CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-283/S011

Combined Medical and Statistical Review

Introduction:

Several ACE inhibitors, including captopril, ramipril, trandolapril, and lisinopril, have been approved for long-term use, based on survival benefit, in the post-myocardial infarction (MI) setting. Three ACE inhibitors, ramipril, captopril and trandolapril were studied, in double-blind, placebo-controlled outcome trials, in selected higher risk subsets of post-MI patients.

Table 1. ACE inhibitors with a post-MI indication.

Drug	Study	Findings
Captopril	SAVE (Survival and Ventricular Enlargement)	↓mortality ↓CHF hospitalization ↓overt CHF
Ramipril	AIRE (Acute Infarction Ramipril Efficacy)	↓mortality ↓CHF hospitalization ↓severe CHF
Trandolapril	TRACE (Trandolapril Cardiac Evaluation)	↓mortality ↓CHF hospitalization
Lisinopril	GISSI-3*	↓mortality

Source: Respective drug labeling.
See Tables 36 and 37 for comparisons of the SAVE, AIRE and TRACE studies.
*Based on GISSI-3, the indication is for hemodynamically stable patients within 24 hours of MI. The other studies selected higher risk patients based on clinical or imaging criteria (see Table 37).

Thus far, however, no angiotensin-receptor antagonist (ARB) has received an approval for post-MI patients.

It is worth noting an active-control ARB study which did not achieve its objective in this setting: OPTIMAAL (Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan):[1] This was a 5477 patient (mean age 67.4 years) double-blind, randomized, parallel-group active controlled non-inferiority study of losartan (up to 50 mg qd) and captopril (up to 50 mg tid) in patients with a new Q-wave MI and heart failure. Patients treated with ACEI or ARB prior to the MI were excluded. The primary endpoint was all-cause mortality, and the study was event-driven, designed to continue until at least 937 patients reached the primary endpoint. The enrollment for OPTIMAAL (similar to VALIANT) occurred between 1998 and 2002. The non-inferiority hypothesis was based on comparison of the upper one-sided 95% boundary for the relative risk for losartan vs. captopril to the prespecified constant of 1.10[2]. According to the publication, the all-cause mortality rate for losartan (n=2744) was 18.2% compared to captopril (n=2733) 16.4%, with a relative risk 1.13 (95% CI 0.99-1.28) favoring captopril.[3]

Background: VALIANT study:

In a 1998 Agency review of the VALIANT protocol, the primary (superiority) analysis was felt acceptable. However, the Agency did not agree with the non-inferiority boundary of 1.13, proposed by the sponsor, based the upper confidence interval of the hazard ratio. A boundary of 1.09 was proposed, based on the upper confidence limit (95%) from the analysis of the 3 index trials as estimate of the treatment effect whereas the sponsor used the point estimate.

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[1] Source: Dickstein K et. al. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomized trial. Lancet 2002; 360: 752-760.
[2] This constant was based on results of SAVE, AIRE, TRACE and the anterior acute MI subsets of SMILE, GISSI III, CONSENSUS II and ISIS IV.
[3] An outstanding question is whether losartan 50 mg qd represented an adequate dose.

The VALIANT (VALsartan In Acute myocardial iNfarcTion) protocol:
Title: Multinational, multicenter, double-blind, randomized, active controlled, parallel group study comparing the efficacy and safety of long-term treatment with valsartan, captopril and their combination in high-risk patients after myocardial infarction. (Protocol date: August 13, 1998)

Primary Objectives:
1. Demonstrate superiority of long-term valsartan monotherapy to captopril monotherapy in the reduction of total mortality after an acute myocardial infarction (MI);
2. Demonstrate superiority of long-term administration of a valsartan and captopril combination to captopril monotherapy in the reduction of total mortality post-MI;
3. If valsartan monotherapy cannot be shown to be superior to captopril as in objective #1, then to demonstrate that long-term valsartan monotherapy is at least as effective as captopril monotherapy in the reduction of total mortality post-MI.

Secondary Objective: Demonstrate superiority of the combination of valsartan and captopril to valsartan monotherapy in the reduction of total mortality after an acute MI.

Other key parameters:
1. To compare resource utilization and quality of life of the three treatment groups;[4]
2. To compare safety and tolerability of the three treatment arms.

Sample size: A total of 14,500 patients, allocated in a 1:1:1 ratio to captopril monotherapy, valsartan monotherapy, or the combination of valsartan and captopril, respectively.

Inclusion criteria:
1. Men; women who are not of childbearing potential or using effective contraception;
2. Age $\geq$ 18 years old;
3. Who have sustained an acute MI and are no less than 12 hours and no more than 10 days after the onset of symptoms;
4. Presence of either clinical or radiological signs of heart failure and/or evidence of LV systolic dysfunction (see definitions, below).

Definitions:
Acute MI:
In order to fulfill criteria for acute MI:[5]
1. All patients must have an increase in the plasma concentration of cardiac enzymes:
    1. Either CK at least 2x the upper limit of normal range, or CK-MB above the upper limit of normal and at least 5% of the total CK.
    2. If total CK or CK-MB not available, then troponin T or I at least 3 x upper limit of normal range.

    (**Reviewer note**: biomarker definitions were changed in Protocol Amendments 2 and 3).

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[4] Results not included in this submission.
[5] The VALIANT protocol was not designed to include silent MI (e.g. EKG changes only) as either an index or recurrent non-fatal MI.
According to the sponsor, if MI was suspected, based on the ECG, but the patient died prior to hospitalization, the cause of death could be adjudicated as a fatal MI based on chest pain and ECG changes without having met the strict definition of MI.)

3. All patients must have either typical ECG changes or typical clinical presentation: typical ECG changes include evolving ST or T changes in two or more contiguous leads, development of new pathological Q/QS waves in two or more contiguous leads, or the development of new left bundle branch block.

Heart failure:
Heart failure was defined by at least one of the following:
1. Radiological evidence of left ventricular (LV) failure: pulmonary venous congestion with interstitial or alveolar edema (must be supported by at least one chest radiograph);
2. Clinical evidence of LV failure: pulmonary edema (bilateral post-tussive crackles extending at least one-third of the way up the lung fields in the absence of pulmonary disease) or the presence of a third heart sound with persistent tachycardia.

Clinical or radiological evidence of LV failure following the qualifying acute MI could be transient and may not have been present at the time of randomization.

LV systolic dysfunction:
At least one of the following was sufficient for the criterion of LV systolic dysfunction:
1. Echocardiography: LV ejection fraction (EF) $\leq$35% or a wall motion index $\leq$ 1.2;
2. Radionuclide ventriculography: LVEF $\leq$ 40%;
3. Ventricular contrast angiography: LVEF $\leq$ 35%.

Relevant Exclusion criteria:
(1) Cardiogenic shock within 24 hours prior to randomization; (2) systolic BP < 100 mm Hg; (3) serum creatinine > 221 µmol/L (2.5 mg/dl); known/suspected renal artery stenosis; (4) stroke/TIA within previous month;(5) refractory or potential lethal ventricular arrhythmia;(6) refractory angina; (7) planned cardiac surgery within 15 days after randomization; (8) known intolerance to ACE inhibitor or angiotensin receptor antagonist; (9) clinically significant right ventricular (RV) infarction; (10) obstructive cardiomyopathy; (11) serious non-cardiovascular disease limiting life expectancy; (12) previous major organ transplantation or awaiting transplantation; (13) other condition associated with poor compliance; (14) current participation in investigational drug or device trial (except for non-coated or heparin-coated stents).

In the original protocol, treatment with an ACE inhibitor or angiotensin II blocker (ARB) prior to randomization was not an exclusion, "provided that this treatment is discontinued at least 12 hours before randomization." **(Reviewer**: this criterion was changed, in amendment 2, to allow ACE inhibitor or ARB use).

Study treatment:
1. Captopril monotherapy, with a target dose of 50 mg three times daily (tid);
2. Valsartan monotherapy, with a target dose of 160 mg twice daily (bid);
3. The combination of captopril and valsartan; the target doses are captopril 50 mg tid and valsartan 80 mg bid. [6]

Medication was dispensed tid with placebo tablets/capsules (double dummy).
The treatment objective was to ensure that each patient received the maximal tolerated dose of study medication up to the target dose. Study medication was administered in a stepwise titration

[6] According to the sponsor, the half-maximal dose of valsartan was chosen for the combination arm because of safety concerns (hemodynamic instability, increase in prespecified adverse events as well as other serious adverse events) due to excessive renin-angiotensin system blockade.

with four titration steps. The decision whether or not to up-titrate was left to the investigator's discretion based on the patient's status.

Titration criteria: The criteria for upward titration of study medication were:

1. Persistent SBP > 90 mm Hg;
2. No symptoms of hypotension (e.g., syncope, orthostatic dizziness, faintness, lightheadedness);
3. Serum creatinine (measurement required before the initial titration from Step I to II and from Step II to III; an additional creatinine measurement was added, in Amendment 1, before up-titration to Step IV) must be < 265 µmol/L (3.0 mg/dl) and must not have increased by more than 1.0 mg/dl from baseline (Visit 1 value).

Down-titration or temporary interruption was permitted if a patient could not tolerate a particular dose or if the study medication cannot be continued for a concomitant medical condition/surgery.

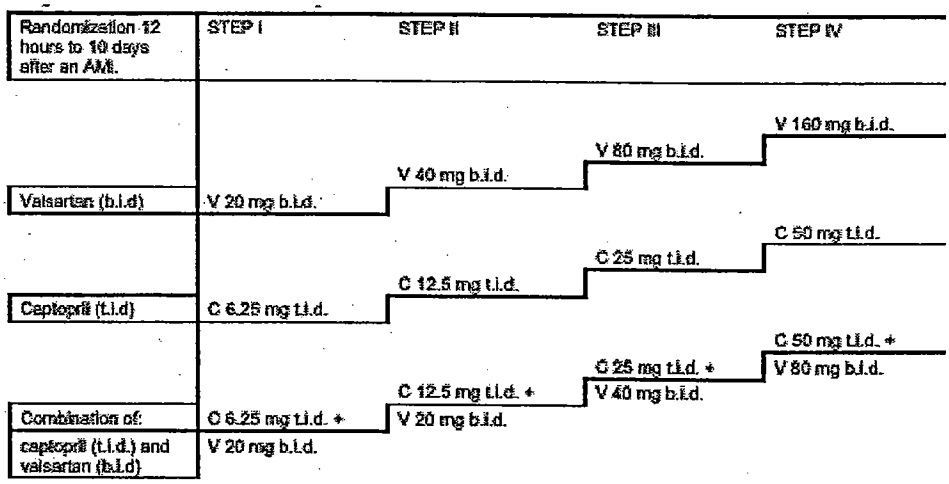

Figure 1. Treatment regimen (C= captopril; V= valsartan)

Study design: This was an active-controlled study. The AIRE, SAVE and TRACE studies were chosen for external validation since, according to the sponsor, these were the definitive placebo-controlled long-term mortality trials that have defined a survival benefit in a high-risk group of post-MI patients.

The study consisted of two phases: 1. Medication initiation and titration phase; and 2. Maintenance phase. Initiation of study medication occurred at Visit 1 on Day 1. Dose titration and maintenance occurred at Visits 2-16. Visit 2 occurred on Day 15 or hospital discharge, whichever occurred first.

Study duration: The study was event-driven and planned to continue until 2700 patients reached the primary endpoint (death). On that date, the vital status of all randomized patients was collected and the study was considered completed.

Discontinuation of study medication: Permanent discontinuation of study medication was considered if the patient withdrew consent, an investigator considered it advisable, an intolerable or life-threatening adverse event (AE) occurred that was suspected to be a drug effect, or if the study medication was unblinded. Patients discontinued from study medication were to continue the visit schedule and undergo evaluation for the occurrence of endpoints. In cases where

patients withdrew consent, vital status was followed to the end of the study. If a patient was lost to follow-up, then the status of the patient at the last visit or contact was used for the final analysis.

The following committees were employed in the VALIANT study:
1. Executive Committee[7]
2. Steering Committee[8]
3. Endpoint Committee (independent of the sponsor and without direct contact with randomized patients): agreed on endpoint definitions/ procedures and provided an independent and blinded assessment of causes of death, reinfarctions and CHF hospitalizations;
4. Data and Safety Monitoring Board (DSMB) (independent of Novartis, study management organizations and investigators): monitored safety based on initial analysis after the first 1000 patients completed $\geq$ 1 month in the study and on subsequent safety analyses every 6 months thereafter; monitored efficacy based on two planned interim analyses, performed when 900 and 1800 primary endpoints (deaths) have been observed.

Efficacy evaluations: The Endpoint Committee adjudicated causes of death and selected secondary endpoints based upon predefined definitions and procedures for this study. The process of endpoint adjudication, as well as definitions and required documentation, were included in an Endpoint Manual.

Primary efficacy parameter: The primary efficacy parameter was all-cause mortality (time to death).

Secondary efficacy parameters: **(Reviewer note**: Secondary endpoints were changed to tertiary endpoints in Protocol Amendment 5).
1. All-cause (unplanned and elective) hospitalization;
2. All-cause mortality and all-cause hospitalization;
3. Hospitalization for heart failure (defined as unplanned iv treatment of new or worsening heart failure with inotropic agents, diuretics or vasodilators requiring or occurring during any hospital admission or overnight stay in a health care facility);
4. All-cause mortality and hospitalization for heart failure;
5. Cardiovascular mortality (defined as sudden death, or death attributed to recurrent MI, heart failure, cardiovascular procedure, stroke or other cardiovascular etiology);
6. Cardiovascular mortality and hospitalization for heart failure;
7. Cardiovascular mortality, hospitalization for heart failure, and recurrent non-fatal MI;
8. Cardiovascular mortality, hospitalization for heart failure, recurrent non-fatal MI, and coronary revascularization procedures (defined as unplanned and elective percutaneous coronary angioplasty, stent, other percutaneous coronary revascularization, and coronary artery bypass surgery);
9. Cardiovascular morbidity (defined as hospitalization for heart failure, unplanned hospitalization for non-fatal recurrent MI, unstable angina, sudden cardiac arrest with

[7] The role of the Executive Committee was to develop scientific rationale and protocol, review and approve protocol amendments, lead Steering Committee, approve membership of the other committees, oversee study conduct, serve as liaison between DSMB and Steering Committee as well as between Novartis and other committees.

[8] The role of the Steering Committee was to review study progress, serve as liaison between investigators and the Executive Committee, and make ethical, scientific and policy decisions regarding study conduct, act on DSMB recommendations, review protocol amendments, review and approve presentations and publications.

resuscitation, transient ischemic attack (TIA), other cardiovascular-related unplanned hospitalization);
10. All cause mortality and cardiovascular morbidity;
11. Sudden death and cardiac arrest with resuscitation;
12. Coronary revascularization procedures;
13. Cardiovascular procedures (defined as coronary revascularization procedures, cardiovascular procedures for heart failure, heart transplant, or other vascular procedures);
14. All cause mortality at 30 days.

The Process of Endpoint Adjudication:
A Guideline Document (version dated February 21, 2003) outlined the procedure for clinical event classification, which was planned as a collaborative effort between the Clinical Events Classification group at the Duke Clinical Research Institute (DCRI CEC) and the Endpoint Committee at Brigham and Women's Hospital Clinical Endpoint Center (BWH CEC). The DCRI CEC identified patients with suspected endpoint events, coordinated the collection of required documentation, and confirmed suspected rehospitalizations. The role of the BWH CEC was to define and adjudicate important non-fatal events of CHF hospitalization, MI, stroke, and sudden cardiac arrest with resuscitation. In addition, the BWH CEC classified all reports of death in the VALIANT trial.

All hospitalizations, other than MI, CHF, stroke and sudden cardiac arrest with resuscitation were reviewed by DCRI CEC to determine primary reason for hospitalization; if the primary reason was determined to be MI, CHF or stroke and an endpoint was not triggered by the site, BWH reviewed all such rehospitalizations in order to make a determination as to whether a VALIANT endpoint occurred.

The DCRI CEC group was responsible for providing BWC CEC with adequate information, including endpoint review forms, required source documents (including clinical hospital summaries translated into English), and appropriate CRF pages.

The goal of the BWC CEC was to adjudicate all events within 2 weeks from the time a complete patient folder was received, and to resolve any outstanding source document request by BWH within 2 weeks.[9]

The analysis cutoff date was January 7, 2003; events occurring after this date were not adjudicated.

The Chairman of the BWH CEC was Marc Pfeffer, MD, PhD. The Co-Chairman was Scott Solomon, MD. The DCRI Clinical Faculty Leader was Kenneth W. Mahaffey, MD.

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[9] For multiple events or any event occurring during Visit 2, the reviewer would present all events in each hospitalization to the Committee for a consensus opinion. For interesting, difficult or particularly noteworthy events, the Chairman or Co-Chairman would dictate an event summary that will be maintained at the BWH CEC in the Case Precedent Listing.
For quality assurance, the BWC CEC re-reviewed 100 previously adjudicated events randomly selected by DCRI; two events out of 100 required a change in the original classification. A subset of rehospitalization events coded by DCRI CEC was randomly selected for blinded re-review by BWH CEC. Of the 55 cases, there was agreement in all but 3/55 cases as to "cardiac" vs. "noncardiac" reasons.

Reviewer note: In addition to his roles as member of the Steering Committee and Chairman of the Executive Committee, Marc Pfeffer, MD, PhD was Chairman of the BWH Clinical Endpoint Committee.

Reviewer: The procedure of adjudication appears acceptable.

Safety assessments: These consisted of monitoring pre-defined safety/tolerability endpoints, all serious AE, and regular measurements of vital signs. Pre-defined safety/tolerability endpoints were known side effects of either captopril or valsartan. These included:

--Symptomatic hypotension (defined as hypotension, including first dose hypotension, accompanied by symptoms (i.e., dizziness, faintness, and diaphoresis) or persistent hypotension leading to dose reduction, temporary interruption or permanent discontinuation of medication (not a reason for unblinding).

--Renal dysfunction, defined as death from renal failure, end-stage renal disease requiring dialysis/ transplant or increase in serum creatinine leading to temporary or permanent discontinuation of medication (not a reason for unblinding).

--Dry cough, defined as dry, either persistent or paroxysmal, and usually developing between 1 week and 6 months after initiation of therapy (not a reason for unblinding).

--Angioedema, characterized by rapid swelling in the nose, throat, mouth, glottis, larynx, lips/tongue. Study treatment must be permanently discontinued; unblinding could be considered in this circumstance.

Pharmacokinetics: No drug levels or pharmacokinetic assessments were planned.

Database management: Database management and quality control for this study were the responsibility of Duke Clinical Research Institute, Durham, NC.

Statistics:
Primary hypotheses:
According to the sponsor, the primary hypotheses were whether valsartan was either superior to or as effective as ("non-inferior to") captopril, and whether the combination of captopril and valsartan was superior to captopril monotherapy with respect to all-cause mortality. The primary efficacy variable for these comparisons was time to death, and these hypotheses were to be tested using a Cox regression analysis. Cox regression analyses were also planned for secondary efficacy variables. The data were analyzed by the sponsor.

Analysis populations: In the original protocol, the primary analysis population consisted of all randomized patients who received study medication. (**Reviewer**: This definition was changed in Protocol Amendment 5). In analyses based on this population, all events occurring up to and including the time of trial completed were to be included in analyses, regardless of whether the events occurred before or after discontinuation of double-blind treatment.

The per-protocol population consisted of all patients receiving, at least once, titration Step II of study medication (**Note**: this definition was changed in Protocol Amendment 5). Since use of an ACE inhibitor or angiotensin II blocker other than study medication prior to permanent discontinuation of trial medication was considered a major protocol violation, patients in per-protocol time-to-event analyses who were event-free up to the first date on which they received a

drug in one of these classes was considered censored as of that date. In the per-protocol analyses, if a patient permanently discontinued double-blind treatment and an event had not occurred by the date of discontinuation, then the time-to-event for that patient would be considered censored as of the date of discontinuation, regardless of reason for discontinuation.

Interim analyses were planned based on the primary analysis population.

Efficacy evaluation:
The primary efficacy variable was time to death. This was to be calculated for each non-surviving patient as the difference between the date of death and the date of randomization.

Adjustment for multiple comparisons:
In the protocol, an overall significance level of 0.0253 (Sidak adjustment) was planned; for the superiority hypotheses two-sided tests were planned, and a one-sided test was planned for the non-inferiority hypothesis.

For the superiority comparison, the null hypothesis was that the risk ratio (hazard ratio for mortality) between captopril and valsartan was equal to 1, versus the alternative hypothesis that it is not equal to 1.

For the non-inferiority comparison, the null hypothesis was that the risk ratio between captopril and valsartan was at least $1 + \Delta$, where Δ is the acceptance range within which the two treatments are considered to be equivalent (defined by the sponsor to be 0.13). The Δ value was selected by the sponsor based on a meta-analysis of the AIRE, TRACE and SAVE studies, which indicated an estimated 22.5% hazard ratio benefit for an ACE inhibitor relative to placebo, with a 95% confidence interval of 14.4% to 29.8%.

A superiority test was planned for the primary comparison between the captopril-valsartan combination and captopril monotherapy. The null hypothesis was that the risk ratio between the combination therapy and captopril was equal to 1.

The primary analysis model for each comparison contained treatment group, age (as a continuous covariate) and the occurrence of a previous myocardial infarction. The assumption of proportionality of the treatment arm hazard functions (i.e., constant hazard ratio) will be investigated, and implications for the primary analysis results of any non-proportionality will be considered. Supplemental log rank tests were also planned.
Valsartan monotherapy was considered superior to captopril monotherapy if the difference between these treatment arms, using the primary analysis population and the Cox regression analysis of the primary variable, was statistically significant in favor of valsartan using a two-sided level of 2.53%.
If valsartan was not shown to be superior to captopril then, according to the protocol, valsartan would be concluded to be non-inferior to captopril if the upper limit of the confidence interval for the hazard ratio (derived from the Cox regression estimate and using a one-sided significance level of 2.53%) was less than 1.13.
The combination of captopril and valsartan was considered superior to captopril if the difference between these treatment arms, using the primary analysis population and the Cox regression analysis of the primary variable, was statistically significant in favor of the combination using a two-sided significance level of 2.53%.

Exploratory subgroup analyses: As prespecified in the protocol, these analyses included the possibility of differential treatment effects in subgroups defined by age, gender, race, prior MI,

history of hypertension, diabetes, hyperlipidemia or smoking, time to randomization, Killip class, infarct location and type, history of coronary revascularization procedures, evidence of LV dysfunction or heart failure, and use of beta blockers, aspirin, ACE inhibitors or ARBs, or thrombolytics prior to randomization.

Interim analyses:
Two formal interim analyses for the primary efficacy endpoint were planned. Cutoff dates for the first and second interim analyses were approximately equally spaced with respect to the targeted total number of deaths prior to study completed; the interim analyses were thus planned to be performed at the time roughly 900 and 1800 deaths have been reported. A cumulative two-sided significance level of 2.53% was planned to indicate formal statistical significance for each of the three pairwise comparisons of the treatment arms. The interim analyses were performed by an independent statistical center, and the results reviewed by the independent DSMB.

Sample size and power considerations:
In sample size calculations, an annual mortality rate of 6.9% for captopril patients was assumed, based on results in the AIRE, SAVE and TRACE studies, and the use of a similar high-risk population.

In the protocol, it was desired that the non-inferiority comparison have adequate power to demonstrate that valsartan was as effective as captopril if the true benefit for valsartan was in the range 0-2.5%. Using a one-sided significance level of 0.0253, a total of 1850 primary events in these two treatment arms would provide 88.1% power if valsartan was actually 2.5% better than captopril, and 74% power if the mortality risk was identical in these two treatment groups. When the power considerations for superiority were taken into account, the sponsor concluded that 2700 events would provide adequate power to address the primary objectives.

Laboratory abnormalities:
Except for serum creatinine, results of routine laboratory measurements were not recorded in the CRF. Laboratory values obtained as part of patient care and evaluation were kept in the patient's study chart (source document).

Amendments to the Protocol:
1) Amendment 1: January 7, 1999:
   a) Changed titration threshold to SBP $\geq$ 100 mm Hg within 72 hours after the onset of MI;
   b) Added serum creatinine measurement prior to up-titration to Step IV; Step III should not be exceeded if serum creatinine rose above 2.5 mg/dl;
   c) Up-titration was allowed at any time during the day;
   d) Clarified supplemental information to DSMB for their review of interim efficacy data and statistical adjustment;
   e) Gave DSMB the option of unblinding certain safety events (i.e., angioedema, dry cough, renal dysfunction, symptomatic hypotension);

2) Amendment 2: June 8, 1999:
   a) Amended enzyme definition of MI to include rise in CK-MB of at least 2x ULN where total CK is unavailable (clinical/ECG criteria remain as before);
   b) Changed prohibition to "strong discouragement" to use of open-label ACEI/ARB;

c) Patients previously on a stable higher dose of ACEI/ARB prior to study start could be given Step II therapy as initial dose and be up-titrated, if eligible, after a 12-hour observation period (previous ACEI/ARB therapy must have been withdrawn at least 12 hours prior to randomization);
d) Per-protocol population definition amended to include inclusion criteria of having sustained an MI;
e) In the per-protocol analysis, censoring of data occurred for patients off study medication or who have taken open-label ACEI/ARB (either continuously or intermittently) for at least two consecutive visits. For the patient temporarily discontinuing from double-blind treatment for two consecutive visits, the censoring will begin subsequent to the second visit; for the patient taking ACEI/ARB other than study medication for two consecutive visits, the censoring will begin at the date of the second of the two visits.

3) Amendment 3: November 17, 1999: According to the sponsor, the wording change in Amendment 2 [redacted] had the unintended consequence of significantly changing the overall sensitivity/specificity of entry criteria. This Amendment was made to correct that unintended change.
   a) Amended serum biomarker/enzyme definition of MI as follows:

Table 2. Cardiac biomarker criteria for MI (each patient must satisfy a row in order to qualify)

CK	CK-MB	Troponin
> ULN	≥ 2 x ULN	--
≥ 2 x ULN	> ULN	--
> ULN	> ULN	≥ 3 x ULN
NA	≥ 2 x ULN	--
--	> ULN	≥ 3 x ULN
≥ 2 x ULN	NA	--
> ULN	--	≥ 3 x ULN
NA	NA	≥ 5 x ULN

Clinical/EKG criteria remained unchanged.

4) Amendment 4: December 17, 1999: included five substudies (echocardiography substudy, neurohormone substudy, genetic marker substudy, microalbuminuria substudy, and registry substudy) to be performed at selected sites.[10]

5) Amendment 5: August 13, 1998:
   a) The primary analysis population was amended to include all randomized patients; the original protocol defined the primary analysis population as randomized patients who received study medication (modified intent-to-treat). As a result of this amendment, 77 patients were added to the primary analysis population. The modified intent-to-treat population would undergo supplementary analysis.
   b) The per-protocol population was amended to include all patients who received at least one dose of study medication at any titration step (Amendment 2 specified inclusion of patients who received, at least once, titration Step II medication).

[10] Results of these substudies were not included in this submission.

c) It was decided that the Endpoint Committee would adjudicate occurrences of stroke. Stroke was added as a component of one of the secondary efficacy variables; in addition, stroke was added as a tertiary efficacy variable. The new secondary efficacy variables were thus changed to:
   i) Cardiovascular mortality (defined as sudden death, or death attributed to recurrent MI, heart failure, cardiovascular procedure, stroke, or other cardiovascular etiology);
   ii) Cardiovascular mortality, recurrent non-fatal MI, and hospitalization for heart failure (defined as unplanned intravenous treatment of new or worsening heart failure with inotropic agents, diuretics, or vasodilators requiring or occurring during any hospital admission or overnight stay in a health care facility);
   iii) Cardiovascular mortality, recurrent non-fatal MI, hospitalization for heart failure, sudden cardiac arrest with resuscitation, and non-fatal stroke.
d) The other 14 secondary endpoints were now treated as tertiary endpoints. Additional tertiary endpoints included: 1) fatal and non-fatal stroke; and 2) all cause mortality, non-fatal recurrent MI, and hospitalization for heart failure.
e) In the per-protocol analysis, time-to-event will be considered censored as of the 31st date after the date of permanent discontinuation of study medication, regardless of the status of off-protocol medication.

Data Safety and Monitoring Board (DSMB):
The DSMB was responsible for monitoring study progress with regard to patient safety; monitoring efficacy and safety according to two planned interim analyses to be performed on the primary efficacy endpoint; and review study protocol and review and approve the DSMB manual. The statistical report to the DSMB was provided by an Independent Statistical Center, which was to function independently from investigators, Executive Committee, Steering Committee, the Sponsor and the coordinating center.

The DSMB was composed of 5 physicians and 1 biostatistician who were not involved in the conduct of the study or employees of Novartis or Duke CRI.

The initial DSMB members were: Alain Leizorovicz, MD; Robert J. Cody, MD; Henry Dargie, MD; Charles Hennekens, MD; Jean-Louis Imbs, MD; Stuart Pocock (statistician). The ISC was headed by F. Boutitie (statistician). Prior to the first review of safety data on August 26, 1999, Dr. Jean-Louis Imbs declined participation due to a conflict of interest and was not replaced.

Interim analyses:
According to DSMB minutes as well as a letter from the sponsor, the DSMB reviewed 6 safety interim analyses, 2 efficacy interim analyses and an ad hoc review of results from another valsartan trial, as outlined below:

Table 3. Schedule of DSMB meetings

Date of meeting	Subject
August 24, 1999	Safety interim analysis #1
February 25, 2000	Safety interim analysis #2
September 8, 2000	Safety interim analysis #3
November 22, 2000	Ad Hoc meeting/Review of Val-Heft results (regarding effects of beta-blocker with an ACE inhibitor)
March 17, 2001	Efficacy interim analysis #1 Safety interim analysis #4

October 2, 2001	Safety interim analysis #5
March 16, 2002	Efficacy interim analysis #2 Safety interim analysis #6

Reviewer: DSMB minutes were requested and reviewed; the DSMB appeared to perform independently and without evidence of bias.

Other changes to the Conduct of the Study: None

Note: Information from one site in the Czech Republic (105 patients) was excluded from analysis, prior to unblinding, because the adequacy of informed consent could not be assured. These data were removed from the datasets prior to transfer from DCRI to the sponsor for unblinding and analysis. CRFs and endpoint documentation were sequestered and returned to the Czech Republic.

Results: As this was an event-driven trial, the completion date, when the 2700th death occurred, was estimated to be October 29, 2002. As a result of follow-up attempts, the final number of deaths was ascertained to be 2879. Vital status was ascertained for all patients as of October 1, 2002.
This study involved 931 centers (excluding the above-mentioned site in the Czech Republic) in 24 countries. The United States randomized the highest percentage (27%) followed by the Russian Federation (21.3%) and Canada (7.4%).
Unless otherwise noted, results will be presented for the primary analysis population.

Patient Disposition: The following tables display patient disposition. The percentages of patients who completed the study, withdrew consent, and lost to follow-up appear balanced across treatment groups.

Table 4. Patient Disposition (primary analysis population)

Disposition	Valsartan (N=4909) n (%)	Valsartan + Captopril (N=4885) n (%)	Captopril (N=4909) n (%)
Total Randomized	4909 (100)	4885 (100)	4909 (100)
Completed *	4683 (95.4)	4656 (95.3)	4691 (95.6)
Dead	941 (19.2)	911 (18.6)	933 (19)
Alive	3742 (76.2)	3745 (76.7)	3758 (76.6)
Premature Study Termination	226 (4.6)	229 (4.7)	218 (4.4)
Withdrew consent	195 (4)	197 (4)	197 (4)
Dead	39 (0.8)	30 (0.6)	25 (0.5)
Alive	134 (2.7)	151 (3.1)	155 (3.2)
Unknown	22 (0.4)	16 (0.3)	17 (0.3)
Lost to follow-up	31 (0.6)	32 (0.7)	21 (0.4)

*Patients who did not withdraw consent or patients whose vital status were known after October 1, 2002. This table does not include one patient (2415-008) on valsartan who died on February 21, 2003 (after the cut-off date January 1, 2003); this patient's cause of death was not adjudicated.

The percentage of patients discontinuing prematurely appear highest in the combination arm and lowest in the valsartan group.

Table 5. Premature permanent discontinuation of study drug by treatment (primary analysis population)

	Valsartan	Valsartan +Captopril	Captopril
Total # randomized	4909	4885	4909
# prematurely discontinued study drug but received at least one dose study drug	1001 (20.4)	1139 (23.3)	1055 (21.5)
Principal reasons:			
Adverse event	282 (5.7)	438 (9)	375 (7.6)
Withdrew consent	380 (7.7)	373 (7.6)	355 (7.2)
Lost to follow-up at time of study drug discontinuation (vital status determined at study completion for some)	31 (0.6)	35 (0.7)	30 (0.6)
Treatment failure	3 (0.1)	3 (0.1)	2 (0)
Unknown	132 (2.7)	145 (3)	143 (2.9)

Protocol Deviations:
For the primary analysis population, protocol deviations were noted in about 16% (n=774) of valsartan patients and about 17% of patients randomized to captopril (n=856) or the combination arm (n=832). About 4% (n=190) valsartan patients, 3.4% (n=168) captopril patients, and 3.6% (n=177) of those taking the combination were noted to have some admission criteria deviation; the most common of these was "MI enzyme criteria not fulfilled" (2.3-2.5%) with no gross differences across treatment groups.

After premature (permanent) discontinuation of study drug, 45.7% (n=466) of valsartan patients (n=1020), 42.9% (n=463) of captopril patients (n=1078), and 41.7% (n=482) of those on the combination (n=1156) were taking open-label ACEI; in this population, about 11% of patients discontinuing from valsartan, and about 18% of patients discontinuing from captopril or the combination took open-label ARB.
In the primary analysis population, about 0.5-0.6% of patients did not receive trial medication with no imbalances across treatment groups.

Baseline characteristics:
As presented below, this population was mainly male (69-70%) and mostly Caucasian (93-94%). More than half were 65 years and older. Over half had a history of hypertension; however, overall mean baseline BPs were within acceptable control. About 28-29% had a history of prior MI.

In terms of cardiovascular history, the incidence of CHF was slightly higher in the valsartan group; otherwise, no imbalance was seen across treatment groups with respect to cardiovascular, demographic and other baseline characteristics

Table 6. Cardiovascular history: (prespecified with check boxes on CRF) (primary analysis population)

Cardiovascular history / disease factor	Valsartan (N=4909)	Valsartan + Captopril (N=4885)	Captopril (N=4909)
	n (%)	n (%)	n (%)
Angina pectoris	1972 (40.2)	1922 (39.3)	1947 (39.7)
Unstable angina	1029 (21.0)	1066 (21.8)	1034 (21.1)
MI	1395 (28.4)	1376 (28.2)	1333 (27.2)
PTCR	376 (7.7)	337 (6.9)	354 (7.2)
CABG	355 (7.2)	327 (6.7)	344 (7.0)
CHF	759 (15.5)	701 (14.4)	714 (14.5)
TIA	138 (2.8)	126 (2.6)	149 (3.0)
Stroke	292 (5.9)	305 (6.2)	298 (6.1)
Atrial fibrillation	334 (6.8)	314 (6.4)	312 (6.4)
Automatic implantable cardiac defibrillator	17 (0.3)	16 (0.3)	17 (0.3)
Peripheral vascular disease	433 (8.8)	402 (8.2)	402 (8.2)
Dyslipidemia	1500 (30.6)	1416 (29.0)	1419 (28.9)
Chronic obstructive pulmonary disease	429 (8.7)	416 (8.5)	413 (8.4)
Chronic renal insufficiency	89 (1.8)	86 (1.8)	91 (1.9)
Chronic alcohol abuse	80 (1.6)	89 (1.8)	80 (1.6)
History of cancer within 5 years	122 (2.5)	95 (1.9)	102 (2.1)
Hypertension	2726 (55.5)	2693 (55.1)	2681 (54.6)
Treated	2180 (44.4)	2153 (44.1)	2153 (43.9)
Diabetes	1134 (23.1)	1146 (23.5)	1120 (22.8)
Insulin treated	346 (7.0)	336 (6.9)	313 (6.4)
Smoking status (current/past)	3135 (63.9)	3090 (63.3)	3119 (63.5)

Table 7. Baseline characteristics (primary analysis population)

	Valsartan (N=4909) n (%)	Valsartan + Captopril (N=4885) n (%)	Captopril (N=4909) n (%)
Sex N (%)			
Male	3365 (68.5)	3395 (69.5)	3373 (68.7)
Female	1544 (31.5)	1490 (30.5)	1536 (31.3)
Race N (%)			
Caucasian	4604 (93.8)	4553 (93.2)	4591 (93.5)
Black	125 (2.5)	137 (2.8)	145 (3.0)
Asian	44 (0.9)	53 (1.1)	44 (0.9)
Other	136 (2.8)	142 (2.9)	129 (2.6)
Age group N (%)			
< 65 years	2313 (47.1)	2370 (48.5)	2305 (47.0)
≥ 65 years	2596 (52.9)	2515 (51.5)	2604 (53.0)
Height (cm) N	4819	4778	4804
Mean (SD)	169.4 (9.44)	169.8 (9.74)	169.6 (9.5)
Weight (kg) N	4839	4801	4833
Mean (SD)	80.5 (16.59)	80.4 (16.40)	80.1 (16.35)
Systolic BP (mm Hg) N	4905	4882	4909
Mean (SD)	122.7 (16.85)	122.5 (17.10)	122.8 (16.99)

Diastolic BP (mm Hg) N Mean (SD)	 4899 72.3 (11.29)	 4879 72.3 (11.35)	 4909 72.4 (11.18)
Heart rate (bpm) N Mean (SD)	4897 76.2 (12.98)	4872 76.2 (12.74)	4900 76.2 (12.76)

Mean baseline serum creatinine was 1.1 mg/dl for all 3 groups.

Characteristics of the qualifying MI follow. About 81% of patients in each treatment group presented with typical ECG changes, symptoms and increased enzymes (biomarkers). A majority were Q-wave MIs. About 44-46% of the myocardial infarctions were anterior; 23-25% were inferior. Almost half of the patient population were Killip class II. Documentation of LV dysfunction appeared most commonly in relationship to clinical or imaging criteria.
Mean (SD) time from qualifying MI to randomization was 6.1 (SD 2.5-1.6) days for all treatment groups.

Table 8. MI characteristics (primary analysis population)

Characteristic / therapy	Valsartan (N=4909)	Valsartan + Captopril (N=4885)	Captopril (N=4909)
	n (%)	n (%)	n (%)
MI documentation:			
Increased cardiac enzymes, typical ECG symptoms, and typical clinical presentation	3985 (81.2)	3978 (81.4)	3990 (81.3)
Increased cardiac enzymes and typical clinical presentation	584 (11.9)	539 (11.0)	551 (11.2)
Increased cardiac enzymes and typical ECG symptoms	335 (6.8)	362 (7.4)	363 (7.4)
Other	5 (0.1)	6 (0.1)	5 (0.1)
MI site:			
1. Anterior	2134 (43.5)	2174 (44.5)	2155 (43.9)
2. Inferior	1136 (23.1)	1119 (22.9)	1162 (23.7)
3. Other	445 (9.1)	385 (7.9)	416 (8.5)
1. and 2.	122 (2.5)	134 (2.7)	143 (2.9)
1. and 3.	464 (9.5)	470 (9.6)	455 (9.3)
2. and 3.	283 (5.8)	295 (6.0)	270 (5.5)
1., 2. and 3.	45 (0.9)	53 (1.1)	43 (0.9)
Missing	280 (5.7)	255 (5.2)	265 (5.4)
MI type:			
1. Q-wave	3050 (62.1)	3068 (62.8)	3141 (64.0)
2. Non-Q-wave	1437 (29.3)	1429 (29.3)	1374 (28.0)
3. New LBBB	82 (1.7)	77 (1.6)	89 (1.8)
1. and 2.	6 (0.1)	6 (0.1)	9 (0.2)
1. and 3.	60 (1.2)	58 (1.2)	45 (0.9)
2. and 3.	69 (1.4)	59 (1.2)	69 (1.4)
Missing	205 (4.2)	188 (3.8)	182 (3.7)
Killip class			
I	1294 (26.4)	1381(28.3)	1424(29.0)
II	2401 (48.9)	2329 (47.7)	2346 (47.8)
III	874 (17.8)	842 (17.2)	813 (16.6)
IV	313 (6.4)	312 (6.4)	306 (6.2)
Missing	27 (0.6)	21 (0.4)	20 (0.4)

Cardiac enzyme results are presented below; the highest sample size (non-missing) is available for total CK. Most of the mean values, except troponin T, are slightly lower in the valsartan

group compared to the results in patients randomized to captopril; however, not every patient underwent the same enzyme testing.

Table 9. MI documentation by cardiac enzymes (primary analysis population)

	Valsartan (N=4909)	Valsartan + Captopril (N=4885)	Captopril (N=4909)
Highest total CK (U/L) N (non-missing)	4418	4426	4460
Mean (SD)	1766.3 (1980.4)	1830.5 (2102.3)	1818.6 (2009.1)
Highest CK-MB (U/L) N (non-missing)	809	830	845
Mean (SD)	148.4 (148.9)	162.5 (197.1)	167.6 (182.4)
Highest CK-MB (µg/L) N (non-missing)	828	831	800
Mean (SD)	189.6 (221)	197.4 (236.6)	190.1 (225.5)
Highest troponin I (ng/ml) N (non-missing)	1718	1745	1746
Mean (SD)	126.1 (320.8)	144.5 (414.8)	163.4 (781.5)
Highest troponin T (ng/ml) N (non-missing)	579	558	570
Mean (SD)	5.6 (18.2)	4.5 (7.5)	5.3 (10.1)

Local laboratories at the 931 sites were used for the analysis of cardiac enzymes.

Table 10. MI documentation and characteristics by treatment group (primary analysis population)

Characteristic	Valsartan (N=4909)	Valsartan + Captopril (N=4885)	Captopril (N=4909)
CHF/LV dysfunction documentation			
1. Clinical evidence	1065 (21.7)	1046 (21.4)	1010 (20.6)
2. Radiologic evidence	143 (2.9)	132 (2.7)	144 (2.9)
3. Quantitative imaging evidence	1111 (22.6)	1161 (23.8)	1125 (22.9)
1 and 2	906 (18.5)	914 (18.7)	976 (19.9)
1 and 3	816 (16.6)	805 (16.5)	797 (16.2)
1, 2 and 3	691 (14.1)	639 (13.1)	687 (14)
No evidence	7 (0.1)	11 (0.2)	7 (0.1)

Mean ejection fractions (EF) were 35.6-35.7 % via echocardiography, 35.5-35.7% by radionuclide ventriculogram and 34.3-34.6 by ventricular angiography (SD 10-12 range) across the three groups. No gross imbalances were seen across treatment groups with respect to MI site, MI documentation, Killip class, NYHA class or CHF/LVD documentation. (Note: the sponsor

claims that there is an increased incidence of higher Killip class patients randomized to valsartan; according to the sponsor, this may explain the hypotension seen with valsartan patients—see Safety section).
For each treatment group, about 27-28% presented with NYHA class I, 40% with NYHA class II, 21-22% NYHA class III, and 4% with class IV symptoms; 8-9% per group were missing NYHA classification.

Table 11. Use of therapies in association with qualifying MI (primary analysis population)

	Valsartan (N= 4909) n (%)	Valsartan + Captopril (N=4885) n (%)	Captopril (N=4909) n (%)
Aspirin	4544 (88.5)	4367 (89.4)	4372 (89.1)
ACEI	2044 (41.6)	2104 (43.1)	2023 (41.2)
IIb/IIIa inhibitor	656 (13.4)	611 (12.5)	657 (13.4)
ARB	73 (1.5)	59 (1.2)	53 (1.1)
Beta-blocker	2865 (58.4)	2908 (59.5)	2938 (59.8)
Thrombolytic therapy	1741 (35.5)	1711 (35)	1718(35)
Primary PTCR	731(14.9)	730 (14.9)	717 (14.6)
None	208 (4.2)	183 (3.7)	216 (4.4)

The use of MI-related therapies (above) appears similar across treatment groups.

CHF was the most common complication of the qualifying MI, and similar across treatment groups. There was a slight increase in PTCA (PTCR) as a complication in the valsartan group; otherwise, complications appeared similar across treatment groups.

Table 12. Complications, procedures and risk factors associated with the qualifying MI

Table 7-8 Complications, procedures, and risk factors associated with the qualifying MI by treatment (primary analysis population)

Complication	Valsartan (N=4909)	Valsartan + Captopril (N=4885)	Captopril (N=4909)	All (N=14,703)
	n (%)	n (%)	n (%)	n (%)
Post-infarct angina	1030 (21.0)	1039 (21.3)	1011 (20.6)	3080 (20.9)
Cardiac catheterization	1385 (28.2)	1377 (28.2)	1359 (27.7)	4121 (28.0)
PTCR	1012 (20.6)	949 (19.4)	955 (19.5)	2916 (19.8)
CABG	91 (1.9)	113 (2.3)	110 (2.2)	314 (2.1)
CHF	2668 (58.4)	2825 (57.8)	2856 (58.2)	8549 (58.1)
Atrial fibrilation	594 (12.1)	612 (12.5)	608 (12.4)	1814 (12.3)
Sustained ventricular tachycardia	156 (3.2)	159 (3.3)	141 (2.9)	456 (3.1)
Ventricular fibrillation	187 (3.8)	184 (3.8)	203 (4.1)	574 (3.9)
Automatic implantable cardiac defibrillator	16 (0.3)	13 (0.3)	21 (0.4)	49 (0.3)
Pacemaker placement	58 (1.2)	47 (1.0)	54 (1.1)	159 (1.1)
Intra-aortic balloon pump	179 (3.6)	184 (3.8)	180 (3.7)	543 (3.7)
Renal insufficiency	208 (4.2)	217 (4.4)	210 (4.3)	635 (4.3)
Dyslipidemia	1806 (36.8)	1791 (36.7)	1804 (36.7)	5401 (36.7)
Hypertension	1709 (34.8)	1715 (35.1)	1704 (34.7)	5128 (34.9)
Treated	1609 (32.8)	1616 (33.1)	1618 (33.0)	4843 (32.9)
Diabetes	1178 (24.0)	1213 (24.8)	1164 (23.7)	3555 (24.2)
Insulin treated	652 (13.3)	627 (12.8)	616 (12.5)	1895 (12.9)

Background therapies taken in the 24 hours prior to randomization are shown in the next table:

Table 13. Background therapies at baseline (24 hours prior to randomization) (primary analysis population)

Therapy	Valsartan (N=4909)	Valsartan-Captopril (N=4885)	Captopril (N=4909)
Cardiovascular drugs			
ACE inhibitor	1936 (39.4)	1993 (40.8)	1888 (38.5)
ARB	54 (1.1)	53 (1.1)	67 (1.4)
Beta-blocker	3468 (70.6)	3439 (70.4)	3443 (70.1)
Calcium channel blocker	421 (8.6)	429 (8.8)	411 (8.4)
Potassium-sparing diuretic	447 (9.1)	438 (9)	445 (9.1)
Other diuretic	2517 (51.3)	2459 (50.3)	2424 (49.4)
Digitalis	625 (12.7)	618 (12.7)	613 (12.5)
Amiodarone	281 (5.7)	275 (5.6)	269 (5.5)
Other antiarrhythmic	86 (1.8)	75 (1.5)	108 (2.2)
Nitrate (excluding prophylaxis)	2144 (43.7)	2150 (44)	2133 (43.5)
Other vasodilator	87(1.8)	85 (1.7)	109 (2.2)
IV inotrope/vasopressor	98 (2)	91 (1.9)	83 (1.7)
Antithrombotics			
Aspirin	4481 (91.3)	4452 (91.1)	4485 (91.4)
IIb/IIIa inhibitor	328 (6.7)	331 (6.8)	313 (6.4)
Other antiplatelet	1232 (25.1)	1205 (24.7)	1210 (24.6)
Heparin	2529 (51.5)	2547 (52.1)	2519 (51.3)
Oral anticoagulant	473 (9.6)	474 (9.7)	439 (8.9)
Lipid lowering agents			
Statin	1658 (33.8)	1665 (34.1)	1691 (34.4)
Antidiabetic drugs			
Insulin	654 (13.3)	633 (13)	585 (11.9)
Oral hypoglycemic	574 (11.7)	96 (2.0)	584 (11.9)
Other			
Potassium supplement	1220 (24.9)	1186 (24.3)	1206 (24.6)

Concomitant Medications:

It should be noted that 21% (1008/4909) of valsartan patients, 23% percent (1138/4909) of captopril patients, and 23.8% (1162/4885) of those on the combination received one or more doses of open-label ACEI or ARB during the double-blind period. In the primary analysis population, about 19% of all valsartan patients, 20% of captopril patients, and 24% of combination patients took open-label ACEI (see table 16 for analysis of primary endpoint after censoring open-label ACEI/ARB use).

In the analysis of concomitant medications (check boxes in the CRF) given post-randomization, there were no differences seen across treatment groups. About 83-85% received beta-blockers, 22-23% calcium channel blockers, 26% potassium-sparing diuretic, 24% digitalis, 11-12%

amiodarone, 4% IV inotrope or vasopressor, 95% aspirin, 4-5% IIb/IIIa inhibitor, 34% other antiplatelet, 19-20% heparin, 20-21% oral anticoagulant, 62-64% statin, 12-13% insulin, 19-20% oral hypoglycemic agent, 5% hormone replacement therapy, 26-27% potassium supplement, and 7-8% serotonin re-uptake inhibitor.

Patient Exposure:
For the primary analysis population, the mean (709.1-711.6 days; SD 309-312) and median (739-743 days) time in the trial (including days on and off drug and regardless of permanent discontinuation) were similar across the three treatment groups. The frequency distribution (time on trial) also was similar across treatment groups.

The mean (SD) exposure to study drug was 612.8 (353.4) days for valsartan, 585.7 (365) days for valsartan + captopril, and 599.2 (358.3) days for captopril. The median exposure was 665 days for captopril and 672 days for valsartan.

Exposure to dose levels:
It is not clear whether each "step" is comparable across treatment groups.

Table 14. Daily dose and titration step by treatment (primary analysis population)

	Valsartan (N=4909)	Valsartan + Captopril (N=4885)	Captopril (N=4909)
Mean daily dose/patient (mg/d)*			
n**	4885	4862	4879
Mean (SD)	216.9 (107.2)	103.2 (V) +93.1(C) (50.57 (V) + 51.8 (C))	103.5 (49.38)
Mean titration step/patient***			
n**	4885	4862	4879
Mean (SD)	3.1 (1.04)	2.9 (1.10)	3.1 (1.01)
Exposure time on each titration step ¶			
N	4909	4885	4909
Mean no. days on step 0	52.4	50.3	57.1
Mean no. days on step 1	61.5	81.8	52.5
Mean no. days on step 2	77.9	98.6	75.4
Mean no. days on step 3	123.3	128.0	116.4
Mean no. days on step 4	598.0	549.3	580.9

* mean daily dose = (no. days on step 1 x step 1 dose) +.... (no. days on step 4 x step 4 dose)/no. days on study drug. Step 0 dose level is excluded from numerator and denominator.
**n= Patients who received at least one dose of study drug
***No. days on step 0 is excluded from numerator and denominator.
¶ No. days on specified step/No. days on study drug (mean percent) per patient. For step 0, number of days on step 0 is included in the denominator.

Efficacy:

Primary Endpoint:

The primary endpoint, all-cause mortality, is presented below for the ITT population. Similar results were obtained in the per-protocol and safety populations. The Kaplan-Meier curve is also presented below.

Table 15. Primary Endpoint (primary analysis population)

Table 9-1 Analysis results for the primary endpoint – all-cause mortality (primary analysis population)

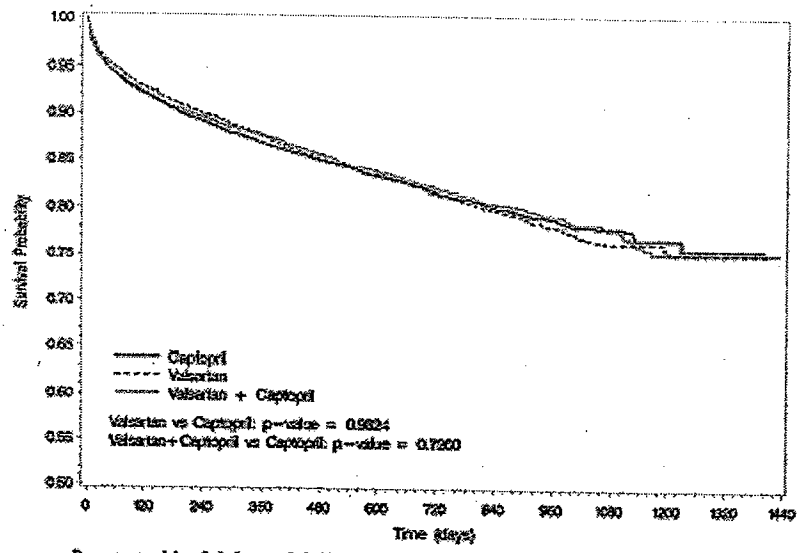
	Valsartan vs. Captopril (N=4909) (N=4909)			Valsartan + Captopril vs. Captopril (N=4885) (N=4909)		
	No. of deaths (%)[1] valsartan/captopril	Hazard ratio CI [2]	p-value	No. of deaths (%)[1] comb/captopril	Hazard ratio CI [2]	p-value
All-cause mortality	979 (19.9) /958 (19.5)	1.001 (0.902, 1.111) (0, 1.094)[4]	0.9824[3] 0.0038[4]	941 (19.3) /958 (19.5)	0.984 (0.886, 1.093)	0.7260[3]

Source: Post-text table 9.1-1a

1. Percent = raw estimate of the mortality rate: (number of deaths / number of patients in each group)*100%.
2. Hazard ratio = valsartan or valsartan + captopril / captopril. A value less than 1.0 is in favor of valsartan or valsartan + captopril. The two-sided CI (97.82%) has been adjusted for all interim analyses.
3. P-value is from Cox regression model with factor of treatment group and covariates of age (continuous) and previous MI (yes/no) for a two-sided null hypothesis with no treatment difference.
4. One-sided 97.47% CI for non-inferiority analysis of valsartan vs. captopril. The p-value is one-sided and is based on a pre-defined non-inferiority threshold of 1.13 for hazard ratio from a meta-analysis.

[*Source: Sponsor's results. Results confirmed by the reviewers*]

Figure 9-1 Kaplan-Meier estimates for all-cause mortality by treatment (primary analysis population)



Source: Post-text tables 9.1-1a and 9.1-1b, Post-text figure 9.1-1a

Figure 2. Kaplan-Meier curve for the primary endpoint

From the log/log plot of survival in Figure 3, the hazard ratio appeared to be constant over time.

log(-log(survival))

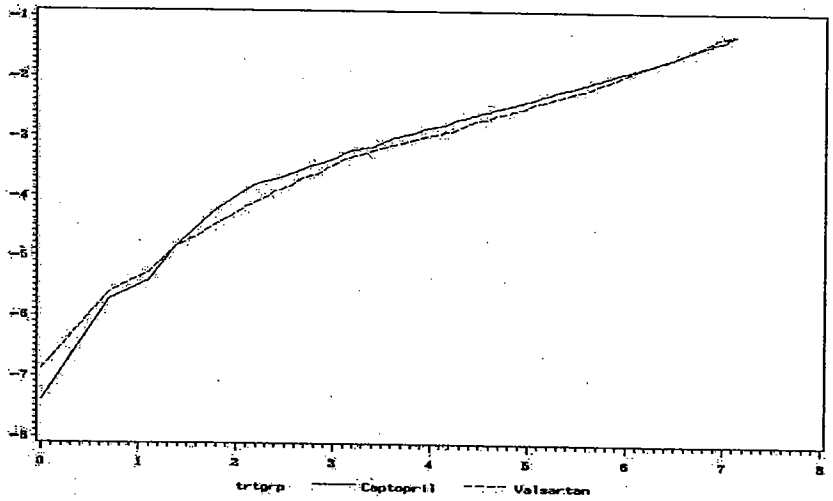


Figure 3. Plot of log (-log (survival)) versus log (time)

Superiority analyses: Superiority was not demonstrated in either the all-cause mortality analyses of valsartan vs. captopril, or the analysis of the combination arm vs. captopril.

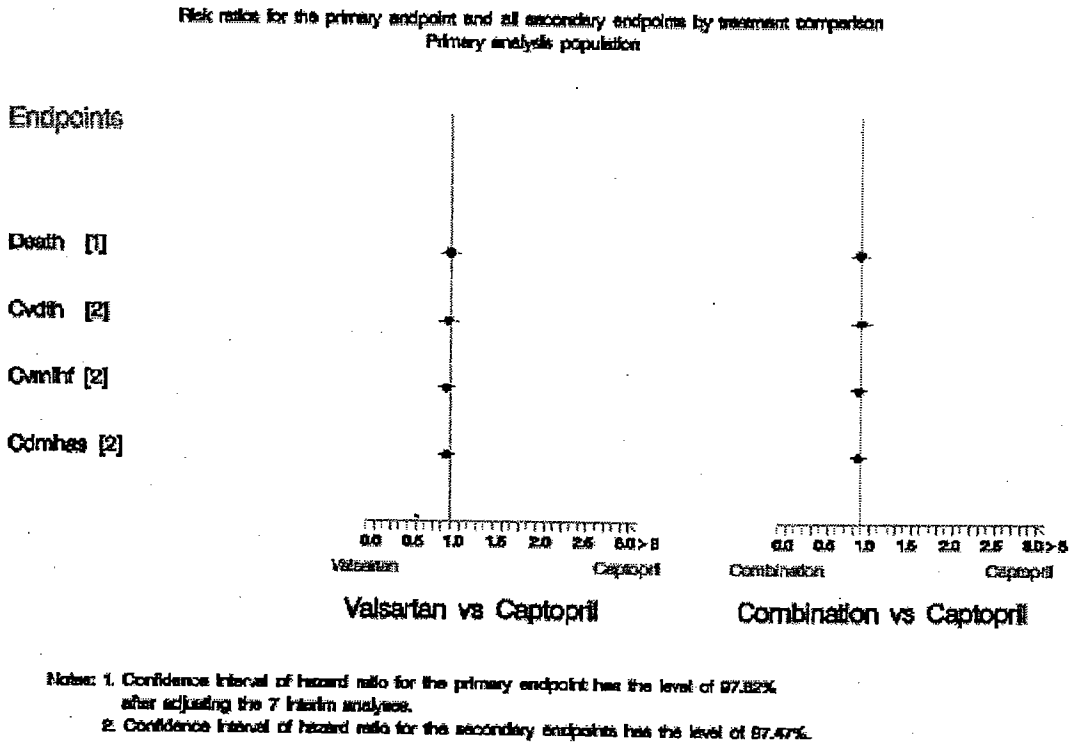


Figure 4. Risk ratios for the primary and secondary endpoints by treatment comparison (primary analysis population) Cvdth = cardiovascular (CV) mortality; Cvmlhf = 3 event composite (CV mortality, recurrent non-fatal MI, CHF hospitalization; Cdmhas = 5 event composite (CV mortality, recurrent non-fatal MI, CHF hospitalization, sudden cardiac arrest with resuscitation, non-fatal stroke)

Primary analysis with censoring for open-label ACE inhibitor/ARB use:
A sensitivity analysis for the primary endpoint was performed with censoring for open-label ACE inhibitor as well as open-label ACE/ARB use. Results are shown below:

Table 16. Cox regression analysis results for the primary endpoint—all cause mortality (primary analysis population) with open-label ACE inhibitor/ARB censoring

All-cause mortality	n* (%) deaths valsartan (N=4909) / captopril (N=4909)	Hazard ratio** CI	p-value**
Valsartan/captopril	773 (15.7%)/742 (15.1%)	0.9965 (0.8857, 1.1213)	0.9464

*n=number of patients with event before analysis cut-off date (Jan. 7, 2003), N=number of patients in that treatment group.
**P-value is calculated from Cox model with factor of treatment (three levels), covariates of age (continuous), and previous MI (y/n). Hazard ratio is formed as valsartan/captopril, derived from the Cox model. CI are two-sided with a level of 97.82% after adjusting for the 7 interim analyses.

Consistent results were also obtained when the analysis was repeated with censoring for open-label ACE inhibitor use only.

A sensitivity (per-protocol) analysis was also performed using cardiac enzyme criteria as defined by the original protocol and protocol amendment 2. Numerically, the hazard ratio was in favor of valsartan. Results are shown below:

Table 17. All-cause mortality using MI definitions in the original protocol and Amendment 2 (per-protocol population)

All-cause mortality	N (%) deaths valsartan/captopril	Hazard ratio CI*	p-value
Per-protocol (original protocol)	738 (16.2)/746 (16.3)	0.965 (0.856, 1.087)	0.4875**
Per-protocol (Amendment 2)	656 (16.1)/666 (16.2)	0.959 (0.846, 1.088)	0.4496**

*The two-sided CI (97.82%) was adjusted for all interim analyses.
**P-value from Cox regression model with factor of treatment group and covariates of age (continuous) and previous MI (yes/no) for a two-sided null hypothesis with no treatment difference.
Source: sponsor

Subgroup analyses of the primary efficacy parameter:

Higher event rates are seen, across treatment groups, in the older and female subgroups. In addition, a consistently higher event rate is seen (for all treatment groups) in the non-US population. The event rates are small, with wide CI, in non-Caucasian subgroups. An increased mortality rate, regardless of treatment group, is seen in subgroups with previous MI, history of hypertension or diabetes, and higher Killip/NYHA class with qualifying MI (these would be expected findings). In addition, a lower event rate was seen in the subgroups receiving beta-blocker, aspirin, or thrombolytic therapy compared to the subgroups not receiving these therapies. The event rates in the smoker (vs. nonsmoker) and dyslipidemia (vs. no dyslipidemia) subgroups are not consistent with expected outcomes, although other factors (i.e., other characteristics of these subgroups) may certainly be at play. The subgroup on HRT (hormone replacement therapy) is small compared to the group not receiving HRT. For the examined subgroups, no significant difference was seen between valsartan and captopril, or between the combination and captopril (analysis not shown).

Table 18. Rates of all-cause mortality in subgroups (primary analysis population):

Subgroup	Valsartan event rate n/N (%)	Val + Cap event rate n/N (%)	Captopril event rate n/N (%)	Val vs. Cap HR (95% CI)
Age				
< 65 years	268/2313 (11.6)	273/2370 (11.5)	275/2305 (11.9)	0.935 (0.79, 1.106)
≥ 65 years	711/2596 (27.4)	668/2515 (26.6)	683/2604 (26.2)	1.026 (0.924,1.140)
Gender				
Male	620/3365 (18.4)	598/3395 (17.6)	594/3373 (17.6)	1.029 (0.920, 1.152)
Female	359/1544 (23.3)	343/1490 (23.0)	364/1536 (23.7)	0.954 (0.824,1.103)
Race				

Caucasian	924/4604 (20.1)	884/4553 (19.4)	902/4591 (19.6)	1.003 (0.915, 1.099)
Black	27/125 (21.6)	32/137 (23.4)	34/145 (23.4)	0.795 (0.479, 1.321)
Asian	6/44 (13.6)	7/53 (13.2)	5/44 (11.4)	1.744 (0.510, 5.962)
Other	22/136 (16.2)	18/142 (12.7)	17/129 (13.2)	1.197 (0.635, 2.254)
Location				
US	242/1324 (18.3)	238/1311 (18.2)	235/1329 (17.7)	0.998 (0.834, 1.194)
Non-US	737/3585 (20.6)	703/3574 (19.7)	723/3580 (20.2)	1.003 (0.905, 1.111)
Disease history/risk factors				
Previous MI	417/1395 (29.9)	412/1376 (29.9)	402/1333 (30.2)	0.978 (0.853, 1.122)
No previous MI	562/3512 (16.0)	529/3509 (15.1)	556/3576 (15.5)	1.015 (0.903, 1.142)
Hypertension	620/2726 (22.7)	622/2693 (22.7)	614/2681 (22.9)	0.978 (0.875, 1.094)
No hypertension	359/2181 (16.5)	329/2192 (15.0)	344/2226 (15.5)	1.032 (0.890, 1.197)
Diabetes	325/1134 (28.7)	298/1146 (26.0)	294/1120 (26.3)	1.120 (0.957, 1.312)
No diabetes	654/3775 (17.3)	643/3739 (17.2)	664/3789 (17.5)	0.954 (0.856, 1.062)
Dyslipidemia	286/1500 (19.1)	269/1416 (19.0)	296/1419 (20.9)	0.903 (0.768, 1.063)
No dyslipidemia	678/3340 (20.3)	653/3401 (19.2)	636/3406 (18.7)	1.056 (0.948, 1.177)
Smoker	595/3135 (19.0)	556/3090 (18.0)	580/3119 (18.6)	1.002 (0.894, 1.123)
Non-smoker	382/1768 (21.6)	380/1788 (21.3)	377/1780 (21.2)	0.995 (0.863, 1.147)
Qualifying MI characteristics				
Anterior MI	542/2765 (19.6)	530/2831 (18.7)	523/2796 (18.7)	1.017 (0.902, 1.147)
Inferior MI	280/1586 (17.7)	284/1601 (17.7)	307/1618 (19.0)	0.927 (0.789, 1.091)
Other MI	255/1237 (20.6)	270/1203 (22.4)	272/1184 (23.0)	0.869 (0.733, 1.031)
Q-wave MI	528/3116 (16.9)	499/3132 (15.9)	555/3195 (17.4)	0.964 (0.856, 1.086)
Non-Q-wave MI	356/1512 (23.5)	365/1494 (24.4)	322/1452 (22.2)	1.014 (0.872, 1.179)
New LBBB MI	70/211 (33.2)	61/194 (31.4)	71/203 (35.0)	0.928 (0.667, 1.292)
Killip class I	159/1294 (12.3)	169/1381 (12.2)	176/1424 (12.4)	0.969 (0.782, 1.200)
Killip class II	450/2401 (18.7)	446/2329 (19.1)	436/2346 (18.6)	0.999 (0.875, 1.139)
Killip class III	270/874 (30.9)	231/842 (27.4)	250/813 (30.8)	0.970 (0.817, 1.153)
Killip class IV	97/313 (31.0)	91/312 (29.2)	93/306 (30.4)	1.016 (0.762, 1.25)
NYHA class I	158/1314 (12.0)	155/301 (11.9)	188/1348 (13.9)	0.859 (0.693, 1.062)
NYHA class II	365/1933 (18.9)	336/1965 (17.1)	328/1958 (16.8)	1.123 (0.968, 1.304)
NYHA class III	283/1060 (26.7)	289/1023 (28.3)	288/1021 (28.2)	0.898 (0.762, 1.059)
NYHA class IV	74/184 (40.2)	76/194 (39.2)	66/190 (34.7)	1.169 (0.838, 1.629)
Baseline medications (within 24 hrs of randomization)				
Beta-blocker	565/3468 (16.3)	560/3439 (16.3)	550/3443 (16.0)	1.003 (0.892, 1.128)
No beta-blocker	414/1441 (28.7)	381/1444 (26.4)	408/1466 (27.8)	1.003 (0.874, 1.049)
Aspirin	865/4481 (19.3)	833/4452 (18.7)	845/4485 (28.8)	1.008 (0.916, 1.108)
No aspirin	114/428 (26.6)	108/431 (25.1)	113/424 (26.7)	0.948 (0.731, 1.230)
ACEI/ARB	419/1984 (21.1)	385/2031 (19.0)	394/1939 (20.3)	1.020 (0.889, 1.170)
No ACEI/ARB	560/2925 (19.1)	556/2852 (19.5)	564/2970 (19.0)	0.987 (0.878, 1.109)
Thrombolytics*	238/1741 (13.7)	226/1711 (13.2)	229/1718 (13.3)	1.005 (0.838, 1.205)
No thrombolytics	741/3168 (23.4)	715/3174 (22.5)	729/3191 (22.8)	1.002 (0.905, 1.110)
HRT	19/87 (21.8)	14/82 (17.1)	18/87 (20.7)	0.903 (0.473, 1.724)
No HRT	340/1457 (23.3)	329/1407 (23.4)	346/1449 (23.9)	0.957 (0.824, 1.111)
Procedures/Other factors				
Prior	146/611 (23.9)	125/560 (22.3)	143/576 (24.8)	0.968 (0.769, 1.219)
CABG/PTCR	92/731 (12.6)	61/730 (8.4)	72/717 (10.0)	1.30 (0.955, 1.770)
Primary PTCR	129/1096 (11.8)	111/1048 (10.6)	116/1053 (11.0)	1.078 (0.839, 1.386)
PTCR/CABG post				
Clinical evidence	189/1065 (17.7)	170/1046 (16.3)	160/1010 (15.8)	1.091 (0.884, 1.347)

of heart failure only				
LV dysfunction via radiologic/imaging	700/3342 (20.9)	673/3398 (19.8)	688/3426 (20.1)	0.985 (0.893, 1.087)

*used to treat qualifying MI.

The secondary endpoints were numerically similar across treatment groups.

Table 19. Secondary Endpoints (primary analysis population):

Endpoint	Valsartan (N=4909) n (%)	Valsartan + Captopril (N=4885) n (%)	Captopril (N=4909) n (%)
Cardiovascular mortality	827 (16.8)	827 (16.8)	830 (16.9)
Three-event composite*	1529 (31.1)	1518 (31.1)	1567 (31.9)
Cardiovascular mortality	827 (16.8)	827 (16.9)	830 (16.9)
Hospitalization for heart failure	813 (16.6)	774 (15.8)	801 (16.3)
Recurrent non-fatal MI**	397 (8.1)	365 (7.5)	402 (8.2)
Five-event composite*	1612 (32.8)	1580 (32.3)	1641 (33.4)
Additional variables: non-fatal stroke***	131 (2.7)	119 (2.4)	123 (2.5)
Cardiac arrest with resuscitation	56 (1.1)	52 (1.1)	59 (1.2)

*Only the first event was counted toward the composite endpoints if a patient experienced two or more events.
** Only MI occurring ≥ 15 days before death is included.
*** Only stroke occurring > 15 days before death is included.
Source: Sponsor's analysis confirmed by the reviewers.

Figure 9-5 Kaplan-Meier estimates for cardiovascular mortality by treatment (primary analysis population)

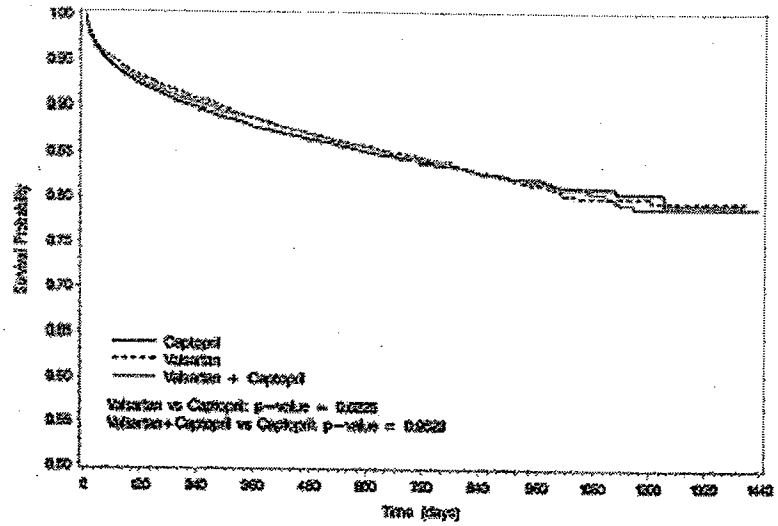


Figure 5. Kaplan-Meier curve for cardiovascular mortality by treatment

Figure 9-6 Kaplan-Meier estimates for the first cardiovascular mortality, hospitalization for heart failure, or recurrent non-fatal myocardial infarction by treatment (primary analysis population)

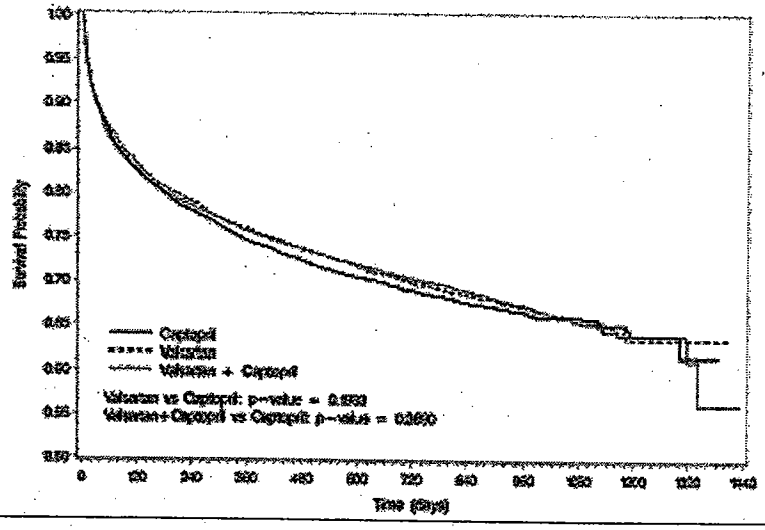


Figure 6. Kaplan-Meier curve for the time to cardiovascular (CV) mortality, hospitalization for heart failure, or recurrent non-fatal MI by treatment (primary analysis population)

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Figure 9-7 Kaplan-Meier estimates for the first cardiovascular mortality, hospitalization for heart failure, recurrent non-fatal myocardial infarction, non-fatal stroke, or sudden cardiac arrest with resuscitation by treatment (primary analysis population)

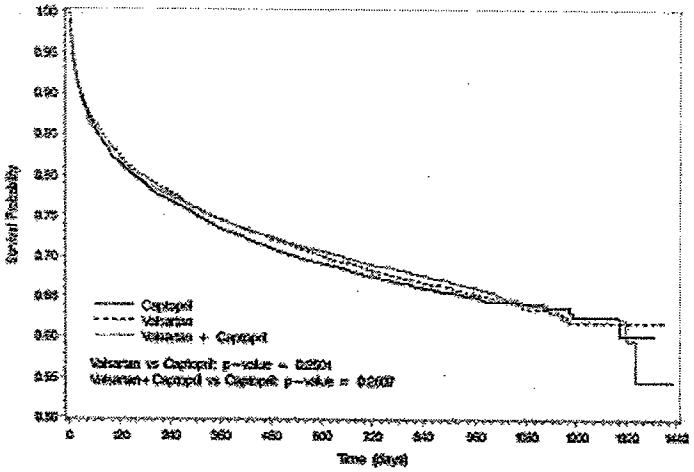


Figure 7. Kaplan-Meier curve for the time to first CV mortality, hospitalization for heart failure, recurrent non-fatal MI, non-fatal stroke, or sudden cardiac arrest with resuscitation by treatment group (primary analysis population)

Tertiary Efficacy Results:

Analysis results are presented for valsartan vs. captopril. There were no significant differences in the analysis of valsartan + captopril vs. captopril. Results of hazard ratios appear consistent.

Table 20. Tertiary Efficacy results (primary analysis population)

Tertiary efficacy endpoint	Valsartan (N=4909) vs: Captopril (N=4909)	
	N (%) of events V/C	Hazard ratio (95% CI)
All-cause hosp (unplanned and elective)*	2712 (55.2)/2714 (55.3)	0.984 (0.933, 1.037)
All-cause mortality and all-cause hospitalization*	3045 (62.0)/3086 (62.9)	0.969 (0.922, 1.019)
Hosp for CHF*	813 (16.6)/801 (16.3)	0.997 (0.905, 1.099)
All-cause mortality and hosp for CHF*	1326 (27)/1335 (27.2)	0.975 (0.922, 1.068)
CV mortality, hosp for CHF, recur nonfatal MI, and coronary revascularization procedures *	2241 (45.7)/2310 (47.1)	0.954 (0.9, 1.011)
CV morbidity	2507 (51.1)/2523 (51.4)	0.973 (0.921, 1.028)
All-cause mortality and CV morbidity	2843 (57.9)/2877 (58.6)	0.967 (0.918, 1.019)
CV mortality and CV morbidity	2777 (56.6)/2830 (57.6)	0.963 (0.859, 1.079)

Sudden death and sudden cardiac arrest with resuscitation*	342 (7)/349 (7.1)	0.958 (0.826, 1.112)
Fatal and non-fatal MI	587 (12)/599 (12.2)	0.963 (0.876, 1.038)
Coronary revascularization procedures	1052 (21.4)/1097 (22.3)	0.953 (0.876, 1.038)
CV procedures	1270 (25.9)/1318 (26.8)	0.959 (0.888, 1.036)
All-cause mortality at 30 days*	189 (3.9)/201 (4.1)	0.930 (0.762, 1.162)
Fatal and non-fatal stroke*	157 (3.2)/166 (3.4)	0.932 (0.751, 1.162)
All-cause mortality, MI and hosp for CHF	1635 (33.3)/1649 (33.6)	0.97 (0.906, 1.039)

* included CEC adjudicated events. No p-values are presented because all p-values were ≥ 0.10).

Safety:

Safety assessments consisted of serious AE, AE leading to down-titration of study drug, AE leading to permanent discontinuation of study drug, and 4 predefined (in the protocol) safety/tolerability endpoints (symptomatic hypotension, renal dysfunction, dry cough, or angioedema). Serum creatinine, performed at local laboratories, was recorded at baseline, prior to titration, and at the final visit; other laboratory values were not collected.

Deaths: All-cause mortality was a primary endpoint; see the section on Efficacy for further discussion.
Below are deaths (investigator assessments), serious AE, and hospitalizations:

Table 21. Number (%) of patients who died (investigator assessment), had other SAE, or who discontinued due to AE (safety population)

	Valsartan (N=4885)	Valsartan + Captopril (N=4862)	Captopril (N = 4879)
Deaths*	970 (19.9)	928 (19.1)	946 (19.4)
Serious adverse events (total, not including death)	2358 (48.3)	2290 (47.1)	2310 (47.3)
Serious adverse events during the first month of study treatment	949 (19.4)	1003 (20.6)	918 (18.8)
Hospitalizations	2709 (55.5)	2622 (53.9)	2709 (55.5)
Permanent discontinuation of study drug for any reason	1001 (20.5)	1139 (23.4)	1055 (21.6)
Permanent discontinuation due to adverse events	282 (5.8)	438 (9)	375 (7.7)
Down-titration or temporary	1443 (29.5)	1641 (33.8)	1379 (28.3)

discontinuation for any reason			

*In the investigator assessments (unadjudicated) of causes of death, no imbalance between groups appeared for the various cardiovascular and non-cardiovascular causes of death; in 40 (valsartan), 40 (combination) and 35 (captopril) cases, the cause of death was unknown; in 41 (valsartan), 29 (combination) and 28 (captopril) cases, the cause of death was missing. The adjudicated deaths (primary analysis population) resulted in 42 (valsartan), 29 (combination) and 32 (captopril) deaths where the cause was unknown, and only 1 case where the cause was missing.

Causes of Death/Effects of adjudication:

Below are listed the investigator and CEC-adjudicated causes of death for the safety population. Cardiovascular deaths were most common (both investigator and CEC assessments); of these, sudden death was most frequent (both investigator and CEC assessments). The CEC reclassified deaths originally classified as "missing" (no cause of death identified by investigator); in addition, the CEC reclassified many investigator-assessed "other cardiovascular deaths" into specific causes such as fatal MI and CV procedure-related deaths. After sudden death, CEC adjudication resulted in fatal MI and fatal pump failure as second and third most common causes of death. By investigator assessment, the most frequent causes of death were sudden death, followed by heart failure (2.8-3.5%), and followed by fatal MI (2.4-2.6%).

Twenty-four, twenty-three and thirty patients randomized to valsartan, combination therapy and captopril, respectively, did not receive study drug. Of these patients, there were 10, 13 and 12 deaths in the valsartan, combination, and captopril groups, respectively. About 50-58% of these deaths occurred within the first 30 days after qualifying MI.

Table 22. Number (%) patients who died with adjudicated cause of death (safety population)

	Valsartan (N=4885)	Valsartan + Captopril (N=4862)	Captopril (N=4879)
No. deaths with CEC adjudicated cause of death†	969 (19.8)	928 (19.1)	946 (19.4)
Causes of death:◊			
Total cardiovascular death	818 (16.7)	815 (16.8)	820 (16.8)
Sudden death	292 (6.0)	335 (6.9)	293 (6.0)
Fatal pump failure	156 (3.2)	122 (2.5)	156 (3.2)
CV procedure-related	34 (0.7)	29 (0.6)	32 (0.7)
Other CV death‡	20 (0.4)	13 (0.3)	9 (0.2)
Stroke-related death	40 (0.8)	34 (0.7)	51 (1.0)
Presumed CV death	29 (0.6)	41 (0.8)	38 (0.8)
Unknown*	42 (0.9)	29 (0.6)	32 (0.7)
Total non-CV death	151 (3.1)	113 (2.3)	126 (2.6)
Malignancy	67 (1.4)	42 (0.9)	55 (1.1)
Pulmonary	19 (0.4)	11 (0.2)	19 (0.4)
Gastrointestinal	12 (0.2)	11 (0.2)	19 (0.4)
Hepatobiliary	0	3 (0.1)	2 (<0.1)
Infection	22 (0.5)	18 (0.4)	11 (0.2)
Accident	6 (0.1)	6 (0.1)	9 (0.2)
Suicide	3 (0.1)	5 (0.1)	1 (<0.1)

Drug overdose	1 (<0.1)	1(<0.1)	0
Other	21 (0.4)	16 (0.3)	14 (0.3)

†One valsartan patient died after the cutoff date for CEC adjudication and was not included in this table.
◊Each patient has only one cause of death.
*All unknown causes of death were classified as cardiovascular deaths.
‡ Examples of "other" CV death: pulmonary embolus, peripheral vascular disease, abdominal aortic aneurysm, malignant ventricular tachycardia, etc.

Table 23. Number (%) patients who died with causes of death (investigator assessment) (safety population)

	Valsartan (N=4885)	Valsartan + Captopril (N=4862)	Captopril (N=4879)
Total number deaths	970 (19.9)	928 (19.1)	946 (19.4)
Sudden death	302 (6.2)	355 (7.3)	318 (6.5)
Presumed cardiovascular death	43 (0.9)	43 (0.9)	45 (0.9)
Heart failure	169 (3.5)	135 (2.8)	167 (3.4)
Fatal MI	129 (2.6)	126 (2.6)	115 (3.4)
CV procedure-related	13 (0.3)	13 (0.3)	16 (0.3)
Fatal stroke	36 (0.7)	26 (0.5)	47 (1.0)
Other cardiovascular death	55 (1.1)	46 (0.9)	43 (0.9)
Non-CV death	142 (2.29)	115 (2.4)	132 (2.7)
Unknown	40 (0.8)	40 (0.8)	35 (0.7)
Missing cause of death	41 (0.8)	29 (0.6)	28 (0.6)

The investigator may have indicated more than one cause of death; if so, the patient is counted once in each category.

Serious Adverse Events:

Below are listed serious adverse events, not including death (regardless of drug relationship).

Table 24. Serious adverse events, not including death, regardless of drug relationship by preferred term and treatment (safety population), occurring ≥ 1.0 % in any treatment group.

	Valsartan (N=4885)	Valsartan + Captopril (N=4862)	Captopril (N=4879)
Chest pain	34 (0.7)	60 (1.2)	46 (0.9)
Pneumonia NOS	54 (1.1)	46 (0.9)	49 (1.0)
Cardiac failure NOS	1095 (22.4)	1014 (20.9)	1038 (21.3)
Unstable angina	812 (16.6)	796 (16.4)	787 (16.1)
Myocardial infarction	677 (13.9)	626 (12.9)	680 (13.9)
Atrial fibrillation	47 (1.0)	34 (0.7)	37 (0.8)
Cardiac arrest	200 (4.1)	205 (4.2)	207 (4.2)
Renal impairment NOS	55 (1.1)	57 (1.2)	34 (0.7)
Cerebrovascular accident	156 (3.2)	145 (3.0)	159 (3.3)
Cerebral infarction	108 (2.2)	106 (2.2)	112 (2.3)
Transient ischemic attack	60 (1.2)	62 (1.3)	112 (2.3)

Some of the above events might be expected in this post-MI study population (congestive heart failure would be an example). Cardiac failure NOS appears slightly increased in the valsartan group; otherwise, no gross imbalances across treatment groups were noted.

Serious adverse events occurring during the first month by treatment (excluding death and reasons for hospitalization) were also analyzed. The incidence of cardiac failure NOS (9.3% in the valsartan group, 8.7% in the combination group, and 8.4% in the captopril group), unstable angina (5.8% incidence in the combination arm, 5.2-5.3% incidence in the other groups, and hypotension NOS (1.3% incidence in the valsartan group, 1.8% in the combination group, 0.8% incidence in the captopril group) showed slight imbalances; otherwise, no differences were seen across treatment groups.

Hospitalizations:
The primary reasons for hospitalization were categorized by the CEC. Results are shown below. Gross imbalances between captopril and valsartan were not identified.

Table 25. Number (%) patients (incidence ≥ 2.0% in any treatment group) hospitalized with CEC-categorized reasons for hospitalization by treatment (safety population): safety population

	Valsartan (N=4885) n (%)	Valsartan + Captopril (N=4862) n (%)	Captopril (N=4879) n (%)
# with at least one hospitalization	2709 (55.5)	2622 (53.9)	2709 (55.5)
Other, cardiovascular	675 (13.8)	708 (14.6)	726 (14.9)
Congestive heart failure	586 (12.0)	534 (11.0)	581 (11.9)
Unstable angina	517 (12.0)	531 (10.9)	513 (10.5)
Other, non-cardiovascular	491 (10.1)	486 (10.0)	496 (10.2)
Myocardial infarction	448 (9.2)	406 (8.4)	477 (9.8)
Cardiac catheterization	291 (6.0)	262 (5.4)	253 (5.2)
Gastrointestinal, hepatic	241 (4.9)	212 (4.4)	226 (4.6)
Pulmonary	236 (4.8)	208 (4.3)	251 (5.1)
CABG	187 (3.8)	231 (4.8)	226 (4.6)
Non-cardiovascular surgery	173 (3.5)	183 (3.8)	161 (3.3)
Percutaneous intervention	171 (3.5)	156 (3.2)	144 (3.0)

A patient can have more than one event; each patient is counted once in each category.

Discontinuations due to Adverse Events (AE):
Below are listed premature discontinuations (≥ 1.0% in any treatment group) from study drug due to an adverse event. The incidence of these listed AE appeared highest in the group receiving combination therapy. There is a higher incidence of hypotension-related discontinuations in the

valsartan group compared to those on captopril; however, the incidence is under 2%. Discontinuations due to cough are higher in patients receiving captopril.

Table 26. Premature discontinuations (occurring ≥ 1.0% in any treatment group) from study drug due to adverse events by preferred term and treatment group (safety population)

	Valsartan (N=4885)	Valsartan + Captopril (N=4862)	Captopril (N=4879)
Total	282 (5.8)	438 (9.0)	375 (7.7)
Cough	31 (0.6)	101 (2.1)	120 (2.5)
Hypotension NOS	66 (1.4)	87 (1.8)	41 (0.8)

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

There were 8 (0.2%) cases of angioedema in the valsartan group, 11 (0.2%) cases in the combination group, and 13 (0.3%) cases in the captopril group. The number of premature discontinuations due to renal/urinary disorders was 28 (0.6%) for valsartan, 29 (0.6%) for the combination, and 22 (0.5%) for captopril.

Downward Titration due to AE:

As in the previous table, the group receiving combination therapy had the highest incidence of at least one downward dose titration. Consistent with the previous table, patients on valsartan had a higher incidence of downward titration due to symptomatic hypotension compared to those receiving captopril; the group receiving combination therapy had the highest incidence of symptomatic hypotension requiring downward titration. The incidence of downward titration due to cough was higher in the captopril group.

Table 27. Number (%) of patients with at least one downward dose titration by primary reason for change and treatment group (safety population)

Primary reason	Valsartan (N=4885)	Valsartan + Captopril (N=4862)	Captopril (N=4879)
Patients with at least one downward dose titration*	1443 (29.5)	1641 (33.8)	1379 (28.3)
Symptomatic hypotension	593 (12.1)	689 (14.2)	474 (9.7)
Dry cough	49 (1.0)	137 (2.8)	136 (2.8)
Hyperkalemia	49 (1.0)	45 (0.9)	32 (0.7)
Elevated creatinine	148 (3.0)	159 (3.3)	93 (1.9)
Other AE**	278 (5.7)	304 (6.3)	272 (5.6)
Other	587 (12.0)	628 (12.9)	610 (12.5)

*A patient with multiple primary reasons is counted only once in at least one downward dose titration. End-of-study titration to step 0 is excluded. **Other AE includes non-AE items associated with MedDRA codes.

Prespecified AE:

Numbers and incidence (per treatment group) with prespecified AE are listed below. The percentage of patients with dry cough is higher in groups taking captopril; the percentage of

patients with renal dysfunction and symptomatic hypotension is higher in patients taking valsartan (compared to those on captopril) and highest in the patients taking combination therapy. The incidence of angioedema appears comparable (0.9-1.0%) in the three treatment groups.

Table 28. Number (%) of patients with pre-specified checklist adverse events by treatment (safety population)

	Valsartan (N=4885)	Valsartan +Captopril (N=4862)	Captopril (N=4879)
Symptomatic hypotension	N=4885	N=4862	N=4879
	n= 1500 (30.7%)	n=1757 (36.1%)	n=1291 (26.5%)
Renal dysfunction	N= 4880	N=4857	N=4871
	n=595 (12.2%)	n= 612 (12.6%)	n= 465 (9.5%)
Dry cough	N=4880	N=4857	N= 4871
	n=543 (11.1%)	n=886 (18.2%)	n=919 (18.9%)
Angioedema	N=4880	N=4857	N=4871
	n=48 (1.0%)	n=42 (0.9%)	n=46 (0.9%)

These AE were check boxes on the CRF.

Lab Results: Serum creatinines, analyzed at local laboratories, were collected at baseline, prior to upward titrations, and at the final visit. For the safety population, mean values for all treatment groups were 1.1 (SD 0.3-0.4) mg/dL at baseline and prior to upward titrations. Mean values at the final visit (treatment group N=575-605) were 1.2-1.3 (SD 0.5-0.7). Median values were 1.1 mg/dL at all time points for all treatment groups.
Please see table 34 for an analysis of those patients with doubling of serum creatinine at any time point.

Safety analyses by Subgroups (Age, Gender, and Race):

Age: Most frequent serious adverse events are presented (below) by treatment and age. The incidence of cardiac failure, MI, cardiac arrest, cerebral infarction, cerebrovascular accidents, hypotension NOS, atrial fibrillation and renal impairments appear higher in the $\geq$ 65 year subgroup, regardless of treatment arm. The incidence of hypotension NOS appears highest in the $\geq$ 65 group receiving valsartan therapy, compared to the other treatment groups; otherwise, no imbalances were noted.

Table 29. Number (%) of patients with serious adverse events (> 1.0% in any treatment subgroup) by age and treatment (safety population; death and reasons for hospitalization are excluded)

	Valsartan (N=4885) n (%)		Valsartan + Captopril (N=4862) n (%)		Captopril (N=4879) n (%)	
	< 65 yr	≥ 65 yr	< 65 yr	≥ 65 yr	< 65 yr	≥ 65 yr
Total # patients	2306 (100)	2579 (100)	2363 (100)	2499 (100)	2293 (100)	2586 (100)
# with at least 1 SAE	921 (39.9)	1437 (55.7)	937 (39.7)	1353 (54.1)	903 (39.4)	1407 (54.4)
Unstable angina	363 (15.7)	449 (17.4)	373 (15.8)	423 (16.9)	351 (15.3)	436 (16.9)
Cardiac failure NOS	314	781	320 (13.5)	694 (27.8)	285	753 (29.1)

	(13.6)	(30.3)			(12.4)	
Myocardial infarction	228 (9.9)	449 (17.4)	221 (9.4)	405 (16.2)	245 (10.7)	435 (16.8)
Cardiac arrest	72 (3.1)	128 (5.0)	78 (3.3)	127 (5.1)	84 (3.7)	123 (4.8)
Cerebrovascular accident	56 (2.4)	100 (3.9)	44 (1.9)	101 (4.0)	38 (1.7)	121 (4.7)
Cerebral infarction	42 (1.8)	66 (2.6)	32 (1.4)	74 (3.0)	30 (1.3)	82 (3.2)
Hypotension NOS	33 (1.4)	95 (3.7)	70 (3.0)	85 (3.4)	35 (1.5)	61 (2.4)
Transient ischemic attack	23 (1.0)	37 (1.4)	23 (1.0)	39 (1.6)	15 (0.7)	65 (2.5)
Chest pain	20 (0.9)	14 (0.5)	32 (1.4)	28 (1.1)	23 (1.0)	23 (0.9)
Atrial fibrillation	12 (0.5)	35 (1.4)	9 (0.4)	15 (1.0)	6 (0.3)	31 (1.2)
Acute renal failure	12 (0.5)	29 (1.1)	12 (0.5)	24 (1.0)	4 (0.2)	20 (0.8)
Renal impairment NOS	7 (0.3)	48 (1.9)	17 (0.7)	40 (1.6)	5 (0.2)	29 (1.1)

A patient can have more than one event; each patient is counted once in each category.

In addition, results for the prespecified checklist adverse events by age/treatment are presented below. In all treatment groups, the incidence of renal dysfunction appears higher in the elderly population (about three times the rate seen in the younger population) and highest in the combination arm. The incidence of angioedema appears comparable across groups.

Table 30. Number (%) with pre-specified checklist adverse events by age/treatment (safety population)

		Valsartan (N=4885)		Valsartan + Captopril (N=4862)		Captopril (N=4879)	
		<65 yr	≥ 65 yr	<65 yr	≥ 65 yr	<65 yr	≥ 65 yr
Total # patients	n (%)	2306 (100)	2579 (100)	2363 (100)	2499 (100)	2293 (100)	2586 (100)
Symptomatic hypotension*	n (%) N	701 (30.4) 2306	799 (31.0) 2579	890 (37.7) 2363	867 (34.7) 2499	595 (25.9) 2293	696 (26.9) 2586
Renal dysfunction	n (%) N	153 (6.6) 2304	442 (17.2) 2576	152 (6.4) 2360	459 (18.4) 2497	104 (4.6) 2289	360 (13.9) 2582
Dry cough	n (%) N	241 (10.5) 2304	302 (11.7) 2576	427 (18.1) 2360	459 (18.4) 2497	419 (18.3) 2289	500 (19.4) 2582
Angioedema	n (%) N	22 (1.0) 2304	26 (1.0) 2576	25 (1.1) 2360	17 (0.7) 2497	22 (1.0) 2289	24 (0.9) 2582

A patient can have more than one event; each patient is counted once in each category.
*includes patients with first-dose hypotension at Visit 1.

Gender:

The next table lists most frequent serious adverse events (> 2.0% in any treatment subgroup) by gender and treatment.

Table 31. Number (%) of patients with most frequent serious adverse events (≥ 2.0% in any treatment subgroup) by gender and treatment (safety population; excludes death and reasons for hospitalization)

	Valsartan (N=4885)		Valsartan + Captopril (N=4862)		Captopril (N=4879	
	Male n (%)	Female n (%)	Male n (%)	Female n (%)	Male n (%)	Female n (%)
Total # patients	3351 (100)	1534 (100)	3383 (100)	1479 (100)	3355 (100)	1524 (100)
# with at least one SAE	1527 (45.6)	831 (54.2)	1501 (44.4)	789 (53.3)	1496 (44.6)	814 (53.4)
Preferred term						
Cardiac failure NOS	651 (19.4)	444 (28.9)	614 (18.1)	400 (27.0)	607 (18.1)	431 (28.3)
Unstable angina	516 (15.4)	296 (19.3)	511(15.1)	285(19.3)	500 (14.9)	287 (18.8)
Myocardial infarction	447 (13.3)	230 (15.0)	412 (12.2)	214 (14.5)	446 (13.3)	234 (15.4)
Cardiac arrest	136 (4.1)	64 (4.2)	139 (4.1)	66 (4.5)	148 (4.4)	59 (3.9)
Cerebrovascular accident	97 (2.9)	59 (3.8)	82 (2.4)	63 (4.3)	94 (2.8)	65 (4.3)
Hypotension NOS	79 (2.4)	49 (3.2)	101 (3.0)	54 (3.7)	62 (1.8)	34 (2.2)
Cerebral infarction	65 (1.9)	43 (2.8)	59 (1.7)	47 (3.2)	69 (2.1)	43 (2.8)

Each patient is counted once in each category.

As seen in the above table, the incidences of the listed SAE appeared higher in the female subgroup, regardless of treatment. The incidence of hypotension (both male and female subgroups) was higher in the valsartan group compared with the captopril group. Otherwise, differences between valsartan and captopril were seen.

Below are the pre-specified (check box) adverse events by gender/treatment. The incidence of symptomatic hypotension appears higher in males. No difference by gender is seen for angioedema. In all treatment groups, the incidence of renal dysfunction and dry cough is higher in females.

Table 32. Number (%) of patients with pre-specified checklist adverse events by sex and treatment (safety population)

		Valsartan (N=4885)		Valsartan + Captopril (N=4862)		Captopril (N=4879)	
		Male	Female	Male	Female	Male	Female
Total # patients	n (%)	3351 (100)	1534 (100)	3383 (100)	1479 (100)	3355 (100)	1524 (100)
Symptomatic hypotension*	n (%) N	1061 (31.7) 3351	439 (28.6) 1534	1267 (37.5) 3383	490 (33.1)	909 (27.1)	382 (25.1) 1524

					1479	3355	
Renal dysfunction	n (%) N	391 (11.7) 3347	204 (13.3) 1533	417 (12.3) 3379	195 (13.2) 1478	298 (8.9) 3347	167 (11.0) 1524
Dry cough	n (%) N	321 (9.6) 3347	222 (14.5) 1533	567 (16.8) 3379	319 (21.6) 1478	570 (17.0) 3347	349 (22.9) 1524
Angioedema	n (%) N	31 (0.9) 3347	17 (1.1) 1533	23 (0.7) 3379	19 (1.3) 1478	33 (1.0) 3347	13 (0.9) 1524

N=number of patients with assessment of adverse event. A patient can have more than one event; each patient is counted once in each category.
*Include patients with first-dose hypotension at Visit 1.

Race: An analysis by race was not performed due to the baseline imbalances and insufficient numbers of non-Caucasians in the study population.

Hypotension:
At each visit, the investigator determined whether the patient had experienced a serious adverse event. Hypotension meeting these criteria were recorded on the CRF as "hypotension NOS". In addition, at each visit, the investigator completed a checklist of four known adverse effects (one of which was "symptomatic hypotension") of ACE inhibitors/ARBs. Criteria for symptomatic hypotension were defined in the protocol. At the first visit, the investigator indicated if first-dose hypotension had occurred.

Table 33. Summary of adverse events associated with hypotension (safety population)

	Valsartan (N=4885) n (%)	Valsartan + Captopril (N=4862) n (%)	Captopril (N=4879) n (%)
Serious adverse events			
Hypotension NOS (all)	128 (2.6)	155 (3.2)	96 (2.0)
Hypotension NOS on study drug	100 (2.0)	128 (2.6)	77 (1.6)
Hypotension NOS during first month	64 (1.3)	88 (1.8)	37 (0.8)
Pre-specified adverse events			
Symptomatic hypotension	1500 (30.7)	1757 (36.1)	1291 (26.5)
First dose hypotension	65/4836 (1.3)	137/4817 (2.8)	55/4826 (1.1)
Change in study drug			
Permanent discontinuation due to hypotension NOS	66 (1.4)	87 (1.8)	41 (0.8)
Temporary discontinuation due to: Symptomatic hypotension Hypotension NOS	168 (3.4) 19 (0.4)	183 (3.8) 24 (0.5)	115 (2.4) 11 (0.2)
Down-titration due to: Symptomatic hypotension Hypotension NOS	593 (12.1) 43 (0.9)	689 (14.1) 55 (1.1)	474 (9.7) 25 (0.5)
Mean change (SD) (mm Hg) from baseline to Visit 2			

SBP	-4.6 (17.1)	-5.6 (17.1)	-3.3 (16.9)
N	4734	4705	4729
DBP	-2.0 (11.8)	-2.8 (11.6)	-1.2 (11.9)
N	4725	4702	4727

For mean change in BP from baseline to final visit, please see figure 9.
Hypotension NOS= MedDRA preferred term coded from investigator terminology.
Symptomatic hypotension =pre-specified checklist adverse event, protocol-defined.
First-dose hypotension = check box on CRF.
Temporary discontinuation = down-titration to step 0 with subsequent restart.

Hypotension was more frequent in the valsartan group compared to those on captopril, and most frequent in the group treated with combination therapy. The sponsor has made the point that symptomatic hypotension was a frequent reason for down-titration but < 2% of patients permanently discontinued therapy due to hypotension. The sponsor has also claimed that, although not statistically significantly different, valsartan patients had more prior cardiovascular diseases and higher baseline Killip class, which may have caused more susceptibility to hypotension.

Renal dysfunction:
The sponsor included an analysis of major renal dysfunction, defined as one or more of: death from renal cause (investigator assessment), serious AE suggestive of renal failure, or temporary or permanent discontinuation due to a renal cause (increased creatinine was a checklist item as a reason for down-titration).

Table 34. Renal adverse events by treatment (safety population)

		Valsartan (N=4885) n (%)	Valsartan + Captopril (N=4862) n (%)	Captopril (N=4879) n (%)
Deaths (investigator assessment)	Renal failure NOS	5 (0.1)	1 (0)	2 (0)
	Azotemia	1 (0)	0	0
	Renal failure acute	1 (0)	0	0
	Total renal causes of death	**7 (0.1)**	**1 (0)**	**2 (0)**
Serious AE	Renal impairment NOS	55 (1.1)	57 (1.2)	34 (0.7)
	Renal failure acute	41 (0.8)	36 (0.7)	24 (0.5)
	Renal failure NOS	32 (0.7)	29 (0.6)	20 (0.4)
	Total renal serious AE	**87 (1.8)**	**71 (1.5)**	**51 (1.0)**
Permanent discontinuation	Blood creatinine increased	27 (0.6)	33 (0.7)	19 (0.4)
	Renal failure NOS	14 (0.3)	9 (0.2)	8 (0.2)
	Renal failure acute	5 (0.1)	7 (0.1)	2 (0)
	Renal impairment NOS	4 (0.1)	12 (0.2)	9 (0.2)
	Total permanent discontinuations due to renal AE	**54 (1.1)**	**62 (1.3)**	**40 (0.8)**
Temporary discontinuation	Elevated creatinine	79 (1.6)	82 (1.7)	50 (1.0)
	Total temporary	**88 (1.8)**	**82 (1.7)**	**50 (1.0)**

	discontinuations due to renal cause			
Down-titration	Elevated creatinine	148 (3.0)	159 (3.3)	93 (1.9)
Total patients with major renal dysfunction*		**187 (3.8)**	**182 (3.7)**	**126 (2.6)**
Pre-specified AE**	Renal dysfunction	595 (12.2)	612 (12.6)	465 (9.5)
Change in serum creatinine n (%)	Doubling of serum creatinine at any time point—all patients	202 (4.2) N=4879	229 (4.8) N=4733	162 (3.4) N=4771

*defined as one or more of: death from renal cause (investigator assessment), serious AE suggestive of renal failure, or temporary or permanent discontinuation due to a renal cause
** pre-specified checklist AE, protocol-defined.

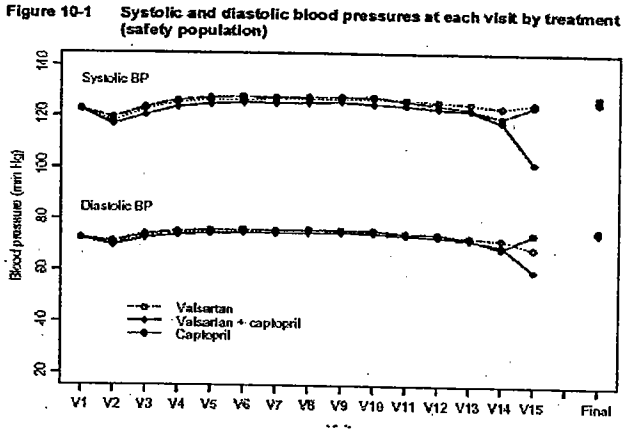
Compared to captopril, patients randomized to valsartan or the combination arm had a higher incidence of doubling of serum creatinine, pre-specified renal dysfunction, temporary/permanent discontinuations due to renal causes, and renal serious AE.

NYHA class: NYHA class was recorded at every visit. From Visit 1 to Visit 2 (hospital discharge or 15 days post-randomization), the percentage of patients increased in NYHA class I and decreased in class III and IV in all treatment groups. At the final visit, about 40% (across treatment groups) were class I, 28-30% class II, 8-9% class III, 3-4% class IV, and about 19% were missing NYHA classification. There were no differences across treatment groups.

Pregnancy/Overdose: None reported in this submission.

Vital Signs (safety population): For mean blood pressures and heart rates, no imbalances were seen across treatment groups.

Figure 8. Blood pressures by visit and treatment



APPEARS THIS WAY
ON ORIGINAL

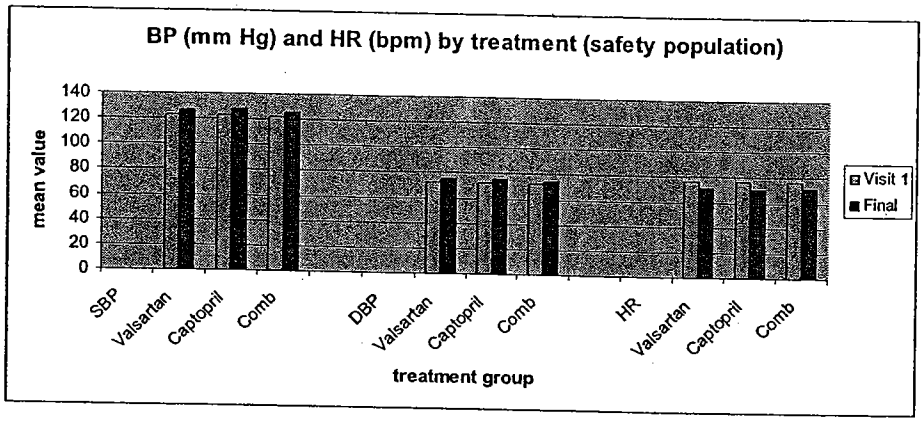


Figure 9. Vitals signs at baseline and endpoint by treatment

Source: Tables 10.4-1, 10.4-2, 10.4-3

Reviewer safety comments/conclusions:

1. The most common serious adverse event, in all three treatment groups, was heart failure.
2. There were no gross imbalances across treatment groups in serious adverse events and hospitalizations.
3. Compared to patients receiving monotherapy, there was a higher discontinuation rate in patients receiving the combination, whether for any reason or due to adverse events. The highest down-titration or temporary discontinuation rate was seen in patients receiving the combination.
4. Compared to captopril, there was a higher discontinuation rate due to hypotension in patients receiving valsartan (either as monotherapy or in combination).
5. Compared to valsartan, there was a higher discontinuation rate due to cough in patients receiving captopril (either as monotherapy or in combination).
6. There were higher rates of down-titration due to hypotension or increased creatinine[11] in patients receiving valsartan.
7. Compared to captopril, there were higher rates of renal dysfunction (prespecified AE) in patients receiving valsartan (either alone or in combination)
8. No imbalances were seen across treatment groups with respect to blood pressure or heart rate.
9. The incidence of angioedema was 0.9-1.0%. No differences were seen across treatment groups.

REVIEWERS' EVALUATION

All-cause Mortality – Primary Efficacy Endpoint

Three major objectives of the VALIANT trial are:

1) Superiority of valsartan monotherapy (at 160 mg bid) to captopril monotherapy (at 50 mg tid) in the reduction of total mortality after an acute MI,

[11] Hypotension and increased creatinine appear in valsartan labeling.

2) Superiority of the combination of valsartan (at 80 mg bid) and captopril (at 50 mg tid) to captopril monotherapy (at 50 mg tid) in the reduction of total mortality post-MI,
3) If valsartan monotherapy (at 160 mg bid) cannot be shown to be superior to captopril (at 50 mg tid) as in objective 1), then to demonstrate that long-term valsartan monotherapy is at least as effective as (or non-inferior to) captopril monotherapy in the reduction of total mortality post-MI.

The sponsor's results of the VALIANT trial, confirmed by the reviewer's analyses, demonstrate that neither objective 1) nor objective 2) was achieved. Numerically, the combination of valsartan 80 mg bid and captopril 50 mg tid was very similar to captopril 50 mg tid with respect to total mortality and so was valsartan 160 mg bid to captopril 50 mg tid; see Table 15 (9-1). The remaining question is whether valsartan 160 mg bid is as effective as captopril 50 mg tid. This is a non-inferiority analysis to be stipulated below.

The first issue concerns the alpha level for the non-inferiority analysis. As stated in the protocol, the alpha level for either the valsartan – captopril comparison or the comparison of valsartan/captopril combination versus captopril was set to 0.0253 (based on Sidak criterion which is essentially identical to Bonferroni criterion). This is acceptable. For the comparison of valsartan monotherapy versus captopril monotherapy, the superiority test and the non-inferiority test are performed. If both tests are based on a single confidence interval, then no further correction of alpha is needed[12]. For this reason and consistency, the same two-sided 97.47% confidence interval should be used for testing non-inferiority and superiority, rather than using a two-sided 97.47% confidence interval for superiority testing but a one-sided 97.47% confidence interval for non-inferiority testing as elected by the sponsor.

Two-sided Confidence Interval analysis:

The following table includes the two-sided 97.47% confidence interval for the hazard ratio of valsartan versus captopril for sponsor's non-inferiority analysis (this table is almost identical to the sponsor's Table 9-1, except that their table contains one-sided 97.47% confidence interval).

Table 35. Analysis results for the primary endpoint – all-cause mortality (primary analysis population; reviewer's analysis)

	Valsartan vs. Captopril (N=4904) (N=4909)			Valsartan+Captopril vs. Captopril (N=4885) (N=4909)		
	No. of deaths (%)[1] valsartan/captopril	Hazard ratio CI[2]	p-value	No. of deaths (%)[1] combo/captopril	Hazard ratio CI[2]	p-value
All-cause mortality	979 (19.9) / 958 (19.5)	1.001 (0.902, 1.111) (0.904, 1.108)[4]	0.98[3]	941 (19.3)/ 958 (19.5)	0.984 (0.886, 1.093)	0.73[3]

1. Percent = raw estimate of mortality rate: (number of deaths / number of patients in each group)*100%
2. Hazard ratio = valsartan or combo / captopril. The two-sided CI (97.82%) has been adjusted for all interim analyses
3. P-value is from Cox regression model with factor of treatment group and covariates of age (continuous) and previous MI (yes/no) for a two-sided null hypothesis with no treatment difference
4. Two-sided 97.47% CI for non-inferiority analysis of valsartan vs. captopril.

[12] Based on several published articles, e.g., Morikawa and Yoshida (1995, Journal of Biopharmaceutical Statistics, 297-306) and confirmed by this statistical reviewer

The second issue pertains to the non-inferiority analysis. For the non-inferiority comparison, the null hypothesis to reject was that the hazard ratio (or risk ratio) of valsartan versus captopril is at least $1+\Delta$, where Δ is the acceptance range within which the two treatments are considered equivalent. The sponsor defined Δ to be 0.13 which resulted in the non-inferiority margin of $1+\Delta = 1.13$. According to the sponsor's more detailed explanation dated 2/10/2004, this non-inferiority margin was determined using the meta analysis results from three previous placebo-controlled MI studies (SAVE, AIRE, and TRACE) on a believed-to-be similar patient population. Based on the reviewer's analysis, the random-effect analysis leads to the results similar to those of the fixed-effect analysis performed by the sponsor. The published estimates and 95% confidence intervals for hazard ratio are summarized in the following table.

Table 36. Mortality results of three historical trials (SAVE, AIRE, TRACE)

	SAVE (N=2221)	AIRE (N=1986)	TRACE (N=1749)
Year	1987-1990	1989-1992	1990-1992
ACE inhibitor tested	Captopril	Ramipril	Trandolapril
Mortality on placebo	25%	23%	42%
Mortality on ACEI	20%	17%	35%
Hazard ratio 95% CI	0.81 0.68 – 0.97	0.73 0.60 – 0.89	0.78 0.67 – 0.91

By pooling the three trials with equal weight, the hazard ratio for ACE inhibitor versus placebo was estimated to be 0.773 with a 95% confidence interval of (0.698, 0.856) from meta-analysis.

The non-inferiority margin was determined to ensure the following considerations:

1) In the worst scenario of possible non-inferiority results from VALIANT, the result would indicate that the benefit of valsartan was to preserve at least 50% of the expected ACE inhibitor (captopril) benefit in mortality reduction at the allowed significance level. With the hazard ratio margin of 1.13 for valsartan versus captopril comparison, the estimated benefit of valsartan was expected to preserve about 55.7% (= (1-1.13*0.773)/ (1-0.773)*100% of the expected ACE inhibitor (captopril) benefit in mortality risk reduction.
2) In the worst scenario of possible non-inferiority results from VALIANT, the result would still ensure that valsartan is effective (i.e., better than placebo) in reduction of mortality risk at the allowed significance level. This is because the 95% confidence interval for the hazard ratio of placebo versus ACE inhibitor would be 1.168-1.433 by inversion from the 95% confidence interval for the hazard ratio of ACE inhibitor versus placebo, 0.698-0.856 and the 1.13 non-inferiority margin from VALIANT would be able to conclude that valsartan is effective at the allowed significance level.

The sponsor's arguments are based on the point estimate of the captopril effect but the variance of the point estimate which measures the precision of the estimate was not considered in defining the non-inferiority margin. This critical point will be addressed later.

The sponsor's non-inferiority analysis was based on the following assumptions:

1. Captopril benefits in patients post-MI with LV dysfunction or congestion is a "class effect" and similar across ACE inhibitors;
2. The captopril effect, as demonstrated in the older SAVE trial, has not changed over time;
3. SAVE, AIRE and TRACE populations are comparable to the current VALIANT population.

These assumptions are critical to the assessment of the validity of the non-inferiority analysis as also to be articulated below.

Comparability of VALIANT to the SAVE, AIRE and TRACE studies:

VALIANT, SAVE, AIRE and TRACE were not identical studies. Important differences between the trials include:

1. Enrollment periods: VALIANT began enrollment about 8-9 years after the three index trials;
2. Entry criteria: Compared to the other three studies, VALIANT employed the broadest entry criteria, using either clinical, radiologic or imaging evidence of LV dysfunction as a basis for study entry. The AIRE study, for example did not require imaging evidence of LV dysfunction and may have included patients with preserved LV function;
3. Cardiac enzymes: Only the VALIANT trial employed troponins as a criterion for MI.
4. Time to randomization: Mean time from MI to randomization ranged from 4.5 to 11 days[13];
5. Background disease: Compared to the other studies, VALIANT patients had higher rates of hypertension and diabetes.
6. Medication use: The VALIANT population showed a higher incidence of beta blocker and aspirin use and lower calcium channel blocker use compared to the other study populations.
7. The mean age in the TRACE population was older compared with the other studies. The TRACE population had a higher history of previous angina and CHF compared with the other studies. In addition, the TRACE population was randomized a mean of 4.5 days post-MI. According to labeling, the TRACE population was entirely Caucasian. In addition, BP control, especially in the placebo group, was poor; about 47-53% of placebo patients and about 32-40% of trandolapril patients had BP> 140/95 at 90-day follow-up visits.
8. The use of primary angioplasty as therapy for MI was not consistently reported and therefore was not used as a basis for comparison in this table. According to labeling, about 6.7% of the TRACE population underwent PTCA or CABG during the entire follow-up period.
9. Mean follow-up was different across the studies as outlined below:

Table 37. Comparisons of VALIANT, SAVE, AIRE, TRACE

	SAVE	AIRE	TRACE	VALIANT
Enrollment period	1987-1990	1989-1992	1990-1992	1998-2001
Regions	USA/Canada	Multinational	Denmark	Multinational
Entry criteria:	1. 3-16 days post-MI; 2. 21-79 years old	1. 2-9 days post-MI. 2. ≥ 18 years old	1. 1-5 days post-MI. 2. > 18 years old.	1. 12 hours-10 days post-MI. 2. ≥ 18 years old
	3. LV EF ≤ 40% by radionuclide ventriculography (RVG)	3. Clinical evidence of heart failure (could be transient); LV EF was not an inclusion criterion.	3. LV systolic dysfunction defined as wall motion index ≤ 1.2 by echocardiography	3. Clinical evidence of heart failure (could be transient) or radiologic or systolic dysfunction defined by echo, RVG, or contrast angiography

[13] It could be argued that the study with a shorter mean time from MI to randomization may have enrolled a sicker population, whereas the SAVE population may have excluded patients who died within the first week post-MI.

	Excluded: Patients with clinical course/ETT highly suggestive of ischemia w/o further evaluation (angiography); patients s with coronary stenosis warranting revascularization; overt heart failure.		Excluded: Patients with NYHA Class IV CHF.		Patients with need for an ACE inhibitor were excluded. Randomized patients were stratified according to wall motion index. Patients with NYHA Class IV CHF were included.		Use of ACE inhibitor was "strongly discouraged." Patients with heart failure (except cardiogenic shock within 24 hours of randomization) were included.	
Randomized	PBO (n=1116)	Captopril (n=1115)	Ram (n=1004)	PBO (n=982)	Trandolapril (n=876)	PBO (n=873)	Valsartan (n=4909)	Captopril (n=4909)
Mean (range) follow-up (months)	42 (24-60)		15 (6-46)		24 months[14]		23 (0.3- 47)[15]	
Mean age (yr)	59		65		67-68		64-65	
Males (%)	82-83		73-74		71-72		69	
Previous MI (%)	35-36		22-23		34-37		27-28	
Previous angina	25-26		35-37		44-47		39-40	
History of CHF	6		8		21-23		14-16	
Diabetes (%)	21-23		12		13-14		23	
Hypertension (%)	42-44		27-29		23		55-56	
History of Smoking (%)	78-79		NR		73-75		64	
Events between MI and randomization								
Mean days from MI to randomization	11		5		4.5		6	
Killip class I (%)	59-60		NR		79-80		26-29	
Thrombolytic (%)	32		56-59		44-45		35-36	
PTCA (%)	17		NR		NR		15	
CABG (%)	8-10		NR		NR		7	
Infarct type (%)								
Anterior Q wave	54-56*		59-62		47		44-45	
Inferior Q wave	17-18**		38-41		18-19		23-24	
Q wave	NR		62-65		78-79		62-64	
Non Q wave	10		35-38		14-15		28-29	

[14] According to the TRACE publication (Kober L. et al. NEJM 1995: 333: 1670-1676), the duration of follow-up was 24- 50 months. According to the Agency primary medical review, follow-up out to the protocol-specified 24 month endpoint was missing for hundreds of subjects; according to the sponsor, mortality was ascertained, through the full follow-up period, via inquiries to the Danish Civil Registration Service.

[15] Follow-up means and ranges were supplied by the sponsor in days and converted to months by the following formula: n (days) x 12/365.

Mean radionuclide EF	31	NR	NR (reported as wall motion index =1.0)***	36

*reported as anterolateral **reported as inferoposterior *** by echocardiography, not radionuclide

Medication use w/in 24 hrs of randomization (%)				
	SAVE	AIRE	TRACE	VALIANT
Aspirin	59	77-78	90-92	91
Other antiplatelet agents	14	NR	NR	IIb/IIIa = 6-7% Other antiplatelet = 25%
Beta blockers	35-36	21-24	15-17	70-71
Calcium channel blockers	42	16	28	8-9
Digitalis	25-27	12	26-29	13
Diuretics	35	58-61	64-68	Potassium-sparing diuretic = 9% Other diuretic = 49-51%
Nitrates	50-53	55-56	50-56	44*
Mean BP (mm Hg)				
Systolic	112-113	NR	120-122	123
Diastolic	70	NR	75-76	72
Mean heart rate (bpm)	78	NR	81	76.2

Sources: NDA 18-343/S-048 (SAVE), NDA 19-901/S-010 (AIRE), NDA 20-528/S-001 (TRACE), in addition to the study report publications. NR= Not reported in publication nor found in the reviews. PBO= placebo
*excluding nitrate prophylaxis.

Non-inferiority margin:

The sponsor's non-inferiority margin (1.13) was derived from the three historical trials using the point estimate of the captopril effect to be expected for the VALIANT population. The variance of the estimate was not incorporated in the non-inferiority analysis.

This approach is known to be problematic[16]. That is, using the 97.47% confidence interval for the hazard ratio of valsartan versus captopril to rule out 1.13, the probability of type I error associated with falsely concluding that valsartan retains > 50% of the captopril effect is larger than 0.0253, the allowed level of significance (split of 0.05 for the two comparisons - valsartan versus captopril and valsartan/captopril combination versus captopril). Thus, to deal with this problem, one way is finding a non-inferiority margin smaller than 1.13 by incorporating the uncertainty of the point estimate of the captopril effect in calculation of the margin. Another way is inflating the confidence interval for the hazard ratio of valsartan versus captopril by incorporating the variance of the point estimate of the captopril effect into the confidence interval; this is similar to the concept of discounting[17]. Technical details are provided in the appendix.

To incorporate the uncertainty in the point estimate of the active control's effect, the Agency had experiences with the approach[18] of using the worst confidence limit of some high-level confidence interval for the hazard ratio of the control's effect to define the margin. If the meta analysis of the three trials is acceptable, then the worst limit of the 95% confidence interval for the hazard ratio of captopril versus placebo is 0.856. Using this limit leads to a conservative non-inferiority margin, 1.08. That is, if the 97.43% confidence interval for the hazard ratio of

[16] Wang, Hung and Tsong (2002, Controlled Clinical Trials, 15-28)
[17] Snapinn (2004, Journal of Biopharmaceutical Statistics, 263-273)
[18] CBER/FDA Memorandum (June 1999)

valsartan versus captopril rules out the 1.08 margin, then one can statistically conclude that valsartan preserves > 50% of the captopril effect.

Equivalently, one can conservatively inflate the 97.43% confidence interval to a wider interval by incorporating the uncertainty in the point estimate of the hazard ratio of the captopril effect in the interval. If the wider interval rules out the 1.13 margin, then one can statistically conclude >50% retention of the captopril effect by valsartan. This conservative approach is statistically valid with a very small type I error rate (<< 0.0253) if the above three assumptions hold. Technical details are provided in the appendix.

When this highly conservative approach is performed, it cannot be concluded from VALIANT that valsartan preserves > 50% of the captopril effect since the two-sided 97.43% confidence interval (0.904, 1.108) for the hazard ratio of valsartan versus captopril includes the conservative margin 1.08, or equivalently, the conservatively inflated interval (0.859, 1.166) for the hazard ratio of valsartan versus captopril includes the margin 1.13.

If the three assumptions given above hold, then a less conservative approach of non-inferiority analysis can be derived. This is the so-called the synthesis method[19]. This method can be expressed in two ways. One way is to derive a "working" margin for the 97.43% confidence interval to rule out (Note: such a margin cannot be used to plan a non-inferiority trial[20]). The other way is to inflate the 97.43% confidence interval properly and then compare the inflated interval with the 1.13 margin; see Appendix for details. Based on the calculation with this less conservative approach, the "working" margin is 1.12 and the properly inflated interval is (0.890, 1.125) which is less conservative than the interval (0.859, 1.166) of the worst limit approach previously described. The synthesis method can lead us to conclude (if the constancy assumption holds) that valsartan preserves > 50% of the captopril effect, since the two-sided 97.43% confidence interval (0.904, 1.108) for the hazard ratio of valsartan versus captopril rules out the less conservative margin 1.12 or, equivalently, the less conservatively inflated interval (0.890, 1.125) for the hazard ratio of valsartan versus captopril rules out the margin 1.13.

The event rate seen in the TRACE trial was almost double the event rates of the SAVE and the AIRE trials. This may raise the concerns of whether TRACE and other two trials are comparable and whether TRACE should ever be combined with other two trials to estimate the captopril effect or the effect of ACE inhibitors.

We looked into combining only SAVE and AIRE in estimating the effect of captopril. By pooling the two trials in the same way as the sponsor pooled the three trials, the estimated hazard ratio of captopril versus placebo is 0.769 with 95% confidence interval (0.673, 0.879). Use of the worst confidence limit of this confidence interval will result in a conservative non-inferiority margin 1.067 which cannot be ruled out by the 97.43% confidence interval (0.904, 1.108) for the hazard ratio of valsartan versus captopril, or equivalently, a point-estimate non-inferiority margin 1.140 that cannot be ruled out by the conservatively inflated interval (0.846, 1.185). If the three assumptions hold, the synthesis method will result in a less conservatively inflated interval (0.881, 1.137) which rules out the margin 1.140. So the synthesis method can lead us to conclude that valsartan retains > 50% of the captopril effect, if the constancy assumption holds.

VALIANT employed only captopril as the active control comparator. So it can be argued whether, strictly speaking, only the SAVE trial can provide a relevant estimate of the captopril effect and that AIRE and TRACE trials are supportive in the sense of shedding some light on whether the effect of captopril, if deemed similar to those of other ACE inhibitors, is likely to

[19] Holmgren (1999, Journal of Biopharmaceutical Statistics, 651-659)
Hung, Wang, Tsong, Lawrence, O'Neill (2003, Statistics in Medicine, 213-225)
Rothmann, Li, Chen, Chi, Temple, Tsou (2003, Statistics in Medicine, 239-264)

[20] Hung, Wang, Tsong, Lawrence, O'Neill (2003, Statistics in Medicine, 213-225)

have worsen over time. Under these assumptions, the captopril effect in terms of mortality risk ratio did not seem to worsen over the years. If the worst confidence limit of the 95% confidence interval (0.68, 0.97) for the hazard ratio of captopril versus placebo from the SAVE trial is used, then the non-inferiority margin will be 1.02. Based on this conservative approach, the 97.43% confidence interval (0.904, 1.108) for the hazard ratio of valsartan versus captopril failed to rule out the margin 1.02. If only SAVE trial can be used to estimate the effect of captopril, the synthesis method will result in the comparison of a less conservatively inflated interval (0.866, 1.157) with the 1.111 margin and also failed to rule out the margin.
Thus, if only SAVE trial can be used to estimate the effect of captopril, then it cannot be concluded that valsartan preserves > 50% of the captopril effect.

On the other hand, the reviewers recognize that the mortality hazard ratios across the three index studies are similar despite the seeming differences in study design and patient population.

Secondary Endpoints

Numerically, valsartan seemed to be similar to captopril with respect to all the secondary endpoints as seen in the following table.

Table 38. Number (%) of secondary endpoints (primary analysis population; sponsor's results confirmed by the reviewers)

	Valsartan (N=4909)	Captopril (N=4909)
Cardiovascular mortality	827 (16.8%)	830 (16.9%)
Three-event composite Cardiovascular mortality Hospitalization for heart failure Recurrent non-fatal MI	1529 (31.1%) 827 (16.8%) 813 (16.6%) 397 (8.1%)	1567 (31.9%) 830 (16.9%) 801 (16.3%) 402 (8.2%)
Five-event composite Additional variables: Non-fatal stroke Cardiac arrest with resuscitation	1612 (32.8%) 131 (2.7%) 56 (1.1%)	1641 (33.4%) 123 (2.5%) 59 (1.1%)

Though these results might be viewed to support the results of all-cause mortality in some sense, the interpretation of non-inferiority analysis with respect to these endpoints is even more difficult and probably impossible since these endpoints were never studied in the three historical trials. In our view, non-inferiority analysis with respect to the secondary endpoints should not be entertained.

Tertiary Endpoints:

Numerically, valsartan appeared similar to captopril with respect to the tertiary endpoints.

CONCLUSIONS

For any type of non-inferiority analysis, since the placebo arm is not studied in the non-inferiority trial, there are no data to prove or disprove that the effect of the selected positive control in the historical trials remains unchanged under the non-inferiority setting. [21] The interpretation of the results of the non-inferiority analysis in the VALIANT trial is no exception.
The following issues would need to be dealt with based on judgment since there is no data to support the judgment.
1. Since VALIANT involved only captopril as the selected active control comparator, can AIRE and TRACE (neither involved captopril) be also used to estimate the effect of captopril?
2. The mortality rate in TRACE is almost double the mortality rates of SAVE and AIRE. Does this indicate that the type of heterogeneity needs to be of concern between VALIANT and TRACE? That is, should the TRACE mortality result ever be used to estimate the effect of captopril?
3. There are always differences among trials in patient populations, concomitant medications, etc. Will the constancy assumption that the captopril effect remains unchanged from the historical trials to the VALIANT trial hold because of these differences?

These questions or issues are fundamental to challenge the following assumptions (labeled as S1-S3) made by the sponsor which are also critical to the interpretability of any of the non-inferiority analyses.
S1) Captopril benefits in patients post-MI with LV dysfunction or congestion is a "class effect" and similar across ACE inhibitors;
S2) The captopril effect, as demonstrated in the older SAVE trial, has not changed over time;
S3) SAVE, AIRE and TRACE populations are comparable to the current VALIANT population.

Based on the result of VALIANT, the point estimate for the risk of all-cause mortality in the valsartan 160 mg bid group is almost identical to that in the captopril group (hazard ratio = 1.001). The per protocol analysis gave very similar results. However, whether the result is sufficient for us to assert that valsartan preserves at least 50% of the effect of the captopril depends on which analysis results to take and the underlying assumptions, S1-S3. If these assumptions hold, then it can be concluded with more than 95% confidence that valsartan retains > 50% of the captopril effect (i.e., based on synthesis method, the inflated interval (0.890, 1.125) for valsartan versus captopril rules out the margin 1.13). If there is any doubt about these assumptions, then a more conservative method that the CBER/FDA had experience with cannot lead to this conclusion [i.e., the 97.43% confidence interval (0.904, 1.108) for valsartan versus captopril includes the conservative margin 1.08].

If it is deemed that TRACE cannot be used in estimation of the captopril effect (i.e., only SAVE and AIRE are combined to estimated the captopril effect) and if the assumptions S1-S3 hold, then it <u>can</u> be concluded that valsartan retains > 50% of the captopril effect (i.e., based on the synthesis method, the inflated interval (0.881, 1.137) for valsartan versus captopril ruled out the appropriate margin 1.140). If these assumptions are in doubt, then a more conservative method that CBER/FDA had experience with <u>cannot</u> lead to this conclusion (i.e., the 97.43% confidence interval for valsartan versus captopril included the conservative margin 1.067).

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[21] Note that the captopril mortality rate in VALIANT (19.5%) is about the same as, and certainly not worse than, the captopril mortality rate in SAVE (20%). One might have hoped that the mortality rate in VALIANT would have been even lower, given the higher use of beta blockers and aspirin.

If it is deemed that only SAVE can be used to estimate the captopril effect, then neither method can lead to the assertion that valsartan retains > 50% of the captopril effect.

The results of the non-inferiority analyses using the worst confidence limit method and the synthesis method are summarized in Table 39. Note that the results of both methods require the constancy assumption to be interpretable. The synthesis method is much more sensitive to the constancy assumption than the worst confidence limit method.

Table 39. Results of non-inferiority analyses for retention of >50% captopril (C) by valsartan (V)

Historical trials	Method of non-inferiority analysis	Non-inferiority analysis result	Conclude that V retains >50% of C effect?
SAVE, AIRE, TRACE combined	Worst CI limit	(0.904, 1.108)* contains 1.08	Fail
	Synthesis	(0.890, 1.125)** rules out 1.13	Succeed
SAVE, AIRE combined	Worst CI limit	(0.904, 1.108)* contains 1.067	Fail
	Synthesis	(0.881, 1.137)** rules out 1.140	Succeed
SAVE only	Worst CI limit	(0.904, 1.108)* contains 1.02	Fail
	Synthesis	(0.866, 1.157)** contains 1.111	Fail

*With worst CI limit method, 97.47% confidence interval is compared to the conservative margin
**With synthesis method, inflated interval wider than 97.47% confidence interval is compared to the point-estimate margin (see Appendix for details)

So one pathway involves deciding which study or studies to accept (SAVE alone, SAVE + AIRE, or the three studies) and which margins/analyses to accept in order to estimate a captopril effect. One might then decide either that valsartan meets criteria for "non-inferiority" or, more basically, to decide whether valsartan is even effective in this selected post-MI population. Depending on which assumptions one accepts, one could then write labeling for effectiveness without accepting a non-inferiority claim. Or one could decide that this study does not provide the weight of evidence to support an approval.

Another consideration is that there are currently no alternatives to ACE inhibitors in the post-MI population with LV dysfunction. In a population unable to take ACE inhibitors, it would be attractive to offer an alternative, such as an ARB, if convincing benefit could be demonstrated and if the safety and tolerability were not an issue. The question, then, is what percent retention of captopril benefit is acceptable to conclude that valsartan is effective in this patient population unable to take ACE inhibitors.

For superiority testing, two positive trials or the strength of evidence equivalent to two positive trials are normally required. For non-inferiority analysis, this requirement may even be more compelling. If the goal of the non-inferiority analysis is to assert retention of >50% of the captopril with valsartan, then the result of VALIANT probably is insufficient in terms of the strength of evidence. This raises the option of asking the sponsor to perform an additional confirmatory study. However, the exact kind of confirmatory study, including study design and comparator (s) would have to be discussed within the Agency. For the sponsor to perform such a study, there should be a reasonable expectation that this study will support the sponsor's proposed valsartan indication.

Appendix

Let

C_0/P_0 = hazard ratio of captopril versus placebo in historical trial populations (SAVE, AIRE, TRACE);

C/P = hazard ratio of captopril versus placebo in the VALIANT population;

V/C = hazard ratio of valsartan versus captopril in the VALIANT population.

Let log denote the natural logarithm and exp denote the anti-log.

The sponsor's approach of comparing the one-sided 97.47% confidence interval with the 1.13 non-inferiority margin can be viewed, at least approximately, as

$$\exp\{\log(\hat{V}/\hat{C}) + 1.955\sqrt{\mathrm{var}(\log(\hat{V}/\hat{C}))}\} < 1.13 \cong \exp(-0.5\log(\tilde{C}_0/\tilde{P}_0))$$

where var is the estimated variance, $\hat{V}/\hat{C}$ and $\tilde{C}_0/\tilde{P}_0$ are the estimators of V/C and C_0/P_0, respectively. As we argued on page ??, the two-sided 97.47% confidence interval should be used for non-inferiority analysis; consequently, the critical value 1.955 in the above inequality should be changed to 2.237.

By use of the two-sided 97.47% confidence interval for V/C, the method of using the worst confidence limit of the 95% confidence interval for the hazard ratio of the captopril effect to define the non-inferiority margin will result in the critical region

$$\exp\{\log(\hat{V}/\hat{C}) + 2.237\sqrt{\mathrm{var}(\log(\hat{V}/\hat{C}))}\}$$
$$< \exp(-0.5[\log(\tilde{C}_0/\tilde{P}_0) + 1.96\sqrt{\mathrm{var}(\log(\tilde{C}_0/\tilde{P}_0))}])$$

For example, by the sponsor's meta analysis, combining SAVE, AIRE and TRACE will lead to 1.08 for the right-hand side of this inequality. From Table ??, the two-sided 97.47% confidence interval for the hazard ratio of valsartan versus captopril in the VALIANT trial is (0.902, 1.111). Thus, the non-inferiority in the sense of retaining >50% of the captopril effect is to be tested by determining whether the interval (0.902, 1.111) rules out 1.08. Alternatively, one could move the variance term of the right-hand side of this inequality to the left-hand side and obtain

$$\exp\{\log(\hat{V}/\hat{C}) + 2.237\sqrt{\mathrm{var}(\log(\hat{V}/\hat{C}))} + 0.5\times 1.96\sqrt{\mathrm{var}(\log(\tilde{C}_0/\tilde{P}_0))}\}$$
$$< \exp(-0.5\log(\tilde{C}_0/\tilde{P}_0))$$

Now, the right-hand side becomes the 1.13 margin but the left-hand side is an interval inflated by incorporating the variance term in the 97.47% confidence interval. This is similar to the concept of discounting[22]. That is, the comparison of the 97.47% confidence interval (0.902, 1.111) with 1.08 is equivalent to the comparison of the conservatively inflated interval (0.857, 1.169) with 1.13.

[22] Snapinn (2004, Journal of Biopharmaceutical Statistics, 263-273)

Another method is the so-called synthesis method which is originated from the critical region using the test statistic

$$Z = \frac{\log(\hat{V}/\hat{C}) + 0.5\log(\tilde{C}_0/\tilde{P}_0)}{\sqrt{\text{var}(\log(\hat{V}/\hat{C})) + 0.25\,\text{var}(\log(\tilde{C}_0/\tilde{P}_0))}} < -2.237 \quad ,$$

for asserting that valsartan preserves > 50% of the captopril effect. By the same algebraic manipulation, this critical region can be expressed as

$$\exp\{\log(\hat{V}/\hat{C}) + 2.237\sqrt{\text{var}(\log(\hat{V}/\hat{C})) + 0.25\,\text{var}(\log(\tilde{C}_0/\tilde{P}_0))}\} < \exp(-0.5\log(\tilde{C}_0/\tilde{P}_0))$$

or

$$\exp\{\log(\hat{V}/\hat{C}) + 2.237\sqrt{\text{var}(\log(\hat{V}/\hat{C}))}\}$$
$$< \exp(-0.5\log(\tilde{C}_0/\tilde{P}_0)$$
$$- 2.237[\sqrt{\text{var}(\log(\hat{V}/\hat{C})) + 0.25\,\text{var}(\log(\tilde{C}_0/\tilde{P}_0))} - \sqrt{\text{var}(\log(\hat{V}/\hat{C}))}]\}.$$

The first inequality leads to the comparison of the less conservatively inflated interval (0.889, 1.128) with 1.13 whereas the second inequality leads to the comparison of the 97.47% confidence interval (0.902, 1.111) with the "working" margin 1.12 [note: this "working" margin depends on the sample size of the current non-inferiority trial and can be problematic for interpretation and for designing the non-inferiority trial[23].

[23] Hung, Wang, Tsong, Lawrence, O'Neill (2003, Statistics in Medicine, 213-225)

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