→ At maternally toxic doses in rats, pantoprazole was embryo/fetotoxic and caused reduced pup survival. At lower doses, it produced reduced fetal and pup weights and delayed development.

- By comparison, the following is reproduced from the PRILOSEC® (omeprazole) delayed-release capsules, PREGNANCY CATEGORY C section: "In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/Kg/day (ca. 17 to 172 times the human dose) produced dose-related increases in embryo-lethality, fetal resorptions and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal development toxicity were observed in offspring resulting from parents treated with omeprazole 13.8 to 138.0 mg/Kg/day (ca. 35 to 345 times the human dose). There are no adequate or well-controlled studies...."

- According to the sponsor, at the highest dosages used in rat carcinogenicity studies, the AUC for PANTO was ~20 times higher than that for OME and ~40 times higher than that (extrapolated) for LANSO. At the highest dosages used in mouse carcinogenicity studies, the AUC for PANTO was ~25 times higher than that for OME and ~6 times higher than that for LANSO.

  → AUC gives a better measure of exposure than other PK parameters.

  The reviewer wishes to point out that comparison of the L-T effects of PPIs in animals is of interest but the most relevant data are obtained from controlled L-T therapeutic exposure in humans.

- As summarized in Fig. 1, PANTO metabolism is extensive in mice, rats, and dogs. First-pass metabolism rather than absorption reduces systemic availability in these species. **Sulfone** formation is the major metabolic pathway in rats and dogs. There are over 20 metabolites in rats, dogs, and monkeys. PANTO is metabolized primarily by the CYP3A and CYP2C isozymes systems in rats.

  → However, for PANTO no inhibition of metabolism has been shown to occur in humans.

- At very high doses (≥200 mg/Kg) and after repeated-dose administration, PANTO induced hepatic enzyme activities in rats.

  → Both OME and LANSO exhibited mixed CYP1A and CYP2B1/2 induction, whereas, PANTO demonstrated a more pronounced induction of CYP2B1/2.

II. SUMMARY OF HUMAN PKs AND BIOAVAILABILITY

The sponsor summarized this information in their Table 3.6A; a total of 45 Phase I clinical PK trials, involving ca. 1000 subjects, has been carried out. Included were studies on General PKs (Pilot and Background), Bioavailability/~~Bioequivalence~~, ~~Drug~~ Interaction, Special Populations and Food Effects. The information from these studies is briefly summarized below.

- Oral and I.V. PANTO PKs were linear and dose proportional over the dose range of 10 to 80 mg and, based on limited I.V. data, up to 240 mg.

- PANTO was rapidly and well absorbed after oral administration as a pH-adjusted solution; as expected, delayed, but consistent, absorption resulted from the enteric coated PANTO tablet formulation.

- With the enteric coated tablet, t_{max} was ca. 2.5 h and the absolute bioavailability was ca. 77%.

- The drug is extensively bound to plasma proteins (98%), undergoes little first-pass metabolism (19%) and does not accumulate after multiple doses.

- The concomitant intake of food or antacids had no significant effect on the PKs of this PPI.

- According to the sponsor, all tablet formulations were bioequivalent in terms of rate and extent of absorption. The dosage form used in Phase II efficacy trials was the same formulation which is expected to be marketed. This formulation also exhibited appropriate pH-related dissolution characteristics for an enteric coated dosage form.

- PANTO had a small steady-state volume of distribution (11 L) and was rapidly cleared (8 L/h) from the systemic circulation with a $t_{½}$ of approximately 1 h in normal PANTO metabolizers. Despite the short elimination half-life, this drug provided dose-related, 24-h duration of activity, due to its irreversible action on the gastric parietal cell proton pumps.

- PANTO was metabolized extensively by demethylation (CYP2C19) and subsequent sulfation and by oxidation/reduction (CYP3A4) to several inactive metabolites that are mostly renally excreted. About 3% of the population studied were slow CYP 2C19 metabolizers; compared to normal metabolizers, this group had lower clearance (<2.0 L/h) and greater $t_{½}$ (>3.5h) values, but still exhibited minimal accumulation with once daily dosing.

- PANTO PKs for patients with renal impairment were similar to those for healthy subjects.

  → There is no dosage adjustment recommended based on gender, age and renal function.

- Even though pantoprazole elimination was diminished in patients with cirrhosis or Child-Pugh Class A or B liver impairment, there was minimal accumulation and plasma concentrations were no greater than those observed with slow CYP2C19 metabolizers, where no dosage adjustment is warranted.

→ A reduction in dosage frequency in severe hepatically impaired patients should be considered.

- 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 oral contraceptive. Furthermore, PANTO did not induce hepatic enzymes, as shown with theophylline, antipyrine and caffeine markers.

→ Overall, PANTO appears to have a very low potential for drug-drug interaction.

III. SUMMARY OF HUMAN PHARMACODYNAMIC STUDIES

These studies were undertaken to determine the dose response, onset and duration of action and effects of single and repeated doses for both oral and I.V. dosage forms of acid secretory datameters.

Study 3001K1-100US

In this healthy volunteers model, acid secretion was stimulated maximally by pentagastrin and acid output measured over a 25-h period.

PANTO had a rapid onset of activity following I.V. administration. By 2h, the mean percent inhibitions of PSAO (pentagastrin-stimulated acid output) for the 20-, 40-, and 80-mg doses were 47, 82 and 97, respectively. The 40-mg dose reduced PSAO to <10 mEq/h by 2 h, and this level of inhibition lasted for 16 h. No further suppression was seen with the 120-mg dose.

→ Oral administration of 40 mg of PANTO produced acid suppression consistent with that produced by the I.V. form.

BvK Gulden Studies

These investigated the PD effects on PSAO of the drug after oral or I.V. administration. and after single or repeated doses.

Inhibition of PSAO increased on successive days during once-daily administration of 15 or 30 mg of PANTO administered **intravenously** for 5 days. Nearly complete inhibition of PSAO was seen on days 4 and 5 with a 30-mg dose. Maximal inhibition was achieved with 40 mg per day of oral PANTO given for 7 days. The inhibitory effect of pantoprazole was reversible. Seven days after the last oral dose of a 7-day treatment period, the acid secretory response to pentagastrin had returned to pretreatment values. No evidence of rebound hypersecretion was observed.

Following the initial **oral dose** of 40 mg PANTO, a 51% mean inhibition was achieved by 2.5 h. With once a day dosing for 7 days the mean inhibition was increased to 85%. The drug suppressed acid secretion in excess of 95% in half of the subjects. Acid secretion had returned to normal within a week after the last dose of PANTO; as in the case following I.V. dosage, there was no evidence of rebound hypersecretion.

pH metry Studies

These were undertaken to evaluate the effect of PANTO, orally or I.V., on **intragastric acidity**.

PANTO, at oral doses ranging from 20 to 120 mg, caused dose-related increases in median basal gastric pH and in the percent of time gastric pH was >3 and >4.

40 mg of PANTO produced optimal increases in gastric pH which were significantly greater than those seen with the 20-mg dose. Doses higher than 40 mg (60, 80, 120 mg) did not result in further significant increases in median gastric pH. The effects of orally administered PANTO on median pH from one double-blind crossover study are shown in Table 2.

TABLE 2

Effect of Single Doses of Oral Pantoprazole on Intragastric pH

	Median pH			
		PANTO (mg)		
Time	PL	20	40	80
8 a.m. – 8 a.m. [24 h]	1.3	2.9*	3.8*#	3.9*#
8 a.m. – 10 p.m. [Daytime]	1.6	3.2*	4.4*#	4.8*#
10 p.m. – 8 a.m. [Nighttime]	1.2	2.1*	3.0*	2.6*

* Significantly different from PL
\# Significantly different from 20 mg

In addition, study GMR-29730, compared the antisecretory effects of PANTO 40 mg with OME 20 mg, each administered daily for 7 days, in a double-blind, crossover design. For both one day and one week treatment periods, PANTO administered in the morning produced significantly greater increases in median pH during 24 h than did OME.

Serum Gastrin, Enterochromaffin-Like (ECL) Cell, and Other (cardiovascular, respiratory, ophthalmic or CNS function) Effects

These data are further reveiwed as part of the Integrated Summary of Safety. In addition, in Clinical Pharmacology study GMR-30077, PANTO 40 mg given once daily for 2

weeks had no effect on the following endocrine parameters: cortisol, testosterone, triodothyropine (T3), thyroxine (T4), TSH, thyronine-binding protein, PTH, insulin, glucagon, renin, aldosterone, FSH, LH, prolactin and GH.

IV. REQUESTED LABELING FOR SHORT-TERM HEALING OF EROSIVE ESOPHAGITIS

Wyeth-Ayerst Labs., Inc. is requesting approval for the healing of erosions/ulcerations of erosive esophagitis associated with GERD.

The language requested for labeling inclusion is:

"INDICATIONS AND USAGE

"Short-Term Treatment of Erosive Esophagitis Associated With Gastroesophageal Reflux Disease (GERD)

[

]

DOSAGE AND ADMINISTRATION

"Treatment of Erosive Esophagitis

[

V. MARKETING OF PANTOPRAZOLE

The sponsor notes that as of February 1998, oran PANTO **in the form of a 40 mg tablet** is marketed in over 50 countries by Byk Gulden Pharmaceuticals of Konstanz, Germany, and its affilates and licensees. [redacted] **moderate to severe erosive esophagitis** [redacted] Wyeth-Ayerst Research (W-AR) has licensed the development and marketing right in the United States for both the oral and intravenous forms of PANTO to the U.K., Canada, Germany and France are among the countries where the drug has been approved for indications that are the same or very similar to the indication sought in the U.S.

Country	Wording Under INDICATIONS AND USAGE

U.K. [Protium or Panselect] For symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion. Moderate and severe reflux esophagitis [DU, GU].

A 4-week period is usually required for the treatment of gastro-esophageal reflux. If this is not sufficient healing will usually be achieved within a further 4 weeks.

CANADA PANTOLOC™ (pantoprazole) is indicated for the treatment of conditions where a reduction of gastric acid secretion is required, such as the following: reflux esophagitis [DU, GU].

The recommended adult oral dose of pantoprazole is 40 mg, given once daily in the morning. In most patients, healing usually occurs within 4 weeks. For patients not healed after this initial course of therapy, an additional 4 weeks of treatment is recommended.

Pantoprazole is not indicated for maintenance therapy. Until adequate long term clinical data are available, pantoprazole should be prescribed only according to the recommended dosage regimens.

Pantoprazole is formulated as an enteric-coated tablet. A whole tablet should not be chewed or crushed, and should be swallowed with water in the morning either before, during or after breakfast.

FRANCE EUPANTOL Therapeutic Indications – reflux esophagitis (the diagnosis of esophagitis must be confirmed endoscopically by the presence of erosions or ulceration). [Progressing DU, Progressing GU].

4 weeks of treatment with one 40 mg tablet daily are usually required for the treatment of gastro-esophageal reflux esophagitis. If this is not sufficient, then treatment can be extended for a further 4 weeks, depending on the endoscopic results.

GERMANY TRADENAME® Therapeutic Indications: - moderate and severe reflux esophagitis [DU, GU].

A 4-week period is usually required for the treatment of reflux esophagitis [and GUs]. If this is not sufficient, healing will usually be achieved within a further 4 weeks.

VI. RATIONALE FOR TESTING PANTO 20 and PANTO 40 mg

The sponsor has not satisfactorily addressed the rationale for testing the doses of PPI employed in the critical clinical trials, for the GERD indication. It is noted above that, as of February 1998, the 40 mg tablet formulation is marketed in more than 50 countries for acid-related indications and *H. Pylori* infection eradication. The current application seeks to support the approval to market PANTO enteric-coated tablets for a) the S-T treatment — 8 weeks) of ——— erosive esophagitis ———

——— All in all, the clinical program consists of a combination of Wyeth-Ayerst (W-A) studies submitted as primary evidence of safety and efficacy, plus supportive data from PK, PD, and clinical efficacy and safety trials conducted primarily by Byk Gulden Pharmaceuticals.

As previously noted, in GERD, the primary goal is to decrease the volume and increase the pH of secretions refluxed into the esophagus. The measurement of **intraesophageal** pH is one of the parameters that may be useful in determining a dose for the treatment of GERD. But, to the reviewer's knowledge, no data from such an evaluation have been submitted for review. Instead, the sponsor tested the effects of graded daily doses of PANTO (20, 40 or 80 vs PL) on **intragastric pH** (Table 2). The latter evaluations demonstrated that doses higher than 40 mg per day did not result in further significant increases in median intragastric pH testing. From these results, testing of the dose of 40 mg once-a-day as the highest dose in efficacy and safety studies in GERD, and including lower doses such as 20 and 10 mg, for comparison, appears justified.

VII. CRITICAL TRIALS IN NDA 20-987

In support of the approval of PANTO for the S-T treatment — 8 weeks) for healing of all grades of erosive esophagitis (EE) ——— the sponsor presents results of two

(2) critical trials. The main experimental features of design and execution and an initial appraisal of the utility of these pivotal studies in our recommendations for regulatory action, are summarized in Table 3.

TABLE 3

Main Features of Design and Execution of and Initial Assessment of the Utility of the Two Pivotal Trials Submitted by the Sponsor in Support of the Approval of the Marketing of LANSO for the S-T Healing of Erosive Esophagitis

Protocol No. # of Centers	No. of Patients Enrolled Per Gender	Main Features of the Trial	Group Being Compared	REMARKS
(GMR-32022) 3001A1-300-US	M = 400 F = 203 Total n 603	Randomized, double-blind, parallel-groups, 4-arm, PL-controlled, dose range. Study Population: patients with symptomatic endoscopically proven erosive esophagitis. Upper g.i. endoscopy at 0, 4 and 8 weeks. The primary endpoint of efficacy was the healing of EE lesions to grade 1 or 0 in the Hetzel-Dent scale. Secondary efficacy endpoints were the persistent absence of symptoms[a] Antacid (Gelusil) tablets allowed for relief of heartburn [max. of 12 tablets in a 24-h period].	All given QD and PO PANTO 10 mg [n=174] vs PANTO 20 mg [n=174] vs PANTO 40 mg [n=173] vs PL [n=82]	• Useful design. • The inclusion of the PL arm is important to demonstrate that PANTO is efficacious. • Efficacy of the 40 or 20 mg PANTO is shown by demonstrating statistical superiority of each of these PANTO doses over PL. • In addition, the dose-response approach is important to test efficacy of the 40 mg PANTO in comparison to the 20 mg dose and choose the best of these two doses.
GMR-32023 3001A1-301-US	M = 169 F = 74 Total n 243[b]	Randomized, double-blind, double-dummy, PL-controlled, parallel-group, 3-arm Study Population: patients with symptomatic, endoscopically proven erosive esophagitis. Upper g.i. endoscopy at 0, 4 and 8 weeks. Primary and secondary endpoints of efficacy as above. Antacid (Gelusil) tablets allowed for relief of heartburn [maximum of 12 tablets in a 24-h period].	PANTO 20 mg QD PO [n=80] vs PANTO 40 mg QD PO [n-81] vs NIZ 150 mg b.i.d. [n=82]	• Useful design. • Efficacy at the 40 mg (at 8 weeks) is shown by demonstrating statistical superiority of this PANTO dose over NIZ 150 mg b.i.d.. • Efficacy of the 20 mg (at 8 weeks) is shown by demonstrating statistical superiority of this PANTO dose over NIZ 150 mg b.i.d. • Comparison to an approved dose of NIZ and demonstrating that the PPI is better than the H2 receptor antagonist in a very robust study is important to decide if only one trial of PANTO against the H_2-receptor antagonist is sufficient to grant a superiority claim.

a) These included: nighttime heartburn, daytime heartburn, acid regurgitation and dysphagia, and Gelusil usage associated with EE.
b) The total n was really 244. One pt. did not receive test medication.

At the end of the assessment of the evidence, the reviewer expects to be able to answer the questions listed below. These questions are related to treatment of erosive esophagitis with this PPI at the oral dose of 40 mg given once-a-day for 4 to 8 weeks.

1. Is 40 mg PANTO **(the proposed dose)** safe and effective?
2. Is 20 mg PANTO safe and effective?
3. Is 40 mg PANTO superior to 20 mg PANTO for the proposed indication?
4. Is 40 mg once-a-day PANTO superior to NIZ 150 mg b.i.d.? [Should this claim be granted on the basis of **one study** only?]
5. Is 20 mg once-a-day PANTO superior to NIZ 150 mg b.i.d.?

VIII. STUDY GMR-32022 (3001A1-300-US)

"Comparison of the Clinical Safety and Efficacy of Pantoprazole 10 mg, 20 mg, or 40 mg Once Daily and Placebo in Patients With Symptomatic Erosive Esophagitis"

1. Hypothesis Four to eight weeks of PANTO 40 mg once-daily or 20 mg once daily will be more effective than PL in the healing of EE and in the rapid relief of associated daytime and nighttime heartburn.

2. Objective: To evaluate the safety and efficacy of PANTO 10 mg, 20 mg, and 40 mg taken once daily in the morning compared with that of PL in patients with reflux symptoms and endoscopically proven erosive esophagitis at grade 2 or greater according to the Hetzel-Dent Scale.[2]

3. Study Population (Table 4)

This was adequate for this type of study. The study population consisted of patients with **symptomatic erosive esophagitis**. Listed in this Table are a) the criteria for randomization of EE patients into the study; and b) the criteria used to exclude patients from participation in the trial.

[D.J. Hetzel et al. Healing and relapse of severe peptic esophagitis after treatment with omeprazole. Gastroenterology 95:903-912 (1988)]

TABLE 4
Study GMR-32022 (3001A1-300-US)

Characteristics of the Study Population

INCLUSION CRITERIA	REASONS FOR EXCLUSION
• Men and nonpregnant, non-nursing women, aged 18 y or older, who had signed IRB-approved written IC documents. • Women of childbearing potential could be included in the study. A woman of childbearing potential was defined as a F who was capable of becoming pregnant. All women of childbearing potential – this included women who were single and women whose sexual partners had been vasectomized – were required to use medically acceptable contraception[a] during their participation in the trial. • Outpatients and inpatients not confined to bed (ie, patients who were admitted to the hospital for not more than 2 days for diagnostic procedures). • Endoscopically demonstrated erosive esophagitis, grade 2 or greater according to the following Hetzel-Dent scale. Grade – Description 0 – Normal mucosa, no abnormalities noted 1 – No macroscopic erosions, but with visible erythema, hypermia, or friability of the esophageal mucosa 2 – Superficial erosion/ulceration affecting less than 10% of the mucosal surface of the distal 5 cm of the esophageal mucosa 3 – Superficial erosion/ulceration affecting 10% to 50% of the mucosal surface of the distal 5 cm of the esophageal mucosa 4 – Deep ulceration anywhere in the esophagus or confluent erosion/ulceration of more than 50% of the mucosal surface of the distal 5 cm of the esophageal mucosa • Symptoms that are typical for RE: acid regurgitation, HB (daytime and/or nighttime: defined as a retrosternal burning pain that rises from the epigastrium and that may radiate into the pharynx), and dysphagia (discomfort swallowing). The patient must have experienced a single episode of at least one of these three symptoms for at least 4 of the previous 7 days.	• Therapeutic doses of PPIs within 1 month of administration of test medication • Esophageal strictures that require dilation for endoscopy • Esophageal diverticulum • Esophageal varices • Barrett's esophagus greater than 3 cm or with high-grade dysplasia • Gastric, pyloric channel, or DU • Hx of Zollinger-Ellison syndrome or mastocytosis • Previous surgery of the esophagus and/or upper g.i. tract except appendectomy, cholecystectomy, or polypectomy • Unstable cardiovascular, pulmonary, or endocrine disease; clinically significant renal or hepatic disease or dysfunction; hematologic, neurologic, or psychiatric disorder, presence of any other unstable clinically significant medical or surgical illness. • Scleroderma or other connective tissue disorder • Achalasia • Suggested or confirmed malignancy, except successfully resected basal cell skin cancer, Hx of chemotherapy or radiation Tx • Clinically significant abnormal laboratory values as assessed by the investigator • Chronic use of glucocorticoids or NSAIDs (other than daily low-dose aspirin for cardiovascular protection) • Simultaneous use of drugs with pH-dependent absorption (eg, ketoconazole, ampicillin esters, iron salts) • Use of drugs that could potentially interact with test medication: oral anticoagulants (warfarin), phenytoin, benzodiazepines. Medication used during endoscopy were allowed. • Clinically significant drug allergies or hypersensitivities • Hx or presence of alcohol or drug abuse • For women, pregnancy or nursing • Participation in any other investigational drug or experimental medical trial within 2 months before the administration of test medication. • Diets that might alter metabolism; clinically significant weight loss or gain within the past month; chronic use of therapeutic vitamin B_{12} injections • Uncooperative patient or a Hx of poor compliance • Known heavy metal toxicity • Hx of a positive test for human immunodeficiency virus (HIV)

Abbreviations used: IC=Informed consent; F=Female; RE=Reflux Esophagitis; HB=Heartburn; DU=Duodenal ulcer; Hx=History; g.i.=gastrointestinal; Tx=Treatment; NSAID=Nonsteroidal anti-inflammatory drug

a- Medically acceptable contraception included oral, injectable, or mechanical devices (eg, condoms).

4. Overall Study Design and Schedule of Evaluations

From the review of the evidence this was a multicenter, randomized, double-blind, 4-arm, parallel trial that investigated the efficacy of ——— (10, 20 or 40 mg once-a-day) in comparison to a PL control in patients with symptomatic erosive esophagitis. The allocation to Tx was 2:2:2:1 with respect to the number of patients that received test medication or PL. The three doses of PANTO were chosen to examine dose-related differences in healing rates. The PL arm provide a negative control for the trial conduct and methodology and a standard against which to compare the safety and efficacy of the experimental drug. Patients received Gelusil (antacid tablets to be taken as needed for symptomatic relief after 5 or more minutes of retrosternal pain, acid regurgitation, or dysphagia, but not within 1 h before or after taking test med. No more than 12 tablets were to be taken in a 24-h period. The initially planned total enrollment was 560 at ca. 50 investigative centers. The expected completed number was 455 patients. Instead, 603 patients were enrolled; of these, 538 completed the trial.

In Table 5, a checklist of clinical and laboratory measurements is given. Randomized into the trial were out- or inpatients who were not confined to bed and had endoscopically demonstrated EE, grade 2 or greater in the Hetzel-Dent scale, and at least a single episode, on at least 4 of the previous 7 days, of one of the symptoms typical for RE (i.e. daytime or nighttime HB, acid regurgitation, or dysphagia). All in all, there were 5 visits (at weeks 0, 2, 4, 6 and 8) and 3 endoscopies [at initial visit (study week 0), visit 2 (study week 4) and visit 4 (study week 8)]. Final efficacy and safety determinations were to be made for all patients with endoscopic evidence of healing to grade 1 or less at study week 4 or 8 or on the last day they took a full dose of medication. Patients could be removed from the trial at any time at their own request, because of lack of efficacy, because of an AE, or for other reasons unrelated to treatment. Patients were to be withdrawn from the study as nonresponders if esophageal lesions deteriorated by at least 2 grades. Patients withdrawn from the trial were not replaced. If a patient decided to withdraw from the study or failed to return, every effort was made to determine the reason.

TABLE 5
Study GMR-32022 (3001A1-300-US)

Study Flowchart Checklist of Clinical and Laboratory Measurements

Visit Number →	(Initial) 0	1[a]	2	3	4
Study Week →	**0**	**2**	**4**	**6**	**8**
Procedure/data collection					
Demography	x				
IC	x				
Hx	x				
Inclusion/exclusion criteria	x				
Complete P.E.	x		x[b]		x
Endoscopy	x		x		x
Gastric Bxs	x		x[c]		x
Serology for *H. pylori*	x		x[c]		x
Brief P.E.		x		x	
EKG	x		x[b]		x
Symptom Questionnaire	x	x	x	x	x
Prior and current medication	x				
Concomitant medication		x	x	x	x
AEs		x	x	x	x
Laboratory evaluation	x	x	x	x	x
Fasting serum gastrin	x		x[c]		x
Dispense test medication and antacids	x	x	x[d]	x	
Collect unused test medication and antacids		x	x	x	x
Dispense daily diary cards	x	x	x[d]	x	
Collect daily diary cards		x	x	x	x

a) All visits were to occur within –2/+3 days of the scheduled study visit and be synchronized to the date of the first administration of the study medication.
b) A complete P.E. including an EKG was to be performed if the patient's lesions had healed or had deteriorated by at least 2 grades. Otherwise, a brief P.E. was to be performed. The EKG was to be performed at the final visit.
c) Gastric Bxs, *H. pylori* tests, and serum gastrin levels were to be performed at visit 2 (study week 4) if the patient's lesions had healed to grade 1 or 0 (became baseline for maintenance study), or if the patient had deteriorated by at least 2 grades. Otherwise these tests were to be performed at the final visit.
d) If healing to at least grade 1 or 0, or deterioration by at least 2 grades had not occurred.

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5. **Clinical Supplies/Randomization/Selection of Timing of Dose for Each Patient/Blinding**

- The source of all medications was Byk Gulden Pharmaceuticals, from Konstanz, Germany. The dosage strengths, formulation and lot numbers of the test medications were as follows:

Test Medication Formulation
and Lot Numbers

Test Medication (Study Arm)	Strength (mg)	Formulation Number	Lot Number
Placebo tablet	--	0930666C	296540
Pantoprazole tablet	10	0930663C	296120
Pantoprazole tablet	20	0930664C	296060
Pantaprazole tablet	40	0930665C	296440

- A computerized randomization schedule was provided by the Biostatistics section of W-AR. A program based on the SAS® PLAN procedure was used to generate the randomization table. The study was designed so that the number of patients assigned to each of the PANTO dose groups would be twice as great as the number assigned to PL. Block randomization was done and each study site was provided with a block (or blocks) of random numbers. Each block consisted of **seven numbers**, two for each PANTO dose group and one for the PL group. This was to ensure that after every seventh patient randomized at a site, the desired balance of two patients in each PANTO group and one in the PL group would be achieved. At each site, randomization numbers were to be assigned consecutively in ascending numerical order at the time the patient was given his or her first package of test medication. Sponsor's Appendix A provided a listing by patient of their patient number, their randomization number, the treatment group to which they were assigned, and the date on which study drug was dispensed. If the randomization process was carried out as planned, then as the randomization numbers increase, the date of study drug dispensation should increase chronologically. A review of the listing showed this was true in all but a few instances.

- Patients were administered either PL or 10, 20 or 40 mg of PANTO once daily in the morning. The timing of dose for each patient was based on the finding that over a 24-h period, gastric acid inhibition was significantly more pronounced when a 40-mg dose of PANTO was administered in the morning rather than in the evening. The increase from baseline in 24-h median pH values was greater after morning administration of PANTO than after evening administration.

- Adequate procedures were used to institute and preserve the blinding of the trial. PANTO and the matching PL were packaged and coded by Wyeth-Ayerst Laboratories, and were supplied to the investigator as identical-appearing blister packs. At the commencement of the trial and at each follow-up visit, each patient received one blister pack containing a 17-day supply of yellow oval PANTO tablets (10, 20, or 40 mg) or

identical appear PL, and one box of 100 Gelusil antacid tablets. Preprinted labels on the packets of investigational drug[3] and box of Gelusil antacid tablets contained the study number and randomization number.

6. **Prior and Concomitant Therapy; Compliance**

- Medication deemed indispensable because of intercurrent acute or chronic disease could be administered provided that it was not prohibited by the study protocol. The dose of the concomitant medication required for chronic conditions was to be kept constant throughout the study. All concomitant treatment, including the name of the drug (trade name or generic name and total daily dose) or procedure, and the start and stop dates were to be recorded on the appropriate CRF throughout the study.

- Supportive medication for the management of EE except for the antacid provided (Gelusil tablets) was proscribed during the study. Concurrent treatment with any of the following medications during any period of the study was prohibited:

  - H_2 receptor antagonists - other PPIs - oral anticoagulants (eg, warfarin)
  - phenytoin - benzodiazepines (except medication used during endoscopy)
  - pH absorption-dependent drugs (eg, ketoconazole, ampicillin esters, iron salts)
  - chronic use of glucocorticoids
  - chronic use of nonsteroidal anti-inflammatory agents (other than daily low-dose aspirin for cardiovascular protection) - prostaglandins
  - prokinetic drugs (eg, MCP, cisapride, bethanechol) - anticholinergics
  - sucralfate - chronic treatment with vitamin B_{12} injections -

- Patient compliance with the dosage regimen was to be assessed by a count of the test medication performed at the study site. Percent compliance was calculated from the number of tablets dispensed and the number returned. Antacid usage was accounted for in the same manner and recorded on the CRF. Patients were considered compliant if they consumed **80% or more of the test medication.**

7. **Evaluation Criteria**

a) **Efficacy**

- The **primary endpoint** for demonstrating efficacy was the resolution of all macroscopic esophageal erosions or ulcerations to **grade 1 or less** by the Hetzel-Dent scale, as confirmed by endoscopy. Endoscopy was to be performed at baseline, at 4 weeks (visit 2) and, if necessary, at 8 weeks (visit 4). All patients whose esophageal

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[3] At the time that the medication was dispensed to the patient, the patient's initials and number, date, and directions for taking the medications were indicated on the label. The medication code for each patient was provided in individual sealed envelopes that were code labeled according to the randomization schedule. In the event of an emergency, the individual patient's envelope could be opened to identify the medication being taken. All envelopes and unused medication wqere to be returned to W-AR at the end of the trial.

lesions were grade 1 or 0 at 4 weeks were classified as responders and as having completed the study. All patients whose esophageal lesions were not healed to grade 1 or 0 after 4 weeks were to continue for an additional 4 weeks. Patients who continued beyond 4 weeks were to have a final endoscopy at 8 weeks. Those patients whose lesions had healed to grade 1 or 0 at 8 weeks were also classified as responders. All patients whose esophageal lesions were grade 2 or greater after 8 weeks were to be classified as nonresponders. **Deterioration by at least two grades at any time** during the trial required withdrawal of the patient as a nonresponder.

- The **secondary endpoint** for demonstrating efficacy was the **absence of typical reflux symptoms.** The patients maintained daily diary cards on which they scored the frequency and severity of acid regurgitation, dysphagia, and daytime and nighttime symptoms of HB by using the following four-point scale.

  0 = no symptoms
  1 = mild symptoms
  2 = moderate symptoms interfering with usual activity
  3 = disabling symptoms interfering with daily routine or sleep

  Patients were to record their daily consumption of Gelusil tablets.

b) Safety

All aspects of safety assessment were adequate. This included evaluations of reports of AEs, results of routine P.E., EKGs, endoscopy, gastric Bx and laboratory determinations.

8. Data Quality Assurance

The procedures instituted to ensure that the data collected were accurate, consistent, complete and reliable were all adequate. The database was properly verified through a series of steps and at the end, was of high quality.

9. Statistical Methodology

a) Determination of Sample Size

- 560 patients were to be enrolled with a sample size ratio of 1:2:2:2 specified for the respective therapy groups. The objective of this study was to demonstrate a significant ($p \leq 0.05$) difference in healing rates between the highest dose (40 mg) of PANTO and PL. Assuming an estimated healing rate of 70% to 90% for PANTO and 20% for PL (therapeutic gains of 50% to 70%), and depending on the cose, the planned sample size was expected to provide greater than 95% power to declare a significant difference between a dose of PANTO and PL. It is important to note that the power exceeds the usual target of 90% due to the **secondary objective** of demonstrating a **difference between doses** of PANTO and also due to sample size considerations for a subsequent follow-up maintenance study

b) Details of Statistical and Analytical Procedures

- Analyses of the primary efficacy measurement were performed on three patient populations; intent-to-treat **(ITT)** patients, modified intent-to-treat patients **(MITT)** and evaluable or valid-for-efficacy **(VFE)** patients. ITT patients were defined as all patients randomized to receive test medication. MITT patients were defined as those who had at least one post-baseline endoscopic evaluation. VFE patients included all patients who satisfied the MITT definition except those who were less than 80% compliant in their test medication, did not have at least one endoscopy at week 4 or beyond, or who had serious protocol violations. Decisions about exclusion from VFE analyses were made on a patient-by-patient basis before Tx group assignments were unblinded. Analysis of the secondary efficacy measurements were based on all patients who provided data for at least one day while on test medication.

- The primary efficacy endpoint was the endoscopic resolution of all macroscopic esophageal erosion or ulceration to grade 1 or 0 according to the Hetzel-Dent scale. Endoscopy assessments were to be made at baseline (week 0) and week 4. Patients whose lesions were healed at week 4 were considered study completers and were classified as healed for the week 4 endpoint.

NOTE Although valid, the above-described approach precluded the gathering of important information. It would have been of interest to determine if patients that healed at Week 4 remained healed at Week 8. EE that has "healed" at Week 4 may recur at Week 8. This may have been due to a) poor quality of healing; or b) the definition of healed ulcer was not standardized. Different results may be obtained if the endoscopy is carried out by the Principal Investigator instead of an inexperienced gastroenterologist since endoscopic visualization of the upper g.i. mucosa is a **subjective approach that requires training.** In addition, there are convincing data available in the literature that once a PPI (i.e. omeprazole) is discontinued, the GERD-related symptoms and endoscopic lesions of GERD return within 48h; during this interval, normalization of serum gastrin levels is concomittantly observed.

- Those patients whose lesions had not healed at week 4 were to continue in the study with an endoscopy at week 8. If the lesions were healed at week 8, the patients were considered healed for this endpoint. Patients who were healed at week 4 were included in the analysis at week 8 and counted as healed.

  The healing rates in each of the four treatment groups were compared at the week 4 and 8 endpoints by using Fisher's Exact Probability Test; data from all sites were pooled. A significant difference among the Tx groups was further examined by comparing the healing rates found in specific pairs of Tx groups by using Fisher's Exact Probability Test. Pairwise comparisons were planned only if the overall test comparing the four Tx groups was significant at the 0.05 level.

- The effect of Tx groups on healing rates while controlling for investigational sites was examined using the Cochran-Mantel-Haenszel (CMH) method with stratification by investigator. The Breslow-Day test associated with each pairwise comparison provides a test of consistency of results across investigative sites. The results of this analysis should be viewed with caution. The number of patients at any given site was small, and as with the Chi-square test, small cell frequencies may lead to difficulties in interpretation.

- Two additional analyses of healing rates were performed. First, the relationship between healing rate and the severity of EE at baseline was examined. Second, healing rates were compared in two patient subgroups defined by whether patients' test results were positive or negative for *H. pylori* at baseline as determined by histology. Patients were divided into subgroups according to their Hetzel-Dent score (score of 2 or score of 3 or 4). Comparisons between and among Tx groups were done within each subgroup using Fisher's exact test. Additionally, stratified CMH analyses were done to obtain Tx comparisons separately controlling for baseline severity and *H. pylori* status. Again, the Breslow-Day test was used to check the consistency of results across subgroups.

- The secondary efficacy endpoint was the **absence of typical reflux symptoms.** Patients were to record, on a daily basis, the frequency and severity of daytime HB, nighttime HB, acid regurgitation, and dysphagia. The patients scored these symptoms daily on a four-point scale. The lowest scale value, 0, indicates the absence of symptoms. A patient was classified as having obtained persistent absence of symptoms on the first day on which no symptoms were reported for that day or any subsequent day. The rates for persistent absence of symptoms were tested for proportional differences in the same manner as the primary efficacy endpoint variable using Fisher's exact test. Analyses of this type were done for the presence or absence of any symptom as well as individually for each of the four symptoms.

- Gelusil use was recorded and analyzed by the Kruskal-Wallis test to determine if the use of antacid tablets differed among the Tx groups.

- Comparisons of the incidence of individual AEs across Tx groups were made using Fisher's Exact Probability Test.

c) Changes in Planned Analyses

[NOTE: An appraisal by our statisticians is needed on the impact of these changes in planned analysis on the conclusion that can be drawn from this trial.]

- The statistical analysis in section b) above differed from that specified in the protocol in several respects. The changes to the planned analyses were made prior to the unblinding of the study.

- With regard to efficacy populations to be analyzed, the protocol referred to ITT, evaluable and completer populations. As defined in the protocol, the ITT population was to include any patient enrolled in the study who had at least one post-baseline endoscopic evaluation. These populations differed somewhat from those actually analyzed.

The ITT population was redefined to include all patients enrolled and randomized to Tx regardless of whether they had a post-baseline endoscopy. This population was analyzed in two ways. In the ITT [+] analyses, a patient with no post-baseline endoscopy was considered healed at weeks 4 and 8. In the ITT [-] analyses, these patients were considered not healed at weeks 4 and 8. The ITT population defined in the protocol was analyzed as planned, but was renamed the MITT population. The evaluable patient population was also analyzed as planned but is referred to as the VFE population in this report. The completer population was discarded from the list of potential populations for analysis because it was expected to be similar to the VFE analysis and would not provide any additional insight.

- Some additional analyses of the symptom data were performed beyond those originally planned. Analyses were done separately for each of the 4 individual symptoms as well as the planned analysis of any symptom. Survival analysis methods were used to evaluate the time to persistent absence of symptoms. This approach provided a comparison among all the groups in the overall distribution of time to persistent absence of symptoms and allowed for censored data (i.e., patients who discontinued without becoming symptom-free) to be taken into account.

- The Kaplan-Meier product-limit method was used to estimate the survival curves. The Wilcoxon test was used for comparison between groups of the survival curves. The survival analyses were supplemented by tabulations by Tx group of the number of patients who had reached a persistent symptom-free state by specific points in time (daily through day 7 and weekly through week 9). This provided further perspective on the difference between groups in the time to becoming symptom-free. Fisher's exact test was used in comparison between groups of the cumulative proportion of symptom-free patients at each time point.

- The original plan for evaluation of Gelusil tablet usage was to base the analysis on the total number of tablets used. It later became apparent that it could be misleading to treat totals based on patients who completed 4 or 8 weeks of therapy the same as totals based on patients who discontinued after 1 or 2 weeks. The total tablet usage was divided by the number of days on study to obtain an average number of tablets taken per day. Both total tablets and average tablets per day were analyzed using the originally planned Kruskal-Wallis test.

10. Results

a) Disposition of Patients/Number of Patients by Site

- The disposition of the 603 patients that were **randomized** into the trial can be summarized as follows:

	Study Arm	Disposition		Total
		Withdrawn	Completed	
TOTAL ENROLLED [n=603]	PL	14	68	82
	PANTO 10 mg	22	152	174
	PANTO 20 mg	17	157	174
	PANTO 40 mg	12	161	173
		63	538	603

Definitions of Study Populations analyzed for Efficacy:
ITT = Received at least one dose of test med.
[Also included in the safety analysis]

MITT = Received at least one dose of test med. + had at least one post-baseline endoscopic assessment

VFE = All patients from the MITT population who were 80% compliant, had at least one endoscopy at week 4 or beyond, and had no major protocol violations.

- Test medication was shipped to the 48 sites listed in Table 6. Three of these sites [Achord ($300K_4$), Dr. Nucci (300 LI) and Verne (30007)]. The 45 remaining sites randomized a total of 603 patients.

TABLE 6
Study GMR-32022 (3001A1-300-US)

Number of Patients Randomized by Investigator

		PANTO (mg)			
	PL	10	20	40	Total
Aaronson (300K3)	2	4	4	2	12
Achord (300K4)	0	0	0	0	0
Behar (300K5)	1	1	2	2	6
Berenson (300K6)	2	5	4	4	15
Bruns (300K8)	1	3	4	4	12
Castell (300K9)	1	3	3	2	9
Cheng (300L0)	2	3	3	2	10
Chiao (300M1)	3	6	6	6	21
DeNucci (300L1)	0	0	0	0	0
Diamant (300P2)	1	3	3	3	10
DiPalma (300L2)	3	6	6	6	21
Feldman (300L3)	1	2	2	3	8
Gremillion (300L4)	2	4	3	4	13
Harford (300L6)	2	4	4	4	14
Jones (300L7)	2	4	4	4	14
Karras (300L8)	0	1	1	0	2
Kogut (300L9)	2	4	4	5	15
Koval (300L5)	3	6	6	7	22
Kugelmas (300M6)	0	1	2	2	5
Levine (300M2)	1	3	3	3	10
Lieberman (300M3)	2	5	6	5	18
Maton (300M4)	4	8	8	7	27
McCarthy (300M5)	1	2	2	4	9
Metz (300M7)	1	2	2	2	7
Movva (300M8	4	7	7	8	26
Ortego (300N0)	0	1	0	2	3
Pambianco (300 N1)	3	6	6	4	19
Person (300N2)	3	6	6	6	21
Rai (300M9)	0	1	0	1	2
Redinger (300N3)	2	2	4	2	10
Richter (300N4)	2	4	3	4	13
Riff (300N5)	4	8	8	8	28
Rosenberg (30006)	0	0	0	1	1
Rudolph (300N6)	1	4	2	2	9
Sabesin (300N7)	4	8	8	7	27
Safdi (300N8)	3	6	8	8	25
Sahba (300N9)	1	4	3	3	11
Schlesinger (300O0)	0	0	0	1	1
Schwartz (300O1)	2	4	4	4	14
Schwartz (300O2)	2	5	4	4	15
Shaker (300O3)	2	4	3	2	11
Sobieski (300O4)	1	1	2	2	6
Sontag (300O5)	1	2	2	1	6
Verne (300O7)	0	0	0	0	0
Wagonfeld (300O8)	4	8	8	8	28
Wilkofsky (300O9)	1	3	4	3	11
Wruble (300P0)	4	8	8	8	28
Wu (300P1)	1	2	2	3	8
Total n	**82**	**174**	**174**	**173**	**603**

The following 11 centers enrolled more than 20 patients each:

Riff (300N5)	28
Wagonfeld (300O8)	28
Wruble (300P0)	28
Maton (300M4)	27
Sabesin (300N7)	27
Movva (300M8)	26
Sadfi (300N8)	25
Koval (300L5)	22
Chiao (300M1)	21
DiPalma (300L2)	21
Person (300N2)	21

- The following 5 centers enrolled less than 4 patients each: Karras (300L8), Ortigo (300N0), Rai (300M9), Rosenberg (300O6), Schlesinger (300 O0).

- The remaining 39 centers enrolled between 5 and 19 patients each.

b) **Reasons for Withdrawal (Table 7)**

Adverse events and failure to return were the most common primary reasons for discontinuation. The greatest rate of discontinuation occurred in the PL group (lack of efficacy and AEs). In Table 7, a statistically significant difference is noted among the treatment groups in the proportion of patients who discontinued due to unsatisfactory response-efficacy. The rate was greater for PL (8.5%) than any of the PANTO groups (0.6% to 1.1%). Conclusions based on these comparisons do not essentially change if minor adjustments are introduced because some patients were classified as experiencing AEs when in reality they represented examples of insufficient therapeutic effect.

TABLE 7
Study GMR-32022 (3001A1-300-US)

NUMBER AND PROPORTION (%) OF PATIENTS WHO WITHDREW BY PRIMARY REASON

Primary Reason	PL [n=82]	PANTO (mg) 10 [n=174]	PANTO (mg) 20 [n=174]	PANTO (mg) 40 [n=173]	p-Value[a]
Any	14 (17.1)	22 (12.6)	17 (9.8)	12 (6.9)	N.S.
AE	5 (6.1)	7 (4.0)	7 (4.0)	3 (1.7)	N.S.
Other nonmedical events	0	1 (0.6)	1 (0.6)	0	N.S.
Protocol violations	0	3 (1.7)	1 (0.6)	1 (0.6)	N.S.
Failed to return	2 (2.4)	7 (4.0)	6 (3.4)	6 (3.5)	N.S.
Patient/subject request	0	2 (1.1)	1 (0.6)	1 (0.6)	N.S.
Unsatisfactory response-efficacy	7 (8.5)	2 (1.1)	1 (0.6)	1 (0.6)	0.004

Data based on sponsor's supportive Table 2 which showed specific reason(s) for discontinuation after randomization, listed by study site and treatment group.

a) Fisher's exact test.

c) **Protocol Deviations**

This information was presented in sponsor's supportive Table 3 and these data were examined in conjunction with sponsor's supportive Table 2. A detailed examination of these data revealed:

- 10 pts. had important protocol violations:
  - Pt. 300M4-0030 completed the trial but was excluded from the VFE analyses
  - 9 pts. were prematurely W/D from the study as protocol violators; 5 of these (300K6-007, 300L0-0013, 300L3-0010, 300L5-0008 and 300N8-0024) had protocol violations as the primary reason for withdrawal and are listed in Table 17; the other 4 pts. (300L3-0002, 300L9-0003, 300L9-0009 and 300M1-0002) had protocol violations as a secondary reason for withdrawal.
  - 1 additional pt. (300N8-0020) was given the wrong dosage and was W/D from the trial [this pt. was included in the VFE analysis at Week 4 but not at Week 8].

d) **Data Showing Comparability of Treatment Groups at Baseline**

1) **Demographic and Disease Baseline Characteristics (Table 8)**

As shown in this Table, at baseline, the four treatment groups were similar (to each other) for age, gender, ethnic origin, height, weight, body mass index, data related to EE severity [64.5% of the patients had grade 2, 27.5% had grade 4 esophagitis; 1 patient (0.2%) had no EE (grade 1)], *H. pylori* status [80% were **H. P.(-)** and 20% **H.P.(+)**] and concomitant medications [97% of the patients received concomitant meds]. As listed in Table 8, common concomitant medications (>20%) were: hypnotic and sedatives, opioids (both prescribed for endoscopic procedures), oral analgesic and antipyretics, antipruritics (including antihistamines, anesthetics, etc.) and antihemorrhoidals for topical use.

TABLE 8
Study GMR-32022 (3001A1-300-US)

Data Showing Comparability of Treatment Group at Baseline: Demographic Pre-Treatment Characteristics and Concomitant Medications Intent-to-Treat Patients

Characteristic		PL [n=82]	PANTO (mg) 10 [n=174]	PANTO (mg) 20 [n-174]	PANTO (mg) 40 [n=173]	Total [n=603]	p-value
I. Demographics							
Age (y)	Mean	48.3	49.6	48.7	49.3	49.1±13.4[a]	N.S.
Age group	18-64	86.6%	82.2%	89.1%	83.8%	14 (85.2%)	N.S.
	>64	13.4%	17.8%	10.9%	16.2%	89 (14.8%)	
Gender (%)	F	35.4%	36.2%	33.9%	30.1%	203 (33.7%)	N.S.
	M	64.6%	63.8%	66.1%	69.9%	400 (66.3%)	
Ethnic Origin (%)	White	81.7%	86.8%	89.7%	86.7%	524 (86.9%)	N.S.
	Black	13.4%	5.7%	5.7%	4.6%	39 (6.5%)	
	Asian	1.2%	0	0.6%	0	2 (0.3%)	
	Hispanic	2.4%	7.5%	3.4%	6.9%	33 (5.5%)	
	Other	1.2%	0	0.6%	1.7%	5 (0.8%)	
Height (cm)	Mean	[n=81] 170.9	[n=172] 172.0	[n=172] 172.9	[n=172] 173.4	[n=597] 172.5±10.4[b]	N.S.[d]
Weight (Kg)	Mean	84.7	87.5	90.9	88.8	88.4±18.2	N.S.[d]
Body Mass index [Kg/(cm**0.01)^2]	Mean	[n=81] 28.9	[n=172] 29.5	[n=172] 30.3	[n=172] 29.5	[n=597] 29.7±5.3[c]	N.S.[d]
II. REFLUX ESOPHAGITIS SEVERITY							
Grade (Hetzel-Dent scale)	1	0	0	0.6%[f]	0	1 (0.2%)	N.S.[e]
	2	65.9%	65.5%	62.1%	65.3%	389 (64.5%)	
	3	28.0%	24.7%	29.9%	27.7%	166 (27.5%)	
	4	6.1%	9.8%	7.5%	6.9%	47 (7.8%)	
III. *H. PYLORI* STATUS							
Status	Negative	79.3%	82.2%	82.2%	75.1%	481 (79.8%)	N.S.[e]
	Positive	20.7%	17.8%	17.3%	24.9%	122 (20.2%)	
IV. COMMON CONCOMITANT MEDICATIONS >20%							
Any non-study medication		98.7%	94.8%	96.5%	98.2%	584 (96.8%)	N.S.[g]
Hypnotics and sedatives[h]		76.8%	75.2%	74.4%	74.5%	453 (75.1%)	N.S.[g]
Opioids[h]		63.4%	60.3%	56.8%	60.6%	361 (59.8%)	N.S.[g]
Other analgesics and antipyretics		31.7%	25.8%	31.0%	30.6%	178 (29.5%)	N.S.[g]
Antipruritics: includes anti-histamines, anesthetics, etc.		24.3%	28.7%	27.0%	28.3%	166 (27.5%)	N.S.[g]
Antihemorrhoidals for topical use		19.5%	18.9%	23.5%	19.6%	124 (20.5%)	N.S.[g]

a,b,c) ± SD
d) Based on one-way ANOVA
e) Based on Fisher's exact test (two categories) or Chi-square (>two categories)
f) One patient (300M4-0003) was enrolled in study despite a Grade 1 evaluation at baseline and at week 4. This patient was included in the ITT and MITT populations but was excluded from VFE analyses because of a protocol violation
g) Fisher's exact test
h) Non-study medications prescribed for endoscopic procedures

This Table is a composite of sponsor's Tables 8.2A and 8.3A with substantial modifications.

2) Number of Patients in the Three Population Analyses

The number of patients comprising each of the three populations analyzed (ITT, MITT and VFE) for primary efficacy parameters and those analyzed for secondary assessment of efficacy is given in Table 9.

- As stated in Section VIII. 9. of this review, the study was designed to allow for completion of 80 patients in the PL group and 160 in each of the PANTO arms (1:2:2:2) for a total of 560 patients.

- In fact, the number of patients randomized into the trial (603) exceeded the original goals of the study by 43 patients.

- As shown in Table 9, 31 patients from the ITT population failed to make it into the MITT population group; 12 pts. from the MITT population group were excluded from VFE analysis.

TABLE 9
Study GMR-32022 (3001A1-300-US)

Number of Patients Analyzed for Efficacy

I. ANALYSES OF PRIMARY EFFICACY ASSESSMENT					
		PANTO (mg)			
Population Subset	PL	10	20	40	Total
Intent-to-treat analysis	82	174	174	173	603
Modified intent-to-treat analysis	78	162	165	167	572
Valid-for-efficacy analysis	77	158	160	165	560[a]
II. PATIENTS ANALYZED FOR SECONDARY ASSESSMENTS[b]					
Any EE symptom	80	170	170	170	590
Gelusil tablet usage	78	171	167	168	584

This Table is a composite of sponsor's Tables 9.1A and 9.1B, with major modifications.

a) The distribution of the 43 patients that were excluded from the VFE analysis was

	(mg)		
PL	10	20	40
5	16	14	8

There were no significant differences among the treatment groups in the proportion of patients excluded from VFE analysis (p=0.372, Fisher's exact test)

- 7 pts. were excluded from some or all of the VFE analysis solely because of **noncompliance** with respect to test med. (some of these pts. were D/C from the trial because of protocol violations)
- Pts. 300L4-0006, 300M3-0009, 300N8-0024 and 300O9-0025 were included in the VFE analysis for Week 4 but excluded at Week 8. These 4 pts. met the compliance criteria for Week 4, but failed to meet it at Week 8.

b) The analyses for the secondary assessments were based on all patients who had at least one day of on-therapy data for the given assessment.

e) Endoscopy Relative Ranges

For analysis purposes, the endoscopy data were grouped into the following time intervals.

TIME INTERVALS FOR ENDOSCOPY DATA

Time Interval	Days Relative to Start of Study Drug
Pre-therapy	-10 through –1
Week	
1	1 through 7
2	8 through 21
4	22 through 35
6	36 through 49
8	50 through last day of therapy

- The sponsor noted that every patient who received test medication was included in the ITT population. If there was no post-baseline endoscopy for a given patient, both weeks 4 and 8 were assigned values. They were assigned a value of healed for the ITT [+] analysis and a value of not-healed for the ITT [-] analysis. For those patients who did have post-baseline data, the following rules were applied: if the patient had weeks 4 and 8 data, the data was left "as-is". If the patient's last endoscopy was at week 2, that observation was carried forward to be the week 4 and week 8 value. If the patient's last data was for week 4 or week 6, that observation was carried forward to be the week 8 value. If the patient had week 8 data but not week 4 data, that patient was left out of the week 4 analysis.

[NOTE: It is clear that the ITT [-] analysis was the most conservative, since patients who only had baseline data were identified similarly to the ITT [+] patients except that their missing data was expressed as **patients not being healed**. Therefore, the reviewer's main conclusions on efficacy are based on analysis of the ITT [-] population. Results of analysis of the ITT [+] population are also included here, for completeness. However, neither results of analyses of the MITT nor the VFE population are considered here.]

f) Additional Statistical Considerations

- In the protocol, it was stated that an analysis based on **completer patients** would be done. This was later abandoned in favor of other analyses that were thought to be more meaningful. The results of an analysis based on completer patients were presented in the sponsor's Statistical Appendix. The reviewer agrees with the sponsor's statement that the conclusions about the relative effectiveness of the four treatments are the same for the completer patients as those discussed for the ITT, MITT and VFE populations.

- It is worth reiterating that the primary objective of this trial was to compare PANTO at three different dose levels to PL. The approach used to control the overall alpha level of the experiment was to initially do overall comparisons looking for differences among the four treatment groups. Pairwise comparisons were done only if the overall test yielded a significant result at the 0.05 level. It is noted that if a more conservative multiple comparisons procedure had been used it would not have affected the study conclusions since all differences between PANTO and PL in the primary analyses of

healing rates were significant at the 0.001 level. The secondary objective of the trial was to investigate the relationship between the different doses of PANTO. The three pairwise comparisons between the PANTO dose groups were each done at the 0.05 level.

g) Healing of Erosive Esophagitis (Table 10)

i) Healing of EE in ITT [-] and [+] populations analysis

Because the results of all four population analyses were similar, only results for the ITT [-] population and those for the ITT [+] population are displayed in Table 10. The comments that follow apply to results for the ITT [-] population (upper panel of Table 10). In addition to the EE healing rates per treatment group, the therapeutic gains resulting from comparisons between pertinent Tx groups are shown on the right hand side of this Table.

After 4 weeks of treatment, each of the three dose levels of PANTO (10, 20 and 40 mg) were significantly more effective than PL in the healing of the EE lesions. A dose response relationship was seen with therapeutic gains [over PL] of 28.5%, 41.5% and 58.6% for the 10, 20 and 40 mg PANTO, respectively. In addition, both the 20 and 40 mg of PANTO were superior to the lowest dose (10 mg) with a therapeutic gain of 13% and 30.1%, respectively. Furthermore, the 40 mg PANTO dose was superior to the 20 mg dose, with a therapeutic gain of 17.1%.

Similar conclusions can be drawn when considering EE healing after 8 weeks of treatment. Each of the three dose levels of PANTO (20, 20 and 40 mg) were significantly more effective than PL in the healing of EE lesions. A dose response relationship was shown, with therapeutic gains [over PL] of 25.7%, 44.7% and 55% for the 10, 20 and 40 mg PANTO, respectively. Both the 20 and 40 PANTO doses were superior to the lowest dose (10 mg), with a therapeutic gain of 19% and 29.3%, respectively. In addition, the 40 mg PANTO dose was superior to the 20 mg dose, with a therapeutic gain of 10.3%.

In summary, although all three doses of PANTO were significantly more effective than PL in the healing of EE lesions (at both 4 and 8 weeks of treatment), the highest therapeutic gains were seen with the 40 mg PANTO dose. In addition, this dose of the drug produced higher therapeutic gain than the 20 mg dose in comparison to the lowest dose (10 mg). Furthermore, the 40 mg dose was also significantly more effective than the 20 mg dose. Similar conclusions were reached when evaluating results of analysis of the ITT [+] population (see lower panel of Table 10).