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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-283/S011

Statistical Review(s)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

ADDENDUM #2

NDA #/Serial #:	21-283/S-011
DRUG NAME:	Diovan (valsartan) Tablets
INDICATION:	Improving survival following myocardial infarction in clinically stable patients with signs, symptoms or radiological evidence of left ventricular failure and/or with left ventricular systolic dysfunction
APPLICANT:	Norvatis Pharmaceuticals
DATE OF DOCUMENT:	March 3, 2005
REVIEW PRIORITY:	P
BIOMETRICS DIVISION:	Division of Biometrics I
STATISTICAL REVIEWER:	H.M. James Hung, Ph.D. (HFD-710)
MEDICAL DIVISION:	Division of Cardio-Renal Drug Product (HFD-110)
CLINICAL TEAM:	Shari Targum, M.D. (HFD-110)
PROJECT MANAGER:	Ed Fromm (HFD-110)

KEY WORDS: non-inferiority margin, percent preservation, 95-95 method, 97.47-95 method, constancy assumption

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TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

There is no data to support the constancy assumption that the effect of captopril estimated from the three historical trials is applicable to VALIANT. However, there appear to be some pieces of data that seem to suggest that this assumption may not hold. Thus, use of a more conservative method is needed for non-inferiority analysis in this application. Based on the traditional approach using the worst limit of 95% two-sided confidence interval to estimate the captopril effect, VALIANT appears to support that valsartan retains at least 36%-44% of the mortality benefit of captopril, depending on whether adjusting for the difference in beta blockers use between VALIANT and the three historical trials is necessary. If the mortality effect of captopril is not much smaller in VALIANT than in the three historical trials, use of the worst limit of 90% two-sided confidence interval may be considered, based on which VALIANT appears to support that valsartan retains at least 42%-53% of the mortality benefit of captopril. Valsartan seems to preserve more than 50% of the effect of captopril on the composite of cardiovascular mortality, heart failure hospitalization and recurrent myocardial infarction (a pre-specified endpoint).

1.2 Brief Overview of Clinical Studies

The overview of the clinical studies of concern is provided in the 6/30/2004 joint clinical/statistical review and the 1/10/2005 statistical review addendum. Following the meeting with the Agency dated February 9, 2005, the sponsor submitted a document on March 3, 2005 that contains a number of additional analyses to support unrestricted use of valsartan to treat post-myocardial-infarction patients.

1.3 Statistical Issues and Findings

The key question is whether we can believe with great comfort that the effect of captopril, estimated by borrowing the estimated effects of ramipril from AIRE and trandolapril from TRACE, can apply to the effect of captopril in VALIANT. There is no data to answer this question. All we have are some pieces of data that generate discomfort, such as, that the captopril effect seen in SAVE is numerically smaller than those of ramipirl and trandolapril in AIRE and TRACE, that CCS-1 and ISIS-4 trials seem to show a much smaller effect with captopril. Therefore, in this reviewer's view, the results of some of the sponsor's additional analyses using synthesis methods to estimate the fraction of preservation are difficult to interpret. And it is more compelling to use a more conservative method to assess the fraction of preservation, as also commented in the 6/30/2004 joint clinical/statistical review and 1/10/2005 statistical review addendum.

2. INTRODUCTION

2.1 Overview

Following the meeting with the Agency dated February 9, 2005, the sponsor submitted a document on March 3, 2005 that contains a number of additional analyses to support unrestricted use of valsartan to treat post-myocardial-infarction patients. This review pertains to this document.

2.2 Data Sources

No additional SAS dataset is provided for the sponsor's results reported in the 3/3/2005 document.

3.1 Evaluation of Efficacy

The 03/03/2005 document reviews the strength of the non-inferiority results (valsartan versus captopril) with a focus on preservation of the captopril benefit provided by valsartan in reducing mortality and morbidity. This document is also intended to consolidate key data and the sponsor's assessments that have been submitted previously with relevance to this document. In addition, this document includes new analyses and assessments for the pre-specified secondary endpoints (CV mortality and two composite mortality/morbidity endpoints), using available data from the reference trials (SAVE, TRACE, and AIRE). The sponsor concludes that these additional results reinforce the evidence that valsartan preserves more than 50% of captopril's benefit in reducing mortality/morbidity risk and strongly support the conclusion that valsartan is non-inferior to captopril as an effective treatment for a general post-myocardial-infarction population with left ventricular dysfunction.

The 3/3/05 document contains several tables and figures for

1) the primary endpoint: all cause mortality
2) three pre-specified secondary endpoints:
   cardiovascular (CV) mortality
   composite of CV death, HF hospitalization, recurrent myocardial infarction (MI)
   composite of CV death, HF hospitalization, MI, stroke, cardiac arrest with resuscitation
3) composite of all-cause death, MI and CHF.

All-cause mortality (primary endpoint)

Throughout all the submitted documents including the 03/03/2005 document, the 95% confidence interval of valsartan versus captopril from VALIANT was used to assess non-inferiority (e.g., Sponsor's Figures 1, 2, 3 of the 03/03/2005 document). As stated in the joint medical/statistical review of 6/30/2005, the 97.5% confidence interval rather than 95% CI should be used because of the necessary adjustment for multiple comparisons (valsartan versus captopril comparison and the combination of valsartan plus captopril versus captoril comparison).

In addition, the sponsor's non-inferiority margin 1.13 is computed using the point estimate of the captopril effect from the three historical trials (Sponsor's Figure 1, page 4 of the document), which is not acceptable because its standard error is completely ignored in defining the margin.

As per the reviewer's analysis, the 97.5% confidence interval (0.904, 1.108) from VALIANT fails to rule out the margin 1.084 (50% of the worst limit of 95% confidence interval from SAVE, AIRE, TRACE combined) or the margin 1.094 (50% of the worst limit of 90% confidence interval from the three historical trials combined). Using the 95% CI worst limit as the estimate of the captopril effect, VALIANT appears to support that valsartan retains more than 36% of the captopril effect, whereas using the 90% CI worst limit, the retention level can be 42%; see Table R1 below. Use of the 90% CI worst limit to estimate the captopril effect may be considered if the mortality effect of captopril is not much smaller in VALIANT than that in the three historical trials combined (this assumption requires subjective judgment without any data for verification).

Table R1. Non-inferiority (NI) analyses for % retention of captopril (C) effect by valsartan (V) [ITT population; confidence interval versus fixed NI margin analysis]
[Source: Reviewer's analysis]

Method of NI analysis*	CI of V vs. C	NI margin (retaining 50% of C effect)	Concluding 'V retains >50% of C effect'?	Estimated % of retention**
Use of SAVE alone to define NI margin				
97.5-95	(0.904, 1.108)	1.015	Fail	NE
97.5-90	(0.904, 1.108)	1.031	Fail	NE
Use of SAVE+AIRE to define NI margin				
97.5-95	(0.904, 1.108)	1.069	Fail	22%
97.5-90	(0.904, 1.108)	1.081	Fail	33%
USE of SAVE+AIRE+TRACE to define NI margin				
97.5-95	**(0.904, 1.108)**	**1.084**	**Fail**	**36%**
97.5-90	**(0.904, 1.108)**	**1.094**	**Fail**	**42%**

* e.g., for the 97.5-90 method, 97.5% CI of VALIANT for valsartan versus captopril is compared against the NI margin that is derived by preserving 50% of the worst limit of 90% CI of the historical trials for the effect of captopril (or ACE inhibitor)
** % retention is estimated, treating the upper limit of confidence interval of V vs. C as if it were the NI margin to rule out; e.g., when three historical trials are combined to estimate the captopril effect, based on 97.5-90 method, if the study were to rule out the margin 1.108, then one would be able to claim at least 42% of the captopril effect (estimated by the worst limit of 90% CI) is preserved by valsartan. NE: not estimable

The sponsor's analyses in Tables 1 and 2 in estimating percent preservation are based on the so-called synthesis methods that are still being explored in the literature. A well-known fact is that these methods are highly sensitive to the constancy assumption, i.e., the effect of captopril in VALIANT is equal to that in the historical trials. In addition, these methods cannot provide a non-inferiority margin for evaluation. Since the constancy assumption is very much uncertain in this case (only SAVE provided the historical estimate of the effect of captopril two decades ago, the later AIRE and TRACE studies provided no estimate for captopril effect but the estimated effect for other ACE inhibitors are larger than that for captopril), the interpretability of the analysis results using these methods may be highly questionable.

Per-protocol analysis yields a larger percent retention (Sponsor's Table 3 of the 03/03/2005 document); however, it is unclear whether that is a result of overestimation due to bias that can easily incur in per-protocol analysis. In Table 3, the sponsor's post hoc analysis adjusting for the difference in % of beta-blocker use between VALIANT and the three historical trials also gives a larger percent retention.

Cardiovascular mortality (pre-specified secondary endpoint)

According to the 03/03/2005 document, SAVE and TRACE provide data for this endpoint. The alpha adjustment for cardiovascular mortality is probably little after all-cause mortality is analyzed. From VALIANT, the worst limit of the 97.5% confidence interval for valsartan versus captopril is 1.090. Using the worst limit of 95% CI of the SAVE and TRACE combined gives a non-inferiority margin of 1.071. Using the worst limit of 90% CI gives a non-inferiority margin of 1.083. In either way, the margin cannot be ruled out by the 97.5% CI; thus, 50% retention on cardiovascular mortality cannot be concluded. In fact, cardiovascular mortality essentially gives the results similar to those of all-cause mortality (Sponsor's Table 8 and Figure 4 in the 03/03/2005 document).

The sponsor's Tables 6 and 7 give the results of synthesis methods. As commented above, the interpretability of these results may be highly questionable for the same reasons.

Composite of CV mortality, HF hospitalization and MI (pre-specified secondary endpoint)

This is one of the two pre-specified composite endpoints as a secondary endpoint. It is not clear what alpha should be used to analyze this endpoint. If we think that the result of the primary endpoint is conclusive, this endpoint may be analyzed using the 98.75% CI of VALIANT (i.e., by Bonferroni adjustment). Based on this reviewer's calculation using the result of the sponsor's Table 9, the upper limit of the 98.75% confidence interval for valsartan versus captopril from VALIANT on this composite endpoint is 1.045. According to the 03/03/2005 document, among the three historical trials, only SAVE has available data for this composite endpoint. From the sponsor's Table 13, using the worst limit of the 95% CI for the captopril effect yields a 50%-retention non-inferiority margin of 1.074, which is ruled out by the 98.75% CI of VALIANT. Thus, valsartan appears to retain more than 50% of the captopril effect on this composite endpoint, provided that the result of the primary endpoint is conclusive.

Composite of CV mortality, HF hospitalization, MI, stroke, and cardiac arrest with resuscitation (pre-specified secondary endpoint)

Since no data for this composite endpoint in the three historical trials is available, the non-inferiority assessment cannot be performed.

Composite of all-cause mortality, morbidity endpoints

Two additional composite endpoints are post hoc analyzed in the 03/03/2005 document to strengthen the support for the non-inferiority results. In this reviewer's view, these analyses add little to support.

3.2 Evaluation of Safety

Please refer to the combined medical/statistical review dated June 30, 2004 for safety assessment.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Please refer to the combined medical/statistical review dated June 30, 2004.

4.2 Other Special/Subgroup Populations

Please refer to the combined medical/statistical review dated June 30, 2004.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The key question is whether we can believe with great comfort that the effect of captopril, estimated by borrowing the estimated effects of ramipril from AIRE and trandolapril from TRACE, can apply to the effect of captopril in VALIANT. There is no data to answer this question. All we have are some pieces of data that generate discomfort, such as, that the captopril effect seen in SAVE is numerically smaller than those of ramipirl and trandolapril in AIRE and TRACE, that CCS-1 and ISIS-4 trials seem to show a much smaller effect with captopril. Therefore, in this reviewer's view, the results of some of the sponsor's additional analyses using synthesis methods to estimate the fraction of preservation are difficult to interpret. And it is more compelling to use a more conservative method to assess the fraction of

preservation, as also commented in the 6/30/2004 joint clinical/statistical review and 1/10/2005 statistical review addendum.

5.2 Conclusions and Recommendations

As commented earlier, there is no data to support the constancy assumption that the effect of captopril estimated from the three historical trials is applicable to VALIANT. However, there appear to be some pieces of data that seem to suggest that this assumption may not hold. Thus, use of a more conservative method is needed for non-inferiority analysis in this application. Based on the traditional approach using the worst limit of 95% two-sided confidence interval to estimate the captopril effect, VALIANT appears to support that valsartan retains at least 36%-44% of the mortality benefit of captopril, depending on whether adjusting for the difference in beta blockers use between VALIANT and the three historical trials is necessary. If the mortality effect of captopril is not much smaller in VALIANT than in the three historical trials, use of the worst limit of 90% two-sided confidence interval may be considered, based on which VALIANT appears to support that valsartan retains at least 42%-53% of the mortality benefit of captopril. Valsartan seems to preserve more than 50% of the effect of captopril on the composite of cardiovascular mortality, heart failure hospitalization and recurrent myocardial infarction (a pre-specified endpoint).

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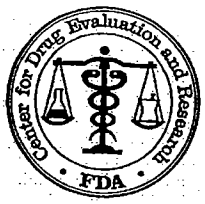

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STATISTICAL REVIEW AND EVALUATION

ADDENDUM

NDA #/Serial #:	21-283/S-011
DRUG NAME:	Diovan (valsartan) Tablets
INDICATION:	Improving survival following myocardial infarction in clinically stable patients with signs, symptoms or radiological evidence of left ventricular failure and/or with left ventricular systolic dysfunction
APPLICANT:	Norvatis Pharmaceuticals
DATE:	October 1, 2003
REVIEW PRIORITY:	P
BIOMETRICS DIVISION:	Division of Biometrics I
STATISTICAL REVIEWER:	H.M. James Hung, Ph.D. (HFD-710)
MEDICAL DIVISION:	Division of Cardio-Renal Drug Product (HFD-110)
CLINICAL TEAM:	Shari Targum, M.D. (HFD-110)
PROJECT MANAGER:	Ed Fromm (HFD-110)

KEY WORDS: non-inferiority margin, percent preservation, 95-95 method, 97.47-95 method, constancy assumption

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TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The sponsor's analyses appear to support that the beneficial effects of ACE inhibitors and beta blockers are independent, additive and consistent across all three historical trials (SAVE, AIRE, TRACE). The data for these analyses are not available for statistical review.

Regarding the sponsor's statistical assessment of percent preservation, the key clinical question is whether the captopril's mortality effect is smaller in VALIANT than in the historical trials. The captopril effect shown in SAVE appears to be smaller than that of ramipril in AIRE and that of trandolapril in TRACE, though the differences are not statistically significant. This raises the issue of whether the point estimate and the standard error produced from the three historical trials (SAVE, AIRE, TRACE) combined can provide a proper estimate for the effect of captopril. Moreover, the results of the Chinese Cardiac Study (CCS-1) and Fourth International Study of Infarct Survival (ISIS-4) provided in the 11/30/2004 document (Table 3 in that document) show a much smaller mortality effect with captorpril (the designs and trial characteristics of these two studies are different from SAVE). Nonetheless, these differences in the mortality risk reduction need be considered in judging whether the constancy assumption can be seriously violated. Unless the constancy assumption is deemed not to be a big problem, the sponsor's statistical assessment of percent retention cannot be properly interpreted and adds little support to their assertion of more than 50% retention. Based on the analysis suggested by Dr. Temple on 7/14/1998, VALIANT can at best support that valsartan retains more than 36% of the mortality benefit of captopril.

1.2 Brief Overview of Clinical Studies

The supplemental new drug application dated December 17, 2003 pertains to VALIANT, a large active controlled non-inferiority trial for pursuing an indication of improving survival following myocardial infarction in clinically stable patients with signs, symptoms or radiological evidence of left ventricular failure and/or with left ventricular systolic dysfunction. The Agency completed the combined medical/statistical review of VALIANT on June 30, 2004. In the teleconference with the sponsor on September 9, 2004, the Agency outlined several issues that need a resolution. In response the sponsor submitted a document adding more analyses on October 1, 2004 to address the issues.

1.3 Statistical Issues and Findings

The sponsor's analyses appear to support that the beneficial effects of ACE inhibitors and beta blockers are independent, additive and consistent across all three trials (SAVE, AIRE, TRACE). The data for their analyses have not been submitted for review.

Regarding the sponsor's statistical assessment of percent preservation, several issues are raised in this review addendum (see pages 7-9). Their assessment is performed under the critical

unverifiable constancy assumption that the effect of captopril in VALIANT population is similar to the effect in the historical trial population. If the effect of captopril in VALIANT is smaller than that in the historical trials, then these point estimates as well as the confidence intervals may be biased for falsely asserting that valsartan preserves more than 50% effect of captopril; the bias can be serious, depending on how much smaller the captopril effect is in VALIANT. So the key clinical question is whether the captopril's mortality effect is smaller in VALIANT. The captopril effect shown in SAVE appears to be smaller than that of ramipril in AIRE as well as that of trandolapril in TRACE. This raises the issue of whether the point estimate and the standard error produced from the three historical trials combined are proper to estimate the effect of captopril. In addition, some technical issues make the submitted results difficult to interpret (page 8).

Three historical trials, SAVE, AIRE and TRACE, estimate the effects of three ACE inhibitors (captopril, ramipril, trandolapril) on mortality, respectively. The sponsor combined the three studies to estimate the captopril effect; thus, it was implicitly assumed that the effects of the three ACE inhibitors are similar or exchangeable. Based on the combination of the three trials, the risk (or hazard) ratio for death is 0.773 with a 95% confidence interval (0.698, 0.856). The study objective of the non-inferiority analysis as per the VALIANT protocol is to demonstrate that valsartan retains more than 50% of the captopril effect. According to Dr. Ganley's review dated 7/22/98 that summarized some major points discussed in the industry meeting on 7/14/98, the sponsor proposed planning VALIANT with a non-inferiority margin of 1.13, but Dr. Temple proposed a margin of 1.09 based on the worst limit of 95% confidence interval for the ACE inhibitor's effect estimated from the composite of the three historical trials. The sponsor's non-inferiority margin of 1.13 was determined by retaining 50% of the captopril effect estimated by the point estimate derived from the three historical trials combined. Such a margin determined using the point estimate is certainly problematic since the variance of the estimate is completely ignored. The margin of 1.09 proposed by Dr. Temple in that meeting was determined by retaining 50% of the captopril effect estimated by the worst limit of the 95% confidence interval. In order to assert 50% retention, this margin needs to be ruled out by the two-sided 97.47% confidence interval for the risk ratio of valsartan versus captopril in VALIANT (use 97.47% confidence interval rather than 95% confidence interval because of the Bonferroni-Sidak multiple comparison adjustment due to another comparison made for the valsartan plus captopril versus captopril). The two-sided 97.47% confidence level cannot be compromised in order to ensure that the error rate of making a false claim that VALIANT has a positive finding is no greater than 0.05 (two-sided). From VALIANT, the 97.47% confidence interval for the risk ratio of valsartan versus captopril is (0.904, 1.108) and thus the margin to be ruled out is 1.108. With the 97.47-95 method (which can often protect statistical inference from being severely biased due to violation of constancy assumption), VALIANT can only support that valsartan retains more than 36% of the mortality benefit of captopril, if the three historical studies combined can be accepted to estimate the captopril effect.

2. INTRODUCTION

2.1 Overview

The supplemental new drug application dated December 17, 2003 pertains to VALIANT, a large active controlled non-inferiority trial for pursuing an indication of improving survival following myocardial infarction in clinically stable patients with signs, symptoms or radiological evidence of left ventricular failure and/or with left ventricular systolic dysfunction. The Agency completed the combined medical/statistical review of VALIANT on June 30, 2004. In the teleconference with the sponsor on September 9, 2004, the Agency outlined several issues that need a resolution. In response the sponsor submitted a document on October 1, 2004 to address the issues and another document containing additional information on November 30, 2004. This addendum is to provide additional comments pertaining Issues #1 and #2 outlined in Section 3.

2.2 Data Sources

No SAS dataset is provided for the sponsor's results reported in the 10/1/2004 document and the 11/30/2004 document.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Issue #1
Historical constancy-is the treatment effect of SAVE relevant to the background therapy in the VALIANT trial? It was noted that the use of beta-blockers in SAVE was low (20%), yet around 80% in VALIANT. This is a concern for the Division because there is expectation (at least partly from Val-HeFT) that use of beta-blockers and ACE inhibitors have no additive effect and in fact may be adverse to one another.

The sponsor's 10/1/2004 document provides Figure A1 and Table A1 to indicate that the beneficial effects of ACE inhibitors and beta blockers are independent, additive and consistent across all three historical trials (SAVE, AIRE, TRACE). Their additional analyses on hazard ratio in the 11/30/2004 document give similar results. All these results appear to support the sponsor's explanation. The data for these analyses are not available for statistical review.

Figure A1. Kaplan-Meier estimates for all-cause mortality in SAVE by beta-blocker use and treatment

[Source: Sponsor's Figure 1, page 2, document of October 1, 2004]

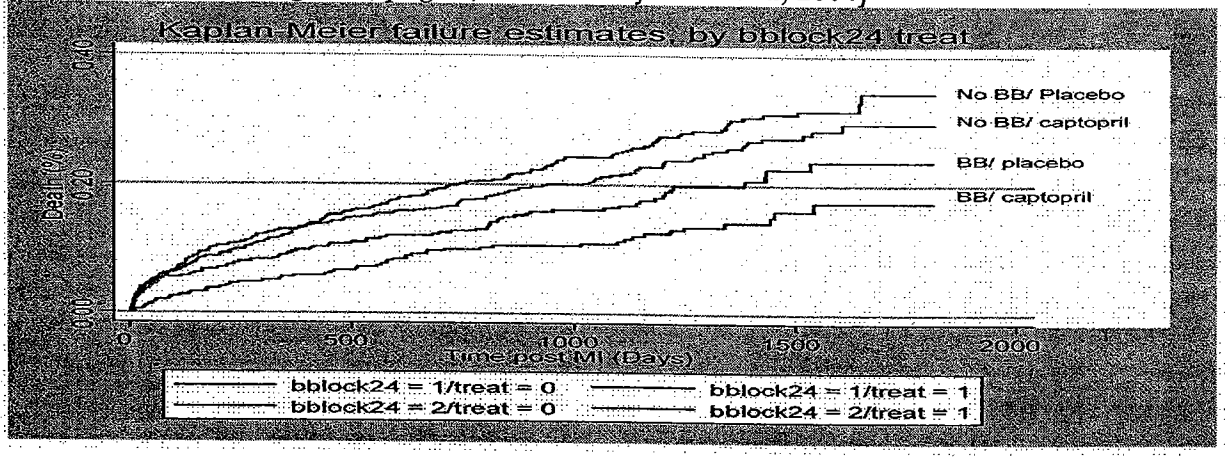

Table A1. Mortality and ACEI treatment benefit in patients treated with beta-blockers in VALIANT, SAVE, AIRE and TRACE, and the SAVE, AIRE, and TRACE pooled-analysis

[Source: Sponsor's Table 1, page 2, document of October 1, 2004]

	VALIANT N = 14,703	SAVE N = 2231	AIRE N = 1986	TRACE N = 1749	SAVE,AIRE,TRACE N = 5966 [4]
Beta blocker use, % [1]	70	35	22	17	25
Mortality in patients on beta-blocker, n/N (%)*					
ACEI	550/3443 (16.0)	52/391 (13.3)	23/236 (9.7)	26/148 (17.6)	101/775 (13.0)
Control [2]	565/3468 (16.3)	76/398 (19.1)	29/207 (14.0)	36/130 (27.7)	141/735 (19.2)
Odds ratio (95% CI) [3]	0.98 (0.86-1.11)	0.65 (0.44-0.95)	0.66 (0.37-1.19)	0.56 (0.31-0.99)	0.63 (0.48-0.83)
p-value		0.0272	0.1642	0.0430	0.0011
Mortality in patients not on beta-blocker, n/N (%)*					
ACEI	408/1466 (27.8)	176/724 (24.3)	147/768 (19.1)	278/728 (38.2)	601/2220 (27.1)
Control [2]	414/1441 (28.7)	199/718 (27.7)	193/775 (24.9)	333/743 (44.8)	725/2236 (32.4)
Odds ratio (95% CI) [3]	0.96 (0.81-1.12)	0.84 (0.66-1.06)	0.71 (0.56-0.91)	0.76 (0.62-0.94)	0.77 (0.68-0.88)
p-value		0.1404	0.0063	0.0099	0.0001

n = number of deaths; N = number of patients on beta-blocker in each treatment group

* Event rates are not normalized for duration of follow-up; mean duration of follow-up was 24, 42, 15, and 36 months for VALIANT, SAVE, AIRE, and TRACE, respectively.'

[1] Percent in ACEI treatment group

[2] VALIANT control agent = valsartan; SAVE, AIRE, and TRACE control agent = placebo

[3] Odds ratios calculated from mortality rates presented in published results. In VALIANT column, the control is valsartan.

[4] Analysis provided by Dr. M. Pfeffer, Brigham and Women's Hospital, Boston, MA

Issue #2

The historical basis for the effect of captopril was the SAVE trial, which used captopril alone, along with a combination of the AIRE and TRACE trials, which did not use captopril and had larger treatment effects. An analysis of the VALIANT data based on SAVE alone for historical context does not show compelling evidence for preservation of even 50% of the

effects of captopril, so there is no way to establish "non-inferiority" of valsartan with captopril, especially given the endpoints of mortality or hospitalization.

The sponsor's 10/1/2004 document provides detailed arguments to support the use of SAVE, AIRE and TRACE combined to give a better estimate of the captopril effect on mortality. Numerically, the estimated effect of captopril in SAVE is smaller than that of ramipril in AIRE and that of trandolapril in TRACE, though the differences in these estimates are not statistically significant. However, clinical assessments are still needed to determine whether the apparently smaller effect of captopril is very likely to be real and whether the differences in the effects of these ACE inhibitors are too large to ignore.

The 10/1/2004 document provides the following two tables (Tables A2 and A3) to support the sponsor's statistical assessment for preservation of the mortality benefit of captopril. Several issues need to be addressed. First, all the point estimates and confidence intervals for % preservation in Table A2 are generated using the point estimates of the captopril effect derived from the selected historical trials. For example, in the 1st row of Table A2 (i.e., SAVE, AIRE, and TRACE are used), the point estimate 0.773 of the mortality risk of captopril from the three trials combined is used to estimate the % retention. The calculation is

$$\begin{aligned} \%\,retention &= \frac{1-(\text{risk ratio of valsartan vs.placebo})}{1-(\text{risk ratio of captopril vs.placebo})} \\ &= \frac{1-(\text{risk ratio of valsartan vs.captopril})\times(\text{risk ratio of captopril vs.placebo})}{1-(\text{risk ratio of captopril vs.placebo})} \\ &= \frac{1-1.001\times 0.773}{1-0.773} \\ &= 99.6\% \end{aligned}$$

In calculating the confidence interval, the standard error derived from the three historical trials combined is used. It is well known and as also noted in the sponsor's document that **these calculations are performed under the critical unverifiable constancy assumption that the effect of captopril in VALIANT population is similar to the effect in the historical trial population.** If the effect of captopril in VALIANT is smaller than that in the historical trials, then these point estimates as well as the confidence intervals may be biased for mistakenly asserting that valsartan preserves more than 50% effect of captopril; the bias can be serious, depending on how much smaller the captopril effect is in VALIANT. So **the key clinical question is whether the captopril's mortality effect is smaller in VALIANT conducted in two decades after the SAVE trial**. The captopril effect in SAVE appears to be smaller than that of ramipril in AIRE and that of trandolapril in TRACE. This raises the issue of whether the point estimate and the standard error produced from the three trials combined are proper to estimate the effect of captopril. Moreover, the results of the Chinese Cardiac Study (CCS-1) and Fourth International Study of Infarct Survival (ISIS-4) provided in the 11/30/2004 document (Table 3 in that document) show a much smaller mortality effect with captorpril (the designs and trial characteristics of these two studies are different from SAVE). Nonetheless, these differences in the mortality risk reduction need be considered in judging whether the constancy assumption can

be seriously violated. Unless the constancy assumption is deemed not a big problem, these estimates for percent preservation cannot be properly interpreted.

Secondly, normal approximation appears to have been used in calculating the confidence intervals. It is well known that normal approximation for such a ratio statistic is often very poor. The sponsor needs to conduct extensive simulations to assess the validity of these confidence intervals. Moreover, because of another comparison made for valsartan plus captopril versus captopril, the multiple comparison adjustment as proposed in the study protocol (i.e., using 97.47% confidence interval instead of 95% confidence interval) needs to be incorporated for the confidence interval. That is, a 97.47% confidence interval should have been used in Table A2, not 95% confidence interval. Thirdly, the p-values in Table A3 are difficult to interpret since they are produced by synthesizing the VALIANT data and the historical trial data and they have little statistical meaning under the traditional framework of statistical inference for clinical trials.

Table A2. Preservation (%) of the mortality benefit of captopril provided by valsartan *[Source: Sponsor's Table 7, page 11, document of October 1, 2004]*

Historical reference for mortality benefit of captopril	% preservation of mortality benefit, (95% confidence interval)	
	ITT population	Per-protocol population
Both estimate and variability of effect size from meta analysis of SAVE, AIRE, and TRACE trials	99.6% (65.1%, 134.1%) [included in the original submission]	108.3% (69.7%, 146.8%)
Estimate of effect size from SAVE alone; variability from meta analysis of SAVE, AIRE, and TRACE	99.5% (57.2%, 141.8%)	110.1% (62.8%, 157.4%)
Both estimate and variability of effect size from SAVE alone	99.5% (57.2%, 141.8%)	110.1% (62.3%, 157.9%)

**** There might be an error in the table. Under ITT, the 3rd row and the 2nd row are completely identical but we know that the variability of effect size from SAVE alone is much smaller than that from the three trials combined.**

Table A3. P-value of the preservation test for the hypothesis that valsartan preserves more than 50% of mortality benefit of captopril *[Source: Sponsor's Table 8, page 11, document of 10/1/04]*

Historical reference for mortality benefit of captopril	P-value (> 50% reservation of mortality benefit of captopril)	
	ITT population	Per-protocol population
Both estimate and variability of effect size from meta analysis of SAVE, AIRE, and TRACE trials	0.007	0.004
Estimate of effect size from SAVE alone; variability from meta analysis of SAVE, AIRE, and TRACE	0.023	0.013
Both estimate and variability of effect size from SAVE alone	0.053	0.031

Additional Comments from Reviewer

At several places of the combined medical/statistical review dated 6/30/2004, 97.43 percent for confidence interval is a typographical error and should be changed to 97.47 percent.

Three historical trials, SAVE; AIRE and TRACE, estimate the effects of three ACE inhibitors (captopril, ramipril, trandolapril) on mortality, respectively. The sponsor combined the three studies to estimate the captopril effect; thus, it was implicitly assumed that the effects of the three ACE inhibitors are similar or exchangeable. Based on the combination of the three trials, the risk (or hazard) ratio for death is 0.773 with a 95% confidence interval (0.698, 0.856). The study objective of the non-inferiority analysis as per the VALIANT protocol is to demonstrate that valsartan retains more than 50% of the captopril effect. According to Dr. Ganley's review dated 7/22/98 that summarized some major points discussed in the industry meeting on 7/14/98, the sponsor proposed planning VALIANT with a non-inferiority margin of 1.13, but Dr. Temple proposed a margin of 1.09 based on the worst limit of 95% confidence interval for the ACE inhibitor's effect estimated from the composite of these three historical trials. The sponsor's non-inferiority margin of 1.13 was determined by retaining 50% of the captopril effect estimated by the point estimate derived from the three historical trials combined. The margin determined using the point estimate is certainly problematic since the variance of the estimate is completely ignored. The margin of 1.09 proposed by Dr. Temple in that meeting was determined by retaining 50% of the captopril effect estimated by the worst limit of the 95% confidence interval. In order to assert 50% retention, traditionally, this margin needs to be ruled out by the 95% confidence interval for the risk ratio of the test drug versus the selected control generated from the non-inferiority trial. This is often known to be 95-95 method, where the first 95 means two-sided 95% confidence interval for treatment (valsartan) versus control (captopril) from the non-inferiority trial and the second 95 means use of the worst limit of two-sided 95% confidence interval of the control (captopril) versus placebo from the historical trial(s) to construct the fixed margin. In VALIANT, the first 95 is changed to 97.47 (i.e., use two-sided 97.47% confidence interval rather than 95% confidence interval from VALIANT) because of another comparison made for the valsartan plus captopril versus captopril, using the Bonferroni-Sidak multiple comparison adjustment. The two-sided 97.47% confidence level cannot be compromised in order to ensure that the error of making a false claim that VALIANT has a positive finding is no greater than 0.05. From VALIANT, the 97.47% confidence interval for the risk ratio of valsartan versus captopril is (0.904, 1.108) and thus the margin to be ruled out is 1.108. With the 97.47-95 method (which can often protect statistical inference from being severely biased due to violation of constancy assumption), VALIANT can only support that valsartan retains more than 36% of the mortality benefit of captopril, if the three historical studies combined can be accepted to estimate the captopril effect.

3.2 Evaluation of Safety

Please refer to the combined medical/statistical review dated June 30, 2004 for safety assessment.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Please refer to the combined medical/statistical review dated June 30, 2004.

4.2 Other Special/Subgroup Populations

Please refer to the combined medical/statistical review dated June 30, 2004.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The combined medical/statistical review for this supplemental NDA was completed on June 30, 2004. The statistical issues discussed in this addendum are which of the three historical trials (SAVE, AIRE, TRACE) are relevant for estimating the captopril effect on mortality and whether VALIANT meets its goal of concluding that valsartan preserves more than 50% of the mortality benefit of the control effect. Numerically, the estimated effect of captopril in SAVE is smaller than that of ramipril in AIRE and that of trandolapril in TRACE, though the differences in these estimates are not statistically significant. However, clinical assessments are still needed to determine whether the apparently smaller effect with captopril is very likely to be real and whether the differences in these estimates are too large to ignore. Unless the constancy assumption that the effect of captopril in VALIANT is similar to that in historical trials is not a big problem, the sponsor's statistical assessment of percent preservation provided in the 10/1/2004 document cannot be properly interpreted.

5.2 Conclusions and Recommendations

The sponsor's analyses appear to support that the beneficial effects of ACE inhibitors and beta blockers are independent, additive and consistent across all three historical trials (the data for these analyses are not available for statistical review).

Regarding the sponsor's statistical assessment of percent preservation, the key clinical question is whether the captopril's mortality effect is smaller in VALIANT than in the historical trials. The captopril effect shown in SAVE appears to be smaller than that of ramipril in AIRE and that of trandolapril in TRACE, though the differences are not statistically significant. This raises the issue of whether the point estimate and the standard error produced from the three historical trials (SAVE, AIRE, TRACE) combined can provide a proper estimate for the effect of captopril. Moreover, the results of the Chinese Cardiac Study (CCS-1) and Fourth International Study of Infarct Survival (ISIS-4) provided in the 11/30/2004 document (Table 3 in that document) show a much smaller mortality effect with captorpril (the designs and trial characteristics of these two studies are different from SAVE). Nonetheless, these differences in the mortality risk reduction need be considered in judging whether the constancy assumption can be seriously violated. Unless the constancy assumption is deemed not a big problem, the sponsor's statistical assessment of percent retention cannot be properly interpreted and adds little support to their assertion of more than 50% retention. Based on the analysis suggested by Dr. Temple on 7/14/1998, VALIANT can at best support that valsartan retains more than 36% of the mortality benefit of captopril.