CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20988

MEDICAL REVIEW

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

MAY 28 1999

NDA:	20-988
Sponsor:	Wyeth-Ayerst Labs. Inc. Philadelphia, PA
Drug:	PROTONIX™ I.V. (sterile pantoprazole sodium)
Formulation:	PROTONIX I.V. is supplied as a freezed-dried powder for reconstitution in a 40 mg/vial strength. The freeze-dried powder is readily reconstituted with 10 ml of 0.9% sodium chloride injection, USP
Pharmacological Category:	Gastric Acid Antisecretory; Anti-GERD, Anti-Ulcer Inhibitor of the H^+-K^+/ATPase
Proposed Indication:	Short-term gastric acid suppression in GERD patients who are unable to take oral medication
Material Submitted/Reviewed:	a) Parts of Item 5: Nonclinical Pharmacology and Toxicology (vol. 1.010 to 1.047) b) Item 6: Human Pharmacokinetics and Bioavailability (vol. 1.048 to 1.089) c) Item 8: Clinical (vol. 1.091 through 1.178) d) Item 10: Statistical (vol. 1.172 to 1.178) e) Item 11: Case Report Tabulations (Electronic File) f) Item 12: Case Report Forms (Electronic File) In addition: Item 1 (Index, vol. 1.001) Item 2 (Labeling, vol. 1.001) Item 3 (Application Summary, vol. 1.002)
Reviewer:	Hugo E. Gallo-Torres, M.D., Ph.D.

EXECUTIVE SUMMARY

Wyeth-Ayerst Laboratories, Inc. has submitted NDA 20-988 and requested approval of PROTONIX™ I.V., a sterile formulation of the proton pump inhibitor pantoprazole sodium, 40 mg once-a-day for the short-term (up to 7 days) gastric acid suppression in GERD patients who are unable to take oral medication. In support of this request, the sponsor has submitted data from two well-designed and apparently well-executed clinical trials using pharmacodynamic response (inhibition of gastric acid secretion) as the main parameter of efficacy. In one trial (-309-US) the study population consisted of erosive esophagitis patients; gastric acid secretion was stimulated by subcutaneous administration of maximally stimulating doses of pentagastrin (6 μg/Kg/h). This secretogue was given after the last day of oral and the first and last days of I.V. dosage. Whether using maximal acid output (MAO) or basal acid output (BAO) as the PD parameter of comparison, equivalence on inhibition of AO on the last day of 40 mg I.V. PANTO to the last day of oral PANTO (40 mg; the dose found to be safe and effective for healing of erosive esophagitis and resolution of symptoms associated with GERD) was established; 20 mg PANTO I.V. was not consistently equivalent to the 40 mg PANTO PO.

The second trial (-100-US) was carried out in apparently healthy volunteers in whom gastric acid secretion was **submaximally** stimulated by continuous I.V. infusion of pentagastrin (1 μg/Kg/h at a rate of 10 ml/h). PD parameters evaluated included onset, duration and magnitude of response of acid output, cumulative AO and gastric pH over time. The 40 mg PANTO I.V. was at least as effective than the 40 mg PANTO PO. The 20 mg PANTO I.V. was less effective than the 40 mg PANTO I.V. Safety was similar to that of the control groups in these two trials.

It is concluded that the intravenous dose of 40 mg PANTO demonstrates the same [equipotent/equivalent] antisecretory effects as the 40 mg oral PANTO formulation. The 40 mg I.V. once-a-day dose of the drug can maintain the same degree of antisecretory activity already obtained after a 7-day regimen of 40 mg PO.

Approval of I.V. PANTO 40 mg once-a-day is recommended. This I.V. form of the drug is to be used as an alternate to 40 mg oral PANTO per day in those erosive esophagitis patients who are unable to take oral medication. This is a significant unmet medical need.

TABLE OF CONTENTS

I. BACKGROUND INFORMATION/SCIENTIFIC RATIONALE

PANTOPRAZOLE (PANTO; PROTONIX™) would be the fourth proton pump inhibitor (PPI) to be introduced in the U.S. and abroad. An oral form of PANTO (enteric coated tablets) is presently under reivew (NDA 20-987) for approval for the short-term treatment of erosive esophagitis (EE) associated with gastroesophageal reflux disease (GERD). Based on the review of the evidence, the MO (Hugo E. Gallo-Torres, MOR of April 9, 1999) has recommended[1] approval of a regimen of 40 mg once-a-day PANTO for the short-term treatment (4 to 8 weeks) of EE and the relief of daytime and nighttime heartburn and regurgitation associated with GERD. The scientific rationale behind the use of oral PANTO in the treatment of EE is the ability of this PPI to inhibit both basal and stimulated acid secretion irrespective of the stimulus. This pronounced PD effect is important because, although associations do not necessarily establish cause-to-effect relationship, EE is nearly always associated with reflux of gastric acid contents into the esophagus and the consensus is that acid causes esophagitis, although other causes, such as reflux of biliary secretions, need to be considered under certain clinical conditions. It follows that the major rationale for the use of orally administered PANTO in the treatment of EE is its well-documented antisecretory effect.

PANTO shares these antisecretory properties with the two approved PPIs [omeprazole (PRILOSEC®) and lansoprazole (PREVACID®)] and an approvable PPI [rabeprazole (ACIPHEX®)]. PPIs suppress gastric acid secretion by inhibiting the enzyme H^+/K^+-ATPase. This exzyme, the proton pump which exchanges luminal hydrogen ions, and constitutes the final common pathway of gastric acid secretion, is abundant in the gastric mucosa where it is involved with the acid-producing parietal cell. After binding to this enzyme irreversibly, PANTO inactivates it and thereby abolishes response to all types of acid secretion stimulation. This profound and long lasting (>24h) PD effect results in a reduction of the potency of the refluxed material. The propensity for reflux is likewise reduced by a significant decrease in gastric volume; acid refluxed into the esophagus would otherwise be injurious to the esophageal mucosa. In addition, an increase in pH (to >4) favors the inactivation of pepsin, a proteolytic enzyme produced by the oxynthic cells of the stomach which, somehow, contributes to esophageal mucosal damage. Normal salivary flow may facilitate the neutralization of the reduced total output and acid concentration and esophageal motility may hasten the removal of the refluxed gastric contents.[2]

Through the present NDA (20-988), the sponsor is seeking approval of a parenteral (intravenous=i.v.) form of PANTO. This intravenous formulation is intended for short-term use to suppress gastric acid secretion in EE patients that are unable to take oral medication. This i.v. formulation is expected to act through the same mechanism of action than that proposed for the orally administered material, described in detail above. The proposed i.v. dose is 40 mg once-a-day. To be declared effective, this dose of intravenously administered PANTO should produce

---

[1] This recommendation is based on results of two well-designed and well-controlled trials: Study –300-US [comparing three dose levels of the drug, 10, 20, or 40 mg/day to placebo (PL)] and –301-US [comparing 20 or 40 mg PANTO to the recommended dose/regimen of nizatidine, 150 mg twice-a-day].

[2] Based on the available evidence, orally administered PANTO does not seem to have an influence on other pathophysiological factors (decreased LES pressure, inefficiency of esophageal clearance, motility-antimotility effects, decreased resistance of the esophageal tissue to injury, ability of the esophageal tissue to repair, etc.) known to play a role in determining whether a patient with GER (gastroesophageal reflux) will have esophagitis.

the same or reasonably similar PD response to that observed with the 40 mg oral PANTO per day, the dose recommended for approval for the short-term treatment (up to 8 weeks) of EE and the relief of daytime and nighttime heartburn and regurgitation associated with GERD.

II. REGULATORY HISTORY (MILESTONES)

December 10, 1996: IND No. [redacted], for lyophilized PANTO for i.v. use was submitted, including **Protocol No. 3001K1-100-US,** a dose range study in normal subjects to assess the inhibition of pentagastrin-stimulated gastric acid secretion by single doses of i.v. PANTO. This protocol was later amended to provide for a comparison with oral PANTO.

April 29, 1997: Meeting between representatives of HFD-180 and the firm. Agreement was reached on the main features of **Protocol No. 3001K1 -309-US,** a double-blind, PL-controlled critical trial comparing pharmacodynamic efficacy responses in GERD patients that were switched from oral to i.v. PANTO.

May 27, 1998: Letter from HFD-180 to sponsor informing them that the clinical information obtained from **Protocol No. 309** in conjunction with data from **Protocol No. 100** would be adequate to support the filing of NDA 20-988.

October 15, 1997: Pre-NDA meeting. Discussed were the (usual) format and content of the proposed NDA for i.v. PANTO. Based on discussions at this meeting, the sponsor has included a section in the ISS and the SU that reviews and summarizes the optic safety data for PANTO sodium.

III. PERTINENT SECTIONS OF THE SPONSOR'S PROPOSED LABELING

(See comments in the last Section of this review)

IV. FOREIGN MARKETING HISTORY

As listed below, i.v. PANTO has been registered (approved for marketing) in five countries, but as of 23 February 1998 (the data cutoff date for the NDA submission) this dosage form of the drug is only marketed in Germany. In all 5 instances, the approved indications include GERD (moderate to severe) in addition to duodenal ulcer (DU) and gastric ulcer (GU).

Commercial Marketing History of Pantoprazole I.V.

Country	Trade Name	Company	Registration Date	Indications	Marketed (yes/no)
Brazil	Pantozol		02 May 1995	GERD (moderate and severe) DU, GU	NO
Finland	Somac 40 mg powder for injection		09 Feb 1998	GERD (moderate and severe) DU, GU	NO
Germany	**Pantozol i.v.** **Pantoprazole-Byk i.v.** **Pantoloc i.v.**		**31 July 1997**	**GERD (moderate and severe) DU, GU**	**YES** NO NO
Netherlands	Pantozol i.v.		11 Feb 1998	GERD (moderate and severe) DU, GU	NO
U.K.	Protium i.v.		04 Dec 1996	GERD (moderate and severe) DU, GU	NO

By 23 February 1998, registration was pending in 16 other countries. I.V. PANTO was approved (marketed) in 4 of these countries (Austria, Denmark, France and Mexico) after the cutoff date.

V. SUMMARY (SELECTED) INFORMATION ON DRUG SUBSTANCE/ PRODUCT

- In an acidic environment PANTO undergoes a molecular rearrangement that is necessary for biologic activity. Although it is amphoteric, PANTO acts as a weak base (approximate pKa of 4.0) that is protonated in the low pH environment of the parietal cell secretory canaliculi. The protonated species forms a tetracyclic sulfenamide, which then becomes covalently bound to cysteine residues of the H^+,K^+ ATPase, or gastric proton pump.

- The solubility of PANTO sodium sesquihydrate is low at neutral pH and increases with increasing pH. The molecule possesses one stereogenic center located at the sulfur atom. Under physiological conditions, each enantiomer is converted to the achiral cyclic sulfenamide product. It is this product which is responsible for the pharmacologic activity of PANTO. Enantiomers have been separated analytically via capillary electrophoresis. The ratio of the enantiomers was 1:1 in all cases. PANTO sodium sesquihydrate does not exhibit evidence of polymorphic behavior. Other hydrates have been prepared, but none offer any formulation advantage.

PANTO has been demonstrated to be very stable:

- At *25 °C/60% RH*, for 5 years when stored as bulk in polyethylene bags/fiber drums.
- At *30 °C/70% RH*, for up to 36 months when packaged in polyethylene bags.
- When stored under *accelerated conditions of 37 °C/75% RH* for up to 20 months in polyethylene bags/fiber drums.
- When stored under *stress conditions of 50 °C* for up to 25 weeks in brown glass bottles.

Pantoprazole sodium sesquihydrate is sensitive:

- To light exposure.
- To acidic media (depending on the pH). In a strong acidic medium (pH ca. 1), the pseudo first order half-life for degradation is only a few minutes. The drug is more stable in basic media.
- When exposed to temperatures higher than 60°C.

The stability of PANTO sodium sesquihydrate with respect to assay as well as purity (related substances, specific optical rotation and water content) and appearance has been demonstrated in long term studies with specific stability-indicating analytical methods. Only the color changes slightly over time from white to orange-white, but this is not critical for the quality of the drug substance due to the extremely low levels (less than 0.01%) of the color-causing impurity. Therefore, the bulk drug substance should be stored at room temperature in tightly closed containers, protected from direct light and heat. The current packaging materials (polyethylene bags in HDPE drums) are suitable for this purpose.

The stability of PANTO in solution was investigated as a function of pH in the range of pH 1 to 8, using mixtures of methanol and an aqueous buffer or 0.1 N HCl as solvents. At pH 1.25, the half-life was estimated at 5 min., while at pH 5.0, the half-life was 2.8 h and at pH 7.8, the half-life was 220 h. The decrease in PANTO concentration follows pseudo first order kinetics. In a second experiment, after 30 min. in simulated gastric fluid (pH 1.2), several degradation products were detected.

Drug Product: Description/Composition of the Dosage Form

- PROTONIX™ I.V. (Sterile Pantoprazole Sodium) is a freeze-dried powder to be reconstituted and further diluted for intravenous injection. The product is manufactured in a 40 mg/vial strength packaged in a clear glass vial fitted with a rubber stopper and aluminum crimp seal. The freeze-dried powder is reconstituted with 10 mL of 0.9% NaCl. PROTONIX™ is addressed by several different terms throughout the sponsor's documentation: PROTONIX™, Sterile Pantoprazole Sodium; Sterile Pantoprazole; Pantoprazole for Injection; Pantoprazole Lyophile; Lyophilized Pantoprazole; I.V.; Pantoprazole I.V.

- The 40 mg/vial presentation of Sterile PANTO Sodium has the following quantitative composition. The commercial batch size is approximately ___ vials.

Active Ingredient	mg/vial[a]	Input/vial
Pantoprazole sodium	42.3 mg	45.1 mg[b]
Inactive Ingredients		
Water for Injection, USP[c]	--	--
Nitrogen, NF[d]	--	--

a) Equivalent to 40 mg as PANTO free acid. If the potency of the active ingredient is not 100%, the amount added to the batch must be adjusted to assure label claim.
b) Vials of Sterile PANTO Sodium contains 42.3 mg PANTO sodium (freeze-dried).
c) Removed during freeze-drying process; not present in final formulation.
d) Nitrogen is used during the stoppering process for the vials in the freeze-dryer.

Identification of formulations used in important clinical trials:

	Formulation Used
Study 3001K1-309-US	20 mg tablet (I)
(Pivotal)	40 mg tablet (J)
Batch No. 296310	40 mg lyophile (L2)
Study 3001K1-100	40 mg tablet (J)
(Supportive PD)	40 mg lyophile (L2)
Batch No. 296310	
Study BAT010	40 mg tablet (E)
("Supportive" Clinical)	40 mg tablet (L2)
Study FK3050	40 mg tablet (E)
("Supportive" Clinical)	40 mg lyophile (L2)
Batch No. 195230	

VI. BRIEF SUMMARY ON PHARMACOKINETICS

At this point in time, a Biopharm. review is not available. The information that follows was transposed from the September 8, 1998 memorandum from Dr. Alfredo R. Sancho to Drs. Chen, Hunt and Lee, on the subject of filability of NDA 20-988.

Pharmacokinetics

The sponsor states that the i.v. PANTO PKs seem to be linear and dose proportional over the dose range of 10 to 80 mg and up to 120-mg with limited data. PANTO has a small steady-state volume of distribution (0.2 L/kg) and is rapidly cleared (8 L/h) from the systemic circulation with a $t_{1/2}$ of ca. 1-hour in healthy subjects. Despite the short elimination half-life. PANTO provides dose-related 24-h duration of activity, due to its irreversible action on the gastric parietal cell proton pumps. The drug is metabolized extensively by demethylation (CYP 2C19) and subsequent sulfation and by oxidation/reduction (CYP3A4) to several inactive metabolites that are mostly renally excreted.

Metabolites

PANTO is metabolized through the cytochrome P450 (CYP) system to a series of metabolites, none of which, according to the sponsor, were found to contribute to the overall pharmacological activity of the parent compound. Metabolites are excreted primarily in the urine and there is no renal excretion of unchanged drug. The main metabolite, M2, which is formed by the CYP 2C19 isozyme, was quantified in most studies along with the sulfone metabolite. The CYP 2C19 isozyme exhibits genetic polymorphism; therefore, the metabolism of PANTO seems to be slower in some subjects ("poor metabolizers"). The sponsor identified both the slow-metabolizers and the rapid-metabolizers with the population of these studies. The AUC, $t_{1/2}$ and CL values for the slow metabolizers were reported separately from those for the normal, rapid metabolizers; the values for the slow metabolizers were marked by the superscript "c".

Drug-Drug Interactions

In the present NDA submission, according to the sponsor, there were no PK or PD interactions when PANTO was coadministered with cisapride, ethanol, glibenclamide (glyburide), theophylline, diazepam, phenytoin, carbamazepine, digoxin, warfarin, phenprocoumon, nifedipine, metoprolol, diclofenac, antacids or an oral contraceptive. No drug-to-drug studies were done with antibiotics, which are commonly used in the treatment of H. pylori.

Assay Method/s

- Listed below are the number of PK/PD studies submitted by the sponsor of NDA 20-988, by category.

[3] The first of these methods with an . The other method used Following further chromatographic separation . **The sulfone metabolite** was quantitated analogously to PANTO using method. The same method allowed metabolites M1-M3, for which no synthetic reference compounds were available. These concentrations were expressed in the sponsor's submittion as *mg-equivalents/L* of PANTO. Internal and external standards were used for quantitation purposes. The recovery of PANTO ranged from %. The lower limit of quantitation (LOQ) was either mg/ml with respective standard curves from mg/ml. From quality control samples, the within-day precision was %. The between-day precision was %.

Category	Total No. of Studies
General PK [Pks, crossover, absolute bioavailability, ADME, bolus, continuous infusion, study of dose linearity, pentagastrin-stimulated acid output]	8
Special Population [elderly, renally impaired patients before and after hemodialysis, severe renal impairment, verified liver cirrhosis, impaired hepatic function]	7
Bioavailability/Bioequivalence [PK after oral vs i.v., tolerability and PK after i.v. infusion over 15 min.]	2
Drug-Drug Interaction [antipyrine, activities of CYP 1A2, N-acetyl transferase (NAT) and xanthine oxidase (XO) enzymes, ethanol, teophylline, diazepam, carbamazepine, phenytoin, digoxin, metoprolol, nifepidine, warfarin, phenprocoumon, cisapride, antacid coadministration, diclofenac gibenclamide (glyburide), oral contraceptive]	20
Total No. of Phase I Clinical PK Trials	37

VII. CONTRASTING PKs OF 40 mg PANTO AFTER ORAL vs I.V. ADMINISTRATION

[Byk-Gulden Report 7E/91; Byk-Gulden Protocol A9915-GER]

"A study in healthy subjects to describe and compare the plasma pharmacokinetics of SK&F 96022 after a single 40 mg dose administered either orally (Phase 11B formulation) or by constant rate 15 minute IV infusion"

Period of investigation: 11/89 to 12/89

1. Investigator:

2. Objectives:

This study was set to describe and compare the plasma PKs of SK&F 96022 (PANTO) after a single dose of 40 mg administered either orally as an investigational Phase IIb (enteric-coated) formulation or by constant rate i.v. infusion over 15 min.

3. Study Design, Methods and Data Analysis

- 12 HMVs participated in a randomized period-balanced crossover study in which each subject received SK&F 96022 (as the sodium salt, SK&F 96022-Z) on 2 occasions at least 5 days apart, either as a single oral dose of 40 mg or a single 40 mg dose administered by constant rate 15 min. i.v. infusion (doses expressed as free acid). Serial blood samples were obtained following each dose administration and plasma assayed for concentrations of SK&F 96022 using a specific reverse phase system (limit of quantification= μg/ml.

- SK&F 96022 plasma concentration-time data were analyzed using Estimates of T_{max} and C_{max} were made from visual inspection of the individual plasma concentration-time profiles. The area under the individual SK&F 96022 plasma concentration-time curves was estimated using Apparent terminal plasma elimination half-life values for SK&F 96022 were calculated from the elimination rate constants. The mean residence time for SK&F 96022 (MRT) was estimated for each profile. Total systemic plasma clearance and the apparent volume of distribution at steady state for SK&F 96022 were estimated following i.v. administration.

- Descriptive statistics were tabulated for the PK parameter estimates for i.v. and oral administration. Log-transformed AUC(0-i) values were analyzed by ANOVA taking account of subject, sequence, period and treatment. The mean difference in AUC(0-i) values between the two treatments was estimated and the 95% confidence intervals for the difference calculated using the residual mean square value. The difference and the 95% confidence interval on the log-scale were then back transformed to give ratios on the original scale to give estimates for the absolute bioavailability of SK&F 96022.

4. Results (Table 1)

a. Intravenous Administration

- Following i.v. infusion of SK&F 96022-Z at a dose of 40 mg (expressed as free acid) administered at a constant rate over 15 min., concentrations of SK&F 96022 at the end of the infusion (C_{max}) ranged from $\mu g.ml^{-1}$ (mean 4.615, S.D. 0.980 $\mu g.ml^{-1}$). Thereafter, SK&F 96022 plasma concentrations declined in manner consistent with a rapid distribution phase followed by 2 plasma elimination phases. The area under the individual SK&F 96022 plasma concentration-time profiles represented by the apparent terminal elimination phase accounted for up to approximately % of the respective AUC(0-T_{last}) values. Estimates of the apparent terminal plasma elimination hafl-life ranged from min (mean 115.8 min, median 104.8 min). Estimates of the plasma elimination half-life for the phase which preceeded the apparent terminal phase ranged from min.

- Values of AUC(0-i)[4] ranged from $\mu g.ml^{-1}.min$ (mean 367.4, S.D. 314.0 $\mu g.ml^{-1}.min$). Mean MRT value was 111.0 min (S.D. 94.9). Mean Vd_{ss} and Cl values were 12623 ml (S.D. 2345) and 159.9 $ml.min^{-1}$ (S.D. 78.9).

[4] Excluding Subject 5, the range of values for AUC(0-i) $\mu f.ml^{-1}.min$) decreased. Similarly, the range of values for the apparent terminal plasma elimination half-life min) and the mean MRT value (85.6 min) was reduced. The means for the remaining PK parameters showed little change when the data for Subject 5 were excluded.

TABLE 1
Study SK&F 96022/A9915-GER

Summary Statistics Following Single 40 mg Dose of SK&F 96022 (PANTO) Either by Oral or I.V. Administration (12 subjects)

	n	mean	S.D.	median	min	max
AUC(0-i) (μg/ml.min)						
i.v.	12	367.4	314.0	240.8		
oral	12	311.6	317.3	190.5		
C_{max} (μg/ml)						
i.v.	12	4.615	0.980	4.419		
oral	12	2.088	0.659	2.126		
T_{max} (min)						
i.v.	12	15	0	15		
oral	12	163	35	165		
Half-life (min)						
i.v.	12	115.8	72.3	104.8		
oral	12	114.3	80.5	74.8		
MRT (min)						
i.v.	12	111.0	94.9	78.3		
oral	12	268.2	122.1	229.6		
Vd_{ss} (ml)						
i.v.	12	12623	2345	12321		
Cl (ml/min)						
i.v.	12	159.9	78.9	166.3		

Materials used in this study
Enteric coated tablets of 20 mg SK&F 96022-A/B 8610-23 (Batch 4/1/1. Ca. No.: 895 107) and a solution of SK&F 96022/B 8510-29 (SK&F 96022 injection concentrate 120 mg.ml^{-1}, Formula 16, Batch 18 F) for parenteral administration were supplied by the SK&F Department of Pharmaceutical Development. Welwyn, UK.

b. Oral Administration

- Following single oral administration of SK&F 96022-Z as the investigational phase IIb tablet at a dose of 40 mg (expressed as free acid), maximum plasma concentrations of SK&F 96022 ranged from μg.ml^{-1} (mean 2.088, S.D. 0.659 μg.ml^{-1}) and occurred at 120-240 min (median 165 min) post-dose. Thereafter, plasma concentrations of SK&F 96022 declined from peak with an apparent terminal elimination half-life of min (mean 114.3 min, median 74.8 min). Values of AUC(0-i)[5] ranged from μg.ml^{-1}.min (mean 311.6, S.D. 317.3 μg.ml^{-1}.min). Mean MRT value was 268.2 min (S.D. 122.1 min).

- The sponsor notes that estimates of T_{max} and C_{max} values were based upon the SK&F 96022 plasma concentration-time curves which were characterized by relatively few data points on the absorption phase of the curves, due to rapid absorption of SK&F 96022 from the

[5] Excluding Subject 5, the range of values for AUC(o-i) μg.ml^{-1}.min) decreased. In addition, the mean MRT value (237.1 min) was reduced. The means for the remaining PK parameters showed little change when the data for Subject 5 were excluded.

oral formulation once absorption had started at a time when blood sampling was every 30-60 min. This factor increases the uncertainty in the estimation of true C_{max} and T_{max} values.

- Estimates of MRT values following oral administration were based upon SK&F 96022 plasma concentration-time curves which were characterized by a substantial and variable delay in the onset of absorption (sponsor's figures 1 through 12) and the reported MRT values include a significant component for the time lag of absorption. The time lag for absorption of SK&F 96022, estimated as the last of the initial time points in each profile at which SK&F 96022 was non-quantifiable, ranged from 60 to 180 min.

c. Absolute Bioavailability[6]

- The ratio of the individual values for AUC(0-i) following i.v. and oral administration were used to estimate the absolute bioavailability of SK&F 96022 from the investigational phase IIb tablet used in this study, the same dose having been administered via the 2 dose routes. This calculation assumes constant clearance for SK&F 96055 between the 2 dose routes. After back transformation of the difference of the log transformed AUC(0-i) values, the estimated absolute bioavailability was 0.77 (95% CI: 0.67, 0.89). The intra-subject coefficient of variation for AUC(o-i) was 15.3% (sponsor's Appendix 5).

5. Results of Safety Evaluations

a. Subject #6 (Apparent positive rechallenge)

Half an hour after oral administration of PANTO subject 6 complained of **"blurred vision"**, combined with a feeling of pressure behind the eyes and difficulties to recognize objects. On his second study day (i.v. infusion), he again had a feeling of pressure behind the eyes especially when moving or closing the eyes. These symptoms appeared about 10 min. after the start of the i.v. infusion and cleared during the next hours.

b. Subjects #10 and #12

These two subjects felt very tired about 10 min. after the start of the i.v. infusion of SK&F 96022.

c. Subject #4

SK&F 96022 was administered as the i.v. infusion on the first study day for Subject 4. During the infusion, he was anxious. About half an hour after the end of the infusion, he complained of cold and pale hands. During the following 3 h of the study day, the symptoms cleared. At 3:00 am the next morning, he awoke because of nausea, meteorism, diarrhea and dizziness. At 4:45 am he reported in the study unit and complained of persistent nausea, meteorism, light diarrhea and dizziness. His BP was between 117/71 mmHg and 155/65 mmHg with a HR of 96 and 98 bpm. respectively. He was put supine; 3 h later he still suffered from light nausea and

[6] Excluding the data for Subject 5, the estimated absolute bioavailability was 0.82 (95% CI: 0.66, 0.89) and the intrasubject coefficient of variation for AUC(0-i) was 15.7% (sponsor's Appendix 5).

dizziness. BP in supine position was 136/66 mmHg with a HR of 97 bpm. When standing, blood pressure fell to 87/74 mmHg and 97/63 mmHg with HRs of 120 bpm and 106 bpm, respectively; 30 min. later, he left the study unit on his own initiative. On his second study day, he had no problems.

d. Laboratory Safety Data

These were presented for each subject in sponsor's Appendix 7. Values outside of the laboratory normal reference ranges were indicated. None of these were judged to be treatment related and/or to affect interpretation of the data.

6. Conclusions

- The i.v. plasma PKs of SK&F 96022 were characterized by a rapid distribution phase followed by 2 elimination phases in the decline from maximum plasma concentrations of SK&F 96022 at the end of the infusion. Estimates for the apparent terminal plasma elimination half-life values ranged from min. The mean estimate of the total plasma clearance of SK&F 96022 was 160 $ml.min^{-1}$ (S.D. 78.9).

- The oral plasma PKs of SK&F 96022 following administration as the investigational Phase IIb (enteric coated) formulation were characterized by a variable delay in the onset of absorption followed by a rapid attainment of maximum plasma concentrations at post-dose. Thereafter, plasma concentrations of SK&F 96022 declined with an apparent terminal plasma elimination half-life of : min. The absolute bioavailability of SK&F 96022 from the oral tablet formulation was **0.77** with a relatively small degree of variability as reflected by the 95% confidence interval on this estimate (0.67, 0.89) and an intra-subject coefficient of variation of 15.3%.

- AEs that were regarded as possibly treatment- and compound-related included a) disturbance of vision and pressure behind the eyes following both I.V. and oral treatments (presitive rechallenge) in one subject, and b) nausea, meteorism, diarrhea and dizziness on the morning following i.v. administration in another. No changes in laboratory safety parameters were evident which were considered treatment related and/or to affect interpretation of the results.

VIII. BRIEF SUMMARY ON PHARMACODYNAMICS

1. Pre-clinical Pharmacology

From experiments where PANTO was administered orally (NDA 20-987), it has been established that this PPI is a potent and long-acting inhibitor of spontaneous gastric acid secretion in rats and dogs.

24-h gastric lumen pH after i.v. administration

This study was carried out in dogs with chronic gastric fistulae in order to establish a range of therapeutic ranges. In this animal model, a dose of 0.38 mg/Kg was not effective. At dosages of 0.95, 1.9 and 3.8 mg/Kg, PANTO rapidly caused increases of at least 1 pH unit (>90% inhibition of acid secretion) with the 3.8 mg/Kg dosage the antisecretory effect lasted 8 h.

According to the sponsor, the doses of the drug administered i.v. were very similar to those needed to produce strong and long-lasting inhibition of spontaneous gastric acid secretion when PANTO was administered orally [PANTO has good PO bioavailability].

Secretagogue-Induced Gastric Acid Secretion

- The ED_{50} for i.v. PANTO as an inhibitor of gastric acid secretion induced by pentagastrin infusion in rats was 0.23 mg/Kg.

- Results of studies in rats stimulated with an infusion of pentagastrin showed that pantoprazole, omeprazole, and lansoprazole had similar gastric acid antisecretory potencies.

- When administered as an i.v. bolus injection, both the (+) and (-) enantiomers of PANTO had antisecretory potencies comparable to the racemate in inhibiting pentagastrin induced gastric acid secretion in the rat model.

- PANTO administered i.v. or PO was potent as an inhibitor of the gastric secretory effect of bethanecol (a muscarinic receptor agonist) in the Acute Gastric Fistula rat model:

	I.V.	PO
ED_{50} (mg/Kg)	0.5	0.7

- Results of inhibition of impromidine-induced gastric acid secretion in the dog model, where PANTO was administered as an i.v. bolus injection demonstrated that this route of administration is effective in inducing antisecretory effects:

	I.V.	PO
ED_{50} (mg/Kg)	0.17	1.4

NOTE: These results are in agreement with those previously shown in the anesthetized rat model.

Need of Acidic Environment for PANTO Activation

- Experiments were carried out to verify the importance of a strongly-acidic environment for activation of PANTO in the activated parietal cell canaliculi. PANTO was administered i.v., either alone or after i.v. administration of famotidine (an histamine H_2-receptor antagonist) to conscious dogs with gastric fistulas that were stimulated with pentagastrin.

When gastric acid secretion was inhibited by pretreatment with the H_2-blocker, the duration of PANTO's gastric antisecretory effect was reduced in a dose related manner. The reduced effect can be attributed to a decrease in chemical transformation of PANTO to the **active sulfenamide** in the intracellular canaliculi where acidity had been reduced by famotidine pretreatment.

- The potency and duration of the gastric acid inhibitory effect of PANTO was also assessed by continuously measuring the pH in the lumen of the stomach of dogs with gastric fistulas. I.V. administration of PANTO at dosages of 0.38, 1.15, and 3.83 mg/Kg caused a dose-related inhibition of gastric acid secretion induced by a 20-h pentagastrin infusion. In this animal model, the duration of the antisecretory effect was dose related and lasted about 13 h for the highest dosage.

Prevention of Ulcer Formation

- The similarity of antisecretory effects obtained when PANTO is administered intravenously to those seen when the drug is given orally (or intraduodenally) was also shown in animal models of gastric ulcer formation (e.g. ___ rat):

	I.V. (Administered at the time pylorus ligation)	I.D. (Administered at the time of ligation)	PO (Administered 1 h prior to ligation)
Antiulcerogenic ED_{50} (mg/Kg) in the rat model	0.21	0.25	0.23

a) In this ulcer prevention model, occlusion of the pylorus with a ligature results in vagal stimulation of acid secretion and accumulation of acid in the lumen of the stomach. Aspirin is ulcerogenic to the gastric mucosa and, under these experimental conditions, enhances the ulcerogenic activity of the gastric acid accumulated in the lumen of the stomach after pylorus ligation and occlusion.

Healing of Preformed Ulcers

- Orally administered PANTO was also shown to be effective in accelerating the healing of acetic acid-induced gastric and duodenal ulcers. Although no data are available, intravenously administered PANTO is expected to show the same pharmacodynamic effect.

2. Pre-clinical Pharmacology Related to the Side Effect Profile

The material that follows was taken from sponsor's volume 1.002, ITEM 3 (Nonclinical Pharmacology and Toxicology Summary), Section 3.5.1.7.

- PANTO was evaluated in a battery of pharmacology tests designed to identify side effects due to the drug itself or due to interactions with other pharmacological agents. In most of these tests, the dosages used were much higher than the intended therapeutic dosage.

- **Cardiovascular parameters** were only moderately affected after i.v. administration of up to 26.6 mg/Kg of PANTO to anesthetized cats or to conscious dogs. The effects consisted of a 10 to 20% reduction in BP in both species and inconsistent changes in HR.

- In the isolated guinea pig heart, i.v. bolus injections of 100 μL PANTO at dosages of 10^{-8} mol to 10^{-7} mol, did not alter any of the standard cardiovascular parameters measured.

- Renal function was not affected by i.v. administration of 26.6 mg/Kg PANTO in dogs.

- PANTO was shown not to have CNS activity either by PO or parenteral administration in locomotive and exploratory activity tests and tests which assessed muscle strength and coordination, such as the rotarod test and the grip strength test in mice. At dosages up to 53.2 mg/Kg PO, PANTO had no effect on spontaneous exploratory motility of mice placed in light beam cages, on motor coordination of mice in the rotarod test, or on grip strength of mice. I.V. PANTO at 88.7 mg/Kg had no effect on motor coordination or grip strength in mice.

- PANTO at PO dosages up to 106.4 mg/Kg had no effect on the duration of pentobarbital-, hexobarbital-, or ethanol-induced hypnosis in rodents, suggesting a lack of an acute effect on drug metabolizing enzymes or a pharmacological interaction with the CNS depressants.

- No significant effects of PANTO were observed on functions that are dependent on the autonomic nervous system. PANTO had no effect on intestinal propulsion in mice or rats at PO dosages up to 266 or 53.2 mg/Kg, respectively. At PO dosages of 88.7 mg/Kg and 266 mg/Kg, a delay in gastric emptying was observed in mice. However, in a subsequent experiement in which i.v. dosages of 26.6 and 88.7 mg/Kg were administered, PANTO had no effect on gastric emptying or intestinal propulsion in mice.

- At 38 mg/Kg i.v. PANTO did not produce any reflux of stomach contents into the esophagus of anesthetized rats, suggesting that the gastroesophageal sphincter tone was not affected.

- PANTO at i.v. dosages of 3.8 and 11.5 mg/Kg did not cause any effect on pancreatic or biliary secretions in anesthetized rats.

- [Blood levels of glucose in fasted mature rats were not altered by single PO administration of PANTO at dosages up to 26.6 mg/Kg. At 53.2 mg/Kg, pantoprazole increased blood glucose by 8%.]

- [The body temperature of rats was not consistently affected by PO administration of pantoprazole up to 53.2 mg/Kg.]

- In pentobarbital-anesthetized dogs, i.v. infusion of PANTO at 26.6 mg/Kg did not cause any statistically significant change in respiratory flow, tidal volume, respiratory rate, transpulmonary pressure, dynamic compliance or pulmonary resistance.

- In conscious dogs, 26.6 mg/Kg i.v. PANTO did not cause any consistent changes in electroencephalogram or electrocardiogram recordings. Occasional vomiting was noted in some dogs, but this effect was not considered to be compound related.

- At dosages up to 88.7 mg/Kg PO, PANTO had no antinociceptive effect (hot plate test) in mice. The threshold for pentetrazole-induced seizures in mice also was not affected by dosages of PANTO up to 88.7 mg/Kg PO. PANTO (2% solution) injected intramuscularly in the region of the sciatic nerve trunk of rats did not affect the motility of the rats nor did it have local anesthetic activity when instilled on the cornea of rabbits.

  - [In *in vitro* studies of isolated tissues maintained in media at physiological pH, pantoprazole did not interact with muscarinic (M_1, M_2, and M_3), histaminergic (H_1) or adrenergic (α_{1B}, β_2) receptors.]

- [The effect of pantoprazole on ATPase systems at organ locations other than the gastric parietal cell was investigated using Na^+/K^+-ATPase obtained from dog kidney. PANTO was a much weaker inhibitor of this type of ATPase system than of the proton pump of the gastric parietal cell.]

Reviewer's Conclusions on Pre-clinical Pharmacology

In a variety of animal models, in rats and dogs, intravenously administered PANTO was shown to be a potent and long-acting inhibitor of spontaneous as well as secretagogue-induced gastric acid secretion. These secretagogues are known to act at different receptors of the parietal cell, neurons, or paracrine cells. Activity in either the prevention or the treatment of preformed ulcers induced in animal models was also demonstrated. In general, similarity of effects were seen between the i.v. and the PO dosages of the drug needed to show an effect. This indicates that PANTO has good PO bioavailability. The reviewer agrees with the sponsor's conclusion that at minimum i.v. or PO dosage levels needed to produce a strong and long-lasting inhibition of gastric acid secretion in rats and dogs, PANTO was devoid of adverse effects. At high i.v. dosages, modest lowering of BP was seen in dogs and cats.

3. Antisecretory Activity in Humans

Study FHP001 (Germany) Dr. B. Simon Dr. P. Müller	This was the first study in humans. The trial was set to obtain PK data and to investigate safety, tolerability, and efficacy under pentagastrin infusion. The design was that of S-B PL-controlled, ascending dose trial with random PL dose in schedule. Subjects were 12 HMVs (mean age-28y); there was a one week wash out period between doses. Pentagastrin at the rate of 0.6 μg/Kg/h was infused from 1h before to 3h after the beginning of PANTO or PL infusion.

The dose and groups investigated were:

	Group 1 [n=4]	Group 2 [n=4]	Group 3 [n=4]
PANTO (mg)[a]	0,[b] 1, 2.5 and 5	0[c], 10, 20 and 40	0[d], 30, 60 and 80

a) Administered as 25 ml infusion (in 0.9% NaCl) over 15 min.
b,c,d) I.V. placebo consisted of 25 ml of 0.9% NaCl, infused over 15 min.

- Acid output and volume were reduced in a dose dependent manner. Gastric pH increased with the higher doses. Dose linearity was seen for AUC over the dose range from 5 to 80 mg. Elimination half-life, total clearance, and volume of distribution were independent of the dose.

- PANTO was well tolerated.

Study FHP016E (Germany) Dr. G. Brunner

The main design consisted of an open-label evaluation of the effect of a loading dose followed by 3x/day dosing on intragastric pH in 8 (4M, 4F; aged 25-42y), fasting, drip -fed, healthy volunteers.. The study included 48 h pH-metry.

PANTO 80 mg bolus injection loading dose was followed by PANTO 40 mg bolus injection every 8h for 5 doses (six doses total).

In the Clinical Report, the results were summarized as follows:

Pharmacokinetics: the following median (min/max) values were determined: AUC (O-Inf.): 8.49 (4.64/16.05) μgxh/ml, t1/2: 1.06 (0.48/2.1) h, Cl: 0.135 (0.083/0.203) 1/h/Kg, Wdarea: 0.191 (0.112/0.536) 1/Kg. A thiol metabolite was not found in any of the serum samples.

Efficacy: median pH (1./3. quartil) was 3.14 (2.42/4.28) on day 1 and 3.96 (3.01/4.84) on day 2.

Safety and tolerability: in general, PANTO was well tolerated. There were no clinically relevant changes in BP, HR, EKG and routine clinical laboratory tests. In two female subjects, the study was terminated prematurely due to AEs (edema, swelling). Both AEs were classified as moderate and considered to be possibly drug related.

Study FHP024E (Germany) Dr. G. Brunner

This D-B, randomized, PL-controlled, two-period crossover study was set to investigate the effect of loading dose and subsequent "L-T" intravenous infusion of PANTO on intragastric pH in 6 (3M, 3F) volunteers, aged 23 to 30 years. The two groups being compared were:

Test	Reference
PANTO 40 mg i.v. bolus, then continuous infusion of 4 mg/h over 48h	PL i.v. bolus, then continuous PL infusion over 48h

There was a washout of at least 1 week between periods.

- Steady state concentrations were attained within 24h of the start of the infusion. The mean C_{ss} value was 0.45 mg/d. Mean PANTO clearance was close to 10 l/h (range: 4.9 to 14.5 l/h). The mean C_{ss} value for the M2 metabolite was 0.25 mg/l; this was attained also within 24h of the start of the PANTO infusion.

- PANTO "L-T" infusion was well tolerated.

Study CH001 (Germany) Dr. C. Beqlinger	This S-B, randomized, multiple dose, two-period, crossover study compared two different dosage regimens of PANTO in 13 healthy volunteers (7M, 6F) aged 19 to 33y. Two 24-h infusions were separated by a 14-day washout period. The PANTO lyophile was administered with sucrose.

The two groups being compared were:

Group A	Group B
PANTO 40 mg i.v. loading dose (as bolus), then 6 mg/h continuous infusion for 24h	PANTO 40 mg i.v. loading dose (as bolus), then 4 to 8 mg feed-back controlled infusion for 24h

Efficacy was assessed as the percentage of time (% of time) with pH > 5 during 24 h (primary criterion); secondary criteria: % of time with pH > 5 during 0-4, 5-8, 9-12, and 13-24 h after start of infusion; median pH during 24 h, 0-12 h and 13-24 h; PANTO consumption.

Summary of Results:

1) The median percentage of time (% of time) during 24 h with pH > 5 was 3.9 without medication, 47.7 under constant and 45.5 under variable infusion. The difference between measurements without medication and both treatment groups was significant, while the difference between the treatment groups was not (sign-rank test, two-sided).

2) The median % of time with pH > 5 during the first four hours (1-4 h) was 2.8 without medication, 29.0 under constant and 23.2 under variable infusion. The respective values for the second four hours (5-8 h) were 0, 33.9 and 20.5 for the third four hours (9-12 h) 2.2, 62 and 51.4, and for the second twelve hours (13-24 h) 3.1, 53.6 and 47.6.

3) The median pH over 24 was 1.6 without medication, 4.8 under constant and 4.8 under variable infusion. At day time (1-12 h), the respective values were 1.7, 4.6 and 4.5, and at night time (13-24 h) 1.5, 5.0 and 4.9.

4) The average consumption of pantoprazole after initial injection of 40 mg was 35.3 ml – 141.2 mg in the constant and 42.5 ml = 170.4 mg in the variable treatment group.

5) Both treatments were well tolerated. Seven participants complained of AEs, all of them of mild or moderate intensity. No serious AEs were reported. No laboratory parameter changes of clinical relevance were observed.

The sponsor concluded that after a 40 mg i.v. loading dose, 6 mg/h I.V. PANTO is very effective in controlling intragastric pH in healthy volunteers, fed standard meals, at daytime and nighttime. A variable pH feedback controlled infusion did not improve efficacy further.

Study FH029E (Germany) Dr. G. Brunner	This open-label, parallel group study evaluated in 12 HMV [6 (3M, 3F) for each group; median age 28y] the effect of i.v. PANTO on intragastric pH: initial i.v. bolus, followed by continuous infusion over 2 days. The PANTO lyophile was administered with sucrose.

The two groups being compared were:

Group 1	Group 2
[n=6]	[n=6]
40 mg loading dose, then 8 mg/h for 48h	80-mg loading dose, then 8 mg/h for 48h

The following is a summary of results, according to the Clinical Report:

Pharmacokinetics: PANTO-Na steady-state serum concentrations were reached approximately 4-6 h following the beginning of the infusion and the initial loading dose. The median steady-state serum concentrations of PANTO-Na and metabolite M2 were 1.23 mg/l and 0.45 mg-equiv./l (Group 1) and 1.31 mg/l and 0.42 mg-equiv./l (Group 2), respectively. For the median clearance of PANTO 0.099 l/h/Kg and 0.088 l/h/Kg (40 mg and 80 mg loading doses), respectively, were calculated. C_{ss} and CL thus seemed to be independent of the loading dose.

Efficacy: Median pH of Group 1 was 5.99, that of Group 2 was 4.37. Median % time pH > 3, 4, 5 and 6 were 972.%, 94.4%, 93.1% and 79.9% for Group 1 and 83.3%, 53.5%, 34% and 10.4% for Group 2, respectively

Safety: PANTO did not influence BP, HR or clinical laboraotry parameters.

Study BF002 (France) J.P. Galmiche	The objective of this study was to compare the effects of i.v. PANTO, OME, and PL on gastric acid output and intragastric pH; a double-blind, randomized, three-period study was carried out in two Phases:

	Treatment		
Phase I:	A	B	C
	PANTO 80 mg i.v. bolus at 8 AM, 40 mg i.v bolus at 4 PM and midnight	OME 80 mg i.v. bolus at 8 AM, 40 mg i.v. bolus at 4PM andmidnight	PL i.v. bolus at 8AM, 4 PM and midnight

Each of the 12 participating HMVs received each of the 3 treatments
Gastric and secretion was maximally stimulated with pentagastrin (6μg/Kg, given I.M.)
PANTO lyophile was administered with sucrose.

Phaee II: The purpose of this phase of the trial was to compare the 24h pH-metric profiles of PANTO [loading dose: 96 mg in 2h at the rate of 12 ml/h then 8 gm/h throughout the 22 following hours].

- Compared with PL, PANTO (bolus and infusion) and OME significantly decreased acid secretion and increased intragastric pH. None of the drug regimens was able to maintain the intra-gastric pH above 4 during the first 16h. One possible explanation for these results is that, in this study, the secretagogue pentagastrin was administered at maximally stimulating doses.

Studies Comparing PD Effects of 40 mg PANTO Administered Either Intravenously or Orally

Study A9918
(U.K.)
Dr. C. Broom
Dr. S. Daniels

This open-label, two-period crossover study was set to assess the effect of repeated once daily i.v. and oral administration of PANTO on 24-h intragastric pH. The study population consisted of 17 healthy volunteers (8M, 9F, aged 24-43y). The final n was 11 since 6 subjects were W/D due to reasons unrelated to test medication. The criteria for evaluation were a) % time pH>3, b) median pH•AUC, c) C_{max}, $t_{½}$, and t_{max} of PANTO. Equivalence between the effect of the i.v. vs oral treatment was concluded if the 90% CI was completely within (-15%, +15%). The groups being compared were:

Group A	Group B
PANTO (tablets) 40 mg QD PO for 5 days	PANTO 40 mg QD (in 10 ml as slow injection over 5-min) for 5 days

There was a washout of 10 days between periods.

- Summary of results:

	I.V.	PO	Δ
% time pH > 3 (least square means)	67.7%	64.1%	3.6% [90% CI: -2.9, 10.2]
median pH (least square means)	3.78	3.63	0.15 [90% CI: -0.19, 0.49]

The mean estimate of the absolute bioavailability was 0.72 (range 0.57 to 0.89)

CONCLUSION: Following once daily administration, PANTO 40 mg i.v. was equipotent to PANTO 40 mg PO in reducing intragastric acidity. Based on this information, similar healing rates in GERD patients are to be expected: 40 mg i.v. may be given as an alternative dosage form instead of 40 mg orally. There were no clinically relevant changes or changes in laboratory or II lead EKG.

Study FHP047
(Germany)
Dr. W. Lucker

This open-label, randomized, two-period, crossover trial compared PD effects of 40 mg PANTO i.v. and 40 mg tablet (enteric coated) formulations on intragastric pH. Twenty (21 ITT) HMVs aged 23-42y participated. Equivalence was assessed through the parameter % of time below pH 4. Secondary objectives were % of time pH <3 of PK characteristics of PANTO after single and repeated doses intravenous and oral administration. For the % times, an equivalence range of ±20% was defined. For the pH-median the equivalence range was set to ± 1 pH unit.

Summary of results:

	Median		90% CI for difference I.V. – Oral	
	I.V.[a]	Oral		
% time pH <4	65.3	71.1	0.57	8.31
% time pH <3	45.3	56.0	1.83	9.64
24-h median pH	3.2	2.7	-0.03	0.44

The parameters were analyzed by means of an ANOVA.
a) Saccharose-free lyophile 40 mg reconstituted with 10 ml normal saline solution, 5 min. i.v. administration. PKs: absolute bioavailability (90% CI) was 66% (60%, 73%).

CONCLUSION

The respective 90% CI for the ratio of the difference i.v. – PO were well within the prespecified equivalence range (about one-half of the predefined range only). It is concluded that both formulations are equipotent. A dose of 40 mg PANTO administered once-a-day for 5 days is considered to be an alternative dosage form to oral administration. PANTO 40 mg once-a-day, administered by either route is safe and well-tolerated.

Study 3001K1-100-US (U.S.) J. Pisegna Los Angeles	Because the sponsor has submitted it as supportive, results of this study will be evaluated in detail (see Section below).

IX. CRITICAL TRIALS IN NDA 20-988

In support of the approval of PROTONIX® I.V. for the short-term gastric acid suppression in GERD patients who are unable to take oral medication, the sponsor submitted results of four clinical trials. The main experimental features of design and execution and an initial appraisal of the utility of these studies in the reviewer's recommendations for regulatory action, are summarized in Table 2. At the end of the assessment of the evidence, the reviewer expects to be able to answer the following questions, related to treatment of erosive esophagitis with intravenously administered PANTO.

1. Is 40 mg I.V. PANTO once-a-day effective?

2. Can an "adequate" antisecretory activity be maintained?

3. Can 40 mg I.V. PANTO once-a-day be used as an alternate to 40 mg oral PANTO per day in those patients who are unable to take oral medication?

4. Is 40 mg I.V. PANTO once-a-day safe?

5. Can approval of 40 mg I.V. PANTO be recommended on the basis of one critical clinical trial (3001K1-309-US)?

6. Can approval of 20 mg I.V. PANTO also be recommended?

7. Can approval of 40 mg I.V. PANTO be recommended for use?

TABLE 2

Main Features of Design and Execution of and Initial Assessment of the Utility of the Trials Submitted by the Sponsor in Support of the Approval of the Marketing of 40 mg PROTONIX® I.V. as an Alternate to 40 mg PANTO

Protocol No. # of Centers	No. of Patients/ Subjects Enrolled per Gender	Main Features of the Trial	Groups Being Compared	Remarks
I. PIVOTAL TRIAL				
3001K1-309-US Multicenter U.S.	M = 30 F = 35 Total # of Pts. 65 Age: 26-64y (mean 45y)	**Aim** To compare gastric acid secretion responses in patients with GERD who were switched from PO to I.V. PANTO. Double-blind, randomized, two-period, placebo-controlled unbalanced parallel group comparison. The trial included a 10 to 14-day oral treatment period and a 7-day i.v. treatment period. Gastric acid secretion was stimulated by subcutaneous administration of pentagastrin 6 μg/Kg after the last day of oral and after the first and last day of i.v. dosage.	20 or 40 mg QD oral PANTO on Days 1 through up to 14 vs 20 or 40 mg QD i.v. PANTO (infused over 15 min. on Days 11 through 17	• Useful Design • This design is adequate to answer the critical question of whether patients who have been stabilized on 40 mg oral PANTO can be safely switched to 40 mg i.v. PANTO for one week. • Efficacy is demonstrated by showing that the 40 mg i.v. PANTO dose formulation is equivalent to the 40 mg oral PANTO in the suppression of both basal (BAO) suppression and maximal (MAO) acid secretion in erosive esophagitis patients.
II. SUPPORTIVE STUDIES				
3001K1-100-US Dr. J. Pisegna (CURE/West LA VA Med. Center)	Enrolled 39 (All males) Completed the Study 33	**Aim** To assess the magnitude and time course of inhibition, by various single doses of i.v. PANTO, of pentagastrin-stimulated gastric acid secretion of HMVs. Secondary objectives were to compare these variables with those mediated by PANTO tablets, famotidine i.v. and PL and to determine the PD dose response of PANTO i.v. over a sixfold dose range (20, 40, 80 and 120 mg doses). Gastric acid secretion was stimulated by intravenous administration of pentagastrin (1 μg/Kg/h) at a rate of 10 ml/h. Open-label, single dose PL-controlled, rising-dose, in healthy male subjects.	PANTO I.V. (QD) 0 mg (n=40 20 mg (n=6) 40 mg (n=8) 80 mg (n=8) 120 mg (n=5) vs PANTO 40 mg I.V. vs FAM 20 mg I.V. a) 1h before i.v. test med., b) simultaneously with oral test med., for total of 24 or 25h.	• Useful design • Onset and duration of acid suppression can be determined and used for comparison purposes. • The design is adequate to confirm if i.v. administration of 40 mg PANTO produces acid suppression consistent with that produced by the oral formulation. • Comparisons of onset and duration of acid suppression with i.v. PANTO with those obtained with intravenously administered FAM can also be made.

II. SUPPORTIVE STUDIES (Continued)				
BAT010 Multicenter Dr. R. Fischer (Austria)	M = 72 F = 38 Total # of patients 110 Age: 20-88y Median 58y	**Aim:** Open-label, multicenter trial set to assess healing plus symptom relief in patients with endoscopically established erosive esophagitis grade II/III (Savary-Miller system) who were given initial i.v. followed by oral therapy. Efficacy was assessed by historical comparison with oral only PANTO therapy (pooled data from two oral-only performed earlier, FK 3005 and FK 3009 in which patients with EE grade II or III received 40 mg oral PANTO daily for 4 or 8 weeks).	PANTO lyophile, 40 mg QD as short infusion over 4 min. for 5-7 days then PANTO enteric coated tablets 40 mg QD, 3 or 7 weeks (following i.v.) depending on healing (4 or 8 weeks total)	• Not very useful design (for the proposed indication), for a number of reasons including: • Open-label observations are not adequate to minimize bias • The order of administration of PANTO dosage form (i.v. first followed by oral) is different from that in the proposed indication (oral followed by i.v.). so, this study is designed to answer a different question that the question of interest: can 40 mg i.v. PANTO once-a-day be used as an alternate to 40 mg oral PANTO per day in those patients who are unable to take oral medication? • Establishing "efficacy" by showing equivalence in complete healing of esophageal lesions or relief of symptoms to a historical comparator is not appropriate without proper validation of such historical positive control. • The design of this and the study below is useful as hypothesis generating. The sought indication may be eventually expanded.
FK3050 Dr. R. Fischer (Germany)	M = 94 F = 82 Total # of patients 176 Age: 21-84y Median 59y	This study had identical design to the one described in detail above, except for the fact that in FK3050, PANTO lyophile 40 mg QD was administered as a longer infusion (15 instead of 4 min.)	Same as above	• Not very useful design (same reasons as listed above) NOTE: Neither study BAT010 nor FK3050 is considered supportive. None of these two trials will be reviewed here.
Reviewer's Table				

X. STUDY 3001K1-309-US GMR-32141

"A comparison of gastric acid secretion responses in patients with gastroesophageal reflux disease who are switched from oral to intravenous pantoprazole"

Date of Report: 18 June 1998.

1. Hypothesis

40 mg PANTO i.v. formulation is equivalent to 40 mg oral PANTO in the suppression of basal and maximal acid secretion in erosive esophagitis patients. Patients who have been stabilized on 40 mg oral PANTO can be safely switched to 40 mg i.v. PANTO for one week.

2. Objective

This trial was set to compare the basal gastric acid output (BAO) and the maximum pentagastrin-stimulated acid output (MAO) response in GERD patients with a history of erosive esophagitis who were switched from oral to i.v. PANTO dose formulations. Results from this study are expected to provide pivotal data to support an indication for i.v. PANTO use as an alternate dose formulation in patients who cannot take oral medication.

3. Study Population (Table 3)

This was adequate for this type of study. After screening, patients with GERD and a documented history of EE who had been on a regimen of acid suppressants (i.e., H_2-receptor antagonists or proton pump inhibitors) or antacids and who satisfied the inclusion-exclusion criteria listed in Table 3 were randomized. In the main, the patient population used in this study is representative of the adult EE population in which use of i.v. PANTO would be indicated. Generalizations to this larger patient population would be reasonable.

TABLE 3
Study 30001K1-309-US

Characteristics of the Study Population

INCLUSION CRITERIA	REASONS FOR EXCLUSION
• Signed informed IC • Men or nonpregnant, nonlacting women[a], aged 18 to 65y inclusive • Hx of EE documented by endoscopy and a previous diagnosis of GERD • Treatment with acid suppressants (i.e., H_2 antagonists or proton pump inhibitors) or antacids • Clinical laboratory values WNL of the investigator's laboratory and normal results for a 12-lead EKG, unless the investigator documented that the deviations were not clinically important or were directly related to an allowable pre-existing medical condition • High probability for compliance and completion of the trial.	• Obstructive esophageal strictures[b] • Esophageal diverticuli[c] • Esophageal varices[d] • Barrett's esophagus[e] greater than 3 cm or with high-grade dysplasia • Active gastric, pyloric channel, or DU[f] • Hx of ZES or mastocytosis • Hx of high suspicion of scleroderma or other connective tissue disorder • Hx or high suspicion of achalasia • Previous surgery of the esophagus and/or UGIT; [appendectomy, cholecystectomy, or colonic polypectomy were permitted] • Unstable[g,h] cardiovascular, pulmonary, or endocrine disease; clinically important renal or hepatic disease or

	dysfunction; hematologic, 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 • Chronic use of systemic glucocorticoids within 1 month of study day 1 • Use of NSAIDs (other than daily low-dose aspirin for 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 B_{12} injections • Inability to tolerate a nasogastric (NG) or orogastric tube • Consumption of green leafy vegatables within 12 h before NG tube placement • Hx 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 PANTO • Hx of, or treatment for, alcohol abuse within the past year; consumption of alcoholic beverages within 24 h of gastric acid measurements • 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 PANTO administration[i] • Presence of any acute disease state (eg, 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)

a) 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).
b through f) Discovered on screening endoscopy.
g) An imprecise category, not defined in the protocol.
h) Certain patients with chronic stable medical conditions (eg, 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.
i) Exception: patients completing an ongoing W-AR sponsored study of oral PANTO could be enrolled immediately without the 1 month clinical trial exclusion.

ABBREVIATIONS
IC=Informed Consent; Y=years; Hx=History; EE=Erosive Esophagitis: WNL=Within the normal limits; DU=duodenal ulcer; ZES=Zollinger-Ellison Syndrome; UGIT=Upper gastrointestinal tract; NSAIDs=Non-steroidal anti-inflammatory drugs

4. Study Design

From the review of the evidence, this was a randomized, double-blind, multiple-dose, four-arm/two-period, placebo-controlled trial.

5. Study Periods (Table 4)

Each patient participated in this trial for ca. 42 days. This included a pre-study screening period of approximately 3 weeks, a 10 to 24-day oral PANTO treatment period and a 7-day i.v. treatment period.

a. Pre-study (Screening) Period

This period included a complete clinical evaluation composed of medical Hx, complete P.E., EKG, ophthalmological examination, laboratory evaluation and vital sign measurements. On November 27, 1997, the protocol was amended to include an endoscopy to verify patient exclusion criteria. However, since enrollment of subjects was well underway when the amendment was implemented, not all screened patients underwent the endoscopic examination.

b. Study (Treatment) Period

1) Treatment Period 1 (Oral Phase) (Table 4)

Patients took their last dose of prestudy acid suppressant or antacid on the day before study day 1. Patients were randomly assigned to one of the following four treatment groups, where the most important sequence of treatment, oral in Period 1, I.V. in Period 2, is highlighted.

Treatment Period 1	Treatment Period 2
PANTO, 20 mg PO	PANTO, 20 mg I.V.
PANTO, 20 mg PO	PL, 20 mg I.V.
PANTO, 40 mg PO	**PANTO, 40 mg I.V.**
PANTO, 40 mg PO	PL, 40 mg I.V.
PANTO = Pantoprazole PL=Placebo	

After the prestudy (screening) period and a brief P.E. and laboratory evaluation on day 1 (Table 4), patients received their first dose of oral PANTO under double-blinded conditions. They were then released from the site with a sufficient supply of test medication to be self-administered once daily on an outpatient basis up to day 14. A diary card was provided for recording the date and time that the patients took test medication, antacids, or concomitant medications, or experienced any GERD symptoms or AEs.

TABLE 4

Study 3001K1-309-US

Flow Chart of Study Assessments

Procedure	Prestudy Screening	Period 1: Oral								Period 2: Intravenous														Final Eval[a]
Study Day	-21 to -1	1	2-9		10				11					12			13-16			17				18	
Study Hour				0		14	22	23	24	0	14	22	23		24	0		0			14	22	23	24	
Inpatient Period (h)[i]						x-			-x	-----							x-							-x	
Outpatient Visit			x														x								
Medical History	x																								x
Complete Physical	x																								
Brief Physical			x		x													x							
Lab Evaluation	x		x		x													x							x
Thyroid Evaluation	x		x		x													x							x
EKG (12 lead)	x		x																						x
Vital Signs[b]	x		x		x					x						x	x	x							x
Urine Drug Screen	x																								
Serum Preg. Test[c]	x		x																						x
Fecal Occult Blood	x																								
Endo. Examination	x																								
Ophthal. Exam	x																								x
Prev. Acid Sup. Ther.	<-------x																								x--->
Oral Panto Admin[d]			x----------x																						
IV PANTO/PL Adm[e]										x						x	x	x							
NPO (h)[f]						x-			-x		x----------x										x-			-x	
NG Tube Placement[g]							x				x										x				
BAO (h) Collection							x-----x				x--------x										x--------x				
PG Injection[h]							x				x										x				
MAO (h) Collection							x-----x				x---------x										x-----x				
Discharge[i]																									x

This Table corresponds to sponsor's Figure 6.1A, with some modifications.

a) Final evaluation done after last gastric acid measurement, or if patient withdraw early and did not finish the study.

b) Oral temperature, respiratory rate, sitting BP and pulse.

c) Female subjects only.

d) If a patient received oral PANTO for more than 10 days (up to 14 days maximum), subsequent study days referred to in the flow chart and protocol were to be adjusted appropriately to reflect this modification (ie, day 11 – first IV dose – became day 12-15 depending on the number of days of oral dose administration)

e) The I.V. test medication was given as a 15-min. I.V. infusion.

f) Nothing by mouth (NPO). Patients were not allowed to consume foods or fluids for at least 8 h before NG tube placement; or to consume green leafy vegatables for 12 h before tube placement.

g) Nasogastric (NG)

h) Pentagastrin (PG) was administered subcutaneously at a dose of 6.0 μg/Kg.

i) Discharge after final study procedures on day 18.

The patients were to return to the clinic on the morning of day 10 and were to undergo the procedures listed on Table 4 before receiving their final dose of oral PANTO at hour 0 (day 10). Last-day **oral BAO (BAO_{LPO})** and last-day **oral MAO (MAO_{LPO})** were obtained as follows

- At hour 14, the patients were not allowed to consume food or liquids (NPO)
- An NG tube was inserted and positioned properly by hour 22 and BAO_{LPO} measurement was obtained from hours 22 to 23
- At hour 23, a pentagastrin injection was administered and MAO_{LPO} measurement was obtained from hours 23 to 24
- For both BAO and MAO, acid output measurements were obtained every 15 min. and then summed to determine the hourly acid output.

2) <u>Treatment Period 2 (I.V. Phase) Table 4</u>

At the end of day 10, immediately after the MAO_{LPO} collection and vital signs measurements. patients received their first dose of I.V. PANTO or PL at hour 0 (day 11). The first-day **I.V. BAO ($BAO_{FI.V.}$** and the first-day **I.V. $MAO_{FI.V.}$** were obtained as follows on day 11:

- At hour 14, the patients started the NPO period
- At hour 22, an NG tube was inserted and from hours 22 to 23 the $BAO_{FI.V.}$ measurement was obtained
- At hour 23, a PG injection was administered and $MAO_{FI.V.}$ measurement was obtained from hours 23 to 24.
- After all day 11 gastric acid collection procedures were completed and vital signs were measured, patients received their second dose of I.V. study drug (hour 0, day 12) before being discharged from the clinic.
- A diary card was provided for recording use of antacids or concomitant medications, symptoms of GERD, or AEs.
- Patients were to return to the clinic each morning on days 13 to 16 to receive their i.v. infusion of test medication.
- Vital signs were taken on each of these days before administration of the i.v. infusions.
- On the morning of day 17, patients were to return to the clinic to undergo the same procedures performed on day 10 before they received their last dose of i.v. test

medication at 0 hour (day 17). The last-day I.V. BAO ($BAO_{LI.V.}$) and the last day I.V. MAO ($MAO_{LI.V.}$) were obtained as follows on day 17.

- At hour 14 the patients started the NPO period.
- At hour 22, an NG tube was inserted and $BAO_{LI.V.}$ was obtained from hours 22 to 30.
- At hour 23, a PG injection was administered and $MAO_{LI.V.}$ was obtained from hours 23 to 24.
- Patients then underwent a final safety evaluation and were discharged from the trial.

6. Clinical Supplies, Randomization/Blinding

The information on the identity of investigational product is summarized below:

DRUG INFORMATION

Drug and Dosage	Dosage Formulation	Batch No.	Formulation No.	Manufactured by:
PANTO Lyophile	40 mg/Vial	9620679	09306621	Byk Gulden
PANTO Lyophile	20 mg Tablets	W22341A	0930664C	Byk Gulden
PANTO Lyophile	40 mg Tablets	W22341B	0930665C	Byk Gulden
Pentagastrin	2 ml/ampule, 0.25 mg/ml	Lot No. LO42		Trade package (Wyeth-Ayerst) NDC No. 0046-3290-10

This Table corresponds to sponsor's Table 6.4.2A., with minor modifications

From the review of the evidence, the process of randomization and assigning of patients to treatment groups, and the procedures to ensure and maintain blinding (the study can be considered double-blind with respect to the dose level of test medication) were adequately executed. In summary, a screening number was assigned when the patient was first seen and evaluated for inclusion into the study. After meeting eligibility requirements, a patient was then assigned a patient number and was randomized into the study on or before day –1. A computerized randomization/enrollment (CORE) system of automatic randomization[7] was used. The randomization table was constructed in **blocks of eight,** consisting of 3 assignments of

[7] Randomizations were provided on page 197 of sponsor's supplemental volume 1 (Study Documentation).

40 mg PO PANTO + 40 mg I.V. PANTO, 1 assignment of 40 mg PO PANTO + 40 mg I.V. PL, 3 assignments of 20 mg PO PANTO + 20 mg I.V. PANTO, and 1 assignment of 20 mg PO PANTO + 20 mg I.V. PL. The system assigned the randomization number and combination therapy for a given patient by selecting the next sequential number from the central table.[8]

With regard to blinding, PANTO for i.v. infusion was supplied by W-AR as a lyophilized powder formulation in open-label, sealed glass vials containing 40 mg of drug. The final dose was reconstituted with 0.9% sodium chloride before administration. PL for i.v. infusion was composed of 0.9% sodium chloride and was supplied by each site. Oral PANTO was supplied by W-AR as identically appearing tablets containing 20 or 40 mg of the drug. Pentagastrin was supplied by W-AR in ampules containing 0.5 mg (0.25 mg/mL). **The pharmacist at the site was responsible for blinding and labeling each patient's assigned treatments and for ensuring that the double-blinded randomization schedule was followed.**

Potentially eligible patients were assigned a patient number and were randomly assigned to treatment on or before day –1. A CORE system of automatic transtelephonic randomization was used. If, after screening, the patient was found to be eligible for the trial, the unblinded dispenser called the telephone number provided at the time of initiation. The caller was required to enter an investigator ID, a password, the patient number, and the patient's date of birth. In return, the caller was given the oral dose level (20 or 40 mg) and the i.v. treatment ("active" of PL) assignments. The CORE system also sent confirmation of the treatment assignments by telefax to the third-party unblinded dispenser.

7. Prior and Permitted/Prohibited Concomitant Therapy/Compliance

The sponsor states that reasonable efforts were made to determine any treatment received by the patient within 1 month before administration of the test medication. All such information, including the name of the procedure or drug and duration of treatment, was specified and recorded on the patient's CRF.

- Participating patients were required to be taking oral acid suppression or antacid therapy before being randomized into the trial. Although antacids were allowed during the study if needed for symptomatic relief of GERD symptoms, antacid use was discontinued for at least 12 h before and throughout the gastric acid output collection procedure. Patients continued their other usual medical therapies according to standard clinical practice with approval from the medical monitor. However, on gastric acid measurement days concomitant medications were withheld for at least 12 h before and throughout gastric acid collection procedure.

---

[8] In the case where the next default assignment was the third PL in a row for the calling site, the system skipped over that assignment and assigned an active number (i.e., assigned the "active" test medication). Alternatively, if the next default assignment was the seventh consecutive active for the calling site, the system skipped it and searched for a PL assignment. The numbers which were skipped were utilized for the next call. This maintained a balance of patients receiving PL and "active" medication at each site. In order to maintain the desired balance among the completor patients, the system automatically inserted into the initial 48 slots a replacement randomization number each time a patient was dropped. Each replacement number matched the therapy of the randomization number of the dropped patient.

Any medically necessary concomitant medications were approved by the medical monitor. All concomitant medication taken from study day 1 until discharge from the study was recorded on the patient's CRF. The name of the drug and duration of treatment was recorded on the CRF. On gastric acid measurement days, the time of each dose of concomitant medication was also recorded.

- Patients were not to receive any of the following:

  a) Systemic glucocorticoids within 1 month of study day 1.
  b) NSAIDs within 1 week of study day 1. [Low-dose aspirin for cardiovascular protection was permitted].

  c) Drugs whose absorption is pH dependent, eg, ketoconazole, ampicillin esters, iron salts.

- As depicted in Table 4, the first and last two oral PANTO doses and all of the i.v. test medications were administered at the study site. For the remaining outpatients oral PANTO doses, patient compliance was assessed at the study site by a count of the study medication. In addition, the dosing schedule was tracked on a diary card and by telephone contact with the patient.

8. Evaluation Criteria

a. Efficacy

Refer to Section X, 5. b) and Table 4 for the precise times and details of acid secretion collection[9] and measurements, which included BAO (basal acid output) and MAO (maximal pentagastrin-stimulated acid output). BAO and MAO were obtained following the last dose of oral PANTO, the first and last dose of i.v. test medication (at 22 to 24 h after their dose of test medication on the previous day).

- The primary efficacy endpoint was comparison of the mean MAO following the last dose of i.v. PANTO with that after the last dose of oral PANTO ($MAO_{LI.V.}$ vs MAO_{LPO}) for the 20 and 40 mg treatment groups.

- The secondary efficacy endpoint was the comparison between the first i.v. dose mean and the last oral dose mean ($MAO_{FI.V.}$ vs MAO_{LPO}).

- Other secondary comparisons were the first i.v. mean BAO with the last oral mean BAO ($BAO_{FI.V.}$ vs BAO_{LPO}) and the last i.v. mean BAO with the last oral mean BAO ($BAO_{LI.V.}$ vs BAO_{LPO}).

[9] Detailed instructions for collection and analysis of the samples were provided in an Operations Manual (sponsor's Attachment 1) in order to standardize the procedure across sites. In addition, an Investigator's Meeting was held and included a demonstration of the collection and analysis procedures.

b. Safety

The recording, handling, grading and reporting of AEs and laboratory determinations to evaluate safety, were all adequate.

9. Details of Statistical Methodology for the Efficacy Analyses

a. Determination of Sample Size

The sponsor cites published data which suggest 5 mEq/h as a reasonable estimate of the standard deviation of the difference between groups when the acid output is in the range of 15 to 20 mEq/h.[10] Given that the following assumptions were met, the probability of rejecting the null hypothesis and concluding the two dose formulations are comparable[11] will be approximately 0.80:

1) The MAO for the oral formulation will be 17.5 mEq/h.

2) The upper limit of the 95% confidence interval difference that one would be willing to accept to declare the two formulations comparable is 3.5.

3) The true difference between the two formulations is 0.

4) The number of patients per treatment group is 18.

b. Study Populations Analyzed

Three approaches to the selection of eligible patients were used:

- **ITT:** Patients who had at least one MAO measurement in each study period (i.e., MAO_{LPO} and either $MAO_{FI.V.}$ or $MAO_{LI.V.}$). This population included patients with protocol violations.
- **MITT:** Same as ITT but excluded patients who received an incorrect dose of i.v. PANTO or pentagastrin. This population included any patient with any other protocol violation.
- **VFE:** Patients who complied with and completed all aspects of the protocol.

c. Comparisons Within Dose Groups

- The main focus of the analysis was the comparison of gastric acid output between the oral and i.v. dose formulations.

---

[10] [W.D. White and K. Juniper. Repeatability of Gastric Analysis. Digestive Diseases 18:7-13 (1973)].

[11] There were two primary comparisons between i.v. and the oral dose formulations for both doses. One was based on the 40 mg dose and the other on the 20 mg dose. Each comparison was based on ca. 18 patients who were to receive the oral and i.v. formulation of each dose.

- The primary endpoint comparison was the mean intrapatient difference between the MAO_{LPO} and the $MAO_{LI.V.}$.

- The null hypothesis was that $MAO_{LI.V.} - MAO_{LPO} \geq 0.2 \times MAO_{PO}$ ($MAO_{LI.V.} - 1.2 \times MAO_{LPO} \geq$) and the alternative was that $MAO_{LI.V.} - 1.2 \times MAO_{LPO} < 0$.

- If the null hypothesis was rejected, then it would be concluded that the acid output for the i.v. form was at most 20% greater than that of the oral form and that therefore, the two forms of pantoprazole were equivalent.

- For each patient the equivalence difference $MAO_{LI.V.} - 1.2 \times MAO_{LPO}$ was calculated. The one-sided t-test was then applied to check the null hypothesis that the i.v. and oral forms were *not* equivalent. Separate comparisons were done for the 20 and 40 mg groups at a one-sided α-level of 0.025. In addition the normality of the equivalence difference was tested by the method of Shapiro and Wilk, and the nonparametric sign and signed-rank tests were also run. Since the equivalence difference was generally not normally distributed, the p-values of the signed-rank test were quoted in this report. P-values from all tests were given in the sponsor's Statistical Appendix, Volume 2.

- A similar testing procedure was used to compare the $MAO_{FI.V.}$ with the MAO_{LPO} and to compare either $BAO_{FI.V.}$ or $BAO_{LI.V.}$ with the BAO_{LPO}. [These comparisons were declared secondary in the protocol and were done separately for the 20 and 40 mg dose groups.]

- For each patient the following was also calculated in order to compare acid output after one day of i.v. PANTO with 7 days of i.v. PANTO $MAO_{LI.V.} - MAO_{FI.V.}$, and $BAO_{LI.V.} - BAO_{FI.V.}$. The mean for each difference was determined separately for each PANTO dose group and compared to 0 by the signed-rank test. This was a two-tailed test with significance declared at $p<0.05$.

d. <u>Comparisons Across Dose Groups</u>

- Other analyses were run across treatment groups. Since the two forms could be therapeutically comparable but ineffective, an analysis of covariance was used to compare MAO and BAO between each of the two PANTO i.v. groups and PL following the first i.v. dose and the last i.v. dose; the two PL groups (one had received 20 mg PANTO PO and the other 40 mg PANTO PO in the first period of the study) were pooled for this analysis. The BAO_{LPO} or MAO_{LPO} was used as the covariate. There were four analyses run: $MAO_{FI.V.}$, $MAO_{LI.V.}$, $BAO_{FI.V.}$ and $BAO_{LI.V.}$

- Because patients had received different treatments during the oral phase of the trial, the covariate was not randomly distributed across i.v. treatment groups. As a result, the highest individual acid output rates were observed in the 20 mg PANTO PO group. In order to better balance the covariates, the largest acid output rate from the last oral day was determined for each of the three treatment groups (20 mg i.v. PANTO, 40 mg i.v. PANTO, and i.v. PL). The smallest rate of the three was identified and individual patients with an oral acid output rate above this value were removed from the analysis. The analysis of covariance was performed on the original data as well as on the ranks of the data.

- Another analysis involving the PL groups was to compare the difference $MAO_{LI.V.} - MAO_{LPO}$ between the PANTO and PL groups that started with the same oral dose. This was also done with BAO (ie, $BAO_{LI.V.} - BAO_{LPO}$). The Wilcoxon rank-sum test was used for these comparisons.

- The BAO_{LPO} and MAO_{LPO} were also compared between the 20 and 40 mg dose groups by a Wilcoxon rank-sum test.

- Significance was declared at $p<0.05$ for all comparisons among [or between] treatment groups.

10. Results

a. Number of Patients per Site

At each participating site, either the Principal Investigator or the Subinvestigator was a qualified gastroenterologist. As shown below, two of the 8 sites enrolled no patients:

M. Feldman, M.D. (309A6)
Dallas, VA Medical Center
[n=0]

E. Kelly, M.D. (309A3)
PPD Pharmaco, NC
[n=8]

P. Maton, M.D. (309A5)
Inst. Dig. Dis. Special., OK
[n=9]

D. Metz, M.D. (309D3)
Univ. Penn. Med. Center
[n=2]

G. Ohning, M.D. (309D4)
WLA VA Medical Center
[n=0]

J. Pisegna, M.D. (309A4)
CURE.West LA Medical Center
[n=6]

V. Pratha, M.D. (309A7)
Clin. Appl. Labs., San Diego, CA
[n=20]

S. Wason, M.D. (309A2)
Phoeniz Internat., Cincinnati, OH
[n=20]

[Total n=65]

b. Patient Disposition

- All 65 patients enrolled in the trial received the oral dose of PANTO (Period 1, Oral Phase) and were included in the safety population.

	PANTO mg per day PO	
	20	40
Received Last Day Oral BAO_{LPO}/MAO_{LPO}	[n=34]	[n=31]

- During Period 2, I.V. Phase, 2 patients (309D3-0001 in the 20 mg i.v. group and 309A5-0002 in the 40 mg i.v. group) D/C after receiving the first dose of i.v. PANTO but before the $BAO_{FI.V.}/MAO_{FI.V.}$ determination. At this point, the distribution of patients was:

	PANTO 20 mg I.V.	PL 20 mg I.V.	PANTO 40 mg I.V.	PL 40 mg I.V.
First Day I.V. $BAO_{FI.V.}/MAO_{FI.V.}$	[n=24][a]	[n=7][b]	[n=23]	[n=7]
a) Pt. 309A3-0008, had no 1st day i.v. BAO/MAO determination but did have last day i.v. BAO/MAO determination.				
b) Pt. 309A7-0014, had no 1st day i.v. BAO/MAO determination but did have last day i.v. BAO/MAO determination.				

Pt. 309A5-0005 in the 20 mg i.v. PANTO group D/C before the $BAO_{LI.V.}/MAO_{LI.V.}$ determination. The remaining 62 patients completed the trial. Although one pt. in the 20 mg i.v. PANTO group and one in the 20 mg I.V. PL group missed their $BAO_{FI.V.}/MAO_{FI.V.}$ determinations, both had their last day i.v. $BAO_{LI.V.}/MAO_{LI.V.}$ determinations and both are listed as having completed the trial.

- The number of patients who discontinued tratment during the trial and the total number of patients analyzed, per group was:

NUMBER (%) OF PATIENTS WHO DISCONTINUED BY PRIMARY REASON

	Treatment Group				
Reason	20 mg PO PANTO 20 mg I.V. PANTO [n=26]	20 mg PO PANTO 20 mg I.V. PL [n=8]	40 mg PO PANTO 40 mg I.V. PANTO [n=24]	40 mg PO PANTO 40 mg I.V. PL [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)
Pts. Completing Last Day I.V. $BAO_{LI.V.}/MAO_{LI.V.}$	[n=24]	[n=8]	[n=23]	[n=7]	[n=62]

c. Demographic and Other Baseline Characteristics

The sponsor presented these data in a series of Tables, on all patients (sponsor's Table 8.2A), ITT patients (sponsor's Tables 8.2B), MITT and VFE populations (sponsor's Supportive Tables 3 and 4). The four treatment groups were comparable to each other in demographic characteristics. All were less than 65 years of age (mean age of 44.5y), 54% were F, 46% M, mostly white (68%), with average weight of 86.5 Kg, height 168 cm and mean body mass index of 30.7 Kg/m^2. Aside of a previous history of GERD, none of the patients were known to have any illness at baseline that might interfere with the effect of test medication or the interpretation of the results. Many patients had a history of chronic, stable medical conditions that would not interfere with the conduct of the trial.

d. Previous and Concomitant Medication

- Prior non-study medication was taken by virtually all 65 patients (at least 1 or more medication category). From sponsor's supportive Table 6, the following categories of medications were taken by 20% or more of the patients, with no statistically significant differences among the four treatment groups:

Drugs for treatment of Peptic Ulcer	89.2%
Antacids	33.8%
Other Analgesics and Antipyretics	24.6%
Hypnotics and Sedatives	20.0%
Antidepressants	20.0%

- Similarly, on average, 93.8% of the patients took at least 1 or more medications during the trial, with no significant differences among the four treatment groups. From sponsor's Table 8.3A, the following categories of medications were taken by 10% or more of the patients, with no statistically significant differences among the four treatment groups:

Other analgesics and antipyretics	50.7%
Antacids	47.6%
Antidepressants	15.3%
Anti-inflammatory/antirheumatics, non-steroids	15.3%
Antihistamines for systemic use	13.8%
Hormones and related agents	10.7%

e. Protocol Violations/Populations Analyzed

- 3 previously defined study populations (i.e., ITT, MITT and VFE) were analyzed for efficacy. A listing of efficacy exclusions by patient and a summary of patient evaluability is given in Table 5. The trial was designed to allow for the completion of 48 patients in total, with at least 24 in each of the two dose groups (i.e. the 20 and 40 mg of PANTO). All 65 patients received PANTO in either oral or intravenous formulation and were considered valid for the safety analysis. As mentioned above, 62 patients completed the trial.

- According to the sponsor, all exclusions were made while the study was still blinded. Data for 12 patients were excluded from the VFE population (Table 5): 5 patients from the analysis of the I.V. PANTO 20-mg group, 4 from the analysis of the I.V. PANTO 40-mg group, 1 from the analysis of the I.V. PL 20-mg group and 2 from the analysis of the I.V. PL 40-mg group.

TABLE 5
Study 3001K1-309-US
Listing of Efficacy Exclusions by Patient

Treatment Group Patient ID	Age (y), Gender	Included in ITT	MITT	VFE	Reason for Efficacy Exclusion
PANTO 20 mg PO, 20 mg I.V. [n=5]					
309A5-0005	43 F	Y	N	N	Discontinued
309A5-0009	43 M	Y	Y	N	Late MAO_{LPO}
309A7-0001	30 F	Y	N	N	Dosing error-test medication
309A7-0003	48 M	Y	N	N	Dosing error-test medication
309D3-0001	53 F	N	N	N	Discontinued
PANTO 20 mg PO, Placebo I.V. [n=1]					
309A5-0001	48 F	Y	N	N	Dosing error-pentagastrin
PANTO 40 mg PO, 40 mg I.V. [n=4]					
309A2-0014	51 F	Y	Y	N	Early MAO_{LIV}
309A5-0002	34 F	N	N	N	Dosing error-pentagastrin/discontinued
309A5-0004	49 M	Y	N	N	Dosing error-pentagastrin
309A7-0004	26 M	Y	N	N	Dosing error-test medication
PANTO 40 mg PO, Placebo I.V. [n=2]					
309A5-0003	40 F	Y	N	N	Dosing error-pentagastrin
309A7-0002	45 F	Y	N	N	Dosing error-test medication

SUMMARY OF PATIENT EVALUABILITY

Population Subset	Patients All	Patients Not Included in the Analysis	PANTO (mg) 20	PANTO (mg) 40	I.V. PL Combined
Enrolled	65	0	26	24	15
Valid-for-safety analysis	65	0	26	24	15
Intent-to-treat analysis (ITT)	63	2	25	23	15
Modified intent-to-treat analysis (MITT)	55	10	22	21	12
Valid-for-efficacy analysis (VFE)	53	12	21	20	12

This Table is a composite of sponsor's Tables 9.1B and 9.1A, with major modifications. There were no exclusions based on lack of compliance.

f. Results of Efficacy Evaluations[12]

In this section, emphasis is put on results with the 40 mg PANTO given intravenously because, according to the draft labeling proposed by the sponsor, this is the recommended adult i.v. dose. Summarized will be results on MAO (the primary parameter of efficady) but also BAO (a secondary parameter of efficacy). Although all of the comparisons tested below will be commented upon, detailed data in tabular form is presented only for the most clinically interesting comparisons.

[12] A listing of the individual patient response data for gastric acid aspiration was provided in sponsor's supportive Table 15.