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Statistical Review and Evaluation

CLINICAL STUDIES

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Candesartan cilexetil (Candesartan) significantly reduced cardiovascular (CV) death or Chronic Heart Failure (CHF) hospitalization in patients with depressed left ventricular (LV) systolic function and ejection fraction (EF) < 40% treated with an angiotensin converting enzyme (ACE) inhibitor. In the confirmatory analysis, Candesartan also significantly reduced the risk of all-cause death or CHF hospitalization, and the risk of CV death or CHF hospitalization or non-fatal MI.

The benefits of Candesartan appeared to be very small in North America relative to Western Europe (Table 7). The secondary endpoints showed similar results (Tables 8 and 9).

1.2 Brief Overview of Clinical Studies

This review is based on Study SH-AHS-0006, which is one of the three pivotal studies for the CHARM (Candesartan in Heart Failure Assessment of Reduction in Mortality and mobility) program. The CHARM program consists of 3 pivotal studies (SH-AHS-0003, SH-AHS-0006 and SH-AHS-0007) with the same primary endpoint and different patient populations. The common primary endpoint was time to the first CV death or CHF hospitalization. SH-AHS-0006 studied patients with heart failure who were treated with ACE inhibitors and had depressed LV systolic function, SH-AHS-0003 treated patients with heart failure who were ACE inhibitor intolerant and had depressed LV function, and SH-AHS-0007 had patients with heart failure and preserved LV systolic function. The Sponsor is seeking indication that Candesartan reduces the risk of CV death or CHF hospitalization in the three patient populations based on each of the three individual studies. The Sponsor is also seeking the indication that Candesartan reduces the risk of all-cause mortality based on the data combining all three studies.

This indication for the patients treated with an ACE inhibitor (SH-AHS-0006) was granted with priority review status and this review was based on this study. A separate review will consider the other indications.

This study (SH-AHS-0006) was a randomized, double-blind, placebo controlled, parallel group, multicenter study to evaluate the influence of candesartan cilexetil with a target dose of 32 mg once daily on mortality and morbidity in patients with depressed LV systolic function and EF <40% treated with an ACE inhibitor. A total of 2548 patients were randomized in a 1:1 ratio into Candesartan group (n = 1276) and placebo group (n = 1272). All patients remained in the study until the last randomized patient had been in the CHARM program for two years. Patient follow-up time ranged from 41 to 48 months, with the median follow-up time around 41 months.

1.3 Statistical Issues and Findings

Candesartan significantly reduced CV death or CHF hospitalization with a relative risk reduction of 15% over placebo. The relative risk reductions were 2% in North America and 26% in Western Europe, respectively.

It also significantly reduced the all-cause death or CHF hospitalization with a 13% relative risk reduction. It significantly reduced the relative risk of CV death or CHF hospitalization or non-fatal MI, with a 15% relative risk reduction.

2 INTRODUCTION

2.1 Overview

Candesartan is indicated for the treatment of hypertension and it is available for oral use as tablets containing either 4 mg, 8 mg, 16 mg, or 32 mg of Candesartan cilexetil. In this efficacy supplement application, the Sponsor is seeking indications that Candesartan reduces the combined endpoint of CV mortality or hospitalization for the management of chronic heart failure. Results from the CHARM program are submitted in this application. CHARM was an international (26 countries including the US) program comprised of 3 independent concurrent double-blind, placebo-controlled trials (SH-AHS-0003, SH-AHS-0006 and SH-AHS-0007) in which a total of 7601 patients (7599 with data) with NYHA class II-IV heart failure. Study SH-AHS-0006 (CHARM-Added trial) studied the patients with depressed LV systolic function and EF <40% treated with an ACE inhibitor. The patients in Study SH-AHS-0003 (CHARM-Alternative) were ACE inhibitor intolerant with depressed LV systolic function and EF <40%. Study SH-AHS-0007 (CHARM-Preserved) studied patients with heart failure and preserved LV systolic function and EF > 40%.

2.1.1 HISTORY OF DRUG DEVELOPMENT

The Sponsor was seeking priority review for all 3 pivotal studies. After negotiation with the Sponsor, the Division granted the priority review status for the review of Study SH-AHS-0006. The other two studies are under standard review.

2.1.2 SPECIFIC STUDIES REVIEWED

Study SH-AHS-0006 was fully reviewed for this priority review. This study enrolled patients with depressed LV systolic function (EF ≤ 40%) treated with ACE inhibitors. It is also called CHARM-added trial.

2.1.3 MAJOR STATISTICAL ISSUES

The primary endpoint of this study is the composite of CV mortality and CV hospitalization for the management of CHF, and this single study is intended for the indication that Candesartan reduces the risk of the composite endpoint when compared with placebo. The data from this study, together with the other two studies in the CHARM program, are also used for the indication that Candesartan reduces the risk of all-cause mortality for the pooled patient population. Six interim analyses were conducted on all-cause mortality at intervals of approximately 6 months over a total of recruitment and follow-up period of around 48 months. In order to stop for efficacy, one required a p-value < 0.0001 for any interim analysis within 18 months, or a p-value < 0.001 for any subsequent interim analysis.

The hypothesis for the test of the primary endpoint is tested at alpha = 0.05 in this study, and the analysis for all-cause mortality is also performed at alpha = 0.05 level based on the pooled data. Since this is a single study, the evidence for the indication of the primary endpoint should be strong and the p-value should be smaller. Some adjustment of the p-value should be made for the all-cause mortality for the pooled data of the 3 studies. Six interim analyses were conducted on all-cause mortality, which was not the primary endpoint. It is not clear how the interim analyses would affect the alpha level for the analysis of the primary endpoint. Since the Type I error rates allocated for the interim analyses were very small, the effect should be small.

2.2 Data Sources

This application was submitted electronically. All the materials are located at \\Cdseub1\n20838\S_022\2004-06-30. The final reports for this study and the summary of clinical efficacy for all the 3 studies were fully reviewed. They are located at \\Cdseub1\n20838\S_022\2004-06-30\clinstat\indication\controlled. The main analyses were independently performed by this reviewer. SAS data sets are located at \\Cdseub1\n20838\S_022\2004-06-30\crt\datasets\SH-AHS-0006.

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 STUDY DESIGN AND ENDPOINT

This was a randomized, double-blind, placebo controlled, parallel group, multicenter study to evaluate the influence of Candesartan with a target dose of 32 mg once daily on mortality and morbidity in patients with depressed LV systolic function and EF < 40% treated with an ACE inhibitor. The patient population was male and female patients, over or equal to 18 years of age,

with symptomatic CHF corresponding to NYHA class II-IV and with depressed LV systolic function and treated with ACE inhibitors. A total of 2548 patients were randomized in a 1-1 ratio into Candesartan group (n = 1276) or placebo group (n = 1272). All patients remained in the study until the last randomized patient had been in the CHARM program for two years. The patients were followed from 41 to 48 months, with a median follow-up time of 41 months. The study was conducted in 25 countries at a total of 473 sites, including 123 sites in the United States. The first patient was randomized on March 22, 1999 and the last patient was completed on March 31, 2003.

The primary endpoint was time to the first CV death or hospitalization due to symptomatic chronic heart failure. Secondary endpoints were time to the first all-cause mortality or hospitalization due to chronic heart failure, time to the first CV death or hospitalization due to chronic heart failure or nonfatal MI.

3.1.2 PATIENT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Table 1 is the summary of the patient participation, demographic and baseline characteristics. Almost everybody completed the study, with 99.8% of the patients completed the study in the Candesartan group and 99.9% of the patients completed in the placebo group, respectively. The demographic and baseline characteristics seem to be comparable between the two treatment groups for the variables listed in the table.

Table 1. Patient Participation, Demographic and Baseline Characteristics

	Placebo N = 1272	Cand. Cil. N = 1276	Total N = 2548
Disposition N (%)			
Completed	1271 (99.9)	1273 (99.8)	2544 (99.8)
Lost to Follow-up	1 (0.1)	3 (0.2)	4 (0.2)
Demographic Characteristics			
Sex N (%)			
Male	1000 (78.6)	1006 (78.8)	2006 (78.7)
Female	272 (21.4)	270 (21.2)	542 (21.3)
Age Mean (SD) Years	64.1 (11.3)	64.0 (10.7)	64.1 (11.0)
Ethnicity N (%)			
European Origin	1164 (91.5)	1143 (89.6)	2307 (90.5)
Black	62 (4.9)	65 (5.1)	127 (5.0)
South Asia	8 (0.6)	19 (1.5)	27 (1.1)
Arab/Middle East	4 (0.3)	8 (0.6)	12 (0.5)
Oriental	13 (1.0)	22 (1.7)	35 (1.4)
Malay	7 (0.6)	11 (0.9)	18 (0.7)
Other	14 (1.1)	8 (0.6)	22 (0.9)
Baseline Characteristics			
Ejection Fraction, Mean (SD)	0.28 (0.07)	0.28 (0.08)	0.28 (0.07)
Diabetes Mellitus, N (%)	382 (30.0)	376 (29.5)	758 (29.7)
Hypertension, N (%)	619 (48.7)	609 (47.7)	1228 (48.2)
Atrial Fibrillation, N (%)	341 (26.8)	346 (27.1)	687 (27.0)
Previous MI, N (%)	703 (55.3)	714 (56.0)	1417 (55.6)

	Placebo N = 1272	Cand. Cil. N = 1276	Total N = 2548
Angina Pectoris, N (%)	684 (53.8)	666 (52.2)	1350 (53.0)
Stroke, N (%)	112 (8.8)	108 (8.5)	220 (8.6)
NYHA II, N (%)	302 (23.7)	312 (24.5)	614 (24.1)
NYHA III, N (%)	925 (72.7)	931 (73.0)	1856 (72.8)
NYHA IV, N (%)	45 (3.5)	33 (2.6)	78 (3.1)
Current Smoker, N (%)	235 (18.5)	194 (15.2)	429 (16.8)

Source: Table S1 of the clinical study report of Study SH-AHS-0006 by AstraZeneca.

3.1.3 STATISTICAL METHODOLOGIES

The primary endpoint, time to the first CV death or hospitalization due to symptomatic chronic heart failure, was compared between the two treatment groups using the log-rank test. The hazard ratio and its 95% CI was obtained by a Cox proportional hazards model. The survival distribution by treatment group was plotted using the Kaplan-Meier product limit estimator. The analyses were conducted on the ITT population, which included all the randomized patients.

The primary and two secondary endpoints were analyzed based on the principal of closed tests. The analyses were conducted in a hierarchical sequence. The primary endpoint was tested first and the two secondary endpoints were tested sequentially, conditional on a significant result of the preceding test.

3.1.4 RESULTS AND CONCLUSION

Table 2 presents the results of the analysis of the primary endpoint and two secondary endpoints, including the analysis of the components of the composite endpoints. For the primary endpoint, time to the first CV death or CHF hospitalization, Candesartan had a relative risk reduction of 15% over placebo, with p-value = 0.011. Candesartan also reduced the risk of the two secondary endpoints. The relative risk reduction was 13% (nominal P = 0.021) for all-cause death or CHF hospitalization and 15% (nominal P = 0.010) for CV death or CHF hospitalization or nonfatal MI. It seemed that each individual component contributed to the benefit of Candesartan.

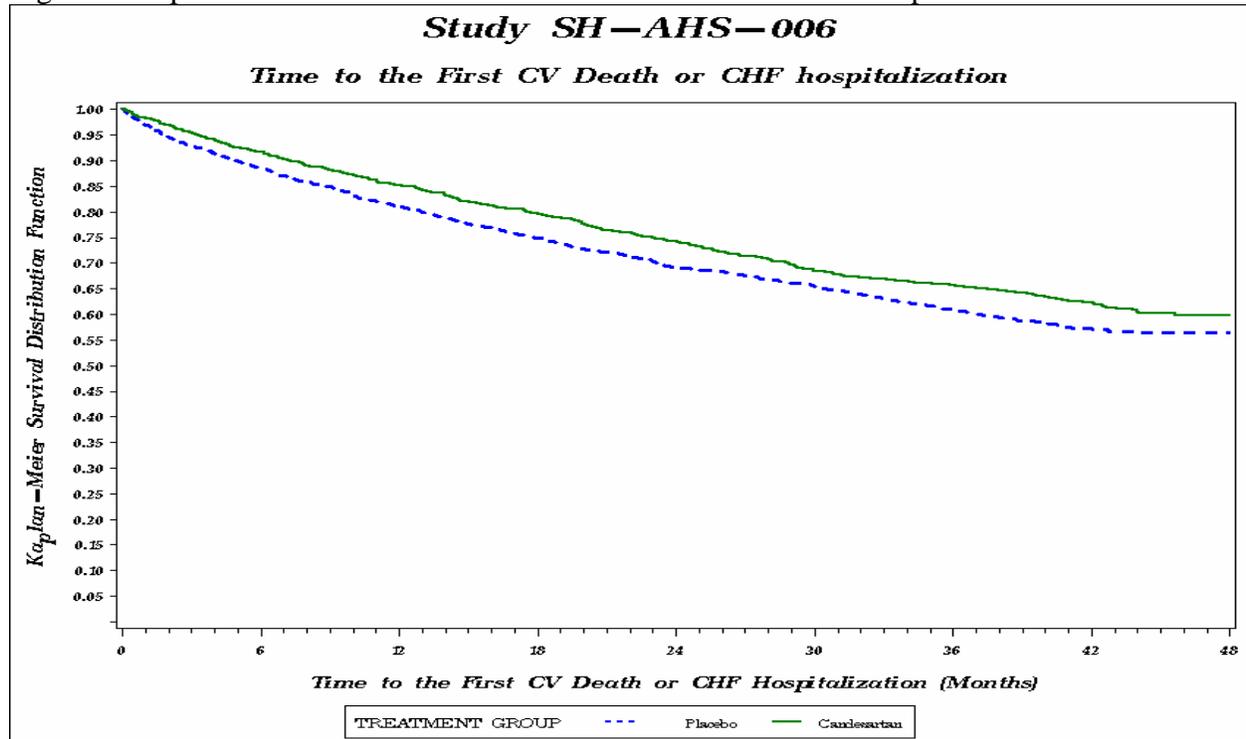
Table 2. Analysis of the Primary and Secondary Endpoints

Endpoint	No. of Patients with event		Hazard Ratio (95%CI)	P-value
	Candesartan N = 1276	Placebo N = 1272		
Primary CV death or CHF hospitalization	483	538	0.85 (0.75–0.96)	0.011
Secondary All-cause death or CHF hospitalization	539	587	0.87 (0.78-0.98)	0.021
CV death or CHF hospitalization or non-fatal MI	495	550	0.85 (0.76-0.96)	0.010
Components of the composite endpoints CV death	302	347	0.84 (0.72-0.98)	0.029
CHF hospitalization	309	356	0.83 (0.71-0.96)	0.013
All-cause mortality	377	412	0.89 (0.77-1.02)	0.086
Nonfatal MI	26	49	0.51 (0.32-0.82)	0.005

Source: Table 8 of the Sponsor’s summary of clinical efficacy. The results were confirmed independently by this reviewer, with minor difference for nonfatal MI. Nominal P-values were from log-rank test and hazard ratios were from Cox regression model with treatment as the only independent variable.

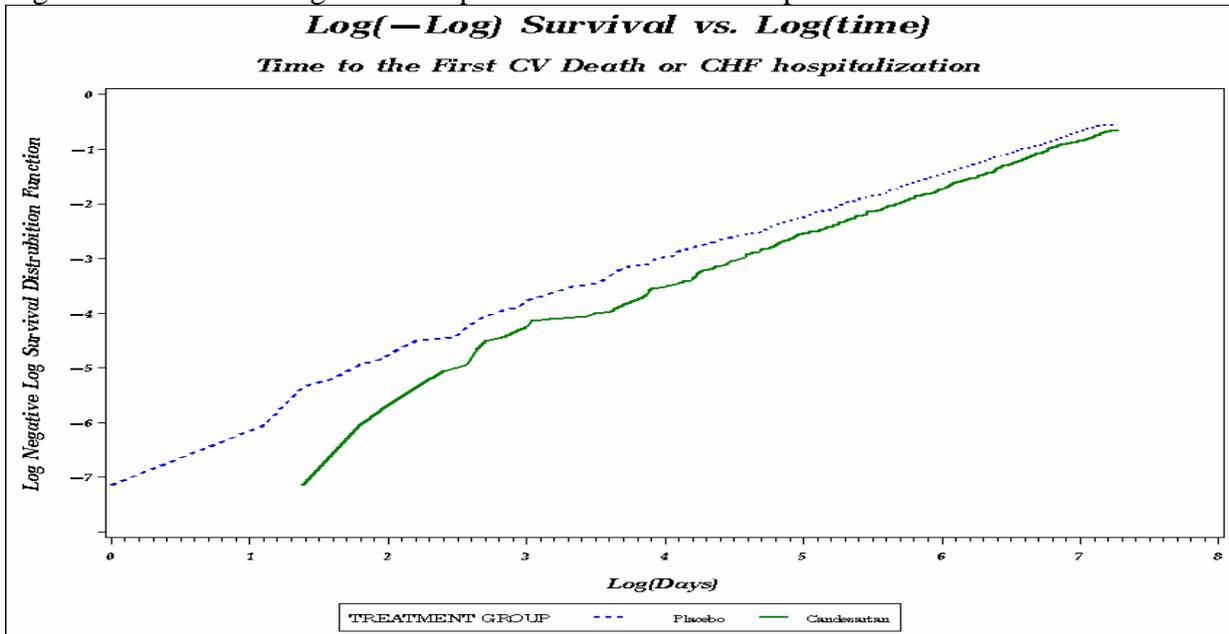
Figure 1 is the Kaplan-Meier estimates for time to the first CV death or CHF hospitalization. It seemed that the benefit of Candesartan appeared early and was maintained throughout the study period. Based on Figure 2, it appeared that it was reasonable to use the proportional hazards model, although the proportion might not be a constant over time.

Figure 1. Kaplan-Meier Estimate of Time to 1st CV Death or CHF Hospitalization



Source: Reviewer’s analysis.

Figure 2. Plot of Testing of the Proportional Hazards Assumption



Source: Reviewer’s Analysis.

The results of the analysis of the primary endpoint for some subgroups are in Table 3. Based on Table 3, it seemed that Candesartan was more effective when the patients took recommended ACE inhibitor doses.

Table 3. Some Sugroup Analysis of the Primary Endpoint

Subgroup	Total N (n with events)		Hazard Ratio (95%CI)	P-value
	Candesartan N (n)	Placebo N (n)		
Patients with recommended ACE inhibitors at baseline	643 (232)	648 (275)	0.79 (0.67-0.95)	0.010
Patients without recommended ACE inhibitors at baseline	633 (251)	624 (263)	0.92 (0.77-1.09)	0.314
Patients with recommended ACE inhibitors during study	748 (270)	787 (330)	0.81 (0.69-0.95)	0.010
Patients without recommended ACE inhibitor during study	528 (213)	485 (208)	0.91 (0.75-1.10)	0.345

Source: Table 102 of the Sponsor’s clinical study report of study SH-AHS-0006, independently confirmed by this reviewer. The nominal P-value, hazard ratio and CI were from Cox regression model with treatment as the only independent variable.

3.2 Evaluation of Safety

The most commonly reported adverse events (AE) are in Table 5. Table 6 lists the most commonly reported AEs leading to death, and the most commonly reported severe AEs other than death are reported in Table 7. Tables 5 and 7 use a cut-off of 3% AEs in the total population during the study (N = 2548), and Table 6 uses a cut-off of 0.3% in the total population during the study (N = 2548). Candesartan reduced the risk of death, so there are fewer deaths in the Candesartan group. It seemed that most of reported AEs are comparable among the two treatment groups. Among the AEs that occurred more in the Candesartan group

during the study, Hypotension occurred in 23% and 15% of the patients in Candesartan group and Placebo group, respectively, and renal function abnormal/renal dysfunction aggravated occurred in 15% and 9% of the patients in Candesartan group and Placebo group, respectively. The two AEs also occurred more often in the Candesartan group among the most often reported non-fatal SAEs.

Table 4. Most Commonly Reported AEs

Preferred Term	Placebo on treatment (N = 1272)		Candesartan on treatment (N = 1276)		Placebo during study (N = 1272)		Candesartan during study (N = 1276)	
	n	%	n	%	n	%	n	%
Cardiac failure/cardiac failure aggravated	435	(34.2)	350	(27.4)	472	(37.1)	421	(33.0)
Hypotension	176	(13.8)	288	(22.6)	184	(14.5)	296	(23.2)
Angina pectoris/angina pectoris aggravated	153	(12.0)	127	(10.0)	169	(13.3)	150	(11.8)
Sudden death	140	(11.0)	114	(8.9)	174	(13.7)	143	(11.2)
Renal function abnormal/renal dysfunction aggravated	115	(9.0)	192	(15.0)	119	(9.4)	196	(15.4)
Arrhythmia ventricular	107	(8.4)	78	(6.1)	121	(9.5)	88	(6.9)
Pneumonia	88	(6.9)	57	(4.5)	108	(8.5)	76	(6.0)
Hyperkalaemia	44	(3.5)	121	(9.5)	46	(3.6)	123	(9.6)
Myocardial infarction	73	(5.7)	60	(4.7)	88	(6.9)	70	(5.5)
Atrial fibrillation	69	(5.4)	52	(4.1)	73	(5.7)	66	(5.2)
Arrhythmia atrial	61	(4.8)	59	(4.6)	71	(5.6)	67	(5.3)
Tachycardia ventricular/arrhythmia/ arrhythmia aggravated	63	(5.0)	52	(4.1)	68	(5.3)	65	(5.1)
Cerebrovascular disorder	48	(3.8)	55	(4.3)	58	(4.6)	69	(5.4)
Chest pain	64	(5.0)	45	(3.5)	71	(5.6)	54	(4.2)
Coronary artery disorder	42	(3.3)	58	(4.5)	50	(3.9)	73	(5.7)
Syncope	45	(3.5)	49	(3.8)	49	(3.9)	59	(4.6)
Tachycardia supraventricular	46	(3.6)	47	(3.7)	50	(3.9)	54	(4.2)
Cardiomyopathy	38	(3.0)	33	(2.6)	48	(3.8)	51	(4.0)
Dizziness/vertigo	35	(2.8)	49	(3.8)	40	(3.1)	57	(4.5)
Pulmonary oedema	41	(3.2)	39	(3.1)	47	(3.7)	48	(3.8)
Renal failure acute	29	(2.3)	45	(3.5)	38	(3.0)	54	(4.2)
Anaemia	36	(2.8)	35	(2.7)	43	(3.4)	46	(3.6)
Accident and/or injury	32	(2.5)	34	(2.7)	43	(3.4)	44	(3.4)
Diabetes mellitus/diabetes mellitus aggravated	41	(3.2)	30	(2.4)	42	(3.3)	37	(2.9)
Dehydration	18	(1.4)	40	(3.1)	22	(1.7)	55	(4.3)

Source: Table S4 of the Sponsor's clinical study report of study SH-AHS-0006.

On treatment = on treatment with investigational product; During study = total study period, irrespective of treatment with investigational product or not.

Table 5. Number of Patients with Most Commonly Reported AEs Leading to Death

Preferred Term	Placebo on treatment (N = 1272)		Candesartan on treatment (N = 1276)		Placebo during study (N = 1272)		Candesartan during study (N = 1276)	
	n	%	n	%	n	%	n	%
Sudden death	139	(10.9)	113	(8.9)	174	(13.7)	143	(11.2)
Cardiac failure/cardiac failure aggravated	61	(4.8)	28	(2.2)	112	(8.8)	74	(5.8)
Myocardial infarction	12	(0.9)	15	(1.2)	20	(1.6)	21	(1.6)
Death	5	(0.4)	7	(0.5)	13	(1.0)	19	(1.5)
Pneumonia	11	(0.9)	3	(0.2)	19	(1.5)	10	(0.8)
Cardiac arrest	8	(0.6)	8	(0.6)	13	(1.0)	13	(1.0)
Fibrillation ventricular	14	(1.1)	6	(0.5)	16	(1.3)	9	(0.7)

Preferred Term	Placebo	Candesartan	Placebo	Candesartan
	on treatment (N = 1272) n %	on treatment (N = 1276) n %	during study (N = 1272) n %	during study (N = 1276) n %
Cerebrovascular disorder	7 (0.6)	8 (0.6)	11 (0.9)	12 (0.9)
Sepsis	6 (0.5)	5 (0.4)	10 (0.8)	11 (0.9)
Cardiomyopathy	3 (0.2)	2 (0.2)	8 (0.6)	8 (0.6)
Pulmonary carcinoma	4 (0.3)	5 (0.4)	5 (0.4)	10 (0.8)
Pulmonary oedema	4 (0.3)	3 (0.2)	8 (0.6)	6 (0.5)
Renal failure nos	3 (0.2)	0 (0)	8 (0.6)	4 (0.3)
Accident and/or injury	3 (0.2)	3 (0.2)	5 (0.4)	5 (0.4)
Renal failure acute	3 (0.2)	2 (0.2)	5 (0.4)	5 (0.4)
Multiorgan failure	0 (0)	1 (0.1)	4 (0.3)	4 (0.3)
Colon carcinoma	0 (0)	1 (0.1)	0 (0)	7 (0.5)
Coronary artery disorder	2 (0.2)	1 (0.1)	2 (0.2)	5 (0.4)
Renal function abnormal	2 (0.2)	0 (0)	5 (0.4)	2 (0.2)

Source: Table 67 of the Sponsor's clinical study report of study SH-AHS-0006.

On treatment = on treatment with investigational product; During study = total study period, irrespective of treatment with investigational product or not.

Table 6. Number of Patients with Most Commonly Reported SAEs Other Than Death

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

Source: Table 68 of the Sponsor's clinical study report of study SH-AHS-0006.

On treatment = on treatment with investigational product; During study = total study period, irrespective of treatment with investigational product or not.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age, Gender and Ethnic group

Subgroup analysis of the primary endpoint was performed by age, gender and ethnic group. The results are presented in Table 7. The hazard ratios were less than 1 (in favor of Candesartan) in all the subgroups except for the oriental, South Asian, Malay subgroups. The sample sizes were very small in the three groups. The results of the subgroup analysis of the secondary endpoints are presented in Tables 8 and 9. Since the secondary endpoints are highly correlated with the primary endpoint, the results were similar.

Table 7. Subgroup Analysis of Time to the First CV Death or CHF hospitalization

Variable	Group	Total N	Candesartan # of events	Placebo # of Events	Hazard Ratio (95% CI)	P-value
Age(Years)	< 65	1268	192	211	0.879 (0.723, 1.069)	0.197
	>= 65 -< 75	823	176	193	0.782 (0.637, 0.959)	0.018
	>= 75	457	115	134	0.945 (0.736, 1.212)	0.654
Age (Years)	< 75	2091	368	404	0.842 (0.732, 0.970)	0.017
	>= 75	457	115	134	0.945 (0.736, 1.212)	0.654
Sex	Male	2006	387	427	0.862 (0.752, 0.990)	0.035
	Female	542	96	111	0.815 (0.620, 1.072)	0.143
Ethnic Group	European	2307	427	490	0.845 (0.742, 0.962)	0.011
	Black	127	24	29	0.655 (0.381, 1.126)	0.126
	South Asian	27	11	4	1.264 (0.400, 3.998)	0.690
	Arab/Middle East	12	3	0		
	Oriental	35	10	4	1.804 (0.564, 5.768)	0.320
	Malay	18	5	3	1.104 (0.263, 4.636)	0.892
	Other	22	3	8	0.573 (0.152, 2.165)	0.412
Region	Western Europe	1193	194	255	0.739 (0.613, 0.891)	0.002
	Eastern Europe	219	41	43	0.825 (0.538, 1.266)	0.378
	North America (US and Canada)	954	205	204	0.984 (0.811, 1.194)	0.870
	USA	597	128	128	1.019 (0.798, 1.303)	0.877
	Asia	59	19	8	1.282 (0.561, 2.930)	0.556
	Russia	15	2	5	0.787 (0.152, 4.073)	0.775
	Other	108	22	23	0.800 (0.446, 1.435)	0.454
NYHA	II	614	93	104	0.841 (0.636, 1.112)	0.225
	III	1856	367	399	0.868 (0.753, 1.000)	0.051
	IV	78	23	35	0.847 (0.500, 1.435)	0.536
LVEF	< 0.25	770	186	203	0.851 (0.698, 1.039)	0.113
	>= 0.25	1778	297	335	0.849 (0.726, 0.993)	0.040

Source: Table 102 of the Sponsor's clinical study report of study SH-AHS-0006, independently confirmed by this reviewer. The nominal P-value, hazard ratio and CI were from Cox regression model with treatment as the only independent variable.

Table 8. Subgroup Analysis of Time to the All-cause Death or CHF hospitalization

Variable	Group	Total N	Candesartan # of events	Placebo # of Events	Hazard Ratio (95% CI)	P-value
Age(Years)	< 65	1268	204	223	0.883 (0.730, 1.068)	0.200

Variable	Group	Total N	Candesartan # of events	Placebo # of Events	Hazard Ratio (95% CI)	P-value
	>= 65 -< 75	823	205	208	0.844 (0.696, 1.023)	0.084
	>= 75	457	130	156	0.917 (0.727, 1.157)	0.466
Age (Years)	< 75	2091	409	431	0.877 (0.766, 1.004)	0.057
	>= 75	457	130	156	0.917 (0.727, 1.157)	0.466
Sex	Male	2006	433	468	0.880 (0.772, 1.003)	0.055
	Female	542	106	119	0.839 (0.646, 1.091)	0.190
Ethnic Group	European	2307	480	531	0.876 (0.774, 0.991)	0.036
	Black	127	25	35	0.564 (0.337, 0.943)	0.029
	South Asian	27	11	4	1.264 (0.400, 3.998)	0.690
	Arab/Middle East	12	3	0		
	Oriental	35	12	5	1.729 (0.608, 4.917)	0.305
	Malay	18	5	4	0.828 (0.222, 3.091)	0.779
	Other	22	3	8	0.573 (0.152, 2.165)	0.412
Region	Western Europe	1193	220	278	0.767 (0.643, 0.916)	0.003
	Eastern Europe	219	46	47	0.843 (0.562, 1.267)	0.412
	North America (US and Canada)	954	225	224	0.983 (0.817, 1.183)	0.858
	USA	597	143	138	1.056 (0.836, 1.334)	0.648
	Asia	59	21	10	1.122 (0.528, 2.384)	0.765
	Russia	15	3	5	1.158 (0.276, 4.864)	0.841
	Other	108	24	23	0.870 (0.491, 1.541)	0.632
NYHA	II	614	108	113	0.899 (0.690, 1.170)	0.427
	III	1856	407	437	0.878 (0.767, 1.005)	0.059
	IV	78	24	37	0.841 (0.502, 1.408)	0.510
LVEF	< 0.25	770	202	218	0.860 (0.710, 1.042)	0.123
	>= 0.25	1778	337	369	0.874 (0.754, 1.013)	0.073

Source: Table 110 of the Sponsor's clinical study report of study SH-AHS-0006. The nominal P-value, hazard ratio and CI were from Cox regression model with treatment as the only independent variable.

Table 9. Subgroup Analysis of Time to the CV Death or CHF hospitalization or Nonfatal MI

Variable	Group	Total N	Candesartan # of events	Placebo # of Events	Hazard Ratio (95% CI)	P-value
Age(Years)	< 65	1268	198	217	0.883 (0.728 1.071)	0.205
	>= 65 -< 75	823	180	197	0.777 (0.634, 0.951)	0.014
	>= 75	457	117	136	0.940 (0.734, 1.204)	0.625
Age (Years)	< 75	2091	378	414	0.843 (0.733, 0.969)	0.016
	>= 75	457	117	136	0.940 (0.734, 1.204)	0.625
Sex	Male	2006	395	436	0.860 (0.751, 0.986)	0.030
	Female	542	100	114	0.822 (0.629, 1.076)	0.154
Ethnic Group	European	2307	439	499	0.852 (0.750, 0.969)	0.014
	Black	127	24	31	0.598 (0.351, 1.020)	0.059
	South Asian	27	11	4	1.264 (0.400, 3.998)	0.690
	Arab/Middle East	12	3	0		
	Oriental	35	10	4	1.804 (0.564, 5.768)	0.320
	Malay	18	5	4	0.761 (0.204, 2.847)	0.685
	Other	22	3	8	0.573 (0.152, 2.165)	0.412
Region	Western Europe	1193	200	257	0.756 (0.629, 0.910)	0.003
	Eastern Europe	219	41	43	0.826 (0.538, 1.267)	0.380
	North America (US and Canada)	954	211	212	0.969 (0.801, 1.173)	0.747

Variable	Group	Total N	Candesartan # of events	Placebo # of Events	Hazard Ratio (95% CI)	P-value
	USA	597	131	135	0.978 (0.769, 1.244)	0.856
	Asia	59	19	9	1.108 (0.501, 2.452)	0.800
	Russia	15	2	5	0.787 (0.152, 4.073)	0.775
	Other	108	22	24	0.753 (0.422, 1.342)	0.336
NYHA	II	614	98	107	0.863 (0.656, 1.136)	0.294
	III	1856	374	408	0.862 (0.749, 0.992)	0.038
	IV	78	23	35	0.809 (0.477, 1.370)	0.430
LVEF	< 0.25	770	189	208	0.836 (0.686, 1.018)	0.074
	>= 0.25	1778	306	342	0.857 (0.734, 1.000)	0.049

Source: Table 112 of the Sponsor's clinical study report of study SH-AHS-0006. The nominal P-value, hazard ratio and CI were from Cox regression model with treatment as the only independent variable.

4.2 Other Subgroup Populations

The results of subgroup analysis of the primary endpoint by region, classification of NYHA and LVEF are presented in Table 7. The hazard ratios were less than 1 (in favor of Candesartan) in all the subgroups except for the USA and Asia subgroups. The sample size was too small in Asia. The estimate of the hazard ratio was 1.02 in the USA subgroup, which was very close to 1. It should be noted that the hazard ratios were 0.74 (N = 1193) and 0.98 (N = 954) in the Western Europe and North America with similar sample size, respectively. The results of the subgroup analysis for the two secondary endpoints are similar to those for the primary endpoint.

Some other subgroup analysis results of the primary endpoint are presented in Table 3. In Table 3, the patients were divided into whether they took recommended ACE inhibitor doses at baseline or during the study. It seemed that Candesartan reduced the risk of the CV death or CHF hospitalization in each of the subgroups.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The primary endpoint, time to the first CV death or CHF hospitalization, achieved statistical significance (P = 0.011) with a relative risk reduction of 15% over placebo. It seemed that both CV death and CHF hospitalization contributed to the benefit. The benefits of Candesartan seemed consistent among various subgroups except between North America and Western Europe, where the hazard ratios were 0.98 (N = 954) and 0.74 (N = 1193), respectively. Six interim analyses were conducted on all-cause mortality and it is not clear how these analyses would affect the Type I error rate for the primary endpoint. However, since the allocated Type I error rates were very small for the interim analyses, the effect should be small if any.

In the pre-specified analysis of the two secondary endpoints, statistical significance was also achieved for each of the two secondary endpoints. Candesartan reduced the risk of all-cause death or CHF hospitalization with a 13% relative risk reduction (nominal P = 0.021) and the risk of CV death or CHF hospitalization or nonfatal MI with a 15% relative risk reduction (nominal P = 0.010).

5.2 Conclusions and Recommendations

Candesartan significantly reduced CV death or CHF hospitalization in patients with depressed LV systolic function treated with an ACE inhibitor. Candesartan also significantly reduced the risk of all-cause death or CHF hospitalization, and the risk of CV death or CHF hospitalization or non-fatal MI in the same patient population.

The benefits of Candesartan appeared to be very small in North America when compared with Western Europe (Tables 7, 8 and 9).