AstraZeneca

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ATACAND® (candesartan cilexetil) Tablets
Briefing Document

NDA 20-838/S-022, S-024, S-025

Indication: Heart failure

Cardiovascular and Renal Drugs Advisory Committee Meeting
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OVERVIEW

This document summarizes the clinical data presented in the Supplemental New Drug Applications for ATACAND® (candesartan cilexetil) Tablets in which AstraZeneca LP requested approval for the use of candesartan cilexetil, an angiotensin II receptor blocker (ARB), to treat patients with chronic heart failure (CHF) based on the 3 trials comprising the CHARM program (CHARM-Added, CHARM-Alternative, and CHARM-Preserved). AstraZeneca received an approvable letter in December 2004 for the supplemental application containing the CHARM-Added study. FDA has posed the question whether the beneficial effects of candesartan are evident in the CHARM-Added study for patients receiving a maximum dose of an ACE inhibitor. Please note that Sections 1 to 8 of this document address the pre-specified analyses conducted by the sponsor for the CHARM program. Section 9 of this document, referred to as CHARM-Added Supplemental Analyses, addresses the question from the FDA regarding the beneficial effects of candesartan when added to a maximum dose of an ACE inhibitor.

Heart failure is a serious, progressive, and debilitating condition. Following a first hospital admission for heart failure, only 1 in 2 patients will survive 5 years, with most dying suddenly or from progressive pump failure - a prognosis far worse than many forms of cancer. Furthermore, patients living with CHF typically suffer functional limitations due to shortness of breath, chronic fatigue, and generalized weakness, and these patients face an ever-present risk of hospitalization for recurrent, decompensated heart failure. The burden to patients and to health-care systems is enormous and growing. Therapies that can reduce cardiovascular (CV) mortality and heart failure hospitalizations remain a priority for health care providers as well as for afflicted patients and society.

In spite of the introduction of some effective CHF treatments, notably angiotensin-converting enzyme (ACE) inhibitors and beta-blockers, a pressing need for additional, alternative, and more effective treatments persists:

- CHF mortality rates remain high; patients living with heart failure typically suffer incapacitating symptoms punctuated by repetitive hospitalization. In the United States (US), decompensated heart failure is a leading cause for hospitalization and explains, in part, why CHF accounts for a substantial portion of the cost of caring for older Americans.

- Current treatments are insufficient. Inhibition of the renin-angiotensin-aldosterone-system (RAAS) with ACE inhibitors is established as an effective intervention for CHF patients with left ventricular (LV) systolic dysfunction but many patients do not receive this therapy. Approximately 10% of patients are intolerant to ACE inhibitors. Even patients who tolerate and receive ACE inhibitors are still at risk for sudden or heart failure death and recurrent hospitalization, indicating that ACE inhibitor therapy alone, or in combination with beta-blocker therapy, is often

inadequate. Physicians and their patients require alternative and additional effective treatments.

- Almost half of CHF patients do not have reduced LV systolic function, a traditional clinical diagnostic marker for heart failure. As this is a relatively recent clinical observation, there is a paucity of scientific evidence upon which to formulate 'preserved' systolic function treatment guidelines. CHF patients with preserved LV systolic function have typically been excluded from clinical trials, yet they carry an increased risk for death and heart failure hospitalization. It is now appropriate to evaluate treatments for this understudied segment of the CHF population.

Given the established benefit of inhibiting the RAAS in the CHF patient and recognizing the limitations of current therapy, AstraZeneca undertook a comprehensive program to evaluate candesartan as treatment for CHF. Candesartan is a non-peptide antagonist that selectively binds tightly to, and slowly dissociates from, the angiotensin II type 1 (AT_1) receptor. The ARB heart failure hypothesis suggests that candesartan would benefit patients with CHF as it blocks the effects of angiotensin II at the AT_1-receptor level. Angiotensin II is a primary effector hormone of the RAAS. Angiotensin II is activated in CHF and is a key factor contributing to the symptoms and progression of heart failure. Specifically, angiotensin II induces vasoconstriction, sodium retention with volume overload, norepinephrine release, and cardiac hypertrophy, and increases aldosterone. In patients not receiving RAAS-inhibiting agents, the magnitude of angiotensin II activation is proportional to the degree of CHF, and it relates inversely to survival. These observations suggest that effective angiotensin II blockade could alleviate the morbid and mortal consequences of CHF. Moreover, it is known that angiotensin II production continues in patients receiving ACE inhibitors. Consequently, there might be advantages to the addition of an ARB to an ACE inhibitor.

The clinical investigation of candesartan as a treatment for CHF was conducted by AstraZeneca in cooperation with Takeda Pharmaceuticals and included a total of 12 studies involving more than 10,000 CHF patients: 3 of these trials comprise the CHARM program, "**C**andesartan in **H**eart failure – **A**ssessment of **R**eduction in **M**ortality and morbidity", which included 7601 (7599 with data) New York Heart Association (NYHA) class II to IV CHF patients.

The CHARM trials were initiated following completion of focused pilot/feasibility studies that were used to define a target dose of candesartan and patient populations. In the CHARM program, 3 independent, concurrently conducted, placebo-controlled trials each sought to test the ability of candesartan to improve CV mortality and morbidity for heart failure patients. The trials were conducted by a multinational cohort of investigators with an objective of establishing, collectively, whether candesartan, given together with standard CHF medical therapy, reduces CV mortality and hospitalizations due to CHF, and improves symptoms in a very broad CHF population.

The CHARM trials demonstrated that the ARB, candesartan, as an add-on to standard therapy, is an effective heart failure treatment. Candesartan was effective in patients not receiving an ACE inhibitor (Trial SH-AHS-0003, CHARM-Alternative) and it was incrementally effective

in CHF patients already receiving an ACE inhibitor (Trial SH-AHS-0006, CHARM-Added). These findings were established in a population traditional for heart failure clinical trials, ie, patients with LV systolic dysfunction. A 3rd trial evaluated candesartan in patients with 'preserved' LV systolic function (Trial SH-AHS-0007, CHARM-Preserved); a trend directionally favoring candesartan treatment but which was not statistically significant was observed for the primary endpoint, CV mortality or CHF hospitalization and for the component CHF hospitalization. Lastly, pre-specified analyses evaluated additional hypotheses, including effects on all-cause mortality, based on data pooled across the CHARM trials.

The CHARM program of trials enrolled symptomatic (NYHA class II-IV) CHF patients and determined specifically that:

In CHF patients with depressed LV systolic function receiving an ACE inhibitor (1276 candesartan and 1272 placebo patients) (CHARM-Added)

- Candesartan reduced the risk of 1st occurrence of CV death or CHF hospitalization (primary endpoint) by 15% (hazard ratio [HR]=0.85, 95% confidence interval [CI]=0.75-0.96, p=0.011) over a median follow-up of 41 months. There were 166.3 events/1000 follow-up years in the placebo group and 141.2 events/1000 follow-up years in the candesartan group. To prevent 1 CV death or 1st CHF hospitalization, the number needed to treat with candesartan for 1 year is 40 patients.

- The benefit of candesartan was evident for patients receiving recommended doses of an ACE inhibitor as well as for patients taking lesser doses, as well as for patients taking an ACE inhibitor with or without a beta-blocker.

In CHF patients with depressed LV systolic function and not receiving an ACE inhibitor because of intolerance (1013 candesartan and 1015 placebo patients) (CHARM-Alternative)

- Candesartan reduced the risk of 1st occurrence of CV death or CHF hospitalization (primary endpoint) by 23% (HR=0.77, 95% CI=0.67-0.89, p=0.0003) over a median follow-up of 34 months. There were 182.1 events/1000 follow-up years in the placebo group and 138.1 events/1000 follow-up years in the candesartan group. To prevent 1 CV death or 1st CHF hospitalization, the number needed to treat with candesartan for 1 year is 23 patients.

In patients with depressed LV systolic function (2289 candesartan and 2287 placebo) (2-trials pooled: CHARM-Added plus CHARM-Alternative)

- Candesartan reduced the risk of 1st occurrence of CV death or CHF hospitalization by 18% (HR=0.82, 95% CI=0.74-0.90, p<0.001) over a median follow-up of 40 months. Candesartan also reduced risks for the individual components: CV mortality (HR=0.84, 95% CI=0.75-0.95, p=0.005) and CHF hospitalization (HR=0.76, 95% CI=0.68-0.85, p<0.001). Reductions in sudden death (20% risk

reduction, p=0.013) and death due to heart failure (16% risk reduction, p=0.005) accounted for most of the reduction in CV mortality.

- Total mortality was lower with candesartan (12% relative risk reduction, HR=0.88, 95% CI=0.79-0.98, nominal p=0.018). There were 112.3 deaths/1000 follow-up years in the placebo group and 98.7 deaths/1000 follow-up years in the candesartan group.

In CHF patients with preserved LV systolic function (1514 candesartan and 1509 placebo patients) (CHARM-Preserved)

- Candesartan showed a trend (not statistically significant) to reduce the risk of 1st occurrence of CV mortality or CHF hospitalization (primary endpoint) (HR=0.89, 95% CI=0.77-1.03, p=0.118) and a directionally favorable but not statistically significant trend for reduction in CHF hospitalization.

In CHARM 3-trials pooled (3803 candesartan and 3796 placebo patients), total mortality was lower with candesartan (but not statistically significant) relative to placebo (9% relative risk reduction, HR=0.91, 95% CI=0.83-1.00, p=0.055). There were 88.4 deaths/1000 follow-up years in the placebo group and 81.0 deaths/1000 follow-up years in the candesartan group.

The CHARM program also demonstrated that:

- Candesartan is safe and generally well tolerated as treatment for CHF. This safety and tolerability profile is consistent across population subgroups including the elderly and very elderly, patients intolerant to ACE inhibitors, and patients taking concomitant heart failure treatments including ACE inhibitors (irrespective of dose) and beta-blockers.

- The most common adverse events prompting candesartan discontinuation include hypotension, hyperkalemia, and abnormal renal function and reflect the known pharmacological effects of RAAS inhibition as well as the underlying clinical status of heart failure patients.

- These common adverse events in CHF patients are well recognized, are rarely accompanied by severe consequences and are manageable by usual clinical practices for care of CHF patients, including the very elderly. AstraZeneca has proposed instructions in the labeling suggesting that usual clinical practices include assessments of blood pressure, serum creatinine and serum potassium at baseline, and monitoring with initiation of treatment, during dose escalation, and periodically thereafter.

AstraZeneca proposes an indication for heart failure based on the CHARM-Added and CHARM-Alternative trials in patients with CHF and LV systolic dysfunction showing that candesartan reduces the risk of CV death or CHF hospitalization.

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACE	Angiotensin-converting enzyme
ACE_i	Angiotensin-converting enzyme inhibitor
AE	Adverse event
ARB	Angiotensin II receptor blocker
AT_1 receptor	Angiotensin II subtype 1 receptor
bid	Twice daily
Candesartan	Candesartan cilexetil; the tradename is ATACAND
CEC	Clinical Endpoint Committee
CHARM	Candesartan in Heart failure - Assessment of Reduction in Mortality and morbidity
CHARM-Alternative	Also referred to as Trial SH-AHS-0003, where patients had a left ventricular ejection fraction of ≤0.40 and were not receiving an ACE inhibitor because of a history of intolerance to ACE inhibitors
CHARM-Added	Also referred to as Trial SH-AHS-0006, where patients had a left ventricular ejection fraction of ≤0.40 and were receiving an ACE inhibitor (at their individualized optimal dose)
CHARM-Preserved	Also referred to as Trial SH-AHS-0007, where patients had a left ventricular ejection fraction of >0.40 and an ACE inhibitor was allowed for high risk patients
CHARM 2-trials pooled	Also referred to as the population with depressed left ventricular systolic function or low left ventricular ejection fraction, which includes pooled data from CHARM-Alternative and CHARM-Added
CHARM 3-trials pooled	Also referred to as the overall CHARM population, which includes pooled data from CHARM-Alternative, CHARM-Added, and CHARM-Preserved
CHF	Chronic heart failure
CI	Confidence interval
CPMP	Committee for Proprietary Medicinal Products
CV	Cardiovascular
DRG	Diagnosis-related groups
eGFR	estimated Glomerular Filtration Rate
FDA	Food and Drug Administration

Abbreviation or special term	Explanation
HR	Hazard ratio
IND	Investigational new drug application
ITT	Intention to treat
LVCF	Last value carried forward
LV	Left ventricular
LV ejection fraction	Left ventricular ejection fraction
MDRD equation	Modified Diet Renal Disease equation
MI	Myocardial infarction
NYHA	New York Heart Association
NOS	Not otherwise specified
RAAS	Renin-angiotensin-aldosterone system
RESOLVD	Randomized Evaluation of Strategies for Left Ventricular Dysfunction
SAE	Serious adverse event
SBP	Systolic blood pressure
SPICE	Study of Patients Intolerant of Converting Enzyme Inhibitors
Study SH-AHS-008	This is a pilot study that is also known as Protocol 211 under IND 50,115 since there was a dual numbering system in use prior to the merger between AstraMerck, Inc. and Astra Pharmaceuticals LP
Swedish MPA	Swedish Medical Products Agency
tid	Three times daily
UK MHRA	United Kingdom Medicines and Healthcare products Regulatory Agency
US	United States

1. SCIENTIFIC BACKGROUND AND PROGRAM RATIONALE

CHF is a common, life-threatening, progressive, disabling clinical syndrome, which is usually consequent to underlying ischemic, hypertensive, or idiopathic cardiomyopathic heart disease. More than 5 million Americans suffer from CHF and 500,000 new cases are identified each year (Jessup and Brozena 2003). In contrast to the overall decline in cardiovascular morbidity and mortality since the 1970's, incident CHF remains unchanged in men and has only slightly declined for women (Levy et al 2002). Moreover, after adjusting for competing risks, the lifetime risk for developing CHF remains almost 25%, no matter what an individual's age (Lloyd-Jones et al 2002). In spite of the introduction of some very effective therapies, notably ACE inhibitors and beta-blockers, the prognosis for the CHF patient remains dismal. Once diagnosed with CHF, a patient has only about a 50% chance of surviving an additional 5 years (Vasan et al 1999) and patients 'living with heart failure' typically suffer functional limitations due to dyspnea on exertion, fatigue, edema, and pulmonary congestion, and require repetitive hospitalization. It is not surprising, then, that in the US heart failure is a leading diagnosis-related groups (DRG) reason for hospitalization and that heart failure accounts for a substantial portion of the cost of caring for older Americans (Jessup and Brozena 2003).

Historically, heart failure treatment relied on salt restriction, digitalis, and then diuretics to alleviate symptoms and congestion. The advent of ACE inhibitors and subsequent clinical trials demonstrated that drug therapy could also prolong survival and reduce the burden of CHF hospitalization (The CONSENSUS Trial Study Group 1987, The SOLVD Investigators 1991). With the introduction of agents that directly block the angiotensin II receptor, new questions were raised. Could ARBs effectively inhibit the RAAS in the CHF patient? Could they do so and avoid some of the bothersome ACE inhibitor side effects such as protracted cough? Would there be an incremental benefit if an ARB were used together with an ACE inhibitor? The scientific basis for the expectation of additive benefits followed the discovery of alternative pathways for angiotensin I conversion to angiotensin II, and the potential for 'ACE inhibitor escape' in patients receiving ACE inhibitor monotherapy. These therapeutic questions persist and the role of pharmacologic blockade of the angiotensin receptor has remained an unresolved issue for contemporary heart failure treatment guidelines.

Further clinical trial research also demonstrated survival benefits with the beta-blockers metoprolol succinate (extended release), carvedilol, and bisoprolol (MERIT-HF Study Group 1999, Packer et al 2001, CIBIS II Investigators and Committees 1999), and reduced CHF hospitalization rates with digitalis, but without a mortality benefit (The Digitalis Investigation Group 1997).

Despite the availability of diuretics, ACE inhibitors, beta-blockers, and digitalis, mortality and CHF hospitalization rates remain high among CHF patients, and even those receiving optimal treatment may experience incapacitating symptoms (McMurray 2000, Swedberg 2002). These facts illustrate the need for CHF treatments that further reduce CV mortality and CHF hospitalization and improve functional status. In addition, side effects prohibit treatment of approximately 10% of CHF patients with ACE inhibitors (Kostis et al 1996, Bart et al 1999)

and deter the use of these agents for even more patients (Masoudi et al 2004), findings that further underscore the need for agents that effectively inhibit the RAAS but which carry a lower risk for troublesome side effects.

ARBs provide an additional therapeutic option for attenuation of the deleterious effects of the RAAS in CHF patients. One hypothesis, that addition of an ARB to the therapy of CHF patients already taking an ACE inhibitor would provide additional benefit, was tested in the Valsartan Heart Failure Trial (Cohn et al 2001). The Val-HeFT trial found that adding valsartan (target dose 160 mg twice daily [bid]) to conventional treatment (including ACE inhibitors in 93% of patients and beta-blockers in 35%) for CHF patients with low ejection fraction (<40%) decreased the risk of the primary, composite endpoint of death or cardiovascular morbidity by 13%. However, there was no apparent effect of valsartan on either total or cardiovascular mortality. The beneficial effect on the composite endpoint was attributable to a 24% reduction in first adjudicated hospitalization for heart failure. However, subgroup analyses suggested little evidence of additional benefit with valsartan among patients receiving higher doses of an ACE inhibitor. In another subset analysis of 1610 patients (32% of the trial population) who were given both ACE inhibitors and beta-blockers at baseline, the addition of valsartan was unexpectedly associated with worse outcomes. A subset analysis of 366 patients who were not taking ACE inhibitors at baseline ostensibly because of intolerance (7% of the trial population), indicated that the addition of valsartan provided mortality and morbidity benefits. In August 2002, the FDA approved the supplemental application containing the Val-HeFT study for the use of valsartan for the treatment of heart failure (NYHA class II-IV) in patients who are intolerant of ACE inhibitors based on the data on reduction in heart failure hospitalizations. In the FDA review-documentation supporting the approval of valsartan for use in the treatment of heart failure, FDA commented that because of the limited data (n=366 patients) available for valsartan, the valsartan indication was limited to patients who are intolerant rather than for use as a substitution for treatment with ACE inhibitor. Also, the approved labeling for valsartan indicates that 1) there is no evidence that valsartan provides added benefits when it is used with an adequate dose of an ACE inhibitor and, 2) concomitant use with an ACE inhibitor and a beta-blocker is not recommended.

In addition, Novartis announced in December 2003 that it had filed a supplemental application with the FDA based on the results of the VALIANT trial (Pfeffer et al 2003), which evaluated valsartan compared to or when added to an ACE inhibitor in post (0.5 to 10 days) myocardial infarction (MI) patients with LV systolic dysfunction. In VALIANT, valsartan (target dose 160 mg bid) and captopril (target dose 50 mg 3 times daily [tid]) had virtually identical effects on the primary endpoint of all-cause mortality. However, valsartan (80 mg bid) in combination with a full dose of ACE inhibitor (captopril) provided no more benefit on all-cause mortality than monotherapy with either the ACE inhibitor or valsartan (160 mg bid), but the combination did increase the incidence of adverse events. There was no negative interaction of valsartan in combination with an ACE inhibitor and beta-blocker reported in this study. In VALIANT, only approximately 15% of this post-MI population had a history of CHF and only a minority were on an ACE inhibitor prior to the index MI.

The traditional pathophysiologic heart failure model attributes the clinical syndrome of heart failure to depressed LV systolic function (usually a LV ejection fraction <0.40), and to its attendant consequences. In fact, patients fulfilling this criterion constitute the population evaluated in nearly all heart failure clinical trials to date. However, almost half the patients with clinical heart failure have 'preserved' LV systolic function, which for the purposes of the CHARM program was defined as an LV ejection fraction >0.40 (Redfield et al 2003). In these patients, cardiac contractility appears close to normal or normal but cardiac function is abnormal, with impaired cardiac output, especially during activity. The patients experience elevated ventricular filling pressures, pulmonary congestion, and edema, but they do not typically develop large dilated hearts characteristic of CHF patients with depressed LV systolic function (Redfield 2004, Zile et al 2004). Observational data indicate that the CHF patient with preserved LV systolic function is older, more likely female, more likely to have underlying hypertension, and relatively less likely to die from a CV cause. Although mortality among these patients is not as high as for patients with depressed LV systolic function, it is elevated about 3-fold relative to individuals free of CHF (Vasan et al 1999). Recurrent heart failure hospitalizations, which are generally similar in frequency to those in patients with depressed LV systolic function, are a hallmark of the preserved LV systolic function population. Because CHF patients with preserved LV systolic function have traditionally been excluded from major clinical trials, there is little direct evidence to guide treatment recommendations for these patients.

When undertaking evaluations of a CHF population with LV systolic function impairment, it is important to note that most CHF clinical trials that have demonstrated benefit have done so in patients with LV ejection fraction ≤0.35 or <0.40 (The SOLVD Investigators 1991, Cohn and Tognoni for the Valsartan Heart Failure Trial Investigators, 2001). However, strict demarcation of benefit based on any specific LV ejection fraction cut-point still remains arbitrary and fails to recognize that in all likelihood, patients represent a spectrum of LV dysfunction severity and differing pathophysiological mechanisms.

Given the established benefit of RAAS inhibition in the management of the CHF patient and the recognized limitations of contemporary treatments, AstraZeneca undertook a comprehensive program to evaluate candesartan as treatment for CHF in a program of studies known as CHARM.. Candesartan, a non-peptide analogue of angiotensin II, selectively binds to the angiotensin II type 1 (AT_1) receptor with high affinity and slow dissociation, blocking access of angiotensin II. Angiotensin II is activated in CHF and is a key factor contributing to the symptoms and progression of CHF. Specifically, angiotensin II induces vasoconstriction, sodium retention with volume overload, norepinephrine release, and cardiac hypertrophy, and increases aldosterone. In patients not receiving RAAS-inhibiting agents, the magnitude of angiotensin II activation is proportional to the degree of CHF, and it relates inversely to survival (Francis et al 1990, Swedberg 2000), a finding that suggests that direct therapeutic blockade of angiotensin II could alleviate the mortal and morbid consequences of CHF.

1.1 Regulatory background

Candesartan was approved in the US in 1998 for the treatment of hypertension and is currently approved for this indication in 92 countries, including European countries, Canada, Australia,

and Japan. For treating hypertension in the US, the approved maximum daily dose of candesartan is 32 mg and the usual starting dose is 16 mg. Fixed-dose combination tablets containing candesartan and hydrochlorothiazide (16 mg-12.5 mg, and 32 mg-12.5 mg tablets) were approved in the US in 2000 for the treatment of hypertension and are currently available in 60 countries. In September 2002, the Division of Cardio-Renal Drug Products revised the labeling for candesartan to include information comparing the antihypertensive effects of candesartan cilexetil and another ARB, losartan potassium, at their highest recommended doses when administered once-daily. Candesartan 32 mg lowered systolic and diastolic blood pressure by 2 to 3 mm Hg on average more than losartan potassium 100 mg, when measured at the time of either peak or trough effect.

In November 2004, candesartan was approved in 14 European countries for the treatment of heart failure. Other countries have also granted approval to use candesartan for the treatment of heart failure as follows: Latvia (October 2004), Mexico (October 2004), Slovakia (December 2004), and New Zealand (December 2004).

Investigational New Drug (IND) application (IND 50,115) for candesartan as treatment for heart failure was submitted to the Division of Cardio-Renal Drug Products of the FDA in March 1996. Under this IND, AstraZeneca conducted the pilot studies RESOLVD (Study SH-AHS-0001), SPICE (Study SH-AHS-0002), and Study SH-AHS-0008 to define key design elements, including dose and study population, for the definitive efficacy, safety, and tolerability program, known as CHARM, Candesartan in Heart failure – Assessment of Reduction in Mortality and morbidity". Three trials comprise the CHARM program, which included New York Heart Association (NYHA) class II to IV CHF patients. The trial protocols specified broadly inclusive, common eligibility criteria except for the following key distinguishing features:

> CHARM-Added (Trial SH-AHS-0006) - LV ejection fraction ≤0.40 and already receiving an ACE inhibitor at an optimum individualized dose
>
> CHARM-Alternative (Trial SH-AHS-0003) - LV ejection fraction ≤0.40 and not receiving an ACE inhibitor because of a history of intolerance to ACE inhibitors
>
> CHARM-Preserved (Trial SH-AHS-0007) - LV ejection fraction >0.40 and ACE inhibitors allowed in high-risk patients

Before program initiation, the design of the CHARM trials was discussed with the Division of Cardio-Renal Drug Products and with the Swedish Medical Products Agency (MPA); the design was considered adequate to support a claim for heart failure. An End-of-Phase II meeting between the sponsor and the Division of Cardio-Renal Drug Products was held on 20 October 1998. This meeting included a discussion of the proposed claim structure, endpoints, statistical analysis, collection of safety data, monitoring and reporting approach, and collection of concomitant medication data.

The Division of Cardio-Renal Drug Products provided the following key comments at the End-of-Phase II meeting in regard to the proposals made by AstraZeneca:

- The descriptions of the trials (in labeling) would depend upon the results of the trials.

- There should be some adjustment of the p-value for the total mortality endpoint from the pooled data.

- The trials should be stopped only for all-cause mortality, not morbidity. The decision to stop a trial should be independent of the other trials (the decision to stop 1 trial does not mean that the other trials should also stop).

- The 2 low ejection fraction studies (patients with LV ejection fraction ≤40%) could support a claim. Although drugs are currently labeled for the treatment of heart failure, generally, without reference to ejection fraction, the Division summarized that most patients are in fact low ejection fraction patients.

- The Division would like medications routinely prescribed for non-serious adverse event (AE) conditions and in addition concomitant medications for the treatment of CHF or other cardiovascular diseases to be recorded (the dose need not be recorded for these medications).

- The Division agreed with the proposal to collect routine laboratory data at baseline, at the end of the study dose titration, and at yearly intervals for the North American subset of patients.

While the trials were in progress in the Spring of 2002 (with the blinding maintained), AstraZeneca also met with the United Kingdom Medicines and Healthcare products Regulatory Agency (UK MHRA) to obtain agreement about the organization of the clinical data from the CHARM trials, potential interpretation of these data, and an overall submission filing strategy.

The draft Statistical Analysis Plan for the CHARM program was submitted to the Division of Cardio-Renal Drug Products for review in February 2003. The Division returned comments in March 2003, and these comments were taken into consideration before completion of the statistical plan in advance of analysis of the data.

In August 2004, the Division informed AstraZeneca that the supplemental application supported by the CHARM-Added study was assigned a "Priority (P)" review classification since these results demonstrated the potential to demonstrate a significant medical improvement over other available therapies currently on the market.

In December 2004, the FDA issued an approvable letter for the supplemental application containing the CHARM-Added study. FDA has posed the question of whether the beneficial effects of treatment with candesartan are evident when candesartan is used in a patient receiving a maximum dose of an ACE inhibitor in the CHARM-Added study. Sections 1 to 8 presented in this document were prepared to assist the Cardiovascular and Renal Drugs Advisory Committee with background information on the CHARM program and Section 9

contains the supplemental analyses for CHARM-Added that were conducted to assist with review of the questions raised by FDA.

1.2 CHARM program

As an overall goal, the candesartan heart failure program sought to investigate the effect of candesartan on the unmet medical need associated with RAAS inhibition in CHF. One of the major goals of the candesartan heart failure program was to address the therapeutic hypothesis of incremental benefit of AT II type 1 receptor blockade plus inhibition of AT II generation. This facet of the program was designed to compare candesartan to placebo in a population already treated with ACE inhibitors, to perform the necessary pilot studies to determine the feasibility of this approach and of the proposed dosing regimen, and to estimate the tolerability of adding candesartan to a therapeutic regimen that also included an ACE inhibitor at a dose proven to be effective in CHF. Accordingly, the RESOLVD pilot study (SH-AHS-0001) in a total of 768 patients demonstrated that candesartan at doses up to 16 mg once daily was generally well tolerated in patients taking the ACE inhibitor enalapril (10 mg bid). In addition, this study described additive effects of candesartan and enalapril on neurohormonal responses and a dose-related decrease in LV systolic volume with candesartan plus enalapril compared with enalapril alone. Furthermore, co-administration of metoprolol succinate (an extended release beta-blocker) with candesartan and enalapril decreased LV systolic volume and increased LV ejection fraction compared to the combination of candesartan and enalapril alone. However, it was not apparent from RESOLVD that maximum efficacy was achieved with the 16 mg candesartan dose, or whether higher doses would be tolerated. Subsequently, pilot Study SH-AHS-0008 (98 patients) established the tolerability of a dosing regimen starting at 8 mg and escalating biweekly to 32 mg once daily in NYHA Class IIb - IV CHF patients already receiving an ACE inhibitor.

Another major goal of the CHARM program was to address the hypothesis of the benefit of direct inhibition of the AT II type 1 receptor and to quantify the effect by comparing candesartan treatment with placebo in the absence of background ACE inhibitor treatment, a therapy that has been proven beneficial in CHF patients with LV systolic dysfunction. The ethical constraint of prohibiting ACE inhibitor treatment in CHF study subjects led to the proposal to conduct the investigation in LV systolic dysfunction patients with known intolerance to ACE inhibitors as a suitable population, a proposal which was reviewed and deemed acceptable to the Division of Cardio-Renal Drug Products. The AstraZeneca proposal was based on the scientific rationale that patients who are ACE inhibitor intolerant are not more likely to tolerate candesartan than “ACE inhibitor-naive patients” and, patients who are ACE inhibitor intolerant are not more likely to benefit from candesartan than “ACE inhibitor-naive patients”. Therefore, the ethically driven strategy to establish a benefit of treatment with candesartan in the CHARM-Alternative trial would support the use of candesartan in patients as an alternative to an ACE inhibitor and not be exclusively limited to use in ACE inhibitor-intolerant patients. Secondly, if tolerability was established, CHARM-Alternative would address another important unmet medical need. Initially, when the CHARM program was designed, it was not known if it was feasible to identify or to recruit such a population, or whether patients intolerant to ACE inhibitors could, in fact, tolerate the ARB, candesartan. Accordingly, pilot studies addressed these questions.

Specifically, in the SPICE study of 270 CHF patients with depressed LV systolic function and intolerance to ACE inhibitors, candesartan was generally well tolerated (Study SH-AHS-0002). A SPICE registry of 9580 patients also estimated that 9% of heart failure patients experience intolerable side effects with ACE inhibitors and enumerated the most common reasons for ACE inhibitor intolerance (Bart et al 1999).

A third goal of the CHARM program was to evaluate candesartan as treatment for CHF patients with preserved LV systolic function. No pilot studies specific to this therapeutic hypothesis were undertaken; rather, the trial assumptions were based on the limited data available at the time, largely the recently published DIG study (The Digitalis Investigation Group 1997).

The CHARM program investigators estimated that by 'bundling' the 3 trials into a single program conducted with the same cohort of investigators, it was feasible to collectively include the broadest possible population of patients, to follow patients long-term, and to do so in an acceptable, contemporary framework and acceptable timeframe.

Recognizing the importance of all-cause mortality as an endpoint and the increasing interest in total mortality by regulatory authorities, the 3 CHARM trial protocols were amended to include the composite endpoint of all-cause mortality or CHF hospitalization and the component all-cause mortality as 'high-level' secondary endpoints. In addition, the original study protocols analysis plans pre-specified all-cause mortality in the broadest population (CHARM 3-trials pooled) and in the population with LV systolic dysfunction (CHARM 2-trials pooled).

Trial design features

The CHARM trials (SH-AHS-0006, SH-AHS-0003, and SH-AHS-0007) were randomized, double-blind, placebo-controlled, parallel-group, multicenter, multinational trials that were conducted concurrently at the same trial sites, using uniform procedures for randomization and ascertainment of endpoints. The trial design was typical for 'survival' studies where every effort is made to follow-up all patients to the final, common closing date and to analyze data according to the intent-to-treat (ITT) principle.

The clinical trials began on 22 March 1999 and the last patient completed on 31 March 2003. To assure that trial findings would prove representative of long-term treatment, the trial protocols specified a minimum patient follow-up time of 2 years (estimated median follow-up of about 3 years). Participation continued for all enrolled patients until a date no later than 31 March 2003.

Figure 1 provides the key design features in the CHARM trials and Figure 2 outlines the study dose titration and visit schedules.

Figure 1 **Diagram of the key design features of the CHARM program**

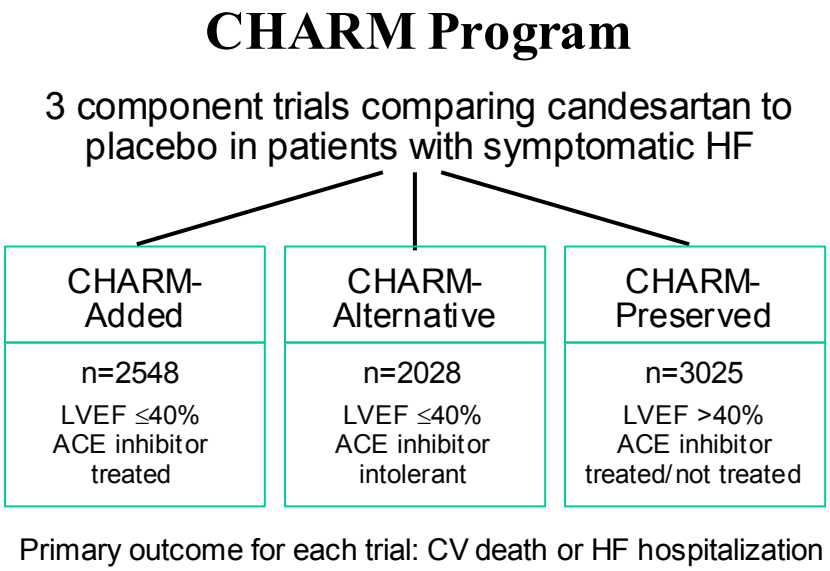
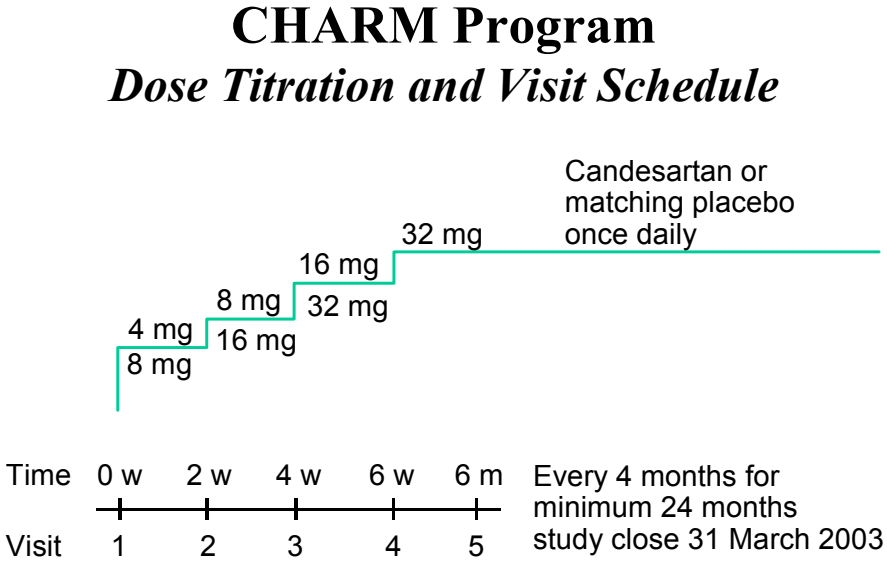


Figure 2 **CHARM dose titration and visit schedule**



Efficacy endpoints

The composite endpoint of CV mortality or hospitalization for CHF served as the primary endpoint in each of the 3 CHARM trials. This composite endpoint was specified as primary within each trial as it best reflects the chief mortal and morbid consequences of CHF and it is the principal therapeutic target of the drug under study.

Secondary endpoints included all-cause mortality or CHF hospitalization, and CV mortality or CHF hospitalization or nonfatal MI (Table 1). The composite of all-cause mortality or CHF hospitalization was included as a secondary endpoint because of the emphasis placed on all-cause mortality by the European Regulatory Authorities (Committee for Proprietary Medicinal Products [CPMP] guidelines [CPMP, 1999]). This endpoint was also selected with the intent of supporting an all-cause mortality claim based on 1 or more trials, consistent with the CPMP guidelines. Nonfatal MI was added to the primary composite endpoint (CV mortality or hospitalization for CHF) due to the established role of RAAS inhibitors as a post-MI treatment. The protocol-specified endpoints in the confirmatory analyses were identical for each of the 3 CHARM studies and are outlined in Table 1.

Table 1 Primary and secondary endpoints for CHARM trials

	Endpoints[a] in CHARM-Added, CHARM-Alternative, and CHARM-Preserved
Primary endpoint	CV mortality or hospitalization for CHF
Secondary endpoints	All-cause mortality or hospitalization for CHF
	CV mortality or hospitalization for CHF or nonfatal MI

[a] Protocol-specified endpoints for confirmatory analysis.

The primary and secondary endpoints were based on the final Clinical Endpoint Committee (CEC) classification of trial events (adjudicated events). In its classification of trial events, the CEC was directed to classify all deaths as cardiovascular unless there was compelling evidence to the contrary. The CEC criteria for a CHF hospitalization required evidence of hospital admission primarily for worsening of chronic heart failure, necessitating at least intravenous diuretic treatment and an overnight stay.

Time from randomization to the 1st occurrence of a trial endpoint served as the analysis efficacy variable. Patients who did not reach the endpoint or who reached a competing terminal endpoint (eg, death for a different cause) were censored at the end of the trial or the time when they ceased to remain at risk.

The components of the composite endpoints (CV mortality, CHF hospitalization, all-cause mortality, and nonfatal MI) were also analyzed as individual endpoints.

The primary and secondary trial endpoints were analyzed in a hierarchical sequential manner (confirmatory strategy) using a closed test procedure (to control the overall alpha level at 0.05 for the overall analysis) according to the order listed in Table 1. Pre-specified analyses were

also performed on the overall pooled population of the CHARM 3-trials pooled to determine whether candesartan reduced all-cause mortality in this broad CHF population. Another pooled analysis was pre-specified to determine whether candesartan reduced all-cause mortality in the population of patients with depressed LV systolic function (2-trials pooled, CHARM-Alternative and CHARM-Added). These 2 mortality endpoints were also analyzed in a hierarchical, confirmatory testing strategy using a closed test procedure (Table 2).

Table 2 Primary and secondary endpoints for pooled populations

	Endpoints[a] in the pooled populations
Primary endpoint	All-cause mortality in the 3-trial pooled population (CHARM-Added, CHARM-Alternative, and CHARM-Preserved)
Secondary endpoint	All-cause mortality in patients with depressed LV systolic function in the 2-trial pooled population (CHARM-Added and CHARM-Alternative)

[a] Protocol-specified endpoints for confirmatory analysis.

Treatments and doses

In the CHARM trials, the target dose of candesartan was 32 mg once daily (the tolerability of the 32 mg dose was established in the pilot study SH-AHS-0008 in NYHA class IIb - IV CHF patients). Patients received candesartan (or matching placebo) beginning at 4 mg or 8 mg once daily, with dose escalation (by doubling the dose) at 2-week intervals to the target dose of 32 mg once daily or the highest tolerated dose. The dose could be lowered when considered necessary. The trial protocols suggested that investigators start with 4 mg for patients at higher risk for hypotension or other adverse effects.

Except for ARBs, investigators were encouraged to treat patients with other heart failure treatment drugs as appropriate, including diuretics, digitalis, beta-blockers, an aldosterone antagonist, and any combination of these drugs. As mentioned above, there were protocol-specified directives regarding ACE inhibitors. CHARM-Added required treatment with an ACE inhibitor at a stable dose considered optimal for each individual patient. CHARM-Alternative prohibited the use of ACE inhibitors (for ethical reasons, the trial was limited to patients known to be intolerant of these agents). CHARM-Preserved allowed ACE inhibitors for high-risk patients according to the inclusion criteria for the HOPE study (The HOPE investigators 2000).

Trial populations

Overall, the CHARM program was designed to include a wide population of CHF patients receiving treatment currently considered as standard. The 3 independent CHARM trials included essentially different, complementary populations of CHF patients in order to address similar hypotheses relevant to the efficacy of candesartan in the treatment of CHF. Furthermore, within each trial, eligibility criteria imposed as few restrictions as possible.

Common inclusion criteria for all 3 studies included symptomatic CHF (NYHA class II to IV) for ≥4 weeks and age ≥18 years. Assignment to the individual studies was dependent on the patient's LV ejection fraction and tolerance to ACE inhibitor treatment.

The exclusion criteria in the CHARM trials were minimal but specified usual criteria for CV mortality/morbidity outcome studies, such as presence of any non-cardiac disease (eg, cancer) that was likely to shorten life expectancy to less than 2 years, significant liver disease, or severe pulmonary disease. Patients were also excluded for the following reasons: stroke, MI, or performed (or planned) cardiac surgery within 4 weeks, uncontrolled hypertension or symptomatic hypotension, serum creatinine ≥265 μmol/L (≥3 mg/dl), serum potassium ≥5.5 mmol/L, a history of marked ACE inhibitor-induced hyperkalemia, or known bilateral renal artery stenosis. Consistent with prescribing admonitions for all ARBs and ACE inhibitors, the trials excluded women of childbearing potential who were not using an accepted method of contraception.

In CHARM-Added, patients were eligible for randomization if they had an LV ejection fraction ≤0.40 and NYHA class II to IV CHF. (Patients in NYHA class II had an additional requirement for a hospitalization for a cardiac condition within the past 6 months). In addition, patients were required to receive an ACE inhibitor at a dose that the investigator determined was optimal, taking into consideration target dose levels proven effective in clinical outcome trials as well as the patient's ability to tolerate the ACE inhibitor. Investigators were directed to document that each patient was receiving an individualized optimum dose of an ACE inhibitor and to maintain the dose for 30 days prior to randomization.

CHARM-Alternative specified enrollment of NYHA class II-IV patients with LV ejection fraction ≤0.40 and who were intolerant to ACE inhibitors. Treatments other than ARBs and ACE inhibitors (eg, beta-blockers and diuretics) were encouraged, but the protocol recommended stabilization of dose levels before trial entry.

The CHARM-Preserved trial enrolled NYHA class II to IV patients with preserved LV systolic function, ie, LV ejection fraction >0.40. The protocol required that patients have a history of hospitalization for a cardiac condition and that the patients' signs and symptoms were primarily due to heart failure and not explained by other conditions. Initially, only patients who did not require ACE inhibitor treatment were included. Following publication of the HOPE trial (The HOPE Investigators 2000), the protocol was amended to allow ACE inhibitor treatment under specified (HOPE trial) criteria defining high-risk patients.

Statistical considerations

Each of the 3 trials in the CHARM program was powered to detect a clinically meaningful reduction in the primary composite endpoint of cardiovascular mortality or hospitalization for heart failure. Pooling the trials also provided an opportunity to analyze all-cause mortality as an endpoint with sufficient power. The sample size for the pooled analysis was not, however,

determined specifically for the all-cause mortality endpoint; rather, the sample size was 'inherited' as the sum of the sizes in the individual trials.

The trial protocols allowed for an interim re-examination of the sample size calculation assumptions for the 3 trials based on blinded event rate estimates. Accordingly, there was a one-time increase in trial sample sizes because observed blinded event rates were lower than pre-trial estimates.

The primary efficacy analyses were based on the ITT population, using events adjudicated and confirmed by the CEC. The primary analyses were performed on the time-to-event variables using a logrank test (stratified by study in the pooled populations). Hazard ratios (HRs) and confidence intervals (CIs) were derived from Cox proportional hazards models, stratified by study in pooled analyses, with treatment as the only explanatory factor. Treatment-by-covariate interactions were also evaluated with Cox models. Time-to-event variables were summarized graphically using the complementary probabilities estimated by the Kaplan-Meier method. Numbers needed-to-treat per year were calculated as the reciprocal of the difference in event rates per thousand patient-years, using the cumulative follow-up time in each study.

A confirmatory testing strategy was employed in the analysis of the primary and 2 secondary efficacy endpoints. The overall alpha level (0.05) for the 3 significance tests was controlled by way of a closed testing procedure, in accordance with guidance provided in CPMP "Points to consider on multiplicity issues in clinical trials" (CPMP 2002). The closed testing procedure applies the same nominal alpha level to the secondary endpoints in a fixed stepwise fashion provided the primary endpoint is significant at the same level. The CPMP document notes that this would allow significant effects on secondary endpoints to serve as the basis for additional claims. (Specifically, the CPMP guidelines recommend inclusion of all-cause mortality as a high-level endpoint or component of a high-level endpoint to support approval for a heart failure indication.) In the individual CHARM trials, there were 3 endpoints in the confirmatory analysis: the primary endpoint (CV mortality or CHF hospitalization), and 2 secondary endpoints (1st, all-cause mortality or CHF hospitalization, and 2nd, CV mortality, CHF hospitalization, or nonfatal myocardial infarction). A confirmatory strategy was also used for analysis of all-cause mortality in the pooled population analyses, with all-cause mortality in the 3-trials pooled as the first level, and all-cause mortality in the 2-trials pooled in patients with depressed LV systolic function as the second level. Other endpoints, including components of the previously noted composite endpoints, were analyzed with the same statistical tests and regression methods but without correction for multiplicity. Unless otherwise indicated, all p-values less than 0.05 were deemed to be statistically significant. Nominal p-values and confidence intervals are reported throughout this document.

Recurring CHF hospitalizations were also analyzed using investigator-reported evaluations because adjudication by the CEC stopped at the 1st determined CHF hospitalization. For each patient, the number of events divided by the total follow-up time on investigational product was calculated. The distribution of these frequencies within each treatment group was compared with a 2-sided Wilcoxon rank sum test. Also, change from baseline in number of

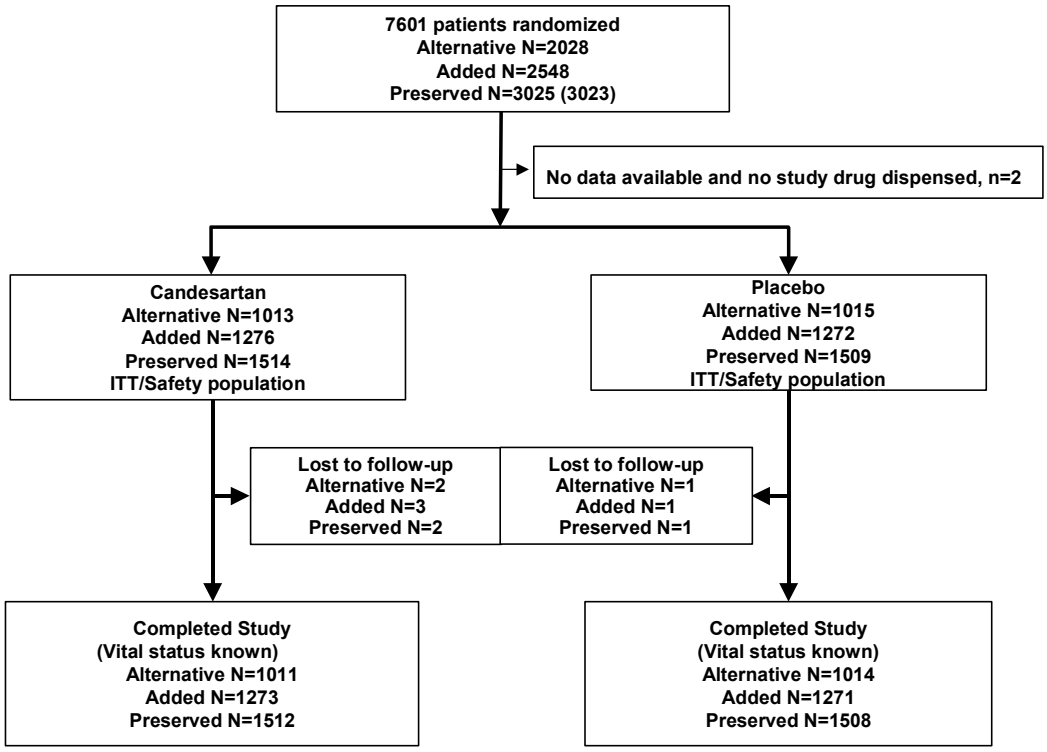
NYHA classes was compared between treatments using a Wilcoxon rank sum test, carrying forward the value of the last visit (LVCF).

A Data Monitoring Committee performed 6 planned interim analyses for safety/efficacy based on the endpoint of all-cause mortality for the pooled population of all CHARM patients. The recommendation at each interim analysis was to continue all CHARM trials. To account for sequential testing of all-cause mortality, p=0.0492 served as the critical value for statistical significance in the final analysis of all-cause mortality in the CHARM 3-trials pooled population.

2. PATIENT DISPOSITION

The CHARM trials began 22 March 1999 (first patient enrolled), and the last patient completed 31 March 2003. During this time the investigators randomized 7601 patients, of whom 7599 (2 patients were mistakenly assigned randomization numbers and no data are available for them) were evaluated for efficacy and safety (3803 candesartan and 3796 placebo). The program ended on a common trial closing date, 31 March 2003. Disposition of the randomized patients by trial is outlined below (Figure 3). At the end of the trials, vital status was available for all but 10 patients.

Figure 3 Patient disposition



3. TRIAL POPULATIONS

The CHARM program study population reflected the goal of the eligibility criteria to include a wide, representative group of patients. Accordingly, patients ranged in age from 21 to 95 years (almost a quarter were ≥75 years of age), and had LV ejection fractions ranging from 0.05 to 0.91. About 1/3 were women, and the trials included approximately 4% blacks (predominantly, African Americans).

Within each trial, the 2 treatment groups were generally well balanced with regard to baseline characteristics. Consistent with published information, patients in the CHARM-Preserved trial were more likely to have hypertension, and less likely to have prior MI and ischemic heart disease, and they had less severe heart failure as assessed by NYHA class. The proportion of women was greater than in CHARM-Alternative and CHARM-Added, (Table 3). Table 4 presents selected continuous baseline characteristics for each CHARM trial.

The CHARM-Added and CHARM-Alternative populations were generally similar although a greater proportion of patients in CHARM-Added had more advanced heart failure. (About 3/4 of patients had NYHA Class III or IV heart failure compared to about 1/2 in CHARM-Alternative; about 30% had an LV ejection fraction <0.25 compared to 22% in CHARM-Alternative.) In CHARM-Alternative, a greater proportion of patients were women, and a larger proportion were aged ≥75 years at baseline.

Table 3 Baseline demographic and clinical characteristics in each CHARM trial

Category[a]	CHARM-Added		CHARM-Alternative		CHARM-Preserved	
	Placebo N=1272	Candesartan N=1276	Placebo N=1015	Candesartan N=1013	Placebo N=1509	Candesartan N=1514
	Percentage (%) of patients					
Age (y)						
<65	50.0	49.5	38.6	40.7	40.7	37.6
≥65 to <75	30.7	33.9	37.8	36.3	32.8	35.5
≥75	19.3	16.6	23.5	23.0	26.5	26.9
Sex						
Men	78.6	78.8	68.1	68.2	59.0	60.8
Women	21.4	21.2	31.9	31.8	41.0	39.2
Race						
European origin[b]	91.5	89.6	88.8	88.4	92.3	90.8
Black	4.9	5.1	4.4	2.8	3.8	4.6
South Asian	0.6	1.5	1.5	2.2	0.7	1.2
Arab/Middle Eastern	0.3	0.6	0.6	0.9	0.3	0.3
Oriental	1.0	1.7	2.7	2.9	1.5	1.3
Malaysian	0.6	0.9	1.0	1.4	0.5	0.9
Other	1.1	0.6	1.1	1.6	0.9	0.9
Smoking status						
Non-smoker	30.7	30.7	37.9	36.7	42.7	39.5
Previously a smoker	50.9	54.1	49.6	48.6	44.9	45.8
Currently a smoker	18.5	15.2	12.5	14.7	12.4	14.7
Severity of heart failure						
NYHA class II	23.7	24.5	47.2	48.1	60.0	61.5
NYHA class III	72.7	73.0	49.2	48.4	38.7	36.7
NYHA class IV	3.5	2.6	3.6	3.6	1.3	1.8
Previous hospitalization for CHF	77.8	76.4	66.3	70.3	68.8	68.6
Previous myocardial infarction	55.3	56.0	60.9	62.1	43.7	45.0

Category[a]	CHARM-Added		CHARM-Alternative		CHARM-Preserved	
	Placebo N=1272	Candesartan N=1276	Placebo N=1015	Candesartan N=1013	Placebo N=1509	Candesartan N=1514
	Percentage (%) of patients					
Medical history						
Hypertension	48.7	47.7	50.7	49.4	63.6	65.0
Diabetes mellitus	30.0	29.5	26.6	27.4	28.0	28.7
Atrial fibrillation	26.8	27.1	25.7	25.1	29.3	29.0
Etiology of heart failure						
Ischemic heart disease	62.6	62.2	66.9	69.7	56.5	56.4
Idiopathic dilated cardiomyopathy	25.8	26.6	20.3	18.8	8.7	8.7
Hypertension	6.2	6.8	7.2	5.7	23.0	22.3
Valvular heart disease	1.7	1.3	2.0	2.5	3.2	2.7
Diabetes mellitus	0.2	0.2	0.3	0.3	0.3	0.5
Alcohol-related	1.2	1.0	1.1	1.0	0.3	0.8
Atrial fibrillation	0.4	0.4	1.0	1.2	4.2	4.6
Other cause	2.0	1.5	1.3	0.9	3.8	4.1
Cardiac function						
Left ventricular ejection fraction						
<0.25	30.0	30.4	21.1	23.6	0	0
≥0.25	70.0	69.6	78.9	76.4	100	100
<0.50	100	99.8	100	100	35.5	35.4
≥0.50	0	0.2	0	0	64.5	64.6
Geographic location						
US patients	23.7	23.1	23.4	22.9	23.9	24.6
Non-US patients	76.3	76.9	76.6	77.1	76.1	75.4

[a] Not all sub-categories are mutually exclusive.
[b] Includes white (Caucasian).
N Total number of patients. CHF Chronic heart failure. NYHA New York Heart Association.

Table 4 Selected continuous baseline characteristics in each CHARM trial

Variable	Statistic	CHARM-Added		CHARM-Alternative		Charm-Preserved	
		Placebo	Candesartan	Placebo	Candesartan	Placebo	Candesartan
Age, years	N	1272	1276	1015	1013	1509	1514
	Mean	64.1	64.0	66.8	66.3	67.1	67.2
	(SD)	(11.3)	(10.7)	(10.5)	(11.0)	(11.1)	(11.1)
	Min, max	24, 94	26, 93	23, 89	24, 91	21, 94	26, 95
DBP, mm Hg	N	1271	1276	1015	1013	1508	1514
	Mean	75.2	75.0	76.9	76.6	77.8	77.8
	(SD)	(10.7)	(10.8)	(10.5)	(10.9)	(10.5)	(10.9)
	Min, max	40, 110	40, 110	40, 120	37, 110	30, 110	50, 110
SBP, mm Hg	N	1272	1276	1015	1013	1508	1514
	Mean	125.6	124.7	130.3	129.9	136.3	136.0
	(SD)	(18.6)	(18.6)	(18.5)	(19.0)	(18.3)	(18.6)
	Min, max	80, 180	75, 185	80, 200	80, 198	85, 210	80, 202
Ejection fraction	N	1272	1276	1015	1012	1509	1514
	Mean	0.28	0.28	0.30	0.30	0.54	0.54
	(SD)	(0.07)	(0.08)	(0.07)	(0.08)	(0.09)	(0.09)
	Min, max	0.05, 0.47	0.08, 0.62	0.08, 0.40	0.07, 0.45	0.30, 0.89	0.40, 0.91

DBP Diastolic blood pressure.
SBP Systolic blood pressure.

The treatment groups were also generally well balanced with regard to concomitant heart failure treatments. At baseline, most patients were receiving diuretics and over half were receiving beta-blockers (Table 5).

Table 5 Heart failure and key cardiovascular concomitant medications in each CHARM trial at baseline

Concomitant medications	CHARM-Added		CHARM-Alternative		CHARM-Preserved	
	Placebo N=1272 %	Candesartan N=1276 %	Placebo N=1015 %	Candesartan N=1013 %	Placebo N=1509 %	Candesartan N=1514 %
ACE inhibitor	99.8	100	0.2	0.1	18.6	19.6
ACE inbitor at recommended heart failure dose[a]	50.9	50.4	NA	NA	NA	NA
Beta-blocker	55.9	55.0	54.5	54.6	55.5	55.9
Cardiac glycosides[b]	59.2	57.6	46.2	44.9	27.2	28.5
Diuretics	90.1	90.0	85.6	85.3	74.3	75.2
Spironolactone	16.9	17.4	23.0	24.7	12.0	11.3
Calcium channel blockers	11.3	9.6	15.1	17.6	31.6	30.8
Vasodilators[c]	38.7	34.8	43.4	42.2	39.4	37.4
Lipid-lowering drug	41.0	41.4	40.3	42.7	42.7	40.8
Acetylsalicylic acid	51.8	51.1	58.6	57.1	58.8	57.8

[a] For example, daily doses of captopril 150 mg, enalapril 20 mg, lisinopril 20 mg, ramipril 10 mg, perindopril 4 mg, quinapril 20 mg, and fosinopril 20 mg.
[b] Digitalis.
[c] Vasodilators included long-acting nitrates, hydralazine, and other vasodilators.
N Total number of patients in each treatment group, by trial.
NA Not applicable.
Note: Concomitant medications recorded at baseline.

4. EXPOSURE TO INVESTIGATIONAL PRODUCT

4.1 Exposure by time in trial

In total, of the 7599 patients, 3803 patients were randomized to treatment with candesartan and 3796 to treatment with placebo. The numbers of patients on study drug at 12-, 24-, and 36-months is shown in Table 6.

Table 6 **Numbers of patients on study drug, by time in trial for the 3-trials pooled population**

Time on active treatment	Placebo N=3796 n (%)	Candesartan N=3803 n (%)
≥12 months	3105 (81.8)	3071 (80.8)
≥24 months	2701 (71.2)	2659 (69.9)
≥36 months	1766 (46.5)	1715 (45.1)

N Total number of patients, by treatment group.
n Number of patients on study drug.

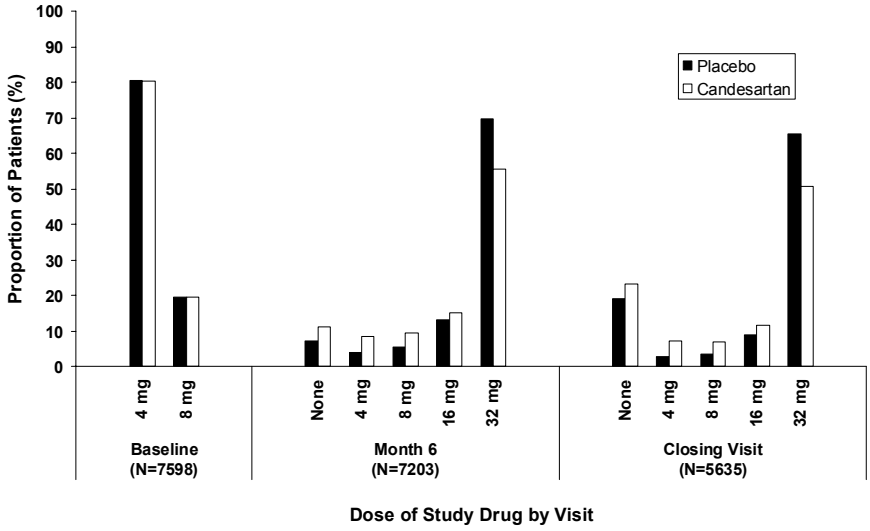
For placebo patients, the median treatment time was 35.0 months and the longest treatment time 47.2 months; for candesartan patients, it was 34.5 months and 47.4 months, respectively.

4.2 Exposure by dose

Approximately 80% of patients began treatment at the 4 mg dose. At 6 months, for those patients receiving study drug, 75.4% of placebo patients (2489/3301 patients) and 62.6% of candesartan patients (2025/3233 patients) were at the 32 mg dose. At the closing visit, for those patients receiving study drug, 80.9% of placebo patients (1827/2259 patients) and 66.1% of candesartan patients (1446/2187 patients) were receiving the 32 mg dose. Figure 4 illustrates study drug dose-specific exposure (the denominator for calculating the proportion of patients includes all patients who had data collected at the specified time point, ie, patients receiving drug as well as those patients not receiving drug).

The mean daily dose for patients taking study drug was 27.1 mg for placebo patients and 24.0 mg for candesartan patients based on data at 6 months, 28.2 mg and 24.7 mg, respectively, based on closing visit data, and 27.0 mg and 23.9 mg, respectively, based on LVCF.

Figure 4 **Exposure to study drug by dose and visit, 3-trials pooled population (CHARM-Added, CHARM-Alternative, plus CHARM-Preserved pooled)**



5. EFFICACY

This efficacy section presents the following: results from 2 individual trials (CHARM-Added and CHARM-Alternative) in patients with depressed LV systolic function; results from the 2-trials pooled of patients with depressed LV systolic function (CHARM-Added and CHARM-Alternative); results from 1 trial in patients with preserved LV systolic function (CHARM-Preserved); and results from analyses in 3-trials pooled (CHARM-Added, CHARM-Alternative, plus CHARM-Preserved). Also in Section 9 the CHARM-Added Supplemental Analyses are presented that address the question posed by the Agency regarding the beneficial effects of candesartan when added to a maximum dose of an ACE inhibitor.

5.1 CHARM-Added, Trial SH-AHS-0006

CHARM-Added enrolled 2548 patients (1272 placebo and 1276 candesartan) with LV systolic dysfunction of whom all but 2 placebo patients were taking ACE inhibitors. Approximately 96% of patients were at an individually optimized ACE inhibitor dose as determined by the patients' investigator. At baseline, half the patients were receiving an ACE inhibitor at a heart failure treatment recommended dose or higher. (Recommended doses were determined prior to data unblinding and were largely consistent with the recommendations of the European Society of Cardiology (Remme et al 2001). At 6 months (Visit 5) by which time study drug titration was largely complete, 50.4% placebo and 46.5% candesartan patients were at or above the recommended dose and at the closing visit, 44.7% of the placebo patients and 38.2% of the candesartan patients were at or above the recommended ACE inhibitor dose, Table 7.

Table 7 **Proportion of patients receiving the recommended heart failure dose of an ACE inhibitor and dose of study drug at the closing visit (CHARM-Added)**

Variable	Placebo n/N (%)	Candesartan n/N (%)
Patients receiving the recommended dose of an ACE inhibitor at baseline	648/1272 (50.9)	643/1276 (50.4)
Patients receiving the recommended dose of an ACE inhibitor at Month 6	603/1196 (50.4)	564/1214 (46.5)
Patients receiving the recommended dose of an ACE inhibitor at the closing visit	386/864 (44.7)	342/896 (38.2)
Patients receiving the target dose (32 mg) of study drug at the closing visit	539/849 (63.5)	410/881 (46.5)

n Number of patients receiving the recommended or target dose of medication, at a specified visit, by treatment group.
N Total number of patients at the specified visit, by treatment group.

The ACE inhibitors used most frequently in CHARM-Added and proportion of patients taking a specific ACE inhibitor and mean doses are listed in Table 8. For those ACE inhibitors which have been studied in heart failure clinical outcome studies (The CONSENSUS Study Group 1987, The SOLVD Investigators 1991, The AIRE Study Investigators 1993), the mean achieved dose established as beneficial in those trials compare very closely with the mean doses used in CHARM-Added.

Table 8 **Most common ACE inhibitors used at baseline (CHARM-Added)**

ACE inhibitor	Proportion of patients taking a specific ACE inhibitor, at baseline in CHARM-Added	Mean doses at baseline in CHARM-Added	Recommended heart failure target dose in CHARM-Added mg/day
Enalapril	26.7%	17 mg	20 mg
Lisinopril	10.1%	18 mg	20 mg
Captopril	16.8%	83 mg	150 mg
Ramipril	11.0%	7 mg	10 mg
Perindopril	6.4%	4 mg	4 mg
Trandolapril	5.9%	2 mg	2 mg
Quinapril	5.4%	25 mg	20 mg
Fosinopril	5.1%	20 mg	20 mg
Benazepril	2.6%	26 mg	20 mg
Other ACE inhibitors	1.1%		

In CHARM-Added, candesartan treatment significantly reduced the risk for the primary endpoint, CV mortality or CHF hospitalization (Figure 5 and Table 9). Controlling for testing of multiple endpoints, candesartan also reduced the risk for each of the secondary endpoints:

all-cause mortality or CHF hospitalization, and CV mortality or CHF hospitalization or nonfatal MI (Table 9).

Figure 5 **Candesartan versus placebo for the primary endpoint: CV mortality or CHF hospitalization (CHARM-Added)**

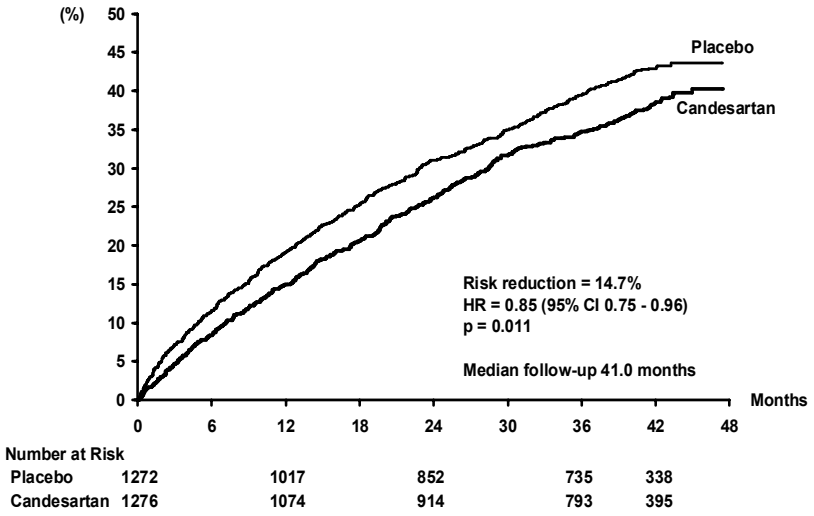


Table 9 **Candesartan versus placebo for the primary and secondary endpoints (CHARM-Added)**

	Placebo N=1272 n	Placebo Events/1000 follow-up years	Cand N=1276 n	Cand Events/1000 follow-up years	Hazard ratio (95% CI)	p-value (logrank test)
CV mortality or hospitalization due to CHF (primary variable)	538	166.3	483	141.2	0.85 (0.75-0.96)	p=0.011
All-cause mortality or CHF hospitalization	587	181.5	539	157.5	0.87 (0.78-0.98)	p=0.021
CV mortality or CHF hospitalization or nonfatal MI	550	172.0	495	145.8	0.85 (0.76-0.96)	p=0.010

N Total number of patients in each treatment group for CHARM-Added.
n Number of events.
Cand Candesartan.

A beneficial effect favoring candesartan was observed for each component of the composite primary and secondary endpoints (CV mortality, CHF hospitalization, all-cause mortality, and nonfatal MI) (Table 10).

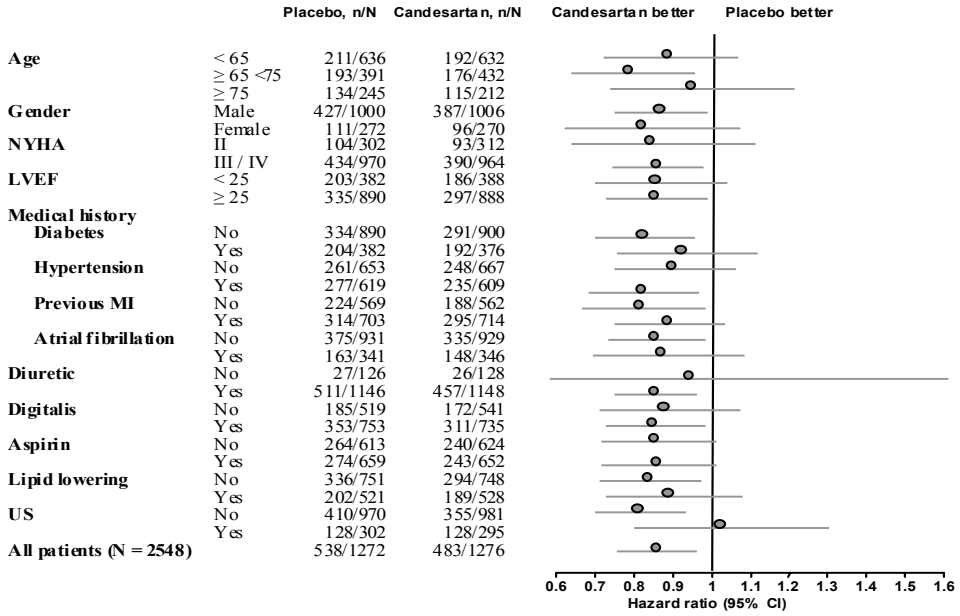
Table 10 **Candesartan versus placebo for the components of the primary and secondary endpoints (CHARM-Added)**

	Placebo N=1272 n	Placebo Events/1000 follow-up years	Candesartan N=1276 n	Candesartan Events/1000 follow-up years	Hazard ratio (95% CI)	p-value (logrank test)
CV mortality	347	93.3	302	78.5	0.84 (0.72-0.98)	p=0.029
CHF hospitalization	356	110.1	309	90.3	0.83 (0.71-0.96)	p=0.013
All-cause mortality	412	110.7	377	98.0	0.89 (0.77-1.02)	p=0.086
Nonfatal MI	49	13.4	26	6.8	0.51 (0.32-0.82)	p=0.005

N Total number of patients in each treatment group for CHARM-Added.
n Number of events.

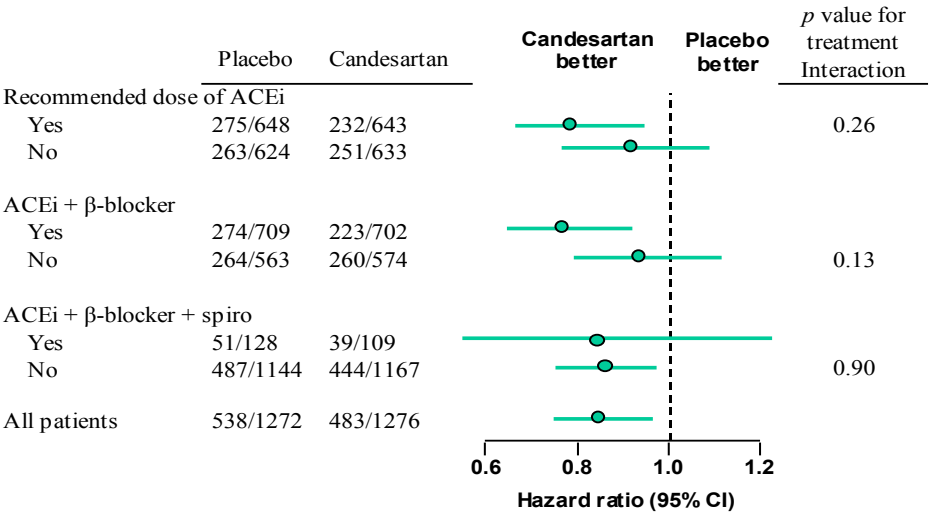
Among subgroups, the point-estimates for the primary endpoint, CV mortality or CHF hospitalization, were consistent with the findings for all patients, and were without statistical evidence of effect modification (Figure 6). The point-estimate for the US subgroup was 1.02 (95% CI=0.80-1.30, p=0.877), while the point-estimate for the North American population was 0.98 (95% CI=0.81-1.19, p=0.870). For Black patients, the point-estimate for the treatment effect was 0.66 (95% CI=0.38-1.13, p=0.126).

Figure 6 **CV mortality or CHF hospitalization subgroup analysis (CHARM-Added)**



In addition, the beneficial effect of candesartan on the primary endpoint was evident for patients on ACE inhibitors whether receiving the recommended dose proven effective in previous positive trials for heart failure (eg, daily doses of captopril 150 mg, enalapril 20 mg, lisinopril 20 mg, ramipril 10 mg, perindopril 4 mg, quinapril 20 mg, or fosinopril 20 mg) or receiving lesser doses at baseline, whether on a beta-blocker or not, and whether receiving a combination of an ACE inhibitor plus beta-blocker plus spironolactone (Figure 7).

Figure 7 **Primary endpoint CV death or CHF hospitalization by background therapy (CHARM-Added)**



Note: Recommended dose of ACE inhibitor (eg, daily doses of captopril 150 mg, enalapril 20 mg, lisinopril 20 mg, ramipril 10 mg, perindopril 4 mg, quinapril 20 mg, or fosinopril 20 mg).

5.2 CHARM-Alternative, Trial SH-AHS-0003

CHARM-Alternative enrolled 2028 (1015 placebo and 1013 candesartan) patients with LV systolic dysfunction and not receiving an ACE inhibitor because of a history of intolerance. The most common reasons cited for ACE inhibitor intolerance included: cough (n=1455, 72%), hypotension (n=262, 13%), abnormal renal function (n=234, 12%), and angioedema (n=83, 4%).

In CHARM-Alternative, candesartan treatment significantly reduced the risk for the primary endpoint, CV mortality or CHF hospitalization (Figure 8 and Table 11). Controlling for testing of multiple endpoints, candesartan also reduced the risk for each of the secondary endpoints: all-cause mortality or CHF hospitalization, and CV mortality or CHF hospitalization or nonfatal MI (Table 11).

Figure 8 **Candesartan versus placebo for the primary endpoint: CV mortality or CHF hospitalization (CHARM-Alternative)**

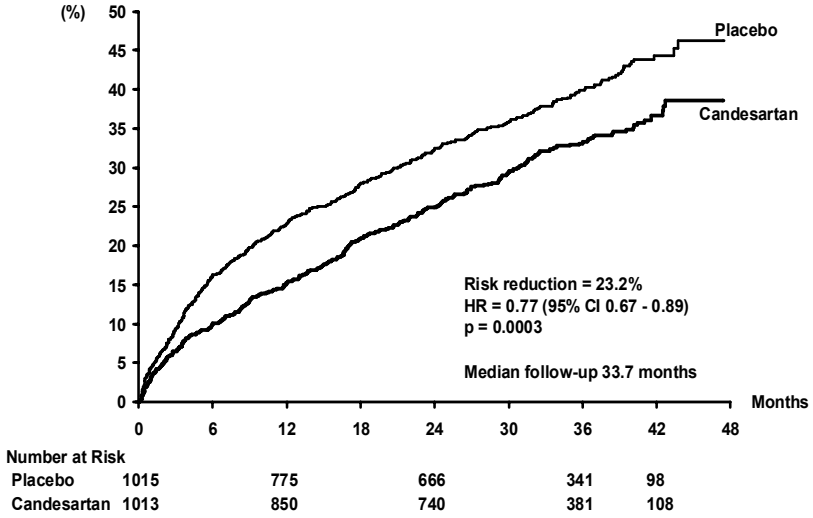


Table 11 **Candesartan versus placebo for the primary and secondary endpoints (CHARM-Alternative)**

	Placebo N=1015 n	Placebo Events/1000 follow-up years	Candesartan N=1013 n	Candesartan Events/1000 follow-up years	Hazard ratio (95% CI)	p-value (logrank test)
CV mortality or hospitalization due to CHF	406	182.1	334	138.1	0.77 (0.67-0.89)	p<0.001[a]
All-cause mortality or CHF hospitalization	433	194.2	371	153.4	0.80 (0.70-0.92)	p=0.001
CV mortality or CHF hospitalization or nonfatal MI	420	191.2	353	147.8	0.78 (0.68-0.90)	p<0.001

[a] p-value=0.0003.
N Total number of patients in each treatment group.
n Number of events.

A beneficial effect favoring candesartan was observed for each of the 3 major components of the composite primary and secondary endpoints (CV mortality, CHF hospitalization, and all-cause mortality) (Table 12). For the nonfatal MI component there were relatively few events, resulting in a wide confidence interval.

Table 12 Candesartan versus placebo for the components of the primary and secondary endpoints (CHARM-Alternative)

	Placebo N=1015 n	Placebo Events/1000 follow-up years	Candesartan N=1013 n	Candesartan Events/1000 follow-up years	Hazard ratio (95% CI)	p-value (logrank test)
CV mortality	252	97.6	219	82.4	0.85 (0.71-1.02)	p=0.072
CHF hospitalization	286	128.3	207	85.6	0.68 (0.57-0.81)	p<0.001
All-cause mortality	296	114.6	265	99.7	0.87 (0.74-1.03)	p=0.104
Nonfatal MI	36	14.2	41	15.7	1.11 (0.71-1.73)	p=0.655

N Total number of patients in each treatment group, in CHARM-Alternative.
n Number of events.

Among subgroups, the point-estimates for the primary endpoint, CV mortality or CHF hospitalisation, were consistent with the estimate for all patients, with no statistical evidence of effect modification. The point-estimate for the US subgroup was 0.88, (95% CI=0.61-1.09, p=0.162), and for North American patients it was 0.77 (95% CI=0.60-0.98, p=0.034). For Black patients the point-estimate for the treatment effect was 0.45 (95% CI=0.18-1.13, p=0.088).

5.3 CHARM-Added (Trial SH-AHS-0006) plus CHARM- Alternative (Trial SH-AHS-0003)

This section details further analyses for patients with LV systolic dysfunction: 2-trials pooled, CHARM-Added plus CHARM-Alternative, the population traditionally included in most heart failure studies.

5.3.1 Primary and secondary composite endpoint analyses (CHARM 2-trials pooled)

Table 13 summarizes the primary and secondary endpoints for patients with depressed LV systolic function (2-trials pooled) and provides estimates of the effect in the combined population. In the 2-trials pooled CHARM population, candesartan reduced the risk for all 3 composite endpoints comprising the confirmatory analysis: CV mortality or CHF hospitalization, all-cause mortality or CHF hospitalization, and CV death or CHF hospitalization or nonfatal MI (Table 13). Additionally, candesartan treatment reduced the risk for each of the components, although the effect on nonfatal MI was not nominally significant (Table 14).

Table 13 Candesartan versus placebo for the individual trial primary and secondary endpoints (CHARM 2-trials pooled)

	Placebo N=2287 n	Placebo Events/1000 follow-up years	Candesartan N=2289 n	Candesartan Events/1000 follow-up years	Hazard ratio (95% CI)	p-value (logrank test)[a]
CV mortality or hospitalization due to CHF	944	172.8	817	139.9	0.82 (0.74-0.90)	p<0.001
All-cause mortality or CHF hospitalization	1020	186.7	910	155.8	0.84 (0.77-0.92)	p<0.001
CV mortality or CHF hospitalization or nonfatal MI	970	179.8	848	146.6	0.82 (0.75-0.90)	p<0.001

[a] Nominal p-values are provided without multiplicity adjustment.
N Total number of patients in each treatment group for CHARM 2-trials pooled.
n Number of events.

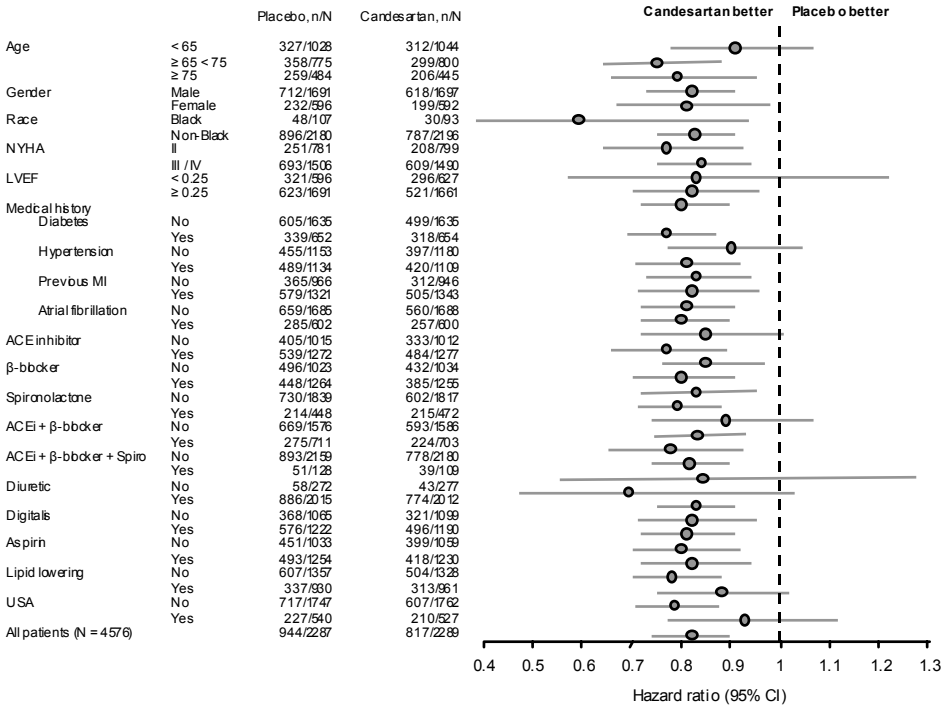
Table 14 Candesartan versus placebo for the components of the individual trial primary and secondary endpoints (CHARM 2-trials pooled)

	Placebo N=2287 n	Placebo Events/1000 follow-up years	Candesartan N=2289 n	Candesartan Events/1000 follow-up years	Hazard ratio (95% CI)	p-value (logrank test)[a]
CV mortality	599	95.0	521	80.1	0.84 (0.75-0.95)	p=0.005
CHF hospitalization	642	117.5	516	88.3	0.76 (0.68-0.85)	p<0.001
All-cause mortality	708	112.3	642	98.7	0.88 (0.79-0.98)	p=0.018
Nonfatal MI	85	13.7	67	10.4	0.76 (0.55-1.05)	p=0.097

[a] Nominal p-values are provided without multiplicity adjustment.
N Total number of patients in each treatment group for CHARM 2-trials pooled.
n Number with events

Among subgroups, the point-estimates for the primary endpoint of CV mortality or CHF hospitalization were consistent with the estimate for all patients, with no statistical evidence of effect modification (Figure 9). The point-estimate for the US subgroup was 0.93, (95% CI=0.77-1.12, p=0.433), and for North American patients it was 0.89 (95% CI=0.77-1.04, p=0.148). For Black patients, the point-estimate for the treatment effect was 0.59 (95% CI=0.37-0.94, p=0.025).

Figure 9 **CV mortality or CHF hospitalization subgroup analysis (CHARM 2-trials pooled)**



5.3.2 Causes of death (individual trials and CHARM 2-trials pooled)

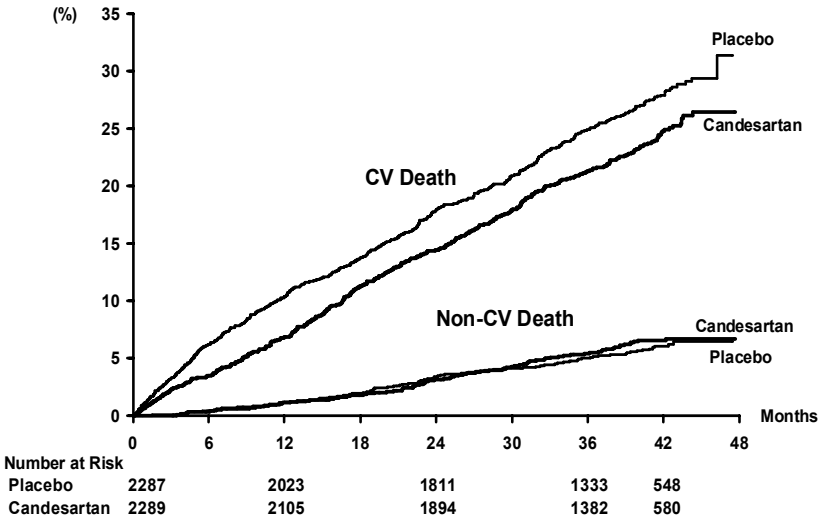
The CEC classified deaths as either cardiovascular or non-cardiovascular events. The rules governing the CEC specified classification of all deaths as CV unless there was compelling evidence to the contrary. As expected, most deaths were attributed to CV causes (Table 15), Figure 10 displays the findings of the analyses of time to CV mortality and the time to non-CV mortality for the pooled data of patients with LV systolic dysfunction (CHARM-Added plus CHARM-Alternative).

Table 15 **Candesartan versus placebo for the endpoint all-cause mortality, and cardiovascular and non-cardiovascular causes of death (CHARM-Added, CHARM-Alternative, and 2-trials pooled, CHARM-Added plus CHARM-Alternative)**

Endpoint	Number of patients with event		Hazard ratio	95% CI	p-value (logrank test)[a]
CHARM-Added	Placebo N=1272 n	Candesartan N=1276 n			
All-cause mortality	412	377	0.89	0.77, 1.02	0.086
Cardiovascular mortality	347	302	0.84	0.72, 0.98	0.029
Non-cardiovascular mortality	65	75	1.11	0.80, 1.55	0.528
CHARM-Alternative	Placebo N=1015 n	Candesartan N=1013 n			
All-cause mortality	296	265	0.87	0.74, 1.03	0.104
Cardiovascular mortality	252	219	0.85	0.71, 1.02	0.072
Non-cardiovascular mortality	44	46	1.01	0.67, 1.53	0.948
2-trials pooled (CHARM-Added plus CHARM-Alternative)	Placebo N=2287 n	Candesartan N=2289 n			
All-cause mortality	708	642	0.88	0.79, 0.98	0.018
Cardiovascular mortality	599	521	0.84	0.75, 0.95	0.005
Non-cardiovascular mortality	109	121	1.07	0.83, 1.39	0.594

[a] Nominal p-values are provided without multiplicity adjustment.
Note: These events were classified by the CEC.
N Total number of patients in a treatment group.
n Number of events.

Figure 10 **Cardiovascular and non-cardiovascular mortality, in 2-trials pooled (CHARM-Added plus CHARM-Alternative)**



The CEC also sub-classified CV causes of death as sudden, heart failure, myocardial infarction, stroke, and other CV causes. Non-CV deaths were classified as death due to cancer or other non-CV death.

Most deaths were classified as cardiovascular in origin and sub-classified as sudden death or heart failure deaths. Non-cardiovascular deaths were less common and were about equally divided between death due to cancer and other non-cardiovascular causes.

Risk reductions in sudden death (20% reduction, HR=0.80, CI=0.67-0.95, p=0.013) and deaths attributed to worsening heart failure (24% reduction, HR=0.76, CI=0.62-0.93, p=0.008) each contributed to the beneficial effects of candesartan in reducing cardiovascular deaths (16% reduction, HR=0.84, CI=0.75-0.95, p=0.005) and all-cause mortality (12% reduction, HR=0.88, CI=0.79-0.98, nominal p=0.018).

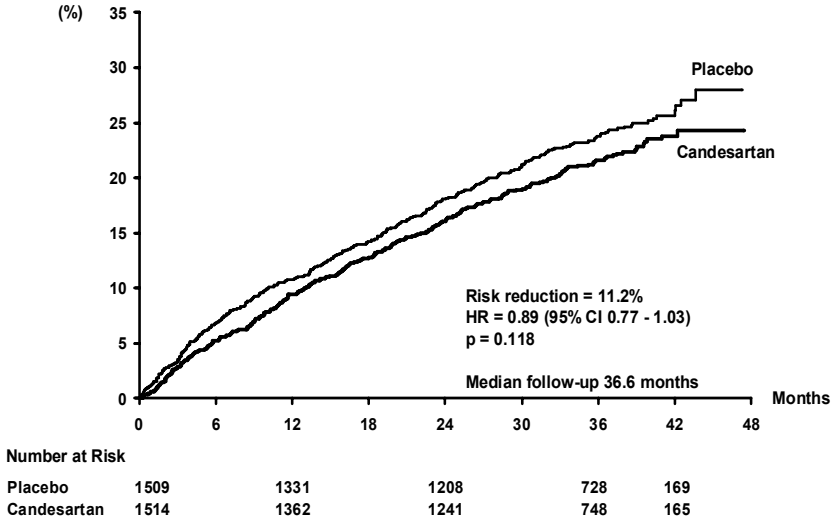
5.4 CHARM-Preserved (Trial SH-AHS-0007)

CHARM-Preserved assigned randomization numbers to 3025 symptomatic CHF patients with preserved LV systolic function, of whom 3023 (2 patients were mistakenly randomized and no data were collected) were included in the ITT population (placebo, 1509; candesartan, 1514); 18.6% of placebo patients and 19.6% of candesartan patients were receiving ACE inhibitor treatment at baseline.

In CHARM-Preserved, there was a trend directionally favoring candesartan for the primary endpoint of CV mortality or CHF hospitalization (Figure 11 and Table 16) but it was not statistically significant. The findings were similar for the secondary composite endpoints: all-

cause mortality or CHF hospitalization, and CV mortality or CHF hospitalization or nonfatal MI.

Figure 11 **Candesartan versus placebo for the primary endpoint: CV mortality or CHF hospitalization (CHARM-Preserved)**



For the component CHF hospitalization, candesartan reduced (not statistically significant) the number of 1st admissions for CHF (p=0.071) (see Table 16). However, as noted in Table 18, where all CHF hospitalizations are presented based on the investigator assessment, candesartan reduced the total number of hospital admissions for CHF (566 admissions for placebo and 402 for candesartan, p=0.013).

Table 16 Candesartan versus placebo for the primary and secondary endpoints and components of the primary endpoint (CHARM-Preserved)

	Placebo N=1509 n	Candesartan N=1514 n	Hazard ratio (95% CI)	p-value (logrank test)
CV mortality or CHF hospitalization (confirmed adjudicated)	366	333	0.89 (0.77-1.03)	p=0.118
All-cause mortality or CHF hospitalization	411	386	0.92 (0.80-1.05)	p=0.221
CV mortality or CHF hospitalization or nonfatal MI	399	365	0.90 (0.78-1.03)	p=0.126
Components of the primary endpoint				
CV mortality	170	170	0.99 (0.80-1.22)	p=0.918
CHF hospitalization	276	241	0.85 (0.72-1.01)	p=0.071

N Total number of patients in each treatment group.
n Number of events.

5.5 All-cause mortality in CHARM: pooled analyses

The CHARM pooled analysis plan specified all-cause mortality for the entire CHF population (3-trials pooled: CHARM-Added, CHARM-Alternative, plus CHARM-Preserved) as the primary endpoint and then in the population with LV systolic dysfunction (2-trials pooled: CHARM-Added plus CHARM-Alternative) as the secondary endpoint.

Candesartan treatment in this broad spectrum of heart failure patients over a median follow-up of 38 months resulted in an 8.6% relative risk reduction in all-cause death (HR=0.91, 95% CI=0.83-1.00, p=0.055) (Figure 12 and Table 17), largely attributable to a 12% relative risk reduction in CV deaths (HR=0.88, 95% CI=0.79-0.97, p=0.012.

Figure 12 **Candesartan versus placebo for the endpoint all-cause mortality, in the 3-trials pooled population**

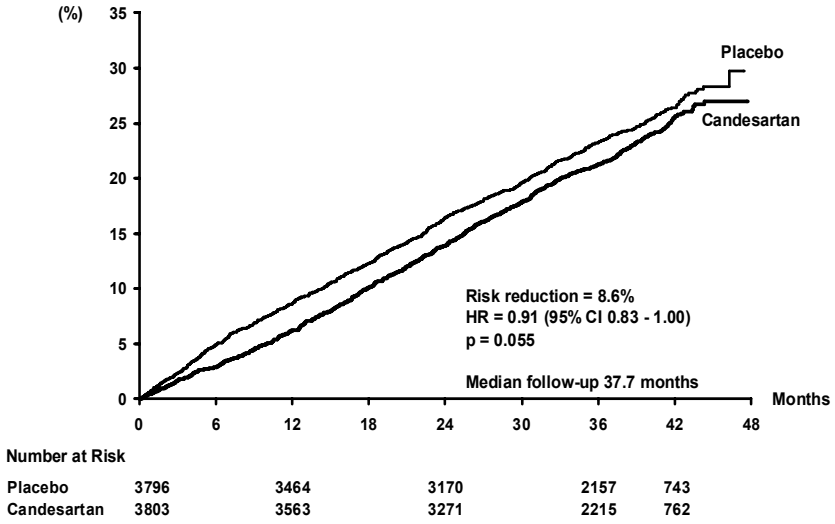


Table 17 **Candesartan versus placebo for the endpoint all-cause mortality in the CHARM 3-trials pooled**

	Placebo N=3796	Candesartan N=3803	Hazard ratio (95% CI)	p-value (logrank test)
All-cause mortality	945	886	0.91 (0.83-1.00)	p=0.055

All-cause mortality based on the pooled analysis of the 2 trials of patients with left ventricular systolic dysfunction is presented in Table 15, above.

Similar to the findings in the analysis of the 2-trials pooled summarized in Section 5.3 and Figure 10, most causes of death in the 3-trials pooled analyses were cardiovascular. There was no apparent effect on non-cardiovascular deaths, which were about equally divided between death due to cancer and other non-CV causes of death.

5.6 CHF hospitalizations in the CHARM pooled populations

The CHARM trial-specific results presented earlier describe CHF hospitalization as a component of the primary endpoint and in terms of time from randomization to the first CHF hospitalization based on the CEC adjudicated classification. (The CEC only confirmed the 1st CHF hospitalization; investigators reported all CHF and other hospitalizations.) Table 18 illustrates the candesartan benefit in reducing investigator-reported hospitalizations in terms of the numbers of hospitalizations where heart failure was the primary reason for admission.

Candesartan significantly reduced the frequency of investigator-reported heart failure hospitalizations in each of the 3 CHARM trials.

Table 18 Number of patients with hospital admissions and total number of hospital admissions for CHF, investigator-reported events for the individual CHARM trials and the 3-trials pooled (CHARM-Alternative, CHARM-Added, and CHARM-Preserved)

	Number of patients with admissions [a] (%)				Total number of admissions	p-value[b]
	None	1	2	≥3	n[a]	
CHARM-Alternative						
Placebo, n=1015	724 (71.3)	155 (15.3)	65 (6.4)	71 (7.0)	608	<0.001
Candesartan, n=1013	801 (79.1)	110 (10.9)	49 (4.8)	53 (5.2)	445	
CHARM-Added						
Placebo, n=1272	890 (70.0)	184 (14.5)	100 (7.9)	98 (7.7)	836	0.002
Candesartan, n=1276	953 (74.7)	184 (14.4)	76 (6.0)	63 (4.9)	607	
CHARM-Preserved						
Placebo, n=1509	1230 (81.5)	157 (10.4)	59 (3.9)	63 (4.2)	566	0.013
Candesartan, n=1514	1284 (84.8)	132 (8.7)	54 (3.6)	44 (2.9)	402	
CHARM-3 pooled (CHARM-Alternative, CHARM Added, and CHARM-Preserved)						
Placebo, n=3796	2844 (74.9)	496 (13.1)	224 (5.9)	232 (6.1)	2010	<0.001
Candesartan, n=3803	3038 (79.9)	426 (11.2)	179 (4.7)	160 (4.2)	1454	

[a] Investigator reported, with heart failure as primary reason.
[b] Test for difference in distribution of hospital admissions for CHF (adjusted for follow-up time) using the Wilcoxon rank sum test.

5.7 Heart failure related symptoms

The NYHA functional class served as the tool for assessing candesartan treatment effects on heart failure related symptoms. In CHARM-Added, the distribution of changes in NYHA class favored candesartan (p=0.020): in the placebo group, 495 (39.3%) patients improved 1 or 2 NYHA classes compared to the candesartan group where 548 (43.3%) patients improved. Fewer candesartan patients deteriorated by 1 or 2 classes compared to placebo patients: in the placebo group, 111 (8.8%) patients deteriorated compared to the candesartan group where 83 (6.5%) patients deteriorated by 1 or 2 NYHA classes.

Similarly in CHARM-Alternative there was an improvement in NYHA functional class that favored candesartan (p=0.008). In placebo patients, 298 (29.7%) improved 1 or 2 NYHA classes compared to the candesartan group where 359 (35.7%) patients improved. Fewer candesartan patients deteriorated by 1 or 2 classes compared to placebo patients: in the

placebo group, 109 (10.9%) patients deteriorated compared to the candesartan group where 101 (10.0%) patients deteriorated by 1 or 2 NYHA classes

In patients with preserved LV systolic function, the effect of candesartan on NYHA classification was non-significant.

5.8 Efficacy findings

In CHF patients with depressed LV systolic function receiving an ACE inhibitor (1276 candesartan and 1272 placebo patients) (CHARM-Added):

- Candesartan reduced the risk of 1st occurrence of CV death or CHF hospitalization (primary endpoint) by 15% (HR=0.85, 95% CI=0.75-0.96, p=0.011) over a median follow-up of 41 months. There were 166.3 events/1000 follow-up years in the placebo group and 141.2 events/1000 follow-up years in the candesartan group. To prevent 1 CV death or 1st CHF hospitalization, the number needed to treat with candesartan for 1 year is 40 patients.

- Candesartan treatment also reduced the risk of 1st occurrence of all-cause mortality or hospital admission for CHF (1st secondary endpoint) (HR=0.87, 95% CI=0.78-0.98, p=0.021). There were 181.5 events/1000 follow-up years in the placebo group and 157.5/1000 follow-up years with candesartan. To prevent 1 death or 1st CHF hospitalization, the number needed to treat with candesartan for 1 year is 42 patients.

- Candesartan treatment also reduced the risk for CV mortality, CHF hospitalization, or nonfatal MI (2nd secondary endpoint) (HR=0.85, 95% CI=0.76-0.96, p=0.010).

- A beneficial effect favoring candesartan was observed for each component of the composite primary and secondary endpoints: CV death, CHF hospitalization, all-cause mortality, and nonfatal MI.

- The benefit of candesartan was evident for patients receiving recommended doses of an ACE inhibitor as well as for patients taking lesser doses, as well as for patients taking an ACE inhibitor with or without a beta-blocker.

- Symptoms of heart failure as assessed by NYHA functional class improved in patients treated with candesartan.

In CHF patients with depressed LV systolic function and not receiving an ACE inhibitor because of intolerance (1013 candesartan, 1015 placebo patients) (CHARM-Alternative):

- Candesartan reduced the risk of 1st occurrence of CV death or CHF hospitalization (primary endpoint) by 23% (HR=0.77, 95% CI=0.67-0.89, p=0.0003) over a median follow-up of 34 months. There were 182.1 events/1000 follow-up years in the placebo group and 138.1/1000 follow-up years in the candesartan group. To

prevent 1 CV death or 1st CHF hospitalization, the number needed to treat with candesartan for 1 year is 23 patients.

- Candesartan treatment also reduced the risk of 1st occurrence of all-cause mortality or hospital admission for CHF (1st secondary endpoint) (HR=0.80, 95% CI=0.70-0.92, p=0.001). There were 194.2 events/1000 follow-up years in the placebo group and 153.4/1000 follow-up years in the candesartan group. To prevent 1 death or 1st CHF hospitalization, the number needed to treat with candesartan for 1 year is 25 patients.

- Candesartan treatment also reduced the risk for CV mortality, CHF hospitalization, or nonfatal MI (2nd secondary endpoint) (HR=0.78, 95% CI=0.68-0.90, p<0.001).

- A beneficial effect favoring candesartan was observed for the following components of the composite primary and secondary endpoints: CV death, CHF hospitalization, and all-cause mortality. The nonfatal MI component did not contribute to this benefit, but there were relatively few events resulting in a wide confidence interval.

- Symptoms of heart failure as assessed by NYHA functional class improved in patients treated with candesartan.

In patients with depressed LV systolic function (2289 candesartan and 2287 placebo) (2-trials pooled: CHARM-Added plus CHARM-Alternative):

- Candesartan reduced the risk of 1st occurrence of CV death or CHF hospitalization by 18% (HR=0.82, 95% CI=0.74-0.90, p<0.001) over a median follow-up of 40 months. Candesartan treatment also reduced risks for the individual components: CV mortality (HR=0.84, 95% CI=0.75-0.95, p=0.005) and CHF hospitalization (HR=0.76, 95% CI=0.68-0.85, p<0.001). Reductions in sudden death (20% reduction, p=0.013) and death due to heart failure (16% reduction, p=0.005) contributed to the reduction in CV mortality.

- Candesartan reduced the risk of 1st occurrence of all-cause mortality or CHF hospitalization by 16% (HR=0.84, 95% CI=0.77-0.92, p <0.001). Candesartan treatment also reduced the risk by 12% for the component, all-cause mortality (HR=0.88, 95% CI=0.79-0.98, p=0.018); there were 112.3 deaths/1000 follow-up years in the placebo group and 98.7 deaths/1000 follow-up years with candesartan.

- Symptoms of heart failure, as assessed by NYHA functional class, improved with candesartan treatment.

- The benefits of candesartan on the 1st occurrence of CV death or CHF hospitalization were evident across subgroups of clinical interest including sex, age, and concomitant medications (including beta-blockers, ACE inhibitors, and beta-blockers plus ACE inhibitors).

In CHF patients with preserved LV systolic function (1514 candesartan and 1509 placebo patients) (CHARM-Preserved):

- Candesartan treatment showed a directionally favorable but not statistically significant trend to reduce the risk of 1st occurrence of CV mortality or CHF hospitalization (primary endpoint) (HR=0.89, 95% CI=0.77-1.03, p=0.118), and for the component, CHF hospitalization, a similar trend was observed.

In the CHARM 3-trials pooled (3803 candesartan and 3796 placebo patients), total mortality was lower with candesartan (but not statistically significant) relative to placebo (9% relative risk reduction, HR=0.91,95% CI=0.83-1.00, nominal p=0.055).

6. SAFETY

6.1 Introduction

The principal candesartan heart failure safety evaluations are derived from the 3 CHARM trials (7599 total patients: 3803 candesartan, 3796 placebo). Nine other short-term clinical studies evaluated candesartan in an additional 3102 CHF patients. The safety data from these 9 studies are consistent with those from the CHARM program.

The CHARM trials collected all serious adverse events (SAEs) and all adverse events (serious or non-serious) that led to a dose reduction or discontinuation of study treatment. Investigators were instructed to assess serum creatinine and potassium prior to drug initiation, within 2 weeks of a dose escalation, at the end of dose titration, yearly thereafter, and at their discretion. Blood samples were collected for these analyses at North American sites as a representative sample for the CHARM program.

The focus of the safety aspects of the CHARM program was on SAEs and adverse events that led to discontinuation of or reduction in the dose of investigational product. The CHARM trial case report forms did, however, specifically query for adverse events commonly associated with CHF and RAAS inhibitors: these included hyperkalemia, abnormal renal function, and hypotension. The SAEs in this safety section reflect the investigators' description, independent of the classification by the CEC adjudication process.

Throughout the safety section, discontinuation refers to permanent discontinuation.

6.1.1 Pharmacological class effects

Candesartan is a selective angiotensin II type 1 (AT_1) receptor blocker with tight binding to and slow dissociation from the receptor. It has no agonist activity and no effect on ACE activity. Because candesartan is an AT_1-receptor blocker, pharmacological effects due to modification of the RAAS homeostasis are not unexpected when it is administered to patients with CHF. These effects can include increases in serum potassium levels and reductions in blood pressure.

In patients whose vascular tone and glomerular filtration rate depend predominantly on the activity of the RAAS (eg, patients with severe heart failure or with underlying renal disease, including renal artery stenosis), treatment with drugs that inhibit the RAAS has been associated with hypotension, azotemia, oliguria, and rarely, acute renal failure.

Symptomatic hypotension and decline in renal function are also more likely to occur in patients who are volume and salt depleted, including patients being treated for CHF and patients receiving diuretics. Co-administration of spironolactone or other potassium sparing diuretics, potassium supplements or other drugs affecting potassium homeostasis also predispose to hyperkalemia. Initiating or escalating the dose of inhibitors of the RAAS in these patients requires appropriate clinical oversight.

6.2 Overview of safety findings

Safety data from the CHARM program indicate that candesartan treatment beginning at 4 mg or 8 mg and titrated to 32 mg (or the highest tolerated dose) administered orally once a day is generally a well-tolerated and safe treatment for patients with CHF. The adverse events hypotension, abnormal renal function (increase in serum creatinine), and hyperkalemia, which are well-recognized findings in patients with CHF, particularly when they are treated with inhibitors of the RAAS, occur more frequently as reasons for discontinuation of candesartan treatment compared with placebo. These events are detectable by routine testing and are manageable by the usual clinical practices for the care of patients with CHF.

Concomitant treatment with other 'heart failure' drugs including ACE inhibitors, beta-blockers, spironolactone, or combinations of these treatments is not associated with increased mortality or a notable increase in hospitalizations.

Table 19 summarizes the candesartan and placebo adverse event experience for the CHARM-Added trial and the CHARM 3-trials pooled population.

Table 19 Summary of adverse events in the CHARM-Added trial and CHARM 3-trials pooled

	CHARM-Added				CHARM 3-trials pooled			
	Placebo[a]		Candesartan[a]		Placebo[a]		Candesartan[a]	
	N=1272		N=1276		N=3796		N=3803	
Categories of patients[b]	n, and percentage (%) of patients							
Any adverse events (AEs)	992	(78.0)	1026	(80.4)	2799	(73.7)	2841	(74.7)
Serious AEs (SAEs)	966	(75.9)	969	(75.9)	2698	(71.1)	2624	(69.0)
SAEs that led to death	413	(32.5)	377	(29.5)	947	(24.9)	887	(23.3)
SAEs that did not lead to death	870	(68.4)	874	(68.5)	2487	(65.5)	2432	(63.9)
Discontinuation of investigational product because of AEs[c]	224	(17.6)	310	(24.3)	613	(16.1)	799	(21.0)
Dose reduction of the investigational product because of AEs	123	(9.7)	220	(17.2)	324	(8.5)	569	(15.0)

[a] Only 1 occurrence of an event is counted during the study period, for categories of patients.
[b] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each category. Adverse events include all serious adverse events and all adverse events that led to discontinuation or reduction of the dose of study treatment.
[c] Permanent discontinuation is discontinuation by patients who were still alive more than 5 days later and were not taking study drug at the closing visit.
N Total number of patients in each treatment group.
n Subset of patients.

6.3 Safety in CHARM-Added

6.3.1 Common adverse events (CHARM-Added)

For CHARM-Added, among the most common adverse events, cardiac failure/cardiac failure-aggravated, angina pectoris/angina pectoris-aggravated, and sudden death occurred more often in the placebo group; in the candesartan group, hypotension, renal function abnormal, and hyperkalemia occurred more often (Table 20). The median follow-up time was 41.1 months for candesartan and 40.9 months for placebo.

Table 20 Most commonly reported adverse events in the total population (CHARM-Added)

Adverse event[a]	Placebo N=1272		Candesartan N=1276	
	n and percentage (%) of patients			
Cardiac failure/cardiac failure, aggravated	472	(37.1)	421	(33.0)
Hypotension	184	(14.5)	296	(23.2)
Angina pectoris/angina pectoris, aggravated	169	(13.3)	150	(11.8)
Sudden death	174	(13.7)	143	(11.2)
Renal function abnormal/renal dysfunction, aggravated	119	(9.4)	196	(15.4)
Arrhythmia ventricular	121	(9.5)	88	(6.9)
Pneumonia	108	(8.5)	76	(6.0)
Hyperkalemia	46	(3.6)	123	(9.6)
Myocardial infarction	88	(6.9)	70	(5.5)
Fibrillation atrial	73	(5.7)	66	(5.2)

[a] Adverse events are defined as all serious adverse events and all adverse events that led to discontinuation or reduction of the investigational product.

Note: This table presents the 10 most frequently reported adverse events.

N Total number of patients in each treatment group.

n Subset of patients with most commonly reported adverse events.

6.3.2 Serious, fatal adverse events (CHARM-Added)

The most frequently cited serious fatal adverse events were sudden death and cardiac failure/cardiac failure-aggravated, which occurred more frequently in placebo patients. Myocardial infarction occurred in a similar proportion of patients in both treatment groups (Table 21). Other serious fatal adverse events were less common and occurred at about equal frequency for the 2 treatment groups.

Table 21 Most common adverse events leading to death (CHARM-Added)

Adverse event	Placebo N=1272		Candesartan N=1276	
	n and percentage (%) of patients			
Sudden death	174	(13.7)	143	(11.2)
Cardiac failure/cardiac failure, aggravated	112	(8.8)	74	(5.8)
Myocardial infarction	20	(1.6)	21	(1.6)
Death	13	(1.0)	19	(1.5)
Pneumonia	19	(1.5)	10	(0.8)
Cardiac arrest	13	(1.0)	13	(1.0)
Fibrillation ventricular	16	(1.3)	9	(0.7)
Cerebrovascular disorder	11	(0.9)	12	(0.9)
Sepsis	10	(0.8)	11	(0.9)
Cardiomyopathy	8	(0.6)	8	(0.6)

Note: This table presents the 10 most frequently reported adverse events leading to death in the total population.
N Total number of patients in each treatment group.
n Subset of patients with most commonly reported adverse events.

6.3.3 Adverse events leading to permanent study drug discontinuation (CHARM-Added)

In CHARM-Added, among the most common adverse events leading to discontinuation of study drug, cardiac failure/cardiac failure-aggravated occurred more often in the placebo group, and renal function abnormal, hypotension, and hyperkalemia occurred more often in the candesartan group (Table 22). Other reasons for discontinuation were less common, occurring at about equal rates for the 2 treatment groups.

Table 22 Most common adverse events leading to discontinuation of study drug in the total population (CHARM-Added)

	Placebo N=1272		Candesartan N=1276	
	n and percentage (%) of patients			
Discontinued treatment because of adverse events				
Renal function abnormal	53	(4.2)	105	(8.2)
Cardiac failure/cardiac failure, aggravated	81	(6.4)	69	(5.4)
Hypotension	44	(3.5)	69	(5.4)
Hyperkalemia	11	(0.9)	49	(3.8)
Renal failure acute	14	(1.1)	15	(1.2)
Cerebrovascular disorder	7	(0.6)	9	(0.7)
Diarrhea	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)

Note: This table presents the 10 most frequently reported adverse events leading to discontinuation of study drug.
N Total number of patients in each treatment group.
n Subset of patients with most commonly reported adverse events.

6.4 Safety in CHARM-Alternative

6.4.1 Categories of adverse events

In general, the safety findings in CHARM-Alternative (Table 23), in which the median follow-up time was 33.6 months for the placebo group and 33.8 months for the candesartan group, were similar to those summarized in Table 19 for CHARM-Added, and for the 3-trials pooled (Table 28).

Table 23 Summary of adverse events (CHARM-Alternative)

Categories of patients[a]	Placebo[b] N=1015 n (%)		Candesartan N=1013 N (%)	
Any adverse events (AEs)	747	(73.6)	741	(73.1)
Serious AEs (SAEs)	722	(71.1)	682	(67.3)
SAEs that led to death	296	(29.2)	266	(26.3)
SAEs that did not lead to death	654	(64.4)	619	(61.1)
Discontinuation of investigational product because of AEs[c]	197	(19.4)	220	(21.7)
Dose reduction of the investigational product because of AEs	76	(7.5)	157	(15.5)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each category. Adverse events include all serious adverse events and all adverse events that led to discontinuation or reduction of the dose of study treatment.
[b] Only 1 occurrence of an event is counted during the study period, for categories of patients.
[c] Permanent discontinuation is discontinuation by patients who were still alive more than 5 days later and were not taking study drug at the closing visit.
N Total number of patients in each treatment group.
n Subset of patients.

6.4.2 Common adverse events (CHARM-Alternative)

The most common adverse events profile in CHARM-Alternative was similar to that of CHARM-Added in that cardiac failure/cardiac failure-aggravated occurred more often in placebo patients, while hypotension and abnormal renal function were reported more frequently for the candesartan group (Table 24).

Table 24 Most commonly reported adverse events in the total population (CHARM-Alternative)

Adverse event[a]	Placebo N=1015		Candesartan N=1013	
	n and percentage (%) of patients			
Cardiac failure/cardiac failure, aggravated	359	(35.4)	280	(27.6)
Hypotension	90	(8.9)	193	(19.1)
Angina pectoris/angina pectoris, aggravated	120	(11.8)	127	(12.5)
Renal function abnormal/renal dysfunction, aggravated	50	(4.9)	141	(13.9)
Sudden death	106	(10.4)	80	(7.9)
Pneumonia	75	(7.4)	83	(8.2)
Myocardial infarction	68	(6.7)	85	(8.4)
Arrhythmia ventricular	79	(7.8)	73	(7.2)
Cerebrovascular disorder	61	(6.0)	52	(5.1)
Arrhythmia atrial	44	(4.3)	56	(5.5)

[a] Adverse events are defined as all serious adverse events and all adverse events that led to discontinuation or reduction of the investigational product.

Note: This table presents the 10 most frequently reported adverse events.

N Total number of patients in each treatment group.

n Subset of patients with most commonly reported adverse events.

6.4.3 Discontinuations according to reason for ACE inhibitor intolerance (CHARM-Alternative)

In the CHARM-Alternative trial, enrollment was restricted to patients with a history of intolerance to ACE inhibitors. Table 25 displays study drug discontinuation in CHARM-Alternative according to corresponding reasons for ACE-inhibitor intolerance.

Table 25 Reasons for ACE-inhibitor intolerance at study entry and study drug discontinuation for the corresponding reason, CHARM-Alternative

	Placebo (N_1=1015)		Candesartan (N_1=1013)	
Reason for ACE-inhibitor intolerance at entry	**Patients intolerant to ACE inhibitors at entry N_2 (%),**	**Patients who discontinued study drug for the same reason[a] n (%)**	**Patients intolerant to ACE inhibitors at entry N_2 (%),**	**Patients who discontinued study drug for the same reason[a] n (%)**
Cough	751 (74.0)	4 (0.5)	704 (69.5)	2 (0.3)
Hypotension	119 (11.7)	5 (4.2)	143 (14.1)	13 (9.1)
Renal dysfunction	100 (9.9)	12 (12.0)	134 (13.2)	31 (23.1)
Angioedema	44 (4.3)	0	39 (3.8)	1 (2.6)

[a] Calculated with respect to patients with the same reason for ACE intolerance at entry.
ACE Angiotensin-converting enzyme.
N_1 Total number of patients in treatment groups.
N_2 Total number of patients intolerant to ACE inhibitors at entry (a patient may have more than 1 reason for ACE inhibitor intolerance). Calculated with respect to total patients in the treatment group.
n Subset of patients. Calculated with respect to total patients in the treatment group with the same reason for ACEi intolerance.

Cough was the most frequently cited reason for ACE-inhibitor intolerance. Cough as a recurring event in these patients led to discontinuation of study treatment in 4 of 751 patients in the placebo group and 2 of 704 patients in the candesartan group, ie, less than a 1% recurrence rate in both groups. For patients with a history of symptomatic hypotension recorded as a reason for ACE-inhibitor intolerance, 4.2% in the placebo group and 9.1% in the candesartan group discontinued study treatment because of hypotension. Among the patients with abnormal renal function as reason for ACE-inhibitor intolerance, discontinuation for abnormal renal function as a recurring event was reported for 12.0% of patients in the placebo group and 23.1% in the candesartan group.

Of the 83 patients who entered CHARM-Alternative with a history of angioedema as the reason for ACE intolerance, 1 of 39 candesartan-treated patients discontinued study treatment because of angioedema. Another 2 of these 39 patients developed angioedema but the episodes did not necessitate study drug discontinuation. None of the 44 placebo-treated patients discontinued study treatment because of angioedema.

Of patients who had no previous history of angioedema as a reason for ACE inhibitor intolerance, none developed angioedema, or required study drug discontinuation for angioedema.

6.5 Safety in CHARM-Preserved

6.5.1 Categories of adverse events

A summary of adverse events by category for CHARM-Preserved is presented in Table 26. Median follow-up in CHARM-Preserved was 36.5 months for the placebo group and 36.6 months for the candesartan group. Mortality overall was lower in CHARM-Preserved

than in CHARM-Added and CHARM-Alternative. In CHARM-Preserved, the proportion of fatal SAEs was similar in both treatment groups; otherwise, the pattern of adverse events was similar to that of the other 2 trials.

Table 26 Summary of adverse events (CHARM-Preserved)

Categories of patients[a]	Placebo[b] N=1509 n (%)		Candesartan[b] N=1514 n (%)	
Any adverse events (AEs)	1060	(70.2)	1074	(70.9)
Serious AEs (SAEs)	1010	(66.9)	973	(64.3)
SAEs that led to death	238	(15.8)	244	(16.1)
SAEs that did not lead to death	963	(63.8)	939	(62.0)
Discontinuation of investigational product because of AEs[c]	192	(12.7)	269	(17.8)
Dose reduction of the investigational product because of AEs	125	(8.3)	192	(12.7)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each category. Adverse events include all serious adverse events and all adverse events that led to discontinuation or reduction of the dose of study treatment.
[b] Only 1 occurrence of an event is counted during the study period, for categories of patients.
[c] Permanent discontinuation is discontinuation by patients who were still alive more than 5 days later and were not taking study drug at the closing visit.
N Total number of patients in each treatment group.
n Subset of patients.

6.5.2 Common adverse events in CHARM-Preserved

The common adverse event profile in CHARM-Preserved was generally similar to that of CHARM-Added and CHARM-Alternative. Among the most common adverse events, cardiac failure/cardiac failure-aggravated and angina pectoris/angina pectoris-aggravated occurred more often in placebo patients, and hypotension and renal function abnormal occurred more often in candesartan patients (Table 27).

Table 27 Most commonly reported adverse events in the total population (CHARM-Preserved)

Adverse event[a]	Placebo N=1509		Candesartan N=1514	
	n and percentage (%) of patients			
Cardiac failure/cardiac failure, aggravated	356	(23.6)	300	(19.8)
Angina pectoris/angina pectoris, aggravated	217	(14.4)	213	(14.1)
Hypotension	125	(8.3)	247	(16.3)
Renal function abnormal/renal dysfunction, aggravated	79	(5.2)	150	(9.9)
Pneumonia	116	(7.7)	102	(6.7)
Fibrillation atrial	119	(7.9)	93	(6.1)
Myocardial infarction	101	(6.7)	87	(5.7)
Coronary artery disorder	102	(6.8)	83	(5.5)
Cerebrovascular disorder	97	(6.4)	82	(5.4)
Chest pain	81	(5.4)	82	(5.4)

[a] Adverse events are defined as all serious adverse events and all adverse events that led to discontinuation or reduction of the investigational product.

Note: This table presents the 10 most frequently reported adverse events.

N Total number of patients in each treatment group.

n Subset of patients with most commonly reported adverse events.

6.6 Safety overall (CHARM 3-trials pooled)

6.6.1 Categories of adverse events

In the CHARM 3-trials pooled population, slightly more deaths and non-fatal SAEs occurred in the placebo group than in the candesartan group but more patients were discontinued due to an adverse event in the candesartan group (Table 28).

Table 28 Summary of adverse events (CHARM 3-trials pooled)

Categories of patients[a]	Placebo[b] N=3796 n (%)		Candesartan[b] N=3803 n (%)	
Any adverse events (AEs)	2799	(73.7)	2841	(74.7)
Serious AEs (SAEs)	2698	(71.1)	2624	(69.0)
SAEs that led to death	947	(24.9)	887	(23.3)
SAEs that did not lead to death	2487	(65.5)	2432	(63.9)
Discontinuation of investigational product because of AEs[c]	613	(16.1)	799	(21.0)
Dose reduction of the investigational product because of AEs	324	(8.5)	569	(15.0)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each category. Adverse events include all serious adverse events and all adverse events that led to discontinuation or reduction of the dose of study treatment.
[b] Only 1 occurrence of an event is counted during the study period, for categories of patients.
[c] Permanent discontinuation is discontinuation by patients who were still alive more than 5 days later and were not taking study drug at the closing visit.
N Total number of patients in each treatment group.
n Subset of patients.

6.6.2 Common adverse events (CHARM 3-trials pooled)

The most common adverse events in the CHARM 3-trials pooled population are presented in Table 29. Among the 5 most common adverse events, cardiac failure/cardiac failure-aggravated, angina pectoris/angina pectoris-aggravated, and sudden death occurred more often in the placebo group; hypotension and renal failure/renal failure-aggravated occurred more often in the candesartan group. Hyperkalemia was also more frequently reported for the candesartan patients. The adverse events of hypotension, abnormal renal function, and hyperkalemia are also discussed in Section 6.7. The median follow-up time for placebo was 37.6 months and for candesartan it was 37.9 months.

Table 29 Most commonly reported adverse events, sorted by descending frequency (CHARM 3-trials pooled)

Adverse event[a]	Placebo N=3796		Candesartan N=3803	
	n and percentage (%) of patients			
Patients who had at least 1 adverse event	**2799**	**(73.7)**	**2841**	**(74.7)**
Cardiac failure/cardiac failure, aggravated	1187	(31.3)	1001	(26.3)
Hypotension	399	(10.5)	736	(19.4)
Angina pectoris/angina pectoris, aggravated	506	(13.3)	490	(12.9)
Renal function abnormal/renal dysfunction, aggravated	248	(6.5)	487	(12.8)
Sudden death	348	(9.2)	291	(7.7)
Pneumonia	299	(7.9)	261	(6.9)
Myocardial infarction	257	(6.8)	242	(6.4)
Fibrillation atrial	249	(6.6)	202	(5.3)
Arrhythmia ventricular	239	(6.3)	193	(5.1)
Cerebrovascular disorder	216	(5.7)	203	(5.3)
Coronary artery disorder	200	(5.3)	205	(5.4)
Chest pain	202	(5.3)	183	(4.8)
Arrhythmia atrial	197	(5.2)	187	(4.9)
Hyperkalemia	84	(2.2)	242	(6.4)
Tachycardia supraventricular	177	(4.7)	148	(3.9)
Dizziness/vertigo	115	(3.0)	168	(4.4)
Accident and/or injury	143	(3.8)	125	(3.3)
Tachycardia ventricular/arrhythmia/arrhythmia, aggravated	132	(3.5)	128	(3.4)
Syncope	119	(3.1)	139	(3.7)
Anemia	110	(2.9)	145	(3.8)
Dyspnea/dyspnea (aggravated)	123	(3.2)	100	(2.6)
Pulmonary edema	109	(2.9)	109	(2.9)
Renal failure acute	91	(2.4)	121	(3.2)
Cardiomyopathy	101	(2.7)	98	(2.6)
Diabetes mellitus/diabetes mellitus aggravated	102	(2.7)	90	(2.4)
Bronchitis/bronchitis aggravated	85	(2.2)	81	(2.1)
Renal failure, not otherwise specified	74	(1.9)	88	(2.3)
Dehydration	54	(1.4)	106	(2.8)
Chronic obstructive airways disease	80	(2.1)	76	(2.0)
Bradycardia	78	(2.1)	75	(2.0)
Diarrhea	54	(1.4)	98	(2.6)

[a] Adverse events are defined as all serious adverse events and all adverse events that led to discontinuation or reduction of the investigational product. This table uses a ≥2.0 % cut-off in the total population .

N Total number of patients in each treatment group.

n Subset of patients with most commonly reported adverse events.

6.6.3 Serious, fatal adverse events (CHARM 3-trials pooled)

Overall, fatal adverse events occurred more frequently in the placebo group than in the candesartan group. Sudden death and cardiac failure/cardiac failure-aggravated were the most commonly cited SAEs leading to death; these occurred more frequently in the placebo group (Table 30). Other specific fatal adverse events were less common (≤2%) and between-treatment frequency differences were small; these included myocardial infarction, pneumonia, cerebrovascular disorder, and death.

Table 30 Most common adverse events leading to death, sorted by decreasing frequency (CHARM 3-trials pooled)

	Placebo N=3796		Candesartan N=3803	
	n and percentage (%) of patients			
Patients who had fatal serious adverse events	947	(24.9)	887	(23.3)
Sudden death	348	(9.2)	291	(7.7)
Cardiac failure/cardiac failure, aggravated	256	(6.7)	192	(5.0)
Myocardial infarction	57	(1.5)	77	(2.0)
Pneumonia	47	(1.2)	30	(0.8)
Cerebrovascular disorder	39	(1.0)	36	(0.9)
Death	31	(0.8)	35	(0.9)
Cardiac arrest	24	(0.6)	27	(0.7)
Sepsis	26	(0.7)	19	(0.5)
Fibrillation ventricular	23	(0.6)	17	(0.4)
Cardiomyopathy	19	(0.5)	14	(0.4)

Note: This table presents the 10 most frequently reported adverse events leading to death.
N Total number of patients in each treatment group.
n Subset of patients with serious adverse events that led to death. (An additional 3 patients are listed in the safety analyses because efficacy data included only patients with onset of the serious adverse event occurring prior to 31 March, the last day of the study).

6.6.4 Adverse events leading to permanent study drug discontinuation and adverse events leading to dose reduction (CHARM 3-trials pooled)

The most common reason for stopping study drug was cardiac failure/cardiac failure-aggravated, which occurred more frequently among placebo patients. Abnormal renal function, hypotension, and hyperkalemia were the next most common discontinuation reasons and these occurred more frequently in the candesartan group (Table 31).

Table 31 **Most common adverse events leading to discontinuation of study drug, sorted by decreasing frequency (CHARM 3-trials pooled)**

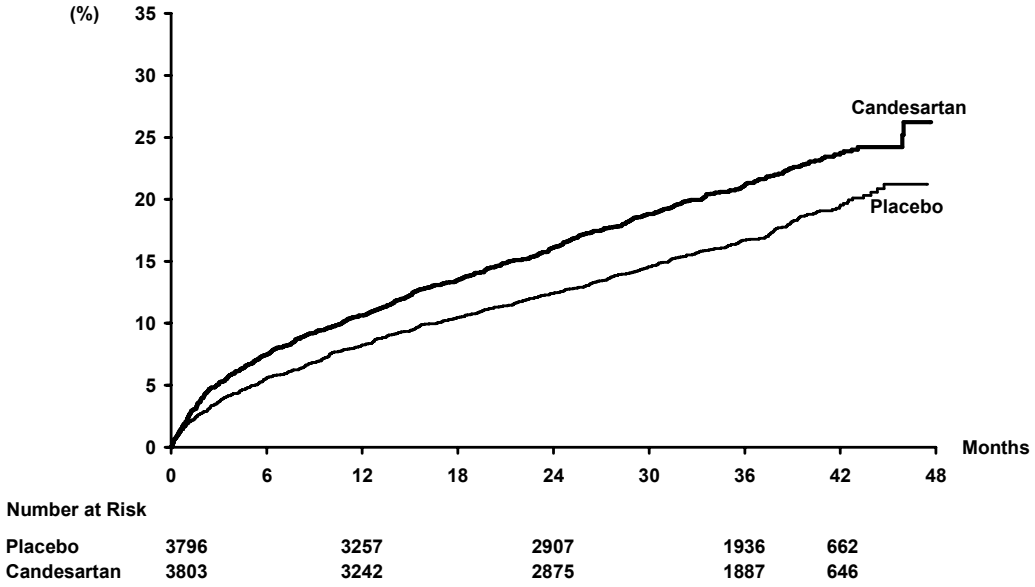
	Placebo N=3796		Candesartan N=3803	
	n and percentage (%) of patients			
Discontinued treatment because of adverse events	613	(16.1)	799	(21.0)
Cardiac failure/cardiac failure, aggravated	186	(4.9)	165	(4.3)
Renal function abnormal/renal dysfunction, aggravated	110	(2.9)	238	(6.3)
Hypotension	76	(2.0)	155	(4.1)
Hyperkalemia	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	20	(0.5)	30	(0.8)
Dizziness/vertigo	14	(0.4)	32	(0.8)
Pneumonia	22	(0.6)	21	(0.6)

Note: This table presents the 10 most frequently reported adverse events leading to discontinuation of study drug.
N Total number of patients in each treatment group.
n Subset of patients with adverse events that led to permanent discontinuation from study drug.

Overall, the study drug discontinuation rate with placebo was 130.4/1000 follow-up years and with candesartan it was 164.4/1000 follow-up years.

The discontinuation rate for adverse events during the first 6 months was 3.7% and 6.3% in the placebo and candesartan groups, respectively. Figure 13 below illustrates permanent discontinuation of investigational product for the CHARM 3-trials pooled population based on the Kaplan-Meier method and suggests a rather constant discontinuation rate over the trial time for both treatment groups once initial dose escalation was completed.

Figure 13 **Discontinuation of investigational product because of an adverse event (CHARM 3-trials pooled)**



The most common adverse events leading to a candesartan dose reduction were similar to those leading to study drug discontinuation, ie, hypotension, renal function abnormal/renal dysfunction-aggravated, hyperkalemia, as well as dizziness/vertigo (Table 32).

Table 32 **Adverse events leading to dosage reduction, sorted by decreasing frequency (CHARM 3-trials pooled)**

	Placebo N=3796	Candesartan N=3803
	n and percentage (%) of patients	
Dose of study drug was reduced because of adverse events[a]	324 (8.5)	569 (15.0)
Hypotension	136 (3.6)	315 (8.3)
Renal function abnormal/renal dysfunction, aggravated	50 (1.3)	99 (2.6)
Dizziness/vertigo	38 (1.0)	54 (1.4)
Hyperkalemia	17 (0.4)	60 (1.6)
Cardiac failure, aggravated	29 (0.8)	30 (0.8)

[a] Does not include patients who permanently discontinued because of an adverse event. This table presents the 5 most frequently reported reasons for dose reduction.
N Total number of patients in each treatment group.
n Subset of patients with adverse events that led to reduction of dose of study drug.

6.7 Adverse events of hypotension, renal function abnormal, hyperkalemia, and angioedema (CHARM 3-trials pooled)

6.7.1 Hypotension

Hypotension was cited as an adverse event for 10.5% of placebo patients and 19.4% of candesartan patients but it was cause for stopping treatment in 2.0% and 4.1% of patients, respectively. There was a higher rate of discontinuations because of hypotension in the very elderly compared to patients less than 75 years, and in patients entering the trial with a low systolic blood pressure (SBP) (<100 mm Hg) compared to patients with SBP above 100 mm Hg. Hypotension was reported as the reason for hospitalization for 2.0% of the candesartan patients and 4.1% of placebo patients.

Hypotension was rarely reported as cause of death (4 [0.1%] placebo patients and 6 [0.2%] candesartan patients) (Table 33).

Table 33 Patients with hypotension as an adverse event in the CHARM 3-trials pooled population

		Placebo		Candesartan	
	Subgroup	**N**	**n (%)**	**N**	**n (%)**
Hypotension as an AE		3796[a]	399 (10.5)	3803[a]	736 (19.4)
Discontinued due to hypotension		3796[a]	76 (2.0)	3803[a]	155 (4.1)
Age, years[b]	≥75	884[c]	28 (3.2)	852[c]	44 (5.2)
	<75	2912[c]	48 (1.6)	2951[c]	111 (3.8)
SBP, mm Hg[b]	<100	92[c]	4 (4.4)	126[c]	19 (15.1)
	≥100	3703[c]	72 (1.9)	3677[c]	136 (3.7)
Hospitalization for hypotension		2423[d]	49 (2.0)	2374[d]	98 (4.1)
Fatal events due to hypotension		3796[a]	4 (0.1)	3803[a]	6 (0.2)

[a] Total number of patients in the treatment group.
[b] At baseline.
[c] Total number of patients in a specific subgroup regardless of adverse event status or discontinuation status.
[d] Number of patients with at least one hospitalization for any reason.
n Subset of patients.

6.7.2 Abnormal renal function

Abnormal renal function was reported for 6.5% of placebo patients and 12.8% of candesartan patients but was a cause for study drug discontinuation for 2.9% and 6.3% of patients, respectively. Patients with abnormal renal function were more likely to discontinue study drug if they were elderly, taking an ACE inhibitor, or taking spironolactone. Patients entering the CHARM program with a serum creatinine level ≥2.0 mg/dl had a higher discontinuation rate for abnormal renal function compared to patients with creatinine levels less than 2.0 mg/dl whether in the placebo or the candesartan group. Adverse renal events including renal

failure led to hospitalization for 2.8% of the placebo patients and 5.2% of the candesartan patients.

A small proportion of patients required dialysis (1.3 % placebo and 1.4% candesartan) and a small proportion of patients died of renal adverse events (0.9% placebo and 0.8% candesartan). Typically, patients who required dialysis or who died of a renal event had multiple other co-morbid conditions and contributing causes of death (Table 34).

Table 34 Patients with adverse renal events in the CHARM 3-trials pooled

		Placebo		Candesartan	
	Subgroup	**N**	**n (%)**	**N**	**n (%)**
Abnormal renal function/aggravated renal dysfunction as an AE		3796[a]	248 (6.5)	3803[a]	487 (12.8)
Discontinued due to AE of abnormal renal function/aggravated renal dysfunction		3796[a]	110 (2.9)	3803[a]	238 (6.3)
Age, years[b]	≥75	884[c]	35 (4.0)	852[c]	67 (7.9)
	<75	2912[c]	75 (2.6)	2951[c]	171 (5.8)
ACE inhibitor[b]	Yes	1552[c]	61 (3.9)	1573[c]	125 (8.0)
	No	2244[c]	49 (2.2)	2230[c]	113 (5.1)
Spironolactone[b]	Yes	629[c]	26 (4.1)	643[c]	63 (9.8)
	No	3167[c]	84 (2.6)	3160[c]	175 (5.5)
Creatinine ≥2.0 mg/dl[b]	Yes	70[c,d]	16 (22.9)	84[c,d]	22 (26.2)
	No	1271[c,d]	45 (3.5)	1250[c,d]	88 (7.0)
Hospitalization for renal adverse events		2423[e]	68 (2.8)	2374[e]	124 (5.2)
Dialysis		3796[a]	49 (1.3)	3803[a]	55 (1.4)
Serious, fatal outcome[f]		3796[a]	36 (0.9)	3803 [a]	31 (0.8)
Creatinine value ≥2 times the baseline value		1279[c,d]	47 (3.7)	1263[c,d]	82 (6.5)

[a] Total number of patients in the treatment group
[b] At baseline.
[c] Total number of patients in a specific subgroup regardless of adverse event status or discontinuation status.
[d] Patients who had baseline and follow-up values from North American sites.
[e] Number of patients hospitalized for any reason.
[f] Fatal outcomes are reported for patients with any of the following adverse event terms: renal failure acute; renal failure, not otherwise specified (NOS); and renal function abnormal/renal dysfunction-aggravated. Number of fatal outcomes because of renal disease may not indicate the primary reason for death.
n Subset of patients.

6.7.2.1 Change in renal function

Patients who developed a renal adverse event typically did not develop progressive decline in renal function to end-stage renal disease; this is illustrated in Table 35 which presents a post hoc analysis of the change in renal function from baseline to last visit as determined by

change in eGFR (MDRD equation) using the patients for whom serum creatinine levels were collected (North American sites).

Patients in both treatment groups, who experienced a renal adverse event or who discontinued for a renal adverse event, exhibited small to modest declines in eGFR.

Table 35 Change in estimated eGFR, baseline to last value carried forward, North American patients (CHARM 3-trials pooled)

Variable:eGFR	Placebo		Candesartan	
	Patients with AE of abnormal renal function N=161	Patients who discontinued due to AE of abnormal renal function N=62	Patients with AE of abnormal renal function N=233	Patients who discontinued due to AE of abnormal renal function N=116
Baseline, ml/min/1.73 m^2				
Mean (SD)	54.1 (25.8)	45.7 (18.4)	55.1 (22.3)	53.4 (22.5)
Median (min, max)	49.5 (3.2, 180.9)	42.1 (3.2, 112.7)	51.9 (21.4, 130.2)	48.7 (21.4, 124.9)
LVCF, ml/min/1.73 m^2				
Mean (SD)	44.7 (22.1)	35.1 (14.3)	43.1 (19.7)	38.7 (16.8)
Median (min, max)	42.3 (5.5, 136.7)	34.8 (5.5, 81.6)	39.2 (7.7, 146.8)	37.1 (7.7, 90.0)
Change from baseline to LVCF, ml/min/1.73 m^2				
Mean (SD)	–9.4 (17.9)	–10.6 (15.3)	–12.0 (18.4)	–14.7 (19.9)
Median (min, max)	–8.1(–62.5, 36.1)	–9.5 (–48.5, 19.0)	–10.3 (–97.3, 37.1)	–12.3 (–97.3, 22.6)

[a] Abnormal renal function includes the following adverse events: Renal function abnormal, renal dysfunction aggravated, renal failure not otherwise specified (NOS), renal failure acute, renal failure aggravated. Adverse events are not mutually exclusive, a patient may have more than 1 renal-related adverse event counted.

Note: Glomerular filtration rate estimated by Modification of Diet in Renal Disease (MDRD) equation.

AE Adverse event.

LVCF Last value carried forward.

6.7.3 Hyperkalemia

Hyperkalemia was reported as an adverse event for 2.2% of placebo patients and 6.4% of the candesartan patients and was a cause for study drug discontinuation in 0.6% and 2.4% of patients, respectively. The elderly, patients taking ACE inhibitors, patients taking spironolactone, or patients who were diabetic discontinued study drug at slightly higher rates; those with a baseline serum creatinine ≥2.0 mg/dl or those with a potassium ≥5.0 mEq/L had moderately greater discontinuation rates than patients with lower values. Hospitalization for hyperkalemia was reported for 0.6% of placebo patients and 1.5% of candesartan patients.

Fatal hyperkalemia events were uncommon: 1 patient in the placebo group and 2 in the candesartan group. In the subset of patients (N=2604) with scheduled laboratory measures performed by the central laboratory, 1.1% of placebo and 2.4% of candesartan patients had at least 1 post-randomization serum potassium level >6.0 mEq/L, Table 36.

Table 36 Patients with hyperkalemia as an adverse event (CHARM 3-trials pooled)

		Placebo		Candesartan	
	Subgroup	**N**	**n (%)**	**N**	**n (%)**
Hyperkalemia as an AE		3796[a]	84 (2.2)	3803	242 (6.4)
Discontinued due to an AE of hyperkalemia		3796[a]	22 (0.6)	3803	93 (2.4)
Age, years[b]	≥75	884[c]	8 (0.9)	852[c]	36 (4.2)
	<75	2912[c]	14 (0.5)	2951[c]	57 (1.9)
ACE inhibitor[b]	Yes	1552[c]	16 (1.0)	1573[c]	57 (3.6)
	No	2244[c]	6 (0.3)	2230[c]	36 (1.6)
Spironolactone[b]	Yes	629[c]	7 (1.1)	643[c]	23 (3.6)
	No	3167[c]	15 (0.5)	3160[c]	70 (2.2)
Creatinine ≥2.0 mg/dl[b]	Yes	70[c,d]	4 (5.7)	84[c,d]	9 (10.7)
	No	1271[c,d]	10 (0.8)	1250[c,d]	31 (2.5)
Potassium ≥5.0 mEq/L[b]	Yes	125[c,d]	5 (4.0)	135[c,d]	13 (9.6)
	No	1213[c,d]	9 (0.7)	1197[c,d]	27 (2.3)
History of diabetes[b]		1075[c]	13 (1.2)	1088[c]	31 (2.8%)
Hospitalization for hyperkalemia		2423[e]	14 (0.6)	2374[e]	36 (1.5)
Fatal outcome due to an AE of hyperkalemia		3796[a]	1 (<0.1)	3803[a]	2 (<0.1)
Potassium value ≥6.0 mEq/L after randomization[d]		1310[c,d]	15 (1.1)	1294[c,d]	31 (2.4)

[a] Total number of patients in the treatment group
[b] At baseline.
[c] Total number of patients in a specific subgroup regardless of adverse event status or discontinuation status.
[d] North American sites.
[e] Number of patients hospitalized for any reason.
n Subset of patients.

6.7.4 Angioedema

In the CHARM 3-trials pooled population, 8 events of angioedema were reported: 5 in the candesartan group and 3 in the placebo group (Table 37).

Three of the patients in the candesartan group who reported angioedema as an adverse event had angioedema stated as the reason for ACE inhibitor intolerance at baseline. The remaining 2 patients in the candesartan group who had angioedema were receiving an ACE inhibitor at the start of the event. One event led to hospitalization (a patient in CHARM-Added had candesartan continued but the ACE inhibitor discontinued) and for 2 patients the events led to study drug discontinuation. Thus, for 3 of the 5 patients, treatment with candesartan

continued, and angioedema did not recur; for 1 of these patients, the dose of candesartan treatment was reduced.

There were no reports of angioedema among 326 black patients (164 placebo and 162 candesartan patients) in the CHARM pooled population.

Table 37 Patients who developed angioedema (CHARM 3-trials pooled)

	Placebo	Candesartan
	Developed angioedema	Developed angioedema
CHARM-Alternative[a]	0 of 1015	3 of 1013
CHARM-Added[b]	3 of 1272	2 of 1276
CHARM-Preserved[c]	0 of 1509	0 of 1514

[a] Of the patients with no history of angioedema with ACE inhibitor at study initiation (974 candesartan patients and 971 placebo patients), none developed angioedema in this trial.

[b] Patients were required to receive an ACE inhibitor in the trial; 1 patient in each treatment group had an event of angioedema that led to permanent discontinuation.

[c] A total of 576 (19.1%) patients (280 placebo and 296 candesartan) were receiving ACE inhibitors at baseline. A total of 634 (25.2%) patients (337 placebo and 297 candesartan) were receiving ACE inhibitors at the closing visit.

6.8 Safety in subgroups (CHARM 3-trials pooled population)

6.8.1 Age

The most common adverse events leading to death by age group are presented in Table 38. Similar to the analyses of deaths in the overall CHARM 3-trials pooled population (Table 30), most deaths within subgroups were attributed to sudden death and to cardiac failure. As expected, these CV causes of death were more common in older patients. Cause-specific CV mortality tended to be lower with candesartan than with placebo, with the possible exception of death due to MI, regardless of age group.

Table 38 **All-cause mortality - most common adverse events leading to death, by age groups and sorted by descending frequency in the total population (CHARM 3-trials pooled)**

Adverse event	Placebo				Candesartan			
	<75 years		≥75 years		<75 years		≥75 years	
	N=2912		N=884		N=2951		N=852	
	n	(%)	n	(%)	n	(%)	n	(%)
Sudden death	204	(7.0)	72	(8.1)	168	(5.7)	63	(7.4)
Cardiac failure/cardiac failure aggravated	89	(3.1)	60	(6.8)	53	(1.8)	26	(3.1)
Myocardial infarction	21	(0.7)	14	(1.6)	39	(1.3)	17	(2.0)
Cerebrovascular disorder	14	(0.5)	9	(1.0)	12	(0.4)	7	(0.8)
Pneumonia	12	(0.4)	13	(1.5)	6	(0.2)	5	0.6)

Note: This tables presents the 5 most frequently reported adverse events leading to death, by age group. Data were derived while patients were on active treatment.
N Total number of patients in each age group.
n Subset of patients with adverse events leading to death, by age.

Subgroup analyses of study drug discontinuations stratified by age failed to identify any notable subgroup by treatment differences (Table 39). Elderly patients (≥75 years) as a group, however, were more likely to discontinue study drug than were younger patients.

Table 39 **Most common adverse events leading to discontinuation of study drug by age groups, sorted by decreasing frequency in the total population (CHARM 3-trials pooled)**

Adverse event	Placebo				Candesartan			
	<75 years		≥75 years		<75 years		≥75 years	
	N=2912		N=884		N=2951		N=852	
	n	(%)	n	(%)	n	(%)	n	(%)
Cardiac failure/cardiac failure aggravated	136	(4.7)	50	(5.7)	121	(4.1)	44	(5.2)
Renal function abnormal/renal dysfunction aggravated	75	(2.6)	35	(4.0)	171	(5.8)	67	(7.9)
Hypotension	48	(1.6)	28	(3.2)	111	(3.8)	44	(5.2)
Hyperkalemia	14	(0.5)	8	(0.9)	57	(1.9)	36	(4.2)
Myocardial infarction	22	(0.8)	9	(1.0)	17	(0.6)	9	(1.1)

Note: This tables presents the 5 most frequently reported adverse events leading to discontinuation of study drug, by age group.
N Total number of patients in each age group.
n Subset of patients who discontinued study drug because of an adverse event, by age.

6.8.2 Safety in patients with abnormal renal function

The proportion of patients who died or discontinued the study, stratified by eGFR is presented in Table 40. (eGFR data could only be determined at North American sites.) While the proportion of patients who died tended to be higher among patients with lower eGFRs, there were no notable placebo vs candesartan differences across eGFR strata. Study drug discontinuation rates tended to be higher among patients with lower eGFRs; there were no notable placebo vs candesartan differences across eGFR strata other than the overall trend for fewer placebo patients than candesartan patients to discontinue study drug.

Table 40 Patients in North America who died or discontinued study drug, stratified by glomerular filtration rate (CHARM 3-trials pooled)

Adverse event	Placebo N=1376					Candesartan N=1367				
	<30 ml/min	≥30-<60 ml/min	≥60-<90 ml/min	≥90 ml/min	NA	<30 ml/min	≥30-<60 ml/min	≥60-<90 ml/min	≥90 ml/min	NA
Number of patients in group	43	444	566	288	35	50	428	570	285	34
Number and % of patients who died	14 (32.6)	158 (35.6)	115 (20.3)	39 (13.5)	6 (17.1)	23 (46.0)	136 (31.8)	103 (18.1)	37 (13.0)	8 (23.5)
Number and % of patients who discontinued study drug	19 (44.2)	137 (30.9)	84 (14.9)	33 (11.5)	8 (22.9)	28 (56.0)	162 (37.9)	128 (22.5)	39 (13.7)	8 (23.5)

N Total number of patients in North America with glomerular filtration rate calculated at baseline, by treatment group.
NA Patients with missing data.

6.8.3 Safety with concomitant use of other heart failure treatment medications

Consistent with the lower mortality findings with candesartan treatment described in Section 5.5, patients treated with candesartan experienced a lower mortality risk relative to placebo even if they received other concomitant heart failure treatments including: digitalis, diuretics, ACE inhibitors, beta-blockers, spironolactone, or combinations of these agents. Mortality was lower with candesartan treatment relative to placebo for patients taking an ACE inhibitor plus a beta-blocker ('triple therapy') (23.1% candesartan, 76.4 deaths/1000 follow-up years; and 25.0% placebo, 84.5 deaths/1000 follow-up years), and those taking an ACE inhibitor plus a beta-blocker plus spironolactone ('quadruple therapy') (23.7% candesartan, 78.0 deaths/1000 follow-up year; and 29.4% placebo, 104.3 deaths/1000 follow-up years) (Table 41).

Table 41 Candesartan versus placebo for serious adverse events leading to death, by concomitant heart failure therapy (CHARM 3-trials pooled)

Category of baseline concomitant therapy		Event: all-cause mortality						
			Placebo			Candesartan		
		N	N_p	n_p(%)[a]	Events/ 1000 years	N_c	n_c(%)[a]	Events/ 1000 years
All fatal SAEs		7599	3796	947 (24.9)	88.4	3803	887 (23.3)	81.0
Digitalis glycoside	No	4345	2164	419 (19.4)	66.4	2181	426 (19.5)	67.5
	Yes	3254	1632	528 (32.3)	119.8	1622	461 (28.4)	99.5
Diuretics	No	1313	660	75 (11.4)	36.8	653	63 (9.6)	31.4
	Yes	6286	3136	872 (27.8)	100.3	3150	824 (26.2)	92.2
ACE inhibitors	No	4474	2244	491 (21.9)	78.6	2230	456 (20.5)	72.1
	Yes	3125	1552	456 (29.4)	102.1	1573	431 (27.4)	93.2
Beta-blocker	No	3396	1695	519 (30.6)	112.8	1701	481 (28.3)	101.3
	Yes	4203	2101	428 (20.4)	70.1	2102	406 (19.3)	65.5
Spironolactone	No	6327	3167	730 (23.1)	80.2	3160	698 (22.1)	75.8
	Yes	1272	629	217 (34.5)	134.6	643	189 (29.4)	108.5
ACE inhibitors and β-blocker	No	5853	2924	729 (25.0)	89.6	2929	685 (23.4)	82.5
	Yes	1746	872	218 (25.0)	84.5	874	202 (23.1)	76.4
ACE inhibitors and β-blocker and spironolactone	No	7315	3643	902 (24.8)	87.7	3672	856 (23.3)	81.1
	Yes	284	153	45 (29.4)	104.3	131	31 (23.7)	78.0

[a] Includes 2 placebo-treated patients and 1 candesartan-treated patient who died after the 31 March 2003 CHARM studies completion date.
N Total number of patients (placebo plus candesartan) by category of concomitant therapy, by therapy use (no or yes).
N_p Total number of patients in the placebo group by category of concomitant therapy, by therapy use (no or yes).
n_p Number of patients who died in the placebo group by category of concomitant therapy, by therapy use (no or yes).
N_c Total number of patients in the candesartan group by category of concomitant therapy, by therapy use (no or yes).
n_c Number of patients who died in the candesartan group by category of concomitant therapy, by therapy use (no or yes).
SAE Serious adverse event.

Patients receiving concomitant heart failure drugs, including triple therapy and quadruple therapy, did not exhibit a notably excessive risk for hospitalization, although hospitalization rates were slightly lower for placebo than candesartan for patients taking spironolactone or spironolactone plus an ACE inhibitor plus a beta-blocker (Table 42).

Table 42 Candesartan versus placebo for the endpoint all-cause hospitalization, by concomitant therapy (CHARM 3-trials pooled)

Category of baseline concomitant therapy		Event: All-cause hospitalization						
			Placebo			Candesartan		
		N	N_p	n_p(%)	Events/ 1000 years	N_c	n_c(%)	Events/ 1000 years
Hospitalization (any cause)		7599	3796	2423 (63.8)	373.9	3803	2374 (62.4)	352.1
Digitalis glycoside	No	4345	2164	1360 (62.8)	357.2	2181	1321 (60.6)	334.0
	Yes	3254	1632	1063 (65.1)	397.7	1622	1053 (64.9)	377.8
Diuretics	No	1313	660	358 (54.2)	268.0	653	353 (54.1)	267.1
	Yes	6286	3136	2065 (65.8)	401.4	3150	2021 (64.2)	372.9
ACE inhibitors	No	4474	2244	1399 (62.3)	365.6	2230	1321 (59.2)	330.4
	Yes	3125	1552	1024 (66.0)	386.0	1573	1053 (66.9)	383.8
Beta-blocker	No	3396	1695	1140 (67.3)	429.2	1701	1129 (66.4)	402.4
	Yes	4203	2101	1283 (61.1)	335.5	2102	1245 (59.2)	316.3
Spironolactone	No	6327	3167	2004 (63.3)	363.9	3160	1935 (61.2)	336.3
	Yes	1272	629	419 (66.6)	430.5	643	439 (68.3)	444.0
ACE inhibitors and β-blocker	No	5853	2924	1856 (63.5)	378.4	2929	1820 (62.1)	355.8
	Yes	1746	872	567 (65.0)	360.1	874	554 (63.4)	340.6
ACE inhibitors and β-blocker and spironolactone	No	7315	3643	2326 (63.8)	374.7	3672	2283 (62.2)	350.5
	Yes	284	153	97 (63.4)	356.0	131	91 (69.5)	399.6

Note: Follow-up time is calculated to first hospitalization.
N Total number of patients (placebo plus candesartan) by category of concomitant therapy, by therapy use (no or yes).
N_p Total number of patients in the placebo group by category of concomitant therapy, by therapy use (no or yes).
n_p Number of patients who were hospitalized in the placebo group by category of concomitant therapy, by therapy use (no or yes).
N_c Total number of patients in the candesartan group by category of concomitant therapy, by therapy use (no or yes).
n_c Number of patients who were hospitalized in the candesartan group by category of concomitant therapy, by therapy use (no or yes).

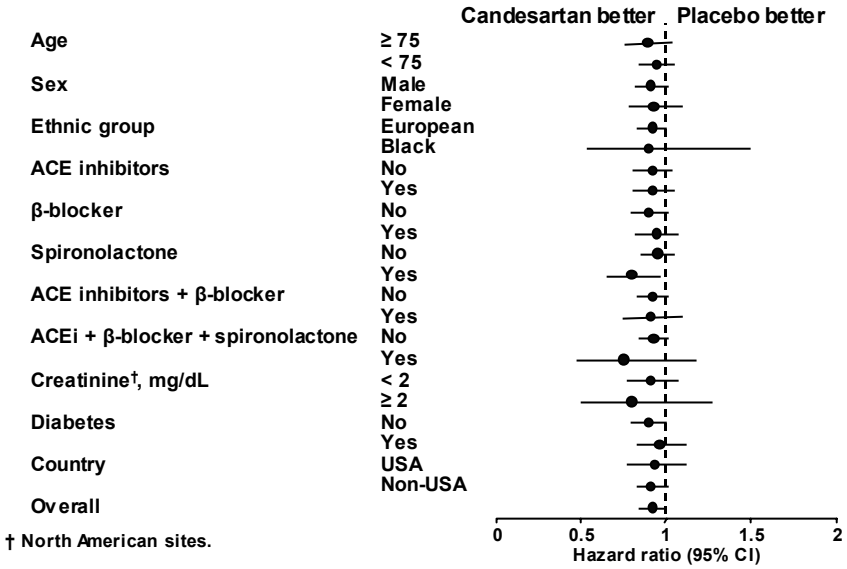
6.9 All-cause mortality and all-cause hospitalization–individual trials and CHARM 2-pooled and CHARM 3-pooled populations

Administration of candesartan to patients with heart failure does not carry an increased risk for mortal consequences. All-cause mortality was lower in candesartan patients than in placebo patients (Table 43). Furthermore, for all key subgroups, there were no subpopulations that appeared to have a higher mortality risk with candesartan (Figure 14).

Table 43 All-cause mortality, events per 1000 years follow-up

Variable	Treatment	N	Events, (Number of patients)	Total follow-up time (years)	Events/1000 follow-up years	Mean follow-up time (years)
CHARM-Added	Placebo	1272	412	3720.8	110.7	2.9
	Candesartan	1276	377	3845.8	98.0	3.0
CHARM-Alternative	Placebo	1015	296	2582.4	114.6	2.5
	Candesartan	1013	265	2658.1	99.7	2.6
CHARM-Preserved	Placebo	1509	237	4387.1	54.0	2.9
	Candesartan	1514	244	4434.3	55.0	2.9
CHARM, 2-trials pooled	Placebo	2287	708	6303.2	112.3	2.8
	Candesartan	2289	642	6503.9	98.7	2.8
CHARM, 3-trials pooled	Placebo	3796	945	10690.3	88.4	2.8
	Candesartan	3803	886	10938.2	81.0	2.9

Figure 14 All-cause mortality by subgroups, CHARM 3-trials pooled population

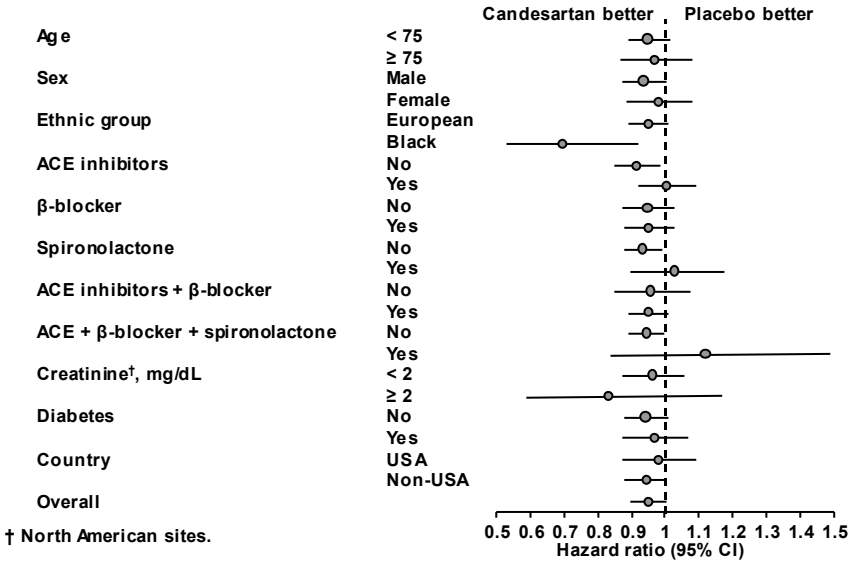


Overall, all-cause hospitalization rates were higher for placebo than for candesartan patients and there was no subgroup at excess risk for hospitalization although the rates were slightly higher for patients in the spironolactone group and spironolactone plus beta-blocker plus ACE-inhibitor group, (Table 44 and Figure 15).

Table 44 All-cause hospitalization, events per 1000 years follow-up

Variable	Treatment	N	Events, (Number of patients)	Total follow-up time (years)	Events/1000 follow-up years	Mean follow-up time (years)
CHARM-Added	Placebo	1272	858	2190.7	391.6	1.7
	Candesartan	1276	852	2296.0	371.1	1.8
CHARM-Alternative	Placebo	1015	643	1606.2	400.3	1.6
	Candesartan	1013	610	1681.6	362.7	1.7
CHARM-Preserved	Placebo	1509	922	2682.9	343.7	1.8
	Candesartan	1514	912	2764.2	329.9	1.8
CHARM, 2-trials pooled	Placebo	2287	1501	3796.9	395.3	1.7
	Candesartan	2289	1462	3977.7	367.6	1.7
CHARM, 3-trials pooled	Placebo	3796	2423	6479.8	373.9	1.7
	Candesartan	3803	2374	6741.9	352.1	1.8

Figure 15 All-cause hospitalization by subgroups, CHARM 3-trials pooled



† North American sites.

6.10 Safety findings

In CHF patients with depressed LV systolic function receiving an ACE inhibitor (CHARM-Added)

- More candesartan than placebo patients discontinued treatment due to adverse events, principally for hypotension, abnormal renal function, and hyperkalemia.

- However, all-cause mortality (110.7 deaths/1000 follow-up years, placebo; 98.0 deaths/1000 follow-up years, candesartan), and all-cause hospitalization (391.6 events/1000 follow-up years, placebo; 371.1 events/1000 follow-up years, candesartan) remained lower with candesartan than placebo.

In CHF patients with depressed LV systolic function and not receiving an ACE inhibitor because of intolerance (CHARM-Alternative)

- More candesartan than placebo patients discontinued treatment due to adverse events, principally for hypotension, abnormal renal function and hyperkalemia.

- However, all-cause mortality (114.6 deaths/1000 follow-up years, placebo; 99.7 deaths/1000 follow-up years candesartan) and all-cause hospitalization (400.3 events/1000 follow-up years, placebo; 362.7 events/1000 follow-up years candesartan) remained lower with candesartan than placebo.

Overall, in patients with CHF (CHARM–3 trials pooled):

- Adverse events of hypotension, abnormal renal function and hyperkalemia occurred more frequently in patients treated with candesartan than with placebo. These events resulted in candesartan discontinuation in 4.1% (hypotension), 6.3% (abnormal renal function), and 2.4% (hyperkalemia) patients. Patients who were elderly (>75 years of age), had low blood pressure (SBP <100 mmHg), or impaired renal function (creatinine >2.0 mg/dl) were more likely to require study drug discontinuation for these reasons. More candesartan than placebo patients were hospitalized for these reasons.

- Hospitalization (for any cause) risk was lower for heart failure patients treated with candesartan (352.1 hospitalizations/1000 patient years) than for patients treated with placebo (373.9 hospitalizations/1000 patient years). Except for patients taking spironolactone (444.0 events/1000 follow-up years for candesartan patients vs 430.5 events/1000 follow-up years for placebo patients) or spironolactone in combination with a beta-blocker and an ACE inhibitor (399.6 events/1000 follow-up years for candesartan patients vs 356.0 events/1000 follow-up years for placebo patients), there were no key subgroups that exhibited a higher risk for all-cause hospitalization with candesartan than with placebo.

- Mortality in heart failure patients was lower for patients treated with candesartan (81.0 deaths/1000 follow-up years) than in patients treated with placebo (88.4 deaths/1000 follow-up years). There were no subgroups that exhibited a higher mortality risk with candesartan than with placebo including those based on age, gender, and concomitant heart failure treatments

7. BENEFIT/RISK

The overall CHARM program of clinical trials clearly delineates new benefits for the heart failure patient treated with candesartan and it comprehensively characterizes the risks associated with the treatment. The CHARM clinical investigation included an extended observation period so as to characterize the benefits of treatment long term. The CHARM program, by design, facilitated a comprehensive safety assessment as it included a broad study population, and deliberately included potentially vulnerable patients including those unable to tolerate ACE inhibitors and patients already receiving ACE inhibitors at their individually optimized dose level. In addition, CHARM included a large proportion of elderly and very elderly patients. As a consequence, the CHARM trials established that candesartan provides a meaningful incremental contribution to contemporary treatment regimens in CHF patients with LV systolic dysfunction. Specifically:

- Candesartan reduces CV mortality and heart failure hospitalizations. It provides a benefit that is incremental to other heart failure treatments including ACE inhibitors and beta-blockers.

- Candesartan is an effective alternative heart failure treatment for patients not receiving an ACE inhibitor. In addition, candesartan is generally well tolerated by patients previously intolerant to ACE inhibitors.

The **CHARM-Added trial** addresses the previously unresolved question as to whether adding the ARB candesartan to ACE inhibitor therapy in CHF patients with LV systolic dysfunction provides incremental benefit for reducing the leading mortal and morbid consequences of heart failure without introducing excess risk. Support for a positive benefit-risk profile is evidenced by the following observations:

- The hazard ratio for the primary endpoint, CV death or hospitalization for heart failure, with a 41-month median follow-up time was 0.853 (p=0.011), which equates to a 15% relative risk reduction

- Per 1000 follow-up years, candesartan reduced CV death or 1st CHF hospitalization events:

  – 166.3 vs.141.2 (placebo vs candesartan)

- Per 1000 follow-up years, candesartan reduced both components of the composite primary endpoint

- CV mortality: 93.3 vs78.5 (placebo vs candesartan)
- 1st heart failure hospitalization: 110.1 vs 90.3 (placebo vs candesartan)

- Fewer primary endpoint events were observed for the candesartan group whether or not patients were using recommended doses of ACE inhibitors, and with or without beta-blockers, and whether receiving a beta-blocker and spironolactone in addition to an ACE inhibitor.
  - Recommended dose of ACE inhibitor: 167.1 vs 131.7 /1000 follow-up years (placebo vs candesartan)
  - Less than recommended dose of ACE inhibitor:165.5 vs 151.2 /1000 follow-up years (placebo vs. candesartan)
  - Receiving a beta-blocker: 144.2 vs 111.3/1000 follow-up years (placebo vs candesartan)
  - Not receiving a beta-blocker: 197.7 vs 183.4/1000 follow-up years (placebo vs candesartan)
  - Receiving ACE inhibitor plus beta-blocker plus spironolactone: 154.6 vs 128.1/1000 follow-up years (placebo vs candesartan)
  - Not receiving ACE inhibitor plus beta-blocker plus spironolactone: 167.7 vs 142.4/1000 follow-up years.

- Although discontinuations and hospitalization for hypotension, abnormal renal function, and hyperkalemia were more common for the candesartan group, event rates per 1000 follow-up years for the candesartan group remained lower for:
  - all-cause hospitalization: 391.6 vs 371.1 (placebo vs candesartan)
  - all-cause mortality: 110.7 vs 98.0 (placebo vs candesartan)
  - all-cause mortality or all-cause hospitalization: 431.4 vs 411.1 (placebo vs candesartan)

- To prevent a 1st event of 1 CV death or CHF hospitalization, the number needed to treat with candesartan for 1 year is 40 patients

The **CHARM-Alternative trial** addresses the question as to whether using candesartan in CHF patients with LV dysfunction not receiving an ACE inhibitor provides incremental benefit for reducing the leading mortal and morbid consequences of heart failure without introducing excess risk. For ethical reasons, this placebo-controlled trial enrolled only patients with a history of intolerance to ACE inhibitors. Prospectively, CHARM-Alternative

enrolled patients who did not tolerate an ACE inhibitor because of side effects such as cough, hypotension, abnormal renal function, and angioedema. Although a minority of CHARM-Alternative patients did require discontinuation of candesartan for the same corresponding reasons, most of the patients did successfully tolerate candesartan treatment. Support for a positive benefit-risk profile is evidenced by the following observations:

- The hazard ratio for the primary endpoint, CV death or hospitalization for heart failure, with a 33.7-month median follow-up time was 0.768 (p=0.0003), which equates to a 23% relative risk reduction.

- Per 1000 follow-up years, candesartan reduced CV death or 1st CHF hospitalization events:

  – 182.1 vs 138.1 (placebo vs candesartan)

- Per 1000 follow-up years, candesartan reduced both components of the composite primary endpoint

  – CV mortality 97.6 vs 82.4 (placebo vs candesartan)

  – CHF hospitalization 128.3 vs 85.6 (placebo vs candesartan)

- Although discontinuations and hospitalization for hypotension, abnormal renal function and hyperkalemia was more common for the candesartan group, event rates per 1000 follow-up years for the candesartan group remained lower for:

  – all-cause hospitalization: 400.3 vs 362.7 (placebo vs candesartan)

  – all-cause mortality: 114.6 vs 99.7 (placebo vs candesartan)

  – all-cause mortality or all-cause hospitalization: 433.3 vs. 394.9 (placebo vs candesartan)

- To prevent a 1st event of CV death or CHF hospitalization, the number needed to treat with candesartan for 1 year is 23 patients

The **CHARM-Preserved trial** addresses the question as to whether using candesartan in patients with CHF and preserved LV systolic function (LV ejection fraction >40%) provides incremental benefit for reducing the leading mortal and morbid consequences of heart failure without introducing excess risk. This is a patient population previously excluded from most clinical trials. In CHARM-Preserved, a reduction in mortality with candesartan was not evident. Nonetheless, the CHARM-Preserved trial generally supports the findings in the 2 trials in patients with LV systolic dysfunction in that CHF patients with preserved LV systolic function treated with candesartan required fewer hospital admissions for heart failure. The reduction in CHF hospitalizations for these patients was of the same order of magnitude as in

the other 2 CHARM trials. The safety and tolerability of candesartan treatment in CHARM-Preserved was generally consistent with that of the other 2 trials. Per 1000 follow-up years, all-cause hospitalization rates were less in the candesartan group (placebo = 343.7 vs candesartan = 329.9). In the context of the overall CHARM program, CHARM-Preserved further suggests that patient selection, strictly on the basis of such criteria as LV ejection fraction, may not be an absolute prerequisite for benefit with candesartan treatment.

Together, **CHARM-Added and CHARM-Alternative** comprise 2 large, placebo-controlled trials in CHF patients with LV systolic dysfunction that complement each other and demonstrate that candesartan, at a target dose of 32 mg once daily, substantially reduces the mortal and morbid consequences of heart failure when used with other contemporary therapies. These benefits were observed across major subgroups, and with concomitant treatment with other heart failure drugs, including ACE inhibitors and/or beta-blockers.

The benefit of treating heart failure patients with candesartan is clearly quantifiable, as is the associated risk. These risks are, however, predictable and manageable. Accordingly, treatment prognosis is favorable when physicians are instructed to start treatment of heart failure patients with candesartan 4 mg once daily and to double the dose at 2 week intervals to a target of 32 mg once daily or the highest tolerated dose. AstraZeneca has proposed instructions in the labeling that are consistent with those provided to the CHARM investigators and are consistent with good clinical management of the heart failure patient. These emphasize attention to intravascular volume depletion, checking blood pressure, serum creatinine, and serum potassium prior to treatment, and monitoring of these measures when initiating candesartan treatment, during dose escalation, and periodically thereafter.

Thus, the use of candesartan in patients with CHF and LV dysfunction results in clear benefit as evidenced by reduction in CV mortality and CHF hospitalizations. Furthermore, the use of candesartan in patients with CHF and LV dysfunction as was done in the CHARM program results in a positive benefit-risk profile as evidenced by numerical reductions in both all-cause hospitalization and all-cause mortality. Therefore, AstraZeneca requests the approval of candesartan for the treatment of heart failure so that it can be incorporated into the routine management of patients with CHF and LV systolic dysfunction.

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9. CHARM-ADDED SUPPLEMENTAL ANALYSES

CHARM-Added Supplemental Analyses

9.1 Overview

These supplemental post-hoc analyses for the CHARM-Added study address the questions posed by the FDA related to whether the beneficial effects of candesartan are evident when candesartan is added to a maximum dose of an ACE inhibitor.

According to the statistical analysis plan for CHARM, pre-specified subgroup analyses were done based on ACE inhibitor dose levels, with patients classified according to whether or not they were receiving recommended target doses. AstraZeneca specified the recommended doses used for these analyses prior to data unblinding and these doses aligned closely with the 2001 European Society of Cardiology Heart Failure Recommendations (Remme et al 2001), (Table 45).

The FDA has suggested an additional ACE inhibitor 'maximum' dose classification. The doses used for classifying patients receiving the most commonly used ACE inhibitors in CHARM-Added and as detailed by the FDA are summarized in Table 45.

FDA raised an additional related question regarding the interpretation of the results of CHARM-Added – specifically whether the benefit observed with candesartan could be attributed to a substantial attrition in use of ACE inhibitors during initiation and titration of study drug and thereafter during the study.

In response, AstraZeneca is providing data on the use of ACE inhibitors at baseline and during the course of the study, and efficacy subgroup analyses based on these data.

These supplemental analyses demonstrate that 1) candesartan provides incremental benefit when added to an ACE inhibitor at either the recommended dose or the maximum dose, ie, the benefit is independent of the ACE inhibitor dose and, 2) ACE inhibitor use over the course of the trial was quite stable and confirms only minimal attrition, particularly during the early period of dose titration with the investigational drug.

9.2 Background

CHARM-Added was designed to evaluate the benefits of candesartan when added to optimal conventional treatments including an ACE inhibitor. The protocol recommended that investigators give ACE inhibitors at doses based on target doses proven effective in controlled clinical trials of heart failure and individual patient tolerability. The protocol included a list of target doses of these ACE inhibitors and noted that other ACE inhibitors should be used at comparable doses. Furthermore, patients were to be on a stable dose of an ACE inhibitor for at least 30 days prior to study entry. The case report form for the baseline visit specifically asked the investigators to confirm that each patient was on an "optimum individualized dose of an ACE inhibitor", and this dosing plan was confirmed for 96% of patients. The statistical analysis plan for the CHARM program included an exploratory analysis of outcomes based on whether patients were on (at least) a recommended dose of an ACE inhibitor or less than a recommended dose. For this analysis, a complete list of recommended doses was detailed for each ACE inhibitor used in CHARM while the study was still blinded. These recommended doses were based, in part, on those proven effective in clinical trials and based in part on the

ESC guidelines published in 2001 (Remme et al 2001). Within this document, the sponsor has designated these doses of ACE inhibitors as "recommended" doses for analysis.

The FDA has requested supplemental post-hoc analyses using a list of "maximum" ACE inhibitor doses. This list of maximum doses is drawn from various indications in US labels, previous heart failure trials, and FDA databases. The FDA list included 9 ACE inhibitors, representing approximately 99% of those used in CHARM-Added. For 3 of the 4 (enalapril, captopril and ramipril) most commonly used ACE inhibitors in CHARM-Added, representing 73% of the patients, the CHARM-Added "recommended" target doses and the FDA's designated "maximum" doses were the same. For most ACE inhibitors, other than captopril, the mean doses at baseline in CHARM-Added were very similar to the mean doses proven effective in previous positive trials (Table 45 and Table 46).

Table 45 Recommended ACE inhibitor heart failure treatment doses as defined in CHARM analyses, and maximum doses as defined by FDA (CHARM-Added)

ACE inhibitor	Proportion of patients taking a specific ACE inhibitor, at baseline in CHARM-Added	Recommended heart failure target dose[a] mg/day	Maximum dose as provided by FDA mg/day
Enalapril	26.7%	20 mg	20 mg
Lisinopril	19.1%	20 mg	40 mg
Captopril	16.8%	150 mg	150 mg
Ramipril	11.0%	10 mg	10 mg
Perindopril	6.4%	4 mg	16 mg
Trandolapril	5.9%	2 mg	4 mg
Quinapril	5.4%	20 mg	80 mg
Fosinopril	5.1%	20 mg	40 mg
Benazepril	2.6%	20 mg	80 mg
Other ACE inhibitors[b]	1.1%	-	-

[a] CHARM-Added recommended heart failure dose for subgroup analyses in the submission.
[b] For 'Other ACE inhibitors' not attributed a maximum dose by the FDA, the sponsor selected a maximum dose based on product labeling, (see Appendix, Table 54 for the complete list of ACE inhibitors).

Table 46 ACE inhibitor doses in CHF and post myocardial infarction trials

Trial	Drug	Daily target dose	Mean daily dose	Final mean daily dose
Heart failure trials				
CONSENSUS	Enalapril	40 mg	18.4 mg	NA
SOLVD-T	Enalapril	20 mg	16.6 mg	11.2 mg
Val-HeFT	Enalapril	20 mg		15 mg
ATLAS	Lisinopril	35 mg high dose group	33.2 mg	22.5 mg
		5 mg low dose group	4.5 mg	3.2 mg
Post MI trials				
AIRE	Ramipril	10 mg	8.1 mg	NA
TRACE	Trandolapril	4 mg	NA	NA
GISSI-3	Lisinopril	10 mg	NA	NA
SAVE	Captopril	75/150 mg	135 mg (1 year)	127 mg

NA Not available.

Captopril is a distinctive case. It is intended to be used 3 times daily (tid). In studies that included it as a comparator, target doses have usually been 50 mg tid (150 mg daily), with mean achieved doses typically 110 mg to 130 mg daily. However, in heart failure trials of other treatments such as beta-blockers, or in clinical use, achieved doses are often in the range of 60 mg to 80 mg daily (Hjalmarson et al 2000, Pitt et al 1999, Cleland et al 2002). For other ACE inhibitors such as enalapril, lisinopril, or ramipril, the mean doses observed in CHARM-Added were very similar to those achieved in trials designed with force-titration to a target dose as tolerated (see Table 46). These doses are also typically slightly higher than the mean doses used in clinical practice settings (Cleland et al 2002, Gattis et al 2004). Consequently, with the possible exception of captopril, it is difficult to speculate as to the relevance of titrating to maximum doses that exceed the mean doses achieved by force-titration in previous positive trials. Of note, it has not been a requirement for the approval of previous heart failure treatments that the investigational drug must be proven effective when added to maximum doses of other conventional or established treatments.

In the case of candesartan, the partially overlapping mechanism of action of ARBs and ACE inhibitors has led the FDA to raise the burden of proof of efficacy for the use of these 2 drugs classes together. The FDA has asked whether the addition of candesartan is more effective than an alternative strategy of increasing the ACE inhibitor to a maximum dose defined by the label or by tolerability. CHARM-Added was not designed to require force-titration of ACE inhibitors to a maximum dose. However, approximately 28% of patients at baseline were receiving an FDA defined maximum dose of an ACE inhibitor or greater. At the request of the FDA, post-hoc analyses have been done in this subset to confirm the consistency of the effects of candesartan, irrespective of the dose of ACE inhibitor, and to confirm incremental benefit even when added to a maximum dose of ACE inhibitor. Although such post-hoc subgroup analyses have limitations of interpretability and lack the usual statistical power for

clinical trials or regulatory evidence of effect, they do provide further evidence of the consistency of benefit of adding candesartan to an ACE inhibitor, independent of dose.

In addition, the FDA has raised concerns that the results of CHARM-Added should be interpreted with consideration of an analysis of ACE inhibitor use during the trial. Specifically, if it were revealed that there was substantial attrition in ACE inhibitor dose, this could be considered analogous to an ACE inhibitor "withdrawal" study in the placebo group, or to a "switch" study in the candesartan group. This analysis has been done to demonstrate maintenance of the mean doses of ACE inhibitors and the proportions of patients maintaining either the recommended or maximum dose during the trial, including the early period of dose escalation with investigational drug.

Implicit in the questions posed by the FDA is the underlying assumption that ACE inhibitors and ARBs are interchangeable, based on the presumption that each has the potential to completely inhibit the RAAS. The available pharmacologic, preclinical, and clinical evidence supports an alternative view that with respect to efficacy, there are differences between ACE inhibitors and ARBs that make them complementary drug classes when used together resulting in more complete inhibition of the RAAS. It is biologically plausible therefore, that together an ACE inhibitor plus ARB would provide incremental benefit over either class alone. Since angiotensin II is believed to be a major mediator of deleterious effects of the RAAS in CHF, the complementary actions of ACE inhibitors and ARBs for both reducing the formation of angiotensin II and preventing residual angiotensin II from binding to the AT1 receptor is highly relevant in the context of CHF.

The FDA has commented that the results of the Val-HeFT study in CHF patients (and possibly the results of the VALIANT trial in post-myocardial infarction [MI] patients with left ventricular (LV) systolic dysfunction) using the ARB valsartan have created uncertainty regarding the interpretation of the positive findings in the CHARM-Added trial with respect to the "added" benefit of candesartan.

Although CHARM-Added and Val-HeFT have some similarities, drawing conclusions from comparisons of candesartan and valsartan from separate studies rather than from head to head comparisons suffers from fundamental limitations. When specific head-to-head comparisons within the ARB class have been conducted, differences in efficacy within the class have been demonstrated. For example, candesartan at a once daily maximum dose of 32 mg was more effective in lowering blood pressure than losartan at a once daily maximum dose of 100 mg in the 2 CLAIM trials (Bakris et al 2001, Vidt et al 2001). The distinctive receptor binding properties of candesartan (non-competitive tight receptor binding with slow dissociation not overcome by increasing levels of angiotensin II]) may have contributed to the additional effects demonstrated with candesartan. Thus, there is specific clinical trial evidence demonstrating differences in efficacy within the ARB class, notably showing superiority of candesartan to an ARB comparator at once daily maximum doses.

9.3 Rationale for using an ACE inhibitor and an ARB together

9.3.1 Mechanisms of action and clinical implications

The main common action of ACE inhibitors and ARBs is the reduction of the stimulation of the AT_1 receptor by its ligand angiotensin II. ACE inhibitors block angiotensin II formation from angiotensin I, while ARBs directly inhibit the binding of angiotensin II to AT_1. Both drug classes induce a compensatory increase of renin release and more angiotensin I is formed. When the angiotensin-converting enzyme is blocked, several other enzymes, including cathepsins and chymase, are able to generate angiotensin II and other angiotensin peptides from angiotensin I (Hilgers and Mann 2002). The two major pharmacologic differences between ACE inhibitors and ARBs are the inhibition of bradykinin degradation by the former and the unopposed activation of the angiotensin II type 2 receptor (AT_2) by the latter. Stimulation of AT_2 receptors by angiotensin II can slightly increase bradykinin levels. Kinins contribute significantly to the blood pressure-lowering effects of ACE inhibitors in animals and in humans; up to 50% of the acute effect of a single ACE inhibitor dose may be due to kinins (Gainer et al 1998).

Kinins may also contribute to 2 of the most bothersome adverse effects associated with the use of ACE inhibitors. Cough, typically a dry nonproductive cough, may occur in an estimated 5% to 20% of patients receiving an ACE inhibitor and is the most common reason for ACE inhibitor intolerance in patients with CHF (Bart et al 1999). Its relation to dose has not been clearly defined. This can be particularly problematic in patients with CHF, since cough may also be a manifestation of worsening heart failure or common co-morbidities such as chronic obstructive pulmonary disease or bronchitis. A 2nd and less common adverse effect that has been attributed in part to increased kinins and use of ACE inhibitors is an increased frequency of angioedema, which can be potentially life threatening.

9.3.2 Pharmacologic effects

The pharmacologic differences between ACE inhibitors and ARBs have additional relevance in the context of CHF. Evidence suggests that ACE inhibitors prevent myocardial fibrosis as a result of inhibition of angiotensin II production (Francis et al 1990). However, ACE inhibitors do not always suppress concentrations of angiotensin II in patients with CHF, presumably a reflection of the existence of other enzyme pathways (eg, chymase) that escape ACE inhibition (Jorde et al 2000). The rationale for therapy with both an ARB and ACE inhibitor is based on the assumption that these non-classical pathways of the RAAS are important. ARBs counteract the AT_1-mediated effects of residual angiotensin II formation by non-ACE enzymes, and ACE inhibitors additionally increase kinins. Thus, using both drug classes together in the context of CHF should provide a higher degree of blockade of RAAS pathways than either drug class can achieve alone, even at the maximum pharmacologic doses.

9.3.3 Preclinical data

Preclinical evidence supports this hypothesis. In a study of dogs using a model of pacing-induced congestive heart failure, it was found that an ARB plus ACE inhibitor synergistically

prevented myocardial fibrosis and decreased LV stiffness during the progression of CHF in an animal model that has additional pathways in the heart for generating angiotensin II as well as angiotensin-converting enzyme (Funabiki et al 2004). Specifically, an ARB plus ACE inhibitor in CHF suppressed the RAAS and the activation of the bradykinin-NO system thereby, decreasing the expression of collagen I and III mRNA, and preventing myocardial fibrosis. Combined therapy also decreased LV stiffness as estimated using LV pressure-volume loops. These findings suggest that use of an ARB plus ACE inhibitor together has the advantage of preventing myocardial fibrosis and decreasing LV stiffness in CHF compared with an ARB or ACE inhibitor alone.

9.3.4 Clinical evidence (cardiovascular and renal)

In the 43-week RESOLVD pilot study (n=768), symptomatic heart failure patients were randomized to receive the ACE inhibitor enalapril (target dose of 20 mg daily, a dose proven effective in previous heart failure trials), or the ARB candesartan (4 mg, 8 mg, or 16 mg once daily), or enalapril (20 mg daily) plus candesartan (4 or 8 mg daily) with or without a beta-blocker (metoprolol CR/XL) to evaluate the effects of these agents alone or together on various measures of cardiac function, LV geometry, or neurohormones. Patients receiving candesartan plus enalapril showed evidence of beneficial effect in reducing LV systolic volumes and on neurohormones compared to either monotherapy. All 3 drugs together showed the greatest favorable effect on LV geometry and neurohormones. No effect on clinical outcomes was evident in this pilot study (McKelvie et al 2003)

The beneficial effect of using an ACE inhibitor plus ARB together has been evaluated in clinical trials in patients with renal disease using proteinuria as the primary measure of effect, in which a greater reduction of proteinuria has been reported with the 2 together than with either an ACE inhibitor or ARB alone (Nakao et al 2003, Laverman et al 2002). The COOPERATE trial (Nakao et al 2003) was a comparative study on clinical endpoints in 263 patients with proteinuric nondiabetic renal insufficiency followed up for 3 years. The chosen ACE inhibitor dose was based on the dose above which no additional benefit resulted with respect to proteinuria reduction in the initial forced titration phase of the trial. Blood pressure was very well controlled and not different between groups. Proteinuria was less with the use of ACE inhibitor plus ARB than with either monotherapy and not different between single drug treatments. Based on this evidence, it was concluded that the use of ACE inhibitor plus ARB together was significantly better than each individual drug in preventing the primary endpoint of doubling of serum creatinine or development of end stage renal disease in non-diabetic patients with moderately reduced renal function and moderate daily urine protein excretion.

Thus, there is substantial evidence to support the assumptions made at the time that the CHARM trials were initiated: 1) ACE inhibitors and ARBs have distinctive pharmacologic actions and, 2) use of ACE inhibitors and ARBs together can result in additional benefits incremental to those of either monotherapy. The available evidence supports the biologic plausibility for the potential benefits of using ACE inhibitors and ARBs together in patients with cardiovascular disease including CHF.

9.4 Maximum dose of ACE inhibitor as treatment for CHF

The request to demonstrate a candesartan benefit when added to 'maximum' ACE inhibitor doses contains the implicit assumption that maximum doses are superior to doses proven effective in clinical heart failure trials. This assumption is difficult to validate. For most heart failure treatments, recommendations call for starting at 'low' doses with careful dose escalation to a target dose or the maximal tolerated dose (Remme et al 2001). Data are rarely provided to indicate that these target doses are pharmacologically maximal doses, or maximal doses for the treatment of chronic heart failure. Moreover, in previous positive trials evaluating ACE inhibitors in patients with CHF or in post MI patients (usually with LV systolic dysfunction), mean achieved doses have uniformly fallen short of the target doses (see Table 46). It is therefore not surprising that the literature is devoid of dose-response ACE inhibitor clinical trials of heart failure.

Several trials have failed to show that higher doses of an ACE inhibitor are more effective than doses proven effective in clinical trials (The NETWORK Investigators 1998, Nanas et al 2000). One trial attempted to compare a proven effective target dose of the ACE inhibitor enalapril (20 mg daily) to a very high dose (60 mg daily). However, mean achieved doses were 17.9 mg and 19.3 mg daily, respectively, and there were no differences in survival or clinical or hemodynamic variables (Nanas et al 2000). One trial (ATLAS) showed that a very low dose of lisinopril (target dose: 2.5 mg to 5.0 mg/day, mean achieved dose 4.5 mg) was less effective than a high dose (target dose 32.5 mg to 35 mg, mean achieved dose 33.2 mg) for the secondary outcome, death or hospitalization for any reason by 12% (nominal p=0.002) (Packer et al 1999), but with no significant reduction (p=0.128) for the primary endpoint of all-cause mortality. Accordingly, the approved US label for lisinopril (ZESTRIL®) states that: "A large (over 3000 patients) survival study, the ATLAS Trial, comparing 2.5 and 35 mg of lisinopril in patients with heart failure, showed that the higher dose of lisinopril had outcomes at least as favorable as the lower doses".

Thus, there is no compelling evidence that a maximum ACE inhibitor dose is therapeutically superior to the mean doses proven effective in clinical trials. Rather, the bulk of clinical heart failure trial data would suggest that the optimal doses are those determined by investigators according to recommendations to start at a low dose and to escalate doses to a proven target dose unless limited by tolerability (The CONSENSUS Trial Group 1987, The SOLVD Investigators 1991, The AIRE Study Investigators 1993).

9.5 Concomitant ACE inhibitor treatment over study time in CHARM-Added

As indicated in the supplemental application, in the CHARM-Added study, about half of the patients entered the trial receiving an ACE inhibitor at a recommended dose. To further describe concomitant ACE inhibitor treatment in CHARM-Added, concomitant ACE inhibitor treatment for the most commonly used ACE inhibitors is presented in Table 47. This table provides for representative visits, 1) the number of patients on each dose level of each of the 4 most commonly used ACE inhibitors, 2) the percentage of patients at the recommended dose (CHARM definition), 3) the percentage of patients at the maximum dose (FDA definition), 4)

the mean dose, 5) the mean proportion of maximum normalized dose where the maximum dose of each ACE inhibitor is assigned the value 1.0 and, 6) the mean proportion of recommended dose where recommended dose is assigned a value of 1.0.

Table 47 ACE inhibitor use by visit (CHARM-Added)

ACE inhibitor (n/N and % of patients on specific ACE inhibitor at baseline) Percent of patients at recommended and maximum doses, by visit	Baseline Visit 1	Visit 4 Week 6	Visit 5 Month 6	Visit 7 Month 14	Visit 10 Month 26	Visit 13 Month 38	Visit 19 Closing visit
	P, C	P, C	P, C	P, C	P, C	P, C	P, C
Enalapril (680/2548 = 26.7%)							
Mean dose at specific visit, mg	17, 17	17, 16	18, 17	17, 16	17, 16	16, 17	17, 16
And number of patients at each visit	335, 345	319, 331	298, 313	269, 282	239, 250	200, 204	185, 185
% at recommended dose (≥20 mg)	54, 50	54, 47	54, 46	53, 45	51, 46	48, 47	48, 44
% at maximum dose (≥20 mg)	54, 50	54, 47	54, 46	53, 45	51, 46	48, 47	48, 44
Mean normalized to recommended dose	0.86, 0.84	0.86, 0.81	0.88, 0.83	0.86, 0.78	0.84, 0.82	0.82, 0.86	0.83, 0.79
Mean normalized to maximum dose	0.86, 0.84	0.86, 0.81	0.88, 0.83	0.86, 0.78	0.84, 0.82	0.82, 0.86	0.83, 0.79
Lisinopril (486/2548 = 19.1%)							
Mean dose at specific visit, mg	18, 18	17, 18	18, 18	18, 17	18, 18	18, 18	19, 18
And number of patients at each visit	243, 243	241, 234	231, 225	216, 196	190, 176	160, 149	143, 145
% at recommended dose (≥20 mg)	52, 52	50, 53	51, 53	52, 54	54, 53	52, 54	60, 55
% at maximum dose (≥40 mg)	13, 16	13, 14	13, 15	11, 13	13, 15	12, 14	13, 15
Mean normalized to recommended dose	0.88, 0.89	0.87, 0.88	0.89, 0.88	0.88, 0.86	0.90, 0.88	0.88, 0.87	0.97, 0.90
Mean normalized to maximum dose	0.44, 0.44	0.43, 0.44	0.44, 0.44	0.44, 0.43	0.45, 0.44	0.44, 0.44	0.48, 0.45
Captopril (429/2548 = 16.8%)							
Mean dose at specific visit, mg	83, 82	81, 81	81, 79	81, 77	83, 73	83, 72	77, 69
And number of patients at each visit	237, 192	228, 181	214, 178	192, 156	158, 131	130, 118	109, 98
% at recommended dose (≥150 mg)	21, 22	19, 20	20, 20	19, 20	21, 19	22, 20	20, 18
% at maximum dose (≥150 mg)	21, 22	19, 20	20, 20	19, 20	21, 19	22, 20	20, 18
Mean normalized to recommended dose	0.55, 0.55	0.54, 0.54	0.54, 0.53	0.54, 0.51	0.55, 0.49	0.55, 0.48	0.51, 0.46
Mean normalized to maximum dose	0.55, 0.55	0.54, 0.54	0.54, 0.53	0.54, 0.51	0.55, 0.49	0.55, 0.48	0.51, 0.46
Ramipril (281/2548 = 11.0%)							
Mean dose at specific visit, mg	7, 7	8, 7	8, 7	8, 7	9, 7	8, 7	8, 7
And number of patients at each visit	120, 161	118, 157	114, 145	107, 143	104, 126	99, 111	91, 100
% at recommended dose (≥10 mg)	43, 35	47, 34	47, 35	49, 38	49, 37	53, 40	54, 43

Table 47 ACE inhibitor use by visit (CHARM-Added)

ACE inhibitor (n/N and % of patients on specific ACE inhibitor at baseline) Percent of patients at recommended and maximum doses, by visit	Baseline Visit 1	Visit 4 Week 6	Visit 5 Month 6	Visit 7 Month 14	Visit 10 Month 26	Visit 13 Month 38	Visit 19 Closing visit
	P, C	P, C	P, C	P, C	P, C	P, C	P, C
% at maximum dose (≥10 mg)	43, 35	47, 34	47, 35	49, 38	49, 37	53, 40	54, 43
Mean normalized to recommended dose	0.73, 0.68	0.75 0.67	0.75, 0.53	0.54, 0.67	0.78, 0.67	0.79, 0.68	0.79, 0.72
Mean normalized to maximum dose	0.73, 0.68	0.75 0.67	0.75, 0.53	0.54, 0.67	0.78, 0.67	0.79, 0.68	0.79, 0.72

n/N number of placebo plus candesartan patients on a specific ACE inhibitor/total number of patients in the CHARM-Added trial.
P, C Placebo/candesartan.

The cross-sectional tabulations of concomitant ACE inhibitor use are summarized for all ACE inhibitors used in the trial in Table 48 and demonstrate that, in CHARM-Added, the doses of ACE inhibitors over the course of the trial were quite stable. While the proportions of patients at the recommended dose or at the maximum dose at closing visit were somewhat less than at baseline, there was very little change in ACE inhibitor treatment from baseline through Month 6 (Visit 5), during the initial period of study drug dose escalation. For the placebo group, 28.2% were at maximum ACE inhibitor dose at baseline and 27.5% were at maximum dose at Visit 5. For the candesartan group, 28.4% were at maximum dose at baseline, and 25.1% were at maximum dose at Visit 5.

Table 48 Summary table of concomitant ACE inhibitor use (CHARM- Added)

Visit	Summary statistic	Placebo n (%)	Candesartan n (%)	Total n (%)
Visit 1 (Baseline)	Number of patients	1272	1276	2548
	Recommended dose or above	648 (50.9)	643 (50.4)	1291 (50.7)
	Maximum dose or above	359 (28.2)	362 (28.4)	721 (28.3)
	Mean normalized to recommended dose	0.87	0.87	0.87
	Mean normalized to maximum dose	0.60	0.59	0.60
Visit 2 (Week 2)	Number of patients	1259	1269	2528
	Recommended dose or above	639 (50.8)	636 (50.1)	1275 (50.4)
	Maximum dose or above	353 (28.0)	354 (27.9)	707 (28.0)
	Mean normalized to recommended dose	0.86	0.86	0.86
	Mean normalized to maximum dose	0.59	0.59	0.59
Visit 3 (Week 4)	Number of patients	1255	1257	2512
	Recommended dose or above	636 (50.7)	623 (49.6)	1259 (50.1)

Table 48 Summary table of concomitant ACE inhibitor use (CHARM- Added)

Visit	Summary statistic	Placebo n (%)	Candesartan n (%)	Total n (%)
	Maximum dose or above	352 (28.0)	342 (27.2)	694 (27.6)
	Mean normalized to recommended dose	0.86	0.85	0.86
	Mean normalized to maximum dose	0.59	0.58	0.58
Visit 4 (Week 6)	Number of patients	1248	1251	2499
	Recommended dose or above	629 (50.4)	605 (48.4)	1234 (49.4)
	Maximum dose or above	345 (27.6)	325 (26.0)	670 (26.8)
	Mean normalized to recommended dose	0.86	0.84	0.85
	Mean normalized to maximum dose	0.59	0.57	0.58
Visit 5 (Month 6)	Number of patients	1196	1214	2410
	Recommended dose or above	603 (50.4)	564 (46.5)	1167 (48.4)
	Maximum dose or above	329 (27.5)	305 (25.1)	634 (26.3)
	Mean normalized to recommended dose	0.86	0.81	0.84
	Mean normalized to maximum dose	0.59	0.56	0.57
Visit 6 (Month 10)	Number of patients	1157	1179	2336
	Recommended dose or above	563 (48.7)	534 (45.3)	1097 (47.0)
	Maximum dose or above	307 (26.5)	292 (24.8)	599 (25.6)
	Mean normalized to recommended dose	0.84	0.80	0.82
	Mean normalized to maximum dose	0.57	0.55	0.56
Visit 7 (Month 14)	Number of patients	1110	1141	2251
	Recommended dose or above	550 (49.5)	516 (45.2)	1066 (47.4)
	Maximum dose or above	300 (27.0)	276 (24.2)	576 (25.6)
	Mean normalized to recommended dose	0.85	0.77	0.81
	Mean normalized to maximum dose	0.58	0.52	0.55
Visit 8 (Month 18)	Number of patients	1068	1094	2162
	Recommended dose or above	522 (48.9)	499 (45.6)	1021 (47.2)
	Maximum dose or above	293 (27.4)	274 (25.0)	567 (26.2)
	Mean normalized to recommended dose	0.84	0.77	0.81
	Mean normalized to maximum dose	0.58	0.53	0.55
Visit 9 (Month 22)	Number of patients	1038	1050	2088
	Recommended dose or above	513 (49.4)	476 (45.3)	989 (47.4)
	Maximum dose or above	294 (28.3)	270 (25.7)	564 (27.0)
	Mean normalized to recommended dose	0.86	0.78	0.82
	Mean normalized to maximum dose	0.59	0.53	0.56
Visit 10 (Month 26)	Number of patients	993	999	1992
	Recommended dose or above	483 (48.6)	443 (44.3)	926 (46.5)

Table 48 Summary table of concomitant ACE inhibitor use (CHARM- Added)

Visit	Summary statistic	Placebo n (%)	Candesartan n (%)	Total n (%)
	Maximum dose or above	274 (27.6)	247 (24.7)	521 (26.2)
	Mean normalized to recommended dose	0.85	0.77	0.81
	Mean normalized to maximum dose	0.58	0.53	0.56
Visit 11 (Month 30)	Number of patients	954	963	1917
	Recommended dose or above	456 (47.8)	417 (43.3)	873 (45.5)
	Maximum dose or above	262 (27.5)	230 (23.9)	492 (25.7)
	Mean normalized to recommended dose	0.82	0.76	0.79
	Mean normalized to maximum dose	0.57	0.52	0.54
Visit 12 (Month 34)	Number of patients	916	927	1843
	Recommended dose or above	442 (48.3)	399 (43.0)	841 (45.6)
	Maximum dose or above	253 (27.6)	215 (23.2)	468 (25.4)
	Mean normalized to recommended dose	0.82	0.75	0.78
	Mean normalized to maximum dose	0.57	0.51	0.54
Visit 13 (Month 38)	Number of patients	852	890	1742
	Recommended dose or above	409 (48.0)	381 (42.8)	790 (45.4)
	Maximum dose or above	232 (27.2)	212 (23.8)	444 (25.5)
	Mean normalized to recommended dose	0.81	0.74	0.78
	Mean normalized to maximum dose	0.56	0.52	0.54
Visit 14 (Month 42)	Number of patients	285	299	584
	Recommended dose or above	122 (42.8)	129 (43.1)	251 (43.0)
	Maximum dose or above	81 (28.4)	69 (23.1)	150 (25.7)
	Mean normalized to recommended dose	0.76	0.71	0.73
	Mean normalized to maximum dose	0.56	0.50	0.53
Closing visit	Number of patients	864	896	1760
	Recommended dose or above	386 (44.7)	343 (38.3)	729 (41.4)
	Maximum dose or above	214 (24.8)	185 (20.6)	399 (22.7)
	Mean normalized to recommended dose	0.75	0.66	0.70
	Mean normalized to maximum dose	0.51	0.45	0.48

The mean "normalized to maximum" dose changed little over the course of the trial (0.60, placebo and 0.59 candesartan at baseline; 0.51, placebo and 0.45 candesartan at closing visit). The mean achieved ACE inhibitor doses were also relatively constant over the course of the trial (Table 47). Furthermore, the mean doses of enalapril and ramipril compare favorably with the mean doses attained in the clinical trials that established benefit of these agents in the

treatment of heart failure (Table 46) (The CONSENSUS Study Group 1987, The SOLVD Investigators 1991, The AIRE Study Investigators 1993).

9.6 ACE inhibitor subgroup analyses

9.6.1 ACE inhibitor subgroup efficacy analyses

9.6.1.1 Subgroup analyses based on ACE inhibitor dose at baseline

The original CHARM submission described whether there were differential treatment effects associated with concomitant ACE inhibitor dose. The subgroup analyses, as conducted, indicate that the benefit of candesartan vs. placebo is evident whether patients are taking an ACE inhibitor at a recommended dose or at a lower dose. There was no suggestion of a treatment-by-recommended dose interaction (p=0.26). In fact, for the primary endpoint, CV death or CHF hospitalization, there was significant benefit observed within the population taking ACE inhibitors at the recommended dose (HR=0.794, 95% CI 0.666-0.945, p=0.010). In patients taking a maximum dose of ACE inhibitor at baseline, there was also evidence of a directionally consistent incremental benefit from treatment with candesartan (Table 49).

Table 49 **Subgroup analyses based on the recommended ACE inhibitor heart failure treatment doses and maximum ACE inhibitor doses, at baseline for the primary and 2 secondary endpoints (CHARM-Added)**

Event/dose of ACE inhibitor at baseline		N	Placebo Events/1000 follow-up years	Candesartan Events/1000 follow-up years	Hazard Ratio	95% CI	p-value
CV death or CHF hospitalization							
All patients		2548	166.3	141.2	0.85	0.75, 0.96	0.011
Recommended dose of ACEi	No	1257	165.5	151.2	0.92	0.77, 1.09	0.314
	Yes	1291	167.1	131.7	0.79	0.67, 0.95	0.010
Maximum dose of ACEi	No	1827	172.1	144.5	0.84	0.73, 0.98	0.021
	Yes	721	152.2	133.0	0.88	0.69, 1.11	0.273
All cause death or CHF hospitalization							
All patients		2548	181.5	157.5	0.87	0.78, 0.98	0.021
Recommended dose of ACEi	No	1257	179.4	166.2	0.93	0.79, 1.10	0.378
	Yes	1291	183.5	149.3	0.82	0.69, 0.97	0.017
Maximum dose of ACEi	No	1827	186.9	161.9	0.87	0.76, 1.00	0.046
	Yes	721	168.2	147.0	0.88	0.70, 1.10	0.249
CV death or CHF hospitalization or non-fatal MI							
All patients		2548	172.0	145.8	0.85	0.76, 0.96	0.010
Recommended dose of ACEi	No	1257	170.8	153.4	0.90	0.76, 1.07	0.233
	Yes	1291	173.2	138.7	0.81	0.68, 0.96	0.014
Maximum dose of ACEi	No	1827	177.5	147.8	0.84	0.73, 0.97	0.015
	Yes	721	158.6	141.0	0.89	0.71, 1.12	0.332

ACEi Angiotensin-converting enzyme inhibitor.

A directionally consistent benefit of candesartan was also evident for the component endpoints, CV death, CHF hospitalization, and all-cause mortality, whether or not patients were receiving the ACE inhibitor at a recommended dose or at a maximum dose (Table 50).

Table 50 Subgroup analyses based on the recommended ACE inhibitor heart failure treatment doses and maximum ACE inhibitor doses at baseline for the components CV death, CHF hospitalization, and all-cause death (CHARM-Added)

Event/dose of ACE inhibitor at baseline		N	Placebo Events/1000 follow-up years	Candesartan Events/1000 follow-up years	Hazard Ratio	95% CI	p-value
CV death							
All patients		2548	93.3	78.5	0.84	0.72, 0.98	0.029
Recommended dose of ACEi	No	1257	97.0	81.0	0.84	0.67, 1.04	0.101
	Yes	1291	89.7	76.1	0.85	0.68, 1.06	0.146
Maximum dose of ACEi	No	1827	97.5	79.6	0.82	0.68, 0.98	0.027
	Yes	721	82.6	75.8	0.92	0.68, 1.24	0.577
CHF hospitalization							
All patients		2548	110.1	90.3	0.83	0.71, 0.96	0.014
Recommended dose of ACEi	No	1257	106.4	97.0	0.91	0.74, 1.13	0.411
	Yes	1291	113.6	84.0	0.75	0.60, 0.93	0.008
Maximum dose of ACEi	No	1827	112.4	93.7	0.84	0.70, 1.00	0.054
	Yes	721	104.3	82.0	0.79	0.59, 1.06	0.116
All cause death							
All patients		2548	110.7	98.0	0.89	0.77, 1.02	0.086
Recommended dose of ACEi	No	1257	111.2	99.9	0.90	0.74, 1.09	0.283
	Yes	1291	110.2	96.2	0.87	0.72, 1.06	0.175
Maximum dose of ACEi	No	1827	114.9	100.1	0.87	0.74, 1.03	0.096
	Yes	721	100.4	93.0	0.93	0.71, 1.22	0.582

ACEi Angiotensin-converting enzyme inhibitor.

9.6.1.2 Subgroup analyses based on ACE inhibitor dose at baseline and over the course of the trial

A 2nd analysis was performed to investigate the effect of candesartan in patients who received recommended or maximum dose of ACE inhibitors over time. For each endpoint, the analysis was limited to the cohort of patients who were on a recommended or maximum dose of ACE inhibitor at baseline and up to the time of each specific event or to the end of study if the patient was event-free. These analyses, although not assured of being unbiased due to selection criteria which use the post-randomization experience of patients, support a directionally consistent benefit of candesartan on top of concomitant use of ACE inhibitors at recommended or maximum doses over time.

Table 51 shows analyses for the primary and 2 secondary endpoints. Of the 721 patients in CHARM-Added who were taking a maximum dose of ACE inhibitor at baseline, over 90%

(659) were on a maximum dose at all visits up to the time of each specific event or at the end of the study for the primary and secondary endpoints.

Table 51 Subgroup analyses based on the recommended ACE inhibitor heart failure treatment doses and maximum ACE inhibitor doses, at baseline and throughout all visits for the primary and 2 secondary endpoints (CHARM-Added)

Event/dose of ACE inhibitor at baseline and at all visits prior to a specific event or to the end of the study if patient was event-free		N	Placebo Events/1000 follow-up years	Candesartan Events/1000 follow-up years	Hazard Ratio	95% CI	p-value
CV death or CHF hospitalization							
Recommended dose of ACEi	Yes	1165	177.2	134.0	0.76	0.64, 0.92	0.004
Maximum dose of ACEi	Yes	659	160.2	133.7	0.84	0.66, 1.07	0.161
All cause death or CHF hospitalization							
Recommended dose of ACEi	Yes	1165	191.5	148.1	0.78	0.66, 0.93	0.005
Maximum dose of ACEi	Yes	659	175.3	144.9	0.83	0.66, 1.05	0.121
CV death or CHF hospitalization or non-fatal MI							
Recommended dose of ACEi	Yes	1168	183.8	141.9	0.78	0.65, 0.93	0.006
Maximum dose of ACEi	Yes	659	167.3	142.7	0.86	0.67, 1.09	0.209

ACEi Angiotensin-converting enzyme inhibitor.

A directionally consistent benefit of candesartan was also evident for the component endpoints, CV death, CHF hospitalization, and all-cause mortality, in the cohort of patients who were on a maximum dose of ACE inhibitor at baseline as well as all visits up to the time of an event, or to the end of study if the patient was event-free (Table 52).

Table 52 Subgroup analyses based on the recommended ACE inhibitor heart failure treatment doses and maximum ACE inhibitor doses, throughout all visits for the components CV death, CHF hospitalization, and all-cause death (CHARM-Added)

Event/dose of ACE inhibitor at baseline and at all visits prior to a specific event or to the end of the study if patient was event-free		N	Placebo Events/1000 follow-up years	Candesartan Events/1000 follow-up years	Hazard Ratio	95% CI	p-value
CV death							
Recommended dose of ACEi	Yes	1116	93.6	71.2	0.76	0.60, 0.97	0.026
Maximum dose of ACEi	Yes	634	87.9	73.9	0.84	0.61, 1.16	0.290
CHF hospitalization							
Recommended dose of ACEi	Yes	1165	119.7	83.3	0.70	0.56, 0.88	0.002
Maximum dose of ACEi	Yes	659	109.1	79.8	0.74	0.54, 1.00	0.052
All cause death							
Recommended dose of ACEi	Yes	1116	112.3	87.4	0.78	0.63, 0.97	0.024
Maximum dose of ACEi	Yes	634	103.6	87.6	0.85	0.63, 1.13	0.266

ACEi Angiotensin-converting enzyme inhibitor.

9.6.2 ACE inhibitor subgroup safety analyses

The safety experience in both the "maximum" and "recommended" dose cohorts of patients was consistent with that of the overall CHARM-Added population. The risk of death and the risk of hospitalization were both lower with candesartan than placebo but the rate of study drug discontinuation was higher (Table 53). Discontinuation rates in the "maximum" dose cohort for the specific adverse events, hypotension (placebo 2.5%, candesartan 2.2%), abnormal renal function (placebo 5.3%; candesartan 8.6%) and hyperkalemia (placebo 0.8%; candesartan 3.9%), were also similar to those of the overall CHARM-Added population.

Table 53 Subgroup analyses based on the recommended ACE inhibitor heart failure treatment doses, and maximum dose, at baseline for key safety endpoints (CHARM-Added)

Event/dose of ACE inhibitor at baseline		N	Placebo Events/1000 follow-up years	Candesartan Events/1000 follow-up years	Hazard Ratio	95% CI	p-value
All cause death							
Recommended dose of ACEi	No	1257	111.2	99.9	0.90	0.74, 1.09	0.283
	Yes	1291	110.2	96.2	0.87	0.72, 1.06	0.175
Maximum dose of ACEi	No	1827	114.9	100.1	0.87	0.74, 1.03	0.096
	Yes	721	100.4	93.0	0.93	0.71, 1.22	0.582
All cause hospitalization							
Recommended dose of ACEi	No	1257	373.4	372.3	0.10	0.87, 1.14	0.982
	Yes	1291	409.7	369.9	0.92	0.80, 1.05	0.191
Maximum dose of ACEi	No	1827	380.3	361.0	0.96	0.86, 1.07	0.453
	Yes	721	420.9	398.2	0.95	0.80, 1.13	0.580
Permanent discontinuation of study drug due to AE or abnormal lab value							
Recommended dose of ACEi	No	1257	66.8	95.3	1.42	1.12, 1.81	0.004
	Yes	1291	67.8	88.2	1.29	1.02, 1.64	0.035
Maximum dose of ACEi	No	1827	70.6	95.1	1.34	1.10, 1.64	0.003
	Yes	721	59.3	83.3	1.40	1.00, 1.95	0.050

9.6.3 Benefit/Risk

In response to FDA's questions about the CHARM-Added trial for patients receiving maximum ACE inhibitor dose, a supplemental benefit/risk assessment is provided for these specific subgroups. Whether considering the maximum ACE inhibitor dose at baseline or throughout the trial, all efficacy analyses on the composite endpoints and their components demonstrate consistency of risk reduction that mirrors that observed for the entire CHARM-Added patient population. As would be expected, the smaller subgroup analyses do not reveal significant p-values. However, the consistency of the point estimates for risk reduction provides strong evidence that the beneficial effects of candesartan added to ACE inhibitors are not modified by ACE inhibitor dose throughout a broad dose range. Although drug discontinuation rates due to adverse events were higher in the candesartan group, as was the case for the entire CHARM-Added trial, the risk of discontinuation was not substantially modified by the use of maximum doses of ACE inhibitor. Using all-cause hospitalization and all-cause mortality as aggregate measures of benefit/risk for the maximum ACE inhibitor doses subgroups, it may again be observed that the point estimate of relative risk favors

candesartan. Furthermore, the point estimates for these aggregate measures are consistent with those observed when the same analyses are applied to the entire CHARM-Added patient population. Therefore, the totality of the evidence indicates that candesartan added to ACE inhibitors at maximum doses shows the same positive benefit-risk profile as the entire CHARM-Added trial.

9.7 Discussion of subgroups and Val-heft

9.7.1 Limitations of subgroup analyses

With respect to the interpretation of subgroups, in general we support the concept that the best estimate of the effect of intervention in any subgroup is the effect observed in the overall study population. In the absence of a predefined biologically plausible hypothesis that would have anticipated a directionally different and meaningful heterogeneous effect in a specific subgroup, any apparent differences in one of multiple subgroups should be interpreted most cautiously and should be assumed to be a chance finding, or due to under powering. Such subgroup analyses may provide a stimulus for generating a hypothesis but cannot be considered a reliable indicator of a likely reproducible effect in that subgroup (Wedel et al 2001). As concluded by Wedel et al based on subgroup analyses in the MERIT-HF trial "The best estimate of the treatment effect on total mortality [the primary endpoint of the trial] for any subgroup is the estimate of the hazard ratio for the overall trial".

The Val-HeFT trial was subjected to considerable subgroup analyses. In the Val-HeFT trial, the addition of the ARB valsartan or placebo to standard treatment was compared in 5010 patients with CHF (NYHA II-IV). There was no effect on all-cause mortality, one of the primary outcomes, but there was a 13.2% relative risk reduction ($p=0.009$) in the combined endpoint that included mortality, CHF hospitalizations, and morbidity, the other primary outcome. The risk reduction was attributable predominantly to a 24% reduction in CHF hospitalizations ($p<0.001$). However, the study was subjected to several subgroup analyses (mostly post-hoc), which revealed several findings that eroded confidence in ascribing a beneficial effect to valsartan in the overall trial. These included an unexpected worse outcome with respect to both primary endpoints in the 1610 patients (32%) receiving both an ACE inhibitor and beta-blocker at baseline with the addition of valsartan compared to placebo. In addition, analyses suggested that most of the benefit was seen either in patients not receiving an ACE inhibitor (n=366, 7%) or an ACE inhibitor at less than the median dose. However, there was a consistent numerical reduction in heart failure hospitalizations even in the group receiving an ACE inhibitor at a dose above the median. Consequently, based predominantly on the Val-HeFT trial and an unmet medical need, valsartan was the first ARB approved for the treatment of heart failure. The approval was for patients intolerant of an ACE inhibitor (although this group was not formally studied in Val-HeFT) to reduce hospitalizations for heart failure. However, the heart failure indication also includes the statement," There is no evidence that Diovan® (valsartan) provides added benefits when it is used with an adequate dose of ACE inhibitors". Moreover, the description of the Val-HeFT trial includes the statement, "Concomitant use of an ACE inhibitor, a beta-blocker, and valsartan was associated with a worse outcome for heart failure morbidity. It is not known if this is a reproducible effect or a chance occurrence. Use of a beta-blocker did not appear to influence the effect of

valsartan in patients not receiving an ACE inhibitor". As one might expect, the results of Val-HeFT and the subsequent labeling for Diovan® (valsartan) have led to much discussion and commentary among those who write guidelines, academicians, and clinicians regarding the potential utility of adding the ARB valsartan to conventional treatment that typically includes an ACE inhibitor plus beta-blocker. The results of the VALIANT post MI trial with valsartan were awaited to refute what was presumed to be a spurious negative interaction finding of valsartan with a beta-blocker plus an ACE inhibitor. Moreover, CHARM has been considered to be a more definitive study with respect to the beta-blocker plus ACE inhibitor issue (55% on a beta-blocker at baseline).

With respect to Val-HeFT and CHARM-Added, such subgroups may differ for many reasons other than the variable upon which the subgroups are formed, and these population differences may be related to the clinical outcomes. This is undoubtedly true for subgroups based on ACE inhibitor dose, as a patient's attained ACE inhibitor dose reflects clinical response and tolerability to the attained dose.

Thus we conclude that the best estimate of the benefits of candesartan in various subgroups should be based on the effect observed in the total study population applicable to that analysis. Based on such an analysis, benefit would be predicted to occur in all subgroups including those on a maximum dose of ACE inhibitor.

9.7.2 Comparison of Val-HeFT and CHARM-Added

The FDA has expressed interest in interpreting the results of CHARM-Added in light of the findings of the Val-HeFT trial with valsartan. In the absence of a head to head trial, it is hazardous to draw inferences regarding relative benefits or risk between any 2 treatments even 2 drugs of the same class. Consequently, one should be cautious in drawing conclusions regarding the effects of a maximum dose of candesartan in CHARM-Added (target dose 32 mg once daily, mean dose 24 mg daily) compared to a maximum dose of valsartan (target dose 160 mg bid, mean dose 254 mg daily) in Val-HeFT. The patients in CHARM-Added were somewhat sicker (eg, a higher proportion were in NYHA Class III [73% vs 36%]; and higher annualized mortality rates in the placebo groups [11% vs 9%]), a higher proportion were on beta-blockers (55% vs 35%), and the follow-up period was longer (CHARM-Added, median 41 months; Val-HeFT, mean 23 months).

Importantly, in both Val-HeFT and CHARM-Added there were substantial reductions in the risk of CHF hospitalization. In Val-HeFT these were directionally consistent in both the high-dose and low-dose ACE inhibitor groups, whereas in CHARM-Added the benefits of adding candesartan were consistent regardless of dose, including maximal doses. The single major additional benefit that was evident in CHARM-Added was the risk reduction in CV mortality and a directionally favorable effect on all-cause mortality. The other major difference between Val-HeFT and CHARM-Added was the unexpected and probably spurious negative interaction in patients receiving valsartan with an ACE inhibitor plus a beta-blocker and that was refuted indirectly by VALIANT and by inference in CHARM.

This negative interaction in 1610 of 5010 patients in the Val-HeFT trial may have undermined any potential beneficial effect on either all-cause mortality or CV mortality in that overall population, since the patients that appeared to benefit most in CHARM-Added were those using an ACE inhibitor, beta-blocker, and candesartan together.

While the best evidence for the effect of any drug is based on the specific drug studied at the specific doses in the population studied, we suggest that the totality of the evidence suggests a strong foundation for recommending the addition of candesartan at a target dose of 32 mg once daily to other heart failure treatments including an ACE inhibitor.

9.8 Summary statement

We believe that the supplemental analyses and background information presented in this section directly address the concerns raised by the FDA in the approvable letter for CHARM-Added. Specifically, these data support the conclusion that patients with CHF and LV systolic dysfunction who are receiving an ACE inhibitor at their individualized optimum dose, in the judgment of the treating physician, and who have candesartan added to their treatment regimen, will have an added benefit in terms of a reduced risk for CV death or CHF hospitalization. Furthermore, there is evidence of additional benefit of candesartan when added to concomitant use of the maximum dose of an ACE inhibitor. In this setting, the benefit of candesartan is independent of the dose of the ACE inhibitor.

9.9 References

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9.10 Appendix

The recommended ACE inhibitor heart failure treatment doses as defined in CHARM analyses, and maximum doses as defined by FDA are presented in Table 54.

Table 54 Recommended ACE inhibitor heart failure treatment doses as defined in CHARM analyses, and maximum doses as defined by FDA

ACE inhibitor	Recommended heart failure target dose[a] mg/day	Maximum doses provided by FDA[b] mg/day
Benazepril	20	80
Captopril	150	150
Enalapril	20	20
Fosinopril	20	40
Lisinopril	20	40
Perindopril	4	16
Quinapril	20	80
Ramipril	10	10
Trandolapril	2	4
Cilazapril	5	5
Moexipril	15	15
Moexipril hydrocholoride	15	15
Moexipril (Univasc)	15	15
Spirapril	20	20
Perinodopril See Perindopril	4	16
Coversyl	4	4
Accupril	20	20
Asig	20	20
Zestril	20	40
Prinivil	20	40
Monopril	20	20
Zestoretic	20	40
Trandolapril See above	2	4
Mavik	2	4
Monoplus	20	20

[a] CHARM program recommended heart failure doses.

[b] For ACE inhibitors not attributed a maximum dose by the FDA, the sponsor selected a maximum dose based on product labeling.