including diuretics and β-blockers.

Among the patients that discontinued the investigational products due to hypotensive events, a greater proportion had SBP < 100 mmHg at baseline in the candesartan group (placebo 3, 7.5%, candesartan 11, 24.1%).

In patients aged younger than 75 years, discontinuation because of the preferred term hypotension was reported in 30 (2.9%) of patients in the placebo group and 53 (5.0%) of patients on candesartan.

For patients aged 75 years or older the discontinuation rates were 14 (5.7%) in the placebo group and 16 (7.5%) in the candesartan group.

In the placebo group, permanent discontinuation of the investigational product due to hypotension was reported in 34 (3.4%) males and 10 (3.7%) females. In the candesartan treatment group there were 59 (5.9%) males and 10 (3.7%) females who were permanently discontinued due to hypotension.

Although over the entire study period patients in both treatment groups discontinued taking the investigational product because of hypotension, the candesartan discontinuation rate, shown in the exploratory analysis, was greatest during the first 6 to 12 months of treatment (Figure 103).

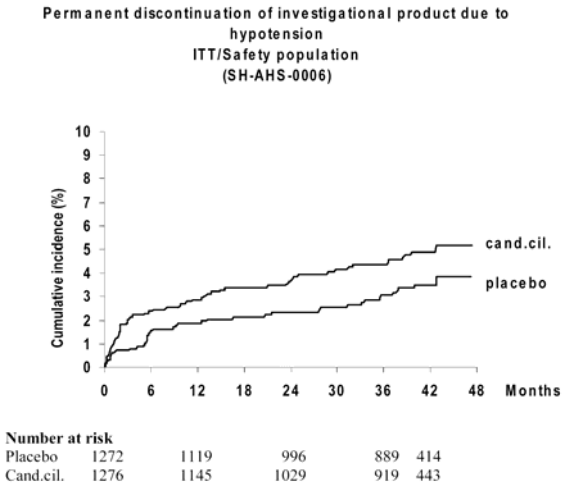


Figure 103 Cumulative incidence (%) of permanent discontinuation of investigational product due to hypotension (Ref. - Table 221). ITT/Safety population

Among the 382 (30.0%) placebo patients and 376 (29.5 %) candesartan patients entering the study with a history of diabetes, investigational product discontinuation for the specific preferred term hypotension was noted for 15 (3.9%) placebo patient and 17 (4.5%) candesartan patients.

<u>Abnormal renal function</u>:

To summarize abnormal renal function, the following AE terms (AAED preferred terms) were

selected and analyzed as a single composite event: renal function, abnormal/ renal dysfunction, aggravated; renal failure acute; renal failure, NOS; uremia; non-protein nitrogen, increased; renal failure, aggravated; blood urea nitrogen, increased; acute pre-renal failure and anuria. For this composite AE, patients with multiple events including any of the selected AE terms were counted only once.

At baseline, prior to study entry, there were a slightly higher proportion of patients in the candesartan group with s-creatinine ≥ 2.0 mg/ dl at baseline (placebo 20, 4.3%; candesartan 26, 5.6%) (North American study population).

AEs suggesting 'abnormal renal function' occurred in 151 (11.9%) patients in the placebo group and 231 (18.3 %) patients in the candesartan group during study (Table 226).

Table 226 Number (%) of patients with any of the preferred terms renal function abnormal/ renal dysfunction aggravated, renal failure acute, renal failure not otherwise specified (NOS), uremia, non-protein nitrogen increased, renal failure aggravated, blood urea nitrogen increased, acute pre-renal failure or anuria. ITT/Safety population (SH-AHS-0006)

Placebo on treatment N=1272	Cand. cil. on treatment N=1276	Placebo during study N=1272	Cand. cil. during study N=1276
139 (10.9)	220 (17.3)	151 (11.9)	231 (18.3)

The AE terms that predominately contributed to this composite AE term was renal function abnormal which was reported in 118 (9.3%) of patients given placebo and 195 (15.3%) given candesartan during study. Renal failure, acute (placebo, 38 patients, 3.0%; candesartan, 54 patients, 4.2%) and uremia (placebo, 10 patients, 0.8%; candesartan, 18 patients, 1.4%) were also numerically more frequent in patients given active treatment.

A fatal renal function event was reported for a higher proportion of patients in the placebo group, both 'on treatment' (placebo, 8 patients; candesartan, 2 patients) and 'during study' (placebo, 20 patients; candesartan 15 patients). In both treatment groups, the majority of renal events that led to death were reported in association with other causes of death such as worsening heart failure.

The preferred term renal function abnormal used in this descriptive safety analysis correspond to the term increased creatinine used in the exploratory safety analyses. Both terms refer to 'Abnormal renal function (e.g. creatinine increased), pre-specified in the CRF.

In the descriptive safety analysis (Table 219), on investigational product discontinuation in the overall study population, the specified AE term renal function abnormal was the most common reason for permanent discontinuation of the investigational product in both treatment groups (placebo 53, 4.2%; candesartan 105, 8.2%).

In the exploratory analysis the term increased creatinine was reported for 52 (4.1%) placebo patients and 100 (7.8%) candesartan patients (Table 223). The higher rate for discontinuation of the investigational product due to 'abnormal renal function' in the candesartan group could not

be explained by higher use of concomitant medication when the event started. Among the patients who discontinued the investigational product due to 'abnormal renal function events', a higher proportion of patients in the placebo group had a serum creatinine level equal to or greater than 2 mg/dL at baseline (placebo 8, 15.4%); candesartan 9 (9.0%) (North American study population).

In patients aged younger than 75 years, discontinuation because of the AE term renal function abnormal was reported in 40 (3.9%) of patients in the placebo group and 82 (7.7%) of patients on candesartan. For patients aged 75 years or older the discontinuation rates were 13 (5.3%) in the placebo group and 23 (10.8%) in the candesartan group.

In the placebo treatment group 43 (4.3%) males and 10 (3.7%) females discontinued due to renal function abnormal. In the candesartan treatment group 82 (8.2%) males and 23 (8.5%) females reported the renal event.

In the exploratory analysis, patients discontinued study treatment because of the term 'increased creatinine' over the entire study period, and the rate was greater for candesartan-treated patients (Figure 104).

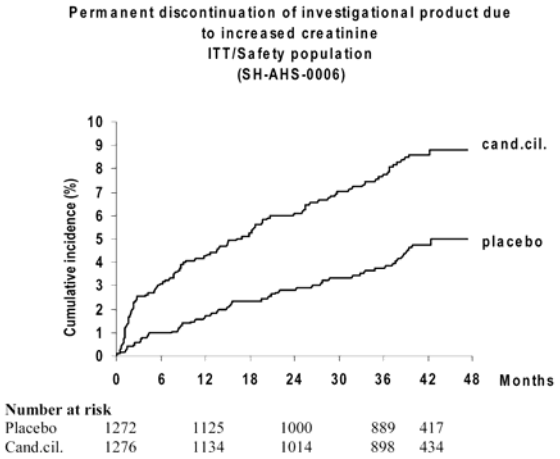


Figure 104 Cumulative incidence (%) of permanent discontinuation of investigational product due to increased creatinine (Ref. - Table 221). ITT/Safety population

Among the 382 (30.0%) placebo patients and 376 (29.5 %) candesartan patients entering the study with a history of diabetes, investigational product discontinuation for the specific term increased creatinine was noted for 25 (6.5%) placebo and 42 (11.2%) candesartan patients. Compared to the overall population (placebo 4.1%, candesartan 7.8%) diabetics were slightly more likely to discontinue the investigational product for increased creatinine levels (Table 223 and Table 224).

Hyperkalemia:

In this section hyperkalemia is discussed 'on treatment' rather than 'during study' as a more clinically meaningful measure of possible relationship to the investigational product.

At baseline, a slightly higher proportion of patients in the candesartan treatment group had a serum potassium ≥ 5 mmol/L (North American study population).

Hyperkalemia was reported for 44 patients (3.5%) in the placebo group and 121 patients (9.5%) in the candesartan group on treatment with the investigational product Table 216).

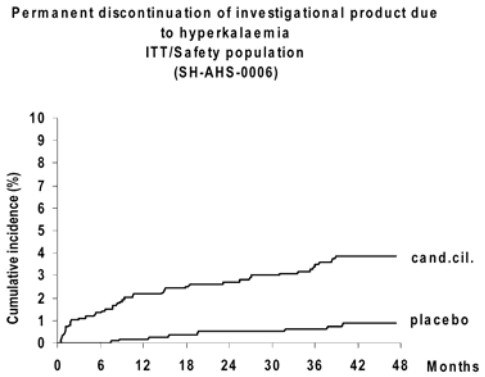
Fatal hyperkalemia was reported during the study for 2 patients in the candesartan group and no patient in the placebo group. Patient 155-10493 died of sudden death and hyperkalemia (potassium concentration, 6.2 mmol/ L) after approximately two years of candesartan treatment. Patient 201-12699 had abnormal renal function 20 days after starting treatment with candesartan, and died of sudden death and hyperkalemia (potassium concentration, 6.1 mmol/ L) after 52 days of treatment. Both patients had a concomitant unspecified increase in serum creatinine. The Investigators assessed the AEs as probably and possibly, respectively, related to the investigational product.

In Table 219, discontinuation of the investigational product because of hyperkalemia was more frequent with candesartan (placebo 11, 0.9%; candesartan 49, 3.8%). In the exploratory analysis the corresponding numbers were 9 (0.7%) for placebo patients and 44 (3.4%) for candesartan patients (Table 223). The higher rate for hyperkalemia causing discontinuation in the candesartan group could not be explained by higher use of concomitant medication when the event started, including potassium-sparing diuretics. There was no between treatment difference regarding baseline serum potassium levels in patients who discontinued investigational product due to hyperkalemia (North American study population).

In patients < 75 years old, discontinuation because of the AE term hyperkalemia was reported in 8 (0.8%) patients in the placebo group and 31 (2.9%) of patients on candesartan. For patients aged 75 years or older the discontinuation rates were 3 (1.2%) in the placebo group and 18 (8.5%) in the candesartan group.

In the placebo group the majority of events were seen in male patients, in the candesartan group the events were equally distributed between.

The discontinuation rate for candesartan-treated patients because of hyperkalemia, presented from exploratory analysis, was greater during the first 6 to 12 months of treatment, but discontinuations still occurred over the entire study period (Figure 105)



Number at risk					
Placebo	1272	1136	1011	904	421
Cand.cil.	1276	1152	1039	923	443

Figure 105 Cumulative incidence (%) of permanent discontinuation of investigational product due to hyperkalemia. ITT/Safety population (Ref. - Table 221).

Among the 382 (30.0%) placebo patients and 376 (29.5 %) candesartan patients entering the study with a history of diabetes, investigational product discontinuation for the specific preferred term hyperkalemia was noted for 10 (2.6%) placebo and 31 (8.2%) candesartan patients.

Abnormal hepatic function:

The most common AE terms suggesting liver dysfunction during treatment were hepatic enzymes increased (placebo 1 patient; candesartan 6 patients) and hepatic function abnormal (placebo 1 patient; candesartan 4 patients). The AE term hepatic failure was reported for 4 patients in the placebo group and 2 patients in the candesartan group.

Neoplasms:

AEs indicative of neoplasms, whether benign or malignant, were pooled from the SOC (System organ class) 'Neoplasms', plus 3 neoplastic AE terms from other SOCs (Melanoma malignant, Myelomatosis multiple and Pleural mesothelioma). Neoplasms were reported for 68 patients (5.3%) in the placebo treatment group compared with 90 (7.1%) in the candesartan group. One patient in the placebo group (Site 1532, Patient number 21520) had both Myeloid dysplasia (included in the SOC Neoplasms) and Myelomatosis multiple. In the total numbers presented above this patient is counted only once. Neoplasms proved fatal for 20 patients (1.6%) in the placebo group and 39 patients (3.0%) in the candesartan group.

In the overall study population, the majority of patients did not have a history of cancer at baseline (placebo 94.1%; candesartan 93.9%).

The majority of reported neoplasms were malignant. The most common neoplasms during study were pulmonary cancer (placebo, 7 patients; candesartan, 12 patients), prostatic cancer (placebo, 9 patients; candesartan, 7 patients) and colon cancer (placebo 5 patients; candesartan 8 patients.

Angioedema:

During study, two cases of angioedema were reported for patients in the candesartan group. Both patients were Caucasian with concomitant medication with an ACE-inhibitor at the start of the event. One of these patients developed angioedema that required discontinuation of candesartan treatment. For the other patient ACE inhibitor medication was stopped but treatment with candesartan continued. In the placebo group three patients reported angioedema, in one case leading to discontinuation of the investigational product.

Discussion of deaths, serious adverse events, discontinuation due to adverse events, and other significant adverse events:

Both CV mortality and overall mortality were lower for patients given candesartan. There were no statistically significant differences between the candesartan group and the placebo group in proportion of patients with non-CV death or non-CV hospitalization.

SAE reports were a common occurrence during the study, an expected finding for a study population with CHF and a long follow-up period. SAEs were reported for more than two thirds of study patients (75.9% in both treatment groups) and most SAEs were CV disorders, reflecting the underlying conditions and risk factors of the study population.

Greater than one fourth of study patients died during the study (placebo 32.5%; candesartan 29.5%), but overall mortality was lower with candesartan treatment (placebo 21.7 %; candesartan, 16.5 %). As expected, most deaths were attributed to CV causes, the most frequent of which were sudden death; cardiac failure/cardiac failure, aggravated; and MI.

Among CV deaths, specific causes such as sudden death and death from heart failure were less common with candesartan treatment. This is an expected finding given that candesartan significantly reduced overall CV death and the most common causes of death in patients with CHF are typically sudden (arrhythmic) death and death from heart failure. Prevention of these causes of CV death is consistent with the survival beneficial effect of candesartan treatment observed in patients with CHF. Death from MI was a less common cause of death in this population (placebo 0.9%; candesartan 1.2%). The overall incidence of MI was 5.7% for placebo and 4.7% for candesartan. The mortality findings in the study population were relatively consistent across subgroups on the basis of age, sex and race. As expected, mortality was higher in older patients.

Also, as expected, some of the most common non-fatal SAEs were cardiovascular (cardiac failure/cardiac failure aggravated; angina pectoris and arrhythmia ventricular), and they generally occurred less frequently in patients in the candesartan group. Pneumonia, also an expected finding in an older population with CHF, was frequently cited with a higher frequency in the placebo treatment group (placebo 7.3%; candesartan 5.7%). 'Renal failure, acute' as a non-fatal SAE was reported for 32 of placebo-treated patients and for 50 of candesartan-treated patients during study.

There was no difference in frequency between treatment groups for AE terms suggesting liver dysfunction.

Of 1,276 candesartan-treated patients in the study, 39 (3.0%) died of cancer; 20 (1.6%) of 1,272 placebo-treated patients also died of cancer. More equal proportions developed a neoplasm during the study (placebo, 5.3%; candesartan, 7.0%). The types of cancer (lung, prostate, colon) were typical for patients in the age group of the study population. In the overall assessment of safety data from the CHARM program (SH-AHS-0003, SH-AHS-0006, SH-AHS-0007), no significant differences in the incidence of malignant neoplasms were identified.

Tolerability of investigational product was not different between patients treated with candesartan and patients treated with placebo. Overall, 71.4% of patients completed participation in the study without discontinuing treatment (74.9% in the placebo and 67.8% in the candesartan groups). Small differences existed between treatment groups for specific causes of investigational product discontinuation.

Discontinuation due to aggravation of cardiac failure was more common in placebo- treated patients (6.4% compared with 5.4% for candesartan-treated patients).

Abnormal renal function, hypotension and hyperkalemia were cited more frequently as reasons for discontinuation with candesartan treatment (8.2% compared with 4.2%, 5.4% compared with 3.5% and 3.8% compared with 0.9%, respectively). Discontinuation of candesartan because of these three reasons was most notable in the first 6 to 12 months of treatment. Hypotension, progressive renal dysfunction and hyperkalemia are well recognized as likely adverse events in patients with CHF, particularly when they are treated with inhibiters of the RAAS.

Safety analyses for subgroups based on sex and race were similar compared to the overall population. As expected, event rates increased with age for both treatment groups. For abnormal renal function and hypotension there were no differences between the treatment groups. In patients aged 75 and younger, discontinuation because of hyperkalemia was reported in 0.8% of patients in the placebo group and 2.9% of patients on candesartan. Corresponding figures for patients aged 75 years or older were 1.2% in the placebo group and 8.5 % in the candesartan group. Generally the frequency of events was higher for males in both treatment groups. The majority of the patients were Caucasians (placebo 92.5%; candesartan 91.7%). Only 4.9% in the placebo group and 5.1% on candesartan treatment were Blacks, among whom a correspondingly smaller number of events was observed. Concomitant medication with ACE-inhibitors, β-blockers and/or spironolactone at the time of the event did not seem to affect the outcome regarding the AEs specifically studied.

For patients with a history of diabetes, the between-treatment difference in frequency of discontinuations caused by increase in creatinine was slightly higher compared to the total population in the study. This is not an unexpected finding in a subpopulation with possible underlying renal dysfunction and autonomic dysregulation.

Study investigators chose to reduce the dose of the investigational product to manage AEs for

17.2% of candesartan-treated patients and 9.7% of placebo-treated patients. In general, AEs cited as prompting investigational product discontinuation were also cited as reasons for dose reductions (hypotension, hyperkalemia and abnormal renal function). However, dose reduction due to aggravated cardiac failure was comparatively rare.

In this study of patients treated with ACE inhibitors, events relatively specific to candesartan (by its being an inhibitor of the RAAS) such as hypotensive events, abnormal renal function and hyperkalemia occurred in the candesartan treatment group.

Clinical laboratory results:

Serial laboratory data were collected from patients participating at investigational sites in North America (placebo 477 patients, candesartan 477 patients).

Changes in mean laboratory values were generally small, of minor clinical significance, and occurred primarily in parameters that previously showed changes in studies with inhibitors of the renin-angiotensin-aldosterone system (RAAS), such as creatinine and potassium.

The mean value for creatinine in the placebo group increased 13.64 µmol/L from the baseline value to the LVCF. In the candesartan group, the value increased 19.63 µmol/L. At baseline, 86 (18.5%) of placebo patients had values above the reference range compared with 83 (17.8%) of patients in the candesartan group. For the last values carried forward that were above the upper level of normal, frequency increased in both treatment groups (placebo 140, 30.4%; candesartan 145, 32.4%). For patients who had serial measurements (placebo 447 patients, candesartan 436 patients) baseline serum creatinine was at least doubled in 27 (6.0%) patients in the placebo group, compared with 32 (7.3%) patients in the candesartan group.

For potassium, the mean value for patients treated with placebo increased 0.02 mmol/L from the baseline value to the LVCF compared with 0.12 mmol/L for patients treated with candesartan. During the study, the proportions of patients with values above the reference range increased in the placebo group (14, 3.0% at baseline, 20, 4.4% LVCF) and increased from 21 (4.5%) to 31 (6.9%) in the candesartan group. Potassium levels increased to ≥ 6 mmol/L at any time after randomization in 1.1% (5) of 459 patients valid for evaluation in the placebo group and 2.7% (12) of 447 patients in the candesartan group.

Mean sodium measurements increased 0.10 mmol/L for patients treated with placebo and decreased 0.28 mmol/L for patients in the candesartan group. The AE term hyponatremia was reported for 5 patients treated with placebo compared with 6 patient treated with candesartan.

Minor decreases were seen for mean hemoglobin values for patients treated with placebo (0.30 mmol/L) and candesartan (0.35 mmol/L). The proportion of patients with anemia reported as an AE during treatment with the investigational product was similar for placebo-treated patients (36, 2.8%) compared with candesartan-treated patients (35, 2.7%). One patient (0.2%) in each treatment group had a hemoglobin value below the defined level of abnormality (male ≤ 80 g/L (4.96 mmol/L), female ≤ 70 g/L (4.34 mmol/L)).

Glycohemoglobin A_{1c} levels decreased slightly and no major difference was seen between the placebo (-0.36%) and candesartan groups (-0.38%).

In summary, both the small differences in mean laboratory values (candesartan compared with placebo) and the frequency of outliers was in keeping with the expected findings for treatment with inhibitors of the renin- angiotensin-aldosterone system, i. e., effects on serum creatinine and potassium levels.

Discussion of vital signs, ECG, physical findings and other observations related to safety:

Vital signs consist of diastolic blood pressure (DBP), systolic blood pressure (SBP), pulse pressure and heart rate. For physical findings, data for body weight are presented.

Blood pressure declined in both treatment groups. Mean DBP decreased 2.6 mmHg from the baseline value to the LVCF in the placebo group and 3.5 mmHg from the baseline value to the LVCF in the candesartan group. Corresponding values for SBP were 2.5 mmHg for patients treated with placebo and 5.0 mmHg for patients treated with candesartan. The effect on blood pressure in the candesartan group was established during the first 6 months while in the placebo group a trend towards lowering could be seen for a longer time period.

A DBP value less than 40 mmHg at any time during the study was reported for 32 (2.5%) patient in the placebo group and 42 (3.3%) patients in the candesartan group. 67 (5.3%) patients treated with placebo and 104 (8.2%) patients treated with candesartan had a recorded SBP value less than 80 mmHg at any time after randomization.

At LVCF mean heart rate was unchanged in patients in the placebo group and 0.3 bpm lower in patients in the candesartan group compared to baseline

In the placebo group, mean body weight decreased by 0.2 kg from baseline to LVCF. In the candesartan population an increase of 0.3 kg was seen.

Is there is relationship between the dose of candesartan and the important adverse events?

Following a Telecon with the sponsor on Nov 2, 2004, I requested the sponsor to provide information on the CHARM-Added (SH-AHS-0006) Study regarding the proportion of patients receiving low dose (4 or 8 mg) or high dose (16 or 32 mg) candesartan *at the time of the event* or *at the last visit (if no event occurred)* in the each of the sub-populations of patients receiving high dose ACE inhibitors and those receiving low dose ACE inhibitors in relation to the adverse events of: (a) aggravated heart failure, (b) hypotension, (c) hyperkalemia, (d) deterioration of renal function, (e) study drug discontinuation, and (f) reduction in dose of study drug

On Nov 12, 2004, I received the sponsor's response containing the information related to the adverse event endpoints according to dose level of candesartan. These analyses consider dose level of candesartan consistent with the sub-group analyses presented in the submission. For the

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

Relationship of dose of candesartan to permanent study drug discontinuation due to an adverse event or an abnormal laboratory value

In Table 227, no relationship is apparent between the dose of candesartan and the numbers and frequencies of permanent study drug discontinuation due to an adverse event or an abnormal laboratory value.

Table 227 The numbers and frequencies of permanent study drug discontinuation due to an adverse event or an abnormal laboratory value[a] in patients who received high or low dose candesartan plus ACE inhibitors at heart failure dose or low dose– CHARM-Added (SH-AHS-0006) Study

	$ACEi_{HFD}$ (N=643)			**$ACEi_{LD}$ (N=633)**		
Candesartan cilexetil[b]	**CC_{HD} + $ACEi_{HFD}$** N = 426 n = 86 (20.2%)	**CC_{LD} + $ACEi_{HFD}$** N = 138 n = 58 (42.0%)	**CC_{00} + $ACEi_{HFD}$** N = 79 n = 7 (8.9%)	**CC_{HD} + $ACEi_{LD}$** N = 393 n = 75 (19.1%)	**CC_{LD} + $ACEi_{LD}$** N = 162 n = 64 (39.5%)	CC_{00} + $ACEi_{LD}$ N = 78 n = 20 (25.6%)

$ACEi_{HFD}$ = ACE inhibitor at heart failure dose; $ACEi_{LD}$ = ACE inhibitor at lower than heart failure dose;
CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC_{00} =Not on candesartan at event or last visit
[a] Definition used in exploratory safety analyses; [b]Dose of candesartan preceding the event (or at last visit if no event occurred)
n = number of patients with one or more events (proportion (%) of patients at the dose)

Relationship of dose of candesartan to permanent study drug discontinuation due to hypotension

In Table 228, no relationship is apparent between the dose of candesartan and the numbers and frequencies of permanent study drug discontinuation due to hypotension.

Table 228 The numbers and frequencies of permanent study drug discontinuation due to hypotension[a] in patients who received high or low dose candesartan plus ACE inhibitors at heart failure dose or low dose– CHARM-Added (SH-AHS-0006) Study

	$ACEi_{HFD}$ (N=643)			**$ACEi_{LD}$ (N=633)**		
Candesartan cilexetil[b]	**CC_{HD} + $ACEi_{HFD}$** N = 364 n = 8 (2.2%)	**CC_{LD} + $ACEi_{HFD}$** N = 98 n = 13 (13.3%)	**CC_{00} + $ACEi_{HFD}$** N = 181 n = 1 (0.6%)	**CC_{HD} + $ACEi_{LD}$** N = 342 n = 12 (3.5%)	**CC_{LD} + $ACEi_{LD}$** N = 131 n = 22 (16.8%)	CC_{00} + $ACEi_{LD}$ N = 160 n = 2 (1.3%)

$ACEi_{HFD}$ = ACE inhibitor at heart failure dose; $ACEi_{LD}$ = ACE inhibitor at lower than heart failure dose;
CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC_{00} =Not on candesartan at event or last visit
[a] Definition used in exploratory safety analyses; [b]Dose of candesartan preceding the event (or at last visit if no event occurred)
n = number of patients with one or more events (proportion (%) of patients at the dose)

Relationship of dose of candesartan to permanent study drug discontinuation due to hyperkalemia

In Table 229, no relationship is apparent between the dose of candesartan and the numbers and frequencies of permanent study drug discontinuation due to hyperkalemia.

Table 229 The numbers and frequencies of permanent study drug discontinuation due to hyperkalemia[a] in patients who received high or low dose candesartan plus ACE inhibitors at heart failure dose or low dose– CHARM-Added (SH-AHS-0006) Study

	$ACEi_{HFD}$ (N=643)			$ACEi_{LD}$ (N=633)		
Candesartan cilexetil[b]	CC_{HD} + $ACEi_{HFD}$ N = 372 n = 16 (4.3%)	CC_{LD} + $ACEi_{HFD}$ N = 94 n = 7 (7.5%)	CC_{00} + $ACEi_{HFD}$ N = 177 n = 1 (0.6%)	CC_{HD} + $ACEi_{LD}$ N = 342 n = 12 (3.5%)	CC_{LD} + $ACEi_{LD}$ N = 117 n = 8 (6.8%)	CC_{00} + $ACEi_{LD}$ N = 174 n = 0 (0.0%)

$ACEi_{HFD}$ = ACE inhibitor at heart failure dose; $ACEi_{LD}$ = ACE inhibitor at lower than heart failure dose;
CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC_{00} =Not on candesartan at event or last visit
[a] Definition used in exploratory safety analyses; [b] Dose of candesartan preceding the event (or at last visit if no event occurred)
n = number of patients with one or more events (proportion (%) of patients at the dose)

Relationship of dose of candesartan to permanent study drug discontinuation due to increased serum creatinine

In Table 230, no relationship is apparent between the dose of candesartan and the numbers and frequencies of permanent study drug discontinuation due to increased serum creatinine.

Table 230 The numbers and frequencies of permanent study drug discontinuation due to increased serum creatinine[a] in patients who received high or low dose candesartan plus ACE inhibitors at heart failure dose or low dose– CHARM-Added (SH-AHS-0006) Study

	$ACEi_{HFD}$ (N=643)			$ACEi_{LD}$ (N=633)		
Candesartan cilexetil[b]	CC_{HD} + $ACEi_{HFD}$ N = 385 n = 32 (8.3%)	CC_{LD} + $ACEi_{HFD}$ N = 105 n = 20 (19.1%)	CC_{00} + $ACEi_{HFD}$ N = 153 n = 2 (1.3%)	CC_{HD} + $ACEi_{LD}$ N = 351 n = 25 (7.1%)	CC_{LD} + $ACEi_{LD}$ N = 127 n = 20 (15.8%)	CC_{00} + $ACEi_{LD}$ N = 155 n = 1 (0.7%)

$ACEi_{HFD}$ = ACE inhibitor at heart failure dose; $ACEi_{LD}$ = ACE inhibitor at lower than heart failure dose;
CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC_{00} =Not on candesartan at event or last visit
[a] Definition used in exploratory safety analyses; [b] Dose of candesartan preceding the event (or at last visit if no event occurred)
n = number of patients with one or more events (proportion (%) of patients at the dose)

Relationship of dose of candesartan to dose reductions of study drug due to an adverse event or an abnormal laboratory value

In Table 231, no relationship is apparent between the dose of candesartan and the numbers and frequencies of dose reductions of study drug due to an adverse event or an abnormal laboratory value.

Table 231 The numbers and frequencies of dose reductions[a] of study drug due to an adverse event or an abnormal laboratory value[a] in patients who received high or low dose candesartan plus ACE inhibitors at heart failure dose or low dose– CHARM-Added (SH-AHS-0006) Study

	$ACEi_{HFD}$ (N=643)			$ACEi_{LD}$ (N=633)		
Candesartan cilexetil[b]	CC_{HD} + $ACEi_{HFD}$ N = 403 n = 88 (21.8%)	CC_{LD} + $ACEi_{HFD}$ N = 83 n = 35 (42.2%)	CC_{00} + $ACEi_{HFD}$ N = 157 n = 1 (0.6%)	CC_{HD} + $ACEi_{LD}$ N = 380 n = 95 (25.0%)	CC_{LD} + $ACEi_{LD}$ N = 101 n = 43 (42.6%)	CC_{00} + $ACEi_{LD}$ N = 152 n = 3 (2.0%)

$ACEi_{HFD}$ = ACE inhibitor at heart failure dose; $ACEi_{LD}$ = ACE inhibitor at lower than heart failure dose;
CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC_{00} =Not on candesartan at event or last visit
[a] Definition used in exploratory safety analyses; [b] Dose of candesartan preceding the event (or at last visit if no event occurred)
n = number of patients with one or more events (proportion (%) of patients at the dose)

Conclusions on safety results:

Candesartan appears to be safe and well tolerated. **Discontinuations and dose reductions attributed to a decline in renal function, hypotension and hyperkalemia occur more frequently with candesartan than placebo.** The AE profile of candesartan in heart failure patients is consistent with the pharmacology of the drug and the health status of the patients.

Standard safety assessments included serious adverse events, serious and non-serious adverse events causing discontinuation of investigational product or dose reduction, clinical laboratory data (North America), vital signs and physical examination. The following were found:

- Serious adverse events occurred in equal frequency in both treatment groups during study (placebo 75.9%, candesartan 75.9%).
- 24.3% of the patients in the candesartan group and 17.6% of the placebo group permanently discontinued treatment with the investigational product due to an AE or an abnormal laboratory finding.
- 17.2% of the patients receiving candesartan and 9.7% receiving placebo required a reduction in the investigational product dose.
- Discontinuations and dose reductions attributed to decline in renal function, hypotension and hyperkalemia were more frequent in the candesartan group.
- Differences in mean laboratory values across the treatment groups were small and in keeping with expectations for inhibitors of the renin-angiotensin-aldosterone system, i.e. increase in creatinine and potassium.
- Mean blood pressure from baseline to LVCF (SBP and DBP) was lowered in both treatment groups. Mean body weight was slightly decreased in the placebo group and increased in the candesartan group.
- Candesartan reduced time to permanent investigational product discontinuation due to any cause (P=< 0.001).
- Candesartan increased the number of investigational product discontinuations due to any cause (P=< 0.001).
- Candesartan reduced time to permanent investigational product discontinuation due to an AE or an abnormal laboratory value (P=< 0.001).
- Candesartan increased the number of permanent investigational product discontinuations due to an AE or an abnormal laboratory value (P=< 0.001).
- Candesartan increased the number of dose reductions due to an AE or an abnormal laboratory value at least once (P=< 0.001).
- Candesartan did not influence time to non-CV death (P= 0.529).
- Candesartan did not increase the number of non-CV deaths (P= 0.395).
- Candesartan did not increase the number of non-CV hospitalizations (P= 0.895).

8.1 Summary of safety

Adverse events (AEs) were reported for approximately equal proportions of patients in the two treatment groups, both as analyzed during treatment with the investigational product (placebo 979, 77.0%; candesartan 1007, 78.9%) and over the entire study period (placebo 992, 78.0%; candesartan 1026, 80.4%).

Serious adverse events (SAEs), fatal and non-fatal, occurred less frequently on treatment with candesartan (placebo 930, 73.1%; candesartan 883, 69.2%) and at equal frequency during the study, whether on or off treatment (placebo 966, 75.9%; candesartan 969, 75.9%).

Fatal SAEs were also less common with candesartan, on treatment with the investigational product (placebo 276, 21.7%; candesartan 210, 16.5%) as well as during the study (placebo 413, 32.5%; candesartan 377, 29.5%). The most common fatal SAEs were CV events and these occurred less frequently in the candesartan treatment group during study (placebo 347, 27.3%; candesartan 302, 23.7%).

A total of 534 (21.0%) of the patients permanently discontinued taking the investigational product because of an AE or abnormal laboratory value (placebo 224, 17.6%; candesartan 310, 24.3%).

Study investigators chose to reduce the investigational product dose because of an AE for 123 (9.7%) of patients taking placebo and 220 (17.2)% taking candesartan.

Abnormal renal function (placebo 53, 4.2%; candesartan 105, 8.2%), cardiac failure aggravated (placebo 81, 6.4%; candesartan 69, 5.4%), hypotension (placebo 44, 3.5%; candesartan 69, 5.4%) and hyperkalemia (placebo 11, 0.9%; candesartan 49, 3.8%) were the most commonly reported AE, given as reasons for discontinuing the investigational product.

Differences in mean laboratory values (candesartan compared with placebo) were small and in keeping with expected values for treatment with inhibitors of the renin-angiotensin-aldosterone system, i.e., slightly higher serum potassium and creatinine levels.

DISCUSSION AND OVERALL CONCLUSIONS

Discussion

In patients with CHF using an ACE inhibitor, the addition of candesartan significantly reduced cardiovascular mortality or hospitalization due to heart failure. The effect appeared early and was sustained throughout the duration of the study. Also the other outcomes included in the confirmatory analysis; all cause mortality or hospitalization due to heart failure as well as cardiovascular mortality or hospitalization due to heart failure or non- fatal myocardial infarction were significantly reduced by candesartan treatment. There were substantial reductions in the individual components of the composite outcomes. Moreover, symptoms of heart failure as

evaluated by the NYHA-classification were reduced by candesartan as compared to placebo.

The reduction in cardiovascular mortality and hospitalization due to heart failure with candesartan treatment was also evident in those patients being treated with recommended doses of ACE-inhibitors as well as in those treated with β-blockers. The finding that treatment with candesartan in combination with β-blockers provided these patients with additional beneficial efficacy is particularly noteworthy, since a large proportion (55% at baseline) of the patients were receiving this lifesaving therapy. A prior subgroup analysis from the Val-HeFT[16] study suggested lack of benefit of an ARB (valsartan) in patients already receiving ACE-inhibitors and β-blockers, but the results of study SH-AHS-0006 suggest that this finding may be specific to the treatments studied in Val-HeFT.

The candesartan treatment benefit observed in the current study is consistent with observations suggesting that blockade of angiotensin II generation is incomplete with chronic ACE inhibitor therapy[1,2,3]. Mechanistic studies show favorable neurohumoral, hemodynamic and left ventricular remodeling effects when an ARB is administered to patients already treated with an ACE inhibitor[6,75]. These potentially beneficial effects are also seen in patients treated with both a β-blocker and an ACE inhibitor. For example, in the RESOLVD pilot study, the greatest left ventricular "reverse-remodeling" was seen with the combination of enalapril, metoprolol and candesartan[5].

When comparing the overall Val-HeFT[16] population (where 93% of the patients were treated with an ACE inhibitor) to the present study, the findings of the two studies can to some extent be considered consistent in that both demonstrated that adding an ARB to conventional therapy reduces hospitalization due to heart failure. However, in Val-HeFT there was no effect on cardiovascular mortality in contrast to the present study with candesartan[16]. Further, in the present study there were statistically significant reductions in cardiovascular mortality as well as in CHF hospitalizations in patients receiving candesartan in addition to ACE-inhibitor and β-blocker suggesting that there is no negative interaction between the ARB (candesartan), ACE-inhibitors and β-blocker therapy as was seen with valsartan in Val-HeFT[16].

The benefit of candesartan in this study was evident even with substantial background treatment with ACE inhibitors at recommended doses. For example, the mean daily dose of enalapril at baseline was 17 mg, which compares to 16.6 mg (in those taking drug) in the treatment arm of the Studies Of Left Ventricular Dysfunction (SOLVD)[32] and 17 mg in Val-HeFT[16]. The present study also shows that this benefit is clinically important. There were consistent and clinically important reductions in both cardiovascular mortality and CHF hospitalizations when patients received candesartan. In addition to prolongation of time to first CHF hospitalization, the number of patients admitted to hospital for CHF and the total numbers of hospital admissions that were primarily for CHF were lower in the candesartan group. Furthermore, the magnitude of the benefit in reducing cardiovascular death or CHF hospitalization translates into an absolute reduction of 4.4 major events per 100 patients treated, which means that one needs to treat 23 patients with candesartan to prevent one patient from suffering this outcome.

There was a statistically significant reduction in cardiovascular mortality attributed primarily to a reduction in sudden deaths and deaths due to heart failure, which are the most common modes of death in patients with CHF. The study was not powered to assess the effect on all cause mortality but since there was no difference in non-cardiovascular deaths, all cause death clearly trended in the direction favoring treatment with candesartan. Although more cancer deaths occurred in the candesartan group, the investigator-reported rate of non-fatal neoplasms was more equal between treatment groups. In the total CHARM population (SH-AHS-003, SH-AHS-0006, SH-AHS-0007) no significant differences in the incidence of neoplasms were identified.

Candesartan in addition to treatment with an ACE-inhibitor, was well tolerated in this study, although dose reduction and discontinuation of investigational product were more common with candesartan than placebo which was primarily attributable to renal function impairment, hyperkalemia, or hypotension. This distribution of events could be expected from the pharmacodynamic profile of inhibitors of the RAAS and the underlying conditions in the CHF population. Monitoring patients for these expected events is already well-established practice for care of the CHF patient.

Overall conclusions

Candesartan reduces mortality and hospitalization due to heart failure and improves symptoms in CHF patients who are receiving an ACE inhibitor. The reduced mortality is attributable to a reduction in cardiovascular deaths. Patients receiving other treatments, including a beta-blocker, also benefit. Candesartan is safe and well tolerated. Discontinuations and dose reductions attributed to a decline in renal function, hypotension and hyperkalemia occur more frequently with candesartan than placebo. The AE profile of candesartan in heart failure patients is consistent with the pharmacology of the drug and the health status of the patients.

10.1.20 Appendix 16 CHARM-Pooled studies

Candesartan cilexetil (candesartan) in heart failure. Assessment of reduction in mortality and morbidity (CHARM) Analysis of two pooled populations of clinical studies SH-AHS-0003, SH-AHS-0006 and SH-AHS–0007

Study program sites: The CHARM program was conducted in 26 countries at a total of 618 sites (Australia 18, Belgium/Luxembourg 18, Canada 72, Czech Republic 12, Denmark 20, Finland 10, France 27, Germany 53, Hungary 10, Iceland 2, Italy 20, Malaysia 3, Netherlands 22, Norway 19, Poland 14, Portugal 17, Russia 10, Singapore 3, South Africa 12, Spain 16, Sweden 18, Switzerland 13, United Kingdom/Ireland 38, and USA 171 sites)

Objectives

Primary objective

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

Secondary objective

To determine whether candesartan, compared to placebo, reduced all- cause mortality in the pooled population of patients with depressed left ventricular (LV) systolic dysfunction (studies SH-AHS-0003 and SH-AHS-0006).

Other objectives

To determine whether candesartan, compared to placebo,

- reduced the combined endpoint of all-cause mortality or all-cause hospitalization in the pooled population of patients with symptomatic chronic heart failure (studies SH-AHS-0003, SH-AHS-0006 and SH-AHS-0007).
- reduced the combined endpoint of all- cause mortality or all-cause hospitalization in the pooled population of patients with depressed LV systolic dysfunction (studies SH-AHS-0003 and SH-AHS-0006).

Component study design

The component studies were randomized, double-blind placebo controlled parallel group multicenter studies. The program was designed to evaluate the influence on mortality and morbidity of candesartan cilexetil (hereafter referred to as candesartan) with a target dose of 32 mg once daily, in three target populations of patients with symptomatic chronic heart failure.

The figure illustrating the component studies is the same as Figure 94 (Appendix 10.1.19 of this review).

Target patient population

Male and female patients, over or equal to 18 years of age, with symptomatic CHF corresponding to New York Heart Association (NYHA) class II-IV and:

- depressed LV systolic function and ejection fraction (EF) < 40% and an intolerance to angiotensin converting enzyme (ACE) inhibitors (study SH-AHS-0003)
- depressed LV systolic function EF< 40% treated with an ACE inhibitor (study SH-AHS-0006)
- preserved LV systolic function EF> 40% (study SH-AHS-0007)

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for enrollment into the CHARM Program studies are similar for all component CHARM-studies except that for enrollment into study SH-AHS-0007, the LVEF must be >40%. The detailed inclusion and exclusion criteria are similar to that described for study SH-AHS-0006 in Appendix 10.1.19

Investigational product

The active treatment group received candesartan (Atacand®) tablets 4 mg (white) and 16 mg (pink) once daily. A starting dose of 4 mg or 8 mg once daily was up-titrated by doubling the dose at 2-week intervals to a maximum of 32 mg once daily or the highest tolerated level. Tablets were swallowed with water in the morning. The batch numbers for candesartan 4 mg used in the study program were: H 1155-02-01-07, -09, -10, -11, -12, -13, -14 and -16. The batch numbers for candesartan 16 mg were: H 1191-01-01-06, -12, -13, -14, -15, -16, -17, -18, -19, -20, -21, -22, -24, -25 and -28.

The comparator group received placebo tablets identical to the active tablets, with the exception of the active ingredient. The batch numbers for placebo candesartan 4 mg were: H 1242-01-01-02, -03, -04, -05, -06, -07, -08 and 09. The batch numbers for placebo candesartan 16 mg were: H 1203-03-01-05, -07, -08, -09, -10, -11, -12, -13, -14, -15, -16, -17, -21, -22 and 23.

Duration of CHARM program

The patient recruitment period was 23 months. All patients remained in their respective studies until the last randomized patient had been in the study for two years. Individual time in the study for surviving patients not lost to follow-up could last from 25 to 48 months depending on when the patient was randomized. The median follow-up time for the total population was 37.9 months in the candesartan group and 37.6 months in the placebo group. The median exposure to the investigational product in the total population was 35.0 months in the placebo group and 34.5 months in the candesartan group.

Criteria for evaluation (main variables)

Efficacy

- Primary efficacy endpoint: Time from randomization to all-cause death in patients with symptomatic chronic heart failure.
- Secondary efficacy endpoint: Time from randomization to all-cause death in patients with depressed LV systolic function.

Safety

- Investigational product discontinuation.
- Reduction in dose of investigational product.
- Occurrence of non- cardiovascular death and hospitalization.

- Standard safety assessments including adverse event reports, clinical laboratory data (North America), vital signs and physical examination.

Patient-reported outcomes

- The patients' global evaluation of change from baseline to the patient's last visit or closing visit using OTE (overall treatment evaluation) in the US and Canadian sites.
- The change in the physical functioning dimension of the disease-specific patient-reported outcomes questionnaire, the Minnesota Living with Heart Failure (LIhFE), from baseline to last/closing visit evaluated in the US and Canadian sites.

Study sample size

With a total of 7200 patients randomized in the pooled population a 16- 20% decrease in the annual placebo incidence rate of all-cause death, assuming an annual placebo rate of 9 to 11%, could be detected with a statistical power of at least 94%. The patients were to be equally distributed between the two treatment groups. The number of randomized patients was 7601; two of the patients were randomized in error (study SH-AHS-0007). These patients received no investigational product and no data were collected; so the actual number of patients was 7599.

Statistical methods

All analyses were made on an intention-to-treat basis.

The time from randomization to an event variable was analyzed with a two-sided Logrank test and for estimation in a Cox proportional hazards model. Kaplan-Meier plots were used to graphically display the time-to-event distributions by treatments.

Secondary analysis was made using a Cox-regression model with pre-specified prognostic factors (baseline covariates).

A Chi-square test was used to test the difference between the proportions of patients with a specific characteristic/outcome.

Changes in the NYHA classification were tested using a Wilcoxon rank-sum test.

For continuous variables, the mean change from baseline to last observed value was tested in an analysis of covariance (ANCOVA) model.

Estimates with 95% confidence intervals (CIs) for each treatment and the difference between the treatments were calculated, as appropriate.

All tests were two-sided. The multiple significance levels were controlled for the primary and secondary objectives using a closed test procedure.

Method of statistical analysis

The primary objective was to determine whether candesartan compared to placebo, reduced all-cause death in the total patient population (SH-AHS-0003, -0006, and -0007), as translated into a

hypothesis problem: time from randomization to the death of any cause. The null hypothesis (H0) was:

H0: The distribution function for the time from randomization to the endpoint when treated with candesartan equals the distribution function for the time from randomization to the endpoint when treated with placebo.

The alternative hypothesis (H1) was:

H1: The distribution functions differ.

The H0 was tested using the two-sided stratified Logrank test for comparing the time from randomization to event distributions. If the P-value was less than 0.0492 (corresponding to a significance level of 0.05 adjusted for six interim analyses performed by the SC) it was considered as a confirmation that there was a true difference between the two distributions.

In addition, estimates of the treatment hazards were calculated as the number of events per 1,000 patient years. The size of the treatment effect was estimated by means of a Cox proportional hazards model with treatment as the only factor. The hazard ratio, with a 95% CI based on the Wald estimate of the standard error, and corresponding relative risk reduction estimate are reported.

The secondary objective was translated into the null hypothesis:

Time from randomization to the endpoint all-cause death in patients with low LVEF (SH-AHS-0003 and -0006).

The H0 was equality of the distribution functions for the time from randomization to event for candesartan and placebo versus the H1 that they were different.

The null-hypothesis was tested with a stratified Logrank test in exactly the same way as described above for the primary variable. Similarly, the treatment hazards were estimated and the hazard ratios were calculated in a Cox regression model.

If the P-value was less than 0.0492 and if the test for the primary variable was significant at the 0.0492 level, then this test was also considered as a confirmation of a true treatment effect.

This follows from the theory of closed test procedures and will guarantee a multiple α level of 0.05 (Bauer 1991).

The Kaplan-Meier estimated time from randomization to event distribution was plotted for each treatment. This graph was used to interpret the likely difference in the true distributions.

<u>Protocol amendments</u>

These are similar to that already presented in Appendix 10.1.19 of this review.

Changes to planned analyses

These are similar to that already described in Appendix 10.1.19 of this review.

Re-opening of CHARM program database

The issues are similar to that already described in Appendix 10.1.19 of this review.

CHARM-POOLED STUDY POPULATIONS

In total 7,601 patients were recruited from 618 sites. The first patient was randomized in the CHARM program on 22 March 1999, and the last patient completed on 31 March 2003. All patients, except two who had no investigational product administered and no data available after randomization (study SH-AHS-0007), were analyzed for safety and efficacy. Of the 7,599 patients in the ITT/safety population, 3,803 were randomized to candesartan and 3,796 to placebo (Table 232). Overall, the treatment groups were comparable for demographic characteristics and baseline data.

Baseline characteristics of patients in studies SH-AHS-0003 and SH-AHS-0006 were similar to those in other studies on patients with CHF and reduced left ventricular systolic function, and were considered to be representative of a general population of patients with CHF. Almost a quarter of the patients were older than 75 years and almost a third were females. A large proportion had accompanying atherosclerotic CV disease.

Patients in study SH-AHS-0007 constituted a group that has not been studied in large intervention trials previously, but the characteristics of patients were consistent with the epidemiological studies in patients with CHF and an ejection fraction of more than 40%.

The treatment groups were in general well balanced. However, in the total population there were more patients that had a previous diagnosis of cancer in the candesartan group compared to the placebo group (270; 7.1% vs. 243; 6.4%).

Table 232 Total-pooled patient population and disposition

		Placebo		Cand. cil.		Total	
Population							
N randomised (N planned)		3796	(3600)	3803	(3600)	7599	(7200)
Demographic characteristics							
Sex, N (%)	Male	2582	(68.0)	2617	(68.8)	5199	(68.4)
	Female	1214	(32.0)	1186	(31.2)	2400	(31.6)
Age, mean (SD)	Years	66.0	(11.1)	65.9	(11.0)	66.0	(11.0)
Ethnicity, N (%)	European origin	3458	(91.1)	3412	(89.7)	6870	(90.4)
	Black	164	(4.3)	162	(4.3)	326	(4.3)
	South Asian	34	(0.9)	59	(1.6)	93	(1.2)
	Arab/Middle East	15	(0.4)	22	(0.6)	37	(0.5)
	Oriental	62	(1.6)	71	(1.9)	133	(1.8)
	Malay	25	(0.7)	39	(1.0)	64	(0.8)
	Other	38	(1.0)	38	(1.0)	76	(1.0)
Baseline characteristics							
Ejection fraction, mean (SD)		0.39	(0.15)	0.39	(0.15)	0.39	(0.15)
Diabetes mellitus, N (%)		1075	(28.3)	1088	(28.6	2163	(28.5)
Hypertension, N (%)		2093	(55.1)	2093	(55.0)	4186	(55.1)
Atrial fibrillation, N (%)		1044	(27.5)	1039	(27.3)	2083	(27.4)
Previous myocardial infarction, N (%)		1980	(52.2)	2024	(53.2)	4004	(52.7)
Angina pectoris, N (%)		2178	(57.4)	2174	(57.2)	4352	(57.3)
Stroke, N (%)		330	(8.7)	333	(8.8)	663	(8.7)
NYHA II, N (%)		1686	(44.4)	1730	(45.5)	3416	(45.0)
NYHA III, N (%)		2008	(52.9)	1977	(52.0)	3985	(52.4)
NYHA IV, N (%)		102	(2.7)	96	(2.5)	198	(2.6)
Current smoker, N (%)		549	(14.5)	565	(14.9)	1114	(14.7)
Disposition							
N (%) of patients	Completing the programme	3793	(99.9)	3796	(99.8)	7589	(99.8)
	Lost to follow-up	3	(0.01)	7	(0.02)	10	(0.02)
N analysed for safety (ITT/Safety population[a])		3796		3803		7599	
N analysed for efficacy (ITT/Safety population[a])		3796		3803		7599	

[a] Safety and ITT population was defined as all randomised patients. ITT Intention to treat; N number

In the total population, 3,052 (80.3%) patients in the candesartan group started treatment on 4 mg once daily and 751 (19.7%) patients started on 8 mg once daily. In a total of 5,360 (70.5%) patients, 2,659 (69.9%) who were on candesartan treatment received the investigational product for 24 months or more. Of those patients still on the investigational product at 6 months, (3,233, 88.9% in the candesartan group), 62.6% of the candesartan patients were treated with the target dose 32 mg once daily. The mean dose in the candesartan group was 24.0 mg at 6 months and 23.9 at LVEF.

The countries participating in the program, number of sites and number of patients with symptomatic CHF are shown in Table 233 (studies SH-AHS-0003, -0006 and -0007).

Table 233 Number of sites and randomized patients by country for patients with symptomatic CHF. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Country	No. of sites	No. of patients randomised to placebo	No. of patients randomised to cand. cil.	Total
All	618	3796	3803	7599
Sweden	18	103	89	192
Norway	19	105	112	217
Denmark	20	253	234	487
Finland	10	55	47	102
Iceland	2	38	44	82
Italy	20	78	73	151
Spain	16	64	61	125
Portugal	17	43	50	93
The Netherlands	22	212	207	419
France	27	108	117	225
Czech Republic	12	90	104	194
Poland	14	113	102	215
Hungary	10	101	103	204
Switzerland	13	32	36	68
Belgium/Luxembourg	18	113	136	249
Malaysia	3	54	86	140
Singapore	3	25	37	62
United Kingdom/Ireland	38	138	143	281
Germany	53	425	378	803
Canada	72	475	467	942
USA	171	901	900	1801
Australia	18	108	120	228
South Africa	12	61	58	119
Russia	10	101	99	200

Disposition of patients

The disposition of patients with symptomatic CHF is summarized in Figure 2.

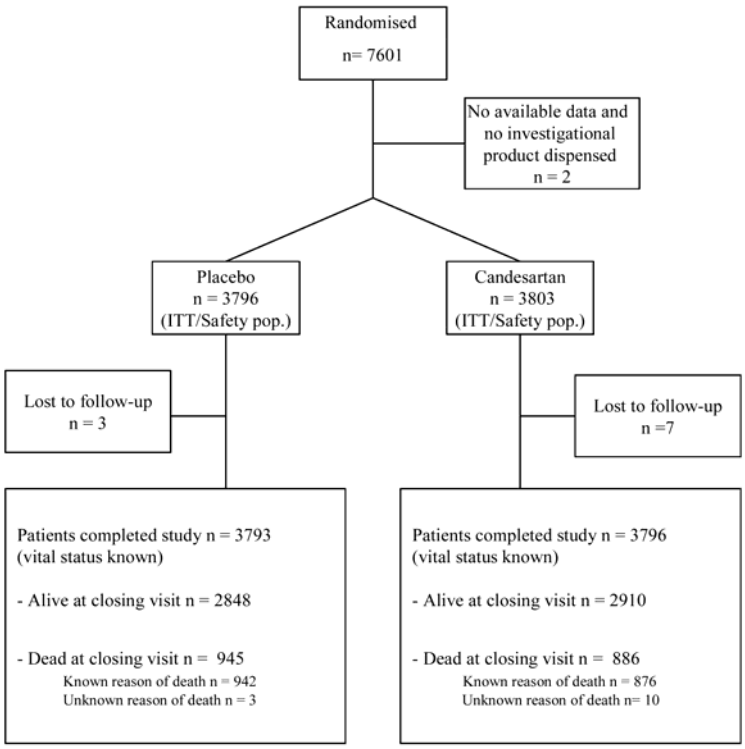


Figure 106 Disposition of patients with symptomatic CHF (completion or discontinuation) (SH-AHS-0003, -0006 and -0007)

Protocol deviations

The numbers of patients with protocol deviations in each treatment group are summarized in Table 234. (N.B. One patient could have more than one protocol deviation throughout the study.)

Table 234 Number of patients with protocol deviations in CHARM-Pooled patient population

	Placebo (N=361)	Cand. cil. (N=341)
Inclusion criteria deviation	103	100
Exclusion criteria deviation	151	120
Patient's consent withdrawn (continued in study or with the investigational product)	0	1
Pregnancy	1	0
Investigational product given without randomisation	0	0
Investigational product never given	0	0
Wrong investigational product given, wrong bottle and wrong investigational product	7	15
Wrong investigational product given, wrong bottle and correct investigational product	40	44
Wrong dose of investigational product given (dose<4 or >32mg)	3	9
Incorrect dose of the investigational product given (dose ≠4, 8, 16, 32 mg)	3	1
Pre-randomisation (randomisation date before visit 1)	38	32
Treatment code prematurely broken	14	14
Less than two years in the study (patients lost to follow-up)	1	5

Patient populations analyzed

Two pooled patient populations were analyzed:

- Total population: Patients with symptomatic CHF (ITT/Safety population in studies SH-AHS-0003, -0006 and -0007).
- Subpopulation: Patients with depressed LV systolic dysfunction (ITT/Safety population in studies SH-AHS-0003 and -0006).

Treatment compliance

Compliance was assessed (> 80%, 20- 80% or < 20%) by the treating investigator by estimation of returned tablets and after discussion with the patient. Pill- counts were not done unless required by local regulatory authorities. A listing of estimated individual compliance data is shown in Appendix 12.2.5 for the individual study reports. The vast majority of patients had a compliance of > 80% at all visits.

Concomitant medications

The patients in the total pooled population were receiving conventional heart failure treatments at baseline including diuretics (6,286, 83%), β-blockers (4,203, 55%), digoxin (3,254, 43%), ACE-inhibitor (3,125, 41%) and spironolactone (1,272, 17%). The most frequently used β-blockers were metoprolol and carvedilol that were taken, respectively, by 26% (1,945 patients) and 13% (980 patients) of the patient population. These two β-blockers accounted for about 70% of the β-blocker use within this patient population.

At the closing visit, there were more patients in the placebo group receiving diuretics (2,195, 77% vs. 2,171, 75%), β-blockers (1,812, 64% vs. 1,765, 61%), digoxin (1,018, 36% vs. 978, 34%), ACE-inhibitors (1,110, 39% vs. 1,051, 36%) and spironolactone (625, 22% vs. 501, 17%).

EFFICACY RESULTS

Primary endpoint: Time from randomization to all-cause death in patients with symptomatic CHF

Of the 7,599 patients in the population pooled across the three CHARM component studies a total of 1831 patients died: 886 (23.3%) in the candesartan group and 945 (24.9%) in the placebo group. The HR for the time to death was 0.91 (95% CI 0.83 to 1.00, P= 0.055 unadjusted for interim analyses), which equates to a relative risk reduction of 8.6%. The average annualized death rates were 8.1% and 8.8% respectively (Table 235 and Table 236).

Table 235 Confirmed adjudicated all-cause death in patients with symptomatic CHF. Number of patients with an event by treatment group and events per 1000 years of follow-up. Follow-up time is calculated to event. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Variable	Treatment	N	Events (no of patients)	Total follow-up time (years)	Events / 1000 follow-up years	Mean follow-up time (years)
All-cause death (confirmed adjudicated)	Placebo	3796	945	10690.3	88.4	2.8
	Cand. cil.	3803	886	10938.2	81.0	2.9

Table 236 Confirmed adjudicated all-cause death in patients with symptomatic CHF. Comparison of candesartan versus placebo with Cox regression. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Variable	N	Events cand. cil.	Events placebo	Hazard Ratio	95% CI		p-value
					Lower	Upper	
All-cause death (confirmed adjudicated)	7599	886	945	0.914	0.834	1.002	0.055

The sponsor submitted that in a pre-specified covariate-adjusted analysis the relative risk reduction for all-cause death with candesartan treatment was 10% (HR= 0.90, 95% CI 0.82 to 0.99, P=0.032).

The Kaplan-Meier plot illustrates the mortality in the two treatment groups over time (Figure 107).

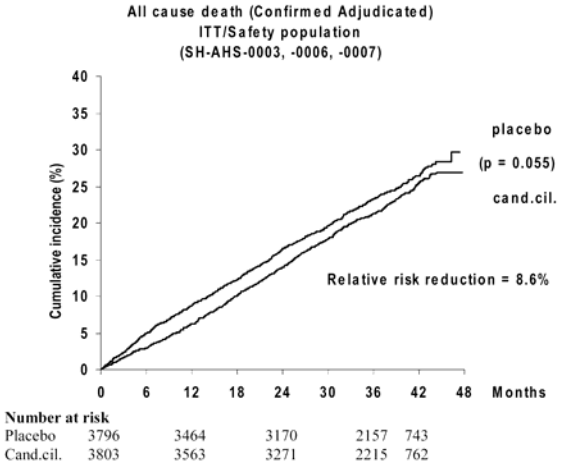


Figure 107 Cumulative incidence (%) of confirmed adjudicated all-cause death in patients with symptomatic CHF over time. ITT/Safety population

<u>Secondary variable: Time from randomization to all-cause death in patients with depressed LV systolic function</u>

Of the 4,576 patients in the population pooled across the two CHARM component studies in patients with depressed systolic LV function a total of 1,350 patients died: 642 (28.0%) in the candesartan group and 708 (30.9%) in the placebo group. The HR for the time to death was 0.88 (95% CI 0.79 to 0.98, P= 0.018), which equates to a relative risk reduction of 12%. The average annualized death rates were 9.9% and 11.2% respectively (Table 237 and Table 238).

Table 237 Confirmed adjudicated all-cause death in patients with depressed LV systolic function. Number of patients with an event by treatment group and events per 1000 years of follow-up. Follow-up time is calculated to event. ITT/Safety population (SH-AHS-0003, -0006)

Variable	Treatment	N	Events (No of patients)	Total follow-up time (years)	Events / 1000 follow-up years	Mean follow-up time (years)
All-cause death (confirmed adjudicated)	Placebo	2287	708	6303.2	112.3	2.8
	Cand. cil.	2289	642	6503.9	98.7	2.8

Table 238 Confirmed adjudicated all-cause death in patients with depressed LV systolic function. Comparison of candesartan versus placebo with Cox regression. ITT/Safety population (SH-AHS-0003,-0006)

Variable	N	Events cand. cil.	Events placebo	Hazard Ratio	95% CI		p-value
					Lower	Upper	
All-cause death (confirmed adjudicated)	4576	642	708	0.880	0.790	0.979	0.018

The Kaplan-Meier plot illustrates the mortality in the two groups over time (Figure 108).

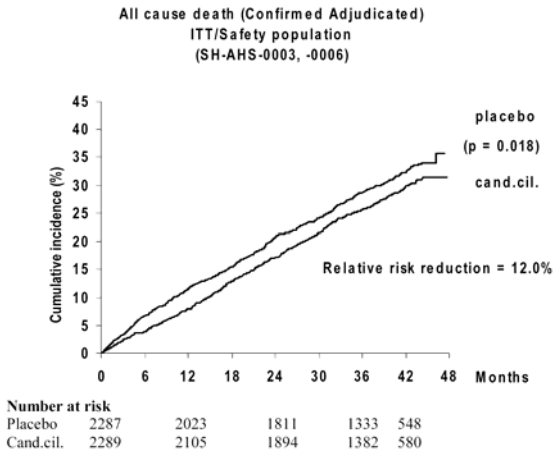


Figure 108 Cumulative incidence (%) of confirmed adjudicated all-cause death in patients with depressed LV systolic function over time. ITT/Safety population

Analysis of components of all-cause death

Patients with symptomatic CHF

The lower mortality in the candesartan group was attributable to a reduction in deaths from cardiovascular causes (HR=0.88, 95% CI 0.79 to 0.97, P=0.012: relative risk reduction 12.4%). There was no apparent difference in non-CV mortality (Figure 109and Table 240). The two most common reasons for CV death were both reduced by treatment with candesartan, sudden death (P=0.037) and death due to CHF (P=0.008) (Table 239 and Table 240).

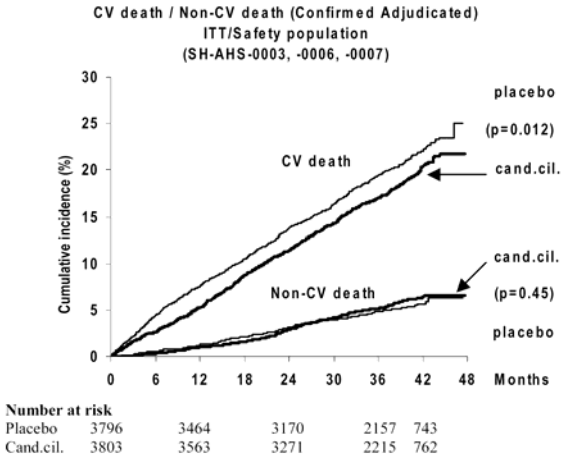


Figure 109 Cumulative incidence (%) of confirmed adjudicated cardiovascular death and non-cardiovascular death patients with symptomatic CHF over time. ITT/Safety population

Table 239 Confirmed adjudicated components of the primary variable. Number of patients with event by treatment group and events per 1000 years of follow-up. Follow-up time is calculated to event. ITT/ Safety population (SH-AHS-0003, -0006, -0007)

Variable	Treatment	N	Events (No of patients)	Total follow-up time (years)	Events / 1000 Follow-up years	Mean follow-up time (years)
CV death	Placebo	3796	769	10690.3	71.9	2.8
	Cand. cil.	3803	691	10938.2	63.2	2.9
Death due to CHF	Placebo	3796	260	10690.3	24.3	2.8
	Cand. cil.	3803	209	10938.2	19.1	2.9
Sudden death	Placebo	3796	344	10690.3	32.2	2.8
	Cand. cil.	3803	299	10938.2	27.3	2.9
Death due to MI	Placebo	3796	50	10690.3	4.7	2.8
	Cand. cil.	3803	61	10938.2	5.6	2.9
Death due to stroke	Placebo	3796	44	10690.3	4.1	2.8
	Cand. cil.	3803	45	10938.2	4.1	2.9
Death due to other CV cause	Placebo	3796	71	10690.3	6.6	2.8
	Cand. cil.	3803	77	10938.2	7.0	2.9
Non-CV death	Placebo	3796	176	10690.3	16.5	2.8
	Cand. cil.	3803	195	10938.2	17.8	2.9

Table 240 Confirmed adjudicated components of primary variable. Comparison of candesartan versus placebo with Cox regression. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Variable	N	Events cand. cil.	Events placebo	Hazard Ratio	95% CI		p-value
					Lower	Upper	
CV death	7599	691	769	0.876	0.790	0.971	0.012[a]
Death due to CHF	7599	209	260	0.783	0.653	0.939	0.008
Sudden death	7599	299	344	0.848	0.726	0.990	0.037[b]
Death due to MI	7599	61	50	1.187	0.817	1.726	0.368
Death due to stroke	7599	45	44	1.001	0.661	1.517	0.996
Death due to other CV cause	7599	77	71	1.057	0.766	1.460	0.734
Non-CV death	7599	195	176	1.081	0.882	1.326	0.452

[a] Logrank test p=0.011
[b] Logrank test p=0.036

Patients with depressed LV systolic function

The lower mortality in the candesartan group was attributable to a reduction in deaths from cardiovascular causes (HR=0.84, 95% CI 0.75 to 0.95, P=0.005: relative risk reduction 15.6%). There was no apparent difference in non- CV mortality. The two most common reasons for CV

death were both reduced by treatment with candesartan, sudden death (P=0.013) and death due to CHF (P=0.008) (Table 241 and Table 242).

Table 241 Confirmed adjudicated components of the primary variable. Number of patients with at least one event by treatment group and events per 1000 years of follow-up. Follow-up time is calculated to first event. ITT/Safety population (SH-AHS-0003, -0006)

Variable	Treatment	N	Events (No of patients)	Total follow-up time (years)	Events / 1000 Follow-up years	Mean follow-up time (years)
CV death	placebo	2287	599	6303.2	95.0	2.8
	cand.cil.	2289	521	6503.9	80.1	2.8
Death due to CHF	placebo	2287	206	6303.2	32.7	2.8
	cand.cil.	2289	161	6503.9	24.8	2.8
Sudden death	placebo	2287	279	6303.2	44.3	2.8
	cand.cil.	2289	230	6503.9	35.4	2.8
Death due to MI	placebo	2287	38	6303.2	6.0	2.8
	cand.cil.	2289	52	6503.9	8.0	2.8
Death due to stroke	placebo	2287	28	6303.2	4.4	2.8
	cand.cil.	2289	28	6503.9	4.3	2.8
Death due to other CV cause	placebo	2287	48	6303.2	7.6	2.8
	cand.cil.	2289	50	6503.9	7.7	2.8
Non-CV death	placebo	2287	109	6303.2	17.3	2.8
	cand.cil.	2289	121	6503.9	18.6	2.8

Table 242 Confirmed adjudicated components of primary variable. Comparison of candesartan versus placebo with Cox regression. ITT/Safety population (SH-AHS-0003, -0006)

Variable	N	Events cand. cil.	Events placebo	Hazard Ratio	95% CI		p-value
					Lower	Upper	
CV death	4576	521	599	0.844	0.751	0.950	0.005
Death due to CHF	4576	161	206	0.758	0.617	0.932	0.008
Sudden death	4576	230	279	0.801	0.673	0.954	0.013
Death due to MI	4576	52	38	1.327	0.873	2.016	0.185
Death due to stroke	4576	28	28	0.973	0.576	1.643	0.919
Death due to other CV cause	4576	50	48	1.007	0.678	1.497	0.972
Non-CV death	4576	121	109	1.073	0.828	1.390	0.595

NYHA classification of heart failure

Patients with symptomatic CHF

There was an improvement in NYHA functional class in candesartan patients compared to placebo patients (P= 0.004, Wilcoxon rank-sum test) (Table 243).

Table 243 Number of patients and change from baseline to LVEF in NYHA class by treatment in patients with symptomatic CHF. ITT/Safety Population. (SH-AHS-0003, -0006, -0007)

Visit	NYHA class	Placebo	Cand.cil.	Total
Baseline	NYHA II	1686 (44.4%)	1730 (45.5%)	3416 (45.0%)
	NYHA III	2008 (52.9%)	1977 (52.0%)	3985 (52.4%)
	NYHA IV	102 (2.7%)	96 (2.5%)	198 (2.6%)
LVCF	NYHA I	415 (11.0%)	470 (12.4%)	885 (11.7%)
	NYHA II	1881 (49.9%)	1929 (51.0%)	3810 (50.5%)
	NYHA III	1302 (34.6%)	1260 (33.3%)	2562 (33.9%)
	NYHA IV	170 (4.5%)	120 (3.2%)	290 (3.8%)
Change from Baseline to LVCF[a]	NYHA Improved by 3 classes	3 (0.1%)	3 (0.1%)	6 (0.1%)
	NYHA Improved by 2 classes	140 (3.7%)	140 (3.7%)	280 (3.7%)
	NYHA Improved by 1 class	1081 (28.7%)	1196 (31.6%)	2277 (30.2%)
	NYHA Same as baseline	2156 (57.2%)	2100 (55.6%)	4256 (56.4%)
	NYHA Deteriorated by 1 class	368 (9.8%)	319 (8.4%)	687 (9.1%)
	NYHA Deteriorated by 2 classes	20 (0.5%)	21 (0.6%)	41 (0.5%)
	Total	3765	3776	7541

a Wilcoxon rank-sum test, p=0.004

Patients with depressed LV systolic function

There was an improvement in NYHA functional class in candesartan patients compared to placebo patients (P< 0.001, Wilcoxon rank-sum test) (Table 244).

Table 244 Number of patients and change from baseline to LVEF in NYHA class by treatment in patients with depressed LV systolic function. ITT/Safety Population. (SH-AHS-0003, -0006)

Visit	NYHA class	Placebo	Cand.cil.	Total
Baseline	NYHA II	781 (34.1%)	799 (34.9%)	1580 (34.5%)
	NYHA III	1424 (62.3%)	1421 (62.1%)	2845 (62.2%)
	NYHA IV	82 (3.6%)	69 (3.0%)	151 (3.3%)
LVCF	NYHA I	210 (9.3%)	280 (12.3%)	490 (10.8%)
	NYHA II	1069 (47.2%)	1083 (47.7%)	2152 (47.4%)
	NYHA III	860 (38.0%)	821 (36.1%)	1681 (37.0%)
	NYHA IV	127 (5.6%)	88 (3.9%)	215 (4.7%)
Change from Baseline to LVCF[a]	NYHA Improved by 3 classes	2 (0.1%)	3 (0.1%)	5 (0.1%)
	NYHA Improved by 2 classes	98 (4.3%)	108 (4.8%)	206 (4.5%)
	NYHA Improved by 1 class	695 (30.7%)	799 (35.2%)	1494 (32.9%)
	NYHA Same as baseline	1251 (55.2%)	1178 (51.8%)	2429 (53.5%)
	NYHA Deteriorated by 1 class	209 (9.2%)	173 (7.6%)	382 (8.4%)
	NYHA Deteriorated by 2 classes	11 (0.5%)	11 (0.5%)	22 (0.5%)
	Total	2264	2269	4533

a Wilcoxon rank-sum test, p<0.001

Analyses of subgroups

The primary efficacy variable of each of the three component studies was time to CV death or hospitalization due to heart failure. This endpoint indicated a definite benefit with candesartan treatment as assessed in the pooled population of chronic heart failure patients (HR= 0.84, 95% CI 0.77 to 0.91, p< 0.001). The finding was similar across a wide range of subgroups, i.e., there was no apparent indication that the results in any subgroup were notably different from those described for the overall population.

The analyses considered subgroups based on gender, age cohorts, (a substantial number of participating patients were over 75 years of age.), diabetes, concomitant CHF medications and race. The number of black patients randomized in the program was relatively low but there was no indication that the treatment effect was different for Blacks. The beneficial effects of candesartan in the CHARM program were not altered by concomitant treatment with ACE inhibitors, β-blockers, spironolactone, digoxin, aspirin or lipid-lowering therapies (Figure 110).

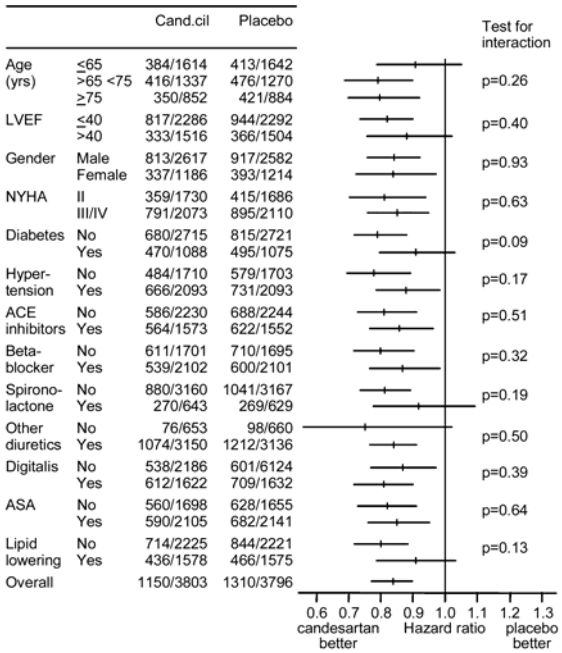


Figure 110 Overall effect of candesartan on cardiovascular death or first admission for CHF in pre-specified subgroups. Point estimates of hazard ratios given with 95 % confidence interval. P-values are for heterogeneity. ITT/ Safety population (SH-AHS-0003, -0006, -0007)

There was no increase in all-cause mortality in any subgroup (Figure 111).

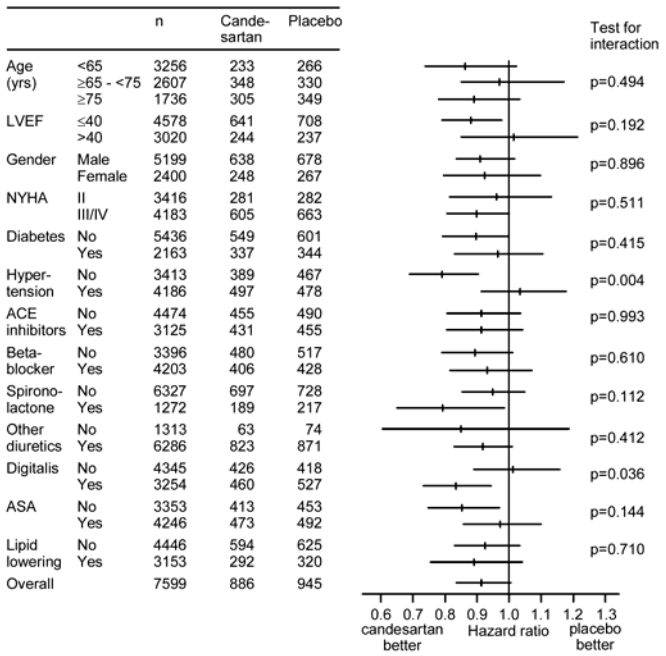


Figure 111 Overall effect of candesartan on all-cause death in pre-specified subgroups. Point estimates of hazard ratios given with 95% confidence interval. P-values are for heterogeneity. ITT/Safety population (SH- AHS-0003, -0006, -0007)

Patient-reported outcome results

Primary Quality of Life variables

Overall treatment evaluation

The patients' global evaluation of treatment effect (OTE) suggests that more patients treated with candesartan rated themselves as improved (Table 245).

Table 245 Frequency of patients by the outcome of the OTE questionnaire at last visit. ITT/Safety population

	Cand. cil.		Placebo	
	n	%	n	%
A very great deal worse	6	0.5	9	0.7
A great deal worse	18	1.4	25	2.0
A good deal worse	26	2.1	33	2.6
Moderately worse	42	3.4	41	3.3
Somewhat worse	21	1.7	19	1.5
A little worse	19	1.5	16	1.3
Almost the same, hardly worse at all	3	0.2	8	0.6
About the same	642	51.4	679	54.4
Almost the same, hardly better at all	16	1.3	16	1.3
A little better	52	4.2	57	4.6
Somewhat better	58	4.6	46	3.7
Moderately better	108	8.6	104	8.3
A good deal better	146	11.7	109	8.7
A great deal better	54	4.3	56	4.5
A very great deal better	38	3.0	30	2.4

Table 246 shows that this difference was significantly in favor of candesartan. In order to estimate the difference between the treatment groups, the OTE items were combined to form an overall 15- point scale, ranging from the worst deterioration (-7) to the highest improvement (+7) with "No change" (0) as the middle score. The overall score was then analyzed using the stratified Wilcoxon- Mann-Whitney test.

Table 246 OTE for patients with symptomatic CHF as assessed by a stratified Wilcoxon-Mann-Whitney test for comparison of the change for the two treatment groups. The data are stratified according to study. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Variable	Treatment	Estimate	Lower 95 % limit	Upper 95 % limit	p-value
Overall treatment effect	Cand. cil.-placebo	0.28	0.04	0.51	0.0167

Change in the physical functioning dimension in LIhFE

Patients in both treatment groups were comparatively little affected at baseline as reflected in the emotional dimension in LIhFE (mean around 8.5 out of 25) and in terms of the total score (mean around 40 out of 105). There was no significant difference between treatment groups in LIhFE emotional dimension or total score.

The physical dimension was slightly more affected (mean around 18.8 out of 45), i.e., a modest impairment. The mean change over time indicates a small improvement in all LIhFE outcomes; however, there was no significant difference between treatment groups in LIhFE physical dimension.

Change in frequency and severity of cough measured by VAS

Cough improved to a small extent during the program with no difference between treatment groups.

CHARM Program overall results

The overall CHARM Program wins on "**all-cause mortality"** when only the two studies involving patients with depressed LV systolic function – CHARM-Alternative (SH-AHS-0003) and CHARM-Added (SH-AHS-0006) – are pooled. When the CHARM-Preserved (SH-AHS-0007) study is added to the pooled analysis, the CHARM Program does not win on "all-cause mortality," unless covariate adjustment is allowed (then hazard ratio = 0.904, P = 0.031). However, this covariate adjustment is not agreed upon by FDA *apriori*.

CHARM Program Primary Efficacy Endpoint Finding: For the primary efficacy endpoint "all-cause mortality in the pooled population of patients with symptomatic CHF (pooled studies SH-AHS-0003, SH-AHS-0006 and SH-AHS-0007)", the CHARM-Program endpoint analysis showed that candesartan reduced (by 8.6%) all-cause mortality in patients with symptomatic CHF (Figure 112 and Table 247). This was NOT statistically significant (P=0.055).

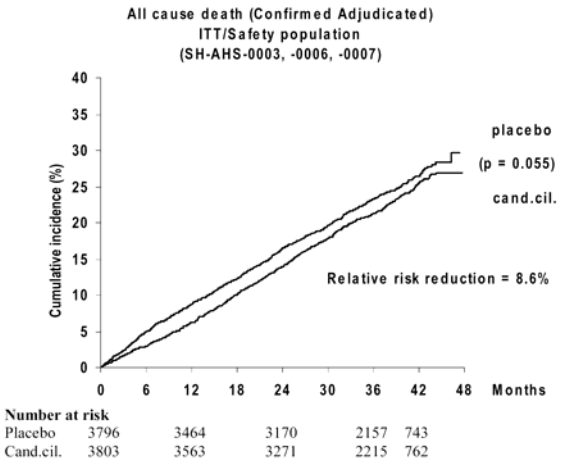


Figure 112 Cumulative incidence (%) of confirmed adjudicated all-cause death in patients with symptomatic CHF over time. ITT/Safety population.

Table 247 Endpoints in the CHARM-Alternative study (SH-AHS-0003), CHARM-Added study (SH-AHS-0006) and the CHARM Program (Pooled studies SH-AHS-0003, SH-AHS-0006 and SH-AHS-0007)

Endpoints	SH-AHS-0003 (CHARM-Alternative)	SH-AHS-0006 (CHARM-Added)	Pooled SH-AHS-0003 + SH-AHS-0006	Pooled SH-AHS-0003 + SH-AHS-0006+ SH-AHS-0007
P°: CV deaths or CHF hospitalizations	HR =0.768; P<0.001	**HR =0.853; P=0.011**	HR = 0.816; P<0.001	HR = 0.836; P<0.001
S°: All-cause deaths or CHF hospitalizations	HR =0.798; P=0.001	**HR =0.871; P=0.021**	HR = 0.840; P<0.001	HR = 0.862; P<0.001
S°: CV death/CHF hospitalization/non-fatal MI	HR =0.782; P<0.001	**HR =0.852; P=0.008**	HR = 0.822; P<0.001	HR = 0.843; P<0.001
All-cause Mortality	HR =0.872; P=0.105 (Covar. adj: P=0.033)	**HR =0.885; P=0.086 (Covar. adj: P=0.105)**	HR =0.886; P=0.018	HR =0.914; P=0.055 (Covar. adj: P=0.032)
All-cause deaths or all-cause hospitalizations	HR =0.918; P=0.114 (Covar. adj: P=0.028)	**HR =0.961; P=0.387**	HR =0.943; P=0.092	HR =0.948; P=0.055
All-cause hospitalizations	HR =0.913; P=0.107 (Covar. adj: P=0.030)	**HR =0.955; P=0.346**	HR =0.937; P=0.078	HR =0.948; P=0.064
CHF hospitalizations	HR =0.677; P<0.001	**HR =0.825; P=0.014**	HR = 0.76 ; P<0.001	HR = 0.79 ; P<0.001
Non-fatal MI	HR =1.107; P=0.656	**HR =0.512; P=0.006**	HR = 0.--- ; P<0.097	HR = 0.--- ; P<0.267
CV deaths	HR =0.847; P=0.072	**HR =0.842; P=0.029**	HR =0.844; P=0.005	HR =0.876; P=0.011
CHF death	HR =0.766; P=0.095	**HR =0.752; P=0.041**	HR =0.758; P=0.008	HR =0.783; P=0.008
Sudden death	HR =0.704; P=0.017	**HR =0.865; P=0.196**	HR =0.801; P=0.013	HR =0.848; P=0.037
Death due to MI	HR =1.942; P=0.025*	**HR =0.830; P=0.562**	HR =1.327; P=0.185	HR =1.187; P=0.368
Death due to stroke	HR =0.846; P=0.658	**HR =1.120; P=0.765**	HR =0.973; P=0.919	HR =1.001; P=0.996
Death due to other CV cause	HR =1.066; P=0.836	**HR =0.965; P=0.894**	HR =1.007; P=0.972	HR =1.057; P=0.734
Non-CV death	HR =1.014; P=0.948	**HR =1.112; P=0.529**	HR =1.073; P=0.595	HR =1.081; P=0.452

CHARM Program Secondary Efficacy Endpoint Finding: For the secondary efficacy endpoint "all-cause mortality in the pooled population of patients with CHF and left ventricular systolic dysfunction (pooled studies SH-AHS-0003 and SH-AHS-0006)", the CHARM-Program endpoint analysis showed that candesartan significantly (P=0.018) reduced (by 11.4%) all-cause mortality in patients with symptomatic CHF and left ventricular systolic dysfunction (Figure 113 and Table 247).

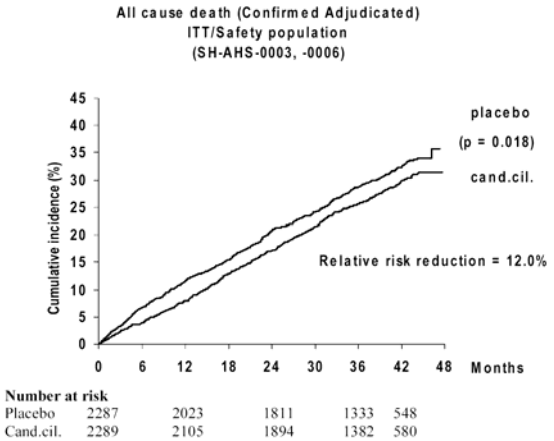


Figure 113 Cumulative incidence (%) of confirmed adjudicated all-cause death in patients with LV systolic dysfunction over time. ITT/Safety population.

CHARM Program – Other Efficacy Endpoint Findings: For the efficacy endpoint "all-cause mortality or all cause hospitalization in the pooled population of patients with symptomatic CHF (pooled studies SH-AHS-0003, SH-AHS-0006 and SH-AHS-0007)", the CHARM-Program endpoint analysis showed that candesartan reduced (by 5.2%) all-cause mortality or all cause hospitalization in patients with symptomatic CHF (Table 247). This was NOT statistically significant (P=0.055).

For the efficacy endpoint "all-cause death or all-cause hospitalization in the pooled population of patients with CHF and left ventricular systolic dysfunction (pooled studies SH-AHS-0003 and SH-AHS-0006)", the CHARM-Program endpoint analysis showed that candesartan reduced (by 5.7%) all-cause death or all-cause hospitalization" in patients with symptomatic CHF and left ventricular systolic dysfunction (Table 247). This was NOT statistically significant (P=0.092).

Please note that the CHARM Program does **NOT** win on the composite endpoint "**all-cause mortality or hospitalization**" or on "**all-cause hospitalization**" (regardless of whether 2 or all 3 studies are pooled).

Summary of efficacy results

Of the 7,599 patients in the population formed by pooling across the three CHARM component studies a total of 1,831 patients died: 886 (23.3%) in the candesartan group and 945 (24.9%) in the placebo group. The HR for the time to death was 0.91 (95% CI 0.83 to 1.00, P= 0.055 unadjusted for interim analyses), which equates to a relative risk reduction of 8.6%. The lower mortality in the candesartan group was attributable to a reduction in deaths from cardiovascular causes (HR=0.88, 95% CI 0.79 to 0.97, P=0.012: relative risk reduction=12.4%).

The sponsor submitted that a pre-specified covariate-adjusted analysis indicated a 10% relative risk reduction for all-cause death with candesartan treatment (HR=0.90, 95% CI 0.82 to 0.99, P=0.032).

In the pooled population of the two studies of patients with depressed LV systolic function (LVEF ≤ 40%) the all-cause mortality relative risk reduction with candesartan was 12% (HR=0.88, 95% CI 0.79 to 0.98, P=0.018). As noted above for the 3-study pooled analysis, the reduction in all cause mortality in the population with depressed LV systolic function was attributable to lower CV mortality (HR=0.88, 95% CI 0.79 to 0.97, P=0.012; relative risk reduction=12%).

During the follow-up period a total of 5,159 patients with symptomatic CHF died or were hospitalized for any reason; 2,554 (67.2%) in the candesartan group and 2,605 (68.6%) in the placebo group The relative risk reduction with candesartan treatment was 5.2% and the HR was 0.95 (95% CI 0.90 to 1.00, P=0.055).

In the population of patients with depressed LV systolic function, 1,608 (70.2%) patients in the candesartan group and 1,641 (71.8%) in the placebo group died or were hospitalized for any

reason. The HR was 0.94 (95% CI 0.88 to 1.01, P=0.092) and the corresponding relative risk reduction was 5.7%

In the total pooled population, 163 patients in the candesartan group and 202 patients in the placebo group developed diabetes during the follow-up period. The relative risk reduction for development of diabetes in patients without a pre-study diagnosis was 22% with candesartan treatment (HR=0.78, 95% CI 0.64 to 0.96, P=0.020).

In the total pooled population, fewer patients in the candesartan group (179, 4.7%) than in the placebo group (216, 5.7%) developed AF (95% CI for difference in proportions 2.0 to 0.0, P=0.054).

For the composite endpoint CV death or hospitalization due to CHF, which was the primary endpoint in the individual studies, the relative risk reduction with candesartan was 16.4% in the total pooled population (HR= 0.84, 95% CI 0.77 to 0.91, P< 0.001) and 18.4% in the population with depressed LV systolic function (HR= 0.82, 95% CI 0.74 to 0.90, P< 0.001).

The relative risk reduction for hospitalization due to CHF was 21% in the pooled population of patients across all studies (HR= 0.79, 95% CI 0.79 to 0.87, P< 0.001) and 24% in patients with depressed LV systolic function (HR= 0.76, 95% CI 0.68 to 0.85, P< 0.001).

Symptoms of heart failure according to NYHA classification improved significantly in patients with symptomatic CHF with candesartan treatment compared to placebo (P= 0.004).

The effect of candesartan with regard to the combined CV mortality CHF hospitalization outcome across sub groups according to age, gender, EF and concomitant CHF medications, was not inconsistent with the effect described for the overall population.

In the total population, the overall treatment evaluation (OTE questionnaire) showed a statistically significant advantage in favor of candesartan over placebo. Health related quality of life was maintained throughout the program with no significant difference between the treatments in any of LIhFE questionnaire outcomes.

SAFETY RESULTS

Deaths

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

Table 248 Number (%) of patients with symptomatic CHF with the most commonly reported[a] AEs leading to death, sorted by descending frequency in the total population during study. ITT/Safety population (SH-AHS-0003, -0006, -0007)

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

a The table uses a cut-off of ≥0.3% in the total population during study (N=7599).
b Patients having both or all events are counted once only.

The most commonly reported fatal AEs (Table 248) in the placebo and candesartan groups during study were sudden death (348, 9.2% and 291, 7.7% respectively), cardiac failure/cardiac failure aggravated (256, 6.7% and 192, 5.0% respectively) and MI (57, 1.5% and 77, 2.0% respectively).

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

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

Other Serious Adverse Events

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

The most commonly reported non-fatal SAEs during study were cardiac failure/cardiac failure aggravated (1,118, 29.5%), angina pectoris/angina pectoris aggravated (502, 13.2%) and pneumonia (268, 7.1%) in the placebo group, and cardiac failure/cardiac failure aggravated (931,

24.5%), angina pectoris/angina pectoris aggravated (480, 12.6%) and hypotension (318, 8.4%) in the candesartan group (Table 249).

Table 249 Number (%) of patients with symptomatic CHF with the most commonly reportedaa SAEs other than death, sorted by descending frequency in the total population during study. ITT/Safety population (SH-AHS-0003, -0006, -0007)

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

a The table uses a cut-off of ≥3.0% in the total population during study (N=7599).
b Patients having both or all events are counted once only.

Discontinuations and Other Significant Adverse Events

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

Overall profile of discontinuations

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

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

Thus, discontinuation of study medication due to AEs was more frequent in the candesartan

group in the CHARM-Pooled studies.

Adverse events associated with discontinuations

The most common AEs leading to discontinuation of the investigational product (Table 250) in the placebo group in the total population were cardiac failure/cardiac failure aggravated (186, 4.9%), renal function abnormal/renal dysfunction aggravated (110, 2.9%) and hypotension (76, 2.0%). The most commonly reported AEs leading to discontinuation in the candesartan group were renal function abnormal/renal dysfunction aggravated (238, 6.3%), cardiac failure/ cardiac failure aggravated (165, 4.3%) and hypotension (155, 4.1%).

Table 250 Number (%) of patients with symptomatic CHF with the most commonly reporteda AEs leading to discontinuation of the investigational product, sorted by descending frequency in the total population on treatment. ITT/Safety population (SH-AHS-0003, -0006, -0007)

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

a The table uses a cut-off of ≥0.5% in the total population on treatment (N=7599).
b Patients having both or all events are counted once only.

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

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

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

In this exploratory presentation of data permanent discontinuation of the investigational product due to an AE or abnormal lab value occurred in 633 (16.7%) patients in the placebo group and 798 (21.0%) patients in the candesartan group. Both the difference in time to event (P< 0.001) (Table 251, Table 252 and Figure 114) and the difference in proportions between treatments of 4.3% (P< 0.001) (Table 70 and Table 71) were statistically significant.

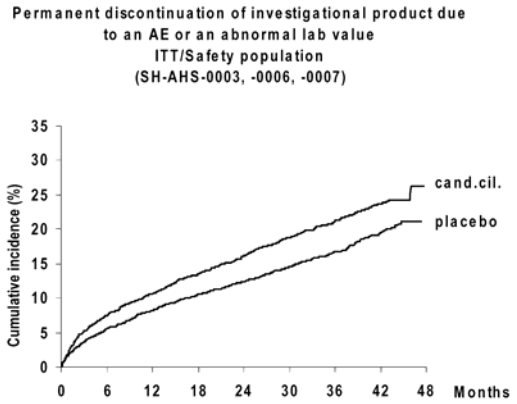
Table 251 Exploratory safety variables for patients with symptomatic CHF. Number of patients with at least one event by treatment group and events per 1000 years of follow-up. Follow-up time is calculated to first event. ITT/Safety population. (SH-AHS-0003, -0006, -0007)

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

Table 252 Exploratory safety variables for patients with symptomatic CHF. Comparison of candesartan versus placebo with Logrank test. ITT/Safety population. (SH-AHS-0003, -0006, -0007)

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

Specific causes of investigational product discontinuation are shown in Table 253, Table 254, Table 255 and Table 256. Hypotension, hyperkalemia and increased creatinine as causes for the investigational product discontinuation were statistically significantly more frequent for candesartan. Absolute differences in these cause-specific discontinuations relative to placebo were 1.7%, 1.7% and 3.1%, respectively.



Number at risk

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

Figure 114 Cumulative incidence (%) of permanent discontinuation of the investigational product due to an AE or an abnormal laboratory value. ITT/Safety population

Table 253 Exploratory safety variables for patients with symptomatic CHF. The proportions of patients (%) with an event. ITT/Safety population. (SH-AHS-0003, -0006, -0007)

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

Table 254 Exploratory safety variables for patients with symptomatic CHF. The difference in proportion (%) between treatments. Chi-square test. ITT/ Safety population. (SH-AHS-0003, -0006, -0007)

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

Table 255 Exploratory safety variables. Comparison of candesartan cilexetil versus placebo with Cox regression test with 33 pre-specified baseline factors as covariates for the total population. ITT/Safety Population. (SH-AHS-0003, -0006, -0007)

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

Table 256 Exploratory safety variables. Comparison of candesartan cilexetil versus placebo with Cox regression with 33 pre-specified baseline factors as covariates for the subpopulation. ITT/Safety Population. (SH-AHS-0003, -0006)

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

Investigational product discontinuation due to an AE or lab abnormality was also examined as an endpoint across the array of subgroups. There was an approximate 1.3 fold excess risk for

candesartan discontinuation relative to placebo for the entire study population which was characteristic of the relative discontinuation rates across most subgroups including concomitant medication with ACE-inhibitors, β-blockers and spironolactone.

For patients with a history of diabetes, there was a higher frequency of discontinuation of the investigational product caused by hypotension, hyperkalemia or increased serum creatinine (Table 257 and Table 258), which is an expected finding in these diabetics with possible underlying renal dysfunction and autonomic dysregulation.

Table 257 Discontinuation of investigational product due to hypertension, hyperkalemia and increased creatinine in patients with a history of diabetes for the total population. The proportions of patients (%) with an event. ITT/Safety Population. (SH-AHS-0003, -0006, -0007)

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

Table 258 Permanent discontinuation of investigational product in patients with a history of diabetes for the total population. The difference in proportion (%) between treatments. Chi square test. ITT/Safety Population (SH-AHS-0003, -0006, -0007)

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

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

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

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

The dose of the investigational product was reduced due to AEs in 324 (8.5%) patients in the placebo group and in 569 (15.0%) patients in the candesartan group. The most commonly reported AEs leading to dose reduction were hypotension (136, 3.6%), renal function abnormal/renal dysfunction aggravated (0, 1.3%) and dizziness/vertigo (38, 1.0%) in the placebo group, and hypotension (315, 8.3%), renal function abnormal/renal dysfunction aggravated (99, 2.6%) and hyperkalemia (60, 1.6%) in the candesartan group (Table 259).

Table 259 Number (%) of patients with symptomatic CHF with the most commonly reported[a] AEs leading to dose reduction of the investigational product, sorted by descending frequency in the total population on treatment. ITT/Safety population (SH-AHS-0003, -0006, -0007)

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

a The table uses a cut-off of ≥0.3% in the total population on treatment (N=7599).
b Patients having both or all events are counted once only.

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

A higher frequency of dose reduction is presented in the exploratory safety analysis which is due to the fact that patients experiencing both dose reduction and later permanent discontinuation for the same reason are counted once in each category in the exploratory analysis. In the descriptive safety analysis above these patients are only included in the discontinuation category.

Dose reduction of the investigational product due to an AE or abnormal lab value occurred in 385 (10.1%) patients in the placebo group and 693 (18.2%) patients in the candesartan group (Table 253). This between- treatment difference in dose reductions for an AE of 8.1% was statistically significant ($P < 0.001$), (Table 254). As shown in Figure 115, the majority of events occurred during the first 6 to 12 months of treatment with the investigational product.

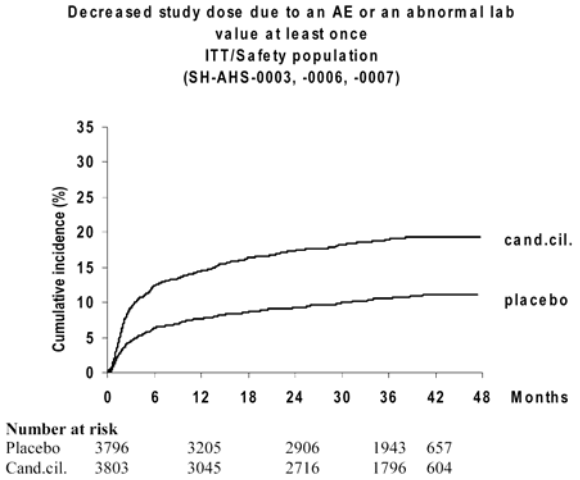


Figure 115 Cumulative incidence (%) of dose reduction of the investigational product due to an AE or an abnormal laboratory value. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Common Adverse Events

Adverse events (AEs) collected during the component studies in the total population (SH-AHS-0003, SH-AHS-0006 and SH-AHS-0007) are described depending on whether they were reported during treatment with the investigational product (referred to as "on treatment" in tables) or reported over the entire study period (referred to as "during study"). AEs during study include all AEs reported for each patient, i.e., those reported on treatment as well as any new-onset AEs during the period following discontinuation of the study drug and new-onset SAEs after the patient completed or withdrew from a component study. AEs are organized according to the AAED preferred term level, i.e., AEs of a similar kind share the same preferred term.

Appropriateness of adverse event categorization and preferred terms

Categories of adverse events in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies: During study, in the total population AEs were reported by 2,799 (73.7%) patients randomized to placebo, and by 2,841 (74.7%) patients randomized to candesartan. In the placebo group 947 (24.9%) patients had fatal SAEs and 2,487 (65.5%) patients experienced non-fatal SAEs, compared with the candesartan group where 887 (23.3%) patients had fatal SAEs and 2,432 (63.9%) patients had non-fatal SAEs. The investigational product was prematurely discontinued due to AEs for 613 (16.1%) patients in the placebo group and for 799 (21.0%) patients in the candesartan group. The investigational product was reduced in dose due to AEs for 324 (8.5%) patients in the placebo group and for 569 (15.0%) patients in the candesartan group. A summary of AEs by category in the total population is presented in Table 260, and for CHF patients with depressed LV function is given in Table 261.

Table 260 Number (%) of patients with symptomatic CHF with at least one adverse event in any category, and total numbers of adverse events. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Category of adverse event	N (%) of patients who had an adverse event in each category[a]							
	Placebo on treatment (N=3796)		Cand. cil. on treatment (N=3803)		Placebo during study[b] (N=3796)		Cand. cil. during study[b] (N=3803)	
Any AE	2732	(72.0)	2788	(73.3)	2799	(73.7)	2841	(74.7)
Serious AEs	2562	(67.5)	2410	(63.4)	2698	(71.1)	2624	(69.0)
Serious AEs leading to death	616	(16.2)	504	(13.3)	947	(24.9)	887	(23.3)
Serious AEs not leading to death	2369	(62.4)	2246	(59.1)	2487	(65.5)	2432	(63.9)
Discontinuations of the investigational product due to AEs	613	(16.1)	799	(21.0)	-	-	-	-
Dose reductions of the investigational product due to AEs	324	(8.5)	569	(15.0)	-	-	-	-
	Total number of adverse events							
All AEs[c]	9317		9378		10814		11261	
Serious AEs[c]	8390		7730		9895		9634	

a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

b Only one occurrence of an event during the study period is counted

c Events are counted by preferred term, ie, for patients with multiple events falling under the same preferred term, only one occurrence of the event is counted.

Table 261 Number (%) of patients who had at least one adverse event in any category, and total numbers of adverse events for the subpopulation ITT/Safety population (SH-AHS-0003, -0006)

Category of adverse event	N(%) of patients who had an adverse event in each category[a]							
	Placebo on treatment (N=2287)		Cand.cil. on treatment (N=2289)		Placebo during study[b] (N=2287)		Cand.cil. during study[b] (N=2289)	
Any AE	1703	(74.5)	1732	(75.7)	1739	(76.0)	1767	(77.2)
Serious AEs	1605	(70.2)	1506	(65.8)	1688	(73.8)	1651	(72.1)
Serious AEs leading to death	463	(20.2)	375	(16.4)	709	(31.0)	643	(28.1)
Serious AEs not leading to death	1453	(63.5)	1373	(60.0)	1524	(66.6)	1493	(65.2)
Discontinuations of investigational product due to AEs	421	(18,4)	530	(23,2)	-	-	-	-
Dose reductions of investigational product due to AEs	199	(8.7)	377	(16.5)	-	-	-	-
	Total number of adverse events							
All AEs[c]	5875		5928		6885		7123	
Serious AEs[c]	5276		4885		6291		6092	

a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

b Only one occurrence of an event during the study period is counted.

c Events are counted by preferred term, ie, for patients with multiple events falling under the same preferred term, only one occurrence of the event is counted.

Incidence of common adverse events and common adverse event tables

The most common AEs (Table 262) in the placebo and candesartan groups during study were cardiac failure/cardiac failure aggravated (1,187, 31.3% and 1001, 26.3% respectively), angina pectoris/angina pectoris aggravated (506, 13.3% and 490, 12.9%, respectively), hypotension (399, 10.5% and 736, 19.4% respectively) and renal function abnormal/renal dysfunction aggravated (248, 6.5% and 487, 12.8% respectively).

A similar pattern was seen in the subpopulation of patients with depressed LV systolic function.

Table 262 Number (%) of patients with symptomatic CHF with the most commonly reported[a] AEs, sorted by descending frequency. ITT/ Safety population (SH-AHS-0003, -0006, -0007)

Preferred term	Placebo on treatment (N=3796)		Cand. cil. on treatment (N=3803)		Placebo during study (N=3796)		Cand. cil. during study (N=3803)	
	N	(%)	N	(%)	N	(%)	N	(%)
Cardiac failure/cardiac failure aggravated[b]	1073	(28.3)	831	(21.9)	1187	(31.3)	1001	(26.3)
Hypotension	372	(9.8)	714	(18.8)	399	(10.5)	736	(19.4)
Angina pectoris/angina pectoris aggravated[b]	461	(12.1)	414	(10.9)	506	(13.3)	490	(12.9)
Renal function abnormal/renal dysfunction aggravated[b]	238	(6.3)	474	(12.5)	248	(6.5)	487	(12.8)
Sudden death	282	(7.4)	234	(6.2)	348	(9.2)	291	(7.7)
Pneumonia	243	(6.4)	200	(5.3)	299	(7.9)	261	(6.9)
Myocardial infarction	216	(5.7)	205	(5.4)	257	(6.8)	242	(6.4)
Fibrillation atrial	218	(5.7)	165	(4.3)	249	(6.6)	202	(5.3)
Arrhythmia ventricular	207	(5.5)	159	(4.2)	239	(6.3)	193	(5.1)
Cerebrovascular disorder	189	(5.0)	164	(4.3)	216	(5.7)	203	(5.3)
Coronary artery disorder	170	(4.5)	169	(4.4)	200	(5.3)	205	(5.4)
Chest pain	177	(4.7)	154	(4.0)	202	(5.3)	183	(4.8)
Arrhythmia atrial	175	(4.6)	156	(4.1)	197	(5.2)	187	(4.9)
Hyperkalaemia	78	(2.1)	238	(6.3)	84	(2.2)	242	(6.4)
Tachycardia supraventricular	152	(4.0)	129	(3.4)	177	(4.7)	148	(3.9)
Dizziness/vertigo[b]	107	(2.8)	154	(4.0)	115	(3.0)	168	(4.4)
Accident and/or injury	112	(3.0)	99	(2.6)	143	(3.8)	125	(3.3)
Tachycardia ventricular/arrhythmia/arrhythmia aggravated[b]	110	(2.9)	100	(2.6)	132	(3.5)	128	(3.4)
Syncope	105	(2.8)	121	(3.2)	119	(3.1)	139	(3.7)
Anaemia	87	(2.3)	110	(2.9)	110	(2.9)	145	(3.8)

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

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

Laboratory Findings

For the total population, serial laboratory data were collected from patients participating at investigational sites in North America (placebo 1,376 patients, candesartan 1,367 patients).

Changes in mean laboratory values were generally small, of minor clinical significance, and occurred primarily in parameters that previously showed changes in studies with inhibitors of the RAAS, such as creatinine and potassium. As a consequence of the large number of observations, some laboratory variables showed statistically significant between treatment differences, even though the absolute differences were small and may not be clinically significant.

From the results for all clinical laboratory tests in the total population, only clinical important abnormalities in the laboratory tests are presented below.

The number of patients with increase in serum creatinine ≥ 2 times from baseline, and of patients with serum potassium ≥ 6mmol/l after randomization are shown in Table 263 and Table 264 for the total CHARM-Pooled population, and in Table 265 and Table 266 for the subpopulation of CHF patients with LV dysfunction.

Table 263 Number (%) of patients with increase in serum creatinine ≥ 2 x from baseline value. ITT/Safety population (North America) (SH-AHS-0003, -0006,-0007)

Abnormal Laboratory variable	Placebo (N=1279)		Cand.cil. (N=1263)	
	N	%	N	%
Creatinine	47	3.7	82	6.5

Table 264 Number (%) of patients with serum potassium to ≥ 6 mmol/L at any time after randomization. ITT/Safety population (North America) (SH-AHS-0003, -0006,-0007)

Abnormal Laboratory variable	Placebo (N=1310)		Cand.cil. (N=1294)	
	N	%	N	%
Potassium	15	1.1	31	2.4

Table 265 Number (%) of patients with increase in serum creatinine ≥ 2 x from baseline value. ITT/Safety population (North America) (SH- AHS- 0003, -0006)

Abnormal Laboratory variable	Placebo (N=754)		Cand.cil. (N=747)	
	N	%	N	%
Creatinine	32	4.2	49	6.6

Table 266 Number (%) of patients with serum potassium to ≥ 6 mmol/L at any time after randomization. ITT/Safety population (North America) (SH-AHS-0003, -0006)

Abnormal Laboratory variable	Placebo (N=774)		Cand.cil. (N=768)	
	N	%	N	%
Potassium	9	1.2	21	2.7

The mean value for creatinine in the placebo group increased 7.7 µmol/L from the baseline value to the LVCF. In the candesartan group, the mean value increased 17.0 µmol/L. At baseline, 252 (18.8%) of placebo patients had values above the reference range compared with 251 (18.8%) of patients in the candesartan group. For the last values carried forward that were above the upper level of normal, frequency increased in both treatment groups (placebo 358, 27.3%; candesartan 399, 30.8%). For patients who had baseline value and at least one measurement after randomization (placebo 1279 patients, candesartan 1263 patients) baseline serum creatinine was at least doubled in 47 (3.7%) patients in the placebo group, compared with 82 (6.5%) patients in the candesartan group (Table 263).

For potassium, the mean value for patients treated with placebo increased 0.02 mmol/ L from the baseline value to the LVCF compared with 0.24 mmol/L for patients treated with candesartan. The proportions of patients with values above the reference range increased from 32 (2.4%) to 44 (3.4%) in the placebo group and increased from 38 (2.8%) to 83 (6.4%) in the candesartan group. Potassium levels increased to = 6 mmol/L at any time after randomization in 15 (1.1%) of 1,310 patients valid for evaluation in the placebo group and 31 (2.4%) of 1,294 patients in the candesartan group (Table 264).

AE reports of hypokalemia were rare and occurred more often in the placebo group (placebo 36, 0.9%; candesartan 16, 0.4%).

Mean sodium measurements decreased 0.07 mmol/L for patients treated with placebo and decreased 0.12 mmol/L for patients in the candesartan. The AE term hyponatremia was reported for 13 patients treated with placebo compared with 9 patients treated with candesartan.

Minor decreases were seen for mean hemoglobin values for patients treated with placebo (0.18 mmol/L) and candesartan (0.31 mmol/L). The proportion of patients with anemia reported as an AE on treatment with the investigational product was slightly lower for placebo-treated patients (87, 2.3%) compared with candesartan-treated patients (110, 2.9%). One patient in the placebo treatment group and 4 (0.3%) of 1,290 patients in the candesartan group had a hemoglobin value below the defined level of abnormality (male = 80 g/L (4.96 mmol/L), female = 70 g/L (4.34 mmol/L)).

Glycohemoglobin A_{1c} levels decreased slightly and no major difference was seen between the placebo (-0.31%) and candesartan groups (-0.32%).

In summary, it appears that the small differences in mean laboratory values (candesartan compared with placebo) and the frequency of critical abnormal values was in keeping with the expected findings for treatment with inhibitors of the RAAS.

Vital Signs

For the CHARM Program studies' safety report, vital signs consist of diastolic blood pressure (DBP), systolic blood pressure (SBP), pulse pressure and heart rate. For physical findings, only the data for body weight are presented.
Changes in vital signs over time in the total population are shown in Figure 116, Figure 117, Figure 118, and Figure 119.

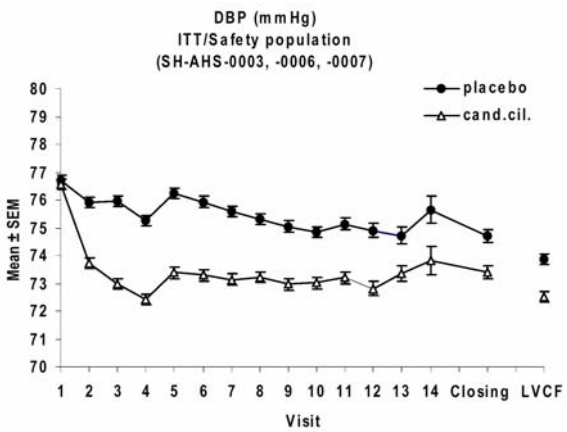


Figure 116 Mean DBP ± SEM (mmHg) by visit for the total population. ITT/Safety population

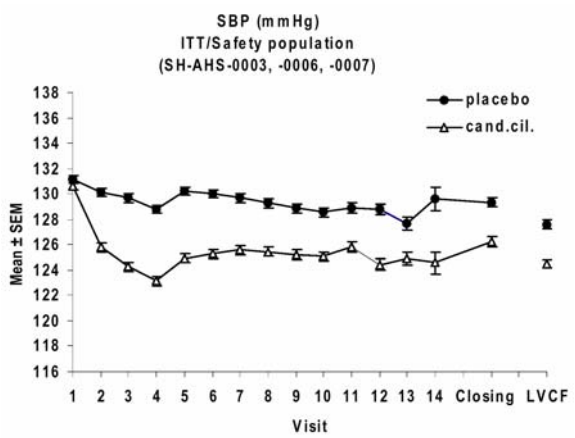


Figure 117 Mean SBP ± SEM (mmHg) by visit for the total population. ITT/Safety population

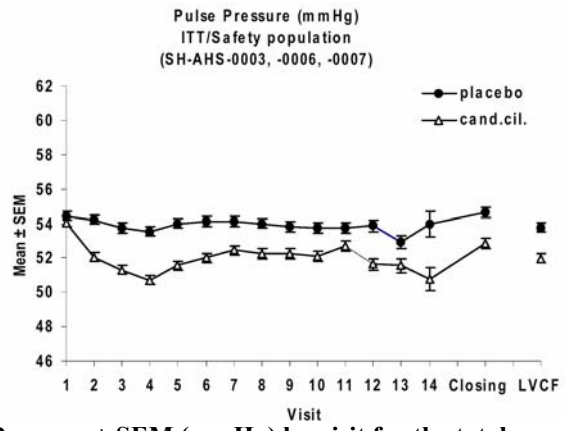


Figure 118 Mean Pulse Pressure ± SEM (mmHg) by visit for the total population. ITT/Safety population

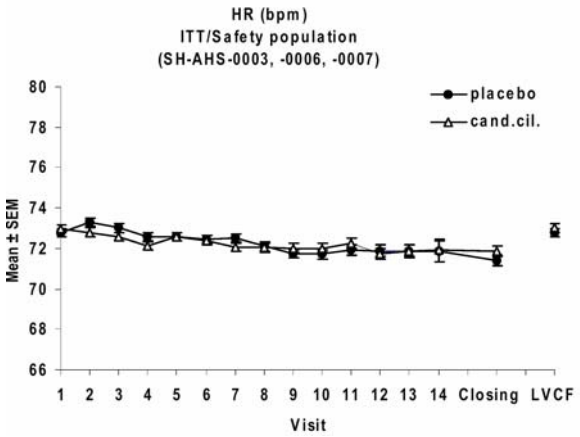


Figure 119 Mean heart rate ± SEM (bpm) by visit for the total population. ITT/Safety population

Changes in vital signs over time in the subpopulation of patients with depressed LV systolic function are shown in Figure 120, Figure 121, Figure 122and Figure 123.

The number of patients with clinically important changes in vital signs in the total population are shown in (Table 267, Table 268 and Table 269) and the number of patients with clinically important changes in vital signs in the subpopulation of patients with depressed LV systolic function are shown in (Table 270 and Table 271).

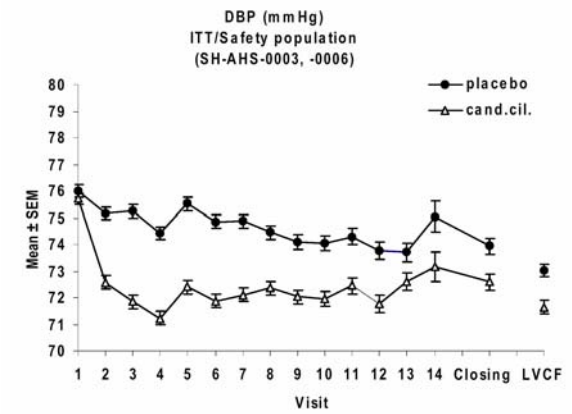


Figure 120 Mean DBP ± SEM (mmHg) by visit for the depressed LV systolic function subpopulation. ITT/Safety population

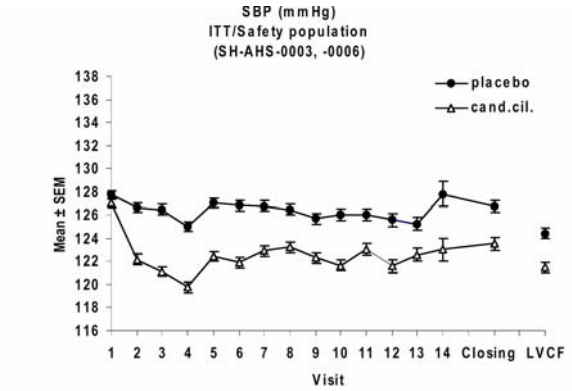


Figure 121 Mean SBP ± SEM (mmHg) by visit for the depressed LV systolic function subpopulation. ITT/Safety population

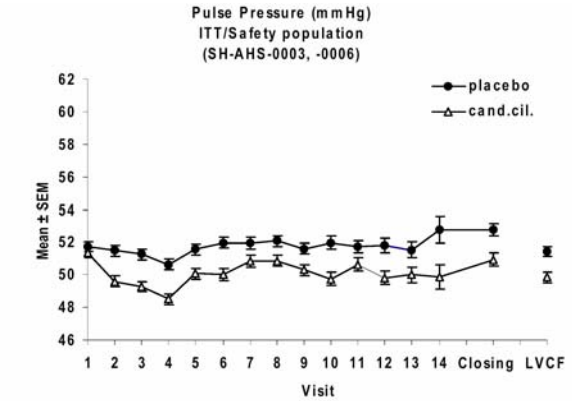


Figure 122 Mean Pulse Pressure ± SEM (mmHg) by visit for the depressed LV systolic function subpopulation. ITT/Safety population

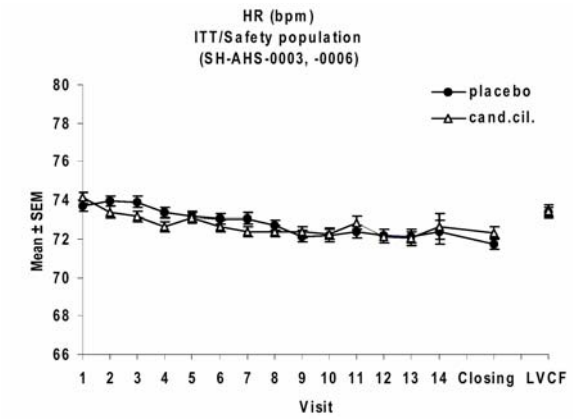


Figure 123 Mean heart rate ± SEM (bpm) by visit for the depressed LV systolic function subpopulation. ITT/Safety population

Table 267 Estimated Means and 95% CI for the change from baseline to LVCF for BP variables with Region as an ANOVA factor for the total population. ITT/Safety Population. (SH-AHS-0003, -0006, -0007)

Variable	Treat-ment	N	Estimated Mean	95% CI	
				Lower	Upper
DBP (mmHg)	placebo	3755	-2.21	-2.66	-1.75
	cand.cil.	3774	-3.66	-4.10	-3.23
SBP (mmHg)	placebo	3756	-2.69	-3.48	-1.89
	cand.cil.	3774	-5.95	-6.70	-5.19
Pulse Pressure (mmHg)	placebo	3755	-0.42	-1.05	0.21
	cand.cil.	3774	-2.22	-2.83	-1.62
Heart rate (bpm)	placebo	3756	0.22	-0.30	0.73
	cand.cil.	3773	0.37	-0.12	0.86

Table 268 Comparison for Change in BP variables with Region as an ANOVA factor for the total population. ITT/Safety Population. (SH-AHS-0003, -0006, -0007)

Variable	Comparison	Estimated Mean	95% CI		p-value
			Lower	Upper	
DBP (mmHg)	cand.cil. - placebo	-1.45	-2.08	-0.82	<0.001
SBP (mmHg)	cand.cil. - placebo	-3.26	-4.35	-2.16	<0.001
Pulse Pressure (mmHg)	cand.cil. - placebo	-1.81	-2.68	-0.93	<0.001
Heart rate (bpm)	cand.cil. - placebo	0.15	-0.56	0.86	0.680

Table 269 Number (%) of patients with decrease in SBP to ≤ 80 mm Hg or DBP to ≤40 mm Hg at any time after randomization for the total population. ITT/safety population. (SH-AHS-0003,-0006, -0007)

Abnormal Vital Sign variable	Placebo (n=3757)		Cand.cil. (n=3774)	
	N	%	N	%
DBP	50	1.3	77	2.0
SBP	109	2.9	201	5.3

Table 270 Number (%) of patients with decrease in SBP to ≤ 80 mm Hg at any time after randomization for the subpopulation. ITT/safety population. (SH-AHS-0003, -0006)

Abnormal Vital Sign variable	Placebo (n=2260)		Cand.cil. (n=2271)	
	N	%	N	%
SBP	87	3.8	158	7.0

Table 271 Number (%) of patients with decrease in DBP to ≤ 40 mm Hg at any time after randomization for the subpopulation. ITT/safety population. (SH-AHS-0003, -0006)

Abnormal Vital Sign variable	Placebo (n=2259)		Cand.cil. (n=2271)	
	N	%	N	%
DBP	37	1.6	58	2.6

Discussion of vital signs, physical findings and other observations related to safety in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

In the total population, blood pressure declined in both treatment groups. Mean DBP decreased 2.9 mmHg from the baseline value to the LVCF in the placebo group and 4.0 mmHg from the baseline value to the LVCF in the candesartan group. Corresponding values for SBP were 3.6 mmHg for patients treated with placebo and 6.1 mmHg for patients treated with candesartan.

The effect on blood pressure in the candesartan group was established during the first 6 months while in the placebo group a trend towards lowering could be seen for a longer time period. Mean heart rate was unchanged during study in both treatment groups. A DBP value less than 40 mmHg at any time during study was reported for 50 (1.4%) patient in the placebo group and 77 (2.0%) patients in the candesartan group. 109 (2.9%) patients treated with placebo and 201 (5.3%) patients treated with candesartan had a recorded SBP value less than 80 mmHg at any time after randomization (Table 269).

In the placebo group, mean body weight decreased by 0.4 kg from baseline to LVCF. In the candesartan population an increase of 0.3 kg was seen.

Overdose Experience

In case reports of overdose (up to 672 mg of candesartan), patient recovery was uneventful. The main manifestation of overdose is symptomatic hypotension and dizziness, which may require placing the patient supine, elevation of legs and, if required, infusion of isotonic saline solution and, sympathomimetic drugs. Candesartan is not removed by hemodialysis.

Post marketing Experience

The sponsor submits that candesartan has been available in worldwide markets for the treatment of hypertension since 1997. The majority of patients have been treated with 8 to 16 mg dose of

candesartan. Since its first approval for treatment of hypertension in 1997, the approved once/day doses of 2 to 32 mg candesartan are available in 84 countries including the United States. In Canada, a 32-mg dose in hypertension was approved in 2002. In 1998, the fixed-dose tablets of candesartan and hydrochlorothiazide was first approved; this formulation is now approved in 56 countries.

During the post marketing period, no unexpected organ-specific toxicity has been reported. Rarely reported reactions include leucopenia, neutropenia, agranulocytosis, hyperkalemia, hyponatremia, increased liver enzymes, abnormal liver function or hepatitis, angioedema, rash, urticaria, pruritus, and renal impairment including renal failure.

Adequacy of Patient Exposure and Safety Assessments

Please also see section 5.3.1 of the review (Total exposure of candesartan). The sponsor submits that the cumulative exposure to candesartan as of October 2003 exceeds 14 million patient-years.

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

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

(i) 5 randomized, double-blind, placebo-controlled clinical trials with duration of 2 to 12 months, comprising a total of 1,893 patients,

(ii) one randomized, double-blind, active-treatment (enalapril)-controlled study (RESOLVD) comprising 768 patients, and

(iii) one open, uncontrolled, long-term (6 month) study comprising 355 patients,

(iv) 3 clinical pharmacology studies comprising 262 patients,

(v) 11 clinical studies comprising a total of 677 patients under the Japanese study program (for which FDA granted the sponsor a waiver from providing case report tabulations and case report forms, and 10 studies were pertinent to efficacy), and

(vi) 4 investigator-initiated clinical studies comprising 107 patients.

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

Extent of exposure (dose/duration)

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

A total of 2,028 patients were randomized into SH-AHS-0003, 2,548 patients to SH-AHS-0006 and 3,025 patients to SH-AHS 0007. The total ITT/safety population for patients with symptomatic CHF (SH-AHS-0003, SH-AHS-0006 and SH- AHS-0007) comprised 7,599 patients (2,400 females and 5,199 males) and the corresponding figures for SH-AHS-0003 and SH-AHS-0006 are 4,576 (1,188 females and 3,388 males). Two patients were randomized in error and were therefore excluded from the ITT/safety population in SH-AHS-0007 (because no investigational product was dispensed and no data were collected). Patients who received incorrect investigational product during any part of the studies (22 patients in SH-AHS-0007) are included in the analyses according to the group to which they were randomized. The incorrect investigational product administration lasted for a maximum of 21 days.

An overview of exposure in the total ITT/safety population including the numbers of patients who completed or discontinued the CHARM program is presented in Table 272. Table 273 presents the exposure and number of patients by time in the component studies.

A total of 5,360 (70.5%) received the investigational product for ≥ 24 months, among which 2,659 (69.9%) on candesartan received the investigational product for ≥ 24 months.

Table 272 Overview of exposure in patients with symptomatic CHF. ITT/Safety population (SH-AHS-0003, -0006, -0007)

		Placebo (N=3796)		Cand.cil. (N=3803)	
No. (%) of patients evaluable for safety	Male	2582	(68.0)	2617	(68.8)
	Female	1214	(32.0)	1186	(31.2)
Age (years)	<65	1642	(43.3)	1614	(42.4)
	≥65	2154	(56.7)	2189	(57.6)
	<75	2912	(76.7)	2951	(77.6)
	≥75	884	(23.3)	852	(22.4)
Race[a]	Caucasian	3507	(92.4)	3493	(91.8)
	Black	164	(4.3)	162	(4.3)
	Oriental	87	(2.3)	110	(2.9)
	Other	38	(1.0)	38	(1.0)
Exposure by discontinuation due to AE of investigational product and/or study (N and %)	Discontinued investigational product due to AEs	613	(16.1)	799	(21.0)
	Patients who withdrew consent	51	(1.3)	66	(1.7)

[a] Race is presented according to the four race groups Caucasian (including European origin, South Asian and Arab/Middle East), Black, Oriental (including Oriental and Malay) and Other. See Section 8.3.

The median duration of patient follow-up for the total population in the CHARM program was 37.9 months for patients randomized to candesartan and 37.6 months for patients randomized to placebo (Table 273). The longest follow-up time was 47.6 months.

Table 273 Exposure and number of patients with symptomatic CHF by time in the component studies. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Period	Time	Placebo	Cand. cil.	Total
From baseline to last visit	>= 0 days	3796	3803	7599
	>= 1 months	3765	3779	7544
	>= 3 months	3707	3738	7445
	>= 6 months	3673	3721	7394
	>= 12 months	3464	3563	7027
	>= 24 months	3170	3271	6441
	>= 36 months	2157	2215	4372
	>= 48 months	0	0	0
	Patient years	10690.3	10938.2	21628.5
	Mean (months)	33.8	34.5	34.2
	Median (months)	37.6	37.9	37.7
	Min/max (months)	0.1/47.4	0.1/47.6	0.1/47.6
From baseline to last day on double-blind investigational product	>= 0 days	3796	3803	7599
	>= 1 months	3653	3660	7313
	>= 3 months	3501	3475	6976
	>= 6 months	3451	3419	6870
	>= 12 months	3105	3071	6176
	>= 24 months	2701	2659	5360
	>= 36 months	1766	1715	3481
	>= 48 months	0	0	0
	Patient years	9371.2	9221.9	18593.1
	Mean (months)	29.6	29.1	29.4
	Median (months)	35.0	34.5	34.8
	Min/max (months)	0.0/47.2	0.0/47.4	0.0/47.4

Corresponding data for the subpopulation of patients with depressed LV systolic function is shown in Table 274 and Table 275.

The median duration of patient follow-up for the two treatment groups in the subpopulation of patients with depressed LV systolic function were 40.2 and 39.9 months respectively (Table 275).

Table 274 Overview of exposure in the ITT/Safety population for the subpopulation. (SH-AHS-0003, -0006)

		Placebo (N=2287)		Cand.cil. (N=2289)	
No. (%) of patients evaluable for	Male	1691	(73.9)	1697	(74.1)
	Female	596	(26.1)	592	(25.9)
Age	<65	1028	(44.9)	1044	(45.6)
	≥65	1259	(55.1)	1245	(54.4)
	<75	1803	(78.8)	1844	(80.6)
	≥75	484	(21.2)	445	(19.4)
Race[a]	Caucasian	2098	(91.7)	2096	(91.6)
	Black	107	(4.7)	93	(4.1)
	Oriental	57	(2.5)	76	(3.3)
	Other	25	(1.1)	24	(1.0)
Exposure by study completion or	Discontinued investigational	421	(18.4)	530	(23.2)
	Discontinued the study[b]	31	(1.4)	43	(1.9)
	Completed the study	2256	(98.6)	2246	(98.1)

a Race is presented according to the four race groups Caucasian (including European origin, South Asian and Arab/ Middle East), Black, Oriental (including Oriental and Malay) and Other.
b Patients who withdrew consent.

Table 275 Exposure and number of patients for the subpopulation by time in the study. ITT/Safety population. (SH-AHS-0003, -0006)

Period	Time	Placebo	Cand.cil.	Total
From Baseline to Last visit	>= 0 days	2287	2289	4576
	>= 1 months	2259	2269	4528
	>= 3 months	2210	2235	4445
	>= 6 months	2185	2223	4408
	>= 12 months	2023	2105	4128
	>= 24 months	1811	1894	3705
	>= 36 months	1333	1382	2715
	>= 48 months	0	0	0
	Patient years	6303.2	6503.9	12807.1
	Mean (months)	33.1	34.1	
	Median (months)	39.9	40.1	
	Min/max (months)	0.1/47.4	0.1/47.6	
From Baseline to last day on double-blind study medication	>= 0 days	2287	2289	4576
	>= 1 months	2181	2191	4372
	>= 3 months	2077	2066	4143
	>= 6 months	2048	2031	4079
	>= 12 months	1813	1798	3611
	>= 24 months	1546	1523	3069
	>= 36 months	1083	1050	2133
	>= 48 months	0	0	0
	Patient years	5513.3	5420.1	10933.4

The median exposure to the investigational product in the total population was 35.0 months in the placebo group and 34.5 months in the candesartan group.

In the total CHARM-Program population, 3,052 (80.3%) patients in the candesartan group started treatment on 4 mg once daily and 751 (19.7%) patients started on 8 mg once daily at randomization (baseline). Among patients still on the investigational product at 6 months (visit 5), (3,233 patients or 88.9% in the candesartan group and 3,301 patients 92.6% in the placebo group), 62.6% of the candesartan patients were treated with the target dose 32 mg once daily. The mean dose in the candesartan group was 24.0 mg at 6 months. At the end of treatment (LVCF) 62.3% of those still treated with candesartan (2,769, 73.1%) received 32 mg of candesartan once daily. The mean candesartan LVCF dose was 23.9 mg.

Literature

The medical literature reviewed (References, section 10) did not reveal reports of unexpected organ-specific toxicity. In this review, I have presented, with tables and figures where necessary, and discussed the information from the medical literature in the context of the data from the CHARM-Added and CHARM-Pooled Studies under each heading in the safety review template.

Additional submissions, including safety update

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

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

This section summarizes AEs of special interest relevant to blockade of RAAS in the treatment of CHF by using AT_1-receptor blockers (ARBs) and ACE inhibitors. These AEs of special interest include hypotension, abnormal renal function or worsening of renal function, hyperkalemia, angioedema and myocardial ischemia. In addition, a brief description of abnormal hepatic function and neoplasms reported in the safety report is presented.

Hypotensive events

'Hypotension' as an adverse clinical event include a composite of the following AAED preferred terms: hypotension; hypotension, postural; dizziness/vertigo; syncope; circulatory failure; and collapse, not otherwise specified (NOS). For this composite AE, patients with multiple events including any of the selected AE terms were counted only once.

At baseline, there were slightly more patients in the candesartan treatment group with SBP < 100 mmHg (placebo 92, 2.4%; candesartan 126, 3.3%) (North American study population).

AEs suggesting a 'hypotensive' event were reported more frequently in the candesartan group (875, 23.0%) than in the placebo group (519, 13.7%) for patients than on treatment with the investigational product (Table 276).

Table 276 Number (%) of patients with any of the preferred terms hypotension, hypotension postural, dizziness/vertigo, syncope, circulatory failure or collapse not otherwise specified (NOS). ITT/Safety population (SH-AHS-0003, -0006, -0007)

Placebo on treatment (N=3796)	Cand. cil. on treatment (N=3803)	Placebo during study (N=3796)	Cand. cil. during study (N=3803)
519 (13.7)	875 (23.0)	560 (14.8)	914 (24.1)

The individual AE term contributing the largest numbers to this composite AE was hypotension, which was reported for 372 (9.8%) patients given placebo and 714 (18.8%) patients given candesartan (Table 277).

Table 277 Number (%) of patients with symptomatic CHF with the most commonly reported[a] AEs, sorted by descending frequency in the total population during study. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Preferred term	Placebo on treatment (N=3796)		Cand. cil. on treatment (N=3803)		Placebo during study (N=3796)		Cand. cil. during study (N=3803)	
	N	(%)	N	(%)	N	(%)	N	(%)
Cardiac failure/cardiac failure aggravated[b]	1073	(28.3)	831	(21.9)	1187	(31.3)	1001	(26.3)
Hypotension	372	(9.8)	714	(18.8)	399	(10.5)	736	(19.4)
Angina pectoris/angina pectoris aggravated[b]	461	(12.1)	414	(10.9)	506	(13.3)	490	(12.9)
Renal function abnormal/renal dysfunction aggravated[b]	238	(6.3)	474	(12.5)	248	(6.5)	487	(12.8)
Sudden death	282	(7.4)	234	(6.2)	348	(9.2)	291	(7.7)
Pneumonia	243	(6.4)	200	(5.3)	299	(7.9)	261	(6.9)
Myocardial infarction	216	(5.7)	205	(5.4)	257	(6.8)	242	(6.4)
Fibrillation atrial	218	(5.7)	165	(4.3)	249	(6.6)	202	(5.3)
Arrhythmia ventricular	207	(5.5)	159	(4.2)	239	(6.3)	193	(5.1)
Cerebrovascular disorder	189	(5.0)	164	(4.3)	216	(5.7)	203	(5.3)
Coronary artery disorder	170	(4.5)	169	(4.4)	200	(5.3)	205	(5.4)
Chest pain	177	(4.7)	154	(4.0)	202	(5.3)	183	(4.8)
Arrhythmia atrial	175	(4.6)	156	(4.1)	197	(5.2)	187	(4.9)
Hyperkalaemia	78	(2.1)	238	(6.3)	84	(2.2)	242	(6.4)
Tachycardia supraventricular	152	(4.0)	129	(3.4)	177	(4.7)	148	(3.9)
Dizziness/vertigo[b]	107	(2.8)	154	(4.0)	115	(3.0)	168	(4.4)
Accident and/or injury	112	(3.0)	99	(2.6)	143	(3.8)	125	(3.3)
Tachycardia ventricular/arrhythmia/arrhythmia aggravated[b]	110	(2.9)	100	(2.6)	132	(3.5)	128	(3.4)
Syncope	105	(2.8)	121	(3.2)	119	(3.1)	139	(3.7)
Anaemia	87	(2.3)	110	(2.9)	110	(2.9)	145	(3.8)

a This table uses a cut-off of ≥3.0% in the total population during study (N=7599).
b Patients having both or all events are counted once only.

A fatal hypotensive event was reported in a comparable proportion of patients in each treatment group (Table 278). In both treatment groups, hypotensive events that led to death were reported in association with other causes of death; notably in the candesartan patients, associated events included electromechanical dissociation, ventricular tachycardia and gastrointestinal bleeding, and were thus assessed by the investigators as unlikely related to the investigational product.

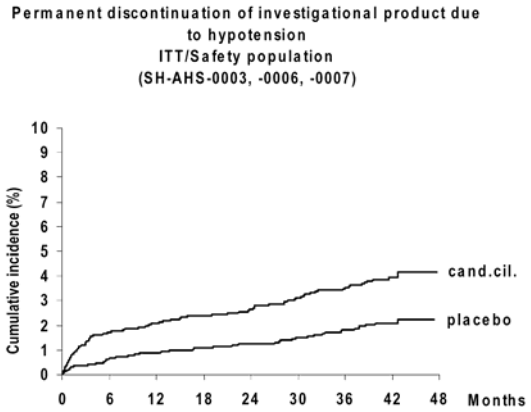
Table 278 Number (%) of patients with fatal preferred terms hypotension, hypotension postural, dizziness/ vertigo, syncope, circulatory failure or collapse not otherwise specified (NOS). ITT/ Safety population (SH-AHS-0003, -0006, -0007)

Placebo on treatment (N=3796)	Cand.cil on treatment (N =3803)	Placebo during study (N =3796)	Cand.cil during study (N =3803)
5 (0.1)	6 (0.2)	10 (0.3)	12 (0.3)

As noted in the descriptive analysis for the total population, the investigational product was discontinued for hypotension in 76 (2.0%) placebo patients and 155 (4.1%) candesartan patients (Table 250). Corresponding figures for the exploratory analysis were 66 (1.7%) placebo patients and 132 (3.5%) candesartan patients (Table 253). The higher proportion of permanent discontinuation of the investigational product due to hypotensive events in the candesartan group could not be explained by higher use of concomitant medication when the event started,

including diuretics, β-blockers and ACE-inhibitors. Among the patients that discontinued the investigational product due to hypotensive events, a greater proportion had SBP < 100 mmHg at baseline in the candesartan group (placebo, 7.5%; candesartan, 13.6%).

In patients aged < 75 years, discontinuation because of hypotension was reported in 48 (1.6%) patients in the placebo group and 111 (3.8%) patients on candesartan. For patients aged ≥ 75 years the discontinuation rates were 28 (3.2%) patients in the placebo group and 44 (5.2%) patients in the candesartan group. Permanent discontinuation of the investigational product due to hypotension was reported in 56 (2.2%) males and 20 (1.6%) females in the placebo group, and 107 (4.1%) males and 48 (4.0%) females in the candesartan treatment group.



Number at risk					
Placebo	3796	3440	3139	2129	732
Cand.cil.	3803	3497	3202	2157	738

Figure 124 Cumulative incidence (%) of permanent discontinuation of the investigational product due to hypotension. ITT/Safety population

Although patients in both treatment groups discontinued taking the investigational product because of hypotension over the entire study period, the candesartan discontinuation rate shown in the exploratory analysis, was greatest during the first 6 to 12 months of treatment (Figure 124).

Among the 1,075 (28.3%) placebo patients and 1,088 (28.6%) candesartan patients entering the study with a history of diabetes, investigational product discontinuation for hypotension was noted for 22 (2.0%) placebo patients and 34 (3.1%) candesartan patients.

Abnormal renal function

To summarize abnormal renal function, the following AAED preferred terms were selected and analyzed as a single composite event: renal function, abnormal/renal dysfunction, aggravated; renal failure acute; renal failure, NOS; uremia; non-protein nitrogen, increased; renal failure, aggravated; blood urea nitrogen, increased; increased creatinine, acute pre-renal failure and anuria. For this composite AE, patients with multiple events of any of the selected AE terms were counted only once.

At baseline, there were more patients in the candesartan group with serum creatinine > 2.0 mg/ dl (placebo 70, 5.2%; candesartan 84, 6.3%) (North American study population).

AEs suggesting 'abnormal renal function' occurred in 349 (9.2%) in the placebo group and 576 (15.1%) patients in the candesartan group during study (Table 279).

Table 279 Number (%) of patients with any of the preferred terms renal function abnormal/renal dysfunction aggravated, renal failure acute, renal failure NOS, uremia, non-protein nitrogen increased, renal failure aggravated, blood urea nitrogen increased, acute pre-renal failure or anuria. ITT/Safety population (SH-AHS-0003, -0006 and -0007)

Placebo on treatment (N=3796)	Cand. cil. on treatment (N=3803)	Placebo during study (N=3796)	Cand. cil. during study (N=3803)
316 (8.3)	546 (14.4)	349 (9.2)	576 (15.1)

The AE terms that predominately contributed to this composite AE term was renal function abnormal which was reported in 247 (6.5%) of patients given placebo and 485 (12.8%) given candesartan during study. Renal failure, acute (placebo, 91 patients, 2.4%; candesartan, 121 patients, 3.2%) and uremia (placebo, 28 patients, 0.7%; candesartan, 43 patients, 1.1%) were also numerically more frequently in patients given active treatment.

Table 280 Number (%) of patients with fatal renal function, abnormal/renal dysfunction, aggravated, renal failure acute, renal failure, NOS, uremia, non-protein nitrogen increased, renal failure aggravated, blood urea nitrogen increased, acute pre-renal failure or anuria. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Placebo on treatment (N=3796)	Cand.cil on treatment (N=3803)	Placebo during study (N=3796)	Cand.cil during study (N=3803)
18 (0.5)	7 (0.2)	41 (1.1)	36 (0.9)

Fatal renal function events 'during study' and 'on treatment' were reported for a higher proportion of patients in the placebo group (Table 280). In both treatment groups, the majority of renal events that led to death were reported in association with other causes of death such as worsening heart failure.

In the descriptive safety analysis, renal function abnormal/renal dysfunction aggravated was the second most common reason for permanent discontinuation of the investigational product (second only to cardiac failure aggravated,) in both treatment groups (placebo 110, 2.9%; candesartan 238, 6.3%) (Table 250). In the exploratory analysis the term increased creatinine was reported for 115 (3.0%) placebo patients and 234 (6.2%) candesartan patients (Table 253). The higher discontinuation rate for 'abnormal renal function' in the candesartan group could not be explained by between-treatment differences in concomitant medications when the event started or baseline serum creatinine levels (North American study population) (Table 281).

Table 281 Permanent discontinuation due to pooled adverse events related to abnormal renal function[a] or hypotensive events[b] or hyperkalemia[c] on treatment with candesartan cilexetil or placebo. Specified concomitant medication at the start of the event. ITT/safety population (SH-AHS-0003, -0006, -0007)[d]

	Placebo Abn renal N=126		Cand cil Abn renal N=266		Placebo Hypotensive N=93		Cand cil Hypotensive N=188		Placebo Hyperkalae N=22		Cand cil Hyperkalae N=93	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Loop diuretics	117	(92.9)	258	(97.0)	83	(89.2)	169	(89.9)	20	(90.9)	84	(90.3)
Potassium - sparing diuretics	59	(46.8)	105	(39.5)	29	(31.2)	80	(42.6)	10	(45.5)	34	(36.6)
Thiazide diuretics	22	(17.5)	52	(19.5)	22	(23.7)	35	(18.6)	3	(13.6)	11	(11.8)
Any β-blocker	72	(57.1)	146	(54.9)	54	(58.1)	93	(49.5)	13	(59.1)	54	(58.1)
Calcium channel blocker	36	(28.6)	67	(25.2)	11	(11.8)	29	(15.4)	1	(4.5)	23	(24.7)
Any ACE-inhibitor	79	(62.7)	141	(53.0)	63	(67.7)	88	(46.8)	18	(81.8)	59	(63.4)

a Preferred terms included in abnormal renal function: Renal function abnormal/renal dysfunction aggravated, renal failure acute, renal failure nos, uraemia, non-protein nitrogen increased, renal failure aggravated, acute pre-renal failure or anuria.
b Preferred terms included in hypotensive events: Hypotension, hypotension postural, dizziness/vertigo, syncope, circulatory failure or collapse not otherwise specified (nos).
c Hyperkalaemia is a single Preferred term.
d Exploratory safety analysis

In patients aged younger than 75 years, discontinuation because renal function abnormal/renal dysfunction aggravated was reported in 75 (2.6%) patients in the placebo group and 171 (5.8%) patients in the candesartan group on treatment with the investigational product. For patients aged 75 years or older the discontinuation rates were 35 (4.0%) patients in the placebo group and 67 (7.9%) patients in the candesartan group. In the placebo group the majority of events were seen in male patients (81, 3.1%) compared to 29 (2.4%) female patients. Corresponding values for the candesartan treatment group were 169 (6.5%) males and 69 (5.8%) females. The majority of patients in both treatment groups were Caucasians.

As shown in the exploratory analysis, patients discontinued study treatment because of 'increased creatinine' over the entire study period, and the rate was greater for candesartan-treated patients (Figure 125).

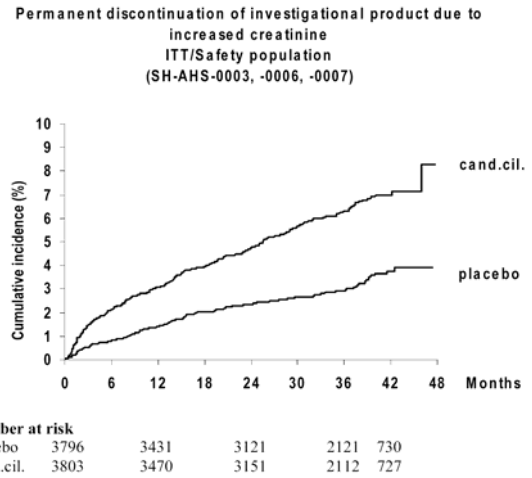


Figure 125 Cumulative incidence (%) of permanent discontinuation of the investigational product due to increased creatinine. ITT/Safety population

Among the 1,075 (28.3%) placebo patients and 1,088 (28.6%) candesartan patients entering the CHARM program study with a history of diabetes, investigational product discontinuation for increased creatinine was noted for 57 (5.3%) placebo and 99 (9.1%) candesartan patients (Table 257 and Table 258). Compared to the total population (placebo 3.0%, candesartan 6.2%) (Table 253), diabetic patients were slightly more likely to discontinue the investigational product for increased creatinine levels.

Hyperkalemia

Hyperkalemia is reported as observed 'on treatment' rather than 'during study' to present a more clinically meaningful measure of possible relationship to the investigational product.

At baseline, there were more patients in the candesartan treatment group with serum potassium = 5 mmol/L (placebo 125, 9.3%; candesartan 135, 10.1%) (North American study population).

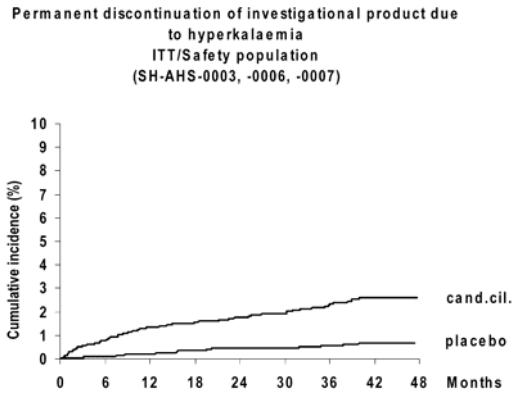
Hyperkalemia was reported for 78 patients (2.1%) in the placebo group and 238 patients (6.3%) in the candesartan group on treatment with the investigational product (Table 262).

Fatal hyperkalemia 'during study' was reported for 2 patients in the candesartan group, and in 1 patient in the placebo group. Both candesartan treated patients were on active treatment in SH-AHS-0006 as described above. The one patient in the placebo group in SH-AHS-0003 was not on treatment with the investigational product and had concomitant renal failure (with an increase in serum creatinine) which could have contributed to the hyperkalemia.

In Table 250, discontinuation of the investigational product because of hyperkalemia occurred more frequently in patients treated with candesartan (placebo 22, 0.6%; candesartan 93, 2.4%). In the exploratory analysis the corresponding numbers were 21 (0.6%) for placebo patients and 85 (2.2%) for candesartan patients (Table 253). The higher rate for hyperkalemia causing discontinuation in the candesartan group could not be explained by between treatment differences in concomitant medications at the start of the event, including potassium – sparing diuretics or baseline serum potassium levels (North American study population) (Table 281).

In patients aged younger than 75 years, discontinuation because of the AE term hyperkalemia was reported in 14 (0.5%) patients in the placebo group and 57 (1.9%) patients on candesartan. For patients aged 75 years or older the discontinuation rates were 8 (0.9%) patients in the placebo group and 36 (4.2%) patients in the candesartan group. In the placebo treatment group 16 (0.6%) males and 6 (0.5%) females discontinued due to hyperkalemia. In the candesartan group the majority of events were seen in male patients (72, 2.8%) compared to female patients (21, 1.8%).

The discontinuation rate for candesartan-treated patients because of hyperkalemia, presented from exploratory analysis, (Figure 126), was somewhat greater during the first 6 to 12 months of treatment, but discontinuations still occurred over the entire study period.



Number at risk					
Placebo	3796	3459	3159	2154	742
Cand.cil.	3803	3520	3223	2171	741

Figure 126 Cumulative incidence (%) of permanent discontinuation of the investigational product due to hyperkalemia. ITT/ Safety population

Among the 1,075 (28.3%) placebo patients and 1,088 (28.6%) candesartan patients entering the CHARM program with a history of diabetes, investigational product discontinuation for the specific preferred term hyperkalemia was noted for 13 (1.2%) placebo and 31 (2.8%) candesartan patients (Table 257 and Table 258).

Angioedema

During study 5 cases of angioedema were reported for patients in the candesartan group compared with 3 cases in the placebo treatment group.

All patients in the candesartan treatment group were Caucasian. Three of these patients in the candesartan group had a history of previous angioedema reactions while taking ACE-inhibitors. The remaining two patients in the candesartan group had concomitant medication with an ACE-inhibitor at the start of the event. None of the events was considered life threatening or led to hospitalization. Two patients who developed angioedema required discontinuation of candesartan treatment. For the remaining 3 patients with angioedema, candesartan treatment continued without recurrence of angioedema, and for 1 of these the dose was reduced.

Myocardial ischemia

'Myocardial ischemia' was evaluated as a composite of the AAED preferred terms: angina pectoris/angina pectoris aggravated, MI and coronary artery disorder. For this composite AE, patients with multiple events including any of the selected AE terms were counted only once.

At baseline prior to enrollment, there were no differences between the treatment groups in the frequencies of patients with previous MI and angina pectoris. Slightly more patients in the candesartan treatment group reported a history of coronary artery bypass grafting (placebo 870, 22.9%; candesartan 921, 24.2%).

The proportions of patients with 'myocardial ischemia' 'on treatment' were approximately equal

in the two groups (18.1% in the placebo vs. 16.7% in the candesartan group) (Table 282).

Table 282 Number (%) of patients with any of the preferred terms angina pectoris/angina pectoris aggravated, myocardial infarction or coronary artery disorder. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Placebo on treatment (N=3796)	Cand. cil. on treatment (N=3803)	Placebo during study (N=3796)	Cand. cil. during study (N=3803)
688 (18.1)	637 (16.7)	774 (20.4)	755 (19.9)

The AE term accounting for the greatest number of patients in this composite AE was angina pectoris which was more frequently reported in the placebo treatment group (placebo 460, 12.1%; candesartan 405, 10.6%). The AE term MI occurred in 216 (5.7%) patients in the placebo group and in 205 (5.4%) in the candesartan group 'on treatment.'

'Myocardial ischemic' events that were fatal were reported for 70 (1.8%) patients in the placebo group and 97 (2.6%) patients in the candesartan group during study (Table 283).

Table 283 Number (%) of patients with any of the preferred terms angina pectoris/angina pectoris aggravated, myocardial infarction or coronary artery disorder leading to death. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Placebo on treatment (N=3796)	Cand. cil. on treatment (N=3803)	Placebo during study (N=3796)	Cand. cil. during study (N=3803)
44 (1.2)	66 (1.7)	70 (1.8)	97 (2.6)

Most of the fatal 'myocardial ischemic' events 'during study' were attributed to fatal MI (57 patients in the placebo group and 77 in the candesartan group).

Abnormal hepatic function

The most common AE terms suggesting liver dysfunction were hepatic enzymes, increased NOS and hepatic function, abnormal; which were reported for 7 and 4 patients, respectively, given placebo treatment and 12 and 10 patients, respectively, given candesartan. The AE term hepatic failure was reported for 5 patients in the placebo group and 6 patients in the candesartan group.

In the candesartan group there was one fatal case of hepatic necrosis which the investigator and the sponsor considered related to amiodarone (SH-AHS-0003-373-15108), and one fatal case of cholestatic hepatitis considered related to septic cholangitis (SH-AHS-0003-1476-21109).

Neoplasms

AEs indicative of neoplasms, whether benign or malignant, were pooled from the SOC (system organ class) 'Neoplasms', plus 3 neoplastic AE terms from other SOCs (Melanoma malignant, Myelomatosis multiple and Pleural mesothelioma).

In the total population slightly more patients in the candesartan treatment group had a history of cancer at baseline (placebo 243, 6.4%, candesartan 270, 7.1%).

Neoplasms were reported for 230 (6.0%) in the placebo group and 244 (6.4%) in the candesartan group. One patient in the placebo group in the component study SH-AHS-0003 (Site 558, Patient number 13436) had Breast neoplasm malignant female and Carcinomatosis (included in the SOC Neoplasms) together with Pleural mesothelioma. One patient in the candesartan group in the component study SH-AHS-0006 (Site 1532, Patient number 21520) had both Myeloid metaplasia (included in the SOC Neoplasms) and Myelomatosis multiple. In the total numbers presented above these patients are counted only once. Neoplasms proved fatal for 59 patients (1.8%) in the placebo group and 84 patients (2.2%) in the candesartan group.

The majority of reported neoplasms were malignant. The most common neoplasm's were prostatic carcinoma (placebo, 27 patients; candesartan, 32 patients), pulmonary carcinoma (placebo, 25 patients; candesartan, 31 patients), colon carcinoma (placebo, 24 patients; candesartan, 26 patients) and breast neoplasm malignant (17 patients in each group). The AE term 'gastrointestinal neoplasm benign' had a higher event rate in the candesartan group during study (placebo, 5; candesartan, 19) whereas 'renal carcinoma' was more frequent in the control group (placebo, 11; candesartan, 5).

Rare Adverse events in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

Rare adverse events reported include:
- pancytopenia (placebo 1 patient; candesartan 3 patients),
- aplastic anemia (candesartan 1 patient),
- anaphylactic shock and anaphylactoid reaction (placebo 1 patient; candesartan 2 patients),
- Stevens- Johnson syndrome (placebo 2 patients),
- rhabdomyolysis (placebo 2 patients; candesartan 3 patients),
- sarcoidosis (candesartan 2 patients), and
- scleroderma (candesartan 1 patient).

In most cases an alternative cause was identified. There was no sufficient evidence to support a causal relationship to the investigational product.

Summary of Safety

Summary of safety for CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies

Summary of safety in the total population of patients with symptomatic CHF (SH-AHS-0003, 0006, 0007)

In the total population of patients with symptomatic CHF (SH-AHS-0003, SH-AHS-0006, SH-AHS-0007) AEs were reported for almost equal proportions of patients in the two treatment groups, both during treatment with the investigational drug (placebo 2732, 72.0%; candesartan 2788, 73.3%) and over the entire study period (placebo 2799, 73.7%; candesartan 2841, 74.7%).

SAEs, fatal and non-fatal, occurred less frequently on treatment with candesartan than with placebo (placebo 67.5%; candesartan 63.4%) as well as during the study, whether on or off treatment (placebo 71.1%; candesartan 69.0%). Fatal SAEs were also less common on treatment with candesartan (placebo 16.2%; candesartan 13.3%) as well as during the study (placebo 24.9%; candesartan 23.3%). The most common fatal SAEs were CV events which occurred less frequently in the candesartan treatment group during study (placebo 20.3%; candesartan 18.2%)

16.1% in the placebo group and 21.0% of the patients in the candesartan group permanently discontinued the investigational product due to an AE or an abnormal laboratory finding.

8.5% of the patients receiving placebo and 15.0% of the patients receiving candesartan required a reduction in the investigational product dose.

Discontinuations and dose reductions attributed to decline in renal function, hypotension and hyperkalemia were more frequent in the candesartan group. Cardiac failure aggravated (placebo 4.9%; candesartan 4.3%), abnormal renal function (placebo 2.9%; candesartan 6.3%), hypotension (placebo 2.0%; candesartan 4.1%) and hyperkalemia (placebo 0.6%; candesartan 2.4%) were the most commonly reported AEs associated with discontinuation of the investigational product.

The differences in mean laboratory values (candesartan compared with placebo), and the frequency of abnormal values were within expected findings for treatment with inhibitors of the RAAS, i.e., slightly higher serum potassium and creatinine levels.

Mean blood pressure from baseline to LVCF (SBP and DBP) was lowered in both treatment groups.

Mean body weight was slightly decreased in the placebo group and increased in the candesartan group.

<u>Summary of safety in the population of patients with depressed LV systolic function (SH-AHS 0003, 0006)</u>

The safety findings in the subpopulation of patients with depressed LV systolic function (SHAHS-0003, SH-AHS-0006) were similar to those in the total population, although the absolute AE rate in the patients with depressed LV systolic function were somewhat higher than in the total population. Between-treatment differences (candesartan versus placebo) were very similar to those noted for the total population.

AEs were reported for approximately equal numbers of patients in the two treatment groups (placebo 76.0%; candesartan 77.2%), over the entire study period.

SAEs, fatal and non-fatal, occurred less frequently with candesartan treatment (placebo 70.2%; candesartan 65.8%). Fatal SAEs were also less common with candesartan treatment (placebo 20.2%; candesartan 16.4%). The most common fatal SAEs were CV events.

18.4% in the placebo group and 23.2%of the patients in the candesartan group permanently discontinued treatment with the investigational product due to an AE or an abnormal laboratory finding.

Discontinuations and dose reductions attributed to decline in renal function, hypotension and hyperkalemia were more frequent in the candesartan group. Abnormal renal function (placebo, 3.4%; candesartan, 7.4%), hypotension (placebo, 2.5%; candesartan, 5.0%) and hyperkalemia (placebo, 0.6%; candesartan, 3.1%) were the most commonly reported AEs associated with discontinuation of the investigational product. In the candesartan group the frequency of discontinuation for hyperkalemia relative to placebo was greater in the oldest age groups.

The following findings are significantly different between the two treatment groups:

- Candesartan reduced *time* to permanent discontinuation of investigational product due to any cause ($p < 0.001$).
- Candesartan increased the *number* of investigational product discontinuations due to any cause ($p < 0.001$).
- Candesartan reduced *time* to permanent discontinuation of investigational product due to an AE or an abnormal laboratory value ($p < 0.001$).
- Candesartan increased the *number* of permanent investigational product discontinuations due to an AE or an abnormal laboratory value ($p < 0.001$).
- Candesartan increased the *number* of dose reductions due to any cause ($p < 0.001$).
- Candesartan increased the *number* of dose reductions due to an AE or an abnormal laboratory value ($p < 0.001$).

Thus, candesartan appears to be safe and well tolerated. Discontinuations and dose reductions attributed to a decline in renal function, hypotension and hyperkalemia occur more frequently with candesartan than placebo. The AE profile of candesartan in heart failure patients is consistent with the pharmacology of the drug and the health status of the patients.

Overall conclusions

Candesartan appears to be safe and well tolerated in this population of patients with chronic heart failure. Discontinuations and dose reductions attributed to a decline in renal function, hypotension and hyperkalemia occur more frequently with candesartan than placebo. The AE profile of candesartan in heart failure patients is consistent with the pharmacology of the drug and the health status of the patients.

10.2 Line-by-Line Labeling Review

NDA 20-838

The prescribing information has been updated to include information for the heart failure supplemental New Drug Application.

Additions are indication by double underlining and deletions are indicated by ~~strikethrough~~.

Reviewer's annotations are in italics, with shaded background, and additions are also wriggly underlined.

XXXXX-XX

ATACAND®
(candesartan cilexetil)
TABLETS

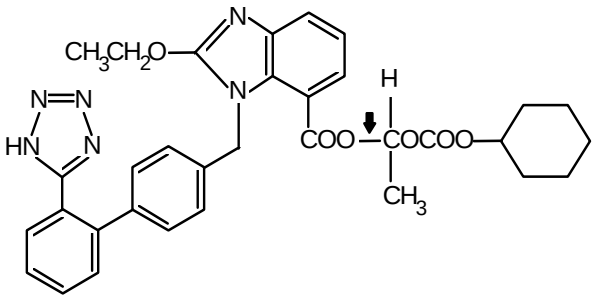
USE IN PREGNANCY-
When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, ATACAND should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

ATACAND® (candesartan cilexetil), a prodrug, is hydrolyzed to candesartan during absorption from the gastrointestinal tract. Candesartan is a selective AT_1 subtype angiotensin II receptor antagonist.

Candesartan cilexetil, a nonpeptide, is chemically described as (±)-1-Hydroxyethyl 2-ethoxy-1-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]-7-benzimidazolecarboxylate, cyclohexyl carbonate (ester).

Its empirical formula is $C_{33}H_{34}N_6O_6$, and its structural formula is



site of ester hydrolysis.

Candesartan cilexetil is a white to off-white powder with a molecular weight of 610.67. It is practically insoluble in water and sparingly soluble in methanol. Candesartan cilexetil is a racemic mixture containing one chiral center at the cyclohexyloxycarbonyloxy ethyl ester group. Following oral administration, candesartan cilexetil undergoes hydrolysis at the ester link to form the active drug, candesartan, which is achiral.

ATACAND is available for oral use as tablets containing either 4 mg, 8 mg, 16 mg, or 32 mg of candesartan cilexetil and the following inactive ingredients: hydroxypropyl cellulose, polyethylene glycol, lactose, corn starch, carboxymethylcellulose calcium, and magnesium stearate. Ferric oxide (reddish brown) is added to the 8-mg, 16-mg, and 32-mg tablets as a colorant.

CLINICAL PHARMACOLOGY

Mechanism of Action

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Candesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is, therefore, independent of the pathways for angiotensin II synthesis.

There is also an AT_2 receptor found in many tissues, but AT_2 is not known to be associated with cardiovascular homeostasis. Candesartan has much greater affinity (>10,000-fold) for the AT_1 receptor than for the AT_2 receptor.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because candesartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Candesartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of candesartan on blood pressure.

Pharmacokinetics

General

Candesartan cilexetil is rapidly and completely bioactivated by ester hydrolysis during absorption from the gastrointestinal tract to candesartan, a selective AT_1 subtype angiotensin II receptor antagonist. Candesartan is mainly excreted unchanged in urine and feces (via bile). It undergoes minor hepatic metabolism by O-deethylation to an inactive metabolite. The elimination half-life of candesartan is approximately 9 hours. After single and repeated administration, the pharmacokinetics of candesartan are linear for oral doses up to 32 mg of candesartan cilexetil. Candesartan and its inactive metabolite do not accumulate in serum upon repeated once-daily dosing.

Following administration of candesartan cilexetil, the absolute bioavailability of candesartan was estimated to be 15%. After tablet ingestion, the peak serum concentration (C_{max}) is reached after 3 to 4 hours. Food with a high fat content does not affect the bioavailability of candesartan after candesartan cilexetil administration.

Metabolism and Excretion

Total plasma clearance of candesartan is 0.37 mL/min/kg, with a renal clearance of 0.19 mL/min/kg. When candesartan is administered orally, about 26% of the dose is excreted unchanged in urine. Following an oral dose of ^{14}C-labeled

candesartan cilexetil, approximately 33% of radioactivity is recovered in urine and approximately 67% in feces. Following an intravenous dose of ^{14}C-labeled candesartan, approximately 59% of radioactivity is recovered in urine and approximately 36% in feces. Biliary excretion contributes to the elimination of candesartan.

Distribution

The volume of distribution of candesartan is 0.13 L/kg. Candesartan is highly bound to plasma proteins (>99%) and does not penetrate red blood cells. The protein binding is constant at candesartan plasma concentrations well above the range achieved with recommended doses. In rats, it has been demonstrated that candesartan crosses the blood-brain barrier poorly, if at all. It has also been demonstrated in rats that candesartan passes across the placental barrier and is distributed in the fetus.

Special Populations

Pediatric — The pharmacokinetics of candesartan cilexetil have not been investigated in patients <18 years of age.

Geriatric and Gender— The pharmacokinetics of candesartan have been studied in the elderly (≥ 65 years) and in both sexes. The plasma concentration of candesartan was higher in the elderly (C_{max} was approximately 50% higher, and AUC was approximately 80% higher) compared to younger subjects administered the same dose. The pharmacokinetics of candesartan were linear in the elderly, and candesartan and its inactive metabolite did not accumulate in the serum of these subjects upon repeated, once-daily administration. No initial dosage adjustment is necessary. (See DOSAGE AND ADMINISTRATION.) There is no difference in the pharmacokinetics of candesartan between male and female subjects.

Renal Insufficiency— In hypertensive patients with renal insufficiency, serum concentrations of candesartan were elevated. After repeated dosing, the AUC and C_{max} were approximately doubled in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73m^2) compared to patients with normal kidney function. The pharmacokinetics of candesartan in hypertensive patients undergoing hemodialysis are similar to those in hypertensive

patients with severe renal impairment. Candesartan cannot be removed by hemodialysis. No initial dosage adjustment is necessary in patients with renal insufficiency. (See DOSAGE AND ADMINISTRATION.)

Hepatic Insufficiency— The pharmacokinetics of candesartan were compared in patients with mild and moderate hepatic impairment to matched healthy volunteers following a single oral dose of 16 mg candesartan cilexetil. The increase in AUC for candesartan was 30% in patients with mild hepatic impairment (Child-Pugh A) and 145% in patients with moderate hepatic impairment (Child-Pugh B). The increase in C_{max} for candesartan was 56% in patients with mild hepatic impairment and 73% in patients with moderate hepatic impairment. The pharmacokinetics after candesartan cilexetil administration have not been investigated in patients with severe hepatic impairment. No initial dosage adjustment is necessary in patients with mild hepatic impairment. In hypertensive patients with moderate hepatic impairment, consideration should be given to initiation of ATACAND at a lower dose. (See DOSAGE AND ADMINISTRATION.)

Editorial

Heart Failure— The pharmacokinetics of candesartan were linear in patients with heart failure (NYHA class II and III) after candesartan cilexetil doses of 4, 8, and 16 mg. After repeated dosing, the AUC was approximately doubled in ~~these~~ patients *with heart failure > 65 years old* compared with healthy, younger subjects. (See DOSAGE AND ADMINISTRATION, Heart Failure).[1]

[1] Module 2, Clinical Summary: Summary of Clinical Pharmacology Studies, 2.7.2.3, Figures 1 and 2, Clinical Study Report EC002, 4.6.1 submitted in original NDA

Studies EC602, EC605-A and EC608 (reviewer's addition)

Drug Interactions

See PRECAUTIONS, Drug Interactions.

Pharmacodynamics

Candesartan inhibits the pressor effects of angiotensin II infusion in a dose-dependent manner. After 1 week of once daily dosing with 8 mg of candesartan cilexetil, the pressor effect was inhibited by approximately 90% at peak with approximately 50% inhibition persisting for 24 hours.

Plasma concentrations of angiotensin I and angiotensin II, and plasma renin activity (PRA), increased in a dose-dependent manner after single and repeated administration of candesartan cilexetil to healthy subjects, hypertensive, and heart failure patients.[2] ACE activity was not altered in healthy subjects after repeated candesartan cilexetil administration. The once-daily administration of up to 16 mg of candesartan cilexetil to healthy subjects did not influence plasma aldosterone concentrations, but a decrease in the plasma concentration of aldosterone was observed when 32 mg of candesartan cilexetil was administered to hypertensive patients. In spite of the effect of candesartan cilexetil on aldosterone secretion, very little effect on serum potassium was observed.

[2] Clinical Study Report EC604, 7.4.1 and Clinical Study Report EC605. 7.4.1.3

In multiple-dose studies with hypertensive patients, there were no clinically significant changes in metabolic function, including serum levels of total cholesterol, triglycerides, glucose, or uric acid. In a 12-week study of 161 patients with non-insulin-dependent (type 2) diabetes mellitus and hypertension, there was no change in the level of HbA_{1c}.

In heart failure patients, candesartan cilexetil administration at doses of 8 mg and 16 mg resulted in ~~dose related~~ significant decreases in systemic vascular resistance and pulmonary capillary wedge pressure.[3]

[3]Clinical Study Report EC605, 7.4.1.3 and Clinical Study Report EC604, 7.4.1

Studies: EC602 and EC605

In heart failure patients, candesartan cilexetil 8 mg in combination with enalapril 20 mg resulted in a ~~dose related~~ significant decrease in left ventricular end systolic volume compared with enalapril 20 mg alone.[4,5] Co-administration of metoprolol succinate (extended-release tablets) with candesartan cilexetil plus enalapril resulted in a decrease in left ventricular systolic volume and an increase in left ventricular ejection fraction compared with the combination of candesartan plus enalapril.[6]

[4]McKelvie RS, *Yusuf S, Pericak D,* et al. Circulation 1999; 100: 1056-64.

[5]Clinical study Report SH-AHS-0001,11.4.1.5 *(RESOLVD)*

[6]McKelvie RS, *Rouleau JL, White M,* et al. Eur Heart J 2003; 24:1727-34.

Reviewer's additions are based on data from the same above references.

Clinical Trials

Hypertension

The antihypertensive effects of ATACAND were examined in 14 placebo-controlled trials of 4- to 12-weeks duration, primarily at daily doses of 2 to 32 mg per day in patients with baseline diastolic blood pressures of 95 to 114 mm Hg. Most of the trials were of candesartan cilexetil as a single agent, but it was also studied as add-on to hydrochlorothiazide and

amlodipine. These studies included a total of 2350 patients randomized to one of several doses of candesartan cilexetil and 1027 to placebo. Except for a study in diabetics, all studies showed significant effects, generally dose related, of 2 to 32 mg on trough (24 hour) systolic and diastolic pressures compared to placebo, with doses of 8 to 32 mg giving effects of about 8-12/4-8 mm Hg. There were no exaggerated first-dose effects in these patients. Most of the antihypertensive effect was seen within 2 weeks of initial dosing and the full effect in 4 weeks. With once-daily dosing, blood pressure effect was maintained over 24 hours, with trough to peak ratios of blood pressure effect generally over 80%. Candesartan cilexetil had an additional blood pressure lowering effect when added to hydrochlorothiazide.

The antihypertensive effects of candesartan cilexetil and losartan potassium at their highest recommended doses administered once- daily were compared in two randomized, double-blind trials. In a total of 1268 patients with mild to moderate hypertension who were not receiving other antihypertensive therapy, candesartan cilexetil 32 mg lowered systolic and diastolic blood pressure by 2 to 3 mm Hg on average more than losartan potassium 100 mg, when measured at the time of either peak or trough effect. The antihypertensive effects of twice daily dosing of either candesartan cilexetil or losartan potassium were not studied.

The antihypertensive effect was similar in men and women and in patients older and younger than 65. Candesartan was effective in reducing blood pressure regardless of race, although the effect was somewhat less in blacks (usually a low-renin population). This has been generally true for angiotensin II antagonists and ACE inhibitors.

In long-term studies of up to 1 year, the antihypertensive effectiveness of candesartan cilexetil was maintained, and there was no rebound after abrupt withdrawal.

There were no changes in the heart rate of patients treated with candesartan cilexetil in controlled trials.

Heart Failure

Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity (CHARM) was an international (26

countries including the US) program comprised of 3 independent concurrent double-blind, placebo-controlled trials in which a total of 7601 patients (7599 with data) with NYHA class II - IV heart failure of at least 4 weeks duration, on standard baseline therapy, were randomized to ATACAND (titrated from 4 mg or 8 mg once daily, to a target dose of 32 mg once daily as tolerated) or matching placebo, and followed for at least 2 (up to 4) years. Patients with serum creatinine > 3 mg/dL, serum potassium > 5.5 mg/dL, symptomatic hypotension or known bilateral renal artery stenosis were to be excluded. Baseline characteristics of patients in the 3 CHARM trials are detailed in Table 1.[7]

[7]Module 2, Summary of Clinical Efficacy, 2.7.3.2.1

Table 1. CHARM: Baseline Characteristics[8]

	CHARM-Alternative	CHARM-Added	CHARM-Preserved
Number of patients	2028	2548	3023
Mean age (years)	67	64	67
Female (%)	32	21	40
NYHA class II (%)	48	24	61
III (%)	49	73	38
IV (%)	4	3	2
Mean LVEF (%)	30	28	54
Mean BP (mm Hg)	130/77	125/75	136/78
Medical history (%):			
Myocardial infarction	62	56	44
Hypertension	50	48	64
Diabetes	27	30	28
Atrial fibrillation	25	27	29
Concomitant therapy (%):			
ACE inhibitor	0	100	19
Diuretic	85	90	75
Digitalis	46	58	28
Beta-blocker	55	55	56
Spironolactone	24	17	12

[8]Module 2, Summary of Clinical Efficacy, 2.7.3.1 Table 4

The CHARM – Alternative trial included patients with LVEF ≤40% not receiving an ACE inhibitor due to prior intolerance; the CHARM – Added trial included patients with LVEF ≤40% receiving an ACE inhibitor (96% on an optimum individualized dose); and the CHARM – Preserved trial included patients with LVEF >40%. Most patients were on background diuretic therapy and about 55% on a beta-blocker in all 3 trials.[9]

[9]Module 2, Summary of Clinical Efficacy, 2.7.3.1.1.4 Table 2

The primary endpoint in each of the 3 trials, assessed as time to first event, was cardiovascular (CV) mortality or hospitalization for heart failure (defined as a hospital admission primarily for worsening of chronic heart failure [CHF], requiring intravenous diuretic and an overnight stay).[10] Secondary and other endpoints included other cardiovascular endpoints, as well as effects on NYHA functional class.[11] The initial dose of ATACAND was 4 mg for 80% of patients, the mean daily dose was 24 mg, and 63% of patients were titrated to the target dose of 32 mg once daily.[12] In the CHARM – Alternative trial, the most common reasons for previous ACE inhibitor intolerance (patients could report 1 or more reasons) were cough (n=1455, 72%), hypotension (n=262, 13%), abnormal renal function (n=234, 12%), and angioedema (n=83, 4%).[13]

[10]Module 2, Summary of Clinical Efficacy, 2.7.3.1.1.1

[11]Module 2, Summary of Clinical Efficacy, 2.7.3.1.1.1

[12]Module 2, Summary of Clinical Efficacy, 2.7.3.1.1.3

[13]Module 2, Summary of Clinical Efficacy, 2.7.4.2.1.5 Table 63

CHARM - Alternative Trial

In the CHARM – Alternative trial, the use of ATACAND over a median follow up of 34 months[14] resulted in a 23% (p <0.001) relative risk reduction in the primary endpoint of cardiovascular death or heart failure hospitalization, with each of the components contributing to this effect (Table 2).[15] Risk reductions in deaths attributed to worsening heart failure and sudden deaths both contributed to the effect on cardiovascular death. The use of ATACAND also resulted in a 32% relative risk reduction (hazard ratio 0.68, CI 0.57-0.81, p<0.001)[16] in CHF hospitalizations as a first event, and a reduction in the total number of investigator reported CHF hospitalizations (445 vs. 608, p<0.001).[17] Symptoms of heart failure as assessed by NYHA functional class were also significantly improved in patients treated with ATACAND (p=0.008).[18]

[14]Clinical Study Report SH-AHS-0003, 8.2

[15]Clinical Study Report SH-AHS-0003, 7.1

[16]Clinical Study Report SH-AHS-0003, 7.2.2

[17]Clinical Study Report SH-AHS-0003, 7.2.3.1

[18]Clinical Study Report SH-AHS-0003, 7.2.3.6

[19]Module 2, Summary of Clinical Efficacy, 2.7.3.3.2.1 Table 8 and Figure 4

Table 2. CHARM – Alternative: Primary Endpoint and its Components[19]

Endpoint (time to first event)	ATACAND (n=1013)	Placebo (n=1015)	Hazard Ratio (95% CI)	p-value (logrank)	Relative Risk Reduction
CV death or CHF hospitalization	334	406	0.77 (0.67-0.89)	<0.001	23%
CV death	219	252	0.85 (0.71-1.02)	0.072	15%
CHF hospitalization	207	286	0.68 (0.57-0.81)	<0.001	32%

CHARM - Added Trial

In the CHARM-Added trial, the use of ATACAND over a median follow up of 41 months[20] resulted in a 15% (p = 0.011) relative risk reduction in the primary endpoint of cardiovascular death or heart failure hospitalization with each of the components contributing to this effect (Table 3).[21] Risk reductions in deaths attributed to worsening heart failure and sudden deaths both contributed to the effect on cardiovascular death. This favourable effect in reducing cardiovascular mortality or CHF hospitalization was evident consistently in patients receiving ACE inhibitors at doses recommended for heart failure as well as in patients on lower doses. A beneficial effect on cardiovascular mortality or CHF hospitalization was also evident with concomitant use of an ACE inhibitor, a beta-blocker and ATACAND.[22] The use of ATACAND also resulted in a 17% relative risk reduction (hazard ratio 0.83, CI 0.71-0.97, p=0.014) for CHF hospitalizations as a first event,[23] and a reduction in the total number of investigator reported CHF hospitalizations (607 vs. 836, p=0.002).[24] Symptoms of heart failure as assessed by NYHA functional class were also significantly improved in patients treated with ATACAND (p=0.020).[25]

[20]Clinical Study Report SH-AHS-0006, 8.2

[21]Clinical Study Report SH-AHS-0006, 7.2.1.1

[22]Clinical Study Report SH-AHS-0006, 7.6.3 Figure 11

[23]Clinical Study Report SH-AHS-0006, 7.2.4.1 Table 54

[24] Module 2, Summary of Clinical Efficacy, 2.7.3.3.2.1 Table 10

[25] Module 2, Summary of Clinical Efficacy, 2.7.3.3.2.2 Table 17 and Figure 20

Table 3. CHARM – Added: Primary Endpoint and its Components[26]

Endpoint (time to first event)	ATACAND (n=1276)	Placebo (n=1272)	Hazard Ratio (95% CI)	p-value (logrank)	Relative Risk Reduction
CV death or CHF hospitalization	483	538	0.85 (0.75-0.96)	0.011	15%
CV death	302	347	0.84 (0.72-0.98)	0.029	16%
CHF hospitalization	309	356	0.83 (0.71-0.96)	0.013	17%

[26]Module 2, Summary of Clinical Efficacy, 2.7.3.3.2.1 Table 8 and Figure 5

CHARM: CHF with LV Systolic Dysfunction Trials—Pooled

In a prespecified analysis of the pooled results of the 4576[27] patients from the CHARM-Alternative and CHARM-Added trials (LVEF <40%), over a median follow up of 40 months,[28] ATACAND demonstrated a 12% relative risk reduction in all-cause mortality (hazard ratio 0.88 95% CI 0.79-0.98; p= 0.018).[29] This improvement in survival was attributable to a 16% relative risk reduction in cardiovascular deaths, (hazard ratio 0.84, CI 0.75-0.95, p=0.005). Risk reductions in heart failure deaths (24 %, hazard ratio 0.76, CI 0.62-0.93, p=0.008)[30] and sudden deaths (20%, hazard ratio 0.80, CI 0.67-0.95, p=0.013)[31] both contributed to this effect on cardiovascular death.[32] No effect was seen on cardiovascular deaths due to other causes or on non-cardiovascular deaths. The use of ATACAND also resulted in a 24% relative risk reduction in hospitalizations for heart failure as a first event (hazard ratio 0.76, CI 0.68-0.85, p<0.001),[33] and a reduction in the total number of investigator reported CHF hospitalizations (1052 vs. 1444, p<0.001).[34] Symptoms of heart failure as assessed by NYHA functional class were also improved (p<0.001).[35]

[27]Clinical Study Report SH-AHS-pooled, 6.2 Figure 3

[28]Clinical Study Report SH-AHS-pooled, 8.2

[29]Clinical Study Report SH-AHS-pooled, 7.2.1.2

[30]Clinical Study Report SH-AHS-pooled, 7.2.2 Table 30

[31]Clinical Study Report SH-AHS-pooled, 7.2.2 Table 30

[32]Clinical Study Report SH-AHS-pooled, 7.2.2 Table 30

[33]Clinical Study Report SH-AHS-pooled, 11.2.8.1 Table 134

[34]Module 2, Summary of Clinical Efficacy, 2.7.3.3.2.1 Table 10

[35]Module 2, Summary of Clinical Efficacy, 2.7.3.3.2.2 Table 17 and Figure 23

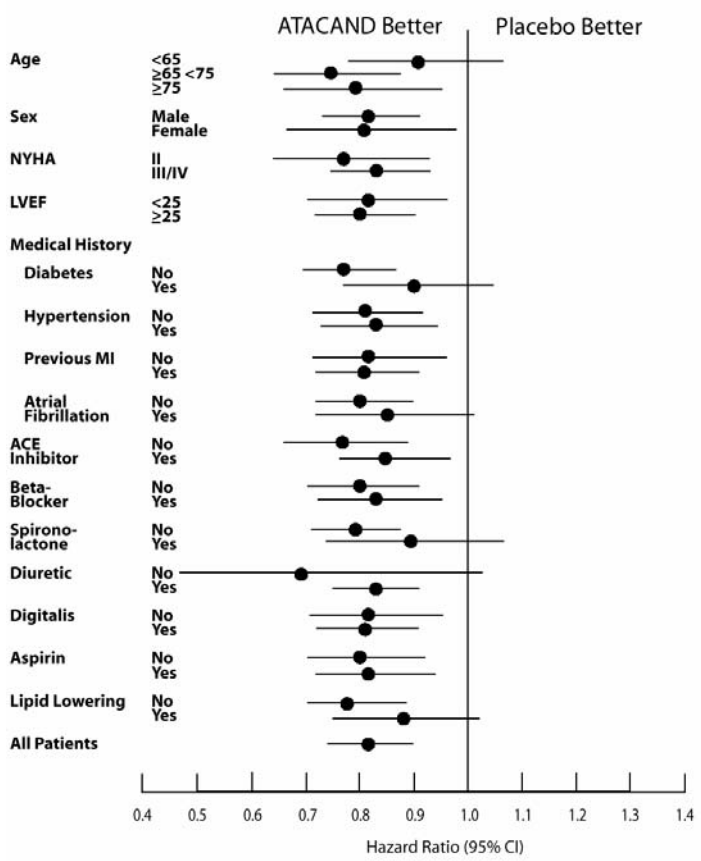
The benefits of ATACAND in reducing CV death or heart failure hospitalization (hazard ratio 0.82, CI 0.74-0.90, p<0.001) were evident in major subgroups and in patients on various combinations of other cardiovascular and heart failure treatments, including ACE inhibitors, beta-blockers, and spironolactone (see Figure 1).[36]

[36]Module 2, Summary of Clinical Efficacy, 2.7.3.3.3 Table 23

[37]Module 2, Summary of Clinical Efficacy, 2.7.3.3.3 Table 23

[38]Clinical Study Report SH-AHS-pooled, 12.1.9.4.126 and 12.1.9.4.172

Figure 1[37,38]



CHARM - Preserved

In the CHARM - Preserved trial, the use of ATACAND over a median follow up of 37 months[39] resulted in an 11% (non-significant, p = 0.118) relative risk reduction in the primary endpoint of cardiovascular death or heart failure hospitalization.[40] Although ATACAND had no apparent effect on cardiovascular mortality, there was a trend in reducing by 15% the relative risk for CHF hospitalizations as a first event (hazard ratio 0.85, CI 0.72-1.01, p=0.072, (Table 4),[41] and a

[39]Clinical Study Report SH-AHS-0007, 8.2

[40]Module 2, Summary of Clinical Efficacy, 2.7.3.3.2.1 Figure 5

[41]Module 2, Summary of Clinical Efficacy, 2.7.3.3.2.1 Table 8

[42]Module 2, Summary of Clinical Efficacy, 2.7.3.3.2.1 Table 10

reduction in total investigator reported heart failure hospitalizations (402 vs. 566, p= 0.013).[42]

Table 4. CHARM–Preserved: Primary Endpoint and its Components:[43]

Endpoint (time to first event)	ATACAND (n=1514)	Placebo (n=1509)	Hazard Ratio (95% CI)	p value (logrank)	Relative Risk Reduction
CV death or CHF hospitalization	333	366	0.89 (0.77-1.03)	0.118	11%
CV death	170	170	0.99 (0.80-1.22)	0.918	1%
CHF hospitalization	241	276	0.85 (0.72-1.01)	0.072	15%

[43]Module 2, Summary of Clinical Efficacy, 2.7.3.3.2.1 Table 8 and Figure 6

CHARM Overall Program—Three Component Trials-Pooled

In a prespecified analysis of the pooled data from the 3 component trials (n=7599),[44] treatment of a broad spectrum of heart failure patients with ATACAND over a median follow up of 38 months[45] resulted in a 9% relative risk reduction[46] (p=0.055) in all-cause death, attributable to a 12% (p = 0.011) relative risk reduction in cardiovascular deaths. No effect was seen on non-cardiovascular deaths.[47]

The beneficial effects of ATACAND on the composite endpoint of cardiovascular death or heart failure hospitalization, the primary endpoint of each of the 3 CHARM trials, were evident across all major subgroups regardless of age, race, sex, ejection fraction, medical history, and concomitant treatments (see Figure 2). The number of black patients in the CHARM program was relatively small (n=326),[48] but the benefits of ATACAND appeared to be consistent with the effects in the Caucasian population, both in the CHARM Overall program and in the component trials.[49]

[44]Clinical Study Report SH-AHS-pooled, 6.1

[45]Clinical Study Report SH-AHS-pooled, 8.2

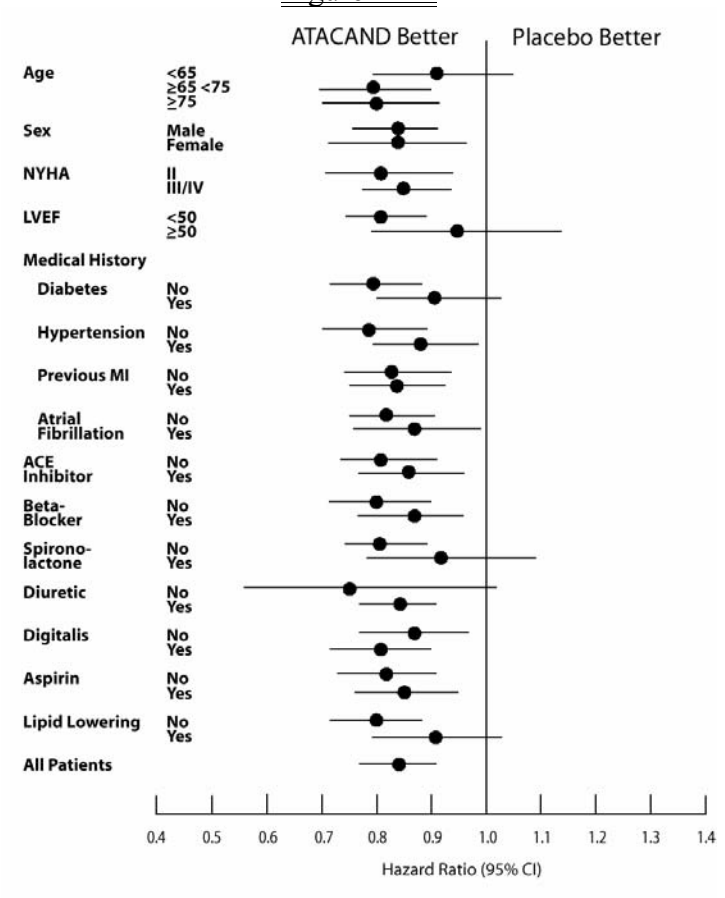
[46]Clinical Study Report SH-AHS-pooled, 7.1

[47]Module 2, Summary of Clinical Efficacy, 2.7.3.3.2.1 Table 11

[48]Clinical Study Report SH-AHS-pooled, 6.5 Table 16

[49]Module 2, Summary of Clinical Efficacy, 2.7.3.3.3 Table 23

Figure 2[50,51]



[50]Module 2, Summary of Clinical Efficacy, 2.7.3.3.3 Table 23

[51]Clinical Study Report SH-AHS-pooled, 6.5 Tables 12.1.9.4.40 and 12.1.9.4.86

INDICATIONS AND USAGE

Hypertension

ATACAND is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

Editorial

Heart Failure

ATACAND is indicated for the treatment of heart failure (NYHA class II-IV) *with left ventricular systolic dysfunction (ejection fraction ≤40%).* ATACAND reduces the risk of death from cardiovascular causes, ~~and~~ improves symptoms ~~*in patients with left ventricular systolic dysfunction,*~~ and reduces hospitalizations for heart failure in patients with depressed ~~*or preserved*~~ left ventricular systolic function. These effects occur in patients receiving other heart failure treatments with or without ACE inhibitors, including patients intolerant to ACE inhibitors, and with or without beta-blockers (see Clinical Trials).[52]

Per inclusion and exclusion criteria.

Benefits not found in patients with preserved left ventricular systolic function.

[52]Module 2, Clinical Overview, 2.5.4.3

CONTRAINDICATIONS

ATACAND is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS

Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin- converting enzyme inhibitors. Post-marketing experience has identified reports of fetal and neonatal toxicity in babies born to women treated with ATACAND during pregnancy. When pregnancy is detected, ATACAND should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of ATACAND as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, ATACAND should be discontinued unless it is considered life saving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

Oral doses ≥ 10 mg of candesartan cilexetil/kg/day administered to pregnant rats during late gestation and continued through lactation were associated with reduced survival and an increased incidence of hydronephrosis in the offspring. The 10-mg/kg/day dose in rats is approximately 2.8 times the maximum recommended daily human dose (MRHD) of 32 mg on a mg/m^2 basis (comparison assumes human body weight of 50 kg). Candesartan cilexetil given to pregnant rabbits at an oral dose of 3 mg/kg/day (approximately 1.7 times the MRHD on a mg/m^2 basis) caused maternal toxicity (decreased body weight and death) but, in surviving dams, had no adverse effects on fetal survival, fetal weight, or external, visceral, or skeletal development. No maternal toxicity or adverse effects on fetal development were observed when oral doses up to 1000 mg of candesartan cilexetil/kg/day (approximately 138 times the MRHD on a mg/m^2 basis) were administered to pregnant mice.

Hypotension in Volume-and Salt-Depleted Patients

In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g., those being treated with diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of ATACAND, or the treatment should start under close medical supervision (see DOSAGE AND ADMINISTRATION).

If hypotension occurs, the patients should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment which usually can be continued without difficulty once the blood pressure has stabilized.

Hypotension in Heart Failure Patients

Caution should be observed when initiating therapy in patients with heart failure. Patients with heart failure given ATACAND commonly have some reduction in blood pressure.[53] In patients with symptomatic hypotension this may require temporarily reducing the dose of ATACAND, or diuretic, or both, and/or volume repletion. In the CHARM program, *hypotension was the second most frequently reported adverse event (aggravated heart failure was the most frequently reported adverse event), constituting 18.8% of patients on candesartan versus 9.8% of patients on placebo*; the incidence of hypotension leading to drug discontinuation in candesartan-treated patients was 4.1% compared with 2.0% in placebo-treated patients.[54] Monitoring of blood pressure is recommended during dose escalation and periodically thereafter.

[53]Module 2, Summary of Clinical Safety, 2.7.4.4.1 Table 67

Table 22, page 59, of ISS.

[54]Module 2, Summary of Clinical Safety, 2.7.4.2.1.4.1 Table 44

PRECAUTIONS

General

Impaired Hepatic Function— Based on pharmacokinetic data which demonstrate significant increases in candesartan AUC and C_{max} in patients with moderate hepatic impairment, a lower initiating dose should be considered for patients with moderate hepatic impairment. (See DOSAGE AND ADMINISTRATION, and CLINICAL PHARMACOLOGY, Special Populations.)

Impaired Renal Function— As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals treated with ATACAND. In patients whose renal function may depend upon the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe ~~congestive~~ heart failure), treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results may be anticipated in patients treated with ATACAND. (See CLINICAL PHARMACOLOGY, Special Populations.)

Editorial

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen (BUN) have been reported. There has been no long-term use of ATACAND in patients with unilateral or bilateral renal artery stenosis, but similar results may be expected.

In heart failure patients treated with ATACAND, increases in serum creatinine may occur. Dosage reduction, and/or discontinuation of the diuretic, and/or ATACAND, and/or volume repletion may be required.[55] In the CHARM program, *the incidence of abnormal renal function (e.g., creatinine increase) was 12.5% in patients treated with candesartan versus 6.3% inpatients treated with placebo*; the incidence of abnormal renal function (e.g., creatinine increase) leading to drug discontinuation in candesartan-treated patients was 6.3% compared with 2.9% in placebo-treated patients.[56] Evaluation of patients with heart failure should always include assessment of renal function. Monitoring of serum creatinine is recommended during dose escalation and periodically thereafter.

[55]ClinicalStudy Report, SH-AHS-pooled, 11.3.9

Table 22, page 59, of ISS.

[56]Module 2, Summary of Clinical Safety, 2.7.4.2.1.4.1 Table 44

Hyperkalemia

In heart failure patients treated with ATACAND, hyperkalemia may occur,[57] especially when taken concomitantly with ACE inhibitors[58] and potassium-sparing diuretics such as spironolactone. In the CHARM program, *the incidence of hyperkalemia was 6.3% in patients treated with candesartan versus 2.1% in patients treated with placebo;* the incidence of hyperkalemia leading to drug discontinuation in candesartan-treated patients was 2.4% compared with 0.6% in placebo-treated patients.[59] During treatment with ATACAND in patients with heart failure, monitoring of serum potassium is recommended during dose escalation and periodically thereafter.

Table 22, page 59, of ISS.

[57]Module 2, Summary of Clinical Safety, 2.7.4.2.1.1.1 Table 22

[58]Module 2, Summary of Clinical Safety, 2.7.4.5.2.1 Table 78

[59]Module 2, Summary of Clinical Safety, 2.7.4.2.1.4.1 Table 44

Information for Patients

Pregnancy— Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Drug Interactions

No significant drug interactions have been reported in studies of candesartan cilexetil given with other drugs such as glyburide, nifedipine, digoxin, warfarin, hydrochlorothiazide, and oral contraceptives in healthy volunteers, or given with enalapril to patients with heart failure (NYHA class II and III).[60] Because candesartan is not significantly metabolized by the cytochrome P450 system and at therapeutic concentrations has no effects on P450 enzymes, interactions with drugs that inhibit or are metabolized by those enzymes would not be expected.

[60]Clinical Study Report EC608, 6.7.1 and 8.1

Lithium— Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors, and with some angiotensin II receptor antagonists. An increase in serum lithium concentration has been reported during concomitant administration of lithium with ATACAND, so careful monitoring of serum lithium levels is recommended during concomitant use.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of carcinogenicity when candesartan cilexetil was orally administered to mice and rats for up to 104 weeks at doses up to 100 and 1000 mg/kg/day, respectively. Rats received the drug by gavage, whereas mice received the drug by dietary administration. These (maximally-tolerated) doses of candesartan cilexetil provided systemic exposures to candesartan (AUCs) that were, in mice, approximately 7 times and, in rats, more than 70 times the exposure in man at the maximum recommended daily human dose (32 mg).

Candesartan and its O-deethyl metabolite tested positive for genotoxicity in the *in vitro* Chinese hamster lung (CHL) chromosomal aberration assay. Neither compound tested positive in the Ames microbial mutagenesis assay or the *in vitro* mouse lymphoma cell assay. Candesartan (but not its O-deethyl metabolite) was also evaluated *in vivo* in the mouse micronucleus test and *in vitro* in the Chinese hamster ovary (CHO) gene mutation assay, in both cases with negative results. Candesartan cilexetil was evaluated in the Ames test, the *in vitro* mouse lymphoma cell and rat hepatocyte unscheduled DNA synthesis assays and the *in vivo* mouse micronucleus test, in each case with negative results. Candesartan cilexetil was not evaluated in the CHL chromosomal aberration or CHO gene mutation assay.

Fertility and reproductive performance were not affected in studies with male and female rats given oral doses of up to 300 mg/kg/day (83 times the maximum daily human dose of 32 mg on a body surface area basis).

Pregnancy

Pregnancy Categories C (first trimester) *and D* (second and third trimesters)—See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers

It is not known whether candesartan is excreted in human milk, but candesartan has been shown to be present in rat milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Editorial

Hypertension

Of the total number of subjects in clinical studies of ATACAND, 21% (683/3260) were 65 and over, while 3% (87/3260) were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. In a placebo-controlled trial of about 200 elderly hypertensive patients (ages 65 to 87 years), administration of candesartan cilexetil was well tolerated and lowered blood pressure by about 12/6 mm Hg more than placebo.

Heart Failure

Of the 7599 patients with heart failure in the 3 trials of the CHARM program, 4343 (57 %) were age 65 years or older and 1736 (23 %) were 75 years or older.[61] ~~*In general, there were no notable differences in efficacy or safety between older and younger patients.*~~[62] In patients ≥ 75 years of age, the incidence of drug discontinuations due to adverse events was higher for those treated with ATACAND or placebo compared with patients <75 years of age.[63] In these patients, the most common adverse events leading to drug discontinuation at an incidence of at least 3%, and more frequent with ATACAND than placebo, were abnormal renal function (7.9% vs. 4.0%), hypotension (5.2% vs. 3.2%) and hyperkalemia (4.2% vs. 0.9%).[64] In addition to monitoring of serum creatinine, potassium, and blood pressure during dose escalation and periodically thereafter, greater sensitivity of some older individuals with heart failure must be considered.

No evidence for this statement.

[61]Module 2, Summary of Clinical Safety, 2.7.4.1.3 Table 6

[62]Module 2, Summary of Clinical Efficacy, 2.7.3.3.3 Table 23

[63]Clinical Study Report SH-AHS-pooled, 11.3.5.3 Table 168

[64]Clinical Study Report SH-AHS-pooled, 11.3.5.3 Table 168

ADVERSE REACTIONS

Editorial

Hypertension

ATACAND has been evaluated for safety in more than 3600 patients/subjects, including more than 3200 patients treated for hypertension. About 600 of these patients were studied for at least 6 months and about 200 for at least 1 year. In general, treatment with ATACAND was well tolerated. The overall incidence of adverse events reported with ATACAND was similar to placebo.

The rate of withdrawals due to adverse events in all trials in patients (7510 total) was 3.3% (i.e., 108 of 3260) of patients treated with candesartan cilexetil as monotherapy and 3.5% (i.e., 39 of 1106) of patients treated with placebo. In placebo-controlled trials, discontinuation of therapy due to clinical adverse events occurred in 2.4% (i.e., 57 of 2350) of patients treated with ATACAND and 3.4% (i.e., 35 of 1027) of patients treated with placebo.

The most common reasons for discontinuation of therapy with ATACAND were headache (0.6%) and dizziness (0.3%).

The adverse events that occurred in placebo-controlled clinical trials in at least 1% of patients treated with ATACAND and at a higher incidence in candesartan cilexetil (n = 2350) than placebo (n = 1027) patients included back pain (3% vs. 2%), dizziness (4% vs. 3%), upper respiratory tract infection (6% vs. 4%), pharyngitis (2% vs. 1%), and rhinitis (2% vs. 1%).

The following adverse events occurred in placebo-controlled clinical trials at a more than 1% rate but at about the same or greater incidence in patients receiving placebo compared to candesartan cilexetil: fatigue, peripheral edema, chest pain, headache, bronchitis, coughing, sinusitis, nausea, abdominal pain, diarrhea, vomiting, arthralgia, and albuminuria.

Other potentially important adverse events that have been reported, whether or not attributed to treatment, with an incidence of 0.5% or greater from the 3260 patients worldwide treated in clinical trials with ATACAND are listed below. It cannot be determined whether these events were causally related to ATACAND. **Body as a Whole:** asthenia, fever; **Central and Peripheral Nervous System:** paresthesia, vertigo; **Gastrointestinal System Disorder:** dyspepsia, gastroenteritis; **Heart Rate and Rhythm Disorders:** tachycardia, palpitation; **Metabolic and Nutritional Disorders:** creatine phosphokinase increased, hyperglycemia, hypertriglyceridemia, hyperuricemia; **Musculoskeletal System Disorders:** myalgia; **Platelet/Bleeding-Clotting Disorders:** epistaxis; **Psychiatric Disorders:** anxiety, depression, somnolence; **Respiratory System Disorders:** dyspnea; **Skin and Appendages Disorders:** rash, sweating increased; **Urinary System Disorders:** hematuria.

Other reported events seen less frequently included angina pectoris, myocardial infarction, and angioedema.

Adverse events occurred at about the same rates in men and women, older and younger patients, and black and non-black patients.

Heart Failure

The adverse event profile of ATACAND in heart failure patients was consistent with the pharmacology of the drug and the health status of the patients. In the CHARM program, comparing ATACAND in total daily doses up to 32 mg once daily (n=3803) with placebo (n=3796), 21.0% of ATACAND patients discontinued for adverse events vs. 16.1% of placebo patients.[65]

[65]Module 2, Summary of Clinical Safety, 2.7.4.2.1.1.1 Table 21

[66]Module 2, Summary of Clinical Efficacy, 2.7.4.2.1.4.1 Table 44

In the CHARM program, adverse events leading to drug discontinuation at an incidence of at least 1% and more frequent with ATACAND than placebo were abnormal renal function (6.3% vs. 2.9%), hypotension (4.1% vs. 2.0%), and hyperkalemia (2.4% vs. 0.6%).[66] *Aggravated heart failure was found to lead to study drug discontinuation at an incidence of 4.3% (versus 4.9% with placebo); also, aggravated heart failure was the most frequent adverse event (observed in 21.9% of patients treated with candesartan versus 28.3% of patients treated with placebo).*

Table 44, page 91, of ISS.

Post-Marketing Experience:

The following have been very rarely reported in post-marketing experience:

Digestive: Abnormal hepatic function and hepatitis.

Hematologic: Neutropenia, leukopenia, and agranulocytosis.

Metabolic and Nutritional Disorders: hyperkalemia, hyponatremia.

Renal: renal impairment, renal failure.

Skin and Appendages Disorders: Pruritus and urticaria.

Editorial

Laboratory Test Findings

Hypertension

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with the administration of ATACAND.

Creatinine, Blood Urea Nitrogen— Minor increases in blood urea nitrogen (BUN) and serum creatinine were observed infrequently.

Hyperuricemia— Hyperuricemia was rarely found (19 or 0.6% of 3260 patients treated with candesartan cilexetil and 5 or 0.5% of 1106 patients treated with placebo).

Hemoglobin and Hematocrit— Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.2 grams/dL and 0.5 volume percent, respectively) were observed in patients treated with ATACAND alone but were rarely of clinical importance. Anemia, leukopenia, and thrombocytopenia were associated with withdrawal of one patient each from clinical trials.

Potassium— A small increase (mean increase of 0.1 mEq/L) was observed in patients treated with ATACAND alone but was rarely of clinical importance. One patient from a congestive heart failure trial was withdrawn for hyperkalemia (serum potassium = 7.5 mEq/L). This patient was also receiving spironolactone.

Liver Function Tests— Elevations of liver enzymes and/or serum bilirubin were observed infrequently. Five patients assigned to candesartan cilexetil in clinical trials were withdrawn because of abnormal liver chemistries. All had elevated transaminases. Two had mildly elevated total bilirubin, but one of these patients was diagnosed with Hepatitis A.

Heart Failure

In the CHARM program, small increases in serum creatinine (mean increase 0.2 mg/dL in candesartan-treated patients and 0.1mg/dL in placebo-treated patients) and serum potassium (mean increase 0.15 mEq/L in candesartan-treated patients and 0.02 mEq/L in placebo-treated patients), and small decreases in hemoglobin (mean decrease 0.5 gm/dL in

candesartan-treated patients and 0.3 gm/dL in placebo-treated patients) and hematocrit (mean decrease 1.6% in candesartan-treated patients and 0.9% in placebo-treated patients) were observed.[67]

[67]Clinical Study Report SH-AHS-pooled, 11.3.9

OVERDOSAGE

No lethality was observed in acute toxicity studies in mice, rats, and dogs given single oral doses of up to 2000 mg/kg of candesartan cilexetil. In mice given single oral doses of the primary metabolite, candesartan, the minimum lethal dose was greater than 1000 mg/kg but less than 2000 mg/kg.

The most likely manifestation of overdosage with ATACAND would be hypotension, dizziness, and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Candesartan cannot be removed by hemodialysis.

Treatment: To obtain up-to-date information about the treatment of overdose, consult your Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*. In managing overdose, consider the possibilities of multiple-drug overdoses, drug-drug interactions, and altered pharmacokinetics in your patient.

DOSAGE AND ADMINISTRATION

Editorial

Hypertension

Dosage must be individualized. Blood pressure response is dose related over the range of 2 to 32 mg. The usual recommended starting dose of ATACAND is 16 mg once daily when it is used as monotherapy in patients who are not volume depleted. ATACAND can be administered once or twice daily with total daily doses ranging from 8 mg to 32 mg. Larger doses do not appear to have a greater effect, and there is relatively little experience with such doses. Most of the antihypertensive effect is present within 2 weeks, and maximal blood pressure reduction is generally obtained within 4 to 6 weeks of treatment with ATACAND.

No initial dosage adjustment is necessary for elderly patients, for patients with mildly impaired renal function, or for patients with mildly impaired hepatic function (see CLINICAL PHARMACOLOGY, Special Populations). In patients with moderate hepatic impairment, consideration should be given to initiation of ATACAND at a lower dose (See CLINICAL PHARMACOLOGY, Special Populations). For patients with possible depletion of intravascular volume (e.g., patients treated with diuretics, particularly those with impaired renal function), ATACAND should be initiated under close medical supervision and consideration should be given to administration of a lower dose (see WARNINGS, Hypotension in Volume- and Salt-Depleted Patients).

ATACAND may be administered with or without food.

If blood pressure is not controlled by ATACAND alone, a diuretic may be added. ATACAND may be administered with other antihypertensive agents.

Heart Failure

The usual initial dose for treating heart failure is 4 mg once daily. The target dose is 32 mg once daily, which is achieved by doubling the dose at approximately 2 week intervals, as tolerated by the patient.[68] ATACAND can be administered with other heart failure treatments including ACE inhibitors, beta-blockers, diuretics, *and/or* digoxin~~, *and/or aldosterone antagonist*~~.[69]

[68]Module 2, Clinical Overview, 2.5.6

[69]Module 2, Clinical Overview, 2.5.5.4.3

No beneficial effect on CV mortality or CHF hospitalization was found with candesartan treatment among CHF patients who were receiving spironolactone (See Figures 1 & 2).

HOW SUPPLIED

No. 3782 — Tablets ATACAND, 4 mg, are white to off-white, circular/biconvex-shaped, non-film-coated tablets, coded ACF on one side and 004 on the other. They are supplied as follows:

NDC 0186-0004-31 unit of use bottles of 30.

No. 3780 — Tablets ATACAND, 8 mg, are light pink, circular/biconvex-shaped, non-film-coated tablets, coded ACG on one side and 008 on the other. They are supplied as follows:

NDC 0186-0008-31 unit of use bottles of 30.

No. 3781 — Tablets ATACAND, 16 mg, are pink, circular/biconvex-shaped, non-film-coated tablets, coded ACH on one side and 016 on the other. They are supplied as follows:

NDC 0186-0016-31 unit of use bottles of 30
NDC 0186-0016-54 unit of use bottles of 90
NDC 0186-0016-28 unit dose packages of 100.

No. 3791 — Tablets ATACAND, 32 mg, are pink, circular/biconvex-shaped, non-film-coated tablets, coded ACL on one side and 032 on the other. They are supplied as follows:

NDC 0186-0032-31 unit of use bottles of 30
NDC 0186-0032-54 unit of use bottles of 90
NDC 0186-0032-28 unit dose packages of 100.

Storage:
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Keep container tightly closed.

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Rev. XX/XX

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Made in Sweden

AstraZeneca

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