AstraZeneca

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ATACAND® (candesartan cilexetil) Tablets
Briefing Document
ADDENDUM

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

Indication: Heart failure

Cardiovascular and Renal Drugs Advisory Committee Meeting
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10. ADDENDUM: JANUARY 2005 - CHARM-ADDED SUPPLEMENTAL ANALYSES

Addendum to Section 9 - CHARM-Added Supplemental Analyses

10.1 Overview

Section 10 is provided as an addendum to the 21 January 2005 Briefing Document to provide additional supplemental analyses and the reader may utilize this addendum as a replacement for Section 9 of the briefing document. An additional supplemental analysis is included in Section 10 based on a request from FDA to change the recommendations for the maximum doses of 3 ACE inhibitors: lisinopril, enalapril, and captopril, which are shown in Table 55 in Section 10 and referred to as 'Analysis 2'. The tables throughout this addendum reflect the FDA's first request made in December 2004 for an analysis of maximum suggested doses for ACE inhibitors (herein referred to as Analysis 1) and the additional supplemental analysis using the recently revised maximum dose recommendations for ACE inhibitors (herein referred to as Analysis 2).

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

According to the statistical analysis plan for CHARM, pre-specified subgroup analyses were done based on ACE inhibitor dose levels, with patients classified according to whether or not they were receiving recommended target doses. AstraZeneca specified the recommended doses used for these analyses prior to data unblinding and these doses aligned closely with the 2001 European Society of Cardiology (ESC) Heart Failure Recommendations (Remme et al 2001), (Table 55).

The FDA has suggested an additional ACE inhibitor 'maximum' dose classification. The doses used for classifying patients receiving the most commonly used ACE inhibitors in CHARM-Added and as detailed by the FDA are summarized in Table 55. In this table and throughout Section 10, the column labeled 'Analysis 1' represents analyses performed at FDA's request in December 2004 using suggested maximum doses for ACE inhibitors (Section 9 of the Briefing Document). After review of these data, the FDA subsequently asked for an additional supplemental analysis based on a change in the recommendations for the maximum doses of 3 ACE inhibitors: lisinopril, enalapril, and captopril, which are shown in Table 55.

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

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

These supplemental analyses demonstrate that 1) candesartan provides incremental benefit when added to an ACE inhibitor at either the recommended dose or the maximum dose, ie, the benefit is independent of the ACE inhibitor dose and, 2) ACE inhibitor use over the course of

the trial was quite stable and confirms only minimal attrition, particularly during the early period of dose titration with the investigational drug.

10.2 Background

CHARM-Added was designed to evaluate the benefits of candesartan when added to optimal conventional treatments including an ACE inhibitor. The protocol recommended that investigators give ACE inhibitors at doses based on target doses proven effective in controlled clinical trials of heart failure and individual patient tolerability. The protocol included a list of target doses of these ACE inhibitors and noted that other ACE inhibitors should be used at comparable doses. Furthermore, patients were to be on a stable dose of an ACE inhibitor for at least 30 days prior to study entry. The case report form for the baseline visit specifically asked the investigators to confirm that each patient was on an "optimum individualized dose of an ACE inhibitor", and this dosing plan was confirmed for 96% of patients. The statistical analysis plan for the CHARM program included an exploratory analysis of outcomes based on whether patients were on (at least) a recommended dose of an ACE inhibitor or less than a recommended dose. For this analysis, a complete list of recommended doses was detailed for each ACE inhibitor used in CHARM while the study was still blinded. These recommended doses were based, in part, on those proven effective in clinical trials and based in part on the ESC guidelines published in 2001 (Remme et al 2001). Within this document, the sponsor has designated these doses of ACE inhibitors as "recommended" doses for analysis.

The FDA has requested supplemental post-hoc analyses using a list of "maximum" ACE inhibitor doses. This list of maximum doses is drawn from various indications in US labels, previous heart failure trials, and FDA databases. The FDA list included 9 ACE inhibitors, representing approximately 99% of those used in CHARM-Added. For most ACE inhibitors, other than captopril, the mean doses at baseline in CHARM-Added were very similar to the mean doses proven effective in previous positive trials (Table 55 and Table 56).

Table 55 Recommended ACE inhibitor heart failure treatment doses as defined in CHARM analyses, and maximum doses as defined by FDA (CHARM-Added)

ACE inhibitor	Proportion of patients taking a specific ACE inhibitor, at baseline in CHARM-Added	Recommended heart failure target dose[a] mg/day	Maximum dose as provided by FDA Analysis 1 mg/day	Maximum dose as provided by FDA Analysis 2 mg/day
Enalapril	26.7%	20 mg	**20 mg**	**40 mg**
Lisinopril	19.1%	20 mg	**40 mg**	**20 mg**
Captopril	16.8%	150 mg	**150 mg**	**300 mg**
Ramipril	11.0%	10 mg	10 mg	10 mg
Perindopril	6.4%	4 mg	16 mg	16 mg
Trandolapril	5.9%	2 mg	4 mg	4 mg
Quinapril	5.4%	20 mg	80 mg	80 mg
Fosinopril	5.1%	20 mg	40 mg	40 mg
Benazepril	2.6%	20 mg	80 mg	80 mg
Other ACE inhibitors[b]	1.1%	-	-	-

[a] CHARM-Added recommended heart failure dose for subgroup analyses in the submission.
[b] For 'Other ACE inhibitors' not attributed a maximum dose by the FDA, the sponsor selected a maximum dose based on product labeling, (see Appendix, Table 64 for the complete list of ACE inhibitors).

Table 56 ACE inhibitor doses in CHF and post myocardial infarction trials

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

NA Not available.
Note: References for these trials are provided in Section 10.9.

Captopril is a distinctive case. It is intended to be used 3 times daily (tid). In studies that included it as a comparator, target doses have usually been 50 mg tid (150 mg daily), with

mean achieved doses typically 110 mg to 130 mg daily. However, in heart failure trials of other treatments such as beta-blockers, or in clinical use, achieved doses are often in the range of 60 mg to 80 mg daily (Hjalmarson et al 2000, Pitt et al 1999, Cleland et al 2002). For other ACE inhibitors such as enalapril, lisinopril, or ramipril, the mean doses observed in CHARM-Added were very similar to those achieved in trials designed with force-titration to a target dose as tolerated (see Table 56). These doses are also typically slightly higher than the mean doses used in clinical practice settings (Cleland et al 2002, Gattis et al 2004). Consequently, with the possible exception of captopril, it is difficult to speculate as to the relevance of titrating to maximum doses that exceed the mean doses achieved by force-titration in previous positive trials. Of note, it has not been a requirement for the approval of previous heart failure treatments that the investigational drug must be proven effective when added to maximum doses of other conventional or established treatments.

In the case of candesartan, the partially overlapping mechanism of action of ARBs and ACE inhibitors has led the FDA to raise the burden of proof of efficacy for the use of these 2 drugs classes together. The FDA has asked whether the addition of candesartan is more effective than an alternative strategy of increasing the ACE inhibitor to a maximum dose defined by the label or by tolerability. CHARM-Added was not designed to require force-titration of ACE inhibitors to a maximum dose. However, approximately 28% of patients (Analysis 1) or 21% of patients (Analysis 2) at baseline were receiving an FDA defined maximum dose of an ACE inhibitor or greater. At the request of the FDA, post-hoc analyses have been done in this subset to confirm the consistency of the effects of candesartan, irrespective of the dose of ACE inhibitor, and to confirm incremental benefit even when added to a maximum dose of ACE inhibitor. Although such post-hoc subgroup analyses have limitations of interpretability and lack the usual statistical power for clinical trials or regulatory evidence of effect, they do provide further evidence of the consistency of benefit of adding candesartan to an ACE inhibitor, independent of dose.

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

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

RAAS in CHF, the complementary actions of ACE inhibitors and ARBs for both reducing the formation of angiotensin II and preventing residual angiotensin II from binding to the AT1 receptor is highly relevant in the context of CHF.

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

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

10.3 Rationale for using an ACE inhibitor and an ARB together

10.3.1 Mechanisms of action and clinical implications

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

Kinins may also contribute to 2 of the most bothersome adverse effects associated with the use of ACE inhibitors. Cough, typically a dry nonproductive cough, may occur in an estimated 5% to 20% of patients receiving an ACE inhibitor and is the most common reason for ACE inhibitor intolerance in patients with CHF (Bart et al 1999). Its relation to dose has not been clearly defined. This can be particularly problematic in patients with CHF, since cough may

also be a manifestation of worsening heart failure or common co-morbidities such as chronic obstructive pulmonary disease or bronchitis. A 2nd and less common adverse effect that has been attributed in part to increased kinins and use of ACE inhibitors is an increased frequency of angioedema, which can be potentially life threatening.

10.3.2 Pharmacologic effects

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

10.3.3 Preclinical data

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

10.3.4 Clinical evidence (cardiovascular and renal)

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

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

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

10.4 Maximum dose of ACE inhibitor as treatment for CHF

The request to demonstrate a candesartan benefit when added to ‘maximum’ ACE inhibitor doses contains the implicit assumption that maximum doses are superior to doses proven effective in clinical heart failure trials. This assumption is difficult to validate. For most heart failure treatments, recommendations call for starting at 'low' doses with careful dose escalation to a target dose or the maximal tolerated dose (Remme et al 2001). Data are rarely provided to indicate that these target doses are pharmacologically maximal doses, or maximal doses for the treatment of chronic heart failure. Moreover, in previous positive trials evaluating ACE inhibitors in patients with CHF or in post MI patients (usually with LV systolic dysfunction), mean achieved doses have uniformly fallen short of the target doses (see Table 56). It is therefore not surprising that the literature is devoid of dose-response ACE inhibitor clinical trials of heart failure.

Several trials have failed to show that higher doses of an ACE inhibitor are more effective than doses proven effective in clinical trials (The NETWORK Investigators 1998, Nanas et al 2000). One trial attempted to compare a proven effective target dose of the ACE inhibitor enalapril (20 mg daily) to a very high dose (60 mg daily). However, mean achieved doses were 17.9 mg and 19.3 mg daily, respectively, and there were no differences in survival or clinical or hemodynamic variables (Nanas et al 2000). One trial (ATLAS) showed that a very low dose of lisinopril (target dose: 2.5 mg to 5.0 mg/day, mean achieved dose 4.5 mg) was less effective than a high dose (target dose 32.5 mg to 35 mg, mean achieved dose 33.2 mg) for the secondary outcome, death or hospitalization for any reason, by 12% (nominal p=0.002)

(Packer et al 1999), but with no significant reduction (p=0.128) for the primary endpoint of all-cause mortality. Accordingly, the approved US label for lisinopril (ZESTRIL®) states that: "A large (over 3000 patients) survival study, the ATLAS Trial, comparing 2.5 and 35 mg of lisinopril in patients with heart failure, showed that the higher dose of lisinopril had outcomes at least as favorable as the lower doses".

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

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

As indicated in the supplemental application, in the CHARM-Added study, about half of the patients entered the trial receiving an ACE inhibitor at a recommended dose. To further describe concomitant ACE inhibitor treatment in CHARM-Added, concomitant ACE inhibitor treatment for the most commonly used ACE inhibitors is presented in Table 57. This table provides for representative visits, 1) the number of patients on each dose level of each of the 4 most commonly used ACE inhibitors, 2) the percentage of patients at the recommended dose (CHARM definition), 3) the percentage of patients at the maximum dose (FDA definition), 4) the mean dose, 5) the mean proportion of maximum normalized dose where the maximum dose of each ACE inhibitor is assigned the value 1.0 and, 6) the mean proportion of recommended dose where recommended dose is assigned a value of 1.0.

Table 57 ACE inhibitor use by visit (CHARM-Added)

ACE inhibitor (n/N and % of patients on specific ACE inhibitor at baseline) **Percent of patients at recommended and maximum doses, by visit**	**Baseline Visit 1**	**Visit 4 Week 6**	**Visit 5 Month 6**	**Visit 7 Month 14**	**Visit 10 Month 26**	**Visit 13 Month 38**	**Visit 19 Closing visit**
	P, C	**P, C**	**P, C**	**P, C**	**P, C**	**P, C**	**P, C**
Enalapril (680/2548 = 26.7%)							
Mean dose at specific visit, mg	17, 17	17, 16	18, 17	17, 16	17, 16	16, 17	17, 16
And number of patients at each visit	335, 345	319, 331	298, 313	269, 282	239, 250	200, 204	185, 185
% at recommended dose (≥20 mg)	54, 50	54, 47	54, 46	53, 45	51, 46	48, 47	48, 44
% at maximum dose **(≥20 mg)** Analysis 1	54, 50	54, 47	54, 46	53, 45	51, 46	48, 47	48, 44
% at maximum dose **(≥40 mg)** Analysis 2	10, 9	11, 9	12, 11	11, 9	11, 12	10, 16	10, 11
Mean normalized to recommended dose	0.86, 0.84	0.86, 0.81	0.88, 0.83	0.86, 0.78	0.84, 0.82	0.82, 0.86	0.83, 0.79

Table 57 ACE inhibitor use by visit (CHARM-Added)

ACE inhibitor (n/N and % of patients on specific ACE inhibitor at baseline) Percent of patients at recommended and maximum doses, by visit	Baseline Visit 1	Visit 4 Week 6	Visit 5 Month 6	Visit 7 Month 14	Visit 10 Month 26	Visit 13 Month 38	Visit 19 Closing visit
	P, C	P, C	P, C	P, C	P, C	P, C	P, C
Mean normalized to maximum dose Analysis 1	0.86, 0.84	0.86, 0.81	0.88, 0.83	0.86, 0.78	0.84, 0.82	0.82, 0.86	0.83, 0.79
Mean normalized to maximum dose Analysis 2	0.43, 0.42	0.43, 0.41	0.44, 0.41	0.43, 0.39	0.42, 0.41	0.41, 0.43	0.41, 0.40
Lisinopril (486/2548 = 19.1%)							
Mean dose at specific visit, mg	18, 18	17, 18	18, 18	18, 17	18, 18	18, 18	19, 18
And number of patients at each visit	243, 243	241, 234	231, 225	216, 196	190, 176	160, 149	143, 145
% at recommended dose (≥20 mg)	52, 52	50, 53	51, 53	52, 54	54, 53	52, 54	60, 55
% at maximum dose **(≥40 mg)** Analysis 1	13, 16	13, 14	13, 15	11, 13	13, 15	12, 14	13, 15
% at maximum dose **(≥20 mg)** Analysis 2	52, 52	50, 53	51, 53	52, 54	54, 53	52, 54	60, 55
Mean normalized to recommended dose	0.88, 0.89	0.87, 0.88	0.89, 0.88	0.88, 0.86	0.90, 0.88	0.88, 0.87	0.97, 0.90
Mean normalized to maximum dose Analysis 1	0.44, 0.44	0.43, 0.44	0.44, 0.44	0.44, 0.43	0.45, 0.44	0.44, 0.44	0.48, 0.45
Mean normalized to maximum dose Analysis 2	0.88, 0.89	0.87, 0.88	0.89, 0.88	0.88, 0.86	0.90, 0.88	0.88, 0.87	0.97, 0.90
Captopril (429/2548 = 16.8%)							
Mean dose at specific visit, mg	83, 82	81, 81	81, 79	81, 77	83, 73	83, 72	77, 69
And number of patients at each visit	237, 192	228, 181	214, 178	192, 156	158, 131	130, 118	109, 98
% at recommended dose (≥150 mg)	21, 22	19, 20	20, 20	19, 20	21, 19	22, 20	20, 18
% at maximum dose **(≥150 mg)** Analysis 1	21, 22	19, 20	20, 20	19, 20	21, 19	22, 20	20, 18
% at maximum dose **(≥300 mg)** Analysis 2	1, 2	1, 2	1, 2	1, 1	1, 0	0, 0	0, 0
Mean normalized to recommended dose	0.55, 0.55	0.54, 0.54	0.54, 0.53	0.54, 0.51	0.55, 0.49	0.55, 0.48	0.51, 0.46
Mean normalized to maximum dose Analysis 1	0.55, 0.55	0.54, 0.54	0.54, 0.53	0.54, 0.51	0.55, 0.49	0.55, 0.48	0.51, 0.46
Mean normalized to maximum dose Analysis 2	0.28, 0.27	0.27, 0.27	0.27, 0.26	0.27, 0.26	0.28, 0.24	0.28, 0.24	0.26, 0.23
Ramipril (281/2548 = 11.0%)							
Mean dose at specific visit, mg	7, 7	8, 7	8, 7	8, 7	9, 7	8, 7	8, 7
And number of patients at each visit	120, 161	118, 157	114, 145	107, 143	104, 126	99, 111	91, 100
% at recommended dose (≥10 mg)	43, 35	47, 34	47, 35	49, 38	49, 37	53, 40	54, 43

Table 57 ACE inhibitor use by visit (CHARM-Added)

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

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

The cross-sectional tabulations of concomitant ACE inhibitor use are summarized for all ACE inhibitors used in the trial in Table 58 and demonstrate that, in CHARM-Added, the doses of ACE inhibitors over the course of the trial were quite stable. While the proportions of patients at the recommended dose or at the maximum dose at closing visit were somewhat less than at baseline, there was very little change in ACE inhibitor treatment from baseline through Month 6 (Visit 5), during the initial period of study drug dose escalation.

For Analysis 1, for the placebo group, 28.2% were at maximum ACE inhibitor dose at baseline and 27.5% were at maximum dose at Visit 5. For the candesartan group, 28.4% were at maximum dose at baseline, and 25.1% were at maximum dose at Visit 5.

For Analysis 2, for the placebo group, 20.4% were at maximum ACE inhibitor dose at baseline and 21.0% were at maximum dose at Visit 5. For the candesartan group, 21.1% were at maximum dose at baseline, and 20.6% were at maximum dose at Visit 5.

Table 58 Summary table of concomitant ACE inhibitor use (CHARM- Added)

Visit	Summary statistic	Placebo n (%)	Candesartan n (%)	Total n (%)
Visit 1 (Baseline)	Number of patients	1272	1276	2548
	Recommended dose or above	648 (50.9)	643 (50.4)	1291 (50.7)
	Maximum dose or above – Analysis 1	359 (28.2)	362 (28.4)	721 (28.3)
	Maximum dose or above –Analysis 2	260 (20.4)	269 (21.1)	529 (20.8)
	Mean normalized to recommended dose	0.87	0.87	0.87
	Mean normalized to maximum dose Analysis 1	0.60	0.59	0.60
	Mean normalized to maximum dose Analysis 2	0.52	0.52	0.52

Table 58 Summary table of concomitant ACE inhibitor use (CHARM- Added)

Visit	Summary statistic	Placebo n (%)	Candesartan n (%)	Total n (%)
Visit 2 (Week 2)	Number of patients	1259	1269	2528
	Recommended dose or above	639 (50.8)	636 (50.1)	1275 (50.4)
	Maximum dose or above – Analysis 1	353 (28.0)	354 (27.9)	707 (28.0)
	Maximum dose or above – Analysis 2	255 (20.3)	266 (21.0)	521 (20.6)
	Mean normalized to recommended dose	0.86	0.86	0.86
	Mean normalized to maximum dose Analysis 1	0.59	0.59	0.59
	Mean normalized to maximum dose Analysis 2	0.51	0.52	0.52
Visit 3 (Week 4)	Number of patients	1255	1257	2512
	Recommended dose or above	636 (50.7)	623 (49.6)	1259 (50.1)
	Maximum dose or above – Analysis 1	352 (28.0)	342 (27.2)	694 (27.6)
	Maximum dose or above – Analysis 2	255 (20.3)	262 (20.8)	517 (20.6)
	Mean normalized to recommended dose	0.86	0.85	0.86
	Mean normalized to maximum dose Analysis 1	0.59	0.58	0.58
	Mean normalized to maximum dose Analysis 2	0.51	0.51	0.51
Visit 4 (Week 6)	Number of patients	1248	1251	2499
	Recommended dose or above	629 (50.4)	605 (48.4)	1234 (49.4)
	Maximum dose or above – Analysis 1	345 (27.6)	325 (26.0)	670 (26.8)
	Maximum dose or above- Analysis 2	257 (20.6)	259 (20.7)	516 (20.6)
	Mean normalized to recommended dose	0.86	0.84	0.85
	Mean normalized to maximum dose Analysis 1	0.59	0.57	0.58
	Mean normalized to maximum dose Analysis 2	0.51	0.51	0.51
Visit 5 (Month 6)	Number of patients	1196	1214	2410
	Recommended dose or above	603 (50.4)	564 (46.5)	1167 (48.4)
	Maximum dose or above – Analysis 1	329 (27.5)	305 (25.1)	634 (26.3)
	Maximum dose or above – Analysis 2	251 (21.0)	250 (20.6)	501 (20.8)
	Mean normalized to recommended dose	0.86	0.81	0.84
	Mean normalized to maximum dose Analysis 1	0.59	0.56	0.57
	Mean normalized to maximum dose Analysis 2	0.51	0.49	0.50
Visit 6 (Month 10)	Number of patients	1157	1179	2336
	Recommended dose or above	563 (48.7)	534 (45.3)	1097 (47.0)

Table 58 Summary table of concomitant ACE inhibitor use (CHARM- Added)

Visit	Summary statistic	Placebo n (%)	Candesartan n (%)	Total n (%)
	Maximum dose or above – Analysis 1	307 (26.5)	292 (24.8)	599 (25.6)
	Maximum dose or above – Analysis 2	242 (20.9)	234 (19.8)	476 (20.4)
	Mean normalized to recommended dose	0.84	0.80	0.82
	Mean normalized to maximum dose Analysis 1	0.57	0.55	0.56
	Mean normalized to maximum dose Analysis 2	0.50	0.49	0.50
Visit 7 (Month 14)	Number of patients	1110	1141	2251
	Recommended dose or above	550 (49.5)	516 (45.2)	1066 (47.4)
	Maximum dose or above – Analysis 1	300 (27.0)	276 (24.2)	576 (25.6)
	Maximum dose or above – Analysis 2	241 (21.7)	226 (19.8)	467 (20.7)
	Mean normalized to recommended dose	0.85	0.77	0.81
	Mean normalized to maximum dose Analysis 1	0.58	0.52	0.55
	Mean normalized to maximum dose Analysis 2	0.51	0.47	0.49
Visit 8 (Month 18)	Number of patients	1068	1094	2162
	Recommended dose or above	522 (48.9)	499 (45.6)	1021 (47.2)
	Maximum dose or above – Analysis 1	293 (27.4)	274 (25.0)	567 (26.2)
	Maximum dose or above – Analysis 2	229 (21.4)	222 (20.3)	451 (20.9)
	Mean normalized to recommended dose	0.84	0.77	0.81
	Mean normalized to maximum dose Analysis 1	0.58	0.53	0.55
	Mean normalized to maximum dose Analysis 2	0.51	0.47	0.49
Visit 9 (Month 22)	Number of patients	1038	1050	2088
	Recommended dose or above	513 (49.4)	476 (45.3)	989 (47.4)
	Maximum dose or above – Analysis 1	294 (28.3)	270 (25.7)	564 (27.0)
	Maximum dose or above – Analysis 2	238 (22.9)	222 (21.1)	460 (22.0)
	Mean normalized to recommended dose	0.86	0.78	0.82
	Mean normalized to maximum dose Analysis 1	0.59	0.53	0.56
	Mean normalized to maximum dose Analysis 2	0.53	0.48	0.50
Visit 10 (Month 26)	Number of patients	993	999	1992
	Recommended dose or above	483 (48.6)	443 (44.3)	926 (46.5)
	Maximum dose or above – Analysis 1	274 (27.6)	247 (24.7)	521 (26.2)
	Maximum dose or above – Analysis 2	225 (22.7)	206 (20.6)	431 (21.6)

Table 58 Summary table of concomitant ACE inhibitor use (CHARM- Added)

Visit	Summary statistic	Placebo n (%)	Candesartan n (%)	Total n (%)
	Mean normalized to recommended dose	0.85	0.77	0.81
	Mean normalized to maximum dose Analysis 1	0.58	0.53	0.56
	Mean normalized to maximum dose Analysis 2	0.52	0.47	0.50
Visit 11 (Month 30)	Number of patients	954	963	1917
	Recommended dose or above	456 (47.8)	417 (43.3)	873 (45.5)
	Maximum dose or above – Analysis 1	262 (27.5)	230 (23.9)	492 (25.7)
	Maximum dose or above – Analysis 2	215 (22.5)	195 (20.2)	410 (21.4)
	Mean normalized to recommended dose	0.82	0.76	0.79
	Mean normalized to maximum dose Analysis 1	0.57	0.52	0.54
	Mean normalized to maximum dose Analysis 2	0.51	0.46	0.49
Visit 12 (Month 34)	Number of patients	916	927	1843
	Recommended dose or above	442 (48.3)	399 (43.0)	841 (45.6)
	Maximum dose or above – Analysis 1	253 (27.6)	215 (23.2)	468 (25.4)
	Maximum dose or above – Analysis 2	211 (23.0)	188 (20.3)	399 (21.6)
	Mean normalized to recommended dose	0.82	0.75	0.78
	Mean normalized to maximum dose Analysis 1	0.57	0.51	0.54
	Mean normalized to maximum dose Analysis 2	0.51	0.46	0.48
Visit 13 (Month 38)	Number of patients	852	890	1742
	Recommended dose or above	409 (48.0)	381 (42.8)	790 (45.4)
	Maximum dose or above – Analysis 1	232 (27.2)	212 (23.8)	444 (25.5)
	Maximum dose or above – Analysis 2	192 (22.5)	185 (20.8)	377 (21.6)
	Mean normalized to recommended dose	0.81	0.74	0.78
	Mean normalized to maximum dose Analysis 1	0.56	0.52	0.54
	Mean normalized to maximum dose Analysis 2	0.51	0.46	0.48
Visit 14 (Month 42)	Number of patients	285	299	584
	Recommended dose or above	122 (42.8)	129 (43.1)	251 (43.0)
	Maximum dose or above – Analysis 1	81 (28.4)	69 (23.1)	150 (25.7)
	Maximum dose or above – Analysis 2	60 (21.1)	56 (18.7)	116 (19.9)
	Mean normalized to recommended dose	0.76	0.71	0.73
	Mean normalized to maximum dose	0.56	0.50	0.53

Table 58 Summary table of concomitant ACE inhibitor use (CHARM- Added)

Visit	Summary statistic	Placebo n (%)	Candesartan n (%)	Total n (%)
Closing visit	Analysis 1			
	Mean normalized to maximum dose Analysis 2	0.47	0.42	0.44
	Number of patients	864	896	1760
	Recommended dose or above	386 (44.7)	343 (38.3)	729 (41.4)
	Maximum dose or above – Analysis 1	214 (24.8)	185 (20.6)	399 (22.7)
	Maximum dose or above – Analysis 2	188 (21.8)	164 (18.3)	352 (20.0)
	Mean normalized to recommended dose	0.75	0.66	0.70
	Mean normalized to maximum dose Analysis 1	0.51	0.45	0.48
	Mean normalized to maximum dose Analysis 2	0.47	0.41	0.44

For Analysis 1, the mean "normalized to maximum" dose changed little over the course of the trial (0.60, placebo and 0.59candesartan at baseline;0.51, placebo and 0.45 candesartan at closing visit). For Analysis 2, the mean "normalized to maximum" dose changed little over the course of the trial (0.52, placebo and 0.52 candesartan at baseline; 0.47, placebo and 0.41 candesartan at closing visit).

The mean achieved ACE inhibitor doses were also relatively constant over the course of the trial (Table 57). Furthermore, the mean doses of enalapril and ramipril compare favorably with the mean doses attained in the clinical trials that established benefit of these agents in the treatment of heart failure (Table 56) (The CONSENSUS Study Group 1987, The SOLVD Investigators 1991, The AIRE Study Investigators 1993).

10.6 ACE inhibitor subgroup analyses

10.6.1 ACE inhibitor subgroup efficacy analyses

10.6.1.1 Subgroup analyses based on ACE inhibitor dose at baseline

The original CHARM submission described whether there were differential treatment effects associated with concomitant ACE inhibitor dose. The subgroup analyses, as conducted, indicate that the benefit of candesartan vs. placebo is evident whether patients are taking an ACE inhibitor at a recommended dose or at a lower dose. There was no suggestion of a treatment-by-recommended dose interaction (p=0.26). In fact, for the primary endpoint, CV death or CHF hospitalization, there was significant benefit observed within the population taking ACE inhibitors at the recommended dose (HR=0.794, 95% CI 0.666-0.945, p=0.010). In patients taking a maximum dose of ACE inhibitor at baseline, there was also evidence of a directionally consistent incremental benefit from treatment with candesartan (Table 59).

Table 59 Subgroup analyses based on the recommended ACE inhibitor heart failure treatment doses and maximum ACE inhibitor doses, at baseline for the primary and 2 secondary endpoints (CHARM-Added)

Event/dose of ACE inhibitor at baseline		N	Placebo Events/1000 follow-up years	Candesartan Events/1000 follow-up years	Hazard Ratio	95% CI	p-value
CV death or CHF hospitalization							
All patients		2548	166.3	141.2	0.85	0.75, 0.96	0.011
Recommended dose of ACEi	No	1257	165.5	151.2	0.92	0.77, 1.09	0.314
	Yes	1291	167.1	131.7	0.79	0.67, 0.95	0.010
Maximum dose of ACEi – Analysis 1	No	1827	172.1	144.5	0.84	0.73, 0.98	0.021
	Yes	721	152.2	133.0	0.88	0.69, 1.11	0.273
Maximum dose of ACEi – Analysis 2	No	2019	162.5	142.8	0.88	0.77, 1.01	0.077
	Yes	529	181.4	135.3	0.75	0.57, 0.98	0.034
All cause death or CHF hospitalization							
All patients		2548	181.5	157.5	0.87	0.78, 0.98	0.021
Recommended dose of ACEi	No	1257	179.4	166.2	0.93	0.79, 1.10	0.378
	Yes	1291	183.5	149.3	0.82	0.69, 0.97	0.017
Maximum dose of ACEi – Analysis 1	No	1827	186.9	161.9	0.87	0.76, 1.00	0.046
	Yes	721	168.2	147.0	0.88	0.70, 1.10	0.249
Maximum dose of ACEi – Analysis 2	No	2019	178.0	159.2	0.90	0.79, 1.02	0.109
	Yes	529	195.2	151.6	0.78	0.60, 1.00	0.054
CV death or CHF hospitalization or non-fatal MI							
All patients		2548	172.0	145.8	0.85	0.76, 0.96	0.010
Recommended dose of ACEi	No	1257	170.8	153.4	0.90	0.76, 1.07	0.233
	Yes	1291	173.2	138.7	0.81	0.68, 0.96	0.014
Maximum dose of ACEi – Analysis 1	No	1827	177.5	147.8	0.84	0.73, 0.97	0.015
	Yes	721	158.6	141.0	0.89	0.71, 1.12	0.332
Maximum dose of ACEi – Analysis 2	No	2019	167.3	147.0	0.88	0.77, 1.01	0.076
	Yes	529	191.0	141.8	0.75	0.57, 0.97	0.028

ACEi Angiotensin-converting enzyme inhibitor.
CI Confidence interval.

A directionally consistent benefit of candesartan was also evident for the component endpoints, CV death, CHF hospitalization, and all-cause mortality, whether or not patients were receiving the ACE inhibitor at a recommended dose or at a maximum dose (Table 60).

Table 60 Subgroup analyses based on the recommended ACE inhibitor heart failure treatment doses and maximum ACE inhibitor doses at baseline for the components CV death, CHF hospitalization, and all-cause death (CHARM-Added)

Event/dose of ACE inhibitor at baseline		N	Placebo Events/1000 follow-up years	Candesartan Events/1000 follow-up years	Hazard Ratio	95% CI	p-value
CV death							
All patients		2548	93.3	78.5	0.84	0.72, 0.98	0.029
Recommended dose of ACEi	No	1257	97.0	81.0	0.84	0.67, 1.04	0.101
	Yes	1291	89.7	76.1	0.85	0.68, 1.06	0.146
Maximum dose of ACEi – Analysis 1	No	1827	97.5	79.6	0.82	0.68, 0.98	0.027
	Yes	721	82.6	75.8	0.92	0.68, 1.24	0.577
Maximum dose of ACEi – Analysis 2	No	2019	92.4	79.8	0.86	0.73, 1.03	0.098
	Yes	529	96.5	73.7	0.76	0.54, 1.08	0.123
CHF hospitalization							
All patients		2548	110.1	90.3	0.83	0.71, 0.96	0.014
Recommended dose of ACEi	No	1257	106.4	97.0	0.91	0.74, 1.13	0.411
	Yes	1291	113.6	84.0	0.75	0.60, 0.93	0.008
Maximum dose of ACEi – Analysis 1	No	1827	112.4	93.7	0.84	0.70, 1.00	0.054
	Yes	721	104.3	82.0	0.79	0.59, 1.06	0.116
Maximum dose of ACEi – Analysis 2	No	2019	104.9	90.2	0.87	0.73, 1.03	0.102
	Yes	529	130.7	90.7	0.70	0.51, 0.96	0.028
All cause death							
All patients		2548	110.7	98.0	0.89	0.77, 1.02	0.086
Recommended dose of ACEi	No	1257	111.2	99.9	0.90	0.74, 1.09	0.283
	Yes	1291	110.2	96.2	0.87	0.72, 1.06	0.175
Maximum dose of ACEi – Analysis 1	No	1827	114.9	100.1	0.87	0.74, 1.03	0.096
	Yes	721	100.4	93.0	0.93	0.71, 1.22	0.582
Maximum dose of ACEi – Analysis 2	No	2019	109.6	99.6	0.91	0.78, 1.06	0.230
	Yes	529	115.0	92.1	0.80	0.59, 1.09	0.157

ACEi Angiotensin-converting enzyme inhibitor.

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

The supplemental analyses were performed to investigate the effect of candesartan in patients who received recommended or maximum dose of ACE inhibitors over time (Analyses 1 and 2). For each endpoint, the analysis was limited to the cohort of patients who were on a recommended or maximum dose of ACE inhibitor at baseline and up to the time of each specific event or to the end of study if the patient was event-free. These analyses, although not assured of being unbiased due to selection criteria which use the post-randomization experience of patients, support a directionally consistent benefit of candesartan on top of concomitant use of ACE inhibitors at recommended or maximum doses over time.

Table 61 shows analyses for the primary and 2 secondary endpoints.

In Analysis 1, of the 721 patients in CHARM-Added who were taking a maximum dose of ACE inhibitor at baseline, over 90% (659) were on a maximum dose at all visits up to the time of each specific event or at the end of the study for the primary and secondary endpoints.

In Analysis 2, of the 529 patients in CHARM-Added who were taking a maximum dose of ACE inhibitor at baseline, 90% (476) were on a maximum dose at all visits up to the time of each specific event or at the end of the study for the primary and secondary endpoints.

Table 61 Subgroup analyses based on the recommended ACE inhibitor heart failure treatment doses and maximum ACE inhibitor doses, at baseline and throughout all visits for the primary and 2 secondary endpoints (CHARM-Added)

Event/dose of ACE inhibitor at baseline and at all visits prior to a specific event or to the end of the study if patient was event-free		N	Placebo Events/1000 follow-up years	Candesartan Events/1000 follow-up years	Hazard Ratio	95% CI	p-value
CV death or CHF hospitalization							
Recommended dose of ACEi	Yes	1165	177.2	134.0	0.76	0.64, 0.92	0.004
Maximum dose of ACEi Analysis 1	Yes	659	160.2	133.7	0.84	0.66, 1.07	0.161
Maximum dose of ACEi Analysis 2	Yes	476	186.0	136.1	0.74	0.56, 0.98	0.033
All cause death or CHF hospitalization							
Recommended dose of ACEi	Yes	1165	191.5	148.1	0.78	0.66, 0.93	0.005
Maximum dose of ACEi Analysis 1	Yes	659	175.3	144.9	0.83	0.66, 1.05	0.121
Maximum dose of ACEi Analysis 2	Yes	476	197.8	150.2	0.76	0.58, 1.00	0.050
CV death or CHF hospitalization or non-fatal MI							
Recommended dose of ACEi	Yes	1168	183.8	141.9	0.78	0.65, 0.93	0.006
Maximum dose of ACEi Analysis 1	Yes	659	167.3	142.7	0.86	0.67, 1.09	0.209
Maximum dose of ACEi Analysis 2	Yes	476	196.6	143.6	0.74	0.56, 0.97	0.028

ACEi Angiotensin-converting enzyme inhibitor.
CI Confidence interval.

A directionally consistent benefit of candesartan was also evident for the component endpoints, CV death, CHF hospitalization, and all-cause mortality, in the cohort of patients who were on a maximum dose of ACE inhibitor at baseline as well as all visits up to the time of an event, or to the end of study if the patient was event-free (Table 62).

Table 62 Subgroup analyses based on the recommended ACE inhibitor heart failure treatment doses and maximum ACE inhibitor doses, throughout all visits for the components CV death, CHF hospitalization, and all-cause death (CHARM-Added)

Event/dose of ACE inhibitor at baseline and at all visits prior to a specific event or to the end of the study if patient was event-free		N	Placebo Events/1000 follow-up years	Candesartan Events/1000 follow-up years	Hazard Ratio	95% CI	p-value
CV death							
Recommended dose of ACEi	Yes	1116	93.6	71.2	0.76	0.60, 0.97	0.026
Maximum dose of ACEi Analysis 1	Yes	634	87.9	73.9	0.84	0.61, 1.16	0.290
Maximum dose of ACEi Analysis 2	Yes	459	95.9	71.5	0.75	0.52, 1.08	0.123
CHF hospitalization							
Recommended dose of ACEi	Yes	1165	119.7	83.3	0.70	0.56, 0.88	0.002
Maximum dose of ACEi Analysis 1	Yes	659	109.1	79.8	0.74	0.54, 1.00	0.052
Maximum dose of ACEi Analysis 2	Yes	476	134.1	92.3	0.69	0.50, 0.97	0.033
All cause death							
Recommended dose of ACEi	Yes	1116	112.3	87.4	0.78	0.63, 0.97	0.024
Maximum dose of ACEi Analysis 1	Yes	634	103.6	87.6	0.85	0.63, 1.13	0.266
Maximum dose of ACEi Analysis 2	Yes	459	112.2	87.6	0.78	0.56, 1.10	0.152

ACEi Angiotensin-converting enzyme inhibitor.

10.6.2 ACE inhibitor subgroup safety analyses

The safety experience in both the "maximum" and "recommended" dose cohorts of patients was consistent with that of the overall CHARM-Added population. The risk of death and the risk of hospitalization were both lower with candesartan than placebo but the rate of study drug discontinuation was higher (Table 63).

In Analysis 1, discontinuation rates in the "maximum" dose cohort for the specific adverse events, hypotension (placebo 2.5%, candesartan 2.2%), abnormal renal function (placebo 5.3%; candesartan 8.6%) and hyperkalemia (placebo 0.8%; candesartan 3.9%), were also similar to those of the overall CHARM-Added population

In Analysis 2, discontinuation rates in the "maximum" dose cohort for the specific adverse events, hypotension (placebo 3.1%, candesartan 4.5%), abnormal renal function (placebo 8.1%; candesartan 7.4%) and hyperkalemia (placebo 1.5%; candesartan 4.1%), were also similar to those of the overall CHARM-Added population

Table 63 Subgroup analyses based on the recommended ACE inhibitor heart failure treatment doses, and maximum dose, at baseline for key safety endpoints (CHARM-Added)

Event/dose of ACE inhibitor at baseline		N	Placebo Events/1000 follow-up years	Candesartan Events/1000 follow-up years	Hazard Ratio	95% CI	p-value
All cause death							
Recommended dose of ACEi	No	1257	111.2	99.9	0.90	0.74, 1.09	0.283
	Yes	1291	110.2	96.2	0.87	0.72, 1.06	0.175
Maximum dose of ACEi Analysis 1	No	1827	114.9	100.1	0.87	0.74, 1.03	0.096
	Yes	721	100.4	93.0	0.93	0.71, 1.22	0.582
Maximum dose of ACEi Analysis 2	No	2019	109.6	99.6	0.91	0.78, 1.06	0.230
	Yes	529	115.0	92.1	0.80	0.59, 1.09	0.157
All cause hospitalization							
Recommended dose of ACEi	No	1257	373.4	372.3	0.10	0.87, 1.14	0.982
	Yes	1291	409.7	369.9	0.92	0.80, 1.05	0.191
Maximum dose of ACEi Analysis 1	No	1827	380.3	361.0	0.96	0.86, 1.07	0.453
	Yes	721	420.9	398.2	0.95	0.80, 1.13	0.580
Maximum dose of ACEi Analysis 2	No	2019	370.7	362.3	0.98	0.88, 1.10	0.772
	Yes	529	483.4	406.0	0.85	0.70, 1.04	0.119
Permanent discontinuation of study drug due to AE or abnormal lab value							
Recommended dose of ACEi	No	1257	66.8	95.3	1.42	1.12, 1.81	0.004
	Yes	1291	67.8	88.2	1.29	1.02, 1.64	0.035
Maximum dose of ACEi Analysis 1	No	1827	70.6	95.1	1.34	1.10, 1.64	0.003
	Yes	721	59.3	83.3	1.40	1.00, 1.95	0.050
Maximum dose of ACEi Analysis 2	No	2019	62.0	93.5	1.50	1.24, 1.83	<0.001
	Yes	529	88.0	85.0	0.97	0.68, 1.37	0.842

10.6.3 Benefit/Risk

In response to FDA's questions about the CHARM-Added trial for patients receiving maximum ACE inhibitor dose, a supplemental benefit/risk assessment is provided for these specific subgroups. Whether considering the maximum ACE inhibitor dose at baseline or throughout the trial, all efficacy analyses on the composite endpoints and their components

demonstrate consistency of risk reduction that mirrors that observed for the entire CHARM-Added patient population. As would be expected, the smaller subgroup analyses do not reveal significant p-values. However, the consistency of the point estimates for risk reduction provides strong evidence that the beneficial effects of candesartan added to ACE inhibitors are not modified by ACE inhibitor dose throughout a broad dose range.

Although drug discontinuation rates due to adverse events were higher in the candesartan group, as was the case for the entire CHARM-Added trial, the risk of discontinuation was not substantially modified by the use of maximum doses of ACE inhibitor. Using all-cause hospitalization and all-cause mortality as aggregate measures of benefit/risk for the maximum ACE inhibitor doses subgroups, it may again be observed that the point estimate of relative risk favors candesartan. Furthermore, the point estimates for these aggregate measures are consistent with those observed when the same analyses are applied to the entire CHARM-Added patient population. Therefore, the totality of the evidence indicates that candesartan added to ACE inhibitors at maximum doses shows the same positive benefit-risk profile as the entire CHARM-Added trial.

10.7 Discussion of subgroups and Val-heft

10.7.1 Limitations of subgroup analyses

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

The Val-HeFT trial was subjected to considerable subgroup analyses. In the Val-HeFT trial, the addition of the ARB valsartan or placebo to standard treatment was compared in 5010 patients with CHF (NYHA II-IV). There was no effect on all-cause mortality, one of the primary outcomes, but there was a 13.2% relative risk reduction ($p=0.009$) in the combined endpoint that included mortality, CHF hospitalizations, and morbidity, the other primary outcome. The risk reduction was attributable predominantly to a 24% reduction in CHF hospitalizations ($p<0.001$). However, the study was subjected to several subgroup analyses (mostly post-hoc), which revealed several findings that eroded confidence in ascribing a beneficial effect to valsartan in the overall trial. These included an unexpected worse outcome with respect to both primary endpoints in the 1610 patients (32%) receiving both an ACE inhibitor and beta-blocker at baseline with the addition of valsartan compared to placebo. In addition, analyses suggested that most of the benefit was seen either in patients not receiving an ACE inhibitor (n=366, 7%) or an ACE inhibitor at less than the median dose. However,

there was a consistent numerical reduction in heart failure hospitalizations even in the group receiving an ACE inhibitor at a dose above the median. Consequently, based predominantly on the Val-HeFT trial and an unmet medical need, valsartan was the first ARB approved for the treatment of heart failure. The approval was for patients intolerant of an ACE inhibitor (although this group was not formally studied in Val-HeFT) to reduce hospitalizations for heart failure. However, the heart failure indication also includes the statement," There is no evidence that Diovan® (valsartan) provides added benefits when it is used with an adequate dose of ACE inhibitors". Moreover, the description of the Val-HeFT trial includes the statement, "Concomitant use of an ACE inhibitor, a beta-blocker, and valsartan was associated with a worse outcome for heart failure morbidity. It is not known if this is a reproducible effect or a chance occurrence. Use of a beta-blocker did not appear to influence the effect of valsartan in patients not receiving an ACE inhibitor". As one might expect, the results of Val-HeFT and the subsequent labeling for Diovan® (valsartan) have led to much discussion and commentary among those who write guidelines, academicians, and clinicians regarding the potential utility of adding the ARB valsartan to conventional treatment that typically includes an ACE inhibitor plus beta-blocker. The results of the VALIANT post MI trial with valsartan were awaited to refute what was presumed to be a spurious negative interaction finding of valsartan with a beta-blocker plus an ACE inhibitor. Moreover, CHARM has been considered to be a more definitive study with respect to the beta-blocker plus ACE inhibitor issue (55% on a beta-blocker at baseline).

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

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

10.7.2 Comparison of Val-HeFT and CHARM-Added

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

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

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

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

10.8 Summary statement

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

10.9 References

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10.10 Appendix

The recommended ACE inhibitor heart failure treatment doses as defined in CHARM analyses, and maximum doses as defined by FDA are presented in Table 64.

Table 64 Recommended ACE inhibitor heart failure treatment doses as defined in CHARM analyses, and maximum doses as defined by FDA

ACE inhibitor	Recommended heart failure target dose[a] mg/day	Maximum doses provided by FDA[b] Analysis 1 mg/day	Maximum doses provided by FDA[b] Analysis 2 mg/day
Benazepril	20	80	80
Captopril	150	**150**	**300**[c]
Enalapril	20	**20**	**40**[c]
Fosinopril	20	40	40
Lisinopril	20	**40**	**20**[c]
Perindopril	4	16	16
Quinapril	20	80	80
Ramipril	10	10	10
Trandolapril	2	4	4
Cilazapril	5	5	5
Moexipril	15	15	15
Moexipril hydrocholoride	15	15	15
Moexipril (Univasc)	15	15	15
Spirapril	20	20	20
Perinodopril See Perindopril	4	16	16
Coversyl	4	4	4
Accupril	20	20	20
Asig	20	20	20
Zestril	20	20	20
Prinivil	20	20	20
Monopril	20	20	20
Zestoretic	20	20	20
Trandolapril See above	2	2	2
Mavik	2	2	2
Monoplus	20	20	20

[a] CHARM program recommended heart failure doses.

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

[c] FDA revised doses of ACE inhibitors for Analysis 2.