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NDA 21-283/S-001

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

NDA #/Serial #: 20-665/SE1-016 21-283/SE1-001

DRUG NAME: Diovan (valsartan) Tablets

INDICATION: Heart Failure

SPONSOR: Norvatis Pharmaceuticals

DOCUMENT REVIEWED:

Volume 1 of Supplement Amendment SE1-016 (BL) (CDER REC'D Date: January 23, 2002)

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0. SUMMARY

Val-HeFT gave a statistically significant finding on the composite morbidity endpoint in favor of valsartan. However, the large contrast between the results of the ACEI and the results of the No-ACEI subgroup casts serious doubt about the internal consistency of the trial results. The results of the No-ACEI subgroup provide a basis for the Agency's consideration of the possibility that valsartan might be approvable for the patients who cannot tolerate ACE inhibitors. The sponsor provided the results of additional analyses in this supplement amendment. The results of all the secondary endpoints and others provided by the sponsor appeared to lend a strong support for the suggestion that valsartan might have a significant benefit with respect to composite morbidity endpoint in the patients not receiving ACE inhibitors.

Regarding mortality, however, in my view, the trial results are inconclusive and too weak to render conclusive evidence for the No-ACEI subgroup. Firstly, in the overall population the mortality risk was dead even between valsartan and placebo and trended slightly against valsartan with a hazard ratio of 1.02. Secondly, neither the ACEI subgroup nor No-ACEI subgroup was the pre-specified subgroup. The small sample size for the No-ACEI subgroup contradicts the argument that the potential benefit of valsartan in the patients not receiving ACE inhibitors was a priori anticipated when designing Val-HeFT. Thirdly, with a small number of deaths in the No-ACEI subgroup, the nominal p-value of 0.017 is not impressive. The original study report examined many subgroups, including ACEI (yes/no) subgroups, beta blockers (yes/no), the combination of ACEI (yes/no) and beta-blockers (yes/no), and thus at least eight subgroups. Since the decision tree was not provided in advance for how to analyze these subgroups and interpret the results, one cannot assign a proper weight to the No-ACEI subgroup that was deemed the most relevant subgroup after examination of the trial results. A simple Bonferroni adjustment for examining at least eight subgroups lifted the nominal p-value to a level of ≥ 0.14 . In addition, with the small size in the No-ACEI subgroup, the p-value can be sensitive to a very small change in number of deaths and thus statistical significance of this nominal p-value cannot meet the challenge from a small change of number of deaths. In all, Val-HeFT failed to provide conclusive statistical evidence to support that valsartan gives a mortality benefit in patients not receiving ACE inhibitors.

1. INTRODUCTION

In response to the Agency's approvable letter dated 10/24/01, the sponsor further submitted the results of their additional analyses in support of final approval and their claim in the proposed label. This review is written to address some of their claim.

2. BACKGROUND AND ISSUES

The results of Val-HeFT were reviewed by the Agency and discussed in the Cardio-Renal Advisory Committee Meeting on 10/11/01. See the joint medical/statistical review (dated 09/13/01) by Dr. Shari Targum and me and secondary review (dated 10/15/01) by Dr. Norman

Stockbridge. The Agency issued the approvable letter on 10/24/01 in which a number of concerns regarding interpretation of the trial results were raised. In brief, the letter conveys that the Agency believes that valsartan cannot be approved as add-on therapy for patients already receiving an appropriate dose of an ACE inhibitor (ACEI) and that another study, or possibility additional analyses, is needed before valsartan can be approved for patients not receiving ACEI. The data of the "no ACEI" subgroup seem to represent a single study suggesting effectiveness in patients not receiving ACEI's. This single study, a subset finding from a much larger study does not appear to constitute the substantial evidence of effectiveness needed for approval. The letter leaves the possibility that examination of the Val-HeFT exercise substudy and the many secondary endpoints in the no-ACEI patients in Val-HeFT could strengthen the subset findings further.

Results of Sponsor's Additional Analyses

The sponsor reported a statistically significant reduction in risk for time to death (33%) and first morbid event (44%) as adjudicated by the Endpoint Committee with valsartan compared to placebo in the subgroup of patients not receiving an ACE inhibitor (see Table 1). In addition, there was a statistically significant reduction in risk for time to cardiovascular death (24%), first non-fatal morbid event (54%), and first heart failure hospitalization (53%) with valsartan in this subgroup. The contrast between the No-ACEI subgroup and ACEI subgroup is also seen in Table 1.

Table 1. Results of mortality and morbidity endpoints of Val-HeFT

	Valsartan	Placebo	Hazard ratio ^a	p-value ^b
Overall population	(N=2511)	(N=2499)		
Primary endpoint				
Mortality	495 (19.7%)	484 (19.4%)	1.02	0.80 [#]
Morbidity	723 (28.8%)	801 (32.1%)	0.87	0.009 [#]
Secondary endpoint				
CV mortality	427 (17.0%)	419 (16.8%)	1.01	0.86
Non-fatal morbidity	367 (14.6%)	486 (19.4%)	0.73	0.00001
CHF hospitalization	349 (13.9%)	463 (18.5%)	0.73	0.00001
No-ACEI group	(N=185)	(N=181)		
Primary endpoint				
Mortality	32 (17.3%)	49 (27.1%)	0.67	0.017
Morbidity	46 (24.9%)	77 (42.5%)	0.56	0.0002
Secondary endpoint				
CV mortality	29 (15.7%)	40 (22.1%)	0.76	0.074
Non-fatal morbidity	24 (13.0%)	49 (27.1%)	0.46	0.0004
CHF hospitalization	24 (13.0%)	48 (26.5%)	0.47	0.0006
ACEI group	(N=2326)	(N=2318)		
Primary endpoint				
Mortality	463 (19.9%)	435 (18.8%)	1.06	0.35
Morbidity	677 (29.1%)	724 (31.2%)	0.90	0.096

Secondary endpoint				
CV mortality	398 (17.1%)	194 (16.4%)	1.04	0.49
Non-fatal morbidity	343 (14.7%)	247 (18.9%)	0.76	0.0003
CHF hospitalization	325 (14.0%)	230 (17.9%)	0.76	0.0004

* hazard ratio computed from Cox regression

§ nominal p-value based on logrank test

p-value of either primary endpoint in overall population is compared with $\alpha = 0.0253$

Table 2 summarizes the results of the treatment comparisons in the low ACEI subgroup (patients whose dose at baseline was less than the median dose) and in the high ACEI subgroup (patients whose dose at baseline was at least the median dose). A total of 19 patients in the valsartan group and 18 patients in the placebo group who received ACE inhibitors at baseline were missing doses, and were not included in this table. The exploratory analysis appeared to show a numerical trend suggesting a greater risk of all cause and CV mortality with valsartan compared to placebo in the patients whose ACE inhibitor dose at baseline was at least the median dose (high ACEI subgroup).

Table 2. Results of mortality and morbidity endpoints by ACEI dose

	Valsartan	Placebo	Hazard ratio*	p-value [§]
Low ACEI group	(N=1034)	(N=1001)		
Primary endpoint				
Mortality	208 (20.1%)	206 (20.6%)	0.99	0.74
Morbidity	290 (28.0%)	321 (32.1%)	0.86	0.040
Secondary endpoint				
CV mortality	175 (16.9%)	181 (18.1%)	0.95	0.48
Non-fatal morbidity	144 (13.9%)	187 (18.7%)	0.73	0.0032
CHF hospitalization	135 (13.1%)	182 (18.2%)	0.71	0.0013
High ACEI group	(N=1273)	(N=1299)		
Primary endpoint				
Mortality	254 (20.0%)	225 (17.3%)	1.15	0.088
Morbidity	386 (30.3%)	396 (30.5%)	0.96	0.88
Secondary endpoint				
CV mortality	223 (17.5%)	379 (14.9%)	1.17	0.076
Non-fatal morbidity	199 (15.6%)	437 (19.0%)	0.79	0.036
CHF hospitalization	190 (14.9%)	415 (17.7%)	0.81	0.080

* hazard ratio computed from Cox regression

§ nominal p-value based on logrank test

Hospitalizations

The study report provided the results (see the sponsor's Table 2.6) of total number of hospitalizations based on investigator assessment. CHF hospitalizations were fewer in the valsartan group than in the placebo group in both No-ACEI and ACEI subgroups (both $p \leq 0.012$), the valsartan effect was much larger in the No-ACEI subgroup (56% greater reduction in

the no-ACEI subgroup versus 19% greater reduction in the ACEI subgroup). CHF hospitalizations were about 35% of total hospitalizations. Numerically, valsartan was associated with a much greater reduction of all cause hospitalization in the no-ACEI subgroup (24% greater reduction in the no-ACEI subgroup versus 7% greater reduction in the ACEI subgroup); the valsartan effect on all cause hospitalization was not statistically significant (all $p > 0.23$).

Quality of life

The study report provided the results of quality of life data in Australia, Italy, UK and US (these countries had a validated Minnesota Living with Heart Failure questionnaire). There appeared to be a statistically significant benefit in quality of life with valsartan compared to placebo ($p = 0.005$). The No-ACEI subgroup appeared to show a greater change from baseline in QOL score in favor of valsartan (the sponsor's Table 2.12). A similar trend was seen with respect to number of patients who had >5 unit change in overall QOL score at endpoint (the sponsor's Table 2.13).

Left ventricular function and structure

Valsartan appeared to be associated with a statistically significant increase in left ventricular ejection fraction and reduction in left ventricular end diastolic volume in both ACEI and No-ACEI subgroups and in overall population (the sponsor's Tables 2.14 and 2.15). The treatment difference appeared to be greater in favor of valsartan in No-ACEI subgroup.

Neurohormones

There appeared to be a statistically significant reduction in brain natriuretic peptide with valsartan compared to placebo in the overall population and in both ACEI and No-ACEI subgroups ($p < 0.0005$). The treatment difference in favor of valsartan is much greater in the No-ACEI subgroup (the sponsor's Table 2.17). There was less of an increase in norepinephrine with valsartan than placebo but the treatment difference was not statistically significant in the No-ACEI subgroup ($p = 0.21$, the sponsor's Table 2.16).

NYHA class and signs/symptoms

In the No-ACEI subgroup, there were generally higher percentages of patients who improved and lower percentages of patients who deteriorated with valsartan compared to placebo for NYHA class and the majority of the individual heart failure signs and symptoms at endpoint (the sponsor's Table 2.18).

Exercise capacity

The Val-HeFT substudy of a total of 633 patients evaluated exercise capacity measured by the six-minute walk test. In the No-ACEI subgroup, there appeared to be a statistically significant increase in walk distance with valsartan compared to placebo ($p = 0.022$). The treatment difference in favor of valsartan was greater in the Non-ACEI subgroup. The exercise time of Study 106 showed a similar trend (Table 4).

Table 3. Mean change from baseline in six-minute walk distance at endpoint (Val-HeFT)

	Valsartan	Placebo
Overall population		
N	320	313
LS mean change	14.9	13.7
LS mean treatment difference	1.2	
p-value	0.85	
No-ACEI group		
N	18	17
LS mean change	50.3	-34.2
LS mean treatment difference	84.4	
p-value	0.022	
ACEI group		
N	302	296
LS mean change	8.5	12.3
LS mean treatment difference	-3.8	
p-value	0.55	

Taken from the sponsor's Table 2.19

Table 4. Mean change from baseline in exercise duration (seconds) at endpoint (Study 106)

	Val 80	Val 160	Val 320	Placebo
Overall population				
N	168	180	182	179
LS mean change	85.1	85.4	68.6	65.7
LS mean treatment difference	19.4	19.7	2.9	
p-value	0.23	0.21	0.85	
No-ACEI group				
N	19	25	28	25
LS mean change	132.7	62.7	78.5	12.6
LS mean treatment difference	120.1	50.1	65.9	
p-value	0.044	0.36	0.21	
ACEI group				
N	149	155	154	154
LS mean change	77.5	82.0	61.5	68.3
LS mean treatment difference	9.2	13.7	-6.8	
p-value	0.59	0.41	0.69	

Taken from the sponsor's Table 2.20

3. REVIEWER'S EVALUATION AND CONCLUSION

Val-HeFT gave a statistically significant finding on the composite morbidity endpoint in favor of valsartan. However, the large contrast between the results of the ACEI and the results of the No-ACEI subgroup casts serious doubt about the internal consistency of the trial results. The results of the No-ACEI subgroup provide a basis for the Agency's consideration of the possibility that valsartan might be approvable for the patients who cannot tolerate ACE inhibitors. The sponsor provided the results of additional analyses in this supplement amendment. The results of all the secondary endpoints and others provided by the sponsor appeared to lend a strong support for the suggestion that valsartan might have a significant benefit with respect to morbidity in the patients not receiving ACE inhibitors.

Regarding mortality, however, in my view, the trial results are inconclusive and too weak to render conclusive evidence for the No-ACEI subgroup for the following reasons. Firstly, in the overall population the mortality risk was dead even between valsartan and placebo and trended slightly against valsartan with a hazard ratio of 1.02. Secondly, neither the ACEI subgroup nor No-ACEI subgroup was the pre-specified subgroup. The small sample size for the No-ACEI subgroup contradicts the argument that the potential benefit of valsartan in the patients not receiving ACE inhibitors was a priori anticipated in designing Val-HeFT. Thirdly, with a small number of deaths in the No-ACEI subgroup, the nominal p-value of 0.017 is not impressive. The original study report examined many subgroups, including ACEI (yes/no) subgroups, beta blockers (yes/no), the combination of ACEI (yes/no) and beta-blockers (yes/no), and thus at least eight subgroups. Since the decision tree was not provided in advance for how to analyze these subgroups and interpret the results, one cannot assign a proper weight to the No-ACEI subgroup that was thought the most relevant subgroup after the trial results were examined. A simple Bonferroni adjustment for examining at least eight subgroups would lift the nominal p-value to a level of ≥ 0.14 . In addition, with the small size of the No-ACEI subgroup, the p-value can be sensitive to a very small change in number of deaths and thus statistical significance of this nominal p-value cannot meet the challenge of a small change of deaths. In all, this reviewer finds it inconclusive that valsartan gives a mortality benefit in the patients not receiving ACE inhibitors.

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**STATISTICAL REVIEW AND EVALUATION
(ADDENDUM)**

NDA #: 20,665 S-016

Applicant: Novartis Pharmaceuticals

Drug Name: Diovan (valsartan)

Indication: Heart failure

Document Reviewed: The sponsor's response to FDA request, SAS data set, and SAS codes (CDER REC'D Date: 9/13/01)

This review pertains to the hospitalization endpoints evaluated in the medical/statistical review of 09/13/01. During the analysis of the hospitalization data, the reviewers found that many data records had date of admission or date of discharge missing and thus requested that the sponsor submit their SAS codes to resolve this issue. Based on the sponsor's SAS codes, the reviewers' observations have been confirmed. In fact, there are some other problems in the hospitalization data, such as, missing reason for hospitalization. To deal with these problems, the sponsor devised an algorithm to impute missing dates of admission, missing dates of discharge, etc. (as shown in the Appendix). The algorithm is complex. A total of 468 hospitalization records out of 5962 data records from 351 (7%) patients (175 in the valsartan group and 176 in the placebo group) were imputed because of missing date of admission, date of discharges, etc. The quality of hospitalization data is questionable despite the tremendous effort of the sponsor in trying to resolve the deficiencies in the data. At least, it cannot be certain that the first hospitalization (CHF, CV or all-cause) in the sponsor's analyses was indeed the first hospitalization that should be analyzed. Thus, based on the investigator assessment data, there is a concern about the analysis of time to the first hospitalization due to any reason. This reviewer analyzed the number of patients who had at least one all cause hospitalization and the number of patients who had at least one CHF hospitalization prior to the study end or death. The results of this analysis are summarized in the following table.

Table A.1. Number (or %) of the patients who had at least one hospitalization based on investigator assessment

Cause of hospitalization	Valsartan (N=2511)		Placebo (N=2499)		Relative risk (95% CI)	p-value*
	n	%	n	%		
All cause	1236	49	1273	51	0.97 (0.91, 1.02)	0.22
CHF	525	21	613	25	0.85 (0.77, 0.94)	0.002

* Chi-square test

Clearly, all cause hospitalization failed to show a statistically significant benefit in favor of valsartan. The incidence of CHF hospitalization, analyzed using both investigator assessment data and EC adjudicated data, seemed to be smaller in the valsartan group than in the placebo group. Numerically, the valsartan group had slightly more patients who were hospitalized only due to non-CHF reasons [711 (28%) in the valsartan group versus 660 (26%) in the placebo group].

The results on total number of hospitalizations (including multiple hospitalizations per subject) based on the investigator assessment in the sponsor's table FDA-3-D-3-2 and in Table 107.16 of the medical/statistical review of 9/13/01 have been confirmed by this reviewer assisted by the SAS codes the sponsor provided. These results show similar trends as the results of Table A.1.

H.M. James Hung, Ph.D.
Acting Team Leader

This review consists of 4 pages of text.

Concur: Dr. Chi

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JHung/594-5436/DB1/valhat3.doc/09-26-2001

Appendix

The following is excerpted from the document FDA-3-C-1.DOC submitted by the sponsor on September 7, 2001.

Programming specification for hospitalization data (by steps)

0.1 If randomization date after admission date then delete.

Mean duration for imputation purpose

- 0.2 Select only all the cases where admission date and discharge date are complete (non-missing) and calculate the duration for each case by (discharge date) - (admission date) + 1.
- 0.3 Average the duration by patient, and by country and hospitalization reason.
- 0.4 Round off the mean duration to an integer.

Imputation for missing admission date by patient

- 1 Only the day of admission date is missing, use the first day of the month
- 2 If more than the day of admission date is missing, and discharge date is complete (non-missing), admission date will be imputed as (discharge date) - (mean duration - 1) by country and hospitalization reason
- 3 Patient = 11111, both admission date and discharge date = "1999", patient = 978, both admission date and discharge date = ". The previous visit date will be used for admission date.

Imputation for hospitalization reason

- 4 Patient = 3160, visit = 60, both the hospitalization reason and the diagnosis are missing. "Non-CHF" will be used (only one case).

Creating an order for both discharge date imputation and overlapping/duplicate handling

- 5 Sort the data by patient, admission date, discharge (No/Yes), discharge date, and visit.

Imputation for discharge date

- 6 If the discharge date of last record is missing regardless of discharge (Yes/No), and patient died and $(\text{death date}) - (\text{admission date}) \leq 14$, the death date will be used.
- 7 For the following cases, the discharge date will be imputed by $(\text{admission date}) + (\text{mean duration date} - 1)$.
 - 7.1 The discharge date of last record is missing regardless of discharge (Yes/No) including death beyond 14 days.
 - 7.2 Last record, and $(\text{discharge date}) < (\text{admission date})$.
 - 7.3 Discharge = Yes, and $(\text{discharge date}) < (\text{admission date})$.

Handling overlapping/duplicates by patient

- 8 Link next record information to current record (for programming purpose only)
- 9 Previous discharge is not Yes, and overlapping (i.e., previous discharge date is missing, or previous discharge date \geq next admission date).
 - 9.1 If hospitalization reason (CHF-related or not): previous reason = next reason, merge with next record. The combined record will be [previous admission date, next discharge date].
 - 9.2 If hospitalization reason (CHF-related or not): previous reason not = next reason, check the difference = $(\text{next admission date}) - (\text{previous admission date})$.
 - If = 0, reset previous discharge date to next admission date.
 - If >0 and ≤ 14 , reset previous discharge date by $(\text{next admission date} - 1)$.
 - If > 14 , reset previous discharge date by $(\text{previous admission date} + (\text{mean duration} - 1))$
- 10 Previous discharge is Yes (for those records, no more missing discharge date), and not the last record, and overlapping (i.e., next admission date \leq previous discharge date).
 - 10.1 If previous admission date = next admission date, and previous discharge date = next discharge date regardless of changing hospitalization reasons, merge to next record (delete previous record)
 - 10.2 If the time intervals for previous record and next record are not identical and they are overlapping, repeat Step 9.2.
- 11 If previous admission date = next admission date (overlapping on 1 day), reset next admission date to next admission + 1.

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/s/

James Hung
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need prompt attention because the NDA is going to Oct 11-12 AC meeting

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