CLINICAL REVIEW

Application Type	NDA #20-838
Submission Number	S-025
Submission Code	

Reviewer Name	Mehul Desai, M.D.
Review Completion Date	3-Jan-2005

Established Name	Candesartan Cilexitil
(Proposed) Trade Name	Atacand®
Therapeutic Class	angiotensin receptor antagonist
Applicant	AstraZeneca
Priority Designation	Standard
Formulation	oral
Dosing Regimen	initial dose of 4 mg qd up titrated to 32 mg qd

Indication	heart failure
Intended Population	“preserved EF (> 40%)”

Table of Contents

List of Figures

List of Tables

Abbreviations

AE = adverse event
ARB = angiotensin receptor blocker
CHF = congestive heart failure
CRF = case report form
CSR = clinical study report
CTD = common technical document
CV = cardiovascular
DBP = diastolic blood pressure
EF = ejection fraction
MI = myocardial infarction
NDA = new drug application
NYHA = New York Heart Association
SAE(’s) = serious adverse event
SBP = systolic blood pressure

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The CHARM Program was a prospective, randomized clinical trial of the use of candesartan, a selective angiotensin II receptor blocker, in patients with congestive heart failure to decrease cardiovascular morbidity and mortality. The 3 sub studies within the CHARM Program were: CHARM Alternative, CHARM Added, and CHARM Preserved. The focus of this review is CHARM Preserved. Please refer to the review by Dr. Khin U for details on CHARM Alternative and CHARM Added.

CHARM Preserved was a prospective, randomized, double-blind, placebo controlled study to evaluate the effectiveness of candesartan in reducing cardiovascular mortality and/or morbidity in congestive heart failure patients (NYHA Class II through IV) with a preserved ejection fraction (EF > 40%). It is important to note that the choice of an EF > 40% to define a subset of the heart failure population as having "preserved EF" is arbitrary but very relevant to this review. It is possible for patients with an EF around 40% (e.g. 41% to 45% or possibly even higher) to have some degree of systolic dysfunction making them similar to patients in either the CHARM Alternative or CHARM Added study.

In CHARM preserved, an EF > 40% was used as a surrogate to describe heart failure patients as having "diastolic dysfunction." However, a purist would require evidence of an upward shift in the end-diastolic pressure-volume relation (EDPVR)[1,2] to describe such a population. The characterization of the EDPVR is complicated and is not routinely done in clinical practice. The medical literature suggests that CHF patients with an EF > 40% comprise between 20% to 50% of all patients with CHF[3]. It seems to be widely accepted that patients with diastolic heart failure have a better prognosis compared to patients with systolic heart failure, although recent reports seem to refute this notion[4].

The vast majority of research in CHF patients has focused on those with an EF $\leq$ 40% while the optimal medical management of patients with EF > 40% has yet to be defined. CHARM Preserved represents one of the first attempts to study the effects of a renin angiotensin system blocker in patients with a preserved EF in a prospective, controlled clinical trial.

The CHARM Preserved study was the sole study submitted by the sponsor to support approval in patients with a preserved EF. There were no supportive studies for this indication. More than 3000 patients with predominantly NYHA Class II and III heart failure were randomly assigned to placebo or candesartan and followed up for 2 to 4 years. This was a multi-national study enrolling patients from Europe, Asia, Africa, and North America. Patients were started on candesartan once daily doses of 4 to 8 mg and titrated every two weeks to a maximum dosage of 32 mg once daily as tolerated. The primary endpoint was CV death or CHF hospitalization. In terms of relevant demographics, the mean age of patients enrolled was 67 years, 40 % were female, and more than 4% were Black. The most prevalent background therapy in this patient population was diuretics. The primary endpoint was reached in 333 patients in the candesartan arm and 366 patients in the placebo arm: hazard ratio 0.89 (0.77, 1.03), p-value 0.12. CHARM Preserved did

not achieve its primary pre-specified endpoint. The observed trend appears to be driven by patients with an EF between 40 and 50%. By arbitrarily defining patients with an EF > 40% as having a "preserved EF", the study likely included patients with systolic dysfunction into CHARM Preserved. Based on the CHARM Added and CHARM Preserved components reviewed by Dr. U, it is evident that patients with systolic dysfunction will benefit from candesartan in terms of CV mortality and morbidity. Another possibility for the observed trend is that patients with an EF > 40% represent a unique heart failure sub-population that could respond to candesartan but that CHARM Preserved was simply underpowered to detect a significant difference. Differentiating these two possibilities would require further studies by the sponsor.

Candesartan has been approved for the treatment of hypertension since 1997 and thus has a large post marketing safety experience. Patients in the CHARM Preserved study were followed for a minimum duration of 24 months and a mean duration of 35 months. Study drug discontinuations were higher in the candesartan arm (18%) versus the placebo arm (13%). Three common adverse events of special interest that led to discontinuation of study drug were hyperkalemia, hypotension, and abnormal renal function. Other common AE's that led to study drug discontinuation were dizziness/vertigo and diarrhea. The frequencies of the adverse events leading to study drug discontinuation were higher on candesartan compared to placebo and were consistent across the entire CHARM Program. Other commonly occurring adverse events that occurred with a greater frequency on candesartan compared to placebo were anemia, dehydration, and fatigue and were consistent across the CHARM Program.

In summary, given the single study that failed to meet its primary endpoint, of candesartan for use in a subset of heart failure patients with "preserved" EF.

1.2 Recommendation on Postmarketing Actions

N/A

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

CHARM Preserved was one component of the overall CHARM program that evaluated the efficacy of candesartan to reduce cardiovascular morbidity and mortality in patients with congestive heart failure. CHARM Preserved focused on the subset of patients with an arbitrarily defined EF of greater than 40%. The sponsor provided results from one adequate and well controlled study to support the use of candesartan in this subset population. There were no supportive studies in this subpopulation.

CHARM Preserved was a prospective, randomized, double-blind, placebo controlled study to evaluate the effectiveness of candesartan in reducing cardiovascular mortality and CHF

hospitalizations in congestive heart failure patients (NYHA Class II through IV) with a preserved ejection fraction (EF > 40%).

1.3.2 Efficacy

The CHARM Preserved study was the sole study submitted by the sponsor to support approval in patients with a preserved EF. There were no supportive studies for this particular subset of heart failure patients. More than 3000 patients with predominantly NYHA Class II and III heart failure were randomly assigned to placebo or candesartan and followed up for 2 to 4 years. The primary endpoint was time to CV death or CHF hospitalization. The patients in the two arms of the study were similar at baseline in terms of demographics and pre-study medications. The mean age of patients enrolled was 67 years and the mean EF was 54%. More than 1/3 of the patients enrolled had an EF between 40 and 50. Approximately 75% of patients were being treated with diuretics at the time of randomization. The primary endpoint was reached in 333 patients in the candesartan arm and 366 patients in the placebo arm: hazard ratio 0.89 (0.77, 1.03), p-value 0.12. CHARM Preserved did not achieve its primary pre-specified endpoint. Neither component of the primary endpoint reached a statistically significant p-value of < 0.05.

1.3.3 Safety

Candesartan has been approved for the treatment of hypertension since 1997 and thus has a large post marketing safety experience. There were no unexpected safety findings from CHARM Preserved. The mean duration in study was 35 months. Study drug discontinuations were higher on candesartan arm versus placebo. Three common adverse events of special interest that led to discontinuation of study drug were hyperkalemia, hypotension, and abnormal renal function. Other common AE's that led to study drug discontinuation included dizziness/vertigo and diarrhea.
Other commonly occurring adverse events that occurred with a greater frequency on candesartan compared to placebo were anemia, dehydration, and fatigue and were consistent across the CHARM Program.

1.3.4 Dosing Regimen and Administration

Patients randomized to the candesartan arm were started on daily doses of either 4 or 8 mg and titrated every two weeks to a maximum dose of 32 mg once daily.

1.3.5 Drug-Drug Interactions

N/A

1.3.6 Special Populations

CHARM Preserved was not designed to evaluate the efficacy of candesartan as a function of sex or ethnicity. The effect of candesartan appeared similar in female and male patients. A subgroup analysis of the primary endpoint by ethnicity revealed that in Orientals, the effect of candesartan was negative. The hazard ratio for cardiovascular mortality and CHF hospitalizations was 3.7 [95%CI (1.2, 12), p-value 0.026.]. A total of 42 Oriental patients contributed 14 primary events. The negative effect of candesartan on the primary endpoint in the Oriental subgroup seen in CHARM Preserved was consistent when analyzing pooled data across the entire CHARM Program. In the overall CHARM Program, 133 Oriental patients contributed 51 primary events. There is evidence of statistical heterogeneity in this subgroup.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Candesartan (ATACAND®) is a selective angiotensin II type 1 (AT_1) receptor blocker that is currently approved for the treatment of hypertensive patients. In the current supplemental NDA, the sponsor has submitted clinical data in support of the use of candesartan in patients with congestive heart failure.

2.2 Currently Available Treatment for Indications

Nearly all of the guidelines for the management of heart failure are in patients with left ventricular systolic dysfunction (EF $\leq$ 40%). Currently there are no consensus guidelines for the treatment of heart failure patients with preserved ejection fraction (EF > 40%). Until CHARM Preserved, there have been no studies of adequate size evaluating clinically meaningful endpoints to guide management in the subset of patients with preserved systolic function.

In general terms, management of heart failure patients with preserved EF (referred to as diastolic heart failure by many) is to reverse the consequences of diastolic dysfunction (e.g. venous congestion and exercise intolerance) and secondly to eliminate or reduce factors that are responsible for diastolic dysfunction (e.g. hypertrophy, fibrosis, ischemia)[5]. Diuretics are the mainstay of management for venous congestion while calcium channel blockers are used for their beneficial effects in terms of myocardial ischemia, hypertension, and/or hypertrophy. However, neither of these two classes of drugs is labeled for use in patients with diastolic heart failure. Other agents that may also be potentially beneficial include beta blockers or renin angiotensin system blockers.

2.3 Availability of Proposed Active Ingredient in the United States

Candesartan was approved in 1998 for the treatment of hypertension.

2.4 Important Issues With Pharmacologically Related Products

N/A

2.5 Presubmission Regulatory Activity

Discussed here are key regulatory highlights. Please refer to Dr. Khin U's review for further details. Table 1 below summarizes major regulatory highlights for this supplemental NDA application.

Table 1: Presubmission Regulatory highlights

March 1993	Patent issued for candesartan cilexetil
June 1998	Candesartan cilexetil approved for the treatment of hypertension
October 1998	EOP2 meeting regarding the heart failure program
March 1999	The sponsor submitted the CHARM Program (studies SH-AHS-0003, 0006, and 0007)
November 2003	Pre supplemental NDA teleconference between Sponsor and FDA to discuss plans for filing.
June 2004	Supplemental NDA filed

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

No chemistry issues affecting approvability were identified.

3.2 Animal Pharmacology/Toxicology

No animal pharmacology/toxicology issues affecting approvability were identified.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sponsor submitted one pivotal study (CHARM Preserved) for the use of candesartan in patients with a preserved ejection fraction. The sponsor's sNDA submission was in the electronic CTD format. Case report forms (CRF's) for death and study drug discontinuations due to AE's, case report tabulations, and clinical study report were provided by the sponsor for patients in CHARM Preserved.

4.2 Tables of Clinical Studies

The following table lists the one study that was submitted by the sponsor in support of the use of candesartan in heart failure patients with preserved EF. Unlike for the other two components of

the CHARM Program, there were no supportive studies conducted in this subset of patients with heart failure.

Table 2: Table of Clinical Studies in CHARM Preserved

Study	Title
SH-AHS-0007 (CHARM Preserved)	"Clinical Study of Candesartan in Patients With Heart Failure and Preserved Left Ventricular Systolic Function"

4.3 Review Strategy

The focus of this review is CHARM Preserved. The other components of the CHARM Program (CHARM Alternative and CHARM Added) have been reviewed by Dr. Khin U. I initially read over the original CHARM protocols and subsequent protocol amendments. I then read over the sponsor's clinical study report for CHARM Preserved. This review is primarily based on the sponsor's clinical study report for CHARM Preserved. With the help of the Statistical Reviewer Dr. Charles Le, the results of the primary efficacy variable were validated. Case report forms for death and study drug discontinuation due to AE's were provided. Selected CRF's were reviewed in depth.

4.4 Data Quality and Integrity

DSI audits were not felt to be relevant to this efficacy supplement (Please refer to Dr. Khin U's review of CHARM Added for a detailed rationale).

4.5 Compliance with Good Clinical Practices

A debarment certification was signed by a representative of the sponsor.

4.6 Financial Disclosures

Please refer to Dr. Khin U's review of CHARM Added for further details. His review of financial disclosures is applicable to CHARM Preserved.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Please refer to the detailed "Clinical Pharmacology and Biopharmaceutics Review" completed by Dr. Nhi Beasley.

The pharmacokinetics (PK) of candesartan were studied in NYHA Class II and III heart failure over the dose range of 2 to 16 mg once daily. The PK was linear over this dose range. No attempt was made to examine PK differences based on low EF or preserved EF and there is no

clear rationale of why such a difference should exist. In general, the exposure (as measured by plasma concentration area under the curve) to candesartan was approximately doubled in patients with NYHA Class II and III heart failure compared to healthy, young patients. As candesartan is not a narrow therapeutic index drug, this change in exposure is not expected to significantly alter its safety profile.

5.2 Pharmacodynamics

Please refer to the detailed "Clinical Pharmacology and Biopharmaceutics Review" completed by Dr. Nhi Beasley. No specific pharmacodynamic studies were conducted in patients with preserved EF.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication: Preserved EF

The indication as transcribed from the sponsor's proposed label is shown below. Highlighted and italicized are sections in the proposed labeling specifically referring to the patient population with a preserved ejection fraction.

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

In essence the claim the sponsor seeks based on CHARM Preserved is a reduction in heart failure hospitalizations in patients with a preserved EF.

6.1.1 Methods

In support of the indication for Preserved EF stated above, there was one adequate and well controlled trial submitted to NDA 20-863, SH-AHS-0007, "Clinical Study of Candesartan in Patients With Heart Failure and Preserved Left Ventricular Systolic Function." There were no supportive studies (e.g. Phase 2 studies) submitted for this indication.

6.1.2 General Discussion of Endpoints

The endpoints collected during this trial were clinically relevant and included both morbidity and mortality. The endpoints chosen in the CHARM program were not inconsistent with endpoints utilized in other large outcome studies involving patients with heart failure. The components of the primary and other secondary endpoints collected during the CHARM program are described below.

Cardiovascular (CV) death: All deaths were considered CV unless an unequivocal non-CV cause could be established. This category included sudden death, death due to MI, death due to heart failure, death due to stroke, death due to a CV investigation/procedure/operation, death due to other CV causes, presumed CV deaths and deaths from unknown causes.

Hospitalization for heart failure: A hospitalization was defined as any overnight stay in a hospital. A CHF hospitalization was defined as admission to hospital necessitated by heart failure and primarily for the treatment of heart failure. A patient admitted for this reason was to demonstrate signs and symptoms of worsening heart failure and require treatment with intravenous diuretics.

Signs or symptoms of worsening heart failure could include at least one of the following:

- Increasing dyspnea on exertion
- Orthopnea
- Nocturnal dyspnea
- Increasing peripheral edema
- Increasing fatigue/decreasing exercise tolerance
- Renal hypoperfusion/ worsening renal function
- Elevated JVP
- Radiologic signs of CHF

All cause mortality: Death from any cause

Myocardial infarction (MI): A diagnosis of MI was to be made if the following conditions were met:

- Creatinine kinase (CK) or CKMB > 2x upper limit of normal (ULN) ***or***
- CK > 3 x ULN immediately following PTCA ***or***
- Troponin I or troponin T > 2 x ULN in hospitals where CK measurement unavailable

AND

- ECG demonstrated development of pathological Q waves and/or the development or disappearance of localized ST-elevations combined with the development of T inversion in at least two of the routine standard leads and clinical history consistent with myocardial infarction.

The CHARM Program utilized a Clinical Endpoints Committee (CEC). The Chair of the Committee was Dr. Scott Solomon. The objectives of the Committee were to classify deaths and to adjudicate CHF hospitalizations and MI's in a consistent and unbiased manner. The adjudication process was identical for all three components of the CHARM Program. The CEC adjudicated data were used in the analyses of the primary and secondary endpoints. Adjudication was done in a blinded manner. One member of the Committee reviewed each case that was submitted for adjudication. If the CEC member agreed with the principal investigator's (PI) endpoint diagnosis, the endpoint was considered adjudicated. If the CEC member disagreed

with the PI, the endpoint was given to the Chairman for review, discussion, and final adjudication.

6.1.3 Study Design

CHARM Preserved (SH-AHS-0007) was an adequate and well controlled study submitted in support of the use of candesartan in patients with preserved systolic function (EF > 40%.)

CHARM Preserved was a randomized, double-blind, placebo controlled, parallel group, multi-centered study to evaluate the influence of candesartan (4 mg once daily titrated to target dose of 32 mg once daily) on mortality and morbidity endpoints in patients with preserved left ventricular (LV) systolic function.

A pictorial of the study design is shown in Figure 1 below. Following randomization, patients were to have study drug titrated every two weeks as tolerated to a maximum dose of 32 mg once daily.

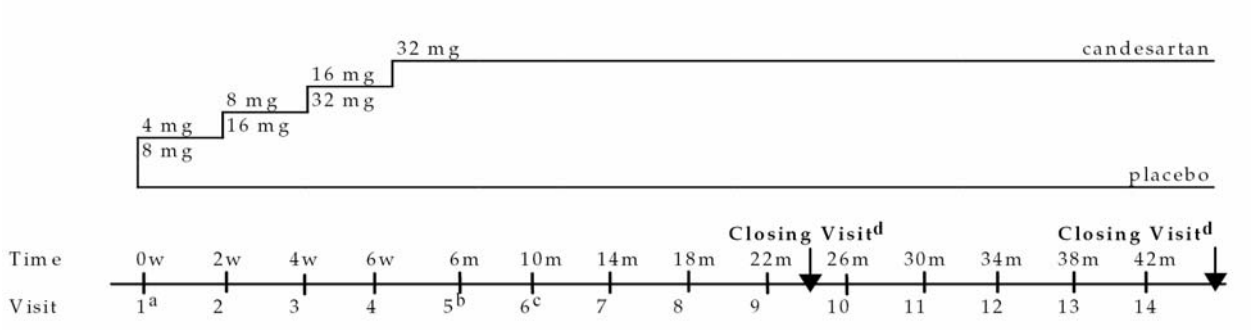

Figure 1: Study Design of CHARM (SH-AHS-0003, 0006, 0007)

Source: Figure 1 of SH-AHS-0007 CSR

In order to preserve the blind, placebo tablets were identical in appearance to the active drug. The biostatistician of the Safety Committee was the only person that could be unblinded to the data while the CHARM program was in process.

Study randomization was done centrally using an Interactive Voice Response System. Patients were randomized in blocks of four. Patients were randomized to candesartan or placebo in a ratio of 1:1.

As discussed above, the CHARM Program also consisted of a CEC, which adjudicated endpoint events in a blinded manner. In addition, there was also a Data Safety Committee that functioned independently of all other individuals and bodies associated with the conduct of the CHARM Program (e.g. investigators, Steering Committee, and Study Sponsor). The Safety Committee received safety data on a monthly basis and was responsible for reviewing the safety data continually during the program.

A data analysis plan was formulated but not finalized until approximately 2 weeks after study closure.

Placebo was the control treatment in all 3 components of the CHARM program including CHARM Preserved.

The duration of the studies the CHARM Program appeared to be adequate. The patient recruitment period was 16 months. The total study duration could range from 32 to 48 months depending on when a patient was randomized. The minimum duration of patient follow-up post randomization was to be 2 years.

The CHARM Program enrolled patients 18 years of age or older with symptomatic heart failure (NYHA Class II – IV). There were additional study specific inclusion criteria for each component of the CHARM Program. Please refer to section 10.1.1.2 in the Appendix for details regarding inclusion/exclusion criteria.

The current maximum approved dose of candesartan for the approved indication of hypertension is 32 mg once daily. The CHARM Program was designed as a dose titration study utilizing maximally tolerated doses of candesartan up to 32 mg.

6.1.4 Efficacy Findings

CHARM Preserved was the lone study in support of the proposed indication in patients with preserved left ventricular systolic function. The study did not achieve its primary pre-specified endpoint of a statistically significant reduction in CV mortality or CHF hospitalizations (p-value of 0.12.)

CHARM Preserved randomized a total of 3025 patients of whom 2 did not receive any study drug. Thus, a total of 3023 patients were evaluable in the ITT population. Three patients in the ITT population were lost to follow-up (2 on placebo, 1 on candesartan). The mean age of study patients was 67 $\pm$ 11 years. Forty percent of the patients were female, 90% were European, and more than 98% were of Class II/III NYHA class. The etiology of CHF was ischemic heart disease in more than 50% of patients followed by hypertension in approximately 23% of patients. The mean ejection fraction in randomized patients was 54%. The percentage of patients on digitalis glycosides, diuretics, beta-blockers, calcium channel blockers, vasodilators, long acting nitrates, and ACE inhibitors was 28%, 75%, 56%, 69%, 38%, 33%, and 19% respectively.

The baseline characteristics of the two treatment groups were generally similar as shown in Table 28 and Table 29 in the Appendix of this review. Shown in these tables are risk factors for congestive heart failure as well as risk factors for cardiovascular disease for the two treatment groups. The use of various medications at baseline and at study closure are listed in Table 30 located in the Appendix.

The results of the primary efficacy variable are shown below. The results were confirmed independently by Dr. Charles Le, FDA statistician.

Table 3: Efficacy results of primary variable

	Candesartan (N = 1514)	Placebo (N = 1509)	Hazard ratio (95% CI)	p-Value
CV death or CHF hospitalization	333	366	0.89 (0.77, 1.03)	0.12

Note: This data in this table obtained from Table 24 of SH-AHS-0007 CSR

The primary endpoint is displayed graphically in a Kaplan-Meier plot in Figure 2 below.

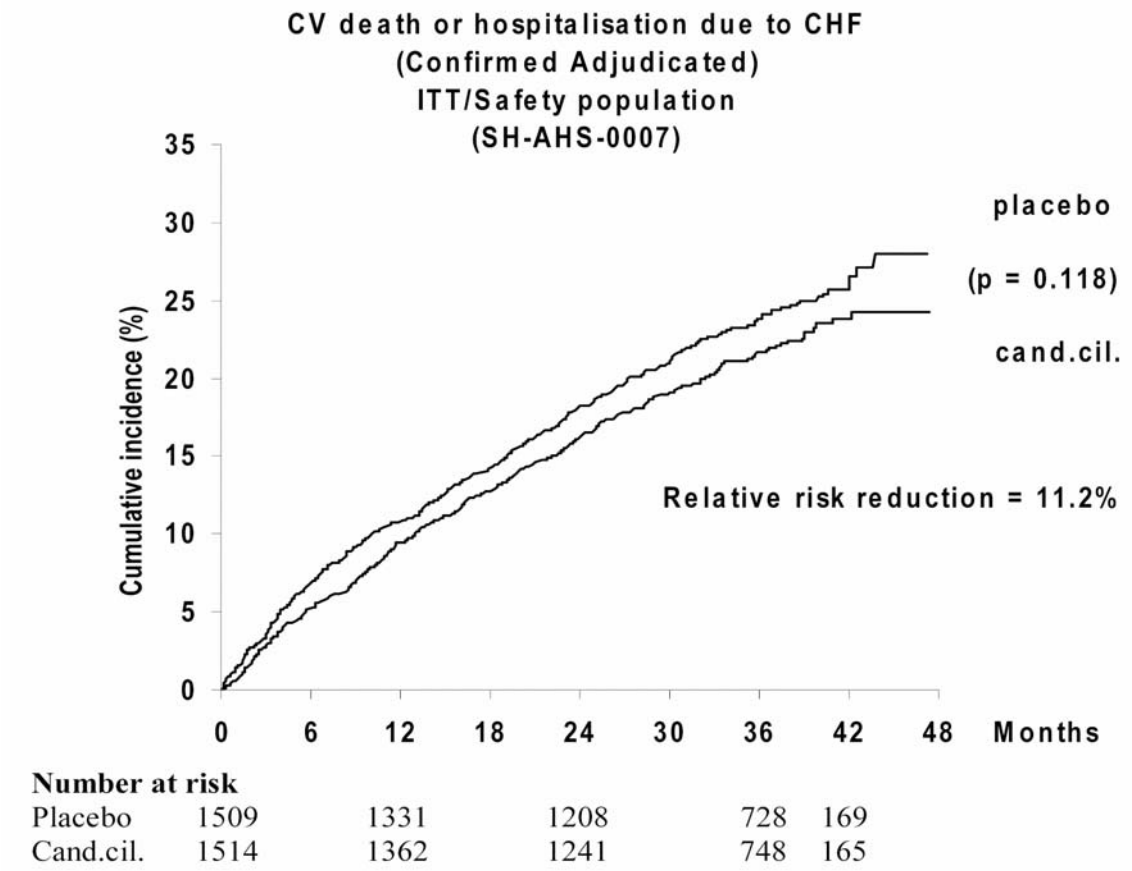

Figure 2: Cumulative incidence (%) of confirmed adjudicated CV death or hospitalization due to CHF over time

Source: Figure 4 of SH-AHS-0007 CSR

As seen in the table and figure above, the CHARM Preserved study did not meet its primary objective. It is important to note that the incidence of cardiovascular mortality and morbidity

was lower in CHARM Preserved compared to the other two components of the CHARM Program as shown in Table 4 below.

Table 4: Comparative event rates in the components of the CHARM Program

	Events per 1000 follow-up years	
	Placebo	**Candesartan**
SH-AHS-003 ("Alternative")	182	138
SH-AHS-006 ("Added")	166	141
SH-AHS-0007 ("Preserved")	91	81

Note: Data in this table obtained from Table 24, Table 23, and Table 23 of SH-AHS-0003, SH-AHS-0006, and SH-AHS-0007 CSR respectively.

In terms of the individual components contributing to the primary endpoints, there was no statistically significant difference in terms of CV death or in terms of CHF hospitalization as shown in the table below.

Table 5: Components of Primary endpoint

	Candesartan (N = 1514)	**Placebo (N = 1509)**	**Hazard ratio (95% CI)**	**p-Value**
CV death	170	170	0.989 (0.80, 1.22)	0.918
CHF hospitalization	241	276	0.853 (0.718, 1.014)	0.072

Note: The data in this table obtained from Table 30 of SH-AHS-0007 CSR

Various subgroup analyses (e.g. age, sex, and ethnicity) of the primary endpoint are discussed in detail in the Appendix of this review.

The result of one relevant subgroup analysis is shown in Table 6 below.

Table 6: Primary endpoint (CV death, CHF hospitalizations) by baseline EF

Variable	**Group**	**N**	**Cand # of events**	**Placebo # of events**	**Hazard ratio (95% CI)**	**P-value**
LVEF	< 0.50	1072	106	131	0.78 (0.60, 1.01)	0.055
	≥ 0.50	1951	227	235	0.95 (0.79, 1.14)	0.592

The tabular results of the secondary endpoints are not displayed in this review. The pre-specified secondary endpoint of time from randomization to all cause death and CHF hospitalization was not statistically significant between the two study groups. Similarly the other secondary endpoint consisting of time from randomization to CV death, CHF hospitalization or non-fatal MI was not statistically significant between the two study arms.

6.1.5 Efficacy Conclusions

The CHARM Preserved study was the sole study submitted by the sponsor to support approval in patients with a preserved EF. There were no supportive studies for this particular subset of heart failure patients. More than 3000 patients with predominantly NYHA Class II and III heart

failure were randomly assigned to placebo or candesartan and followed up for 2 to 4 years. The primary endpoint was CV death or CHF hospitalization. The patients in the two arms of the study were similar at baseline in terms of demographics and pre-study medications. The mean EF of patients enrolled was 54%. The primary endpoint was reached in 333 patients in the candesartan arm and 366 patients in the placebo arm: hazard ratio 0.89 (0.77, 1.03), p-value 0.12. CHARM Preserved did not achieve its primary pre-specified endpoint.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The information presented in the safety section of this review was primarily obtained from the sponsor's clinical study report. Line listings of all patient deaths in the candesartan arm were reviewed. Death narratives of selected cases were also reviewed with referencing of the case report forms.

Table 7 below summarizes the overall AE experience in CHARM preserved. There were nominally more deaths on the candesartan arm compared to the placebo arm during the study period (238 P vs 244 C). The were a greater number of discontinuations due to AE's and dose reductions due to AE's in the candesartan arm compared to the placebo arm. A more detailed discussion of these safety findings are provided later in this review.

Table 7: Summary of AE's, SAE's, and Discontinuations/dose reductions of study drug due to AE's

	Placebo (n = 1509)	**Candesartan (n = 1514)**
Any AE during study	1060 (70%)	1074 (71%)
Serious AE's leading to death during study	238 (16%)	244 (16%)
Serious AE's not leading to death during study	963 (64%)	939 (62%)
Discontinuations due to AE's	192 (13%)	269 (18%)
Dose reductions due to AE's	125 (8%)	192 (13%)

Note: This data in this table obtained from Table 65 of SH-AHS-0007 CSR

7.1.1 Deaths

There were a total of 482 deaths during the study of which 238 occurred in patients randomized to placebo and 244 in patients randomized to candesartan. Table 8 shows the most common AE's leading to death. The etiologies of death in the two treatment arms were similar. The most common etiologies of death were not unexpected given the patient population enrolled into the study. The most common etiologies of death in CHARM Preserved were similar to the etiologies in the overall CHARM Program and were mainly cardiovascular in nature (e.g. sudden

death, heart failure, myocardial infarction). Line listings of all deaths, located in the sponsor's clinical study report SH-AHS-0007, Appendix 12.2.7.2, that included the sponsors "Preferred Term" and the investigator's terms were reviewed. In general, the sponsor's coding of adverse events based on the investigator's verbatim term was acceptable. Line listings from all deaths in the candesartan arm were reviewed. Narratives of death from selected cases and their respective case report forms (CRF's) were also reviewed.

Table 8: AE's leading to death in CHARM preserved (cutoff ≥ 0.3%)

Preferred term	Placebo (N=1509) N	(%)	Cand (N=1514) N	(%)
Sudden death	68	(4.5)	68	(4.5)
Cardiac failure/cardiac failure aggravated[b]	53	(3.5)	41	(2.7)
Myocardial infarction	20	(1.3)	18	(1.2)
Pneumonia	19	(1.3)	14	(0.9)
Cerebrovascular disorder	14	(0.9)	11	(0.7)
Death	11	(0.7)	7	(0.5)
Sepsis	9	(0.6)	6	(0.4)
Respiratory insufficiency	8	(0.5)	5	(0.3)
Pulmonary oedema	6	(0.4)	6	(0.4)
Renal failure acute	6	(0.4)	5	(0.3)
Accident and/or injury	6	(0.4)	4	(0.3)
Pulmonary carcinoma	5	(0.3)	5	(0.3)
Renal failure nos	4	(0.3)	5	(0.3)
Coronary artery disorder	5	(0.3)	3	(0.2)

Note: This data in this table obtained from Table 67 of SH-AHS-0007 CSR

7.1.2 Other Serious Adverse Events

Table 9 below lists serious adverse events (SAE's) other than death that occurred on treatment in CHARM preserved. The table lists SAE's occurring at a frequency of at least 1% based on the candesartan arm. The 4 most common serious adverse events not leading to death on the candesartan arm were cardiac failure, angina pectoris, atrial fibrillation, and pneumonia. In general the frequency of these SAE's was similar or lower to that observed in the placebo arm. Adverse events that occurred with frequency that was nominally higher on candesartan compared to placebo included hypotension, anemia, syncope, renal failure (acute), GI hemorrhage, renal function abnormal, skin cellulitis, bradycardia, renal failure NOS, dehydration, respiratory infection, diarrhea, ventricular tachycardia/arrhythmias, atrial flutter, hyperkalemia, arteriosclerosis, AV block, hernia, and fracture. Of these listed AE's, three occurred with a frequency that was 2 fold higher on candesartan compared to placebo and are highlighted in the table below. These include dehydration, hyperkalemia, and fracture.

Three adverse events of special interest, hypotension, hyperkalemia, and renal dysfunction/renal failure occurred more frequently on candesartan compared to placebo. The adverse events of hypotension and hyperkalemia were notably higher in the candesartan arm compared to the placebo arm: hypotension (4.9% vs. 3.6%), hyperkalemia (1.5% vs. 0.4%). The adverse events

of “renal failure acute”, “renal function abnormal/renal dysfunction aggravated”, and “renal failure NOS” occurred with a higher incidence on candesartan compared to placebo.

Another SAE worth noting that occurred with a greater frequency on candesartan compared to placebo was anemia. There is more discussion of this AE later in this review.

Table 9: Serious Adverse Events other than Death (Frequency ≥ 1% on candesartan)

Preferred term	Placebo on Treatment (n=1509)		Cand on Treatment (n=1514)	
	n	(%)	N	(%)
Cardiac failure/cardiac failure aggravated	303	(20.1)	234	(15.5)
Angina pectoris/angina pectoris aggravated	195	(12.9)	179	(11.8)
Fibrillation atrial	103	(6.8)	77	(5.1)
Pneumonia	81	(5.4)	76	(5.0)
Coronary artery disorder	85	(5.6)	69	(4.6)
Cerebrovascular disorder	83	(5.5)	65	(4.3)
Myocardial infarction	74	(4.9)	63	(4.2)
Chest pain	69	(4.6)	66	(4.4)
Tachycardia supraventricular	76	(5.0)	55	(3.6)
Arrhythmia atrial	73	(4.8)	53	(3.5)
Hypotension	54	(3.6)	74	(4.9)
Accident and/or injury	46	(3.0)	45	(3.0)
Anaemia	35	(2.3)	45	(3.0)
Syncope	32	(2.1)	43	(2.8)
Dyspnoea/dyspnea (aggravated)	39	(2.6)	24	(1.6)
Arrhythmia ventricular	36	(2.4)	23	(1.5)
Diabetes mellitus/diabetes mellitus aggravated	30	(2.0)	26	(1.7)
Renal failure acute	24	(1.6)	30	(2.0)
Gi haemorrhage	20	(1.3)	25	(1.7)
Bronchitis/bronchitis aggravated	25	(1.7)	24	(1.6)
Chronic obstruct airways Disease	27	(1.8)	23	(1.5)
Pulmonary oedema	26	(1.7)	21	(1.4)
Renal function abnormal/renal dysfunction aggravated	18	(1.2)	28	(1.8)
Cellulitis skin	20	(1.3)	24	(1.6)
Dizziness/vertigo	24	(1.6)	23	(1.5)
Hypertension	32	(2.1)	12	(0.8)
Bradycardia	16	(1.1)	25	(1.7)
Renal failure nos	14	(0.9)	23	(1.5)
Urinary tract infection	18	(1.2)	18	(1.2)
Arthrosis	21	(1.4)	19	(1.3)
Dehydration	10	(0.7)	25	(1.7)
Respiratory infection	16	(1.1)	20	(1.3)
Diarrhoea	15	(1.0)	20	(1.3)
Tachycardia ventricular/arrhythmia	14	(0.9)	19	(1.3)

Preferred term	Placebo on Treatment (n=1509)		Cand on Treatment (n=1514)	
	n	(%)	N	(%)
Atrial flutter	13	(0.9)	17	(1.1)
Sick sinus syndrome	16	(1.1)	17	(1.1)
Hyperkalaemia	6	(0.4)	22	(1.5)
Arteriosclerosis	10	(0.7)	17	(1.1)
Av block	12	(0.8)	16	(1.1)
Hernia	11	(0.7)	17	(1.1)
Fracture	9	(0.6)	18	(1.2)

Taken from Table 129 of SH-AHS-0007 CSR

7.1.3 Dropouts and Other Significant Adverse Events

Dropouts due to AE's and dose reductions due to AE's were greater on the candesartan arm compared to the placebo arm in CHARM Preserved. This pattern was observed in all 3 components of the CHARM Program. More details are provided below.

7.1.3.1 Adverse events associated with dropouts

As shown earlier, the study drug was permanently discontinued due to AE's in 192 patients randomized to placebo and 269 patients randomized to candesartan. As shown in Table 10 below, AE's leading to study drug discontinuation that were at least twice as common on candesartan compared to placebo were abnormal renal function, hypotension, hyperkalemia, dizziness/vertigo, renal failure, diarrhea, and nausea. The sponsor's coding of adverse events based on the investigator's verbatim terms were acceptable.

Table 10: Summary of discontinuations due to AE's in CHARMED preserved (cutoff ≥ 0.5%)

Preferred term	Placebo (N=1509)		Cand (N=1514)	
	N	(%)	N	(%)
Renal function abnormal	32	(2.1)	68	(4.5)
Cardiac failure/cardiac failure aggravated	33	(2.2)	43	(2.8)
Hypotension	18	(1.2)	40	(2.6)
Hyperkalaemia	8	(0.5)	23	(1.5)
Cerebrovascular disorder	11	(0.7)	14	(0.9)
Angina pectoris	7	(0.5)	12	(0.8)
Myocardial infarction	13	(0.9)	6	(0.4)
Dizziness/vertigo	4	(0.3)	14	(0.9)
Renal failure nos	4	(0.3)	12	(0.8)
Diarrhoea	3	(0.2)	11	(0.7)
Dyspnoea/dyspnoea (aggravated)	6	(0.4)	8	(0.5)
Nausea	4	(0.3)	10	(0.7)
Pneumonia	8	(0.5)	6	(0.4)

Note: This data in this table obtained from Table 69 of SH-AHS-0007 CSR

Table 11 below summarizes the reductions in dosages of study drugs due to adverse events. Several of the findings in this table are consistent with those in Table 10. AE's leading to a

reduction in study drug dose that were at least twice as common on candesartan compared to placebo were hypotension and hyperkalemia. The frequency of abnormal renal function was also higher in patients randomized to candesartan compared to placebo but just missed the two fold threshold. Fatigue was also a reason for reduction in study drug dose that was twice as frequent on candesartan relative to placebo.

Table 11: Summary of dose reductions due to AE's in CHARMED preserved (cutoff ≥ 0.3%)

Preferred term	Placebo (N=1509)		Cand (N=1514)	
	N	(%)	N	(%)
Hypotension	52	(3.4)	106	(7.0)
Renal function abnormal	17	(1.1)	30	(2.0)
Dizziness/vertigo	21	(1.4)	16	(1.1)
Hyperkalaemia	5	(0.3)	16	(1.1)
Fatigue	5	(0.3)	12	(0.8)
Cardiac failure aggravated	13	(0.9)	10	(0.7)
Nausea	5	(0.3)	6	(0.4)
Dyspnoea/dyspnoea (aggravated)	6	(0.4)	5	(0.3)
Asthenia	3	(0.2)	5	(0.3)

Note: This data in this table obtained from Table 70 of SH-AHS-0007 CSR

7.1.4 Common Adverse Events

Common AE's causing study drug discontinuation or down-titration were recorded in the CRF. Non-serious AE's that did not lead to drug discontinuation or dose reduction were not recorded. Assessments for AE's were made during the up titration period and every 4 months until the end of the study as shown in Figure 5 in the Appendix.

7.1.4.1 Common adverse event tables

The table below lists AE's occurring with a frequency of ≥ 1% in the candesartan arm on treatment and the corresponding frequency on the placebo comparator.
Three adverse events that are worth noting and that occurred with a significantly higher frequency on candesartan compared to placebo were hypotension, abnormal renal function, and hyperkalemia. These AE's have also been discussed in a previous section dealing with discontinuation/dose reduction due to AE's. These AE's occurred at a consistently higher frequency on candesartan compared to placebo for the entire CHARM Program.
Other AE's that occurred more frequently on candesartan compared to placebo and were consistent across the CHARM Program included dizziness/vertigo, syncope, diarrhea, fatigue, and anemia.

Table 12: Common AE's occurring in CHARM Preserved (AE's with a frequency ≥ 1% in the candesartan arm)

Preferred term	Placebo on treatment (N=1509)		Cand. cil. on treatment (N=1514)	
	N	(%)	N	(%)
Cardiac failure/cardiac failure				

Preferred term	Placebo on treatment (N=1509)		Cand. cil. on treatment (N=1514)	
	N	(%)	N	(%)
aggravated[b]	321	(21.3)	247	(16.3)
Angina pectoris/angina pectoris aggravated[b]	198	(13.1)	182	(12.0)
Hypotension	120	(8.0)	236	(15.6)
Renal function abnormal/renal dysfunction aggravated[b]	74	(4.9)	146	(9.6)
Pneumonia	91	(6.0)	78	(5.2)
Fibrillation atrial	103	(6.8)	79	(5.2)
Myocardial infarction	85	(5.6)	74	(4.9)
Coronary artery disorder	89	(5.9)	73	(4.8)
Cerebrovascular disorder	86	(5.7)	68	(4.5)
Chest pain	71	(4.7)	72	(4.8)
Hyperkalemia	18	(1.2)	63	(4.2)
Tachycardia supraventricular	76	(5.0)	55	(3.6)
Arrhythmia atrial	73	(4.8)	53	(3.5)
Sudden death	57	(3.8)	55	(3.6)
Accident and/or injury	49	(3.2)	46	(3.0)
Dizziness/vertigo[b]	51	(3.4)	62	(4.1)
Anaemia	35	(2.3)	46	(3.0)
Syncope	32	(2.1)	46	(3.0)
Dyspnoea/dyspnoea (aggravated)[b]	48	(3.2)	39	(2.6)
Dyspnea	45	(3.0)	34	(2.2)
Diarrhea	23	(1.5)	33	(2.2)
Acute renal failure	26	(1.7)	31	(2.0)
Renal failure NOS	17	(1.1)	25	(1.7)
Pulmonary edema	28	(1.9)	26	(1.7)
Bronchitis	24	(1.6)	26	(1.7)
Bradycardia	16	(1.1)	25	(1.7)
Diabetes mellitus	27	(1.8)	26	(1.7)
Dehydration	10	(0.7)	25	(1.7)
GI hemorrhage	22	(1.5)	26	(1.7)
Cellulitis skin	20	(1.3)	24	(1.6)
Ventricular arrhythmia	36	(2.4)	23	(1.5)
Chronic obstr airways disease	27	(1.8)	23	(1.5)
Nausea	15	(1.0)	23	(1.5)
Fatigue	12	(0.8)	21	(1.4)
Respiratory infection	16	(1.1)	21	(1.4)
Abdominal pain	13	(0.9)	21	(1.4)
Arthrosis	21	(1.4)	19	(1.3)
Fracture	12	(0.8)	19	(1.3)
Atrial flutter	13	(0.9)	19	(1.3)
Urinary tract infection	18	(1.2)	18	(1.2)
Sick sinus syndrome	16	(1.1)	18	(1.2)
Hernia	11	(0.7)	17	(1.1)
AV block	12	(0.8)	16	(1.1)
Arteriosclerosis	10	(0.7)	17	(1.1)
Headache	13	(0.9)	15	(1.0)

Note: The data in this table taken from Table 120 of SH-AHs-0007 CSR

7.1.5 Laboratory Findings

Laboratory tests were obtained at the local hospital laboratory at the discretion of the investigator when deemed necessary. It was recommended that the investigator check serum creatinine and serum potassium approximately 2 weeks after each increase in dose. In a subset of sites in the study (specifically the North American sites), samples were to be sent to a core laboratory at the following time points: randomization, end of dose titration, thereafter yearly and, where possible, if the study medication is stopped. The labs included CBC, electrolytes, serum creatinine, serum ASAT, serum ALAT, serum ALP, and serum bilirubin. Please refer to the schedule of study activities in Figure 5 of the Appendix.

There are 3 laboratory abnormalities I will discuss in this section: 1) hyperkalemia, 2) increased serum creatinine and 3) anemia.

HYPERKALEMIA
Serum potassium changes from baseline in the two study arms are noted in Table 13 below. With regards to hyperkalemia, a placebo subtracted 0.09 mmol/L (95%CI → 0.03, 0.14) increase in serum potassium was noted on patients randomized to candesartan. This is consistent with what is currently noted in the approved candesartan product labeling.

Table 13: Change from baseline in serum potassium (last value carried forward)

Preferred term	**Placebo on Treatment (n=523)**		**Cand.cil. on Treatment (n=515)**	
	N	**(95%CI)**	**N**	**(95%CI)**
Potassium change from baseline (mmol/L)	0.03	(-0.01, 0.07))	0.12	(0.08, 0.16))

Taken from Table 161 of Sponsor's SH-AHS-0007 CSR

Table 14 below summarizes the frequency of elevated serum potassium outliers (as defined by serum $K^+ > 6$ mmol/L) in CHARM persevered. It is important to note that this table reflects outliers that were captured by routine blood sampling and does not reflect patients with hyperkalemia that were reported on CRF's. As shown in Table 15 below, there was at least once instance of hyperkalemia that was picked up via review of selected CRF's but that was not reported in the sponsor's list of serum potassium outliers. Case report forms were not provided in several cases of hyperkalemia including this patient. As discussed in earlier portions of this review, CRF's were only provided for deaths and discontinuations due to AE's. CRF's for serious adverse events and dose reductions due to AE's were not provided.

Table 14: Number (%) of patients with serum $K^+ \geq 6$ mmol/L any time after randomization

Preferred term	Placebo on Treatment (n=523)		Cand.cil. on Treatment (n=515)	
	N	(%)	N	(%)
Potassium > 6 mmol/L	6	1.1	10	1.9

Taken from Table 165 of Sponsor's SH-AHS-0007 CSR

The table below lists patient outliers with respect to serum potassium. Please refer to Figure 5 for information relating visit number to time in study. At baseline, 7 of these 10 patients had a serum potassium less than 5 mmol/L, 2 of 10 had serum potassium > 5 mmol/L (5.5, 5.6), and in one a baseline serum potassium was not reported.

Table 15[a]: Listing of patient outliers with respect to serum K^+

Center	Patient	Sex	Age	Visit	K^+ (mmol/L)	CRF available
1200	22596	Male	57	10	6.3	No
1232	30232	Male	60	19	6.2	No
1233	30136	Female	76	13	6.2	Yes
1239	23881	Male	76	7	6.0	Yes
1258	23159	Male	77	10	6.3	No
1410	20067	Female	68	10	6.2	Yes
1422	20821	Male	74	4	6.3	Yes
1532	23948	Male	66	4	6.5	No
1561	22157	Female	72	7	6.4	No
1587	22281	Female	70	4	7.0	No
852[b]	14173	Female	88		6.6	Yes

[a]This table obtained in part from Table 167 of SH-AHS-0007 CSR

[b]This patient was not reported in the sponsor's list of serum potassium outliers and was discovered through review of selected CRF's of death. This patient died, reportedly due to ischemic heart disease and renal failure, and was noted to have a serum potassium of 6.6 mmol/L prior to her death. This patient's initial visit was on 8/16/99 while her date of death was 2/2/01.

INCREASED CREATININE

An increase in serum creatinine to $\geq$ 2x the baseline value occurred more frequently on candesartan compared to placebo as shown in Table 16 below. This finding is consistent with the greater frequency of adverse event reports of abnormal renal function, renal impairment, or renal failure seen with candesartan compared to placebo.

Table 16: Number (%) of patients with serum creatinine ≥ 2x baseline value during study

Preferred term	Placebo on Treatment (n=525)		Cand.cil. on Treatment (n=516)	
	N	(%)	N	(%)
Creatinine ≥ 2x baseline	15	2.9	33	6.4

Taken from Table 164 of Sponsor's SH-AHS-0007 CSR

DECREASED HEMATOCRIT

A decrease in hematocrit was noted with candesartan as shown in Table 17 below. A statistically significant decrease in hematocrit was seen on candesartan compared to placebo. Placebo subtracted change in hematocrit was -1.13 (95%CI → -1.57, -0.68). Although not shown below, changes in red cell count and hemoglobin were consistent with the changes seen in the hematocrit.

Table 17: Change from baseline in hematocrit (%)(last value carried forward)

Preferred term	Placebo on Treatment (n=512)		Cand.cil. on Treatment (n=505)	
	N	(95%CI)	N	(95%CI)
Hematocrit change from baseline (%)	-0.40	(-0.71, -0.08))	-1.52	(-1.84, -1.21)

Taken from Table 161 of Sponsor's SH-AHS-0007 CSR

Outliers with respect to hematocrit are summarized below. A case report form was not available for either of these two cases.

Table 18: Listing of patient outliers with respect to serum hemoglobin

Center	Patient	Sex	Age	Hematocrit (%)	Hematocrit (%)	CRF available
1413	22766	Male	49	21.5 (visit 7)	35.3 (visit 1)	No
1455	22874	Female	79	19.8 (visit 4)	30.3 (visit 1)	No

7.1.6 Vital Signs

The effects of placebo and candesartan on diastolic blood pressure (DBP) and systolic blood pressure (SBP) over time are reported in Figure 3 and Figure 4 below. As would be expected, blood pressure reduction was greater in the candesartan arm compared to the placebo arm throughout the study duration.

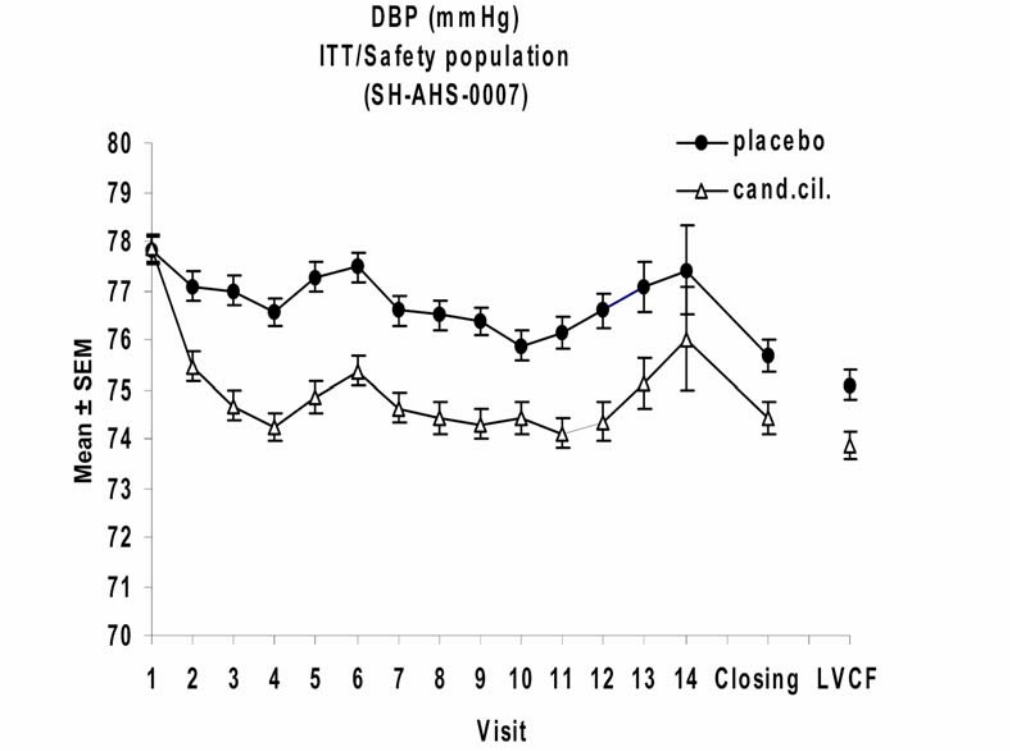

Figure 3: DBP in CHARM Preserved

Source: Figure 63 of Sponsors SH-AHS-0007 CSR

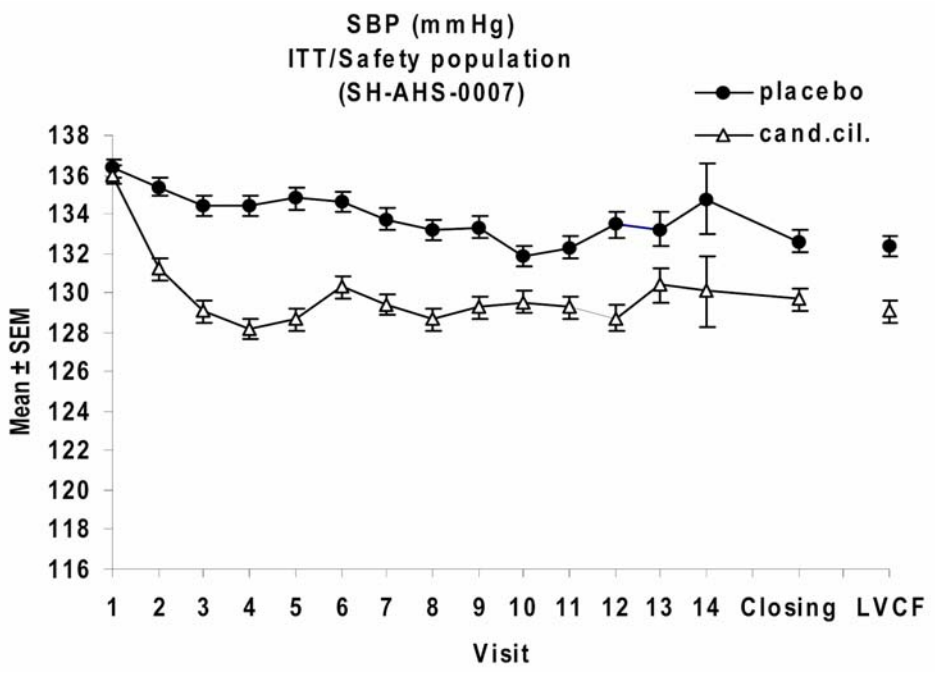

Figure 4: SBP in CHARM Preserved

Source: Figure 64 of Sponsor's SH-AHS-0007 CSR

The table below summarizes number (%) of patients with decrease in SBP to < 80 mmHg or DBP < 40 mmHg at any time after randomization. This physical exam finding is supported by reported adverse events of hypotension that were greater on candesartan compared to placebo: 236 vs. 120 events. In addition, symptoms of dizziness/vertigo were more common on candesartan compared to placebo (62 vs. 51) as were cases of syncope (46 vs. 32). Please refer to Table 12 that was described earlier in this review.

Table 19: Summary of SBP and DBP outliers

Preferred term	Placebo (N=1508) N (%)	Cand (N=1514) N (%)
DBP (< 40 mm Hg)	22 (1.5)	43 (2.8)
SBP (<80 mm Hg)	13 (0.9)	19 (1.3)

(Obtained from Table 177 of SH-AHS-0007 CSR)

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Demographics

Please refer to Appendix, Table 28 and Table 29 for further details.

7.2.1.2 Extent of exposure (dose/duration)

A summary of the patient exposure is shown in Table 20 below. As shown in the table below, duration in study and exposure to study drug were similar in both treatment arms. Patients were exposed to candesartan on average for approximately 2 ½ years. No one in the study was exposed to candesartan for more than 4 years.

Table 20: Summary of Exposure in CHARM preserved

	Time in Study			**Time on study drug**		
Time	**Placebo (n = 1509)**	**Cand (n= 1514)**	**Total (n = 3023)**	**Placebo (n = 1509)**	**Cand (n= 1514)**	**Total (n = 3023)**
≥ 6 months	1488	1498	2968	1403	1388	2791
≥ 12 months	1441	1458	2899	1292	1273	2565
≥ 24 months	1359	1377	2736	1155	1136	2291
≥ 36 months	824	833	1657	683	665	1348
≥ 48 months	0	0	0	0	0	0
Patient years	4387	4434	8821	3858	3802	7660
Mean (months)	35	35[a]	35	31	30	30
Median (months)	37	37	37	35	35	35

Note: This data in this table obtained from Table 63 of SH-AHS-0007 CSR
[a]The table in the original sNDA submission reported this time as 47 months but the sponsor's response to an information request corrected this value as being 35.1 months.

CHARM preserved was a dose titration trial. Patients were started on doses of either 4 mg or 8 mg and titrated to a maximum of 32 mg once daily as tolerated. Table 21 below summarizes the doses that patients were exposed to in CHARM preserved. Approximately 60% of patients were on the maximum dose of 32 mg candesartan permitted in the trial by month 6 post randomization (Visit 5). Beyond month 6, the percentage of patients remaining on the 32 mg dose was relatively stable between 55% and 60% (these data are not shown in this review).

Table 21: % of patients and investigational drug dose by visit and treatment

	Baseline visit		**Visit 2**		**Visit 3**		**Visit 4**		**Visit 5 (month 6)**	
	Plac	**Cand**	**Plac**	**Cand**	**Plac**	**Cand**	**Plac**	**Cand**	**Plac**	**Cand**
No study drug			31 (2.1%)	42 (2.8%)	37 (2.5%)	61 (4.1%)	44 (3.0%)	71 (4.8%)	113 (7.8%)	157 (10.7%)
4 mg	1128 (75%)	1132 (75%)	1100 (73.2%)	1095 (72.6%)	99 (6.7%)	173 (11.5%)	62 (4.2%)	117 (7.9%)	46 (3.2%)	95 (6.5%)

	Baseline visit		Visit 2		Visit 3		Visit 4		Visit 5 (month 6)	
	Plac	**Cand**	**Plac**	**Cand**	**Plac**	**Cand**	**Plac**	**Cand**	**Plac**	**Cand**
8 mg	381 (25%)	382 (25%)	370 (24.6%)	372 (24.7%)	1019 (68.5%)	945 (63.1%)	172 (11.6%)	217 (14.6%)	72 (4.9%)	135 (9.2%)
16 mg	0	0	1 (0.1%)	0	329 (22.1%)	317 (21.2%)	899 (60.7%)	810 (54.4%)	165 (11.3%)	206 (14.0%)
32 mg	0	0	0	0	3 (0.2%)	2 (0.1%)	304 (20.5%)	275 (18.5%)	1061 (72.8%)	876 (59.6%)

Note: This data in this table obtained from Table 64 of SH-AHS-0007 CSR

In general the exposure duration was adequate based on guidelines provided in ICH E1for a drug intended for chronic use.

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

Three adverse events of special interest that are unequivocally drug related include:

1) hyperkalemia
2) hypotension
3) abnormal renal function

These adverse events are discussed in detail elsewhere in this review. The dose titration study design used in the CHARM Program make defining a dose response relationship with respect to these AE's problematic. It is worth noting again that the patterns of these AE's was consistent across the CHARM Program.

Other adverse events that are likely related to candesartan include anemia, fatigue, diarrhea, dizziness/vertigo and dehydration. These AE's were consistently higher on candesartan compared to placebo across the CHARM Program.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The CHARM Program in general used a regimen of dose titration. The highest dose of candesartan currently approved is 32 mg. The currently available tablet strengths are 4, 8, 16, and 32 mg. In CHARM Preserved, patients randomized to the candesartan arm were started on daily doses of either 4 or 8 mg and titrated every two weeks to a maximum dose of 32 mg once daily as tolerated.

8.2 Drug-Drug Interactions

N/A

8.3 Special Populations

The responses to candesartan were similar for different age and sex subgroups. However, there were differences in response to candesartan seen among different ethnic groups. Table 22 below shows the results of the primary endpoint (CV mortality and CHF hospitalization) as a function of ethnicity. Orientals were adversely affected by candesartan with a statistically significant hazard ratio of 3.73.

Table 22: CV death and CHF hospitalization by ethnicity in CHARM Preserved

Variable	Group	N	Cand # of events	Placebo # of events	Hazard ratio (95% CI)	P-value
Ethnicity	European	2767	289	336	0.85 (0.72, 0.99)	0.036
	Black	126	16	11	1.20 (0.56, 2.59)	0.637
	Oriental	42	10	4	3.73 (1.17, 11.93)	0.026
	South Asian	29	6	2	2.26 (0.46, 11.24)	0.32

Note: The data in this table obtained from Table 102 of SH-AHS-0007 CSR

The adverse effect of candesartan in Orientals seen in CHARM Preserved was consistent across the overall CHARM Program as shown in Table 23 below.

Table 23: CV death and CHF hospitalization by ethnicity in overall CHARM Program

Variable	Group	N	Cand # of events	Placebo # of events	Hazard ratio (95% CI)	P-value
Ethnicity	European	6870	1002	1180	0.82 (0.75, 0.89)	<0.001
	Black	326	46	59	0.71 (0.48, 1.05)	0.090
	Oriental	133	34	17	2.14 (1.19, 3.85)	0.012
	South Asian	93	31	15	1.36 (0.73, 2.54)	0.330

Note: The data in this table obtained from Table 12.1.9.4.40 of CHARM Pooled CSR

The following table summarizes the results in Orientals only by components of the primary endpoint and also all cause mortality.

Table 24: CV death, CHF hospitalizations, and All cause mortality in Orientals in overall CHARM Program

Variable	Group	N	Cand # of events	Placebo # of events	Hazard ratio (95% CI)	P-value
CV death	Oriental	133	19	9	1.90 (0.85, 4.22)	0.116
CHF hospitalization	Oriental	133	23	11	2.16 (1.05, 4.46)	0.038
All cause mortality	Oriental	133	24	13	1.62 (0.82, 3.20)	0.166

Note: The data in this table obtained from Tables 12.1.9.4.47, 12.1.9.4.48, and 12.1.9.4.49 of CHARM Pooled CSR

8.4 Pediatrics

N/A

8.5 Advisory Committee Meeting

There has been no previous Advisory Committee meeting to discuss the CHARM program.

8.6 Literature Review

Table 25 below summarizes the studies published in the literature to date regarding the use of angiotensin receptor blockers (ARB's) other than candesartan in patients with congestive heart failure. The studies summarized below all evaluated heart failure patients with NYHA Class II-IV and ejection fractions $\leq$ 40%. The key point is that no prospective clinical trials evaluating the effects of ARB's in patients with a preserved ejection fraction have been conducted to date.

Table 25: Summary of clinical trials of ARB use in heart failure patients

Clinical trial	ARB used	Study design	Population studied	Literature reference
ELITE 1	Losartan	P, R, DB, AC (captopril)	NYHA II-IV, ***LVEF < 40%***	Pitt B et. al, Lancet 1997; 349:747-52
ELITE 2	Losartan	P, R, DB, AC (captopril)	NYHA II-IV, ***LVEF < 40%***	Pitt B et. al, Lancet 2000; 355:1582-87
Val-HEFT	Valsartan	P, R, DB, PC	NYHA II-IV, ***LVEF < 40%***	Cohn J et. al, NEJM 2001; 345-1667-75

Note: P = prospective, R = randomized, DB = double blind, AC = active controlled, PC = placebo controlled
ELITE 1, ELITE 2, and Val-HEFT are references 6, 7, 8 in the References section

9 OVERALL ASSESSMENT

9.1 Conclusions

The CHARM Preserved study was the sole study submitted by the sponsor to support approval in patients with a preserved EF. There were no supportive studies for this particular subset of heart failure patients. More than 3000 patients with predominantly NYHA Class II and III heart failure were randomly assigned to placebo or candesartan and followed up for 2 to 4 years. This was a multi-national study enrolling patients from Europe, Asia, Africa, and North America. Patients were started on candesartan once daily doses of 4 to 8 mg and titrated every two weeks to a maximum dosage of 32 mg once daily. The primary endpoint was CV death or CHF hospitalization. In terms of relevant demographics, the mean age of patients enrolled was 67 years, 40 % were female, and more than 4% were Black. The most prevalent background therapy in this patient population was diuretics. The primary endpoint was reached in 333 patients in the candesartan arm and 366 patients in the placebo arm: hazard ratio 0.89 (0.77, 1.03), p-value 0.12. CHARM Preserved did not achieve its primary pre-specified endpoint. The observed trend appears to be driven by patients with an EF between 40 and 50%. By somewhat arbitrarily defining patients with an EF > 40% as having a "preserved EF", this study likely included some patients more closely related to those in either of the other two components of the CHARM program with systolic dysfunction, notwithstanding an EF > 40%. Based on the CHARM Added and CHARM Alternative components reviewed by Dr. U, it is evident that patients with systolic dysfunction will benefit from candesartan in terms of CV mortality and morbidity. Another possibility is that CHARM Preserved was simply underpowered to detect a significant difference. Differentiating these two possibilities would require further studies by the sponsor.

With regard to safety it is important to note that Oriental patients had worse outcomes when treated with candesartan compared to Caucasians. There was evidence of statistical heterogeneity in the Oriental subgroup. It is acknowledged that post hoc subgroup analyses may be problematic and may give rise to false positive signals. The clinical significance of this finding is unclear and it is uncertain whether any specific labeling changes should be incorporated.

9.2 Recommendation on Regulatory Action

Based on CHARM Preserved (SH-AHS-0007), the sponsor is seeking approval of candesartan for use in patients with heart failure with a "Preserved" EF to decrease the need for hospitalization. Given that the single study submitted in support of the proposed indication failed to meet its primary endpoint with a p-value less than 0.05,
for the proposed indication.

9.3 Recommendation on Postmarketing Actions

N/A

9.4 Labeling Review

My labeling recommendations are as follows:

1) Acknowledge the existence of CHARM Preserved
2) Remove pooled study data that incorporates CHARM Preserved.
3) In the "Indications" section remove the reference to use of candesartan in patients with "preserved" left ventricular systolic function.

A more detailed line by line review of labeling will be discussed with other team members during labeling meetings.

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 CHARM Preserved

10.1.1.1 Study dates

Table 26: Chronology of the CHARM Program highlights

Original Protocol	November 13, 1998
Amendment #1	December 10, 1998
First Patient randomized	March 22, 1999
Amendment #2	March 31, 1999
Amendment #3	December 21, 1999
Amendment #4	March 7, 2000
Study Closure	March 31, 2003
Statistical Analysis Plan finalized	April 15, 2003
Database Lock	June 12, 2003
Database Re-Locked	July 4, 2003

10.1.1.2 Protocol

Overall Program Title:

"Candesartan Cilexitil (Candesartan) In Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM)"

Individual Study Title:

"Clinical Study (SH-AHS-0003) of Candesartan in Patients With Heart Failure Who Are ACE Inhibitor Intolerant and Have Depressed Left Ventricular Systolic Function"

"Clinical Study (SH-AHS-0006) of Candesartan in Patients With Heart Failure Who Are Treated With ACE Inhibitors and Have Depressed Left Ventricular Systolic Function"

"Clinical Study (SH-AHS-0007) of Candesartan in Patients With Heart Failure and Preserved Left Ventricular Systolic Function"

Objectives of Overall Program (Pooled Analyses):

Primary: To determine whether candesartan, compared to placebo, reduces all cause mortality in the pooled population of patients with symptomatic chronic heart failure (studies SH-AHS-0003, SH-AHS-0006, SH-AHS-0007).

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

Objectives of Each Study

Primary: To determine whether candesartan, compared to placebo, reduces the combined endpoint of cardiovascular mortality or hospitalization for the management of CHF.

Secondary: To determine whether candesartan, compared to placebo,

- Reduces the combined endpoint of all cause mortality or hospitalization for the management of CHF
- Reduces the combined endpoint of cardiovascular mortality or hospitalization for the management of CHF or nonfatal myocardial infarction (MI).

Inclusion Criteria (Common to all 3 studies in the CHARM Program)

1. Male or female, > 18 years old.
2. Symptomatic CHF corresponding to NYHA class II-IV for > 4 weeks before randomization.
3. Informed consent. (Obtained before any study specific procedures were carried out).

Criteria specific to CHARM Preserved (SH-AHS-0007)

- Documentation of left ventricular ejection fraction (LVEF) > 40% by contrast ventriculography, radionuclide ventriculography or quantitative echocardiography within the previous month (<31 days). The most recent measurement was used.
- A history of hospitalisation for a cardiac reason.
- No current treatment, or continued need for treatment, with an ACE inhibitor, except if the patient fulfils one or more of the following conditions (a-d) in which case treatment with an ACE inhibitor was allowed at the discretion of the investigator. a) Coronary artery disease defined as previous myocardial infarction, unstable angina or angina pectoris with a positive stress test or at least two-vessel disease demonstrated on coronary angiogram (>50% stenosis in at least 2 major vessels). b) Previous stroke. c) Peripheral vascular disease (angiographically proven or prior vascular surgery, amputation or intermittent claudication with an ankle-brachial pressure index below 0.9). d) Diabetes mellitus with at least one other coronary risk factor; s-total cholesterol >5.2 mmol/l (200 mg/dL), HDL-cholesterol <0.9 mmol/l (<35 mg/dL), smoking, treated hypertension, albuminuria or microalbuminuria, or any evidence of vascular disease.

  All patients must have heart failure of NYHA class II-IV at the time of enrolment. If the patient was being treated with an ACE inhibitor, the patient had to have heart failure of NYHA functional class III-IV in the last 6 months and should have been treated with a constant dose of an ACE inhibitor for at least 30 days before randomization.

- Signs and symptoms of CHF not caused by renal or liver failure, chronic lung disease, anaemia, thyroid or other primary disease.

Exclusion Criteria (Common to all 3 studies in the CHARM Program)

1. Treatment with an angiotensin II type 1 (AT_1) receptor blocker within 2 weeks before randomization.
2. Known hypersensitivity to AT_1-receptor blocker.
3. Current serum-creatinine $\geq$265 μmol/L ($\geq$3 mg/dL). If the patient was in a stable condition the sample could be taken within one month before randomization. For unstable patients a new sample was recommended.
4. Current serum-potassium $\geq$5.5 mmol/L ($\geq$5.5 mEq/L) or a history of marked ACE inhibitor induced hyperkalemia resulting in either a serum-potassium $\geq$6.0 mmol/L ($\geq$6.0 mEq/L) or a life-threatening adverse event. If the patient was in a stable condition, the sample could be taken within one month before randomization. For unstable patients a new sample was recommended.
5. Known bilateral renal artery stenosis.
6. Current symptomatic hypotension.
7. Persistent systolic or diastolic hypertension (systolic >170 mmHg; diastolic >100 mmHg) despite use of antihypertensive therapy.
8. CHF secondary to any of the following conditions: a) Critical aortic or mitral stenosis b) Non-cardiac disease (eg uncorrected thyroid disease) c) Pericardial disease.
9. Stroke, acute myocardial infarction or open-heart surgery within the last 4 weeks before randomization.
10. History of severe obstructive, restrictive or other chronic pulmonary disease.
11. Significant liver disease.
12. The following procedures: a) Planned cardiac surgery expected to be performed within 4 weeks after randomization. b) Previous heart transplants; or heart transplants expected to be performed within the next 6 months
13. Presence of any non-cardiac disease (eg cancer) that was likely to significantly shorten life expectancy to <2 years.
14. Pregnant or lactating women or women of childbearing potential who were not protected from pregnancy by an accepted method of contraception, such as the oral contraceptive pill, an intrauterine device or surgical sterilization (all women of childbearing potential must have a negative pregnancy test before randomization).
15. Any condition that in the opinion of the investigator would jeopardize the evaluation of efficacy or safety or be associated with poor adherence to the protocol.
16. Treatment with any investigational agents within 4 weeks before randomization.

Summary of Study Plan

Figure 5: Study Plan for CHARM Program

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Closing visit
Week/Month	0	2 w	4 w	6 w	6 m	10 m	14 m	18 m	22 m	26 m	30 m	34 m	38 m	42 m	
Randomisation	X														
Informed consent	X														
Medical history	X														X[g]
Physical examination[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical events/AE[b]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
NYHA class	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X														
Current therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical chemistry/haematology[c]	X[e]			X			X			X			X		
Urinalysis[d]	X						X						X		X
Creatinine/potassium[f]		X	X	X											
Health economics		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life: LihFE and VAS (North America)	X				X		X	X	X	X					X
Quality of Life: OTE (North America)					X		X			X					X

[a] Comprehensive physical examination at visit 1. Assessment of heart rate, blood pressure and body weight at each scheduled visit.
[b] Collection of serious AE and AE leading to study medication discontinuation and/or dose reduction.
[c] Samples for lab screen (blood) collected and analysed at a central laboratory. Applied to sites in North America.
[d] Collection of urine. Results of analyses are not included in this report.
[e] Blood samples also used for analyses of genetic markers. Results of analyses are not included in this report.
[f] Monitoring of S-creatinine and S-potassium was recommended 2 weeks after each dose increase and during the study at the discretion of the investigator (not recorded in the CRF).
[g] Including documentation about diagnosed diabetes mellitus and or atrial fibrillation/flutter after randomisation.

10.1.1.3 Protocol Amendments

The protocol amendments to the CHARM program are summarized in Table 27 below. The table below includes the specific date of implementation of each amendment and its relationship to patient recruitment. Particular attention should be paid to Amendment 4 that is described in the table below. The change involved increasing the sample size in the overall CHARM program by 950 patients (15% increase). The increase in sample size affected each component of CHARM differentially. This change occurred more than 15 months after the original protocol was first approved and approximately 12 months after the first patient was randomized.

Table 27: Summary of Protocol Amendments in the CHARM program

Number (date of internal approval)	Key details of amendment (Section of this report affected)	Reason for amendment	Persons who initiated Amendment
Amendment made before the start of patient recruitment			
1	Another secondary objective was	To meet planned changes	AstraZeneca

Number (date of internal approval)	Key details of amendment (Section of this report affected)	Reason for amendment	Persons who initiated Amendment
(10 December 1998)	added: To determine whether candesartan, compared to placebo, reduced the combined endpoint of all-cause death and hospitalisation for the management of CHF. Changes in the primary analysis were made to reflect changes in the secondary endpoint described above.	in European guidelines for heart failure studies, recommending that "all-cause death" is part of any combined Endpoints.	Clinical Study Team
Amendments made after the start of patient recruitment			
2 (31 March 1999)	No substantive changes made via this amendment. There were no changes to the primary/secondary endpoints, analysis, inclusion/exclusion criteria that were made	Editorial/Clarification changes	Executive Committee Astra Zeneca Clinical Study Team
3 (21 December 1999)	A reference was made to the Clinical Endpoint Committee Manual of Operations (adjudication plan). Inclusion criteria (Section 5.3.1) ACE inhibitors were allowed as concomitant treatment for patients fulfilling the HOPE-study inclusion criteria.	The detailed adjudication plan had not been developed at the time of the original protocol. Publication of the HOPE-study results	Executive Committee
4 (7 March 2000)	The number of randomised patients in the overall CHARM program was increased by 950 patients (6500 to 7450). For CHARM alternative this increase was 300 patients. For CHARM added this was 250 patients. For CHARM preserved this was 400 patients.	To safeguard statistical power due to lower than expected event rates in blinded data.	Executive Committee

Note: Data in this table adapted from Table 12 of SH-AHS-0007 study report

10.1.1.4 Statistical Considerations

Please refer to the Statistical Review by Dr. Charles Le for a more detailed discussion.

Interim efficacy analyses were made every 6 months and recommendations were made to the Steering Committee and Sponsor as to stopping the study for benefit or harm. The pre-specified primary monitoring variable for the interim analyses was all-cause mortality. A total of 6 interim analyses were conducted. According to the statistical review of this application by Dr. Charles

Le, it was felt that the effect of the interim analyses on the alpha level for the analysis of the primary endpoint would not be substantial.

Primary Analyses (of each component study of CHARM):

The primary variable (time from randomization to a CV event or the first occurrence of a CHF hospitalization) was to be analyzed by a two-sided log rank test. For patients with multiple occurrences of events, the time to first occurrence was to be used. A p-value below 0.05 was to be considered statistically significant.

To meet the secondary objectives in each study a log rank test was to be performed to first compare the incidence curves for the combined endpoint of all cause mortality or CHF hospitalization and then for the combined endpoint of CV mortality, CHF hospitalization or non-fatal MI. A statistically significant difference was to be declared if the p-value was below 0.05.

The primary and secondary endpoints were to be analyzed using a step down procedure in which if and only if the previous analysis was significant at a p value below 0.05, were subsequent analyses of the secondary endpoints were to occur.

Primary Pooled Analyses (CHARM studies pooled)

Data on all cause mortality was to be pooled from all three component studies of the CHARM Program (SH-AHS-0003, SH-AHS-0006, SH-AHS-0007). The primary endpoint of the pooled analysis was to determine if candesartan, compared to placebo, reduces all cause mortality in this patient population. A p-value less than 0.05 for the two-sided log-rank test was to be considered as a confirmation of different incidence curves for the pooled population.

It was estimated that the annual event rate in the overall CHARM program would be approximately 11%. It was anticipated that the event rates in the patient population with a depressed ejection fraction would be higher: 14% and 11.6% for studies SH-AHS-0003 and SH-AHS-0006 respectively. It was anticipated that the annual event rate in the patients with preserved ejection fraction would be 8.3%. It was also anticipated that candesartan arm would reduce the incidence of all cause mortality relative to the placebo by a minimum of 16%. Under these assumptions the power of the study was greater than 90% (even if one were to assume an even smaller overall event rate of 9%). It was originally expected that 6,500 patients would be required to achieve the endpoint. However, as discussed above in the protocol amendments section, the sample size was increased approximately 1 year after the initiation of the overall CHARM program.

10.1.1.5 Results

Patient Disposition

A total of 3025 patients were recruited from 514 sites. Of the 3025 patients, 2 had no study drug administered and no data available post randomization. Consequently there were 3023 patients that were analyzed in the ITT/Safety population. As this was a multi-national study, patients were enrolled from Europe, Asia, Africa, and North America. More than one-third of the patients in the study were from the U.S. and Canada (N = 1112).

As seen in Figure 6 below, 1509 patients were randomized to placebo and 1514 patients were randomized to candesartan. In CHARM preserved, follow up with respect to vital status was excellent. Of the 3023 patients in the ITT population, only 1 person was lost to follow-up in the placebo arm and 2 in the candesartan arm.

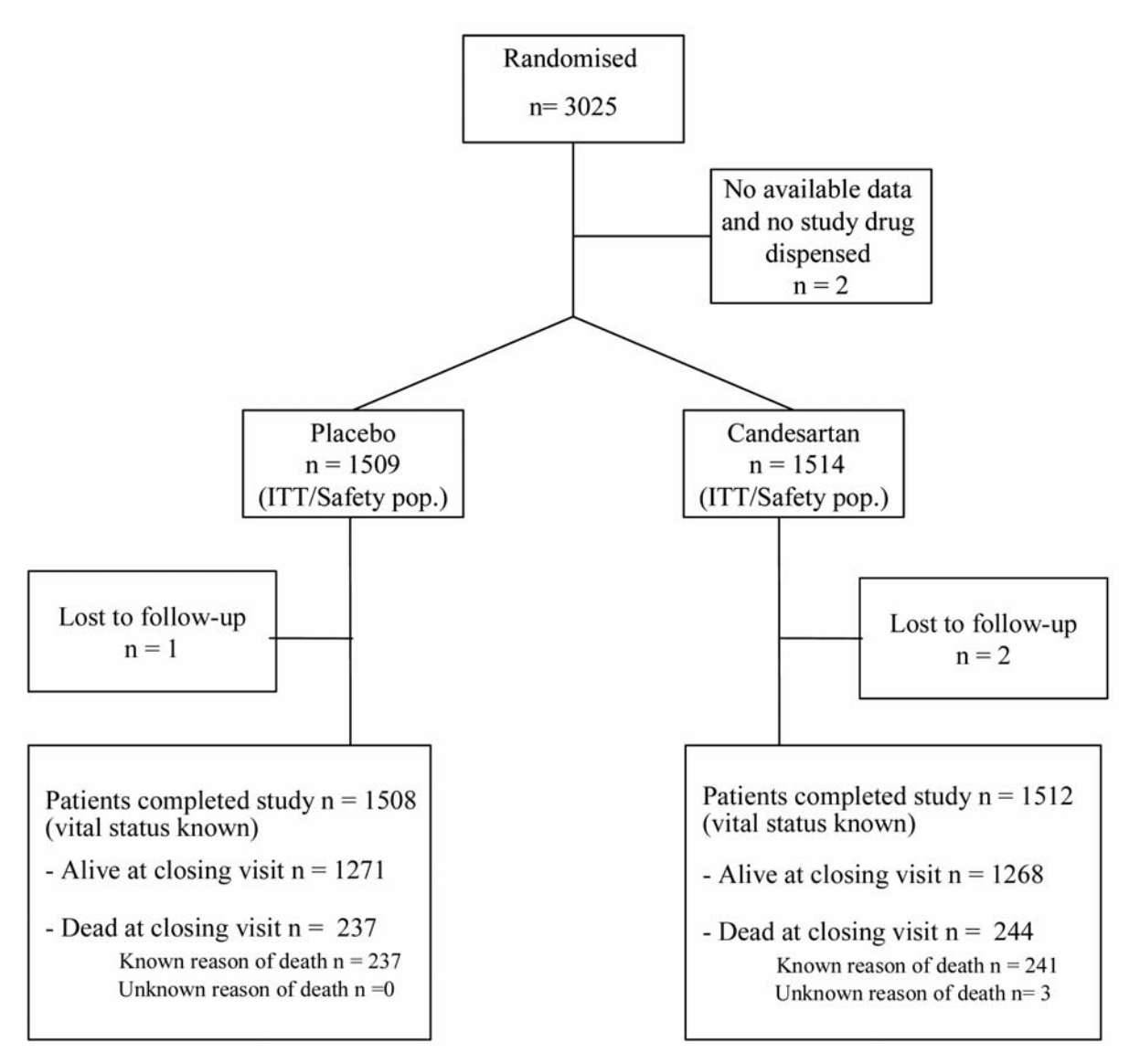

Figure 6: Patient Disposition in CHARM Preserved

Source: Figure 2 of Sponsor's CSR for SH-AHS-0007

Protocol Deviations

There were a total of 324 patients with protocol deviations – 165 on placebo and 159 on candesartan. The top two protocol deviations were inclusion and exclusion criteria deviations

and accounted for 75% of the total protocol deviations. The other common protocol deviations were the wrong investigational product given and randomization before visit 1.

Baseline patient characteristics

In general, patients were well balanced at baseline suggesting randomization was effective. As shown in Table 28 below, approximately 2/5 of the population was female. Caucasians were the predominant racial group in the study. Blacks comprised less than 5% of the study population. The majority of patients were Class II/III heart failure at baseline. In terms of the etiology of heart failure, the majority of patients had ischemic heart disease followed by hypertension. These two etiologies accounted for more than 75% of the etiologies of heart failure in this population.

Table 28: CHARM Preserved patient baseline characteristics

		Placebo	**Candesartan**	**Total**
Total number		1509 (100%)	1514 (100%)	3023 (100%)
Sex (male)		891 (59%)	920 (61%)	1811 (60%)
Age	< 65 years	614 (41%)	570 (38%)	1184 (39%)
	≥ 65 years	895 (59%)	944 (62%)	1839 (61%)
Race	European	1393 (92%)	1374 (91%)	2767 (92%)
	Black	57 (4%)	69 (5%)	126 (4%)
	Oriental	22 (2%)	20 (1%)	42 (1%)
Cigarette smoking	Non-smoker	644 (43%)	598 (40%)	1242 (41%)
	Current smoker	187 (12%)	222 (15%)	409 (14%)
NYHA Class	II	905 (60%)	931 (62%)	1836 (61%)
	III	584 (39%)	556 (37%)	1128 (38%)
	IV	20 (1.3%)	27 (2%)	47 (2%)
h/o previous CHF hospitalization		1038 (69%)	1038 (69%)	2076 (69%)
h/o previous MI		659 (44%)	681 (45%)	1340 (44%)
h/o hypertension		959 (64%)	984 (65%)	1943 (64%)
h/o diabetes mellitus		423 (28%)	434 (29%)	857 (28%)
CHF etiology	Ischemic heart disease	852 (57%)	854 (56%)	1706 (56%)
	Hypertension	347 (23%)	337 (22%)	684 (23%)
	Idiopathic dilated cardiomyopathy	132 (9%)	131 (9%)	263 (9%)

Note: data in this table obtained from Table 18 of Sponsor's SH-AHS-0007 clinical study report

As shown in Table 29 below, patients were similar in the two treatment arms with respect to age, BMI, blood pressure, and ejection fraction. The mean age of patients studied was approximately 67 years of age. The mean ejection fraction was 54%.

Table 29: CHARM preserved patient baseline characteristics

	Placebo	**Candesartan**	**Total**
Mean Age (years)	67.1 ± 11.1	67.2 ± 11.1	67.2 ± 11.1
Mean Height (cm)	168.1 ± 10.1	168.1 ± 10.1	168.1 ± 10.1
Mean Weight (kg)	82.3 ± 18.8	83.0 ± 19.1	82.7 ± 19.0
Mean BMI ((kg/m^2))	29.0 ± 5.6	29.3 ± 5.9	29.2 ± 5.8
Mean ejection fraction	0.54 ± 0.09	0.54 ± 0.09	0.54 ± 0.09
Mean SBP (mm Hg)	136.3 ± 18.3	136.0 ± 18.6	136.2 ± 18.4
Mean DBP (mm Hg)	77.8 ± 10.5	77.8 ± 10.9	77.8 ± 10.7

Note: data in this table obtained from Table 19 of Sponsor's SH-AHS-0007 clinical study report

Table 30 below summarizes the major classes of medicine being used by patients in the CHARM preserved study at the time of study randomization and at the closing visit. The use of various medications was similar between the two treatment groups at the time of randomization. Approximately ¾ of the study population enrolled were on diuretics at baseline. Beta blockers and aspirin were used by more than half of the study population at baseline. Calcium channel blockers were used by less than 1/3 of the patients at baseline. Of the beta blockers, metoprolol was the most commonly used agent followed by atenolol. Of the calcium channel blockers, amlodipine was the most commonly used agent followed by diltiazem. Of the vasodilators, long acting nitrates was the most commonly used agent.

At the time of the closing visit, the use of digitalis glycosides, diuretics, calcium channel blockers, vasodilators, and acetylsalicylic acid had generally decreased relative to the time of randomization in both study arms (the exception was calcium channel blocker use in the placebo arm). The decreased use of digitalis, diuretics, and calcium channel blockers was disproportionately greater in the candesartan arm relative to placebo. The use of beta-blockers, ACE inhibitors, and lipid lowering agents was increased at the closing visit relative to the randomization visit in both study arms. The increased use was proportional in both treatment arms.

Table 30: Patients (%) using the listed class of drug at the time of study entry

	At randomization			At closing visit		
	Placebo	**Candesartan**	**Total**	**Placebo**	**Candesartan**	**Total**
Digitalis glycoside	410 (27%)	432 (29%)	842 (28%)	321 (26%)	292 (23%)	613 (24%)
Diuretics	1121 (74%)	1138 (75%)	2259 (75%)	914 (73%)	873 (70%)	1787 (71%)
Beta-blocker	837 (56%)	847 (56%)	1684 (56%)	746 (59%)	712 (57%)	1458 (58%)
Calcium channel blocker	477 (32%)	467 (31%)	944 (31%)	409 (33%)	349 (28%)	758 (30%)
ACE inhibitors	280 (19%)	296 (20%)	576 (19%)	337 (27%)	297 (24%)	634 (25%)
Vasodilators (including nitrates, hydralazine, and other agents)	594 (39%)	566 (37%)	1160 (38%)	445 (35%)	419 (33%)	864 (34%)
Lipid lowering drugs	645 (43%)	617 (41%)	1262 (42%)	651 (52%)	644 (51%)	1295 (52%)
Acetylsalicylic acid	887 (59%)	875 (58%)	1762 (58%)	653 (52%)	663 (53%)	1316 (52%)

Note: data in this table obtained from Table 20 of Sponsor's SH-AHS-0007 clinical study report

Efficacy

Table 31 below summarizes the results of efficacy in subgroups of interest based on ITT analysis. The effect on candesartan in various age and sex subgroups was similar in CHARM Preserved. In Orientals, there appeared to be a negative effect of candesartan on CV mortality and CHF hospitalizations.

Another interesting finding based on the table below is that patients with a baseline EF < 0.50 seemed to derive benefit whereas patients with a baseline EF $\geq$ 0.50 did not. It should be noted that the sponsor's choice of an EF > 0.40 to define "preserved ejection fraction" is an arbitrary one. It is likely that at least some patients with an EF between 0.40 and 0.50 had reduced systolic function and could have derived benefit from candesartan similar to patients studied in CHARM Added.

Table 31: Subgroup analysis of CV death or CHF hospitalization

Variable	Group	N	Cand # of events	Placebo # of events	Hazard ratio (95% CI)	P-value
Age (years)	< 65	1184	72	86	0.90 (0.66, 1.23)	0.513
	≥ 65 - < 75	1032	117	118	0.90 (0.70, 1.16)	0.424
	≥ 75	807	144	162	0.82 (0.65, 1.02)	0.074
Sex	Male	1811	195	205	0.91 (0.75, 1.11)	0.341
	Female	1212	138	161	0.87 (0.69, 1.09)	0.220
Ethnicity	European	2767	289	336	0.85 (0.72, 0.99)	0.036
	Black	126	16	11	1.20 (0.56, 2.59)	0.637
	Oriental	42	10	4	3.73 (1.17, 11.93)	0.026
	South Asian	29	6	2	2.26 (0.46, 11.24)	0.32
Region	Western Europe	1377	125	143	0.87 (0.69, 1.11)	0.262
	Eastern Europe	196	18	12	1.39 (0.67, 2.88)	0.379
	North America	1112	142	167	0.83 (0.66, 1.03)	0.096
	USA	734	95	105	0.85 (0.65, 1.13)	0.261
NYHA	II	1836	151	164	0.88 (0.71, 1.10)	0.269
	III	1140	166	195	0.87 (0.71, 1.07)	0.188
	IV	47	16	7	1.60 (0.66, 3.91)	0.300
LVEF	< 0.50	1072	106	131	0.78 (0.60, 1.01)	0.055
	≥ 0.50	1951	227	235	0.95 (0.79, 1.14)	0.592
Digitalis during study	No	1984	187	186	0.98 (0.80, 1.20)	0.817
	Yes	1039	146	180	0.80 (0.64, 1.00)	0.045
Diuretic during study	No	492	15	19	0.77 (0.39, 1.51)	0.441
	Yes	2531	318	347	0.90 (0.77, 1.04)	0.154
Calcium channel blocker during study	No	1718	176	196	0.80 (0.65, 0.98)	0.033
	Yes	1305	157	170	1.01 (0.82, 1.26)	0.901
Spironolactone during study	No	2239	219	228	0.90 (0.75, 1.08)	0.249
	Yes	684	114	138	0.96 (0.75, 1.23)	0.754
ACE inhibitors during study	No	2008	200	205	0.93 (0.77, 1.13)	0.470
	Yes	1015	133	161	0.85 (0.67, 1.07)	0.159

Note: This table taken from Table 102 of SH-AHS-0007 CSR

10.2 Line-by-Line Labeling Review

To be discussed during team meetings.

REFERENCES

1) Burkhoff D, Maurer MS, Packer M. Heart Failure With a Normal Ejection Fraction, Is It Really a Disorder of Diastolic Dysfunction? Circulation 2003; 107: 656-58.

2) Zile MR, Baicu CF, Gaasch WH. Diastolic Heart Failure – Abnormalities in Active Relaxation and Passive Stiffness of the Left Ventricle. NEJM 2004; 350: 1953-59.

3) Jessup M, Brozena S. Heart Failure. NEJM 2003; 348: 2007-18.

4) Senni M, Redfield MM. Heart Failure with Preserved Systolic Function. A Different Natural History? J. Am Coll Cardiol 2001; 38:1277-82.

5) Gaasch WH, Zile MR. Left Ventricular Diastolic Dysfunction and Diastolic Heart Failure. Ann Rev. Med 2004; 55:373-94.

6) Pitt B, Segal R, Martinez FA, Meurers G, Cowley AJ, Thomas I, et. al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). Lancet 1997; 349 (9054): 747-52.

7) Pitt B, Poole-Wilson PA, Segal R, Martinez FA, Dickstein K, Camm AJ, et. al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial--the Losartan Heart Failure Survival Study ELITE II. Lancet 2000; 355 (9215): 1582-87.

8) Cohn JN, Tognoni G; Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. NEJM 2001; 345(23): 1667-75.