

STAT

Statistical Review and Evaluation

Date: DEC 10

NDA #: 18-998/Drug Class:1B

Applicant: Merck, Sharp & Dohme Research Laboratories

Name of Drug: VASORIL (Enalapril Maleate, MSD) Tablets

Documents Reviewed: Volumes 1.1-1.7 of the "Biostatistical Package" dated November 9, 1983, five volumes of additional analysis requested by this reviewer dated March 12 & 26, 1984, two volumes of corrected tables to study Protocol #2 dated March 12, 1984, two volumes of 2 studies on the congestive heart failure patients dated March 23, 1984, and additional information and data listing on NYHA cardiac status and exercise duration for the International Congestive Heart Failure study dated October 26 and November 30, 1984.

This NDA contains five multicenter hypertension studies and two multiclinic congestive heart failure studies (one USA and one International). Most of these hypertension studies had multiple periods in the sense that patients who were not responding in the initial treatment period received additional therapy in the subsequent period(s). Since the main objective of this NDA is to demonstrate the safety and efficacy of enalapril, this review will focus on just the first treatment periods of these studies. The medical reviewer of this NDA is Dr. Sollymossy, HFN-110 with whom the content of this review has been discussed. He accepts this reviewer's conclusion.

Hypertension Studies

Protocol #0 (Dose-Response Study)

Five investigators were involved in this double-blind, randomized, parallel, placebo-controlled study assessing the anti-hypertensive dose-response relationship of four levels of enalapril at fixed doses of 2.5, 10, 20, and 40 mg/bid given for four weeks to patients with mild to moderate hypertension (sitting diastolic blood pressure between 90 and 110 mmHg at the end of the placebo washout period). A total of 136 patients were randomized into the five treatment groups which were fairly well balanced with respect to the baseline characteristics of age, sex, race, blood pressure and sample size.

Safety

No death occurred in this study. Six patients were discontinued from the study due to adverse reactions, one patient from the placebo group, and one patient each from the enalapril 10, 20, 40 mg/bid groups. The reactions for the enalapril treated patients were fatigue/dizziness, rash and facial edema. Two other patients had muscle cramps while under the enalapril/HCTZ .

combination treatment in the second period which was considered more likely to be associated with HCTZ.

No significant differences were detected between the enalapril groups and the placebo group with respect to either the overall frequencies of reported adverse effects (27% for enalapril vs. 14% for placebo, $p=0.16$) or frequencies by body systems. However, generally, enalapril-treated patients experienced more fatigue, dizziness, musculoskeletal pain, headache, nausea, rash, and edema than did placebo treated patients. With respect to the laboratory safety parameters, there were generally no significant differences between the treatment groups in their changes from baseline in the enalapril groups. However, it should be noted that at week 4, both hemoglobin and hematocrit had significant reduction from baseline in the enalapril groups. The results also suggest that hemoglobin and hematocrit reduction may be dose-related (see Table 13). Eight patients had a significant drop in white blood cell count to less than 4.0 ths/mm^3 during treatment. Two of these were placebo patients. One of the enalapril patients was discontinued from the study at week 4 due to low WBC.

Dose-Response Relationship

Based on the data file supplied by the firm, this reviewer reassessed the dose-response relationship using Jonckheere's nonparametric statistic to test the hypothesis of equal treatment responses among the enalapril groups against the one-sided alternative hypothesis that increasing doses of enalapril result in greater reduction in sitting diastolic blood pressure. It should be pointed out that this method does not address the magnitude of the differences between groups and thus does not define the nature of the dose-response curve, but only addresses the simpler question of whether a dose-response relationship exists. Despite some minor discrepancies, the results as given in Table 1 basically confirm the sponsor's finding of a significant dose-response relationship at weeks 1 and 3, a marginal one at week 4, and a nonsignificant one at week 2.

Table 1
Dose Response Relationship for Enalapril
Based on Reduction in Sitting Diastolic Blood Pressure
(Protocol #0)

Treatment Group	Mean Reduction in Sitting Diastolic Blood Pressure* (mmHg)			
	Week 1	Week 2	Week 3	Week 4
40 mg/bid	-13.7	-11.4	-16.5	-15.5
20 mg/bid	-12.2	-10.4	-12.4	-11.5
10 mg/bid	- 8.9	-11.6	-10.0	- 9.3
2.5 mg/bid	- 8.1	- 9.9	- 8.3	-10.7
Placebo	- 3.1	- 2.7	- 3.0	- 3.8
Jonckheere's Statistic+	2.8	0.2	2.5	1.6
significance level	0.003	0.42	0.006	0.054

* All reductions for enalapril treated groups were significantly greater (p < 0.05) than the corresponding reduction for placebo group at all four weeks.

+ Not including placebo treatment group.

Efficacy

Since only 8 patients dropped out of the study (3 from enalapril groups, 4 from placebo) and since the results of the endpoint analysis are similar to those based on evaluable patients, only the latter will be discussed here.

For the evaluable patients, the sponsor used a nonparametric randomized block procedure (extension of Friedman's test) for between treatment groups comparisons and an analysis of variance on the rank transformed values with a randomized complete block design (with investigators as blocks) for assessing treatment x block interactions and block differences. The sponsor reported no significant investigator differences or treatment x investigator interactions. For between treatment groups comparisons, all enalapril groups had significantly greater diastolic blood pressure reductions than the placebo group at all weeks (see Table 1). This reviewer reanalyzed the data at week 4 allowing a narrower window (week 4 + 3 days, instead of the sponsor's 25-33 day range) by multifactorial analysis of variance. The result of this analysis (Table 2) confirms the sponsor's findings except it also indicates a significant racial difference in treatment response (-12.3 mmHg reduction in sitting diastolic blood pressure for whites vs. -7.1 mmHg reduction for blacks, p = 0.012).

Table 2
 Comparison of Reduction in Sitting Diastolic Blood Pressure at Week 4
 Between Different Doses of Enalapril and Placebo
 (Protocol #10)
 (mmHg)
 Treatment Group

	Placebo	2.5 mg	Enalapril		40 mg
			10 mg	20 mg	
Sponsor's Analysis	- 3.8	-10.7 (< 0.001)*	- 9.3 (0.013)*	-11.5 (0.002)*	-15.5 (< 0.001)*
No. of Patients	24	29	26	23	22
Reviewer's Analysis	- 2.1	-10.7 (0.003)*	- 7.4 (0.021)*	-12.2 (< 0.001)*	-16.0 (< 0.001)*
No. of Patients	21	24	24	21	20

* two-sided significance level for comparison between enalapril and placebo

Protocol #1

The primary objective of this study was to compare the safety and anti-hypertensive efficacy of enalapril taken once-a-day and twice-a-day to placebo in mild to moderate hypertensive outpatients. A secondary purpose was to compare the efficacy of once-a-day administration to the twice a day administration.

This was a 16-week, double-blind, randomized, parallel, placebo-controlled, six-clinic study of 169 mild to moderate hypertensive patients with supine diastolic blood pressure between 90 and 104 mmHg. Fifty-seven patients were randomized to enalapril once-daily with titration from 10 to 20 to 40 mg/qd at 4-week intervals. Fifty-six patients were assigned to enalapril twice-daily with titration from 5 to 10 to 20 mg/bid at 4-week intervals. Fifty-six patients were given placebo.

Safety

No death was reported in this study. Twenty-one of the 57 patients (37%) in the enalapril once-a-day group, 19 out of the 56 patients (34%) in the enalapril twice-a-day group, and 24 out of the 56 patients (43%) in the placebo group had one or more adverse experiences at some time during the 12-week treatment period. These reported overall incidence rates were not significantly different between treatment groups. With regard to specific adverse effects, the only significant difference between groups was in the

frequency of headache; the incidence rate was 1/56 (1.8%) for enalapril twice-a-day group and 9/56 (16.1%) in the placebo group. All together, one patient each from the enalapril groups, and two from the placebo group were discontinued from the study due to adverse reactions. As suggested by the complication resulted from the concurrent administration of enalapril and lithium (a manic depressant) to one patient, the sponsor noted that such combination treatment may lead to lithium toxicity.

With respect to the laboratory safety parameters, a significant ($p < 0.05$) decrease from baseline in hemoglobin was observed at Weeks 4, 8, and 12 for the enalapril groups, and these reductions were significantly different from the corresponding increases observed for the placebo group (see Table 13 for week 12 results). A similar trend was also observed for hematocrit. No statistically significant reduction in WBC was observed.

Efficacy

Using the same nonparametric procedures as in the preceding study, the sponsor analyzed the standing and supine systolic/diastolic blood pressures, and percentage of responders (SDBP < 90 mmHg) based on both the evaluable and the all patient data. Despite an imbalance in the number of dropouts among treatment groups (2 from enal/qd, 4 from enal/bid, and 11 from placebo), all results indicated that enalapril/qd and enalapril/bid were significantly superior to placebo at all time points. A multifactorial analysis of variance was also carried out by this reviewer on the 12-week data allowing a slightly narrower window of (78, 91)-day range. No significant treatment by investigator interaction was detected. This analysis agreed closely with the sponsor's findings as shown in Table 3. A marginally significant difference in treatment effect was detected between nonblack and black patients (-7.0 mmHg reduction in SDBP for nonblack and -4.3 mmHg reduction for black, $p = 0.05$).

Table 3
Comparisons of Mean Reductions in Supine Diastolic Blood Pressure from Baseline between Enalapril Treatment Groups and Placebo Group at Week 12 (Protocol #1) (mmHg)

	<u>Placebo</u>	<u>QD</u>	<u>BID</u>
Sponsor's Efficacy Analysis	-0.8	-8.7*	-8.4*
	40+	52	46
Sponsor's Endpoint Analysis	0.0	-9.4*	-8.0*
	54	57	56
Reviewer's Analysis	-0.5	-8.7*	-8.2*
	40	50	44

* significantly superior to placebo, $p < 0.001$.
+ number of patients

Protocol #2

Study Design:

This was a double-blind, randomized, parallel, active-control 24-clinic study comparing the anti-hypertensive effects of enalapril, hydrochlorothiazide and their combination in patients with mild to moderate essential hypertension (100-120 mm Hg SDBP).

At the end of a 4-week placebo washout period, 221 patients were randomly assigned to the enalapril group, 222 to the HCTZ group, and 103 to the enalapril/HCTZ group making a total of 546 patients. For the first four weeks, the enalapril group received 10mg/bid, the HCTZ group received 25mg/bid, and the combination group received (10/25mg)/bid. The dose for each of these groups was doubled after four weeks for patients whose SDBP remained above 90 mm Hg. At the end of 8 weeks (period 1), if a patient's blood pressure was still not under control, then he was given the combination therapy at (10/25mg)/bid in the second period for 4 weeks. The dose was again doubled after 4 weeks if necessary. Patients who initially received the combination therapy and did not come under control at the end of period 1 were discontinued from the study. No upward titration occurred if SDBP < 90 mm Hg.

Safety

Two deaths occurred during this study. A 58 year old white male was admitted to emergency room 10 days after treatment with 10 mg/bid of enalapril. He died five days later of myocardial infarction. The second death occurred to a 59 year old white male who was first treated with enalapril and then switched to the combination therapy enal/HCTZ in the second period. He suffered a myocardial infarction during week 11 (second period) and died six weeks later. It is not clear whether enalapril contributed to the cause of death in these cases.

A tabulation of the total number of patients discontinued from the study broken down by reason for discontinuation is given in Table 4. They were about equally distributed between treatment groups. The enalapril group had a slightly higher number of patients who discontinued due to adverse effects. The reasons for enalapril discontinuation included dizziness, rash, hives, abdominal pain, breathlessness, palpitation, angioneurotic edema, nausea, vomiting, myocardial infarction, tachycardia, shortness of breath, chest pain, decreased appetite, and cramps in hands and feet.

In the first period (8-week), the total frequencies of individuals reporting one or more adverse clinical experiences were not significantly different between treatment groups: 34% (74/221) for enalapril, 28% (63/222) for HCTZ, and 38% (39/103) for the combination. Relative to body systems, enalapril had a significantly higher percentage of respiratory system related side effects

(7.7%) than HCTZ (2.3%). This also appeared to be the case in the later periods among the responders. The musculoskeletal system related side effects also occurred significantly more frequently among the enalapril patients (5.0%) than the HCTZ patients (2.7%). Although occurrence of side effects involving skin or skin appendage were not significantly different between the treatment groups, two patient discontinuations due to angioneurotic edema were thought to be related to enalapril.

With respect to the safety parameters, the enalapril treated group had a reduction over baseline in hemoglobin concentration at week 8 which was significantly different from a corresponding increase observed in the HCTZ group (see Table 13). Among the enalapril responders, this reduction became statistically significant at week 16 (-0.47, $p < 0.05$) and week 32 (-0.38, $p < 0.05$). Due to the lack of a placebo control group, it is not possible to assess the significance of these reductions.

Table 4
Number of patients Discontinued from the Study
(Protocol #2)

Reason	Treatment Group		
	Enal	HCTZ	ENAL/HCTZ
Adverse Experience	17(7.7%)	14(6.3%)	5(4.9%)
Lost to Follow-up	6	5	2
Nonresponders	6	3	3
Protocol Violation	3	5	1
Adverse Lab Paramters	2	3	3
Others		1	2
Total	34(15.4%)	31(14.0%)	16(15.5%)

Efficacy

Using nonparametric procedures previously described, the sponsor evaluated the relative effectiveness of enalapril as compared to HCTZ and Enal/HCTZ with respect to standing and supine blood pressures, and the proportion of responders at weeks 2, 4, 5, and 8 in period 1 both with and without patient exclusion. Since the enalapril group had significantly fewer black patients than the HCTZ group (38% vs. 50%, $p = 0.012$), and since preliminary analysis based on all races combined indicated the presence of significant race x treatment interactions, the sponsor carried out similar analysis within each racial subgroup. The sponsor's results at week 8 (period 1) for supine diastolic blood pressure are given in Table 5. This reviewer's own analysis at week 8 is not much different from that of the sponsor's and hence will not be presented here. The sponsor's results for the other weeks exhibited similar patterns.

This study shows that for nonblacks, enalapril was slightly but not significantly favored over HCTZ (-14.3 mmHg vs. -11.8 mmHg, $p = 0.17$), while for blacks, enalapril was significantly less effective than HCTZ (-6.8 mmHg vs. -14.6 mmHg, $p = 0.001$). The combination Enal/HCTZ was significantly better than enalapril alone in either racial subgroup ($p=0.001$), and it was more effective than HCTZ alone in nonblacks ($p=0.001$) and marginally so in blacks ($p=0.09$). Because of the absence of a concurrent placebo control, this study only provides indirect evidence in support of the efficacy of enalapril.

Table 5
Reduction* of Supine Diastolic Blood Pressure at Week 8 over Baseline
(Protocol #2)
(mmHg)

Sponsor's Analysis		Enalapril	HCTZ	Enal/HCTZ
With Exclusion	All Races+	- 9.9	-12.0	-19.7
	Nonblack	-14.3	-11.8 (0.125)	-21.7 (0.001, 0.001)
	Black	- 6.8	-14.6 (0.001)	-21.0 (0.001**, 0.001***)
Without Exclusion	All Races+, ++	-10.7	-12.6	-20.7
	Nonblack	-13.7	-11.5 (0.238)	-21.8 (0.001, 0.001)
	Black	- 6.4	-13.6 (0.001)	-20.0 (0.001, 0.085)

+ Significant race x treatment interaction

++ Significant investigator x treatment interaction ($p = 0.012$)

* All reductions were significant at $p = 0.05$ level (two-sided)

** Two-sided p-value for comparison with enalapril

*** Two-sided p-value for comparison with HCTZ

Protocol #3

This was a 16-week double-blind, randomized, parallel, 6-clinic study with a design similar to the previous study to compare the antihypertensive effects of enalapril 10-40 mg per day and metoprolol 100-400 mg per day with and without hydrochlorothiazide (50mg/per day) in mild to moderate essential hypertensive outpatients.

After a 4 week placebo baseline period 150 patients with supine diastolic blood pressures between 95 and 115 mm Hg were randomly assigned to treatment with either enalapril (75 patients) or metoprolol (75 patients). Enalapril was titrated from 5 mg/bid to 10 and 20 mg/bid at 2-week intervals for those patients whose supine diastolic blood pressure remained above 90 mmHg. Metoprolol was similarly titrated beginning with 50 mg/bid. At the end of the sixth week (period 1), patients who were under control maintained their optimal dose, and patients with SDBP > 90 mmHg received a concurrent administration of HCTZ (50mg/day) for six more weeks.

Safety

No death was reported during this study. There were four patients from the enalapril group and six from the metoprolol group who were discontinued from the study due to adverse reactions. The overall frequencies of adverse reactions were similar between the two treatment groups in Period 1. However, during Period 1, the enalapril group appeared to have higher incidences of adverse effects in cardiovascular system (5.3% vs. 1.3%), musculoskeletal system (4.0% vs. 1.3%), dizziness (4.0% vs. 2.7%), and cough (4.0% vs. 0%).

With respect to the laboratory safety parameters, mean reduction over baseline in hemoglobin, was observed in Period 1 for enalapril, but it achieved statistical significance ($p < 0.05$) only in Period 2 for the non-responders under the combination therapy of Enalapril/HCTZ (see Table 13).

Efficacy

The sponsor's analysis at the end of the sixth week based on both the efficacy and the all patient data (10 from enalapril group and 13 from metoprolol group dropped out), and the reviewer's fixed-effect analysis of variance all demonstrated that both treatments effected significant and comparable reductions in supine diastolic blood pressure from their respective baselines (see Table 6). Race was the only factor found to have a significant effect. Blacks did not respond well to either treatment when compared to nonblacks. Again due to the lack of a placebo control, this study only provided indirect evidence supporting the efficacy claim for enalapril.

Table 6
Mean Reduction from Baseline in Supine Diastolic
Blood Pressure at Week 6 Based on the Efficacy Data
(Protocol #3)
(mmHg)

Treatment	Race	# Patients	Mean Reduction in SDBP (mmHg)
Enalapril	Black	20	- 5.0
	Nonblack	42	-15.1
	Combined	62	-11.8
Metoprolol	Black	18	- 6.1
	Nonblack	41	-13.7
	Combined	59	-11.3

Protocols #4 and 5

These were two studies with the same design and were treated by the sponsor as a single study. It was a 17-center, randomized, double-blind, captopril-controlled, parallel study to compare the antihypertensive effects of enalapril and captopril each combined with HCTZ in the treatment of essential hypertensive patients who had a supine diastolic blood pressure between 100 and 120 mmHg at the end of a 4-week 50 mg/bid HCTZ baseline treatment. At the end of 5 weeks (first period), aldomet (in protocol #4 or timolol (in protocol #5) was added to the treatment regimen of nonresponders (SDBP > 90 mmHg). A total of 175 patients entered the active treatment phase of this study. Eighty-five patients were randomly assigned to the HCTZ/enalapril group and 90 to the HCTZ/captopril group. The two groups were similar with respect to the various baseline characteristics.

Safety

No deaths occurred in this study. Two patients from the HCTZ/enalapril group and 9 patients from the HCTZ captopril group were discontinued from the study due to adverse clinical experiences. Four additional patients from HCTZ/enalapril group were dropped out for other reasons. The overall frequencies of adverse clinical experiences were comparable between the two groups in period 1 (30.6% for HCTZ/Enalapril vs. 36.7% for HCTZ/Captopril) and in period 2 (17.4% vs. 14.0% respectively). It should be noted that the HCTZ/enalapril group appeared to have a higher incidence of adverse clinical experiences involving the musculoskeletal system (3.5% vs. 1.1% in period 1, 6.5% vs. 2.3% in period 2).

With respect to laboratory safety parameters, there were significant reductions from baseline in hemoglobin and hematocrit at all weeks and for all combination therapies involving enalapril (see Table 13 for week 6 results).

Efficacy

An analysis of variance was carried out for supine diastolic blood pressure data at week 6 to study the effects of the baseline factors and their interactions. No significant interactions were found. Factors that did have a significant effect on the change in SDBP at week 6 included race, age and SDBP stratum.

Based on the same nonparametric procedure as used in the preceding studies, the sponsor found that the reductions in blood pressures from baseline were not significantly different between the treatments at all three visits during period 1 (e.g. -16.3 mmHg for HCTZ/enalapril vs. -16.5 mmHg for HCTZ/captopril at week 6).

Except for the higher incidence of adverse clinical experiences involving the musculoskeletal system and the significant reductions in hemoglobin and hematocrit observed in the HCTZ/enalapril group (see Table 13), the results of this study showed that enalapril at increasing doses of 5, 10 and 20 mg/bid and captopril at the corresponding doses of 25, 50 and 100 mg/bid were equally safe and effective when combined with 50 mg/bid of HCTZ in the treatment of hypertensive patients whose supine diastolic blood pressure remained between 100 and 120 mmHg after four weeks of 50 mg/bid HCTZ treatment at baseline.

Chronic Congestive Heart Failure Studies

The importance of ventricular outflow resistance on the performance of the left ventricle has been recognized and lends physiological support to the use of vasodilators in the treatment of congestive heart failure (CHF). The objectives of the next two studies were to evaluate the acute and chronic hemodynamic effect, the efficacy, safety, and tolerability of enalapril in the treatment of patients with CHF who had failed to respond adequately to therapy with digitalis and diuretics and who did not show a clinically important hypotension during two days of open-label treatment with enalapril.

U.S. Study

This was a double-blind, randomized, parallel, placebo-controlled, multicenter (12) study of patients with chronic congestive heart failure. Chronic congestive heart failure patients with N.Y.H.A. cardiac status 2 to 4, prognosis 1 to 3 were eligible for the study.

The duration of the study was 14 weeks. The baseline period consisted of one or two weeks during which the patient's cardiac status had to remain stable without changing the dose of digitalis and diuretics. Patients were randomized into two groups. One group was to receive enalapril/bid plus digitalis and diuretic and the other group was to receive placebo/bid plus digitalis and diuretic for the 12-week double-blind treatment period.

Patients were hospitalized for the first and second day of the 12-week period. On the first day, patients in both groups received enalapril 5 mg/bid, and on the second day the dose was increased to 10 mg/bid, if there had not been an adequate hemodynamic response and/or clinically important hypotension on the first day after receiving enalapril 5 mg/bid. On the third day, the patients began to receive either enalapril or placebo according to the random allocation schedule. Patients were scheduled for biweekly visits during this treatment period. Upward titration of enalapril to 10 mg or 20 mg/bid was made at the end of second week if no improvement in exercise capacity was observed provided that the patient's SDBP \geq 95 mmHg. Reduction in dosage was allowed at any time during the course of the treatment period.

Baseline differences between the two groups were generally slight except for the greater frequencies of secondary diagnosis of hyperlipidemia ($p < 0.05$) and obesity ($p < 0.01$) in the enalapril group. Prior drug therapy and concomitant drug therapy were not remarkably different between the treatment groups.

Results of Sponsor's Efficacy Analysis

The overall assessment of the efficacy of enalapril for the congestive heart failure patients was based upon the following key parameters as specified in the protocol: duration of exercise, N.Y.H.A. cardiac status and diagnosis, and left ventricular resting ejection fraction. These parameters were analyzed in three ways at the end of weeks 2, 6, and 12: (1) A "completers" analysis excluding patients judged to have serious protocol violations, (2) an endpoint analysis at each treatment period where all patients who were randomized to treatment were included by assigning any missing data the value of the efficacy parameter recorded during the treatment period immediately preceding, and (3) a dropout analysis in which therapy-related withdrawals were assigned the worse value and the two treatment groups were compared.

Since the efficacy results at week 2 and 6 are generally less favorable to enalapril than the result at week 12, only the latter result will be presented below for the "completers" and endpoint analysis.

Duration of Exercise

Exercise capacity (tolerance) quantified by exercise duration was used as an objective measure of congestive heart failure severity. A modified Naughton treadmill protocol with exercise time measured in seconds was utilized in this study. Data were first analyzed for all patients (with N.Y.H.A. 2-4), and then for sicker patients (with N.Y.H.A. 3-4). The within treatment group comparisons were evaluated using the Wilcoxon signed-rank test, while the between-group comparisons were performed using a one-way analysis of variance on the rank transformed values. The results are summarized in Table 7. Both the enalapril and placebo groups had significant increases from baseline in duration of exercise except for the sicker patients in the placebo group.

However, there is no significant difference between the two treatment groups even at the one-tailed .05 significance level.

Table 7
Mean Duration of Exercise in Seconds (\pm S.D.)
At the End of Week 12 of Treatment Period
(U.S. Congestive Heart Failure Study)

Type of Analysis		Treatment Group	# of Patients	Pre	Post	Adjusted Change	Percent Change
All Patients (NYHA 1-4)	Completers	Enalapril+	24	597	687	92	18*
		Placebo	22	582	672	88	18
	Endpoint	Enalapril+	42	580	680	103	21**
		Placebo	45	547	610	61	17*
Sicker Patients (NYHA 3-4)	Completers	Enalapril+	17	567	645	77	18 Δ
		Placebo	15	590	658	70	12 Δ
	Endpoint	Enalapril+	28	545	636	92	22**
		Placebo	32	527	570	42	10

** , * , Δ p < 0.01, 0.05, 0.10 for change over baseline.

+ Between treatment groups comparisons were not statistically significant at $\alpha = 0.05$ level.

Ejection Fraction

Resting left ventricular ejection fraction was evaluated by radionuclide gated blood scan or by echocardiogram at baseline and at the end of weeks 4 and 12. The same methods of analysis were used here as in the evaluation of duration of exercise. Except for the enalapril group at week 4, both groups registered positive changes in ejection fraction from their respective baselines. However, only the placebo group at week 4 had a significant change from baseline (p < 0.05). No significant differences in changes between the two treatment groups were observed (Table 8).

Table 8
Resting Ejection Fraction
(U.S. Congestive Heart Failure Study)

Technique	Week	# of Patients	Treatment Group	Pre	Post	Change
Radionuclide gated blood scan	4	15	Enalapril	27.4	26.9	- 0.5
		17	Placebo	26.5	29.7	+ 3.2*
	12	20	Enalapril	27.2	29.6	+ 2.4
		21	Placebo	26.2	26.7	+ 0.5
Echocardiogram	4	9	Enalapril	43.4	44.4	+ 1.0
		10	Placebo	37.5	47.9	+10.4
	12	11	Enalapril	39.1	46.8	+ 7.7
		12	Placebo	38.9	45.3	+ 6.3

* p < 0.05 for change over baseline

NYHA Functional Change

The NYHA cardiac status was evaluated with respect to the number of patients improving or worsening from their baseline cardiac status. Fisher's exact test was used to compare between group differences. The results for Week 12 are summarized in Table 9. As indicated there, the sponsor's dropout analysis showed that 12 of the 33 placebo treated patients worsened in cardiac status as compared to none of the 28 patients receiving enalapril (p < 0.01). However, the validity of this dropout analysis is questionable for the following reasons.

1. The sponsor reported a total of 12 placebo and 6 enalapril related withdrawals. However, it appears from Table 9 that at most 1 of the enalapril-related dropout was included in the analysis. While 10 of the 12 placebo-related dropouts were included in the same analysis. Since in the dropout analysis the dropouts were assigned the worse values, the failure to include all the therapy-related dropouts introduced a bias in favor of enalapril.
2. The sponsor should have included other forms of dropouts in the analysis instead of just the therapy-related dropouts.
3. Most of the placebo dropouts whether therapy-related or not had completed either the 2 or 6-week visits, and they had either maintained or improved their NYHA cardiac status over the periods prior to their last visits

(6 improved, 13 same, 6 had no information past baseline). On the other hand, most of the enalapril dropouts whether therapy-related or not, had no information past baseline (1 improved, 3 same, 6 had no information past baseline). Therefore, assigning the worse values to dropouts in general does not appear to be an acceptable strategy here.

Table 9
Between Treatment Group Comparisons of the Change from Baseline
in NYHA Cardiac Status as Week 12
(U.S. Congestive Heart Failure Study)

Type of Analysis	Improved		p	Worsened		p
	Enalapril	Placebo		Enalapril	Placebo	
Completers	12/27	8/23	NS	0/27	2/23	NS
Endpoint	15/43	16/46	NS	0/43	3/46	NS
Dropout*	12/28	8/33	NS	0/28	12/33	p < 0.01

*Only therapy-related dropouts were included in this analysis.

Other supportive clinical efficacy variables included improvement in clinical condition (Yale scale), weight, change in liver size, ventricular rate (beats/min. during ECG), distention of jugular veins (lying down and 45° tilt), liver condition, and edema. There were no statistically significant differences between treatment groups in the changes from baseline for these variables.

Safety Results

Of the 43 patients on enalapril, thirty-six completed the study, two discontinued due to death, three to treatment ineffectiveness, one to adverse clinical experience, and one to patient withdrawal. Of the 46 patients on placebo, thirty-two completed the study, four discontinued due to death, one to treatment ineffectiveness, six to adverse clinical experience, one each to adverse laboratory experience, patient uncooperativeness, and lost-to-followup, and two patients' data were received past cut-off date. During the randomized phase of the study, 16 (37%) patients on enalapril vs. 21 (46%) patients on placebo reported at least one adverse clinical experience. There was no significant difference between the treatment groups in the frequency of occurrence of these outcomes except for the higher frequency of adverse clinical experience observed in the placebo group (8 vs. 1).

With respect to the hematology parameters, there were significant reductions from baseline for the enalapril group on hemoglobin, hematocrit and eosinophils, and for the placebo group on eosinophils and basophils. Furthermore, the reduction from baseline for hemoglobin and hematocrit were significantly greater for the enalapril group (p < 0.01) (see Table 14).

Relative to the blood chemistry and clinical safety parameters, there were significant changes from baseline in the enalapril group for plasma renin activity and for supine and standing systolic/diastolic blood pressures. These changes which were expected of enalapril were significantly different between the two treatment groups ($p < 0.01$).

International Study

This was a multicenter (19 investigators from 11 countries), double-blind, randomized, parallel, placebo-controlled study to determine the effect of enalapril in patients with congestive heart failure. The design of this study was similar to that of the previous US study, but there were some differences in both the design and conduct of these two studies. Patients were eligible if their ejection fraction were less than 60% instead of the 40% used in the US study. Also, in this study, investigators could substitute a bicycle exercise machine for a treadmill exercise machine if the latter was not available. A patient eligibility criterion required that preliminary exercise duration should be at least 240 seconds but not more than 960 seconds on the Naughton scale. However, the Naughton scale was with reference only to the treadmill exercise machine. Additional information requested from the sponsor by this reviewer indicates that the two forms of exercises are essentially equivalent. In total, 119 patients entered the treatment period (57 in the enalapril group and 62 in the placebo group), and 98 patients completed the study (48 in the enalapril group and 50 in the placebo group).

Efficacy Results

The same efficacy measures and methods of analysis as in the U.S. study were used to evaluate the effectiveness of enalapril in the treatment of patients with congestive heart failure. The analysis was performed in two ways: 1) by excluding patients who violated protocol and analyzing only patients who presented "valid" data, and 2) analyzing all patients randomized and using the last available measurement.

Duration of Exercise

Exercise duration was measured by a motor-driven treadmill or a bicycle ergometer. The sponsor's results showed that when bicycle and treadmill were considered separately, there was no significant difference between treatment groups. Since there was no treatment by machine interaction, the sponsor pooled the two groups and demonstrated that there was a significant treatment difference favoring enalapril when various kinds of patients were excluded. However, the validity of this result is doubtful for the following reasons.

1. Nearly 40% of the patients were excluded from the analysis. Reasons for exclusion included protocol violation, no information beyond baseline, early termination, and evaluation made outside the specified time range. For a distribution of reasons for exclusion, see Table 15.

2. Ten of the 20 enalapril patients who were excluded due to either protocol violations or had a 12-week evaluation outside the time range of (78,94) - days had a reduction in exercise duration time of -278 seconds at 12 weeks; while 12 of the 23 placebo patients who were similarly excluded had a net improvement in exercise duration time of 1774 seconds at 12 weeks (see Table 15). Thus, the exclusion of these patients would significantly bias the result in favor of enalapril.

The result of the corresponding analysis without patient exclusion in Table 10 (should have excluded patient with no information beyond baseline) indicates that there was no significant difference between enalapril and placebo in terms of improving patient's exercise capacity.

Table 10
Mean Duration of Exercise in Seconds
At the End of Week 12 of Treatment Period
(International Congestive Heart Failure Study)

Type of Analysis	Type of Exercise	Treatment	Between Treatment		Change	Comparison	
			# Patient	Baseline			
With Exclusion	Bicycle	Enalapril	11	522.6	650.2	127.5**	p=0.051
		Placebo	10	552.0	549.9	-2.1	
	Treadmill	Enalapril	22	629.6	732.6	103.0**	p=0.063
		Placebo	26	563.3	605.4	42.1	
	Combined	Enalapril	33	594.0	705.1	111.2**	p=0.004
		Placebo	36	560.0	590.0	29.8	
No Exclusion	Bicycle	Enalapril	21	506.7	565.2	58.5**	N.S.
		Placebo	21	536.4	585.0	48.7	
	Treadmill	Enalapril	30	602.9	665.2	62.4**	N.S.
		Placebo	37	534.1	581.8	34.6	
	Combined	Enalapril	51	563.3	624.1	60.8**	N.S.
		Placebo	58	530.7	570.4	39.7	

Ejection Fraction

Ejection fraction was also measured by echocardiogram and radionuclide ventriculography methods. There were a few scattered significant changes within treatment groups. However, there were no significant between treatment group differences in these changes.

NYHA Cardiac Status and Prognosis

The sponsor reported significant treatment difference in the improvement in patient cardiac status and prognosis (Table 11) based on data with patient exclusion. Since the enalapril group had a significantly more severe baseline cardiac status than the placebo group, a generalized odds ratio for ordinal data proposed by Agresti (Biometrics 36, 59-67, 1980) was calculated by this reviewer based on the cross-classification of the pre and post-treatment cardiac status by treatment as shown in Table 12. The result confirms the sponsor's finding.

Table 11
 (%) of Patients Improved in Cardiac Status and Prognosis
 (Treatment Week 12 with Exclusion)
 (International Congestive Heart Failure Study)

	Treatment		(%)	Between Group Comparison
Status	Enalapril	16/37	(43)	p < 0.01
	Placebo	3/38	(8)	
Prognosis	Enalapril	12/37	(32)	p < 0.05
	Placebo	4/38	(11)	

Table 12
 Changes in Cardiac Status and Prognosis
 (Treatment Week 12 with Exclusion)
 (International Congestive Heart Failure Study)

Status	Baseline	Enalapril				Placebo			
		2	3	4	Total	2	3	4	Total
	2	12	0	0	12	17	2	0	19
	3	10	8	0	18	3	14	1	18
	4	2	4	1	7	0	0	1	1
	Total	24	12	1	37	20	16	2	38

Generalized Odds Ratio $\chi^2 = 6.5$
 $p = 0.01$

The improvement in cardiac status was also significantly different between treatment groups when data with no exclusion was used.

With respect to other clinical efficacy variables, the only significant difference between treatment groups was observed in liver dullness. The enalapril group showed a significantly greater reduction from baseline in liver dullness than the placebo group (-1.8 vs. -0.1, $p < 0.01$).

Safety Analysis

During the 12 week active treatment period, 16(28%) patients in the enalapril group, and 15(24%) patients in the placebo group reported clinical adverse reactions. There were generally no significant differences between the two groups in either the overall incidence of adverse experiences or the incidence of adverse experiences by body system. There were two deaths each in the enalapril and the placebo groups. With respect to hemoglobin, there were marginally significant between treatment group differences in the respective changes from baseline at weeks 4 and 8 (see Table 14).

Reviewer's Overall Conclusions and Comments Which may be Conveyed to the Sponsor

1. The dose-response study (protocol #0) and the study with Protocol #1 both demonstrated that enalapril at doses ranging from 2.5 mg/bid to 40 mg/bid were significantly more effective than placebo in reducing blood pressures in patients with mild to moderate essential hypertension. Due to the absence of a placebo control, the other hypertension studies provided only indirect evidence in support of the effectiveness of enalapril.
2. The dose-response results in Table 1 suggest that the anti-hypertensive effects of enalapril at doses of 2.5, 10, and 20 mg/bid were not significantly different, particularly at the end of the fourth week. The dose-response relationship might have been strengthened had a lower dose of enalapril (such as 1.0 mg/bid) been chosen.
3. Enalapril is effective among both blacks and nonblacks as demonstrated in the first two studies. However, enalapril is much more effective among nonblacks, than among blacks as shown in the dose response study (-12.3 mmHg vs. -7.1 mmHg reduction in sitting diastolic blood pressure) and the study with protocol #1 (-7.0 mmHg vs. -4.3 mmHg reduction in SDBP).
4. With respect to the congestive heart failure studies, there was no evidence in the U.S study that enalapril was effective relative to any of the efficacy parameters. In the International study, some positive indication favoring enalapril came from the efficacy measures NYHA cardiac status and prognosis based on analyses with and without patient exclusion. The sponsor's analysis of exercise duration time based on

patient data with exclusion showed significant improvement in favor of enalapril. However, the validity of this analysis is questionable for two reasons. First, the analysis excluded nearly 40% of the patient population. Secondly, the exclusion of these patients significantly bias the result in favor of enalapril. More specifically, 10 of the 20 enalapril patients who were excluded due to either protocol violation or having had a 12-week evaluation outside the time range of (78,94) - days had a net reduction in exercise duration time of -278 second at 12 weeks; while 12 of the 23 patients who were similarly excluded had a net improvement in exercise duration time of +1774 seconds at 12 weeks. The result of the corresponding analysis without patient exclusion indicates that there was no significant difference between enalapril and placebo in terms of improving a patient's exercise capacity. Therefore, in summary, there appears to be no substantial evidence favoring enalapril in the treatment of congestive heart failures.

5. There is some evidence suggesting an association between enalapril and a reduction in hemoglobin concentration (see Tables 13 and 14). However, more conclusive evidence is needed, and its clinical implications need to be investigated.

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Mathematical Statistician

cc: Orig., NDA 18-998
 HFN-110
HFN-110/Dr. Solymossy
HFN-344/Dr. Lisook
HFN-713/Dr. Dubey
HFN-713/Dr. Chi
Chron.
File: DRU 1.3.2 NDA
GYHChi/njs/PLT/ebd/rb/12/6/84/34594/#0082n

Concur: Dr. Pledger *gp 12/7/84*

Dr. Dubey *6 12/10/84*

Table 13
 Mean Reduction from Baseline in Hemoglobin (Gm%)
 (Congestive Heart Failure Studies)

Study	Treatment	Mean Reduction		
		Week 4	Week 8	Week 12
U.S.	ENAL (10-20 mg/bid)	-0.8** (43#)		
	Placebo	-0.1 (46)		
	Between Treatment Comparison	p < 0.01		
International	ENAL (10-20 mg/bid)	-0.48* (43#)	-0.56** (38)	-0.35* (38)
	Placebo	-0.07 (49)	-0.17 (43)	-0.16 (41)
	Between Treatment Comparison	p = 0.085	p = 0.072	p > 0.25

*,** p < 0.05, 0.01

Number of Patients

TABLE 14
REDUCTION FROM BASELINE IN HEMOGLOBIN (GM%)
(SPONSOR'S RESULTS)

STUDY	TREATMENT	MEAN REDUCTION	NO. OF PATIENTS WITH REDUCTION					TOTAL
			<-1	(-1, -0.1)	(-0.1, 0.1)	(0.1, 1)	>1	
DOSE-RESPONSE (WEEK 4)	40 MG	-0.49**	7	11	1	7	0	26
	20 MG	-0.21*	1	16	2	4	2	25
	10 MG	-0.19**	4	14	1	8	1	28
	25 MG	-0.28*	2	16	2	8	0	28
	PLACEBO	-0.39	4	13	1	6	1	25
PROTOCOL #1 (WEEK 12)	10-40 MG/QD	-0.31*, ++	14+	17	1	18	4	54
	5-20 MG/BID	-0.03	4	21	2	19	3	49
	PLACEBO	0.07	2	15	2	21	3	43
								ENAL/QD VS. PLACEBO: P < 0.05
PROTOCOL #2 (WEEK 8)	ENAL (10 MG/BID)	-0.10+	21++	84	11	58	16	190
	ENAL/HCTZ	-0.33+	15++	35	2	37	6	95
	HCTZ (25 MG/BID)	0.42**	11	44	9	86	43	193
								ENAL VS. HCTZ: P < 0.01, ENAL/HCTZ VS. HCTZ: P < 0.01
PROTOCOL #3 (WEEK 6)	ENAL (10-40 MG)	-0.18 (P=0.14)	9	27	4	24	3	67
	METO (100-400 MG)	-0.17*	4	38	0	17	5	64
								ENAL VS. METO: P = 0.13
PROTOCOL #4, 5 (WEEK 6)	HCTZ/ENAL	-0.27*, +	13+	34	5	24	2	78
	HCTZ/CAP	0.11	7	36	1	29	9	82
								HCTZ/ENAL VS. HCTZ/CAP: P = 0.02

*, ** P < 0.05, 0.01 FOR WITHIN TREATMENT GROUP COMPARISON
+, ++ P < 0.05, 0.01 FOR BETWEEN TREATMENT GROUPS COMPARISON

Table 15
 Change in Exercise Duration Time for Patients Excluded
 from Sponsor's 12-Week Exercise Duration Analysis
 (International Congestive Heart Failure Study)

Type of Exercise	Enalapril				Placebo			
	Only at Baseline	Only at 4-Week	At 12-Week Outside Range	At 12-Week Protocol Violation	Only At Baseline	Only at 4-Week	At 12-Week Outside Range	At-12 Week Protocol Violation
Bicycle								
# Patients	3	1	5	3	3	3	4	2
Time in Seconds		-35 -30	120 -240 -90 -240 120	-22 -27 270		0 -60 -150	720 600 0 -120	7 132
Treadmill								
# Patients	2	4	1	1	0	5	3	3
Time in Seconds		-160 25 -180 -30	-150	-19		-60 45 -80 80 -70	174 133 -65	180 133 -120
Total Net Change in Seconds		-350	-480	202		-295	1442	322

Statistical Review and Evaluation
(Addendum)

Date: OCT 7 1985

NDA #: 18-998/Drug Class 1B

Applicant: Merck, Sharp & Dohme Research Laboratories

Name of Drug: Vasoril (Enalapril Maleate, MSD) Tablets

Indication: Congestive Heart Failure

Documents Reviewed: Two volumes on the domestic and international congestive heart failure (CHF) studies dated March 23, 1984, additional information and data listing on NYHA cardiac status and exercise duration for the international CHF study dated October 26 and November 30, 1984 and two volumes of additional analyses on both domestic and international CHF studies dated May 15 and June 27, 1985.

Background

The sponsor's original NDA submission dated March 23, 1984 included a domestic (protocol #6) and an international (protocol #520) CHF studies. The overall assessment of the efficacy of enalapril for congestive heart failure patients was based upon the following key parameters as specified in the protocol: duration of exercise, NYHA cardiac status and diagnosis, and left ventricular resting ejection fraction. In the sponsor's original analyses, no treatment difference was detected relative to these efficacy measures in the domestic CHF study (see pp. 12-15 of the original review dated December 10, 1984); in the international CHF study, a significant difference ($p < 0.05$) between enalapril and placebo was detected relative to duration of exercise (completers subset only), and NYHA cardiac status and prognosis. However, in the latter study, the validity of the sponsor's analysis was questioned (see original review pp. 16-21). It was in response to the criticisms and questions raised in the earlier review that the two volumes of additional analyses dated May 15 and June 27, 1985, were submitted. The analyses contained in the June 27 submission superceded the May 15 analyses. In this review, only the June 27 submission will be discussed. In this submission, the sponsor provided a reanalysis of the international CHF study based on the data contained in the original submission (study was still continuing at the time of submission), some summary statistics of the updated data from the since completed study and an analysis of both the domestic and international studies using different composite scores.

Reanalysis of the International CHF Study (Data in Original NDA)

As discussed in the original review (dated December 10, 1984, p. 17) this reviewer's main concern was the actual effect of the bias introduced as a result of excluding 43 patients due to either protocol violations or having had a 12-week evaluation outside the time range of (78,94) - days. In this reanalysis, the sponsor allowed a slightly wider window of (71, 109) - days for the 12-week visit. The earlier results and the results of this reanalysis for exercise duration and NYHA cardiac status are summarized in Table 1. As shown in this table, the significance level for the treatment difference

observed in exercise duration increased from a statistically significant level of 0.004 to a marginally significant level of 0.053. The significance level for the treatment difference in NYHA cardiac status increased from a significant level of <0.01 to <0.05 .

Summary Statistics for the Completed International CHF Study

The sponsor pointed out during a meeting held on June 19, 1985, with this reviewer (see June 19, 1985, memo) that the above analyses would be based on the data submitted in the original NDA. The international CHF study was not completed at that time, and it has since been completed; based on the sponsor's preliminary analysis, the results were highly favorable to enalapril. However, in the interest of time, they would like to avoid submitting a complete reanalysis based on the full data base at this time; this reviewer suggested that the sponsor should at least provide some summary statistics along the line of the preceding reanalysis. The results based on the completed study are shown in Table 2 for exercise duration and NYHA cardiac status. It indicates that the sample size [81 (with exclusion) compared to 40] was more than doubled and the treatment differences in mean exercise duration and in proportion of patients improved in cardiac status were both significantly favoring enalapril ($p < 0.01$). Similar results were observed based on data without exclusions.

Composite Scores Analysis

The sponsor analyzed three composite scores based on the following 6 variables:

1. Change from baseline in exercise duration (in seconds).
2. Change in NYHA cardiac status.
3. Change in physical examination. This was defined as the sum of the non-missing changes in the five variables edema, heart, jugular vein-45°, liver and lungs each coded as 0 for absent/normal and 1 for present/abnormal
4. Changes in Functional Impairment, Magnitudes of Task and Effort as measured in the Yale scale. Each variable was coded as changes ranging from -4 (maximum worsening) to +4 (maximum improvement)

All variables were defined so that a positive value corresponds to improvement and a negative value to worsening. Because these variables were defined in widely differing units, they were all standardized relative to their sample means and standard deviations (without regard to treatment group) prior to computing the composite scores. The first composite score was the first principal component obtained from a principal component analysis of the sample correlation matrix of the above standardized variables. The second composite score was simply the unweighted sum of the standardized variables. The last

composite score was defined as the sum of the non-missing standardized variables divided by the number of non-missing standardized variables. These three scores were computed by the sponsor for both the domestic and the international CHF studies for data with and without exclusions. Comparisons between treatment groups were done relative to these composite scores using the Wilcoxon signed rank test with an adjustment for ties. Since the last two composite scores are not very meaningful (and not any more favorable) only the results for the first composite score are summarized in Tables 3-5.

The sponsor's results for the domestic CHF study (Table 3) show that no mean treatment difference was observed for the first principal component score based on the six variables for data with exclusion at week 12 ($p=0.23$) while a significant difference was observed for data without exclusion ($p=0.03$). For both data with and without exclusions (Table 4) at Week 12, the mean treatment differences observed for the first principal component scores based on three variables (excluding Yale scale variables) did not reach statistical significance ($p=0.46$ and $p=0.15$ respectively). First principal component scores for the international CHF study (Table 5) showed significant treatment differences ($p<0.01$) for both data with or without exclusion based on exercise duration, NYHA cardiac status and physical examination score (Yale scale variables were not available for this study).

Reviewer's Comments

1. Based on the sponsor's reanalysis of the incomplete data from the international CHF study (see Table 1), enalapril appears to be marginally superior to placebo relative to exercise duration ($p=0.053$) and NYHA cardiac status ($p<0.05$). The summary statistics based on the completed data (Table 2) suggested that enalapril was significantly superior to placebo relative to the same measures ($p<0.01$). In view of the marginal nature of the results based on the incomplete data, the sponsor may have to substantiate his claim of enalapril's superiority by submitting a more formal analysis of the completed international CHF study data. Some statistical adjustment appears to be necessary on account of the "interim" analysis performed earlier on the incomplete data.
2. Among the three composite scores defined by the sponsor as either weighted (First principal component score) or unweighted sums of some number (3 or 6) of arbitrarily selected variables, the last two had neither statistical nor clinical meaning. Only the first principal component score will be discussed below.

The purpose of principal component analysis is in data reduction. It is a descriptive analysis for analyzing relationship that may exist in a set of quantitative variables; usually the technique is used for exploratory purposes not as the primary analysis. The method consists in transforming a large set of variables Y_1, Y_2, \dots, Y_p to a new set of p -variables Z_1, Z_2, \dots, Z_p with the following properties:

- (1) Each Z_j , called principal component, is a linear combination (weighted sum) of the Y_j 's, i.e.,

$$Z_j = \sum \alpha_j Y_j \qquad \sum \alpha_j^2 = 1$$

- (2) Of all possible linear combinations, Z_1 accounts for the greatest proportion of the total variation observed.
- (3) Of all possible linear combinations of this type uncorrelated with Z_1 , Z_2 accounts for the greatest proportion of the remaining variation. Similarly Z_3 is uncorrelated with Z_1 , Z_2 and accounts for the greatest proportion of the remaining variation, and so on until the complete set of p -variables, Z_1, Z_2, \dots, Z_p has been defined.

The main idea behind this procedure is that the first few principal components may well account for most of the variability in the original data, and for many purposes it may be reasonable to ignore the remaining principal components and so reduce the number of variables necessary to consider. The method itself is perfectly general; however, the difficulty lies in its execution and subsequent interpretation.

3. Following are some questions and comments directed at the sponsor's principal component analysis and the discussion will focus on the domestic CHF study.
- a. There were at least 17 variables (see Table 6) discussed in the protocol which the sponsor thought might provide relevant information on the condition of a patient with congestive heart failure. Of these 17 variables, only the first five (Duration of Exercise, NYHA cardiac Status and Prognosis, Left Ventricular Ejection Fraction, Transverse Diameter of Heart) were considered by the sponsor as the main efficacy parameters, the remaining variables were only of secondary importance. By what criteria were the 6 variables (marked by asterisks in Table 6) selected for a principal component analysis?
- b. The variable Physical Examination itself is a derived measure. It was defined as the sum of the non-missing values of the last five variables in Table 6 each of which was coded 0 (for absent/normal) and 1 (for present/abnormal). Because of the way it is defined, this variable is informative only with respect to its larger values 4 or 5; for the smaller values, one cannot be sure whether they were indicative of normal condition, or simply reflective of a lot of missing values for its component variables. For example, among the completers, only 15 patients had 12-week values for changes in liver condition, 12 patients had values for changes in jugular vein-45° tilt, 17 patients on edema.

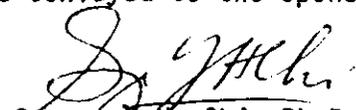
- c. Principal component analysis is sensitive to the units of measurement of the variables involved. Because these variables were not commensurable, the set of principal components obtained based on these variables and the set of principal components obtained based on the standardized variables are likely to be very different and generally no simple relationship could be described between them. This would then lead to the problem of interpreting what these computed principal components actually mean.
- d. Since the first principal component(s) accounted for less than 50% of the observed total variation (see Tables 3 and 4), over 50% of the information was lost by ignoring the remaining components. Were these discarded components (information) relevant to efficacy evaluation? Is the first principal component the only relevant measure?
- e. Is the first principal component(s) itself, as derived by the sponsor, relevant to the efficacy evaluation of enalapril for treatment of congestive heart failure? Recall that the first principal component was determined by a method that was based essentially just on the criterion of optimizing total variation explained and not on other criteria such as relevance, quality and objectivity of the measures involved. Consequently, this method tends to give greater weights to those measures (variables) that treatment had a significant effect on (for example, blood pressures) and/or those measures that were inherently more variable (e.g., Yale scale, due to the subjective nature of the measure). Looking at the weights for the first principal components in Table 3 and Table 4, it is clear that more weights were placed on the measures, Functional Impairment, Magnitude of Task and Magnitude of Effort. This suggests that either the treatment had a significant effect on these measures (indeed the case for Magnitude of Task and Efforts) or that these measures were inherently more variable. Therefore, unless these measures can be considered as primary efficacy measures, the emphasis put on these measures would be misleading. Since the protocol for these studies did not consider these measures to be primary, one cannot take the first principal component as derived by the sponsor seriously as a measure in the efficacy evaluation of enalapril for the treatment of congestive heart failure. If all of the individual measures were relevant and highly correlated, then a large proportion of the variation (>90%) ought to be accounted for by the first principal component. Perhaps only in such cases, may the first principal component be considered as a candidate for efficacy measure, provided it also has a clinically interpretable meaning. Although the sponsor did not display the correlation matrix, in view of the amount of variation (<50%) accounted for by the first principal component, it is suspected that the correlations among the variables were probably not very high.

- f. Principal component analysis used as an exploratory analysis does not require any distributional assumption. However, to use it as a quasi-confirmatory analysis, assumption of multivariate normality is required. Given the kinds of variables involved, it is doubtful that the normality assumption could be met.

Overall Summary and Recommendations

1. Even though the summary statistics (see Table 2) based on the completed data from the international CHF Study (Protocol #520) suggested that enalapril is significantly effective in the treatment for congestive heart failure, in view of the marginal nature of the results based on the incomplete data ($p=0.053$ for Duration of Exercise and $p<0.05$ for NYHA Cardiac Status, see Table 1), the sponsor should submit a formal and complete analysis using the completed data to substantiate the claim of enalapril's superiority. Some statistical adjustment appears to be necessary in view of the "interim" analysis performed.
2. The method of principal component analysis as applied here by the sponsor is not appropriate for the following main reasons. (1) It is exploratory in nature. (2) Because the variables were not commensurable, there is difficulty in interpreting the meaning of the principal components. (3) The weights assigned to the measures in each principal component arose from the desire to maximize total variation explained; they were not based on other criteria such as relevancy, quality and objectivity of the measures. Consequently, those measures that were inherently more variable (e.g. due to its subjective nature) and/or those measures (relevant or not) that treatment had a significant effect on would be given greater weights. This would make the first principal component a misleading efficacy measure. Other reservations concerning its application have been discussed in the preceding section.
3. The sponsor's post-hoc reanalysis of the domestic CHF study (Protocol #6), chiefly based on the principal component analysis, is considered to be inappropriate by this reviewer. Hence, the sponsor still has not provided any convincing evidence from this study to demonstrate the superiority of enalapril to placebo in the treatment of patients with congestive heart failure. This reviewer is of the opinion that further analysis of this data would not be fruitful. Another study may have to be conducted.

This review in its entirety may be conveyed to the sponsor.


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Mathematical Statistician

cc:

Orig. NDA 18-998

HFN-110

HFN-110/Dr. Lipicky

HFN-344/Dr. Lisook

HFN-713/Dr. Dubey

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Chron.

File: DRU 1.3.2 NDA

Dr. Chi/x34594/njs/rp/9/25/85/#0348n

Concur: Dr. Nevius *SN 9/25/85*

Dr. Dubey

D 10-4-85

Table 1
 Treatment Difference in Exercise Duration and NYHA Cardiac
 Status at Week 12 Based on Incomplete Data
 (International CHF Study)

Type of Measure	Type of Analysis	Type of Data	N	Enalapril Baseline Mean	Change at Week 12	N	Placebo Baseline Mean	Change at Week 12	Level of Significance
Exercise Duration	Original	With Exclusion	33	594.0	+111.2	36	560.0	+29.8	p=0.004
		Without Exclusion	51	563.3	+ 60.8	58	530.7	+39.7	Not Significant
	Reanalysis (71,109) Window at Week 12	With Exclusion	40	575.3	+ 83.4	45	547.7	+52.6	p=0.053
		Without Exclusion	Data Not Available						
NYHA Cardiac Status	Original	With Exclusion		16/37	43%*		12/37	32%*	p<0.01
		Without Exclusion		21/52	40%		3/56	5%	p<0.01
	Reanalysis (71,109)- Window at Week 12	With Exclusion		12/43	28%*		4/45	9%*	p<0.05
		Without Exclusion	Data Not Available						

*Percent of patients improved in cardiac status.

Table 2
 Treatment Difference in Exercise Duration and NYHA Cardiac
 Status at Week 12 Based on Completed Data
 (International CHF Study)

Type of Measure	Type of Data	Enalapril			Placebo			Level of Significance
		N	Baseline Mean	Change at Week 12	N	Baseline Mean	Change at Week 12	
Exercise Duration	With Exclusion	81	583.4	+123.6	79	576.1	+46.1	p<0.01
	Without Exclusion	115	572.5	+125.3	116	588.9	+21.4	p<0.01
NYHA Cardiac Status	With Exclusion		45/89	51%		10/82	12%	p<0.01
	Without Exclusion		57/124	46%		13/127	10%	p<0.01

Table 3
 First Principal Component Scores Based on Changes in Exercise Duration,
 NYHA Cardiac Status, Physical Examination Score, Functional Impairment,
 Magnitudes of Task And Effort at Week 12
 (Domestic CHF Study)

Type of Data	N	Enalapril Mean Score	S.D.	N	Placebo Mean Score	S.D.	Level of Significance
With Exclusion	31	0.26	1.59	29	-0.28	1.75	p=0.23
First principal component score = 0.27 (Exercise Duration) + 0.30(NYHA) + 0.21(Physical Exam) + 0.52(Impairment) + 0.50(Task) + 0.53(Effort) Proportion of total variation accounted for = 0.47							
Without Exclusion	43	0.37	1.42	43	-0.37	1.90	p=0.03
First principal component score = 0.27 (Exercise Duration) + 0.20(NYHA) + 0.20(Physical Exam) + 0.53(Impairment) + 0.52(Task) + 0.55(Effort) Proportion of total variation accounted for = 0.49							

Table 4
 First Principal Component Scores Based on Changes in Exercise Duration,
 NYHA Cardiac Status, Physical Examination Score at Week 12
 (Domestic CHF Study)

Type of Data	N	Enalapril Mean Score	S.D.	N	Placebo Mean Score	S.D.	Level of Significance
With Exclusion	31	0.07	0.95	29	-0.08	1.38	p=0.46
First principal component score = 0.58 (Exercise Duration) + 0.74(NYHA) + 0.34(Physical Exam) Proportion of total variation explained = 0.46							
Without Exclusion	43	0.13	0.97	43	-0.13	1.35	p=0.15
First principal component score = 0.59 (Exercise Duration) + 0.69 (NYHA) + 0.41 (Physical Exam) Proportion of total variation explained = 0.46							

Table 5
 First Principal Component Scores Based on Changes in Exercise Duration,
 NYHA Cardiac Status, Physical Examination Score at Week 12
 (International CHF Study)

Type of Data	N	Enalapril Mean Score	S.D.	N	Placebo Mean Score	S.D.	Level of Significance
With Exclusion	40	0.38	1.21	45	-0.34	1.14	0.01
First principal component score = 0.50 (Exercise Duration) + 0.60(NYHA) + 0.62(Physical Exam) Proportion of total variation accounted for = 0.55							
Without Exclusion	51	0.36	1.30	57	-0.32	1.20	<0.01
First principal component score = 0.51 (Exercise Duration) + 0.59 (NYHA) + 0.62 (Physical Exam) Proportion of total variation explained = 0.55							

Table 6

A List of Variables Changes in Which were Considered
By the Sponsor as Indicative of Changes in the Condition
of a Patient with Congestive Heart Failure

I. Objective Measures

- 1.* Duration of exercise
2. Resting left ventricular ejection fraction as measured by echocardiogram or radionuclide gated blood scan
3. Transverse diameter of the heart (only at week 24)

II. Subjective Measures

- 4.* NYHA cardiac status
5. NYHA cardiac prognosis
6. Yale scale
 - a.* functional impairment
 - b.* magnitude of task
 - c.* magnitude of effort

III. Clinical Measures

7. Weight
8. Ventricular rate
9. Liver size
10. Liver condition
11. Jugular distension
 - a. lying down
 - b. 45° tilt
12. Lung
13. Edema
14. Heart

Variables 10-14 (except 11a) were
combined into a single
variable - Physical Examination*

Variables 1, 2, 4, 5 were considered by the sponsor as determining the primary efficacy measures.

Statistical Review and Evaluation

Date: DEC 18

NDA #: 18-988

Applicant: Merck Sharp & Dohme Research Laboratories

Name of Drug: Vasotec (Enalapril Maleate)

Documents Reviewed: Letter to Dr. Raymond J. Lipicky dated October 25, 1984, including a package of updated stability data for 40 mg tablets from Merck Sharp & Dohme Research Laboratories

The Request:

Merck Sharp & Dohme requested a 30-month expiration date for 40 mg tablets based on stability data updated to contain test results of 2-year samples.

Introduction:

On July 30, 1984, in our stability review of the original submission for vasoril (Enalapril Maleate), we recommended that a 2-year expiration date be granted only for 20 mg and 40 mg tablets. For 5 mg and 10 mg tablets, there were a total of five samples which did not support a 2-year expiration date. These samples supported expiration dates of 12 to 15 months.

In a followup on September 6, 1984, we recommended a 30-month expiration date for 5 mg, 10 mg, and 20 mg tablets based on data updated to contain test results of 2-year samples.

The current submission contains additional data for 40 mg tablets and requests an expiration date of 30 months for 40 mg tablets.

Updated Data:

1. Amber glass container, CLIC LOC closure

Lot Number	Strength	Weeks	Percent Label Claim
E004	40 mg	0	102.3
		17	102.8
		30	102
		57	97.7
		111	98.5
E005	40 mg	0	99.3
		19	101.5
		30	100.7
		57	98
		111	97.8

2. Amber glass container, metal screw caps

Lot number	Strength	Weeks	Percent Label Claim
E004	40 mg	0	102.3
		17	102.3
		30	103.2
		57	98.7
		111	96.5
E005	40 mg	0	99.3
		17	100.8
		30	99.5
		57	97
		111	95.3

3. HDPE Bottles, CLIC LOC closure

Lot number	Strength	Weeks	Percent Label Claim
E004	40 mg	0	102.3
		20	99.8
		30	98.5
		57	99.5
		111	95
E005	40 mg	0	99.3
		17	101.8
		30	99
		57	97.2
		111	92.8

4. HDPE bottles, metal screw caps

Lot Number	Strength	Weeks	Percent Label Claim
E004	40 mg	0	102.3
		17	102.8
		30	94
		57	97.2
		60	100.8
		111	98.3
E005	40 mg	0	99.3
		19	101.5
		30	97.2
		57	95.7
		111	96

Methodology:

The same methodology as used in our reviews of July 30, 1984 and September 6, 1984 was used with the additional data for 40 mg tablets.

Results:

There are eight samples for two lots. The eight samples for 40 mg tablets satisfy the conditions for pooling and support an expiration date of 30 months.

Conclusions:

Based on the additional data, regression analysis support a 30-month expiration date.

R. L. Vishnuvajjala
R. Lakshmi Vishnuvajjala, Ph.D.
Mathematical Statistician

Concur: William J. Ferguson

William J. Ferguson

William R. Fairweather *WR7 12/17/84*

cc: Orig. NDA #18-988

HFN-110

HFN-110/Dr. Zimmerman

HFN-715/Mr. Ferguson

HFN-715/Dr. Vishnuvajjala

HFN-715/File: DRU 2.2.1 Stability NDA 18-998

HFN-710/Chron

HFN-715/RKVishnuvajjala/ebd/plt/11/26/84/443-4710/#1112p

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