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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
18-998/S-059

Statistical Review

STATISTICAL REVIEW AND EVALUATION

sNDA #:	18-998
Applicant:	Merck Research Laboratories
Name of Drug:	Vasotec (Enalapril maleate)
Indication:	Hypertension
Document reviewed:	Volume 1, submitted on January 14, 2000
Statistical Reviewer:	John Lawrence, Ph.D. (HFD–710)
Medical Reviewer:	Steve Rodin, M.D. (HFD–110)

1. Introduction

Enalapril is an ACE inhibitor that is commonly used to treat adults, children, and infants. Vasotec is currently supplied in 2.5 mg, 5 mg, 10 mg, and 20 mg tablets. It is indicated for treatment of hypertension, symptomatic heart failure, and asymptomatic left ventricular dysfunction and is currently supplied in 2.5 mg, 5 mg, 10 mg, and 20 mg tablets.

This supplemental NDA submission is for a change in the label to permit the safe and effective use of the drug in hypertensive pediatric patients. In addition, the applicant is requesting an additional six months of marketing exclusivity to the patent protection.

The submission includes the results of two studies recently conducted in pediatric patients and one study in adults. Study MK-0421 Protocol No. 167 and 169 is a double-blind, randomized dose response study of Enalapril in children with hypertension. Study MK-0421 Protocol No. 168 and 172 is an open-label study to investigate the pharmacokinetics in hypertensive children and infants. Study MK-0421 Protocol 170 is an open, two-period, crossover study to determine the relative bioavailability of suspension 10 mg and 10-mg tablets. The remainder of this statistical review will discuss the results from the double-blind, randomized dose response study.

2. Study Design

110 male and female hypertensive patients between the ages of 6 and 16 were enrolled in the study. Patients were enrolled at 19 centers (16 in the US, 1 in Chile, 1 in Colombia, and 1 in Argentina). Overall, 54 patients were from US investigators, 12 from Chile, 31 from Colombia, and 13 from Argentina. Patients had to weigh at least 20 kg, had to have glomerular filtration rate at least 30 mL/min/1.73m^2 based on serum creatinine measurements at the start of the washout period (see below) and had to be able to swallow tablets. Patients with severe hypertension or history of certain other medical complications were excluded.

Each patient first entered a washout period of up to 7 days where any previous anti-hypertensive medication was discontinued. Those completing this washout period who were hypertensive (SiDBP at or above the 95th percentile based on gender, height, and age) were randomly assigned to a low, medium, or high dose. This reviewer could not find the details of the randomization procedure except that it was intended to be a 3:2:5 randomization. In fact, 30 patients were assigned to the low dose, 30 to the medium dose and 50 to the high dose. The definition of low/medium/high was dependent on the patient's body weight. For those patients whose body weight was less than 50 kg: the low dose was 0.625 mg; the medium dose was 2.5 mg; and the high dose was 10 mg titrated upward to 20 mg at day 3. For those patients whose body weight was 50 kg or greater: the low dose was 1.25 mg; the medium dose was 5 mg; and the high dose was 20 mg titrated upward to 40 mg at day 3. For both weight groups, the low dose was administered once daily in a suspension formulation while the medium and high doses were administered once daily with tablets. Following the 14-day treatment period, patients underwent a randomized washout period (placebo or continue active treatment) for up to 14 days. This randomization was determined by the original randomization and each patient was equally likely to continue the active treatment or receive a placebo.

Scheduled blood pressure was measured by office visits occurred on day –7 (the start of the washout period), day 1 (the start of the double-blind treatment period), and days 3, 7, 15, 22, and 29. At the discretion of individual investigators, more frequent clinical observations were performed. Various other laboratory measurements were taken at predefined visits.

3. Primary Efficacy Variable

The primary efficacy variable was the change in trough SiDBP from baseline to Day 15, the end of the double-blind treatment period.

4. Secondary Efficacy Variables

The secondary efficacy was the change in trough SiDBP from day 15 to the end of the randomized washout period.

5. Protocol Specified Planned Statistical Analysis

Intention-to-treat using last-observation-carried-forward was specified as the approach to address the primary hypothesis. The primary analysis was based on the stratified linear regression model on change in trough SiDBP with weight group as the stratified intercepts and dose ratio as the continuous covariate.

In addition, three supportive analyses were planned for the primary efficacy variable: per-protocol analysis excluding protocol violators; ANOVA using covariates for weight, dose group, and the interaction; and a longitudinal model.

The secondary efficacy variable was designed to measure if switching to a placebo (after the initial 14 day treatment period) was associated with an increase in blood pressure. The primary analysis for the secondary efficacy variable was based on a t-test derived from the contrast (1, -1, 1, -1, 1, -1)/3 from a one-way ANOVA with a factor of 6 treatments representing all the combinations of (low, medium, high) dose with (treatment continuation, placebo) washout. In addition, a per-protocol analysis, an ANOVA model with weight as an additional factor, and a longitudinal model were pre-specified as supportive analyses.

6. Analysis of Primary Efficacy Variable

Figure 6.1 shows boxplots of the decrease in trough SiDBP stratified by dose (Low, Medium, High) and patient's weight (Under 50 kg, Over 50 kg).

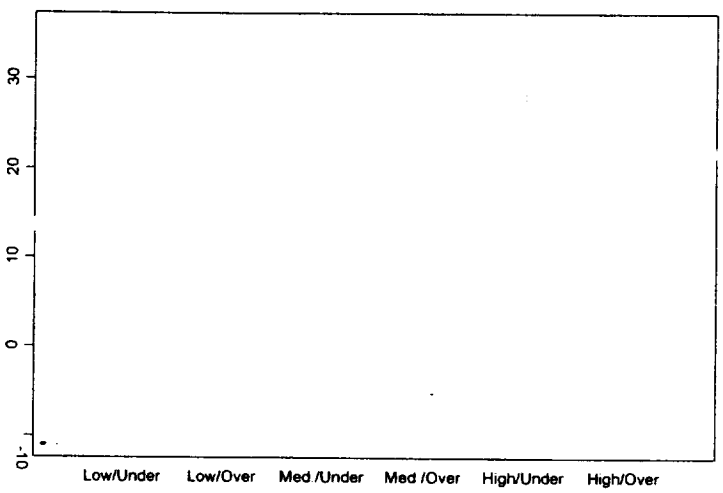

Figure 6.1 Decrease in trough SiDBP stratified by dose and patient's weight.

Within each weight class, an increasing trend is evident. It is also apparent that within each dose, the patients in the higher weight class tend to have a smaller decrease in SiDBP.

The primary analysis that will be described in detail next is a linear regression model that includes terms to adjust for weight and dose. This was the primary analysis pre-specified in the protocol.

For patient i, let

Y_i = decrease in trough SiDBP from baseline to the end of 14 day treatment
W_i = 0 if patient i weighs less than 50 kg and 1 otherwise
D_i = dose ratio 1 (low), 4 (medium), or 32 (high)

A linear regression model of the following form is assumed to describe the relationship between Y and the dependent variables W and D:

$$Y_i = \alpha_0 + \alpha_1 * W_i + \alpha_2 * D_i + \varepsilon_i \; ; \quad \text{where } \varepsilon_i \text{ are iid normal}$$

Table 6.1 shows the estimates of these parameters using the intention-to-treat analysis (specified as the primary analysis) and the per-protocol analysis. The p-values in this table are two-sided. These estimates are from the FDA analysis and they agree with the estimates from Tables 17 and 18 from the Study Report.

Table 6.1 Estimates of parameters from linear regression model.

Parameter	Estimate	Standard Error	p-value
α_0 (intercept)	8.21	1.34	<0.0001
α_1 (adjustment for weight)	-3.31	1.64	0.046
α_2 (adjustment for dose ratio)	0.251	0.054	<0.0001
α_0 (intercept)	8.98	1.35	<0.0001
α_1 (adjustment for weight)	-3.36	1.64	0.042
α_2 (adjustment for dose ratio)	0.225	0.054	<0.0001

Source: FDA analysis.

Assuming the model is correct, the interpretation of the parameters in Table 6.1, is that if everything else is held constant, for each unit increase in dose ratio we would predict that the patient's SiDBP would decrease by an additional 0.251 mm Hg. Also, a patient who weighs less than 50 kg would be expected to have a decrease in SiDBP 3.31 mm Hg more than a patient who weighs at least 50 kg. The remainder of this section explores some supportive analyses specified in the protocol as well as some that were not specified.

In this reviewer's opinion, the dose ratio should be transformed to a log scale before the model is fit. In other words, define a continuous variable by assigning a value

of 0 (= $\log_2$ 1) for the low dose, 2 (= $\log_2$ 4) for the middle dose, and 5 (= $\log_2$ 32) for the high dose. The linear regression using this log-transformed dose ratio variable results in a model that fits the data slightly better as measured by Mallow's C_p or the R^2 criteria. Small values of C_p and large values of R^2 indicate a better fit. The parameter estimates and model fitting criteria are in Table 6.2.

Table 6.2 Estimates of parameters from linear regression model using original dose ratio variable or log-transformed dose ratio.

Original scale (1, 4, and 32)	8.21	-3.31	0.251	2.05	0.193
Log-transformed (0, 2, and 5)	7.26	-3.27	1.75	2.00	0.196

Source: FDA analysis.

The difference of the values for the model fitting criteria is not overwhelming. However, since we might have a predisposition to use this log-transformed scale, we may prefer to use it here. It is worth pointing out that if we use the log-transformed scale for dose, the p-value for the coefficient α_2 is still well below 0.0001. So, this does not effect the conclusion regarding the positive relationship between dose and decrease in SiDBP.

The results of the ANOVA treating dose as a categorical variable appear in Table 6.3. This analysis confirms a highly significant difference between the three doses. The FDA analysis presented here agrees with Table 19 from the Study Report.

Table 6.3 ANOVA Model.

Dose	2	767	<0.0001
Weight	1	281	0.05
Dose * Weight	2	30.7	0.65
Error	103	70.7	

Source: FDA analysis using ITT population.

The longitudinal model described in the protocol combined data from all patients in the first 14 days of treatment with data from the 51 patients who were randomized to continue their enalapril treatment for an additional 14 days. The combined data from the two periods were expected to provide longer-term information. This analysis used a mixed model with terms for period (first 14 days/ second 14 days), slope for first period (as a function of dose-ratio), and slope for second period. The details of the analysis were not very clear in the protocol. From the results presented, one can infer that there was

also an adjustment for patient's weight. The sponsor's results from this analysis that relate to the first period appear in Table 6.4.

Table 6.4 Estimate of slope for first 14 day treatment period (change in trough SiDBP as a function of dose-response) using longitudinal model (ITT approach).

Slope (<50 kg)	-0.40	0.06	<0.001
Slope (≥50 kg)	-0.30	0.07	<0.001
Adjusted SD	8.70		

Source: Table 25 of Study Report.

Finally, one might believe that the response is a function of the amount of drug administered per unit of body mass or amount of drug per unit of height. There are many different models that include terms for Dose/Weight, Dose/Height, Sex, and/or Baseline SiDBP. Since the various models have different numbers of terms, it is more appropriate to use the adjusted-R^2-criteria, rather than R^2, to compare the models. Some of these models with parameter estimates and values of C_p and R^2 appear in Table 6.5.

Table 6.5 Estimates of parameters from various linear regression models using different subsets of covariates.

7.3	12.5				0.09	15.2
6.0	12.7		0.78		1.88	14.6
-1.1	12.1			0.095	1.07	15.3
-1.4	12.2		0.45	0.090	3.00	14.5
7.8		33.9			5.70	10.7
6.7		34.6	0.61		7.58	9.96
-2.2		32.6		0.113	6.24	11.0
-2.4		32.9	0.22	0.11	8.22	10.2

Source: FDA analysis.

The model that seems to fit the data the best includes the single covariate Dose/Weight. The variable Dose is in units of mg of drug per day, Weight is in kilograms, Sex is 1 for Females and 2 for Males, and Baseline SiDBP is measured in mm Hg at Day 1 of the treatment period.

7. Analysis of Secondary Efficacy Variable

The primary analysis for the secondary efficacy variable was based on a t-test derived from the contrast (1, -1, 1, -1, 1, -1)/3 from a one-way ANOVA with a factor of 6 treatments representing all the combinations of (low, medium, high) dose with (treatment continuation, placebo) washout. The results from this analysis using the ITT approach and the per-protocol approach appear in Table 7.1. The FDA analysis agrees with the results reported by the sponsor.

Table 7.1 Estimates of parameters from ANOVA model.

Parameter	Estimate	Standard Error	p-value
Group difference	6.1	1.98	0.0021
Adjusted SD	9.5		
Group difference	6.48	1.99	0.0011
Adjusted SD	9.29		

Source: FDA analysis or Tables 22 and 23 from Study Report.

The estimate of the group difference in Table 7.1 means that, on average, those patients who switched to a placebo experienced a rebound of 6.1 mm Hg relative to those who continued the enalapril treatment. The supportive ANOVA model specified in the protocol that included weight as an additional factor gave similar results (*Source: Table 24 of Study Report*). The p-value reflecting the significance of the difference between the groups that continued treatment and those that switched to a placebo was approximately 0.003 using this model.

The sponsor's results from the longitudinal analysis that relate to the second period appear in Table 7.2.

Table 7.2 Estimate of slope for second treatment period (change in trough SiDBP as a function of dose-response) using longitudinal model (ITT approach).

Slope (<50 kg)	-0.01	0.08	0.936
Slope (≥50 kg)	0.07	0.10	0.503
Adjusted SD	10.23		

Source: Table 25 of Study Report.

The study report states that "there were no significant changes in slopes ... indicating no further blood pressure reductions for enalapril occurred during Period II". However, in this reviewer's opinion, that inference cannot be made from the results from this analysis presented by the sponsor. A better interpretation of the results in Table 7.2 is that any further decrease (or rebound) in SiDBP that occurred during the second two weeks of treatment among those patients who continued enalapril treatment was not dose-dependent.

8. Exploratory Subgroup Analysis

For each subgroup pre-specified in the protocol, the linear regression model that was used for the primary analysis was fit. This model included a term for weight as well as a term for dose-ratio treated as a continuous variable. The estimates of the parameters for each subgroup appear in Table 8.1.

Table 8.1 Estimates of parameters from linear regression model within different subgroups (ITT approach).

Age < 13	56	6.90	0.318	<0.001
Age ≥ 13	53	10.1	0.195	0.009
Tanner < 4	70	7.04	0.297	<0.001
Tanner ≥ 4	38	11.0	0.212	0.016
Male	63	9.29	0.248	0.001
Female	46	6.39	0.284	0.003
Race- White	43	10.8	0.105	0.270
Race- Black	22	6.67	0.319	0.027
Race-Other	44	6.52	0.351	<0.001
Country- U.S.	53	9.6	0.246	0.004
Country- non-U.S.	56	7.06	0.271	<0.001

Source: FDA analysis or Table 20 of Study Report.

Table 8.1 shows that within each subgroup, the numerical estimate of the slope shows a positive relationship between dose and decrease in blood pressure. Moreover, the nominal p-values were significant in each subgroup with the exception of Whites.

The discussion of the results in the specified subgroups should not be extrapolated to the greater population of patients. Rather, it is only a summary of the data that was observed in this study. This is because of the large number of subgroups and the small number in each subgroup. The low dose tended to provide a greater therapeutic effect

among the patients 13 or older. However, the effect of increasing the dose within this subgroup was not as great as the effect in those patients under 13. Recall that the analysis already adjusts for patient's weight (<50 kg/ ≥50 kg). So, this adjustment and the possible confounding of age with weight should be considered when interpreting the results. Similar observations can be made with respect to each stratification factor. Patients with Tanner stage 4 or higher tended to have a higher decrease at the low dose, but those with Tanner stage less than 4 had a higher dose-response. Males tended to have a higher decrease in BP across the board, but females had a slightly higher dose-response. Non-Whites did not respond as well as Whites to the low dose, but seemed to respond better to the high dose than Whites. U.S. patients seemed to respond better to the low dose and tended to have a slightly lower dose response than non-U.S. patients.

9. Adverse events

Safety was characterized by evaluating incidences of adverse experiences during the double-blind period, the randomized washout period, and 14 days following the study. The following events were pre-specified as primary adverse events: cough, renal dysfunction, angioedema, and hyperkalemia. The numbers of adverse experiences within each dose are summarized in Table 9.1. All patients randomized are included.

Table 9.1 Number (and percent) of patients with specific adverse experiences.

≥1 adverse experience	12	(40%)	17	(57%)	22	(44%)
Fever	0		0		2	(4%)
Dizziness	0		1	(3%)	3	(6%)
Headache	4	(13%)	5	(17%)	3	(6%)
Asthma	0		2	(7%)	0	
Infection, respiratory	4	(13%)	2	(7%)	6	(12%)
Pharyngitis	0		4	(13%)	2	(4%)
Pruritis	2	(7%)	0		0	
Nephrotic syndrome	2	(7%)	0		1	(2%)
Cough†	0		1	(3%)	2	(4%)
Renal dysfunction†	0		0		0	
Angioedema†	0		0		0	
Hyperkalemia†	0		0		0	

†Pre-specified as a primary adverse event.

Source: Table 32 and Table 33 of Study Report.

No dose-dependent trend is apparent for any of the adverse experiences listed in Table 9.1. In particular, there is no statistically significant trend for the four adverse experiences pre-specified as primary. Although there is a numerically increasing trend in the incidence of cough, the trend is not significant. More specifically, the p-value from a binomial regression analysis using rate of incidence of cough as the response and the logarithm of dose ratio as the predictor is 0.31.

10. Conclusions

For the pediatric population in the double-blind study, there was a highly significant dose response (p-value less than 0.0001). The positive relationship between dose and decrease in trough SiDBP that was observed in the whole populaiton was also observed in many different subgroups. In addition, there was no dose-dependent trend evident for any of the adverse experiences listed in the study. Combining the data on safety and efficacy, the study shows that the three weight-adjusted doses of enalapril are effective and well tolerated in pediatric patients.

/S/

John Lawrence, Ph.D.
Mathematical Statistician

This review consists of 10 pages of text, tables, and figures.

Concur: James Hung, Ph.D. /S/ 6/30/00
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MAR 22 1999

STATISTICAL REVIEW AND EVALUATION

MAR 22 ..

IND #: [redacted]
Applicant: Merck Research Lab
Drug Name: VASOTEC (Enalapril Maleate)
Indication: Hypertension
Document Reviewed: IND [redacted] for Protocol 167 (CDER REC'D: 02/17/99)

In response to the Agency's request for pediatric studies, the sponsor submitted a statistical data analysis plan for Protocol 167, "A double-blind, randomization dose response study of enalapril in children with hypertension".

The proposed study is a double-blind, randomized, multicenter study in hypertensive children (defined as greater than the 95th percentile for gender, age, and height-adjusted diastolic blood pressure). The study will contain two periods. Period 1 will be a 2-week, double-blind treatment period. Following this period is Period 2 in which half of the patients in each dose arm will be blindly assigned to placebo treatment, and the other patients will continue the same double-blind enalapril medication as that in Period 1 for an additional 14 days. Allocation for patients to such treatment sequences will be determined at randomization on Day 1 in a blinded fashion.

The primary objectives are to determine if a nonzero dose-response slope exists for enalapril in hypertensive children aged 6 to 16 years, after a 14-day, double-blind treatment period, and to characterize the safety and tolerability of enalapril in the dose range 0.625 to 40 mg in children aged 6 to 16 years with hypertension. The dose levels selected in the study will be adjusted by weight. For children with weight < 50kg, the three doses of 0.625 mg, 2.5 mg, and 20 mg will be assigned to 15, 10, and 25 children, respectively; while for children with weight ≥ 50kg, the 3 doses of 1.25 mg, 5 mg, and 40 mg will be assigned to 15, 10, and 25 children, respectively. The secondary objective is to determine whether discontinuation of active enalapril treatment is associated with return of hypertension (i.e., is washout of enalapril associated with loss of antihypertensive efficacy?).

The primary analysis will be the slope analysis on change in SiDBP (Day 15 versus Day 1) with dose ratio (1:4:32) as the continuous covariate using the simple linear regression model. The last-measurement-carried-forward approach will be used for patients who do not have measurements on Day 15, however, the baseline measurement will not be carried forward. An ANOVA model

for change in SiDBP will be performed with dose, weight, and interaction between dose and weight for robustness assessment. For half of the patients who continue the same enalapril treatment in Period 2, the combined data on the two periods will be performed using the mixed model with Period, Period 1 slope, Period 2 slope. The two slopes will be estimated and combined to determine the dose-response relationship.

For the secondary objective, the parameters of interest are the differences of mean change in SiDBP between low-dose and low-dose placebo arms, middle-dose and middle-dose placebo arms, and high-dose and high-dose placebo arms, respectively. When the dose-response relationship cannot be established in Period 1, the objective of the data analysis in the randomized washout period is to show a positive average difference of mean change between enalapril-treated groups versus placebo-treated groups across the 3 dose levels. The primary analysis for the average difference is based on the t-test, derived by the contrast (1 -1 1 -1 1 -1) from a one-way ANOVA with a factor of 6 treatment arms (low-low, low-placebo, middle-middle, middle-placebo, high-high, high-placebo). The blood pressure measurements used in the primary hypothesis on Day 15 will be used as the baseline measurements for the current analysis. The secondary analysis will be ANOVA analysis.

The total sample size of 100 patients is planned to detect a significant common trend at a significant level of 0.05 for a 5 mm Hg difference between the extreme doses, assuming a standard deviation of 8 mm Hg.

No adjustment for multiplicity will be made because there is only one primary efficacy hypothesis (i.e., a positive dose-response slope).

The effect of enalapril will be explored further in specific subgroups of patients characterized as follows:

1) Age ($\leq$ 12, > 12 years old)
2) Gender (male, female)
3) Race (White, Black, Others)
4) Country (U.S., Non-U.S.)

For each subgroup variable, the regression analysis and ANOVA as described in the primary analysis will be performed with the variable plus treatment by variable interaction in the model. The test of treatment by subgroup variable interaction will be performed at 0.05 nominal significance level. Gail and Simon's test will be used to determine whether the interaction is qualitative or quantitative. In the event of a nonsignificant or quantitative interaction, the main treatment effect is

interpreted as the effect averaged over the different levels of the subgroup factor. In the event of a qualitative interaction, the treatment effect will be estimated by each level of the subgroup factor.

Other efficacy variables to be analyzed include sitting systolic and standing diastolic and systolic blood pressures, as well as urinary recovery of study drug at steady state, plasma renin and aldosterone levels. Summary statistics will be provided for these variables.

Reviewer's comments

The sample size calculation is adequate under the given assumption that standard deviation is 8 mm Hg, the dose-response relationship is strictly linear with a mean difference of 5 mm Hg between extreme doses and the dose ratio of 1:4:32. However, from discussion with the medical review team, high dropouts may be expected in pediatric trials and thus the power for detecting the mean difference of 5 mm Hg between enalapril and placebo may be very low for the randomized withdrawal period. Sample size may need to be adjusted.

/S/

H.M. James Hung, Ph.D.
Mathematical Statistician

This review consists of 3 pages of text.

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cc: IND 17,791 N(Im)193
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