

CLINICAL REVIEW

Application Type NDA 20-838
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Established Name Candesartan Cilexetil
(Proposed) Trade Name Atacand[®]
Therapeutic Class Selective AT₁ subtype angiotensin
II receptor antagonist
Applicant AstraZeneca LP

Priority Designation P

Formulation oral
Dosing Regimen Initial dose 4 mg q.d., up-titrated
to a target dose of 32 mg q.d.

Indication Treatment of heart failure
(Labeling claim = Treatment with
Atacand[®] reduces relative risk of death
from cardiovascular causes or
hospitalization for heart failure, and
improves symptoms)

Intended Population Patients with chronic heart failure
(NYHA functional class II – IV)

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Candesartan cilexetil is an angiotensin II type 1 (AT₁)-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 (Candesartan cilexetil (candesartan) in Heart Failure Assessment of Reduction in Mortality and Morbidity) Program consists of three pivotal efficacy trials comprising 7,601 patients with NYHA Class II – IV chronic heart failure (CHF) who were randomized to candesartan (titrated from 4 mg or 8 mg once daily to a target dose of 32 mg once daily as tolerated) or matching placebo, and followed for at least 2 (up to 4) years. The analysis of the CHARM Program was divided into (i) patients with depressed left ventricular systolic function (ejection fraction (EF) ≤40%) who were intolerant to angiotensin converting enzyme (ACE) inhibitors (CHARM-Alternative), (ii) patients with depressed left ventricular systolic function (EF ≤40%) receiving an ACE inhibitor (CHARM-Added), and (iii) patients with Preserved left ventricular systolic function (EF >40%) (CHARM-Preserved). This efficacy supplement #022 pertains to CHARM-Added trial which received priority review.

In CHARM-Added (SH-AHS-0006) Study of 2,548 patients with CHF who were receiving an ACE inhibitor, candesartan significantly (P=0.011) reduced the relative risk of time to CV death or CHF hospitalization by 14.7% (primary efficacy endpoint). This benefit translates into a reduction of 4.4 events per 100 patients treated for two years; i.e., treating 23 patients with candesartan for two years will prevent one patient from suffering the outcome of CV death or CHF hospitalization. The reduction in CV death was attributed to a reduction in sudden death and CHF death, which are the most common modes of death in patients with CHF. The study was not powered to assess the effect on all-cause mortality.

The benefit of candesartan was evident in the presence of treatment with ACE inhibitors at recommended doses. The mean daily dose of enalapril at baseline was 17 mg, which compares to 16.6 mg in the treatment arm of the **Studies Of Left Ventricular Dysfunction (SOLVD)** and 17 mg in the **Valsartan Heart Failure Trial (Val-HeFT)**. This benefit was also evident in patients treated with β-blockers, suggesting that there is no negative interaction between the AT₁-receptor blocker candesartan, ACE-inhibitors and β-blockers as was reported with valsartan in Val-HeFT.

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

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

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

Based on my review limited to NDA 20-838 Efficacy Supplement # 022 with data on the CHARM-Added (SH-AHS-0006) study and the overall CHARM Program (SH-AHS-0003, -0006, -0007) studies, I recommend this application as for the indication of treatment of heart failure (NYHA class II-IV) with left ventricular systolic dysfunction (ejection fraction $\leq 40\%$) in patients who are receiving other heart failure treatments including ACE-inhibitors or β -blockers and for the labeling claim that candesartan reduces the relative risk of time to cardiovascular death or the first occurrence of a hospitalization for heart failure. I suggest that the issues related to (a) the role and dose of AT₁ receptor blockers in the treatment of patients with heart failure (b) the effect on survival of interactions between AT₁ receptor blockers and ACE-inhibitors, β -blockers and digoxin in the treatment of patients with heart failure, be discussed at a Cardio-Renal Drug Advisory Committee Meeting.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

- (i) Analyze data from the CHARM-Program studies to determine dose of candesartan and/or ACE-inhibitor and/or β -blockers and/or spironolactone in relation to AEs (hypotension, hyperkalemia, deterioration of renal function) and study drug discontinuation and/or dose reduction. This information should be provided in the labeling as well as communicated to practicing physicians through educational measures.
- (ii) Ensure educational activities regarding the importance of starting with the lowest initial dose of candesartan and of increasing the dose gradually while monitoring the heart rate, blood pressure, serum creatinine, and serum potassium.

1.2.2 Required Phase 4 Commitments

Not applicable.

1.2.3 Other Phase 4 Requests

- (i) Plan/perform a prospective clinical trial to find the optimal dose combination of ACE-inhibitor (high or low dose) and candesartan (high or low dose) in the treatment of CHF which will provide the most benefit [survival benefit (all-cause death, CV death, sudden death and CHF death) and clinical benefit (reduced hospitalization, improved symptoms, hemodynamics and exercise tolerance)] with the least risk [of AEs such as aggravated heart failure, hypotension, hyperkalemia, and deterioration of renal function].
- (ii) Plan/perform a prospective clinical trial of candesartan in treatment of patients (tolerant and intolerant to ACE inhibitors) with high risk of heart failure without structural heart disease or symptoms (i.e. Stage A heart failure) to determine if candesartan will prevent or delay development of structural heart disease (Stage B), symptomatic heart failure (Stage C) or refractory symptoms of heart failure (Stage D).

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Candesartan cilexetil is an angiotensin II type 1 (AT₁)-receptor blocker. It is currently approved in the United States for the treatment of hypertension with the usual oral starting dose of 16 mg titratable up to 32 mg daily. Candesartan is proposed for the reduction of mortality and morbidity and reduction in hospitalization due to heart failure (NYHA Class II-IV) and improvement in the signs and symptoms of heart failure. The proposed starting dose in heart failure is 4 mg daily, being doubled every two weeks as tolerated to a maximum dose of 32 mg daily.

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

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

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

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

Patients were randomized at visit 1 to candesartan or placebo. The starting dose was 4 mg once daily, which was titrated up to 32 mg once daily or to the highest tolerated dose during a 6-week period. Thereafter, the patients were scheduled to a visit every 4th month. All patients remained in the study until the last randomized patient had been in the study for ≥ 2 years. The median duration of double-blind treatment was 34.8 months, the median time of follow up was 37.7 months, and the longest follow-up time was 47.6 months.

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

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

1.3.2 Efficacy

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

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

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

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

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

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

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

1.3.3 Safety

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

1.3.4 Dosing Regimen and Administration

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

1.3.5 Drug-Drug Interactions

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

1.3.6 Special Populations

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

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

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

2.2 Currently Available Treatment for Indications

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

2.3 Availability of Proposed Active Ingredient in the United States

Not applicable.

2.4 Important Issues with Pharmacologically Related Products

Not applicable

2.5 Pre-submission Regulatory Activity

Not applicable

2.6 Other Relevant Background Information

Not applicable

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Not applicable

3.2 Animal Pharmacology/Toxicology

Not applicable

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

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

- “Clinical Study (SH-AHS-0003) of Candesartan in Patients With Heart Failure Who Are ACE Inhibitor Intolerant and Have Depressed Left Ventricular Systolic Function (CHARM – Alternative study: 2,028 patients)”
- “Clinical Study (SH-AHS-0006) of Candesartan in Patients With Heart Failure Who Are Treated With ACE Inhibitors and Have Depressed Left Ventricular Systolic Function (CHARM – Added study: 2,548 patients)”
- “Clinical Study (SH-AHS-0007) of Candesartan in Patients With Heart Failure and Preserved Left Ventricular Systolic Function (CHARM – Preserved study: 3,023 patients)”

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

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

- (a) seven clinical trials of 3,016 patients with CHF
 - (i) 5 randomized, double-blind, placebo-controlled clinical trials with duration of 2 to 12 months, comprising a total of 1,893 patients,
 - (ii) one randomized, double-blind, active-treatment (enalapril)-controlled study (RESOLVD) comprising 768 patients, and
 - (iii) one open, uncontrolled, long-term (6 month) study comprising 355 patients.
- (b) seventeen clinical trials of 1,046 patients with CHF
 - (i) 3 clinical pharmacology studies comprising 262 patients,
 - (ii) 11 clinical studies comprising a total of 677 patients under the Japanese study program (for which FDA granted the sponsor a waiver from providing case report tabulations and case report forms, and 10 studies were pertinent to efficacy), and
 - (iii) 4 investigator-initiated clinical studies comprising 107 patients.

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

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

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

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

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

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

4.2 Tables of Clinical Studies

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

Table 2 List of Clinical Efficacy Trials

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

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

4.3 Review Strategy

For NDA Supplement #022 (CHARM – Added Study) the sponsor submitted that candesartan incrementally reduces the risk of cardiovascular (CV) mortality or heart failure (CHF) hospitalization when added to an ACE inhibitor containing regimen in CHF patients with left ventricular systolic dysfunction. This is reflected in the sponsor’s claim made in the “Indications and Usage” section of the package insert: *“ATACAND is indicated for the treatment of heart failure (NYHA class II-IV). ATACAND reduces the risk of death from cardiovascular causes and improves symptoms in patients with left ventricular systolic dysfunction, and reduces hospitalizations for heart failure in patients with depressed or preserved left ventricular systolic function. These effects occur in patients receiving other heart failure treatments with or without ACE inhibitors, including patients intolerant to ACE inhibitors, and with or without beta-blockers (see Clinical Trials).”*

With regard to the use of β -blockers, the pharmacodynamics section of the package insert states: *“Co-administration of metoprolol succinate (extended-release tablets) with candesartan cilexetil plus enalapril resulted in a decrease in left ventricular systolic volume and an increase in left ventricular ejection fraction compared with the combination of candesartan plus enalapril.”*

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

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

Study #	Type	Total N=	Patients	Duration	Dose	eCTD
SH-AHS-0006	r, db, pc, pg, mc	2548	chf, EF \leq 40%; ACEi treated	\geq 2 yr	Start CC 4 or 8 mg qd, up-titrate to 32 mg qd or highest tolerated dose	5.3.5.1.2
SH-AHS-0008	r, db, pc, mc	98	chf, EF \leq 40%; ACEi treated	8 wk	CC 2, 4, 8, 16 or 32 mg qd	5.3.5.1.9
SH-AHS-0004	r, pc	33	chf, EF \leq 35%; ACEi treated	4 wk	CC 8 mg qd x 1 wk, up-titrate to 16 mg qd	5.3.5.4.12
EC608 (pk)	r, db, md, co, mc	31	Mild to mod chf	Pt I: 1 day Pt II: 21 d	Pt I: CC 8mg, E 10mg, CC8 + E 10mg Pt II: qd x 7 days, 3 periods	5.3.3.2.2
SH-AHS-0001	r, db, pg, mc control = (E)	768	chf, EF \leq 40%; 6-min walking distance \leq 500 m	43 wk	CC 4 or 8 mg qd, up-titrate to 32 mg qd	5.3.5.1.10
SH-AHS-pooled (2 studies)	r, db, pc, pg, mc	7601	chf, EF \leq 40%; ACEi intol & ACEi treated	\geq 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 \leq 40% & EF $>$ 40%; ACEi intol & ACEi treated	\geq 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 AT₁-receptor blockers (ARBs), including those in which β -blockers are used in combination with ACE inhibitors and ARBs in the treatment of CHF to obtain a broader perspective of the benefits produced by use of candesartan, ACE inhibitors and β -blockers together, and the possible risks (e.g., hypotension, bradycardia, worsening of renal failure) this combination treatment may impose on these relatively sick patients with CHF.

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

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

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

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

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

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

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

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

- (i) RESOLVD trial was not powered to detect deaths as endpoints
- (ii) ELITE II trial no significant effect on mortality
- (iii) Val-HeFT trial reported that β -blockers significantly *increased* the risk of mortality and morbidity
- (iv) COPERNICUS trial was the only clinical trial (other than the CHARM-Added trial in this NDA) that reported a significant reduction in relative risk of all-cause death
- (v) CHARM-Added trial reported that β -blockers reduced relative risk of CV death or CHF hospitalization when used together with ARB plus ACE inhibitor

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

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

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

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

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

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

ACE inhibitor vs. placebo/diuretic trials:

Stage A heart failure:

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

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

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

ARBs vs. ACE inhibitor trials:

Stage A heart failure:

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

Stage B, C or D heart failure:

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

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

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

Stage A heart failure:

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

Stage B, C or D heart failure:

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

Other perspectives:

- (1) Framingham Study did not document any meaningful change in overall death rates from heart failure though ACE inhibitors, B-blockers, spironolactone and ARBs are shown to reduce mortality and morbidity and improve functional status. This lack of survival benefit seen in the general population is attributed to under-use of these agents, and to co-morbid diseases.
- (2) There is no consensus regarding the doses of ACE inhibitors (or ARBs) that can be recommended as effective in heart failure.

4.4 Data Quality and Integrity

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

- (1) this submission is an efficacy supplement of a drug with known safety profile,
- (2) there are 473 sites in 25 countries in this large, multi-center trial, with no specific site showing a positive response that was driving the outcome of the trial, and
- (3) each site enrolled relatively small numbers of patients in this large, double-blind, randomized, clinical trial so that the design of the study would have prevented any investigator bias that could have affected the outcome of the trial.

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

4.5 Compliance with Good Clinical Practices

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

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

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

4.6 Financial Disclosures

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

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

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

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

5 CLINICAL PHARMACOLOGY

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

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

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

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

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

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

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

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

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

5.1 Pharmacokinetics

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

Table 6 Clinical studies of pharmacokinetics

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

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

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

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

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

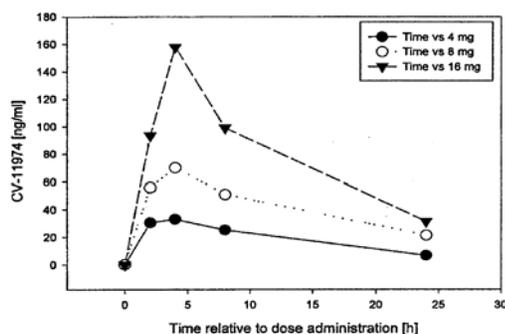


Figure 1 Mean Serum Concentration of CV-11974 (Safety population) – Study EC602

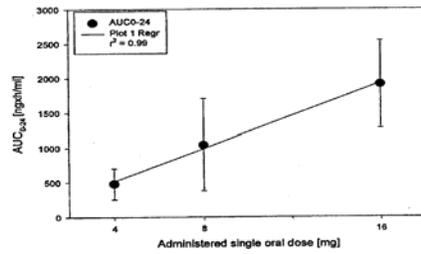


Figure 2 AUC₀₋₂₄ vs. administered dose (Efficacy (ITT) population) – Study EC602

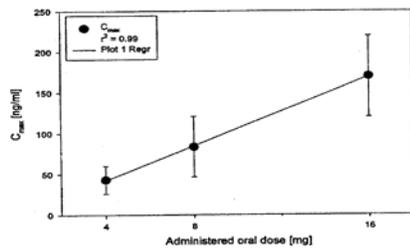
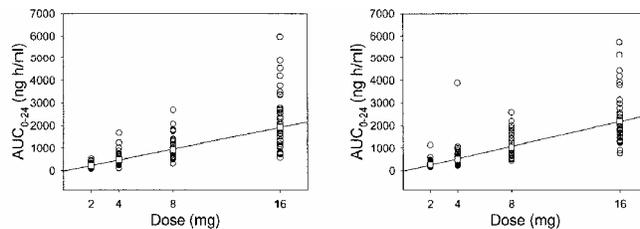


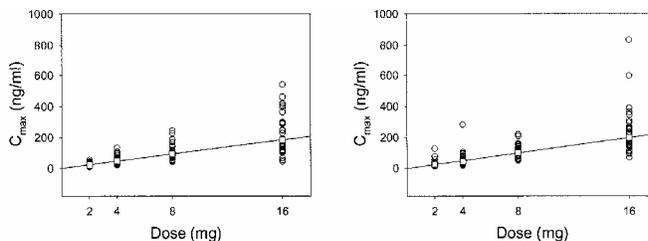
Figure 3 C_{max} vs. administered dose (Efficacy (ITT) population) – Study EC602

In study EC605-A (please see Appendix PK 2), 218 patients with CHF were randomized (44 to placebo and 174 to candesartan), again primarily for PD measurements; PK parameters were also measured for both single dose and multiple-dose (12-week treatment period) situations. Fifteen patients in the candesartan group had missing PK values, so data on 159 patients with evaluable PK data were submitted. For both single-dose and multiple-dose administration of candesartan, dose-proportional increase in AUC₀₋₂₄ and C_{max} of candesartan were reported (Figure 4 and Figure 5). The t_{max} remained constant at around 4 hours after ingestion of oral candesartan in both single dose and multiple-dose situations.



Plots of AUC₀₋₂₄ of CV-11974 versus dose following oral administration of candesartan at doses of 2, 4, 8 and 16 mg o.d. Individual subject values (○) and geometric mean values (◻).

Figure 4 AUC₀₋₂₄ versus dose on visits 2 (left) and 6 (right) – EC605-A



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

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

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

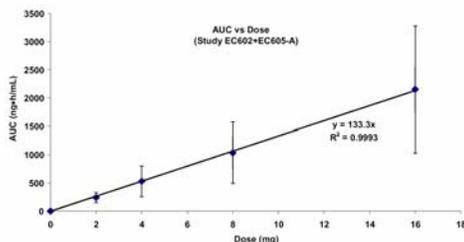


Figure 6 AUC_{0-24h} (following single doses of candesartan) vs. dose of candesartan cilexetil in patients with CHF (studies EC602 and EC605-A)

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

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

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

Notwithstanding these protocol deviations, the study found no interaction between candesartan and enalapril at steady state (apart from a statistically significant increase in AUC₀₋₇₂ of candesartan and enalapril in patients with mild or moderate renal impairment, see Table 7). This study probably provides the rationale for use of candesartan and enalapril in treatment of patients with CHF. In a later communication dated 16-Sep-2004, the sponsor submitted that there are no other studies of the pharmacokinetic interaction of candesartan and enalapril.

Table 7 Study EC608 – Summary statistics for candesartan and enalaprilat pharmacokinetic parameters separated by renal groups after repeat dose administration

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

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

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

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

Com-pounds	No. of pts.		Pharmacokinetic parameters					
			C _{max} (ng/ml)	T _{max} (h)	AUC ₀₋₄₈ (ng.h/ml)	MRT ₀₋₄₈ (h)	t _{1/2α}	t _{1/2β}
M-I	5pts.	Day 1	56.7±21.9	3.6±0.6	825±514	12.8±1.2	2.3±0.6(4)	12.0±2.9(4) 10.5(1)
		Day 9	56.8±16.1	4.3±1.9	892±397	13.5±2.1	3.0±1.9(4)	13.9±5.7(4) 17.6(1)
M-II		Day 1	7.5±4.5	10.0±1.4	223±164	21.2±2.8	-	24.2±14.1
		Day 9	12.5±7.2	7.2±4.6	437±315	20.2±2.6	-	21.0±6.4 ²⁾

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

Table 9 Study CPH102 – Urinary excretions of M-I and M-II

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

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

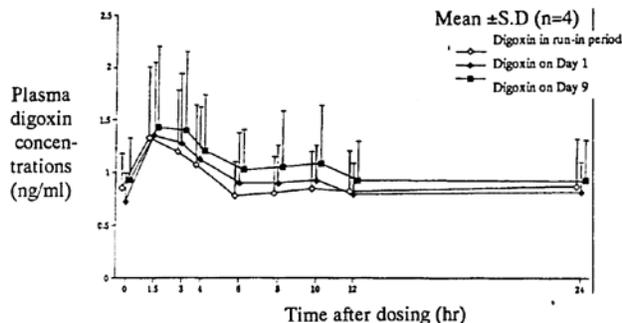


Figure 7 Study CPH102 – Plasma digoxin concentrations

5.2 Pharmacodynamics

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

In study SH-AHS-0004 (Ellis), a similar and statistically significant improvement in peak V_{O_2} was observed in *both* the candesartan and the placebo groups at the end of 1 month.

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

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

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

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

Table 12 Study EC602: PCWP_{mean} – Mean AUC₀₋₁₂ ±SD (difference to pre-dose [0h], Peak Change ±SD (Efficacy (ITT) Population)

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

Table 13 Study EC602: PAP_{mean} – Mean AUC₀₋₁₂ ±SD (difference to pre-dose [0h], Peak Change ±SD (Efficacy (ITT) Population)

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

Table 14 Study EC605-A: Pulmonary capillary wedge pressure – One-way ANCOVA

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

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

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

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

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

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

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

EF (%)	Dose	Time Point	Patients	mean	SD	min	25%	median	75%	max	t-value	p-value
2 & 4 mg combined		Run-in	8	43.16	11.66	29	33.85	42.4	49	65.8		
		End Treatment	8	47.91	15.41	26	35.65	49.5	56.55	73.9		
		Difference	8	4.75	4.81	-5	2.8	5.6	8.5	9.2	2.792	0.027
4mg		Run-in	7	44.09	12.5	29	31	44.5	50.5	65.8		
		End Treatment	7	49.43	15.98	26	34	53.1	59.7	73.9		
		Difference	7	5.34	4.87	-5	5	5.6	8.9	9.2	2.902	0.027
2mg		Run-in	1	36.7		36.7	36.7	36.7	36.7	36.7		
		End Treatment	1	37.3		37.3	37.3	37.3	37.3	37.3		
		Difference	1	0.6		0.6	0.6	0.6	0.6	0.6		

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

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

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

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

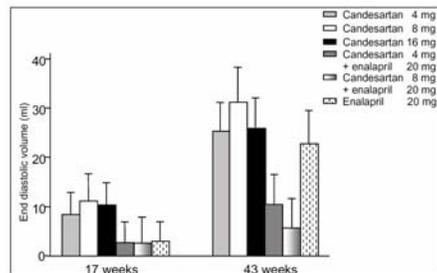


Figure 8 Study SH-AHS-0001 (RESOLVD) – Change in End Diastolic Volume (ml) by different treatments after 17 & 43 weeks.

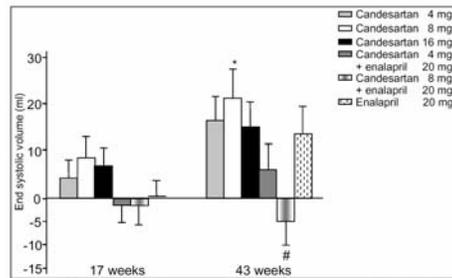


Figure 9 Study SH-AHS-0001 (RESOLVD) – Change in End Systolic Volume (ml) by different treatments after 17 & 43 weeks.

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

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

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

Table 17 Study EC604 – Results of the non-parametric ANCOVA on the change in the cardiothoracic ratio between baseline (Visit 5) and last value – Intent-to-treat population (n= 807)

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

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

Table 18 Study EC604 – Results of the non-parametric ANCOVA on the change in the cardiothoracic ratio between baseline (Visit 5) and last value

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

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

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

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

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

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

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

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

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

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

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

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

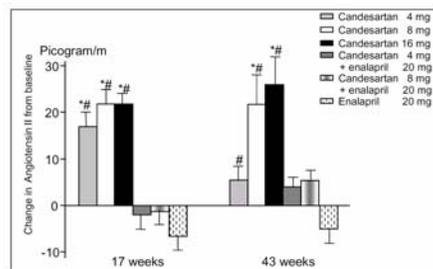


Figure 10 Study SH-AHS-0001 (RESOLVD) – Change in angiotensin II levels after 17 and 43 weeks of treatment with candesartan, candesartan plus enalapril or enalapril
 P< 0.01 compared with 0 weeks; # P< 0.01 compared with enalapril

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

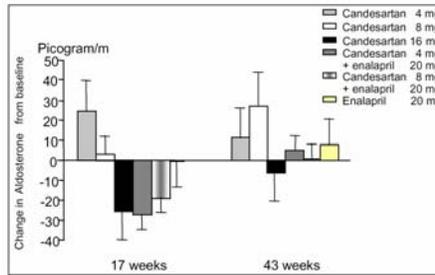


Figure 11 Study SH-AHS-0001 (RESOLVD) – Change in aldosterone levels after 17 and 43 weeks of treatment with candesartan, candesartan plus enalapril or enalapril
 P< 0.01compared with 0 weeks; # P< 0.01 compared with enalapril

Table 19 Study EC605-A Neurohormonal variables

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

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

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

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

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

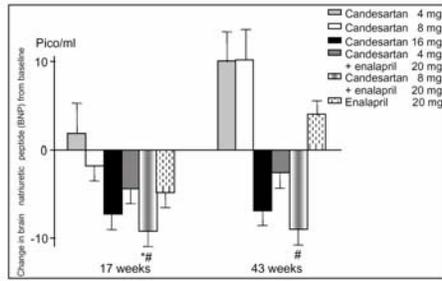


Figure 12 Study SH-AHS-0001 (RESOLVD) – Change in brain natriuretic peptide (BNP) levels after 17 and 43 weeks of treatment with candesartan, candesartan plus enalapril or enalapril
 (* P< 0.01 compared with 0 weeks; # P< 0.01 compared with enalapril)

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

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

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

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

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

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

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

5.3 Exposure-Response Relationships

5.3.1 Total exposure of candesartan

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

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

The median time of follow up for the total population was 37.7 months, and the longest follow-up time was 47.6 months. The median exposure to double-blind treatment was 34.8 months. A total of 5,360 patients (of which 2,659 patients were in the candesartan group) received study medication for 24 months or longer. Also, the sponsor stated that from the 6-month visit onwards, >50% of patients still receiving candesartan were on a dose of 32 mg/day.

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

- (i) 5 randomized, double-blind, placebo-controlled clinical trials with duration of 2 to 12 months, comprising a total of 1,893 patients,
- (ii) one randomized, double-blind, active-treatment (enalapril)-controlled study (RESOLVD) comprising 768 patients, and
- (iii) one open, uncontrolled, long-term (6 month) study comprising 355 patients.
- (iv) 3 clinical pharmacology studies comprising 262 patients,
- (v) 11 clinical studies comprising a total of 677 patients under the Japanese study program (for which FDA granted the sponsor a waiver from providing case report tabulations and case report forms, and 10 studies were pertinent to efficacy), and
- (vi) 4 investigator-initiated clinical studies comprising 107 patients.

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

5.3.2 Dose Selection

The approved doses of candesartan for treatment of hypertension range from 2 mg to 32 mg once daily. For organ-protective effect (e.g., cardio-protection from remodeling), a higher degree of AT₁-receptor blockade than that required for an anti-hypertensive effect is expected. Thus, higher doses than those optimal for hypertension treatment were thought to be required. The selection of dose of candesartan for treatment of CHF was based on the following studies:

- (1) SH-AHS-0001 (RESOLVD) study: In this pilot study of 768 patients with CHF, candesartan 4 mg to 16 mg was found as effective as enalapril 10 mg bid on improving left ventricular function (with or without addition of metoprolol). This study was terminated early because of increased clinical events (deaths) in the treatment groups receiving candesartan and candesartan plus enalapril.
- (2) SH-AHS-0002 (SPICE) study: This pilot study of 270 patients with CHF showed that patients intolerant to ACE-inhibitors could be treated for 12 weeks with candesartan 4 mg to 16 mg, with a tolerability similar to placebo.
- (3) EC604 study: In this relatively large study of 844 patients with CHF, 4 mg, 8 mg and 16 mg doses of candesartan were given over 12 weeks and, the 16 mg dose was found to improve exercise tolerance (bicycle ergometry only).
- (4) SH-AHS-0008 study: In this 8-week study of 98 patients with CHF, candesartan was added to conventional heart failure treatment regimen, starting at 8 mg once daily, titrated at 2-week intervals to doses of 16 mg once daily and to a maximum dose of 32 mg once daily (the highest dose for candesartan in the treatment of essential hypertension approved in the United States). This study showed that the 32 mg dose was generally safe and well-tolerated by these patients with CHF.

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

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

For this pivotal study SH-AHS-0006 (CHARM-Added trial), a starting dose of 4 or 8 mg candesartan was chosen (at the discretion of the clinical investigator), and this was up-titrated by doubling the dose at intervals of 2 weeks up to a maximum dose of 32 mg once daily or the highest tolerable dose to ensure as complete blockade as possible of AT₁-receptors. The protocol specified monitoring serum potassium and creatinine levels at each dose escalation.

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

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

The submission shows that a total of 1,096 (85.9%) patients in the candesartan group started treatment on 4 mg once daily, and 180 (14.1%) patients started on 8 mg once daily. 53.6% of patients treated with candesartan were receiving the target dose of 32 mg once daily at 6 months (visit 5). 1,756 (68.9%) patients (candesartan = 857, 67.2%; placebo = 899, 70.7%) received the investigational product for 24 months or more. The mean dose in the candesartan treatment group was 23.5 mg at 6 months.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The sponsor applied for the following indication and labeling under the umbrella of the CHARM Program:

“ATACAND (candesartan cilexetil) is indicated for the treatment of heart failure (NYHA class II-IV). ATACAND (1) reduces the risk of death from cardiovascular causes and (2) improves symptoms in patients with left ventricular systolic dysfunction, and (3) reduces hospitalizations for heart failure in patients with depressed or preserved left ventricular systolic function. These effects occur in patients receiving other heart failure treatments (4) with or without ACE inhibitors, (5) including patients intolerant to ACE inhibitors, and (6) with or without beta-blockers.”

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

With regard to the use of β -blockers, the pharmacodynamics section of the package insert states: *“Co-administration of metoprolol succinate (extended-release tablets) with candesartan cilexetil plus enalapril resulted in a decrease in left ventricular systolic volume and an increase in left ventricular ejection fraction compared with the combination of candesartan plus enalapril.”*

6.1.1 Methods

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

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

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

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

patients with left ventricular systolic dysfunction appears to have scientific basis. It is known that ACE inhibitors only partially block the production of angiotensin II. One or more ACE-independent pathways^{1,2} for the synthesis of angiotensin II has been demonstrated, including the “chymase pathway” which produces angiotensin II at the tissue level; about 90% of angiotensin produced in the heart is believed to be produced via this pathway^{3,4}. Thus, local production of angiotensin II can occur despite the use of an ACE inhibitor. AT₁-receptor blockers (ARBs), by inhibiting angiotensin II at the AT₁-receptor level, may exert a more complete inhibition of the local adverse effects of angiotensin II. Also, blocking AT₁-receptors causes unopposed stimulation of AT₂-receptors which may produce an additional beneficial effect on cardiac remodeling⁵ and vascular epithelial changes. Thus, ACE inhibitors and ARBs such as candesartan may exert different effects at the cardiac and vascular levels, which may be complementary in the treatment of CHF⁶.

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

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

- (1) The effect of candesartan vs. placebo in CHF patients treated with ACE inhibitor (ACEi) *any dose* (sponsor’s primary efficacy analysis) is derived from (A+B) vs. (C+D)
- (2) The effect of candesartan vs. placebo in CHF patients already on treatment with ACEi *heart failure dose* (i.e., the incremental effect of candesartan added to the effect of heart failure dose of ACEi in CHF) is derived from A vs. C
- (3) The effect of ACEi at *heart failure dose* vs. *low dose* in CHF patients treated with candesartan (i.e., the incremental effect of heart failure dose of ACEi added to the effect of candesartan in CHF, the low dose ACEi being, hypothetically, considered as producing no effect) is derived from A vs. B

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

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

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

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

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

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

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

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

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

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

N.B. Please 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 31-34 of this review.

6.1.2 General Discussion of Endpoints

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

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

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

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

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

A hospitalization was defined as any overnight stay in a hospital (different dates for admission and discharge). A CHF hospitalization was defined as admission to hospital necessitated by heart failure (i.e., signs and symptoms of worsening heart failure), and primarily for the treatment of heart failure. Evidence of worsening heart failure must include at least one of the following: increasing dyspnea on exertion, orthopnea, nocturnal dyspnea, increasing peripheral edema, increasing fatigue/decreasing exercise tolerance, renal hypoperfusion (worsening renal function), elevated jugular venous pressure and radiological signs of CHF.

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

6.1.2.1.1 *Protocol amendments*

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

The first amendment came into effect before patients were recruited. Another secondary endpoint was added to bring the study into line with European guidelines for studies in heart failure following discussions with regulatory agencies. The change made use of endpoints that were collected but had not been combined in the original protocol. The first amendment did not affect the study procedure, only the analysis of the result.

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

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

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

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

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

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

6.1.2.1.2 *Changes to planned analyses:*

Prior to unblinding of data:

- In amendment 1, the closed test procedure was changed due to an addition to the secondary endpoint. The original closed test procedure was modified to contain three steps with one primary and two secondary endpoints in a hierarchical order.
- In amendment 4, a re-calculation of the power was done to increase the sample sizes in the two other component studies in the CHARM program (SH-AHS-0003 and SH-AHS-0007).
- Several efficacy and safety variables for analysis were added to those described in the study protocol, and were finalized before database lock was declared.
- Additional analyses were made for the time-to-event variables adjusting for 33 pre-specified covariates used in the interim analyses. This was included as a part of the analysis plan for

the manuscripts approved by the Executive Committee.

- Analyses in subgroups were made even if the P-value for the interaction treatment by subgroup was greater than 0.1. The interaction P-values were calculated in a regression model for each subgroup separately.
- The non-CV death component, cancer death was included as a separate analysis.
- The planned calculation of medians and percentiles for the cumulative incidence curves were not performed.

After unblinding of data:

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

6.1.2.1.3 *Re-opening of study database*

The sponsor submitted that shortly before the Clean File meeting and Database Lock on 12 June 2003, death reports and other CRF-pages for patients classified as ‘withdrew consent’ were removed from the database. However, based on a recommendation from the Executive Committee the data were re-entered and database was revised to include these data and database lock was declared on July 4, 2003. The cases re-entered into the study database were adjudicated by the endpoint committee as for all other cases. In three cases the death reports sent in were crossed out by the investigator with a comment that the information should not be entered into the database. In these cases the information in the reports was not used and it was decided by the Study Team that the date of death was to be estimated by imputation. The number of patients with events added or reclassified in the study database is shown in Table 22.

Table 22 Number of patients with events added (+) or subtracted (-) due to reclassification at the re- opening of the database.

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

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

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

- Patients lost to follow-up/incomplete patient data: Last date known to be alive was used in the analyses;
- Patients who withdrew the consent: Patients alive up to 31 March 2003 were analyzed as being alive 31 March 2003; for dead patients, the death date was estimated by imputation;
- When date of death was unknown, if occurring before 31 March 2003, a death date was estimated by imputation to a date exactly between the date of withdrawal of consent (alternatively last date known to be alive) and 31 March 2003. In the present study there was only one patient for whom the date of death was unknown i.e., the procedure of imputation was only applied in one case.

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

6.1.2.2 Endpoints for the overall CHARM Program

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

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

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

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

Interim Analysis:

The protocol specified that the Safety Committee formally compared the treatment groups in the CHARM Program trials with regard to all-cause death. While the all-cause mortality in the three CHARM trials combined was the emphasis, the data from the treatment groups were compared at approximately 6-months intervals with a logrank test, stratified by study. In order to stop the trials for benefit in the overall population, the stopping rule required $P < 0.0001$ for analyses performed within 18 months of the first patient randomized, and $P < 0.001$ for all subsequent analyses. If the test for heterogeneity between trials indicated a differential benefit of candesartan across the individual trials, consideration was to be given to continuing randomization or follow-up for those trials in which findings were less pronounced. In order to stop for safety, should candesartan exhibit greater mortality, the same general principles applied except that the plan required $p < 0.001$ for analyses performed within 18 months of the first patient randomized and $p < 0.01$ for any subsequent analysis. In addition, the logrank test for a treatment difference in mortality was performed separately for each trial at each interim analysis. Stopping a single trial for benefit required (1) the same boundary values as for the overall analysis, and (2) statistical evidence of heterogeneity between trials of sufficient strength to justify termination of the trial. The results of 6 interim analyses are summarized in (Table 23).

Table 23 Interim results for CHARM-Pooled

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

^aData taken from source other than CHARM Interim Reports (personal communication).

^bBoundary crossed for efficacy.

N.B. First patient randomized was 22 March 1999. The initial meeting of the SC was on 22 August 1999 where no formal analyses were performed due to the small number of events observed.

The stopping boundary for efficacy was crossed at the third interim analysis (Table 23). However, the Committee recommended that the program continue based on the following considerations:-

- The treatment difference in mortality was most marked in one study (66 vs 100 deaths [$P = 0.006$ by logrank test], SH-AHS-0003; CHARM-Alternative Study)) and not statistically

significant in the other two (140 vs. 168 deaths [P= 0.070], SH-AHS-0006 (CHARM-Added) study; and, 54 vs. 71 deaths [P= 0.136], SH-AHS-0007 (CHARM-Preserved) Study).

- At that point in time, data on the primary study endpoint, CV death or hospitalization, were incomplete with many such endpoints awaiting adjudication, thus making it difficult to reliably assess the totality of evidence for efficacy.

6.1.3 Study Design

This was a randomized, double-blind placebo controlled parallel group multicenter study to evaluate the influence of candesartan (4 mg titrated to target dose of 32 mg once daily) on mortality and morbidity in patients with depressed LV systolic function and ejection fraction (EF ≤ 40%) and simultaneously treated with an ACE inhibitor. The primary variable for this evaluation was time from randomization to CV mortality or the first occurrence of a CHF hospitalization. A total of 2,548 patients were randomized at 473 sites in 25 countries.

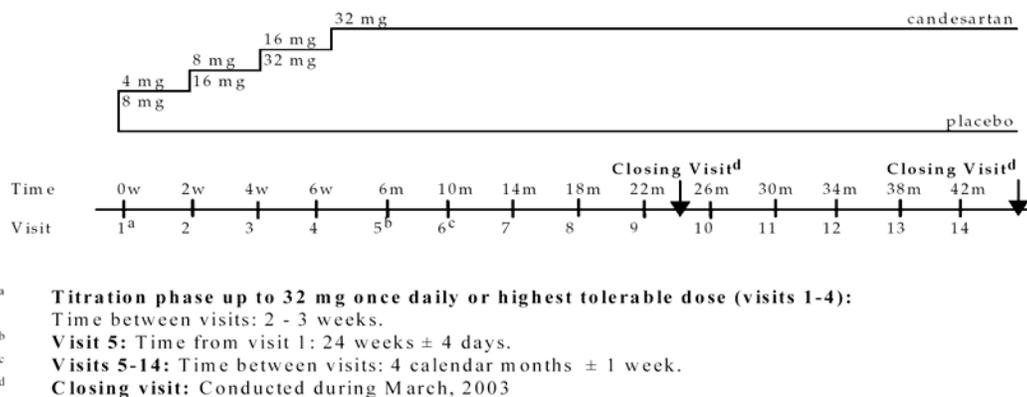


Figure 13 Study design

Figure 13 shows the design of the study and the sequence of treatment periods. Randomization was carried out at visit 1. The patients were randomized to candesartan or placebo, and titrated up to 32 mg once daily or to the highest tolerated dose during a 6- week period. Thereafter, the patients were scheduled to a visit every 4th month. The information in the CRF for visits 2 to 14 was similar. The recruitment period was 8 months. All patients remained in the study until the last randomized patient had been in the study for at least 2 years. Thus, individual time in the study for surviving patients not lost to follow-up may be 41 to 48 months. The median duration of the double-blind treatment was 34.8 months, the median time of follow up was 37.7 months, and the longest follow-up time was 47.6 months.

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

6.1.4 Efficacy Findings

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

During the follow-up period, a total of 1,021 patients experienced the primary efficacy outcome of CV death or hospitalization due to CHF, 483 (37.9%) in the candesartan group and 538 (42.3%) in the placebo group. The average annualized events rates were 14.1% and 16.6%, respectively (Table 24).

Table 24 Confirmed adjudicated CV death or hospitalization due to CHF. Number of patients with at least one event by treatment group and events per 1000 years of follow-up. Follow-up time is calculated to first event. ITT/Safety population (SH-AHS-0006)

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

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

Table 25 Confirmed adjudicated CV death or hospitalization due to CHF. Comparison of candesartan versus placebo with Cox regression. ITT/Safety population (SH-AHS-0006)

Variable	N	Events cand. cil.	Events placebo	Hazard Ratio	95% CI		p-value
					Lower	Upper	
CV death or hospitalisation due to CHF (confirmed adjudicated)	2548	483	538	0.853	0.754	0.964	0.011

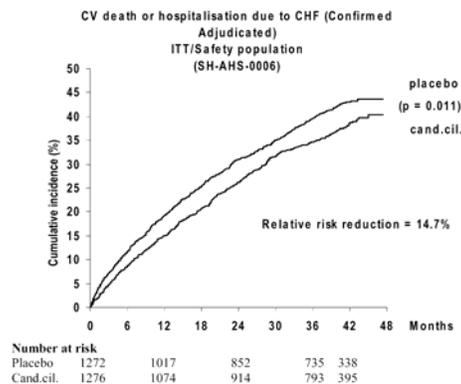


Figure 14 Cumulative incidence (%) of confirmed adjudicated CV death or hospitalization due to CHF over time (ITT/Safety population)

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

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

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

6.1.4.2 Secondary efficacy endpoint

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

During the follow-up period, a total of 1,126 patients experienced the secondary efficacy outcome of all-cause death or hospitalization due to CHF, 539 (42.2%) in the candesartan group and 587 (46.1%) in the placebo group. The average annualized events rates were 15.8% and 18.2%, respectively (Table 26).

Table 26 Confirmed adjudicated all-cause death or hospitalization due to CHF. Number of patients with at least one event by treatment group and events per 1000 years of follow-up. Follow-up time is calculated to first event. ITT/Safety population (SH-AHS-0006)

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

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

Table 27 Confirmed adjudicated all-cause death or hospitalization due to CHF. Comparison of candesartan versus placebo with Cox regression. ITT/ Safety population (SH-AHS-0006)

Variable	N	Events cand. cil.	Events placebo	Hazard Ratio	95% CI		p- value
					Lower	Upper	
All-cause death or hospitalisation due to CHF (confirmed adjudicated)	2548	539	587	0.871	0.775	0.980	0.021

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

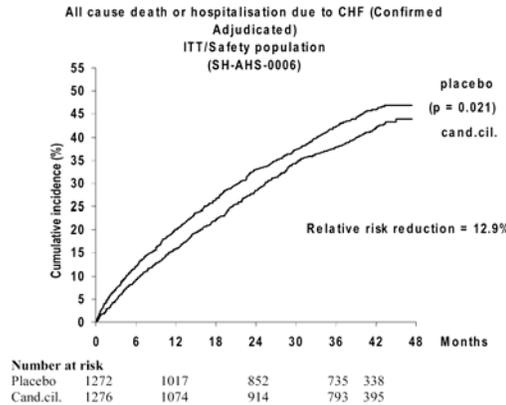


Figure 15 Cumulative incidence (%) of confirmed adjudicated all-cause death or hospitalization due to CHF over time (ITT/Safety population)

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

During the follow-up period a total of 1,045 patients experienced the secondary efficacy outcome of CV death or hospitalization due to CHF or non-fatal MI, 495 (38.8%) in the candesartan group and 550 (43.2%) in the placebo group. The average annualized events rates were 14.6% and 17.2%, respectively (Table 28).

Table 28 Confirmed adjudicated CV death or hospitalization due to CHF or nonfatal MI. Number of patients with at least one event by treatment group and events per 1000 years of follow-up. Follow-up time is calculated to first event. ITT/Safety population (SH-AHS-0006)

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

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

Table 29 Confirmed adjudicated CV death or hospitalization due to CHF or non-fatal MI. Comparison of candesartan vs. placebo with Cox regression. ITT/Safety population (SH-AHS-0006)

Variable	N	Events cand. cil.	Events placebo	Hazard Ratio	95% CI		p-value
					Lower	Upper	
CV death or hospitalisation due to CHF or non-fatal MI (confirmed adjudicated)	2548	495	550	0.852	0.755	0.962	0.010

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

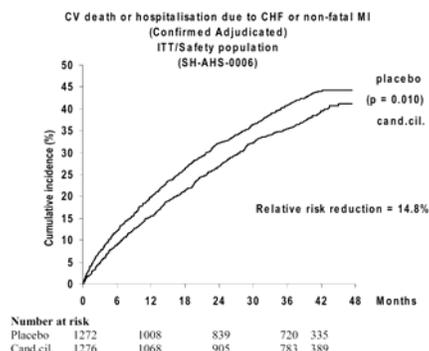


Figure 16 Cumulative incidence (%) of confirmed adjudicated CV death or hospitalization due to CHF or non-fatal MI over time (ITT/Safety population)

6.1.4.3 Components of the primary and secondary variables

The individual components:-

- (i) CV death (relative risk reduction 15.8%, P= 0.029),
- (ii) hospitalization due to CHF (relative risk reduction 17.5%, P= 0.014),
- (iii) all-cause death (relative risk reduction 11.5%, P= 0.086) and
- (iv) non- fatal MI (relative risk reduction 48.8%, P= 0.006)

all contributed to the benefit of candesartan as described by the respective composite endpoints (Table 30 and Table 31).

Table 30 Components of primary and secondary variables. Number of patients with at least one event by treatment group and events per 1000 years of follow-up. Follow-up time is calculated to first event. ITT/Safety population (SH-AHS-0006)

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

Table 31 Components of primary and secondary variables. Comparison of candesartan versus placebo with Cox regression. ITT/ Safety population (SH-AHS-0006)

Variable	N	Events cand. cil.	Events placebo	Hazard Ratio	95% CI		p-value
					Lower	Upper	
CV death (confirmed adjudicated)	2548	302	347	0.842	0.722	0.983	0.029
Hospitalisation due to CHF (confirmed adjudicated)	2548	309	356	0.825	0.709	0.961	0.014
All-cause death (confirmed adjudicated)	2548	377	412	0.885	0.770	1.018	0.086
Non-fatal MI (confirmed adjudicated)	2548	26	49	0.512	0.318	0.823	0.006

The number and rate of deaths by cause are calculated for each of the component trials of the CHARM Program and the overall CHARM Program and all-cause and cause-specific mortality results⁸ are shown in Table 32. There were 1,831 deaths, of which 1,460 were cardiovascular deaths. The three leading causes of death are sudden death (8.5% of patients, or 35% of all deaths), progressive heart failure (6.2% of patients, or 26% of all deaths), and MI (1.5% of patients, 6.1% of all deaths).

Table 32 Number, proportion, and annualized incidence of deaths attributed to different causes in the 3 CHARM Trials and the overall CHARM Program⁸ (based on data from Circulation 2004; 110:2180-3)

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

*Per 100 person-years.

The reduction in CV death with candesartan (relative risk reduction = 12%, P = 0.012) is largely attributable to a reduction in sudden death (relative risk reduction = 15%, P = 0.036), and progressive heart failure death (relative risk reduction = 22%, P = 0.008). These reductions were observed only in the two left ventricular systolic dysfunction trials (CHARM-Alternative (SH-AHS-0003) and CHARM-Added (SH-AHS-0006)) where patient had LVEF ≤ 40%. The mechanism by which ARBs (candesartan) reduce the incidence of sudden death is not clear (but ACE inhibitors also have been shown to reduce sudden death in patients following acute myocardial infarction⁹). 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 remodeling⁵ may also directly or indirectly decrease the propensity to fatal ventricular arrhythmias¹⁰. 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 suddenly¹¹. Autopsy data were available in only a few patients in the CHARM trials.

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

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

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

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

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

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

Table 34 summarizes the number of hospitalizations and overall length of stay for hospitalized patients where the primary reason for the hospitalization was stated by the investigator as cardiovascular.

Table 34 Total number and total duration (days) of hospitalizations and percentage of time on each unit of care subdivided with respect to treatment and primary reason for hospitalization. ITT/Safety population (SH-AHS-0006)

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

^a As stated by investigator

Regarding improvement in symptoms, there was an improvement in NYHA functional class in candesartan patients compared to placebo patients (P= 0.020, Wilcoxon rank-sum test). 548 (43.3%) patients in the candesartan group improved 1 or 2 NYHA classes compared to 495 (37.3%) in the placebo group (Table 35).

Table 35 Number of patients and change from baseline to LVCF in NYHA class by treatment. ITT/ Safety population (SH- AHS- 0006)

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

^a Wilcoxon rank-sum test, p=0.020

The shift in NYHA functional class from baseline to last known class is presented in Table 36.

Table 36 NYHA class shift table by treatment. ITT/Safety Population. (SH-AHS-0006)

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

6.1.4.4 Overview of Efficacy Findings

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

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

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

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

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

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

- (2) The effect of candesartan vs. placebo in CHF patients treated with ACEi *heart failure dose* (i.e., the incremental effect of candesartan added to the effect of *heart failure dose* of ACEi in CHF) is derived from A vs. C. This showed a reduction in relative risk of **20.6%**, which is the largest reduction found for study SH-AHS-0006. This is a statistically significant finding ($P = 0.010$), even for this smaller subgroup of fewer patients (with, therefore, less statistical power). This finding, together with the finding in (1) above, suggests that there is an incremental effect of candesartan added to the effect of ACE inhibitors at *heart failure doses* in the treatment of CHF.
- (3) The effect of ACEi at *heart failure dose* vs. ACEi *low dose* in CHF patients treated with candesartan (i.e., the incremental effect of *heart failure dose* of ACEi on top of the effect of candesartan in CHF, the *low dose* ACEi being, hypothetically, considered as producing negligible effect) is derived from A vs. B. This showed a reduction in relative risk of **12.6%**, but the results are not statistically significant (because of the loss of statistical power from the smaller sample size in this subgroup). The results are still in the positive direction, so this is a consistent finding in relation to the findings in (1) and (2) above. This suggests that there is a trend for an incremental effect of *heart failure dose* of ACEi on top of the effect of candesartan in CHF.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The submission shows that 1,756 (68.9%) patients (candesartan = 857, 67.2%; placebo = 899, 70.7%) received the investigational product for 24 months or more. A total of 1,096 (85.9%) patients in the candesartan group started treatment on 4 mg once daily, and 180 (14.1%) patients started on 8 mg once daily. 53.6% of patients treated with candesartan were receiving the target

dose of 32 mg once daily at 6 months (visit 5). Also, the sponsor stated that from the 6-month visit onwards, >50% of patients still receiving candesartan were on a dose of 32 mg/day. The mean dose in the candesartan treatment group was 23.5 mg at 6 months.

In Table 39 and Table 40, the proportions of patients who developed the primary efficacy endpoint events appear to be less in the candesartan-treated groups than the placebo-treated groups, particularly at the lower doses of 4 mg and 8 mg candesartan where the relative risk reduction with candesartan vs placebo was significant (Table 40). However, the results in the table do not take into consideration whether patients were receiving heart failure doses or low doses of ACE-inhibitors.

Table 39 CV death or CHF hospitalization by subgroup: dose of study drug, (events per 1000 years of follow-up), Study SH-AHS-0006

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

Table 40 CV death or CHF hospitalization by subgroup: dose of study drug (Cox regression), Study SH-AHS-0006

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

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

On November 12, 2004, I received the sponsor's response containing the information related to the primary and principal secondary efficacy endpoints, and adverse event endpoints according to dose level of candesartan. These analyses consider dose level of candesartan consistent with

the sub-group analyses presented in the submission. For the dose analyses, high candesartan dose is defined as 16 mg or 32 mg and low dose candesartan as 4 mg or 8 mg. Dose level was determined as described in the submission as a patient's last dose (if the patient had no event), or, if the patient had an event, as the last dose prior to the event. The category “no-study drug” was used to classify patients who were not on study drug at the visit prior to the event or not on study drug at the last visit if they had no event.

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

Primary efficacy endpoint of CV mortality or CHF hospitalization (confirmed, adjudicated): The proportion of patients who reached the primary efficacy endpoint while on high or low dose candesartan plus ACE inhibitors at heart failure dose or low are given in Table 41. It appears that there is a relative dose response, the event rates being significantly ($P < 0.001$) lower in the high dose (16 and 32 mg) candesartan groups compared to the low dose (4 and 8 mg) candesartan groups for both groups of patients receiving heart failure doses and low doses of ACE inhibitors (Table 42).

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

Table 41 The numbers and event rates (primary efficacy endpoint of CV mortality or CHF hospitalization, confirmed, adjudicated) of patients who received high or low dose candesartan plus ACE inhibitors at heart failure dose or low dose – CHARM-Added (SH-AHS-0006) Study

	ACEi _{HFD}			ACEi _{LD}		
Candesartan cilexetil ^a	CC + ACEi _{HFD} N = 643 Events = 232 (36.1%)			CC + ACEi _{LD} N = 633 Events = 251 (39.7%)		
	A			B		
	CC _{HD} + ACEi _{HFD} N = 401 Events = 144 (35.9%) A ₁	CC _{LD} + ACEi _{HFD} N = 98 Events = 46 (46.9%) A ₂	CC ₀₀ + ACEi _{HFD} N = 144 Events = 42 (29.2%) A ₃	CC _{HD} + ACEi _{LD} N = 372 Events = 140 (37.6%) B ₁	CC _{LD} + ACEi _{LD} N = 128 Events = 69 (53.9%) B ₂	CC ₀₀ + ACEi _{LD} N = 133 Events = 42 (31.6%) B ₃
Placebo	Placebo + ACEi _{HFD} N = 648 Events = 275 (42.2%) C			Placebo + ACEi _{LD} N = 624 Events = 263 (42.1%) D		

ACEi_{HFD} = ACE inhibitor at heart failure dose; ACEi_{LD} = ACE inhibitor at lower than heart failure dose;
 CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC₀₀ =Not on candesartan at event or last visit
^a Dose of study drug preceding the event (or at last visit if no event occurred)

Table 42 Comparison of the effect of high or low dose candesartan plus ACE inhibitor at heart failure dose or low dose on the primary endpoint of time to CV mortality or CHF hospitalization (confirmed, adjudicated) using Cox Regression^a – CHARM-Added (SH-AHS-0006) Study

Comparison	Relative risk reduction	Hazard ratio	95% confidence interval	P-value (Wald)
(A ₁ + B ₁) vs (A ₂ + B ₂)	36.9	0.631	(0.508, 0.784)	< 0.001
A ₁ vs B ₁	--	0.934	(0.740, 1.179)	0.567
A ₁ vs A ₂	30.4	0.696	(0.499, 0.970)	0.032
A ₁ vs B ₂	44.6	0.554	(0.416, 0.739)	<0.001
B ₁ vs A ₂	25.8	0.742	(0.532, 1.036)	0.079
B ₁ vs B ₂	40.4	0.596	(0.446, 0.795)	< 0.001
A ₂ vs B ₂	--	0.799	(0.550, 1.160)	0.239

^a Note: P=0.473 for test for interaction between high/low dose candesartan and baseline covariate (cells A₁, B₁, A₂ and B₂ only)
 Cells A₁, B₁, A₂ and B₂ = Reference to cells in Table 41.

Table 43 The numbers and event rates (secondary efficacy endpoint of all-cause mortality or CHF hospitalization, confirmed, adjudicated) of patients who received high or low dose candesartan plus ACE inhibitors at heart failure dose or low dose– CHARM-Added (SH-AHS-0006) Study

	ACEi _{HFD}			ACEi _{LD}		
Candesartan cilexetil ^a	CC + ACEi _{HFD} N = 643 Events = 232 (36.1%)			CC + ACEi _{LD} N = 633 Events = 251 (39.7%)		
	A			B		
	CC _{HD} + ACEi _{HFD} N = 401 Events = 158 9.4% E ₁	CC _{LD} + ACEi _{HFD} N = 99 Events = 49 49.5% E ₂	CC ₀₀ + ACEi _{HFD} N = 143 Events = 56 (39.2%) E ₃	CC _{HD} + ACEi _{LD} N = 375 Events = 155 (41.3%) F ₁	CC _{LD} + ACEi _{LD} N = 128 Events = 72 (56.3%) F ₂	CC ₀₀ + ACEi _{LD} N = 130 Events = 49 (37.7%) F ₃
Placebo	Placebo + ACEi _{HFD} N = 648 Events = 275 (42.2%) C			Placebo + ACEi _{LD} N = 624 Events = 263 (42.1%) D		

ACEi_{HFD} = ACE inhibitor at heart failure dose; ACEi_{LD} = ACE inhibitor at lower than heart failure dose;
 CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC₀₀ =Not on candesartan at event or last visit
^a Dose of study drug preceding the event (or at last visit if no event occurred)

Table 44 Comparison of the effect of high or low dose candesartan plus ACE inhibitor at heart failure dose or low dose on the secondary efficacy endpoint of all-cause mortality or CHF hospitalization (confirmed, adjudicated) using Cox Regression^a – CHARM-Added (SH-AHS-0006) Study

Comparison	Relative risk reduction	Hazard ratio	95% confidence interval	P-value (Wald)
(E ₁ + F ₁) vs (E ₂ + F ₂)	34.0	0.660	(0.535, 0.810)	< 0.001
E ₁ vs F ₁	--	0.930	(0.745, 1.161)	0.521
E ₁ vs E ₂	28.0	0.720	(0.522, 0.992)	0.044
E ₁ vs F ₂	41.8	0.582	(0.440, 0.769)	<0.001
F ₁ vs E ₂	22.8	0.772	(0.560, 1.065)	0.115
F ₁ vs F ₂	37.2	0.628	(0.475, 0.830)	0.001
E ₂ vs F ₂	--	0.810	(0.563, 1.165)	0.255

^a Note: P=0.512 for test for interaction between high/low dose candesartan and baseline covariate (cells E₁, F₁, E₂ and F₂ only)
 Cells E₁, F₁, E₂ and F₂ = Reference to cells in Table 43.

Table 45 The numbers and event rates (secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI, confirmed, adjudicated) of patients who received high or low dose candesartan plus ACE inhibitors at heart failure dose or low dose– CHARM-Added (SH-AHS-0006) Study

	ACEi _{HFD}			ACEi _{LD}		
Candesartan cilexetil ^a	CC + ACEi _{HFD} N = 643 Events = 232 (36.1%)			CC + ACEi _{LD} N = 633 Events = 251 (39.7%)		
	A			B		
	CC _{HD} + ACEi _{HFD} N = 402 Events = 150 (37.3%) G ₁	CC _{LD} + ACEi _{HFD} N = 100 Events = 51 (51.0%) G ₂	CC ₀₀ + ACEi _{HFD} N = 141 Events = 40 (28.4%) G ₃	CC _{HD} + ACEi _{LD} N = 373 Events = 143 (38.3%) H ₁	CC _{LD} + ACEi _{LD} N = 129 Events = 70 (54.3%) H ₂	CC ₀₀ + ACEi _{LD} N = 131 Events = 41 (31.3%) H ₃
Placebo	Placebo + ACEi _{HFD} N = 648 Events = 275 (42.2%) C			Placebo + ACEi _{LD} N = 624 Events = 263 (42.1%) D		

ACEi_{HFD} = ACE inhibitor at heart failure dose; ACEi_{LD} = ACE inhibitor at lower than heart failure dose;
 CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC₀₀ =Not on candesartan at event or last visit
^a Dose of study drug preceding the event (or at last visit if no event occurred)

Table 46 Comparison of the effect of high or low dose candesartan plus ACE inhibitor at heart failure dose or low dose on the secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI (confirmed, adjudicated) using Cox Regression^a – CHARM-Added (SH-AHS-0006) Study

Comparison	Relative risk reduction	Hazard ratio	95% confidence interval	P-value (Wald)
(G ₁ + H ₁) vs (G ₂ + H ₂)	37.7	0.632	(0.504, 0.770)	< 0.001
G ₁ vs H ₁	--	0.959	(0.763, 1.206)	0.720
G ₁ vs G ₂	34.8	0.652	(0.475, 0.896)	0.008
G ₁ vs H ₂	42.0	0.580	(0.437, 0.770)	<0.001
H ₁ vs G ₂	32.1	0.679	(0.493, 0.934)	0.018
H ₁ vs H ₂	39.4	0.606	(0.455, 0.807)	< 0.001
G ₂ vs H ₂	--	0.887	(0.619, 1.273)	0.517

^a Note: P=0.719 for test for interaction between high/low dose candesartan and baseline covariate (cells G₁, H₁, G₂ and H₂ only)
 Cells G₁, H₁, G₂ and H₂ = Reference to cells in Table 45.

However, there are many caveats to these findings:

- (i) The findings are restricted to patients in the candesartan treatment group, i.e., they cannot be analyzed with corresponding placebo groups.
- (ii) Such “within treatment group” analyses are subject to confounding, which limits the ability to interpret findings.
- (iii) Dose level comparisons may not be valid because in the CHARM studies, patients were not randomized to dose level.
- (iv) The observation time will differ by dose level, particularly because the protocol-specified dose escalation treatment regimen means that after the first dose level, the experience at subsequent dose levels is conditional on the experience at the prior dose levels. For

example, a patient hospitalized for CHF in the first 2 weeks would be assigned to the 4 mg dose level and is removed from the risk set. The patient is now no longer at equal risk for hospitalization at any other dose level. Furthermore, this same patient could complete the study at a higher dose and appear in the candesartan high-dose group for the endpoint of discontinuation for an adverse event.

- (v) Please note that for the primary and secondary endpoints, the group with the least events is that receiving NO candesartan at the visit preceding the event or at the last visit if no event occurred.
- (vi) With regard to other heart failure treatments at baseline, there was no randomization to any treatment including ACE inhibitors at recommended dose vs less than heart failure recommended dose.

6.1.6 Efficacy Conclusions

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

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

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

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

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

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

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

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

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

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

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

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

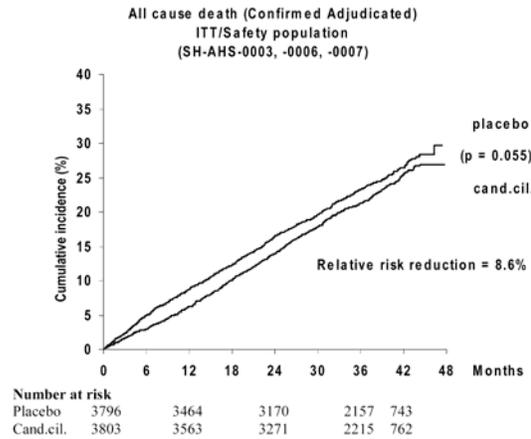


Figure 17 Cumulative incidence (%) of confirmed adjudicated all-cause death in patients with symptomatic CHF over time. ITT/Safety population.

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

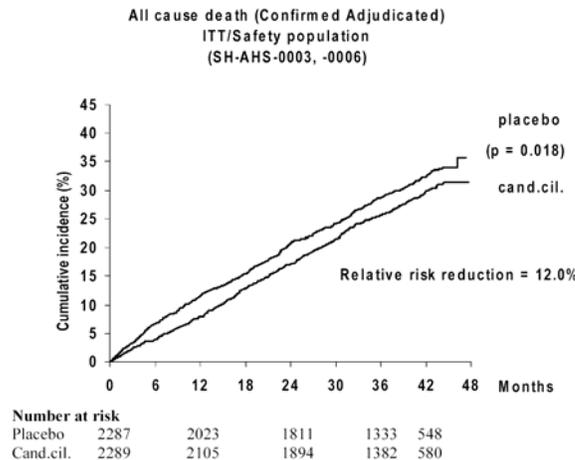


Figure 18 Cumulative incidence (%) of confirmed adjudicated all-cause death in patients with LV systolic dysfunction over time. ITT/Safety population.

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

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

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

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

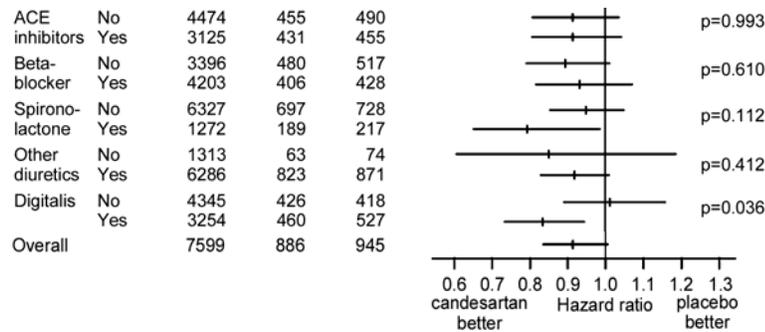


Figure 19 Overall effect of candesartan on all-cause death in subgroups of conventional CHF treatment. Point estimates of hazard ratios given with 95% confidence interval, and P values. ITT/Safety population (SH-AHS-0003, SH-AHS-0006, SH-AHS-0007)

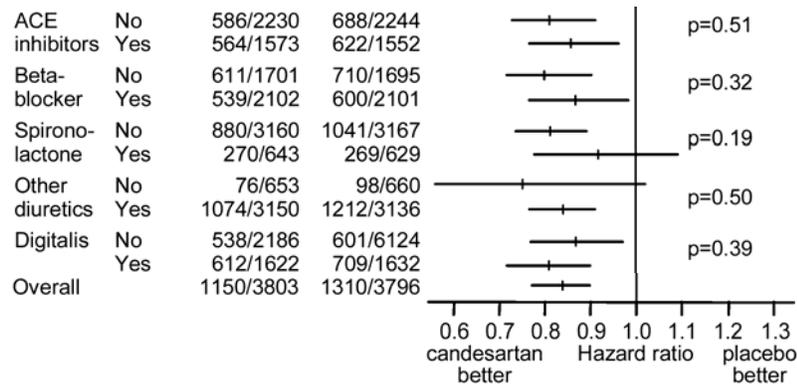


Figure 20 Overall effect of candesartan on CV death or hospitalization in subgroups of conventional CHF treatment. Point estimates of hazard ratios given with 95% confidence interval, and P values. ITT/Safety population (SH-AHS-0003, SH-AHS-0006, SH-AHS-0007).

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

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

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

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

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

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

I think we would need to evaluate the safety findings reported in the CHARM studies in comparison with that observed with use of AT₁-receptor blockers (ARBs) in patients with congestive heart failure as reported in the medical literature, so that we can make an objective assessment of the nature of the adverse events that can arise in patients who have underlying hyperkalemia, hypotension, chronic or acute on chronic renal dysfunction, and other co-morbid diseases such as diabetes, myocardial infarction, etc. In this way, we may be able to evaluate the risk of use of candesartan versus its benefit in the treatment of chronic heart failure in the context of what is occurring with currently available therapies.

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

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

7.1.1 Deaths

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

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

790 patients died during study, of which 413 (32.5%) patients were randomized to placebo and 377 (29.5%) to candesartan. For 6 of the patients who died, the death was incompletely documented (vital status only without specified cause of death). However, all deaths were included in the analysis. One of the patients in the placebo group had an SAE with fatal outcome with date of death after the patient's closing visit. Thus, the death of this patient is included in the descriptive safety results, but not in the exploratory results. I find that this one death is also not included in the efficacy results (Table 30 and Table 31); however, this only makes the statistical analysis more conservative (and less advantageous for candesartan).

The most common fatal AE in both treatment groups during study was sudden death, reported in 174 (13.7%) patients in the placebo group and in 143 (11.2%) patients in the candesartan group (Table 48). Cardiac failure/cardiac failure aggravated was the second most common fatal AE in the placebo and candesartan group (112, 8.8% and 74, 5.8%, respectively).

Table 48 Number (%) of patients with the most commonly reported^a AEs leading to death, sorted by descending frequency in the total population during study. ITT/Safety population (SH-AHS-0006)

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

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

^b Patients having both AEs are counted once only.

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

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

Table 49 Number (%) of patients with symptomatic CHF with the most commonly reported^a AEs leading to death, sorted by descending frequency in the total population during study. ITT/Safety population (SH-AHS-0003, -0006, -0007)

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

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

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

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

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

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

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

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

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

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

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

* percent of all deaths in the treatment group

In the medical literature, death in heart failure trials is usually an efficacy endpoint, and most articles do not discuss deaths under safety. In the only article that describes death under safety, ELITE¹⁹, the primary efficacy endpoint was renal dysfunction, and a composite of death and/or hospitalization was a secondary endpoint. Of 722 patients with NYHA Class II-IV heart failure enrolled, 65 (18.5%) of the losartan-treated patients died or discontinued treatment compared to 111 (30%) captopril-treated patients (P<0.001). In that study, sudden death was the leading cause of death in the captopril-treated group (14 patients, 3.8%) compared to the losartan-treated group (5 patients (1.5%). Progressive heart failure was the cause of death for only 1 patient in each treatment group. The efficacy findings of the ELITE study were not supported by the bigger ELITE II trial²⁰.

7.1.2 Other Serious Adverse Events

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

The most commonly reported non-fatal SAEs during study were cardiac failure/cardiac failure aggravated (450, 35.4%) followed by angina pectoris/angina pectoris aggravated (168, 13.2%) and arrhythmia ventricular (120, 9.4%) in the placebo group, and cardiac failure/cardiac failure aggravated (398, 31.2%), angina pectoris/ angina pectoris aggravated (148, 11.6%) and hypotension (143, 11.2%) in the candesartan group (Table 51).

Table 51 Number (%) of patients with the most commonly reported^a SAEs other than death, sorted by descending frequency. ITT/Safety population (SH-AHS-0006)

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

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

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

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

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

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

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

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

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

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

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

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

7.1.3 Discontinuations and Other Significant Adverse Events

Permanent discontinuations presented descriptively are defined as patients who discontinued treatment with the investigational product permanently, were alive > 5 days after treatment discontinuation and were not on the investigational product at the closing visit. (All patients who died are included in the section on “deaths.”) However, if the investigational product was permanently discontinued, the patient still remained in the study and SAEs were reported during the whole study period. Because of the difference in the definitions of permanent discontinuations in the descriptive and exploratory analyses, there were small differences in the number of patients between the two analyses.

7.1.3.1 Overall profile of discontinuations

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

The study medication was permanently discontinued due to AEs in 224 (17.6%) patients in the placebo group and in 310 (24.3%) patients in the candesartan group.

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

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

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

7.1.3.2 Adverse events associated with discontinuations

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

The most common AEs leading to discontinuation of investigational product are presented in Table 53. A patient could have more than one AE, leading to permanent discontinuation of the investigational product, occurring at the same time.

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

Table 53 Number (%) of patients with the most commonly reported^a AEs leading to discontinuation of investigational product, sorted by descending frequency. ITT/Safety population (SH-AHS-0006)

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

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

b Patients having both AEs are counted once only.

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

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

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

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

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

^a The table uses a cut-off of ≥0.5% in the total population on treatment (N=7599).

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

Reviewer’s comment with data from the literature: Worsening heart failure as the leading cause of discontinuation of study drug is not limited to candesartan (or ARBs). In the Assessment of Treatment with Lisinopril And Survival (ATLAS) trial¹², too, worsening heart failure, dizziness, hypotension and worsening renal function were the leading causes AEs requiring withdrawal of study drug which is an ACE-inhibitor (Table 55).

Table 55 AEs in relation to withdrawal of study drug in ATLAS trial¹² (Based on data from Circulation 1999; 100: 2312-8.)

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

Values in parentheses indicate percentage.

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

In this exploratory presentation of data, the permanent discontinuation of the investigational product due to an AE or abnormal lab value occurred in 233 (18.3%) patients in the placebo group and 310 (24.3%) patients in the candesartan group. Both the difference in time to event (P< 0.001) and the difference in proportions between treatments of 6.0% (P< 0.001) were statistically significant (Table 56, Table 57 and Figure 21).

Table 56 Permanent discontinuation and at least one discontinuation of investigational product due to any cause, an AE or an abnormal laboratory value. Number of patients with at least one event by treatment group and events per 1000 years of follow-up. Follow-up time is calculated to first event. ITT/Safety population (SH-AHS-0006)

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

Table 57 Permanent discontinuation and at least one discontinuation of investigational product due to any cause, an AE or an abnormal laboratory value. Comparison of candesartan versus placebo with Cox regression. ITT/Safety population (SH-AHS-0006)

Variable	N	Events cand. cil.	Events placebo	Hazard Ratio	95% CI		p-value
					Lower	Upper	
Permanent investigational product discontinuation due to any cause	2548	411	319	1.336	1.154	1.547	<0.001
Permanent investigational product discontinuation due to an AE or an abnormal lab value	2548	310	233	1.357	1.145	1.609	<0.001
At least one investigational product discontinuation due to any cause	2548	637	534	1.281	1.142	1.437	<0.001
At least one investigational product discontinuation due to an AE or an abnormal lab value	2548	538	442	1.292	1.139	1.465	<0.001

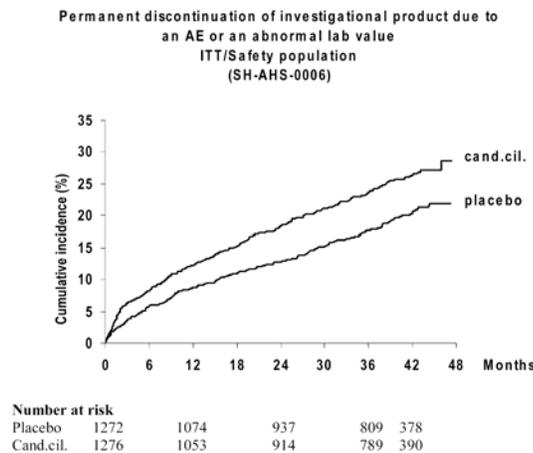


Figure 21 Cumulative incidence (%) of permanent discontinuation of investigational product due to an AE or an abnormal laboratory value. ITT/Safety population

Specific causes of investigational product discontinuation are noted in Table 58. Hyperkalemia and increased creatinine as causes for investigational product discontinuation were statistically significantly more frequent for candesartan; absolute differences in these cause-specific discontinuations relative to placebo were 2.7% and 3.7%, respectively (P< 0.001). For hypotension the absolute difference of 1.4% was not statistically significant (P= 0.066).

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

Table 58 Permanent discontinuation, at least one discontinuation and decreased dose of investigational product due to any cause, an AE, an abnormal laboratory value, hypotension, hyperkalemia or increased creatinine. The difference in proportion (%) between treatments. ITT/Safety population (SH-AHS-0006)

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

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

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

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

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

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

Table 59 Exploratory safety variables for patients with symptomatic CHF. Number of patients with at least one event by treatment group and events per 1000 years of follow-up. Follow-up time is calculated to first event. ITT/Safety population. (SH-AHS-0003, -0006, -0007)

Variable	Treatment	N	Events (No of patients)	Total follow-up time (years)	Events / 1000 follow-up years	Mean follow-up time (years)
Permanent investigational product discontinuation due to any cause	Placebo	3791	969	9355.9	103.6	2.5
	cand.cil.	3788	1135	9177.0	123.7	2.4
Permanent investigational product discontinuation due to an AE or an abnormal lab value	Placebo	3796	633	9937.0	63.7	2.6
	cand.cil.	3803	798	9807.1	81.4	2.6
At least one investigational product discontinuation due to any cause	Placebo	3790	1571	8431.3	186.3	2.2
	cand.cil.	3788	1780	7951.8	223.8	2.1
At least one investigational product discontinuation due to an AE or an abnormal lab value	Placebo	3796	1198	9189.4	130.4	2.4
	cand.cil.	3803	1432	8708.2	164.4	2.3

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

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

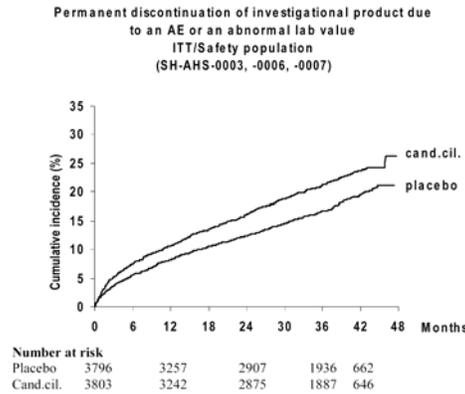


Figure 22 Cumulative incidence (%) of permanent discontinuation of the investigational product due to an AE or an abnormal laboratory value. ITT/Safety population

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

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

Variable	Treatment	N	Number of patients with event	Proportion of patients with event	95% CI	
					Lower	Upper
Permanent investigational product discontinuation due to any cause	Placebo	3796	969	25.5	24.1	26.9
	cand.cil.	3803	1135	29.8	28.4	31.3
Permanent investigational product discontinuation due to an AE or an abnormal lab value	Placebo	3796	633	16.7	15.5	17.9
	cand.cil.	3803	798	21.0	19.7	22.3
Permanent investigational product discontinuation due to hypotension	Placebo	3796	66	1.7	1.3	2.2
	cand.cil.	3803	132	3.5	2.9	4.1
Permanent investigational product discontinuation due to hyperkalaemia	Placebo	3796	21	0.6	0.3	0.8
	cand.cil.	3803	85	2.2	1.8	2.8
Permanent investigational product discontinuation due to increased creatinine	Placebo	3796	115	3.0	2.5	3.6
	cand.cil.	3803	234	6.2	5.4	7.0
At least one investigational product discontinuation due to any cause	Placebo	3796	1571	41.4	39.8	43.0
	cand.cil.	3803	1780	46.8	45.2	48.4
At least one investigational product discontinuation due to an AE or an abnormal lab value	Placebo	3796	1198	31.6	30.1	33.1
	cand.cil.	3803	1432	37.7	36.1	39.2
At least one investigational product discontinuation due to hypotension	Placebo	3796	127	3.3	2.8	4.0
	cand.cil.	3803	274	7.2	6.4	8.1
At least one investigational product discontinuation due to hyperkalaemia	Placebo	3796	42	1.1	0.8	1.5
	cand.cil.	3803	149	3.9	3.3	4.6
At least one investigational product discontinuation due to Increased creatinine	Placebo	3796	182	4.8	4.1	5.5
	cand.cil.	3803	374	9.8	8.9	10.8
Decreased investigational product dose due to any cause at least once	Placebo	3796	482	12.7	11.7	13.8
	cand.cil.	3803	791	20.8	19.5	22.1
Decreased investigational product dose due to an AE or an abnormal lab value at least once	Placebo	3796	385	10.1	9.2	11.1
	cand.cil.	3803	693	18.2	17.0	19.5

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

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

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

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

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

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

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

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

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

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

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

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

Reviewer's comments with data from the medical literature: Adverse events from ARBs in the treatment of patients with CHF appear to lead to more frequent discontinuation of the ARBs (as a class) than placebo. In the Val-HeFT¹⁶ 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 trial²⁵ comparing valsartan, captopril or both in MI complicated by heart failure, LV dysfunction or both, adverse events resulting in permanent discontinuation of study treatment are significantly ($P < 0.05$) more frequent in the Valsartan-plus-captopril group compared to the Valsartan-alone or captopril-alone treatment group (Table 67). Also, dose reductions and permanent discontinuations of study drug for hypotension and renal causes were more frequent in the valsartan-plus-captopril and valsartan-alone groups (Table 67).

Table 67 Adverse Events leading to dose reduction or discontinuation of study treatment in VALIANT trial²⁵ (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)
	<i>number (percent)</i>					
Hypotension	739 (15.1)*	884 (18.2)*	582 (11.9)	70 (1.4)*	90 (1.9)*	41 (0.8)
Renal causes	239 (4.9)*	232 (4.8)*	148 (3.0)	53 (1.1)	61 (1.3)*	40 (0.8)
Hyperkalemia	62 (1.3)	57 (1.2)	43 (0.9)	7 (0.1)	12 (0.2)	4 (0.1)
Cough	85 (1.7)*	225 (4.6)	245 (5.0)	30 (0.6)*	101 (2.1)	122 (2.5)
Rash	32 (0.7)*	53 (1.1)	61 (1.3)	17 (0.3)*	34 (0.7)	39 (0.8)
Taste disturbance	13 (0.3)*	38 (0.8)	31 (0.6)	9 (0.2)*	16 (0.3)	21 (0.4)
Angioedema	12 (0.2)	22 (0.5)	22 (0.5)	9 (0.2)	12 (0.2)	13 (0.3)
Any of the above events†	1112 (22.8)	1404 (28.9)*	1063 (21.8)	197 (4.0)*	332 (6.8)*	280 (5.7)
Any adverse event	1437 (29.4)	1690 (34.8)*	1388 (28.4)	282 (5.8)*	438 (9.0)*	375 (7.7)
Any reason	2103 (43.1)	2342 (48.2)*	2098 (43.0)	1001 (20.5)	1139 (23.4)*	1055 (21.6)

* The difference from the captopril group is significant at $P < 0.05$.

† The totals of the numbers of patients with each type of event are greater than the numbers given for "any of the above events" because in some patients more than one type of event contributed to the decision to reduce the dose or discontinue study treatment.

Table 68 Adverse events causing discontinuation in the OPTIMAAL trial²² (Based on data from Lancet 2002; 360: 752-60.)

	Losartan	Captopril	p
Prespecified events of special interest			
Angio-oedema	10 (0.4%)	22 (0.8%)	0.034
Cough	256 (9.3%)	512 (18.7%)	<0.0001
Hypotension	365 (13.3%)	445 (16.3%)	0.002
Skin rash	86 (3.1%)	126 (4.6%)	0.005
Taste disturbance	16 (0.6%)	73 (2.7%)	<0.0001
Congestive heart failure	401 (14.6%)	383 (14.0%)	0.537
Events causing discontinuation*			
Cough	28 (1.0%)	113 (4.1%)	<0.0001
Hypotension	47 (1.7%)	61 (2.2%)	0.17
Skin rash	3 (0.1%)	18 (0.7%)	0.0008
Dizziness	12 (0.4%)	17 (0.6%)	0.36
Taste disturbance	1 (0.0%)	17 (0.6%)	<0.0001
Angio-oedema	4 (0.1%)	14 (0.5%)	0.019

Information on adverse events was collected during the double-blind treatment period and for 14 days afterwards. Within any category of adverse event, patients could be counted only once, but could be represented more than once across multiple categories of adverse event. *Minimum of 14 patients (0.5%) in either treatment group.

However, in the OPTIMAAL trial²², comparing losartan to captopril on mortality and morbidity in patients with AMI and evidence of heart failure or left ventricular dysfunction, fewer patients on losartan discontinued study medication for any reason (458 patients (17%) on losartan versus 624 (23%) on captopril, HR = 0.70, 95% CI 0.62-0.79, P < 0.0001) or for adverse events (202 patients (7%) on losartan versus 387 patients (14%) on captopril; HR = 0.50; 95% CI 0.42-0.59; P < 0.0001), particularly for AEs such as cough, skin rash, taste disturbance and angioedema (Table 68).

Background treatment with ACE-inhibitors may also be the reason for a high frequency of discontinuation. In the SMILE trial⁶⁰ (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 Study³⁷ of carvedilol on survival in severe chronic heart failure, fewer patients in the carvedilol group than in the placebo group required permanent discontinuation of treatment because of adverse events (P=0.02). The Kaplan-Meier analysis (Figure 23) shows that the cumulative discontinuation rates at one year for the total cohort were 18.5% in the placebo group and 14.8% in the carvedilol groups. The discontinuation rates for patients with recent or recurrent cardiac decompensation or severely depressed cardiac function were 24.2% in the placebo group and 17.5% in the carvedilol group.

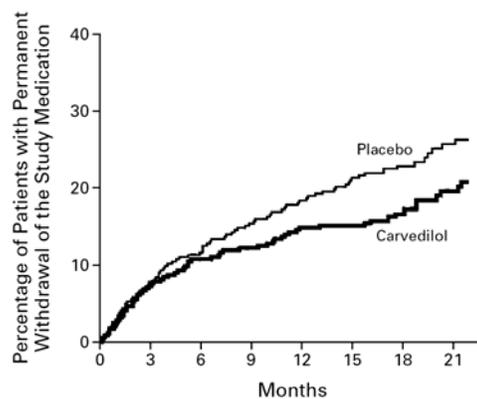


Figure 23 Kaplan–Meier Analysis of the time to permanent withdrawal of the study medication because of adverse reactions or for reasons other than death in placebo and Carvedilol groups in COPERNICUS trial³⁷. The risk of withdrawal was 23% lower in the carvedilol group (95% CI: 4% – 38%; P= 0.02). (Based 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 study²³ comparing losartan versus atenolol in patients with hypertension and ECG evidence of LVH, discontinuations as a result of all AEs, drug-related AEs, and SAEs and drug-related SAEs were significantly less in losartan-treated patients than atenolol-treated patients (Figure 24).

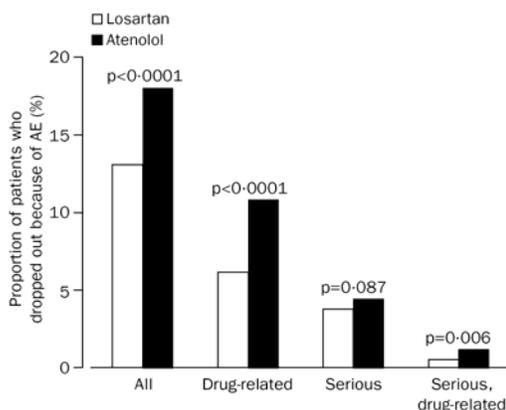


Figure 24 Adverse events resulting in discontinuation of study drug in LIFE study²³ (Based on data from Lancet 2002; 359: 995-1003.)

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

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

In the descriptive analyses, patients who had a reduction of the dose of the investigational product and later permanently discontinued the investigational product for the same reason were counted only in the category of discontinuation; whereas, for the exploratory analysis, these patients were counted as having a reduction of the dose of the investigational product as well as having discontinued treatment with the investigational product. As a result of this difference, the rates of dose reductions were higher in the exploratory safety analyses.

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

The investigational product was reduced in dose due to AEs in 123 (9.7%) patients in the placebo group and in 220 (17.2%) patients in the candesartan group. The most common AEs leading to dose reduction of the investigational product are presented in Table 69.

Table 69 Number (%) of patients with the most commonly reported^a AEs leading to dose reduction of investigational product, sorted by descending frequency in the total population on treatment. ITT/Safety population (SH-AHS-0006)

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

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

^b Patients having both AEs are counted once only.

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

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

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

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

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

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

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

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

Dose reduction of the investigational product due to an AE or abnormal lab value occurred in 153 (12.0%) patients in the placebo group and 265 (20.8%) patients in the candesartan group (Table 58). This between-treatment difference in dose reductions for an AE of 8.8% (Table 58) was statistically significant (P< 0.001). As shown in Figure 25 the majority of events occurred during the first 6 to 12 months of treatment with the investigational product.