# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**20988**

# STATISTICAL REVIEW(S)

# STATISTICAL NDA REVIEW AND EVALUATION

JUN - 7 1999

Date: **June 7, 1999.**

**NDA**: 20-988

**APPLICANT**: Wyeth-Ayerst Research

**NAME OF DRUG**: Protonix I.V. (sterile pantoprazole sodium).

**INDICATION**: Short-term gastric acid suppression in gastroesophageal reflux disease patients who are unable to take oral medication.

**USER FEE DUE DATE**: 7/20/99.

**DRUG CLASSIFICATION**: 1S.

**DOCUMENT REVIEWED**: Volumes 1.001 and 1.172 through 1.178, dated 7/20/1998.

**MEDICAL REVIEWER**: Hugo E. Gallo-Torres, M.D., Ph.D. The issues in this review have been discussed with medical reviewer Dr. Gallo-Torres.

**STATISTICAL REVIEWER**: Wen-Jen Chen, Ph.D.

**Keywords:** Non-Inferiority, Single Study, Bootstrap-t Interval.

## 1.0 . INTRODUCTION

Pantoprazole is a proton pump inhibitor (PPI). Pantoprazole binds covalently to the gastric $H^+$, $K^+$ -ATPase, causing long-lasting inhibition of pump activity, as do other PPIs such as omerprazole or lansoprazole. Pump activity is restored only by de novo protein synthesis of the proton pump. This class of drugs is used in the treatment of gastric acid-related symptoms and pathology, such as Gastroesophageal Reflux Disease (GERD) and the erosive esophagitis (EE) that generally accompanies GERD.

Byk Gulden originally developed intravenous (IV) pantoprazole for the treatment of patients unable to take oral pantoprazole for various reasons, for example, surgery or chemotherapy. Wyeth-Ayerst has licensed the development and marketing rights in the United States for both oral and the IV forms. This submission mainly consists of a single study, Study# 3001K1-309-US, to support the efficacy claim of pantoprazole IV for short-term gastric acid suppression in

GERD patients who are unable to take oral medication. Study# 3001K1-100-US was also submitted as a Phase I study for the pharmacodynamic dose response of pantoprazole IV. In addition, the sponsor also submitted the results of two supportive studies performed by Byk Gulden, Study BAT010 and Study FK3050, to provide related efficacy information for pantoprazole IV. The efficacy results from the two supportive studies were compared with those pooled from the two oral-only studies, Study FK3005 and Study FK3009.

## 2.0 STUDY# 3001K1-309-US

### 2.1 Background Information

**Objectives:** The objective of this Phase III study was to show non-inferiority of pantoprazole IV versus pantoprazole oral, by comparing the maximal pentagastrin-stimulated acid output (MAO) and basal acid output (BAO), in patients with GERD and a history of erosive esophagitis who are switched from pantoprazole oral (PO) to pantoprazole IV dose formulations.

**Study Design**: This was a randomized, placebo & active-controlled, double-blind. multi-dose, two-period study conducted at five clinical sites in United States. There were two dose levels of oral/IV pantoprazole, 20 and 40 mg. The two study periods for the treatment schedules are presented below:

| Group | Treatment Period 1 (Oral) | Treatment Period 2 (IV) | Randomization Weight |
|---|---|---|---|
| 1 | Pantoprazole 20 mg PO | Pantoprazole 20 mg IV | 3 |
| 2 | Pantoprazole 20 mg PO | Placebo 20 mg IV | 1 |
| 3 | Pantoprazole 40 mg PO | Pantoprazole 40 mg IV | 3 |
| 4 | Pantoprazole 40 mg PO | Placebo 40 mg IV. | 1 |

Each patient participated for approximately 42 days, including pre-study screening period (up to 3-week), treatment period 1 (10-14 day oral pantoprazole, 20 or 40 mg, once daily). and treatment period 2 (7-day IV pantoprazole, 20 or 40 mg, once daily; or placebo). During the pre-study screening period, all patients were randomly assigned to one of the above four treatment groups: pantoprazole 20 mg PO+pantoprazole 20 mg IV (Group 1), pantoprazole 20 mg PO + placebo 20 mg IV (Group 2), pantoprazole 40 mg PO+pantoprazole 40 mg IV (Group 3). and pantoprazole 40 mg PO+placebo 40 mg IV (Group 4). Here, + means "followed by".

Randomization was designed so that the ratio of active drug to placebo treatment group size was 3:1. The randomization table was constructed in blocks of eight samples. It consisted of 3 assignments of pantoprazole 20 mg PO + pantoprazole 20 mg IV, 1 assignment of pantoprazole 20 mg PO + placebo 20 mg IV, 3 assignments of pantoprazole 40 mg PO + pantoprazole 40 mg IV, and 1 assignment of pantoprazole 40 mg PO + placebo 40 mg IV.

**Determination of Sample Size**

The sponsor indicated that in order to have approximate 80% power to reject the null hypothesis that MAO of the pantoprazole IV is inferior to that of oral pantoprazole by 20% or more, the sample size for each treatment group was estimated to be 18 patients. The sample size estimation was based on the following assumptions:

1. the MAO for the oral formulation was 17.5 mEq/h,
2. the true difference in MAO between the two formulations was 0, and
3. the difference in MAO between the two formulations, evaluated by the power function, was 20% of MAO from the oral formulation.

In the sponsor's letter, dated May 11, 1999, it indicates that the type I significance level of 0.025 and the published data 5mEq/h as the standard deviation for the difference between groups were used for the sample size estimation.

**Dosing Schedule and Measurements**: On study day 1 (after randomization) through 10, patients received oral administrations of double-blinded (with respect to dose level) study medication, once per day in the morning. Oral dose administration was permitted to continue up to day 14, if necessary, in order to allow patients flexibility in scheduling. Each dose (oral and IV) was taken with the morning meal. After completion of the oral dose, patients received administrations of double-blinded (with respect to dose level and active or placebo treatment) IV infusions once per day in the morning. The IV infusions (90 ml) were administered over a 15 minute period.

Gastric acid output measurement, BAO and pentagastrin (PG)-stimulated MAO, were made 24 hours after the last oral pantoprazole dose, 24 hours after the first IV dose of the study drug, and 24 hours after the last IV dose of the study drug.

**Study Population:** The inclusion criteria for the study population included patients

- having a history of erosive esophagitis documented by endoscopy and a previous diagnosis of GERD,
- receiving treatment with acid suppressants or antacids,
- having clinical laboratory values within the normal limits of the investigator's laboratory and normal results for a 12-lead electrocardiogram (ECG), unless the investigator documented that the deviations were not clinically important or were directly related to an allowable pre-existing medical condition, etc..

The exclusion criteria for the study population included presence on screening endoscopy of

- obstructive esophageal strictures,
- esophageal diverticuli,
- esophageal varices,
- Barrette's esophagus greater than 3 cm or with high-grade dysphasia, and
- active gastric, pyloric channel, or duodenal ulcer, etc..

Minor deviations from the inclusion and exclusion criteria were acceptable if they were judged not clinically important by both the investigator and the sponsor medical monitor and if appropriate documentation was maintained (detailed inclusion and exclusion criteria are attached in Appendix A).

**Clinical Evaluations**: The clinical evaluation was composed of medical history, complete physical examination, ECG, ophthalmologic examination, endoscopic examination, laboratory evaluation, and vital signs measurements.

**Study Hypotheses:** The sponsor proposed that the MAO on the last day of IV pantoprazole treatment ($MAO_{LIV}$) would be no more than 20% greater than that of the last dose of oral pantoprazole ($MAO_{PO}$).

**Primary and Secondary Efficacy Variables**: The primary efficacy endpoint was the difference in the mean MAO following the last dose of IV pantoprazole with that after the last dose of oral pantoprazole ($MAO_{LIV}$ vs $MAO_{PO}$) for the 20 and 40 mg treatment groups.

The secondary efficacy endpoints were: 1. the difference between the first IV dose mean and the last oral dose mean ($MAO_{FIV}$ vs $MAO_{PO}$); 2. the difference between first IV mean BAO and last oral mean BAO ($BAO_{FIV}$ vs $BAO_{PO}$); and 3. the difference between last IV mean BAO and last oral mean BAO ($BAO_{LIV}$ vs $BAO_{PO}$).

**Efficacy analyses**

The efficacy endpoints were analyzed for the following three groups of patients:

Intent-to-treat (ITT) - Patients who had at least one MAO measurements in each study period (i.e. $MAO_{PO}$ and either $MAO_{FIV}$ or $MAO_{LIV}$). This population includes patients with protocol violations.

Modified ITT (MITT) - Same as ITT but excludes patients who received an incorrect dose of IV pantoprazole. This population includes any ITT patient with any other protocol violation.

Valid-for-efficacy (VFE) - patients who complied with and completed all aspects of the protocol.

The primary efficacy analysis was conducted for each primary efficacy endpoint to test the hypothesis that the MAO on the last dose of IV pantoprazole treatment ($MAO_{LIV}$) would be no more than 20% greater than that of the last dose of oral pantoprazole ($MAO_{PO}$).

In order to examine the non-inferiority in MAO between the oral and IV formulations of pantoprazole, the primary analysis is to test the null hypothesis ($H_0$): $MAO_{LIV} - 1.2 * MAO_{PO} \geq 0$ versus the alternative ($H_1$): $MAO_{LIV} - 1.2 * MAO_{PO} < 0$ using all three patient populations. For each patient the difference $MAO_{LIV} - 1.2 * MAO_{PO}$ was calculated. The sponsor then. applied

one-sided T, Sign, and Signed-rank tests to test the null hypothesis that the IV is inferior to oral formulations by 20% of $MAO_{PO}$ or more. Separate comparisons were done for the 20 mg and 40 mg groups at a one-sided $\alpha$-level of 0.025 [The sponsor did not set a plan to perform the p-value adjustments for the multiplicity issue.]

A similar procedure was used to compare the $MAO_{FIV}$ with the $MAO_{PO}$, and to compare either $BAO_{FIV}$ or $BAO_{LIV}$ with $BAO_{PO}$. However, these comparisons were declared secondary in the protocol.

**Disposition of Patients:** A total of 65 patients (30 males and 35 females) were enrolled in this study (period 1, oral phase) and are included in the safety population. Two (2) patients discontinued after receiving the first dose of IV pantoprazole but before the $BAO_{FIV}/MAO_{FIV}$ determination.

The numbers of patients included in each of the efficacy analyses during the entire 8-week treatment period are presented in Table 2.1.1 .

**Table 2.1.1 (Sponsor's) Patient Disposition**

| Disposition | Pan[a] 20 mg PO Pan 20 mg IV | Pan 20 mg PO Pbo[b] 20 mg IV | Pan 40 mg PO Pan 40 mg IV | Pan 40 mg PO Pbo 40 mg IV | Total |
|---|---|---|---|---|---|
| Total Enrolled | 26 | 8 | 24 | 7 | 65 |
| ITT | 25 | 8 | 23 | 7 | 63 |
| MITT | 22 | 7 | 21 | 5 | 55 |
| VFE | 21 | 7 | 20 | 5 | 53 |

**a: Pan - Pantoprazole; b: Pbo - placebo.**

As shown in Table 2.1.1, 12 patients had major protocol deviations and were excluded from VFE population: 5 patients from the group of pantoprazole 20 mg PO and pantoprazole 20 mg IV, 4 from pantoprazol 40 mg PO and pantoprazole 40 mg IV, 1 from patoprazole 20 mg PO and placebo 20 mg IV, and 2 from patoprazole 40 mg PO and placebo 40 mg IV. The sponsor indicated that all exclusions were made while the study was still blinded.

The reasons for efficacy exclusions were: discontinuation from the study (3 patients), late $MAO_{PO}$ (1 patient), dosing error-test medication (4 patients), dosing error-pentagastrin (3 patients), and early $MAO_{LIV}$ (1 patient).

**Premature Discontinuations:** The number of patients who discontinued treatment during the study is shown, by the primary reason for their discontinuities, in Table 2.1.2.

**Table 2.1.2 (Sponsor's) Number (%) of Patients Who Discontinued By Primary Reason of Discontinuity**

| | Treatment Group | | | | |
|---|---|---|---|---|---|
| Reason | 20 mg PO Pan[a] 20 mg IV Pan (N=26) | 20 mg PO Pan 20 mg IV Pbo[b] (N=8) | 40 mg PO Pan 40 mg IV Pan (N=24) | 40 mg PO Pan 40 mg IV Pbo (N=7) | Total (N=65) |
| Any reason | 2 (7.7) | 0 | 1 (4.2) | 0 | 3 (4.6) |
| Adverse reaction | 1 (3.8) | 0 | 1 (4.2) | 0 | 2 (3.1) |
| Patient request | 1 (3.8) | 0 | 0 | 0 | 1 (1.5) |

**Source: Sponsor's Table 8.1A. in Volume 177; a: Pan - Pantoprazole; b: Pbo – Placebo.**

[The sponsor did not specify at which phase (oral or IV) the patient discontinued].

## 2.2 Sponsor's Statistical Analysis and Results

### Analysis of Demographics and Other Baseline Characteristics

Instead of performing statistical inferences on the demographic and baseline variables. the sponsor provided descriptive information on Age, Gender, Ethnic Origin, Weight, Height. and Body Mass Index through tables for all patients, ITT, MITT, and VFE patient populations. Based on these tables, the sponsor concluded that the demographic and baseline characteristics of the patients who were evaluable for efficacy did not differ appreciably from those of the total population and the four treatment groups were comparable in demographic characteristics.

Except the Gender and Ethnic Origin in groups pantoprazole 20 mg PO+placebo 20 mg IV and pantoprazole 40 mg PO+placebo 40 mg IV, this reviewer's preview of the data did not suggest disagreement with the sponsor's conclusions.

### Summary of Sponsor's Efficacy Analysis Results

i)Results of Primary Efficacy Analysis

Table 2.2.1 (extracted from sponsor's Table 9.4A in Volume 1.177) summarizes the means of the $MAO_{LIV}$ and $MAO_{PO}$ for the four treatment groups based on intent-to-treat patient data set.

**Table 2.2.1 (Sponsor's) Maximum Acid Output (MAO, mEQ/H)[a]Response By Pantoprazole Dose and Treatment Period: ITT patient data set**

| Treatment Phase / Value | --- Pantoprazole 20 mg --- IV pantoprazole | IV placebo | ----Pantoprazole 40 mg IV Pantoprazole | IV placebo |
|---|---|---|---|---|
| | N= 33 | | N= 30 | |
| Last Day Oral $MAO_{PO}$ | 14.50 ± 15.51 (0.3 - 69.96) | | 6.49 ± 5.62 (0.0 - 20.3) | |
| Last Day IV $MAO_{LIV}$ | N= 25 | n=8 | n= 23 | n=7 |
| | 11.05± 10.22 (0.2 - 46.2) | 30.50 ± 12.80 (13.3 – 50.6) | 6.62 ± 6.34 (0.0 - 23.1) | 29.19 ± 13.01 (6.9 - 48.7) |

**Source: sponsor's Table 9.4A in Volume 1.177; a: Data presented are mean ± SD and range.**

Table 2.2.2. presents the p-values for testing the null hypothesis that $MAO_{LIV}$ was inferior to $MAO_{PO}$ by 20% of $MAO_{PO}$ or more with respect to the two treatment groups (pantoprazole 40 mg PO+pantoprazole 40 mg IV and pantoprazole 20 mg PO+pantoprazole 20 mg IV).

**Table 2.2.2 (Sponsor's) P-values for testing $MAO_{LIV}$ inferior to $MAO_{PO}$ by 20% or more**

| PATIENT POPULATION | TREATMENT GROUP | P-VALUE FOR T TEST | P-VALUE FOR SIGN TEST | P-VALUE FOR SIGNED-RNK TEST |
|---|---|---|---|---|
| Intent-To-Treat | Pan.[1] 40 mg PO+Pan. 40 mg IV | 0.008* | 0.013* | 0.004* |
| | Pan. 20 mg PO+Pan. 20 mg IV | 0.029 | 0.022* | 0.005* |
| Modified Intent-To-Treat | Pan. 40 mg PO+Pan. 40 mg IV | 0.012* | 0.010* | 0.009* |
| | Pan. 20 mg PO+Pan. 20 mg IV | 0.05 | 0.067 | 0.014* |
| Valid-For-Efficacy | Pan. 40 mg PO+Pan. 40 mg IV | 0.009* | 0.004* | 0.006* |
| | Pan. 20 mg PO+Pan. 20 mg IV | 0.074 | 0.095 | 0.026 |

**1. Pan: Pantoprazole; *: Significance under the level of 0.025.**

For pantoprazole 40 mg IV, under significance level of 0.025, Table 2.2.2 indicates that $MAO_{LIV}$ was not inferior to $MAO_{PO}$ by 20% of $MAO_{PO}$ or more for ITT, MITT, and VFE patient groups, using all three tests: T, Sign and Signed-Rank tests (e.g.: p=0.013, 0.010, and 0.004, for ITT, MITT, and VFE patient populations, based on the Sign test). The mean $MAO_{PO}$ was 6.49 mEq/h compared to the mean $MAO_{LIV}$ 6.62 mEq/h for ITT patient data set; similar results were found for MITT and VFE patient populations.

For the 20 mg pantoprazole analysis, under significance level of 0.025, the sponsor's claim of non-inferiority of the 20 mg IV pantoprazole versus 20 mg oral pantoprazole was demonstrated only for the ITT population. However, the non-inferiority was not validated by MITT and VFE patient groups (p=0.067 and p=0.095, respectively, based on the Sign tests; similar results for the T-tests). [For multiplicity p-value adjustments, refer to this reviewer's comment in section 2.3.]

ii.) Secondary Efficacy Analysis

Under significance level of 0.025, the non-inferiority of $BAO_{LIV}$ and $BAO_{PO}$ for pantoprazole 40 mg was established by the VFE (p=0.024) population; however the p-values from ITT and MITT (p=0.027 and 0.047, respectively) did not support the non-inferiority claim.

For 20 mg pantoprazole, the non-inferiority of $BAO_{LIV}$ and $BAO_{PO}$ was established between the oral and IV formulations only for the ITT population (p=0.02); the non-inferiority claim was not concluded for the MITT and VFE populations (p=0.05 and p=0.09, respectively). [See sponsor's Supportive Table 10 through Supportive Table 12 in Volume 1.77 for detail].

**Results of Adverse Events**

The sponsor indicated that the rate of occurrence of treatment-emergent adverse events was similar among all the treatment groups. Headache and dyspepsia were the most common reported adverse experiences for both treatment groups and occurred at a rate similar to or less than that of placebo group. There were no optic-related adverse events of clinical importance or that would indicate optic liability. There were no deaths reported. Three patients were withdrawn from the study; two of which were due to adverse events. No correlation with drug dose and treatment-emergent adverse events was observed. Both doses of pantoprazole were well tolerated.

**2.3 Reviewer's Analyses and Comments**

In order to validate the robustness of the sponsor's efficacy claim, this reviewer conducted the following three analyses for the ITT, MITT, and VFE patient populations: (1.) P-value multiplicity adjustments, (2.) the Bootstrap-t interval technique to analyze the non-inferiority for pantoprazole IV versus Pantoprazole oral and (3.) rank-based regression analysis using $MAO_{PO}$ as a covariate to compare $MAO_{LIV}$ between the pantoprazole IV dose and the pooled placebo groups.

Note, since there was no wash-out period between pantoprazole oral dose and IV infusion, it is expected that MAO for the IV period would represent the effect of pantoprazole IV in addition to carry over effect from pantoprazole oral.

In addition, this reviewer also performs a subgroup analysis by gender and age to assess the internal consistency of the drug effect. The sponsor in their submission, dated 11 17/1998, submitted data used in this analysis.

**(1.) P-value multiplicity adjustments**

In the protocol, the sponsor did not indicate the preference between the two doses 20 mg and 40 mg. This reviewer therefore, applies the Hochberg step-up procedure to adjust the p-values for drug efficacy testing due to two comparisons for treatment groups pantoprazole 20 mg PO+pantoprazole 20 mg IV and pantoprazole 40 mg PO+pantoprazole 40 mg IV with respect to each of the three patient populations ITT, MITT, or VFE. Since the Sign test needs the least assumptions among the three tests, T, Sign, and Signed-Rank tests, this reviewer uses it to test the non-inferiority of pantoprazole IV versus oral and performs multiplicity adjustments on its p-values. Table 2.3.1 presents the results.

**Table 2.3.1 (Reviewer's) P-value multiplicity adjustments**

| PATIENT POPULATION | TREATMENT GROUP | SIGN TEST RAW-P | SIGN TEST ADJ.-P[1] |
|---|---|---|---|
| Intent-To-Treat | Pan.[2] 40 mg PO+Pan. 40 mg IV | 0.013 | 0.022* |
| | Pan. 20 mg PO+Pan. 20 mg IV | 0.022 | 0.022* |
| Modified Intent-T0-Treat | Pan. 40 mg PO+Pan 40 mg IV | 0.010 | 0.020* |
| | Pan. 20 mg PO+Pan 20 mg IV | 0.067 | 0.067 |
| Valid-For-Efficacy | Pan. 40 mg PO+Pan. 40 mg IV | 0.004 | 0.008* |
| | Pan. 20 mg PO+Pan. 20 mg IV | 0.095 | 0.095 |

**1. ADJ.-P: p-value adjusted by Hochberg procedure; 2. Pan.: Pantoprazole;**
***: Significance under the level of 0.025 determined by Hochberg procedure.**

For pantoprazole 40 mg IV, Table 2.3.1 indicates that after Hochberg p-value adjustments, the results for $MAO_{LIV}$ not inferior to $MAO_{PO}$ by 20% of $MAO_{PO}$ or more are established for ITT, MITT, and VFE patient populations. However, for pantoprazole 20 mg IV, the non-inferiority for IV versus oral dose is significant only by ITT patient population and the adjustment p-values for MITT and VFE, 0.067 and 0.095, are much larger than the significance level 0.025, indicating an unstable significant result of ITT population.

**(2.) Bootstrap-t interval analysis and results**

Due to the following two reasons, this reviewer applies the Bootstrap-t interval technique (Efron, Bradley and Tibshirani, J. Robert (1993), " An Introduction to the Bootstrap". Chapman and Hall) with 1000 Bootstrap loops to develop 95% and 97.5% two-sided confidence intervals for the primary endpoint, $MAO_{LIV}$ - 1.2 * $MAO_{PO}$, to explore the non-inferiority of pantoprazole IV versus pantoprazole oral:

i. a small sample size for treatment group pantoprazole 40 mg PO+pantoprazole 40mg IV (23 patients for ITT population), and
ii. a skew primary endpoint distribution for treatment group pantoprazole 20 mg PO+pantoprazole 20mg IV (skewness = –3.6, -3.9, and –4.0, for ITT, MITT, and VFE populations, respectively).

The upper levels for 95% and 97.5% two-sided confidence intervals are equivalent to the one-sided tests, with significance levels of 0.025 and 0.0125, respectively, for the null hypothesis that $MAO_{LIV}$ is inferior to $MAO_{PO}$ by 20% of $MAO_{PO}$ or more.

Since the analysis of Bootstrap-t interval is employed to assess the robustness of the non-inferiority for pantoprazole IV versus pantoprazole oral, this reviewer does not apply the Hochberg procedure to adjust the p-values for the multiplicity issues.

Table 2.3.2 presents the results of the 95% two-sided confidence intervals using Bootstrap-t interval technique for the non-inferiority of pantoprazole IV versus pantoprazole oral by patient population and treatment group.

**Table 2.3.2 (Reviewer's) The 95% two-sided confidence intervals for $MAO_{LIV}$ - 1.2*$MAO_{PO}$ developed by the Bootstrap-t interval method**

| PATIENT POPULATION | TREATMENT GROUP | 95% TWO-SIDED CONFIDENCE INTERVALS LOWER BND.[2] | UPPER BND. |
|---|---|---|---|
| Intent-To-Treat | Pan.[1] 40 mg PO+Pan. 40 mg IV | -2.52 | -0.173 |
| | Pan. 20 mg PO+Pan. 20 mg IV | -120.0 | 13.15 |
| Modified Intent-T0-Treat | Pan. 40 mg PO+Pan. 40 mg IV | -2.67 | -0.040 |
| | Pan. 20 mg PO+Pan. 20 mg IV | -11.82 | 16.99 |
| Valid-For-Efficacy | Pan. 40 mg PO+Pan. 40 mg IV | -2.78 | -0.139 |
| | Pan. 20 mg PO+Pan. 20 mg IV | -12.05 | 21.14 |

1. Pan.: Pantoprazole; 2. BND.: Bound.

Table 2.3.2 indicates that the upper bounds for treatment pantoprazole 40 mg PO+pantoprazole 40 mg IV are less than zero for ITT, MITT, and VFE populations (upper bound= -0.173, -0.040, and –0.139, respectively). Therefore, the raw p-values for testing the non-inferiority of the pantoprazole 40 mg IV versus pantoprazole 40 mg oral by 20% of $MAO_{PO}$ or more are less than 0.025.

On the contrary, the upper bounds for treatment pantoprazole 20 mg PO+pantoprazole 20 mg IV are greater than zero for ITT, MITT, and VFE populations (upper bound=13.15, 16.99, and 21.4, respectively). Thus, the efficacy of the treatment pantoprazole 20 mg is inferior to pantoprazole 20 mg oral by 20% of $MAO_{PO}$ or more under the significance level of 0.025.

Since the efficacy of pantoprazole 20 mg IV is inferior to pantoprazole 20 mg oral by 20% of $MAO_{PO}$ or more assessed by 95% two-sided confidence intervals, the 97.5% two-sided confidence intervals were used only to assess the robustness of the non-inferiority of pantoprazole 40 mg IV versus pantoprazole 40 mg oral. Table 2.3.3 presents the results of the 97.5% two-sided Bootstrap-t intervals for the difference between $MAO_{LIV}$ and 1.2 * $MAO_{PO}$.

**Table 2.3.3 (Reviewer's) The 97.5% two-sided confidence intervals for $MAO_{LIV}$-1.2* $MAO_{PO}$ developed by the Bootstrap-t interval method**

| PATIENT POPULATION | TREATMENT GROUP | 95% TWO-SIDED CONFIDENCE INTERVALS LOWER BND.[2] | UPPER BND. |
|---|---|---|---|
| Intent-To-Treat | Pan.[1] 40 mg PO+Pan. 40 mg IV | -2.68 | 0.05 |
| Modified Intent-T0-Treat | Pan. 40 mg PO+Pan. 40 mg IV | -2.87 | 0.28 |
| Valid-For-Efficacy | Pan. 40 mg PO+Pan. 40 mg IV | -2.97 | 0.12 |

1. Pan.: Pantoprazole; 2. BND.: Bound.

Table 2.3.3 shows that the upper bounds calculated by Bootstrap-t interval techniques for ITT, MITT, and VFE populations are all greater than zero (upper bounds=0.05, 0.28, and 0.12, respectively). Thus, the non-inferiority of the effect pantoprazole 40 mg IV versus pantoprazole 40 mg oral by 20% of $MAO_{PO}$ or more was not significant under the significance level of 0.0125. Combined with the results from Table 2.3.2, the p-values for testing the non-inferiority of the

effect pantoprazole 40 mg IV versus pantoprazole 40 mg oral by 20% of $MAO_{PO}$ or more are less than 0.025 and greater than 0.0125 for ITT, MITT, and VFE populations.

**(3.) Rank-based linear regression analysis and results**

In this subsection, this reviewer applies the Dispersion test in the rank-based linear regression analysis using $MAO_{PO}$ as a covariate to compare $MAO_{LIV}$ between the pantoprazole 40 mg IV dose and the pooled placebo groups to assess the efficacy for pantoprazole 40 mg IV versus placebo. The purpose of this analysis is to further validate the non-inferiority of pantoprazole IV versus oral by the comparisons of pantoprazole IV versus placebo IV. Since the pantoprazole 20 mg IV is considered to be inferior to pantoprazole 20 mg oral by 20% of $MAO_{PO}$ or more, the efficacy for pantoprazole 20mg IV versus placebo is not performed here.

Table 2.3.4 presents the results for the comparisons of $MAO_{LIV}$ between pantoprazole IV 40 mg and placebo, using rank-based linear regression analysis with $MAO_{PO}$ as a covariate.

**Table 2.3.4 (Reviewer's) P-values for the comparisons of $MAO_{LIV}$ between Pantoprazole 40 mg IV and Placebo groups based on rank-based regression analysis**

| PATIENT POPULATION | P-VALUE FOR PANT.[1] 40 MG IV VS. PLACEBO |
|---|---|
| Intent-To-Treat | <0.001* |
| Modified Intent-To-Treat | <0.001* |
| Valid-For-Efficacy | <0.001* |

**1. PANT.: Pantoprazole; *: Significance under the level of 0.025.**

Table 2.3.4 indicates that the efficacy of treatment pantoprazole 40 mg IV is superior to placebo for ITT, MITT, and VFE patient populations (P<0.001).

**4. Subgroup Analysis**

To assess the consistency of results across subgroups, this reviewer also performed some subgroup analyses for the subgroups listed below.

**Gender**

Table A.1.1 in Appendix I presents this reviewer's gender analysis results for the comparisons of treatment effects.

The results are briefly summarized below:

- The subgroup results indicate at least a positive trend for the male and the female in favor of pantoprazole IV non-inferior to pantoprazole oral by 20% of $MAO_{PO}$ or more.

**Age**

Table A.1.2 in Appendix I presents this reviewer's age group analysis results (age ≤ 45 and age > 45) for the comparisons of treatment effects.

The results are briefly summarized below:

- The subgroup results indicate a significant treatment effect for the lower age group in favor of pantoprazole IV non-inferior to pantoprazole oral by 20% of $MAO_{PO}$ or more. Results for both subgroups however, are not inconsistent, given the small sample size.

**2.4 Comments/Conclusions of treatment effects**

- The effect of pantoprazole 40 mg IV [which might include the carry-over effect from pantoprazole 40 mg oral] is not inferior to pantoprazole 40 mg oral by 20% of $MAO_{PO}$ or more based on ITT, MITT, and VFE patient populations, under the significance level of 0.025.
- The p-values for testing the non-inferiority of the effect pantoprazole 40 mg IV [which might include the carry-over effect from the pantoparzole 40 mg oral] versus pantoprazole 40 mg oral by 20% of $MAO_{PO}$ or more are less than 0.025 and greater than 0.0125 based on ITT. MITT, and VFE patient populations, using Bootstrap-t interval analysis.
- The effect of pantoprazole 20 mg IV [which might include the carryover effect from the pantoparzole 20 mg oral] is inferior to pantoprazole 20 mg oral by 20% or more under significance level of 0.025.

## 3.0 SUPPORTIVE STUDIES

### 3.1 Background Information

**Design**

The designs for the two efficacy studies, BAT010 and FK3050, performed by Byk Gulden, directly examined oral plus IV administration of pantoprazole in the healing of lesions in patients with GERD. Table 3.1.1 summarizes the main features of these two studies.

Table 3.3.1 (Sponsor's) Byk Gulden Healing Studies

| Study No. | Patient Population No. of patients VFE (ITT) | Pantoprazole Regimen | Endpoints |
|---|---|---|---|
| BAT010 | GERD II-III 98 (110) | Pantoprazole lyophile, 40 mg qd as slow injection over 4 minutes, 5 to 7 days, then pantoprazole enteric-coated tablet, 40 mg qd, 3 or 7 weeks, depending on healing (4 or 8 weeks total) | 1. Healing 2. Symptom relief |
| FK3050 | GERD II-III 142 (176) | Pantoprazole lyophile, 40 mg qd as slow injection over 15 minutes, 5 to 7 days, then pantoprazole enteric-coated tablet, 40 mg qd, 3 or 7 weeks, depending on healing (4 or 8 weeks total) | 1. Healing 2. Symptom relief |

These two multi-center studies had identical designs except that pantoprazole IV (lyophile formulation) was administered as a slow injection over 4 minutes in Study BAT010 and as a 15-minute infusion in Study FK3050. Briefly, patients with endoscopically diagnosed erosive esophagitis, grade II or III according to the Savary-Miller system, and typical symptoms of GERD were given a baseline endoscopic examination on the day before the first IV dose. All patients had endoscopic examinations after 4 weeks of treatment (5 or 7 days for IV injection, then 3 for oral tablets). For those patients whose esophageal lesions were not completely healed, treatment with oral pantoprazole continued and another endoscopic examination was performed after 8 weeks of treatment.

**Assessment of Symptom Relief**

The intensity of the 3 primary symptoms of GERD, acid eructation, heartburn, and pain on swallowing, was recorded in each patient's CRF as mild, moderate, or severe. The patient's assessment of these symptoms was recorded for the preceding 24 hours at each visit for IV

pantoprazole administration and at each of the follow-up visits at biweekly intervals.

### 3.2 Sponsor's Statistical Methods and Results

Data from two oral-only studies (FK3005 and FK3009) performed earlier in which patients with erosive esophagitis (grade II or III) received 40 mg oral pantoprazole daily for 4 or 8 weeks. were pooled for the purpose of statistical comparison. The sponsor indicated that the designs of the oral studies were essentially identical to those of the IV+oral studies [Here, + means followed by] , except that the oral studies were double-blind and had groups receiving active comparator. In addition, in Study FK3009, antacids were dispensed to be taken for symptomatic relief as needed. The sponsor claimed that the patient populations for the two IV+oral studies were similar to that of the pooled oral-only study performed approximately 4 years earlier. [This reviewer did not have data to assess the similarities of the demographic populations and baseline characteristics among the four studies: BAT010, FK3050, FK3005, and FK3009]

The sponsor claimed that the main comparison between the healing rates in the oral and the IV+oral studies was at 4 weeks for the VFE population. For both 4- and 8-week rates, the sponsor applied two-sided 95% and 90% confidence intervals (CI) on the difference of the two treatment healing rates to test the equivalence on the esophageal lesion healing rates between the oral-only (Pooled Study FK3005+FK3009) and the IV+oral (Studies BAT010 and FK3050) treatments. [Note: unlike Study# 3001K1-309-US, the two-sided 90% CI was also used here]. If the lower bound of the 90% CI of the two treatment healing rate difference was greater than –15%, then the two treatments IV+oral and oral-only was declared equivalent. [Note: the sponsor actually tested the non-inferiority of treatments IV+oral versus oral only]. However, for the secondary endpoint, symptom relief, the sponsor did not perform statistical inference as for the primary endpoint.

Table 3.2.1 presents the results of the esophageal lesion healing rates for the two IV+oral studies, BAT010 and FK3050. and the pooled oral-only study, FK3005+FK3009.

**Table 3.2.1 Healing Rates Of Esophageal Lesions By the Treatment Groups for the VFE and ITT populations**

| Byk Gulden Study No. | Route of Administration | No. Pts.[a] | % Healing at 4 Weeks[a] | % Healing at 8 Weeks[a] |
|---|---|---|---|---|
| BAT010 | IV + oral | 98 (110) | 87 (77) | 95 (85) |
| FK3050 | IV + oral | 142 (176) | 80 (65) | 93 (75) |
| FK3005 + FK3009 | Oral only | 319 (357) | 72 (64) | 86 (77) |

**a: Both the VFE (and ITT) populations are shown for number of patients and healing rates.**

Table 3.2.1 indicates that the estimate of the difference between Study BAT010 and Pooled Study FK3005+FK3009 in 4-week healing rates using VFE populations was 15%. with CIs ranging from 7 to 23% at the 95% confidence level and 8 to 22 % at the 90% confidence level.

Similarly, the estimate of the difference between Study 3050 and Pooled Study FK3005+FK3009 in 4-week healing rates using VFE populations 8%, with CIs ranging from 0 to 17% at the 95% confidence level and 2 to 15 % at the 90% confidence level.

The sponsor concluded that the efficacy of the IV+oral regimen was shown to be at least equivalent to the oral-only dosage form.

### 3.3 Reviewer's Comments

This reviewer will comment on the following two issues with regard to the efficacy information provided by the supportive studies:

- The clinical efficacy equivalent analysis;
- The drug regimen and primary endpoint.

- **Issue on the clinical equivalence analysis**

The asymptotic 95% confidence interval of the treatment difference on the healing rates for the Study BAT010 versus pooled Study FK3005+FK3009 using VFE populations shows that the lower bound (7%) was greater than -15%, the pre-specified clinical delta, and the upper bound (23%) is greater than 15%. Similarly, for Study FK3050 versus pooled Study FK3005+FK3009, the 95% lower bound (0%) was greater than –15% and the upper bound (17%) was greater than 15%. Therefore, based on these results, one should only declare that the healing rate of the pantoprazole lyophile 40 mg IV+Oral was not inferior to that of the pantoprazole 40 mg oral-only by 15% or more.

- **Issues on the drug regimen and primary endpoint for the supportive studies**

In the supportive studies BAT 010 and FK 3050, the primary efficacy endpoint was the esophageal lesion healing rates following treatment with pantoprazole IV 40 mg for 5-7 days in the first period and pantoprazole tablet 40 mg (oral) for 3 or 7 weeks (depending on healing) in the second period. These results were then, compared to data from pooled studies FK3005 and FK3009, in which pantoprazole was only given in tablet form (PO). However, the primary endpoint for the pivotal study, Study#3001K1-309-US, was the comparison of the mean MAO following the last dose of oral pantoprazole in the first period with that after the last dose of IV pantoprazole in the second period. Thus, there are two issues embedded in the supportive studies:

i) the drug regimen and
ii) the primary efficacy endpoints.

The medical reviewer, Dr. Gallo-Torres, indicated that the primary endpoint, esophageal lesion healing rates. in the supportive studies is a clinical parameter and preferred to the pharmacodynamics parameter, maximal acid output, used in the pivotal study.

However, according to the medical officer, the drug regimen, first period IV ingestion then followed by oral tablet, of the supportive studies is different from that, first period oral tablet then followed by IV injection, of the pivotal study. Therefore, the reviewing medical officer does not recommend to use the efficacy results from the supportive studies to support the indication of pantoprazole IV for short-term gastric acid suppression in GERD patients who are unable to take oral medication.

### 3.4 Conclusions on the supportive studies

- The healing rate of the pantoprazole lyophile 40 mg IV+Oral was not inferior to that of the pantoprazole 40 mg oral-only by 15% or more, under significance level of 0.025. However, these studies were not prospectively designed to assess the efficacy between treatments IV+oral and oral-only.
- Due to different drug regimen between pivotal study and supportive studies, the efficacy results from the supportive studies are not recommended to support the indication of pantoprazole IV for short-term gastric acid suppression in GERD patients who are unable to take oral medication.

## 4.0 OVERALL CONCLUSIONS

- The sponsor's primary analysis in the Study# 3001K1-309-US showed that the effect of pantoprazole 40 mg IV [which might include the carry-over effect from pantoprazole 40 mg oral] is not inferior to pantoprazole 40 mg oral by 20% of $MAO_{PO}$ or more based on ITT, MITT, and VFE patient populations, under the significance level of 0.025.
- The robustness of the sponsor's results for testing the non-inferiority of the effect pantoprazole 40 mg IV versus pantoprazole 40 mg oral by 20% of $MAO_{PO}$ or more is also demonstrated by this reviewer's Bootstrap-t interval analysis indicating the exact p-values are in the range of 0.0125 and 0.025, based on ITT, MITT, and VFE patient populations.
- The null hypothesis that the effect of pantoprazole 20 mg IV [which might include the carryover effect from the pantoparzole 20 mg oral] is inferior to pantoprazole 20 mg oral by 20% or more can not be rejected under the significance level of 0.025.
- Based on the supportive studies, the healing rate of the pantoprazole lyophile 40 mg IV+Oral was not inferior to that of the pantoprazole 40 mg oral-only by 15% or more, under significance level of 0.025.
- Due to different drug regimen between pivotal study and supportive studies, the efficacy results from the supportive studies may not support the indication of pantoprazole IV for short-term gastric acid suppression in GERD patients who are unable to take oral medication.
- Only one pivotal study (Study# 3001K1-309-US) was submitted by the sponsor and the p-values for testing the non-inferiority of the effect pantoprazole 40 mg versus pantoprazole 40 mg oral by 20% of $MAO_{PO}$ or more are between 0.0125 and 0.025. Following Goodman, S. "A Comment on Replication, p-Values and Evidence" Statistics in Medicine, Vol. 11, 875-

879 (1992), the probability of a statistically significant results ($p<0.05$) in a hypothetically duplicated experiment may be as low as 60%.

- In conclusion, since the p-values for the efficacy analyses of the single pivotal study are not statistically persuasive and the supportive studies are not recommended to uphold the intended indication, the sponsor may need to submit another study to confirm the non-inferiority of pantoprazole 40 mg IV versus pantoprazole 40 mg oral by 20% of $MAO_{PO}$ or more. However, the clinical importance of the efficacy results needs to be judged by the medical division.

/S/

Wen-Jen Chen Ph.D.,
Mathematical Statistician

Concur: Dr. Alosh 6/7/99

Dr. Welch 6/7/99

cc: Archival NDA# 20-988
HFD-180 Div File
HFD-180/Dr. Talarico
HFD-180/Dr. Gallo-Torres
HFD-180/Ms. Walsh
HFD-715/Dr. Nevius
HFD-715/Dr. Welch
HFD-715/Dr. Alosh
HFD-715/Dr. Chen
HFD-715/File Copy

This review contains 21 pages of text and tables.

# Appendix A Inclusion and Exclusion Criteria For Study# 3001K1-309-US

**Inclusion Criteria:**

- Signed informed consent form.
- Men or nonpregnant, nonlactating women, aged 18 to 65 years inclusive.
- Women of childbearing potential were required to use a medically acceptable method of contraception. A woman of childbearing potential was defined as a woman who was biologically capable of becoming pregnant—this included women who were single and women whose sexual partners had been vasectomized. Medically acceptable contraception included oral or injectable/implantable, or mechanical devices (e.g., diaphragms, condoms).
- Had a history of erosive esophagitis documented by endoscopy and a previous diagnosis of GERD.
- Were receiving treatment with acid suppressants (i.e., H2 antagonists or proton pump inhibitors) or antacids.
- Had clinical laboratory values within the normal limits of the investigator's laboratory and normal results for a 12-lead electrocardiogram (ECG), unless the investigator documented that the deviations were not clinically important or were directly related to an allowable pre-existing medical condition.
- Patients have a high probability for compliance and completion of the study.

**Exclusion Criteria:**

- Presence on screening endoscopy of obstructive esophageal strictures.
- Presence on screening endoscopy of esophageal diverticuli.
- Presence on screening endoscopy of esophageal varices.
- Presence on screening endoscopy of Barrette's esophagus greater than 3 cm or with high-grade dysphasia.
- Presence on screening endoscopy of active gastric, pyloric channel, or duodenal ulcer.
- History of ZES or mastocytosis.
- History or high suspicion of scleroderma or other connective tissue disorder.
- History or high suspicion of achalasia.
- Previous surgery of the esophagus and/or upper gastrointestinal tract; appendectomy, cholecystectomy, or colonic polypectomy are permitted.
- Unstable cardiovascular, pulmonary, or endocrine disease; clinically important renal or hepatic disease or dysfunction; hematological, neurologic and psychiatric disorder; any clinically important medical condition. including malignancy (except for successfully resected basal cell skin cancer) that could increase the risk to the study participants. Certain patients with chronic stable medical conditions (e.g., mild renal or hepatic dysfunction, essential hypertension, etc.) were permitted to enroll in the study on a case by case basis after documentation of W-AR medical monitor approval.
- Chronic use of systemic glucocorticoids within 1 month of study day 1.
- Use of nonsteroidal anti-inflammatory agents (other than daily low-dose aspirin or cardiovascular protection) within 1 week of study day 1.
- Simultaneous use of drugs with pH-dependent absorption (e.g., ketoconazole, ampicillin esters, iron salts) within 1 week of study day 1.
- Diets that may alter metabolism; chronic use of therapeutic vitamin B12 injections.
- Unable to tolerate a nasogastric (NG) or orogastric tube.
- Consumption of green leafy vegetables within 12 hours before NG tube placement.
- History of any significant allergic condition or drug-related hypersensitivity.
- Any surgical or medical condition that might interfere with the absorption, distribution, metabolism, or excretion of pantoprazole.
- History of, or treatment for, alcohol abuse within the past year; consumption of alcoholic beverages within 24 hours of gastric acid measurements.

## Appendix A Inclusion and Exclusion Criteria For Study# 3001K1-309-US (Continue)

**Exclusion Criteria:**

- Drug abuse within the past year; positive findings on urine drug screen.
- Exposure to any other investigational or recreational drug use within 1 month of pantoprazole administration. Exception: patients completing an ongoing W-AR-sponsored study of oral pantoprazole could be enrolled immediately without the 1 month clinical trial exclusion.
- Presence of any acute disease state (e.g., infection, nausea, diarrhea) within 2 weeks of study day 1; clinically significant weight loss or gain within 1 month before study day 1.
- Positive result for occult blood in stool (prestudy evaluation only).

# APPENDIX I

**Table A.1.1 (Reviewer's) P-values for testing $MAO_{LIV}$ inferior to $MAO_{PO}$ by 20% or more By Gender**

**Female**

| PATIENT POPULATION | TREATMENT GROUP (N) | SIGN TEST | P-VALUE FOR SIGN TEST |
|---|---|---|---|
| Intent-To-Treat | Pant.[1] 40 mg PO+Pant. 40 mg IV (12) | -2.0 | 0.17 |
| | Pant. 20 mg PO+Pant. 20 mg IV (15) | -2.5 | 0.15 |
| Modified Intent-T0-Treat | Pant. 40 mg PO+Pant. 40 mg IV (12) | -2.0 | 0.17 |
| | Pant. 20 mg PO+Pant. 20 mg IV (13) | -1.5 | 0.29 |
| Valid-For-Efficacy | Pant. 40 mg PO+Pant. 40 mg IV (11) | -2.5 | 0.090 |
| | Pant. 20 mg PO+Pant. 20 mg IV (13) | -1.5 | 0.29 |

**Male**

| PATIENT POPULATION | TREATMENT GROUP (N) | SIGN TEST | P-VALUE FOR SIGN TEST |
|---|---|---|---|
| Intent-To-Treat | Pant.[1] 40 mg PO+Pant. 40 mg IV (11) | -3.5 | 0.033 |
| | Pant. 20 mg PO+Pant. 20 mg IV (10) | -3.0 | 0.055 |
| Modified Intent-T0-Treat | Pant. 40 mg PO+Pant. 40 mg IV (9) | -3.5 | 0.020* |
| | Pant. 20 mg PO+Pant. 20 mg IV (9) | -2.5 | 0.090 |
| Valid-For-Efficacy | Pant. 40 mg PO+Pant. 40 mg IV (9) | -3.5 | 0.020* |
| | Pant. 20 mg PO+Pant. 20 mg IV (8) | -2.0 | 0.14 |

*: [1]: Significance under the level of 0.025.

**Table A.1.2 (Reviewer's) P-values for testing $MAO_{LIV}$ inferior to $MAO_{PO}$ by 20% or more By Age Group**

**Age > 45**

| PATIENT POPULATION | TREATMENT GROUP (N) | SIGN TEST | P-VALUE FOR SIGN TEST |
|---|---|---|---|
| Intent-To-Treat | Pant.[1] 40 mg PO+Pant. 40 mg IV (11) | 0.5 | 0.5 |
| | Pant. 20 mg PO+Pant. 20 mg IV (10) | 0.0 | 0.5 |
| Modified Intent-T0-Treat | Pant. 40 mg PO+Pant. 40 mg IV (10) | 0.0 | 0.5 |
| | Pant. 20 mg PO+Pant. 20 mg IV (9) | 0.5 | 0.5 |
| Valid-For-Efficacy | Pant. 40 mg PO+Pant. 40 mg IV (9) | -0.5 | 0.5 |
| | Pant. 20 mg PO+Pant. 20 mg IV (9) | 0.5 | 0.5 |

**Age ≤ 45**

| PATIENT POPULATION | TREATMENT GROUP (N) | SIGN TEST | P-VALUE FOR SIGN TEST |
|---|---|---|---|
| Intent-To-Treat | Pant.[1] 40 mg PO+Pant. 40 mg IV (12) | -6.0 | 0.0002* |
| | Pant. 20 mg PO+Pant. 20 mg IV (15) | -5.5 | 0.0037* |
| Modified Intent-T0-Treat | Pant. 40 mg PO+Pant. 40 mg IV (11) | -5.5 | 0.0005* |
| | Pant. 20 mg PO+Pant. 20 mg IV (13) | - 4.5 | 0.011* |
| Valid-For-Efficacy | Pant. 40 mg PO+Pant. 40 mg IV (11) | -5.5 | 0.0005* |
| | Pant. 20 mg PO+Pant. 20 mg IV (12) | -4.0 | 0.019* |

*: *: Significance under the level of 0.025.

**INFORMATION REQUEST** **September 9, 1998**

**NDA: 20-988**
**Sponsor**: Wyeth-Ayerst Research
**Drug**: Protonix I.V. (sterile pantoprazole sodium)
**Indication**: Short-term gastric acid suppression in gastroesophageal reflux disease patients who are unable to take oral medication.

Dear Ms. Walsh:

In order to continue the review for Drug Protonix I.V. (NDA 20-988), please request the sponsor to provide the following information for Study# 3001K1-309-US.

I. Please create a data set with the following variables :

PROTOCOL - Protocol number.
PATID - Patient identification number.
SEXTXT - F for Female; M for Male.
Age - Patient age at baseline (Unit: Years) .
Weight (cm)
Height (kg)
RANDNO - Patient randomization number.
INVESTID - Investigator ID.
ITT - Y if patient was intent-to-treat ; N otherwise.
MITT - Y if patient was modified intent-to-treat defined in sponsor's document; N otherwise.
VFE - Y if patient was valid-for-efficacy analysis defined in sponsor's document; N otherwise.
EXCOV - Y if patient was excluded from the analysis of covariance described in Section 6.7.1.2; N otherwise.
TRT - Treatment group code: 1 for Pantoprazole 20 mg Oral and Pantoprazole 20 mg IV;
2 for Pantoprazole 20 mg Oral and Placebo, 20 mg IV;
3 for Pantoprazole, 40 mg Oral and Pantoprazole, 40 mg IV; and
4 for Pantoprazole, 40 mg Oral and Placebo, 40 mg IV.
Antacidu - Antacid use: Yes or No.
Antacidp - Percentage of days antacid used during oral and IV treatment phases.
$MAO_{PO}$ - Maximum acid output (MAO) determined after the last oral dose of Pantoprazole.
$MAO_{LIV}$ - MAO determined after the last IV dose of Pantoprazole or placebo.
$MAO_{FIV}$ - MAO determined after the first IV dose of Pantoprazole or placebo.
$BAO_{PO}$ - Basal acid output (BAO) determined after the last oral dose of Pantoprazole.
$BAO_{LIV}$ - BAO determined after the last IV dose of Pantoprazole or placebo.
$BAO_{FIV}$ - BAO determined after the first IV dose of Pantoprazole or placebo.

Leave one space between two adjacent variables.

II. Please provide the SAS programs used to perform the efficacy statistical analyses, for data sets from the three types of populations (ITT, MITT, and VFE), described in the section 6.7.1.1 - Comparisons within dose groups and section 6.7.1.2 - Comparisons across dose groups of the sponsor's volume 1.177. The above SAS programs should be modified to read data from the file defined by request I.

III. A diskette with data set defined in request I and the sponsor's SAS programs specified in request II should be submitted to the agency.

Wen-Jen Chen Ph.D.,
Mathematical Statistician

cc: Original NDA 20-988

HFD-180/Dr. Gallo-Torres
HFD-720/Dr. Sankoh
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