ADMIN

FEB 28 1984

MEMORANDUM OF TELEPHONE CONVERSATION

Date: February 16, 1984

Between: Robert L. Davis, Ph.D.
Merck, Sharp and Dohme Research Laboratories
West Point, Pennsylvania 19486
Tel: (215) 661-6429

and George Y.H. Chi, Ph.D., HFN-713

Subject: NDA 18-998 VASORIL™ (Enalapril Maleate, MSD)

I requested some clarification concerning when a p-value is one-sided or two-sided, what baselines were used for efficacy and safety parameters, and the following additional information described by each individual study.

1. Dose-Response Study
   a. Efficacy (sitting systolic/diastolic b.p.) results for period 1 (weeks 1-4) and period 2 by race (blacks vs. non-blacks).
   b. The dose-response relationship by race.
   c. The mean changes in the five safety parameters: body weight, hemoglobin, hematocrit, serum sodium and potassium by race.
   d. Efficacy data for period 2.

2. Study with Protocol #1
   a. Efficacy (supine systolic/diastolic b.p.) results for weeks 4, 8, 12 by race.
   b. The mean changes for the same set of five safety parameters by race.

3. Study with Protocol #2
   a. Efficacy (supine systolic/diastolic b.p.) results by race for period 2(3).
   b. Safety parameters for period 2(3) and also by race.
   c. The mean supine b.p. at baseline and period 1 (at weeks 2,4,6,8) for both the responders and non-responders (at end of period 1) and also by race.
   d. For responders under treatment Enal and HCTZ, the significance levels for changes in body weight, hemoglobin, hematocrit, serium sodium and potassium at weeks 16, 32, 48 (Period 2).
   e. For non-responders under treatment ENAL and HCTZ, the mean changes and significant levels in the same five safety parameters (Periods 1,2).
   f. For responders under treatment Enal/HCTZ, the mean changes and significance level for the same set of safety parameters at weeks 16, 32, and 48.

4. Study with Protocol #3
   a. Efficacy (supine systolic/diastolic b.p.) by race in period 1 (weeks 2,4,6) and in period 2 (weeks 8,10,12).

b. The results on the five safety parameters in period 1 and period 2 by race.

c. The supine b.p. for responders and non-responders at baseline and at weeks 2,4,6 (Period 1) and weeks 8, 10, 12 (period 2).

d. same in (c) but by race.

5. Study with Protocols #4 and #5

a. HCTZ free baseline information on supine b.p. at week 0.

b. Efficacy results by race.

c. Mean changes and significance levels in the five safety parameters for the treatment groups HCTZ/Enalapril and HCTZ/Captopril (at weeks 6, 12, 16), and the four treatment groups HCTZ/(Enal, Cap)/(Timolol, Aldomet) (at weeks 12, 16).

A data tape was also requested containing some selected items of interest for each of the five studies.

Dr. Davis arranged a conference call (including his staff and their regulatory affairs officer) on February 21, and they agreed to provide the requested information in about 5 weeks.

George Y.H. Chi, Ph.D.
Mathematical Statistician

cc:
Orig. NDA 18-998
HFN-110
HFN-110/Dr. Solymossy
HFN-713/Dr. Chi
Chron
File: DRU 1.3.2 NDA
HFN-713/GYHChi/ebd/plt/2/24/84/#0713r

MEMORANDUM OF MEETING

DATE: June 19, 1985

BETWEEN: Dr. David Blois
Dr. Paul B. Huber (215-834-2530)
Dr. Allen L. Gould
Dr. Robert L. Davis
Ms. Judy Gromovsky
Representing Merck, Sharp and Dohme Research Laboratories

AND: Dr. George Y. Chi, HFN-713

SUBJECT: Enalapril for Congestive Heart Failure Indication, NDA 18-998

Dr. Blois said that they did not have a copy of my review until recently and hence did not respond to the issues raised in my review. They would like to know how they should reanalyze the domestic and international studies. He mentioned that based on principal component analyses performed on the two data sets contained in their original NDA submission, the results came out to be significantly in favor of enalapril (marginally so for the domestic study). He also indicated that their international study had since been completed and the results were also signficantly in favor of enalapril.

I suggested that for the international study, they should:

1. Include in the original data base as many of the patients as possible who were previously excluded due to having measurements taken outside some arbitrarily specified window.

2. Reanalyze this data base relative to the two efficacy measures, exercise tolerance and NYHA status.

3. Provide summary statistics on the same data base but based on the completed study.

They may submit additional analyses on both the domestic and international studies using the method of principal components. However, the validity of these analyses will be subject to review.

The firm agreed and indicated that they will submit these analyses soon.

George Y. Chi, Ph.D.
Mathematical Statistician

cc: Orig. NDA 18-998
HFN-110
HFN-110/Dr. Lipicky
HFN-713/Dr. Dubey
HFN-713/Dr. Chi
Chron.
File: DRU 1.3.2 NDA
GYHChi/plt/njs/06/25/85/34594/#0283n