]. (Based on data from N Engl J Med 2001; 344: 1651-8.)
The 24 percent lower risk in the carvedilol group was significant (P<0.001).

On the other hand, other studies in the medical literature show contradictory findings.

In ELITE II study[36], 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 37).

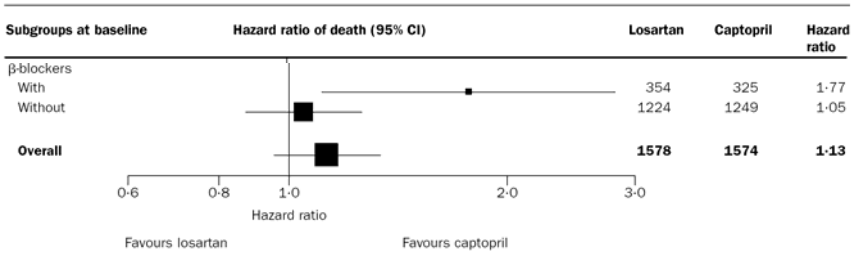


Figure 37 Mortality by subgroup (ELITE II[36]) (Based on data from Lancet 2000; 355: 1582-7.)

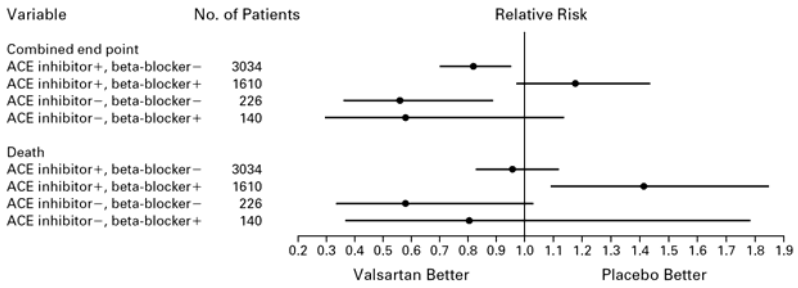


Figure 38 Relative Risks and 95 Percent Confidence Intervals for the Combined End Point (Death from Any Cause, Cardiac Arrest with Resuscitation, Hospitalization for Worsening Heart Failure, or Therapy with Intravenous Inotropes or Vasodilators), According to the Background Therapy at Base Line, in Val-HeFT study[18]. (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[18,50] 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 38): (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[18,50] 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[51].

There are a number of caveats to the use of β-blockers in heart failure.

One caveat that is unique to the use of β-blockers in heart failure is that they may cause initial worsening before improvement occurs[52]; 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[17], MERIT-HF trial[44] and other β-blocker clinical trials have been computed to show (Table 100) 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[53,54].

Table 100 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)[54]

	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.

Secondly, as opposed to the conventional sequence of drug use in the treatment of heart failure (as described above), a small open-label study conducted in Johannesburg, South Africa, showed that initiation of treatment with carvedilol *before* an ACE inhibitor resulted in higher tolerable doses of carvedilol and better improvements in NYHA functional class and LV function. This was a single-center, prospective, randomized trial of initiation of treatment with carvedilol either before (n=39) or after (n=40) perindopril therapy in newly diagnosed patients in NYHA Class II to III heart failure with idiopathic dilated cardiomyopathy, with the addition of the alternative agent after six months[55]. After 12 months, 11 patients died (6 in the group where perindopril was initiated). At 12 months, the group receiving carvedilol as initial therapy achieved a higher tolerable dose of carvedilol (43±17 mg vs. 33±18 mg, P = 0.03), a lower dose of furosemide (P<0.05), and better improvement in symptoms (NYHA functional class, P<0.002), LV ejection fraction (radionuclide: 15±16% vs. 6±13%, P<0.05; echocardiographic, P<0.05), and plasma N-terminal pro-brain natriuretic peptide concentrations (P<0.02) (Table 101).

Table 101 Clinical Parameters and LV Function at 0, 6, and 12 Months of Therapy in Patients With Heart Failure Receiving Either Perindopril (ACEI-First) or Carvedilol (BB-First Group) as Initial Therapy[55] (Based on data from J Am Coll Cardiol 2004; 44: 1825-30.)

Initial Therapy	ACEI-First	BB-First	ACEI-First	BB-First	ACEI-First	BB-First
Months of Treatment	0	0	6	6	12	12
Sample Number	30	27	30	27	30	27
BP (mm Hg)	115 ± 14/76 ± 11	113 ± 15/74 ± 12	121 ± 22/74 ± 16	124 ± 20*/79 ± 15	119 ± 17/73 ± 12	122 ± 19*/75 ± 14
Heart rate (beats/min^{-1})	87 ± 15	88 ± 17	85 ± 16	76 ± 18*‡	76 ± 17*	73 ± 15†
NYHA FC (I/II/II/IV)	4/12/11/1	3/9/12/3	11/11/7/1	13/7/7/0	11/10/9/0	22/3/2/0
LVEDD (mm)	65.5 ± 7.9	65.3 ± 6.8	62.4 ± 7.1	62.0 ± 8.0	62.6 ± 7.9	60.0 ± 11.6†
LVESD (mm)	56.6 ± 7.8	57.6 ± 7.8	53.2 ± 8.2	51.6 ± 10.4†	53.0 ± 8.9	48.5 ± 12.4†
Deceleration time (ms)	154 ± 93	133 ± 45	155 ± 58	207 ± 73†	167 ± 60	204 ± 55†§
E/A	1.46 ± 0.87	1.86 ± 1.25	1.34 ± 0.60	1.27 ± 0.73	1.56 ± 0.79	1.17 ± 0.63*‡

* $p < 0.05$, † $p < 0.005$ versus baseline data; ‡ $p < 0.05$, § $p < 0.01$ versus change from baseline in the ACEI- first group (analysis of covariance). ACEI= angiotensin-converting enzyme inhibitor; BB= beta-blocker; BP= blood pressure; E/A= ratio of E wave to A wave velocity; LVEDD= left ventricular end-diastolic diameter; LVESD= left ventricular end-systolic diameter; NYHA FC= New York Heart Association functional class.

A third caveat is the effect of the ACE D/I polymorphism on heart failure survival. In a study of 479 patients with systolic dysfunction (LVEF 0.25±0.08) who were genotyped for the ACE D/I polymorphism[32] and followed to the endpoint of death or cardiac transplantation, 227 patients received an ACE inhibitor at "low doses" (≤50% of target dose), 201 patients received "high (standard) dose," and 51 patients received ARBs. The ACE-D allele was associated with an increased risk of events and poorer transplant-free survival (1-year percent transplant-free by genotype II/ID/DD = 89/80/74; 2-year = 77/69/62, P=0.026). β-blockers diminished the impact of the ACE-D allele on heart failure survival (reduction in event rate by 29%, P = 0.03), particularly for the DD subjects (relative risk reduction = 53%, P = 0.004) but not for subjects who were ID (RRR = 15%, P=0.46) or II (RRR = 3%, P = 0.94) (Table 102).

Table 102 Relative risk of events by treatment for heart failure in different ACE-genotypes[32] (Based on data from J Am Coll Cardiol 2004; 44: 2019-26.)

	Odds Ratio	95% Confidence Interval	p Value
Beta-blockers			
Overall	0.71	(0.53, 0.96)	0.027
ACE genotype			
II	0.97	(0.47, 2.03)	0.94
ID	0.85	(0.55, 1.31)	0.46
DD	0.47	(0.28, 0.79)	0.004
High-dose ACE inhibitors			
Overall	0.86	(0.64, 1.16)	0.33
ACE genotype			
II	1.35	(0.63, 2.85)	0.44
ID	0.88	(0.57, 1.35)	0.55
DD	0.75	(0.44, 1.27)	0.29
High-dose ACE inhibitors (subject not on beta-blockers)			
Overall	0.88	(0.56, 1.15)	0.24
ACE genotype			
II	1.31	(0.54, 3.22)	0.55
ID	0.86	(0.51, 1.47)	0.59
DD	0.62	(0.33, 1.17)	0.10

ACE = angiotensin-converting enzyme.

CHARM-Alternative (SH-AHS-0003) 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 103 CV death or hospitalization due to CHF (confirmed adjudicated) by use of β-blockers in study SH-AHS-0003. 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	922	172	232	0.657	0.539	0.800	<0.001
	Yes	1106	162	174	0.904	0.730	1.119	0.354
Beta-blocker during study	No	606	120	165	0.610	0.482	0.772	<0.001
	Yes	1422	214	241	0.861	0.716	1.035	0.111
Beta-blocker at the visit preceding the event	No	1647	147	212	0.649	0.526	0.801	<0.001
	Yes	380	187	193	0.958	0.783	1.172	0.678

Table 103 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 ***non-use*** of β-blockers at baseline (RRR =34.3%, P<0.001), during the study (RRR =39.0%, P<0.001) and at the visit preceding the event (RRR=35.1%, P<0.001).

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

On November 24 2004, the sponsor submitted a response to my request for data related to the primary and principal secondary efficacy endpoints according to dose level of candesartan in relation to patients receiving or not receiving β-blockers at baseline. These analyses consider dose level of candesartan consistent with the sub-group analyses presented in the submission. For the dose analyses, I used the definition for high candesartan dose 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): 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 104. It appears that there is a dose-related response, the event rates being lower in the high dose (16 and 32 mg) candesartan groups compared to the low dose (4 and 8 mg) candesartan groups for both patients receiving β-blockers and those not receiving β-blockers.

The event rates in patients receiving β-blockers are generally **lower** than in those not receiving β-blockers for the sub-populations of patients receiving "high dose" candesartan, "low dose" candesartan or no candesartan at the visit prior to the event.

The secondary efficacy endpoint of all-cause mortality or CHF hospitalization (Table 105), and for secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI (Table 106) also show similar findings.

Table 104 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-Alternative (SH-AHS-0003) Study

Beta-blocker at baseline			
Candesartan	**N = 553** **Events = 162 (29.3%)**		
			A
	CC_{HD} n = 343 events = 87 (25.4%)	CC_{LD} n = 106 events = 51 (48.1%)	CC_{00} n = 104 events = 24 (23.1%)
	A1	**A2**	**A3**
Placebo	**N = 553** **Events = 174 (31.5%)**		
			B
	P_{HD} n = 408 events = 120 (29.4%)	P_{LD} n = 63 events = 35 (55.6%)	P_{00} n = 82 events = 19 (23.2%)
	B1	**B2**	**B3**
No beta-blocker at baseline			
Candesartan	**N = 460** **Events = 172 (37.4%)**		
			A
	CC_{HD} n = 252 events = 74 (29.4%)	CC_{LD} n = 107 events = 67 (62.6%)	CC_{00} n = 101 events = 31 (30.7%)
	A1	**A2**	**A3**
Placebo	**N = 462** **Events = 232 (50.2%)**		
			B
	P_{HD} n = 312 events = 150 (48.1%)	P_{LD} n = 67 events = 51 (76.1%)	P_{00} n = 83 events = 31 (37.4%)
	B1	**B2**	**B3**

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 105 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-Alternative (SH-AHS-0003) Study

Beta-blocker at baseline			
Candesartan	**N = 553** **Events = 176 (31.8%)**		
			A
	CC_{HD} n = 343 events = 96 (28.0%)	CC_{LD} n = 106 events = 55 (51.9%)	CC_{00} n = 104 events = 25 (24.0%)
	A1	**A2**	**A3**
Placebo	**N = 553** **Events = 188 (34.0%)**		
			B
	P_{HD} n = 408 events = 126 (30.9%)	P_{LD} n = 63 events = 40 (63.5%)	P_{00} n = 82 events = 22 (26.8%)
	B1	**B2**	**B3**
No beta-blocker at baseline			
Candesartan	**N = 460** **Events = 195 (42.4%)**		
			A
	CC_{HD} n = 254 events = 84 (33.1%)	CC_{LD} n = 107 events = 69 (64.5%)	CC_{00} n = 99 events = 42 (42.4%)
	A1	**A2**	**A3**
Placebo	**N = 462** **Events = 245 (53.0%)**		
			B
	P_{HD} n = 313 events = 156 (49.8%)	P_{LD} n = 68 events = 54 (79.4%)	P_{00} n = 81 events = 35 (43.2%)
	B1	**B2**	**B3**

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 106 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-Alternative (SH-AHS-0003) Study

Beta-blocker at baseline			
Candesartan	**N = 553** **Events = 171 (30.9%)**		
			A
	CC_{HD} n = 345 events = 94 (27.3%)	CC_{LD} n = 106 events = 52 (49.1%)	CC_{00} n = 102 events = 25 (24.5%)
	A1	**A2**	**A3**
Placebo	**N = 553** **Events = 180 (32.6%)**		
			B
	P_{HD} n = 407 events = 124 (30.5%)	P_{LD} n = 64 events = 36 (56.3%)	P_{00} n = 82 events = 20 (24.4%)
	B1	**B2**	**B3**
No beta-blocker at baseline			
Candesartan	**N = 460** **Events = 182 (39.6%)**		
			A
	CC_{HD} n = 254 events = 82 (32.3%)	CC_{LD} n = 109 events = 69 (63.3%)	CC_{00} n = 97 events = 31 (32.0%)
	A1	**A2**	**A3**
Placebo	**N = 462** **Events = 240 (52.0%)**		
			B
	P_{HD} n = 313 events = 155 (49.5%)	P_{LD} n = 70 events = 55 (78.6%)	P_{00} n = 79 events = 30 (38.0%)
	B1	**B2**	**B3**

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)

The above findings suggest that (i) in the absence of candesartan (comparing cells A3 with and without β-blockers), CHF patients treated with β-blockers at baseline have lower event rates than those not treated with β-blockers, and (ii) that when these CHF patients are receiving candesartan at low or high doses, too, those receiving β-blockers at baseline have lower event rates than those not receiving β-blockers.

This finding is also similar to the effect of β-blockers observed in CHF patients treated with ACE inhibitors *plus* candesartan or placebo in the CHARM-Added (SH-AHS-0006) study.

However, the same caveats (as that for the dose-response relationship of candesartan to the primary and secondary efficacy endpoints) apply to these findings:

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

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

(iii) 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.

(iv) With regard to other heart failure treatments at baseline, there was no randomization to any treatment including β-blockers (Yes/No) or spironolactone (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[56]; 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[57] – 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 39).

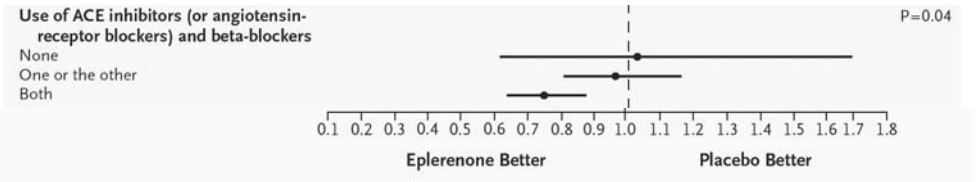


Figure 39 Relative risk of all-cause mortality according to use of and ACE inhibitor (or ARB), a β-blocker or both in EPHESUS study[57] (Based on data from N Engl J Med 2003; 348: 1309-21.)

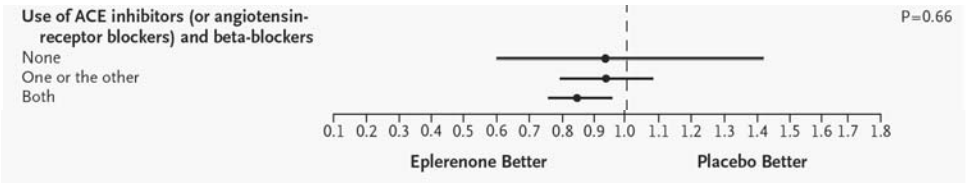


Figure 40 Relative risk of CV death or hospitalization for CV events according to use of an ACE inhibitor (or ARB), a β-blocker or both in EPHESUS study[57] (Based on data from N Engl J Med 2003; 348: 1309-21.)

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 40).

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[58], reducing coronary vascular inflammation and the risk of subsequent development of interstitial fibrosis[59], reducing oxidative stress and improving endothelial dysfunction[60], etc.

CHARM-Alternative (SH-AHS-0003) 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 107 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	1545	224	289	0.742	0.623	0.883	<0.001
	Yes	483	110	117	0.797	0.614	1.034	0.088
Spironolactone during study	No	1193	169	188	0.772	0.627	0.950	0.014
	Yes	835	165	218	0.807	0.659	0.988	0.038
Spironolactone at the visit preceding the event	No	1736	197	251	0.724	0.601	0.873	<0.001
	Yes	291	137	154	0.978	0.776	1.233	0.853

Table 107 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 ***non-use*** of spironolactone at baseline, during the study or at the visit preceding the event.

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

On November 24 2004, the sponsor submitted a response to my request for data related to the primary and principal secondary efficacy endpoints according to dose level of candesartan in relation to patients receiving and not receiving 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 108. It appears that there is a dose-related response, the event rates being lower in the high dose (16 and 32 mg) candesartan groups compared to the low dose (4 and 8 mg) candesartan groups for both patients receiving spironolactone and those not receiving spironolactone.

Table 108 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-Alternative (SH-AHS-0003) Study

Spironolactone at baseline			
Candesartan		**N = 250** **Events = 110 (44.0%)**	
			A
	CC_{HD} n = 107 events = 36 (33.6%)	CC_{LD} n = 79 events = 53 (67.1%)	CC_{00} n = 64 events = 21 (32.8%)
	A1	**A2**	**A3**
Placebo		**N = 233** **Events = 117 (50.2%)**	
			B
	P_{HD} n = 156 events = 74 (47.4%)	P_{LD} n = 39 events = 30 (76.9%)	P_{00} n = 38 events = 13 (34.2%)
	B1	**B2**	**B3**
No spironolactone at baseline			
Candesartan		**N = 763** **Events = 224 (29.4%)**	
			A
	CC_{HD} n = 488 events = 125 (25.6%)	CC_{LD} n = 134 events = 65 (48.5%)	CC_{00} n = 141 events = 34 (24.1%)
	A1	**A2**	**A3**
Placebo		**N = 782** **Events = 289 (37.0%)**	
			B
	P_{HD} n = 564 events = 196 (34.8%)	P_{LD} n = 91 events = 56 (61.5%)	P_{00} n = 127 events = 37 (29.1%)
	B1	**B2**	**B3**

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 109 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-Alternative (SH-AHS-0003) Study

Spironolactone at baseline			
Candesartan		**N = 250** **Events = 118 (47.2%)**	
			A
	CC_{HD} n = 107 events = 38 (35.5%)	CC_{LD} n = 79 events = 56 (70.9%)	CC_{00} n = 64 events = 24 (37.5%)
	A1	**A2**	**A3**
Placebo		**N = 233** **Events = 124 (53.2%)**	
			B
	P_{HD} n = 156 events = 77 (49.4%)	P_{LD} n = 39 events = 31 (79.5%)	P_{00} n = 38 events = 16 (42.1%)
	B1	**B2**	**B3**
No spironolactone at baseline			
Candesartan		**N = 763** **Events = 253 (33.2%)**	
			A
	CC_{HD} n = 490 events = 142 (29.0%)	CC_{LD} n = 134 events = 68 (50.8%)	CC_{00} n = 139 events = 43 (30.9%)
	A1	**A2**	**A3**
Placebo		**N = 782** **Events = 309 (39.5%)**	
			B
	P_{HD} n = 565 events = 205 (36.3%)	P_{LD} n = 92 events = 63 (68.5%)	P_{00} n = 125 events = 41 (32.8%)
	B1	**B2**	**B3**

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 110 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-Alternative (SH-AHS-0003) Study

Spironolactone at baseline			
Candesartan	**N = 250** **Events = 117 (46.8%)**		
			A
	CC_{HD} n = 107 events = 38 (35.5%)	CC_{LD} n = 81 events = 56 (69.1%)	CC_{00} n = 62 events = 23 (37.1%)
	A1	**A2**	**A3**
Placebo	**N = 233** **Events = 119 (51.1%)**		
			B
	P_{HD} n = 156 events = 76 (48.7%)	P_{LD} n = 39 events = 30 (76.9%)	P_{00} n = 38 events = 13 (34.2%)
	B1	**B2**	**B3**
No spironolactone at baseline			
Candesartan	**N = 763** **Events = 236 (30.9%)**		
			A
	CC_{HD} n = 492 events = 138 (28.1%)	CC_{LD} n = 134 events = 65 (48.5%)	CC_{00} n = 137 events = 33 (24.1%)
	A1	**A2**	**A3**
Placebo	**N = 782** **Events = 301 (38.5%)**		
			B
	P_{HD} n = 564 events = 203 (36.0%)	P_{LD} n = 95 events = 61 (64.2%)	P_{00} n = 123 events = 37 (30.1%)
	B1	**B2**	**B3**

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)

However, the event rates are generally **higher** in patients receiving spironolactone than in those not receiving spironolactone for the sub-populations of patients receiving "high dose" candesartan, "low dose" candesartan or no candesartan at the visit prior to the event.

The secondary efficacy endpoint of all-cause mortality or CHF hospitalization (Table 109), and for secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI (Table 110) also show similar findings.

The above findings suggest that (i) in the absence of candesartan, CHF patients treated with spironolactone at baseline had **higher** event rates than those not treated with spironolactone, and (ii) that for both low and high doses of candesartan, CHF patients treated with spironolactone at baseline have **higher** event rates than those not treated with spironolactone. This finding is similar to the effect of spironolactone observed in CHF patients treated with ACE inhibitors *plus* candesartan or placebo in the CHARM-Added (SH-AHS-0006) study.

However, the same caveats (as that for the dose-response relationship of candesartan to the primary and secondary efficacy endpoints) apply to these findings:

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

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

(iii) 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.

(iv) With regard to other heart failure treatments at baseline, there was no randomization to any treatment including β-blockers (Yes/No) or 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[61] showed that combination therapy (of digoxin, diuretic and ACE inhibitor) was better than ACE inhibitor alone (Table 111).

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 111).

Table 111 Deaths due to study group and cause in the DIG Study[61] (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 endarterectomy.

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 41). However, overall mortality was not reduced because an excess of sudden death and ischemic events were observed in patients randomized to digoxin.

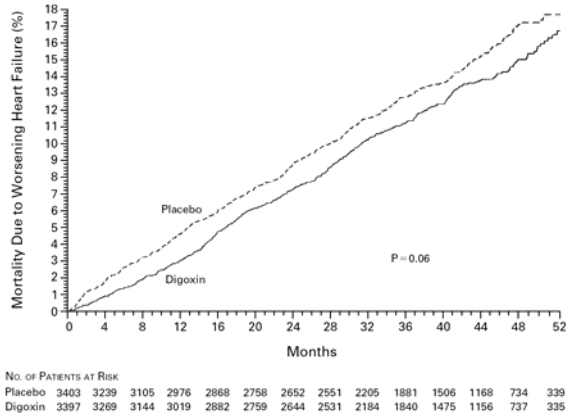


Figure 41 Mortality Due to Worsening Heart Failure in the Digoxin and Placebo Groups[61]. (Based on data from N Engl J Med 1997; 336: 525-33.) The number of patients at risk at each four-month interval is shown below the figure.

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 112). 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[61].

Table 112 Patients hospitalized during the DIG study[61], 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.

CHARM-Alternative (SH-AHS-0003) 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 113 CV death or hospitalization due to CHF (confirmed adjudicated) by use of digitalis glycoside in study SH-AHS-0003. 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	1104	149	183	0.769	0.619	0.954	0.017
	Yes	924	185	223	0.759	0.624	0.922	0.006
Digitalis glycoside during study	No	930	116	119	0.865	0.670	1.117	0.266
	Yes	1098	218	287	0.738	0.619	0.880	<0.001
Digitalis glycoside at the visit preceding the event	No	1585	137	160	0.783	0.623	0.983	0.035
	Yes	442	197	245	0.805	0.666	0.973	0.025

Table 113 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 = 24.1%, P=0.006), during the study (RRR = 26.2%, P<0.001) and at the visit preceding the event (RRR = 19.5%, P=0.025).

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 CHAR-Alternative (SH-AHS-0003) study, hypotension was one of the most frequently reported adverse event constituting 23% of patients on candesartan versus 13.5% of patients on placebo during the study; the incidence of hypotension leading to drug discontinuation in candesartan-treated patients was 4.5% compared with 1.4% 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-Alternative (SH-AHS-0003) study, the incidence of "creatinine increase" was 16.1% in patients treated with candesartan versus 8.1% inpatients treated with placebo; the incidence of "creatinine increase" leading to drug discontinuation in candesartan-treated patients was 6.4% compared with 2.5% 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-Alternative (SH-AHS-0003) study, the incidence of hyperkalemia was 5.3% in patients treated with candesartan versus 1.6% in patients treated with placebo; the incidence of hyperkalemia leading to drug discontinuation in candesartan-treated patients was 2.1% compared with 0.3% 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[62].

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 42.

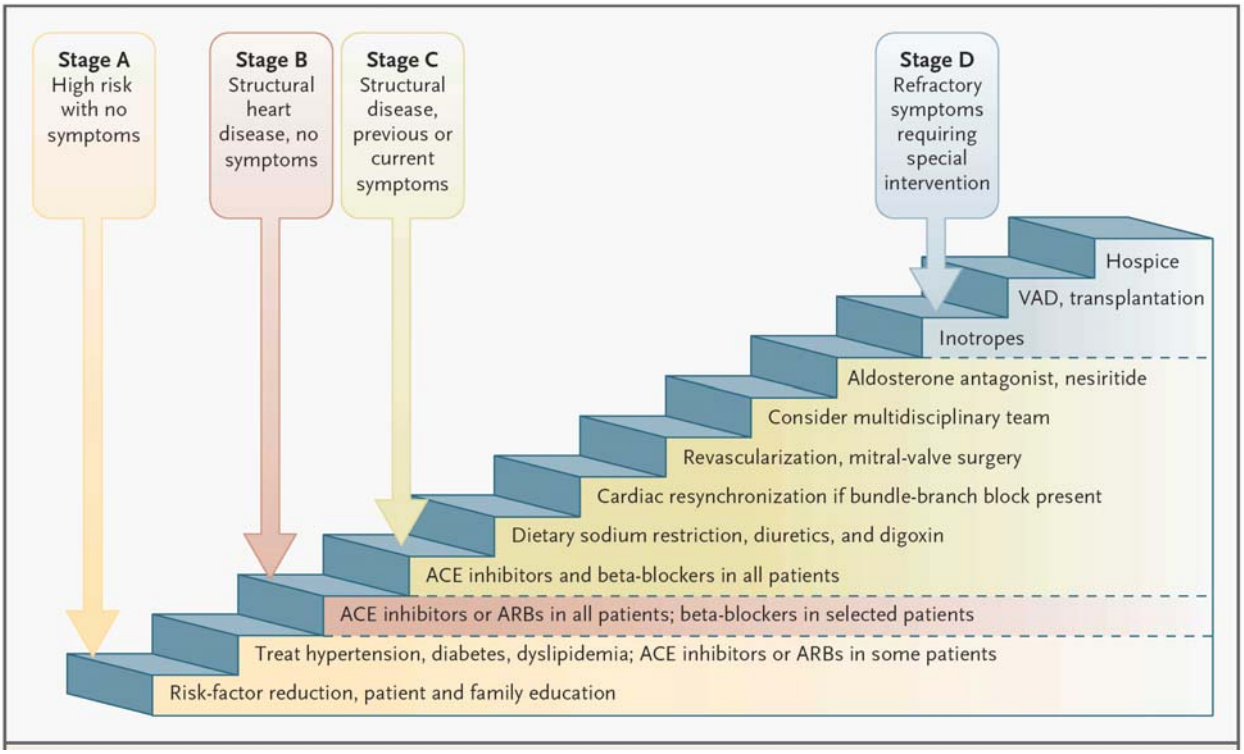


Figure 42 Stages of heart failure and treatment options for systolic heart failure (Based on data from Circulation 2001; 104: 2996-3007)[62].

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 ARBs in the treatment of patients with heart failure who are intolerant to ACE inhibitors.

8.5.1 Are angiotensin II-AT_1-receptor blockers (ARBs) comparable to ACE-inhibitors or superior to ACE inhibitors?

This is the primary issue for the CHARM-Alternative (SH-AHS-0003) study. 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 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[62] 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[42]. 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 43).

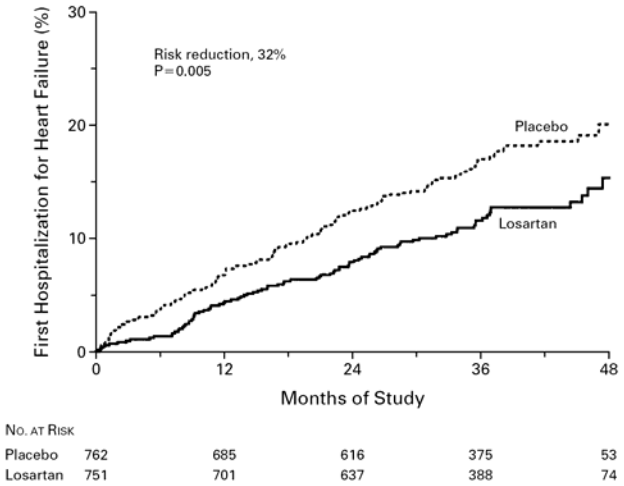


Figure 43 Kaplan-Meier Curves of the Percentage of Patients with a First Hospitalization for Heart Failure in the Losartan and Placebo Groups (RENAAL Study)[42] (Based on data from N Engl J Med 2001;345: 861-9).

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 23.2% reduction (hazard ratio= 0.7687; 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 44 and Table 114).

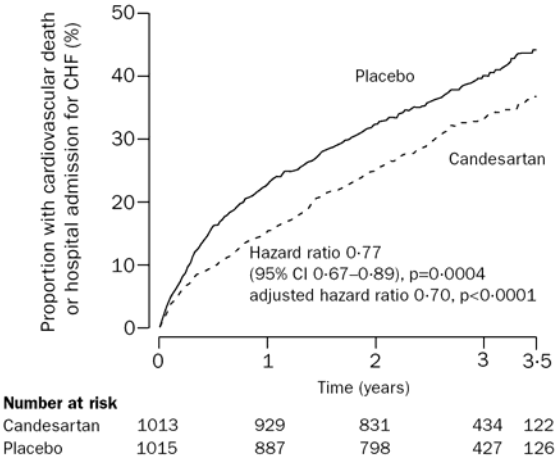


Figure 44 Kaplan-Meier cumulative event curves for primary endpoint (CHARM-Alternative Study)[63] (Based on data from Lancet 2003; 362: 772-6).

Table 114 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 115 shows the endpoints of the Losartan Intervention for Endpoint reduction (LIFE)[41] 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 115).

Table 115 Endpoints of LIFE[41] 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[41] reviewed above where ARBs are compared to placebo (CHARM-Alternative)[63] or a β-blocker (LIFE)[41], in the medical literature, 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)[35] trial demonstrated an unexpected survival benefit of losartan (50mg.day) compared to captopril (150 mg/day) in 722 elderly patients with CHF (Figure 45). However, mortality was neither a pre-specified primary nor a pre-specified secondary endpoint of ELITE[35].

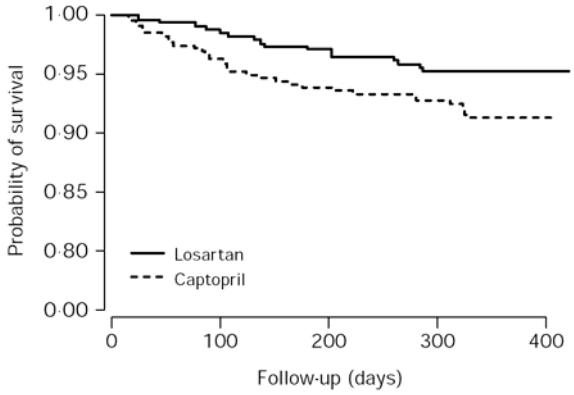


Figure 45 Kaplan-Meier survival curves among patients with CHF in losartan and captopril groups. Patients in losartan group had a 46% lower risk of death than patients in captopril group (p= 0·035). Patients were followed up for 48 weeks (ELITE trial)[35] (Based on data from Lancet 1997; 349: 747-52).

ELITE II[36] 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 116). Thus, ELITE II did not show that losartan was superior to captopril.

Table 116 Endpoint results in ELITE II trial[36] (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[38]. 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 117 and Figure 46).

Table 117 Crude rates and relative risks for pre-specified endpoints in OPTIMAAL Study[38] (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.

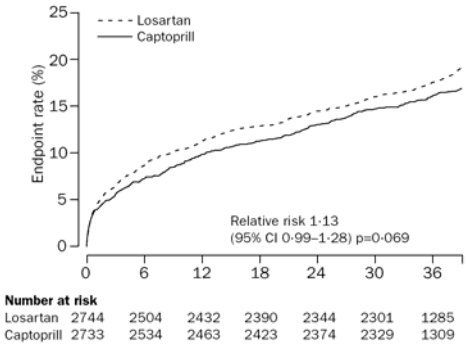


Figure 46 Kaplan- Meier curve for primary endpoint of all-cause mortality. (OPTIMAAL Study)[38] (Based on data from Lancet 2002; 360: 752-60).

The clinical trial of valsartan and captopril in myocardial infarction complicated by heart failure and/or left ventricular dysfunction (VALIANT)[39] 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.

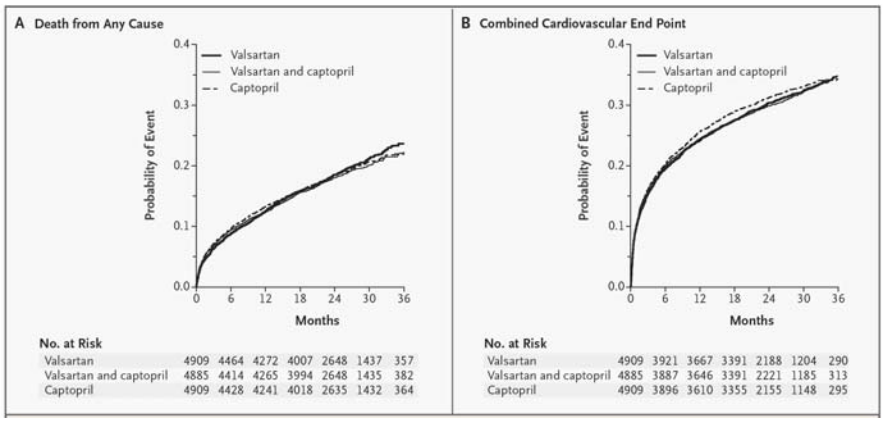


Figure 47 Kaplan-Meier Estimates of the Rate of Death from Any Cause (Panel A) and the Rate of Death from Cardiovascular Causes, Reinfarction, or Hospitalization for Heart Failure (Panel B), According to Treatment Group (VALIANT Study)[39] (Based on data from N Engl J Med 2003; 349; 1893-1906).
For the 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 47 and Table 118). 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[39] (Table 118).

Table 118 Cardiovascular Mortality and Morbidity* in VALIANT Study[39] (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[40]. 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 48); this improvement in oxygen diffusion capacity across the alveolar surface may have provided benefit to heart failure patients treated with ACE inhibitors, which was not shared by ARBs.

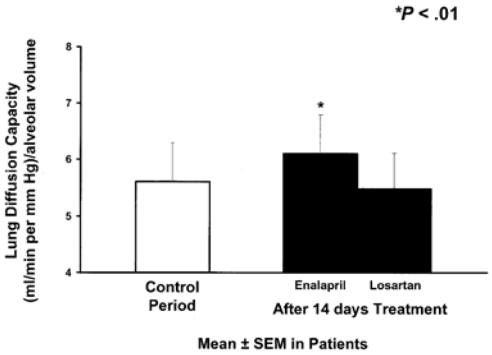


Figure 48 Effect of enalapril or losartan on pulmonary diffusion capacity in heart failure patients[64] (Based on data from J Am Coll Cardiol 2001; 37: 398-406). The bars represent mean±SEM in patients during the control period, after 14 days treatment with enalapril or losartan. * P < 0.01 compared 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.

Recently, two multicenter studies have been initiated in 40 countries to study the effects of ARBs ***and/or*** ACE inhibitors in patients with stage A through D heart failure[65]:

(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 to 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 embedded in the main trials are designed to provide insights to the mechanisms of 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 depressed left ventricular systolic function

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 119.

Table 119 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	
			Chronic Heart Failure	Post-Infarct LV dysfunction
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 HF)	
(ii) in ACE tolerant patients (telmisartan or ramipril or telmisartan plus ramipril)		ONTARGET	ONTARGET (Stage B HF)	

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 119 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[66]. 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, 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[3]. 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[17,67,68,69]. My review of the CHARM-Added (SH-AHS-0006) study (NDA 20-838 Efficacy Supplement SE1 #022) also finds 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%).

Unlike ACE inhibitors, it appears that a survival benefit is found only when ARBs are used at higher doses than those for the treatment of hypertension. Insufficient dose of ARBs may have contributed to the observed lack of beneficial effect of ARBs on mortality in ELITE II[36], OPTIMAAL[38], Val-Heft[18] and VALIANT[39] 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[41] and RENAAL[42] trials.

I think that only when there is a consensus of opinion about using ACE inhibitors and/or ARBs for any type of heart failure, and the dose(s) to be used in the treatment of heart failure, 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-Alternative (SH-AHS-0003) Study

In patients with CHF, with depressed LV systolic function (LV EF≤40%) and intolerance to ACE-inhibitors, the addition of candesartan significantly (P<0.001) reduced the relative risk of the composite primary efficacy outcome of time to CV death or CHF hospitalization by 23.2%. 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 time to all-cause mortality or CHF hospitalization (by 20.2%, P=0.001), and (ii) a composite of time to CV death or CHF hospitalization or non-fatal myocardial infarction (MI) (by 21.8%; P<0.001). The reduction in CV death and CHF hospitalization observed with candesartan treatment was also evident in those patients being treated with β-blockers (55% of patients at baseline) and digoxin (46% at baseline).

The symptoms of heart failure as evaluated by the NYHA-classification were reduced by candesartan as compared to placebo.

The magnitude of the benefit (reduction in CV death or CHF hospitalization) translates into a reduction of 7 events per 100 ACE-inhibitor intolerant patients with CHF and depressed LV systolic function treated with candesartan for two years; that is, treating 14 ACE-inhibitor intolerant patients with CHF and depressed LV systolic function 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, which was the most common fatal adverse event in the CHARM-Alternative study. The study was not powered to assess the effect on all-cause mortality.

Dose reduction and discontinuation of the investigational product attributed to aggravated heart failure, decline in renal function, hypotension and hyperkalemia were more common with candesartan than placebo.

Slightly more cancer deaths occurred in the candesartan group, but the investigator-reported rate of non-fatal neoplasms was approximately 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 CHF (the total CHARM population) treated with candesartan, an 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 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 were 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[18], 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 candesartan- and 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 onset diabetes was lower in the candesartan group, an effect observed in other large populations treated with either an ACE inhibitor[70,71] or AT_1-receptor blockers[41].

Symptoms of heart failure, as classified by the NYHA-classification, improved in more patients treated with candesartan than those treated with placebo (P= 0.004).

Overall, there was no significant safety issue reported with candesartan treatment of CHF other than the expected adverse events typical of the class of drugs and the clinical findings expected for the study populations. Discontinuation due to hyperkalemia, hypotension or renal dysfunction 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 (LV) systolic function (ejection fraction (EF) ≤40%) who were intolerant to angiotensin converting enzyme (ACE) inhibitors (CHARM-Alternative), (ii) patients with depressed LV systolic function (EF ≤40%) receiving an ACE inhibitor (CHARM-Added), and (iii) patients with preserved LV systolic function (EF >40%) (CHARM-Preserved). This review pertains to the efficacy supplement #024 (CHARM-Alternative trial).

In CHARM-Alternative (SH-AHS-0003) Study of 2,028 patients with CHF and depressed LV systolic function who were intolerant to ACE inhibitors, candesartan significantly (P<0.001) reduced the relative risk of time to CV death or CHF hospitalization by 23.2% (primary efficacy endpoint). This benefit translates into a reduction of 7 major events per 100 ACE-inhibitor intolerant patients with CHF and depressed LV systolic function treated with candesartan for two years; i.e., treating 14 ACE-inhibitor intolerant patients with CHF and depressed LV systolic function with candesartan for two years will prevent one patient from suffering the outcome of CV death or CHF hospitalization. This beneficial effect was attributed to a reduction in sudden death, which was the most commonly reported fatal AE in both treatment groups, and CHF hospitalization. The study was not powered to assess the effect on all-cause mortality.

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 the **Val**sartan **He**art **F**ailure **T**rial (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 # 024 with data on the CHARM-Alternative (SH-AHS-0003) 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 intolerant to ACE-inhibitors and receiving other heart failure treatments including β-blockers and digoxin, 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 119 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 (e.g., for high dose and low dose candesartan, and placebo) to determine the effect of candesartan (high or low dose) in the treatment of CHF in patients who are intolerant to ACE-inhibitors in order to 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

Please refer to Chapter 9, Item 9.4 (Pages 200-202) of my clinical review of the efficacy supplement SE 1 #022 of NDA 20-838 (CHARM-Added (SH-AHS-0006) study) in which I presented my labeling review.

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 has been communicated to the sponsor:

(1) Since 44.1% of the CHF patients in the CHARM-Alternative study received the 32 mg/day dose of candesartan, on November 18, 2004, I requested the sponsor to provide information on the CHARM-Alternative (SH-AHS-0003) Study regarding (a) 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 relation to the primary and secondary efficacy endpoints, and (b) in the sub-populations of patients receiving or not receiving β-blockers at baseline, (c) in the sub-populations of patients receiving or not receiving spironolactone at baseline, and (d) at which doses of candesartan the adverse events of aggravated heart failure, hypotension, hyperkalemia, deterioration of renal function, study drug discontinuation, and reduction in dose of study drug, were most frequently observed.

On November 24 2004, I received the sponsor's response containing the information requested with preliminary analyses. These analyses consider dose level of candesartan consistent with the sub-group analyses presented in the submission. For the dose analyses, I used the definition for high dose candesartan 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.

My analysis and interpretation of this additional information is presented in this review.

(2) Use the above information to plan a prospective clinical trial to determine the optimal dose of candesartan in CHF patients with depressed LV systolic function who are intolerant to ACE inhibitors, in order to obtain data which will assist in the selection of the dose of candesartan in the treatment of CHF to 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 a β-blocker and an angiotensin AT_1-receptor blocker may improve symptoms and survival and reduce hospitalizations and adverse events to a greater extent than using high doses of one drug such as an angiotensin AT_1-receptor blocker 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[54] (please see Table 100).

10 APPENDICES

10.1 Review of Individual Study Reports

Please refer to Chapter 10 Appendices section (Pages 204-244) of my clinical review for efficacy supplement SE 1 #022 of NDA 20-838 (CHARM-Added (SH-AHS-0006) study) in which I presented my reviews of the individual clinical studies in Appendices 10.1.1 through 10.1.18.

The following is a listing of the studies I have reviewed:

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)*

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.*

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)*

10.1.4 Appendix PK4 (CPH 102) *Pharmacokinetic Evaluation of Candesartan Cilexetil (TCV-116) in Patients with Chronic Congestive Heart Failure*

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)*

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.*

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)*

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*

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.*

10.1.10 Appendix PD6 (SH-AHS-0001) *The RESOLVD (Randomized Evaluation of Strategies for Left Ventricular Dysfunction) Pilot study.*

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)*

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*

10.1.13 Appendix PD9 (Study CPH101) *Evaluation of the acute effects of TCV-116 on cardiohemodynamics in patients with chronic heart failure*

10.1.14 Appendix PD10 (Study CPH103) *Evaluation of the Influence of TCV-116 on Exercise Tolerability in Patients with Chronic Heart Failure*

10.1.15 Appendix PD11 (Study CPH104) *Evaluation of the influence of TCV-116 on hormones in patients with chronic heart failure*

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*

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*

10.1.18 Appendix PD14 (Study Hikosaka (Publication)) *Candesartan and Arterial Baroreflex Sensitivity and Sympathetic Nerve Activity in Patients with Mild Heart Failure*

10.1.19 Appendix 1 CHARM-Alternative (SH-AHS-0003) Trial

Clinical Study of candesartan in patients with heart failure who are ACE inhibitor intolerant and have depressed left ventricular systolic function

Study dates
Table 120 shows the chronology of the clinical trials conducted under the CHARM Program.

Table 120 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, and SH-AHS-0007).

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

Objectives Specific to Study SH-AHS-0003 (CHARM Alternative 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).

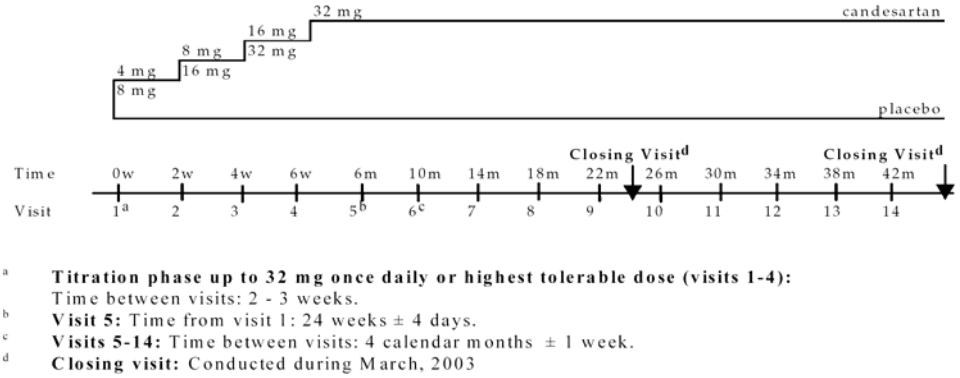
Other objectives: To determine whether candesartan, compared to placebo:

- 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%) intolerant to 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 2028 patients were randomized at 484 sites in 25 countries.

Figure 49 (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 23 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 25 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 49 Study design

Therapy with β-blockers or spironolactone:

Patients receive all other treatments for heart failure including β-blockers or spironolactone except other AT1 receptor blockers and, because of intolerance, ACE-inhibitors. The drugs used for these patients' treatment of CHF 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 Alternative (SH-AHS-0003)

- 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.
- No current treatment with an ACE inhibitor because of a history of intolerance (defined as a decision of the attending investigator to discontinue therapy with the ACE inhibitor for what he/she felt was an ACE inhibitor-related AE, including angioedema, anaphylaxis and/or cough and/or symptomatic hypotension and/or renal dysfunction and/or other AEs such as taste disturbance, rash, neutropenia and gastrointestinal upset.

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 121 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 121 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, and 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-Alternative (SH-AHS-0003) Study Review

The current study is one of three component studies in the CHARM program (SH-AHS-0003, SH-AHS-0006, and 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% intolerant to 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 2028 patients were randomized at 484 sites in 25 countries.

The patient recruitment period was 23 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 25 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 8 patients took expired drug (**Table 122**)**. However, additional stability testing suggested that the drug was still within specifications

Table 122 Patients on expired drug

Country	Site	Pat no	Bottle no	Expiry date	Days on expired drug
France	506	13567	792324	2002-10-01	47
Germany	1076	11354	770754	2002-10-01	5
	1092	12153	614623	2000-11-01	19
Poland	607	12641	602451	2000-11-01	76
	610	12716	621388	2000-11-01	76
	611	12636	659926	2000-11-01	8
South Africa	1855	15239	743817	2002-09-01	3
Sweden	113	11075	680524	2002-09-01	1

Assigning patients to treatment groups: Investigational Products, AstraZeneca R& D Mölndal, Sweden provided a computer generated randomization list (block size = 2) 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, with the exception of ACE inhibitors to which patients were intolerant. Before randomization the investigator was asked to optimize therapy for each patient. 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 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.

Clinical 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.

Three 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.

Patients lost to follow-up/ incomplete patient data:

Patient status	Censoring/ imputation
Date of death unknown	Death date estimated by imputation
Date of death after March 31	Analyzed as being alive 31 March
Patients not reported dead	Last date known to be alive was used in the analyses

Patients who withdrew the consent:

Patient status	Censoring/ imputation
Status alive up to 31 March	Patient analyzed as being alive 31 March
Dead patient	Death date estimated by imputation

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.

Intention-to-Treat (ITT) Population: All randomized patients.

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:
- 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 **1,700** 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 **2,000** 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 123).

Table 123 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.

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 124.

Table 124 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	+2	+4	Seven death reports were added. As a result six patients with CV-deaths were re-classified based on this new information.
Non adjudicated deaths	-2	-5	Due to the new death reports the number of non-adjudicated deaths decreased, they were re-adjudication to CV death.
Confirmed, adjudicated non-CV-deaths	0	+1	One of the seven deaths was re-classified as non-CV death.
Confirmed, adjudicated CHF-hospitalisations	0	+1	One CHF hospitalisations was agreed after adjudication.
Non-fatal MI	0	0	No difference.
Other SAE:s	0	+1	Six SAE-reports were added, but only one patient was re-classified as "other SAE".

STUDY PATIENTS

In total 2,028 patients were recruited from 484 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 2,028 patients recruited, 1,013 were randomized to candesartan and 1,015 to placebo. All 2028 patients were analyzed for safety and efficacy. Overall, the treatment groups were comparable for demographic characteristics and baseline data.

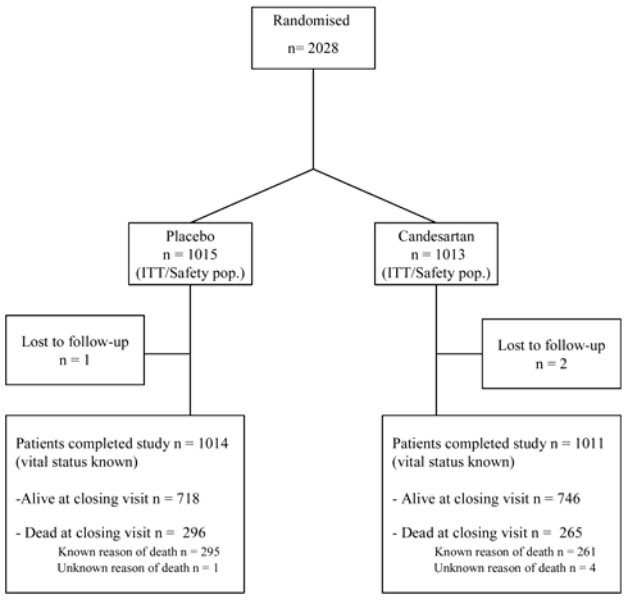


Figure 50 Patient disposition (completion or discontinuation)

Disposition: The disposition of study patients is summarized in Figure 50.

Protocol deviations: The number of patients with protocol deviations in each treatment group are summarized in Table 125. (N.B. One patient could have more than one protocol deviation through out the study.)

Table 125 Number of patients with protocol deviations

	Placebo (N=73)	Cand. cil. (N=63)
Inclusion criteria deviation	6	9
Exclusion criteria deviation	31	28
Patient's consent withdrawn (continued in study or with investigational product)	0	0
Patient pregnant	0	0
Investigational product given without randomisation	0	0
Investigational product never given	0	0
Wrong investigational product given, wrong bottle and wrong investigational product	1	6
Wrong investigational product given, wrong bottle and correct investigational product	12	4
Wrong dose of investigational product given (dose <4 or >32 mg)	0	4
Incorrect dose of investigational product given (dose ≠4, 8, 16, 32 mg)	2	0
Pre-randomisation (randomisation date before visit 1)	16	6
Treatment code prematurely broken	5	4
Less than two years in the study (patients lost to follow up)	0	2

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.

Table 126 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	66	86
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	11	7
ACE inhibitor taken at any time point before the confirmed, adjudicated CV death or hospitalisation for the management of CHF, whichever occurred first	17	7
No investigational product at closing visit – patients without confirmed, adjudicated CV death or hospitalisation for the management of CHF	92	123
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	58	66
ACE inhibitor taken at any time point during the study - patients without confirmed, adjudicated CV death or hospitalisation for the management of CHF	48	53

The reasons for exclusion from the PP population are given in Table 126. (One patient could be listed for more than one reason in this table.) 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 study populations analyzed, and the number of patients in each population, are summarized in Figure 51.

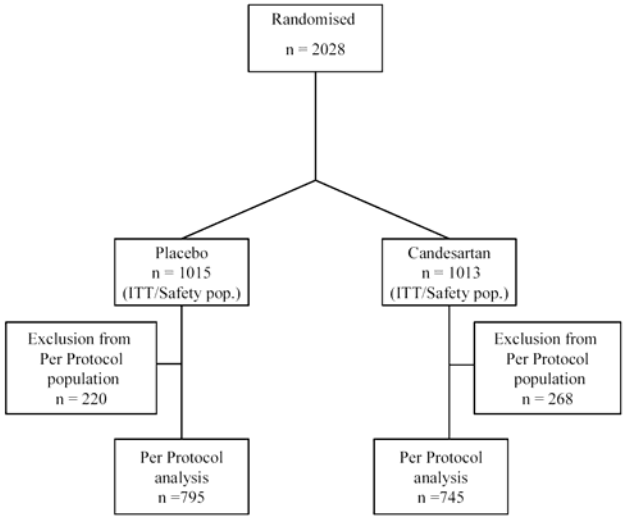


Figure 51 Study populations

Demographic and other patient characteristics:

The treatment groups were generally well balanced with regard to baseline characteristics. However, more patients in the candesartan group had a previous hospitalization for CHF (70.3% vs. 66.3%) and more frequently had a LVEF below 25% (23.6% vs. 21.1%).

Cough was the most common reason for ACE intolerance in both treatment groups. It was more common in the placebo group than in the candesartan group (751, 74.0% vs. 704, 69.5%). ACE intolerance due to hypotension or renal dysfunction was more common in the candesartan group (143, 14.1% vs. 119, 11.7%, and 134, 13.3% vs. 100, 9.9% respectively) (Table 127).

Table 127 Reasons for ACE inhibitor intolerance at randomization. ITT/Safety Population (SH-AHS-0003)

Reason for ACE inhibitor intolerance at randomisation[a]	Treatment	
	Placebo (N=1015)	Cand. cil. (N=1013)
	Number of intolerant patients at randomisation, N (%)	Number of intolerant patients at randomisation, N (%)
Cough	751 (74.0)	704 (69.5)
Hypotension	119 (11.7)	143 (14.1)
Renal dysfunction	100 (9.9)	134 (13.3)
Angioedema	44 (4.3)	39 (3.8)
Other[b]	109 (10.7)	101 (10.0)

[a] A patient may have more than one reason for intolerance
[b] Includes any AE, lab value, or unknown reason.

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.

More than half of patients (1,106, 55%) received β-blockers, 86% (1,733 patients) were treated with diuretics, 46% (924 patients) with digitalis and 24% (483 patients) were treated with spironolactone. Patients were ACE inhibitor intolerant but they were being treated with other therapeutic agents known to provide beneficial effects for the treatment of CHF.

N.B. ACE inhibitors were used by 4 patients at randomization.

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 480 patients (67%) vs. 476 patients (64%), spironolactone in 209 patients (29%) vs. 183 patients (25%) and diuretics in 572 patients (79%) vs. 566 patients (76%)].

EFFICACY RESULTS

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

During the follow-up period, 740 patients experienced the primary outcome of CV death or CHF hospitalization, 334 (33.0%) in the candesartan group and 406 (40.0%) in the placebo group. The average annualized events rates were 13.8% and 18.2% respectively (Table 128).

Table 128 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-0003)

Variable	Treat-ment	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	1015	406	2229.2	182.1	2.2
	Cand. cil.	1013	334	2418.9	138.1	2.4

The relative risk was significantly (P<0.001) reduced by 23.2% for the primary outcome of CV death or hospitalization due to CHF, whichever came first, by candesartan treatment (Table 129).

Table 129 Confirmed adjudicated CV death or hospitalization due to CHF. Comparison of candesartan versus placebo with Cox regression. ITT/Safety population (SH-AHS-0003)

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

The Kaplan-Meier plot implies that the benefit of candesartan appeared early and was maintained throughout the study period (Figure 52).

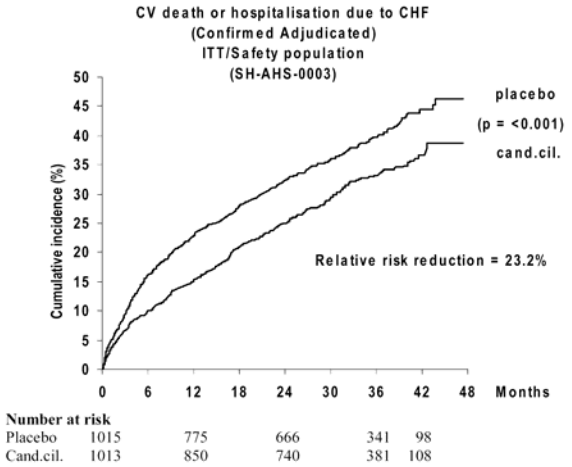


Figure 52 Cumulative incidence (%) of confirmed adjudicated CV death or hospitalization due to CHF over time. ITT/Safety population

The treatment effect of candesartan was similar across geographical regions (test for interaction; P= 0.972).

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

During the follow-up period, 804 patients experienced the secondary outcome of all-cause death or CHF hospitalization, 371 (36.6%) in the candesartan group and 433 (42.7%) in the placebo group. The average annualized events rates were 15.3% and 19.4%, respectively (Table 130).

Table 130 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-0003)

Variable	Treat-ment	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	1015	433	2229.2	194.2	2.2
	Cand. cil.	1013	371	2418.9	153.4	2.4

The relative risk for the secondary outcome of all cause death or hospitalization due to CHF, whichever came first, was significantly reduced by 20.2% by candesartan treatment (Table 131).

Table 131 Confirmed adjudicated all- cause death or hospitalization due to CHF. Comparison of candesartan versus placebo with Cox regression. ITT/Safety population (SH-AHS-0003)

Variable	N	Events cand. cil.	Events placebo	Hazard Ratio	95% CI		p-value
					Lower	Upper	
All-cause death or hospitalisation due to CHF (confirmed adjudicated)	2028	371	433	0.798	0.695	0.917	0.001

The Kaplan-Meier plot implies that the benefit of candesartan appeared early and was maintained throughout the study period (Figure 53).

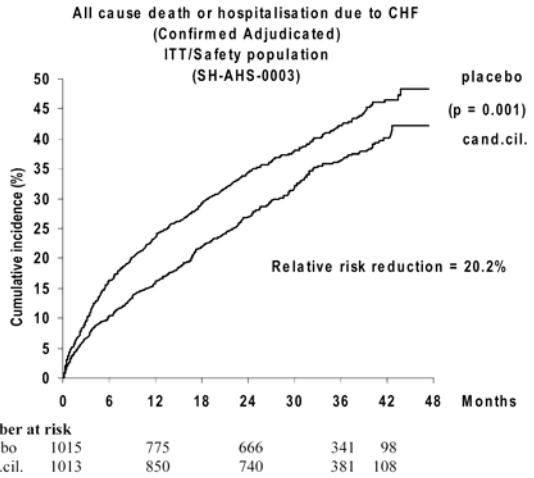


Figure 53 Cumulative incidence (%) of confirmed adjudicated all- cause death or hospitalization due to CHF over time. ITT/Safety population

The treatment effect of candesartan was similar across geographical regions (test for interaction; P= 0.721).

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

During the follow-up period, 773 patients experienced the secondary outcome of CV death or CHF hospitalization or non-fatal MI, 353 (34.8%) in the candesartan group and 420 (41.4%) in the placebo group. The average annualized events rates were 14.8% and 19.1%, respectively (Table 132).

Table 132 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-0003)

Variable	Treat-ment	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	1015	420	2196.4	191.2	2.2
	Cand. cil.	1013	353	2389.2	147.8	2.4

The relative risk for the secondary outcome of CV death or CHF hospitalization or non-fatal MI, whichever came first, was significantly reduced by 21.8% by candesartan treatment (Table 133).

Table 133 Confirmed adjudicated CV death or hospitalization due to CHF or non-fatal MI. Comparison of candesartan versus placebo with Cox regression. ITT/Safety population (SH-AHS-0003)

Variable	N	Events cand. cil.	Events placebo	Hazard Ratio	95% CI		p-value
					Lower	Upper	
CV death or hospitalisation due to CHF or non-fatal MI (confirmed adjudicated)	2028	353	420	0.782	0.679	0.901	<0.001

The Kaplan-Meier plot implies that the benefit of candesartan appeared early and was maintained throughout the study period (Figure 54).

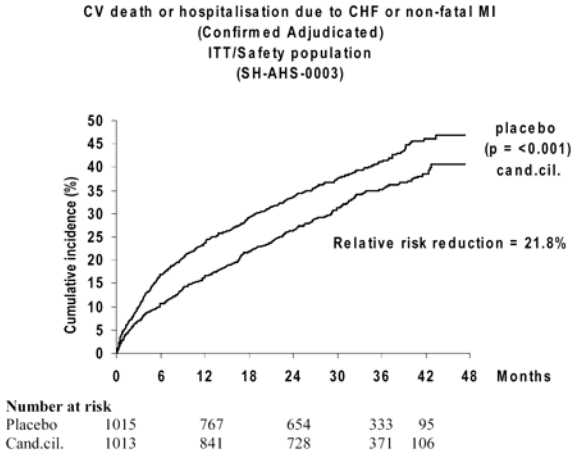


Figure 54 Cumulative incidence (%) of confirmed adjudicated CV death or hospitalization due to CHF or non- fatal MI over time. ITT/Safety population

The treatment effect of candesartan was similar across geographical regions (test for interaction; P= 0.983).

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 134 and Table 135, 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 135). 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 134 CV death or CHF hospitalization by subgroup: dose of study drug, (events per 1000 years of follow-up), Study SH-AHS-0003

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 135 CV death or CHF hospitalization by subgroup: dose of study drug (Cox regression), Study SH-AHS-0003

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 on November 18, 2004, I requested the sponsor to provide information on the CHARM-Alternative (SH-AHS-0003) 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 relation to the primary and secondary efficacy endpoints.

On November 24 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, I used the definition for high candesartan dose 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): 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 136. 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; however, patients receiving and placebo also exhibited the same dose response! (Table 137).

The secondary efficacy endpoint of all-cause mortality or CHF hospitalization (Table 138 and Table 139), and for secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI (Table 140 and Table 141) also show similar findings.

Table 136 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 – CHARM-Alternative (SH-AHS-0003) Study

Candesartan		**N = 1013** **Events = 371 (36.6%)**	
			A
	CC_{HD} n = 597 events = 180 (30.2%)	CC_{LD} n = 213 events = 124 (58.2%)	CC_{00} n = 203 events = 67 (33.0%)
	A1	**A2**	**A3**
Placebo		**N = 1015** **Events = 433 (42.7%)**	
			B
	P_{HD} n = 721 events = 282 (39.1%)	P_{LD} n = 131 events = 94 (71.8%)	P_{00} n = 163 events = 57 (35.0%)
	B1	**B2**	**B3**

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 137 Comparison of the effect of high or low dose candesartan on the primary endpoint of time to CV mortality or CHF hospitalization (confirmed, adjudicated) using Cox Regression– CHARM-Alternative (SH-AHS-0003) Study

Comparison	Relative risk reduction (%)	Hazard ratio	95% confidence interval	p-value (Wald)
A vs B	23.2	0.768	(0.665, 0.888)	<0.001
A_1 vs B	40.7	0.593	(0.494, 0.712)	<0.001
A_1 vs A_2	64.5	0.355	(0.280, 0.451)	<0.001
A_2 vs B	-	1.652	(1.346, 2.028)	<0.001
A_1 vs B_1	34.5	0.655	(0.539, 0.796)	<0.001
A_2 vs B_2	37.6	0.624	(0.472, 0.825)	<0.001

Cells A, B, A_1, B_1, A_2 and B_2 = Reference to cells in Table 136.

Table 138 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 – CHARM-Alternative (SH-AHS-0003) Study

Candesartan	**N = 1013** **Events = 371 (36.6%)**		
			A
	CC_{HD} n = 597 events = 180 (30.2%)	CC_{LD} n = 213 events = 124 (58.2%)	CC_{00} n = 203 events = 67 (33.0%)
	A1	**A2**	**A3**
Placebo	**N = 1015** **Events = 433 (42.7%)**		
			B
	P_{HD} n = 721 events = 282 (39.1%)	P_{LD} n = 131 events = 94 (71.8%)	P_{00} n = 163 events = 57 (35.0%)
	B1	**B2**	**B3**

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 139 Comparison of the effect of high or low dose candesartan on the secondary efficacy endpoint of all-cause mortality or CHF hospitalization (confirmed, adjudicated) using Cox Regression[a] – CHARM-Alternative (SH-AHS-0003) Study

Comparison	Relative risk reduction (%)	Hazard ratio	95% confidence interval	p-value (Wald)
A vs B	20.2	0.798	(0.695, 0.917)	0.001
A_1 vs B	38.2	0.618	(0.519, 0.735)	<0.001
A_1 vs A_2	62.7	0.373	(0.297, 0.470)	<0.001
A_2 vs B	-	1.631	(1.336, 1.992)	<0.001
A_1 vs B_1	30.2	0.698	(0.579, 0.841)	<0.001
A_2 vs B_2	40.1	0.599	(0.458, 0.784)	<0.001

Cells A, B, A_1, B_1, A_2 and B_2 = Reference to cells in Table 138.

Table 140 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 – CHARM-Alternative (SH-AHS-0003) Study

Candesartan	**N = 1013** **Events = 353 (34.9%)**		
			A
	CC_{HD} n = 599 events = 176 (29.4%)	CC_{LD} n = 215 events = 121 (56.3%)	CC_{00} n = 199 events = 56 (28.1%)
	A1	**A2**	**A3**
Placebo	**N = 1015** **Events = 420 (41.4%)**		
			B
	P_{HD} n = 720 events = 279 (38.8%)	P_{LD} n = 134 events = 91 (67.9%)	P_{00} n = 161 events = 50 (31.1%)
	B1	**B2**	**B3**

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 141 Comparison of the effect of high or low dose candesartan on the secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI (confirmed, adjudicated) using Cox Regression[a] – CHARM-Alternative (SH-AHS-0003) Study

Comparison	Relative risk reduction (%)	Hazard ratio	95% confidence interval	p-value (Wald)
A vs B	21.8	0.782	(0.679, 0.901)	<0.001
A_1 vs B	37.9	0.621	(0.521, 0.741)	<0.001
A_1 vs A_2	62.1	0.379	(0.301, 0.478)	<0.001
A_2 vs B	-	1.620	(1.323, 1.983)	<0.001
A_1 vs B_1	30.9	0.691	(0.572, 0.834)	<0.001
A_2 vs B_2	39.5	0.605	(0.460, 0.795)	<0.001

Cells A, B, A_1, B_1, A_2 and B_2 = Reference to cells in Table 140.

However, there are many caveats to these findings:

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

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

(iii) 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.

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

My interpretation of the data provided by the sponsor in Table 136 through Table 141 is as follows.

(i) Patient sub-populations by severity of CHF (presumed): Patients in cells A3 (not receiving candesartan prior to event) and B3 (not receiving "double-blind" placebo (perceived by the clinical investigator and the patient as candesartan) prior to event) were, I think, "the most sick" patients who, for some reason (hypotension, hyperkalemia, deterioration in renal function) could not tolerate candesartan for an unknown period of time prior to the primary or secondary efficacy event. Patients in cells A2 (receiving 4 mg or 8 mg candesartan prior to event) and B2 (receiving "double-blind" placebo (perceived by the clinical investigator and the patient as 4 mg or 8 mg candesartan) prior to event) were "moderately sick" patients who could not tolerate the higher doses of candesartan. Patients in cells A1 (receiving 16 mg or 32 mg candesartan prior to event) and B1 (receiving "double-blind" placebo (perceived by the clinical investigator and the patient as 16 mg or 32 mg candesartan) prior to event) were "the least sick" patients who tolerated the higher doses of candesartan.

(ii) Effect of no drug – internal consistency: Patients in both treatment groups A3 and B3 were not receiving any investigational drug (candesartan or placebo) and had the same

(albeit presumed) severity of CHF. Thus, the events rates in treatment groups A3 and B3 are expected to be similar. The event rates in treatment groups A3 and B3 for the primary and secondary efficacy endpoints are, indeed, similar (Table 136 through Table 141), suggesting internal consistency, and providing some confidence to the logic and integrity of the data.

(iii) Effect of candesartan (1): Comparing the event rates in A2 to B2 allowed the comparison of events in the same population of patients with similar severity of CHF ("moderately sick" patients). A statistically significant reduction in the event rates between A2 vs. B2 for the primary and secondary efficacy endpoints suggests a true difference in this sub-population of moderately sick patients with CHF.

(iv) Effect of candesartan (2): Comparing the event rates in A1 to B1 allow the comparison of event rates in same population of patients with similar degree of CHF ("the least sick" group of patients). A statistically significant reduction in the event rates between A1 vs. B1 for the primary and secondary efficacy endpoints suggests a true difference among patients with the same severity of CHF.

(v) Effect of candesartan (3): The effect of candesartan in the "least sick" and "moderately sick" sub-populations of patients appears to be about the same (for the primary endpoint, a reduction in the relative risk by 34.5% (A1 vs. B1) or 37.6% (A2 vs. B2). This suggests a consistent effect of candesartan for the primary (and also for the secondary) efficacy endpoints.

(vi) Effect of disease: Comparison of the event rates in cells B1 vs. B2 (patients receiving placebo) also shows that the event rates are significantly ($P<0.001$) lower in the "high dose" group compared to the "low dose" group (Table 136 through Table 141). Since neither group (B1 or B2) was receiving candesartan, this finding is clearly due to the severity of CHF.

(vii) Effect of disease severity (or) effect of dose of candesartan? Comparison of cells A1 vs. A2 shows that the event rates are significantly ($P<0.001$) lower in the high dose (16 and 32 mg, A1) candesartan groups compared to the low dose (4 and 8 mg, A2) candesartan groups (Table 136 through Table 141), giving the appearance of a dose-related response. I think that the lower event rate in the "high dose" candesartan group is mainly due to the fact that subjects in cell A1 are "the least sick" of the study population; conversely, the higher event rate in the "low dose" candesartan group is due to the fact that subjects in cell A2 are relatively less sick patients. Thus, rather than a "dose-related" response for candesartan regarding the primary and secondary efficacy endpoints as the data in Table 27 through Table 32 appear to suggest, I think the differences observed between the "high dose" and "low dose" candesartan groups are attributable to the severity of CHF.

Components of primary and secondary variables

The individual components of CV death (relative risk reduction 15%, $P= 0.072$), hospitalization due to CHF (relative risk reduction 32%, $P< 0.001$) and all-cause death (relative risk reduction 13%, $P= 0.105$), all contributed to the benefit of candesartan as described by the respective composite endpoints. There was no reduction in non-fatal MI (Table 142 and Table 143).

Table 142 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-0003)

Variable	Treatment	N	Events (No of pati-ents)	Total follow-up time (years)	Events/ 1000 follow-up years	Mean follow-up time (years)
CV death (confirmed adjudicated)	Placebo	1015	252	2582.4	97.6	2.5
	Cand. cil.	1013	219	2658.1	82.4	2.6
Hospitalisation due to CHF (confirmed adjudicated)	Placebo	1015	286	2229.2	128.3	2.2
	Cand. cil.	1013	207	2418.9	85.6	2.4
All-cause death (confirmed adjudicated)	Placebo	1015	296	2582.4	114.6	2.5
	Cand. cil.	1013	265	2658.1	99.7	2.6
Non-fatal MI (confirmed adjudicated)	Placebo	1015	36	2534.5	14.2	2.5
	Cand.cil.	1013	41	2619.5	15.7	2.6

Table 143 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)	2028	219	252	0.847	0.707	1.015	0.072
Hospitalisation due to CHF (confirmed adjudicated)	2028	207	286	0.677	0.566	0.810	<0.001
All-cause death (confirmed adjudicated)	2028	265	296	0.872	0.739	1.029	0.105[a]
Non-fatal MI (confirmed adjudicated)	2028	41	36	1.107	0.708	1.733	0.656[b]

[a] Logrank test p=0.104
[b] Logrank test p=0.655

Time from randomization to all-cause death:

Time from randomization to all-cause death is a component of a secondary variable, and is presented in Table 142 and Table 143.

Time from randomization to all-cause hospitalization:

During the follow-up period, 610 (60.2%) patients in the candesartan group and 643 (63.3%) patients in the placebo group were hospitalized due to any cause. The average annualized events rates were 36.3% and 40.0% respectively (Table 144). The relative risk of all-cause hospitalization was non-significantly (P= 0.107) reduced by candesartan treatment (Table 145).

Table 144 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-0003)

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	1015	643	1606.2	400.3	1.6
	Cand. cil.	1013	610	1681.6	362.7	1.7

Table 145 Confirmed adjudicated all-cause hospitalization. Comparison of candesartan versus placebo with Cox regression. ITT/Safety population (SH-AHS-0003)

Variable	N	Events cand. cil.	Events placebo	Hazard Ratio	95% CI		p-value
					Lower	Upper	
All-cause hospitalisation	2028	610	643	0.913	0.817	1.020	0.107

Number of patients with fatal or non-fatal MI:

There were significantly fewer patients with fatal or non-fatal MI in the placebo group (48,4.7%) than in the candesartan group (75, 7.4%) (Table 146 and Table 147).

Table 146 The proportion of patients (%) with confirmed adjudicated fatal or nonfatal MI. ITT/Safety population (SH-AHS-0003)

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	1015	48	4.7	3.5	6.2
	Cand. cil.	1013	75	7.4	5.9	9.2

Table 147 The difference in proportion (%) of patients with confirmed adjudicated fatal or non- fatal MI between treatments. Chi-square test. ITT/Safety population (SH-AHS-0003)

Variable	Difference in proportion between treatments	95% CI		p-value
	Cand.cil-placebo	Lower	Upper	
Fatal or non-fatal MI (confirmed adjudicated)	2.7	0.6	4.7	0.012

NYHA classification of heart failure:

Improvement in NYHA functional class by 1 or 2 NYHA classes was observed in 359 (35.7%) patients in the candesartan group compared to 298 (29.7%) in the placebo group (P= 0.008, Wilcoxon rank-sum test) (Table 148).

Table 148 Number of patients and change from baseline to LVCF in NYHA class by treatment. ITT/Safety population (SH-AHS-0003)

Visit	NYHA class	Placebo	Cand. cil.	Total
Baseline	NYHA II	479 (47.2%)	487 (48.1%)	966 (47.6%)
	NYHA III	499 (49.2%)	490 (48.4%)	989 (48.8%)
	NYHA IV	37 (3.6%)	36 (3.6%)	73 (3.6%)
	Total	1015	1013	2028
LVCF	NYHA I	95 (9.5%)	144 (14.3%)	239 (11.9%)
	NYHA II	521 (51.9%)	493 (49.0%)	1014 (50.4%)
	NYHA III	337 (33.6%)	332 (33.0%)	669 (33.3%)
	NYHA IV	51 (5.1%)	37 (3.7%)	88 (4.4%)
	Total	1004	1006	2010
Change from baseline to LVCF[a]	NYHA improved by 3 classes	0	2 (0.2%)	2 (0.1%)
	NYHA improved by 2 classes	33 (3.3%)	40 (4.0%)	73 (3.6%)
	NYHA improved by 1 class	265 (26.4%)	319 (31.7%)	584 (29.1%)
	NYHA same as baseline	597 (59.5%)	544 (54.1%)	1141 (56.8%)
	NYHA deteriorated by 1 class	106 (10.6%)	93 (9.2%)	199 (9.9%)
	NYHA deteriorated by 2 classes	3 (0.3%)	8 (0.8%)	11 (0.5%)
	Total	1004	1006	2010

[a] Wilcoxon rank-sum test, p=0.008

The shift in NYHA functional class from baseline to last known class is presented in Table 149.

Table 149 NYHA class shift table by treatment. ITT/Safety Population. (SH-AHS-0003)

Change in NYHA class from baseline to LVCF	Number of patients (%)	
	Placebo (N=1015)	Cand.cil. (N=1013)
from II to Unknown	4 (0.4%)	4 (0.4%)
from II to I	71 (7.0%)	112 (11.1%)
from II to II	328 (32.3%)	294 (29.0%)
from II to III	73 (7.2%)	69 (6.8%)
from II to IV	3 (0.3%)	8 (0.8%)
from III to Unknown	4 (0.4%)	2 (0.2%)
from III to I	24 (2.4%)	30 (3.0%)
from III to II	184 (18.1%)	189 (18.7%)
from III to III	254 (25.0%)	245 (24.2%)
from III to IV	33 (3.3%)	24 (2.4%)
from IV to Unknown	3 (0.3%)	1 (0.1%)
from IV to I	0	2 (0.2%)
from IV to II	9 (0.9%)	10 (1.0%)
from IV to III	10 (1.0%)	18 (1.8%)
from IV to IV	15 (1.5%)	5 (0.5%)

Time from randomization to diagnosed onset of diabetes:

Analyses include only patients without a pre-study diagnosis of diabetes. During the follow-up period 44 (6.0%) patients in the candesartan group and 53 (7.1%) patients in the placebo group had a diagnosed onset of diabetes during the follow-up period. The average annualized events rates were 2.3% and 2.9% respectively (Table 150). There is a nonsignificant (P= 0.254) relative risk reduction of 20.8% for developing diabetes with candesartan treatment (Table 151).

Table 150 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-0003)

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	745	53	1831.6	28.9	2.5
	Cand. cil.	735	44	1921.0	22.9	2.6

Table 151 Diagnosed onset of diabetes. Comparison of candesartan versus placebo with Cox regression. ITT/Safety population (SH-AHS-0003)

Variable	N	Events cand. cil.	Events placebo	Hazard Ratio	95% CI		p-value
					Lower	Upper	
Diagnosed onset of diabetes	1480	44	53	0.792	0.531	1.182	0.254 [a]

[a] Logrank test p=0.252

Number of patients who developed atrial fibrillation:

Significantly fewer patients in the candesartan group than in the placebo group developed atrial fibrillation (candesartan 49, 4.8%, placebo 70, 6.9%, P= 0.048) during the follow-up period (Table 152 and Table 153).

Table 152 Development of atrial fibrillation. The proportions of patients (%) with an event. ITT/ Safety population (SH-AHS-0003)

Variable	Treatment	N	Number of patients with event	Proportion of patients with event	95% CI	
					Lower	Upper
Development of atrial fibrillation	Placebo	1015	70	6.9	5.4	8.6
	Cand. cil.	1013	49	4.8	3.6	6.3

Table 153 Development of atrial fibrillation. The difference in proportion (%) between treatments. Chi-square test. ITT/Safety population (SH-AHS-0003)

Variable	Difference in proportion between treatments	95% CI		p-value
	Cand.cil-placebo	Lower	Upper	
Development of atrial fibrillation	-2.1	-4.1	0.0	0.048

Frequency of hospitalizations:

The effects on hospitalizations for various reasons are presented in Table 154 and Table 155. 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 154 Total number of clinical events by variable and treatment. ITT/ Safety population (SH-AHS-0003)

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	1015	50	66	2582.4	0.04	25.6
	Cand. cil.	1013	49	62	2658.1	0.03	23.3
All-cause hospitalisation	Placebo	1015	643	1835	2582.4	1.44	710.6
	Cand. cil.	1013	610	1718	2658.1	1.04	646.3
Non-fatal stroke	Placebo	1015	29	34	2582.4	0.06	13.2
	Cand. cil.	1013	25	28	2658.1	0.01	10.5
Non-fatal MI	Placebo	1015	61	92	2582.4	0.12	35.6
	Cand. cil.	1013	62	110	2658.1	0.11	41.4
Hospitalisation due to CHF	Placebo	1015	329	716	2582.4	0.66	277.3
	Cand. cil.	1013	257	539	2658.1	0.44	202.8
Hospitalisation due to CHF (primary reason only)	Placebo	1015	291	608	2582.4	0.53	235.4
	Cand.cil.	1013	212	445	2658.1	0.38	167.4
Number of days alive in hospital	Placebo	1015	586	16008	2582.4	8.11	6199
	Cand. cil.	1013	559	14687	2658.1	7.27	5525

Table 155 Difference between treatments by variable. Wilcoxon rank-sum test. ITT/Safety population (SH-AHS-0003)

Variable	Mean (number of events / follow-up year) by patients.		p-value
	Placebo	Cand. cil.	
Coronary revascularisation procedure	0.04	0.03	0.930
All-cause hospitalisation	1.44	1.04	0.062
Non-fatal stroke	0.06	0.01	0.594
Non-fatal MI	0.12	0.11	0.842
Hospitalisation due to CHF	0.66	0.44	<0.001
Hospitalisation due to CHF (primary reason only)	0.53	0.38	<0.001
Number of days alive in hospital	8.11	7.27	0.176

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, race, region, CHF etiology, baseline NYHA class, baseline LVEF and concomitant medications. While there was a statistically significant interaction for age, the direction of the effect was in favor of candesartan across the age groups.

Reviewer's comment: The United States was the country contributing the largest number of patients to the CHARM-Programme studies. In the CHARM-Alternative (SH-AHS-0003) the treatment effect was in the direction favoring candesartan (HR 0.811, 95% CI 0.605 -1.087, P= 0.162). In the CHARM-Added (SH-AHS-0006) study, the HR for the primary efficacy variable was 1.019 (95% CI 0.798-1.303, P=0.877), which is not consistent with the findings of the CHARM-Alternative study. Taken together, studies SH-AHS-0003 and SH-AHS-0006 (pooled analysis) 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 156 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 156 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-0003)

		Hospitalisations		Intensive care		Intermediate care		General care		All	
Primary reason[a]	Treatment	N	%	Days	%	Days	%	Days	%	Days	%
Worsening CHF	Placebo	523	27.8	572	11.7	1267	26.0	3041	62.3	4880	100
	Cand.cil.	392	20.8	773	21.3	981	27.0	1873	51.6	3627	100
Myocardial infarction	Placebo	48	2.6	176	38.2	151	32.8	134	29.1	461	100
	Cand.cil.	49	2.6	257	51.8	98	19.8	141	28.4	496	100
Unstable angina	Placebo	93	4.9	122	11.8	571	55.2	341	33.0	1034	100
	Cand.cil.	120	6.4	217	29.8	205	28.1	307	42.1	729	100
Stroke	Placebo	17	0.9	44	33.3	22	16.7	66	50.0	132	100
	Cand.cil.	18	1.0	8	3.7	32	14.7	177	81.6	217	100
TIA	Placebo	13	0.7	9	8.3	26	23.9	74	67.9	109	100
	Cand.cil.	9	0.5	0	0.0	5	7.8	59	92.2	64	100
Hypotension	Placebo	8	0.4	9	11.8	5	6.6	62	81.6	76	100
	Cand.cil.	20	1.1	19	12.0	65	41.1	74	46.8	158	100
Atrial tachyarrhythmia	Placebo	37	2.0	38	6.8	62	11.2	456	82.0	556	100
	Cand.cil.	42	2.2	50	25.3	41	20.7	107	54.0	198	100
Ventricular arrhythmia	Placebo	48	2.6	152	36.5	135	32.4	130	31.2	417	100
	Cand.cil.	41	2.2	138	37.3	116	31.4	116	31.4	370	100
Pulmonary embolism	Placebo	6	0.3	0	0.0	15	22.7	51	77.3	66	100
	Cand.cil.	5	0.3	10	22.7	22	50.0	12	27.3	44	100
Other CV event	Placebo	210	11.2	322	21.7	398	26.8	765	51.5	1485	100
	Cand.cil.	183	9.7	269	25.1	235	22.0	566	52.9	1070	100
All CV events	Placebo	1003	53.3	1444	15.7	2652	28.8	5120	55.6	9216	100
	Cand.cil.	879	46.7	1741	25.0	1800	25.8	3432	49.2	6973	100

[a] As stated by investigator

Information on length of stay by type of ward was recorded for 1,882 hospitalizations (879 in the

candesartan group, 1,003 in the placebo group) where the primary reason for hospitalization was reported as cardiovascular. Patients in the candesartan group spent fewer days in hospital (6,973 days) than patients in the placebo group (9,216 days) (Table 156).

When hospitalized, the candesartan patients spent proportionally more days in more resource intensive care than the placebo patients (intensive care 25.0 vs. 15.7% of days, intermediate care 25.8 vs. 28.8% of days and general care 49.2 vs. 55.6% of days). (Table 156)

Reviewer's comment: This is different than the finding in my review of the CHARM-Added (SH-AHA-0006) study (item 6.1.4.3, page 68) which showed that 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), with the candesartan-treated group spending fewer days than the placebo-treated group in higher levels of medical care (intensive care 18.8 vs. 19.4% of days, intermediate care 25.9 vs. 26.2% of days) but not general care (55.3 vs. 54.4% of days).

Drug-drug and drug-disease interactions:

The subgroup analyses showed that the positive effects of candesartan 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 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 157 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 ***non-use*** of β-blockers at baseline (RRR =34.3%, P<0.001), during the study (RRR =39.0%, P<0.001) and at the visit preceding the event (RRR=35.1%, P<0.001).

Table 157 CV death or hospitalization due to CHF (confirmed adjudicated) by use of β-blockers in study SH-AHS-0003. 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	922	172	232	0.657	0.539	0.800	<0.001
	Yes	1106	162	174	0.904	0.730	1.119	0.354
Beta-blocker during study	No	606	120	165	0.610	0.482	0.772	<0.001
	Yes	1422	214	241	0.861	0.716	1.035	0.111
Beta-blocker at the visit preceding the event	No	1647	147	212	0.649	0.526	0.801	<0.001
	Yes	380	187	193	0.958	0.783	1.172	0.678

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

On November 24 2004, the sponsor submitted a response to my request for data related to the primary and principal secondary efficacy endpoints according to dose level of candesartan in relation to patients receiving or not receiving β-blockers at baseline. These analyses consider dose level of candesartan consistent with the sub-group analyses presented in the submission. For the dose analyses, I used the definition for high candesartan dose 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): 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 158. It appears that there is a dose-related response, the event rates being lower in the high dose (16 and 32 mg) candesartan groups compared to the low dose (4 and 8 mg) candesartan groups for both patients receiving β-blockers and those not receiving β-blockers.

The event rates in patients receiving β-blockers are generally **lower** than in those not receiving β-blockers for the sub-populations of patients receiving "high dose" candesartan, "low dose" candesartan or no candesartan at the visit prior to the event.

Table 158 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-Alternative (SH-AHS-0003) Study

Beta-blocker at baseline			
Candesartan	**N = 553** **Events = 162 (29.3%)**		
			A
	CC_{HD} n = 343 events = 87 (25.4%)	CC_{LD} n = 106 events = 51 (48.1%)	CC_{00} n = 104 events = 24 (23.1%)
	A1	**A2**	**A3**
Placebo	**N = 553** **Events = 174 (31.5%)**		
			B
	P_{HD} n = 408 events = 120 (29.4%)	P_{LD} n = 63 events = 35 (55.6%)	P_{00} n = 82 events = 19 (23.2%)
	B1	**B2**	**B3**
No beta-blocker at baseline			
Candesartan	**N = 460** **Events = 172 (37.4%)**		
			A
	CC_{HD} n = 252 events = 74 (29.4%)	CC_{LD} n = 107 events = 67 (62.6%)	CC_{00} n = 101 events = 31 (30.7%)
	A1	**A2**	**A3**
Placebo	**N = 462** **Events = 232 (50.2%)**		
			B
	P_{HD} n = 312 events = 150 (48.1%)	P_{LD} n = 67 events = 51 (76.1%)	P_{00} n = 83 events = 31 (37.4%)
	B1	**B2**	**B3**

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)

The secondary efficacy endpoint of all-cause mortality or CHF hospitalization (Table 159), and for secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI (Table 160) also show similar findings.

The above findings suggest that (i) in the absence of candesartan (cells A3), CHF patients treated with β-blockers at baseline have lower event rates than those not treated with β-blockers, and (ii) that when these CHF patients are receiving candesartan at low or high doses, too, those treated with β-blockers at baseline have lower event rates than those not treated with β-blockers.

This finding is also similar to that in my review of the CHARM-Added (SH-AHS-0006) study.

Table 159 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-Alternative (SH-AHS-0003) Study

Beta-blocker at baseline			
Candesartan		**N = 553** **Events = 176 (31.8%)**	
			A
	CC_{HD} n = 343 events = 96 (28.0%)	CC_{LD} n = 106 events = 55 (51.9%)	CC_{00} n = 104 events = 25 (24.0%)
	A1	**A2**	**A3**
Placebo		**N = 553** **Events = 188 (34.0%)**	
			B
	P_{HD} n = 408 events = 126 (30.9%)	P_{LD} n = 63 events = 40 (63.5%)	P_{00} n = 82 events = 22 (26.8%)
	B1	**B2**	**B3**
No beta-blocker at baseline			
Candesartan		**N = 460** **Events = 195 (42.4%)**	
			A
	CC_{HD} n = 254 events = 84 (33.1%)	CC_{LD} n = 107 events = 69 (64.5%)	CC_{00} n = 99 events = 42 (42.4%)
	A1	**A2**	**A3**
Placebo		**N = 462** **Events = 245 (53.0%)**	
			B
	P_{HD} n = 313 events = 156 (49.8%)	P_{LD} n = 68 events = 54 (79.4%)	P_{00} n = 81 events = 35 (43.2%)
	B1	**B2**	**B3**

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 160 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-Alternative (SH-AHS-0003) Study

Beta-blocker at baseline			
Candesartan		**N = 553** **Events = 171 (30.9%)**	
			A
	CC_{HD} n = 345 events = 94 (27.3%)	CC_{LD} n = 106 events = 52 (49.1%)	CC_{00} n = 102 events = 25 (24.5%)
	A1	**A2**	**A3**
Placebo		**N = 553** **Events = 180 (32.6%)**	
			B
	P_{HD} n = 407 events = 124 (30.5%)	P_{LD} n = 64 events = 36 (56.3%)	P_{00} n = 82 events = 20 (24.4%)
	B1	**B2**	**B3**
No beta-blocker at baseline			
Candesartan		**N = 460** **Events = 182 (39.6%)**	
			A
	CC_{HD} n = 254 events = 82 (32.3%)	CC_{LD} n = 109 events = 69 (63.3%)	CC_{00} n = 97 events = 31 (32.0%)
	A1	**A2**	**A3**
Placebo		**N = 462** **Events = 240 (52.0%)**	
			B
	P_{HD} n = 313 events = 155 (49.5%)	P_{LD} n = 70 events = 55 (78.6%)	P_{00} n = 79 events = 30 (38.0%)
	B1	**B2**	**B3**

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)

However, there are many caveats to these findings:

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

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

(iii) 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.

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

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

Table 161 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 ***non-use*** of spironolactone at baseline, during the study or at the visit preceding the event.

Table 161 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 placebo	Hazard Ratio	95% CI		p-value
						Lower	Upper	
Spironolactone	No	1545	224	289	0.742	0.623	0.883	<0.001
	Yes	483	110	117	0.797	0.614	1.034	0.088
Spironolactone during study	No	1193	169	188	0.772	0.627	0.950	0.014
	Yes	835	165	218	0.807	0.659	0.988	0.038
Spironolactone at the visit preceding the event	No	1736	197	251	0.724	0.601	0.873	<0.001
	Yes	291	137	154	0.978	0.776	1.233	0.853

On November 24 2004, the sponsor submitted a response to my request for data related to the primary and principal secondary efficacy endpoints according to dose level of candesartan in relation to patients receiving and not receiving 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 162. It appears that there is a

dose-related response, the event rates being lower in the high dose (16 and 32 mg) candesartan groups compared to the low dose (4 and 8 mg) candesartan groups for both patients receiving spironolactone and those not receiving spironolactone.

However, the event rates in patients receiving spironolactone are generally **higher** than in those not receiving spironolactone for the sub-populations of patients receiving "high dose" candesartan, "low dose" candesartan or no candesartan at the visit prior to the event.

The secondary efficacy endpoint of all-cause mortality or CHF hospitalization (Table 163), and for secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI (Table 164) also show similar findings.

The above findings suggest that (i) in the absence of candesartan (cells A3), CHF patients treated with spironolactone at baseline had **higher** event rates than those not treated with spironolactone, and (ii) that when these CHF patients are receiving candesartan at low or high doses, too, those treated with spironolactone at baseline have **higher** event rates than those not treated with spironolactone.

This finding is similar to that in my review of the CHARM-Added (SH-AHS-0006) study.

Table 162 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-Alternative (SH-AHS-0003) Study

	Spironolactone at baseline		
Candesartan	**N = 250** **Events = 110 (44.0%)**		
			A
	CC_{HD} n = 107 events = 36 (33.6%)	CC_{LD} n = 79 events = 53 (67.1%)	CC_{00} n = 64 events = 21 (32.8%)
	A1	**A2**	**A3**
Placebo	**N = 233** **Events = 117 (50.2%)**		
			B
	P_{HD} n = 156 events = 74 (47.4%)	P_{LD} n = 39 events = 30 (76.9%)	P_{00} n = 38 events = 13 (34.2%)
	B1	**B2**	**B3**
	No spironolactone at baseline		
Candesartan	**N = 763** **Events = 224 (29.4%)**		
			A
	CC_{HD} n = 488 events = 125 (25.6%)	CC_{LD} n = 134 events = 65 (48.5%)	CC_{00} n = 141 events = 34 (24.1%)
	A1	**A2**	**A3**
Placebo	**N = 782** **Events = 289 (37.0%)**		
			B
	P_{HD} n = 564 events = 196 (34.8%)	P_{LD} n = 91 events = 56 (61.5%)	P_{00} n = 127 events = 37 (29.1%)
	B1	**B2**	**B3**

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 163 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-Alternative (SH-AHS-0003) Study

Spironolactone at baseline			
Candesartan	**N = 250** **Events = 118 (47.2%)**		
			A
	CC_{HD} n = 107 events = 38 (35.5%)	CC_{LD} n = 79 events = 56 (70.9%)	CC_{00} n = 64 events = 24 (37.5%)
	A1	**A2**	**A3**
Placebo	**N = 233** **Events = 124 (53.2%)**		
			B
	P_{HD} n = 156 events = 77 (49.4%)	P_{LD} n = 39 events = 31 (79.5%)	P_{00} n = 38 events = 16 (42.1%)
	B1	**B2**	**B3**
No spironolactone at baseline			
Candesartan	**N = 763** **Events = 253 (33.2%)**		
			A
	CC_{HD} n = 490 events = 142 (29.0%)	CC_{LD} n = 134 events = 68 (50.8%)	CC_{00} n = 139 events = 43 (30.9%)
	A1	**A2**	**A3**
Placebo	**N = 782** **Events = 309 (39.5%)**		
			B
	P_{HD} n = 565 events = 205 (36.3%)	P_{LD} n = 92 events = 63 (68.5%)	P_{00} n = 125 events = 41 (32.8%)
	B1	**B2**	**B3**

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 164 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-Alternative (SH-AHS-0003) Study

Spironolactone at baseline			
Candesartan	**N = 250** **Events = 117 (46.8%)**		
			A
	CC_{HD} n = 107 events = 38 (35.5%)	CC_{LD} n = 81 events = 56 (69.1%)	CC_{00} n = 62 events = 23 (37.1%)
	A1	**A2**	**A3**
Placebo	**N = 233** **Events = 119 (51.1%)**		
			B
	P_{HD} n = 156 events = 76 (48.7%)	P_{LD} n = 39 events = 30 (76.9%)	P_{00} n = 38 events = 13 (34.2%)
	B1	**B2**	**B3**
No spironolactone at baseline			
Candesartan	**N = 763** **Events = 236 (30.9%)**		
			A
	CC_{HD} n = 492 events = 138 (28.1%)	CC_{LD} n = 134 events = 65 (48.5%)	CC_{00} n = 137 events = 33 (24.1%)
	A1	**A2**	**A3**
Placebo	**N = 782** **Events = 301 (38.5%)**		
			B
	P_{HD} n = 564 events = 203 (36.0%)	P_{LD} n = 95 events = 61 (64.2%)	P_{00} n = 123 events = 37 (30.1%)
	B1	**B2**	**B3**

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)

However, the same caveats (as that for the dose-response relationship of candesartan to the primary and secondary efficacy endpoints) apply to these findings:

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

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

(iii) 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.

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

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

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 165 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 = 24.1%, P=0.006), during the study (RRR = 26.2%, P<0.001) and at the visit preceding the event (RRR = 19.5%, P=0.025).

Table 165 CV death or hospitalization due to CHF (confirmed adjudicated) by use of digitalis glycoside in study SH-AHS-0003. 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	1104	149	183	0.769	0.619	0.954	0.017
	Yes	924	185	223	0.759	0.624	0.922	0.006
Digitalis glycoside during study	No	930	116	119	0.865	0.670	1.117	0.266
	Yes	1098	218	287	0.738	0.619	0.880	<0.001
Digitalis glycoside at the visit preceding the event	No	1585	137	160	0.783	0.623	0.983	0.035
	Yes	442	197	245	0.805	0.666	0.973	0.025

Conclusions:

Candesartan significantly reduced CV death or the first occurrence of a CHF hospitalization (P<0.001).

Candesartan significantly reduced all-cause death or the first occurrence of a CHF hospitalization (P= 0.001).

Candesartan significantly reduced all-cause death or the first occurrence of a CHF hospitalization or non-fatal myocardial infarction (P<0.001).

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< 0.001).

Candesartan did not reduce all-cause death or the first occurrence of all-cause hospitalization (P= 0.114).

Candesartan did not reduce all-cause death (P= 0.105).

Candesartan did not reduce the first occurrence of hospitalization (P= 0.107).

Candesartan did not reduce the number of fatal and non-fatal MIs (P= 0.199).

Candesartan significantly improved NYHA classification from randomization to the LVCF (P= 0.008).

Summary of Efficacy Results:

Candesartan treatment significantly reduced cardiovascular death or hospitalization due to CHF (HR 0.77, 95% CI 0.67 to 0.89, P< 0.001). This corresponds to a relative risk reduction of 23.2%. The effect appeared early and was sustained throughout the study period. The two secondary 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 20.2% (HR 0.80, 95% CI 0.70 to 0.92, P= 0.001),and for CV death or hospitalization due to CHF or non-fatal MI the relative risk reduction was 21.8% (HR 0.78, 95% CI 0.68 to 0.90, P< 0.001).

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

Symptoms of heart failure according to NYHA classification improved significantly during candesartan treatment compared to placebo (P= 0.008). The incidence of diagnosed onset of diabetes mellitus during the follow-up period was numerically reduced by candesartan (HR 0.79, 95% CI 0.53 to1.18, P= 0.254). Fewer patients in the candesartan group (49, 4.8%) than in the placebo group (70, 6.9%) developed atrial fibrillation (95% CI – 4.1 to 0.0, P= 0.048).

SAFETY RESULTS

Extent of exposure

A total of 2,028 patients (646 females and 1,382 males) were randomized into the study; all were included in the ITT/safety population. Patients who received incorrect investigational product during any part of the study (7 patients) were 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. Duration of treatment was defined as the time from the first day of treatment 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 of the permanent discontinuation. An overview of exposure is presented in Table 166, including data on the number of patients who completed or discontinued the study.

Table 166 Overview of exposure. ITT/Safety population (SH-AHS-0003)

		Placebo (N=1015)		Cand. cil. (N=1013)	
No. (%) of patients evaluable for safety	Male	691	(68.1)	691	(68.2)
	Female	324	(31.9)	322	(31.8)
Age	<65	392	(38.6)	412	(40.7)
	≥65	623	(61.4)	601	(59.3)
	<75	776	(76.5)	780	(77.0)
	≥75	239	(23.5)	233	(23.0)
Race[a]	Caucasian	922	(90.8)	926	(91.4)
	Black	45	(4.4)	28	(2.8)
	Oriental	37	(3.6)	43	(4.2)
	Other	11	(1.1)	16	(1.6)
Exposure by discontinuation due to AE of investigational product and/or study (N and %)	Discontinued investigational product due to AEs	197	(19.4)	220	(21.7)
	Patients who withdrew consent	16	(1.6)	18	(1.8)

[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 33.8 months for patients randomized to candesartan and 33.6 months for patients randomized to placebo. The median duration of exposure of the investigational product was 29.5 months in the placebo group and 29.4 months in the candesartan group.

A total of 824 (81.3%) patients in the candesartan group started treatment on 4 mg once daily and 189 (18.7%) patients started on 8 mg once daily at randomization (baseline). A total of 1,313 (64.7%) patients (candesartan 666, 65.8%; placebo 647, 63.7%) received the investigational product for 24 months or more. 52.2% of the candesartan patients (58.9% of those still receiving the investigational product) were treated with the target dose 32 mg once daily at 6 months (visit 5). The mean dose in the candesartan group was 23.2 mg at 6 months. At the end of treatment (LVCF) 44.1% (60.3% 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 73.6% (747) of the patients randomized to placebo, and by 73.1% (741) of the patients randomized to candesartan during study. In the placebo group 29.2% (296) of the patients had fatal SAEs and 64.4% (654) of the patients experienced non-fatal SAEs, compared with the candesartan group where 26.3% (266) of the patients had fatal SAEs and 61.1% (619) of the patients had non-fatal SAEs. The investigational product was prematurely discontinued due to AEs for 19.4% (197) of the patients in the placebo group and for 21.7% (220) of the patients in the candesartan group. The investigational product was reduced in dose due to AEs for 76 (7.5%) patients in the placebo group and for 157 (15.5%) patients in the candesartan group. A summary of adverse events by category is presented in Table 167.

Table 167 Number (%) of patients who had at least one adverse event in any category, and total numbers of adverse events. ITT/Safety population (SH-AHS-0003)

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

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

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

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

Most common adverse events**:**

The most commonly reported AEs (Table 168) in the placebo group during study were cardiac failure/cardiac failure aggravated (359, 35.4%), angina pectoris/ angina pectoris aggravated (120,

11.8%), sudden death (106, 10.4%) and renal function abnormal/ renal dysfunction aggravated (50, 4.9%). The most commonly reported AEs in the candesartan group during study were cardiac failure/cardiac failure aggravated (280, 27.6%), hypotension (193, 19.1%) and renal function abnormal/ renal dysfunction aggravated (141, 13.9%).

Table 168 Number (%) of patients with the most commonly reported[a] AEs, sorted by descending frequency in the total population during study. ITT/Safety population (SH-AHS-0003)

Preferred term	Placebo on treatment (N=1015)		Cand. cil. on treatment (N=1013)		Placebo during study (N=1015)		Cand. cil. during study (N=1013)	
	N	(%)	N	(%)	N	(%)	N	(%)
Cardiac failure/cardiac failure aggravated[b]	317	(31.2)	234	(23.1)	359	(35.4)	280	(27.6)
Hypotension	76	(7.5)	190	(18.8)	90	(8.9)	193	(19.1)
Angina pectoris/angina pectoris aggravated[b]	110	(10.8)	105	(10.4)	120	(11.8)	127	(12.5)
Renal function abnormal/renal dysfunction aggravated[b]	49	(4.8)	136	(13.4)	50	(4.9)	141	(13.9)
Sudden death	85	(8.4)	65	(6.4)	106	(10.4)	80	(7.9)
Pneumonia	64	(6.3)	65	(6.4)	75	(7.4)	83	(8.2)
Myocardial infarction	58	(5.7)	71	(7.0)	68	(6.7)	85	(8.4)
Arrhythmia ventricular	64	(6.3)	58	(5.7)	79	(7.8)	73	(7.2)
Cerebrovascular disorder	55	(5.4)	41	(4.0)	61	(6.0)	52	(5.1)
Arrhythmia atrial	41	(4.0)	44	(4.3)	44	(4.3)	56	(5.5)
Fibrillation atrial	46	(4.5)	34	(3.4)	57	(5.6)	43	(4.2)
Chest pain	42	(4.1)	37	(3.7)	50	(4.9)	47	(4.6)
Coronary artery disorder	39	(3.8)	38	(3.8)	48	(4.7)	49	(4.8)
Tachycardia ventricular/arrhythmia[b]	31	(3.1)	28	(2.8)	44	(4.3)	39	(3.8)
Cardiomyopathy	29	(2.9)	25	(2.5)	40	(3.9)	37	(3.7)
Tachycardia supraventricular	30	(3.0)	27	(2.7)	39	(3.8)	34	(3.4)
Hyperkalaemia	16	(1.6)	54	(5.3)	18	(1.8)	54	(5.3)
Dizziness/vertigo[b]	21	(2.1)	43	(4.2)	23	(2.3)	45	(4.4)
Dyspnoea/dyspnoea (aggravated)[b]	39	(3.8)	17	(1.7)	43	(4.2)	22	(2.2)
Syncope	28	(2.8)	26	(2.6)	35	(3.4)	30	(3.0)

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

[b] Patients having both AEs are counted once only.

Deaths:

562 patients died during the study, of whom 296 (29.2%) were randomized to placebo and 266 (26.3%) randomized to candesartan. For 5 of the patients who died (Site-Patient number: 201-13446, 653-12566, 1006-10801, 1406-22827, 1531-20373), 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 candesartan 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 169. The most commonly reported fatal AE in both treatment groups during study was sudden death, reported for 10.4% (106) of the patients in the placebo group and for 7.9% (80) in the candesartan group. Cardiac failure/ cardiac failure aggravated was the second most common fatal AE, reported for 9.0% (91) of the patients in the placebo group and for 7.6% (77) in the candesartan group, respectively.

Table 169 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-0003)

Preferred term	Placebo on treatment (N=1015)		Cand. cil. on treatment (N=1013)		Placebo during study (N=1015)		Cand. cil. during study (N=1013)	
	N	(%)	N	(%)	N	(%)	N	(%)
Sudden death	81	(8.0)	64	(6.3)	106	(10.4)	80	(7.9)
Cardiac failure/cardiac failure aggravated[b]	52	(5.1)	37	(3.7)	91	(9.0)	77	(7.6)
Myocardial infarction	10	(1.0)	29	(2.9)	17	(1.7)	38	(3.8)
Cerebrovascular disorder	9	(0.9)	7	(0.7)	14	(1.4)	13	(1.3)
Cardiac arrest	6	(0.6)	7	(0.7)	9	(0.9)	9	(0.9)
Death	3	(0.3)	2	(0.2)	7	(0.7)	9	(0.9)
Pneumonia	3	(0.3)	2	(0.2)	9	(0.9)	6	(0.6)
Fibrillation ventricular	5	(0.5)	4	(0.4)	7	(0.7)	6	(0.6)
Cardiomyopathy	2	(0.2)	1	(0.1)	6	(0.6)	5	(0.5)
Coronary artery disorder	1	(0.1)	3	(0.3)	4	(0.4)	7	(0.7)
Respiratory insufficiency	2	(0.2)	3	(0.3)	5	(0.5)	6	(0.6)
Sepsis	3	(0.3)	2	(0.2)	7	(0.7)	2	(0.2)
Pulmonary carcinoma	2	(0.2)	5	(0.5)	2	(0.2)	6	(0.6)
Tachycardia ventricular/arrhythmia[b]	1	(0.1)	3	(0.3)	3	(0.3)	4	(0.4)
Accident and/or injury	1	(0.1)	2	(0.2)	4	(0.4)	2	(0.2)
Pulmonary oedema	2	(0.2)	2	(0.2)	3	(0.3)	3	(0.3)

a This table uses a cut-off of ≥0.3% in total population during study (N=2028).

b Patients having both AEs are counted once only.

Serious adverse events other than deaths:

Non-fatal SAEs were reported in 64.4% (654) of the patients in the placebo group during study and in 61.1% (619) of the patients in the candesartan group during study. The most common non-fatal SAEs are presented in Table 170.

Table 170 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-0003)

Preferred term	Placebo on treatment (N=1015)		Cand. cil. on treatment (N=1013)		Placebo during study (N=1015)		Cand. cil. during study (N=1013)	
	N	(%)	N	(%)	N	(%)	N	(%)
Cardiac failure/cardiac failure aggravated[b]	297	(29.3)	209	(20.6)	334	(32.9)	251	(24.8)
Angina pectoris/angina pectoris aggravated[b]	110	(10.8)	100	(9.9)	120	(11.8)	122	(12.0)
Arrhythmia ventricular	64	(6.3)	58	(5.7)	79	(7.8)	73	(7.2)
Pneumonia	62	(6.1)	64	(6.3)	71	(7.0)	81	(8.0)
Hypotension	39	(3.8)	84	(8.3)	51	(5.0)	88	(8.7)
Myocardial infarction	50	(4.9)	46	(4.5)	57	(5.6)	56	(5.5)
Cerebrovascular disorder	50	(4.9)	38	(3.8)	56	(5.5)	46	(4.5)
Arrhythmia atrial	41	(4.0)	44	(4.3)	44	(4.3)	56	(5.5)
Fibrillation atrial	46	(4.5)	32	(3.2)	57	(5.6)	41	(4.0)
Chest pain	41	(4.0)	36	(3.6)	49	(4.8)	45	(4.4)
Coronary artery disorder	39	(3.8)	34	(3.4)	46	(4.5)	42	(4.1)
Tachycardia ventricular/arrhythmia[b]	30	(3.0)	24	(2.4)	42	(4.1)	35	(3.5)
Tachycardia supraventricular	30	(3.0)	27	(2.7)	39	(3.8)	34	(3.4)
Cardiomyopathy	27	(2.7)	24	(2.4)	35	(3.4)	33	(3.3)
Syncope	27	(2.7)	25	(2.5)	34	(3.3)	29	(2.9)

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

b Patients having both AEs are counted once only.

The most commonly reported non-fatal SAEs in the placebo group during study were cardiac failure/cardiac failure aggravated (334, 33.0%), angina pectoris/angina pectoris aggravated (120, 12.0%) and arrhythmia ventricular (79, 7.8%). The most commonly reported non-fatal SAEs in the candesartan group during study were cardiac failure/cardiac failure aggravated (251, 25.0%), angina pectoris/angina pectoris aggravated (122, 12.0%) and hypotension (88, 8.7%).

Discontinuations due to adverse events:

The investigational product was permanently discontinued due to AEs in 19.4% (197) of the patients in the placebo group and in 21.7% (220) of the patients in the candesartan group. The most common AEs leading to discontinuation of investigational product are presented in Table 171. 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 were (a) in the placebo group: cardiac failure/cardiac failure aggravated (72, 7.1%), renal function abnormal/renal dysfunction aggravated (25, 2.5%) and hypotension (14, 1.4%), and (b) in the candesartan group: renal function abnormal/renal dysfunction aggravated (65, 6.4%), cardiac failure/cardiac failure aggravated (53, 5.2%) and hypotension (46, 4.5%).

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 171 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-0003)

Preferred term	Placebo on treatment (N=1015)		Cand. cil. on treatment (N=1013)	
	N	(%)	N	(%)
Cardiac failure/cardiac failure aggravated[b]	72	(7.1)	53	(5.2)
Renal function abnormal/renal dysfunction aggravated[b]	25	(2.5)	65	(6.4)
Hypotension	14	(1.4)	46	(4.5)
Hyperkalaemia	3	(0.3)	21	(2.1)
Myocardial infarction	10	(1.0)	12	(1.2)
Angina pectoris/angina pectoris aggravated[b]	6	(0.6)	10	(1.0)
Pneumonia	9	(0.9)	7	(0.7)
Cerebrovascular disorder	10	(1.0)	4	(0.4)
Dizziness/vertigo[b]	3	(0.3)	11	(1.1)
Coronary artery disorder	7	(0.7)	5	(0.5)
Cardiomyopathy	6	(0.6)	5	(0.5)
Dyspnoea/dyspnoea (aggravated)[b]	8	(0.8)	3	(0.3)
Renal failure acute	3	(0.3)	8	(0.8)
Tachycardia ventricular	7	(0.7)	4	(0.4)
Headache	4	(0.4)	6	(0.6)

a This table uses a cut-off of ≥0.5% in total population on treatment (N=2028).

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 7.5% (76) of the patients in the placebo group and in 15.5% (157) of the patients in the candesartan group. The most common AEs leading to dose reduction of the investigational product are presented in Table 172.

The most commonly reported AEs leading to dose reduction in the placebo group were hypotension (27, 2.7%), renal function abnormal (10, 1.0%) and cardiac failure aggravated and dyspnea (7, 0.7%). The most commonly reported AEs leading to dose reduction in the candesartan group were hypotension (85, 8.4%), renal function abnormal (32, 3.2%) and dizziness/vertigo (23, 2.3%).

Table 172 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=1015)		Cand. cil. on treatment (N=1013)	
	N	(%)	N	(%)
Hypotension	27	(2.7)	85	(8.4)
Renal function abnormal	10	(1.0)	32	(3.2)
Dizziness/vertigo[b]	6	(0.6)	23	(2.3)
Cardiac failure aggravated	7	(0.7)	13	(1.3)
Hyperkalaemia	6	(0.6)	12	(1.2)
Dyspnoea	7	(0.7)	1	(0.1)
Abdominal pain	3	(0.3)	4	(0.4)
Fatigue	2	(0.2)	5	(0.5)
Nausea	3	(0.3)	4	(0.4)
Angina pectoris/angina pectoris aggravated[b]	2	(0.2)	4	(0.4)
Diarrhoea	3	(0.3)	3	(0.3)

a The table uses a cut-off of ≥0.3% in total population on treatment (N=2028).

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 196 (19.3%) patients in the placebo group and 218 (21.5%) patients in the candesartan group. Neither the difference in time to event (P= 0.332), (Table 173, Table 174 and (Figure 55) nor the difference in proportions between treatments of 2.2% (P= 0.217) (Table 175 and Table 176) was statistically significant.

Table 173 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-0003)

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	1013	295	2176.1	135.6	2.1
	Cand. cil.	1011	308	2212.9	139.2	2.2
Permanent investigational product discontinuation due to an AE or an abnormal lab value	Placebo	1015	196	2350.3	83.4	2.3
	Cand. cil.	1013	218	2379.8	91.6	2.3
At least one investigational product discontinuation due to any cause	Placebo	1013	456	1973.3	231.1	1.9
	Cand. cil.	1011	489	1933.0	253.0	1.9
At least one investigational product discontinuation due to an AE or an abnormal lab value	Placebo	1015	355	2177.6	163.0	2.1
	Cand. cil.	1013	399	2115.1	188.6	2.1

Table 174 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-0003)

Variable	N	Events cand. cil.	Events placebo	Hazard Ratio	95% CI		p-value
					Lower	Upper	
Permanent investigational product discontinuation due to any cause	2028	308	295	1.028	0.876	1.207	0.735
Permanent investigational product discontinuation due to an AE or an abnormal lab value	2028	218	196	1.100	0.907	1.334	0.332
At least one investigational product discontinuation due to any cause	2028	489	456	1.090	0.959	1.239	0.187
At least one investigational product discontinuation due to an AE or an abnormal lab value	2028	399	355	1.151	0.997	1.328	0.054

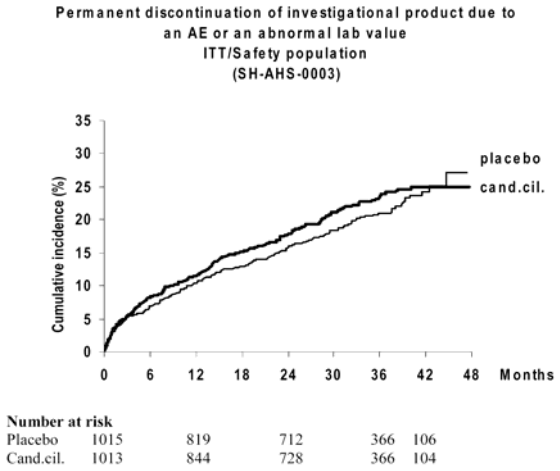


Figure 55 Cumulative incidence (%) of permanent discontinuation of investigational product due to an AE or an abnormal laboratory value. ITT/Safety population

Specific causes of investigational product discontinuation are noted in Table 175 and Table 176. Hypotension, 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 2.8%, 1.6% and 3.5%, respectively.

The approximate 1.1 fold excess risk for candesartan discontinuation relative to placebo for the entire study population was characteristic of the relative discontinuation rates across most subgroups. The approximate 1.5 fold higher risk of candesartan than placebo discontinuation among patients receiving spironolactone at baseline (placebo 47 patients, candesartan 75 patients) was statistically significant (P= 0.022). Also, the approximate 1.3 fold higher risk for candesartan discontinuation among patients receiving spironolactone at the visit prior to investigational product discontinuation (placebo 74 patients, candesartan 90 patients) was

statistically significant (P= 0.003). However, the 1.1 fold excess risk for candesartan discontinuation for patients having spironolactone recorded as a concomitant medication 'during study' was not significant (P= 0.422).

Dose reduction of the investigational product:

Dose reduction of the investigational product due to an AE or abnormal lab value occurred in 89 (8.8%) patients in the placebo group and 182 (18.0%) patients in the candesartan group (Table 175). This between-treatment difference in dose reductions for an AE of 9.2% was statistically significant (P< 0.001) (Table 176). As shown in Figure 56 the majority of events occurred during the first 6 to 12 months of treatment with the investigational product.

Table 175 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-0003)

Variable	Treatment	N	Number of patients with events	Proportion of patients with event	95% CI	
					Lower	Upper
Permanent investigational product discontinuation due to any cause	Placebo	1015	295	29.1	26.3	32.0
	Cand. cil.	1013	308	30.4	27.6	33.3
Permanent investigational product discontinuation due to an AE or an abnormal lab value	Placebo	1015	196	19.3	16.9	21.9
	Cand. cil.	1013	218	21.5	19.0	24.2
Permanent investigational product discontinuation due to hypotension	Placebo	1015	9	0.9	0.4	1.7
	Cand. cil.	1013	37	3.7	2.6	5.0
Permanent investigational product discontinuation due to hyperkalaemia	Placebo	1015	3	0.3	0.1	0.9
	Cand. cil.	1013	19	1.9	1.1	2.9
Permanent investigational product discontinuation due to increased creatinine	Placebo	1015	27	2.7	1.8	3.8
	Cand. cil.	1013	62	6.1	4.7	7.8
At least one investigational product discontinuation due to any cause	Placebo	1015	456	44.9	41.8	48.0
	Cand. cil.	1013	489	48.3	45.2	51.4
At least one investigational product discontinuation due to an AE or an abnormal lab value	Placebo	1015	355	35.0	32.0	38.0
	Cand. cil.	1013	399	39.4	36.4	42.5
At least one investigational product discontinuation due to hypotension	Placebo	1015	23	2.3	1.4	3.4
	Cand. cil.	1013	72	7.1	5.6	8.9
At least one investigational product discontinuation due to hyperkalaemia	Placebo	1015	9	0.9	0.4	1.7
	Cand. cil.	1013	37	3.7	2.6	5.0
At least one investigational product discontinuation due to increased creatinine	Placebo	1015	37	3.6	2.6	5.0
	Cand. cil.	1013	102	10.1	8.3	12.1
Decreased investigational product dose due to any cause at least once	Placebo	1015	106	10.4	8.6	12.5
	Cand. cil.	1013	201	19.8	17.4	22.4
Decreased investigational product dose due to an AE or an abnormal lab value at least once	Placebo	1015	89	8.8	7.1	10.7
	Cand. cil.	1013	182	18.0	15.6	20.5

Table 176 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-0003)

Variable	Difference in proportion between treatments	95% CI		p-value
	Cand.cil. - placebo	Lower	Upper	
Permanent investigational product discontinuation due to any cause	1.3	-2.6	5.3	0.509
Permanent investigational product discontinuation due to an AE or an abnormal lab value	2.2	-1.3	5.7	0.217
Permanent investigational product discontinuation due to hypotension	2.8	1.5	4.1	<0.001
Permanent investigational product discontinuation due to hyperkalaemia	1.6	0.7	2.5	<0.001
Permanent investigational product discontinuation due to increased creatinine	3.5	1.7	5.2	<0.001
At least one investigational product discontinuation due to any cause	3.3	-1.0	7.7	0.131
At least one investigational product discontinuation due to an AE or an abnormal lab value	4.4	0.2	8.6	0.040
At least one investigational product discontinuation due to hypotension	4.8	3.0	6.7	<0.001
At least one investigational product discontinuation due to hyperkalaemia	2.8	1.5	4.1	<0.001
At least one investigational product discontinuation due to increased creatinine	6.4	4.2	8.6	<0.001
Decreased investigational product dose due to any cause at least once	9.4	6.3	12.5	<0.001
Decreased investigational product dose due to an AE or an abnormal lab value at least once	9.2	6.3	12.1	<0.001

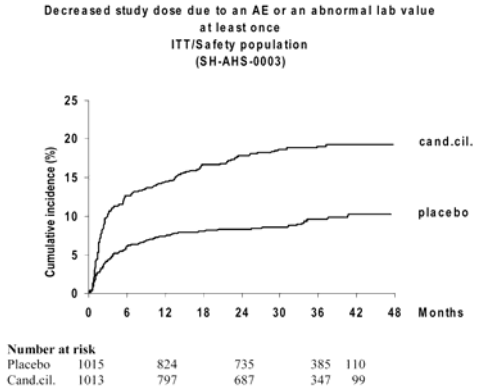


Figure 56 Cumulative incidence (%) of first occurrence of dose decrease of investigational product due to an AE or an abnormal laboratory value. ITT/Safety population

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 44, 4.3%; candesartan 46, 4.5%) or non- CV hospitalization rates (placebo 353, 34.8%; candesartan 362, 35.7%).

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

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, slightly more of the study patients randomized to candesartan cited hypotension as their reason for ACE inhibitor intolerance (placebo 119, 11.7%; candesartan 143, 14.1%). Also, there was a slightly higher proportion of patients in the candesartan group with SBP < 100 mmHg (placebo 22, 2.2%; candesartan 31, 3.1%) (North American study population)
AEs suggesting a ' hypotensive' event were reported less frequently for patients in the placebo group (116, 11.4%) than the candesartan group (228, 22.5%) on treatment with the investigational product (Table 177).

Table 177 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)

Placebo on treatment N=1015	Cand. cil. on treatment N=1013	Placebo during study N=1015	Cand. cil. during study N=1013
116 (11.4)	228 (22.5)	137 (13.5)	233 (23.0)

The individual AE term contributing the largest numbers to this composite AE was hypotension, which was reported for 76 (7.5%) of patients given placebo and 190 (18.8%) of patients given candesartan (Table 168).

Of the patients in the composite 'hypotensive' group, fatal events were reported in the same number of patients in each treatment group (3 in the candesartan group, 3 in the placebo group). In both treatment groups, hypotensive events that led to death were reported in association with other causes of death such as cardiac arrest or failure, ventricular tachycardia and respiratory failure. In the candesartan treated patients, the fatal events occurred well after the titration phase and were assessed by the investigators as related to the investigational product.

The investigational product was discontinued for the specific AE term hypotension in 14 (1.4%) placebo patients and 46 (4.5%) candesartan patients (Table 169). Corresponding figures for the exploratory analysis were 9 (0.9%) placebo patients and 37 (3.7%) candesartan patients (Table 175). The higher proportion of hypotensive events leading to discontinuation in the candesartan group could not be explained by between treatment differences in baseline blood pressure or concomitant medications when the event started, including diuretics and β-blockers As noted above, more candesartan patients had a history of hypotension on an ACE inhibitor.

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. In patients aged younger than 75 years, discontinuation because of the preferred term hypotension was reported in 11 (1.4%) of patients in the placebo group and 32 (4.1%) of patients on candesartan. For patients aged 75 years or older the discontinuation rates were 3 (1.3%) in the placebo group and 14 (6.3%) in the candesartan group. In the placebo group, permanent discontinuation of the investigational product due to hypotension was reported in 11

(1.6%) males and 3 (0.9%) females. In the candesartan treatment group there were 34 (4.9%) males and 12 (3.7%) females who were permanently discontinued due to hypotension). The majority of patients were Caucasians.

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 57).

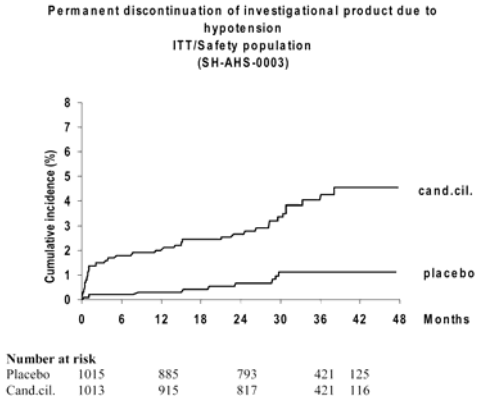


Figure 57 Cumulative incidence (%) of permanent discontinuation of investigational product due to hypotension (Ref. - Table 173). ITT/Safety population

Among the 270 (26.6%) placebo patients and 278 (27.4 %) candesartan patients entering the study with a history of diabetes, investigational product discontinuation for the specific preferred term hypotension was noted for 1 (0.4%) placebo patient and 11 (4.0%) 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, more patients randomized to candesartan (placebo 100, 9.8 %; candesartan 134, 12.8 %) cited 'renal dysfunction' as the reason for ACE-inhibitor intolerance. Also, there were a slightly higher proportion of patients in the candesartan group with serum creatinine > 2.0 mg/dl at baseline placebo 26, 7.8%; candesartan 30, 9.2%)(North American study population).

AEs suggesting 'abnormal renal function' occurred in 82 (8.1%) in the placebo group and 163 (16.1 %) patients in the candesartan group during study (Table 178).

Table 178 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-0003)

Placebo on treatment N=1015	Cand. cil. on treatment N=1013	Placebo during study N=1015	Cand. cil. during study N=1013
74 (7.3)	157 (15.5)	82 (8.1)	163 (16.1)

The AE terms that predominately contributed to this composite AE term was renal function abnormal which was reported in 50 (4.9%) of patients given placebo and 141 (13.9%) given candesartan during study. Renal failure, acute (placebo, 19 patients, 1.9%; candesartan, 31 patients, 3.1%) and uremia (placebo, 7 patients, 0.7%; candesartan, 14 patients, 1.4%) were also numerically more frequent in patients given active treatment.

Among the patients with 'abnormal renal function', similar numbers in both treatment group had an event, which proved a fatal renal function event 'during study' (8 in the candesartan group, 9 in the placebo group). 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 or respiratory failure.

In the descriptive safety analysis (Table 171), on investigational product discontinuation in the overall study population, the specified AE term renal function abnormal/renal dysfunction aggravated was, second to aggravation of cardiac failure, the most common reason for permanent discontinuation of the investigational product in both treatment groups (placebo 25, 2.5%; candesartan 65, 6.4%). In the exploratory analysis the term increased creatinine was reported for 27 (2.7%) placebo patients and 62 (6.1%) candesartan patients (Table 175). The higher rate for discontinuation of the investigational product due to '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). As noted above, more candesartan than placebo patients gave a history of ACE inhibitor intolerance because of abnormal renal function.

In patients aged younger than 75 years, discontinuation because of the AE term renal function abnormal/renal dysfunction aggravated was reported in 20 (2.6%) of patients in the placebo group and 44 (5.6%) of patients on candesartan. For patients aged 75 years or older the discontinuation rates were 5 (2.1%) in the placebo group and 21 (9.4%) in the candesartan group. In the placebo group the majority of events were seen in male patients (24, 3.5%) compared to only one female. In the candesartan treatment group 47 (6.8%) males and 18 (5.6%) females reported the renal event. The vast majority of patients in both treatment groups were Caucasians.

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 58).

Among the 270 (26.6 %) placebo patients and 278 (27.4 %) candesartan patients entering the

study with a history of diabetes, investigational product discontinuation for the specific term increased creatinine was noted for 12 (4.4%) placebo and 25 (9.0%) candesartan patients. Compared to the overall population (placebo 2.7%, candesartan 6.1%) diabetics were slightly more likely to discontinue the investigational product for increased creatinine levels (Table 175 and Table 176).

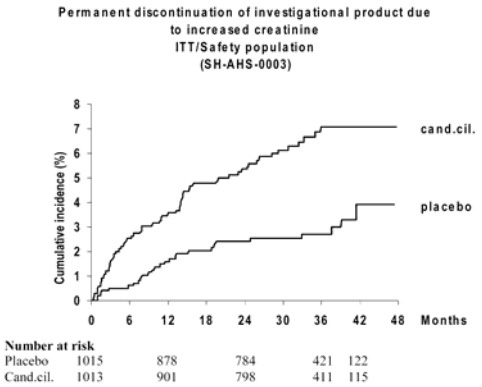


Figure 58 Cumulative incidence (%) of permanent discontinuation of investigational product due to increased creatinine (Ref. - Table 173). ITT/Safety population

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, there was no notable difference between the treatment groups in the proportions of patients with serum potassium ≥ 5 mmol/ L (North American study population).

Hyperkalemia was reported for 16 patients (1.6%) in the placebo group and 54 patients (5.3%) in the candesartan group on treatment with the investigational product (Table 168).

Fatal hyperkalemia 'on treatment' was not reported for any patients in the candesartan group or the placebo group.

In Table 171, discontinuation of the investigational product because of hyperkalemia was predominately limited to patients treated with candesartan (placebo 3, 0.3%; candesartan 21, 2.1%). In the exploratory analysis the corresponding numbers were 3 (0.3%) for placebo patients and 19 (1.9%) for candesartan patients (Table 175). 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).

In patients < 75 years old, discontinuation because of the AE term hyperkalemia was reported in 2 (0.3%) patients in the placebo group and 11 (1.4%) of patients on candesartan. For patients aged 75 years or older the discontinuation rates were 1 (0.4%) in the placebo group and 10

(4.5%) in the candesartan group. In the placebo group there was a low frequency of events for both genders, in the candesartan treatment group the majority of events were seen in male patients (17, 2.5%) compared to females (4, 1.2%). The vast majority of patients in both treatment groups were Caucasians.

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 59).

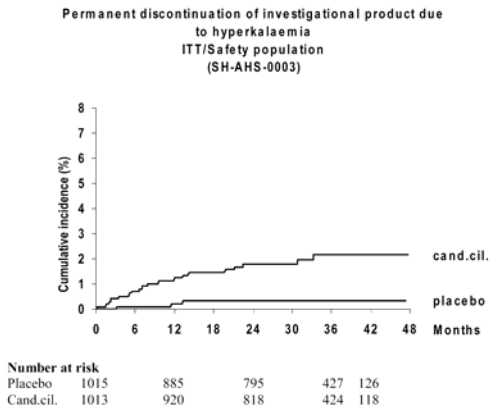


Figure 59 Cumulative incidence (%) of permanent discontinuation of investigational product due to hyperkalemia. ITT/Safety population (Ref. - Table 173).

Among the 270 (26.6 %) placebo patients and 278 (27.4 %) candesartan patients entering the study with a history of diabetes, investigational product discontinuation for the specific preferred term hyperkalemia was noted for 3 (1.1%) placebo and 5 (1.8%) candesartan patients.

Myocardial ischemia

'Myocardial ischemia' was evaluated as a composite of the following AE terms (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 only counted once.

At baseline, prior to study there were no major 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 bypass grafting (placebo 244, 24.0 %; candesartan 269, 26.5 %).

The proportions of patients with 'myocardial ischemia' 'on treatment' were approximately equal in the two treatment groups (16.4% in the placebo group and 18.0% in the candesartan group) (Table 179).

Table 179 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)

Placebo on treatment N=1015	Cand. cil. on treatment N=1013	Placebo during study N=1015	Cand. cil. during study N=1013
166 (16.4)	182 (18.0)	190 (18.7)	217 (21.4)

The AE term accounting for the greatest number of patients in this composite AE was angina pectoris which was also reported for essentially equal proportions of patients in the two groups (placebo 109, 10.7%; candesartan 105, 10.4%). The AE term MI occurred in 58 (5.7%) patients in the placebo group and in 71 (7.0%) in the candesartan group 'on treatment.'

The risk of 'myocardial ischemic' events during candesartan therapy could not be explained by concomitant medication at the start of the event. AEs related to hypotension, reported at the same time as angina pectoris or MI, were more frequent in the candesartan group (angina pectoris 9 patients, MI 7 patients) than in the placebo group (angina pectoris 2 patients, MI 0 patients). For coronary artery disorder there was no difference.

'Myocardial ischemic' events that were fatal were reported for 21 (2.1%) patients in the placebo group and 48 (4.7%) patients in the candesartan group during study (Table 180).

Table 180 Table 79 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)

Placebo on treatment N=1015	Cand. cil. on treatment N=1013	Placebo during study N=1015	Cand. cil. during study N=1013
11 (1.1)	35 (3.5)	21 (2.1)	48 (4.7)

Most of the fatal 'myocardial ischemic' events 'during study' were attributed to fatal MI (17 patients in the placebo group and 38 in the candesartan group).

Abnormal hepatic function:

The most common AE terms suggesting liver dysfunction during treatment were hepatic enzymes increased (placebo 4 patients; candesartan 2 patients) and hepatic function abnormal (placebo 3 patients; candesartan 3 patients). The AE term hepatic failure was reported for 1 patient in the placebo group and 2 patients in the candesartan group.

In the candesartan group there was one fatal case of hepatic necrosis considered related to amiodarone (Site 373, Patient number 15108), and one fatal case of cholestatic hepatitis considered related to septic cholangitis (Site 1476, Patient number 21109; this patient is not included in the listings of AEs of special interest).

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 59 patients (5.8%) in each treatment group. One patient in the placebo group (Site 558, Patient number 13436) had breast neoplasm, malignant, female and carcinomatosis together with pleural mesothelioma. In the total numbers presented above this patient is counted only once. Neoplasms proved fatal for 18 patients (1.8%) in the placebo group and 23 patients (2.3%) in the candesartan group.

In the overall study population, the majority of patients did not have a history of cancer at baseline (placebo 92.9%; candesartan 93.9%).

The majority of reported neoplasms were malignant. The most common neoplasms during study were pulmonary cancer (placebo, 3 patients; candesartan, 10 patients), colon cancer (6 patients in each group), prostatic cancer (placebo, 3 patients; candesartan, 8 patients) and breast neoplasm malignant female (placebo 4 patients; candesartan 5 patients).

Permanent discontinuation and dose reduction of investigational product according to reason for ACE-inhibitor intolerance

Reasons for ACE-inhibitor intolerance, as noted at study entry, were not common reoccurrences as causes for permanent discontinuation or dose reduction of the investigational product (Table 181 and Table 182).

Table 181 Reasons for permanent discontinuation of investigational product compared to reason for ACE inhibitor intolerance at baseline. ITT/Safety Population (SH-AHS-0003)

	Treatment			
	Placebo (N=1015)		Cand. cil. (N=1013)	
Reason for ACE inhibitor intolerance at baseline	Number of patients, who were intolerant at baseline	Number of patients (%), who permanently discontinued treatment with investigational product	Number of patients, who were intolerant at baseline	Number of patients (%), who permanently discontinued treatment with investigational product
Cough	751	4 (<1.0)	704	2 (<1.0)
Hypotension	119	5 (4.2)	143	13 (9.0)
Renal dysfunction[a]	100	12 (12.0)	134	31 (23.0)
Angioedema	44	0 (0)	39	1 (2.6)
Other[b]	109	9 (8.3)	101	8 (7.9)
Any reason	1015	295 (29.1)	1013	308 (30.4)

a Reason for ACE-inhibitor intolerance was defined as renal dysfunction. Reason for permanent discontinuation of investigational product included was defined as abnormal renal function.
b Includes any adverse event, lab value, or unknown reason.

Table 182 Reasons for the first dose reduction of investigational product compared to reason for ACE- inhibitor intolerance at baseline. ITT/Safety Population (SH-AHS-0003)

	Treatment			
	Placebo (N=1015)		Cand. cil. (N=1013)	
Reason for ACE inhibitor intolerance at baseline	Number of patients, who were intolerant at baseline	Number of patients (%), who had at least one dose reduction of investigational product	Number of patients, who were intolerant at baseline	Number of patients (%), who had at least one dose reduction of investigational product
Cough	751	3 (<1.0)	704	4 (<1.0)
Hypotension	119	6 (5.0)	143	25 (17.4)
Renal dysfunction[a]	100	3 (3.0)	134	22 (16.4)
Angioedema	44	0 (0)	39	1 (2.6)
Other[b]	109	1 (<1.0)	101	17 (16.8)
Any reason	1015	106 (10.4)	1013	201 (19.8)

a Reason for ACE-inhibitor intolerance was defined as renal dysfunction. Reason for permanent discontinuation of investigational product was defined as abnormal renal function.
b Includes any adverse event, lab value, or unknown reason.

Cough was the most frequently cited reason for ACE-inhibitor intolerance at baseline (73.9% of placebo-treated patients; 69.5% of candesartan-treated patients) but was associated with a discontinuation rate < 1% in both groups for a recurring event during study. Of patients with a history of symptomatic hypotension as a reason for ACE-inhibitor intolerance, 4.2% in the placebo group and 9.0% in the candesartan group discontinued because of hypotension. Renal dysfunction as a recurrent event was reported for 12.0% of patients in the placebo group compared with 23.0% in the candesartan group.

Regarding dose reductions, the rate for cough was < 1% in both treatment groups for a recurring event during study. In the candesartan group, compared to discontinuation, it was more common to have a dose reduction for recurring hypotension, while it was more common to permanently discontinue candesartan treatment if abnormal renal function was the recurring event.

Angioedema:

During study, three cases of angioedema were reported for patients in the candesartan group. All 3 patients were Caucasian with a history of previous angioedema reactions while taking ACE-inhibitors. None of the three events was considered life threatening or led to hospitalization.

Thirty-nine patients in the candesartan group had a history of ACE-inhibitor intolerance due to angioedema. One of these patients developed angioedema that required discontinuation of candesartan treatment. For the two remaining patients with angioedema, candesartan treatment continued without recurrence, and for one of these the dose was reduced. For two patients, the reaction occurred one month after randomization, and for the third patient the angioedema occurred more than a year after administration of the first dose of candesartan.

Of 44 patients in the placebo group who had a history of angioedema, none discontinued investigational product because of angioedema.

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 (placebo 71.1%, candesartan 67.3%) 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 29.2%; candesartan 26.3%), but overall mortality was lower with candesartan treatment. 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.

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The mortality findings in the study population were relatively consistent across subgroups on the basis of age, gender and race. As expected, mortality was higher in older patients.

Also, as expected, the most common non-fatal SAEs were CV (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 as an AE with an approximately equal frequency in the 2 treatment groups (placebo 7.4 %; candesartan 8.2 %). ‘Renal failure acute’ as a non-fatal SAE was reported for 18 of placebo-treated patients and for 30 of candesartan-treated patients during study.

There was no difference in frequency between treatment groups for AE terms suggesting liver dysfunction. The two fatal cases (hepatic necrosis, cholestatic hepatitis) in the candesartan group were not considered related to the investigational product. Of 1013 candesartan-treated patients in the study, 23 (2.3%) died of cancer; 18 (1.8%) of 1015 placebo-treated patients also died from malignancy. Equal proportions reported a neoplasm during the study (59 patients, 5.8%). The types of cancer (lung, prostate, breast, colon) were typical for patients in the age group of the study population.

Tolerability of the investigational product in this population with CHF and a history of ACE-

inhibitor intolerance, was not remarkably different between patients treated with candesartan and patients treated with placebo. Overall, 70.2% of patients completed participation in the study without discontinuing treatment (70.9% in the placebo and 69.6% 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 (7.1% compared with 5.2% for candesartan). Abnormal renal function, hypotension and hyperkalemia were cited more frequently as reasons for discontinuation with candesartan treatment (6.4% compared with 2.5%; 4.5% compared with 1.4% and 2.1% compared with 0.3%, 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 AEs in patients with CHF, particularly when they are treated with inhibitors of the RAAS. It should also be noted that the study data collection instrument (CRF) included hypotension, increased creatinine and hyperkalemia as pre-specified reason for discontinuation. Furthermore, the majority of AEs reported for these events did not lead to discontinuation of the investigational product.

For hypotension, abnormal renal function and hyperkalemia the rates increased with age in the candesartan treatment group but not for patients in the placebo group. In patients aged younger than 75, discontinuation because of abnormal renal function was reported in 47 (6.0%) of patients on candesartan. Higher incidences were seen for patients aged 75 years or older where 24 patients (10.8%) in the candesartan group discontinued. A similar trend was shown for hypotension and hyperkalemia. Generally the frequency of events was higher for males in both treatment groups. However, the relative risk for renal function impairment with candesartan treatment was increased in women. The proportion of Caucasians in the study was dominant (placebo 90.8 %; candesartan 91.4 %). Only 4.4% in the placebo group and 2.8% on candesartan treatment were Blacks and the number of events were correspondingly small. There was a significant increase in discontinuation rates in the candesartan group for patients treated with spironolactone both at baseline and at the visit preceding the event. This could be expected from another inhibitor of the RAAS. However, concomitant medication with β-blockers and/or spironolactone at the time of the event did not seem to essentially 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.

Patients with previous ACE-inhibitor discontinuation because of renal dysfunction and hypotension were more likely to have recurrence while taking candesartan than placebo, most patients with these histories tolerated candesartan. Importantly, cough (the most common reason for patients not taking an ACE-inhibitor due to ACE-inhibitor intolerance) led to discontinuation and/or dose reduction in only a few patients in each treatment group.

Angioedema occurred in only three patients, all with previous hypersensitivity to ACE inhibitors.

Study investigators chose to reduce the dose of the investigational product to manage AEs for 15.5% of candesartan-treated patients and 7.5% 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 with an established history of ACE-inhibitor intolerance, candesartan was safe, given that it reduced CV-mortality without off-setting non-CV mortality. It was also well tolerated; almost equal proportions of patients in the two treatment groups had AEs leading to permanent discontinuation of the investigational product. As expected for an inhibitor of the RAAS, events relatively specific to candesartan such as hypotensive events, hyperkalemia and increased creatinine occurred. Importantly, for most patients, reactions that prohibited patients from taking ACE inhibitors did not lead to discontinuation of the investigational product.

Clinical laboratory results:

Serial laboratory data were collected from patients participating at investigational sites in North America (placebo 334 patients, candesartan 326 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, such as creatinine and potassium.

The mean value for creatinine in the placebo group decreased 4.73 μmol/L from the baseline value to the LVCF (two extreme values were present at baseline but not at LVCF explaining the decrease). In the candesartan group, the value increased 17.9 μmol/L. At baseline, 75 (22.4%) of placebo patients had values above the reference range compared with 78 (23.9%) 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 94, 29.8%; candesartan 120, 37.3%).m For patients who had serial measurements (placebo 307 patients, candesartan 311 patients) baseline serum creatinine was at least doubled in 5 (1.6%) patients in the placebo group, compared with 17 (5.4%) 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 0.24 mmol/L for patients treated with candesartan. During the study, the proportions of patients with values above the reference range remained approximately the same in the placebo group (6, 1.8% at baseline, 7, 2.2% LVCF) and increased from 7 (2.1%) to 22 (6.8%) in the candesartan group. Potassium levels increased to ≥ 6 mmol/ L at any time after randomization in 1.3% (4) of 315 patients valid for evaluation in the placebo group and 2.8% (9) of 321 patients in the candesartan group.

Mean sodium measurements increased 0.03 mmol/L for patients treated with placebo and decreased 0.39 mmol/L for patients in the candesartan group. The AE term hyponatremia was reported for four patients (Site – Patient number: 358 – 10453, 455 – 16036, 943 – 14360, 1515 – 20840) treated with placebo compared with one patient (Site 1480, Patient number 23729)

treated with candesartan.

Minor decreases were seen for mean hemoglobin values for patients treated with placebo (0.13 mmol/L) and candesartan (0.24 mmol/ L). The proportion of patients with anemia reported as an AE during treatment with the investigational product was slightly lower for placebo-treated patients (16, 1.6%) compared with candesartan-treated patients (29, 2.9%). No patients in the placebo treatment group and 1 (0.3%) of 320 patients valid for evaluation 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 (-0.39%) and candesartan groups (-0.25%).

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.

At LVCF mean heart rate was 0.7 bpm lower in patients in the placebo group and 1.8 bpm lower in patients in the candesartan group compared to baseline.

Blood pressure declined in both treatment groups. Mean DBP decreased 3.5 mmHg from the baseline value to the LVCF in the placebo group and 4.8 mmHg from the baseline value to the LVCF in the candesartan group. Corresponding values for SBP were 4.4 mmHg for patients treated with placebo and 6.5 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 5 (0.5%) patient in the placebo group and 16 (1.6%) patients in the candesartan group. 20 (2.0%) patients treated with placebo and 54 (5.4%) patients treated with candesartan had a recorded SBP value less than 80 mmHg at any time after randomization.

In the placebo group, mean body weight decreased by 0.5 kg from baseline to LVCF. In the candesartan population an increase of 0.7 kg was seen.

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

Following a Telecon on November 18, 2004, I requested the sponsor to provide information on the CHARM-Alternative (SH-AHS-0003) 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 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 November 24, 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, I used the definition for high candesartan dose 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 183, 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 183 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 – CHARM-Alternative (SH-AHS-0003) Study

Candesartan	**N = 1013** **Events = 218 (21.5%)**		
			A
	CC_{HD} n = 626 events = 97 (15.5%)	CC_{LD} n = 260 events = 100 (38.5%)	CC_{00} n = 127 events = 21 (16.5%)
	A1	**A2**	**A3**
Placebo	**N = 1015** **Events = 196 (19.3%)**		
			B
	P_{HD} n = 748 events = 124 (16.6%)	P_{LD} n = 140 events = 60 (42.9%)	P_{00} n = 127 events = 12 (9.5%)
	B1	**B2**	**B3**

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

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

In Table 184, no relationship is apparent between the dose of candesartan and the numbers and frequencies of permanent study drug discontinuation due to hypotension.

Table 184 The numbers and frequencies of permanent study drug discontinuation due to hypotension[a] in patients who received high or low dose candesartan – CHARM-Alternative (SH-AHS-0003) Study

Candesartan	**N = 1013** **Events = 37 (3.7%)**		
			A
	CC_{HD} n = 556 events = 9 (1.6%)	CC_{LD} n = 207 events = 24 (11.6%)	CC_{00} n = 250 events = 4 (1.6%)
	A1	**A2**	**A3**
Placebo	**N = 1015** **Events = 9 (0.9%)**		
			B
	P_{HD} n = 666 events = 5 (0.8%)	P_{LD} n = 102 events = 4 (3.9%)	P_{00} n = 247 events = 0 (0.0%)
	B1	**B2**	**B3**

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

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

In Table 185, no relationship is apparent between the dose of candesartan and the numbers and frequencies of permanent study drug discontinuation due to hyperkalemia.

Table 185 The numbers and frequencies of permanent study drug discontinuation due to hyperkalemia[a] in patients who received high or low dose candesartan – CHARM-Alternative (SH-AHS-0003) Study

Candesartan	**N = 1013** **Events = 19 (1.9%)**		
			A
	CC_{HD} n = 557 events = 10 (1.8%)	CC_{LD} n = 192 events = 8 (4.2%)	CC_{00} n = 264 events = 1 (0.4%)
	A1	**A2**	**A3**
Placebo	**N = 1015** **Events = 3 (0.3%)**		
			B
	P_{HD} n = 665 events = 3 (0.5%)	P_{LD} n = 98 events = 0 (0.0%)	P_{00} n = 252 events = 0 (0.0%)
	B1	**B2**	**B3**

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

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

In Table 186, 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 186 The numbers and frequencies of permanent study drug discontinuation due to <u>increased creatinine</u>[a] in patients who received high or low dose candesartan – CHARM-Alternative (SH-AHS-0003) Study

Candesartan	**N = 1013** **Events = 62 (6.1%)**		
			A
	CC_{HD} n = 578 events = 32 (5.5%)	CC_{LD} n = 209 events = 26 (12.4%)	CC_{00} n = 226 events = 4 (1.8%)
	A1	**A2**	**A3**
Placebo	**N = 1015** **Events = 27 (2.7%)**		
			B
	P_{HD} n = 675 events = 16 (2.4%)	P_{LD} n = 106 events = 9 (8.5%)	P_{00} n = 234 events = 2 (0.9%)
	B1	**B2**	**B3**

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

<u>Relationship of dose of candesartan to dose reductions of study drug due to an adverse event or an abnormal laboratory value</u>

In Table 187, 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 187 The numbers and frequencies of <u>dose reductions</u> of study drug due to an adverse event or an abnormal laboratory value[a] in patients who received high or low dose candesartan – CHARM-Alternative (SH-AHS-0003) Study

Candesartan	**N = 1013** **Events = 182 (18.0%)**		
			A
	CC_{HD} n = 621 events = 120 (19.3%)	CC_{LD} n = 171 events = 60 (35.1%)	CC_{00} n = 221 events = 2 (0.9%)
	A1	**A2**	**A3**
Placebo	**N = 1015** **Events = 89 (8.8%)**		
			B
	P_{HD} n = 693 events = 64 (9.2%)	P_{LD} n = 97 events = 25 (25.8%)	P_{00} n = 225 events = 0 (0.0%)
	B1	**B2**	**B3**

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

<u>Conclusions on safety results</u>:

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 71.1%, candesartan 67.3%).
- 21.7% of the patients in the candesartan group and 19.4% of the placebo group permanently discontinued treatment with the investigational product due to an AE or an abnormal laboratory finding.
- 15.5% of the patients receiving candesartan and 7.5% 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 did not influence time to permanent investigational product discontinuation due to any cause (P=0.735).
- Candesartan did not increase the number of investigational product discontinuations due to any cause (P= 0.509).
- Candesartan did not influence time to permanent investigational product discontinuation due to an AE or an abnormal laboratory value (P= 0.332).
- Candesartan did not increase the number of permanent investigational product discontinuations due to an AE or an abnormal laboratory value (P= 0.217).
- 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= 0.948).
- Candesartan did not increase the number of non-CV deaths (P= 0.822).
- Candesartan did not increase the number of non-CV hospitalizations (P= 0.652).

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

724, 71.3%; candesartan 725, 71.6%) and over the entire study period (placebo 747, 73.6%; candesartan 741, 73.1%)

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

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

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

Apart from cardiac failure aggravated (placebo 72, 7.1%; candesartan 53, 5.2%), abnormal renal function (placebo 25, 2.5%; candesartan 65, 6.4%), hypotension (placebo 14, 1.4%; candesartan 46, 4.5%) and hyperkalemia (placebo 3, 0.3%; candesartan 21, 2.1%) were the most commonly reported AE, given as reasons for discontinuing the investigational product.

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

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

DISCUSSION AND OVERALL CONCLUSIONS

Discussion

In patients with CHF and clinically considered intolerant to an ACE inhibitor candesartan significantly reduced CV 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 for heart failure as well as CV

mortality or hospitalization due to heart failure or non-fatal MI were significantly reduced. There were substantial reductions in the individual components of the composite outcomes except for non-fatal MI. Moreover, symptoms of heart failure as evaluated by the NYHA-classification and development of atrial fibrillation were reduced.

This study evaluated candesartan in a population unable to receive standard ACE inhibitor therapy due to intolerance to this class of drugs. Importantly, the 23% relative risk reduction in CV mortality and heart failure hospitalization with candesartan parallels closely the reduction in mortality and heart failure hospitalization observed with the ACE inhibitor enalapril in the earlier SOLVD study[72] and in an overview of large studies of ACE inhibitors for patients with depressed LV systolic function with or without heart failure[51]. The magnitude of the benefit seen from treatment with candesartan was achieved despite modern concomitant treatment with other effective heart failure drugs such as β-blockers and spironolactone, agents which were not widely prescribed at the time of the earlier ACE-inhibitor trials. The present study has prospectively shown that candesartan provides an important treatment benefit, which appears to be of similar magnitude as that achieved with ACE inhibitors.

There were consistent and clinically important reductions in CHF hospitalizations with candesartan. In addition to prolongation of time to hospitalization due to heart failure, the number of patients admitted to hospital for CHF and the total numbers of hospital admissions primarily for CHF were lower in the candesartan group than in the placebo group.

Over the duration of the trial, 33% of candesartan patients compared with 40% of placebo patients reached the endpoint of CV mortality or first hospitalization due to heart failure. This absolute reduction of 7 major events per 100 patients treated corresponds to the need to treat 14 patients with candesartan to prevent one patient from suffering this outcome.

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. All fatal CV events except fatal MI were lower after treatment with candesartan. Although death due to MI was infrequent compared to death from heart failure-related causes, fatal MI was significantly more common in the candesartan group. There was, however no between- treatment difference in the incidence of non- fatal MI. Furthermore results from all three component studies included in the CHARM programme did not show differences between the treatment groups regarding fatal or non-fatal MI. Non-CV death was not influenced by candesartan.

Candesartan was well tolerated, without a notably increased need for discontinuation overall compared to placebo, despite these patients having a prior history of intolerance to another inhibitor of the renin- angiotensin-aldosterone system. This is consistent with our pilot experience[10]. As may be expected, discontinuation due to renal function impairment, hyperkalemia, or hypotension was more common with candesartan than placebo. This distribution of events could be expected from the pharmacodynamic profile of candesartan and the underlying conditions in the CHF population. Monitoring patients for these risks, especially those receiving concomitant therapy with diuretics or other inhibitors of the RAAS, is an already well-established practice for care of the CHF patient. While patients with prior ACE-inhibitor

discontinuation due to renal insufficiency and hypotension were more likely to have recurrence during treatment with candesartan compared with placebo, the vast majority of these patients were able to tolerate candesartan.

Importantly, cough (the most common reason for patients not taking an ACE-inhibitor due to ACEI-intolerance) led to discontinuation in only a few patients in each treatment group in the current study. Thus, patients who experienced cough as a reason for discontinuation of ACE inhibitor treatment did not experience recurrence of cough during treatment with candesartan.

Although angioedema has been reported with the use of AT1-receptor blockers[73], the incidence of recurrent angioedema among patients who initially had developed angioedema on ACE inhibitors is not well documented[74]. In the present study, the occurrence of angioedema was infrequent, and only 1 of 39 (2.6%) of the patients with a history of angioedema during treatment with ACE inhibitors had recurrence of angioedema leading to permanent discontinuation of treatment with candesartan, and this patient did not require hospitalization nor was the adverse event life threatening.

Overall conclusions

Candesartan reduces mortality and hospitalization due to heart failure and improves symptoms in patients with CHF and intolerance to treatment with ACE inhibitors. The reduction in mortality is attributed to the reduction in CV deaths. 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. Most patients with a history of prior ACE inhibitor intolerance are able to tolerate candesartan.

10.1.20 Appendix 2 CHARM-Pooled studies

Please refer to Chapter 10, Item 10.1.20, Appendix 16 (Pages 314-366) of my clinical review of the efficacy supplement SE 1 #022 of NDA 20-838 (CHARM-Added (SH-AHS-0006) study) in which I presented my reviews of the individual clinical studies in the CHARM-Program.

10.2 Line-by-Line Labeling Review

Please refer to Chapter 10, Item 10.2 (Pages 367-394) of my clinical review of the efficacy supplement SE 1 #022 of NDA 20-838 (CHARM-Added (SH-AHS-0006) study) in which I presented my line-by-line labeling review.

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