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

Section 10.1.20 Appendix 2 CHARM-Pooled studies

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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:

<u>Prior to unblinding of data</u>:

- 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.

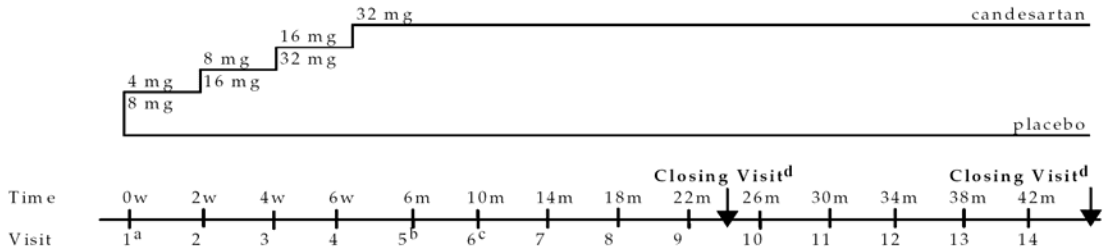
In this patient population, the most common reason for ACE inhibitor intolerance was cough, being more common in the placebo group than in the candesartan group (751, 74.0% vs. 704, 69.5%). ACE intolerance due to hypotension or renal dysfunction was more common in the candesartan group (143, 14.1% vs. 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

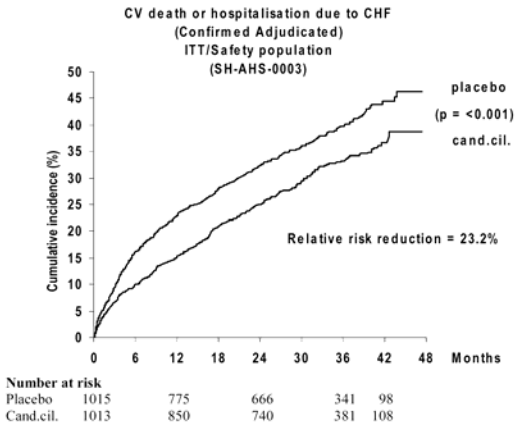


Figure 2 Cumulative incidence (%) of confirmed adjudicated CV death or hospitalization due to CHF over time. ITT/Safety population

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

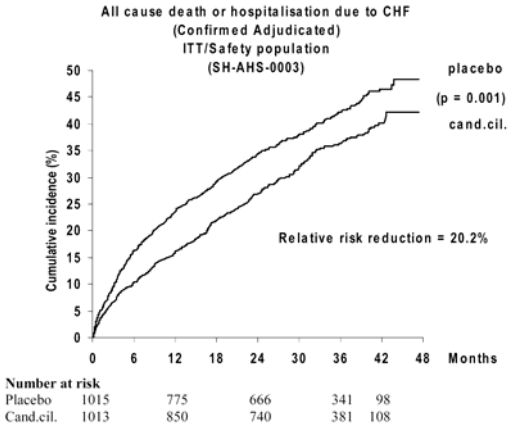


Figure 3 Cumulative incidence (%) of confirmed adjudicated all- cause death or hospitalization due to CHF over time. ITT/Safety population

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

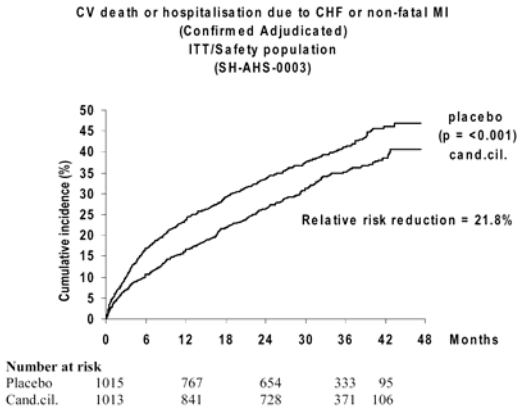


Figure 4 Cumulative incidence (%) of confirmed adjudicated CV death or hospitalization due to CHF or non- fatal MI over time. ITT/Safety population

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.

<u>Primary efficacy endpoint of CV mortality or CHF hospitalization (confirmed, adjudicated):</u> 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%) **A1**	CC_{LD} n = 213 events = 118 (55.4%) **A2**	CC_{00} n = 205 events = 55 (26.8%) **A3**
Placebo		**N = 1015** **Events = 406 (40.0%)**	**B**
	P_{HD} n = 720 events = 270 (37.5%) **B1**	P_{LD} n = 130 events = 86 (66.2%) **B2**	P_{00} n = 165 events = 50 (30.3%) **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%) **A1**	CC_{LD} n = 213 events = 124 (58.2%) **A2**	CC_{00} n = 203 events = 67 (33.0%) **A3**
Placebo		**N = 1015** **Events = 433 (42.7%)**	**B**
	P_{HD} n = 721 events = 282 (39.1%) **B1**	P_{LD} n = 131 events = 94 (71.8%) **B2**	P_{00} n = 163 events = 57 (35.0%) **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%) **A1**	CC_{LD} n = 215 events = 121 (56.3%) **A2**	CC_{00} n = 199 events = 56 (28.1%) **A3**
Placebo		**N = 1015** **Events = 420 (41.4%)**	**B**
	P_{HD} n = 720 events = 279 (38.8%) **B1**	P_{LD} n = 134 events = 91 (67.9%) **B2**	P_{00} n = 161 events = 50 (31.1%) **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).

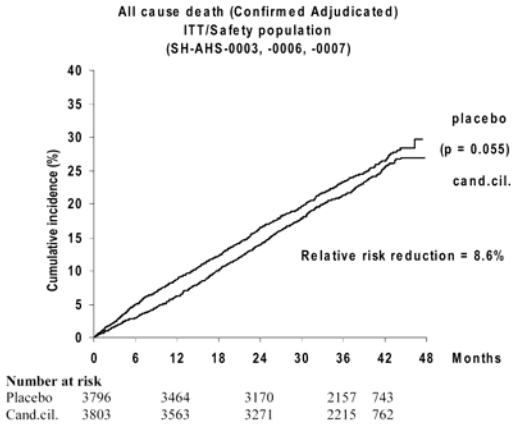


Figure 5 Cumulative incidence (%) of confirmed adjudicated all-cause death in patients with symptomatic CHF over time. ITT/Safety population.

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).

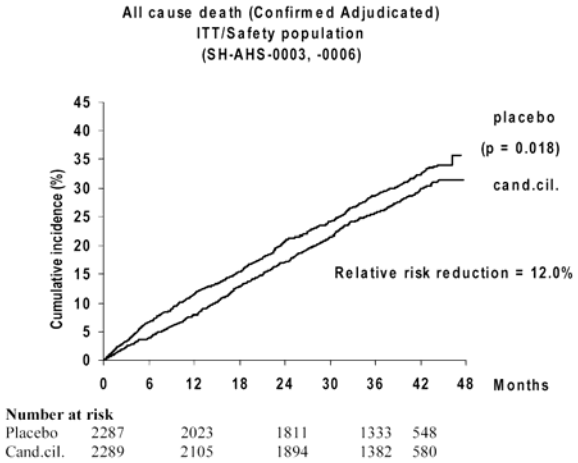


Figure 6 Cumulative incidence (%) of confirmed adjudicated all-cause death in patients with LV systolic dysfunction over time. ITT/Safety population.

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.

<u>Deaths in CHARM-Alternative (SH-AHS-0003) Study</u>

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	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 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.

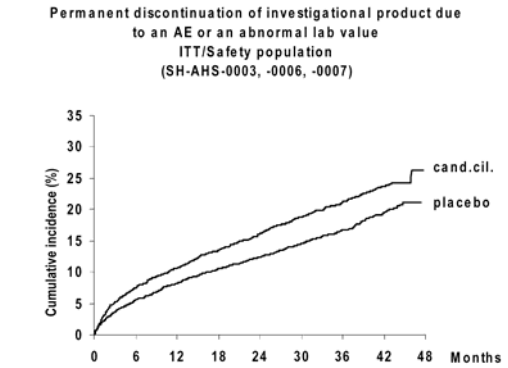
In this exploratory presentation of data permanent discontinuation of the investigational product due to an AE or abnormal lab value occurred in 633 (16.7%) patients in the placebo group and 798 (21.0%) patients in the candesartan group. Both the difference in time to event (P< 0.001) (Table 46, Table 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 Lower	95% CI Upper	p-value
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



Number at risk					
Placebo	3796	3257	2907	1936	662
Cand.cil.	3803	3242	2875	1887	646

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	95% CI 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 Lower	95% CI Upper	p-value
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

<u>Reviewer's comments with data from the medical literature</u>: 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.

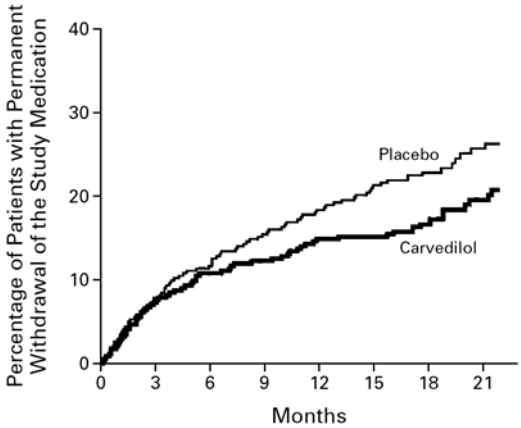


Figure 9 Kaplan–Meier Analysis of the time to permanent withdrawal of the study medication because of adverse reactions or for reasons other than death in placebo and Carvedilol groups in COPERNICUS trial[45]. The risk of withdrawal was 23% lower in the carvedilol group (95% CI: 4% – 38%; P= 0.02). (Based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

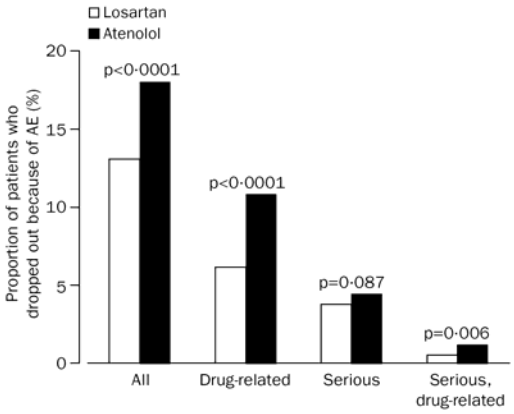


Figure 10 Adverse events resulting in discontinuation of study drug in LIFE study[41] (Based on data from Lancet 2002; 359: 995-1003.)

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.

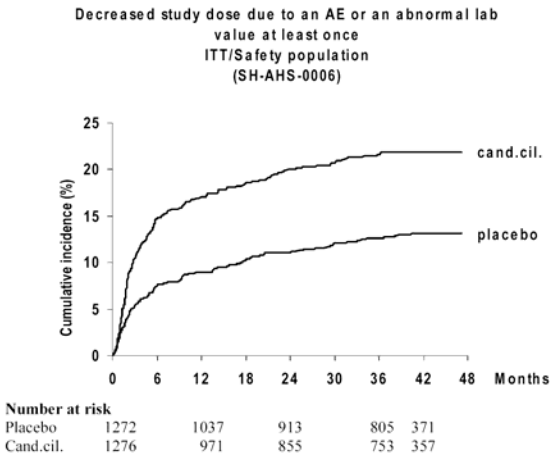


Figure 11 Cumulative incidence (%) of first occurrence of dose decrease of investigational product due to an AE or an abnormal laboratory value. ITT/Safety population

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.

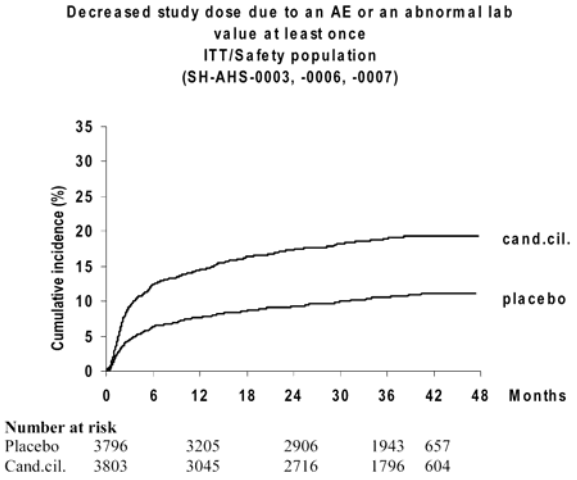


Figure 12 Cumulative incidence (%) of dose reduction of the investigational product due to an AE or an abnormal laboratory value. ITT/Safety population (SH-AHS-0003, -0006, -0007)

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 (N=1015)		Cand. cil. on treatment (N=1013)		Placebo during study[b] (N=1015)		Cand. cil. during study[b] (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 (N=3796)		Cand. cil. on treatment (N=3803)		Placebo during study[b] (N=3796)		Cand. cil. during study[b] (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 (N=2287)		Cand.cil. on treatment (N=2289)		Placebo during study[b] (N=2287)		Cand.cil. during study[b] (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.

<u>Reviewer's comments with data from the medical literature</u>: 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.

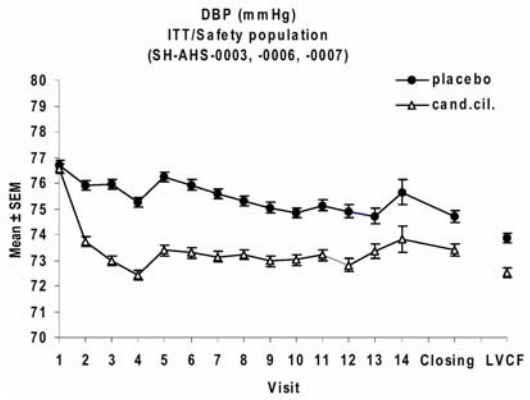


Figure 13 Mean DBP ± SEM (mmHg) by visit for the total population. ITT/Safety population

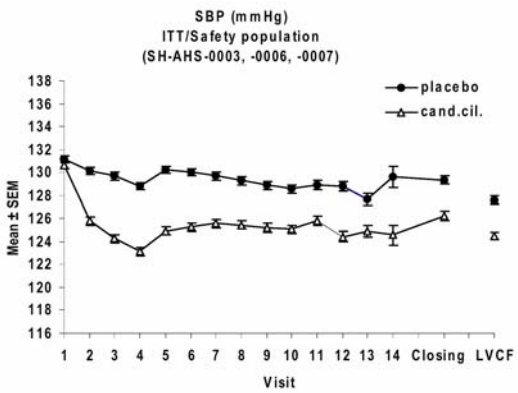


Figure 14 Mean SBP ± SEM (mmHg) by visit for the total population. ITT/Safety population

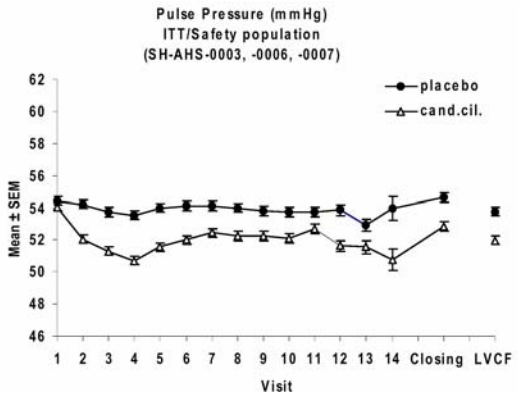


Figure 15 Mean Pulse Pressure ± SEM (mmHg) by visit for the total population. ITT/Safety population

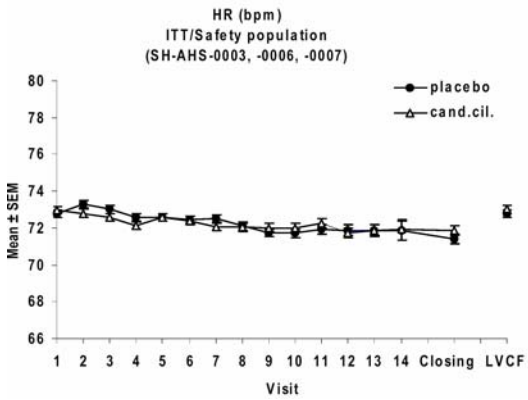


Figure 16 Mean heart rate ± SEM (bpm) by visit for the total population. ITT/Safety population

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).

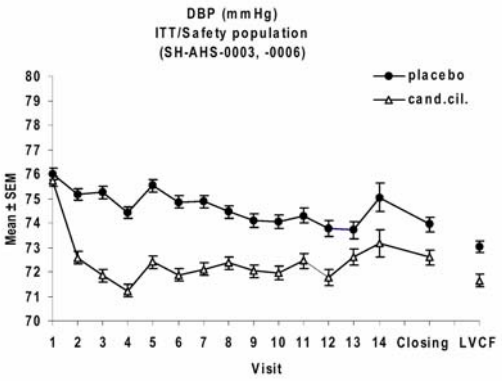


Figure 17 Mean DBP ± SEM (mmHg) by visit for the depressed LV systolic function subpopulation. ITT/Safety population

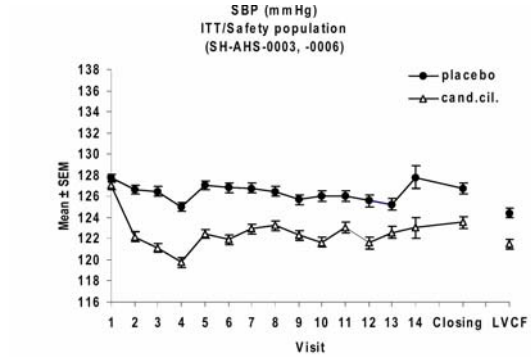


Figure 18 Mean SBP ± SEM (mmHg) by visit for the depressed LV systolic function subpopulation. ITT/Safety population

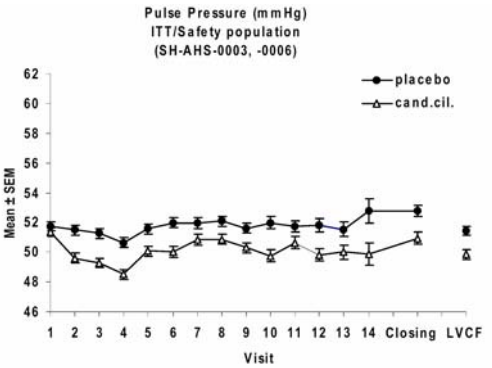


Figure 19 Mean Pulse Pressure ± SEM (mmHg) by visit for the depressed LV systolic function subpopulation. ITT/Safety population

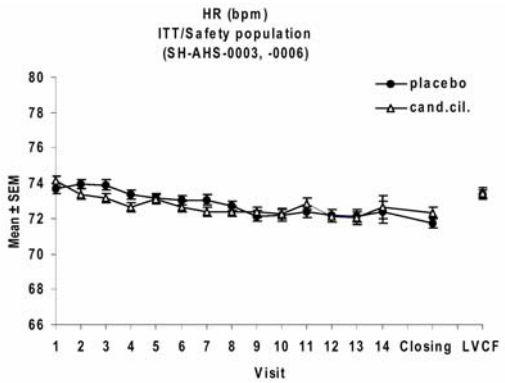


Figure 20 Mean heart rate ± SEM (bpm) by visit for the depressed LV systolic function subpopulation. ITT/Safety population

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.

<u>Extent of exposure in CHARM-Alternative (SH-AHS-0003) Study</u>

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.

<u>Hypotensive events in CHARM-Added (SH-AHS-0006) Study</u>:

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).

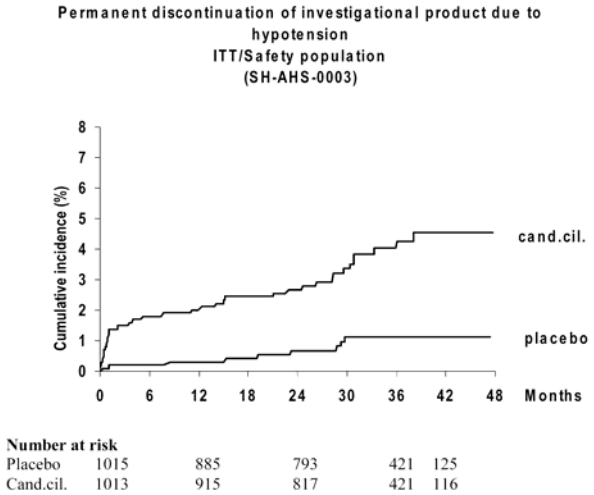


Figure 21 Cumulative incidence (%) of permanent discontinuation of investigational product due to hypotension (Ref. - Table 42). ITT/Safety population

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.

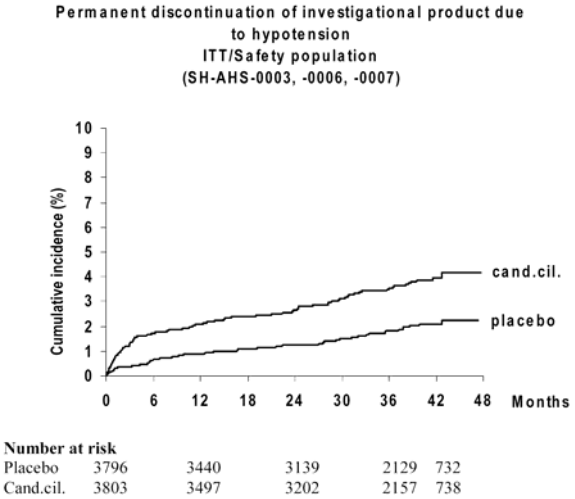


Figure 22 Cumulative incidence (%) of permanent discontinuation of the investigational product due to hypotension. ITT/Safety population

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).

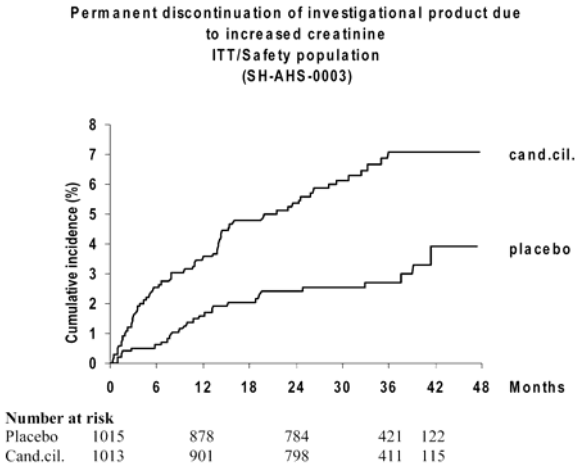


Figure 23 Cumulative incidence (%) of permanent discontinuation of investigational product due to increased creatinine (Ref. - Table 42). ITT/Safety population

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).