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ND A 20-40

Ap Ltr

Draft LBlg

Cso Rvs

Mors

Pharm.

Chem

Stat

Bio

Fons;

Patent Info

Exclusivity Summ.

Memos

Ap Ltr
Draft LBLg

NDA 20-406

MAY 10 1995

TAP Holdings Inc.
Attention: Judy Decker Wargel
Bannockburn Lake Office Plaza
2355 Waukegan Road
Deerfield, IL 60015

Dear Ms. Wargel:

Please refer to your November 12, 1993 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prevacid (lansoprazole) Delayed-Release Capsules.

We also acknowledge receipt of your amendments dated December 22, 1993, February 18, March 14, 25, 29, and 31, April 5 and 6, May 2, 13, 23, and 25, June 14 and 17, July 22, September 14, October 18 and 27, November 3, 15, and 17, and December 20, 21, and 29, 1994, January 4, 18, and 30, February 8, 13, and 24, and April 6 and 13, 1995.

This new drug application provides for the following indications: reflux esophagitis, duodenal ulcer, and pathological hypersecretory conditions.

We have completed the review of this application including the draft labeling submitted April 13, 1995 and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit fifteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-406. Approval of this labeling by FDA is not required before it is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Gastrointestinal

and Coagulation Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and
Communications, HFD-240
5600 Fishers Lane
Rockville, Maryland 20857

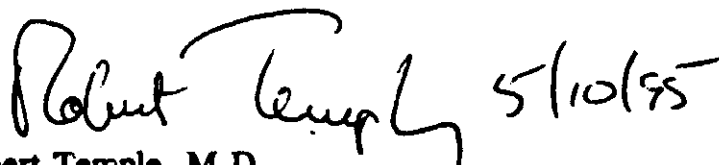
Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any deficiencies that may occur.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Maria R. Walsh
Consumer Safety Officer
(301) 443-0487

Sincerely yours,



Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:

Original NDA

HFD-180/Division file

HFD-180/J.Gibbs

HFD-180/J.Choudary

HFD-181/CSO/M. Walsh

HFD-2/M.Lumpkin

HFD-100 (with labeling)

HFA-100

DISTRICT OFFICE

HF-2/medwatch (with labeling)

HFD-80 (with labeling)

HFD-240/S.Sherman (with labeling)

HFD-613 (with labeling)

Drafted: M. Walsh 4/24/95

R/D init: S.Fredd 4/24/95

Final: M. Walsh 4/25/95

MRW/4/25/95/C:\wpfiles\cso\20406504.AMW

APPROVAL

4/26/95
4/26/95
SF 5/1/95

Submitted: 4/13/1

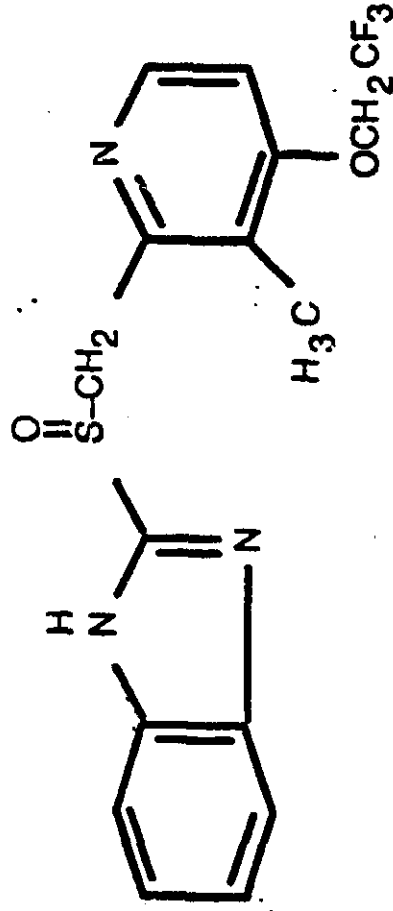
Modified 5/10/1

PREVACID®
(pre-van-sid)
(lansoprazole)

Delayed-Release Capsules

Description

The active ingredient in PREVACID (lansoprazole) Delayed-Release Capsules is a substituted benzimidazole, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl] benzimidazole, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{16}H_{14}F_3N_3O_2S$ with a molecular weight of 369.37. The structural formula is:



lansoprazole

Lansoprazole is a white to brownish-white odorless, crystalline powder which melts with decomposition at approximately 166°C. Lansoprazole is freely soluble in dimethylformamide; soluble in methanol; sparingly soluble in ethanol; slightly soluble in ethyl acetate, dichloromethane and acetonitrile; very slightly soluble in ether; and practically insoluble in hexane and water.

Lansoprazole is stable when exposed to light for up to two months. The compound degrades in aqueous solution, the rate of degradation increasing with decreasing pH. At 25°C the $t_{1/2}$ is approximately 0.5 hour at pH 5.0 and approximately 18 hours at pH 7.0.

PREVACID is supplied in delayed-release capsules for oral administration. The delayed-release capsules contain the active ingredient, lansoprazole, in the form of enteric-coated granules and are available in two dosage strengths: 15 mg and 30 mg of lansoprazole per capsule. Each delayed-release capsule contains enteric coated granules consisting of lansoprazole, hydroxypropyl cellulose, low substituted hydroxypropyl cellulose, colloidal silicon dioxide, magnesium carbonate, methacrylic acid copolymer, starch, talc, sugar sphere, sucrose, polyethylene glycol, polysorbate 80, and titanium dioxide. Components of the gelatin capsule include gelatin, titanium dioxide, D&C Red No. 28, FD&C Blue No. 1, FD&C Green No. 3*, and FD&C Red No. 40.

*PREVACID 15 mg capsules only.

Clinical Pharmacology

Pharmacokinetics and Metabolism

PREVACID Delayed-Release Capsules contain an enteric-coated granule formulation of lansoprazole. Absorption of lansoprazole begins only after the granules leave the stomach. Absorption is rapid, with mean peak plasma levels of lansoprazole occurring after approximately 1.7 hours. Peak plasma concentrations of lansoprazole (C_{max}) and the area under the plasma concentration curve (AUC) of lansoprazole are approximately proportional in doses from 15 mg to 60 mg after single-oral administration. Lansoprazole does not accumulate and its pharmacokinetics are unaltered by multiple dosing.

Absorption

The absorption of lansoprazole is rapid, with mean C_{max} occurring approximately 1.7 hours after oral dosing, and relatively complete with absolute bioavailability over 80%. In healthy subjects, the mean ($\pm$ SD) plasma half-life was 1.5 ($\pm$ 1.0) hours. Both C_{max} and AUC are diminished by about 50% if the drug is given 30 minutes after food as opposed to the fasting condition. There is no significant food effect if the drug is given before meals.

Distribution

Lansoprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 0.05 to 5.0 mcg/mL.

Metabolism

Lansoprazole is extensively metabolized in the liver. Two metabolites have been identified in measurable quantities in plasma (the hydroxylated sulfinyl and sulfone derivatives of lansoprazole). These metabolites have very little or no antisecretory activity. Lansoprazole is thought to be transformed into two active species which inhibit acid secretion by (H⁺.K⁺)-ATPase within the parietal cell canaliculus, but are not present in the systemic circulation. The plasma elimination half-life of lansoprazole does not reflect its duration of suppression of gastric acid secretion. Thus, the plasma elimination half-life is less than two hours while the acid inhibitory effect lasts more than 24 hours.

Elimination

Following single-dose oral administration of lansoprazole, virtually no unchanged lansoprazole was excreted in the urine. In one study, after a single oral dose of ¹⁴C-lansoprazole, approximately one-third of the administered radiation was excreted in the urine and two-thirds was recovered in the feces. This implies a significant biliary excretion of the metabolites of lansoprazole.

Special Populations

Geriatric

The clearance of lansoprazole is decreased in the elderly, with elimination half-life increased approximately 50% to 100%. Because the mean half-life in the elderly remains between 1.9 to 2.9 hours, repeated once daily dosing does not result in accumulation of lansoprazole. Peak plasma levels were not increased in the elderly.

Pediatric

The pharmacokinetics of lansoprazole has not been investigated in patients <18 years of age.

Gender

In a study comparing 12 male and six female human subjects, no gender differences were found in pharmacokinetics and intragastric pH results (also see Use in Women).

Renal Insufficiency

In patients with severe renal insufficiency, plasma protein binding decreased by 1.0%–1.5% after administration of 60 mg of lansoprazole. Patients with renal insufficiency had a shortened elimination half-life and decreased total AUC (free and bound). AUC for free lansoprazole in plasma, however, was not related to the degree of renal impairment, and C_{max} and T_{max} were not different from subjects with healthy kidneys.

Hepatic Insufficiency

In patients with various degrees of chronic hepatic disease, the mean plasma half-life of the drug was prolonged from 1.5 hours to 3.2-7.2 hours. An increase in mean AUC of up to 500% was observed at steady state in hepatically-impaired patients compared to healthy subjects. Dose reduction in patients with severe hepatic disease should be considered.

Pharmacodynamics

Mechanism of action

Lansoprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or histamine H₂-receptor antagonist properties, but that suppress gastric acid secretion by specific inhibition of the (H⁺, K⁺)-ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the parietal cell, lansoprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus.

Antisecretory activity

After oral administration, lansoprazole was shown to significantly decrease the basal acid output and significantly increase the mean gastric pH and percent of time the gastric pH was >5 and >4. Lansoprazole also significantly reduced meal-stimulated gastric acid output and secretion volume, as well as

pentagastrin-stimulated acid output. In patients with hypersecretion of acid, lansoprazole significantly reduced basal and pentagastrin-stimulated gastric acid secretion. Lansoprazole inhibited the normal increases in secretion volume, acidity and acid output induced by insulin.

In a crossover study comparing lansoprazole 15 and 30 mg with omeprazole 20 mg for five days, the following effects on intragastric pH were noted:

Mean Antisecretory Effects after Single and Multiple Daily Dosing

Parameter	Baseline Value	15 mg		30 mg		Omeprazole 20 mg	
		Day 1	Day 5	Day 1	Day 5	Day 1	Day 5
Mean 24-Hour pH	2.1	2.7*	4.0*	3.6*	4.9*	2.5	4.2*
Mean Nighttime pH	1.9	2.4	3.0*	2.6	3.8*	2.2	3.0*
% Time Gastric pH>3	18	33*	59*	51*	72*	30*	61*
% Time Gastric pH>4	12	22*	49*	41*	66*	19	51*

NOTE: An intragastric pH of >4 reflects a reduction in gastric acid by 99%.

* (p<0.05) versus baseline, lansoprazole 15 mg and omeprazole 20 mg.

† (p<0.05) versus baseline only.

After the initial dose in this study, increased gastric pH was seen within 1-2 hours with lansoprazole 30 mg, 2-3 hours with lansoprazole 15 mg, and 3-4 hours with omeprazole 20 mg. After multiple daily dosing, increased gastric pH was seen within the first hour postdosing with lansoprazole 30 mg and within 1-2 hours postdosing with lansoprazole 15 mg and omeprazole 20 mg.

The inhibition of gastric acid secretion as measured by intragastric pH returns gradually to normal over two to four days after multiple doses. There is no indication of rebound gastric acidity.

Enterochromaffin-like (ECL) cell effects

During lifetime exposure of rats with up to 150 mg/kg/day of lansoprazole dosed seven days per week, marked hypergastrinemia was observed followed by ECL cell proliferation and formation of carcinoid tumors, especially in female rats (see PRECAUTIONS, Carcinogenesis, Mutagenesis, and Fertility).

Gastric biopsy specimens from the body of the stomach from approximately 150 patients treated continuously with lansoprazole for at least one year have not shown evidence of ECL cell effects similar to those seen in rat studies. Longer term data are needed to rule out the possibility of an increased risk of the development of gastric tumors in patients receiving long-term therapy with lansoprazole.

Other gastric effects in humans

Lansoprazole did not significantly affect mucosal blood flow in the fundus of the stomach. Due to the normal, physiologic effect caused by the inhibition of gastric acid secretion, a decrease of about 17% in blood flow in the antrum, pylorus and duodenal bulb was seen. Lansoprazole significantly slowed the gastric emptying of digestible solids. Lansoprazole increased serum pepsinogen levels and decreased pepsin activity under basal conditions and in response to meal stimulation or insulin injection. As with other agents that elevate intragastric pH, increases in gastric pH were associated with increases in nitrate-reducing bacteria and elevation of nitrite concentration in gastric juice in patients with gastric ulcer. No significant increase in nitrosamine concentrations was observed.

Serum gastrin effects

In over 2100 patients, median fasting serum gastrin levels increased 50% to 100% from baseline, but remained within normal range after treatment with lansoprazole given orally in doses of 15 mg to 60 mg. These elevations reached a plateau within two months of therapy and returned to pretreatment levels within four weeks after discontinuation of therapy.

Endocrine effects

Human studies for up to eight weeks have not detected any clinically significant effects on the endocrine system. Hormones studied include testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), sex hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEA-S), prolactin,

cortisol, estradiol, insulin, aldosterone, parathormone, glucagon, thyroid stimulating hormone (TSH), triiodothyronine (T₃), thyroxine (T₄), and somatotrophic hormone (STH). Lansoprazole in oral doses of 15 to 60 mg for up to one year, had no clinically significant effect on sexual function. In addition, lansoprazole in oral doses of 15 to 60 mg for two to eight weeks had no clinically significant effect on thyroid function.

In 24-month carcinogenicity studies in Sprague-Dawley rats with daily dosages up to 150 mg/kg, proliferative changes in the Leydig cells of the testes, including benign neoplasms, were increased compared to control rates.

Other effects

No systemic effects of lansoprazole on the central nervous system, lymphoid, hematopoietic, renal, hepatic, cardiovascular or respiratory systems have been found in humans. No visual toxicity was observed among 56 patients who had extensive baseline eye evaluations. were treated with up to 180 mg/day of lansoprazole and were observed for up to 58 months. Other rat-specific findings after lifetime exposure included focal pancreatic atrophy, diffuse lymphoid hyperplasia in the thymus, and spontaneous retinal atrophy.

Clinical Studies

Duodenal Ulcer

In a U.S. multicenter, double-blind, placebo-controlled, dose-response (15, 30, and 60 mg of PREVACID once daily) study of 284 patients with endoscopically documented duodenal ulcer, the percentage of patients healed after two and four weeks was significantly higher with all doses of PREVACID than with placebo. There was no evidence of a greater or earlier response with the two higher doses compared with PREVACID 15 mg. Based on this study and the second study described below, the recommended dose of PREVACID in duodenal ulcer is 15 mg per day.

Duodenal Ulcer Healing Rates

	PREVACID			Placebo
Week	15 mg qd (N=68)	30 mg qd (N=74)	60 mg qd (N=70)	(N=72)
2	42.4%*	35.6%*	39.1%*	11.3%
4	89.4%*	91.7%*	89.9%*	46.1%

* (p<0.001) versus placebo.

PREVACID 15 mg was significantly more effective than placebo in relieving day and nighttime abdominal pain and in decreasing the amount of antacid taken per day.

→ Delete this paragraph and replace with

In a second U.S. multicenter study, also double-blind, placebo-, dose-comparison (15 and 30 mg of PREVACID once daily), and including a comparison with ranitidine, in 280 patients with endoscopically documented duodenal ulcer, the percentage of patients healed after four weeks was significantly higher with both doses of PREVACID than with placebo. There was no evidence of a greater or earlier response with the higher dose of PREVACID. Although the 15 mg dose of PREVACID was superior to ranitidine at 4 weeks, the lack of significant difference at 2 weeks and the absence of a difference between 3 mg of PREVACID and ranitidine leaves the comparative effectiveness of the two agents undetermined.

→ Delete this sentence

Duodenal Ulcer Healing Rates

Week	---PREVACID---			Ranitidine		Placebo (N=41)
	15 mg qd (N=80)	30 mg qd (N=77)	300 mg bis (N=82)	300 mg bis		
2	35.0%	44.2%	30.5%	34.2%		
4	92.3%**	80.3%*	70.5%*	47.5%		

* (p<0.05) versus placebo.
 ** (p<0.05) versus placebo and ranitidine.

Erosive Esophagitis

In a U.S. multicenter, double-blind, placebo-controlled study of 269 patients entering with an endoscopic diagnosis of esophagitis with mucosal grading of 2 or more and grades 3 and 4 signifying erosive disease, the percentages of patients with healing were as follows:

Delete

↓ Esophagitis Healing Rates

Week	PREVACID		Placebo (N=63)
	15 mg qd (N=69)	30 mg qd (N=65)	
4	67.6%*	81.3%**	32.8%
6	87.7%*	95.4%*	52.5%
8	90.9%*	95.4%*	52.5%

* (p<0.001) versus placebo.

** (p<0.05) versus PREVACID 15 mg and placebo.

In this study, all PREVACID groups reported significantly greater relief of heartburn and less day and night abdominal pain along with fewer days of antacid use and fewer antacid tablets taken per day than the placebo group.

Although all doses were effective, the earlier healing in the higher two doses suggest 30 mg qd as the recommended dose.

PREVACID was also compared in a U.S. multicenter, double-blind study to a low dose of ranitidine in 242 patients with erosive reflux esophagitis. PREVACID at a dose of 30 mg was significantly more effective than ranitidine 150 mg bid as shown below.

Delete

and replace with "Erosive"

↓
Esophagitis Healing Rates

Week*	PREVACID 30 mg qd (N=115)	Ranitidine 150 mg bid (N=127)
2	66.7%*	38.7%
4	82.5%*	52.0%
6	93.0%*	67.8%
8	92.1%*	69.9%

* (p<0.001) versus ranitidine.

In addition, patients treated with PREVACID reported less day and nighttime heartburn and took less antacid tablets for fewer days than patients taking ranitidine 150 mg bid.

Although this study demonstrates effectiveness of PREVACID in healing erosive esophagitis, it does not represent an adequate comparison with ranitidine because the recommended ranitidine dose for esophagitis is 150 mg qid, twice the dose used in this study.

Delete this paragraph and replace with:

In the two trials described and in several smaller studies involving patients with moderate to severe erosive esophagitis, PREVACID produced healing rates similar to those shown above.

In a U.S. multicenter, double-blind, active-controlled study, 30 mg of PREVACID was compared with ranitidine 150 mg bid in 151 patients with erosive reflux esophagitis that was poorly responsive to a minimum of 12 weeks of treatment with at least one H₂-receptor antagonist given at the dose indicated for symptom relief or greater, namely cimetidine 800 mg/day, ranitidine 300 mg/day, famotidine 40 mg/day or nizatidine 300 mg/day. PREVACID 30 mg was more effective than ranitidine 150 mg bid in healing reflux esophagitis and the percentage of patients with healing were as follows. Add these sentences:

Reflux Esophagitis Healing Rates in Patients Poorly Responsive to H₂-Receptor Antagonist Therapy

Week	PREVACID 30 mg qd (N=100)	Ranitidine 150 mg bid (N=51)
4	74.7%*	42.6%
8	83.7%*	32.0%

* (p<0.001) versus ranitidine.

This study does not constitute a comparison of the effectiveness of histamine H₂-receptor antagonists with PREVACID as all patients had demonstrated unresponsiveness to the histamine H₂-receptor antagonist mode of treatment. It does indicate, however, that Prevacid may be useful in patients failing on a histamine H₂-receptor antagonist.

histamine

→ Delete this sentence

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

In open studies of 57 patients with pathological hypersecretory conditions, such as Zollinger-Ellison (ZE) syndrome with or without multiple endocrine adenomas, PREVACID significantly inhibited gastric acid secretion and controlled associated symptoms of diarrhea, anorexia and pain. Doses ranging from 15 mg every other day to 180 mg per day maintained basal acid secretion below 10 mEq/hr in patients without prior gastric surgery, and below 5 mEq/hr in patients with prior gastric surgery.

Initial doses were titrated to the individual patient need, and adjustments were necessary with time in some patients (see DOSAGE AND ADMINISTRATION). PREVACID was well tolerated at these high dose levels for prolonged periods (greater than four years in some patients). In most ZE patients, serum gastrin levels were not modified by PREVACID. However, in some patients serum gastrin increased to levels greater than those present prior to initiation of lansoprazole therapy.

Indications and Usage

Short-Term Treatment of Active Duodenal Ulcer

PREVACID Delayed-Release Capsules are indicated for short-term treatment (up to 4 weeks) for healing and symptom relief of active duodenal ulcer.

Delete this sentence

PREVACID SHOULD NOT BE USED AS MAINTENANCE THERAPY FOR TREATMENT OF PATIENTS WITH DUODENAL ULCER DISEASE.

Short-Term Treatment of Erosive Esophagitis

PREVACID Delayed-Release Capsules are indicated for short-term treatment (up to 8 weeks) for healing and symptom relief of all grades of erosive esophagitis.

Revise as follows:

For patients who do not heal with PREVACID for 8 weeks (5-10%) it may be helpful to give an additional course of treatment.

If there is a recurrence of erosive esophagitis an additional 8 week course of PREVACID may be considered.

PREVACID SHOULD NOT BE USED AS MAINTENANCE THERAPY.

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome
PREVACID Delayed-Release Capsules are indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

Contraindications

PREVACID Delayed-Release Capsules are contraindicated in patients with known hypersensitivity to any component of the formulation.

Precautions

General

Symptomatic response to therapy with lansoprazole does not preclude the presence of gastric malignancy.

Information for Patients

PREVACID Delayed-Release Capsules should be taken before eating.

Patients should be cautioned that PREVACID Delayed-Release Capsules should not be opened, chewed or crushed. Capsules should be swallowed whole.

Drug Interactions

Lansoprazole is metabolized through the cytochrome P₄₅₀ system, specifically through the CYP3A and CYP2C19 isozymes. Studies have shown that lansoprazole does not have clinically significant interactions with other drugs

metabolized by the cytochrome P₄₅₀ system, such as warfarin, antiopyrine, indomethacin, ibuprofen, phenytoin, propranolol, prednisone, or diazepam in healthy subjects. These compounds are metabolized through various cytochrome P₄₅₀ isozymes including CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. When lansoprazole was administered concomitantly with theophylline (CYP1A2, CYP3A), a minor increase (10%) in the clearance of theophylline was seen. Because of the small magnitude and the direction of the effect on theophylline clearance, this interaction is unlikely to be of clinical concern. Nonetheless, individual patients may require additional titration of their theophylline dosage when lansoprazole is started or stopped to ensure clinically effective blood levels.

Coadministration of lansoprazole with sucralfate delayed absorption and reduced lansoprazole bioavailability by approximately 30%. Therefore, lansoprazole should be taken at least 30 minutes prior to sucralfate. In clinical trials, antacids were administered concomitantly with PREVACID Delayed-Release Capsules; this did not interfere with its effect.

Lansoprazole causes a profound and long lasting inhibition of gastric acid secretion; therefore, it is theoretically possible that lansoprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g., ketoconazole, ampicillin esters, iron salts, digoxin).

Carcinogenesis, Mutagenesis, and Fertility

In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated orally with doses of 5 to 150 mg/kg/day, about 1 to 40 times the exposure on a body surface (mg/m²) basis, of a 50 kg person of average height (1.46 m² body surface area) given the recommended human dose of 30 mg/day (22.2 mg/m²). Lansoprazole produced dose-related gastric enterochromaffin like (ECL) cell hyperplasia and ECL cell carcinoids in both male and female rats. It also increased the incidence of intestinal metaplasia of the gastric epithelium in both sexes. In male rats, lansoprazole produced a dose-related increase of testicular interstitial cell adenomas. The incidence of these adenomas in rats receiving doses of 15 to 150 mg/kg/day (4 to 40 times the recommended human dose based on body surface area) exceeded the low background incidence (range = 1.4 to 10%) for this strain of rat. Testicular interstitial cell adenoma also occurred in 1 of 30 rats treated with 50 mg/kg/day (13 times the recommended human dose based on body surface area) in a 1-year toxicity study.

In a 24-month carcinogenicity study, CD-1 mice were treated orally with doses of 15 to 600 mg/kg/day, 2 to 80 times the recommended human dose based on body surface area. Lansoprazole produced a dose related increased incidence of gastric ECL cell hyperplasia. It also produced an increased incidence of liver tumors (hepatocellular adenoma plus carcinoma). The tumor incidences in male mice treated with 300 and 600 mg/kg/day (40 to 80 times the recommended human dose based on body surface area) and female mice treated with 150 to 600 mg/kg/day (20 to 80 times the recommended human dose based on body

surface area) exceeded the ranges of background incidences in historical controls for this strain of mice. Lansoprazole treatment produced adenoma of rete testis in male mice receiving 75 to 600 mg/kg/day (10 to 80 times the recommended human dose based on body surface area).

Lansoprazole was not genotoxic in the Ames test, the *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) test, the *in vivo* mouse micronucleus test or the fat bone marrow cell chromosomal aberration test. It was positive in *in vitro* human lymphocyte chromosomal aberration assays.

Lansoprazole at oral doses up to 150 mg/kg/day (40 times the recommended human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

Pregnancy

Revise to "Teratogenic Effects. Pre
Category B"

Teratology studies have been performed in pregnant rats at oral doses up to 150 mg/kg/day (40 times the recommended human dose based on body surface area) and pregnant rabbits at oral doses up to 30 mg/kg/day (16 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to lansoprazole.

There are, however, no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Lansoprazole or its metabolites are excreted in the milk of rats. It is not known whether lansoprazole is excreted in human milk. Because many drugs are excreted in human milk, because of the potential for serious adverse reactions in nursing infants from lansoprazole, and because of the potential for tumorigenicity shown for lansoprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in children have not been established.

Use in Women

Over 800 women were treated with lansoprazole. Ulcer healing rates in females are similar to those in males. The incidence rates of adverse events are also similar to those seen in males.

Use in Elderly Patients

Ulcer healing rates in elderly patients are similar to those in a younger age group. The incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in younger patients. The initial dosing regimen need not be altered for elderly patients, but subsequent doses higher than 30 mg per day should not be administered unless additional gastric acid suppression is necessary.

Adverse Reactions

Worldwide, over 6100 patients have been treated with lansoprazole in Phase II-III clinical trials involving various dosages and duration of treatment. In general, lansoprazole treatment has been well tolerated in both short-term and long-term trials.

Revise as indicated:

Incidence in Clinical Trials

The following adverse events were reported to have a possible or probable relationship to drug [redacted] by the treating physician in 1% or more of PREVACID-treated patients. Adverse events that occurred at a greater rate in PREVACID-treated patients than placebo-treated patients:

Incidence of Possibly or Probably Treatment-Related Adverse Events in Short-term, Placebo-Controlled Studies

Body System/Adverse Event	PREVACID (N=1457) %	Placebo (N=467) %
Body as a Whole		
Abdominal Pain	1.8	1.3
Digestive System		
Diarrhea	3.6	2.6
Nausea	1.4	1.3

Headache was also seen at greater than 1% incidence but was more common on placebo. The incidence of diarrhea is similar between placebo and lansoprazole 15 mg and 30 mg patients, but higher in the lansoprazole 60 mg patients (2.9%, 1.4%, 4.2%, and 7.4%, respectively).

The most commonly reported possibly or probably treatment-related adverse event during maintenance therapy was diarrhea.

In short-term and long-term studies, the following adverse events were reported in <1% of the lansoprazole-treated patients:

Body as a Whole - asthenia, candidiasis, chest pain (not otherwise specified), edema, fever, flu syndrome, halitosis, infection (not otherwise specified), malaise, *Cardiovascular System* - angina, cerebrovascular accident, hypertension/hypotension, myocardial infarction, palpitations, shock (circulatory failure), vasodilation; *Digestive System* - melena, anorexia, bezoar, cardiospasm, cholelithiasis, constipation, dry mouth/thirst, dyspepsia, dysphagia, eructation, esophageal stenosis, esophageal ulcer, esophagitis, fecal discoloration, flatulence, gastric nodules/fundic gland polyps, gastroenteritis, gastrointestinal hemorrhage, hematemesis, increased appetite, increased salivation, rectal hemorrhage, stomatitis, tenesmus, ulcerative colitis; *Endocrine System* - diabetes mellitus, goiter, hyperglycemia/hypoglycemia; *Hematologic and Lymphatic System* - anemia, hemolysis; *Metabolic and Nutritional Disorders* - gout, weight gain/loss;

Delete all crossed-out terms

Musculoskeletal System – arthritis/arthralgia, musculoskeletal pain, myalgia,

Nervous System – agitation, amnesia, anxiety, apathy, confusion, depression, dizziness/syncope, hallucinations, hemiplegia, hostility aggravated, libido decreased, nervousness, paresthesia, thinking abnormality; **Respiratory System** – asthma, bronchitis, cough increased, dyspnea, epistaxis, hemoptysis, hiccup, pneumonia, upper respiratory inflammation/infection; **Skin and Appendages** – acne, alopecia,

pruritis, rash, urticaria; **Special Senses** –

amblyopia, deafness, eye pain, visual field defect, otitis media, taste perversion, tinnitus; **Urogenital System** – abnormal menses, albuminuria, breast enlargement/gynecomastia, breast tenderness, glycosuria, hematuria, impotence, kidney calculus.

Laboratory Values

The following changes in laboratory parameters were reported as adverse events.

Abnormal liver function tests, increased SGOT (AST), increased SGPT (ALT), increased creatinine, increased alkaline phosphatase, increased globulins, increased GGTP, increased/decreased/abnormal WBC, abnormal AG ratio, abnormal RBC, bilirubinemia, eosinophilia, hyperlipemia, increased/decreased electrolytes, increased/decreased cholesterol, increased glucocorticoids, increased LDH, increased/decreased/abnormal platelets, and increased gastrin levels. Additional isolated laboratory abnormalities were reported.

In the placebo controlled studies, when SGOT (ALT) and SGPT (AST) were evaluated, 0.4% (1/250) placebo patients and 0.3% (2/795) lansoprazole patients had enzyme elevations greater than three times the upper limit of normal range at the final treatment visit. None of these patients reported jaundice at any time during the study.

Overdosage

Oral doses up to 5000 mg/kg in rats (approximately 1300 times the recommended human dose based on body surface area) and mice (about 675.7 times the recommended human dose based on body surface area) did not produce deaths or any clinical signs.

Lansoprazole is not removed from the circulation by hemodialysis. In one reported case of overdose, the patient consumed 600 mg of lansoprazole with no adverse reaction.

Dosage and Administration

Treatment of Duodenal Ulcer

The recommended adult oral dose is 15 mg daily before eating for 4 weeks.

AND USAGE).

(see INDICATIONS

Delete this sentence

Treatment of

The recommended adult oral dose is 30 mg daily before eating for up to 8 weeks.

Delete

and replace
"Erosive Esophagitis"

Revise as follows:

For patients who do not heal
PREVACID for 8 weeks (5-10%)
be helpful to give an additio
of treatment.

(See INDICATIONS AND USAGE.)

(If there is a recurrence of erosive esophagitis, an additional 8 week course of
PREVACID may be considered.)

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

The dosage of PREVACID in patients with pathologic hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose is 60 mg once a day. Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Dosages up to 90 mg bid have been administered. Daily dosages of greater than 120 mg should be administered in divided doses. Some patients with Zollinger-Ellison syndrome have been treated continuously with PREVACID for more than four years.

No dosage adjustment is necessary in patients with renal insufficiency or the elderly. For patients with severe liver disease, dosage adjustment should be considered.

How Supplied

PREVACID Delayed-Release Capsules, 15 mg, are opaque, hard gelatin, colored pink and green. The 30 mg are opaque, hard gelatin, pink and black colored capsules. They are available as follows:

NDC 0300-1541-30 Unit of use bottles of 30: 15 mg capsules

NDC 0300-1541-13 Bottles of 100: 15 mg capsules

NDC 0300-1541-11 Unit dose package of 100: 15 mg capsules

NDC 0300-3046-30 Unit of use bottles of 30: 30 mg capsules

NDC 0300-3046-13 Bottles of 100: 30 mg capsules

NDC 0300-3046-11 Unit dose package of 100: 30 mg capsules

Storage: PREVACID capsules should be stored in a tight container protected from moisture. Store between 59°F and 86°F.

Caution: Federal (USA) law prohibits dispensing without a prescription.

U.S. Patent Nos. 4,628,098; 4,689,333; 5,013,743; 5,026,560 and 5,045,321.

Manufactured for
TAP Pharmaceuticals Inc.

Deerfield, Illinois 60015-1595, U.S.A.
by Takeda Chemical Industries Limited,
Osaka, Japan 541

TAKEDA PHARMACEUTICALS, LIMITED

NDA 20-406

wal
FEB 14 1995

**TAP Pharmaceuticals
Attention: Ms. Judy Decker Wargel
Bannockburn Lake Office Plaza
23555 Waukegan Road
Deerfield, Illinois 60015**

Dear Ms. Wargel:

Please refer to your November 12, 1993 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prevacid (lansoprazole) Delayed-Release Capsules.

We acknowledge receipt of your amendments dated December 22, 1993, February 18, March 14, 25, 29, and 31, April 5 and 6, May 2, 13, 23, and 25, June 14 and 17, July 22, September 14, October 18 and 27, November 3, 15, and 17, and December 20, 21, and 29, 1994, January 4, 18, and 30, and February 8, 1995.

This application provides for the following indications: reflux esophagitis, maintenance of healing of reflux esophagitis, duodenal ulcer, and pathological hypersecretory conditions.

We have completed the review of this application as submitted with draft labeling. The indications for reflux esophagitis, duodenal ulcer, and pathological hypersecretory conditions are approvable. However, the indication for maintenance of healing of reflux esophagitis is not approvable at this time. Before this indication can be approved, the following data as requested at the Gastrointestinal Drugs Advisory Committee meeting on December 1, 1994 regarding long-term administration of lansoprazole and the maintenance indication must be provided and reviewed:

- 1. Analyses and considerations of available information to determine whether lansoprazole maintenance therapy in patients with healed erosive esophagitis should be initiated for all patients after healing, or only for those with grade 3/4 or complicated disease during the healing phase and grade 2 patients after a recurrence. You may, for example, analyze the post-acute healing populations by presentation grade to determine rate of relapse and severity of erosive disease at relapse.**
- 2. Analyses of recurrences in studies M88-271 and M89-350 when recurrence is defined as an increase of at least two grades from grade at entrance.**
- 3. Data on atrophic gastritis in helicobacter pylori negative patients on long-term**

lansoprazole.

- 4. Study D75P506 concerning testosterone levels in patients on long-term lansoprazole.**

In addition, the following preclinical reports recently submitted must be reviewed:

- 1. A-29-2097: Taurine Levels in the Retina and Serum in Aged Rats Treated Orally with Lansoprazole for 13 Weeks.**
- 2. A-29-2098: Effects of Taurine Supplementation on Retinal Function and Morphology in Rats Treated with Lansoprazole and Guanidinoethyl Sulfonate (GES).**
- 3. A-29-2099: Effects of Lansoprazole and Its Metabolites on the Hepatic Cysteinesulfinic Acid Decarboxylase Activities of Rat and Mouse (In Vitro).**

If you wish to pursue approval of the maintenance indication in this NDA, please provide the data not yet submitted for our review. Alternatively, you may withdraw this indication from the NDA and submit a supplemental application after approval of the NDA.

Before the application may be approved for the indications specified in the enclosed draft labeling, it will be necessary for you to:

- 1. Submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed draft. If additional information relating to the safety or effectiveness of this drug becomes available, revision of that FPL may be required.**

Please indicate the placement of the expiration date on the carton label for the blister packages.

- 2. Submit a complete response to the January 26, 1995 letter requesting additional biopharmaceutics information.**

In addition, the following submissions must be reviewed:

- 1. The January 18, 1995 amendment submitted in response to the October 11, 1994 letter requesting additional chemistry information.**
- 2. The January 30, 1995 amendment submitted in response to the December 27,**

1994 and January 25, 1995 letters requesting additional biopharmaceutics information.

Please submit fifteen copies of the printed labels and other labeling, ten of which are individually mounted on heavy weight paper or similar material.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Gastrointestinal and Coagulation Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-240
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any deficiencies that may occur.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

Under section 736(a)(1)(B)(ii) of the Prescription Drug User Fee Act of 1992, this letter covers the remaining 50% of the fee assessed for this application. You will receive an invoice for the amount due within the next month. Payment will be due within 30 days of the date of the invoice.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact:

Maria Walsh
Consumer Safety Officer
Telephone: (301) 443-0487

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Draft Labeling

cc:

Original NDA 20-406

HFA-100

HFC-130/J.Allen

HFD-2/M.Lumpkin (with draft labeling)

HFD-5/T.Hassall

HFD-80

HFD-100

HFD-180/Div. Files

HFD-181/M.Walsh

HFD-240/S.Sherman (with draft labeling)

HFD-638 (with draft labeling)

HFD-730 (with draft labeling)

Drafted: M.Walsh 1/18/95

Revised: 1/24/95, 1/26/95, 1/30/95

R/D init: B.Collier 1/18/95

S.Fredd 1/24/95, 1/25/95, 1/30/95

Final: 1/30/95

MRW/1/30/95/C:\wpfiles\cso\n\20406501.AMW

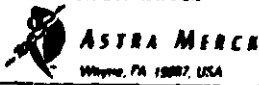
APPROVABLE (AE)

SEA 1/30/95

[Signature] 1/30/95

EF 1/31/95

R Temple 2/4/95



7910812 PRILOSEC[®] (Omeprazole) Delayed-Release Capsules

drug was detected. The plasma clearance of omeprazole was 250 mL/min (about half that of young volunteers) and its plasma half-life averaged one hour, about twice that of young healthy volunteers.

Pharmacodynamics
Mechanism of Action

Omeprazole belongs to a new class of antielectrolytic compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H₂ histamine antagonistic properties, but that suppress gastric acid secretion by specific inhibition of the H⁺/K⁺ ATPase enzyme system at the apical surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the gastric mucosa, omeprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after rapid disappearance from plasma, omeprazole can be found within the gastric mucosa for a day or more.

Antisecretory Activity

After oral administration, the onset of the antisecretory effect of omeprazole occurs within one hour, with the maximum effect occurring within two hours. Inhibition of secretion is about 90% of maximum at 24 hours and the duration of inhibition lasts up to 72 hours. The antisecretory effect thus lasts for longer than would be expected from the very short (less than one hour) plasma half-life, apparently due to prolonged binding to the parietal H⁺/K⁺ ATPase enzyme. When the drug is discontinued, secretory activity returns gradually, over 3 to 5 days. The inhibitory effect of omeprazole on acid secretion increases with repeated once-daily dosing, reaching a plateau after four days.

Results from numerous studies of the antisecretory effect of multiple doses of 20 mg and 40 mg of omeprazole in normal volunteers and patients are shown below. The "max" value represents determinations at a time of maximum effect (7-8 hours after dosing), while "min" values are those 24 hours after the last dose of omeprazole.

Range of Mean Values from Multiple Studies of the Mean Antisecretory Effects of Omeprazole After Multiple Daily Dosing

Parameter	Omeprazole 20 mg		Omeprazole 40 mg	
	Max	Min	Max	Min
% Decrease in Basal Acid Output	78*	58-80	94*	80-82
% Decrease in Peak Acid Output	79*	50-59	86*	67-82
% Decrease in 24 hr Intragastric Acidity		80-87		82-84

*Single Studies

Single daily oral doses of omeprazole ranging from a dose of 10 mg to 40 mg have produced 100% inhibition of 24-hour intragastric acidity in some patients.

Endochromatin like (ECL) Cell Effects

In 24 month carcinogenicity studies in rats, a dose-related significant increase in gastric carcinoid tumors and ECL cell hyperplasia was observed in both male and female animals (see PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility). Hypergastrinemia secondary to prolonged and sustained hypochlorhydria has been postulated to be the mechanism by which ECL cell hyperplasia and gastric carcinoid tumors develop. Omeprazole may also affect other cells in the gastrointestinal tract (e.g., G cells), either directly or by inducing sustained hypochlorhydria, but this possibility has not been extensively studied.

Human gastric biopsy specimens from about 200 patients treated continuously with omeprazole for an average of over 12 months have not detected ECL cell effects of omeprazole similar to those seen in rats. Longer term data are needed to rule out the possibility of an increased risk for the development of gastric tumors in patients receiving long-term therapy with omeprazole.

Serum Gastrin Effects

In studies involving more than 200 patients, serum gastrin levels increased during the first 1 to 2 weeks of once-daily administration of therapeutic doses of omeprazole in parallel with inhibition of acid secretion. No further increase in serum gastrin occurred with continued treatment. In comparison with histamine H₂-receptor antagonists, the median increases produced by 20 mg doses of omeprazole were higher (1.3 to 3.6 fold vs. 1.1 to 1.8 fold increase). Gastrin values returned to pretreatment levels, usually within 1 to 2 weeks after discontinuation of therapy.

Other Effects

Systemic effects of omeprazole in the CNS, cardiovascular and respiratory systems have not been found to date. Omeprazole, given in oral doses of 30 or 40 mg for 2 to 4 weeks, had no effect on thyroid function, carbohydrate metabolism, or circulating levels of parathyroid hormone, cortisol, estradiol, testosterone, prolactin, cholecalciferol or creatinin.

No effect on gastric emptying of the solid and liquid components of a test meal was demonstrated after a single dose of omeprazole 30 mg in healthy subjects; a single 1 V dose of omeprazole (0.35 mg/kg) had no effect on intrinsic factor secretion. No systemic dose dependent effect has been observed on basal or stimulated pepsin output in humans.

PRILOSEC[®] (Omeprazole) Delayed-Release Capsules

However, when intragastric pH is maintained at 4.0 or above, basal pepsin output is low, and pepsin activity is decreased.

As do other agents that elevate intragastric pH, omeprazole administered for 14 days in healthy subjects produced a significant increase in the intragastric concentrations of viable bacteria. The pattern of the bacterial species was unchanged from that commonly found in saliva. All changes resolved within three days of stopping treatment.

Clinical Studies

Duodenal Ulcer Disease

Active Duodenal Ulcer: In a multicenter, double-blind, placebo-controlled study of 147 patients with endoscopically documented duodenal ulcer, the percentage of patients healed (per protocol) at 2 and 4 weeks was significantly higher with PRILOSEC 20 mg once a day than with placebo (p < 0.01).

Treatment of Active Duodenal Ulcer
% of Patients Healed

	PRILOSEC 20 mg q.d. (n = 92)	Placebo q.d. (n = 48)
Week 2	*41	13
Week 4	*75	27

*p < 0.01

Complete daytime and nighttime pain relief occurred significantly faster (p < 0.01) in patients treated with PRILOSEC 20 mg than in patients treated with placebo. At the end of the study, significantly more patients who had received PRILOSEC had complete relief of daytime pain (p < 0.05) and nighttime pain (p < 0.01).

In a multicenter, double-blind study of 283 patients with endoscopically documented duodenal ulcer, the percentage of patients healed (per protocol) at 4 weeks was significantly higher with PRILOSEC 20 mg once a day than with ranitidine 150 mg b.i.d. (p < 0.01).

Treatment of Active Duodenal Ulcer
% of Patients Healed

	PRILOSEC 20 mg q.d. (n = 145)	Ranitidine 150 mg b.i.d. (n = 148)
Week 2	42	34
Week 4	*82	63

*p < 0.01

Healing occurred significantly faster in patients treated with PRILOSEC 20 mg than in those treated with ranitidine 150 mg b.i.d. (p < 0.01).

In a foreign multinational randomized, double-blind study of 105 patients with endoscopically documented duodenal ulcer, 20 mg and 40 mg of PRILOSEC were compared to 150 mg b.i.d. of ranitidine at 2, 4 and 8 weeks. At 2 and 4 weeks both doses of PRILOSEC were statistically superior (per protocol) to ranitidine, but 40 mg was not superior to 20 mg of PRILOSEC, and at 8 weeks there was no significant differences between any of the active drugs.

Treatment of Active Duodenal Ulcer
% of Patients Healed

	PRILOSEC 20 mg (n = 34)	40 mg (n = 36)	Ranitidine 150 mg b.i.d. (n = 35)
Week 2	* 83	* 83	63
Week 4	* 87	* 100	82
Week 8	100	100	94

*p < 0.01

Gastroesophageal Reflux Disease (GERD)

In a U.S. multicenter double-blind placebo controlled study of 20 mg or 40 mg of PRILOSEC Delayed-Release Capsules in patients with symptomatic esophagitis and endoscopically diagnosed erosive esophagitis of grade 2 or above, the percentage healing rates (per protocol) were as follows:

Week	20 mg PRILOSEC (n = 83)	40 mg PRILOSEC (n = 87)	Placebo (n = 43)
4	38**	45**	7
8	74**	78**	14

**p < 0.01) PRILOSEC versus placebo.

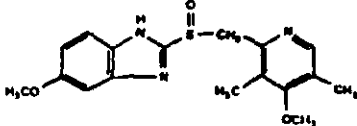
In this study, the 40 mg dose was not superior to the 20 mg dose of PRILOSEC in the percentage healing rate. Other controlled clinical trials have also shown that PRILOSEC is effective in severe GERD. In comparisons with histamine H₂-receptor antagonists in patients with erosive esophagitis of grade 2 or above, PRILOSEC in a dose of 20 mg was significantly more effective than the active controls. Complete daytime and nighttime heartburn relief occurred significantly faster (p < 0.01) in patients treated with PRILOSEC than in those taking placebo or histamine H₂-receptor antagonists.

Pathological Hypersecretory Conditions

In open studies of 136 patients with pathological hypersecretory conditions, such as Zollinger-Ellison (ZE) syndrome with or without multiple endocrine adenomas, PRILOSEC Delayed-Release Capsules significantly inhibited gastric acid secretion and controlled associated symptoms of diarrhea, anorexia, and pain. Doses ranging from 20 mg every other day to 380 mg per day maintained basal acid secretion below 10 mEq/hr in patients without prior gastric

PRILOSEC[®] (OMEPRAZOLE) DELAYED-RELEASE CAPSULES

The active ingredient in PRILOSEC[®] (Omeprazole) Delayed-Release Capsules is a substituted benzimidazole, 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, a compound that inhibits gastric acid secretion. Its empirical formula is C₁₇H₁₉N₃O₃S, with a molecular weight of 345.42. The structural formula is:



Omeprazole is a white to off-white crystalline powder which melts with decomposition at about 155°C. It is a weak base, freely soluble in ethanol and methanol, and slightly soluble in acetone and isopropanol and very slightly soluble in water. The stability of omeprazole is a function of pH; it is rapidly degraded in acid media, but has acceptable stability under alkaline conditions.

PRILOSEC is supplied as delayed-release capsules for oral administration. Each delayed-release capsule contains 20 mg of omeprazole in the form of enteric-coated granules with the following inactive ingredients: cellulose, disodium hydrogen phosphate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, mannitol, sodium lauryl sulfate and other ingredients. The capsule shell has the following inactive ingredients: gelatin, FD&C Blue #1, FD&C Red #40, titanium dioxide, synthetic black iron oxide, iso-propanol, butyl alcohol, FD&C Blue #2, and D&C Red #7 Calcium Lake.

CLINICAL PHARMACOLOGY

Pharmacokinetics and Metabolism

PRILOSEC Delayed-Release Capsules contain an enteric-coated granule formulation of omeprazole (because omeprazole is acid labile), so that absorption of omeprazole begins only after the granules leave the stomach. Absorption is rapid, with peak plasma levels of omeprazole occurring within 0.5 to 3.5 hours. Peak plasma concentrations of omeprazole and AUC are approximately proportional to doses up to 40 mg, but because of a saturable first-pass effect, a greater than linear response in peak plasma concentration and AUC occurs with doses greater than 40 mg. Absolute bioavailability (compared to intravenous administration) is about 30-40% at doses of 20-40 mg, due in large part to presystemic metabolism in healthy subjects (the plasma half-life is 0.5 to 1 hour, and the total body clearance is 500-600 mL/min). Protein binding is approximately 95%. The bioavailability of omeprazole increases slightly upon repeated administration of PRILOSEC Delayed-Release Capsules.

Following single dose oral administration of a buffered solution of omeprazole, little if any unchanged drug was excreted in urine. The majority of the dose (about 77%) was eliminated in urine as at least six metabolites. Two were identified as hydroxyomeprazole and the corresponding carboxylic acid. The remainder of the dose was recoverable in feces. This implies a significant biliary excretion of the metabolites of omeprazole. Three metabolites have been identified in plasma—the sulfide and sulfone derivatives of omeprazole, and hydroxyomeprazole. These metabolites have very little or no antisecretory activity.

In patients with chronic hepatic disease, the bioavailability increased to approximately 100% compared to an I.V. dose, reflecting decreased first-pass effect, and the plasma half-life of the drug increased to nearly 3 hours compared to the half-life in normals of 0.5-1 hour. Plasma clearance averaged 70 mL/min, compared to a value of 500-600 mL/min in normal subjects.

In patients with chronic renal impairment, whose creatinine clearance ranged between 10 and 62 mL/min (1.73 m²), the disposition of omeprazole was very similar to that in healthy volunteers, although there was a slight increase in bioavailability. Because urinary excretion is a primary route of excretion of omeprazole metabolites, their elimination slowed in proportion to the decreased creatinine clearance.

The elimination rate of omeprazole was somewhat decreased in the elderly, and bioavailability was increased. Omeprazole was 76% bioavailable when a single 40 mg oral dose of omeprazole (buffered solution) was administered to healthy elderly volunteers, versus 58% in young volunteers given the same dose. Nearly 70% of the dose was recovered in urine as metabolites of omeprazole and no unchanged

DELAYED-RELEASE CAPSULES
PRILOSEC[®] (OMEPRAZOLE)

Circular Number 7910812



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Submitted: 3/16/95
AP: 3/17/95

PRLOSEC® (Omeprazole) Delayed-Release Capsules

surgery, and below 5 mg/day in patients with prior gastric surgery.

Initial doses were titrated to the individual patient need, and adjustments were necessary with time in some patients (see **DOSE AND ADMINISTRATION**). PRLOSEC was well tolerated at these high dose levels for prolonged periods (>3 years in some patients). In most ZE patients, serum gastrin levels were not modified by PRLOSEC. However, in some patients serum gastrin increased to levels greater than those present prior to initiation of omeprazole therapy. At least 2 patients with ZE syndrome on long-term treatment with PRLOSEC developed gastric carcinoids. This finding was believed to be a manifestation of the underlying condition, which is known to be associated with such tumors, rather than the result of the administration of PRLOSEC.

INDICATIONS AND USAGE

Short-Term Treatment of Active Duodenal Ulcer
PRLOSEC Delayed-Release Capsules are indicated for short-term treatment of active duodenal ulcer. Most patients heal within four weeks; some patients may require an additional four-week course of therapy.

PRLOSEC SHOULD NOT BE USED AS MAINTENANCE THERAPY FOR TREATMENT OF PATIENTS WITH DUODENAL ULCER DISEASE.

Gastroesophageal Reflux Disease (GERD)
Erosive Esophagitis
PRLOSEC Delayed-Release Capsules are indicated for the short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy (see **CLINICAL PHARMACOLOGY, Clinical Studies**).

Poorly Responsive Symptomatic GERD
PRLOSEC Delayed-Release Capsules are also indicated for the short-term treatment (4-8 weeks) of symptomatic gastroesophageal reflux disease (esophagitis) poorly responsive to customary medical treatment, usually including an adequate course of a histamine H₂-receptor antagonist.

The efficacy of PRLOSEC used for longer than 8 weeks in these patients has not been established. In the rare instance of a patient not responding to 8 weeks of treatment, it may be helpful to give up to an additional 4 weeks of treatment. If there is recurrence of erosive esophagitis or symptomatic GERD poorly responsive to customary medical treatment, additional 4-8 week courses of omeprazole may be considered. **THE DRUG SHOULD NOT BE USED AS MAINTENANCE THERAPY.**

Pathological Hypersecretory Conditions
PRLOSEC Delayed-Release Capsules are indicated for the long-term treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome, multiple endocrine adenomas and systemic mastocytosis).

CONTRAINDICATIONS

PRLOSEC Delayed-Release Capsules are contraindicated in patients with known hypersensitivity to any component of the formulation.

PRECAUTIONS

General
Symptomatic response to therapy with omeprazole does not preclude the presence of gastric malignancy.

Information for Patients
PRLOSEC Delayed-Release Capsules should be taken before eating. Patients should be cautioned that the PRLOSEC Delayed-Release Capsule should not be opened, chewed or crushed, and should be swallowed whole.

Drug Interactions
Omeprazole can prolong the elimination of diazepam, warfarin and phenytoin, drugs that are metabolized by oxidation in the liver. Although in normal subjects no interaction with theophylline or propranolol was found, there have been clinical reports of interaction with other drugs metabolized via the cytochrome P-450 system (e.g., cyclosporine, diazepam, benzodiazepines). Patients should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with PRLOSEC.

Because of its profound and long lasting inhibition of gastric acid secretion, it is theoretically possible that omeprazole may interfere with absorption of drugs whose gastric pH is an important determinant of their bioavailability (e.g., bisacodylate, ampicillin esters, and iron salts). In the clinical trials, esterase were used concomitantly with the administration of PRLOSEC.

Carcinogenicity, Mutagenicity, Impairment of Fertility
In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (approximately 4 to 362 times the human dose, based on a patient weight of 80 kg and a human dose of 20 mg) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes in one of these studies. Female rats were treated with 13.8 mg omeprazole/kg/day

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(approximately 36 times the human dose) for one year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of one year (84% treated vs 10% controls). By the second year the difference between treated and control rats was much smaller (48% vs 26%) but still showed more hyperplasia in the treated group. An unusual primary malignant tumor in the stomach was seen in one rat (2%). No similar tumor was seen in male or female rats treated for two years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret. A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive.

Omeprazole was not mutagenic in an *in vitro* Ames *Salmonella typhimurium* assay, an *in vitro* mouse lymphoma cell assay and an *in vivo* rat liver DNA damage assay. A mouse micronucleus test at 625 and 6250 times the human dose gave a borderline result, as did an *in vivo* bone marrow chromosome aberration test. A second mouse micronucleus study at 7000 times the human dose, but with different (suboptimal) sampling times, was negative.

In a rat fertility and general reproductive performance test, omeprazole in a dose range of 13.8 to 138.0 mg/kg/day (approximately 36 to 345 times the human dose) was not toxic or deleterious to the reproductive performance of parental animals.

Pregnancy
Pregnancy Category C
Teratology studies conducted in pregnant rats at doses up to 138 mg/kg/day (approximately 345 times the human dose) and in pregnant rabbits at doses up to 69 mg/kg/day (approximately 172 times the human dose) did not disclose any evidence for a teratogenic potential of omeprazole.

In rabbit, omeprazole in a dose range of 8.9 to 69.1 mg/kg/day (approximately 17 to 172 times the human dose) produced dose-related increases in embryo-toxicity, fetal reabsorptions and pregnancy disruptions. In rats, dose-related embryofetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole 13.8 to 138.0 mg/kg/day (approximately 36 to 345 times the human dose). There are no adequate or well-controlled studies in pregnant women. Sporadic reports have been received of congenital abnormalities occurring in infants born to women who have received omeprazole during pregnancy. Omeprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether omeprazole is excreted in human milk. In rats, omeprazole administration during late gestation and lactation at doses of 13.8 to 138 mg/kg/day (36 to 345 times the human dose) resulted in decreased weight gain in pups. Because many drugs are excreted in human milk, because of the potential for serious adverse reactions in nursing infants from omeprazole, and because of the potential for human carcinogenicity shown for omeprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

PRLOSEC Delayed-Release Capsules were generally well tolerated during domestic and international clinical trials in 3086 patients.

In the U.S. clinical trial population of 465 patients (including duodenal ulcer, Zollinger-Ellison syndrome and resistant ulcer patients), the following adverse experiences were reported to occur in 1% or more of patients on therapy with PRLOSEC. Numbers in parentheses indicate percentages of the adverse experiences considered by investigators as possibly, probably or definitely related to the drug.

	Omeprazole (n=465)	Placebo (n=64)	Ranitidine (n=195)
Headache	6.9 (2.4)	6.3	7.7 (2.6)
Diarrhea	3.0 (1.3)	3.1 (11.6)	2.1 (10.5)
Abdominal Pain	2.4 (0.4)	3.1	2.1
Nausea	2.2 (0.9)	3.7	4.1 (10.5)
URI	1.9	1.6	2.6
Dizziness	1.5 (0.6)	0.0	2.6 (1.0)
Vomiting	1.5 (0.4)	4.7	1.5 (0.5)
Rash	1.5 (1.1)	0.0	0.0
Constipation	1.1 (0.9)	0.0	0.0
Cough	1.1	0.0	1.5
Asthma	1.1 (0.2)	1.6 (1.6)	1.5 (1.0)
Back Pain	1.1	0.0	0.5

The following adverse reactions which occurred in 1% or more of omeprazole treated patients have been reported in international double blind, and open label, clinical trials in which 2,631 patients and subjects received omeprazole.





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PRLOSEC® (Omeprazole) Delayed-Release Capsules

 Incidence of Adverse Experiences ± %
 Causal Relationship not Assessed

	Omeprazole (n=2831)	Placebo (n=120)
<i>Body as a Whole, see unspecified</i>		
Abdominal pain	5.2	3.3
Diathesis	1.3	0.8
<i>Digestive System</i>		
Constipation	1.5	0.8
Diarrhea	3.7	2.5
Flatulence	2.7	5.8
Nausea	4.0	6.7
Vomiting	3.2	10.0
Acid regurgitation	1.9	3.3
<i>Nervous System/Psychiatric</i>		
Headache	2.9	2.5

Additional adverse experiences occurring in < 1% of patients or subjects in domestic and/or international trials, or occurring since the drug was marketed, are shown below within each body system. In many instances, the relationship to PRLOSEC was unclear.

Body As a Whole: Fever, pain, fatigue, malaise, abdominal swelling

Cardiovascular: Chest pain or angina, tachycardia, bradycardia, palpitation, elevated blood pressure, peripheral edema

Gastrointestinal: Pancreatitis (some fatal), anorexia, irritable colon, flatulence, fecal discoloration, esophageal candidiasis, mucosal atrophy of the tongue, dry mouth

Hepatic: Mild and, rarely, marked elevations of liver function tests [ALT (SGPT), AST (SGOT), γ-glutamyl transaminase, alkaline phosphatase, and bilirubin (jaundice)]. In rare instances, overt liver disease has occurred, including hepatocellular, cholestatic, or mixed hepatitis, liver necrosis (some fatal), hepatic failure (some fatal), and hepatic encephalopathy.

Metabolic/Nutritional: Hypoglycemia, weight gain
Musculoskeletal: Muscle cramps, myalgia, muscle weakness, joint pain, leg pain

Nervous System/Psychiatric: Psychic disturbances including depression, aggression, hallucinations, confusion, insomnia, nervousness, tremors, apathy, somnolence, anxiety, dream abnormalities, vertigo, paresthesia, hemispatial dysmetria

Respiratory: Epistaxis, pharyngeal pain
Skin: Rash and, very rarely, cases of severe generalized skin reactions including toxic epidermal necrolysis (TEN; some fatal), Stevens-Johnson syndrome, and erythema multiforme (some severe); skin inflammation, urticaria, angioedema, pruritus, alopecia, dry skin, hyperhidrosis

Special Senses: Tinnitus, taste perversion
Urogenital: Interstitial nephritis (some with positive rechallenge), urinary tract infection, microscopic pyuria, urinary frequency, elevated serum creatinine, proteinuria, hematuria, glycosuria, testicular pain, gynecomastia

Hematologic: Rare instances of pancytopenia, agranulocytosis (some fatal), thrombocytopenia, neutropenia, anemia, leukocytosis, and hemolytic anemia have been reported.
 The incidence of clinical adverse experiences in patients greater than 65 years of age was similar to that in patients 65 years of age or less.

OVERDOSAGE

There is no experience to date with deliberate overdosage. Doses of up to 360 mg/day have been well tolerated. No specific antidote is known. Omeprazole is extensively protein bound and is, therefore, not readily dialyzable. In the event of overdosage, treatment should be symptomatic and supportive.

Lethal doses of omeprazole after single oral administration are about 1500 mg/kg in mice and greater than 6000 mg/kg in rats, and about 100 mg/kg in mice and greater than 40 mg/kg in rats given single intravenous injections. Animals given these doses showed sedation, ptosis, convulsions, and decreased activity, body temperature, and respiratory rate and increased depth of respiration.

DOSEAGE AND ADMINISTRATION

Short-Term Treatment of Active Duodenal Ulcer:
 The recommended adult oral dose is 20 mg once daily. Most patients heal within four weeks. Some patients may require an additional four weeks of therapy. (See INDICATIONS AND USAGE.)

Erosive Esophagitis or Poorly Responsive Gastroesophageal Reflux Disease (GERD):
 The recommended adult oral dose is 20 mg daily for 4 to 8 weeks (see INDICATIONS AND USAGE).

Pathological Hypersecretory Conditions:
 The dosage of PRLOSEC in patients with pathological hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose is 60 mg once a day. Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Doses up to 120 mg i.i.d. have been administered. Daily dosages of greater than 60 mg should be administered in divided doses. Some patients with Zollinger-Ellison syndrome have been treated continuously with PRLOSEC for more than 5 years.

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No dosage adjustment is necessary for patients with renal impairment, hepatic dysfunction or for the elderly.

PRLOSEC Delayed-Release Capsules should be taken before eating. In the clinical trials, antacids were used concomitantly with PRLOSEC.

Patients should be cautioned that the PRLOSEC Delayed-Release Capsule should not be opened, chewed or crushed, and should be swallowed whole.

NOW SUPPLIED

Nc. 3440 — PRLOSEC Delayed-Release Capsules, 20 mg, are opaque, hard gelatin, amethyst colored capsules, coded 742 on cap and PRLOSEC 20 on body. They are supplied as follows:

NDC 61113-742-31 unit of use bottles of 30
 (6505-01-314-2716, 20 mg 30's)
 NDC 61113-742-28 unit dose package of 100
 (6505-01-314-2717, 20 mg individually sealed 100's).

Storage

Store PRLOSEC Delayed-Release Capsules in a tight container protected from light and moisture. Store between 15°C and 30°C (59°F and 86°F).



As to
ASTRA MERCK
 Wayne, PA 19081, USA

Manufactured by MERCK & CO., INC., West Point, PA 19088, USA

Issued February 1995

Printed in USA

Not Approved

Indication

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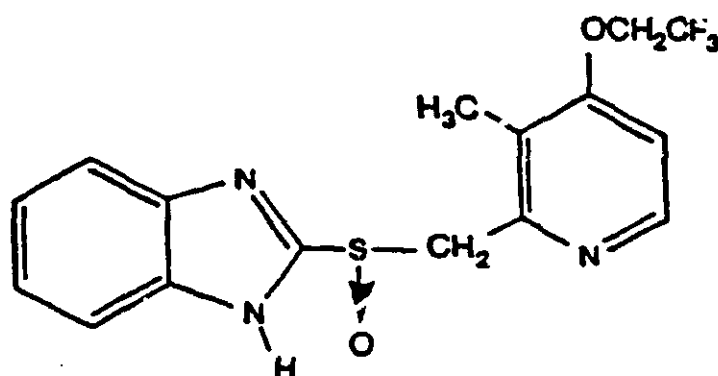
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I. General Information

A. Drug Substance

- (1) INN/USAN Name: Lansoprazole (LANSO)
- (2) Code Names: AG-1749 (Takeda) Abbott-65006 (TAP)
- (3) Trade Name: PREVACID®
- (4) Chem. Abstr. Registry (CAS): 103577-45-3
- (5) Structure



$C_{16}H_{14}F_3N_3O_2S$

M.W. 369.37

2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]benzimidazole

LANSO is a substituted benzimidazole derivative. It has been synthesized and formulated by Takeda Chemical Industries, Ltd., Osaka, Japan. It is being developed by TAP Pharmaceuticals, Inc., Deerfield, Ill.

LANSO has been shown in two polymorphic forms (A and B) by X-ray and differential scanning calorimetry. The fourier-transform IR spectra and thermogravimetric analysis profiles of these polymorphic forms are the same. LANSO can form solvates (pseudopolymorphs) from ethanol, etc. Form A is more stable than form B. LANSO is a stable racemate with respect to the configuration at the S-atom of the sulfinyl group and thus exhibits essentially no optical rotation. LANSO is being developed as a racemate because - according to the sponsor - there are no toxicity issues associated with the drug which "would make it desirable to develop one of the enantiomers separately. Plasma levels of the (+) enantiomer are always higher than those of the (-) enantiomer following administration of racemic LANSO to rats, dogs or humans, but both enantiomers appear to inhibit acid secretion to about the same extent."

NOTE: The statement that plasma levels of one of the enantiomers are always higher than those of the other appears incongruent with the statement that "there are no toxicity issues associated with the drug which would make it desirable to develop one of the enantiomers separately". It is recognized that the criteria by which it is reasonable to develop one enantiomer do not rest on blood level alone. Although there is no toxicity in animals it

seems too early to make such a statement. In addition, blood concentrations may be associated with AEs with one formulation (i.e., I.V.) but not with others. There are no clinical data in support of the sponsor's statement.

B. Drug Product

(See below.)

LANSO is formulated as capsules containing enteric-coated granules that protect the drug substance from acid degradation as it transits the gastric chamber. The inactive components are of compendial quality in the U.S. Pharmacopeia/National Formulary except for methacrylic acid polymer dispersion [an emulsion of MAAP in an aqueous solution of sodium sulfate/polysorbate 80

	15 mg	30 mg	Function
CORE			
LANSO			drug
magnesium carbonate, USP			stabilizer
sugar spheres, NF			diluent
sucrose, NF			diluent
starch, NF			diluent
low substituted, hydroxypropyl cellulose, NF			diluent
hydroxypropyl cellulose, NF			disintegrant
			binder
ENTERIC LAYER			
methacrylic acid copolymer			polymer
polyethylene glycol, NF			plasticizer
titanium dioxide, USP			pigment
polysorbate 80, NF			surfactant
talc, USP			lubricant
colloidal silicon dioxide, NF			anti-static
TOTAL			
CAPSULE SHELLS composition:	gelatin	gelatin	
description: size	#3	#1	
color	bluish-green	black	
markings	pink opaque	pink opaque	
	"TAP" logo	"TAP" logo	
	PREVACID-15	PREVACID-30	

C. Pharmacologically-related Drugs
(Antisecretory, Antiulcer)

1. Proton-pump Inhibitors

Compound	Indications for which these compounds have been approved
Omeprazole (Prilosec™)	Short-term Tx of DU, GERD (severe erosive esophagitis, poorly responsive symptomatic GERD), L-T Tx of Pathological Hypersecretory Conditions (Z-E et al.).

Because, if approved, LANSO would be the second PPI in the U.S. market, it seems important to stress similarities and dissimilarities between this compound and OME. Approved in the U.S. in 1989, OME is now available as an alternative to H₂-inhibition therapy for acid-related diseases, particularly

RE. Just as LANSO, OME is a pro-drug, requiring conversion by an acidic environment before it is able to inhibit the (H⁺, K⁺)-ATPase. Just as LANSO, OME has to be acid protected when given orally. If exposed to gastric juice, OME will convert to the sulfonamide in the lumen of the stomach or duodenum and will not reach its target enzyme [G. Sachs, Current Opinion in Gastroenterology 6:859-866 (1990)]. The half-life of OME in human plasma is ca. 50 min. but through covalent reactions, it accumulates in the acid secretory canaliculi of the parietal cells where it is converted into an active form (a cation that penetrates the cell membrane very slowly) with instantly effective and long-lasting inhibition of acid secretion.

The completeness and long-lasting acid suppression induced by OME is of concern because in long-term (2-year) studies in rats, this compound produced dose-related increase in gastric carcinoid tumors, ECL cell hyperplasia in all treated groups and an unusual primary malignant tumor in the stomach in one rat [OME labeling; Warning]. Reports of possible genotoxicity of OME in the stomach remain controversial. Although most clinical reports indicate no major untoward effects in humans, concerns over the long-term safety of OME continue. Also, potential interactions of OME with some common drugs through potentiation of the P₄₅₀ system are continuously being examined.

2. H₂-Receptor Antagonists

<u>Compounds</u>	<u>Indications for which these compounds have been approved</u>
Cimetidine (Tagamet®)	DU, GU, GERD, Z-E, Maintenance (DU), Prevention of UGIB in critically ill patients
Ranitidine (Zantac®)	DU, GU, GERD, Z-E, Maintenance (DU)
Famotidine (Pepcid®)	DU, GU, GERD, Z-E, Maintenance (DU)
Nizatidine (Axid)	DU, GERD, Maintenance (DU)

NOTE: With the H₂, different dose regimens for symptomatic GERD vs erosive esophagitis are needed. For example, for GERD, the current recommended adult oral dosage is 150 mg ranitidine twice daily. The current recommended adult oral dosage for the treatment of endoscopically diagnosed erosive esophagitis is 150 mg of ranitidine four times a day. It is important to keep these dose and dose regimens in mind. The LANSO clinical trials include comparisons to active drugs, such as ranitidine. Of the latter, 150 mg twice a day relieves symptoms; but 150 mg four times a day are needed to heal esophagitis lesions.

A number of H₂-receptor antagonists have not been fully developed due to toxicity in animals, erratic bioavailability or lack of efficacy in man.

3. <u>Sucralfate</u> (Carafate®)	<u>Approved Indications</u> DU, Maintenance (DU)

4. <u>Prostaglandins</u> Misoprostol (Cytotec®)	<u>Approved Indications</u> Prevention of NSAID-induced GU

II. Summary of Non-Clinical Pharmacology, Toxicology and ADME

A. Pharmacology

As of this writing, non-clinical Pharmacology-Toxicology NDA reviews cannot be consulted because they are not available. The material that follows was abstracted from NDA 20-406 Vol. 2.2, pages 245 through 422. Only salient points are mentioned. To be properly validated the sponsor's statements need to be compared against conclusions from Pharmacology/Toxicology reviews.

The sponsor notes:

- Through a mechanism very similar to that advanced for OME, orally administered LANSO appears to gain access to gastric parietal cells as the uncharged parent with conversion in the secretory canaliculus to charged metabolites that bind directly to a sulfhydryl group on the canalicular (H⁺, K⁺)-ATPase.
- In vitro and in vivo potency antisecretory-antiulcer studies suggest that LANSO is as potent as OME but less potent than H₂-receptor antagonists, particularly famotidine.

NOTE: In addition to PL comparisons, the pivotal clinical trials have included comparisons to customary regimens of ranitidine. Some supportive studies comparing LANSO to FAM or OME are also available.

- Results of general pharmacology studies with LANSO revealed:
 - No counter-indicated effects in the G.I. system
 - Marginal effects on tone and amplitude of rabbit ileum
 - No marked effects on smooth muscle contraction and GI transit at doses X 200 greater than those anticipated in humans (30 mg per day)
 - No untoward effects on gastric hemodynamics in experimental shock; at 10 mg/Kg ip, LANSO reduced the decrease in blood volume, Hb saturation and ulcer index
 - No notable neuropharmacologic effects
 - No effects on motility of rat uterus
 - No effects on:
 - muscle relaxation
 - anticonvulsant activity
 - analgesia or
 - hypothermic responses
 - Marginal effects on tone of guinea pig trachea
 - No effect on central or autonomic responses
 - No notable effects on BP, HR or respiration at doses 600-fold greater than the anticipated dose in humans
 - At 10⁻⁶M, a slight increase in contractile force and 20% decrease in beat rate in guinea pig isolated atria. [No effects were seen at lower concentrations].
 - No perturbation of water-electrolyte balance
- In experiments in which animals were pre-treated with LANSO and then given Pb, prolonged Pb-induced sleeping time was observed at LANSO doses of 30 and 100 mg/Kg in mice and rats, respectively. Shortened sleeping time occurred in mice (100 mg/Kg) by 24h pre-Tx.

NOTE: According to these data some kind of interaction between LANSO and Pb at the CNS level may exist. LANSO appears to potentiate the Pb-induced sleeping time in mice and rats. But it is not known if these pre-clinical findings are clinically relevant.

In addition:

- Study A-29-1170 assessed inhibitory activity against viability of *Helicobacter pylori*. The racemate and acid rearrangement metabolites of LANSO were fourfold more potent than OME; the effects was HP specific.

NOTE: These studies in vitro are of some interest, but far more interesting would be in vivo studies in humans.

B. Summary of Toxicology

- The main target organs for drug-induced effects in subchronic and chronic toxicity studies are listed below. Only main findings are mentioned.

STOMACH

TISSUE/ORGAN	MAIN FINDINGS
RATS (10 to 15 mg/Kg/day or more)	Thickened glandular mucosa, vacuolation and hypertrophy of parietal cells, eosinophilia; hypertrophy and necrosis of chief cells, ↑ in EC-L cell density, ↑ in stomach Wt., ↑ severity of squamous cell hyperplasia, hyperkeratosis, mixed inflammatory Rx. According to the sponsor, these changes in rats were reversible after 26 weeks recovery Post.-Tx.
MICE	↑ stomach Wt., hyperplasia and/or hypertrophy of the glandular mucosa, vacuolar changes and at high doses, EROSIONS OF THE MUCOSA.
DOGS	Thickened gastric mucosa, vacuolation and necrosis of parietal cells.

Carcinogenicity Studies

The sponsor notes:

- In two 2-year rat studies, an ↑ incidence of carcinoid tumors was seen at dosages of 5 mg/Kg/day or more with higher incidence in F compared to M.
- A total of 5 carcinoid tumors were seen in the 2-year mouse study, but the incidence did not show a dose relationship.

In rats, an ↑ in intestinal metaplasia was seen, as follows:

	Control (N=60)	LANSO Dose (mg/Kg)			
		1.5 (N=60)	5 (N=59)	15 (N=60)	50 (N=60)
MALES	0%	0%	3%	5%	10%
FEMALES	2%	0%	0%	0%	10%

According to the sponsor, this effect may be reversible because D/C administration after 18 mo. of Tx resulted in a lower incidence of metaplasia.

LIVER ↑ in liver Wt and hepatocellular hypertrophy

↑ in smooth E.R. (1 and 3-mo. rat and dog studies)

↑ in hepatocellular carcinomas in F rats at 150 mg/Kg/day and F mice at 300 mg/Kg/day. The combined incidence of hepatocellular adenomas/carcinomas was statistically significantly higher in high dose F mice than in controls.

No ↑ in hepatocellular neoplasms were seen for M of either species.

NOTE: The liver carcinogenicity issue is being examined by the Pharmacology Reviewer. In the meantime, it should be pointed out that the sponsor attributes these findings (↑ in hepatocellular carcinomas in two species) to the ability of LANSO to induce hepatic cytochrome P₄₅₀ effects similar to those of Pb). Liver neoplasms are said to occur in animals but not in man. In reality, a) the Pb story is not entirely settled and b) information is needed as to whether cytochrome P₄₅₀ enzymes are required to metabolize LANSO in humans. Some information as to whether LANSO may interact with metabolizing enzymes is available (see Drug-Drug Interactions). But information (i.e. studies involving liver Bx in man) on the effect of LANSO on cytochrome P₄₅₀ monooxygenase- or reductase-dependent ENZ or isoENZ or other ENZ participating in xenobiotic metabolism are not available.

EYE ↑ incidence and severity of retinal atrophy was seen in the 2-year carcinogenicity studies in Sprague-Dawley rats at dosages from 15 to 150 mg/Kg/day in F and 50 to 150 mg/Kg/day in M.

↑ incidence of subcapsular cataracts was seen in one 2-y rat study at the highest dose tested (150 mg/Kg/day).

NOTE: According to the sponsor, careful ophthalmoscopic and electroretinographic examinations are currently being conducted in pts. on L-T Tx with LANSO, to determine the clinical relevance of these pre-clinical eye findings.

TESTIS MICE

↑ incidences of animals with reduced number of sperm in the epididymides and atrophy of seminiferous tubes at doses of LANSO of 1200 to 2400 mg/Kg/day x 3 mo.

RATS

Testicular atrophy and epididymal hypospermia in animals Tx with 300 mg/Kg/day or more x 3 mo.

The 2-y rat studies showed seminiferous tubule degeneration, epididymal hypospermia and seminal vesicle atrophy at 75 mg/Kg/day or more and Leydig cell hyperplasia and benign tumors at 15 mg/Kg/day or more.

In M Tx with 150 mg/Kg/day x 18 mo. and then maintained without Tx for an additional 6 mo., the incidence of Leydig cell tumors was ↓ compared to M rats receiving the same dosage continuously for 2-y.

DOGS

↓ in prostate weights after Tx x 13 weeks and for 1y with 5 mg/Kg/day or more.

NOTE: The sponsor hypothesizes that the mechanism for induction of Leydig cell tumors is a ↓ in circulating levels of testosterone, which interrupts the negative feedback provided by this hormone to the hypothalamus and pituitary.

PANCREAS Pancreatic acinar atrophy was seen in one 2-y rat study at dosages exceeding the MTD and at systemic exposure levels (AUC) of parent drug which exceeded the anticipated clinical AUC with 7 days/week dosing.

ERYTHROCYTE Slight ↓ in erythrocyte count, Hct, Hb in rats Tx with 50 mg/Kg/day x 3 mo. or longer and in mice given 150 mg/Kg/day or more x 3 mo. or 75 mg/Kg/day or more x 2-y.

NOTE: This may occur as a result of interference with iron absorption secondary to reduced gastric acid secretion.

IMMUNE SYSTEM Thymic atrophy or ↓ thymus Wts. was seen consistently in rats given 50 mg/Kg/day or more for 1 mo. or longer

↓ thymic Wt. seen in dogs Tx with 50 mg/Kg/day x 6 mo.

NOTE: The cause of the thymus effect is not known. LANSO has been shown to be non-antigenic in studies in guinea pigs and mice.

THYROID ↑ thyroid Wts. in one 13-week study in rats at 150 mg/Kg/day.
↓ circulating levels of thyroxine; no changes in thyroid Wt., T₃ or TSH, in a second 3-mo. study in rats at of 150 mg/Kg/day or more.

C. Reviewer's Conclusions on L-T Toxicity Studies

Chronic toxicity studies in rats reveal expected similarities between LANSO and OME in that both induce carcinoids and hyperplastic changes of the mucosa, one gastric adenocarcinoma in one rat, liver neoplasms, alterations of erythrocytes and thyroid gland. Both compounds may be mutagenic in some tests. Dissimilarities between these two PPIs included effects with LANSO not noted with OME, such as increase in incidence of a) intestinal metaplasia (seen in the stomach of rats), b) retinal atrophy and subcapsular cataracts seen in rats and c) induction of Leydig cell hyperplasia and benign tumors, preceded by testicular atrophy and epididymal hypospermia in rats and mice and decrease in prostate weight in dogs.

D. Short Summary on ADME in Animals

The sponsor notes:

- After oral doses of ¹⁴C-LANSO in gum arabic suspensions or in gelatin capsules, 27% of the radioactivity was absorbed in mice, 37% in rats, and 63 to 87% in dogs.
- However, due to degradation and hepatic metabolism of the absorbed dose, bioavailability was much lower, representing 4% in mice and rats and 22% in dogs.

- Peak levels of parent drug in mice, rats, and dogs were reached within 24h after dosing, and plasma concentrations generally increased with dose size.
- Considerable interanimal variability was found in monkeys: C_{max} values occurred from 0.5 to 6h after a 50 mg/Kg oral dose in gum arabic.
- Following an oral dose of LANSO, AUC values ranged from
ng·h/mL in mice (mg/Kg),
ng·h/mL in monkeys (mg/Kg),
ng·h/mL in rats (mg/Kg),
ng·h/mL in dogs (mg/Kg), and
ng·h/mL in monkeys (mg/Kg).
- The half-life of LANSO ranged from 0.2 to 1.2 h in mice and rats and had a tendency to increase with dose size.
- The half-life in dogs averaged 0.6 to 1.7 h, and in monkeys 3.3 h.
- The AUC and C_{max} parameters were a) reasonably consistent after multiple doses of LANSO in mice and rats, b) variable in monkeys, and c) decreased appreciably in dogs.

- Following oral or i.v. administration of a 2-mg/Kg dose of racemic LANSO to rats and dogs, C_{max} and/or AUC values were about two to threefold greater for the (+) enantiomer than the (-) enantiomer. In vitro studies with racemic LANSO and the individual isomers using rat and dog liver 9000 x g supernatants suggested that the (-) isomer is metabolized more rapidly than the (+) isomer. This would result in lower plasma concentrations of the (-) isomer. As previously noted, both enantiomers apparently inhibit acid secretion to about the same extent.
- Circulating metabolites in rats and dogs (see Fig. 1) included the

- PK characterization of these metabolites has not been done.
- Studies of total uncharacterized metabolites have demonstrated that, based on C_{max} values after oral doses, the plasma levels exceed those of parent drug by 1.3 to 19 fold in mice, rats and dogs. The half-life of metabolites averaged 1 to 3 h in mice; 8 to 11 h in rats and dogs.

PURGE

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- LANSO was extensively bound to plasma proteins. At LANSO concentrations ranging from _____ ng/mL, protein binding ranged from _____ % in rat and dog plasma.
- LANSO was rapidly distributed throughout the body of rats after a 2-mg/Kg oral dose, with relatively high concentrations in the intestine, stomach, liver, kidney, and thyroid. Tissue to plasma ratios of 2 to 35 were noted in these tissues. Concentrations in the brain and all other tissues examined were lower than circulating levels.
- After multiple oral doses (2 mg/Kg/day) x 7 days, radioactivity in plasma and tissues was slightly elevated, and the overall distribution patterns were similar.
- The cumulative excretion curves paralleled the administered dose, suggesting little accumulation of the drug in tissues with daily dosing.
- In both the single- and multiple-dose studies, most of the drug was cleared from all tissues except the thyroid after 72 h.
- The tissue distribution pattern in mice 24 h after a single, oral 1.5-mg/Kg dose was comparable to that seen in rats.
- Accumulation of the dose in plasma and practically all tissues of mice and rats was observed after large oral doses of 50 mg/Kg/day for 26 days.
- LANSO readily penetrated into the parietal cells of the gastric mucosa of rats and persisted for 24 h.
- Levels of parent drug in the mucosa were 2 to 5 fold greater than those in plasma up to 6 h after a 2-mg/Kg i.v. dose, supporting the concept that LANSO suppresses acid secretion by inhibiting the (H⁺, K⁺)-ATPase enzyme located in these cells.
- Daily, oral administration of a 150-mg/Kg dose of LANSO to rats x 5 days resulted in a moderate induction of microsomal, mixed function oxidase enzymes in the liver. Microsomal protein, total cytochrome P-450, and cytochrome b, levels were increased 12 to 45%, while activities of p-nitroanisole O-demethylase and p-nitrophenyl glucuronyltransferase were elevated about 2 to 3 fold.
- Incubation of LANSO with rat liver microsomes (60 to 1500 µg/g liver) inhibited the in vitro metabolism of aminopyrine, aniline, and p-nitroanisole from 8 to 71%.

On the basis of the above-summarized information, I agree with the sponsor that these data suggest that acute doses of LANSO may inhibit some drug-metabolizing enzymes, while chronic doses appear to induce their formation.

PURGE

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- As noted under fecal metabolites, many of the biliary metabolites have not been characterized.

I.V. Dosing

- ¹⁴C-LANSO administered i.v. was rapidly and widely distributed in tissues, almost completely metabolized, and eliminated from the body preferentially in feces via hepatobiliary route, with the remainder appearing in urine.
- Unchanged LANSO and its metabolites readily entered the gastric mucosa and lasted at relatively high concentrations.
- On repeated administration of the labeled compound to rats, the elimination of radioactivity was almost complete.

III. Human Metabolism and Biopharmaceutics

Again, since a Biopharm. review is not yet available, the material summarized below was taken from sponsor's NDA Summary (Vol. 2.2 of NDA 20-406).

A. PK Parameters of LANSO

PK parameters of LANSO in normal healthy subjects are summarized in Table 1. Since bioavailability studies demonstrated dose proportionality between 15-, 30-, and 60-mg doses, results from 15-, 30-, and 60-mg dose were dose-normalized to a 30-mg dose and pooled. The sponsor also explained that virtually all studies were done using one of three formulations (T1, T2, and T3) and "these have been found to be equivalent". Thus, results from all three formulations were pooled in obtaining the values listed in Table 1.

As shown in Table 1, in normal healthy subjects the mean time of maximum concentration following an oral dose (T_{max}) was 1.68 ± 0.80 h. Since LANSO does not accumulate, T_{max} after a single dose and after multiple doses were virtually the same. The mean area under the curve (AUC), normalized to a 30 mg dose, was 2133 ± 1797 ng·h/mL and the mean normalized maximum concentration (C_{max}) was 824 ± 419 ng/mL. The arithmetic mean half-life was 1.53 ± 1.01 h. The harmonic mean $\pm$ pseudo-SD was determined to be 1.19 ± 0.52 h.

¹Each of the capsule formulations consisted of enteric-coated granules placed in a capsule.

- The T1 formulation was produced in strengths of 7.5 mg and 15 mg; the formulation of the 15-mg capsule contained mg less sucrose and 7.5 mg more LANSO per capsule than did the 7.5-mg capsule.
- T1 and T2 formulations consisted of granules with three layers:
- The T3 formulation has only two layers:

- granules of identical content, which were bioequivalent, yet less complex to manufacture. , resulting in
- T2 and T3 formulations were produced in strengths of 15 and 30 mg. For the T2 formulation, the granules were identical irrespective of the strength of the capsule. The same was true of the T3 formulation.
- The higher strength capsules were produced by placing more of the same granules in a capsule shell.
- According to the sponsor, the three formulations are linked by two definitive bioequivalence studies. Study P90-043 (Germany) established equivalence of the T1 and T2 formulations. Study P90-198 (U.S.) established equivalence of the T2 and T3 formulations. Chiral analysis of a subset of samples from this same study established that the T2 and T3 formulations deliver the two LANSO enantiomers in equal proportions.
- The T3 formulation is the formulation intended for marketing.

TABLE 1

Summary of PK Parameters of LANSO
Pooled Across Phase I Studies

Parameter	T_{max} (h)	$t_{1/2}$ (h)	AUC ^a (ng·h/mL)	C_{max} ^b (ng/mL)
Mean	1.48	1.53	2133	824
Median	1.50	1.24	1644	770
SD	0.80	1.01	1797	419
% CV ^c	47.71	65.92	84.28	50.81
Min	0.50	0.39	213	27
Max	6.00	8.50	14203	2440
Harmonic Mean		1.19		
Pseudo-SD		0.52		
N ^c	345	285	513	515

a,b) Normalized to a 30-mg dose.

T_{max} = time of maximum concentration, $t_{1/2}$ = half-life, AUC = area under the concentration vs time curve, C_{max} = maximum concentration.

c) N represents the number of dosings associated with a particular parameter. For example, if parameters were available from the first and seventh day of dosing for a given subject, then two values were incorporated, one from Day 1 and one from Day 7. Thus, estimates of parameters and their variability are not pure intersubject estimates. Generally, intersubject variability was greater than intrasubject variability. Nonetheless, this table provides a perspective of the PKs of LANSO over a large database.

B. Absorption and Absolute Bioavailability

- LANSO is well-absorbed.
- In Study P91-062 (Germany) the mean absolute bioavailability for the 15-mg LANSO dose was 0.864, and for the 30-mg capsule it was 0.803.
- In light of the high absolute bioavailability, first-pass effect for LANSO is apparently small in man.

C. Effect of Certain Factors on Absorption/Absolute Bioavailability

FACTOR	MAIN EFFECT
<u>Food</u>	• ↓ absorption when dosing with or after food, irrespective of formulation. • Little or no effect on bioavailability when dosing before breakfast. • ∴ Suggest that food can be ingested about one-half hour after dosing.
<u>Antacids</u>	• A Maalox (Al and Mg OH) study examined concomitant dosing and dosing with one hour separation. • A Riopen (megaldrate) study looked at concomitant dosing only. • In both studies, LANSO AUC values were not statistically significantly altered. • Statistically significant ↓ in C_{max} when LANSO was administered concomitantly with either antacid. • When LANSO was administered 1h after Maalox, C_{max} was not statistically significantly different.
<u>Sucralfate</u>	• coadministration resulted in a statistically significantly different LANSO AUC, C_{max} and T_{max}. • Adm. of SUCR 30 min. after LANSO resulted in no statistically significant difference in AUC or T_{max} but C_{max} was statistically significantly lower ($p=0.01$) and $t_{1/2}$ was statistically significantly different ($p=0.05$). The latter difference (14 minutes) may not be of clinical consequence.
<u>AM vs PM Dosing</u>	• Evening dosing (10:00 PM) diminished relative bioavailability by a factor of ca. 2, in comparison to morning dosing (8:00 AM) (Study N87-049 (U.S.), examining 10-, 20-, 30-, and 60-mg doses in MNVs). Diminished absorption (by PM dosing) was also shown in a foreign study including dosing at 9:00 AM and 9:00 PM (comparison of approximate C_{max}).

D. Metabolism and Clearance

- The clearance of LANSO is almost entirely mediated through metabolism, presumably by the liver.
- The mean AUC of 2133 ng·h/mL for a 30-mg dose is equivalent to a CL/F value of 14 L/h, which is low compared to hepatic plasma (~50 L/h). From this it would be expected that the clearance of LANSO would be sensitive to alterations in intrinsic clearance and unbound fraction, but relatively insensitive to alterations in hepatic blood flow.
- Metabolic routes for LANSO involve
 -
 -
 - but its concentrations were generally very low compared to those of LANSO.
- Virtually no unchanged LANSO was found in the urine.

- After oral administration of ^{14}C -LANSO, ca. 2/3 of the dose was recovered in the feces and 1/3 in the urine.
- None of the metabolites found in urine and feces had appreciable pharmacologic activity.
- Within the acidic environment of the parietal cell canaliculus, LANSO was transformed to two metabolites which inhibited acid secretion by $(\text{H}^+, \text{K}^+)\text{-ATPase}$. Neither of these metabolites have been found in the systemic circulation.

E. Human and Interspecies Comparison

- LANSO is extensively metabolized in humans by metabolic pathways common to rats and dogs.
- Both urinary and fecal excretion were involved in the elimination of the drug and its metabolites, although urinary excretion may be more prominent in humans.
- Plasma protein binding was also extensive in all species, including humans, and ranged from 80% to 90%.
- Plasma levels of the (+) enantiomer were always higher than those of the (-) enantiomer following administration of racemic LANSO to rats, dogs, or humans. The degree of stereoselectivity appeared to be different since C_{max} and AUC values for the (+) isomer were 2 to 3 fold greater than those for the (-) isomer in humans, but only two to three fold greater in rats and dogs.
- However, the absorption of the drug from the g.i. tract, whether as total radioactivity or as parent drug, was much less efficient in mice, rats, and dogs than in humans. These data came from studies showing that bioavailability of an oral dose of LANSO was 4% in rats and mice, 22% in dogs, and about 80% in humans.
- In humans, LANSO absorption was subject to large intersubject variability, but the PKs were generally proportional to the dose from 15 to 60 mg.

NOTE: The finding that some people absorb more (or less) than others is of clinical interest. It is possible that outliers re: absorption and metabolism may also be outliers re: efficacy and safety.

- As previously mentioned, LANSO is acid labile; it is administered to humans as enteric-coated granules in capsules to prevent degradation.
- The formulation most used in rodent studies was a suspension of the drug in 5% gum arabic, adjusted to neutral pH, while gum arabic suspensions or gelatin capsules were drug vehicles in the oral dog studies. Studies in rats showed that, with the suspension formulation, the drug underwent degradation in the intestine before reaching the liver. Further hepatic metabolism of the drug, along with possible metabolism in the red blood cells, could account for low bioavailability in rodents.
- In dogs, the absorption of the total dose and parent drug from gum arabic suspensions or gelatin capsules, appeared to be more efficient, but the AUC and C_{max} parameters decreased appreciably with multiple doses of the drug.

- Studies by _____ suggested that the decrease in plasma levels was not related to differences in absorption, but due to increased clearance of the drug by virtue of the induction of drug-metabolizing enzymes.

F. Dose Proportionality

- The sponsor states that dose proportionality was established in Study F90-199 (U.S.).
- Study M88-289 (U.S.) comparing young to middle age vs older subjects, demonstrated dose proportionality between the 15- and 30-mg doses following both single and multiple-doses in both age groups.
- Study M90-485 (U.S.) demonstrated dose proportionality between the 15- and 30-mg doses.
- Dose proportionality was also shown in Study RY-05-0 (Japan). This included dosing of 15-, 30- and 60-mg LANSO via a parallel design.

G. Multiple Dosing

- LANSO PKs were unaltered by multiple dosing. The drug does not accumulate.
- The concentration vs time profile following multiple dosing was the same as that following a single dose. Thus, LANSO is at steady state at the first dose.
- When dosed once-daily, LANSO concentrations were generally back to zero preceding each dose.

Multiple dosing in older subjects, renally or hepatically impaired patients is addressed below.

H. PKs in Special Populations

1) Older Subjects

- Conclusions on two studies [M88-289 (U.S.) and 1900] were virtually identical. The first examined LANSO PKs after 1 and 7 days of dosing 15 or 30 mg LANSO to young to middle age group (mean age=38y) vs older group (mean age=64.8y). In the second study only elderly (mean age=82.5y) subjects were dosed with 30 mg LANSO x 7 days.
- Older subjects exhibited larger AUC and $t_{1/2}$ values than young subjects. These increases were 50% and two-fold, in the first and second study respectively.
- The sponsor proposes that the interstudy difference in the clearance reduction in elderly subjects was probably due to the difference in age of the older populations in the two studies.
- But T_{max} and C_{min} in elderly subjects were not different from those in the young populations.
- The increase in AUC was apparently a result of diminished clearance rather than alteration of absorption.
- In either study, the PKs in the older subjects were constant upon comparison of results in Day 1 to those of Day 7.

- In spite of the longer Tx. LANSO did not accumulate in the older subjects upon multiple dosing. This is not surprising because C_{max} values were not different from that of the young to middle-age group and, in the worse case, the mean $t_{1/2}$ was elevated to a value of only 2.9 h. I agree with the sponsor that given no change in C_{max} values and a maximum $t_{1/2}$ of 2.9 h, only minimal accumulation of LANSO would be expected when dosed once daily.
- The PK results of these studies are consistent with the sponsor's recommendation that doses higher than 30 mg per day should not be administered to the elderly unless there are compelling clinical reasons.

2) Renally Impaired Subjects

Results from studies M90-412 (60 mg x 7 days) and 20200 (single 30 mg dose) examining LANSO PKs in mild, moderate and severely renally impaired subjects are summarized below.

- In study M90-412, AUC values based on total concentration were shown to be reduced by renal impairment but due to differences in protein binding, there was no statistically significant relationship between Cl_r and unbound AUC. Half-life was reduced by renal impairment. Alteration of protein binding probably contributed to this finding. PK parameters were constant across days in these populations.
- In study 20200, T_{max} and C_{max} in the renally impaired subjects were not significantly different from those in the normal reference population. The mean AUC was not significantly different from normal subjects for the moderately and severely impaired subjects. In the mildly (renally) impaired subjects, AUC and half-life were significantly greater than in normals but the differences were thought to be an age effect rather than a result of mild renal impairment. Study conclusions were that a) renal insufficiency does not lead to variations of LANSO PKs and b) dosage modification for patients with this particular pathology is not justified.
- Both studies concluded that no adjustment of LANSO dose is recommended/justified on the basis of impaired renal function.

3) Dialysis

- The impact of dialysis was examined in the first study from three perspectives 1) plasma PKs; 2) concentrations afferent and efferent to the dialyzer; and 3) analysis of dialysate.
- There were no significant differences in AUC, C_{max} , or half-life in the comparison of the dialysis day and dialysis-free day.
- Differences in the arterial and venous plasma concentrations from samples taken across the dialyzer were not statistically significant.
- Dialysate contained no measurable LANSO or metabolite.
- It was concluded that LANSO is not significantly dialyzed and would be a poor candidate for removal by hemodialysis.

4) Hepatically Impaired Subjects

Results from three studies (M90-450, 7000 and 26000) are summarized below.

Study M90-450 (30 mg LANSO x 7 days) examined LANSO PKs in healthy vs Child-Pugh Class A vs Child-Pugh Class B subjects.

- There were no statistically significant differences in the PK parameters of the Class A subjects and the healthy subjects.
- Some numerical differences in C_{max} were statistically significant.
- A statistically significant difference in $t_{1/2}$ and AUC between Class B subjects and healthy subjects was detected, but no difference between these two groups was noted for C_{max} and T_{max} .
- The greatest difference in AUC occurred on Day 7 and was ca. 3.41-fold. This was attributed to a larger $t_{1/2}$ and accumulation [not seen in healthy subjects]. The increase in AUC was apparently due to slower elimination rather than changes in the rate and extent of absorption or bioavailability.

Study 7000 (LANSO 30 mg as a single dose) examined LANSO PKs in healthy subjects vs subjects with hepatitis vs compensated cirrhosis vs decompensated cirrhosis [4 Tx groups].

- A statistically significant difference in AUC and $t_{1/2}$ was seen in subjects of both cirrhosis categories, and a statistically significant difference in C_{max} was seen in compensated cirrhosis subjects.
- The increase in AUC was greater than that seen in study M90-450.

Study 26000 (France; LANSO at 30 mg x 7 days) examined PKs in Child-Pugh Class A vs B vs C subjects.

- PK parameters calculated after the first and final dose revealed significant increases in C_{max} and AUC after the final dose but not change in plasma elimination half-life of LANSO due to multiple dosing.
- T_{max} , C_{max} , and $t_{1/2}$ were similar in the study group and healthy subjects of a previously conducted study.
- AUC was ca. 3.45 fold greater in the hepatically impaired subjects as compared to the healthy subjects following a single dose.

The occurrence of larger differences in AUC and an increase in C_{max} for impaired subjects of studies 7000 and 26000 may have been due to the inclusion of subjects with greater hepatic disease than in the study M90-450.

I. Reviewer's Conclusions on PKs in Special Populations

Although there were minor changes in PK parameters in the healthy elderly, in patients with renal impairment and in those with mild to moderate hepatic impairment (Child-Pugh A and B), I agree with the sponsor that no dosage adjustment is recommended in these patient populations. On the other hand, an adjustment of the dose may be necessary in patients with severe hepatic

impairment (Child-Pugh C). The sponsor has not presented results of studies evaluating if PKs or LANSO in women and children are different from those in males and adults, respectively.

J. Drug-Drug Interactions

- a) R-warfarin [a substrate of P₄₅₀ IA2 and IIIA4]
S-warfarin [a substrate of IIC9]

- There was no significant effect of LANSO co-administration (multiple doses of 60 mg per day) on PK parameters of either R- or S-warfarin.
- PTs were not significantly altered.

- b) Antipyrine [a probe agent widely used to document alteration in some human oxidative metabolism pathways]

- The PKs of antipyrine were not altered by 30 mg LANSO.
- The rate constant of elimination and the volume of distribution of antipyrine were significantly different due to 60 mg LANSO although the change was small.
- In no case, 30 or 60 mg, one, seven, or 16 days of dosing, was the clearance of antipyrine statistically significantly altered.

- c) Theophylline [a drug which metabolism is mediated by P₄₅₀ IA2 and possibly other forms including P₄₅₀ IIIA4 and P₄₅₀ IIE1. But ca. 60% of the metabolism of theophylline is by undetermined pathways].

- Oral theophylline exhibited a small decrease in AUC values following 1 and 7 days of LANSO 6% for a single dose, and 13% for multiple-doses.
- Intravenous theophylline also exhibited a small decrease in AUC values of about 10% following 14 days of theophylline.
- Since the change was a decrease, toxicity of theophylline due to administration of LANSO is not expected. Nonetheless, individual patients may require titration of their theophylline dosage when LANSO is started or stopped to ensure clinical effective blood levels.
- Since, as noted above, about 2/3 of the metabolism of theophylline is by undetermined pathways, inference with regard to the metabolism of other substrates, based on possibly altered metabolism of theophylline, is confounded.

- d) Indomethacin, ibuprofen (substrates of P₄₅₀ IIC9)

- No clinically significant effects of LANSO (multiple doses of 60 mg) on these NSAIDs (as well as aspirin) were found.

- e) Diazepam [a substrate of P₄₅₀ IIC]

- The PKs of this benzodiazepine and desmethyldiazepam (diazepam's metabolite) were not significantly affected by LANSO (multiple doses of 60 mg per day).

f) Phenytoin (metabolized by P₄₅₀ IIC9)

- LANSO (60 mg) changed phenytoin AUC by <3%, a difference of no clinical significance.

g) Prednisone

- Neither the absorption of prednisone, its biotransformation to prednisolone or the disposition of the latter metabolite were significantly changed by the administration of LANSO (multiple doses of 30 mg per day).

h) Triphasil [A low-dose oral contraceptive, containing levonorgestrel and ethinyl-estradiol, a substrate of P₄₅₀ IIIA4]

- The potential for interaction between LANSO and Triphasil was examined in three studies by the monitoring of serum progesterone concentration for which values nmol/L were considered to be an indicator of ovulation.
- Of 50 subjects completing the first two studies, two in the first study and none in the second study had progesterone levels nmol/L.
- The frequency of the occurrence of progesterone concentrations nmol/L was not statistically significant but the results of the first study were inconclusive due to small sample size.
- Upon rechallenge in a third study, neither of the two subjects ovulated.

i) ICG

- ICG PK parameters were unaltered by a single 60-mg LANSO dose or by 7 days of a 30-mg LANSO dose.
- 7 days of 60 mg LANSO produced a small (10.6%) reduction in ICG clearance.
- Significant drug interactions due to alteration of hepatic blood flow are not expected.

j) Vitamin B₁₂

- The absorption of cyanocobalamine was enhanced by LANSO. This effect would not be expected to be of clinical concern.

K. Reviewer's Conclusion on Drug-Drug Interactions

Drug-drug interactions between LANSO and theophylline (THEO) may be more complex than presented by the sponsor. The bronchodilator effect of THEO is related to serum concentrations with the effect beginning at 5 to 8 µg/ml. The therapeutic range is considered to be 10 to 20 µg/ml with titration of dose to achieve levels within the range 10 to 20 µg/ml being optimal. Factors influencing the metabolism of THEO include pronounced interindividual differences in metabolism, illnesses for which THEO is prescribed, other pathological conditions, and other factors such as smoking, age and weight. Thus, the use of THEO and THEO-like compounds requires extremely close attention. Monitoring serum levels as well as the clinical condition of the patient and AEs is stressed. Therefore, although minor (10%) the increase in

the clearance of theophylline may or may not be of clinical concern. Individual patients may require additional titration of their theophylline dosage when LANSO regimens are started or stopped to ensure clinically effective blood levels.

One conclusion from these observations in humans is that the apparent induction of isoenzymes of cytochrome P₄₅₀ by LANSO in in vitro experiments, do not match these in vivo clinical drug interaction studies. This means that the clinical relevance of the in vitro activation of cytochrome P₄₅₀ isoenzymes by LANSO remains to be determined.

The above-summarized clinical trials were designed to evaluate the effects of LANSO on other drugs. These effects were assessed through basic parameters of these drugs after co-administration of multiple doses of LANSO (several days). This multiple dosing procedure has advantages in that it may more closely represent the usual clinical situation. Another advantage of the multiple vs the single dose is that with the former, higher plasma levels are obtained and this facilitates drug analyses. In the present studies, effects of LANSO were measured by calculations of AUC, volume of distribution, clearance, etc. The AUC, being directly proportional to the total amount of unchanged drug in the body, is the most important measure of bioavailability. On the basis of these data I agree with the sponsor's general conclusion that the effects of LANSO (30 to 60 mg) on other drugs were small or nonexistent. In these studies, LANSO did not have important clinical interactions with antacids (Maalox[®] and Riopan[®]), R- or S-warfarin, antipyrine, indomethacin, ibuprofen, aspirin, phenytoin, prednisone or diazepam. But this list of drugs is incomplete.

More clinical experience is needed but - with regard to drug-drug interactions - there seems to be dissimilarities between LANSO and OME. The latter can prolong the elimination of diazepam, warfarin and phenytoin, drugs that are metabolized by oxidation in the liver. There have been reports of OME interaction with drugs metabolized via the cytochrome P₄₅₀ system (e.g. cyclosporine, disulfiram). It must be pointed out however that, although these interactions are real (statistically significant differences in PK parameters are in the laboratory) they are usually not clinically relevant because adjustment of the dose of the drug is seldom needed. The sponsor of the present NDA has not tested possible interaction between LANSO and the latter two drugs. Also, no drug-drug interaction studies between LANSO and antihistamines have been done.

In a fashion similar to that for OME (the approved PPI), because of its profound and long-lasting inhibition of gastric acid secretion, it is theoretically possible that LANSO may interfere with the absorption of drugs where gastric pH is an important determinant of their bioavailability. These drugs include ketoconazole, ampicillin esters, and iron salts. In the clinical trials, antacids were used concomitantly with the administration of PREVACID[®].

IV. Pharmacodynamics

A. Primary Pharmacologic Effect: Inhibition of Gastric Acid Secretion

The sponsor presented results from many studies assessing effects of single and multiple doses, dose-response, effect of times (if AM vs PM), comparisons to OME, etc., etc. In the material that follows, the No. and further identification of the study is listed on the left side. A very succinct account of the main findings and conclusions is given on the right side.

1. Effects on BAO and Mean Gastric pH

<u>Study No.</u>	<u>Main Findings/Conclusions</u>
M88-289 (U.S.) 33000 (FR) KF 4801/03 (GER) /04 (GER) A-1, A-2, RY-11 (JAPAN)	• Studies in healthy subjects. • LANSO [15 to 60 mg] at single and multiple doses significantly decreased BAO.
M90-485 (U.S.) M90-504 (U.S.) M91-642 (U.S.) M91-643 (U.S.) M87-049 (U.S.) AG/III/90/009 (FR) KF 4801/04 (GER) /06 (GER)	• Also studies in healthy subjects. • LANSO [15 to 60 mg] at single and multiple doses significantly increased: - mean gastric pH and - percent of time at pH >3 and 4
M90-504 (U.S.)	• Maximal effect of LANSO on intragastric pH was achieved on the 3rd day of dosing • Evaluation of the duration of effect of LANSO. After 2 weeks of daily Tx, 30 mg was still significantly superior to PL with a greater change in - mean gastric pH and - mean percent of time at pH >3 for up to 2 days after dosing.
M91-643 (U.S.)	• No rebound of gastric acidity: after LANSO Tx was D/C, secretory activity returned to BL levels gradually, by 4 days.

2. Studies Comparing LANSO to OME

On the basis of available information, the antisecretory effects and clinical efficacy of these drugs might be compared at the following dose levels:

<u>LANSO</u>		<u>OME</u>
	(mg)	
15		20
30		20
30		40

- Refer to Fig. 2
 - 5-day study.
- M90-485 (U.S.)
- Effects on intragastric pH with LANSO 15 mg once-a-day were similar to those with OME 20 mg once-a-day.
 - LANSO 30 mg [given daily before breakfast], produced significantly higher mean pH values after the 1st and 5th days of Tx than OME 20 mg [given daily before breakfast].

- It is not known if statistical differences on Days 1 and 5 but not on Days 2, 3 and 4 are clinically important (probably not). Also, it would be interesting to see the effects of 40 mg OME.

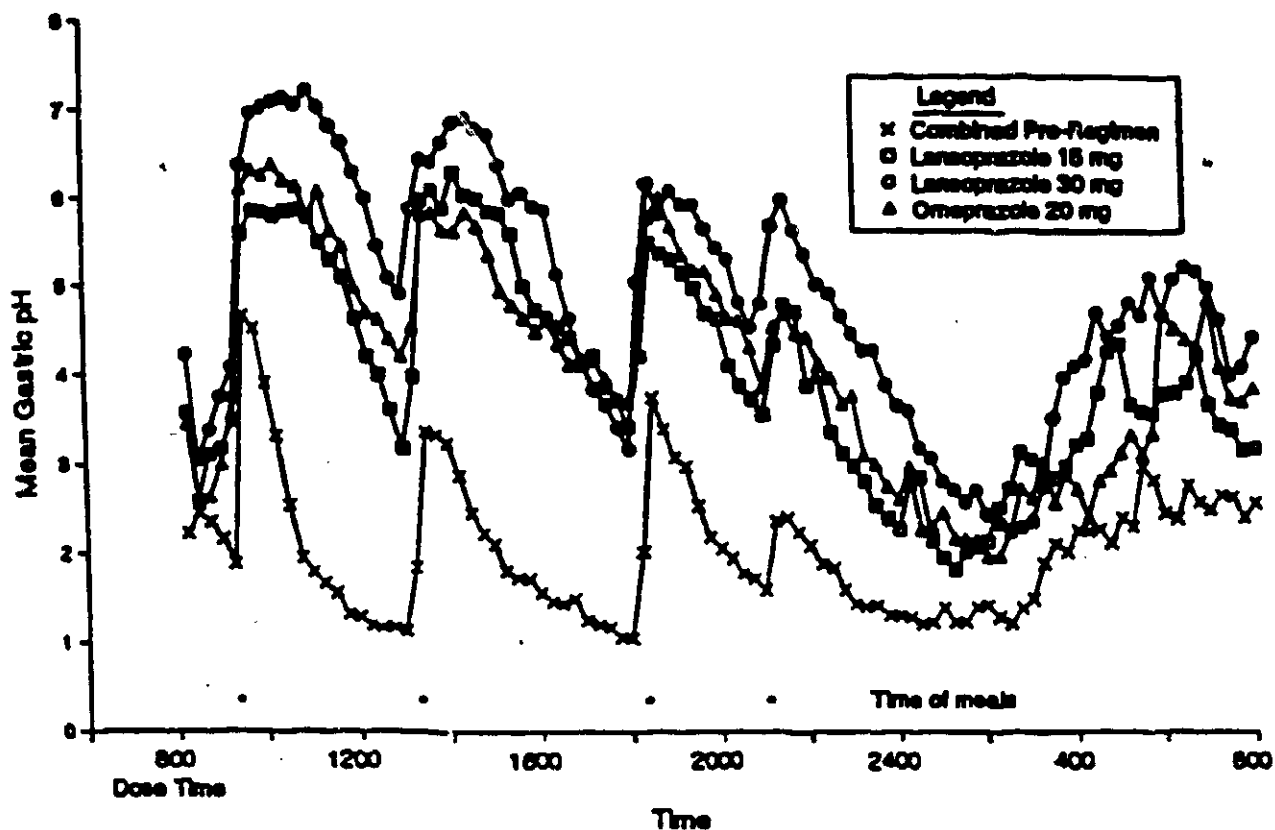


Fig. 2. - Phase I Study M90-85: Mean 24-H Gastric pH After the Fifth Dose of LANSO or OME.

33000 (FR)

- Evaluations after 7 days of Tx.
- Both compounds were given once-a-day before breakfast.
- Although LANSO 30 mg was numerically more effective than OME 20 mg in increasing intragastric pH, this difference was statistically significant only for the percent time spent at pH >3 over the 24-h period. These results are summarized below.
- Again, it is not known if this 10% difference for pH >3 but no differences for higher pHs (>4 and >5) is clinically important.

Phase I Study 33000 (FR)

Percent of Time Spent Above Given pH During the 24-h
Period After Seven Days of Treatment

Percent Time at pH	Mean (S.D.)		
	>3	>4	>5
LANSO 30 mg QD	57.8* (15.2)	39.8* (16.7)	18.8* (11.3)
OME 20 mg QD	48.2* (16.6)	32.4* (16.3)	15.2* (11.6)
PL	21.6 (9.9)	11.6 (6.4)	4.0 (3.3)

* Statistically significantly different from PL (p<0.05)
Statistically significantly different from OME (p<0.05)

AG/III/90/009 (FR) • Results summarized in Table below.

- This was also a 7-day study. LANSO was given in the morning 15 min. before dinner whereas OME was given in the morning before breakfast.
- No significant difference between LANSO 30 mg OME on:
 - mean pH
 - percent time above given pH

Phase I Study AG/III/90/009

Percent of Time Spent Above Given pH: LANSO
30 mg vs OME 20 mg

Percent Time at pH		MEAN PERCENT			
		>2	>3	>4	>5
24h	LANSO	77	67	55	45
	OME	76	62	53	37
Night Time Period	LANSO	80	72	61	49
	OME	70	57	48	32
Day Time Period	LANSO	72	62	50	40
	OME	79	66	57	43
After Breakfast	LANSO	69	58	47	40
	OME	86	69	60	47
After Lunch	LANSO	90	78	63	41
	OME	94	88	81	65
After Dinner	LANSO	83	76	69	56
	OME	89	81	72	46

Results of this study are interesting. There appears to be no substantial pharmacological differences between LANSO 30 mg and OME 20 mg. The sponsor emphasizes the importance of the time of administering the drugs. "These results might differ from the prior two studies because the bioavailability of lansoprazole is significantly decreased with food, and a 30 mg dose given just before dinner is probably not equivalent to 30 mg given in the morning before breakfast." Although this may be true from the bioavailability data discussed above, the important question is whether the AM vs PM dosages (both on a relative empty stomach) result in significantly different efficacy (healing of

RE, DU, etc.). Here the reviewer has more questions than answers. How much acid secretion and for how long does one need to inhibit to heal RE, DU, GU? It seems fair to state that at doses tested (30 mg LANSO vs 20 mg OME), both drugs are profound and long-lasting antisecretories.

3. Inhibition of Stimulated Gastric Acid Secretion

M88-289 (U.S.)

KF 4801/04 (GER)

- [See Table 2]
- LANSO significantly reduced meal-stimulated gastric AO and secretion volume.
- More pronounced antisecretory effects in the older (mean age 64.8y) than in the younger age group (mean age 38.0y).
- While on LANSO Tx, the older group had significantly lower mean gastric acid secretion and meal-stimulated gastric secretion than younger group at Day 7.
- Within the same age group, LANSO 30 mg was superior to 15 mg on Day 1. But on Day 7, inconsistent results were seen because LANSO 30 mg was superior to 15 mg among the younger but not among the older subjects.
- Possible explanations for age being a determinant of pharmacological effect include: a) higher AUCs (see above) and b) slower recovery of secretory activity in the older age group when compared to the younger group.
- As also shown in this Table, at Day 7, the effects of 30 mg LANSO on Basal Gastric Acid Secretion could not be differentiated from those with the 15 mg dose.
- These data provides some - but not very convincing - reasons to choose 30 mg LANSO as "the dose".

TABLE 2
Phase I Study M88-289

Changes in Basal and Meal-Stimulated Gastric Acid Secretion
As a Function of Age

	MEAN (S. D.)	
	Age (y)	
	<60 (N=11)	≥60 (N=12)
<u>Basal Gastric Acid Secretion (mmol/h)</u>		
Day 7 PL	2.65 (2.4)	4.34 (4.9)
• LANSO 15 mg	1.02 (0.8)*	0.59 (0.8)*
• LANSO 30 mg	1.05 (1.1)*	0.32 (0.5)*
<u>Meal-Stimulated Gastric Acid Secretion (mmol/8 h monitoring interval)</u>		
Day 1 PL	115.21 (40.4)	95.72 (51.6)
• LANSO 15 mg	61.07 (48.6)*	27.87 (11.4)*
• LANSO 30 mg	38.33 (47.3)#	12.95 (18.7)#
Day 7 PL	124.44 (43.6)	108.91 (43.9)
• LANSO 15 mg	30.25 (31.5)*	4.89 (7.3)*
• LANSO 30 mg	18.51 (26.6)#	1.51 (2.1)*

* Statistically significantly different (p<0.05) from PL when age groups combined
 + Within a given age group, statistically significantly different (p<0.05) from PL
 # Within a given age group, statistically significantly different (p<0.05) from PL and LANSO 15 mg

M91-643 (U.S.)
KF 4801/03 (GER)
RY-05 (JAPAN)

- LANSO at single or multiple doses of 10 to 60 mg reduced pentagastrin-stimulated gastric AO.

RY-26 (JAPAN)

- LANSO at 30 mg x 7 days inhibited insulin-stimulated secretion volume, acidity and AO.

1000 (FR)
RY-22-3 (JAPAN)
AG/III/90/003(FR)
/004(FR)

- LANSO significantly reduced BAO and increased intragastric pH in hypersecretors, patients with Z-E syndrome and hypersecretors with documented DUD.

AG/III/90/004
(FR)

- In patients with Z-E syndrome, no significant differences between LANSO and OME in their effects on:
 - intragastric pH
 - BAO or
 - serum gastrin levels
- More on this subject under review of LANSO efficacy in Z-E syndrome patients.

4. More on Dose-Response Relationship [Table 3]

RY-11 (JAPAN)
M88-289 (U.S.)
M90-485 (U.S.)
KF 4801/03
/04
/06
(GER)
(GER)

- Results from all of these studies have been described above.
- Very little experience with 7.5 mg.
- There was no clear cut dose-response relationship.
- Differences between LANSO 30 vs 15 mg did not always reach statistical significance. But, in general, the 30 mg LANSO dose appeared more effective than the 15 mg in:
 - mean meal-stimulated gastric acid secretion
 - mean % inhibition of pentagastrin-stimulated AO
 - increase in the average time spent at higher pH values (pH>4)
- As shown in the lower panel of Table 3, there seemed to be little pharmacological advantage when increasing the LANSO dose to 60 mg (in comparison to 30 mg).
- Although statistically significant, the differences between LANSO (30 mg) and OME (20 mg) are of doubtful clinical importance (healing of DU, GERD).
- All in all, these dose-response and comparative data provide a good basis to test clinical effects of LANSO around the 30 mg once-a-day dose.

TABLE 3

Analysis of Dose-Response Relationship on Gastric Acid Inhibition

I. Effects of LANSO at 7.5 mg, 15 mg and 30 mg Doses
(Crossover, except for RY-11)

Study No. (No. of Subjects)	Duration of Dosing (days)	Parameter	PL	ONE	LANSO (mg)		
					7.5	15	30
RY-11* (Japan) (N=8)	7	•Mean $\pm$ 1 in nocturnal acid secretion (2300 to 0600)			73	89	91
MSB-209 (U.S.) Subjects <60 y old (N=11)	7	•Mean $\pm$ 1 in acid secretion				78	87
		•Mean meal-stim. gastric acid secretion day total (mmol/8h)	126.4			30.2 ^b	18.5 ^{cd}
Subjects $\geq$ 60 y old (N=12)		•Mean $\pm$ 1 in acid secretion •Mean meal-stim. acid secretion day total (mmol/8h)	108.9			96	98
WFO-485 (U.S.) (N=14)	5	•Mean gastric pH over 24h		4.16		4.03	4.91 ^{cd}
		•% Time pH>3		60.8		59.2	71.9 ^{cd}
		•% Time pH>4		50.7		49.3	66.0 ^{cd}

II. Effects of LANSO at 15 mg, 30 mg, and 60 mg Doses
(All Crossover)

Study No. (No. of Subjects)	Duration of Dosing (days)	Parameter	PL	LANSO (mg)		
				15	30	60
KF 4801/03* (GER) (N=9)	8	•Mean $\pm$ 1 of BAO •Mean $\pm$ 1 of pentagastrin- stimulated AO		81 ^b 69 ^b	87 ^b 90 ^b	81 ^b 94 ^{bc}
KF 4801/04 (GER) (N=12)	6	•Median Time (min) pH>4 in 24h	144		707 ^b	1038 ^{cd}
		•Meal-stim. AO (median, mmol/h)	43.9		7.3 ^b	3.2 ^b
		•Median BAO (mmol/h)	3.27		0.34 ^b	0.27 ^b
KF 4801/06 (GER) (N=12)	6	•Median Time (min) pH >4 in 24h	67		542 ^b	399 ^b
		•Median Time (min) upright pH>4	41		309	307
		•Median Time (min) supine pH>4	11		237	156

- a) Dose administered in the evening
b) Statistically significantly (p<0.05) different from PL/BL
c) Statistically significantly (p<0.05) different from LANSO 15 mg
d) Statistically significantly (p<0.05) different from LANSO 30 mg

5. Timing of Dose (Table 4)

M87-049 (U.S.)
RY-21
RY-21-3
RY-22
(JAPAN)

- The studies summarized in this Table (normal subjects) used a crossover design to compare the effects of the AM vs PM dosing on gastric acid inhibition.
- Due to the inconsistencies of results, no well founded generalizations are possible.
- The observed inconsistencies may be partly due to the lack of standardization of experimental conditions. For example, in Study M87-049 LANSO was given in the fasting state but in studies RY-21-3 and RY-22 the drug was administered after breakfast. So, some of the differences may be due to differences in PK parameters.
- It is to be noted that the parameter of evaluation chosen for comparison is of great importance. For example, when 24-h gastric acid inhibition was considered, studies [M87-049 (U.S.) and RY-21-3 (Japan)] demonstrated that the morning dose was significantly more effective than the evening dose but study RY-22 found no substantial differences between the dosing regimens. When the parameter of evaluation was nighttime gastric acid inhibition, the dosing regimens were found to be equivalent in study M87-049 while the evening dose was found to be slightly more effective in another study (RY-21).
- In the final analysis, it can be said that LANSO inhibits gastric acid output, regardless of the time of administration.
- Once again, even if some pharmacodynamic difference were to exist between the AM vs the PM dosing, the clinically relevant question is whether this difference translates into significant differences in the healing of DU, GU, GERD, etc.
- The sponsor states: "In view of the bioavailability data, morning doses given to fasting subjects are probably more effective than morning doses given after a meal. Morning doses given before a meal are more effective than evening doses for overall 24-h gastric acid inhibition and probably as effective for nighttime control." But there are no data demonstrating that the part of this statement referring to PD effects has solid scientific support.

TABLE 4
Effect of Timing of Dose of LANSO (AM vs PM)
on Gastric Acid Inhibition

Study Number	Duration (Days)	Parameter (Average over specified time period)	PL		LANSO 30 mg	
			AM	PM	AM	PM
MS7-049 (U.S.)	7	Average pH total 24 h	1.84 (N=5)	1.95 (N=5)	6.72 ^a (N=12)	3.58 (N=12)
		% time pH >3 total 24 h	16.8 (N=5)	19.0 (N=5)	74.7 ^a (N=12)	52.6 (N=12)
		% time pH >3 2400 to 0600 h	1.8 (N=5)	3.2 (N=5)	53.1 (N=12)	43.8 (N=12)
RY-21 (Japan)	7	GAO (mEq/h) 2300 to 0800 h	27.83 (N=11)	23.02 (N=11)	2.52 ^a (N=11)	0.06 (N=11)
		Inhibition rate compared to PL			91.9%	99.8%
RY-21-3 (Japan)	7 ^b	Daily gastric acid concentration (mEq/L)	67.5 (N=5)		6.8 ^a (N=5)	5.5 ^a (N=5)
		Inhibition rate compared to PL			89.9%	92.3%
		Daily GAO (mEq/h)	3.27 (N=5)		0.20 ^{ac} (N=5)	0.25 ^c (N=5)
		Inhibition rate compared to PL			95.7%	93.3%
RY-22 (Japan)	7 ^b	Median time (min) pH ≥4 Total 24 h			790 (N=8)	848 (N=8)
		Median time (min) pH ≥3 Total 24 h			945 (N=8)	1045 (N=8)

a) Statistically significantly different (p ≤ 0.05) from PM dosing
b) Lansoprazole administered after breakfast
c) Statistically significantly different (p ≤ 0.05) from PL or control

V. Other Pharmacologic Effects

A. Summary of Other Gastrointestinal Effects

Study No.
AG/III/90/007
38000
(FR)

Main Findings

- In healthy subjects, LANSO at doses of 30 or 60 mg prevented aspirin-induced gastric lesions

D75p510
(U.K.)

- In healthy subjects, LANSO at doses of 30 or 60 mg reduced aspirin-induced gastric bleeding

RY-23
(JAPAN)

- 30 mg LANSO x 7 days had little effect on mucosal blood flow.

5000
(FR)

- At 30 mg daily x 14 days LANSO did not affect esophageal motility or LES tone.

KF 4801/04 (GER)
RY-26, RY-21,
RY-21-3 (JAPAN)

- In healthy subjects, LANSO at 30 mg x 7 days increased serum pepsinogen concentrations relative to controls under BL conditions as well as in response to meal- or insulin-stimulation.
- Pepsin activity in gastric juice tended to ↓ with LANSO Tx, particularly in response to meal- or insulin-stimulation.

M89-405 (U.S.)
AG/III/90/003
(FR)

- In Z-E syndrome or gastric acid hypersecretory patients, LANSO ↓ basal pepsin output.
- Maximal pepsin output did not change significantly.

RY-27 (JAPAN)

- In GU patients treated for 8 weeks, an ↑ in gastric pH induced by LANSO was seen. This was accompanied by:
 - a) An ↑ in nitrate-reducing bacteria.
 - b) An ↑ in nitrite concentration
 - c) No change in nitrosamine concentration (in gastric juice).

B. Summary of Endocrine Effects

M90-466 (U.S.)

- This study is of interest. The sponsor proposes that the higher incidence of Leydig cell hyperplasia and Leydig cell tumors in LANSO-treated rats (than in control) is occurring through a mechanism involving testosterone.
- This randomized, D-B, PL-controlled, 2-arm, parallel-group study was set to compare effects of LANSO (60 mg) vs PL (both given for 8 weeks) on various aspects of male sexual function in NHVs (16 per group).
- Scoring for gynecomastia was based on the Tanner system used for breast development in puberal girls.

This system uses a 5-score scale where 0=absent, 1=minimal (periareolar), 2=moderate (beyond the areola), 3=marked (filling the entire breast) and 4=severe (complete fullness with anterior development).

To be eligible to participate in the study, the candidate must have had a score of ≤1.

Methods for testes measurement were not described. The endocrine profile consisted of serum concentrations of testosterone, LH, FSH (follicle stimulating hormone), SHBG (sex hormone binding globulin), DHEA-S (dehydroepiandrosterone sulfate), prolactin, estradiol and cortisol.

Blood for the endocrine profile was collected at three separate times during one-hour periods beginning at 1030h (2.5h after dosing), at 2000h (12h after dosing), and at 0700h the following day (23h after dosing). The three samples collected during a given one-hour period were pooled to provide a single endocrine profile at each time

point. Blood was also collected for determination of serum levels of TSH (thyroid stimulating hormone), T₃ and T₄.

- After screening/BL observations, interim medical Hx, interim medical examination, testes measurements and breast examinations, endocrine profile, measurement of vital signs, blood collection for drug assay and routine laboratory evaluations were repeated on days 14, 28 and 56; samples were obtained on the evening of confinement. A sexual function questionnaire and a semen analysis were repeated at the end of the trial. EKGs were repeated on days 28 and at the end of the trial.
- There were no clinically important changes in testicular size (from BL), gynecomastic score, serum concentration of hormones or semen sample determinations.
- No important changes on secondary sex characteristics or on spermatogenesis were demonstrated.
- LANSO appeared to be well tolerated and safe from the endocrinological viewpoint.
- These observations in humans do not shed light on the findings in rats. It is important to remember that the Leydig cell hyperplasia or Leydig cell tumors occurred at doses up to 50 mg/Kg/day and that this doses LANSO did not have an effect on testosterone or LH concentration in the serum of these animals. Therefore, the proposed mechanism for the testicular problem appears to be incorrect.
- From the clinical practice overpoint, findings in this 3-week study do not r/o the possibility that L-T administration of LANSO (months and years?) may have an untoward effect on the endocrine system. If L-T administration of this PPI is being contemplated; yearly evaluations of effects on the endocrine system are recommended.

- KF 4801/06 (GER) • LANSO 30 mg vs LANSO 60 mg vs PL.
- Median values for all endocrine parameters (including M sex hormones) remained within the normal range. Some statistically significant differences were seen but these were not considered to be clinically important.
- M87-049 (U.S.) • LANSO had no clinically significant effect on cortisol levels.
- IR-10 (JAPAN) • In PUD patients, LANSO administered for up to 8 weeks did not have a clinically significant effect on the endocrine parameters evaluated. These included thyroid hormones, prolactin, cortisol and M sex hormones.

Reviewer's Conclusion

I agree with the sponsor's conclusion that Phase I-II clinical studies, of up to 8-weeks duration, have demonstrated LANSO to have no clinically relevant effect(s) on the usual endocrine profile, including M sex hormones.

C. Summary of Cardiovascular Effects

- In a number of PK/Bioavailability and Clinical Pharmacology trials (21 studies in all), administration of LANSO at doses of 10 to 60 mg/day for up to 50 days did not produce clinically significant changes in BP or HR.
- In 9 of these 21 studies the effect of more than one dose of LANSO was evaluated. No dose-related trends were apparent. Findings in some specific studies are briefly noted below.

M90-504 (U.S.) • A statistically significant decrease from BL in mean sitting DBP (from 74 to 69.8 mmHg) was shown. This effect was seen at a post-Tx evaluation in subjects who had been given LANSO 30 mg x 7 days. There were no significant changes in HR.

M91-643 (U.S.) • The mean change from BL to study Day 14 in sitting DBP ↓ significantly for the LANSO group as compared to PL. But the mean sitting DBP for the LANSO group was significantly higher at BL as compared to PL. As a consequence, the mean ↓ of 11.13 mmHg from a mean BL of 81.1 mmHg cannot be considered clinically significant.

- 17 of the aforementioned studies included evaluation of EKG findings.

There were no clinically significant changes associated with administration of LANSO.

2022
M90-412 • There were no clinically significant effects of LANSO on BP or HR in these two PK studies conducted in subjects with varying degrees of renal impairment.

M90-450 • In this PK study, statistically significant differences in mean change from BL in SBP were seen between normal subjects and those with mild or moderate hepatic impairment.

These changes were not accompanied by significant differences in DBP between groups or in HR or EKG parameters. Statistically significant differences are displayed below.

NOTE: During the review of the Safety Update, especial attention will be paid to safety data on long-term effects on bones, eyes and the heart (arrhythmias).

Study M90-450

Summary of Statistically Significant Differences in Mean Changes from BL in SBP After Administration of LANSO 30 mg x 7 Days

Systolic BP (mmHg)	Normal Subjects	Neopatically-impaired Subjects	
		Mild	Moderate
BL ^a	113.5	125.5	134.5
Change from BL			
Day			
2	+6.8	-9.5 ^b	-12.0 ^b
3	+6.0	-13.0 ^b	-6.0
5	+10.5	-4.0	-9.5 ^b
7	+2.3	-9.0	-15.5 ^b

a) Statistically significant tx group difference at BL (p<0.05)
b) Statistically significant vs normal subject (p<0.05)

VI. Summary of PK/PD, Metabolites, Dose Selected for Critical Clinical Trials

A summary of the PKs and main PD profile of LANSO is given in Tables 4a and b, respectively. Comparative urinary, fecal and biliary excretion of LANSO and its metabolites after administration of the compound by oral vs parental routes, etc., are summarized in Table 4c. There appear to be differences between humans and animals (notably rat) in the way the compound is handled by the body. But conclusions on comparative metabolism must await Pharmacology and Biopharm. reviews.

The dose selected for critical clinical trials was 30 mg. According to what follows, there is some justification for choosing this dose. The data in Table 46 in normal subjects show that doses of 7.5, 10 or 12.5 mg (all less than 15 mg) have not been studied or tested in one trial only (7.5 mg). No meaningful conclusion can be drawn on the antisecretory effects of doses <15 mg.

LANSO 30 mg apparently gives the best antisecretory results. These data are in many instances no different from those obtained with LANSO 15 mg but for some parameters the 30 mg appears better than the 15 mg. Although for some parameters the 60 mg was better than the 30 mg dose, in general, there seemed to be no special advantage in increasing the dose from 30 to 60 mg LANSO. The sponsor elected to test in the critical clinical trials daily doses of LANSO from 15 to 60 mg per day.

TABLE 5a
Summary Table of PKs of LAUSD After Single or Multiple Doses of 30 mg Once-a-Day

Variable	T_{max} (h)	C_{max} (ng/mL)	AUC (ng·h/mL)	$t_{1/2}$ (h)	Cl/F (L/h)	Vd/F (L)	Remarks (p-value)
I. NORMAL HEALTHY VOLUNTEERS							
DPV Younger ^a (N=12)	1.5	750	1763 ^a	1.3	...	...	Younger vs Older
	1.5	739	2674	1.4	...	...	
ASD (7-Day Tx) Older ^a (N=12)	1.6	773	2678 ^a	1.9 ^a	...	...	* < 0.05
	1.1	946	2862	2.1 ^a	...	...	* < 0.05
ASD (Single Dose) Older (N=12)	1.5	1033	2668	1.4	16.6	29	Younger vs Older AUC < 0.05 $t_{1/2}$ < 0.001
	1.8	1148	5216	2.9	10.4	36	
II. DATA POOLED ACROSS PHASE I STUDIES							
Pooled	1.68 (N=345)	824 (N=515)	2133 (N=513)	1.53 (N=285)	...	...	C_{max} and AUC normalized to a 30 mg dose
III. HEPATICALLY-IMPAIRED SUBJECTS							
A. Healthy Volunteers (N=6)	1.5	796	2020 ^a	1.2	23	38	vs healthy
B. Subacute Hepatitis (N=8)	1.4	1080	5191	3.2	13 ^a	40	* < 0.05
C. Cirrhosis 1. Compensated (N=3) 2. Decompensated (N=8)	2.1	1438 ^a	11404 ^a	6.1 ^a	2.8 ^a	23 ^a	* < 0.05
	2.1	1160	9251 ^a	7.2 ^a	4.3 ^a	34	* < 0.05

TABLE 4a (Cont)

Subjects (Day 1) Class A/Healthy	1.20	1.38	2.06 ^a	2.71	...	...	Day 1 vs Day 7 *50.05 ^a
Class B/Healthy	1.56	1.07	2.66 ^{a, b}	3.36 ^a	...	...	...
Subjects (Day 7) Class A/Healthy	0.93	1.36	2.55 ^a	2.60	...	...	...
Class B/Healthy	1.31	1.15	3.41 ^{a, c}	3.47 ^a	...	...	*50.05
Subjects (Day 7/Day 1) Healthy Subjects	1.00	1.10	1.11	1.07	...	...	...
Class A'	0.83	1.08	1.37	1.03	...	...	...
Class B'	0.84	1.19	1.41 ^{a, c}	1.11	...	...	*50.05
10-Day 14 in Cirrhosis (Unspecified stage) Day 0 (N=12)	2.3	1050.6	9592	6.5	3.8	35.7	Day 10 vs 0' *50.05
Day 10 (N=12)	1.6	1376.6 ^a	14077 ^a	6.3	...	...	...
IV. RENALLY-IMPAIRED SUBJECTS							
Renal Dysfunction Cl _{cr} (ml/min)							Reference Group Single Dose (Younger)
Normal ^f	1.47	1033	2668	1.44	16.6	29	
Mild	1.58	1279	5534	4.09	7.6	33	
Moderate	1.67	940	3305	2.60	23.3	56	
Severe	1.40	942	2777	1.62	14.4	28	

NOTE: Displayed are means in the number of subjects specified and the column variable. For simplification purposes standard deviations of the mean and Study # have been omitted.

a) AUC_{0-∞} b) <60y c) Subject excluded because of malabsorption on Day 1 d) >60y e) AUC₀₋₈
 f) Mildly impaired hepatic function g) moderately impaired hepatic function h) p-value based on untransformed AUC values. There was no signif. diff. with comparison of log transformed AUC values i) First day of dosing j) Reference parameters from subjects participating in other studies k) Not specified ---=Not determined.

TABLE 4b
Summary Table of Main PD Effects (Inhibition of Gastric Acid Secretion)

PD Parameter of Evaluation	Duration of Dosing (DAYS)	LASTO (mg)				
		PL	7.5	15	30	60
1. BASAL AND MEAL-STIMULATED GAS						
BASAL GAS (mmol/h)	<60y (N=11) ≥60y (N=12)	7	2.65 4.34	1.02 ^a 0.59 ^a	1.05 ^a 0.32 ^a	
MEAL-STIMULATED GAS (mmol/h monitoring interval)	<60y (N=11) ≥60y (N=12)	1	115.21 95.72	61.07 ^a 27.87 ^a	38.33 ^a 12.95 ^a	
Ibid	<60y (N=11) ≥60y (N=12)	7	124.44 108.91	30.25 ^a 4.89 ^a	18.51 ^a 1.51 ^a	

TABLE 4b (Con't)

PD Parameter of Evaluation	Duration of Dosing (DAYS)	LANSD (mg)				
		PL	7.5	15	30	60
II. DOSE-RESPONSE RELATIONSHIP						
Median BAO (mmolH ⁺ /h) (N=12)	6	3.27		0.34 ^b		81 ^b
Mean % i of BAO (N=9)	8			81 ^b	0.27 ^b	87 ^b
Mean % i in Nocturnal Acid Secretion (2300 to 0800) (N=8)	7	73		89	91	91
Mean % i in Acid Secretion <60y (N=11) ≥60y (N=12)	7			78	87	98
Mean Meal-Stim. Acid Secretion Day Total (mmol/Hh) <60y (N=11) ≥60y (N=12)	7	124.4		94	18.5 ^{b,c}	1.5 ^b
Mean % i of Pentagastrin-Stimul. AO (N=9)	8	108.9		30.2 ^b	90 ^b	94 ^b
Median Time (min) pH >4 in 24h One Study (N=12) Another Study (N=12)	6	144		69	707 ^b	1036 ^{b,c}
Median Meal-Stim. AO (mmolH ⁺) (N=12)	6	67			542 ^b	399 ^b
Median Time (min) Upright pH >4 (N=12)	6	43.9			7.5 ^b	3.2 ^b
Median Time (min) Supine pH >4 (N=12)	6	41			309	307
Median Time (min) Supine pH >4 (N=12)	6	11			237	154

a) p<0.05 from PL when age groups combined
b) Within a given age group, p<0.05 from PL
c) Within a given age group p<0.05 from PL and LANSD 15 mg
d) p<0.05 from 30 mg

TABLE 4E
Summary of Urinary, Fecal and Biliary Excretion of LANSO and Its Metabolites^a
in Animals and Humans

Species (Ref.) ^b	Dose (mg/kg)	Percent of Carbon-14 Dose												
		LANSO	M-I	M-II	M-III	M-IV	M-V	M-VI	M-VII	M-VIII	M-IX	M-X	Others	
URINE														
BEI [82] [94]	2, po 2, iv	0.1 0.2	20.1	1.5	1.4	1.9	1.5	0.2	0.3	1.3	0.7	3.6	3.1	21.2
DOG :	2, po	0.1		0.3	0.2	1.1	0.8	1.3	0.2	0.7	0.8	1.3	4.1	16.4
	0.5, po					1.5					0.8		21.5	11.8
	0.5, iv					1.6					0.3			
[94]	2, iv	0.7	0.1	0.5	0.4	2.4	1.1	4.6	<0.1	0.6	2.1			
HUMAN [93]	ca. 0.4, po					6.8							17.1	
FECES														
BEI [82] [94]	2, po 2, iv	0.8 0.3	0.7 0.7	8.7 1.3	1.0 0.7	18.5 20.5	1.7 0.5	0.8 0.5	0.6 <0.1	1.0 1.8	1.1 3.7	1.6	43.6 33.2	
DOG :	2, po	1.2	1.5	14.8	0.7	14.9	2.9	0.7	0.8	1.6	3.2	1.7	38.9	25.1
	0.5, po		1.2			33.4					3.5		14.2	23.2
	0.5, iv		0.4	8.6	0.4	36.1	1.1	0.5	0.3	1.0	6.5			
[94]	2, iv	0.4	0.4			26.2					5.6			
HUMAN [93]	ca. 0.4, po	28	7.2			13.8		0.2	1.0		0.2		11.0	
BILE														
BEI [82]	2, id	0.2	0.1	1.5	0.2	10.7	0.7	1.8	0.6	1.0	4.1		39.7	
DOG [95]	0.5, iv					6.0		8.0			3.7		24.9	

a) Metabolites M-I through M-X are identified in Figure 1.
b) (Ref.) as per sponsor's LANSO/MDA Summary p. 420.

SECTION B

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VII. Clinical Efficacy: Short-Term Treatment of Reflux Esophagitis

A. Indication Sought (as Stated in the Sponsor's Proposed Labeling)

Treatment of Reflux Esophagitis

Reflux Esophagitis

"PREVACID Delayed-Release Capsules are indicated for short-term treatment (4 to 8 weeks) for healing and symptom relief of reflux esophagitis."

NOTE: This is a broad indication. Although erosive esophagitis is not stated, it is implied by the word healing. In reality this indication combines Strata I and II patients.

B. Critical Trials for the Indication Short-term Tx of RE

In support of the efficacy and safety of PREVACID® for the indication "Short-Term Tx (up to 8 weeks) for healing and symptoms of RE" the sponsor has submitted results from two clinical trials. Their main features and an initial assessment of the utility of the experimental design used in these essential trials is given in Table 5.

C. Study M87-092 (Report PPRd/90/003)

"A study to Evaluate the Effects of Abbot-65006 on Acute Gastroesophageal Reflux Disease"

Study dates: February 1988 - June 1989

1. Objectives (as stated on page -3- of the Protocol)

This Phase II PL-controlled study was designed to assess the safety and efficacy of once daily administration of 15, 30, and 60 mg of Abbott-65006 compared to PL in the Tx of R.E. disease and to assess time to recurrence of esophagitis in patients whose esophagitis is healed.

2. Materials/Labeling²/Randomization

- LANSO was supplied in identical capsules containing 7.5 or 15 mg of enteric-coated granules.
- Antacids were supplied to all patients [Gelusil® tablets (Parke-Davis)].
- The bulk NPRO, bulk lot, and finishing subplot numbers for drug supplies used in this trial were:

²Study Supply Quality Control. D-B medications used in this trial were supplied by Takeda Chemical Industries Ltd, Osaka, Japan. The test medication was packaged by Abbott Laboratories, Abbott Park, IL on behalf of YAP Pharmaceuticals Inc.

³Each Gelusil tablet contained g of the combined hydroxides of magnesium and aluminum with mg of simethicone with a neutralizing capacity of mEq/two tablets.

TABLE 3
NDA 20-406
Main Experimental Features and Initial Assessment of the Adequacy of Clinical Trials Submitted in Support of the Indication "Short-Term Treatment of Reflux Esophagitis"

Report No. No. of Pts.	Main Design Features	Study Population	Groups Being Compared	Remarks
I. N87-092 (U.S.) Multicenter (n34) 292 pts.	Randomized, D-B, fixed dose, parallel group, PL-controlled, 4-arm	195 M, 97 F with RE of "at least Grade 2". Endoscopic observations (Healing Rates) at 0, 4, and 8 weeks (weeks 2 and 6 optional)	PL vs LANSO 15 mg vs LANSO 30 mg vs LANSO 60 mg (All administered once-a-day, before breakfast)	- Adequate and useful design. - Efficacy is shown against PL, a negative control - Although the study was apparently not sized to show dose response, effectiveness of the "recommended dose" (30 mg) can also be compared to the effect of lower (15 mg) as well as higher doses (60 mg). - Among the important issues to consider is the esophagitis scale used in this trial. Grade 2 (friability + bleeding...) is not clinically meaningful because it represents some inflammation but not true esophagitis. - It is worth mentioning that Grade 2 esophagitis in this trial is different from Grade 2 in the trial below.
II. N88-269 (U.S.) Multicenter (x 29) 247 pts.	Randomized, D-B, fixed dose, parallel group, 2-arm	156 M, 91 F with RE of "at least Grade 2" Endoscopic mandatory at screening and weeks 2 and 6 (optional at weeks 4 and 6)	LANSO 30 mg (once-a-day) vs RAM 150 mg (b.i.d.)	- Adequate study design, but with some limitations that should be recognized from the start. - Efficacy (of 30 mg) is demonstrated by showing superiority over a "positive" control. - RAM 150 mg b.i.d. is expected to give a PL-like response since, as previously stated, the recommended dose for the healing of esophagitis (PDR) is 150 mg q.i.d. - Consequently, superiority of LANSO over this inadequate dose of RAM would demonstrate activity of LANSO but no superiority over RAM (in advertisement) can be claimed in the healing of lesions. - Did not include a 15 mg arm. Not including a 15 mg arm creates a problem because by 8-weeks of Tx, this dose of LANSO was as effective as 30 mg in the other trial. - Also, it is important to note that this trial made use of a different esophagitis scale than that used in the above trial. - Grade 2 in trial N87-092 did not include erosions. Grade 2 in trial N88-269 included erosions but corresponded to mild esophagitis.

- PL capsules, identical in appearance to the LANSO capsules, were provided. PL contained the ingredients listed in the footnote to this page.

	Bulk NPRO	Bulk Lot Number	Finishing Sublot Number
LANSO 7.5 mg Capsules	4036	10-718-AR	11-827-AR 15-065-AR 16-186-AR
LANSO 15 mg Capsules	4037 4193	10-719-AR 15-072-AR	11-828-AR 15-066-AR 16-187-AR
PL	3978 4035 4198	09-572-AR 10-717-AR 15-077-AR	11-829-AR 11-830-AR 15-067-AR 16-188-AR

- Labeling of materials was adequate.
- Separate randomization schedules for each investigator were used (sponsor's Appendix A - Randomization Schedule).

4

PLACEBO for
15 mg

30 mg

\ Magnesium Carbonate

Stabilizer

\ Sugar Spheres

Diluents

\ Sucrose

\ Starch

Disintegrant

Binder

Coating Materials

\ Titanium Dioxide USP

\ Talc

Antistatic Agent

Total (mg)

Capsule (#1)

1 capsule

(Cap; pink opaque body; black)

Capsule (#3)

1 capsule

(Cap; pink opaque body; bluish green opaque)

a) Low-Substituted Hydroxypropyl Cellulose NF

b) Hydroxypropyl Cellulose NF

c) Methacrylic Acid Copolymer LD ..

d) Also glidants

e) Removed during the manufacturing process

- Drug was shipped to investigators in complete blocks, almost always in quantities greater than the block size (some multiple of block size). The investigators were not informed of the block size used. Randomization was carried out with the following block sizes.

Study M87-092: Block size of 4 (PL; LANSO 15, 30 and 60 mg)

- When all screening procedures were completed and the patient had met all admission criteria, the next successive patient number available for that investigator was assigned to the patient. This number randomly assigned the patient to 1 of the 4 Tx groups. Assignment started with the lowest available number and proceeded in ascending order.

3. Study Design

This was a randomized, D-B, fixed dose, parallel group, 4-arm study. Effectiveness of single daily doses of LANSO of 15, 30 or 60 mg was compared to PL. There was an equal allocation to the four Tx groups.

4. Study Population

This was adequate. It consisted of M or F patients between ages of 21 and 75 years with "active esophagitis" of at least Grade 2. The esophagitis grading scale used in this trial is described below.

<u>Grade</u>	<u>Description at Endoscopy^{a)}</u>
0	No abnormalities
1	Mucosal edema and hyperemia
2	Friability of mucosa with bleeding under instrumentation
3	Isolated ulcerations
4	Confluent ulcerations

a) According to Kaul et al., 21:139-145 (1986)

NOTE: It is important to note the limitations of the classification system for staging RE used in the present trial. Although it may have relevance re symptoms, a Grade as high as 2 has little clinical relevance from the erosive esophagitis viewpoint. This is because this grade includes some signs of inflammation but neither erosions nor "ulcerations". Grades 3 and 4 really include erosions (which is the term that should be used instead of "ulcerations") but these correspond to what may be termed mild (isolated erosions/ulcerations) and moderate esophagitis, respectively. If the patient indeed has an ulcer, in

⁵The randomization schedules were generated by the Clinical Statistics Department at Abbott Laboratories, Abbott Park, IL. The patient numbers and study drug assignments were in the possession of the investigators (D-B portion of the label) and of the Clinical Statistics Department at Abbott Laboratories (sealed envelopes). The study blind could be broken if, in the opinion of the investigator or monitor, it was clearly in the patient's best interest to do so. The time the study blind was broken, by whom, and the reason were to be documented on the CRF.

addition to Grade 4 erosions, then this patient falls under the category of severe esophagitis. During the review of the evidence, it will be important to determine if patients with severe esophagitis were represented in this trial.

Additional inclusion-exclusion criteria - summarized below- were all adequate:

- No evidence of additional clinically significant medical disease (such as Barrett's esophagus, Crohn's disease, Z-E syndrome, regional enteritis, UC, IBS, biliary tract disease, DU, GU, scleroderma, pancreatitis, esophageal stricture requiring dilation procedures, severe esophageal spasm or malignancy except basal cell carcinoma).
- No chronic use of ulcerogenic drugs (such as systemic corticosteroids, within one month prior to the screening endoscopy; or histamine H₂-receptor antagonists or other antiulcer drug therapy (antacids were to be allowed) during the eight weeks prior to the screening endoscopy).
- No use of anticoagulants, hydantoin, theophylline derivatives, or benzodiazepines metabolized by the P-450 enzyme system.
- No current Hx of drug or alcohol abuse.
- For women, no capability of bearing children or a negative pregnancy test along with previous use and agreement of continued use of appropriate means of contraception for the duration of the study.
- No previous surgery for ulcer disease, except for simple closure of perforation.
- No active bleeding or perforation at the time of the screening endoscopy.
- No Laboratory results outside of NLs or clinically acceptable limits determined by the investigator and approved by the sponsor.

5. Study Execution

a) Screening Period

- Within 7 days prior to initially receiving test medication, the patient was to sign the IC and fulfill all admission criteria.
- An assessment of medication taken during the prior 8 weeks was to be performed.
- The patient may have taken antiulcer medication such as histamine H₂ antagonists, sucralfate, etc., for up to 3 days but no ulcerogenic drugs.

⁶According to the Protocol (Amendment No. 1), lora-, nitra-, oxa- and temazepam were to be allowed.

- The following tests were to be completed to qualify the patient for the Tx period: complete medical and social Hx, complete P.E., EKG, symptom assessment, and vital signs, routine laboratory evaluation (including thyroid function studies), pregnancy test (for women of childbearing age), endoscopy and gastric Bx of the greater curvature.

b) Tx Period

Eligible patients were given two bottles of LANSO or PL capsules at BL and at Weeks 2, 4 and 6 of the Tx period. Each bottle contained 38 capsules (10 extra capsules per bottle). Bottles 1A and 1B were dispensed at BL (Study Day 1), bottles 2A and 2B at the Week 2 visit, etc. Each morning before breakfast during the 8-w Tx period, the patient took two capsules orally from each of the two bottles. The bottles contained LANSO or PL in combinations which provided the assigned dose level, as shown below:

Bottle	PL	LANSO DOSE (mg)		
		15	30	60
#1A-4A	PL	7.5 mg cap.	15 mg cap.	15 mg cap.
#1B-4B	PL	PL	PL	15 mg cap.

One replacement bottle for each of the A and B drug bottles (RA and RB) for each patient was supplied to each investigator to be dispensed only as needed. In addition, at the BL and the Weeks 2, 4 and 6 visits (and at the Week 8 visit for patients entering the Post-Tx period), each patient was given one box of Gelusil (containing 50 tablets) to be taken for relief of discomfort as needed.

The Tx period then proceeded as follows.

- The Tx period began with BL Day 1 and ended with Week 8.
- Visits were to be completed at BL, Day 1 and at the end of Weeks 2, 4, 6 and 8.
- Patients were asked to complete a daily diary to document episodes of pain, other symptoms experienced, frequency of taking antacid, concurrent medication and missed medication doses. Diaries were to be issued at the BL Day 1 and at the Week 2, 4 and 6 visit.
- At the Week 2 visit, the diary issued at BL Day 1 was to be collected, reviewed and a Diary Summary was to be completed.
- At the Week 4 visit, the diary issued at the Week 2 visit was to be collected, reviewed and a Diary Summary was to be completed, etc.
- All diaries were to be retained as a part of the patient record.

- During the Tx period, the patient was not to take any ulcerogenic or antiulcer medication. Exceptions were the provided Gelusil and/or continuance of one aspirin per day or one dose of NSAID per week.
- If the esophagitis was completely healed⁷ at the Week 8 visit, the patient was to continue on study for up to 6 mo. of post-Tx F/U.
- If the esophagitis was not healed at Week 8, the patient was to be considered to have completed the study and was not to participate in the 6-mo. post-Tx F/U period. Final Visit Forms and procedures were to be completed at that time.
- Patients who prematurely W/D from the trial during the Tx period should have completed the tests, procedures and examinations listed for the Week 8 visit as soon as possible after D/C Tx.

c) Unscheduled Visits

- If a patient returned to the clinic for evaluation of symptoms or AEs, an Unscheduled Visit Form was to be completed.
- If AEs had occurred, the Adverse Event Form was to be completed.
- If the patient was taken off study, the procedures, tests and examinations specified in the Post-Tx visit: Month 6 Section were to be completed. At that time the Final Visit CRF was to be completed.
- The Unscheduled Visit form was not to be completed if the Final Visit form was completed.

Symptom Assessment

Changes or complaints since the preceding examination were noted for the following symptoms: burning in upper abdomen, heartburn, painful swallowing, belching, GE regurgitation, fullness/bloating/early satiety, abdominal distension, anorexia, nausea, vomiting, day abdominal pain, night abdominal pain, flatulence/abdominal rumbling, diarrhea, constipation, hematemesis, and melena. These symptoms were rated as follows:

- None
- Mild: Symptom did not last long or was easily tolerated.
- Moderate: Symptom caused discomfort and interrupted usual activities.
- Severe: Symptom caused great interference with usual activities and may have been incapacitating.

d) Post-Tx Period

- If the esophagitis was healed at week 8, the patient was to receive up to 6 mo. of Post-Tx follow-up [visits at months 1, 3 and 6, or if esophagitis symptoms recurred].

⁷Complete healing of the esophagitis was defined as a return to Grade 0 [No abnormalities] or 1 [Mucosal edema and hyperemia].

NOTE: This definition of "complete healing" is not adequate. For example a return of friability + bleeding (Grade 2) to either edema + hyperemia (Grade 1) or normal esophageal mucosa (Grade 0) has little clinical relevance.

- The patient may not have taken any ulcerogenic or antiulcer medication with the exception of Gelusil or continuance of one aspirin per day or one dose of NSAID per week.
- Each patient was to be given one box of Gelusil to be taken if he/she experienced pain.
- If the patient experienced pain or suspected a recurrence at any time during the Post-Tx period, he/she was to be instructed to return to the clinic immediately for an unscheduled visit.
- Symptoms were to be evaluated and if recurrence was suspected, an endoscopy was to be performed¹.
- If recurrence was not documented, the patient was to continue on study and an unscheduled visit form was to be completed.
- If the esophagitis had recurred, or if gastric or duodenal ulcer had developed, the patient was to be terminated from the study and Final Visit CRFs and study procedures listed for Post-Tx Visit - Month 6 were to be completed.

NOTE: In summary, in the present trial, endoscopies were mandatory at BL, Weeks 4 and 8 (and Week 6 if the patient had not healed at Week 4). During the Post-Tx F/U endoscopies were mandatory at months 1, 3 and 6.

6. Statistical Methodology

a) Planned Sample Size

The study was designed to enroll sufficient patients such that 260 patients would complete the study and have evaluable efficacy data (65 in each treatment group (sponsor's Appendix A - Clinical Protocol)). This sample size had a 99% chance to detect significant differences between any LANSO group and the PL group if true healing rates were 85% and 50%, respectively ($p < 0.05$, two-tailed test). This assumed a therapeutic gain of 35%.

b) Patient Evaluability

The procedures to establish patient evaluability were adequate but are not discussed in any detail here because - during the present review - efficacy assessment will be based on Intent-To-Treat Population analyses only.

c) Parameters of Evaluation

- The primary efficacy endpoint was the endoscopic assessment (healed/unhealed), as stated in the protocol.
- Additional efficacy parameters were symptom assessments and diary summaries (Gelusil use and day and night abdominal pain).
- The safety variables were assessments of AEs, clinical laboratory data including gastrin levels, Bx results, and additional safety evaluations (P.E., EKG, and vital sign data).

¹Recurrence was defined as a return of esophagitis (Grade 2 to 4) after documented healing.

NOTE: This is an inadequate definition of recurrence. Grade 2 does not really represent erosive esophagitis. Recurrence should be better defined as a return of esophagitis (Grade 3 to 4) after documenting healing.

d) Statistical Analyses

Efficacy

- The principal measurement was the number of patients in each Tx group with endoscopically demonstrated "complete esophagitis healing" after 8 weeks or less of Tx (for all patients).
- The proportions healed on each dose of LANSO at each time point were compared to those healed on PL using Mantel-Haenszel methods for combining (2 x 2) tables across investigators.
- Factors other than Tx which are significantly related to the outcome measures were controlled for in the analyses.
- Secondary analysis compared the Tx groups with respect to pain scores and amount of antacid use as reported at the week 2, 4, 6 and 8 visits.
- Recurrence rates at 8 weeks for those healed at 4 or 6 weeks were tabulated by Tx group.
- For those patients healed at 8 weeks, the number of patients with recurrence in each Tx group after 1, 3 and 6 months as demonstrated endoscopically was analyzed.
- The recurrence rates on each dose of LANSO at each time point was compared to that of the PL group using Mantel-Haenszel methods for combining (2 x 2) tables across investigators.
- Time to recurrence was also compared between Tx groups.
- Factors other than Tx which are significantly related to the outcome measures were controlled for in the analyses.

Safety

- AEs were tabulated separately for each of the four Tx groups and rates were compared between groups with Fisher's Exact Test.
- Safety was also evaluated using BP, PR, B_{12} data, ECL cell densities and clinical laboratory test results. Changes in these variables from BL to the Tx and post-dosing F/U periods were compared between the PL group and the LANSO groups.

7. Study Results

a) Participating Investigators

In this trial, 34 qualified investigators, geographically distributed throughout the United States, enrolled a total of 292 patients (195 M; 97 F).

It is to be noted that 17⁹ of the 34 investigators participating in this trial also enrolled patients in the other RE trial. This has been brought to the attention of Scientific Investigations. It is important to make sure that patients were not studied twice (for the same indication).

b) Number of Patients in the ITT Analysis

Of the total of 292 patients enrolled, 288 were included in the ITT analysis. Four (4) patients (Fisher), (Sahba), (Simmons) and (Thune) had abnormal laboratory values at screening and were terminated from the trial without final endoscopy after 3, 3, 1 and 3 days of Tx, respectively. These four (4) patients were not included in the ITT analysis. The sponsor's definition of ITT population is acceptable because these patients received only days instead of 8 weeks of Tx. More important, inclusion of these patients in the efficacy analyses would not change the conclusions.

c) Data Showing Comparability of Groups

i) Premature Terminations (Table 6)

As shown in this Table, 34 patients - equally distributed among the four groups - W/D from the trial prematurely during the Tx period. The primary reasons for these premature terminations are indicated in this Table.

TABLE 6
Study M87-092

Summary of Primary Reasons for Premature Termination from the Tx Period^{a)}

Termination Reason	PL	LANSO (mg)		
		15	30	60
Number of Patients				
Abnormal Screening Laboratory Values	2	1	1	0
AEs ^{a)}	1	3	3	1
Lost to F/U	2	1	2	4
Tx F	4	2	0	0
Other	2	1	2	2
Total (N=34)	11	8	8	7

a) Sponsor's Table 7.2.1 listed the investigator, patient No., Tx group, No. of completed days of Tx, age, sex, and the reason for termination for each of these patients. Eight of these 34 patients had endoscopically documented healing prior to their termination.

⁹These 17 investigators and their ID Nos. were: Aaronson (2925), Avner (3094), Berry (2927), Bruns (2928), Dorsch (3095), Erling (2934), Fisher (2935), Jones (2940), Koval (2965), Movva (2942), K. Nelson (2947), Oliver (2948), Rowekamp (2950), Sahba (2951), Schwartz (2953), Scowcroft (2954) and Shivakumar (2955).

- b) The study blind was prematurely broken for patient (Novva) on November 2, 1988, by the Clinical Statistics Department due to a BX showing adenocarcinoma. The patient had completed the Tx period having received PL for 56 days.
- c) 2 additional patients (Berry) terminated for personal reasons from the PL group, and (Erflin) Tx F in the 15 mg group were D/C prematurely from the study in part due to an AE; however, the AE was not the primary reason for premature termination.

ii) Demographic and Disease BL Characteristics
(Table 7)

- This Table summarizes the demographic and disease BL characteristics for the 292 patients who entered the D-B Tx period.
- There were no significant differences among the Tx groups - combined across investigators - for age, female body weights, height, sex, race, smoking, alcohol use and caffeine use. There was a significant difference among Tx groups in the mean B_w of M patients [182, 189, 191 and 201 pounds in the PL, 15, 30 and 60 mg LANSO groups, respectively] This difference is not expected to influence efficacy results.
- There were no significant differences among Tx groups, combined across investigators, in the esophagitis grade at entry.
- It is important to remark that, in this trial, the proportion of patients with Grade 2 to 4 lesions was as follows:

Esophagitis Grade	No. of Pts.	Proportion of Pts. (%)	Endoscopic Finding (Clinical Relevance)
2	106	36.3	No erosions (or "ulcerations") (No esophagitis)
3	155	53.1	Isolated erosions (or "ulcerations") (Mild esophagitis)
4	31	10.6	Confluent erosions (or "ulcerations") (Moderate esophagitis)
		100.0%	

The above-displayed data show that, at entry, >36% of the patients did not have erosive esophagitis. Although there were 186 patients divided into four groups with erosions, a little > half had mild disease and only 11% had moderate esophagitis (clinically meaningful disease). The severe esophagitis category did not seem to be represented in this trial.

TABLE 7
Study M87-092
Summary of Demographic and Disease BI Characteristics
(All Patients)

Variable	All Pts. (N=292)	PL (N=68)	LANSO (mg)			Overall p-value
			15 (N=73)	30 (N=72)	60 (N=79)	
Age ^a Mean (SD) (y) Min-Max	44.8 (14.7) 21-75	43.0 (14.9) 21-73	44.9 (14.8) 21-75	47.5 (15.3) 22-74	43.7 (13.6) 23-75	N.S. ^b
Weight-M No. of Pts. Mean (SD) (lbs)	195 191.4 (33.4)	42 182.0 (34.5)	49 189.0 (28.8)	52 191.6 (32.2)	52 201.3 (35.9)	0.041 ^b
Weight-F No. of Pts. Mean (SD) (lbs)	97 171.0 (38.9)	26 174.9 (44.6)	24 168.7 (32.0)	20 172.1 (33.0)	27 168.6 (44.1)	N.S. ^b
Height-M No. of Pts. Mean (SD) (Inch)	195 69.6 (3.1)	42 69.6 (3.0)	49 69.2 (2.9)	52 69.8 (2.9)	52 70.0 (3.6)	N.S. ^b
Height-F No. of Pts. Mean (SD) (Inch)	97 64.2 (2.9)	26 64.4 (3.0)	24 64.2 (3.0)	20 64.8 (2.4)	27 63.6 (3.2)	N.S. ^b
Sex M F	195 97	42 26	49 24	52 20	52 27	N.S. ^c
Race Caucasian Black Other	261 18 13	61 4 3	68 3 2	65 2 5	67 9 3	N.S. ^c
Smoking Non-Smoker ^d Smoker	198 94	42 26	48 25	53 19	55 24	N.S. ^c
Alcohol Use Non-Drinker Drinker	125 167	30 38	31 42	28 44	36 43	N.S. ^c
Caffeine Use No Yes	42 250	10 58	9 64	10 62	13 66	N.S. ^c
Esophageal Stricture Grade 2 3 4	106 155 31	27 36 5	23 41 9	24 39 9	32 39 8	N.S. ^c

TABLE 7 (Con't)

Variables	All Pts. (N=292)	PL (N=68)	LAMEO (BR)		Overall p-value	
			15 (N=73)	30 (N=72)		
SUMMARY OF PRIMARY SYMPTOMS AT BL						
Burning (Upper Abdomen)	NONE (0)	13	16	8	13	N.S.*
	MILD (1)	21	14	24	24	
	MOD (2)	23	26	25	31	
	SEV (3)	11	17	15	11	
Row Mean Score		1.47	1.60	1.65	1.51	
Heart- burn	NONE (0)	12	4	5	10	N.S.*
	MILD (1)	19	16	20	16	
	MED (2)	25	30	28	32	
	SEV (3)	13	23	19	21	
Row Mean Score		1.56	1.99	1.85	1.81	
Painful Swallowing	NONE (0)	43	46	49	62	N.S.*
	MILD (1)	17	15	11	9	
	MCO (2)	5	9	9	5	
	SEV (3)	3	3	3	3	
Row Mean Score		0.53	0.58	0.53	0.35	
Borborygmi (Gastro- intestinal noise)	NONE (0)	30	22	20	23	N.S.*
	MILD (1)	20	22	27	22	
	MOD (2)	15	17	17	26	
	SEV (3)	3	12	6	6	
Row Mean Score		0.87	1.26	1.18	1.24	
Belching	NONE (0)	21	15	20	12	N.S.*
	MILD (1)	21	19	17	29	
	MOD (2)	20	33	23	25	
	SEV (3)	6	6	12	13	
Row Mean Score		1.16	1.41	1.38	1.69	

a) At start of D-B period
b) p-value from F-test for testing equality of means
c) p-value from Chi-square test
d) Includes ex-smokers
e) Based on Cochran-Mantel-Haenszel methods

- Similarly, from 37 to 53 of the patients per group had moderate/severe heartburn; the rest (20 to 31 of the patients) had none/mild heartburn. For other symptoms, listed in Table 7, most patients had non/mild rather than moderate/severe disease. Nonetheless, there were no statistically significant differences among the Tx groups in the number and proportion of patients with symptoms/no symptoms at entry.

d) Primary Efficacy Parameters (Table 8)

i) Treatment Period

- At each time period, the healing rate with each LANSO group was superior than the healing for the PL group. At all time periods the therapeutic gains for the 15, 30 and 60 mg LANSO dose (over PL) were all clinically meaningful. At 8 weeks, these therapeutic gains were 36.3, 40.3 and 41.6%, respectively.
- At 8 (and 6) weeks there were some numerically higher but neither statistically nor clinically significant therapeutic gain of the two highest dose in comparison to the 15 mg LANSO.

ii) Cohort Analysis in Patients With Grade 3 or 4 Esophagitis at Study Entry

- Results at 8 weeks are summarized below.

Study M87-092
Healing Rates for ITT Patients Who Entered the Trial
With Grade 3 (Mild) or 4 (Moderate) Esophagitis

#Healed/N/(%)

Week	PL	LANSO (mg)		
		15	30	60
8	12/40 (30.0)	40/49 (81.6)	40/47 (85.1)	41/47 (87.2)
Therapeutic Gain (%) (over PL)		51.6 (p<0.05)	55.1 (p<0.05)	57.2 (p<0.05)
Therapeutic Gain (%) (over 15 mg)			3.5 (N.S.)	5.6 (N.S.)

- These data show therapeutic gains (over PL) of >50%, which are higher than those seen when Grade 2 "esophagitis" was included.

NOTE: Strictly speaking this evaluation shows that LANSO, at orally administered doses of 15, 30 or 60 mg once-a-day for 8 weeks, heals erosive esophagitis of the mild to moderate type.

TABLE 8
Study M87-092

Healing Rates for ITT Patients
#Healed/Total N/(%)

Week	PL	LANSO (mg)		
		15	30	60
4	20/66 (30.3)	46/72 (63.9)	52/71 (73.2)	60/79 (75.9)
Therapeutic Gain (%) (over PL)		33.6 (p<0.05)	42.9 (p<0.05)	45.6 (p<0.05)
Therapeutic Gain (%) (over 15 mg)			9.3 (N.S.)	12 (p<0.05)
6	32/66 (48.5)	57/72 (79.2)	62/71 (87.3)	68/79 (86.1)
Therapeutic Gain (%) (over PL)		30.7 (p<0.05)	38.8 (p<0.05)	37.5 (p<0.05)
Therapeutic Gain (%) (over 15 mg)			8.1 (N.S.)	6.9 (N.S.)
8	31/66 (47.0)	60/72 (83.3)	62/71 (87.3)	70/79 (88.6)
Therapeutic Gain (%) (over PL)		36.3 (p<0.05)	40.3 (p<0.05)	41.6 (p<0.05)
Therapeutic Gain (%) (over 15 mg)			4.0 (N.S.)	5.3 (N.S.)

iii) Evaluation of Efficacy in Subgroups

- At the primary analysis time point (Week 8), all LANSO doses were significantly superior to PL when healing rates were adjusted for concomitant factors. The latter included sex, age, BL esophagitis grade, alcohol use, tobacco use, caffeine use and whether this was the first episode of R.E.
- No factor-by-Tx group interaction was significant in the analyses based on ITT or evaluable populations.

iv) Patients Healed at Week 4 or 6 But Unhealed at Week 8

Twelve patients (PL=7; LANSO=5) were categorized as unhealed at Week 8 but had been assessed as healed at the endoscopies at Week 4 or Week 6. Data for the five patients receiving LANSO (15 mg, N=1; 30 mg, N=2 and 60 mg, N=2) are shown in Table 9.

TABLE 9
Study M87-092

**LANSO Patients Who Were Healed at Week 4 or 6
But Unhealed at Week 8**

Pt. No. (Inv.)	LANSO Dose (mg)	Endo Grade ^a				Smoking (ppd)	Alcohol Consumption (per day)	History of:	
		Scr	Week		8			Esophagitis	Hiatal Hernia
No.			4	6					
No. (Nano)	15	4	0	NA ^b	2	1-2	1-3 beers	NO	NO
No. (Bruns)	30	2	0	NA	2	Ex (<1)	<1 beer <1 cocktail	NO	YES
No. (Sahba)	30	3	1	NA	2	<1	<1 cocktail <1 beer <1 wine	NO	NO
No. (Nelson, J.)	60	2	0	NA	2	NON	1-3 beers	NO	YES
No. (Sahba)	60	3	2	0	2	Ex (1-2)	1-3 beers <1 wine	NO	YES

a) All endoscopies listed for an individual patient were done by the same endoscopist.

b) NA: Healed at Week 4; therefore, Week 6 endoscopy deferred.

- None of these five patients had a Hx of esophagitis.
- They were apparently compliant with taking test medication during the Tx period.
- These five patients consumed alcohol. In addition, two of them (Nano) and (Sahba) were smokers and three (Bruns), (J. Nelson) and (Sahba) had hiatal hernias. The sponsor speculated that these variables may have affected the esophagitis recurrence. But there are no hard data to prove this assumption.

v) Post-Tx Period (Table 10)

This Table lists the percentages of ITT patients reaching Post-Tx visits [Upper panel=all patients; Lower panel=those patients with Grade 3 or 4 at entry] and remaining healed at 1, 3 or 6 months.

e) Secondary Efficacy Parameters

NOTE: These data are for all patients. The sponsor did not present data on symptomatic relief in patients without erosive esophagitis.

- At Weeks 2, 4 and 6, the 30 and 60 mg groups were superior to PL in relief of:
 - burning in the upper abdomen
 - heartburn
 - belching and
 - GE regurgitation

TABLE 10

Percentages of All Patients (Upper Panel) or Those With Grade 3 or 4 Esophagitis at Study Entry (Lower Panel) Reaching Months 1, 3 and 6 Post-Tx With Endoscopically Documented Healed R.E.

Tx Group	% Remaining Healed (Month Post Tx)			
	0	1	3	6
PL (N=66) % Decrease	47.0	27.3 (-19.7)	25.8 (-21.2)	24.2 (-22.8)
15 (N=72) % Decrease	83.3	51.4 (-31.9)	41.7 (-41.6)	30.6 (-52.7)
30 (N=71) % Decrease	87.3	49.3 (-38.0)	36.5 (-50.7)	27.8 (-59.5)
60 (N=79) % Decrease	88.6	43.0 (-45.6)	32.9 (-55.7)	21.5 (-67.1)
PL (N=40) % Decrease	30.0	15.0 (-15.0)	15.0 (-15.0)	12.5 (-17.5)
15 (N=49) % Decrease	81.6	42.9 (-36.7)	36.7 (-44.9)	28.6 (-53.0)
30 (N=47) % Decrease	85.1	45.0 (-40.1)	27.7 (-57.4)	14.9 (-70.2)
60 (N=47) % Decrease	87.2	34.4 (-52.8)	19.2 (-68.0)	14.9 (-72.3)

- Greater relief of painful swallowing (than PL) was seen in the 30 and 60 mg groups at Week 2 and in the 60 mg group at Week 4.
- At all three evaluation times, the 15 mg LANSO dose produced greater relief than PL for:
 - burning of the upper abdomen and
 - heartburn
 and for
 - belching at Week 2 and
 - GE regurgitation at Week 4.
- At Week 8, all three LANSO groups were superior to PL in producing relief in
 - burning of the upper abdomen
 - heartburn
 - belching and
 - GE regurgitation
- No significant differences in the symptoms of RE at the patient's final Post-Tx visit were seen among the Tx groups.

f) Diary Data

- These data revealed significantly fewer days of Celusil use and significantly fewer tablets used per day and less day and night abdominal pain among patients taking LANSO than PL. There was no significant difference in these parameters among the LANSO groups.

g) Results of Safety Evaluations

i) Adverse Events¹⁰ During Tx Period

- During the Tx period, irrespective of relationship to test medication, 144/224 (or 64.3%) of LANSO pts. reported one or more AE(s), compared to 49/68 (72.1%) PL-treated patients.
- There was no dose relationship. For all the three LANSO groups, the percentages of patients reporting AEs were similar to those of PL patients reporting AEs.
- The percentage of LANSO pts. reporting possibly or probably Tx-related AEs was nearly identical to the percentage of PL patients reporting AEs in the PL group [69/224=30.8% and 21/68=30.9%, respectively]. There was little difference among the three LANSO doses.
- Table 11 lists the numbers of patients reporting possibly or probably Tx-related AEs. The numbers of patients reporting the most common possibly or probably Tx-related AEs are also shown in this Table.
- The data in Table 11 show headache as the most common possibly or probably Tx-related AE reported by PL-treated patients.
- There was more abdominal pain and diarrhea in the LANSO 60 mg than in the lower LANSO groups but this difference was not statistically significant.
- Of the possibly or probably Tx-related AEs reported, the majority were mild to moderate in severity in all of the 4 Tx groups.
- All severe possibly or probably Tx-related AEs were reported by no more than one patient. These severe AEs were not dose related as the highest number of pts. reporting these events (N=3) occurred in the LANSO 15 mg group while all the other 3 groups had only one patient each reporting these AEs.

ii) AEs During the Post-Tx Period

- A larger percentage of patients reported AEs during the Post-Tx period in the PL (13/25=52.0%) than in the LANSO groups combined (56/179=31.3%). All of these were judged to be unrelated to test medication.

¹⁰ AEs reported during the trial were listed by investigator and Tx group in sponsor's Appendix E.14. Appendix D.14.1 listed all medical-term descriptions of AEs (based on medical terms that closely approximated the entry on the CRF) that occurred during the trial. Sponsor's Appendices D.14.2 and D.14.3 summarized patient numbers associated with all AEs and possibly/probably Tx-related AEs, respectively. AEs were summarized in sponsor's Tables 9.1.1 through 9.1.5.

- Listed below are the most common ($\geq 3\%$ incidence in any Tx group) AEs reported during this period by patients who had been on LANSO or PL:

Patients who had been on

<u>LANSO</u>	<u>PL</u>
Headache (14/179=7.8%)	Pharyngitis (5/25=20%)
Dyspepsia (8/179=4.5%)	Diarrhea (4/15=16%)
	Headache (4/25=16%)

TABLE 11
Study M87-092

Number of Patients/(%) With Possibly or Probably Tx-Related AEs

	PL (N=68)	LANSO (mg)		
		15 (N=73)	30 (N=72)	60 (N=79)
Pts. with any Poss/Prob Tx-related AEs	21 (30.9)	25 (34.2)	20 (27.8)	24 (30.4)
<u>Most Frequently^a Reported Poss/Prob Related AEs</u> (COSTART TERM)				
Headache	11 (16.2)	9 (12.3)	6 (8.3)	5 (6.3)
Abdominal Pain	2 (2.9)	4 (5.5)	3 (4.2)	8 (10.1)
Diarrhea	3 (4.4)	1 (1.4)	3 (4.2)	10 (12.7)
Nausea	1 (1.5)	2 (2.7)	3 (4.2)	2 (2.5)
Vomiting	2 (2.9)	1 (1.4)	1 (1.4)	3 (3.8)
Dizziness	1 (1.5)	0	3 (4.2)	0
Eructation	0	0	3 (4.2)	0

a) Defined at $\geq 3.0\%$ incidence rate in any Tx group when rounded to one decimal place.

iii) Withdrawals Due to AEs (Table 12)

- Listed in this Table are the 10 pts. who W/D from the trial during the D-B Tx period at least in part due to an AE.
- 4 pts. (PL=1, 15 mg=2; 30 mg=1) had AEs judged by the investigator to be possibly or probably Tx-related.

- None of these were judged to be severe.
- Three additional patients (Whitaker); (Cozzarelli) and (Nano)] withdrew at least in part due to AEs in the Post-Tx period.

Clinical Summary of Pt. No. (Raforth) [Taken from CRF]

I.M.M. is a 51y old F with a Hx of CABG in 1974, MI in 1985, mild bronchial asthma and an aorto-femoral bypass 3 weeks prior to entering the trial (enrolled on 03/03/88). She had esophagitis Grade 4 and was put on LANSO 15 mg daily. After two doses of test medication, the patient experienced an inferior wall M.I. The investigator considered the AE to be unrelated to test medication.

The patient requested to be W/D from the trial. She had no F/U endoscopy and was counted as a Tx F.

iv) Clinical Laboratory Determinations

- There were no clinically significant differences between any of the LANSO groups and PL for hematology, blood chemistry, urinalysis or thyroid function parameters assessed either during the Tx or Post-Tx intervals.
- There were some statistically significant differences between some of the LANSO groups and PL in some liver enzymes, some metabolic/nutritional and some renal parameters or urinalysis or thyroid function determinations. But these changes were inconsistent, not dose-related and of no clinical concern.

v) Changes in Vital Sign Measurements, Physical Examination and EKG Readings

- There were no clinically significant test medication-related changes in vital signs, P.E. findings or EKG recordings among the LANSO-treated patients.

vi) Fasting Serum Gastrin Concentrations/Gastric Bx Data

NOTE: Fasting serum gastrin values have little clinical utility. The 24-h integrated gastrin AUC is more informative (but this was not done).

- Fasting serum gastrin levels increased in all LANSO groups in a dose-related manner. A plateau was reached by Week 2 and most values returned to near BL values by Month 1 Post-Tx.
- Three patients (Jones)=15 mg; Nos. (Fitch) and (Jones)=30 mg] had gastrin values above the normal range (0 to 100 pg/mL) at screening and throughout the Tx and Post-Tx periods. The investigators were notified. An additional work-up was recommended to rule out Z-E syndrome or G-cell hyperplasia. Two of these patients refused the work-up. The third tested negative for both conditions.
- A very limited number of Bxs was obtained in this study. But results from these Bxs did not suggest an increase in the number of Grimelius-positive cells per mm² during the Tx and/or Post-Tx periods.

TABLE 12
Study H87-092

Patients Who Prematurely D/C During the Tx Period Due to AEs

Pt. No. (Inv)	Total Days on Test Med.	AE(s)/Action Taken	Rx Day of Onset	Rx Day of Stop (S) or Continue (C)	Severity	Relationship to Test Med.
P L G R O U P (N = 2)						
(Berry)	32	Gradual wt. ↓ Fatigue	2 16	32 (C) 32 (C)	Mild Moderate	NO NO
(Weisgn. J.)	7	Headache/No Tx required	5	18 (C)	Moderate	Possible
L A M S O 1 5 M G (N = 4)						
(Erfling)	42	Developed DU/H ₂ started	43	43 (C)	Mild	NO
(Erfling)	42	Esophageal spasms Dry mouth, sore tongue, dry cracked lips/No Tx required	27 ^a 35	43 (C) 43 (C)	Moderate Moderate	Possible Possible
(Rafoth)	2	Inferior wall myocardial infarction/hospitalized	2	6 (S)	Severe	NO
(Scowcroft)	12	Allergic Rx with hives/No Tx required	10	13 (S)	Mild	Possible
L A M S O 3 0 M G (N = 3)						
(Erfling)	34	Skin rash - hives/Sent to dermatologist	32	36 (S)	Moderate	Probably
(Koval)	17	Chest pain on exertion/Sent to cardiologist	2	48 (S)	Moderate	NO
(Simmons)	1	Severe cramping, abdominal pain, leg spasms (Began prior to first dose)/No Tx required	-1	7 (C)	Severe	NO
L A M S O 6 0 M G (N = 1)						
(Thurne)	51	Admitted for alcoholism/ Admitted to alcohol Tx program	21	23 (C)	Severe	NO

a) (C): AE continued as of that date. b) Onset date estimated.

8. Conclusion (Sponsor)

"Lansoprazole, administered once daily before breakfast, healed moderate to severe reflux esophagitis significantly better than did placebo.

"Lansoprazole 30 and 60 mg were equally effective in healing reflux esophagitis and slightly better than the 15 mg dose, with the safety profile suggesting no apparent dose-related effects. Lansoprazole 60 mg was superior to lansoprazole 15 mg in relieving heartburn and upper abdominal burning. All

lansoprazole dose groups (15, 30 and 60 mg) had higher percentages of patients reaching Months 1 and 3 post-treatment with healed reflux esophagitis than the placebo group.

"All lansoprazole groups were superior to placebo in producing relief of upper abdominal burning, heartburn, belching, and gastroesophageal regurgitation.

"Lansoprazole was safe for use in patients with reflux esophagitis at dosages up to 60 mg per day for a period of up to eight weeks, with no lasting effects on fasting serum gastrin levels."

9. Comments

Clinical Trial M87-092 is one of the two critical trials submitted by the sponsor in support of the indication "short-term treatment of reflux esophagitis, all grades". The trial was set to compare the efficacy (and safety) of three dose levels of LANSO (15 vs 30 vs 60 mg, administered once a day before breakfast) to PL under randomized, D-B, parallel conditions in 34 centers throughout the United States.

The inclusion of a PL arm is useful to show efficacy against a negative control. However, strictly speaking, GER was not documented. That is, patients did not undergo 24h of continuous esophageal pH monitoring in relationship to heartburn. Confirmation of reflux previous to randomization would have added quality to the trial. Nonetheless, endoscopic visualization of the esophageal, gastric and duodenal mucosa before randomization allowed the ruling out of other g.i. lesions that may be possibly confounding. Although there is no universally accepted classification system for staging RE, the grading system used in this trial precluded the enrollment of patients with severe esophagitis thereby making it impossible to determine if LANSO is active in this type of esophagitis (severe). In other words, activity is not being tested in "all grades" of esophagitis. The majority of the patients enrolled in this trial were not very sick because a) they had mild to moderate esophagitis and b) mild to moderate disease at entry was also documented on the basis of symptomatology (Table 7). Although 23% of the patients had severe heartburn, anywhere from 20% to 31% of the patients (depending upon the group) had mild or even no heartburn and the rest had moderate heartburn.

Having characterized the study population and the limitations of the most important tool to fulfill one of the aims of the trial, it can be said that other aspects of the study design (blinding, endpoints of efficacy, etc.) were adequate. The trial was apparently well executed. The randomization scheme was properly conducted since it resulted in four groups of patients with similar total numbers and similar demographic and disease baseline characteristics including endoscopic and symptomatologic findings.

Of the parameters evaluated by the sponsor and described with certain detail within the text of this review I have chosen to comment on those which I believe are more meaningful as endpoints for endoscopic and symptomatologic findings. But before we go any further it is important to stress that in this

trial, complete healing of the esophagitis was defined as a return to Grade 0 (no abnormalities) or Grade 1 (mucosal edema and hyperemia). Although a return from Grade 4 (moderate esophagitis) to Grade 0 is clinically meaningful, a return from Grade 2 (friability of mucosa with bleeding under instrumentation but no erosions) to Grade 0 or 1 is not.

Under the experimental conditions described for this trial, activity of LANSO in RE was shown. At all time periods of observation, each of the three LANSO groups showed healing rates superior to PL with clinically meaningful therapeutic gains (36.3, 40.3 and 41.6% for the 15, 30 and 60 mg LANSO, respectively). By 8 weeks there was no advantage in increasing the LANSO dose from 15 to 30 or even 60 mg. The superiority of each of the three LANSO doses was also shown if healing rates were adjusted for concomitant factors including sex, age, BL esophagitis grade, alcohol use, tobacco use, caffeine use and whether this was the first episode of RE.

An analysis of healing in those patients who entered the trial with Grade 3 (Mild) or 4 (Moderate) esophagitis showed that the three orally administered once-a-day doses of LANSO, given for 8 weeks, healed erosive esophagitis of the mild to moderate type.

LANSO was also shown to be effective in relieving symptoms. At Weeks 2, 4 and 6 both the 30 and 60 mg LANSO groups were superior to PL in relief of heartburn, burning in the upper abdomen, belching and GE regurgitation; at these times of evaluation the 15 mg LANSO dose produced greater relief than PL for heartburn and burning of the upper abdomen and for belching at Week 2 and GE regurgitation at Week 4. At Week 8 [why should a patient wait 8 weeks to have his/her symptoms relieved?] all three LANSO groups were superior to PL in the relief of heartburn, burning of the upper abdomen, belching and GE regurgitation. The diary data revealed significantly fewer days of Gelusil use and significantly fewer tablets used per day and less day and night abdominal pain among patients taking LANSO (with no significant difference among the three groups) rather than PL.

It is to be noted that the sponsor analyzed symptom data for all patients combined. Data on symptomatic relief in patients without erosive esophagitis were not presented by the sponsor.

All three LANSO dose groups had higher numerical percentages of patients reaching Months 1 and 3 Post-Tx with healed RE than the PL group. But by 6 months Post-Tx, there was no difference between any LANSO dose and PL.

In this trial, there were no safety concerns. The observed incidence rates of ADRs were similar among the four groups.

D. Study M88-269

"A Study to Evaluate the Effects of Lansoprazole on Acute Gastroesophageal Reflux Disease."

1. Objectives (As stated on page - 4 - of the protocol)

This Phase III study was designed to compare the safety and efficacy of once daily administration of 30 mg of LANSO with those of 300 mg of RAN in the treatment of acute erosive esophagitis.

2. Materials/Labeling¹¹/Randomization

- LANSO and RAN were not matching preparations in this trial. Blinding was done by the use of a double-dummy technique.
- LANSO was supplied in capsules containing 30 mg of enteric-coated granules.
- RAN was supplied in capsules containing 150 mg of RAN as ranitidine hydrochloride¹².
- Matching PL capsules for each LANSO or RAN capsule were provided.
- Antacids were supplied to all patients (Gelusil tablets (Parke-Davis))¹³.
- The bulk NPRO, bulk lot, and finishing subplot numbers for drug supplies used in this trial are shown below.

	Bulk NPRO Number	Bulk Lot Number	Finishing Sublot Number
LANSO 30 mg Capsules	4517N 4517R	24-906-AR 24-967-AR	30-576-AR 35-958-AR
PL for LANSO	4518N	24-907-AR	30-577-AR 35-959-AR
RAN 150 mg Capsules	4495R 4752N	30-532-AR 34-823-AR	30-578-AR 35-960-AR 35-961-AR
PL for RAN	4678N	30-533-AR	30-579-AR 35-962-AR

- Labeling of materials was adequate.
- Separate randomization schedules for each investigator were used (sponsor's Appendix A - Randomization Schedule).

Drug was shipped to investigators in complete blocks, almost always in quantities greater than the block size (some multiple of block size). The investigators were not informed of the block size used. Randomization was carried out with the following block sizes.

M88-269; Block size of 2 (RAN 150 bid; LANSO 30 mg).

¹¹LANSO and PL for LANSO were supplied by Takeda Chemical Industries Ltd, Osaka, Japan and packaged by Abbott Laboratories, Abbott Park, IL on behalf of TAP Pharmaceuticals Inc, Deerfield, IL.

• RAN was supplied by Glaxo, Research Triangle Park, NC and filled into capsules by Abbott Laboratories; PL for RAN was supplied by Abbott Laboratories, Abbott Park, IL.

¹²According to the sponsor, the bioequivalence of the RAN capsules used in this study compared to the commercially available RAN formulation was established in Study F89-154. The Medical Reviewer has not evaluated results from this PK study.

¹³Each Gelusil tablet contained g of the combined hydroxide of magnesium and aluminum with mg of simethicone with a neutralizing capacity of mEq/two tablets.

- When all screening procedures were completed and the patient had met all admission criteria, the next successive patient number available for that investigator was assigned to the patient. This number randomly assigned the patient to 1 of the 2 Tx groups. Assignment started with the lowest available number and proceeded in ascending order¹⁴.

3. Study Design

This was a randomized, D-B, fixed-dose, active-controlled, multicenter study comparing the effectiveness of 30 mg of LANSO when administered orally as a single daily dose before breakfast with that of 150 mg b.i.d. of RAN in patients with acute erosive reflux esophagitis. Test medications were administered for 8 weeks. The study used a parallel-group design with equal allocation to the two Tx groups.

4. Study Population

This was similar to that studied in Trial M87-092. The protocol for the latter study was a bit more explicit in that patients with certain conditions such as Crohn's disease, regional enteritis, UC, IBS or pancreatitis were not included but it did not specify that patients with Gilbert's disease were eligible. Other inclusion-exclusion criteria were as for the previously reviewed R.E. trial. Thus subjects enrolled in the present trial were M or F patients of at least 18y of age with acute erosive R.E. of at least Grade 2. The esophagitis grading scale used in this trial is described below.

Grade	Description
0	Normal-appearing mucosa by endoscopy
1	Mucosal edema, hyperemia, and/or friability
2	One or more erosions/ulcerations in the squamocolumnar junction
3	Erosions/ulcerations involving $\leq 50\%$ of the distal 5 cm of the esophagus proximal to the squamocolumnar junction
4	Multiple erosions/ulcerations involving $>50\%$ of the distal 5 cm of the esophagus or a single large ulcer greater than 5 mm in diameter proximal to the squamocolumnar junction

¹⁴The randomization schedules were generated by the Clinical Statistics Department at Abbott Laboratories, Abbott Park, IL. The patient numbers and study drug assignments were in the possession of the investigators (D-B portion of the label) and of the Clinical Statistics Department at Abbott Laboratories (sealed envelopes). The study blind could be broken if, in the opinion of the investigator or monitor, it was clearly in the patient's best interest to do so. The time the study blind was broken, by whom, and the reason were to be documented on the CRF.

Patient had to be Grade 2 to 4 to be eligible for the trial. It is to be noted that this protocol provided the following adequate definitions:

ulcer:	lesion which is discrete with appreciable depth and greater than 3 mm in diameter
ulceration:	superficial breaks in the esophageal mucosa which are less than 3 mm in diameter, with or without exudate
erosion:	synonymous with ulceration. Red spots without breaks in the mucosa are not considered erosions.
squamocolumnar junction:	includes the 1 cm area proximal to the junction of the esophageal and gastric mucosa
distal 5 cm of the esophagus:	includes the 5 cm area proximal to the squamocolumnar junction

NOTE: It is important to mention that this classification system for staging reflux esophagitis differs substantially from that used in study M87-092. The definitions provided are very helpful in the standardization of procedures and uniform interpretation of findings. Grade 2 of this scale does represent erosive disease, albeit of the mild type. Grades 3 and 4 correspond to moderate and severe disease, respectively. If enough Grade 4 patients were included in the present trial and efficacy in this subgroup were to be demonstrated, then the sponsor request for approval of LANSO use for "all grades of esophagitis" may be justified [although one still needs to consider what the recommended dose is, 15 or 30 mg].

5. Study Execution

In a fashion very similar to the other study, the present trial consisted of two periods: screening (lasting a maximum of 7 days) and treatment (where eligible patients would be enrolled and visits completed at the end of weeks 2, 4, 6 and 8).

Eligible patients were each given three bottles of LANSO, RAN, and/or PL capsules at BL and at Weeks 2, 4 and 6 of the Tx period. Each bottle was labeled AM or PM and contained 19 capsules (five extra capsules per bottle). Bottles 1A, 1B and 1C were dispensed at baseline (Study Day 1); bottles 2A, 2B and 2C at the Week 2 visit, etc. Each morning before breakfast during the eight-week treatment period, the patient took one capsule orally from each of the A and B bottles. At bedtime, the patient took one capsule orally from the C bottle. The bottles contained active drug or PL in combinations that provided the assigned drug and dose level, as shown below.

Bottle	LANSO 30 mg QD	RAN 150 mg b.i.d.
#1A-4A	LANSO 30 mg cap.	LANSO PL
#1B-4B	RAN PL	RAN 150 mg cap.
#1C-4C	RAN PL	RAN 150 mg cap.

One replacement bottle for each of the A, B and C drug bottles (RA, RB and RC) for each patient was supplied to each investigator to be dispensed only as

ed. In addition, at the BL and the Weeks 2, 4 and 6 visits, each patient given one box of Gelusil (containing 50 tablets) to be taken for relief of comfort as needed.

The trial then proceeded in a fashion similar to that of M87-092. In the present trial, endoscopies were mandatory at screening and Weeks 2 and 8. The endoscopy could be deferred at Weeks 4 and 6 if healing was documented at a prior visit.

This trial did not include observation during the Post-Tx period.

6. Statistical Methodology

a) Planned Sample Size

According to the clinical Protocol, the trial was designed to enroll sufficient patients such that 200 would complete the study and have evaluable efficacy data (100 in each Tx group). This sample size had a greater than 97% chance to detect significant differences between the LANSO 30 mg QD and RAN 150 mg b.i.d. groups if true healing rates (at Week 8) were 85% and 60% ($p < 0.05$, two-tailed test). In this trial, a therapeutic gain (LANSO > RAN) of ca. 25% was expected.

b) Patient Evaluability

As shown below, the procedures to establish patient evaluability were adequate. These are discussed in detail here because - during the present review - efficacy assessment will be based both on ITT and Evaluable Population Analyses.

According to the sponsor, classification of patients regarding acceptability of data for efficacy analyses was carried out by the project team prior to their knowledge of the D-B Tx group assignment. Individual data exclusions were also completed at this time. Reasons for excluding patients from efficacy analyses were established as follows:

- Grade 0 or 1 esophagitis at screening [Pt. did not have erosive disease].
- Evidence of uncontrolled, clinically significant medical disease, as determined by review of the patient's medical Hx by the medical monitor. Patients with Barrett's esophagus involving >3 cm of the distal esophagus were not considered evaluable. I agree with this approach, Barrett's esophagus is a different patient population than garden variety erosive esophagitis.
- Chronic use of ulcerogenic medication prior to, or during, Tx (except as allowed by the protocol (=antacids as needed)).
- Use of antiulcer medication during Tx (except as allowed by the protocol (=antacids as needed)).
- Previous vagotomy or GE surgeries. Patients who had had dilation of stricture within 12 weeks of study start were not evaluable but those with simple closure of gastric or duodenal ulcer perforation and fundoplication were considered evaluable.
- Less than 67% of prescribed study drug taken from baseline to each visit, or less than 14 days of study drug taken.

- Screening laboratory values not WNLs and patient terminated upon discovery after receiving less than 14 days of drug.
- No "evaluable" endoscopy after the start of Tx.

c) Parameters of Evaluation

- The primary efficacy endpoint was the endoscopic assessment (healed/unhealed), as stated in the protocol.
- Additional efficacy parameters were symptom assessments and diary summaries (Gelusil use and day and night heartburn).
- The safety variables were assessments of AEs, clinical laboratory data including gastrin and Bx results, P.E. data, EKG data, and vital sign data.

d) Statistical Analysis

Efficacy

- The principal measurement was the number of patients in each Tx group with completed esophagitis healing after 2, 4, 6 or 8 weeks of Tx as demonstrated endoscopically.
- The proportion healed on LANSO at each time point was compared to that healed on RAN using Mantel-Haenszel methods for combining (2x2) tables across investigators.
- Factors other than treatment which are significantly related to the outcome measures were controlled for in the analyses.
- Secondary analysis compared the Tx groups with respect to pain scores and amount of antacid use as reported at the week 2, 4, 6 and 8 visits.

Safety

- AEs were tabulated separately for each of the two Tx groups and rates were compared between groups with Fisher's Exact Test.
- Safety was also evaluated using BP, PR, B₁₂ data, ECL cell densities, G and D cell count and clinical laboratory test results. Changes in these variables from baseline to the final visit evaluation were compared between the LANSO group and the RAN group.
- The protocol stated that "additional statistical methods were to be employed where appropriate" (these are vague statistical approaches).

7. Study Results

a) Participating Investigators

In this trial, 29 qualified investigators, geographically distributed throughout the United States, enrolled a total of 247 patients (156 M, 91 F) all of whom received at least one dose of test medication.

b) Number of Patients in the ITT vs Evaluable¹⁵ Population Analyses

- All 247 patients were included in the analysis of ITT patients.
- 242 (LANSO=115 pts.; RAN=227 pts.) of the 247 pts. who entered the Tx period were included in at least one of the primary efficacy analysis (Week 2, 4, 6 or 8). Reasons for exclusion of the five (5) patients (LANSO=4; RAN=1), who were deemed nonevaluable are given below.

Summary of Patient Evaluability

No. of Pts.	Reason for Exclusions
1	Admission criteria violation: endoscopic grade not appropriate for study entry.
1	Admission criteria violation: previous g.i. surgery and received <14 days of test med.
2	Admission criteria satisfied but received <14 days of test med.
1	Admission criteria satisfied and received >14 days of test med. but had no endoscopy after study start

- 4 Additional pts. had individual endoscopic results excluded from analyses because of failure to comply sufficiently with intended study procedures.
 - 2 patients had taken less than 67% of required test med. between the start of the study and the time of the excluded visits.
 - 2 patients had an endoscopy performed >5 days after the last dose of drug was taken. For these two patients, the endoscopy obtained on the preceding visit was used as the final endoscopy.
- All patients excluded from analyses of endoscopic results were also excluded from analyses of symptom and/or diary data.
- All patients/visits with endoscopy/symptom/diary results excluded and the reasons for their exclusion were listed in sponsor's Table 7.1.1.1.
- The numbers of patients entered at each study site, along with the number included in the ITT and Evaluable Population analyses were summarized in sponsor's Table 7.1.1.b.
- Exclusions from gastrin and Bx analyses were appropriate. The groups were roughly comparable in protocol deviations not resulting in data exclusion.

¹⁵In this Clinical Report, the term "Evaluable patient" refers to patients included in at least one of the primary analyses, who had evaluable endoscopic data at Week 2, 4, 6 or 8, unless specifically referring to a symptom or diary analysis.

c) Data Showing Comparability of Groups

i) Premature Terminations

- A summary of the primary reasons for premature termination from the Tx period is given in Table 13.
- 18 patients [LANSO=10/119 (8.4%); RAN=8/128 (6.3%)] withdrew from the trial prematurely during the Tx period (sponsor's Appendix E.1).

TABLE 13
Study NBB-269

Summary of Primary Reasons for Premature Termination
from the Tx Period

(Number of Patients)

Termination Reason	LANSO 30 mg QD	RAN 150 mg B.I.D.
AE(s) ^a	7	4
Poor Compliance	0	1
TxF	1	0
Personal	1	1
Other	1	2
Total	10	8

a) Sponsor's Table 7.2.1 listed the investigator, patient number, Tx group, number of completed days of treatment, age, sex, and the reason for termination for each of these patients.

- 9 of the 18 patients listed in this Table had endoscopically-documented healing prior to their termination and were flagged in sponsor's Table 7.2.1.

b) In addition to the number of patients indicated as prematurely terminating primarily due to AEs (N=11), (Movva) from the RAN 150 mg b.i.d. group reported dyspepsia as an AE, and this was given as a secondary reason for premature termination. The primary reason was that the patient felt symptomatic despite endoscopic improvement. The patient D/C primarily for this reason, and was listed under the "other" category.

ii) Demographic and Disease Baseline Characteristics
(Table 14)

- This Table summarizes the demographic and disease BL characteristics for the 247 who entered the D-B Tx period.
- There were no significant differences between the LANSO and RAN groups, combined across investigators, for age, body weight, height, sex, race, tobacco use, alcohol use or caffeine use.
- There was no significant difference between Tx groups, combined across investigators, in the esophagitis grade at screening.
- In this trial, the proportion of patients with Grade 1 to 4 lesions was as follows:

Esophagitis Grade	No. of Pts.	Proportion of Pts. (%)	Endoscopic Findings (Clinically Relevance)
1	1	0.4	Mucosal edema, hyperemia, and/or friability [No esophagitis]
2	110	44.5	One or more erosions/ulcerations in the squamocolumnar junction [mild esophagitis]
3	117	47.4	Erosions/ulcerations involving $\leq$ 50% of the distal 5 cm of the esophagus proximal to the squamocolumnar junction [moderate esophagitis] (Clinically meaningful)
4	19	7.7	Multiple erosions/ulcerations involving $>$ 50% of the distal 5 cm of the esophagus or a single large ulcer $>$ 5mm in diameter proximal to the squamocolumnar junction [severe esophagitis] (Clinically important)
	N=247	100.0%	

- The above-summarized data show that - at entry - the bulk of the patients had mild to moderate esophagitis. Only 19 patients (LANSO=8; RAN=11) or - 8% of the enrolled population had endoscopically proven severe esophagitis. The most important clinical condition (severe esophagitis) was poorly represented in this trial.
- Similarly, for night heartburn only roughly 1/4 of the patients in this trial had severe disease. For all of the other symptoms listed in Table 14, patients had either no or up to moderate symptoms. As was the case for the endoscopic lesions, the severe category of symptoms was not well represented in the present trial. Nonetheless, both Tx groups were comparable to each other with regard to the proportion of patients with symptoms/ no symptoms at entry.

d) Primary Efficacy Parameters (Table 15)

i) Overall

- For both the ITT and the Evaluable Populations and at each time period analyzed (Weeks 2, 4, 6 and 8) the healing rates with LANSO 30 mg QD were superior to those with RAN 150 mg B.I.D..
- At all time periods, the therapeutic gains were clinically meaningful. By 8 weeks, these therapeutic gains were 22% (either study population).
- In both ITT and evaluable population analyses, significant lack of homogeneity across investigators (treatment-by-investigator interaction) was not indicated for the comparison of LANSO 30 mg QD and RAN 150 mg BID groups at any evaluation time.

TABLE 14
Study N88-269

Summary of Demographic and Disease Baseline Characteristics
(All Patients)

Variable	All Pts. N=247	LANSO 30 mg QD N=119	RAM 150 mg BID N=128	Overall p-value
Age ^a Mean (S.D.) (y) Min-Max	43.9 (15.0) 18-80	44.7 (15.5) 18-78	43.2 (14.6) 20-80	N.S. ^b
Weight-M ^c No. of Pts. Mean (S.D.) (lbs)	156 196.6 (30.8)	76 192.2 (29.5)	80 200.9 (32.6)	N.S. ^b
Weight-F ^c No. of Pts. Mean (S.D.) (lbs)	91 160.8 (33.1)	43 158.7 (33.6)	48 162.7 (32.8)	N.S. ^b
Height-M ^c No. of Pts. Mean (S.D.) (inch)	154 70.5 (3.0)	75 70.3 (3.0)	79 70.7 (3.0)	N.S. ^b
Height-F ^c No. of Pts. Mean (S.D.) (inch)	91 64.1 (2.2)	43 64.2 (2.2)	48 64.1 (2.3)	N.S. ^b
Sex	M F	76 43	80 48	N.S. ^d
RACE	Caucasian Hispanic Black Other	115 1 2 1	119 5 2 2	N.S. ^d
Tobacco Use	Tobacco Nonuser ^e Tobacco User	83 36	98 30	N.S. ^d
Alcohol Use	Non-drinker Drinker	52 67	60 68	N.S. ^d
Caffeine Use	No Yes	26 93	23 105	N.S. ^d
Esophageal Disease Grade	Grade 1 2 3 4	1 54 56 8	0 56 61 11	N.S. ^d

TABLE 14 (Con't)

Variable	All Pts. N=257	LANSO 30 mg QD N=119	RAM 150 mg BID N=128	Overall p-value
SUMMARY OF PRIMARY SYMPTOMS AT 8L				
Burning Mucos: Abdomen				
NONE (0)		20	24	N.S. ^a
MILD (1)		25	29	
MOD (2)		53	49	
SEV (3)		21	26	
Row Mean Score		1.63	1.60	
Dry Mucos: Buccal				
NONE (0)		10	12	N.S. ^a
MILD (1)		32	35	
MOD (2)		51	61	
SEV (3)		26	20	
Row Mean Score		1.78	1.70	
Light Mucos: Buccal				
NONE (0)		22	21	N.S. ^a
MILD (1)		20	31	
MOD (2)		41	43	
SEV (3)		36	33	
Row Mean Score		1.76	1.69	
Painful Swallowing				
NONE (0)		90	91	N.S. ^a
MILD (1)		16	23	
MOD (2)		6	12	
SEV (3)		5	2	
Row Mean Score		0.39	0.41	
Removal: Sensation (Gumline: Intraoral: Extraoral)				
NONE (0)		36	40	N.S. ^a
MILD (1)		39	49	
MOD (2)		34	30	
SEV (3)		8	9	
Row Mean Score		1.10	1.06	
Belching				
NONE (0)		30	38	N.S. ^a
MILD (1)		32	42	
MOD (2)		41	40	
SEV (3)		16	8	
Row Mean Score		1.35	1.14	

a) At start of 8-8 Period; b) p-value from t-test for testing equality of ix means; c) p-value from Chi-Square Test; d) Includes ex-tobacco users; e) Based on Cochran-Mantel-Haenszel methods

TABLE 15
Study M88-269

Healing Rates^a as a Function of Time and Study Population
Healed/Total N/(%)

Week	ITT Population		Evaluable Population	
	LANSO 30 mg QD	RAN 150 mg BID	LANSO 30 mg QD	RAN 150 mg BID
2	77/119 (64.7)	49/128 (38.3)	76/114 (66.7)	48/124 (38.7)
Therapeutic Gain	26.4 (p<0.001)		28.0 (p<0.001)	
4	95/119 (79.8)	64/128 (50.0)	94/114 (82.5)	64/123 (52.0)
Therapeutic Gain	29.8 (p<0.001)		30.5 (p<0.001)	
6	107/119 (89.9)	80/128 (62.5)	106/114 (93.0)	80/118 (67.8)
Therapeutic Gain	27.4 (p<0.001)		25.2 (p<0.001)	
8	106/119 (89.1)	86/128 (67.2)	105/114 (92.1)	86/123 (69.9)
Therapeutic Gain	21.9 (p<0.001)		22.2 (p<0.001)	

a) In this Table, numerators reflect the cumulative number of patients healed. Denominators reflect the total number of patients in the ITT or Evaluable Population at each of the four time periods.

ii) Cohort Analysis in Patients With Grade 4 Esophagitis at Study Entry

Unfortunately the sponsor did not present efficacy analyses in patients with esophagitis Grade 4 (only). This information, evaluating efficacy in patients with severe disease, should be requested of the sponsor.

iii) Efficacy in subgroups

- At all time points of evaluation (Weeks 2, 4, 6 and 8) and for both ITT and Evaluable Population, LANSO 30 mg QD remained superior to RAN 150 mg BID when healing rates were adjusted for concomitant factors. The latter included sex, age, BL esophagitis grade, alcohol use, tobacco use, caffeine use, whether this was the first episode of R.E. and whether hiatal hernia was present.
- In the ITT analyses, a significant Tx-by-tobacco use interaction was suggested in the comparison of the LANSO vs RAN groups at 8 weeks but not at other times of observation. This as well as other Tx-by-factor interactions seen in the evaluable population were not considered clinically meaningful because they were sporadic, inconsistent and not

very strong (statistically). With so many statistical analyses being carried out, apparently a few significant comparisons of differences are to be expected.

- The sponsor also examined endoscopy results to determine the effect of Barrett's esophagus on healing rates. But the number of patients presenting (LANSO=3; RAN=3) with this condition was too small to allow reaching useful conclusions.

iv) Patients Healed at Week 2, 4 or 6 But Unhealed at Week 8

Eleven (11) patients (LANSO=5; RAN=6) were categorized as unhealed at Week 8 but had been assessed as healed at the Week 2, 4 and/or 6 endoscopy(ies). Data for these 11 patients are summarized in Table 16.

- All of these pts. had a Hx of esophagitis and most of them were found to have a hiatal hernia.
- Some of these patients had healed to Grade 0 (or 1) before they apparently recurred even though they continued taking the test medication.
- They were apparently compliant with taking the test medication.
- Most (although not all) of these patients consumed alcohol and were or had been smokers and had hiatal hernias. The sponsor speculated that these variables may have affected the esophagitis recurrence. But there are no hard data to prove this assumption.
- Two additional patients (LANSO=1; RAN=1, see summary data below) who had a Hx of esophagitis and were noted to have a hiatal hernia at endoscopy, were evaluated as healed at Week 2 and/or 4, unhealed at Week 6 and then healed again at Week 8.

e) Secondary Efficacy Parameters

- At Weeks 2, 4 and 6 the ITT analyses showed LANSO 30 mg QD statistically superior to RAN 150 mg BID in
 - relief of burning in the upper abdomen
 - day heartburn and
 - night heartburn
- At Weeks 2 and 4, greater relief of esophageal regurgitation was seen in the LANSO group compared to the RAN group.
- At Week 8, LANSO was superior to RAN in the relief of:
 - burning of the upper abdomen
 - day heartburn
 - night heartburn
 - pain swallowing and
 - GE regurgitation

TABLE 16
Study M88-269

Patients Who Were Healed at Week 2, 4 or 6 but Unhealed at Week 8

Pt. No. (Inv.)	Endo Grade					Smoking (ppd)	Alcohol Consumption (Per day)	History of:	
	Scr	2	4	6	8			Esophagitis	Hiatal Hernia ^a
LANSO (N = 5)									
(Kovai)	3	1	2	2	3	<1	<1 beer	YES	NO
(Nelson) ^a	4	2	0	NA ^b	3	<1	1-3 wine	YES	NO
(Rowekamp)	3	0	NA	NA	3	<1	1-3 beer	YES	YES
(Scowcroft) ^a	3	0	NA	NA	2	Ex (>2)	>3 beer	YES	YES
(Wu) ^a	3	0	NA	NA	3	NON	NON	YES	YES
RAN (N = 6)									
(Kading) ^a	2	1	2	2	2	Ex (>2)	1-3 beer	YES	NO
(Nelson) ^a	3	1	2	3	2	NON	NON	YES	YES
(Robinson) ^a	2	2	1	NA	2	<1	<1 beer	YES	YES
(Scowcroft) ^a	2	0	NA	NA	2	NON	<1 beer <1 liquor	YES	YES
(Spierling) ^a	3	0	NA	NA	2	Ex (<1)	1-3 wine	YES	YES
(Wu)	3	2	0	NA	3	NON	NON	YES	YES

- a) All endoscopies performed by the same endoscopist.
b) NA: Healed at Week 2 or 4; therefore, Week 6 and/or 8 endoscopy deferred.
c) Hiatal hernia noted at any of the endoscopies.
d) Patient took aspirin on a prn basis (unknown amount) from Study Day 36 to 43.

**Patients Who Were Healed at Week 2 and/or 4,
Unhealed at Week 6, but Healed at Week 8**

Pt. No. (Inv.)	Endo Grade					Smoking (ppd)	Alcohol Consumption (Per day)	History of:	
	Scr	2	4	6	8			Esophagitis	Hiatal Hernia
LANSO (N = 1)									
(Koval) ^a	2	0	0	2	0	NON	<1 beer	YES	YES
RAN (N = 1)									
(Levine) ^a	3	3	1	3	1	Ex (1-2)	Ex (<1 beer) <1 wine <1 liquor	YES	YES

- a) All endoscopies performed by the same endoscopist.

- At Week 8, results in the Evaluable Population showed no differences between LANSO and RAN in the relief of night heartburn or belching. But other findings were similar to those in the ITT population.

f) Diary Data

- Results of the ITT as well as those of the Evaluable Population analyses showed that the LANSO-Tx patients reported significantly

- fewer days of Gelusil and fewer tablets per day
- less day and night heartburn
- fewer days until the last report of day and night heartburn

than the RAN-Tx patients.

g) Results of Safety Evaluations

i) Adverse Events During Tx Period

- During the Tx period (or within 3 days after the last dose), regardless of relationship to test medication, 76/119 (or 63.9%) of the LANSO pts. reported one or more AEs, compared to 75/128 (or 58.6) of RAN patients.
- The percentage of LANSO patients reporting possibly or probably Tx-related AEs [13/119=10.9%] was similar to that with RAN [9/128=7.0%].
- The most frequently ($\geq 2\%$ incidence rate in either group) reported possibly or probably Tx-related AEs were headache and diarrhea, with the following similar distribution:

	LANSO (N=119)	RAN (N=128)
Headache	3 (2.5%)	2 (1.6%)
Diarrhea	4 (3.4%)	2 (1.6%)

- Of the possibly or probably Tx-related AEs reported, the majority were mild to moderate in severity (both groups).

ii) Withdrawals Due to AEs (Table 17)

- Listed in this Table are the 12 patients [LANSO=7; RAN=5] who W/D from the D-B Tx period of the trial at least in part due to an AE.
- 4 pts. (LANSO=3; RAN=1) had AEs judged by the investigator to be possibly or probably Tx-related. Two of these [abnormal LFTs in LANSO-Tx-Pt. (Fisher) and allergic Rx treated with Benadryl, Atarax, calamine lotion in RAN-Tx Pt. (Shivakumar)] were also judged to be severe.
- The AEs causing D/C in the remaining 8 pts. were judged by the investigator to have no relationship to test med.

TABLE 17
Study M08-269

Patients who Prematurely D/C During the Tx Period Due to AEs

Pt. No. (Inv.)	Tx Group	Total Days on Test Med.	AE(s)/Action Taken	Rx Day of Onset	Rx Day of Stop (\$) or Continue (C) ^a	Severity	Relationship to Test Med.
(Aymar)	LANSO	33	↑ Appetite Constipation/Metamucil	2 15	43 (C) 43 (C)	MILD MOD	NO
(Berry)	RAN	32	Flatulence/simethicone, Bentyl Carcinoma of colon/hospitalization	20 32	32 (C) 64 (C)	MOD SEV	NO NO
(DeNicco)	RAN	42	Flu syndrome/erythromycin 250 mg QID, elixir Terpin hydrate/codeine cough syrup prn	42	71 (S)	SEV	NO
(DeNicco)	LANSO	43	Rash/prednisone 20 mg daily	41	56 (S)	SEV	NO
(DeNicco)	LANSO	45	Angina pectoris/cardiac catheterization, coronary angioplasty	44	46 (S)	SEV	NO
(Fisher)	LANSO	18	Abnormal LFTs/allowed to resolution	17	57 (S)	SEV	Possible
(Hee)	LANSO	27	Peripheral edema/Benedryl Urticaria/Benedryl Vasodilation/Benedryl	22 22 22	26 (S) 26 (S) 26 (S)	MOD MOD MOD	Probable Probable Probable
(Hee)	LANSO	52	Chest pain/hospitalization Hypochromic anemia	49 50	65 (S) 72 (S)	SEV MILD	NO NO
(Kovel)	RAN	20	Palpitation/Molter monitor	20	29 (S)	MOD	NO
(Morva)	RAN	29	Dyspepsia/no action taken	2	29 (C)	MOD	NO
(Robinson)	LANSO	30	Abnormal LFTs/allowed to resolution	27	48 (S)	MOD	Probable
(Shivakumar)	RAN	16	Allergic reaction/Benedryl, Atarax, calamine lotion	15	17 (C)	SEV	Probable

a) AE continued as of that date.

- Of the patients listed in Table 17, the following 3 are of special interest (data from CRFs):

(Fisher) (LANSO 30 mg QD) presented with elevated liver enzymes at screening. These levels showed further elevations at Week 2 and at this time they were reported as a severe AE. They showed a gradual return to BL values starting on Study Day 18.

- 2 days after start of test medication, Pt. (Nee) experienced moderate urticarial rash, edema and vasodilation which lasted 1.5h. He reported similar events at Week 4 at which time test med. was D/C. The events resolved the day after the patient stopped test medication.

- Pt. (Robinson) (LANSO) who admitted a 20-y Hx of alcohol use (one to three beers and less than one cocktail per day beginning at seven years of age) had AST/SGOT and ALT/SGPT values that were WNR at screening and Week 2. The patient D/C due to elevation of liver enzymes (AST/SGOT = 238 U/L and ALT/SGPT = 167 U/L). Four days Post-Tx, the patient's AST/SGOT was normal, but the ALT/SGPT value remained elevated (87 U/L). Eighteen (18) days Post-Tx, the patient's AST/SGOT was only slightly elevated (40 U/L) but the total bilirubin (2.0 mg/dL) was now at a level of clinical concern. Further follow-up for this patient was unavailable.

iii) Clinical Laboratory Determinations

- There were no clinically significant differences between the LANSO and RAN groups for hematology, blood chemistry or urinalysis parameters assessed during the Tx period.
- There were some laboratory changes in individual patients but aside of the already described LFTs in two patients, these were of no clinical significance.

iv) Changes in Vital Sign Measurements, Physical Examination and EKG Readings

- There were no clinically significant test medication-related changes in vital signs, P.E. findings or EKG readings between the two Tx groups.

v) Fasting Serum Gastrin Concentrations/Gastric Bx Data

- Again, the utility of fasting gastrin concentrations is limited.
- As expected, fasting serum gastrin concentrations increased in both Tx groups, although they were significantly higher in the LANSO group when compared to the RAN group.
- There were seven (7) pts. (LANSO=6; RAN=1) in whom pre-study serum gastrin levels were WNL but increased to ≥ 2 times the normal range at Week 8.
- The trial included limited analysis of full-thickness Bxs from gastric curvature and antral mucosae.
- Results from these Bxs did not reveal clinically significant histological changes
- For the small number of changes observed, most involved slight increases in inflammation or changes from normal to simple (diffuse) hyperplasia.
- There were also slight, statistically significant, increases in Grimelius-positive and gastrin (G) cell densities in the LANSO group.

8. Conclusion (Sponsor)

"Lansoprazole 30 mg, administered once daily before breakfast, healed acute reflux esophagitis significantly better than did ranitidine 150 mg BID. Lansoprazole 30 mg once daily was also superior to ranitidine 150 mg BID in producing relief of burning in the upper abdomen, day heartburn, painful swallowing, and gastroesophageal regurgitation at the final symptom assessment.

"Lansoprazole 30 mg QD was safe for use in patients with acute reflux esophagitis for a period of eight weeks."

9. Comments

Study under Protocol M88-269 is the second of the two critical trials submitted by the sponsor in support of the use of LANSO for the indication "short-term treatment of reflux esophagitis, all grades". This 2-arm trial was set to compare the efficacy (and safety) of LANSO 30 mg administered once a day before breakfast to RAN 150 mg given twice-a-day, under randomized, D-B, parallel conditions in 29 sites throughout the U.S.

It is important to note that reflux esophagitis is a broader population than erosive esophagitis.

All in all, the trial is of adequate design in that activity of LANSO can be demonstrated through statistical superiority of LANSO over RAN. However, in this trial (nor in the other critical trial) GER pH was not documented. That is, patients did not undergo 24h of continuous esophageal pH monitoring in relationship to the occurrence of heartburn. Confirmation of reflux previous to randomization would have added quality to the trial. In spite of this, and just as in the other trial, endoscopic visualization of the esophageal, gastric and duodenal mucosa before randomization allowed the ruling out of other g.i. lesions that may possibly be confounding. Unlike trial M87-092, the present trial did make use of an adequate classification system for staging RE. Nonetheless, the majority of patients enrolled in the present trial were not very sick because they had mostly mild (Grade 2) to moderate (Grade 3) esophagitis and only a handful (19 patients in total, LANSO=8, RAN=11) had severe esophagitis. Predominance of mild to moderate disease was also documented on the basis of symptomatology (Table 14).

One important clarification is that the dose of RAN (150 mg b.i.d.) tested was not the dose of RAN recommended for the healing of reflux esophagitis (150 mg q.i.d.). Consequently, superiority of LANSO 30 mg over this inadequate dose of RAN would certainly demonstrate activity of LANSO. But no superiority of LANSO over RAN can be claimed in advertisement. In this reviewer's opinion, an additional limitation of this trial is that a LANSO 15 mg OD arm was not included. This is important because this dose of the compound was shown to be active (and safe) in trial M87-092. The latter trial showed that the job (healing of and relief of symptoms of mild to moderate RE) can be accomplished with 15 mg LANSO per day and that there was no real advantage in increasing the dose to 30 or (even less) to 60 mg per day.

Other aspects of Trial M88-269 design (blinding, endpoints of efficacy) were adequate. The randomization scheme and other aspects of the trial were apparently well executed and resulted in two groups of patients with similar total numbers and similar demographic and disease baseline characteristics. These included similar endoscopic and symptomatologic findings before randomization.

Under the experimental conditions described for this trial, activity of LANSO 30 mg once daily in RE was demonstrated, irrespective of the study population (ITT vs Evaluable) being analyzed. At all time periods of observation (Weeks 2, 4, 6 and 8) the healing rates with LANSO 30 mg once daily were clinically and statistically superior to those seen with RAN 150 mg BID, with therapeutic gains of ca. 30% at Week 4 and ca. 22% at Week 8. The superiority of LANSO 30 mg once-a-day was also shown if healing rates were adjusted for concomitant factors that may influence healing. These included gender, age, BL esophagitis grade, alcohol use, tobacco use, caffeine use, whether this was the first episode of R.E. and whether hiatal hernia was present.

LANSO 30 mg once daily was also shown to be effective in relieving symptoms. For example, at Weeks 2, 4 and 6 the ITT analyses showed LANSO 30 mg QD - statistically superior to RAN 150 mg BID in relieving day and night heartburn and burning in upper abdomen. The diary data revealed significantly fewer days of Gelusil and fewer tablets per day, less day and night heartburn and fewer days until the last report of day and night heartburn among LANSO 30 mg once daily-treated patients than those treated with RAN 150 mg QID.

LANSO 30 mg once-a-day was well tolerated. In this trial, there were no safety concerns. The percentage of patients experiencing AEs and those reporting possibly or probably treatment-related AEs were similar between the two groups of patients. The most frequently reported possibly or probably Tx-related AEs for LANSO 30 mg once daily were headache and diarrhea with incidence rates numerically but not statistically higher than for RAN. For both groups, the majority of these possible-probably Tx-related AEs were of moderate severity. Not unexpectedly, fasting serum gastrin concentration increased in both Tx groups, but they were significantly higher in the LANSO when compared to the RAN group. Of note, there were 7 patients (LANSO=6; RAN=1) in whom pre-study serum gastrin concentrations were WNLs but increased to ≥ 2 times the normal range at Week 8.

E. Summary of Section B (Efficacy): S-T Tx of RE

The sponsor is seeking an indication to treat all grades and levels of severity of RE, including RE that responded poorly to a course of H₂-RAs in a dose equivalent to RAN 150 mg b.i.d. or greater and severe RE in patients with co-existing Barrett's epithelium. It is important to reiterate that reflux esophagitis is a broader population than erosive esophagitis. "All grades and levels of severity" includes a) patients with severe esophagitis; b) patients with poorly responsive GERD (although the sponsor's definition of poorly responsive GERD is inadequate (see review below)) and c) esophagitis in patients with Barrett's esophagus. It is not clear why the latter should be a separate indication. On the basis of present knowledge, interfering with the development of, or better yet the reversal of Barrett's esophagus, requires years of pharmacological treatment.

For indications related to RE one needs to focus on at least two aspects. One is symptomatic relief in patients without erosive esophagitis. Evaluations in purely symptomatic patients have not been carried out by the sponsor. The other is healing of erosive esophagitis. In the summary that follows emphasis is put on the healing of lesions. An additional aspect is whether symptom relief is independent of healing or whether these two parameters are correlated. But again, these possible correlations have not been carried out by the sponsor.

Study M87-092 showed that LANSO 15 mg per day given before breakfast for 8 weeks was effective in healing esophageal lesions of the mild to moderate degree. This dose of LANSO was also effective in symptomatic relief in patients with mild to moderate esophagitis. According to the results from this trial there seems to be no advantage in increasing the dose to 30 mg (especially if mild to moderate esophagitis is to be treated) or 60 mg per day. This study does not support the sponsor's proposal of the use of LANSO 30 mg per day for 8 weeks or effectiveness of LANSO (any dose) for "all grades" of esophagitis because effectiveness of the compound in severe esophagitis was not adequately tested. Moreover, the symptoms these patients were experiencing were mild to moderate in severity.

Study M88-269 showed that LANSO 30 mg per day given before breakfast for 8 weeks was effective in healing esophageal lesions that were mostly of the mild to moderate degree. This dose of LANSO was also effective in symptomatic relief of GERD in these patients with mild to moderate esophagitis. This study does support the sponsor's proposal of the use of LANSO 30 mg per day for 8 weeks, although not for "all grades" because - just as in Study M87-092 - patients with severe esophagitis were poorly represented. The sponsor did not present efficacy analysis in patients with Grade 4 (Severe) esophagitis (only). It is to be noted that Study M88-269 did not include a LANSO 15 mg once-a-day group, the dose shown effective and well tolerated in trial M87-092.

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VIII. Clinical Efficacy: Short-Term Treatment of Poorly Responsive ("resistant"), Severe RE

A. Indication sought (as stated in the proposed labeling)

"PREVACID Delayed-Release Capsules are indicated for short-term treatment (up to 8 weeks) for healing and symptom relief of all grades of reflux esophagitis, including severe esophagitis in patients who were poorly responsive to a course of histamine H₂-receptor antagonists in a dose equivalent to ranitidine 150 mg b.i.d. or greater and in patients...."

B. Clinical Trials in Support of This Indication

In support of the efficacy and safety of PREVACID® for the indication "short-term Tx for healing and symptom relief of severe esophagitis in patients who were poorly responsive ("resistant") to H₂-receptor antagonists" the sponsor submitted results from two critical trials, M89-349 and M89-393. The main features of these trials and an initial assessment of the utility of the experimental design used in these essential studies are given in Table 17a.

C. Study M89-349 (Report RED/91/133)

"The Use of Lansoprazole (Abbott-65006) in the Acute Treatment of Erosive Reflux Esophagitis Resistant to Histamine H₂-Receptor Antagonist Therapy".

Study dates: December 1989 to December 1990.

1. Objective (based on page 2 of the Protocol)

This Phase II study was set to assess the safety and efficacy of a LANSO regimen consisting of LANSO 30 mg qd for four weeks with an option of increasing the LANSO dosage to 60 mg qd for four more weeks in those cases where LANSO 30 mg qd Tx did not result in endoscopically-documented healing and in symptom relief. The efficacy of the LANSO 30 mg/60 mg was compared to that of Tx with RAN 150 mg b.i.d. in patients with erosive reflux esophagitis which had "proven resistant" to a minimum of twelve (12) weeks therapy with one or more histamine H₂-receptor antagonists.

A secondary objective of this trial was to compare LANSO 30 mg qd with 60 mg qd among patients who were not healed and/or not symptom-free after 4 weeks of Tx with LANSO 30 mg qd.

The reader is referred to Fig. 3. Randomization was done at Week 0 (pts. meeting all entrance criteria). After 4 weeks of Tx the pts. were not re-randomized after failing 30 mg LANSO. Instead LANSO or PL was administered following the original randomization schedule.

TABLE 17a
NDA 20-406

Main Experimental Features and Initial Assessment of the Adequacy of Clinical Trials Submitted in Support of the Indication "Severe Esophagitis in Patients Who Were Poorly Responsive to a Course of Histamine H₂-receptor Antagonists"

Report No. No. of Pts.	Main Design Features	Study Population	Groups Being Compared	Remarks
I. N89-349 (U.S.) Multicenter (x 9) 159 pts.	Randomized, D-B, active-controlled, 2-arm	133M, 66F with erosive RE "resistant" to one or more histamine H ₂ -receptor antagonists, for a minimum of 12 weeks of therapy	LANSO 30 mg QD vs RAN 150 mg BID (Both x 4 weeks) For unhealed and/or symptomatic pts. at 4 weeks the dose of LANSO was increased to 60 mg QD x 4 weeks. This would allow comparison of LANSO 30 mg QD vs LANSO 60 mg QD	(applicable to both Studies) • During the review of the evidence, the following will be assessed: - "severe esophagitis" means that the study population should consist primarily of patients with Grade 4 esophagitis on endoscopy. This is important because the two pivotal trials already reviewed enrolled primarily patients with mild or at the most moderate esophagitis. A demonstration of efficacy in pts. with severe lesions would support the sponsor's request for all grades of esophagitis. • Both protocols characterize the RE as "resistant". This implies the use of optimal (not customary) doses of H ₂ for about 12 weeks under well documented conditions of compliance. • Comparison to customary doses of RAN (150 mg BID) is inappropriate because: a) This is not an approved dose regimen for erosive [especially "resistant"] esophagitis. b) This RAN dose regimen is not expected to give comparable degrees of acid suppression to those seen with LANSO 30 mg. c) The current recommended dose of RAN for erosive esophagitis is 150 mg QID. • In view of the above, comparison to inadequate doses of RAN in this study population would not allow a superiority claim of LANSO 30 mg to RAN. • The studies did not explore other LANSO regimens (i.e. 15 mg QD, 15 mg b.i.d., LANSO 30 mg b.i.d., etc.).
II. N89-393 (U.S.) Multicenter (x 12) 103 pts.	Randomized, D-B, active-controlled, 2-arm	82M, 21F with erosive RE "resistant" to one or more histamine H ₂ -receptor antagonists, for a minimum of 12 week therapy	LANSO 30 mg QD vs RAN 150 mg BID (Both x 4 weeks) For unhealed and/or symptomatic pts. at 4 weeks, the dose of LANSO was increased to 60 mg QD x 4 weeks. This would allow comparison of LANSO 30 mg QD vs LANSO 60 mg QD	

2. Materials/Labeling/Randomization

All of these were adequate and as described for the two previously reviewed RE trials. Patients received 8 weeks of Tx. The results of the Week 4 endoscopy, in conjunction with the Week 4 symptom assessment, were used to determine the Tx regimen for the subsequent 4 weeks. At Week 4, LANSO and RAN patients who were endoscopically healed and free of symptoms associated with erosive reflux esophagitis continued on the Tx with 30 mg QD and 150 mg BID, respectively. Those who were endoscopically unhealed and/or symptomatic at the time of the Week 4 visit received an additional bottle of medication at Weeks 4 and 6. This bottle contained LANSO 30 mg or matching PL based upon the original randomization schedule. The additional bottles given to patients assigned to receive LANSO 30 mg or RAN throughout the study contained PL; those given to patients assigned to receive LANSO 60 mg during the final four weeks contained LANSO 30 mg.

Throughout this report, the LANSO pts. who were given an extra bottle of medication at Week 4 are referred to as LANSO 30/30 mg if the extra bottle contained PL and LANSO 30/60 if the extra bottle contained LANSO 30 mg.

LANSO patients not receiving an extra bottle of medication at Week 4 are referred to as LANSO 30 mg.

All pts. receiving LANSO (LANSO 30 mg, LANSO 30/30 mg and LANSO 30/60 mg) are referred to as the LANSO group.

3. Study Design

This was a randomized, D-B, active-controlled, 2-arm, multicenter study comparing the effectiveness of LANSO when administered orally as a single daily dose before breakfast with that of RAN in patients with erosive reflux esophagitis supposedly resistant to histamine H₂-receptor antagonist therapy.

The study used a parallel-group design with a 2:1 allocation to the two Tx groups and consisted of a screening period of up to 7 days and a Tx period of 8 weeks.

4. Study Population

The inclusion-exclusion criteria were similar to those for the two pivotal RE protocols already reviewed. Salient differences were as follows.

The present study was to enroll M or F patients at least 18y of age with "resistant" erosive reflux esophagitis of at least Grade 2 (Translation: mild RE, see scale below) without coexisting DU or GU. To be eligible the patients had to have been treated unsuccessfully with at least one histamine H₂-receptor antagonist given at the standard dose or greater:

- CIM 800 mg/day
 - RAN 300 mg/day
 - FAM 40 mg/day or
 - NIZ 300 mg/day
- NOTE:** These regimens are not standard for healing erosive esophagitis. The truly resistant patient may need even higher than the standard doses recommended for the healing of erosive esophagitis.

for a total of at least 12 weeks without healing. The patient must have been compliant during the previous histamine H₂-receptor therapy based upon the physician's opinion and supporting documentation.

NOTE: The sponsor did not submit documentation of compliance of medications taken before enrollment into the trial. This information is needed to document that the patients had followed directions, taken the medication and not responded to it.

- Neither Gilbert's disease nor Barrett's esophagus was reason for exclusion.
- This trial used the following endoscopy grading scale.

Grade	Description at Endoscopy ^a
0	Normal-appearing mucosa by endoscopy
1	Mucosal edema, hyperemia, and/or friability of mucosa
2 (MILD) ^b	One or more erosions/ulcerations involving <10% of the distal 5 cm of the esophagus proximal to the squamocolumnar junction
3 (MODERATE) ^c	Erosions/ulcerations involving 10 to 50% of the distal 5 cm of the esophagus proximal to the squamocolumnar junction or an ulcer measuring 3 to 5 mm in diameter
4 (SEVERE) ^d	Multiple erosions/ulcerations involving >50% of the distal 5 cm of the esophagus or a single large ulcer >5 mm in diameter

a) This scale was developed by TAP Pharmaceuticals Inc. and its Committee of Consultant Gastroenterologists.
b,c,d) Grading according to severity of lesions.

- The definition of distal 5 cm of the esophagus for patients with Barrett's esophagus resulted in the modification of Grades 2, 3 and 4 for these patients, as shown below.

MODIFICATIONS IN ESOPHAGITIS GRADING SCALE FOR PTS. WITH BARRETT'S ESOPHAGUS	
Grade	Description
2	One or more erosions/ulcerations involving <10% of the distal 5 cm of the esophagus proximal to the anatomical gastroesophageal junction
3	Erosions/ulcerations involving 10 to 50% of the distal 5 cm of the esophagus proximal to the anatomical gastroesophageal junction or an ulcer measuring 3 to 5 mm in diameter
4	Multiple erosions/ulcerations involving >50% of the distal 5 cm of the esophagus proximal to the anatomical gastroesophageal junction or a single larger ulcer >5 mm in diameter

5. Study Execution

a) Screening Period

The screening procedures, which were to be performed within 7 days prior to receiving test medication, were as described for the two pivotal RE studies.

b) Tx Period

- LANSO was supplied in capsules containing 30 mg of enteric-coated granules.

- RAN was supplied in capsules containing 150 mg of RAN as RAN•HCl.
- Gelusil® tablets were supplied as described for the two pivotal RE trials.
- Each patient was given 3 bottles of LANSO, RAN and/or PL capsules at screening and at Weeks 2, 4 and 6 of the Tx period.
- Each bottle was labeled AM or PM and contained 19 capsules (five extra capsules per bottle).
- Bottles 1A, 1B and 1C were dispensed at screening; bottles 2A, 2B and 2C at the Week 2 visit, etc.
- Each morning before breakfast during the 8-week Tx period, the patient took one capsule orally from each of the A and B bottles. At bedtime, the patient took one capsule orally from the C bottle.
- The bottles contained active drug or PL in combinations that provided the assigned drug and dose level, as summarized below.

Bottle	LANSO (mg)		RAN 150 mg BID
	30/30 mg QD	30/60 mg QD	
#1A-4A	LANSO 30 mg capsule	LANSO 30 mg capsule	LANSO PL
#1B-4B	RAN PL	RAN PL	RAN 150 mg capsule
#1C-4C	RAN PL	RAN PL	RAN 150 mg capsule
#3D-4D ^{a)}	LANSO PL	LANSO 30 mg capsule	LANSO PL

a) Given to patients who were endoscopically unhealed and/or symptomatic at Week 4.

- All patients who were endoscopically unhealed and/or symptomatic at Week 4 received an additional bottle of medication at Weeks 4 and 6 (Bottles 3D and 4D, respectively). This bottle contained 19 capsules of LANSO 30 mg or matching PL (see Table above), based upon the original randomization schedule ["in order to maintain the D-B nature of the trial"].
- Pts. took one capsule from Bottle D in the morning before breakfast in addition to capsules from Bottles A, B and C.
- One replacement bottle for each of the A, B, C and D drug bottles (RA, RB, RC and RD) for each patient was supplied to each investigator to be dispensed only as needed.
- In addition, at the screening and the Weeks 2, 4 and 6 visits, each patient was given one box of Gelusil (containing 50 tablets) to be taken for relief of discomfort as needed.
- Fig. 3 given a schematic representation of the study design, with emphasis on endoscopic assessments.

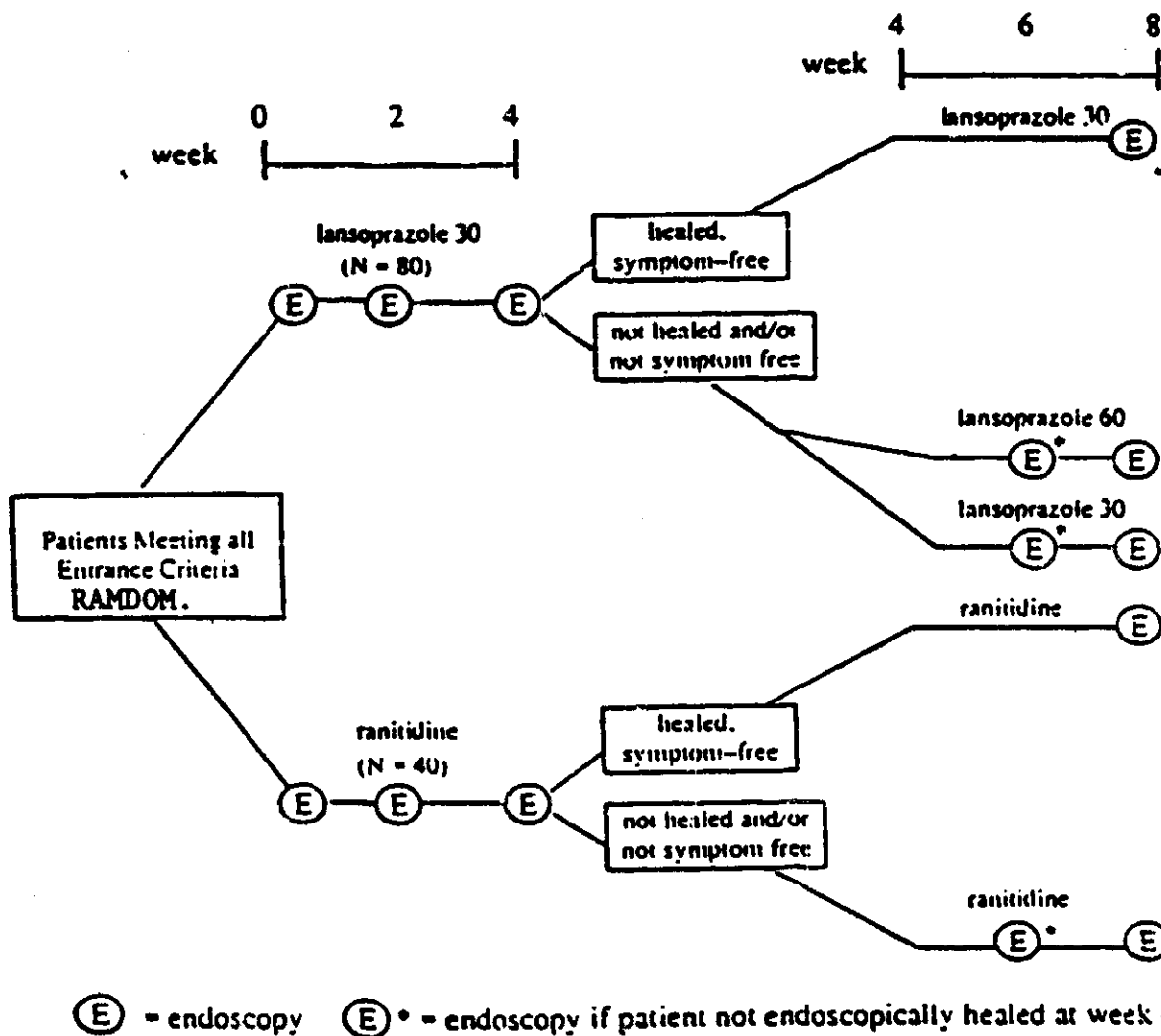


Fig. 3. - Protocol M89-349: Study Design

LANSO 30 = LANSO 30 mg QD

LANSO 60 = LANSO 60 mg QD

RAN = RAN 150 mg BID

RANDOM = Point at which randomization was done

- Complete healing of the "resistant erosive reflux esophagitis" was defined as a return of esophageal mucosa to Grade 0 or 1.
- Symptom(s) assessment and Gelusil use were as described for the pivotal short-term RE studies.

6. Statistical Methodology

a) Planned Sample Size

The study was designed to enroll sufficient patients such that 120 patients would complete the study and have evaluable efficacy data (80 in the LANSO group and 40 in the RAN group). According to the Protocol, this sample size provided a greater than 97% chance to detect significant differences between the LANSO and RAN groups if true healing rates were 85% and 50% ($p < 0.05$, two-tailed test), respectively. A 35% therapeutic gain was anticipated.

b) Efficacy Analyses

- Analysis of intent-to-treat patients: Weeks 2, 4, 6 and 8 endoscopy results were defined as the result closest to the end of Tx obtained on or prior to Study Day 21, Study Day 35, Study Day 49 and Study Day 70, respectively (last value brought forward method). No patients were excluded from this analysis. Patients without an endoscopy within 10 weeks after the start of Tx were included as failing to heal.
- Analysis of evaluable patients: Weeks 2, 4, 6 and 8 endoscopy results were defined as the result closest to the end of Tx obtained during the interval from seven to 21 days, 22 to 35 days, 36 to 49 days, and 50 to 70 days after the start of Tx, respectively, using data considered acceptable for the efficacy evaluation. A patient with no endoscopy in a given time interval was considered healed if healing was documented during the most recent time interval during which an endoscopy was performed. Otherwise, a patient with no endoscopy in a given time interval was not included in the analysis for that time interval.
- For both populations, the proportion healed on LANSO at each time point was compared to the proportion healed on RAN using Mantel-Haenszel methods for combining (2 x 2) tables across investigators, as stated in the protocol.
- Homogeneity of Tx difference across investigators (Tx-by-investigator interaction) was examined using the Breslow-Day test.¹⁰
- Analyses of the proportion healed at each time point were performed to compare LANSO 30/30 mg QD to LANSO 30/60 mg QD in patients who were unhealed and/or symptomatic after four weeks of Tx with LANSO 30 mg QD using Fisher's Exact test. This was done separately for patients healed at Week 4 and those unhealed at Week 4. For the ITT analysis, endoscopy results after 2 and 4 weeks of extra medication were defined as the result closest to the end of Tx obtained on or prior to 21 days and 35 days after the start of extra medication, respectively. For analysis of evaluable patients, endoscopy results after 2 and 4 weeks of extra medication were defined as the result closest to the end of Tx obtained during the interval from seven to 21 days and 22 to 35 days after the start of extra medication, respectively.
- The results of severity of symptoms were analyzed with Cochran-Mantel-Haenszel methodology for ordered response categories using the screening value as the "covariate" to compare the LANSO and RAN groups. Both ITT and Evaluable population analyses were carried out¹⁰.

¹⁰Symptom assessments obtained >5 days after the last day of Tx were not used in the Tx period analyses.

7. Study Results

a) Participating Investigators

In this trial, 9 qualified investigators, geographically located in the United States, enrolled a total of 159 patients (113 M; 46 F).

b) Number of Patients in the ITT vs Evaluable Population Analyses

- All 159 patients enrolled were included in the ITT Population analyses.
- 151 (LANSO=100; RAN=51) of the 159 patients who entered the Tx period were included in at least one of the primary efficacy analyses.
- Reasons for exclusion of the 8 pts. (LANSO=5; RAN=3) who were deemed nonevaluable for the primary efficacy analyses are summarized below.

No. of Pts. (Total N=8)	Reason for Exclusion:
4	Admission criteria satisfied but received <14 days of test med.
2	Admission criteria violation: chronic prestudy use of NSAIDs.
2	No data after start of Tx.

c) Data Showing Comparability of Groups

i) Premature Terminations

- 13 pts. (LANSO=6; RAN=7) W/D prematurely during the Tx period. Of these, 3 pts. in each group W/D primarily due to AEs.

ii) Demographic and Disease Baseline Characteristics (Table 17b)

- This Table summarizes the demographic and disease BL characteristics of the 159 ITT patients who entered the D-B Tx period.
- There were no significant difference between the Tx groups, combined across investigators for age, height, female body weight, sex distribution, race, tobacco use, alcohol use or caffeine use. M in the LANSO group were, on the average, 12 lbs. heavier than M in the RAN and this difference was nearly statistically significant (p=0.054). I agree with the sponsor that this difference is not expected to affect efficacy outcome.

TABLE 17b
Study M89-349

**Summary of Demographic and Disease Baseline Characteristics
(All Patients)**

Variable		All Pts. (N=159)	LANSO (N=105)	RAM (N=54)	Overall p-value
Age	Mean (SD) (y) Min-Max	52.1 (13.6) 22-79	52.6 (13.5) 23-79	51.1 (14.0) 22-75	N.S. ^b
Weight-F	No. of Pts. Mean (S.D.) (lbs)	46 169.1 (32.2)	28 170.5 (33.2)	18 166.9 (31.3)	N.S. ^b
Weight-M	No. of Pts. Mean (S.D.) (lbs)	113 191.7 (30.3)	77 195.5 (30.0)	36 183.7 (30.0)	N.S. ^b
Height-F	No. of Pts. Mean (S.D.) (inch)	46 63.8 (2.4)	28 64.2 (2.5)	18 63.2 (2.3)	N.S. ^b
Height-M	No. of Pts. Mean (S.D.) (inch)	112 69.8 (2.8)	76 69.9 (2.9)	36 69.8 (2.7)	N.S. ^b
Sex	F M	46 113	28 77	18 36	N.S. ^d
Race	Black Caucasian Hispanic	5 151 3	3 99 3	2 52 0	N.S. ^d
Tobacco Use	Tobacco Nonuser ^a Tobacco User	109 50	75 30	34 20	N.S. ^d
Alcohol Use	Drinker Nondrinker	60 99	38 67	22 32	N.S. ^d
Caffeine Use	No Yes	35 124	23 82	12 42	N.S. ^d
Esophagitis Grade	Grade 2 3 4	83 42 34	50 32 23	33 10 11	N.S. ^d
SUMMARY OF PRIMARY SYMPTOMS AT BL					
Burning Upper Abdomen	NONE (0) MILD (1) MOD (2) SEV (3)		34 14 32 25	19 12 15 8	N.S. ^f
Row Mean Score			1.46	1.22	
Day Heartburn	NONE (0) MILD (1) MOD (2) SEV (3)		11 33 39 22	8 17 18 11	N.S. ^f
Row Mean Score			1.69	1.59	
Night Heartburn	NONE (0) MILD (1) MOD (2) SEV (3)		19 20 34 32	17 10 15 12	N.S. ^f
Row Mean Score			1.75	1.41	

Painful Swallowing	NONE (0) MILD (1) MOD (2) SEV (3)		77 14 13 1	43 4 6 1	N.S. ¹
Row Mean Score			0.41	0.35	
Regurgitation (Gastrointestinal)	NONE (0) MILD (1) MOD (2) SEV (3)		31 27 36 11	12 21 15 6	N.S. ¹
Row Mean Score			1.26	1.28	
Belching	NONE (0) MILD (1) MOD (2) SEV (3)		42 33 24 6	23 14 12 5	N.S. ¹
Row Mean Score			0.94	0.98	
PERCENTAGES OF PATIENTS REPORTING GASTROINTESTINAL Ix					
History Of:					
Previous G.I. Surgery			3.8%	1.9%	
DU			21.0%	20.4%	
GU			9.5%	9.3%	
Barrett's Esophagus ^a			18.1%	14.8%	
Hiatal Hernia ^a			81.9%	85.2%	

- a) At start of double-blind period.
b) p-value from F-test for testing equality of Tx means.
c) One patient (Sontag) did not have height measured.
d) p-value from Chi-Square test.
e) Includes ex-tobacco users.
f) Based on Cochran-Mantel-Haenszel methods.
g,h) Noted during endoscopy at any time during the trial.

- It is important to note that in this trial, most of the patients had mild or moderate (Grade 2 or 3) rather than severe (Grade 4) esophagitis:

Study M89-349

Number/(Proportion) of Pts. With Given Grade of Esophagitis at Entry

Grade (Severity)	LANSO (N=105)	RAM (N=54)
2 (MILD)	50/105 (47.6%)	33/54 (61.1%)
3 (MOD)	32/105 (30.5%)	10/54 (18.5%)
4 (SEV)	23/105 (21.9%)	11/54 (20.3%)

- There were no significant differences between Tx groups, combined across investigators, in the esophagitis grade at entry. But, according to the above displayed data, the Study Population of interest, that is, those patients with severe esophagitis, was poorly represented because only ca. 1/5 of the enrolled patients had Grade 4 lesions.

NOTE: These aren't really erosive esophagitis patients unresponsive to adequate doses of H₂-receptor antagonists.

- Likewise, most patients had either no or only mild to moderate rather than severe symptoms.
- There were no significant differences between Tx groups in the proportion of patients reporting G.I. history. Most of the patients (LANSO=82%; RAN=85%) had hiatal hernia.
- 18.1% of the patients in the LANSO group and 14.8% of those in the RAN group had Barrett's esophagus.

d) Primary Efficacy Parameters (Table 17c)

i) LANSO vs RAN

- For both the ITT and the Evaluable Population and at each time period analyzed (Weeks 2, 4, 6 and 8) the healing rates with LANSO were superior to those seen with RAN.
- At all time periods analyzed, the therapeutic gains were clinically meaningful. These varied between 33% to 50% for the ITT Population and 26% to 52% for the Evaluable Population.
- The response to LANSO was as expected. Given the same dose, increased healing rates occurred with additional length of Tx. There was, however, a considerable decrease in efficacy from Week 6 to Week 8 for patients in the RAN group. There is no plausible explanation for this drop in efficacy (-16.7% for the ITT population and -23.6% for the Evaluable Population). This may not represent a real finding.
- The sponsor did not analyze the response in those patients with severe (Grade 4) erosive esophagitis (only) but not much is expected of these ad hoc evaluations because of the small number of patients involved (23 in the LANSO groups vs 11 in the RAN group).
- In both the ITT and Evaluable analyses, significant lack of homogeneity across investigators (Tx-by-investigator interaction) was not indicated for the comparison of the LANSO and RAN groups at any evaluation time.

TABLE 17c
Study N89-349

Healing Rates^a as a Function of Time and Study Population
#Healed/Total N/(%)

Week	ITT Population		Evaluable Population	
	LANSO	RAN	LANSO	RAN
2	62/105 (59.0)	14/54 (25.9)	60/96 (62.5)	14/51 (27.4)
Therapeutic Gain	33.1 (p<0.001)		35.1 (p<0.001)	
4	73/105 (69.5)	20/54 (37.0)	71/95 (74.7)	20/47 (42.6)
Therapeutic Gain	32.5 (p<0.001)		32.1 (p<0.001)	
6	82/105 (78.1)	25/54 (46.3)	80/98 (81.6)	25/45 (55.6)
Therapeutic Gain	31.8 (p<0.001)		26.0 (p<0.001)	
8	84/105 (80.0)	16/54 (29.6)	82/98 (83.7)	16/50 (32.0)
Therapeutic Gain	50.4 (p<0.001)		51.7 (p<0.001)	

a) In this table, numerators reflect the cumulative number of ITT or evaluable patients healed. Denominators reflect the total number of patients in either the ITT or Evaluable Population at each of the four time periods.

ii) Healing Rates Adjusted for Concomitant Factors

- In both the ITT and Evaluable¹⁷ Populations and at all time points (Weeks 2, 4, 6 and 8), LANSO remained superior to RAN when healing rates were adjusted for concomitant factors. These factors included sex, age, BL esophagitis grade, whether hiatal hernia was present, alcohol use, tobacco use, caffeine use, presence of Barrett's esophagus, previous H₂-receptor antagonist use, whether previous H₂-receptor antagonist used was at standard or high dose and duration of previous H₂-receptor antagonist therapy.

iii) Healing in Patients With Barrett's Epithelium

- 27 pts. (LANSO=19; RAN=8) had endoscopically documented Barrett's epithelium involving 0.5 to 17 cm of the distal esophagus. The number of Barrett's patients healed were: LANSO=15 of 19; RAN=4 of 8. The number of observations were too small to draw meaningful conclusions. In addition, Barrett's is not part of claim.

¹⁷ There was one exception. In the evaluable analyses, a significant interaction of BL hiatal hernia with Tx was noted at Week 2 in the comparison of the LANSO and RAN groups (sponsor's Table 8.1.7). This interaction resulted from much higher healing rates among RAN patients without hiatal hernia (71.4%) than those with hiatal hernia (20.5%) compared to little no difference in healing rates among LANSO patients with and without hiatal hernia (61.8% and 65.0%, respectively) (sponsor's Table 8.1.5).

iv) Patients Healed at Week 2, 4 and/or 6 But Unhealed at Week 8 (Table 17d)

- The 16 patients (LANSO=5; RAN=11) under this category are listed in this Table.
- All 11 RAN pts. listed in this Table were considered as healed in the Week 6 analysis but unhealed in the Week 8 analysis.

According to the sponsor, the large percentage of such pts. in the RAN group accounts for most of the difference between Week 6 and Week 8 healing rates in that group in both the ITT (16.7%) and Evaluable Population (23.6%) analyses. The sponsor also stated that in most cases, the endoscopist who performed the endoscopies which showed healed esophagitis at Week 2, 4 and/or 6 did not perform the Week 8 endoscopy showing unhealed erosive esophagitis.

v) LANSO 30/30 mg vs LANSO 30/60 mg

NOTE: These results are not displayed because there were too few patients in these groups.

- Nonetheless, there were no significant differences in healing rates between the LANSO 30/30 and 30/60 mg groups (analyses of LANSO pts. receiving extra medication after Week 4).
- These comparisons are not very meaningful because there were too few patients in these subgroups.

e) Secondary Efficacy Parameters

i) LANSO vs RAN

NOTE: Statistically significant differences in the Evaluable Population analyses are indicated below by an asterisk (*).

- At Weeks 2, 4 and 6, the LANSO group had significantly greater relief of
 - burning in the upper abdomen*
 - day heartburn*
 - night heartburn*
- Additionally, when compared to the RAN group, greater relief of painful swallowing was also seen in the LANSO group at Weeks 4 and 6 and in relief of belching at Week 4.
- At Week 8, the LANSO group had significantly greater relief of
 - burning in the upper abdomen*
 - day heartburn*
 - night heartburn*

than the RAN group. No additional significant differences in the relief of symptoms were detected between LANSO and RAN.

TABLE 7d
Study NS-349

Patients Who Were Healed at Week 2, 4 and/or 6, But Unhealed at Week 8

Pt. No. (Inv.)	Endo Grade					Smoking (ppd)	Alcohol Consumption (per day)	Hiatal Hernia
	scr	W2	W4	W6	W8			
LANSO 30 (N=2)								
(Lehman)	2	0	0	NA ^a	2	1-2	<1 beer <1 liquor	YES
(Sontag)	3	NA ^a	3	0	2	<1	Ex (>3 beer) (>2 liquor)	YES
LANSO 30/30 (N=1)								
(Campbell)	3	2	1	2	3	1-2	Ex (>2 liquor)	NO
LANSO 30/60 (N=2)								
(Sabesin)	4	1	2	2	2	1-2	NON	YES
(Sabesin)	2	2	1	0	2	1-2	NON	YES
RAM (N=11)								
(Campbell)	2	0	0	0	2	Ex (1-2)	NON	YES
(Campbell)	4	2	0	NA ^a	2	Ex (>2 & Pipe 2-3/day)	NON	YES
(Fleischmann)	2	1	2	1	2	Ex (<1)	1-3 wine 1-2 liquor	YES
(Fleischmann)	2	1	1	1	2	Ex (1-2)	NON	YES
(Fleischmann)	2	2	1	0	2	NON	<1 beer	YES
(Kogut)	2	2	2	1	2	1-2	<1 liquor	NO
(Kogut)	2	1	1	NA ^a	2	1-2	NON	NO
(Kogut)	3	3	3	1	3	NON	NON	YES
(Lehman)	2	0	1	NA ^a	2	<1 & Pipe <2/day	Ex (>3 beer)	YES
(Lehman)	2	2	0	NA ^a	2	1-2	<1 beer <1 wine <1 liquor	YES
(Robinson)	2	2	2	0	2	1-2	NON	YES

a) NA: Healed at Week 6; therefore, week 6 endoscopy omitted.
b) Patient prematurely D/C from the study

ii) LANSO 30/30 vs LANSO 30/60 mg

- There were no significant differences between these two LANSO groups in symptom relief after 2 Weeks of the extra-medication period.
- Among the LANSO pts. who received extra-medication at Week 4, patients in the 30/60 mg group had statistically significantly greater relief of
 - day heartburn*
 - night heartburn

f) Diary Results

- Pts. in the LANSO group reported significantly fewer days of Gelusil use and fewer tablets used per day, and significantly less day and night heartburn than the RAN group.
- The LANSO 30/60 mg group had significantly greater improvement in day heartburn severity than the LANSO 30/30 mg group.

g) Results of Safety Evaluations

- In this trial, LANSO patients had similar AE reporting rates as compared to RAN patients. The most frequently reported AEs for the LANSO group were headache, diarrhea, asthenia, and dry mouth. Those in the RAN group were headache and dizziness.
- With the exception of the expected difference in serum gastrin concentrations, there were no clinically significant differences in laboratory parameters between the LANSO and RAN groups.

8. Conclusion (Sponsor)

"Lansoprazole, administered once daily before breakfast, healed erosive reflux esophagitis significantly better than ranitidine 150 mg BID in patients with endoscopically proven reflux esophagitis resistant to histamine H₂-receptor antagonist therapy. Lansoprazole was superior to ranitidine in producing relief of burning in the upper abdomen and day heartburn at Week 8. The lansoprazole group reported significantly fewer days of Gelusil use and fewer tablets used per day, and significantly less day and night heartburn, than the ranitidine group. Based on a quality-of-life questionnaire, lansoprazole patients reported greater improvement in their sleep, with less daytime drowsiness, than ranitidine patients. Both the lansoprazole and ranitidine groups had similar adverse event reporting rates, with no severe adverse events reported as possibly or probably related to study drug.

"Patients unhealed or symptomatic at Week 4 were given an extra bottle of medication for the final four weeks of treatment (extra-medication period). This resulted in either continued treatment with ranitidine 150 mg BID or lansoprazole 30 mg QD (lansoprazole 30/30 mg patients) or an increase to lansoprazole 60 mg QD (lansoprazole 30/60 mg patients). This study was designed to be combined with Study M89-393 for the comparison of the lansoprazole 30/30 mg and lansoprazole 30/60 mg groups (combined analysis will be in the Study M89-393 report). Despite the low power resulting from small sample size, patients in the lansoprazole 30/60 mg group had statistically significantly greater relief of day heartburn during the extra-medication period when compared to the lansoprazole 30/30 mg patients.

"Lansoprazole 30 and 60 mg were safe for use in patients with resistant erosive reflux esophagitis for a period of eight weeks."

9. Comments

Study M89-349 was one of two critical clinical trials submitted by the sponsor in support of the use of LANSO in "severe erosive esophagitis in patients who were poorly responsive to a course of histamine H₂-receptor antagonists". The main objective of the trial was to compare the efficacy (and safety) of LANSO 30 mg administered once a day before breakfast and RAN 150 mg twice daily in the short-term Tx of patients with erosive reflux esophagitis.

Characterization of the esophagitis as "resistant" would imply that this condition was presently severe and had not responded to previous therapy (at least 12 weeks) with optimal doses of H₂. The sponsor has not presented evidence that these patients were resistant since

- a) no compliance data for the 12 weeks prior to enrollment into the present trial have been submitted.
- b) the dose of H₂ that these patients would have had taken per day were the customary doses (CIM=800 mg; RAN=300 mg; FAM=40 mg or NIZ=300 mg). Instead, and on the basis of literature publications for erosive disease, the optimal doses of RAN and CIM are 600 and 1600 mg per day, respectively [E.C. Klinkenberg-Knol et al. 94:A230 (1991)]. These doses of the H₂ are more effective when given in a fractional fashion. Throughout this review we have repeatedly stated that, for RAN, the recommended dose for the healing of erosive RE is 150 mg four times a day (600 mg in divided doses. The dose of CIM for erosive disease is 1600 mg per day).
- c) Another way of assessing or suspecting resistance is to demonstrate that the patients were experiencing complications in spite of the pharmacological approach. But no mention is made about events such as bleeding or stricture in these patients. Indeed, these conditions represented reasons for exclusion in the present trial (this was described in the review of the two studies for the indication of healing of RE).
- d) An additional way of assessing or suspecting resistance is to demonstrate that patients had undergone antireflux surgery. But, again, only a tiny percentage (2 to 4%) of the present study population had undergone previous g.i. surgery (not specified; see Table 17b).
- e) Resistance from the symptomatology viewpoint cannot be claimed. Most of the patients enrolled in this trial had mild to moderate rather than severe intractable symptoms.

One important conclusion is that both from the endoscopic and symptomatological viewpoint, the majority of patients enrolled in this trial were not very sick.

In view of a) through e) above and until convincing data are presented to demonstrate the contrary, this reviewer cannot categorize the study population in trial M89-349 as having resistant erosive reflux esophagitis.

The classification system for staging RE was adequate. The use of such scale was useful to demonstrate that what the patients in trial M89-349 did have was erosive reflux esophagitis. However, this was mostly of the mild to moderate type. Only ca. 1/5 of the enrolled patients had severe disease. Barrett's esophagus, present in 18.1% of the LANSO-treated patients and 14.8% of those treated with RAN, is not a condition expected to respond to such short-term treatment as 8 weeks.

This 2-arm trial was otherwise apparently well executed. It used a parallel design in which the patients were randomly assigned to double-blind treatment with either LANSO 30 mg once daily or RAN 150 mg twice daily. This apparently properly conducted (2:1) randomization process resulted in similar proportions of patients with regards to demographic and baseline disease characteristics.

In this study population, activity of LANSO 30 mg OD was demonstrated, irrespective of whether the assessment was done through ITT or Evaluable Patient analyses. At each time period analyzed (Weeks 2, 4, 6 and 8) the healing rates with LANSO 30 mg OD were clinically meaningful and statistically superior to those seen with RAN 150 mg BID. The therapeutic gains at Week 2 through 6 varied from 26% to 35% and these were comparable to those reported in trial M88-269.

The reported therapeutic gains by 8 weeks (>50%) are not easy to understand because these data suggest a considerable decrease in the efficacy of RAN from the 6th to the 8th week (-16.7% for the ITT and -23.6% for the Evaluable Populations, respectively). How is this possible? The sponsor explained these differences (substantial decrease in RAN efficacy by 8 weeks) by saying that in most cases, the endoscopist who performed the endoscopies which showed healing esophagitis at Week 2, 4 and/or 6 did not perform the Week 8 endoscopy showing unhealing erosive esophagitis. But this explanation actually a) invites questions about the standardization of endoscopic procedures across investigators and b) does not seem tenable because in at least 4 cases no endoscopy was done at Week 6 (Table 17d). If the decrease in RAN efficacy was indeed a problem of standardization of procedures then this was so bad that it resulted in so many RAN-treated but very few LANSO-treated patients as being misdiagnosed as healed, precisely between Weeks 6 and 8!

On the other hand, the superiority of LANSO remained so when healing rates were adjusted for gender, age, esophagitis grade at BL, whether hiatal hernia was present, alcohol use, tobacco use, caffeine use, presence of Barrett's esophagus, previous H₂-receptor antagonist use, whether previous H₂-receptor antagonist used was at standard or higher dose and duration of previous H₂-receptor antagonist therapy.

In this trial, LANSO 30 mg OD was also shown to be effective in relieving symptoms. For example at each of the four points of evaluation (Weeks 2, 4, 6 and 8) and in both ITT and Evaluable Population analyses, the LANSO group had significantly greater relief of day and night heartburn and burning in the upper abdomen than the RAN group.

For both healing or symptom relief, the number of patients in the LANSO 30/60 vs 30/30 was too small to allow sound conclusions. This reviewer does not conclude that 30/60 is better than 30/30.

In this trial, LANSO 30 mg OD was shown to be well tolerated, with AE reporting rates similar to those observed with RAN. Headache, diarrhea, asthenia and dry mouth were the most frequently reported AEs for patients in the LANSO group. For those in the RAN-treated group these were headache and dizziness. Aside from the expected differences in serum gastrin concentrations, there were no clinically significant differences in laboratory parameters in either Tx group.

D. Study M89-393 (R&D/91/529)

"The Use of Lansoprazole (Abbott-65006) in the Acute Treatment of Erosive Reflux Esophagitis Resistant to Histamine H₂-receptor antagonist therapy"

Study Dates: April 1990 to August 1991.

1. through 6.

This study was of nearly identical design to M89-349. Minor differences were a) less total number of patients in the present trial (LANSO=60 pts; RAN=30) for a total of 90 instead of the 120 (LANSO=80; RAN=40) in study M89-349. The sample size in study M89-393 had a 92% probability (as opposed to 97% in the other trial) of detecting significant differences between the two Tx groups if the healing rate in the LANSO group was 85% and the healing rate in the RAN group was 50% (<0.05, two-sided). A therapeutic gain of 35% was anticipated.

This study's execution was also as per trial M89-349. The selection of pts., all procedures including endoscopy and all other aspects and parameters of evaluation used in M89-393 were identical to those used in M89-349.

7. Study Results

a) Participating Investigators

In this trial, 12 qualified investigators, geographically located in the United States, enrolled a total of 103 patients (M=82; F=21).

b) Number of Patients in the ITT vs Evaluable Population Analyses

- All 103 patients enrolled were included in the ITT Population analyses.
- 95 (LANSO=62; RAN=33) of the 103 patients who entered the Tx period were included in at least one of the primary efficacy analyses.
- Reasons for exclusion of the 8 pts (LANSO=7; RAN=1) who were deemed nonevaluable for the primary efficacy analyses are summarized below.

No. of Pts. Total (N=8)	Reasons for Exclusion:
2	Admission criteria satisfied but received <14 days of test med.
2	Use of other anti-ulcer medication during Tx period.
2	Dosing instructions were not followed.
1	Prestudy histamine H ₂ -receptor antagonist therapy was less than the required duration
1	No endoscopic data after start of Tx.

c) Data Showing Comparability of Groups

i) Premature Terminations

- 7 pts. (LANSO=5; RAN=2) W/D prematurely during the Tx period. Of these, 3 pts. in the LANSO and 1 in the RAN group W/D primarily due to AEs.

ii) Demographic and Disease Baseline Characteristics (Table 17e)

- There were less women represented in each of the test groups, especially the RAN group. This difference was statistically significant (p=0.041).
- The groups were otherwise similar in demographic and disease baseline characteristics (Table 17e).
- Once again, it is important to note that, as in the other RE "resistant" trial, the bulk of the patients had mild and at the most, moderate esophagitis rather than severe (Grade 4) esophagitis (see below).

Study M89-393

Number/(Proportion) of Pts. With Given Grade of Esophagitis at Entry

Grade (Severity)	LANSO (N=69)	RAN (N=34)
2 (MILD)	44/69 (63.8%)	23/34 (67.6%)
3 (MOD)	17/69 (24.6%)	8/34 (23.5%)
4 (SEV)	8/69 (11.6%)	3/34 (8.8%)

- There were no significant differences between Tx groups - combined across investigators - in the esophagitis Grade at entry. However, according to the above-displayed data, the study population of interest, that is, those patients with severe esophagitis, was poorly represented since only ca. one-tenth of the enrolled patients had Grade 4 lesions. Nearly 2/3 of the patients in each group had MILD RE.
- Likewise in the symptomatology department. Most of the patients enrolled in this trial were experiencing either no or only mild to moderate symptoms rather than severe symptoms (of RE).
- The groups were also similar in the proportion of patients reporting GI history. Most of the patients (LANSO=80%; RAN=88%) had hiatal hernia.
- 27.5% of the patients in the LANSO group and 32.4% of those in the RAN group had Barrett's esophagus at entry.

d) Primary Efficacy Parameters (Table 17f)

i) LANSO vs RAN

- For both the ITT and Evaluable Population and at each time period analyzed (Weeks 2, 4, 6 and 8) the healing rates with LANSO were superior to those seen with RAN.

TABLE 17a
Study N09-393

Summary of Demographic and Disease Baseline Characteristics
For All Patients

Variable		All Pts. (N=103)	LANSO (N=69)	RAN (N=34)	Overall p-value
Age	Mean (S.D.) (y) Min-Max	56.0 (13.1) 19-82	55.8 (13/2) 19-82	56.3 (13.1) 31-76	N.S. ^b
Weight-F	No. of Pts. Mean (S.D.) (lbs)	21 173.1 (35.5)	18 177.4 (35.9)	3 147.2 (22.5)	N.S. ^b
Weight-M	No. of Pts. Mean (S.D.) (lbs)	80 186.4 (28.4)	49 185.8 (31.8)	31 187.4 (22.5)	N.S. ^b
Height-f	No. of Pts. Mean (S.D.) (inch)	21 63.3 (2.4)	18 63.0 (2.5)	3 65.0 (1.7)	N.S. ^b
Height-M	No. of Pts. Mean (S.D.) (inch)	81 69.3 (2.9)	50 69.3 (2.8)	31 69.3 (3.0)	N.S. ^b
Sex	F M	21 82	18 51	3 31	0.041 ^{ns}
Race	Black Caucasian Hispanic	5 92 6	5 59 5	0 33 1	N.S. ^d
Tobacco Use	Tobacco Nonuser ^a Tobacco User	75 28	48 21	27 7	N.S. ^d
Alcohol Use	Drinker Nondrinker	35 68	25 44	10 24	N.S. ^d
Caffeine Use	NO YES	12 91	7 62	5 29	N.S. ^d
Esophagitis Grade	Grade 2 3 4	67 25 11	44 17 8	23 8 3	N.S. ^d
SUMMARY OF PRIMARY SYMPTOMS AT BL					
Burning Upper Abdomen	NONE (0) MILD (1) MOD (2) SEV (3)		15 21 23 10	11 9 9 5	N.S. ^f
Row Mean Score			1.41	1.24	
Day Heartburn	NONE (0) MILD (1) MOD (2) SEV (3)		7 30 24 8	1 12 16 5	N.S. ^f
Row Mean Score			1.48	1.74	
Night Heartburn	NONE (0) MILD (1) MOD (2) SEV (3)		13 17 23 16	7 12 8 7	N.S. ^f
Row Mean Score			1.61	1.44	

Painful Swallowing	NONE (0) MILD (1) MOD (2) SEV (3)		62 4 1 2	26 4 4 0	N.S. ¹
Row Mean Score			0.17	0.35	
Regurgitation (Gastrointestinal)	NONE (0) MILD (1) MOD (2) SEV (3)		20 28 15 4	6 11 12 5	N.S. ¹
Row Mean Score			1.10	1.47	
Belching	NONE (0) MILD (1) MOD (2) SEV (3)		22 20 24 3	14 11 9 0	N.S. ¹
Row Mean Score			1.12	0.85	
PERCENTAGES OF PATIENTS REPORTING GASTROINTESTINAL IXX					
History Of:					
Previous GI Therapy (N=100)			97.1%	97.1%	N.S. ²
Previous GI Surgery (N=2)			2.9%	0.0%	N.S. ²
DU (N=18)			18.8%	14.7%	N.S. ²
GU (N=9)			10.1%	5.9%	N.S. ²
Miatal Hernia Present ^h (N=85)			79.7%	88.2%	N.S. ²
Barrett's Esophagus Present ⁱ (N=30)			27.5%	32.4%	N.S. ²

- a) At start of double-blind period.
- b) p-value from F-test for testing equality of Tx means.
- c) Statistically significant at p<0.05 level.
- d) p-value from Chi-square test.
- e) Includes ex-tobacco users.
- f) Based on Cochran-Mantel-Haenszel methods
- g) p-value from Fisher's Exact test.
- h,i) Noted during endoscopy at any time during the study.

TABLE 171
Study N89-393

Healing Rates as a Function on Time and Study Population
#Healed/Total N/(%)

Week	ITT Population		Evaluable Population	
	LANSO	RAN	LANSO	RAN
2	46/69 (66.7)	7/34 (20.6)	43/61 (70.5)	7/33 (21.2)
Therapeutic Gain	46.1 (p<0.001)		49.3 (p<0.001)	
4	52/69 (75.4)	11/34 (32.4)	47/59 (79.7)	11/33 (33.3)
Therapeutic Gain	43.0 (p<0.001)		46.4 (p<0.001)	
6	57/69 (82.6)	14/34 (41.2)	51/58 (87.9)	14/31 (45.2)
Therapeutic Gain	41.4 (p<0.001)		42.7 (p<0.001)	
8	59/69 (85.5)	12/34 (35.3)	54/61 (88.5)	12/32 (37.5)
Therapeutic Gain	50.2 (p<0.001)		51.0 (p<0.001)	

- At all time periods analyzed, the therapeutic gains were clinically meaningful. These varied between 41.4% and 50.2% for the ITT Population and 42.7% to 51.0% for the Efficacy Population.
- As in the other "resistant" trial, the response to LANSO was as expected. Given the same dose, increased healing rates occurred with additional length of Tx. There was, however, a decrease in efficacy from Week 6 to Week 8 for patients in the RAN group. Again there is no plausible explanation for this drop in efficacy (-5.9% for the ITT Population and -7.7% for the Evaluable Population). As per the other trial, this reviewer does not believe that this difference between LANSO and RAN is real [with one compound, efficacy increases as time elapses; with the other, efficacy decreases with the passage of time].
- The sponsor did not analyze response in those patients with severe (Grade 4) erosive esophagitis (only). Although this is mentioned here, I am not doing it or suggesting that it should be done because the number of patients with severe esophagitis (8 in one group, 3 in the other) was too small to allow meaningful conclusions.
- This trial showed significant lack of homogeneity across investigators (Tx-by-investigator interaction)¹⁸ for the comparison of the LANSO and

¹⁸This interaction was primarily due to one or two investigators (Cohen and/or Redinger) who had all of their RAN patients heal at these weeks, but at least one LANSO patient unhealed. This finding was in contrast to the other sites where the healing rate in the LANSO group was equal to or better than that in the RAN group. Despite these cases, the healing rates of the LANSO group remained statistically significantly greater than the healing rates of the RAN group, when combined across all investigators. No other significant lack of homogeneity was noted.

RAN groups at Week 4 for both ITT and Evaluable pts. at Week 4 and for ITT patients at Week 8.

ii) Healing Rates Adjusted for Concomitant Factors

- In both the ITT¹⁹ and Evaluable²⁰ Populations and at all time points (Weeks 2, 4, 6 and 8), LANSO remained superior to RAN when healing rates were adjusted for concomitant factors. These factors included sex, age, BL esophagitis grade, whether hiatal hernia was present, alcohol use, tobacco use, caffeine use, presence of Barrett's esophagus, previous H₂-receptor antagonist use, whether previous H₂-receptor antagonist used was at standard or high dose, and duration of previous H₂-receptor antagonist therapy.

*iii) Patients Healed at Week 2, 4 and/or 6,
But Unhealed at Week 8 (Table 17a)*

- The 5 pts. (LANSO=2; RAN=3) under this category are listed in this Table.
- There are no easy explanations (mostly speculations) for these findings. All of these patients were apparently compliant with taking test medication during the Tx period. Once again, the sponsor explains that the endoscopist who performed the endoscopies which showed healed esophagitis at Week 2, 4 and/or 6 did not perform the Week 8 endoscopy showing unhealed erosive esophagitis. [The reviewer Comments re the other "resistant" trial also apply here].

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- In the ITT analyses, a significant interaction of presence of Barrett's esophagus with Tx was noted at Weeks 4 and 6 in comparison of the LANSO and RAN groups (sponsor's Table 8.1.8). According to the sponsor, this interaction resulted from much higher healing rates among RAN patients without Barrett's esophagus (ca. 50%) than among those with Barrett's esophagus (ca. <10%) compared to similar healing rates among LANSO patients with and without Barrett's esophagus (74% - 84%) (sponsor's Table 8.1.6).
- In addition in the ITT analyses, a significant interaction of caffeine use with Tx was noted at Week 2 in comparison of LANSO and RAN groups (sponsor's Table 8.1.8). The sponsor attributed this interaction to much higher healing rates among patients in the RAN group who did not use caffeine (60.0%) than those who did use caffeine (13.8%). In the LANSO group, healing rates were similar with (67.7%) and without (57.1%) caffeine use (sponsor's Table 8.1.6).

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- In the evaluable analyses, a significant interaction of presence of Barrett's esophagus with Tx was noted at Week 4 in comparison of the LANSO and RAN groups (sponsor's Table 8.1.7). As in the ITT analyses, this interaction was said to have resulted from much higher healing rates among RAN patients without Barrett's esophagus (47.8%) than those with Barrett's esophagus (0%) compared to similar healing rates among LANSO patients with and without Barrett's esophagus (87.5% and 76.7%, respectively) (sponsor's Table 8.1.5).
- In addition, in the evaluable analyses, a significant interaction of presence of hiatal hernia with Tx was noted at Week 8 in comparison of the LANSO and RAN groups (sponsor's Table 8.1.7). In the RAN group, all four of the patients without hiatal hernia healed, while only 28.6% of patients with hiatal hernia healed. In the LANSO group, healing rates with and without hiatal hernia were 87.8% and 91.7%, respectively (sponsor's Table 8.1.5).

TABLE 17g
Study M89-393

Patients Who Were Healed at Week 2, 4 and/or 6, But Unhealed at Week 8

Pt. No. (Inv.)	Scr	Endo Grade				Smoking (ppd)	Alcohol Consumption (per day)	Hiatal Hernia
		W2	W4	W6	W8			
LANSO 30 mg (N=2)								
#5601 (Redinger)	2	0	0	NA*	2	NON	1-3 beers	NO
#5006 (Sampliner)	2	0	0	NA*	2	Ex (<1)	Ex (<1 beer)	YES
RAN (N=3)								
(Brand)	3	3	0	NA*	2	Ex (1-2)	<1 beer <1 wine	YES
(Kovacs)	2	1	1	NA*	3	Ex (<1)	Ex (1-3 beers)	YES
(Lind)	2	2	2	1	2	<1	Ex (>3 beers) (>3 wine) (>2 cocktails)	YES

a) NA: Healed at Week 4; therefore, Week 6 endoscopy omitted.

iv) Patients Healed at Week 2, Unhealed at Week 4, But Healed at Weeks 6 and 8 (Table 17h)

- The 4 pts. (LANSO 30/30 = 3; RAN = 1) under this category are listed in this Table.
- There are no easy explanations for these interesting findings in individual patients.

TABLE 17h
Study M89-393

Patients Who Were Healed at Week 2, Unhealed at Week 4, But Healed at Weeks 6 and 8

Pt. No. (Inv.)	Scr	Endo Grade				Smoking (ppd)	Alcohol Consumption (per day)	Hiatal Hernia
		W2	W4	W6	W8			
LANSO 30/30 (N=3)								
(Cohen)	2	0	2	1	0	Ex (1-2)	NON	YES
(Fisher)	2	0	2	1	0	NON	NON	YES
(Lind)	2	1	2	0	0	Ex (1-2)	Ex (>2 cocktails)	YES
RAN N=1)								
(Fisher)	3	1	2	0	0	Ex (>2)	Ex (>2 cocktails)	YES

v) LANSO 30/30 mg vs LANSO 30/60 mg

- Although these data are briefly summarized here, the actual results are not shown because the number of patients falling under these subgroups was too small. Besides, in the analyses of LANSO pts. receiving extra

medication after Week 4, there were no significant differences in healing rates between the LANSO 30/30 mg group vs the LANSO 30/60 mg group.

e) Secondary Efficacy Parameters

i) LANSO vs RAN

NOTE: Statistically significant comparisons in the Evaluable Population are indicated below by an asterisk (*).

- At Week 2, the LANSO group had significantly greater relief of
 - day heartburn*
 - night heartburn
 - GE regurgitation*when compared to the RAN group.
- At Week 4, the LANSO group had significantly greater relief of
 - day heartburn*
 - night heartburn*
 - burning in the upper abdomen* and
 - GE regurgitation*when compared to the RAN group.
- At Week 6, the LANSO group had significantly greater relief of
 - day heartburn* and
 - night heartburn*when compared to the RAN group.
- At Week 8, the LANSO group had significantly greater relief of
 - burning in the upper abdomen*
 - day heartburn*
 - night heartburn*when compared to the RAN group.
- At Week 8, there were no significant differences between the two groups in the relief of
 - pain swallowing
 - belching* or
 - GE regurgitation

ii) LANSO 30/30 vs LANSO 30/60 mg

- In the ITT analyses of symptom relief of patients who received extra medication at Week 4, those in the LANSO 30/60 mg group had statistically significant greater relief of
 - night heartburnwhen compared to the LANSO 30/60 mg group (but this was not confirmed in the Evaluable Population analyses).

f) Diary Results

- The LANSO group reported significantly fewer days of Gelusil use and fewer tablets used per day, and significantly less day and night heartburn, than the RAN group.
- There were no significant differences in diary results between the LANSO 30/30 vs 30/60 mg groups.

g) Results of Safety Evaluations

- In this trial, the most frequently reported AEs for the LANSO group were headache, diarrhea, abdominal pain, nausea and rash. For RAN, headache was most frequently reported. None of the AEs were considered possibly or probably related to test medication.
- No clinically significant differences were found between the LANSO and RAN groups for laboratory parameters, with the exception of fasting serum gastrin concentrations (and this is not surprising).

8. Conclusion (sponsor)

"Lansoprazole, administered once daily before breakfast, healed erosive reflux esophagitis significantly better than ranitidine 150 mg BID in patients with endoscopically proven reflux esophagitis resistant to histamine H₂-receptor antagonist therapy.

"The lansoprazole 30/60 mg group had numerically greater relief of day and night heartburn and less Gelusil use during the extra-medication period when compared to the lansoprazole 30/30 mg group; however, these differences were not statistically significant.

"Lansoprazole 30 and 60 mg was safe for use in patients with resistant erosive reflux esophagitis for a period of eight weeks."

9. Comments

Study under Protocol M89-393 is the second of two critical trials submitted by the sponsor in support of the use of LANSO 30 mg OD for "severe erosive esophagitis in patients who were poorly responsive to a course of histamine H₂-receptor antagonists". This trial was of very similar design and execution to trial M89-349. The major aim of study M89-393 was to compare the efficacy (and safety) of LANSO 30 mg administered once daily before breakfast and RAN 150 mg twice daily in the short-term Tx of patients with "erosive resistant reflux esophagitis". But just as in trial M89-349, no convincing evidence has been presented of these patients being truly resistant either from the endoscopic or symptomatologic viewpoint. The majority of patients enrolled in this trial had mild to moderate esophagitis and only 11.6% of the patients randomized to LANSO and 8.8% of those randomized to RAN had severe esophagitis. Neither were other data suggesting that the patients were "resistant" presented. Only 2.9% of the patients randomized to LANSO and none of the patients randomized to RAN had had previous G.I. surgery. No mention is made of bleeding, strictures or other complications (but these were actually reasons for patient exclusion from the trial). Roughly 3/4 of the patients had hiatal hernia and ca. 1/3 had Barrett's esophagus present. Similarly, most of the patients enrolled in this trial were experiencing either no or only mild to moderate rather than severe symptoms. The important conclusion, similar to that from Study M89-349, is that the study population in trial M89-393 cannot be categorized as having resistant erosive disease.

The adequate system for staging RE used in this trial was useful to demonstrate that most of the randomized patients had mild to moderate esophagitis. In only roughly 10% of the study population the condition was severe.

This 2-arm trial was otherwise apparently well executed. Patients were randomly assigned to D-B treatment with either LANSO 30 mg once daily or RAN 150 mg twice daily. The properly conducted (2:1) randomization process resulted in two groups of patients with similar demographic and baseline disease characteristics. But there are unanswered questions about F/U endoscopies, especially at Week 6 and 8 (similar to those questions mentioned during the review of Study M89-349).

Not unexpectedly, in this study population, LANSO 30 mg OD was shown to be active. The same conclusion was reached whether analyses involved the ITT or the Evaluation Population. At each time period analyzed (Weeks 2, 4, 6 and 8) the healing rates with LANSO 30 mg OD were clinically meaningful and statistically superior to those observed with RAN 150 mg BID. The therapeutic gains in this trial were the highest reported for any of the RE trials and ranged from 41% to 49% at Weeks 2 through 6. By Week 8, even higher therapeutic gains (>50%) were reported. Once again, the effectiveness of RAN was reported as decreasing from Week 6 to 8 while that for LANSO during the same period actually increased although not much.

In this trial, LANSO's superiority over RAN did not change when healing rates were adjusted for factors that may influence outcome, such as gender, age, BL esophagitis grade, whether hiatal hernia was present, alcohol use, tobacco use, caffeine use, presence of Barrett's esophagus, previous H₂-receptor antagonist use, whether previous H₂-receptor antagonist used was at standard or high dose, and duration of previous H₂-receptor antagonist therapy.

Not unexpectedly, this trial also showed that LANSO 30 mg OD is effective in relieving symptoms. Except for night heartburn for the Evaluable population which showed no differences between the two groups, evaluations at all time points (Weeks 2, 4, 6 and 8) demonstrated superiority of LANSO 30 mg OD over RAN 150 mg BID for day and night heartburn in both the ITT and Evaluable population analyses. From diary results, the LANSO group reported significantly fewer days of Galusil use and fewer tablets used per day, and significantly less day and night heartburn, than the RAN group.

Again, not surprisingly, LANSO 30 mg OD was shown to be well tolerated. In this trial, the most frequently reported AEs for the LANSO group were headache, diarrhea, abdominal pain, nausea and rash. Headache was also the most frequently reported AE for the RAN group. But none of these AEs were considered possibly or probably related to test medication by the investigator. Except for the expected increases in serum gastrin concentrations, no other clinically significant differences were reported between the LANSO vs RAN groups for laboratory parameters.

E. Summary of Section C (Efficacy): S-T Tx of Poorly Responsive ("resistant") Severe RE

In this Section, results from two studies (M89-349 and -393) submitted by the sponsor in support of the above-stated indication are evaluated.

Study M89-349 did not fulfill the main objective of the trial because no convincing evidence has been presented that the enrolled patients had resistant erosive reflux esophagitis. The study rather reconfirmed that the dose of LANSO tested (30 mg) given once-a-day before breakfast for 8 weeks is effective in a) healing mild to moderate esophageal lesions and b) inducing symptomatic relief. But we already know this from the results in the two critical RE trials (Section B, Studies M87-092 and M88-269). The important question that remains unanswered is whether 30 mg OD is needed since the same results were obtained with LANSO 15 mg OD (Study M87-092).

An attempt to demonstrate efficacy in Grade 4 (severe) esophagitis could be made by assessing efficacy in this subgroup of patients only. But the reported clinically significant decrease in RAN efficacy from 6 to 8 weeks in this trial needs to be validated by proper examination of the CRFs (Scientific Investigations). Alternatively, a convincing explanation for these findings should be given before results from the present trial can be used to draw valid conclusions.

Study M89-393 showed that LANSO 30 mg per day administered before breakfast for 8 weeks is effective in healing mild to moderate esophageal lesions and in inducing symptomatic relief. But we already know this from data presented in the two critical trials for short-term Tx of RE. Trial M89-393 also failed to fulfill its main objective because no convincing evidence was presented to support the sponsor's contention that these patients had resistant disease.

One recommendation to the sponsor may be to attempt to demonstrate efficacy in severe erosive esophagitis by assessing effects in Grade 4 patients only. But I am very reluctant to make such a recommendation, for a number of reasons. The number of patients in this substratum (Grade 4) was too small so that meaningful statistical conclusions may not be possible. Pooling of the data from this trial with that from trial M89-349 is not recommended unless questions I have raised about the validity of the reported observations at 8 weeks in that trial are satisfactorily answered.

In conclusion then, M89-349 and -393 are two additional studies showing that LANSO 30 mg heals mild to moderate erosive esophagitis and induces symptomatic relief in this patient population. Whether this compound is effective in healing lesions or improving symptoms of resistant (or "poorly responsive") RE is not known.

Not Approved

Indication

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X. Clinical Efficacy: Short-Term Treatment of Duodenal Ulcer

A. Indication sought (as stated in the proposed labeling).

PREVACID Delayed-Release Capsules are indicated for short-term treatment (up to 4 weeks) for healing and symptom relief of duodenal ulcer.

Dosage and Administration

The recommended adult oral dose is 15 mg daily before eating for up to 4 wks.

B. Clinical Trials for the Indication Short-Term Tx of DU

In support of the efficacy and safety of PREVACID® for the indication "short-term Tx of DU" the sponsor submitted results of two clinical trials. The main features of these trials and an initial assessment of the utility of the experimental design used in these essential studies are given in Table 29.

C. Study M87-090 (Report PPRd '90/155)

"A Study to Evaluate the Effects of Abbott-65006 on Acute Duodenal Ulcer"

1. Objective (as stated on page -4- of the Protocol)

This Phase II PL-controlled study was designed to assess the safety and efficacy of once daily administration of 15, 30 and 60 mg of Abbott-65006 in the Tx of DUs and to assess time to recurrence of ulcers in patients who ulcers were healed.

2. Materials/Labeling²⁹/Randomization

- The LANSO and PL capsules and Gelusil tablets were supplied as in Study M87-092.
- The bulk NPRO, bulk lot, and finishing subplot numbers for drug supplies used in this trial were:

	Bulk NPRO	Bulk Lot Number	Finishing Sublot Number
LANSO 7.5 mg Capsules	3979 4036 4195	09-573-AR 10-718-AR 15-074-AR	11-819-AR 15-057-AR 16-176-AR
LANSO 15 mg Capsules	3980 4037	09-574-AR 10-719-AR	11-820-AR 16-177-AR 15-158-AR
PL	3978 4035 3978 ^{a)} 4035 ^{a)} 4197 ^{a)}	09-572-AR 10-717-AR 09-572-AR ^{a)} 10-717-AR ^{a)} 15-076-AR ^{a)}	11-821-AR 15-059-AR 16-178-AR

a) Three lots of bulk PL mixed together and treated as one subplot.

²⁹D-8 medications used in this trial were supplied by Takeda Chemical Industries Ltd, Osaka, Japan. The test medication was packaged by Abbott Laboratories, Abbott Park, IL on behalf of TAP Pharmaceuticals Inc.

TABLE 22
Main Features, Groups Being Compared and Initial Assessment of the Utility of the Experimental Design of Clinical Trials Submitted in Support of the Indication Short-Term Tx of DU

Study No. No. of Investigators	Number of Patients	Study Design	Groups Being Compared	Remarks
187-090 (U.S.) 28 Investigators	195 M 101 F 296 Total	Randomized, D-B, fixed dose, PL-controlled, parallel group, 4-arm Endoscopies at 0, 2 and 4 weeks and then at 1, 3 and 6 mo. Post-Tx	LAM80 15 mg vs LAM80 30 mg vs LAM80 60 mg vs PL All x 4 weeks	- Useful design. - The effects of graded doses of the orally administered drug (15 to 60 mg) are being compared to those of PL, a negative control. - The study was apparently not sized to show differences between the three LAM80 dose levels. But it may be possible to get an initial idea of dose response. - F/U endoscopies were done to assess time to recurrence of ulcers in patients whose DU had healed.
188-268 (U.S.) 30 Investigators	188 M 113 F 301 Total	Randomized, D-B, fixed-dose, active- (RAM) and PL-controlled, parallel group, 4-arms	LAM80 15 mg vs LAM80 30 mg vs RAM 300 mg vs PL All x 4 weeks	- Very useful design. - The effects of two dose levels of the orally administered drug (15 and 30 mg) are being compared to those of a) a positive control (RAM) and b) a negative control (PL). - The study was apparently not sized to show differences between the two LAM80 dose levels. But it may be possible to get an initial idea of dose response. - The dose of RAM being tested (300 mg administered as a single daily dose at bedtime) is recommended as an alternative dosage to 150 mg twice daily. The 300 mg is to be given at bedtime and can be used in patients in whom convenience is important. - No F/U endoscopies after healing. Time of recurrence of ulcers in patients whose DU had healed cannot be assessed.

- Labeling of materials was adequate.
- The randomization schedules used for each investigator were presented in sponsor's Appendix A. As for the other clinical trials, these were provided by the Clinical Statistic Department at Abbott Labs.

3. Study Design

This trial was a randomized, D-B, fixed dose, parallel group, 4-arm comparison of the effectiveness of single oral daily doses of 15, 30 or 60 mg LANSO to PL. There was an equal allocation for Tx groups.

4. Study Population

This was adequate for this type of study.

- M or F patients between the ages of 21 and 75y with endoscopically proven DU with a crater size of at least 3 mm in diameter were eligible for participation in this study if they met the following inclusion-exclusion criteria.
- No evidence of both DU and GU. Multiple ulcerations were acceptable if all were duodenal and/or pyloric channel in location.
- No evidence of additional clinically significant medical disease such as Crohn's disease, regional enteritis, I-E syndrome, UC, IBS, biliary tract disease, GER, or malignancy (but basal cell carcinoma was not reason for exclusion).
- No chronic use of ulcerogenic drugs, such as systemic corticosteroids, within one month prior to the screening endoscopy or histamine H₂-receptor antagonists or other antiulcer drug therapy (antacids were allowed during the trial) during the 8 weeks prior to the screening endoscopy.
- No use of anticoagulants, hydantoin, theophylline derivatives or benzodiazepines metabolized by the P₄₅₀ enzyme system.
- No current Hx of drug or alcohol abuse.
- For women, no capability of bearing children or a negative pregnancy test along with previous use and agreement of continued use of appropriate means of contraception for the duration of the study.
- No previous surgery for ulcer disease, except for simple closure of perforation.
- No active bleeding or perforation at the time of the screening endoscopy.
- No laboratory results outside of NLS or clinically acceptable limits as determined by the investigator and approved by the sponsor.

5. Study Execution

The study consisted of three periods: screening, treatment, and Post-Tx.

a) Screening Period

Standard procedures (see Tx period), including endoscopy to document DU³⁰ were performed within 7 days to receive test medication. The results of these procedures (with the exception of serum gastrin concentrations) were reviewed by the investigator before the pt. entered the Tx period.

b) Tx Period

Eligible patients were given two bottles of LANSO or PL capsules at BL and at Week 2 of the Tx period. Each bottle contained 38 capsules (10 extra capsules per bottle). Bottles 1A and 1B were dispensed at BL (Study Day 1), and bottles 2A and 2B at the Week 2 visit. Each morning before breakfast during the 4-w Tx period, the patient took two capsules orally from each of the two bottles. The bottles contained test medication or PL in combinations which provided the assigned dose level, as shown below.

Bottle	PL	LANSO Dose (mg)		
		15	30	60
#1A, 2A	PL	7.5 mg cap.	15 mg cap.	15 mg cap.
#1B, 2B	PL	PL	PL	15 mg cap.

One replacement bottle for each of the A and B bottles (Bottles RA and RB) for each patient was held at the investigational site to be dispensed only as needed. In addition, at the BL and Week 2 visits (and at the Week 4 visit for patients entering the Post-Tx visit) each patient was given one box of Gelusil (containing 50 tablets) to be taken for relief of discomfort as needed. The study then proceeded as summarized below. Endoscopies were performed at screening Weeks 2 and 4 of Tx.

If the ulcer was completely healed³¹ at the end of 4 weeks of Tx, the patient entered the post-treatment follow-up (6 mo). Patients whose ulcers were not healed at 4 weeks were considered to have completed the study and did not participate in the Post-Tx follow-up period.

Symptom Assessment

Changes or complaints since the preceding examination were noted for the following specific symptoms: burning in the upper abdomen, heartburn, painful swallowing, belching, GE regurgitation, fullness/bloating/early satiety, abdominal distension, anorexia, nausea, vomiting, day abdominal pain, night abdominal pain, flatulence/abdominal rumbling, diarrhea, constipation, hematemesis, and melena.

All symptoms were related through the same scales as those used in the RE trials.

³⁰ Active DU was documented by endoscopy within 7 days preceding entrance into the Tx period of the trial. An ulcer was designed as a lesion with depth. Pts. with a crater size of at least 0.3 cm in the largest diameter were eligible to enter the trial.

³¹ Definition of healed ulcer: duodenal mucosa with re-epithelialization, showing no evidence of an ulcer crater at endoscopy.

c) Post-Tx F/U Period

- If the patient's DU had healed at 4 weeks, he/she was to be followed up with endoscopies for up to 6 mo. Post-Tx (visits at Post-Tx months 1, 3 and 6, or if ulcer symptoms recurred).

Patients Completing the Trial

A patient was considered to have completed the study when

- The ulcer was not healed at Week 4 (Tx F).
- He/she completed the Post-Tx period without recurrence.
- Ulcer recurrence was confirmed by endoscopy at a scheduled or unscheduled visit (at treatment Week 4 or any time during the Post-Tx follow-up period).
- He/she was treated with any ulcerogenic or antiulcer drug that would interfere with evaluation of test medication.
- He/she W/D from the trial for any reason.

6. Statistical Methodology

a) Planned Sample Size

According to the Clinical Protocol, the trial was designed to enroll sufficient patients such that 260 patients would complete the study and be evaluable for efficacy analyses (65 in each Tx group). This sample size had a 99% chance to detect significant differences between any of the three LANSO groups and the PL group if true healing rates were 85% and 50%, respectively ($p < 0.05$, two-tailed tests). A 35% therapeutic gain was anticipated.

b) Patient Evaluability

The procedures to establish patient evaluability were adequate but are not discussed in any detail here because efficacy assessments - during the present review - will be based on Intent-to-Treat Population analyses only.

c) Parameters of Evaluation

- The primary efficacy endpoint was the endoscopic assessment (healed/unhealed) of the ulcer crater, as stated in the Protocol.
- Primary symptoms of DU were defined as day and night abdominal pain. Changes in the severity of the primary symptoms of DU and the additional symptoms were analyzed.
- Safety variables were analyzed as per the RE protocols.

d) Statistical Analyses

- The proportion healed on each dose of LANSO at each time point was compared to the proportion healed on PL using Mantel-Haenszel methods for combining (2 x 2) tables across investigators, as stated in the protocol.

- Similar comparisons among LANSO groups were presented to evaluate dose response. Homogeneity of Tx difference across investigators (Tx-by-investigator interaction) was examined using the Breslow-Day test.
- Months 1, 3 and 6 Post-Tx endoscopy results were defined as the last endoscopy completed 15 to 60 days, 61 to 135 days, and greater than 135 days after the last dose, respectively. A patient with no endoscopy in a given Post-Tx time interval was considered healed if healing was documented during the subsequent time interval.
- Tx group comparisons adjusting for concomitant factors (age, sex, ulcer diameter at screening, alcohol use, caffeine use, smoking, and whether this was the first episode of duodenal ulcer) were made using Mantel-Haenszel methods for combining (2 x 2) tables across levels of each factor.
- Homogeneity of Tx differences across levels of each concomitant factor (treatment-by-factor interaction) was examined using the Breslow-Day test.
- Results of symptom assessments were analyzed with Cochran-Mantel-Haenszel methodology for ordered response categories using the BL value as the "covariate" (analyses of ITT and Evaluable Populations).
- For data from diaries, pairwise comparisons of the mean severity and percentage of days with symptoms were performed using the Wilcoxon two-sample test.
- Adverse events and other safety data were evaluated as described for RE trials.

7. Study Results

a) Participating Investigators

In this trial, 28 qualified investigators, geographically distributed throughout the United States, enrolled a total of 296 patients (195 M; 101 F).

It is to be noted that 16³² of the 28 investigators participating in this DU trial also enrolled patients in the other DU trial. This has been brought to the attention of Scientific Investigations. It is important to make sure that patients were not being studied twice (for the same indication).

b) Data Showing Comparability of Groups

i) Premature Terminations (Table 30)

As shown in this Table, 17 patients, equally distributed among the four Tx groups (except for Tx F, PL=5; each and all LANSO groups=0), W/D from the trial prematurely during the Tx period. The primary reasons for these premature terminations are given in this Table.

³²These 16 investigators were: Aaronson (2925), Avner (3094), Berry (2927), Bruns (2928), Dorsch (3095), Erfling (2934), Jones (2940), Koval (2965), Mavva (2942), Nelson (2947), Oliver (2948), Rowekamp (2950), Sahba (2951), Schwartz (2953), Scowcroft (2954) and Shivakumar (2955).

TABLE 30
Study M87-090

**Summary of Primary Reasons for Premature Termination from
the Tx Period**

(Number of Patients)

Termination Reason	PL	LANSO (mg)		
		15	30	60
AEs*	0	3	1	1
Personal Reasons	1	0	0	0
Poor Compliance	0	2	0	0
Therapeutic Failure	5	0	0	0
Treatment with Another Anti-Ulcer Drug	1	0	1	0
Other	0	0	0	2
Total	7	5	2	3

a) Sponsor's Table 7.2.1 listed the investigator, patient No., Tx group, No. of completed days of Tx, age, sex, and the reason for termination for each of these patients. Two of these 17 patients had endoscopically documented healing prior to their termination.

b) The study blind was prematurely broken for Pt. (Mertesdorf) (PL). The pt. experienced abd. pain + melena 16 days after starting PL and the investigator needed to know in the event surgery was indicated.

c) 3 additional patients (Erfling) (Mertesdorf), and (Oliver) all TxPs in the PL group, were D/C prematurely from the study in part due to AEs; however, the AE(s) were not the primary reason for premature termination.

ii) Demographic and Disease Baseline Characteristics
(Table 31)

- This Table summarizes the demographic and disease BL characteristics for the 296 patients who entered the D-B Tx period.
- There were no significant differences among the 4 Tx groups, combined across investigators, for M or F weights, height, sex, race, smoking, alcohol use or caffeine use. On the average, patients in the LANSO 15 mg group were 3.1y older than those in the PL group. Also, there was a significant difference in the mean age of patients among Tx groups [44.7, 42.8, 41.3 and 43.6 in the PL, 15, 30 and 60 mg LANSO groups, respectively]. But these differences are not expected to influence outcome.
- There were no significant differences, among Tx groups combined across investigators, in the ulcer size at entry.

TABLE 31
Study MB7-090
Summary of Demographic and Disease Baseline Characteristics
(All Patients)

Variable	All Pts. N=206	PL N=73	LANSO (mg)		Overall p-value
			15 N=73	30 N=73	
Age Mean (S.D.) (y) Min-Max	64.3 (13.9) 19-75	64.7 (13.7) 20-72	61.3 (12.9) 21-72	43.6 (13.5) 21-75	0.036 ^a
Weight-F No. of Pts. Mean (S.D.) (lbs)	195 181.1 (29.5)	55 183.3 (35.2)	44 182.9 (28.5)	48 179.5 (27.3)	N.S. ^a
Weight-F No. of Pts. Mean (S.D.) (lbs)	101 144.8 (30.9)	20 152.9 (30.7)	31 144.7 (35.1)	25 144.0 (25.0)	N.S. ^a
Weight-M No. of Pts. Mean (S.D.) (inch)	195 69.8 (2.9)	55 69.8 (3.1)	44 69.7 (2.6)	48 70.1 (2.9)	N.S. ^a
Weight-F No. of Pts. Mean (S.D.) (inch)	101 64.2 (2.8)	20 64.9 (2.6)	25 63.2 (2.8)	25 64.3 (3.2)	N.S. ^a
Sex					
M	195	55	44	48	N.S. ^a
F	101	20	25	25	N.S. ^a
Race					
Caucasian	256	56	64	56	N.S. ^a
Black	40	10	7	14	
Other	20	9	4	3	
Smoking					
Non-smoker ^b	170	47	42	40	N.S. ^a
Smoker	126	28	33	33	
Alcohol Use					
Non-drinker	148	43	35	40	N.S. ^a
Drinker	148	32	40	33	
Caffeine Use					
No	66	23	17	17	N.S. ^a
Yes	239	52	58	56	
Ulcer Size (cm)					
≤5	69	19	19	12	N.S. ^a
>5 to 10	161	39	39	40	
>10	66	17	17	21	

TABLE 31 (Con't)

SUMMARY OF PRIMARY SYMPTOMS AT D2									
Day	13	16	17	9	0.045 ^a				
Abdominal Pain	32	27	34	33					
None (0)	10	7	12	13					
Row Mean Score	1.36	1.34	1.63	1.68					
Milds ^b									
Abdominal Pain	20	16	12	10					
None (0)	15	15	18	19					
MILD (1)	21	29	24	23					
MOD (2)	19	13	21	21					
SEV (3)									
Row Mean Score	1.52	1.53	1.72	1.73	M.S. ^c				
PERCENTAGE OF PATIENTS REPORTING GASTROINTESTINAL ILL									
Medical History Factor	53.6%	49.3%	52.0%	63.0%	M.S. ^d				
Previous DU									
Other GI Disorders (Not Inc. DU)	60.5%	60.3%	66.7%	56.2%	M.S. ^e				
- Previous Undetermined GI Disease	20.3%	17.8%	21.3%	19.2%	M.S. ^f				
- Previous Gastritis	16.9%	13.7%	17.3%	19.2%	M.S. ^g				
- Previous GU	10.5%	6.7%	13.3%	9.6%	M.S. ^h				
- Previous IBD	2.7%	2.7%	2.7%	1.4%	M.S. ⁱ				
- Previous Duodenitis	12.2%	9.6%	16.7%	13.7%	M.S. ^j				
Previous Therapy for any GI disorder(e)	87.8%	85.3%	92.0%	90.4%	M.S. ^k				
Surgical Procedures for GI Dz	2.4%	1.4%	4.0%	0.0%	M.S. ^l				

a) At the start of D-8 period
b) Statistically significant at the 0.05 level
c) p-value from F-test for testing equality of Tx means
d) p-value for Chi-square test
e) Includes ex-smokers
f) Statistically significant at the 0.05 level (Cochran-Mantel-Haenszel methods)
g) (Cochran-Mantel-Haenszel methods)
h) Likelihood ratio Chi-square for difference among Tx groups

- The initial ulcer size was:
 - >5 to 10 mm in 54.4% of the patients
 - >10 mm in 22.3% of the patients
 - ≤5 mm in 23.3% of the patients.
- At BL, the severity of the primary symptoms of DU was similar among all Tx groups for night abdominal pain, but was significantly different among the groups for day abdominal pain among ITT but not among Evaluable patients. This was due to the 30 and 60 mg groups having a larger proportion of patients with moderate symptoms and a lower proportion of patients with no symptoms than the PL and 15 mg groups. The sponsor explained that because the BL severity was used as a stratification factor, this BL imbalance was "adjusted for" in the symptom analyses.
- There were no statistically significant differences among the 4 Tx groups in the percentage of patients reporting G.I. Hx for any of the medical Hx factors. Neither data on previous aspirin nor NSAID use were reported. Similarly, no data on H. Pylori status in these patients were obtained. The addition of these and other information such as comparison of BAO and PAO (both in mEq/h) and fasting serum pepsinogen (ng/ml) would have added quality to the trial.

c) Primary Efficacy Parameters

i) Treatment Period (Table 32)

- As shown in this Table, at both time periods (Weeks 2 and 4) the healing rates for each LANSO group was significantly higher than the healing rate for the PL group. The therapeutic gains were clinically meaningful. By 2 weeks these ranged from 25.3 to 29% and there were no differences among the three LANSO doses. By 4 weeks - these ranged from 40.9% for the LANSO 15 mg to 48% for the LANSO 30 mg group. Although efficacy improved by 7% when the dose was increased from 15 to 30 mg LANSO, this small clinical difference was not statistically significant. Whether one considers Weeks 2 or 4 healing rates, there was no further benefit by increasing the dose from 15 to 30 or even 60 mg.
- Similar responses were noted in the Evaluable Population analyses.

ii) Evaluation of Efficacy in Subgroups

At both evaluation time points (Weeks 2 and 4), all LANSO doses were significantly superior to PL if healing rates were adjusted for concomitant factors. The latter included gender, age, BL ulcer diameter, alcohol use, caffeine use, and whether this was the first episode of DU. Lack of effect of these factors on efficacy was observed in both ITT and Evaluable patients analyses.

TABLE 32
Study N87-090

**Healing Rates as a Function of Time and LANSO Dose
[ITT Population]**

Week	PL	LANSO (mg)		
		15	30	60
2	8/75 (10.7)	29/73 (39.7)	27/75 (36.0)	27/75 (37.0)
Therapeutic Gain		29.0 (<0.001)	25.3 (<0.001)	24.3 (<0.001)
4	31/75 (41.3)	60/73 (82.2)	67/75 (89.3)	64/73 (87.7)
Therapeutic Gain		40.9 (<0.001)	48.0 (<0.001)	46.4 (<0.001)

iii) Patients Healed at Week 2 but Unhealed at Week 4

- Two patients [PL=1; LANSO 15 mg=1] were evaluated as healed at the Week 2 endoscopy but were unhealed at the Week 4 endoscopy.
 - The LANSO pt. had a previous Hx of DU, had been a smoker (<1 ppd) but had not and was not drinking alcohol. The initial ulcer size in this patient was 10x10 mm, this decreased to none at 2 weeks but was 8x7 at 4 weeks. This pt. was apparently compliant with taking test medication during the Tx period.

iv) Post-Tx Period (Table 33)

- This Table lists the Percentages of ITT patients reaching Post-Tx visits who remained healed at months 1, 3 and 6 endoscopy. As time went on greater proportion of patients in the LANSO groups experienced recurrence of the ulcer than those receiving PL.

d) Secondary Efficacy Parameters

- At Week 2 the ITT (and Evaluable) patients in all 3 LANSO groups had significantly greater relief of
 - day abdominal pain and
 - night abdominal pain
 than patients in the PL group.

TABLE 33
Study M87-090

**Percentages of Patients Reaching Months 1, 3 and 6 Post Tx
With Endoscopically Documented Healed DU**

Tx Group mg of LANSO	% Remaining Healed ^a (Month Post-Tx)			
	0	1	3	6
PL (N=73)	41.3	33.3	29.3	25.3
%		(-8.0)	(-12.0)	(-16.0)
15 (N=73)	82.2	65.8	50.7	45.3
%		(-16.4)	(-31.5)	(-36.9)
30 (N=73)	89.3	72.0	49.3	40.0
%		(-17.3)	(-40.0)	(-49.3)
60 (N=73)	87.7	67.1	48.0	38.4
%		(-20.6)	(-39.7)	(-49.3)

a) Percentage of patients healed at the Final Tx Visit.

- At Week 4, the ITT (and Evaluable) patients in all 3 LANSO groups had significantly greater relief of
 - day abdominal pain and
 - night abdominal pain
 than patients in the PL group.
- ITT analyses of change from BL to Week 4 in additional symptoms showed each LANSO dose to be significantly superior to PL in relieving
 - burning in the upper abdomen
 - heartburn (exception: the 15 mg LANSO group was = PL)
 - fullness/bloating/early satiety
 - flatulence/abdominal rumbling
 - G.I. regurgitation
 - anorexia
 - abdominal distension, and
 - nausea.
- The 15 and 60 mg doses were superior to PL in relieving vomiting, and the 15 and 30 mg doses were superior to PL in relieving belching.
- No other significant differences between any LANSO group versus the placebo group were noted.
- Some differences among the LANSO groups were noted:
 - the 30 mg dose was superior to the 15 mg dose in relieving heartburn
 - the 30 mg dose was superior to the 60 mg dose in relieving belching...

- The Evaluable Population analyses gave similar for these additional symptoms, with the exception that the 15 mg group was significantly superior to the PL group in relieving heartburn.
- There were no significant differences in the primary symptoms of DU at the patient's final Post-Tx visit among any of the Tx groups (sponsor's Appendix D.7)

e) Diary Data

- All 3 LANSO groups reported significantly fewer
 - days of Gelusil use
 - tablets used per day
 - day and night abdominal pain

than the PL group.

f) Results of Safety Evaluations

i) Adverse Events³³ During the Tx Period

- During the Tx period, irrespective of relationship to test medication, 117/221 (or 52.9%) of LANSO patients reported one or more AEs compared to 43/75 (or 57.3%) of the PL-Tx patients.
- There was no dose relationship in the reporting of AEs.
- As shown in Table 34, for possibly or probably-related AEs the percentages of LANSO patients reporting AEs were similar than the percentage of PL patients reporting AEs. There were no differences among the LANSO groups.
- The data in Table 34 show headache as the most frequently (23% incidence rate in any Tx group) reported possibly or probably Tx-related AE among the LANSO-Tx patients.
- Of the possibly or probably Tx-related AEs reported, most were mild to moderate in severity (all Tx groups).

ii) AEs During the Post-Tx Period

- There were no differences in the incidence of AEs between the PL group (9/28=32.1%) and the LANSO groups combined (66/180=36.7%) reported in the Post-Tx period.

³³ AEs reported during the trial were listed by investigator and treatment group in sponsor's Appendix E.14. Appendix D.8.1 listed all medical term descriptions of AEs (based on the medical terms that closely approximated the entry on the CRF) that occurred during the trial. Sponsor's Appendices D.8.2 and D.8.3 summarized patients numbers associated with all AEs and possibly/probably Tx-related AEs, respectively. AEs were summarized in sponsor's Tables 9.1.1 through 9.1.5.

TABLE 34
Study NS7-090

Number/(%) of Patients With Possibly or Probably Tx-Related AEs

	PL (N=75)	15 (N=75)	LANSO (mg) 30 (N=75)	60 (N=75)
Patients With Any Poss/Prob Tx-Related AEs				
	18 (24.0)	14 (19.2)	15 (20.0)	11 (15.1)
Most Frequently^a Reported Poss/Prob Related AEs (COSTART Term)				
Headache	10 (13.3)	7 (9.6)	11 (14.7)	7 (9.6)
Nausea	3 (4.0)	0	1 (1.3)	0

a) Defined as ≥3.0% incidence in any Tx group when rounded to one decimal place.

iii) Withdrawals Due to AEs (Table 35)

- Listed in this Table are data from the 8 patients who W/D from the trial during the D-B Tx period at least in part due to AEs (PL=3; LANSO 15 mg=3; 30 mg=1; 60 mg=1).
- In 5 of these patients (one in the PL, two in the 15 mg, one in the 30 mg, and one in the 60 mg groups), the AEs were judged to be possibly related to test medication by the investigator.
- One (1) possibly related AE considered to be severe occurred in a PL patient. This was a case of insufficient therapeutic effect.
- The remaining 4 possibly related AEs were judged to be mild to moderate in severity.
- Finally, 2 patients (Scowcroft) and (Simmons) W/D at least in part due to AEs in the Post-Tx period.

TABLE 35
Study 87-090

Patients Who Prematurely D/C During the Tx Period to AEs

Pt. No. (Investigator)	Total Days on Test Med.	AE(s)/Action Taken	Rx Day of Onset	Rx Day of Stop (S) or Continue (C)	Severity	Relationship to Test Med.
PL GROUP (N=3)						
(Erfiling)	16	Abdominal Pain	16	25 (C)	Moderate	NO
(Hertendorf)	14	Fever Abdominal Pain Melena	11 11 11	17 (S) 17 (S) 17 (S)	Severe Mild Moderate	NO NO NO NO
(Oliver)	16	Peptic Ulcer Syndrome/ Given Domnamel & Bentyl in ER	15	16 (C)	Severe	Possible
LASSO 15 mg (N=3)						
(Auner)	6	Deep Thrombophlebitis	6	14 (C)	Severe	NO
(Oliver)	1	Taste Perversion	1	17 (S)	Mild	Possible
(Simmons)	14	Flatulence, Anorexia, Dizziness, Abdominal Pain, Asthenia, Abdominal Pain, Dyspepsia/Observation	6	14 (C)	Moderate	Possible
LASSO 30 mg (N=1)						
(Simmons)	36	Nausea	29	32 (C)	Moderate	Possible
LASSO 60 mg (N=1)						
(Oliver)	13	Pain & Dizziness	13 -3 ^a	15 (C) 16 (S)	Mild Mild	Possible NO

a) AE continued as of that date. b) Stop date estimated. c) AE occurred intermittently from onset through the stop date.

iv) Clinical Laboratory Determinations

- There were no clinically significant differences between any of the LANSO groups and PL for hematology, blood chemistry or urinalysis parameters assessed during the Tx period.

v) Fasting Serum Gastrin Concentrations

- Fasting serum gastrin concentrations increased in all LANSO groups in a dose-related manner, reaching a plateau by Week 2. Most values returned to near BL values by Month 1 Post-Tx.
- There were no clinically significant drug-related changes in P.E. findings, vital signs or EKG results in any LANSO-Tx patients.

8. Conclusion (Sponsor)

"Lansoprazole, administered once daily before breakfast, healed duodenal ulcer significantly better than did placebo.

"Lansoprazole 15, 30, and 60 mg were similarly effective in healing acute duodenal ulcer as shown by endoscopy, with the safety profile suggesting no apparent dose-related effects. All lansoprazole groups were superior to placebo in producing relief of day and night abdominal pain.

"All lansoprazole dosage groups (15, 30, and 60 mg) had higher percentages of patients reaching Months 1, 3, and 6 posttreatment with healed duodenal ulcer than the placebo group.

"Lansoprazole was safe for use in patients with duodenal ulcer at doses up to 60 mg per day for a period of up to four weeks, with no lasting effects on fasting gastrin levels."

9. Comments

Clinical trial M87-090 is one of the two critical U.S., multicenter trials submitted by the sponsor of this NDA in support of the approval of LANSO 15 mg daily for the healing and symptom relief of duodenal ulcer. The trial was well designed and apparently well executed. The trial was conducted under D-B, randomized conditions and consisted of four parallel arms: three fixed doses of LANSO (15, 30 or 60 mg once daily) vs PL, an adequate negative control. The major aim of the trial was to compare the rate of healing and recurrence (for 6 months) after Tx with either LANSO or PL in DU patients taking antacid for pain relief.

The 296 patients selected for this trial (LANSO 15 mg=73; LANSO 30 mg=75; LANSO 60 mg=73; PL=75 patients) had a primary diagnosis of active DU manifested primarily by mild to moderate symptoms at baseline. The ulcer was primarily of the medium size (>5 to 10 mm) documented by endoscopic visualization of the crater. Additional inclusion-exclusion criteria were also adequate. The trial did not randomize patients with diseases or conditions that may be confounding. Use of ulcerogenic drugs was proscribed for the month prior to entry. The washout period of ca. 8 weeks for H₂ receptor antagonists or other antiulcer drugs allowed >5 half-lives for any H₂-receptor antagonist or PPI.

The randomization process resulted into the four comparatively studied groups of patients that were well-balanced in demographic, disease characteristics and medical g.i. history at baseline. A small statistically significant difference recorded for age is not expected to influence outcome.

Test medication was given in 2-week intervals and Tx continued even if ulcers had healed (completely epithelialized ulcer crater) at 2 weeks for a maximum of 4 weeks. The use of identically appearing LANSO and PL drugs made it possible to conceal the identity of the Tx given to a patient.

At the three dose levels tested LANSO was shown to be significantly more effective than PL in accelerating the short-term healing of and relieving symptoms of DU. This superiority was demonstrated when assessing results in both primary and secondary efficacy parameters and whether the evaluations were carried out using ITT or Evaluable Population analyses. At both points of observation (2 and 4 weeks), healing rates for each of the three LANSO doses were significantly higher than the healing rate with the PL, with therapeutic gains of 25.3 to 29% by 2 weeks and 40.9 to 48% by 4 weeks. The three dose levels of LANSO were equally effective as there was no suggestion of dose-related effects. Increasing the LANSO dose to 30 or even 60 mg once-a-day did not afford further benefit in ulcer healing than that obtained with LANSO 15 mg once-a-day, the dose proposed by the sponsor. These observations are of interest in that given the same length of exposure (2 or 4 weeks) increasing the recommended dose of LANSO (15 mg) by a factor of two or four is not necessary. On the other hand, even after 4 weeks of Tx with the 15 mg LANSO dose, close to 20% of the patients remained unhealed. Based on the findings in this trial, dose duration should be 4 weeks, although some patients healed by 2 weeks but ca. 80% of the patients healed by 4 weeks.

The healing/unhealing rates with the active drug are closely related to the response to PL (the internal control); in this trial, the PL response by 4 weeks (41.3%) was as expected. It can be inferred that the antisecretory effects with 15 mg are as good as those with 30 or even 60 mg of this drug. In this trial, factors suspected or which have been shown to influence ulcer healing in some published trials, added to the analyses, did not significantly interact with treatment.

The six month follow-up study during which the patients may have taken antacids prn for pain, revealed a gradual increase in the proportion of patients experiencing recurrence for all four groups. As time went on, however, a higher proportion of patients in each and all LANSO groups experienced recurrence than in those who had received PL. These data are difficult to interpret in the absence of important information such as histological evaluations at the end of 4 weeks to determine the quality of healing in those patients assessed as healed.

LANSO also influenced secondary effectiveness measures. Whether analyzing ITT or Evaluable Population data each and all three LANSO groups had significantly greater relief of day and night abdominal pain. As was the case for acceleration of ulcer healing, no dose-response was seen for this important symptom. The effectiveness of LANSO 15 mg once-a-day in symptomatic relief could not be further improved by doubling or even quadrupling this dose of the drug.

The data in trial M97-090 also showed that LANSO (15 to 60 mg once-a-day) is well tolerated in the duodenal ulcer population. Headache was the most frequently (≥3% incidence rate in all four Tx groups) reported possibly or probably Tx-related AE among the LANSO-treated patients. But the incidence rate for headache among PL patients was similar to that seen with LANSO. Not unexpectedly, fasting serum gastrin concentrations increased in all LANSO groups (but not in the PL group) in a dose-related manner. Most of these values reached a plateau by Week 2. However, one month after discontinuation of treatment, fasting serum gastrin concentrations were near the concentrations recorded at BL.

D. Study M88-268

"A Study to Evaluate the Effects of Lansoprazole on Acute Duodenal Ulcer."

1. Objective (as stated on page -4- of the Protocol)

This Phase III study was designed to compare the safety and efficacy of once daily administration of 15 mg or 30 mg of LANSO with those of 300 mg of RAN and PL, in the Tx of acute DUs.

2. Materials/Labeling/Randomization

- The LANSO, RAN and matching PL capsules were supplied as in Study - M88-269 for RE.
- The bulk NPRO, bulk lot, and finishing subplot numbers for drug supplies used in this trial were:

	Bulk NPRO Number	Bulk Lot Number	Finishing Sublot Number
LANSO 15 mg Capsules	4515N	24-904-AR	30-571-AR
	4515R	35-948-AR	34-893-AR 40-453-AR
PL for LANSO	4516N	24-905-AR	30-572-AR 34-894-AR 40-454-AR
RAN 150 mg Capsules	4695R	30-532-AR	30-573-AR
	4752R	38-232-AR	34-895-AR 40-455-AR
PL for RAN	4670N	30-533-AR	30-574-AR
	4881N	38-237-AR	34-896-AR 40-456-AR

- Labeling of materials (supplied by Takeda Chemical Industries Ltd., as per previous clinical trials) was adequate.
- Also adequate were the methods of randomization.
- The randomization schedules³⁴ were generated by the Clinical Statistics Department at Abbott Laboratories, Abbott Park, IL. The patient numbers and study drug assignments were in the possession of the investigators (double-blind portion of the label) and of the Clinical Statistics Department at Abbott Laboratories (sealed envelopes). When all screening procedures were completed and the patient had met all admission criteria, the next successive patient number available for that investigator was assigned to the patient. Patients were randomized in blocks of seven (7), with the patient numbers randomly assigning the patient to one of the four (4) treatment groups on a 2:2:2:1 basis. Assignment started with the lowest available number and proceeded in ascending order.

³⁴ Separate randomization schedules for each investigator were used [presented in sponsor's Appendix A].

3. Study Design

This trial in Acute DU, was a randomized, multicenter, D-B, parallel group, fixed-dose, 4-arm, active- and PL-controlled comparison of the effectiveness of LANSO 15 or 30 mg when administered orally as a single daily dose before breakfast to that of a) RAN 300 mg, administered as a single daily dose at bedtime and b) PL. There was an unequal allocation (:1) of pts. to the PL group but equal allocation (2:2:2) to each of the 2 LANSO groups or RAN.

4. Study Population

This was similar to that used in the other DU study (M87-090).

5. Study Execution

The trial consisted of a screening period of up to 7 days and a 4-week Tx period.

a) Screening Period

Standard procedures (see Tx period), including endoscopy to document active DU, were performed within 7 days preceding entrance into the Tx period (starting of test med.). As in the other study, patients were eligible to enter the trial if they presented with a DU with depth and the crater size was at least 3 mm in diameter. Multiple ulcerations were acceptable if all were duodenal and/or pyloric channel in location.

b) Tx Period

- Patients were given four (4) bottles of LANSO, RAN and/or matching PL capsules at BL (Study Day 1), labeled 1A, 1B, 1C and 1D. Each bottle was labeled AM or PM and contained 38 capsules (10 extra capsules per bottle). Each morning before breakfast during the 4-week Tx period, the patient was to take one capsule orally from each of the A and B bottles. At bedtime, the patient was to take one capsule orally from each of the C and D bottles. The bottles contained test medication or PL in combinations that provided the assigned drug and dose level, as shown below.

Bottle	PL	RAN 300 mg Dose	LANSO 15 mg Dose	LANSO 30 mg Dose
#1A	LANSO-PL	LANSO-PL	LANSO 15 mg cap.	LANSO-15 mg cap.
#1B	LANSO-PL	LANSO-PL	LANSO-PL	LANSO-15 mg cap.
#1C	RAN-PL	RAN-150 mg cap.	RAN-PL	RAN-PL
#1D	RAN-PL	RAN-150 mg cap.	RAN-PL	RAN-PL

- One replacement bottle for each A, B, C and D drug bottles (RA, RB, RC and RD) for each patient was supplied to all investigators to be dispensed only as needed. In addition, at BL and Week 2, each patient was given one box of Gelusil (containing 50 tablets) to be taken for relief of discomfort as needed.
- The study then proceeded in a fashion similar (but not identical) to that described for the Tx period of study M87-090 (for both endoscopic and symptom assessments). In the present trial, safety assessments

included Bxs of the stomach to evaluate the effect of LANSO on EC-L, G, EC and D cell densities.

6. Statistical Methodology

a) Planned Sample Size

According to the Protocol, the study was designed to enroll sufficient patients such that 280 patients would complete the study and have evaluable efficacy data (80 in each of the active Tx groups and 40 in the PL group). This sample size had a greater than 98% chance to detect significant differences between the LANSO and PL groups if true healing rates were 85% and 50% ($p < 0.05$, two-tailed test). Expected differences between LANSO and RAN, determining sample size, were not mentioned in the Protocol.

b) Patient Evaluability

A priori listed reasons for excluding patients from efficacy analyses³⁵ were

- DU <3 mm in diameter, or multiple ulcerations if all were not duodenal and/or pyloric channel in location.
- Evidence of additional clinically significant medical Dz, as determined from review of the patient's med. Hx by the medical monitor.
(But no definitions for "clinically significant medical Dz" were given.)
- Chronic use of ulcerogenic medication prior to or during Tx, except as allowed by the protocol.
- Use of antiulcer medication during Tx, except as allowed by the protocol, or equal to or in excess of the standard doses for >3 days within the 2 weeks prior to the start of test medication.
- Current Hx of drug or alcohol abuse.
- Previous G.I. surgery (simple closure of GU or DU perforation were acceptable).
- <67% of prescribed test med. taken from BL to each visit, or <7 days of test med. taken.
- Screening laboratory values not WNLs and patient terminated upon discovery after receiving <7 days of med.
- No endoscopy performed after the start of Tx or all such endoscopies excluded by the above criteria.

c) Parameters of Evaluation

- The primary efficacy endpoint was the endoscopic assessment (ulcer healed/unhealed), as stated in the protocol.
- Additional efficacy endpoints were symptom assessments and diary summaries (Gelusil use and day and night abdominal pain).

³⁵ According to the Clinical Report, classification of patients regarding acceptability of data for efficacy analyses was carried out by the project team (medical, data management, and statistics) prior to their knowledge of the D-B Tx group assignments. Individual data exclusions were also completed at that time.

- Safety variables were assessments of AEs, clinical laboratory data including gastrin and Bx results, and data from P.E., EKG and vital signs.

d) Statistical Analyses

- The proportion healed on each dose of LANSO at each time point was compared to the proportion healed on RAN and PL using Mantel-Haenszel methods for combining (2 x 2) tables across investigators, as stated in the protocol.
- Similar comparisons between LANSO groups were presented to evaluate dose response.
- Homogeneity of Tx difference across investigators (Tx-by-investigator interaction) was examined using the Breslow-Day test.
- ITT³⁶ and Evaluable³⁷ Population analyses were conducted for investigators with at least one patient in each of the 4 test groups.
- Tx-group comparisons, adjusting for concomitant factors (age, sex, ulcer diameter at entry, alcohol use, caffeine use, tobacco use, and whether this was the first episode of duodenal ulcer) were examined using Mantel-Haenszel methods for combining (2 x 2) tables across levels of each factor.
- Homogeneity of Tx differences across levels of each concomitant factor (Tx-by-factor interaction) was examined using the Breslow-Day test.
- Results from symptom assessments were analyzed by Cochran-Mantel-Haenszel methodology for ordered response categories using the BL value as the "covariate" (analyses of ITT and Evaluable Populations).
- For data from diaries, pairwise comparisons of the mean severity, days of Tx until last report of each symptom, and percentage of days with each symptom were performed using the Wilcoxon two sample test.
- Adverse events and other safety data were evaluated as described for RE trials and the DU trial just preceding the review of the present study.

7. Study Results

a) Participating Investigators

In this trial, 30 qualified investigators, geographically distributed throughout the United States, enrolled a total of 301 patients [PL=44; RAN 30 mg HS=86; LANSO 15 mg QD=87; LANSO 30 mg QD=84].

³⁶ Analysis of ITT patients: Weeks 2 and 4 endoscopy results were defined as the result closest to the end of Tx obtained on or prior to Study Day 21 and Study Day 35, respectively (last value brought forward method). Patients without an endoscopy within 5 weeks after the start of Tx were counted as failing to heal.

³⁷ Analysis of evaluable patients: Weeks 2 and 4 endoscopy results were defined as the result closest to the end of Tx obtained during the interval from seven to 21 days and 22 to 35 days from the start of Tx, respectively, using data considered acceptable for the efficacy evaluation. Patients with no endoscopy in a given time interval were considered healed if healing was documented during the most recent time interval during which an endoscopy was performed. Otherwise, a patient with no endoscopy in a given time interval was not included in the analysis for that time interval.

b) Number of Patients in the ITT and Evaluable Population Analyses

- 300 (instead of 301) patients were included in the analysis of ITT patients.
 - Pt. (Koval) was excluded from the analysis of ITT patients due to inappropriate endoscopy at entry (erosive esophagitis Grade 2). Test med. was stopped on Study Day 3. In this patient, no efficacy data were obtained after the start of Tx.
- The Evaluable Population consisted of 280 patients who had entered the Tx period and were included in at least one of the primary efficacy analyses. (Week 2 or 4) [PL=41; RAN=82; LANSO 15 mg=80 and LANSO 30 mg=77 patients].
- Details for each of the 21 patients who were excluded from the evaluable patient analyses are given in Table 36; a summary is included in the lower panel of this Table.

c) Data Showing Comparability of Groups

i) Premature Terminations

- A summary of the primary reasons for premature termination from the Tx period is given in Table 37.

TABLE 37
Study N88-268

Summary of Primary Reasons for Premature Termination
From the Tx Period*

(Number of Patients)

Termination Reason	PL	RAN 300 mg HS	LANSO (mg QD)	
			15	30
AE ^b	0	1	2	0
TxF	3	3	0	1
Personal	0	1	1	1
Lost to F/U	0	1	1	2
Other	0	0	1	0
Total	3	6	5	4

- a) Sponsor's Table 7.2.1 listed the investigator, patient number, Tx group, number of completed days of Tx, age, sex, and the reason for termination for each of these patients.
- b) Two additional patients (Lanza) in the RAN 300 mg HS group and (Koval) in the LANSO 15 mg QD group were D/C from the study in part due to an AE; however, the AE was not the primary reason for premature termination.

TABLE 36
Study NBS-268
Exclusions from Efficacy Analyses: (Complete Patient Data Exclusions)

Pt. # (Inv.)	Date Type Excluded	Excluded Visits (Rx Day)	Reason
PL (N=3)			
(Fumo)	E, S, D	All	Use of other antilucer med. during the Tx period (Bentyl 10mg)
(Goff)	E, S, D	All	Chronic prstudy use of steroids
(Levine)	E, S, D	All	Took 5 days of test med. (<7 days)
RAW 300 mg QD (N=4)			
(Herb)	D	All	No diary data after start of treatment
(Lenze)	E E S	Wk 2 (20) All All	Tx period endoscopy done >5 days after the last dose (13 days) No evaluable endoscopy after start of Tx Only symptom assess. after start of Tx was >5 days after end of Tx (13d)
(Levine)	E, S, D	All	Dosing instructions not followed
(Nelson)	E, S, D	All	Took <67% of test med., dosing instructions not followed
(Oliver)	E	All	No endoscopy after start of Tx
LAJBO 15 mg QD (N=7)			
(Berry)	E, S, D	All	Dosing instructions not followed
(Bruns)	E, S, D	All	Chronic prstudy use of NSAIDs (acetylsalicylic acid)
(Godwala)*	S	All	No BL symptom assessment
(Kogut)	E, S, D	All	Took <67% of test med.
(Kovel)*	E, S, D	All	Endo. grade not approp. for entry, took only 3 days of test med. (<7d)
(Kovel)	E, S, D	All	No data after start of Tx
(Silvers)	E E, S, D	Wk 2 (15) All	Tx period endo. >5 days after the last dose (14 days) Took only 1 day of test med.
(Silvers)	E, S, D	All	Dosing instructions not followed, took <67% of test med.

TABLE 36 (Con't)

LANSO 30 mg QD (N=7)			
(Aarenon)	E, S, D	All	Admission criteria violation-previous hiatal hernia surgery
(Aarenon)	E, S, D	All	Chronic prestudy use of NSAIDs (Mobic for te)
(Bruns)	E, S, D	All	Ibid (Advil and acetylsalicylic acid)
(Bruns)	E, S, D	All	Ibid (Advil)
(Goff)	D	All	No diary data after start of Tx
(Sahba)	E S	All All	No endoscopy after start of Tx The only symptoms assessment completed after start of Tx was at 19d
(Sahba)	E, S, D	All	Posing instructions not followed, took <67% of test med.
(Sperling)	E, S, D	All	Admission criteria violation-drug abuse

a) Endoscopy, b-Symptoms, b-Diary
b) All/all visits completed by that patient
c, d) Also excluded from the ITT analyses for indicated data type

SUMMARY	
No. of Pts.	Reasons for Exclusion
7	Admission criteria violation. Inv. failed to exclude Pt. from study (5 for chronic prestudy use of NSAIDs/steroids; 1 for drug abuse, and 1 for previous surgery)
1	Admission criteria violation. Pt. received <7 days of test med.; (esophagitis grade 2 present at screening)
2	Not admission criteria but took <7 days of test med.
1	Use of other antulcer med. during the Tx period
6	Posing instructions not followed or took <67% of test med. during Tx period
4	Tx period <7 days, but no evaluable data after start of Tx

ii) Demographic and Disease Baseline Characteristics
(Table 38)

- Summarized in this Table are the demographic and disease BL characteristics of the 301 patients who entered the D-B Tx period.
- There were no significant differences among the four Tx groups, combined across investigators for age, body weight, height, sex, race, tobacco use, alcohol use or caffeine use³⁸.
- For the ITT Population there were no significant differences among Tx groups combined across investigators in ulcer diameter at entry (Table 38).
- The initial ulcer size was:
 - >5 to 10 mm in 59.8% of the patients
 - >10 mm in 18.3% of the patients
 - ≤5 mm in 23.9% of the patients.
- At baseline, the severity of both day and night abdominal pain was similar among all 4 Tx groups. Most patients had symptoms mild to moderate in severity.
- There were no significant differences among Tx groups, combined across investigators, in the percentages of patients reporting G.I. history for any of the medical factors that may influence PUD (Table 38, Lower Panel).

d) Primary Efficacy Parameters

1) General (Table 39)

ITT Population

- As shown in this Table, at Week 2, LANSO could not be differentiated from PL. Neither LANSO group was superior to PL or RAN in healing rates [RAN could not be differentiated from PL either].
- At Week 4, the LANSO 15 mg group was superior to both PL (+45.2%) and RAN (+22.1%) in healing rates; LANSO 15 mg was numerically higher (+12.2%) than but not statistically superior to LANSO 30 mg ($p \geq 0.071$). RAN was superior to PL.

³⁸A significant difference was noted among the Tx groups for caffeine use in evaluable patients. The percentages of caffeine users were 44/25 (80.5%) in the PL group; 62/82 (75.6%) in the RAN 300 mg HS group; 74/80 (92.5%) in the LANSO 15 mg QD group; and 61/77 (79.2%) in the LANSO 30 mg QD group (sponsor's Table 7.4.1).

TABLE 30
Study 105-268

Summary of Demographic and Disease Baseline Characteristics
(All Patients)

Variable	All Pts. (N=301)	PL (N=66)	RAM 300 mg (N=66)	LANSO (mg)		Overall P-value
				15 (N=87)	30 (N=68)	
Age Mean (S.D.) (y) Min-Max	43.2 (13.5) 19-81	39.8 (12.8) 21-70	44.5 (13.2) 26-76	43.9 (14.0) 19-81	42.8 (13.7) 19-76	N.S. ^a
Weight-F No. of Pts. Mean (S.D.) (lbs)	163 183.1 (31.7)	28 176.2 (33.1)	54 187.5 (32.3)	56 186.2 (32.0)	50 178.7 (29.7)	N.S. ^b
Weight-F No. of Pts. Mean (S.D.) (lbs)	113 158.6 (32.5)	16 155.9 (29.0)	32 152.1 (29.8)	31 163.1 (40.5)	34 160.1 (28.7)	N.S. ^b
Weight-F No. of Pts. Mean (S.D.) (inch)	106 70.1 (2.6)	28 70.3 (3.4)	54 70.0 (2.5)	56 69.6 (2.3)	50 70.5 (2.4)	N.S. ^b
Weight-F No. of Pts. Mean (S.D.) (inch)	113 63.9 (2.9)	16 65.5 (1.6)	32 63.4 (2.4)	31 63.7 (2.1)	34 63.9 (3.5)	N.S. ^b
Sex M F	108 113	28 16	34 32	36 31	50 34	N.S. ^c
Race Caucasian Black Other	241 41 19	39 3 2	71 13 2	67 13 7	64 12 8	N.S. ^c
Tobacco Tobacco Nonuser ^d Tobacco User	154 147	21 23	41 45	47 40	45 39	N.S. ^c
Alcohol Non-drinker ^d Drinker	135 166	17 27	33 53	40 47	45 39	N.S. ^c
Caffeine No Yes	55 246	8 34	21 65	9 78	17 67	N.S. ^c
Diuretic S.D. >5-10 >10	72 174 55	10 25 9	20 49 17	23 53 11	19 47 16	N.S. ^c

TABLE 38 (Con't)

SUMMARY OF PRIMARY SYMPTOMS AT IN						
Sex						
Abdominal Pain	NONE (0) MILD (1) MED (2) SEV (3)	7 12 17 8	13 23 40 10	16 21 30 9	19 21 31 13	N.S. ^a
Row Mean Score		1.59	1.55	1.44	1.45	
Blight	NONE (0) MILD (1) MED (2) SEV (3)	11 10 12 11	16 14 37 17	24 17 36 9	23 17 25 19	N.S. ^a
Row Mean Score		1.52	1.62	1.35	1.48	
PERCENTAGE OF PTS. REPORTING GASTROINTESTINAL DX						
Medical History Factors						
First Episode of DU		138 (45.8%)	19 (43.2%)	35 (40.7%)	46 (52.9%)	38 (45.2%) N.S. ^b
Previous GU		23 (7.6%)	4 (9.1%)	10 (11.6%)	5 (5.7%)	4 (4.8%) N.S. ^b
Previous RE		37 (12.3%)	5 (11.4%)	10 (11.6%)	12 (13.8%)	10 (11.9%) N.S. ^b
Previous Therapy for Any GI Disorder		273 (91.7%)	39 (86.4%)	79 (91.9%)	80 (92.0%)	75 (89.3%) N.S. ^b
Hiatal Hernia ^c		90 (26.6%)	15 (34.1%)	21 (24.4%)	26 (27.6%)	20 (25.8%) N.S. ^b
Previous GI Surgery ^d		7 (2.3%)	0 (0.0%)	3 (3.5%)	0 (0.0%)	4 (4.8%) N.S. ^b

a) At the start of the 8-8 period
b) p-value from F-test for testing equality of Tx means
c) p-value from Chi-Square test
d) Includes ex-tobacco users
e) Includes ex-drinkers
f, g) Based on Cochran-Mantel-Haenszel methods
h) Likelihood ratio Chi-Square for difference among Tx groups
i) Tested during endoscopy at any time during the study
j) 4 patients (2 in the LA500 30 mg QD group, Kogut and Schwartz) had evidence of ulcer or perforated ulcer and two patients (1 in the LA500 30 mg Herb) and 1 in the 300 mg group (Herb) had esophageal dilations performed, and 1 patient in the LA500 30 mg group (Abramson) had hiatal hernia surgery.

Evaluable Population

- In these analyses, no differences among the 4 groups were noted at Week 2 (again).
- At Week 4, each of the LANSO groups and RAN were superior to PL. In addition, the LANSO 15 mg group was significantly higher in healing rates to the LANSO 30 mg group (+12.0%) and RAN (+21.8%).

NOTE: The FDA biometrician is considering the following statistical matters. What are the ITT and Evaluable p-values exactly for the comparison LANSO 15 mg vs RAN? How should these p-values be corrected for multiple comparisons? For comparisons of the LANSO 30 mg to the other groups why are therapeutic gains of 10% and 9.9% N.S. but 9.8% is significantly different?

ii) Factors Influencing Healing

Tx-By-Investigator Interaction

- At Week 4, for the Evaluable Population, significant lack of homogeneity across investigators was indicated in the comparison of LANSO 15 mg QD vs PL.
- This finding was apparently due to results of one investigator (Bruns). Three patients were entered at this center: although both pts. in the PL group healed the only one in the LANSO 15 mg group did not. The number of patients involved is very small (N=3) but this center presented healing rates higher in the PL group. This was an apparent reversal of healing rates. In spite of this, the healing rates of the LANSO 15 mg QD group remained statistically superior than those of the PL group (sponsor's Table 8.1.1).

Other Factors

[Data Applicable to Both ITT and Evaluable Population Analyses]

- At Week 4, LANSO 15 and 30 mg QD and RAN 300 mg HS were all significantly superior to PL when healing rates were adjusted for the concomitant factors of gender, age, BL ulcer size, alcohol use, tobacco use, caffeine use, and whether this was the first episode of DU.
- Also, at Week 4, LANSO 15 mg QD was superior to both LANSO 30 mg QD and RAN 300 mg HS when other factors were included in the analyses.
- At Week 2, there was no significant difference among the 4 Tx groups in healing rates when other factors were included in the analyses.
- The following numerical disbalances apparently resulted in significant lack of homogeneity across the concomitant factors (Tx-by factor interaction).

TABLE 39
Study M88-268

Healing Rates as a Function of Time and LANSO Dose

Week	PL	RAM	LANSO (mg)	
			15	30
[ITT POPULATION]				
2	14/44 (31.8)	26/86 (30.2)	30/86 (34.9)	35/86 (41.7)
Therapeutic Gain		-1.6 (N.S.)	3.1 (N.S.)	9.9 (N.S.)
4	19/44 (43.2)	57/86 (66.3)	76/86 (88.4)	64/86 (76.2)
Therapeutic Gain	•Over PL	23.1 (p<0.05)	45.2 (p<0.05)	33.0 (p<0.05)
	•Over RAM		22.1 (p<0.05)	9.9 (N.S.)
	•Over LANSO 30 mg		12.2 (p=0.071) (N.S.)	
[EVALUABLE POPULATION]				
2	14/41 (34.2)	25/82 (30.5)	28/80 (35.0)	34/77 (44.2)
Therapeutic Gain		-3.7 (N.S.)	0.8 (N.S.)	10.0 (N.S.)
4	19/40 (47.5)	55/78 (70.5)	72/78 (92.3)	61/76 (80.3)
Therapeutic Gain	•Over PL	23.0 (p<0.05)	44.8 (p<0.05)	32.8 (p<0.05)
	•Over RAM		21.8 (p<0.05)	9.8 (p<0.05)
	•Over LANSO 30 mg		12.0 (p<0.05)	

NOTE: Two patients, (Morva) in the LANSO 15 mg QD group and (Kogut) in the LANSO 30 mg QD group, were unhealed at Week 2 but were reported as healed at their final endoscopies (Study Days 37 and 36, respectively). Because these patients had their final endoscopies performed more than 35 days after the start of Tx, they were considered unhealed in the Week 4 analyses.

NUMERICAL IMBALANCE	APPARENT RESULT
WEEK 2 (BOTH ITT AND EVALUABLE POPULATIONS)	
• Higher healing rates among F than M in the LANSO 15 mg QD group; higher healing rates among M than F in the RAN 300 mg HS group. • Higher healing rates among drinkers than non-drinkers in the PL group; higher healing rates among nondrinkers than drinkers in the LANSO 15 mg QD group. • Higher healing rates among pts. who reported this as a first episode than those who did not in the RAN 300 mg HS group; higher healing rates among pts. who did not report this as a first episode than those who did so in the LANSO 30 mg QD group.	• Significant Tx-by-gender interaction in the comparison LANSO 15 mg QD vs RAN 300 mg HS. • Significant Tx-by-alcohol use interaction in the comparison LANSO 15 mg QD vs PL. • Significant Tx-by-first episode interaction in the comparison LANSO 30 mg QD vs RAN 300 mg HS.
WEEK 4 (BOTH ITT AND EVALUABLE POPULATIONS)	
Although none of the above-mentioned interactions at Week 2 was significant at Week 4, there were "unexpected" responses in healing rates at this time. This is discussed in detail under Comments.	

iii) Patients Healed at Week 2 but Unhealed at Week 4

- 10 pts. [PL=3; RAN=3; LANSO 15 mg=2; LANSO 30 mg=2] were evaluated as healed at Week 2 but unhealed at the Week 4 endoscopy. Data for the 4 LANSO pts. are summarized below.

Study M88-268

LANSO Patients Who Were Healed at Week 2 but Unhealed at Week 4

Pt. (Inv.) ^a	Ulcer Size (mm)			Smoking (ppd)	Alcohol Consumption (per day)	History of:	
	Scr	W2	W4			DU	Hiatal Hernia
LANSO 15 mg QD (N=2)							
(Erfling)	7	NONE	None-erosion	NON	<1 beer	YES	NO
(Sahba)	7	NONE	None-erosion	1-2	Ex (<1 beer <1 cocktail)	YES	YES
LANSO 30 mg QD (N=2)							
(Nelson)	6	NONE	None-erosion	NON	NONE	YES	YES
(Sahba) ^b	15	NONE	None-erosion	1-2	<1 beer	YES	NO

- a) All endoscopies listed were done by the same endoscopist.
 b) There were no erosions reported at Week 2.
 c) Pt. excluded from efficacy analyses for not following instructions and taking <67% of test med.
 - The other 3 pts. were apparently compliant with taking test med. during the Tx period.

e) Secondary Efficacy Parameters

- In the ITT analyses at Week 2, both LANSO 15 and 30 mg QD produced significant greater relief of day abdominal pain than PL. None of the two LANSO groups were superior to RAN or different from each other.
- In the Evaluable Population analyses at Week 2, only the LANSO 30 mg QD group showed significantly better relief of day abdominal pain than the PL group.
 - No other significant differences in the relief of day or night abdominal pain were shown at Week 2.
- In the ITT analyses at Week 4, LANSO 15 mg QD was superior to PL in producing relief of

NOTE: An * denotes analyses not statistically significant in the Evaluable Population.

- burning in the upper abdomen
- day heartburn
- night heartburn*
- fullness/bloating/early satiety and
- overall symptoms

LANSO 15 mg QD was superior to RAN 300 mg HS in the relief of

- burning in the upper abdomen
- night heartburn* and
- nausea

and superior to LANSO 30 mg QD in the relief of

- burning in the upper abdomen.

LANSO 30 mg QD was superior to PL in the relief of

- burning in the upper abdomen
- day heartburn
- fullness/bloating/early satiety and
- flatulence/abdominal rumbling*
- overall symptoms

and superior to RAN 300 mg HS in producing relief of

- day heartburn
- GE regurgitation and nausea*

The RAN 300 mg HS was significantly superior to PL in the relief of

- dysphagia
- abdominal distention
- overall symptoms

NOTE: The following analyses were significant in the 4-Week Evaluable but not the ITT population

- LANSO 15 mg. > LANSO 30 mg in the relief of diarrhea
- RAN > PL for fullness/bloating/early satiety

f) Diary Data

- In comparison to the PL group both the 15 and 30 mg LANSO QD groups reported significantly (ITT Analyses)

NOTE: Again, an * denotes analyses not statistically significant in the Evaluable Population.

- fewer days of Gelusil use
 - fewer tablets used per day
 - less day abdominal pain
 - fewer Tx days until the last report of day pain.
- The LANSO 30 mg QD group had significantly fewer days until the last report of night abdominal pain, fewer nights with abdominal pain* and significantly less severe night abdominal pain* than the PL group and was superior to RAN with respect to Gelusil use, percentage of days with abdominal pain and night abdominal pain.
 - The LANSO 15 mg QD group reported statistically significant fewer days with abdominal pain* and less severe day abdominal pain* than pts. in the RAN group and significantly fewer days until the last report of night pain* than the PL group.

g) Results of Safety Evaluationsi) Adverse Events During Tx Period

- AE reporting rates were similar for all 4 Tx groups.
- The most frequently possibly or probably Tx-related AE was headache (0%, 2%, 1% and 5% for the PL, RAN, LANSO 15 mg and LANSO 30 mg, respectively).
- No other AE was reported by >1 pt. in any Tx group.
- Of the possibly or probably related AEs, the majority were mild to moderate in severity in all Tx groups (sponsor's Table 9.1.4.).
- AEs were rare and distributed similar among the 4 Tx groups. There were 2 possibly/probably related AEs reported during the trial; eructation in Pt. (Sigmund), a 48y old F (PL) and vomiting in Pt. (Sperling), a 22y old M who also experienced a massive headache on Study Day 4 (LANSO 30 mg).

ii) Withdrawals Due to AEs

- 5 Pts. W/D during the D-B Tx period at least in part due to an AE (LANSO 15 mg QD=3; RAN=2). Events in 2 of the 3 LANSO 15 mg patients are summarized below (information taken from CRF).

(Kováč), a 63 y old F, had a medical Hx of hypertension and MI. She was prematurely D/C from the trial after 3 days of Tx in part due to severe chest pains which developed on Study Day 4. Arterial occlusion was considered an alternative etiology. The patient was hospitalized and underwent a triple bypass. The patient, however, was terminated prematurely from the study primarily because she had been inappropriately entered into the study with Grade 2 esophagitis. According to the Clinical Report, the investigator had decided to drop this patient before learning of the AE.

(Lanza), a 35 y old M, was prematurely D/C from the study after 10 days of therapy due to moderate pain and soreness in the upper right pectoral area which developed on Study Day 3. He took it upon himself to stop study drug Tx x 2 days, at which time the pain and soreness subsided. After restarting medication, the discomfort recurred one day later and the patient again stopped his medication. According to the Clinical Report, muscular strain was considered an alternative etiology, but the patient was W/D from the trial because the investigator believed that the study medication aggravated the symptoms (exacerbation of symptoms with drug rechallenge).

iii) Clinical Laboratory Determinations

- There were no clinically significant differences among the 4 Tx groups for routine laboratory parameters (hematology, blood chemistry, electrolytes, metabolic/nutritional, renal or urinalysis).

iv) Fasting Serum Gastrin Concentrations/Gastric Bx

- Fasting serum gastrin concentrations increased in both LANSO groups and RAN with significantly higher fs in both LANSO groups. These fs were seen by Week 2. No further significant fs occurred at Week 4.
- Analyses of data from full-thickness Bxs from gastric curvature and antral mucosae revealed no clinically significant histological changes.
- In both LANSO groups there were small changes observed. These consisted of slight increases in inflammation or small changes in the Solcia scale [from Grade 1 to 2]. There were also slight, although statistically significant, increases from BL in Grimelius-positive and G cell densities.

8. Conclusion (Sponsor)

"Lansoprazole, administered once daily before breakfast, healed duodenal ulcers significantly better than did placebo and ranitidine.

"Lansoprazole was safe for use in patients with duodenal ulcer at doses up to 30 mg per day for a period of up to four weeks."

9. Comments

Clinical trial M88-268 is the second of the two U.S., multicenter clinical trials submitted in support of the approval of LANSO 15 mg daily for the healing and symptom relief of duodenal ulcer. The trial's design used a double-blind, double-dummy, parallel group approach at 30 centers which enrolled a total of 301 patients. In accordance with the Protocol stated objective, a useful design allowed randomization of these DU patients to four groups. Patients in two of these groups received LANSO at either 15 or 30 mg once-a-day. The third group consisted of patients receiving a negative control (PL). Those randomized to the fourth group received RAN 300 mg HS. This constitutes an appropriate active comparator because the dose of H₂-receptor antagonist being tested is approved for this indication.

Just as in the other DU trial, at baseline, the patients randomized into this study [PL=44; RAN=86; LANSO 15 mg=87 and LANSO 30 mg=84] had endoscopically documented ulcer primarily of the medium size (>5 to 10 mm), manifested mostly by mild to moderate symptoms. The inclusion-exclusion criteria were adequate and in the main, similar to those used in Study M87-090.

The randomization process [1:2:2:2 for PL, RAN, LANSO 15 mg and LANSO 30 mg, respectively] resulted in four groups that were comparable in demographics and baseline disease characteristics and medical g.i. history. Test medication was given in 2-week intervals and treatment continued even if ulcers had

healed at 2 weeks, for a maximum of 4 weeks. An identically appearing active and PL drugs, in a double-dummy technique, was used to preserve the D-B character of the trial. Neither the endoscopist nor the specific patient being endoscoped knew the identity of the test medication being administered. These aspects of the execution of this trial are reiterated here because, in spite of these precautions, this reviewer feels that some findings in this trial seem contradictory and not what one would expect from what we already know of this PPI (see below).

In both, ITT and Evaluable Population analyses, LANSO was significantly more effective than PL in accelerating the short-term healing of DU but in this trial, to demonstrate effectiveness, 4 weeks of Tx were needed. Neither of the LANSO groups nor RAN 300 mg HS could be differentiated from PL at Week 2 and this was shown irrespective of the Patient Study Population being analyzed. For LANSO, the therapeutic gains (against PL) with 15 mg per day were 3.1% (ITT) or 0.8% (Evaluable population). These nearly nonexisting therapeutic gains at Week 2 in this trial are in sharp contrast with the 29% reported in trial M87-090 for the ITT Population at the same time. Similarly, for RAN this trial reported no therapeutic gains over PL at Week 2 and this finding was reproduced by analyses of both study populations [ITT = -1.6%; Evaluable Population = -3.7%]. The reviewer realizes that we are talking about different trials but the therapeutic gain of RAN over PL at Week 2 listed in the PDR is 19% [Evaluable Population; No. of Pts. entered=180].

Interpretation of the data from Study M88-268 poses several challenges because there seem to be no easy explanations. For example, the 2-week PL response in the second DU trial was three times higher (31.8%) than the first (10.7%). It is easy to propose that the introduction of an active drug into the design of the trial "inflates" ulcer healing response because this is a well known phenomenon encountered over and over. But, in spite of the 21.1% differential in PL response, the differential in LANSO 15 mg response was much smaller and going in the opposite direction (-4.8%). These findings, I believe, pose a challenge in that contradictory results are seen in regards to activity at Week 2: one trial says - at this time - LANSO 15 mg is well differentiated from PL, the other gave null results (LANSO 15 mg is not different from PL). Which results do we believe? Until a plausible explanation is offered by the sponsor or reanalyses (B) of the data resolve these inconsistencies this reviewer believes that it is reasonable to state that LANSO 15 mg is active in the healing of DU but that a minimum of 4 weeks dose duration is needed. This statement is to be contrasted to that of "up to 4 weeks" proposed by the sponsor.

Another challenge when assessing results from this trial is to offer plausible explanations for the reported statistical superiority of LANSO 15 mg over the 30 mg dose. This finding is not only not a confirmation of what was seen in trial M87-090 but appears to be in defiance of what we know about antisecretory drugs in general. In Study M87-090 the 30 mg LANSO dose was not different from the 15 mg dose at Week 2 (25.3% vs 29%, respectively) and is actually 7.1% more effective than the 15 mg dose at 4 weeks (48% vs 40.99%). The 30 mg dose was certainly not statistically inferior to the 15 mg dose. All of these findings are difficult to interpret. In trial M88-268, at Week 2, the 30 mg gave higher healing rates than those seen with the 15 mg LANSO dose [therapeutic gains=9.9 and 10.0 in the ITT and Evaluable Population, respectively, vs 3.1% and 0.8%]. But before we accept these findings, validation of the data from CRFs and statistical methodology is needed. The reviewer's point is that if one is going to accept a superiority of the 15 mg over the 30 mg dose of LANSO at Week 4 [therapeutic gain=12% (p<0.05)] in the Evaluable and 12.2% (p<0.071) in the ITT population] then one seems to be saying that with LANSO, a plateau of response has been reached with the 15 mg dose already. This 12% difference in healing rates between these two LANSO

dose levels is not trivial. Antiulcer drugs have been approved and recognized as active with similar or even smaller therapeutic gains over PL [see the very initial package insert for TAGAMET (cimetidine)]. Whatever the explanation, if these findings are "real", a corollary of these evaluations is that the label should include the data with the 30 mg to inform the practitioner that this dose of LANSO was actually inferior to the 15 mg (in one trial). This is important because in clinical practice, doctors (and patients themselves) tend to increase the dose to optimize results.

It is possible that these "unexpected differences" are due to numerical imbalances between/among the groups. This and the p-values in ITT and Evaluable Population analyses should be carefully verified by Biometrics. Similarly, scientific investigations should make sure that these findings are "real" and not the results of gross deficiencies in the conduct of the trial. In the absence of original CRFs to examine (and these have not been submitted by the sponsor) the MO cannot entirely validate the assessed data.

This trial showed a quicker healing with LANSO 15 mg once in the morning compared with RAN 300 mg HS. Although no difference between the two drugs was observed in healing rates at Week 2, the Week 4 healing rates [92.3% for LANSO 15 mg and 70.5% for RAN in the Evaluable Population] represents a sizable therapeutic gain (22%) when patients were treated with the PPI rather than the H₂-blocker. If this finding is replicated (in another trial) the sponsor may be entitled to a superiority claim (in advertisement) because the RAN dose treated in trial M88-268 is an approved dose for this indication (healing of DU).

In this trial, it took at least 4 weeks for LANSO 15 mg to influence some secondary effectiveness measures. These findings are not very reassuring. The two LANSO groups (and RAN) were no different from PL in symptom relief at Week 2. Although the reviewer is impressed by the possible sizable therapeutic gain in healing (22%), he is not impressed by the effects on symptoms. This is because even after 4 weeks of treatment, LANSO 15 mg once a day was not different from RAN 300 mg HS in the relief of day or night abdominal pain. The main reason the patient seeks the physician's help is to get rid of his/her symptoms.

The data in Study M88-268 also showed that LANSO (15 or 30 mg once daily) is well tolerated in the DU population. Headache was the most frequently reported possibly or probably Tx-related AE (PL=0%; RAN=2%; LANSO 15 mg=1%; LANSO 30 mg=5%). This insinuation of dose response needs to be properly documented in larger number of patients. Also, the majority of possibly or probably Tx-related AEs were mild to moderate in severity in all Tx groups. Not unexpectedly, fasting serum gastrin concentrations increased in both LANSO groups. These increases were significantly higher than those induced by RAN. These increases in gastrin were already detected by Week 2 with no further significant increases by Week 4. No clinically significant histological changes were reported in analysis of data from full-thickness Bxs from gastric mucosa. Also, this trial did not include F/U endoscopies after the ulcer had healed at 4 weeks. Quality of healing aside, it would have been of interest to compare, side by side, the rate of recurrence of DU in those patients that had healed while on LANSO therapy vs those patients treated with RAN.

E. Summary of Section E (Efficacy): S-T Tx of DU

In support of the approval of LANSO 15 mg once-a-day before eating for up to 4 weeks the sponsor submitted the results of two studies M87-090 and M88-268.

Study M87-090 showed that LANSO 15 mg per day given before breakfast for 2 to 4 weeks is effective in healing DU and in inducing symptomatic relief. There seemed to be no advantage in increasing the once daily LANSO dose to 30 or even 60 mg. This trial supports the sponsor's proposal of the use of LANSO 15 mg per day for the S-T treatment (up to 4 weeks) for healing and symptom relief of duodenal ulcer.

In Study M88-268, LANSO 15 mg per day given before breakfast for 4 weeks was shown effective in healing DU but this dose of PPI did not influence day or night abdominal pain. This dose of LANSO given for the same length of time (4 weeks) accelerated DU healing quicker than RAN 300 mg HS, with a clinically meaningful therapeutic gain of 22%. There was no difference between LANSO 15 mg once daily and RAN 300 mg HS in the relief of day or night abdominal pain. Before these conclusions can be accepted, however, caution is warranted because this trial reported a number of "unexpected" findings and inconsistencies for which no easy interpretation/explanation can be offered mostly questions. These are discussed in detail in the Comments section of the review of Study M88-268. The reviewer feels that to confidently state conclusions from this trial, validation of the raw data from the CRFs (Scientific Investigations) and verification/confirmation of p-values through statistical methodologies (Biometrics) is necessary.

Not Approved

Indication

Pages 225-267

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XII. Clinical Efficacy: Long-Term Tx of Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome (Z-ES)

A. Indication sought (as stated in the proposed labeling).

"PREVACID Delayed-Release Capsules are indicated for the long-term treatment of pathological hypersecretory conditions including Zollinger-Ellison syndrome.

"The dosage of PREVACID in patients with pathologic hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose is 60 mg once a day. Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Dosages of up to 90 mg b.i.d. have been administered. Daily dosages of greater than 120 mg should be administered in divided doses. Some patients with Zollinger-Ellison syndrome have been treated continuously with PREVACID for more than three years."

B. Clinical Trials For This Indication

In support of the efficacy and safety of PREVACID® for this indication the sponsor submitted three critical trials. The three were single-center, U.S., open-label, non-randomized, non-comparative, dose-titration evaluations of the ability of LANSO in treating hypersecretors, including those with Z-ES. Criteria for inclusion into the trials were documented Z-ES with BAO >10 mEq/h, a fasting gastrin level above normal range, and/or rise in serum gastrin concentration of pg/mL in response to secretin⁴⁹. For hypersecretors without Z-ES the BAO needed to be >15 mEq/h with normal serum gastrin levels. For those patients that had undergone prior gastrectomy, the BAO needed to be ≥5 mEq/h with prior documentation of Z-ES.

The primary parameter of efficacy in all three trials was the ability of the PPI to reduce the BAO to a pre-established goal. The latter was 5 mEq/h in studies M89-405 (N=30 pts. in the trial) and M90-436 (N=6 patients in the trial) and 10 mEq/h in Study M88-139 (N=21 pts. in the trial). The trials were expected to explore if the reduction in BAO was accompanied by a reduction in the incidence of acid-related symptoms and/or a decrease in the incidence of acid-induced symptoms in those patients in whom symptoms or mucosal lesions were present before the start of Tx.

It was not expected that LANSO would alter the course of the neoplastic disease in the Z-ES pt. If during the course of Tx in any of the three trials a patient developed clinical signs and symptoms related to the neoplasm, appropriate standard diagnostic and therapeutic procedures were performed as dictated by the patient's clinical condition.

C. Study M89-405

"The Use of Lansoprazole in Patients with Zollinger-Ellison syndrome and patients with Hypersecretion of Gastric Acid"

The PI for this study was B. Hirschowitz, M.D., Univ. of Alabama.

This is an Interim Report (May 1990 to November, 1992). The trial is ongoing.

⁴⁹The secretin test consists in determination of serum gastrin concentration to document a rise in response to an intravenous infusion of 2 units/kg of the g.i. hormone secretin.

All the pts. had been previously treated with histamine H₂-receptor antagonists (H₂) or OME. The dose of LANSO determined to provide adequate control of gastric acid output and symptoms in each patient was compared with the patient's previous dose of H₂ or OME. Before entering the Dose-Titration Phase, pts. stopped Tx with H₂ or OME at least 24h prior to the beginning of the trial and Tx with anticholinergics at least 72h prior to study start. The trial consisted of two Phases: Phase 1 (dose titration) and Phase 2 (long-term maintenance).

1. Dose-Titration Phase

- During this Phase pts. received an initial LANSO dose of 60 mg once-a-day (QD) for at least 3 days (but no longer than 7 days).
- The BAO and MAO were then evaluated during the 2h immediately prior to the next dosing, and the dose was ↑ (if necessary) until a BAO ≤5 mEq/h was obtained and symptoms were controlled.
- The dose of LANSO was ↓ if BAO was <1 mEq/h.
- If the dose required was ≥120 mg QD, the dosage was divided and self-administered at 12-h intervals.
- The dose titration process was repeated until an effective dose was established.
- Pts. who demonstrated adequate inhibition of gastric acid secretion (↓ in BAO to ≤5 mEq/h and control of symptoms during Phase 1), were given the opportunity to enter the maintenance Phase of the trial.

2. Maintenance Phase

This was a long-term assessment of the ability of LANSO to control acid output and symptoms in pts. with S-ES or gastric acid hypersecretion.

- Each patient began the L-T phase at the dosage to which he/she was titrated during Phase 1.
- If at any time the patient developed symptoms consistent with gastric acid hypersecretion and/or BAO increased to >5 mEq/h, control of gastric acid secretion was reassessed and the same dosage adjustments described above were made at this point.
- The dose of LANSO could also be ↓ if a patient's acid secretion and symptoms were well-controlled.
- Patients were seen at the clinic at Months 3, 6, 9, 12 and every 6 mo.
- At each of these visits, BAO, MAO, and pepsin concentration were measured for the 2h immediately preceding the next dose of LANSO, symptoms were assessed, and (except for Month 9) endoscopy was performed.
- BAO and MAO were measured at the Month 9 visit only if the patient presented with symptoms compatible with gastric acid hypersecretion. However, the investigator ended up measuring acid output at the Month 9 visit regardless of symptom assessment results.

3. Study Execution

The procedures to assess BAO, MAO, symptoms and safety, including gastric Bxs for endocrine EC-L cell density, were all adequate. Also adequate were the scales to grade endoscopic findings in the esophagus, stomach and duodenum.

4. Statistical Analyses

- The BL value was defined as the last value obtained prior to the start of the test med. Negative changes from BL represented ↓ from BL. The final value was defined as the last value obtained on or before November 30, 1992.

5. Results

a) Patient Disposition

- 30 pts. (20 M; 10 F; age 22 to 88y) were enrolled in the trial.
 - There were 22 Z-ES pts. and 8 hypersecretion pts.
 - 2 of the 22 Z-ES pts. had MEN-I disease
 - 21 pts. remained active as of November 30, 1992.

b) Premature Terminations

- 9 pts. were terminated from the study prematurely.
- 2 of these were D/C during the dose-titration Phase.
[1 because he did not meet entry criteria; 1 due to ↑ LFTs at BL]
- 7 were D/C prematurely during the maintenance for the following reasons:
 - 3 due to poor compliance
 - 3 due to AEs
 - 1 because neither the pt. nor the PI were willing to repeat endoscopy.

Details in these 9 pts. are given in Table 51.

c) Medical Hx

- 22 of the 30 pts. had been diagnosed with Z-ES; the remaining 8 were hypersecretors (without Z-ES).
- The mean duration of Z-ES or hypersecretion (from diagnosis to start of LANSO) was 1113 days (range: days).
- The mean BL BAO was
 - 28.4 mEq/h (range: mEq/h) for the Z-ES pts.
 - 21.2 mEq/h (range: mEq/h) for the hypersecretors.
- 4 of the 30 pts. had previously undergone a gastrectomy. The mean screening BAO for these pts. was 9.2 mEq/h (range: mEq/h).

TABLE 51
Study N89-405

Premature Terminations

Pt. I.D., Age, Gender	Final LAHSO Regimen	Day of Tx	Reason for Termination
60 M	60 mg QD ^a	2	BAO <5 mEq/h (Did not meet entry criteria)
43 M	60 mg QD ^b	5	Elevated LFTs at screening
39 M	45 mg QD	223	Poor compliance
62 M	60 mg QD	230	Poor compliance
33 M	60 mg QD	302	Poor compliance
31 F	90 mg BID	423	Pregnancy
50 M	30 mg QD	179	Recurrence of malignancy
79 F	75 mg BID	330	Burning sensation in the feet and tremors in the hands
61 M	60 mg QD	105	Pt. and PI unwilling to repeat endoscopy

a,b) Final titration dose not attained

d) Antiulcer Medications Prior to Study Start

This information is summarized in Table 52.

TABLE 52
Study N89-405

Antiulcer Medication Usage Immediately
Prior to Study Start

Antiulcer Medication ^a	No. of Pts. [N=29]
ONE ^b	12
FAM	8
RAM	5
CIM	3 ^c
SUCR	1 ^c
NIZ	1

a) The median doses of antiulcer medication prior to study start were

- ONE 50 mg daily
- FAM 120 mg daily
- RAM 600 mg daily

equivalent dose of histamine H₂-receptor antagonists was obtained by considering 150 mg RAM, 600 mg CIM, 20 mg FAM and 150 mg NIZ to be equivalent doses.

- b) Does not include Pt. #117 who was found to be receiving LASIX[®] instead of LOSEC[®] prior to screening.
- c,d) One patient received both CIM and SUCR.

e) Efficacy Results

i) Dose-Titration Phase (Table 53)

- For the 28 pts. who entered the maintenance Phase of the trial, the median daily end-of-titration dose was 60 mg QD.

TABLE 53

End-of-Titration LANSO Dose^a for Patients Who Entered the Maintenance Phase

LANSO Dose	No. of Pts. (N=28)
15 mg QD	1
45 mg QD	4
60 mg QD	11
75 mg QD	2
90 mg QD	1
45 mg BID	1
105 mg QD	1
60 mg BID	4
75 mg BID	3

- a) Pts. received an initial LANSO dose higher than 60 mg QD because of high values for BAO/MAO at screening.

- There was no significant correlation between end-of-titration dose of LANSO and previous dose of antiulcer medication⁵⁰, BL BAO, or BL MAO.

ii) L-T Maintenance Phase (Table 54)

- The total duration of participation in this trial to the second interim cutoff date for the 28 patients who entered the L-T Maintenance Phase ranged from _____ days, or _____ y (mean 1.4y). This reflects 39.5 patient years of LANSO exposure.
- The median daily dose at the final Tx visit was 60 mg (25 patients)⁵¹.

⁵⁰Too few patients (five or less) on CIM, RAN, NIZ were available to examine the relationship individually for these histamine H₂-receptor antagonists.

⁵¹3 pts.

did not have a maintenance visit on or before November 30, 1992.

TABLE 54
Study N89-405

**Dose of LANSO at the Final Treatment Visit^a for Patients
Who Entered Phase 2 and Had at Least One Maintenance
Visit Before the Interim Cutoff Date**

LANSO Dose	No. of Pts. [N=25]
30 mg QD	3
45 mg QD	2
60 mg QD	7
75 mg QD	1
105 mg QD	1
 	
15 mg BID	1
30 mg BID	3
45 mg BID	2
60 mg BID	2
75 mg BID	2
90 mg BID	1

a) The 3 pts. without gastrectomies who were enrolled into the trial with BAO measurements <15 mEq/h (were receiving doses of 60 mg QD, 30 mg QD and 15 mg BID, respectively, at their final treatment visit.

- Of the 28 pts. who had entered the L-T Maintenance Phase as of November 30, 1992, 17 had been followed for more than one year and 11 of these had been followed for >2y (sponsor's Table 8.1).
- 13 of the 17 patients who remained active for >1y were taking their end-of-titration daily dose or a lower daily dose at Tx visit.
- 9 of the 11 pts. who remained active for >2y were taking their end-of-titration daily dose of a lower daily dose at the final Tx visit.
- The median final maintenance dose was 60 mg daily for the 17 patients who remained active for >1y.
- Dose adjustments are summarized below.

Study N89-405

Summary of Dose Adjustments* During
the Maintenance Phase

Dose Adjustment	No. of Pts.
Dose ↓	6 (24%)
Dose ↑	5 (20%)
No dose adjustment	7 (28%)
Both ↑ and ↓	7 (28%)

a) Of the 25 pts. who had at least one BAO measurement obtained in the Maintenance Phase, the total number of LANSO dose increases per pt. per year was 0.2.

- There was no significant correlation between final maintenance dose of LANSO and previous dose of antiulcer medications, BL BAO or BL MAO (please see footnote No. 50).

Gastric Acid Secretion During Titration/Maintenance Phase

- In the 28 evaluable pts. the BL BAO ranged from _____ mEq/h.
- At the end of the titration phase of the study BAO values for these 28 pts. were all <5 mEq/h [range _____ mEq/h (median 0.55 mEq/h)].
- As of November 30, 1992, 25 pts. had completed at least one maintenance visit. From these,
 - Pt. _____ (31y old F) had a final BAO of 16.5 mEq/h. This was in spite of receiving a final LANSO dose of 90 mg BID before being terminated from the trial.
 - Pt. _____ (28y old M) had a final BAO of 5.5 in spite of receiving the highest single dose of LANSO (105 mg QD).
 - In the Clinical Report the results in Pt. _____ are included when the sponsor states that "for the other 24 patients (median Final Visit BAO 1.4 mEq/h for these 25 pts.)"
 - 18 of these pts. had BAO values <2.0 mEq/h.
 - 6 of these 18 pts. were essentially achlorhydric (BAO ≤0.1 mEq/h) at the Final Tx Visit⁵².

Pepsin Results

- For baseline pepsin output, there were statistically significant differences at Months 3 and 6 and the Final Tx Visit in the analysis of mean change from BL.
- For maximum pepsin output, there was no significant mean change from BL to any subsequent visit.

⁵² I agree with the sponsor that this suggests that a lower dose of LANSO might ultimately control acid secretion in these patients.

Endoscopy Results (Table 55)

- 25 pts. had a BL endoscopy and at least one subsequent endoscopy.
- 4 pts. had only endoscopy at screening and 1 pt. had no BL endoscopy. These 5 pts. are not included in the analysis.
- At screening, 6 pts. presented
with Grade 2 or greater esophagitis, and two patients presented with Grade 1 esophagitis.
 - 7 of these 8 pts. along with the 18 pts. who had Grade 0 esophagitis noted at screening, had normal-appearing mucosa (Grade 0) at the final endoscopy.
 - The remaining patient had Grade 1 esophagitis at the final endoscopy which had been noted as Grade 4 at baseline (see upper panel of Table 55).
- 6 pts. presented with DUs or GUs
at BL, but each healed during the trial (see lower panel of Table 55).

TABLE 55
Study N09-405

Endoscopy Data

Esophagitis Grade	BL	Final
I. Esophagitis		
0	17	24
1	2	1
2	4	0
3	0	0
4	2	0
II. Ulcers		
DU*	5	0
GU*	2	0

- a) Pt. presented with a DU at BL, which subsequently healed during Tx, recurred at Month 24, and again healed by the end of Tx. This DU is not reflected in this Table because the patient had more than one visit in the Month 24 window; by convention, only results from the last visit were included.
- b) Pt. presented with a GU at BL, but his only endoscopy procedure during Tx with LANSO was for dilation of an esophageal stricture and did not include evaluation of the stomach and duodenum (not included in this Table).

Symptom Assessment

- 28 of the 30 pts. enrolled in the trial had symptom assessments at BL and during at least one subsequent visit. The sponsor summarized in a

long Table (8.5.a.) the patient's perceptions of their overall symptoms at BL and at the final Tx visit. This showed improvement in their overall symptoms at the final visit compared to BL:

Study M89-405

Overall Symptom Assessment

	BL (N=28)	Final Tx Visit (N=28)
NONE	4	17
MILD	17	9
MOD	7	2
SEV	0	0

- In the main, symptoms remained well controlled if comparisons for the individual symptoms were made from BL to the Final Tx Visit:
 - 12 pts. remained unchanged (NONE=3; MILD=7; MOD=2).
 - 15 pts. improved (MILD → NONE=10; MOD → MILD=1; MOD → NONE=4).
 - 1 pt. worsened (NONE → MILD).

This pt. had a hiatal hernia and was experiencing day heartburn, belching, regurgitation, fullness/bloating/early satiety, and flatulence/abdominal rumbling at the time of the final Tx visit. His BAD was adequately controlled and he did not have esophagitis or duodenal or gastric ulcers or erosions. His dose of LANSO (60 mg QD) was not increased.

- The patients' assessment of severity of specific symptoms (burning of the upper abdomen, day and night heartburn, painful swallowing, dysphagia, belching, regurgitation, fullness/bloating/early satiety, abdominal distention, anorexia, nausea, vomiting, day and night abdominal pain, flatulence/abdominal rumbling and constipation) indicated that, for the majority of patients, these symptoms were well-controlled throughout the trial and at the final Tx visit.

f) Results of Safety Evaluations

i) Adverse Events

- 20/30 pts. reported one or more AE(s), regardless of relationship to test medication.
- The most frequently reported AEs, regardless of relationship to test med., were headache, diarrhea, nausea and ↑ cough.
- 12 pts. reported possibly or probably Tx-related AEs:

Study M89-405

Possibly or Probably Tx-Related AEs

	LANSO (N=30)
No. of Pts. With any Poss/Prob. Tx-Related AE	12 (40%)
Most Frequently (≥5% incidence rate) Poss/Prob. Related AEs (COSTART TERM)	
Headache	3 (10%)
Diarrhea	2 (6.7%)

- 13 severe AEs were reported by 5 pts.

- None of these were considered poss/prob Tx-related.
- All poss/prob Tx-related AEs reported were MILD to MOD in severity and none resulted in premature termination.

- It is worth summarizing one case of impotence.

- Pt. a 52-y-old Black M with 2-ES had a Hx of gastrectomy and transurethral resection of the prostate. He had been an ex-drinker for more than 20 y. At the screening P.E., the prostate was mildly enlarged and firm, a finding which was unchanged at the Month 12 visit.

The pt. reported impotence on Study Day 117 (estimated), at which time the patient was taking LANSO 45 mg BID. This event, which was considered possibly related to study drug, was continuing as of November 30, 1992 (Study Day 482), at which time the patient had been taking LANSO 60 mg BID for 263 days. Concurrent medications were non-contributory (Tylenol® and butalbital/APAP/caffeine).

ii) D/Cs due to AEs

The following 3 pts. prematurely D/C from the trial due to AEs, none of these considered related to LANSO.

- a 31-y-old Black F: pregnancy test (+); she eventually delivered a healthy term infant.
- a 50-y-old Caucasian M, had a recurrence of alveolar ridge squamous cell carcinoma with extension to the lymph nodes of the neck and skin breakdown on Study Day 144.
- a 79-y-old Caucasian F with a Hx of hypertension and lumbar disc herniation, reported a mild burning sensation in the feet and mild tremors of the hands, both considered to be associated with peripheral neuropathy of unknown origin. These AEs began on Study Days 12 (estimated) and 106, respectively, and eventually caused limitation in mobility such that the patient could not return to the clinic for scheduled appointments. On Study Days 12 and 106 the pt. was taking LANSO 75 mg BID. She reported alcohol consumption of <1 glass of wine per day. Concurrent medications were non-contributory (Vasotec® and Darvocet-N-100®). Both of these events were unresolved as of Study Day 330.

iii) Deaths

There were no deaths during the Trial.

iv) Clinical Laboratory Determinations

There were no clinically significant mean changes from BL in hematology, blood chemistry or urinalysis parameters assessed during the trial period.

v) Fasting Serum Gastrin Concentrations (Table 56)

- There were no statistically significant changes in percent change from BL to subsequent visits in Z-ES pts. Median percent change from Month 3 to any subsequent visit gastrin levels for Z-ES pts. were significantly increased at Month 6.

Hypersecretors

- For these pts., a statistically significant increase was seen at Month 6 and the Final Tx Visit but not at subsequent visits.

TABLE 56
Study M89-405

Fasting Serum Gastrin Results

Visit Month	Median Percent Change from Baseline				Median Percent Change from Month 3			
	Z-ES Pts.		Hypersecretion Pts.		Z-ES Pts.		Hypersecretion Pts.	
	Median BL Gastrin Value (pg/mL)	% Δ	Median BL Gastrin Value (pg/mL)	% Δ	Median BL Gastrin Value (pg/mL)	% Δ	Median BL Gastrin Value (pg/mL)	% Δ
3	625 (N=17)	-7	85 (N=7)	+60				
6	625 (N=15)	+24	85 (N=7)	+82 ^a	641 (N=15)	+22 ^a	132 (N=7)	+14
12	816 (N=13)	-17	96 (N=4)	+33	642 (N=13)	-15	115 (N=4)	+36
18	594 (N=8)	-11	103 (N=3)	-13	956 (N=8)	-5	97 (N=3)	-8
24	625 (N=5)	-26	129 (N=2)	+131	466 (N=5)	-16	115 (N=2)	+156
Final	816 (N=19)	-26	85 (N=7)	+103 ^a	641 (N=15)	-15	132 (N=7)	+44

a,b) Statistically significant increase from BL (p<0.05).

c) Significant increase from Month 3 (p<0.01)

- 9 pts. had serum gastrin levels >100 pg/mL during the trial (all Z-ES pts).
- 5 of these 9 pts. had BL serum gastrin values >1000 pg/mL.
- 2 of these pts. had serum gastrin levels >3000 pg/mL during the trial. One had a 20-y Hx of Z-ES with liver metastasis. His gastric Bx showed MNH at BL and throughout the trial. The other (a 65-y old Caucasian F) had a 1-y Hx of Z-ES, also liver metastasis. At the time of Dx prior to entering the study, the patient had a serum gastrin level of 7000 pg/mL. This value decreased to 425 pg/mL following surgery (splenectomy and partial pancreatectomy), but had increased again to 1499 pg/mL by the time of the patient's BL visit. This high BL value increased to 3201 pg/mL on Study Day 103, and to 4975 pg/mL on Study Day 195 and further at the final Tx visit) to 12,587 pg/mL.

vi) Gastric Bxs

Quantitative Analyses (Table 57)

- There were no statistically significant increases in Grimelius-positive cell density for mean change from BL to any visit for Z-ES pts. or hypersecretors.

TABLE 57
Study N89-405

Grimalius-Positive Cell Densities
(Mean Change in Cells/mm²)

Visit Month	Z-ES Patients ^a			Hypersecretion Patients		
	N	BL Mean	Mean Δ	N	BL Mean	Mean Δ
3	10	285.5	+27.95	3	101.3	+45.60
6	8	257.8	+85.08	2	130.5	+25.48
12	6	317.1	+60.01	2	100.6	+27.17
18	3	321.3	+60.91	2	144.9	-23.02
24	3	302.9	+76.46	1	102.6	+90.54
Final	11	375.6	+36.70	5	127.8	+19.50

a) For the Z-ES patients, correlation analysis did not show correlation between the percent change in fasting serum gastrin level from BL to the final Tx visit and BL fasting gastrin levels, fasting gastrin levels at the final Tx visit, the change in fasting gastrin levels from BL to the final Tx visit, and the change in Grimalius-positive cell density from BL to the final Tx visit (sponsor's Appendix D.2).

Qualitative Analyses (Table 58)

Results of greater curvature Bx examinations for acute inflammation (left side of the Table) and chronic inflammation (right side of the Table) showed no pronounced changes in the 2 groups of pts.

TABLE 58
Study N89-405

Inflammation Changes in Greater Curvature Bxs

Grade	Acute Inflammation (Number of Patients)				Chronic Inflammation (Number of Patients)				
	Z-ES Patients		Hypersecretion Patients		Grade	Z-ES Patients		Hypersecretion Patients	
	BL	Final Tx Visit	BL	Final Tx Visit		BL	Final Tx Visit	BL	Final Tx Visit
0	8	11	4	3	0	3	4	2	2
1	0	1	1	1	1	2	4	1	0
2	7	3	1	2	2	9	6	3	4
3	---	---	---	---	3	1	0	0	0
4	---	---	---	---	4	0	1	0	0

Results Using Modified Solcia's Classification (Table 59)

- Summarized in this Table are data in 11 (all Z-ES) pts. who exhibited

simple hyperplasia or greater at one or more evaluations. None of the 5 hypersecretors changed from BL to the final Tx Visit.

- No pt. had hyperplasia changes higher than MNH.
- No pt. had dysplasia or carcinoid tumor.

TABLE 59
study M89-405

Patients With Simple Hyperplasia or Greater in Greater Curvature Biopsies Using the Solcia Classification (Solcia Classification Grade)*

Pt. #	Screening	Month -----					
		3	6	12	18	24	30
	S	S	N**	S	N**	N	---
	N**	---	N/S (Study Days 141 and 237, respectively)	N**	---	N/N (Study Days 652 and 237, respectively)	---
	MNH	MNH**	MNH	MNH	MNH**	MNH	---
	S	MNH**	MNH**	N**	L**	---	---
	S	S	S	S	S	---	---
	N	N	MNH	N	N	MNH	---
	N	MNH	MNH	MNH**	MNH**	---	---
	N	S	N	S	S	---	---
	MNH	N	N	N**	---	---	---
	L	N**	N**	N**	---	---	---
	S	---	---	-	---	---	---

a) Pt. changed from N to M and focal linear or nodular areas. When data from this pt. are added to those of the 11 pts. above, the changes from BL to Final Tx Visit are summarized as follows:

Histological Classification of Greater Curvature Bxs Using The Solcia Classification for Z-ES Pts.

Solcia Classification	Abbrev.	BL	Final Tx Visit
		Number of Patients	
Normal	[N]	7	6
Simple (Diffuse) Hyperplasia	[S(D)H]	3	2
Linear Hyperplasia [L]	[LH]	0	0
Micronodular Hyperplasia	[MNH]	2	4

* Identifies the 5 pts. that worsened.
** Due to the quality of Bx, not used in Bx analyses

.) Vital Signs, P.E. and EKGs

There were no significant changes from BL in vital sign parameters, P.E. or EKGs

6 Conclusion (Sponsor)

"Lansoprazole provides effective long-term control of gastric acid hypersecretion and symptoms in patients with Zollinger-Ellison syndrome or gastric acid hypersecretion. An initial dose of lansoprazole 60 mg QD, a median end-of-titration dose of 60 mg daily, and a median final maintenance dose of 60 mg daily resulted in a BAO of ≤ 5 mEq/hr at the final treatment visit for 26 of 28 patients who entered the maintenance phase. The duration of treatment for the 28 patients who entered the maintenance phase ranged from 53 to 923 days, representing 39.5 patient years of exposure.

"Currently available evidence from this patient population shows that long-term administration of lansoprazole in doses ranging from 15 mg every other day (QOD) to 90 mg twice daily (BID) is safe. ZES patients showed no significant increase in fasting serum gastrin levels from baseline to any timepoint. Hypersecretion patients showed a median 82% increase from baseline to Month 6, and a median 103% increase from baseline to the final treatment visit, with no significant change found at Months 12, 18, and 24. Long-term administration of lansoprazole to ZES patients was not associated with statistically significant increases in Grimelius-positive cell density from baseline to the final treatment visit. Two patients with ZES, who had the sporadic and not the MEN-I form of ZES, showed a change in gastric endocrine growth from normal to micronodular hyperplasia. No patients, including two MEN-I patients enrolled in the study, developed carcinoids."

7. Comments

The design and execution of this trial were adequate. This is because uncontrolled and open trials in Z-ES are acceptable because of the underlying malignancy in this condition and we know what untreated course is like. The patients had been on histamine H₂-receptor antagonists or OME. When these medications were stopped, the mean BAO increased to 28.4 mEq/h in the Z-ES patients, 21.2 in hypersecretors (without Z-ES) and 9.2 mEq/h in the four that had previously undergone a gastrectomy. In the 28 evaluable pts. the BL BAO ranged from _____ mEq/h. At BL endoscopy 19 of the patients had esophagitis Grade 0 to 1, 5 had DU and 2 had GU. Also, at BL, 21 of the patients had mild to no symptoms, 7 had moderate and none had severe symptoms.

The initial and median final maintenance dose of LANSO to provide effective long-term control of gastric acid hypersecretion, healing and prevention of esophageal, gastric and duodenal lesions (including ulcers) was 60 mg QD. One important advantage of LANSO (over the H₂) was a decrease in the dose and frequency of medication. Once-a-day dosage of the drug was highly effective but, for reasons not presently understood (bioavailability factors?), some patients need the medication in divided doses, in this trial as little as 15 mg BID or as much as 90 mg BID. These dose requirements were usually stable and pts. taking LANSO did not develop tachyphylaxis.

In this trial, LANSO was well tolerated upon long-term administration to these patients. The most frequently reported AEs were headache and diarrhea (which could also be due to the underlying condition). None of the severe AEs were considered poss./probl. related to LANSO. Impotence in a Z-ES ex-drinker with a Hx of gastrectomy and transurethral resection of the prostate was considered possibly related to LANSO. There were no clinically significant changes from BL in vital sign parameters, P.E. or EKGs. Most of the patients, especially

the hypersecretors, did not have pronounced hypergastrinemia. Nonetheless, no significant increases in fasting serum gastrin concentrations from BL to any timepoint were seen among Z-ES patients. The number of observations was small but hypersecretors showed a median 82% increase from BL to Month 6 (N=7) and a median 103% increase from BL to the Final Tx visit but no significant changes at other points of observation.

The most notorious finding (or rather lack of finding) in this trial was that no polyps, nodules or other lesions representing masses were reported among these 30 pts. (even at BL) and this contrasts considerably with the findings reported in Study M88-137 (21 pts.) and even M90-436 (6 pts.) [see below]. This is very surprising but it is unlikely that these lesions were missed because the PI in study M89-405 is one of the most experienced endoscopists in the U.S.

Gastric Bxs from both Z-ES pts. and hypersecretors showed no statistically significant increases in Grimelius-positive cell density for mean change from BL to any visit and only minor changes in acute or chronic inflammation. Pts. had hyperplasia changes that were not higher than MNH (N=4). Neither dysplasia nor carcinoid tumor were reported.

D. Study M90-436

"The use of Lansoprazole in Patients with Zollinger-Ellison syndrome and patients with Hypersecretion of Gastric Acid"

The PI for this study is [the trial is ongoing] M. Feldman, M.D. (Dallas, TX). The trial began on April 1991. Interim Report=11/30/92. This study omitted observations at Month 9 and gave results on BAO only. It was otherwise of similar design and execution to M89-405.

Design/Execution/Results

Six (6) pts. (M=5; F=1, age 35 to 76y) were enrolled into the trial as of the cut-off date. No pt. was prematurely withdrawn. Pts. received a total daily dose of LANSO ranging from 15 mg QOD to 90 mg BID to maintain their gastric acid secretory ratio at ≤ 5 mmol/h to provide adequate symptom relief through the period of time pts. received test med. The median end-of-titration dose was 37.5 mg QD. The median final maintenance dose was 15 mg QD for the 5 pts. who remained active for >9 mo. Three (3) of the 5 pts., who had at least one maintenance visit were essentially achlorhydric (BAO ≤ 0.1 mmol/h) at the final Tx Visit. During Tx, symptoms improved (4 pts.) or were unchanged (2 pts.) from BL in their overall symptoms at their final Tx visit. No pts. developed R.E., ulcers or erosions while on LANSO. One (1) pt. with erosive R.E. and 3 with duodenal ulcers at BL healed by the first maintenance visit and remained healed at subsequent visits.

One Tx-related AE (vasodilation) was reported but it resolved with continued Tx with LANSO. No pt. was W/D from the trial due to an AE. There were no deaths reported during the trial. There were no clinically significant changes from BL for hematology, blood chemistry, urinalysis, or vital sign parameters assessed during the trial period. Abnormalities in and changes between Pre-Tx and final P.E. and EKG results revealed no adverse trends for these LANSO-Tx patients.

Fasting serum gastrin levels decreased from BL (median=728 pg/mL) to the final Tx visit (median=596 pg/mL). Pt. presented at the BL visit with a serum gastrin level >1000 pg/mL. Pts. all Z-ES patients, had serum gastrin levels >1000 pg/mL during the trial.

Gastrointestinal Nodules and Polyps

The following 2 pts. presented with nodules or nodular folds in the fundus of the stomach at the BL endoscopy.

a 35-year-old Black M, had a 0.5-cm nodule in the fundus at the BL endoscopy. Bx of the nodule revealed chronic active atrophic gastritis with intestinal metaplasia and the presence of *H. pylori*. Subsequent endoscopies noted the continued presence of the nodule; the patient did not develop any other nodules or polyps.

NOTE: A more complete clinical Hx, especially dose and length of exposure to antisecretory medication before enrollment into the trial and P/U on this pt's nodule is needed.

a 76-year-old Caucasian M, presented with nodular folds in the fundus at the BL endoscopy. Subsequent endoscopies at Months 5 and 6 revealed the continued presence of the nodular folds. Bx of the nodular areas were not obtained.

NOTE: Same as above.

Conclusion (Sponsor)

"Lansoprazole provides effective long-term control of gastric acid hypersecretion and symptoms in patients with Zollinger-Ellison syndrome (ZES). The BAO of the six patients enrolled was well-controlled (≤ 5 mmol/hr) during the study. At the time of this interim analysis (November 30, 1992 data cut-off date), the duration of treatment for these six patients ranged from 47 to 594 days, which represents 7.3 patient-years of treatment. The median final maintenance dose was 15 mg QD.

"Currently available evidence from these patients demonstrates that long-term administration of lansoprazole in doses ranging from 15 mg QOD to 90 mg BID is safe and efficacious."

Comment

Study M90-436 is the second critical trial submitted by the sponsor in support of the approval of LANSO for the L-T Tx of pathological hypersecretory conditions including Z-ES. Although this trial was of similar design and apparent execution to Study M89-405, the number of pts. studied (N=6) was rather small so that no firm conclusions can be drawn from the data. Nonetheless, the efficacy results appear to go in the same direction as those in the larger trial. Gastric acid secretory ratio of ≤ 5 mmol/h was maintained with doses of LANSO as low as 15 mg once-a-day but some pts. needed 90 mg BID. These doses of the drug provided adequate symptom relief and healing of R.E. or DUs in those pts. who had those conditions at BL.

LANSO appeared to be well tolerated in this small group of pts. Of note, two (2) of these 6 patients presented with nodules or nodular folds in the fundus of the stomach. In both patients the masses were already present at BL. In one, Bx of the 0.5 cm nodule revealed chronic active atrophic gastritis with intestinal metaplasia and the presence of *H. pylori*. This finding needs further clarifications to determine if this apparently pre-malignant condition is a manifestation of the underlying condition or is in any way related to the type and length of exposure to previous antisecretory medication. In the other, nodular folds in the fundus persisted apparently unchanged 6 mo. after Tx with LANSO but Bx of the nodular areas were not obtained. Both these cases and the ones in the trial that follows dictate that histological characterization and follow-up of these nodules be done in every instance.

In summary, data from Study M90-436 in a handful of patients appears to support the effectiveness and safety of LANSO in the Tx of hypersecretory conditions including Z-ES. The most important contribution of this trial is the BL finding of nodules or nodular folds in the fundus of the stomach in two pts. In one of these, in whom Bx was obtained, an apparently pre-malignant condition (chronic active atrophic gastritis + intestinal metaplasia together with the presence of *H. pylori*) is of concern. A thorough investigation of the antisecretory medications and length of administration of drugs in these patients is necessary in view of the many instances of nodules/polyps observed in the trial that follows.

E. Study M88-139

"The Use of Lansoprazole (A-65006) in Patients with Zollinger-Ellison Syndrome"

The PIs for this study were J.D. Gardner, M.D., R.T. Jensen, M.D., and P.N. Maton, M.D. et al. (NIH).

The study is ongoing. The study dates for this Interim Report were February 5, 1989 to November 30, 1992.

1. Study Design and Execution

The design and execution of this trial were similar to those described for Study M89-405 with minor modifications. In the present trial, the Dose Titration Assessment (Phase I) was followed by L-T assessments at Months 6, 12, 18 and 24 and yearly thereafter. The initial Protocol was amended on June 8, 1992 with modifications that included the following.

- Patients who previously used OME were now permitted to participate in this study as long as this Tx was D/C and replaced with H_2 for at least 2 weeks prior to entrance into this study. Also, the requirement that pts. D/C H_2 at least 12h prior to qualifying gastrin evaluation was reduced to 6h.
- The definition of Z-ES was expanded to allow for the inclusion of patients with BAO less than 15 mEq/h if they had prior gastric surgery. Z-ES was now defined as a BAO >15 mEq/h (or >5 mEq/h if the patient had previous gastric surgery), a fasting gastrin level of >100 pg/mL, a positive response to secretin (defined as an increase in serum gastrin concentration of at least 200 pg/mL) or calcium (defined as an increase in serum gastrin concentration of at least 395 pg/mL), histological evidence of a gastrinoma, or a combination of these criteria. Previously, patients had to have a BAO >15 mEq/h to qualify for the study.
- Patients who had a possibility of undergoing a curative resection or those with MEN-1 who were undergoing a parathyroidectomy for hyperparathyroidism were no longer permitted to participate in the trial (such patients had not been explicitly excluded previously).
- It was now explicitly stated that patients would need to be willing to be admitted to the NIH twice yearly in order to be selected for this study.
- The exclusion of pts. with evidence of PUD was dropped.
- The requirement that patients must have received prior therapy with CIM, RAN, or FAM under the protocol entitled "Medical Therapy of Zollinger-Ellison Syndrome" was dropped.
- The control of symptoms was added to the requirement of establishing the optimal LANSO dose during the titration phase. Also, for patients with previous gastric surgery (who were now allowed to enroll), the goal of the titration phase was stated to be BAO <5 mEq/h during the last hour before the next dose and adequate control of symptoms. Prior to this amendment, the titration phase was to reduce BAO to <10 mEq/h during the last hour before the next dose.
- The evaluations of the rate of onset of action and PKs of the first dose, and the duration of action of LANSO were deleted. Duration of action procedures had been carried out on 4 patients under the original protocol and the results were included in this report.

- Maintenance visits were changed to Months 6, 12, 18, 24, and yearly thereafter. In addition, endoscopy evaluations and biopsies were obtained at Months 6, 12, 18, 24 and yearly thereafter. A number of patients entering under the original protocol had visits at Months 3, 30 and 62 prior to the June 1992 protocol amendment. Analyses included these time points.
- It was noted that patients whose acid secretion and symptoms were well-controlled over a period of time could have the dose of LANSO decreased.
- A provision for patients requiring surgery to resect the gastrinoma during the maintenance phase of the study was added. For patients who required such surgery, LANSO Tx was D/C for a maximum of 7 days prior to and 7 following surgery. During this time, the patient received oral and i.v. H_2 which were to be D/C within 7 days following surgery. LANSO Tx was then re-initiated. Three to seven months following surgery, the patient's BAO was reevaluated. If the surgery was successful and BAO and symptom control were well-maintained, the patient was D/C from the study. If the investigator determined that the patient required additional LANSO Tx, he/she could stay in the study and dose adjustments were made as necessary.

2. Results

a) Patients

- 21 pts. were enrolled (F=11; M=10) into this trial, with mean age of 49y (range: y).
- The population was comprised of 14 caucasians, 6 Blacks and 1 Hispanic.

b) Medical Hx

- The duration of Z-ES and previous antisecretory therapy data are summarized in Table 60.
- The mean duration of Z-ES (from diagnosis to start of LANSO Tx) for the patients enrolled in the trial was 1651 days (range: days), and the mean BAO was 38.7 mEq/h (range: mEq/h).
- 20 of the 21 pts. had been treated with RAN (mean daily dosage 4500 mg; range mg).
- The other patient was treated with CIM (daily dosage 6000 mg).

c) Patient Disposition

- 21 pts. were enrolled in this trial; 20 of the 21 pts. were included in at least one primary efficacy analyses; 1 pt. was prematurely terminated from the trial during the titration phase; 5 additional pts. were prematurely D/C during Phase 2.
- 15 pts. remained active as of November 30, 1992.
- 13 of the 21 pts. received >30 mo. of therapy.
- The mean duration of participation for the 20 pts. who entered the maintenance Phase was 2.6y (range: y).

TABLE 60
Study N88-139

Duration of Z-ES and Previous Therapy
(Days from Diagnosis to Start of Test Medication)

Pt. #	Duration (Days)	H ₂ -Blocker	Final H ₂ -Blocker Dose (mg)	Historical BAO (mEq/h)
	505	RAN	6000	38.2
	3740	RAN	7200	62.9
	217	RAN	2400	47.4
	494	RAN	4200	16.0
	2700	RAN	3600	17.8
	855	RAN	2400	17.8
	1064	RAN	6000	29.1
	133	RAN	3000	38.8
	2528	RAN	6000	22.5
	14	RAN	3600	63.3
	2487	CIM	6000	16.2
	40	RAN	14400	55.2
	162	RAN	3600	43.5
	4776	RAN	4800	143.9
	405	RAN	2400	30.8
	4562	RAN	4800	24.6
	1087	RAN	3600	9.9
	3711	RAN	6000	41.7
	3886	RAN	1800	34.4
	134	RAN	1200	24.0
	887	RAN	3000	24.9

Study N88-139

Duration of Treatment

	----- Months on Study Drug -----								
	<3	>3-6	>6-12	>12-18	>18-24	>24-30	>30-36	>36-42	>42
No. of Pts.	1	0	3	0	2	2	4	4	5

- Pt. was dropped from the trial during the titration phase because of suspected noncompliance. He did not have a final titration dose, did not enter Phase 2 and was not included in any efficacy analysis.

- There were a number of Protocol Deviations consisting mostly of procedural departures that did not result in data exclusion.
- In addition 15 pts. took other antisecretory drugs including oral or i.v. doses of H₂, during the study period. Patients were administered the antisecretory medications primarily for acid control prior to and following surgery or angiogram, acid control during an episode of nausea or vomiting, or to stop the duration of action procedure. One patient received OME 60 mg i.v. from Study Day 7 to 20 in preparation for and while recovering from an emergency laparotomy. LANSO was restarted on Study Day 21. Dates and reasons for use were summarized in sponsor's Table 7.6.
- Primary reasons for premature termination of 6 pts. are listed below.

Termination Reason	Number of Patients
Patient Request	1
Patient Death	2
Patient Compliance	2 ^a
Normal GAO After Gastric Surgery	1

a) Pt. was prematurely terminated from the trial due to questionable absorption values (BAO) which led the investigator to believe that the patient was non-compliant.

d) Efficacy Results

i) Dose-Titration Phase

- All patients initially received 60 mg of LANSO QD at the start of the titration phase of the study.
- For the 20 patients who entered the maintenance phase of the study, the end-of-titration-dose was
 - 60 mg QD for 15 patients
 - 75 mg QD for two,
 - 120 mg QD for one, and
 - 60 mg twice daily (BID) for two patients.

(median end-of-titration dose was 60 mg QD)⁵³.

- 14 of the 20 pts. who completed the titration phase required no dose changes to achieve the maintenance dose; 2 required one dose adjustment; 1 required two dose adjustments; 1 required three dose adjustments and 2 pt. required four dose adjustments.
- In this study, a statistically significant positive relationship was found between the titrated dose of LANSO and the historical BAO and

⁵³The end-of-titration dose established for Pt. 314 was 60 mg BID. However, this patient misunderstood the dosing directions and only took 60 mg of LANSO once daily between the end of Phase 1 and his Month 3 visit with Phase 2. This patient's BAO and symptoms were well-controlled at the Month 3 visit, and he continued to take 60 mg QD as his maintenance dose.

historical MAO ($r=0.56$ and $r=0.62$, respectively). This analysis excluded Pt. who previously received CIM. The titrated dose of LANSO was not significantly correlated with the previous RAN dose. According to the sponsor, the relatively high historical BAO values suggested that the previous RAN doses were non-therapeutic.

ii) L-T Maintenance Phase (Table 6L)

- The total duration of participation in this trial for the 20 pts. who entered the L-T Maintenance Phase ranged from 1 to 17 days (mean of 2.6y) which represents a total of 51.4 patient-years of exposure.
- This range includes brief periods of time (maximum of 17 days) when LANSO was temporarily D/C due to scheduled surgery or lack of control of symptoms, such as nausea and vomiting, associated with Z-Es.
- For these 20 patients, the dose of LANSO at the final Tx visit on or before November 30, 1992 was
 - 30 mg QD for 7 pts.
 - 30 mg BID for 2 pts.
 - 45 mg QD for 1 pt.
 - 60 mg QD for 5 pts.
 - 90 mg QD for 1 pt.
 - 120 mg QD for 1 pt., and
 - 60 mg BID for 3 pts.
 (median final maintenance dose of 60 mg QD).
- Dose adjustments are summarized below.

Study N88-139

Summary of Dose Adjustments During the Maintenance Period

Dose Adjustment	No. of Pts.
Dose 1	8 (40%)
Dose 2	2 (10%)
No dose adjustment	6 (30%)
Both 1 and 2 ^{a)}	4 (20%)

a) Pt. was included among these 4 pts. even though he took it upon himself to increase his dosage of LANSO between the end of the titration phase and his Month 3 visit. His acid secretion was well-controlled on 60 mg QD during the titration phase, but he increased his dosage to 90 mg QD before his next visit. At the Month 3 visit, the investigator reduced his dosage to 60 mg QD. The patient has remained at that dose level for over 3y.

TABLE 61
Study M88-139
Summary of LANSO Dosage and BAO Results

Pt. #	Age/Gender	Previous BAO mEq/h	End-of-Titration Dose of LANSO	BAO on Titrated Dose mEq/h	Final Dose of LANSO	Final BAO mEq/h
	45/M	38.2	60 mg q.d.	5.2	90 mg q.d.	0.5
	61/M	62.9	60 mg b.i.d.	4.7	60 mg b.i.d.	1.1
	61/F	47.4	60 mg q.d.	0.1	30 mg q.d.	0.0
	56/M	16.0	60 mg q.d.	0.0	60 mg q.d.	0.0
	57/M	17.8	60 mg q.d.	5.8	30 mg q.d.	4.9
	44/M	17.8	120 mg q.d.	3.8	60 mg b.i.d. ^a	4.1
	51/F	29.1	60 mg q.d.	1.7	60 mg q.d. ^b	0.1
	48/F	38.8	60 mg q.d.	2.5	60 mg b.i.d.	0.0
	39/F	22.5	60 mg q.d.	5.0	30 mg b.i.d.	7.3
	39/F	63.3	60 mg q.d.	0.5	30 mg b.i.d. ^c	0.4
	53/F	16.2	60 mg q.d.	0.0	60 mg q.d.	0.
	40/M	55.2	75 mg q.d.	22.1 ^d	75 mg q.d. ^e	---
	27/F	43.5	75 mg q.d.	2.6	45 mg q.d. ^e	0.0
	61/M	143.9	60 mg b.i.d.	0.2	60 mg q.d.	1.4
	41/M	30.8	60 mg q.d.	0.0	30 mg q.d.	11.1
	68/F	24.6	60 mg q.d.	0.1	30 mg q.d.	0.4
	42/F	9.9	60 mg q.d.	2.2	30 mg q.d.	6.7
	41/F	41.7	60 mg q.d.	0.1	30 mg q.d. ^f	0.0
	45/M	34.4	75 mg q.d.	7.1	120 mg q.d.	6.9
	52/M	24.0	60 mg q.d.	0.0	30 mg q.d.	0.0
	56/F	34.9	60 mg q.d.	0.7	60 mg q.d.	0.8

a through f) Pts. prematurely terminated from trial. Final dose listed is dose at time of premature termination.

g) Never attained a final titration dosage; was taking 75 mg q.d. when dropped from the study for suspected noncompliance. BAO value here reflects value at time of D/C.

h) This pt. was enrolled into the trial despite a BAO <15 mEq/h (9.9 mEq/h) because of a positive secretin test and elevated serum gastrin concentrations.

• All 15 of the patients who remained active in the study as of November 30, 1992, participated for >1y.

- 6 of these 15 pts. had their acid secretion controlled by 30 mg QD
 - 1 required 30 mg BID
 - 4 required 60 mg QD
 - 1 required 90 mg QD
 - 1 required 120 mg QD, and
 - 2 required 60 mg BID
 - 12 of these 15 pts. had their final maintenance daily dose less than or equal to their end-of-titration daily dose.
- There was no statistically significant relationship between the final maintenance dose of LANSO for each patient and either the historical BAO, historical MAO, or the previously established dose of RAN (sponsor's Appendix D). The latter analysis excluded patient who previously received CIM.

Gastric Acid Secretion During Titration/Maintenance Phase
(Refer to Table 61)

- In the 19 evaluable patients the historical BAO values ranged from mEq/h (median of 34.4 mEq/h).
- At the end of the titration phase of the study, BAO values for the 20 patients listed in this Table (obtained during the last hour before the next scheduled dose of LANSO) ranged from mEq/h (median of 1.2 mEq/h).
- 7 pts. were achlorhydric at the end of the titration phase. At the final Tx visit, BAO values ranged from mEq/h (median of 0.5 mEq/h).
- 14 of the 20 pts. had BAO values <2.0 mEq/h.
- 8 of these 20 pts. were essentially achlorhydric (BAO $\leq$ 0.1 mEq/h) at the final Tx visit.

Duration of Action of LANSO

- This information originated from 4 pts. It was obtained by temporarily D/C LANSO administration.
- GAO over a 1-h period was evaluated at 8-h intervals from 24 to 48 h after D/C LANSO until the BAO returned to 30 mEq/h or >50% of the historical BAO value.
- BAO for pts. exceeded 30 mEq/h at measurements obtained 48, 40 and 40 h after the last dose of LANSO, respectively.
- At 48h after her last dose of LANSO, Pt. had a BAO of 11.8 mEq/h. The evaluation was extended to 56h, at which time she had a BAO of 25.8 mEq/h. This patient's historical BAO was 34.9 mEq/h.

Endoscopy Results (Table 62)

- 20 pts. had a BL endoscopy⁵⁴ and at least one subsequent endoscopy.

⁵⁴Pt. had only one endoscopic evaluation (at screening) and he is not included in this analysis.

- The BL endoscopy was evaluated as normal for 14/20 pts.
- Numerous upper G.I. anomalies were detected on endoscopy throughout the trial.
- Only 5/20 pt. had endoscopy evaluated as normal at the Final Tx Visit.
- As shown in this Table, the most frequently reported abnormal endoscopic findings were nodules/polyps. These were located primarily in the duodenum, but there were also instances of antral and gastric nodules.
- In this section, no information is given about results of Bx of the nodules/polyps.

TABLE 62

No. of Pts. With Upper GI Anomalies by
Endoscopy During the Tx Period

Anomaly	No. of Pts. (N=21) ^a
Duodenal nodule/polyp ^a	13
Antral nodule/polyp	3
Gastric nodule	2
Antritis	2
Gastritis	1
Other nodule/polyp/ampulla	3

a) Some patients had more than one type of anomaly.

- There were no patients developing esophagitis, ulcers or erosions during the trial.

Symptom Assessment

- 20 of the 21 pts., enrolled in this trial had symptom assessments at BL and during at least one subsequent visit.
- The pts. perception of their overall well-being at BL and at the final Tx visit is summarized below (there was not much of an effect).

Variable	BL	Final Tx Visit
Overall Well-Being		
Excellent	0	0
Good	19	16
Fair	0	3
Poor	1	1
Very Poor	0	0

Summary: 15 pts. remained unchanged;

- 1 pt. went from poor - good;
- 4 pts. worsened (from good to either fair (3 pts.) or poor (1 pt.))

A brief Clinical Summary for the 4 pts. who had deterioration in their overall well-being assessments is given below. All 4 pts. had their BAD adequately controlled.

- Pt. whose well-being regressed from good to fair, was experiencing abdominal distention, jaundice, ascites, and 1+ to 2+ pitting edema at the time of the evaluation. She also

reported mild abdominal pain and diarrhea at her last symptom assessment; subsequently, this patient died of end-stage liver disease unrelated to test medication.

The pt. had a normal endoscopy at her final Tx visit.

- Pt. whose assessment of well-being regressed from good to fair, reported mild N&V at her final Tx visit assessment was suffering from metastatic liver Dz.

The pt.'s final Tx visit endoscopy was evaluated as abnormal due to a duodenal nodule.

- Pt. whose assessment of well-being regressed from good to poor was suffering from metastatic liver Dz and had been diagnosed with Cushing's syndrome.

This pt.'s final Tx visit endoscopy was evaluated as abnormal due to external compression, bilaterally.

- Pt. whose symptoms deteriorated from good to fair, experienced the following: an infected, indurated cyst in the groin area; hypothyroidism; hypotension; fever; WBC on urinalysis; UTI; and abdominal pain. The patient subsequently died from splenic infarction. All of these events, judged to be of no relationship to study drug, occurred close to the time the patient's symptom assessment deteriorated.

This pt. was evaluated as abnormal due to a 0.5 cm dumbbell shaped polyp in the esophagus at the final endoscopy.

- There were little if any changes in specific symptoms because very few symptoms were reported at BL. The symptoms were well controlled at BL and remained well-controlled throughout the trial and at the final Tx visit.

•) Results of Safety Evaluations

i) Adverse Events

- 18/21 (or 86%) pts. reported one or more AEs, regardless of relationship to test medication.
- The most frequently reported AEs included nausea, vomiting, abdominal pain, pharyngitis and peripheral edema (sponsor's Table 9.1.1.).
- Pt. a 53-y-old Black F, reported AEs that were considered possibly or probably related to LANSO.

The pt. experienced severe nausea, vomiting, diarrhea, and dyspepsia on Study Day 221 that continued to worsen. The next day she was seen in a local hospital emergency room and had the LANSO D/C and was placed on CIM 1500 mg QID. These events resolved spontaneously by Study Day 225. The investigator regarded the events to be possibly related to test med.; he also indicated that the patient may have had an episode of viral gastroenteritis. The patient returned to the NIH on Study Day 234 where she was placed back on LANSO 60 mg QD. One year later, the patient experienced a mild AE of nausea post angiogram that was judged unrelated to study drug by the investigator.

- Pt. a 57-y-old Caucasian M, reported the occurrence of a testicular abnormality. This consisted of moderate right testicular inflammation on Study Day 162 (estimated day of onset). He presented at the screening visit with right-sided testicular pain upon P.E. and was subsequently diagnosed, on Study Day 162, with epididymitis and a hydrocele of the right testicle. The patient was prescribed Bactrim® 80 mg and Septra® 400 mg and was to be followed by a urologist. The investigator judged the event to be unrelated to test med. The patient subsequently presented with chronic prostatitis and a nodule on the prostate on Study Day 593. Additionally, a small polyp was removed from the colon at 50 cm during colonoscopy. The results for the colon bx indicated a normal, mild mucosal thickening. By now, this patient has been treated with LANSO for a total of 1287 days and is currently on LANSO 30 mg QD.

ii) Severe AEs

- 5 pts. experienced AEs that were characterized as severe. As already mentioned, events in pt. were judged as possibly or probably related to LANSO. AEs in the other 4 pts. were judged to be unrelated to LANSO.

iii) D/C Due to AEs

- 2 pts. prematurely D/C from the trial due to an AE. Both pts. died (see below).

iv) Deaths

- Pts. died during the trial. Both had E-ES. The first, died of complications of end-stage liver disease (unrelated to LANSO). The second died of splenic infarction (also unrelated to LANSO).

v) Clinical Laboratory Determinations

- There were no clinically significant mean changes from BL in hematology, blood chemistry, thyroid function or urinalysis parameters.
- There were no clinically significant mean changes from BL seen in any of the individual hepatic chemistry parameters. However, the following 2 pts. experienced elevations that remained abnormal at the end of Tx (Table 63). Clinical Summaries on these 2 pts. are given as footnote to Table 63.

TABLE 63
Study N88-139

Patients With Hepatic Chemistry Values of Clinical Concern

Pt. #	Hepatic Parameter (units)	Study Drug (Months)									Limit of Concern
		BL	3	6	12	18	24	30	36	42	
	AST/SGOT (U/L)	26	15	-	28	32	35	51	71	83	>2 X ULN (62)
	ALT/SGPT (U/L)	33	15	-	28	33	42	63	78	96	>2 X ULN (88)
	AST/SGOT (U/L)	39	21	41	27/ ^a 16 ^b	--	57/ ^a 16 ^b	21	58 ^b	--	>2 X ULN (62)
	ALT/SGPT (U/L)	26	20	28	34/ ^a 15 ^b	--	62/ ^a 10 ^b	19	171	--	>2 X ULN (88)
	AP (U/L)	61	58	70	277/ ^a 93 ^b	--	79	471	1310	--	>2 X ULN (248)
	Total Bil. (mg/dL)	0.2	0.3	0.4	0.4/ ^a 0.3 ^b	--	0.7/ ^a 0.4 ^b	0.5	4.7	--	≥2

a) Study Days 331 and 429, respectively
b) Study Days 632 and 779, respectively

Clinical Summaries for the Two Pts. in This Table

- Pt. a 61-year-old Caucasian F had a Hx of hypothyroidism. She was titrated to a final maintenance dose of LANSO 30 mg QD, had a normal BL AST/SGOT value (26 U/L) that increased to a level of

clinical concern on Study Days 1009 and 1188 (71 U/L and 83 U/L, respectively). In addition, she had a normal BL ALT/SGPT value (33 U/L) that increased to a level of clinical concern on Study Day 1188 (96 U/L). The pt. also had elevated values which did not reach a level of clinical concern for AP on Study Days 1009 and 1188. The investigator indicated that the elevated liver enzymes were due to excessive alcohol consumption. The pt. was repeatedly counseled to reduce alcohol consumption.

- Pt. a 39-y-old Caucasian F titrated to a final maintenance dose of LANSO 30 mg BID, had a normal BL AP value (61 U/L) that increased to a level of clinical concern on Study Day 331 (277 U/L). On Study Days 429 and 779, this patient's AP level returned to NMR (93 U/L and 79 U/L, respectively) but reached a level of clinical concern again on Study Days 928 and 1080 (471 U/L and 1310 U/L, respectively). This patient also had BL AST/SGOT, ALT/SGPT, and total bilirubin values of 39 U/L, 26 U/L and 0.2 mg/dL, respectively (all normal). These increased to a level of clinical concern on Study Day 1080 (585 U/L, 171 U/L, and 4.7 mg/dL, respectively). She had evidence of metastatic liver disease and Cushing's syndrome, was receiving chemotherapy and U/D from the trial on Study Day 1082 because she was unwilling to return to the NIN for required study F/U visits.
- There were no clinically or statistically significant mean changes from BL observed in any of the thyroid parameters. TSH values in Pt. #3, however, were normal at BL but increased to values higher than the limit of concern and remained abnormally high up to 42 mo. after the start of LANSO (see also footnote to Table 63).

Pt. #	Thyroid Parameter (units)										Limit of Concern
		BL	3	6	12	18	24	30	36	42	
	TSH (mIU/mL)	3.2	6.4	-	6.3	9.6	7.9	8.1	13.2	10.1	>5

vi) Fasting Serum Gastrin Determinations (Table 64)

- An analysis of the changes in median serum gastrin levels from BL to each subsequent visit is summarized in this Table.
- A statistically significant median percent change from BL in fasting serum gastrin levels was observed at Months 3, 12, 18, 24 and 30.
- No significant difference from BL was noted in the final visit analysis, although the median gastrin levels increased from 317 pg/mL at BL to 542 pg/mL at the final Tx visit for the 19 patients.
- Analysis of the changes in serum gastrin from Month 3 to each subsequent visit was presented in sponsor's Table 9.5.2. No statistically significant differences were found.
- Thus, fasting serum gastrin levels increased significantly from BL to Month 3 during LANSO administration but showed no further significant increases throughout the remainder of the study period (up to 42 months).
- 10 pts. had serum gastrin concentrations pg/mL during the trial.
 - 5 of these pts. had BL serum gastrin concentrations pg/mL (Pts.
 - Pts. had large, consistent increases in serum gastrin concentrations during the trial.

TABLE 64
Fasting Serum Gastrin Results
(Median Percent Change from BL)

Tx Period (Month)	N	BL Gastrin (pg/mL)	LANSO
3	14	359	-28%*
6	16	381	+17%
12	17	401	+42%*
18	14	359	+60%*
24	13	445	+67%*
30	13	401	+134%*
36	7	401	+81%
42	2	350	+28%
Final	19	317	-5%

a,b) Statistically significant different from BL at the p<0.05 and p<0.01 levels of significance, respectively.

vii) Gastric Bx

Quantitative Analyses (Table 65)

- There were statistically significant decreases in Grimelius-positive cell density for mean change from BL at
 - Month 6 (↓ of 96.99 cells/mm²)
 - Month 24 (↓ of 142.42 cells/mm²)
 - Month 36 (↓ of 150.91 cells/mm²) and
 - Final Tx Visit (↓ of 102.36 cells/mm²)

respectively.

Qualitative Analyses (Table 66)

Results of greater curvature Bx examinations for acute inflammation (left side of Table) and chronic inflammation (right side of Table) showed no pronounced changes. Summary results are given in the lower part of Table 66.

TABLE 65

Giemsa-Positive Cell Densities
(Mean Change in Cells/mm²)

Visit Month	Z-ES Patients		
	N	BL Mean (cells/mm ²)	Mean Δ
3	5	555.3	-50.70
6	9	366.4	-96.99
12	8	397.5	-40.64
18	10	427.8	-97.16
24	7	397.1	-142.42
30	4	314.2	-70.95
36	2	433.6	-150.91
42	1	268.8	+6.40
Final	15	469.9	-102.36

TABLE 66
study N88-139

Inflammation Changes in Greater Curvature Esx

Acute Inflammation (Number of Patients)			Chronic Inflammation (Number of Patients)		
Grade	BL	Final Visit	Grade	BL	Final Visit
0	14	15	0	12	11
1	0	0	1	4	2
2	2	2	2	2	3
3	2	1	3	0	1
4	--	--	4	0	1
<u>Summary (at final Tx Visit):</u> Unchanged: 16 pts. Improved: 2 pts. Similar results were seen at the Months 3, 6, 12, 18, 24, 30, 36 and 42 evaluations			<u>Summary (at Final Tx Visit):</u> Unchanged: 12 pts. Improved: 1 pt. Worsened: 5 pts. Similar results were seen at the months 3, 6, 12, 18, 24, 30, 36 and 42 evaluations		

Results Using Solcia's Classification (Table 67)

Data from 19 pts. who had simple hyperplasia or greater are depicted in this Table.

- 13 pts. exhibited simple hyperplasia (S(D)) or greater at one or more evaluations.
- 11 of these 13 pts. had MNH at one or more evaluations after the screening visit.

Summarized in the lower panel of Table 67 are the changes in the degree of hyperplasia (Solcia's classification) observed. At the final Tx visit:

- 9 pts. had not changed from BL
 - 4 pts. had improved
 - 3 pts. had worsened:
 - L → MNH
 - , L → MNH and
 - N → N/FL or Nodular Areas.
- 4 pts. had MEN-I. Pts. are not included in Table 67. Pts. displayed linear or MNH. In addition, Pt. had a gastric carcinoid cell tumor identified on Study Day 141. Please see footnote to Table 67.

Gastrointestinal Nodules and Polyps (Table 68)

- In this Table, all pts. with G.I. Nodules and polyps³⁵ are listed.
- In this trial, upper g.i. tract lesions were the norm.
- These lesions were variously identified as nodules, polyps, masses or anomalies.
- In pts. nodules/masses in the duodenum and in nodules in the esophagus were already reported at the BL (screening) endoscopy. Other lesions in 3 of these 5 pts. or in the other pts. were observed at least 89 days after the start of tx.
- In all, 15/21 patients enrolled in this trial had g.i. anomalies detected by upper g.i. endoscopy or colonoscopy.

³⁵Dictionary definitions of these terms are:

Nodule = A small node (a circumscribed mass of differentiated tissue)

Polyp = Polypus = a general, descriptive term used with reference to any mass of tissue that bulges or projects outward, or upward, from the normal surface level, thereby being macroscopically visible as a hemispheroidal, spheroidal, or irregularly mound-like structure growing from a relatively broad base or a slender stalk. Polyps may be neoplasms, foci of inflammation, degenerative lesions or malformations.

The adenomatous polyp consists of benign neoplastic tissue derived from glandular epithelium.

TABLE 67
Study MSB-139

Pt. #	Screening	Month												
		3	6	12	18	24	30	36	42					
(MEN-1)	---	N	L	N	N	---	---	---	M	---	---	M/FL-M (Study Days 811 and 934, respectively)	M ^{oo}	---
	---	---	---	L	M/FL	M/FL	M/FL	M/FL	M/FL	M/FL	M/FL	M/FL	L	L
	L	---	L	M/FL	L	M/FL	M/FL	M/FL	M/FL	M/FL	M/FL	M/FL	M	---
	L (Study Day 2)	---	M/FL	N	M/FL	N	M/FL	M/FL	M/FL	N	M	M/FL	M/FL	---
	M/FL	---	---	---	---	---	---	---	---	---	---	---	---	---
	L	---	M/FL	M/FL	M/FL	M/FL	M/FL	M/FL	M/FL	M/FL	M/FL	M/FL	M/FL	M/FL
	L	S(O) ^{oo}	---	M-FL/L (Study Days 331 and 429, respectively)	---	---	---	---	---	---	L	---	---	---
	L	---	---	M/FL	S(O)	M/FL	S(O)	S(O)	S(O)	---	M/FL	M/FL	---	---
(MEN-1)	M/FL	---	L/M/FL (Study Days 141 and 234, respectively)	---	---	---	---	---	---	---	---	---	---	---
	---	N	N	L/M ^{oo} (Study Days 306 and 426, respectively)	---	---	---	---	---	---	M/FL	M/FL	---	---
	L	M/FL	---	M/FL	M/FL	M/FL	M/FL	M/FL	M/FL	M/FL	M/FL	M/FL	M/FL	M/FL
	L	N	---	S(O)/L (Study Days 273 and 448, respectively)	---	---	---	---	---	---	M/FL ^{oo}	M/FL ^{oo}	---	---
	S(O)	S(O)	---	N	---	---	---	---	L	S(O)	L ^{oo}	L ^{oo}	---	---

Table 6Z (Cont.)

Histological Classification of Greater Curvature Biopsies Using the Solcia Classification (Number of Patients)			
Solcia Classification	Abbrev.	BL	Final Visit
Normal	[N]	5	5
Normal and Focal Linear or Nodular Areas	[N/FL]	1	5
Simple (Diffuse) Hyperplasia	[S(D)]	1	1
Linear Hyperplasia	[LW] [L]	7	2
Micronodular Hyperplasia	[MN]	2	3

Clinical Summary of Pt. (61-y-Old Black M)

This pt. entered the study with a Hx of MEN-1, hyperparathyroidism, colon polyps in 1987, and gastric carcinoids in 1988. The screening Bx revealed MEN and the screening endoscopy noted a duodenal nodule. Subsequent Bxs of the gastric greater curvature revealed L or MH at Months 6 and 24. The Month 18 Bx indicated normal mucosa with FL or nodular areas. A Bx taken on Study Day 141 and reviewed by the MH revealed microscopic non-invasive carcinoids of the body of the stomach. No further carcinoids have been detected in this patient. He was titrated to a final maintenance dose of LANSO 60 mg QD and has been on test med. for 1037 days.

²² Due to the quality of Bx, not used in Bx analyses.

- Of the 15 pts.
 - 13 exhibited duodenal nodules
 - 5 had gastric or antral nodules or polyps upon endoscopy. Bxs of the gastric or antral nodules or polyps in these 5 pts. revealed no increase in endocrine cells.
 - 1 pt. had a colon polyp diagnosed upon colonoscopy. Available Bx results reported inflammation with no increase in neuroendocrine cells and no evidence of carcinoid tumors.

TABLE 68
Study N88-139

Patients With Gastrointestinal Nodules or Polyps

Pt. #	Location and Description	Study Day(s) Observed
	Duodenal nodules*	-8, -1, 85, 358, 581, 749, 945, 1267
	Duodenal submucosal mass* Antrum (no location provided) Gastric nodules	-1 517 934
	Duodenal nodule Antral nodule	838 1188
	Pyloric nodules Duodenal nodules Gastric nodule	105, 196 581 1134
	Antral polyp Duodenal nodules	965 965
	Duodenal nodule	954
	Duodenal nodules	728, 1064
	Duodenal nodule	646
	Duodenal nodules Laryngeal nodule Gastroesophageal junction nodule	414, 778, 974 414 974
	Duodenal nodules*	1, 141, 234, 414, 596, 764
	Colon polyp Antral nodule Duodenal nodule	212 426 845
	Duodenal nodules* Duodenal submucosal mass	1, 113, 211, 289, 477, 813 645
	Esophageal nodules* Esophageal polyp	1 843
	Duodenal nodules	405, 611
	Duodenal polyp Duodenal nodule	89 439

* Identifies instances of nodules/mass observed already at BL (screening) endoscopy.

viii) Vital Signs, P.E., EKGs

- There were no clinically significant changes observed in vital sign parameters, P.E. or EKGs.
- 2 pts. had P.E. findings unrelated to LANSO
 - Pt. had atrophic testes on Study Day 762 (a pre-existing condition).
 - Pt. had right-sided testicular pain due to a hydrocele and epididymitis.
- 7 pts. had EKG deteriorations at the final Tx visit (sponsor's Table 9.9). None of the deteriorations experienced by these pts. were considered clinically significant by the investigator.

3. Conclusion (Sponsor)

"Lansoprazole quickly and effectively controlled gastric acid output in ZES patients. Lansoprazole generally maintained a BAO <10 mEq/hr for up to 1386 days in 20 patients. An initial dose of lansoprazole 60 mg QD was effective in rapidly controlling gastric acid output and symptoms related to ZES. No patient developed endoscopic evidence of erosions or ulcers during the study.

"No patient withdrew from the study due to study drug-related adverse events. Three patients had micronodular hyperplasia at the final treatment visit and one MEN-I patient, who had a history of gastric carcinoid tumors, had a gastric carcinoid tumor identified during the study. Median fasting serum gastrin levels were not significantly different at the final treatment visit (542 pg/mL) compared to baseline (317 pg/mL).

"Currently available evidence from these ZES patients indicates that long-term administration of lansoprazole in doses up to 120 mg daily for a total of 51.4 patient-years of exposure in 20 patients is safe and effective."

4. Comments

Study M88-139 is the third critical trial submitted by the sponsor in support of the approval of LANSO for the L-T Tx of pathological hypersecretory conditions, including Z-ES. As the other two, this trial was also uncontrolled and open and this design is acceptable in view of the underlying malignancy of these conditions and we know what untreated course is like. Once again, the need to individually titrate every patient is emphasized as the best approach to treat gastric acid hypersecretors and Z-ES patients.

Twenty (20) of the 21 enrolled pts. had been treated with high doses of RAN, ranging from _____ mg per day and given in divided doses (the additional pt. received 6000 mg of CIM, also in divided doses). The mean historical BAO in these 21 pts. was 38.7 mEq/h (range _____ mEq/h) and the mean diagnosis of Z-ES (up to the start of LANSO Tx) was 1651 days (range _____ days). The mean length of exposure (to LANSO) was 2.6y (range: _____ y).

For pts. in this trial, the median end-of-titration dose was 60 mg QD and the median final maintenance dose was also 60 mg QD. During the dose-titration

Phase one of the pts. required 120 mg once-a-day and two required 60 mg twice-a-day. The lowest amount of L-T maintenance Tx with LANSO was 30 mg once-a-day (N=7), the highest 120 mg (either once-a-day, N=1; or as 60 mg twice-a-day, N=3).

The lack of statistically significant relationship between maintenance dose of LANSO for each pt. and either the historical BAO, historical MAO or the previously established dose of RAN indicates that the adequate therapeutic maintenance dose of this PPI cannot be predicted on the basis of the patient's previous experience. Every pt. needs to be titrated anew.

A measure of the effectiveness of the drug was given by the fact that, at the Final Tx Visit, 8 of 20 pts. in whom BAO values were <2.0 mEq/h were essentially achlorhydric (BAO ≤ 0.1 mEq/h). In a few pts., in whom duration of antisecretory effect was measured, this was shown to last at least 24h in 3 pts. and ca. 48h in one pt. This trial did not show a marked effect on symptoms mainly because very few symptoms were reported at BL. This was not unexpected as these pts. received an H₂ (mainly RAN) up to 6 to 12h prior to their initial dose of LANSO. Similarly, no patients developed acid-related lesions during this trial (esophagitis, ulcers or erosion in the upper g.i. tract).

As the other two trials, this study showed LANSO to be well tolerated. The most frequently reported AEs were nausea, vomiting, abdominal pain, pharyngitis and peripheral edema. There were no clinically significant mean changes from BL in hematology, blood chemistry, thyroid function or urinalysis parameters. However one pt. experienced elevations of transaminases and another experienced elevations of AP + transaminases + bilirubin that remained abnormal at the end of the Tx. In these two patients, all of these parameters of LF had been normal at BL. These biochemical abnormalities were attributed to metastatic liver disease + Cushing's syndrome + chemotherapy in one patient and hypothyroidism + excessive alcohol consumption in the other. The latter pt. also had normal TSH values at BL that increased to values higher than the limit of concern and remained abnormally high up to 42 mo. after the start of LANSO Tx.

In this trial, a statistically significant median percent change from BL in fasting serum gastrin concentrations was seen at Months 3, 12, 18, 24 and 30. For the final visit analysis the difference from BL was numerical (225 pg/mL) but not statistically significant. Actually, fasting serum gastrin concentration showed an increase at Month 3 but no further increases throughout the remainder of the trial (up to 42 mo). In quantitative analyses of gastric Bx, this trial showed statistically significant decreases in Grimelius-positive cell density for mean change from BL at 6, 24 and 36 months and Final Tx Visit (but not at Month 42). Qualitative analyses of the gastric Bxs showed little if any changes in acute and chronic inflammation. No pt. showed higher than MNH (N=11 of 13 at one or more evaluations after the screening visit) or dysplasias. One pt. with a Hx of MEN-I, hyperparathyroidism, colon polyps in 1987 and gastric carcinoids in 1988, had gastric carcinoid tumor identified on Study Day 141.

In this trial a large proportion of the pts. (15 of 21) had g.i. anomalies detected on endoscopy. In 5 of these patients these anomalies were already detected at BL endoscopy (4 pts. with nodules/masses in the duodenum and one pt. with nodules in the esophagus). But in all the others the anomalies (duodenal, gastric or antral nodules/polyps) were not present at BL. The information on this matter is incomplete because Bxs were not done in all instances. Bxs of the gastric or antral nodules in 5 pts. revealed no increase in endocrine cells

F. Summary of Section G (Efficacy): L-T Tx of Pathological Hypersecretory Conditions, Including Z-E Syndrome

There were results from three single-center, U.S., open-label, non-randomized, non-concurrently comparative (but comparative to BL and to historical data), dose-titration trials submitted in support of the approval of LANSO for this indication.

Study M89-405 was one of three ongoing clinical trials showing that LANSO is effective in reducing BAO, decreasing symptomatic manifestations and/or maintaining the pt. free of them and in healing and maintaining endoscopic lesions, including mild to moderate esophagitis, GU and DU in hypersecretors, including patients with Z-ES. As should be the case, individualization of the dose and dose regimen is expected in every patient. But for most, the initial and median final maintenance dose was 60 mg once-a-day. Fractionation of the dose (ranging from 15 to 90 mg BID) was necessary in some. Throughout the duration of the trial no side effects or toxicity related to LANSO were demonstrated. Findings on serum gastrin concentrations of hyperplasia or the EC-L cell of the stomach were neither dramatic, unexpected nor of concern. There were no polyps, nodules, nodular folds or other lesions representing masses or tumors in the upper g.i. tract of these 30 hypersecretory patients.

Data from Study M90-436 in a handful of patients appears to support the effectiveness and safety of LANSO in the Tx of hypersecretory conditions including Z-ES. The most important contribution of this trial was the BL finding of nodules or nodular folds in the fundus of the stomach in two pts. In one of these, in whom Bx was obtained, a pre-malignant condition (chronic active atrophic gastritis together with intestinal metaplasia in the presence of H. pylori) is of concern. Are these lesions due to the underlying condition? Is this their normal/usual evolution? Is their presentation/evolution modified by the profound antisecretory medication given (before LANSO)? A thorough investigation of the antisecretory medication preceding LANSO and the length of administration of hypo- and an acidity-inducing drugs to those patients is necessary in view of the many instances of nodules/polyps observed in the trial that follows.

Study M88-139 supports the sponsor's proposal that LANSO (60 mg once-a-day) is quick and effective in controlling gastric acid output in Z-ES patients, maintaining an adequate BAO of <10 mEq/h for up to 1386 days (N=20). There were little effects on symptoms or acid-related lesions that could be demonstrated but this is not surprising because these pts. had received high-dose RAN up to 6 to 12h prior to their initial dose of LANSO. LANSO was well tolerated in this pt. population. Three pts. had MNH at the Final Tx Visit and one MEN-I pt., who had a Hx of gastric carcinoid tumors, had a gastric carcinoid tumor (identified during the trial). None of this is unexpected.

One finding of concern that needs to be explored further and be put in the proper perspective is the development of endoscopically proven nodules/polyps (some were present pre-dose) in the upper g.i. tract in a large proportion of pts. in trial M88-139. This contrasted to endoscopic findings reported in Study M89-405 (N=30) where no endoscopic anomalies of this type (on any patient, not even at BL observations) were reported. These findings are of concern because in at least one patient, who showed similar lesions in Study M90-436, histopathological evaluations demonstrated findings that can be categorized as pre-malignant [I am referring to the simultaneous presence of chronic atrophic gastritis + intestinal metaplasia together with H. pylori].

Upper g.i. mucosal lesions described in trials M90-436 and M88-139 suggest the need for a thorough assessment of the antisecretory medications (type, dose and dose duration) preceding entrance into the LANSO L-T trials. It is not

altogether clear if these lesions are a manifestation of the natural Hx of the hypersecretory condition(s). But it is very puzzling that none of the 30 patients entered into the M89-405 trial that developed these nodules/polyps; none of these patients developed this type of lesions during the trial.

In summary, the reported EC-L hyperplastic changes, including carcinoids in MEN-I patients are not unexpected. These are most likely due to the natural history of the underlying hypersecretory condition. Whether antiseecretory medication plays a role in the appearance and evolution of these lesions is not known but, based on the overall safety data it would seem that such a role is not very prominent. The pre-existence of nodules or polyps or the development of such lesions, especially if they have the components of a pre-malignant condition (atrophic gastric + intestinal metaplasia + presence of H. pylori) is another matter. These findings dictate histopathological evaluations and follow-up in pts. who already have or develop nodules/polyps during the trial and beyond. It is essential to establish if very high doses of antiseecretory medications (any type, including H₂) given for a long time are not modifying the natural evolution of nodules/polyps in these hypersecretory patients. Until a satisfactory explanation is available, caution is warranted when considering approval of profound antiseecretory drugs such as LANSO for conditions (other than Z-E) where very L-T (years) administration of this antisecretory is needed.

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XIII. REVIEWER'S OVERALL SUMMARY AND CONCLUSIONS

A. Efficacy

A summary of efficacy is given, separately, at the end of the review of clinical trials for each indication, Sections B through G.

B. Safety

In this section, the whole safety database is put together. For information on PK/PD, in normals, PKs in the elderly, women, hepatic or renally impaired subjects as well as drug-drug interactions, the reader is referred to Section A of this review.

1. Number of Pts. Exposed per Database

The safety and tolerance of LANSO have been tested in Phase I through III trials in healthy volunteers and a variety of patient populations (RE, "resistant" RE, maintenance of healed RE, DU, GU, and hypersecretory syndromes. The distribution of total number of patients (worldwide) under the different categories is summarized below (location of Safety Database is given in parenthesis).

- Total No. of Subjects Exposed 9071
- No. of Subjects in Phase I Clin Pharmacol. Trials 1182
 - Of these: 444 (TAP)
 - 464 (European)
 - 274 (Asian)

Of these 1182, 1117 subjects received LANSO on Phase I Clin. Pharmacol. trials

- Worldwide 388 (TAP)
- 455 (European)
- 274 (Asian)

- Total No. of Patients in Phase II/III studies: 7889
 - Of these: 2262 (TAP)
 - 3525 (European)
 - 2102 (Asian)

- Total No. of Patients Tx During Phase II/III, S-T, L-T, and maintenance Tx studies worldwide 5466
 - Of these: 1767 (TAP) Safety
 - 2220 (European)
 - 1479 (Asian)

- Total No. of Patients in S-T studies 4995
 - Of these: 1428 (TAP)
 - 2088 (European)
 - 1479 (Asian)

a) Mean age=50y (range:

y), caucasian=86%, M=64%, Tobacco users=38%, Consumed Alcohol=51%

- Total No. of Patients in L-T studies 223
Of these: 91 (TAP)
132 (European)
- Pts. receiving LANSO at some time during maintenance studies 502
254 of these 502 pts. had received LANSO previously in a short-term study.
- Pts. randomized during S-T, Phase II/III controlled studies in TAP Safety Database 2045
Of these: 1362^a received LANSO
683 received a reference agent

a) Of these, 55 (4.0%) were D/C from one of these controlled studies due to an AE.

2. S-T, Phase II/III Studies in the TAP Safety Database

The duration of Tx and the maximum daily LANSO dose in these studies is summarized in Table 69.

- Most pts. who received LANSO were treated either for >2 but <6 weeks (596 pts.=41.7%) or from 6 to 10 weeks (757 pts.=53%)
- 78.8% of the pts. (657 + 458) received 30 to 60 mg of LANSO daily
- 21.2% of the pts. received a maximum dose of LANSO of 30 mg once-a-day.
- The combined exposure to LANSO during S-T, Phase II/III studies was 176.8 patient years.

3. L-T Phase II/III Studies (Table 70)

- The number of pts. under the different lengths of exposure is small.
- The highest dose administered to any patient was 180 mg once-a-day.
- The combined exposure to LANSO during L-T Phase II/III trials was 173.8 patient-years.

Number of Pts. in Maintenance Studies (Table 71)

A total of 502 pts. received LANSO in maintenance trials; 315 in randomized studies; 187 pts. in open-label Tx for recurrence of disease.

- The overall experience resulted in a total exposure of LANSO of 341.1y.

TABLE 62
NDA 20-406

S-T, Phase II/III Studies in TAP Safety Database: Duration of Tx and Maximum Daily Dose for LANSO Tx Pts.

Length of Tx (Weeks)	PL-Controlled ^a (N=817)	Positive-Controlled ^a (N=545)	Uncontrolled ^a (N=66)	Total Pts. in All S-T Studies (N=1428)
0 - 2	20 (2.4) ^d	15 (2.8)	9 (13.6)	44 (3.1)
>2 - 6	401 (49.1)	152 (27.9)	43 (65.2)	596 (41.7)
>6 - 10	393 (48.1)	358 (65.7)	6 (9.1)	757 (53.0)
>10 - 14	3 (0.4)	20 (3.7)	7 (10.6)	30 (2.1)
>14 - 17	---	---	1 (1.5)	1 (0.1)
Maximum Daily LANSO Dose (mg)				
15	303	---	--	303 (21.2)
30	298	331	28	657 (46.0)
60	216	214	38	468 (32.8)

- a) Studies N87-090, -091, -092 and N88-268. The latter was a positive-controlled and PL-controlled study. In this table it is included only with the PL-controlled studies.
- b) Studies N88-269, N89-349, -393, P91-066 and N90-422.
- c) Study N88-193. Five patients enrolled in this study received an additional course of therapy in study N88-251 which was of 10 to 14 weeks duration.
- d) Figures in parenthesis denote percentages.

TABLE 70
NDA 20-406

L-T, Phase II/III Studies in TAP Safety Database:
Duration of Tx and Maximum Daily Dose for LANSO-Tx Pts.

Length of Tx (Months)	Barrett's Epithelium (N=34) ^a	Hyperscretors/ (Z-ES) (N=57) ^b	Total (N=91)
0 - 6	5 (14.7%)	8 (14.0%)	13 (14.3%)
>6 - 12	2 (5.9%)	11 (19.3%)	13 (14.3%)
>12 - 18	2 (5.9%)	5 (8.8%)	7 (7.7%)
>18 - 24	2 (5.9%)	7 (12.3%)	9 (9.9%)
>24 - 36	15 (44.1%)	17 (29.8%)	32 (35.2%)
>36	8 (23.5%)	9 (15.8%)	17 (18.7%)
Final Daily LANSO Dose (mg)			
<15	--	1	1
15	--	2	2
30	--	13	13
45	--	4	4
60	34	21	55
75	--	2	2
90	--	3	3
105	--	1	1
120	--	6	6
150	--	3	3
180	--	1	1

a) Studies N88-249 and N89-375. The total no. of pts. is the sum of unique patient experience, which includes 34 patients with Barrett's epithelium who received LANSO in Study N88-249, Study N89-375 or both.

Mean age = 61y; the majority were caucasian M.

b) Studies N88-139, N89-405 and N90-436.

Mean age = 51y; 61% were M.

TABLE 71
NDA 20-406

Maintenance Tx Studies in the TAP Safety Databases:
Duration of Tx for Pts. During Continuous
LANSO Therapy^a

Length of Tx (Months)	N (%)
0 - 3	223 ^b (41.5%)
3 - 6	35 (6.5%)
6 - 9	17 (3.2%)
9 - 12	45 (8.4%)
12 - 15	212 (39.5%)
>15	5 (0.9%)

- a) Studies N88-270, -271 and N89-350
- Among the 315 pts. randomized to LANSO, 91% were Caucasian, 64% M. The mean age was 47y (range: 19 to 83y), 31% used tobacco and 47% consumed alcohol.
- b) The total number of patients in this Table is 537. In addition to the 502 mentioned above, included in this Table are 35 pts. who received LANSO in the acute studies and were subsequently randomized to PL in the maintenance trials. These 35 patients are included in the 0-3 months category. The total number of patients that received LANSO for periods longer than 6 months is small (total=279).
- An additional 187 pts. received LANSO in open-label prevention of recurrence trials.

4. AEs

a) S-T Phase II/III Studies (Table 72)

- In the S-T Phase II/III studies, 52.9% of LANSO-Tx pts. reported Tx-emergent AEs. In these studies, 20.8% of LANSO pts. had one or more AEs that were considered to be possibly/probably related to therapy.
- The most frequent AEs considered to be possibly/probably related to LANSO Tx in S-T studies were
 - headache (7.6%)
 - diarrhea (4.4%)
 - abdominal pain (2.0%)
 - nausea (1.3%) and
 - dizziness (1.3%).

- In the PL-controlled studies, the PL group reported statistically significantly higher incidence of possibly/probably Tx-related headaches than the LANSO group.

For Tx-emergent AEs, a statistically significant difference between Tx groups was seen for fever with a lower incidence observed in LANSO patients than in PL patients.

- In the positive-controlled studies, the LANSO group reported statistically significantly higher incidence of both possibly/probably Tx-related and Tx-emergent diarrhea and Tx-emergent myalgia than the RAN group.

- All AEs with an incidence of at least 2% in any Tx group and considered by the investigator to be possibly or probably Tx-related are displayed by body system, COSTART term, and Tx group for PL- and RAN-controlled S-T studies in Table 72.

TABLE 72
NDA 20-406

AEs Possibly/Probably Related to Tx, Reported by ≥2% of Pts. in S-T Phase II/III, PL (Left Side of Column) vs Positive-Controlled Trials

PL-Controlled Trials ^a			RAN-Controlled Trials ^b		
Body System/ COSTART Term	PL (N=254)	LANSO (N=817)	Body System/ COSTART Term	RAN (N=429)	LANSO (N=716)
Total patients Any event	22.0	18.2	Total patients Any event	14.2	19.0
Body as a whole			Body as a whole		
Abdominal pain	1.2	2.3	Headache	3.7	5.3
Headache	12.2	7.7 ^c			
Digestive system			Digestive system		
Diarrhea	2.4	3.5	Diarrhea	1.9	4.3 ^d
Nausea	2.0	1.1			

a) Studies N87-090, -091, 092, N88-268.

b) Studies N88-268, -269, N89-349, -393, N40-422, P91-066

c,d) p<0.05 compared to the PL and RAN group, respectively

- AEs were analyzed by indication. In the positive(RAN)-controlled studies of patients with RE, LANSO patients had a statistically significantly higher incidence of possibly/probably Tx-related AEs than PL patients, but this difference was not observed in the positive(RAN)-controlled DU and GU studies.
- In the subgroup analyses of AEs, there was no apparent evidence that age, gender, race or creatinine clearance influenced the likelihood of developing AEs during Tx with LANSO in the S-T controlled studies.
- When all Tx-emergent AEs were considered in dose-response studies of PL, LANSO 15, 30 and 60 mg there was little difference in AE reporting rates between Tx groups. Specifically, there was no difference between LANSO 15 vs 30 mg.
- When specific AEs were evaluated, a possible dose-response relationship was noted for diarrhea. But this was primarily due to higher incidence in the 60-mg group.
- The use of concomitant therapy did not adversely affect the incidence of AEs in LANSO-Tx pts.

b) L-T Phase II/III Studies (Table 73)

As shown in this Table, the most commonly reported AE considered to be possibly/probably to therapy in pts. with Barrett's epithelium was diarrhea. In Z-ES/hypersecretor pts. these AEs were diarrhea, headache and nausea. Tx-emergent AEs reported while taking concurrent medications in these L-T studies did not show clinically relevant trends. However, these trials did not have a comparator group.

TABLE 73
NDA 20-406

Possibly/Probably Tx-Related AEs Occurring in >1 Pt.
in L-T, Phase II/III Studies

	Barrett's Epithelium ^a	Z-ES/ Hypersecretors ^b
Body System/COSTART Term	LANSO (N=34)	LANSO (N=57)
Total patients Any event	14.7	24.6
Body as a whole Headache	2.9	5.3
Digestive system Diarrhea Nausea	8.8 0	5.3 3.5

a) Studies N88-249 and N89-375

b) Studies N88-139, N89-405 and N90-436

c) Maintenance Tx Studies

When the Tx period until the time of first recurrence of disease was analyzed, 70.5% of LANSO pts. (mean exposure=273 days) reported Tx-emergent AEs. This was higher than the 40.3% of the "PL" patients (mean exposure=114 days) reporting Tx-emergent AEs during this period.

- During maintenance Tx in pts. receiving continuous or intermittent LANSO Tx regimens, Tx-emergent AEs were reported by 75.9% of the LANSO pts and 64.2% of the "PL" pts. One possible explanation for this difference is the substantially longer exposure to maintenance D-B medication in the LANSO Tx-regimens. During maintenance Tx, when "PL" patients could receive open-label LANSO 30 mg QD, there again existed a greater exposure of LANSO pts. (mean 317 days) to their Tx regimen than the "PL" patients (mean 260 days).
- In the subgroup analyses of AEs, there was no apparent evidence that factors such as age, gender, race or creatinine clearance influenced the likelihood of developing AEs during Tx with LANSO in the maintenance Tx studies.

d) Most Commonly Reported AEs (Table 74)

This Table displays the most commonly reported Tx-emergent AEs (≥2%) for S-T, PL- or active-controlled trials. Data from maintenance Tx studies are summarized in Table 75.

TABLE 76
NDA 20-406

ix-Emergent AEs Reported by 22% of Pts. in 2-7, Phase II/III,
PL- or Positive-Controlled Studies in the TAP Safety Database

Body System/COSTART Term	PL (N=254)	LANSO ^a (N=117)	Body System/COSTART Term	RAM (N=429)	LANSO ^b (N=716)
	X of Pts.			X of Pts.	
Total patients Any event	59.1	34.2	Total patients Any event	44.4	47.6
Body as a whole			Body as a whole		
Abdominal pain	5.9	5.3	Abdominal pain	3.0	2.5
Back pain	2.8	2.0	Chest pain	1.4	2.1
Fever	2.4	0.6 ^c	Flu syndrome	3.0	2.0
Flu syndrome	1.4	2.1	Headache	14.0	12.3
Headache	22.8	24.2			
Pain	2.0	2.6			
Digestive system			Digestive system		
Constipation	0.8	2.1	Diarrhea	3.0	6.1 ^d
Diarrhea	5.5	6.0	Nausea	2.1	2.5
Nausea	3.9	3.1			
Vomiting	2.0	2.3			
Respiratory system			Respiratory system		
Pharyngitis	9.1	8.1	Pharyngitis	6.8	6.6
Rhinitis	5.9	4.7	Rhinitis	2.8	1.7
Skin and appendages			Skin and appendages		
Rash	0.8	2.4	Rash	1.9	2.8
			Nervous system		
			Dizziness	2.1	3.1

a) Studies M07-090, -091, -092, M08-268
b) Studies M08-268, -269, M09-349, -393, M00-422, M91-066
c) p<0.05 compared to the PL group.
d) p<0.05 compared to the RAM group.

TABLE 75
NDA 20-406

Tx-Emergent AEs Reported by ≥2% of the "PL" or LANSO Pts.
During the Maintenance Tx Studies^a

Body System/COSTART Term Mean Exposure (Days)	PL ^b (N=201) 259.7	LANSO (n=315) 316.7
Total patients Any event	64.2	75.9
Body as a whole		
Abdominal pain	7.5	6.0
Accidental injury	3.0	5.1
Back pain	5.5	4.1
Chest pain	2.0	3.2
Flu syndrome	7.0	6.0
Headache	10.4	12.4
Infection	2.5	3.2
Pain	2.0	3.5
Cardiovascular		
Hypertension	2.0	1.0
Digestive system		
Diarrhea	12.4	11.4
Dyspepsia	2.5	0.6
Gastroenteritis	1.5	2.5
G.I. anomaly (polyp)	3.0	3.2
Nausea	3.0	2.9
Rectal disorder	1.0	2.5
Tooth disorder	2.5	4.1
Vomiting	1.0	2.9
Musculoskeletal		
Arthralgia	4.0	5.7
Myalgia	3.5	2.9
Nervous system		
Anxiety	1.5	2.5
Depression	2.5	2.2
Dizziness	0.5	3.5
Respiratory		
Bronchitis	4.0	3.8
Cough increased	0.5	2.9
Pharyngitis	17.5	19.7
Rhinitis	3.5	7.0
Sinusitis	8.5	7.9
Skin and Appendages		
Rash	3.5	3.8
Urogenital		
Cystitis	2.0	0
UTI	3.5	6.0

a) Studies N88-270, -271, N89-350

b) Possibly treated with LANSO intermittently

e) Diarrhea and Colonic Findings

- 18 pts. underwent sigmoidoscopy or colonoscopy with Bx during the S-T controlled and maintenance-Tx studies because of an episode of diarrhea or in one case because of severe abdominal pain.

- A prestudy Hx of bowel disease, suggesting a predisposition to diarrhea, was present in 10 of the 18 cases. The preexisting diagnoses in these patients included colitis, IBS, possible helicobacter infection and diverticulitis.
- Of the 18 patients, 15 received LANSO, 1 received PL only, and 2 received RAN and/or PL only.
- Diarrhea occurred at all three LANSO doses and at the 300 mg dose of RAN. The severity of the diarrhea reported among these patients was rated from mild to severe. The duration of treatment at the time the diarrhea began ranged from 4 to 186 days. Three (3) patients were terminated from the study because of the diarrhea.
- Histologic findings from colon Bxs indicated 7 cases of acute superficial colitis or nonspecific reactive changes, 1 case of UC, and one case of Crohn's disease.
- The patient with a Bx consistent with UC developed a recurrence of diarrhea upon rechallenge with LANSO, suggesting a drug-induced AE, possibly an idiosyncratic reaction, as diagnosed by the investigator. However, possible idiosyncratic Rx in one pt. could not explain the other cases of diarrhea seen.
- For the pt. with the Dx of Crohn's disease, the diarrhea and abdominal pain antedated the administration of the drug. The sponsor speculates that exacerbation of diarrhea could have been induced by LANSO by unknown mechanisms or could simply represent a spontaneous relapse that is typical of this IBD. In reality, the pathogenesis of LANSO-induced diarrhea remains unknown.

f) Short- and Long-Term Phase II/III Studies in the European and Asian AE Databases

AEs in these databases were similar to those reported in the U.S. database.

g) Deaths, Premature Terminations Due to AEs and Serious AEs

- A total of 26 deaths occurred worldwide in pts. receiving LANSO (N=22) or blinded test medication (N=4) through June 30, 1993. Two cases, briefly summarized below, but none of the other deaths, were reported as possibly or probably related by the investigator. I agree with the sponsor that the number of deaths is not unexpected if one considers that >9,000 pts. have been enrolled in LANSO studies worldwide.
 - A 79 y old patient with a Hx of hypertension and RE suffered a heart attack and died after 7 weeks of LANSO Tx.
 - A 72 y old woman suffered a sudden CVA and died almost immediately after 58 weeks of LANSO Tx.
- 16 pts. worldwide had serious AEs that have been reported to the FDA as 10-day safety reports. There was no apparent relationship between LANSO and the occurrence of any specific type of serious AEs.
- Of the 57 pts. who enrolled in the Z-ES/hypersecretor studies in the TAP Safety Database, 6 pts. W/D prematurely due to an AE. Two of these premature terminations were deaths (both in Study M88-139) and have been previously presented.

- 8 (PL=2; LANSO=6) of the 36 pts. enrolled in the PL-controlled, L-T study of Barrett's epithelium (Study M88-249) W/D from the study during the D-B Tx period, at least in part due to AEs. None of the patients had AEs causing premature termination which were judged by the investigator to be possibly/probably Tx-related.
- 3 of the 27 Barrett's epithelium-pts. who entered the open-label, LANSO L-T extension (Study M89-375) W/D prematurely due to AEs.

h) Changes in Laboratory Parameters

In general, no trends of concern were found for changes in laboratory parameters. Some small but statistically significant differences were reported for some parameters at some points of observations but these were not consistent between study types and not considered as clinically significant.

5) Safety matters of potential relevance to the L-T Safety of LANSO

These are to be addressed in depth during the MO's review of the LANSO Safety Update (submitted by the sponsor on 7/1/94). This assessment will include review of the following:

- a) Reports of upper gastrointestinal, colonic and other tumors.
- b) Gastric atrophy and intestinal metaplasia.
- c) Eye changes (retinal atrophy; results of electroretinograms)
- d) Impotence.
- e) Abnormalities in LFTs [AP, etc.].
- f) Results of gastric Bxs to monitor ECL cell hyperplasia and carcinoid tumors.
- g) Hypergastrinemia in outliers.

SECTION I

XIV. Recommendations for Regulatory Action.....	316

XII. RECOMMENDATIONS FOR REGULATORY ACTION

The benefit/risk appraisal of LANSO in the various proposed clinical indications took into consideration a number of facts. These include results of carcinogenicity studies in rats showing testicular interstitial cell adenomas in males, gastric fundic carcinoids in females and males and a primary malignant tumor in one rat. This tumor, described as non-argyrophilic adenocarcinoma and seen in the glandular part of the stomach of the rat, is very unusual in this animal species. Also noted were hepatocellular adenomas in male and female rats; these adenomas were higher in incidence but did not reach statistical significance by pairwise testing. Similarly, squamous cell carcinomas were present exclusively in treated rats but the incidence did not reach statistical significance by pairwise comparisons. Carcinogenicity studies in mice showed hepatocellular adenoma and carcinoma in both males and females and testicular rete testis adenomas. It is worth mentioning that gastric carcinoids were exclusively present in treated male mice but the incidence did not reach statistical significance by pairwise testing.

The above-summarized findings demonstrate that LANSO is tumorigenic in animals. These findings, which go over and above carcinoid/gastric adenocarcinoma, are indications of what to look for in humans. There is concern about a potential toxicological hazard to humans based on these animal data with LANSO. This drug should not be used when other treatment modalities are available that are as good and offer less risk. It should be used for conditions where very pronounced acid inhibition is needed (i.e. Z-E syndrome), where available therapeutic modalities are not adequate (i.e. truly intractable DU, truly intractable GU), where additional armamentarium is needed (i.e. severe RE and poorly responsive RE) and in general, where the potential benefits outweigh the perceived risks.

The reviewer's main concern is with long-term use. It seems reasonable to assume that there is no long-term hazard in short-term use provided that the use is indeed short-term. This concept opens the avenue for expansion of the restricted indications to conditions, such as active DU and active GU, where a few weeks treatment of antiseptics/antiulcers is indicated. A recent NIH Consensus recommended short-term use of these drugs in combination with antibiotics for the eradication of H. pylori. In the present state of affairs it appears that there is not going to be much need for maintenance of healing of PU because HP eradication is associated with 10% or less recurrence rate. On this basis, DU is an appropriate indication. Drugs for healing and symptom relief of erosive esophagitis are traditionally approved for "short-term" use. But the impracticability of short-term for erosive esophagitis is widely recognized. The reviewer's major concern for this indication is the consequence of promiscuous usage outside this duration recommendation. For RE, in addition to these safety concerns, the reviewer has concerns over the effectiveness (lack of data for severe or poorly responsive RE), see below.

The recommendations listed below are subject to the adequate resolution of questions brought up during the review of the evidence. These are mentioned with each recommendation. The critical studies submitted in support of the indication are identified. Also included is additional pertinent information, some of which should be included in the labeling.

The following is recommended.

1. Approval of the use of LANSO 15 mg once-a-day before eating for up to 4 weeks for the healing and symptom relief of duodenal ulcer.

(M87-090 and M88--268)

- Studies available to date have not assessed the efficacy of LANSO in uncomplicated DU for periods of more than 4 weeks. No domestic study was performed for >4 weeks for short-term, active DU.
 - The labeling indication should prohibit against maintenance use in DU. If maintenance therapy is deemed appropriate after DU healing, the labeling should indicate that therapy other than LANSO (or OME) should be used.
- For Study M88-268, validation of the raw data from the CRFs (Scientific Investigations) and verification/confirmation of p-values through statistical methodology (Biometrics) is needed.
2. Approval of LANSO (titrated to individual patient needs, starting with 60 mg once-a-day) for the control of hypersecretion in acid hypersecretory conditions, including gastrinomas.

[M89-405, M90-436 and M88-139]

- The development (or pre-existence) of nodules or polyps in patients being treated with very high doses of antisecretories, including H₂-receptor antagonists, other proton pump inhibitors or LANSO, dictates histopathological evaluations of these lesions and follow-up of these patients.
- There is need to explain the presence of so many gastrointestinal polyps or nodules in the NIH trial and the complete absence of these lesions in the Hirschowitz trial.
3. Not approval of LANSO for the short-term healing of GU is recommended (see XI, Section F).

[M87-091 and KF 4801/07]

- For the short-term treatment of benign, uncomplicated GU replication of the effects of LANSO 15 mg once-a-day is needed.
4. It is important to reiterate what the sponsor is requesting when considering the RE indication.

"PREVACID Delayed-Release Capsules are indicated for short-term treatment (4 to 8 weeks) for healing and symptoms of all grades of reflux esophagitis, including severe esophagitis in patients who were poorly responsive to a course of histamine H₂-receptor antagonists in a dose equivalent to ranitidine 150 mg b.i.d. or greater and in patients"...
- a) It is recommended not to approve LANSO for the "short-term" treatment of poorly responsive ("resistant"), severe RE.
 - The severe category of RE was poorly represented in the two critical trials (M89-349 and M89-393) submitted in support of this indication as well as in those submitted in support of erosive esophagitis. No proof has been presented that patients enrolled in trials M89-349 and M89-393 were poorly responsive ("resistant") to optimal doses of antireflux therapy with properly documented compliance. The sponsor failed to give

sufficient information to demonstrate that these patients had erosive esophagitis that was indeed of the poorly responsive type. In all of these trials, the bulk of the study populations consisted of patients with mild to moderate instead of severe esophagitis.

- When treating erosive esophagitis, if a patient has not responded after 8 to 12 weeks of therapy with an H₂-receptor antagonist this could be due to underdosing, need for b.i.d. rather than once-a-day regimens, noncompliance, or to a specific population that - for reasons unknown - was truly poorly responsive. But the sponsor's definition of poorly responsive is not adequate.
- The data from trials M89-349 and M89-393 may be of use in the selection of doses to be tested in patients with severe or poorly responsive RE.

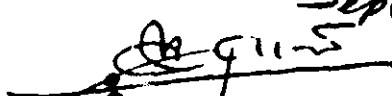
b) It is recommended not to approve LANSO for the indication healing and symptom relief of erosive esophagitis. The deciding factors for the reviewer's recommendation are concerns over demonstrated effectiveness, dose selection, and safety.

[M87-092, M88-269, M89-349 and -393].

- For indications related to RE one needs to focus on at least two aspects. One is symptomatic relief in patients without erosive disease. Evaluations in purely symptomatic patients have not been carried out with LANSO. The other is healing of erosive esophagitis. With the information at hand, approval cannot be granted for all grades of erosive esophagitis. The data from the two critical trials [M87-092 and M88-269] show efficacy in mild to moderate erosive esophagitis. The data from two additional trials [M89-349 and -393] provide further evidence of effectiveness in mild to moderate erosive esophagitis. All of these are well-controlled studies. So, there is plenty of data demonstrating that LANSO is effective in mild to moderate erosive esophagitis. However, if approval of the drug were to be granted, the reviewer is concerned that LANSO might be promoted for mild cases of RE, thereby excluding the concept that (in a fashion similar to the available PPI), only severe RE or poorly responsive GER was the proper indication for LANSO. Because of the toxicological hazard, the use of the drug should be restricted to a patient subgroup of seriously ill patients (severe or truly poorly responsive disease) because erosive esophagitis is not really treated short-term. This is a fact not a conjecture. As pointed out above, the reviewer is concerned with prolonged use.
- Furthermore, the reviewer finds it difficult to recommend a dose (for mild to moderate erosive esophagitis). Although the sponsor proposes 30 mg once-a-day, this dose seems unnecessary according to trial M87-092 because it was not more advantageous than the 15 mg once daily. On the other hand, because the second trial did not include a 15 mg once daily dose, efficacy with this dose of LANSO has not been replicated. There is presently no reason to doubt the fundamental safety of the drug for short-term use in the strict sense. Both doses of LANSO are safe and well tolerated but - although we do not regulate price - the 30 mg dose will be undoubtedly more expensive than half this amount of compound.

5. Not approval of LANSO for the maintenance of healed reflux esophagitis is recommended. This recommendation is based on concerns over safety as well as effectiveness.
- For the indication maintenance of healed RE even higher safety standards than for "short-term" Tx of RE would apply.
 - The reviewer's main concern is with prolonged, continuous use. There is insufficient information to conclude that repeated/intermittent use of LANSO would be worse or better than prolonged, continuous use. The presently available long-term data, although reassuring, is insufficient to mitigate the toxicological hazard arising from animal data. This is because the potential problems may have a long latency period and would need a long term (many years of exposure) to manifest themselves. No standard post-marketing trial can be proposed that can answer the tumorigenic properties question 25 to 30 years down the line.
 - One salient point to factor in the assessment of risk to benefit ratio for this indication is what is being maintained healed. On the basis of the data from studies M88-271 and M89-350, the two critical trials for the maintenance of healed RE, the answer is mild to moderate RE.
 - There is the possibility for these mild to moderate esophageal lesions to be maintained with lower doses of LANSO (i.e., 7.5 mg once-a-day). This possibility should be kept in mind when comparing the results from maintenance trials to the use of other pharmacological approaches.
 - Maintenance of healed severe or complicated RE is, clinically, very important. These situations most likely require treatment with drugs, such as proton pump inhibitors, capable of inducing profound antisecretory activity. But at present, the usefulness of LANSO in these difficult to maintain conditions, is conjectural.
 - Further human data on the effects of sustained hypo- and achlorhydria, hypergastrinemia, etc., are needed to rule out the possibility of an increase risk for tumor development in patients receiving L-T therapy with LANSO and other PPIs.

September 16, 1994


Hugo E. Gallo-Torres, M.D., Ph.D.

cc:
NDA 20-406
HFD-180
HFD-180/SFredd
HFD-180/HGallo-Torres
HFD-181/CSO
HFD-180/Jchoudary
HFD-180/JGibbs
r/d 5/25/94 jgw
f/t 9/15/94 jgw
MED\N\20406404.0HG

9/19/94
will need Advisory Com.
discussion re maint. claim
and safety. 

Wash

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW OF SAFETY UPDATE

NDA: 20-406
Amendment No. 017

Sponsor: TAP Pharmaceuticals Inc.

Date of Submission: June 30, 1994

Drug: PREVACID® (Lansoprazole) capsules

Routing Administration: Oral

Pharmacological Category: Antisecretory/Antiulcer
Inhibitor of the (H⁺, K⁺)-ATPase enzyme (proton pump) of the parietal cell in the gastric mucosa.

Proposed Indications: Short-term Tx of RE,
Pathological Hypersecretory
Conditions, including the Z-E syndrome

First Draft to Supervisor: November 18, 1994

DEC - 5 1994

Material Reviewed:	<u>Vol. No.</u>
Updated Marketing Status, Statement from Eye Safety Subcommittee, Eye Findings from Clinical Studies, Overview of Retinal Atrophy and Results from Mechanistic Studies	1
Preclinical Study Reports + References	2
New PK studies	3-11
New Clinical Studies	12-25
Updated ISS for the Clinical Reviewer	26-30
CRFs for deaths or D/Cs due to AEs	36-39

Reviewer: Hugo E. Gallo-Torres, M.D., Ph.D.

Lansoprazole (PREVACID®)
Review of Safety Update

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I. INTRODUCTION

An initial review of safety database of LANSO was included in MOR of September 19, 1994. The cut-off date for that Integrated Summary of Safety (ISS) was November 30, 1992. The present review assesses data in the updated ISS for NDA 20-406, submitted on June 1994. Special attention is paid to the long-term studies. For these, Tx has been ongoing for >4y in some pts. The data presented includes all data available up to the cut-off date of September 30, 1993. To facilitate review of this document, all section, table, and appendix numbers used throughout this update correspond to those presented in the ISS. Per FDA request, only sections incurring an addition and/or change were presented in this update with the exception of the sections dealing with maintenance of healing studies. These sections were repeated, albeit unchanged, to facilitate review in conjunction with L-T studies for the Tx of patients with Barrett's epithelium and pathological hypersecretory conditions including Z-E syndrome. All data may be referenced in the ISS under the same table and section numbers as presented in the ISS update. For completeness, some information in the MOR of September 19, 1994 is repeated here, with emphasis on updated information.

In response to a request by the FDA, the sponsor presents data and discussions on L-T effects of LANSO on gastric mucosa (atrophic gastritis), intestinal metaplasia, g.i. nodules and polyps, and ophthalmological conditions.

II. SAFETY DATABASE: OVERALL EXTENT OF EXPOSURE**1. Number of Pts. Exposed per Database**

Summarized below is the distribution of total number of patients (worldwide and per geographic zone) under the different Phases (I through III) of development:

- Total No. of Subjects Exposed 9240
- No. of Subjects in Phase I Clin. Pharmacol. Trials 1292
 - Of these: 516 (TAP)
 - 502 (European)
 - 274 (Asian)

Of these 1292, 1227 subjects received LANSO on Phase I Clin. Pharmacol. trials worldwide:

- 460 (TAP)
- 502 (European)
- 274 (Asian)
- Total No. of Pts. in Phase II/III trials: 7948
 - Of these: 2271 (TAP)
 - 3575 (European)
 - 2102 (Asian)
- Of these 7948, 5525 patients received LANSO during Phase II/III, S-T, L-T and maintenance studies worldwide.
 - Of these: 1776 (TAP)
 - 2270 (European)
 - 1479 (Asian)

- Total No. of Pts. in S-T trials: 5045
Of these: 1428^a (TAP)
 2138 (European)
 1479 (Asian)
- Total No. of Pts. in L-T trials 232
Of these: 100 (TAP)
 132 (European)
- Pts. Receiving LANSO at some time during maintenance studies 502
- Of these 502, 254 patients had received LANSO previously
 in a S-T study.
- Pts. randomized during S-T, Phase II/III controlled studies 2045
 in TAP Safety Database.
Of these: 1362^b received LANSO
 683 received a reference agent

-
- a) Mean age = 50y (range: 19 to 83y), Caucasian=86%; M=64%; F=36%;
tobacco users=38%; consumed alcohol=51%.
- b) Of these, 55 (=4%) were D/C from one of these controlled studies
due to an AE.

2. S-T, Phase II/III Studies (Table 1)

- Most pts. who received LANSO were treated either for >2 but <6 weeks
(596 pts.=42.7%) or from 6 to 10 weeks (757 pts.=53%).
- 78.8% of the pts. (657 + 468) received 30 to 60 mg of LANSO daily.
- 21.2% of the pts. received a maximum dose of LANSO of 30 mg once-a-day.
- The combined exposure to LANSO during S-T, Phase II/III studies was
176.8 patient years.

TABLE 1
Updated ISS of NDA 20-406

S-T, Phase II/III Studies in TAP Safety Database: Duration of Tx and Maximum Daily Dose for LANSO Tx Pts.

Length of Tx (Weeks)	PL-Controlled* (N=817)	Positive Controlled* (N=545)	Uncontrolled* (N=66)	Total Pts. in All S-T Studies (N=1428)
0 - 2	20 (2.4) ^d	15 (2.8)	9 (13.6)	44 (3.1)
>2 - 6	401 (49.1)	152 (27.9)	43 (65.2)	596 (41.7)
>6 - 10	393 (48.1)	358 (65.7)	6 (9.1)	757 (53.0)
>10 - 14	3 (0.4)	20 (3.7)	7 (10.6)	30 (2.1)
>14 - 17	----	----	1 (1.5)	1 (0.1)
Maximum Daily LANSO Dose (mg)				
15	303	----	----	305 (21.2)
30	298	331	28	657 (46.0)
60	216	214	38	468 (32.8)

- a) Studies M87-090, -091 and M88-268. The latter was a positive-controlled and PL-controlled study. In this table it is included only with the PL-controlled studies.
b) Studies M88-269, M89-349, -393, P91-066 and M90-422.
c) Study M88-193. Five patients enrolled in this study received an additional course of therapy in Study M88-251 which was of 10 to 14 weeks duration.
d) Figures in parenthesis denote percentages.

3. L-T Phase II/III Studies (Table 2)

- The number of pts. under the various lengths of exposure is still small (Total N=100; total N in initial ISS=91).
- The highest dose administered to any pt. was 180 mg once-a-day (N=1).
- The total exposure to LANSO for the combined Barrett's epithelium studies was 92.0 patient years; for the Z-ES/hypersecretors studies, it was 136.35 patient years.

TABLE 2
Updated ISS of NDA 20-406

L-T, Phase II/III Studies in TAP Safety Database:
Duration of Tx and Maximum Daily Dose for LANSO-Tx Pts.

Length of Tx (Months)	Barrett's Epithelium (N=34) ^a	Hypersecretors/Z-ES (N=66) ^a	Total (N=100)
0 - 6	5 (14.7%)	10 (15.2%)	15 (15.0%)
>6 - 12	2 (5.9%)	13 (19.7%)	15 (15.0%)
>12 - 18	2 (5.9%)	3 (4.5%)	5 (5.0%)
>18 - 24	1 (2.9%)	3 (4.5%)	4 (4.0%)
>24 - 36	5 (14.7%)	17 (25.8%)	22 (22.0%)
>36 - 48	12 (35.3%)	14 (21.2%)	26 (26.0%)
>48 - 54	7 (20.6%)	4 (6.1%)	11 (11.0%)
>54	0	2 (3.0%)	2 (2.0%)
Total Pts.	34	66	100
Final Daily LANSO Dose (mg)			
<15	--	0	0
15	--	7	7
30	--	13	13
45	--	5	5
60	34	22	56
75	--	4	4
90	--	5	5
105	--	0	0
120	--	6	6
150	--	3	3
180	--	1	1

a) Studies M88-249 and M89-375. The total No. of pts. is the sum of unique patient experience. This includes 34 patients with Barrett's epithelium who received LANSO in Study M88-249, Study M89-375 or both.

Mean age = 61y; the majority were Caucasian M.

b) Studies M88-139, M89-405 and M90-436.

Mean age = 51y; 61% were M.

4. Number of Pts. in Maintenance Studies (Table 3)

- A total of 516¹ Pts. were randomized in a double-blind fashion in the maintenance Tx studies (LANSO=315; PL-201).
- The number and proportion of pts. treated with continuous LANSO Tx (alone), as a function of Tx duration are depicted in Table 3.
- The total No. of Pts. that received LANSO for periods >6 mo. is small (Total N=279).

TABLE 3
Updated ISS of NDA 20-406

Maintenance Tx Studies in the TAP Safety Database:
Duration of Tx for Pts. During Continuous
LANSO Therapy^a

Length of Tx (Months)	N (%)
0 - 3	223 ^b (41.5%)
3 - 6	35 (6.5%)
6 - 9	17 (3.2%)
9 - 12	45 (8.4%)
12 - 15	212 (39.5%)
>15	5 (0.9%)

- a) Studies M88-270, -271 and M89-350
- Among the 315 pts. randomized to LANSO, 91% were Caucasian, 64% M. The mean age was 47y (range: 19 to 83y), 31% used tobacco and 47% consumed alcohol.
- b) The total number of patients in this Table is 537. Of these, 502 were Tx either in the listed randomized studies (N=315) or in open-label trials for recurrence of Dz (N=187). Included in this Table are an additional 35 pts. who received LANSO in the acute studies and were subsequently randomized to PL in the maintenance trials. These 35 patients are included in the 0-3 months category.

III. AEs

1. S-T Phase II/III Studies (Table 4)

- In the S-T Phase II/III studies, 52.9% of LANSO-Tx pts. reported Tx-emergent AEs. In these studies, 20.8% of LANSO pts. had one or more AEs that were considered to be possibly/probably related to therapy.
- The most frequent AEs considered to be possibly/probably related to LANSO Tx in S-T studies were

¹A total of 552 pts. entered these maintenance Tx studies.

headache (7.6%)
diarrhea (4.4%)
abdominal pain (2.0%)
nausea (1.3%) and
dizziness (1.3%)

- In the PL-controlled studies, the PL group reported statistically significantly higher incidence of possibly/probably Tx-related headaches than the LANSO group.
- For Tx-emergent AEs, a statistically significant difference between Tx groups was seen for fever with a lower incidence observed in LANSO patients than in PL patients.
- In the positive-controlled studies, the LANSO group reported statistically significantly higher incidence of both possibly/probably Tx-related and Tx-emergent diarrhea and Tx-emergent myalgia than the RAN group.
- All AEs with an incidence of at least 2% in any Tx group and considered by the investigator to be possibly or probably Tx-related are displayed by body system, COSTART term, and Tx group for PL- and RAN-controlled S-T studies in Table 4.

TABLE 4
Updated ISS of NDA 20-406

AEs Possibly/Probably Related to Tx, Reported by ≥2% of Pts. in S-T Phase II/III, PL (Left Side of Column) vs Positive-Controlled Trials

PL-Controlled Trials ^a			RAN-Controlled Trials ^b		
Body System/ COSTART Term	PL [N=254]	LANSO [N=817]	Body System/ COSTART Term	RAN [N=429]	LANSO [N=716]
Total patients any event	22.0	18.2	Total patients any event	14.2	19.0
Body as a whole			Body as a whole		
Abdominal pain	1.2	2.3	Headache	3.7	5.3
Headache	12.2	7.7			
Digestive system			Digestive system		
Diarrhea	2.4	3.5	Diarrhea	1.9	4.3 ^{c,d}
Nausea	2.0	1.1			

a) Studies M87-090, -091, 092, M88-268.

b) Studies M88-268, -269, M89-349, -393, M40-422, P91-066

c,d) p≤0.05 compared to the PL and RAN group, respectively

- AEs were analyzed by indication. In the positive (RAN)-controlled studies of patients with RE, LANSO patients had a statistically significantly higher incidence of possibly/probably Tx-related AEs than PL patients. This difference was not observed in the positive (RAN)-controlled DU and GU studies.
- In the subgroup analyses of AEs, there was no apparent evidence that age, gender, race or creatinine clearance influenced the likelihood of developing AEs during Tx with LANSO in the S-T controlled studies.

- When all Tx-emergent AEs were considered in dose-response studies of PL, LANSO 15, 30 and 60 mg there was little difference in AE reporting rates between Tx groups. Specifically, there was no difference between LANSO 15 vs 30 mg.
- When specific AEs were evaluated, a possible dose-response relationship was noted for diarrhea; this was primarily due to higher incidence in the 60-mg group.
- The use of concomitant therapy did not adversely affect the incidence of AEs in LANSO-Tx pts.

2. L-T Phase II/III Studies (Table 5)

- 31 of these 34 pts. (or 91.2%) experienced Tx-emergent AEs. Of these, 20 (58.8%) experienced severe AEs.
 - 5 Pts. (14.7%) experienced possibly/probably Tx-related AEs but none of these was categorized as severe.
 - As shown in this Table, the most commonly reported AE considered to be possibly/probably related to therapy in pts. with Barrett's epithelium was diarrhea.
- As shown in Table 5, 49 of the Z-ES/Hypersecretor patients (or 74.2%) experienced Tx-emergent AEs. Of these, 13 patients (19.7%) experienced severe AEs.
 - 15 Pts. (22.7%) experienced possibly/probably Tx-related AEs but in only 1 of these patients the AE was categorized as severe.
 - In Z-ES/hypersecretor pts. these AEs were diarrhea, headache and nausea.
- In summary, the reviewer agrees with the sponsor that Tx-emergent AEs reported while taking concurrent medications in these L-T studies did not show clinically relevant trends. However, these trials did not have a comparator group.

TABLE 5
Updated ISS of NDA 20-406

Possibly/Probably Tx-Related AEs Occurring in >1 Pt.
in L-T, Phase II/III Studies

	Barrett's Epithelium ^a	Z-ES/Hypersecretors ^b
Body System/COSTART Term	LANSO (N=34) %	LANSO (N=66) %
Total patients Any event	14.7	22.7
Body as a whole Headache	2.9	4.5
Digestive system Diarrhea Nausea	8.8 0	6.1 4.5

a) Studies M88-249 and M89-375
b) Studies M88-139, M89-405 and M90-436

3. Maintenance Tx Studies

a. AEs Reported until the Time of First Recurrence (Table 6)

- The mean exposure during this period for the LANSO pts. (273 days) was 140% longer in duration than the mean exposure of 114 days for the PL pts.
- The above difference - due to the fact that PL pts. experienced recurrence of Dz earlier than did LANSO pts. - is expected to result in higher AE reporting rates for the LANSO Tx groups (Table 6).

TABLE 6
Updated ISS of NDA 20-406

AEs by Relationship to Tx for PL and LANSO Pts. to the Time of First Recurrence^a of Dz in the Maintenance Tx Studies in the TAP Safety Database^b

Tx Group	No. of Pts.	Mean Days of Exposure	All Tx-Emergent AEs (N (%))		Possibly/Probably Tx-Related AEs (N (%))	
			All	Severe	All	Severe
PL	201	114.0	81 (40.3)	6 (3.0)	10 (5.0)	2 (1.0)
LANSO	315	272.6	222 (70.5)	24 (7.6)	32 (10.2)	3 (1.0)

a) Until time of first recurrence, W/D or end of maintenance Tx.
b) Studies: M88-270, M88-271, M89-350

- The most frequently ($\geq 2\%$) reported possibly/probably Tx-related AE was diarrhea.
- 4/201 (2.0%) of the PL pts. reported diarrhea during this Tx period. This proportion was not statistically significant different from the 10/315 (3.2%) LANSO pts.
- The most commonly reported AEs (those with an incidence of at least 2% in any Tx group of maintenance Tx studies) are listed in Table 7.

TABLE 7
Updated ISS of NDA 20-406

Tx-Emergent AEs Reported by ≥2% of the PL or LANSO Pts. to the Time of First Recurrence of Dz^a in the Maintenance Tx Studies in the TAP Safety Database^b

Mean Exposure (Days)	PL N=201 114.0	LANSO N=315 272.6	Between Groups p-Value ^c
	%	%	
Total patients Any event	40.3	70.5	N.S.
Body as a whole			
Abdominal pain	3.0	6.0	N.S.
Accidental injury	1.5	4.8	N.S.
Back pain	4.5	3.5	0.025 ^d
Chest pain	1.0	2.9	N.S.
Flu syndrome	3.5	5.4	N.S.
Headache	7.5	11.7	N.S.
Infection	1.5	2.5	N.S.
Pain	1.0	2.2	N.S.
Digestive system			
Diarrhea	6.5	9.2	N.S.
Gastroenteritis	0	2.2	N.S.
Gastrointestinal anomaly (polyp)	0.5	2.9	N.S.
Nausea	1.0	2.9	N.S.
Rectal disorder	1.0	2.2	N.S.
Tooth disorder	0.5	2.5	N.S.
Vomiting	0.5	2.9	N.S.
Musculoskeletal system			
Arthralgia	1.5	5.1	N.S.
Myalgia	1.5	2.5	N.S.
Nervous System			
Depression	0.5	2.2	N.S.
Dizziness	0.5	3.2	N.S.
Respiratory system			
Bronchitis	1.5	2.9	N.S.
Cough increased	0	2.2	N.S.
Pharyngitis	10.9	16.5	N.S.
Rhinitis	1.5	6.0	N.S.
Sinusitis	3.0	7.6	N.S.
Skin and appendages			
Rash	1.5	3.5	N.S.
Urogenital system			
Urinary tract infection	2.5	4.8	N.S.

- a) Until time of first recurrence, withdrawal or end of maintenance treatment
- b) Studies: M88-270, M88-271, M89-350
- c) Testing for equality of time of onset using survival curve methodology
- d) Statistical significance at p<0.05

- Sponsor's End-of-Text Tables 44 and 45 summarized the incidence of possibly/probably Tx-related AEs and Tx-emergent AEs, respectively, for each Tx group with onset at any point from the start of maintenance Tx to the time of first recurrence of Dz during the maintenance Tx studies.

End-of-Text Tables 46 and 47 summarized the incidence for all severe Tx-related AEs and severe Tx-emergent AEs, respectively, for each Tx group with onset at any point from the start of maintenance Tx to the time of first recurrence of Dz during the maintenance Tx studies.

- According to these four Tables, there were no frequently reported ($\geq 2.0\%$ incidence) severe AEs in the Tx-emergent or the possibly/probably Tx-related event categories with onset at any point from the start of maintenance Tx to the time of first recurrence of Dz.

b. AEs Reported During Maintenance Tx (Table 8)

- As shown in this Table, the mean duration of maintenance Tx was 317 days for the LANSO pts. and 260 days for the PL pts.
- The most commonly reported ($\geq 2.0\%$ incidence) possibly/probably Tx-related AE was diarrhea [LANSO=14/315 (4.4%); PL=10/201 (5.0%)].

TABLE 8
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AEs by Relationship to Tx for PL or LANSO Pts. in the Maintenance Tx Studies in the TAP Safety Database^a

Tx Group	No. of Pts.	Mean Days of Exposure	All Tx-Emergent AEs N (%)		Possibly/Probably Tx-Related AEs N (%)	
			All	Severe	All	Severe
PL	201	259.7	129 (64.2)	19 (9.5)	21 (10.4)	4 (2.0)
LANSO	315	316.7	239 (75.9)	29 (9.2)	39 (12.4)	3 (1.0)

a) Studies: M88-270, M88-271, M89-350

- The most commonly reported AEs (those with an incidence of at least 2% in any Tx group of maintenance Tx studies) are displayed by COSTART body system and term and by Tx group in Table 9.

TABLE 9
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Tx-Emergent AEs Reported by ≥2% of the PL or LANSO Pts.
During the Maintenance Tx Studies in the
TAP Safety Database^a

Mean Exposure (Days)	PL ^b N=201 259.7	LANSO N=315 316.7
	%	%
Total patients Any event	64.2	75.9
Body as a whole		
Abdominal pain	7.5	6.0
Accidental injury	3.0	5.1
Back pain	5.5	4.1
Chest pain	2.0	3.2
Flu syndrome	7.0	6.0
Headache	10.4	12.4
Infection	2.5	3.2
Pain	2.0	3.5
Cardiovascular system		
Hypertension	2.0	1.0
Digestive system		
Diarrhea	12.4	11.4
Dyspepsia	2.5	0.6
Gastroenteritis	1.5	2.5
Gastrointestinal anomaly (polyp)	3.0	3.2
Nausea	3.0	2.9
Rectal disorder	1.0	2.5
Tooth disorder	2.5	4.1
Vomiting	1.0	2.9
Musculoskeletal system		
Arthralgia	4.0	5.7
Myalgia	3.5	2.9
Nervous system		
Anxiety	1.5	2.5
Depression	2.5	2.2
Dizziness	0.5	3.5
Respiratory system		
Bronchitis	4.0	3.8
Cough increased	0.5	2.9
Pharyngitis	17.4	19.7
Rhinitis	3.5	7.0
Sinusitis	8.5	7.9
Skin and appendages		
Rash	3.5	3.8
Urogenital system		
Cystitis	2.0	0
Urinary tract infection	3.5	6.0

a) Studies: M88-270, M88-271, M89-350

b) Possibly treated with LANSO intermittently

- It should be noted that some of the AEs in the PL group as well as the LANSO group began during open-label LANSO Tx.
 - When the time pts. were Tx with D-B and open-label Tx were evaluated separately, the mean duration of the D-B and open-label treatment periods for the PL pts. was 194 and 65 days and for LANSO pts. was 300 and 16 days, respectively.
 - More patients in the PL group (68%; 136/201) than in the LANSO group (22%; 69/315) required open-label LANSO Tx for recurrence of Dz. Among these patients receiving open-label Tx, the PL group took LANSO for a longer mean duration than the LANSO group (96 and 73 days, respectively). This reflected more repeated recurrences in the PL group.
- The sponsor presented a breakdown of the number of pts. with AEs beginning in D-B or open-label periods in their End-of-Text Table No. 48 for possibly/probably Tx-related AEs and End-of-Text Table No. 49 for all Tx-emergent AEs. All possibly/probably Tx-related and Tx-emergent severe AEs presented by occurrence during D-B or open-label Tx were summarized in sponsor's End-of-Text Tables 50 and 51.
 - From the above, the most commonly reported ($\geq 2.0\%$ incidence) severe Tx-emergent AEs during maintenance Tx were abdominal pain and diarrhea. Severe abdominal pain was reported in 5/201 (2.5%) of the PL-Tx pts. [3 pts. were on open-label LANSO at AE onset] and in 2/315 (0.6%) of the LANSO-Tx pts. Severe diarrhea was reported in 4/201 (2.0%) [3 patients were on open-label LANSO at AE onset] of the PL pts. and in none of the LANSO pts.
- Sponsor's End-of-Text Tables 52 and 53 summarized the incidence for possibly/probably Tx-related and Tx-emergent AEs for each Tx group receiving maintenance Tx. End-of-Text Tables 54 and 55 summarized the incidence for all severe possibly-probably Tx-related and severe Tx-emergent AEs for each Tx group receiving maintenance Tx.
 - There were no commonly reported ($\geq 2.0\%$ incidence) severe possibly/probably Tx-related AEs during Maintenance Tx.
- Listings of AEs reported during the pre-maintenance therapy lead-in Tx with LANSO 30 mg for 4 to 8 weeks and the three-month post-Tx period after completion of maintenance Tx were contained in detail in the individual study summaries in sponsor's Section 8.5, and in End-of-Text Tables 56 through 61.

4. AEs by Study Category

a. Phase I, Clinical Pharmacology Studies (Table 10)

- As shown in this Table these were minor and of no major clinical concern.

TABLE 10
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AEs by Relationship to Tx for all LANSO Subjects in Phase I, Clinical Pharmacology Studies in the TAP Safety Database

Type of Study	No. of Subjects	All Tx-Emergent AEs	Possibly/Probably Tx-Related AEs
Single-dose	178	% 12.9	% 9.0
Multiple-dose ^{a)}	181	35.5	26.5
Drug-interaction	101	54.5	42.6

a) Does not include interaction studies that were multiple-dose.

- The incidence of possibly/probably Tx-related AEs occurring in more than one subject in either the single-dose, multiple-dose or drug-interaction, Phase I, clinical pharmacology studies is summarized by COSTART body system and term and by type of study in Table 11.
- The most frequent (at least 8 patients, ≥2% incidence, reporting across all study types) AEs considered to be possibly/probably related to Tx in the clinical pharmacology studies were headache, dizziness, abdominal pain, diarrhea, and injection site pain.

TABLE 11
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AEs Possibly/Probably Related to Tx Occurring in More than One Subject Tx with LANSO in Single-Dose, Multiple-Dose or Drug-Interaction Phase I, Clinical Pharmacology Studies in the TAP Safety Database

	Single-Dose (N=178)	Multiple-Dose (N=181)	Drug-Interaction (N=101)
Body System/COSTART term	%	%	%
Total subjects Any event	9.0	26.5	42.6
Body as a whole			
Abdominal pain	0.6	3.3	5.0
Asthenia	0	3.9	0
Fever	0	1.1	0
Headache	3.4	9.4	13.9
Injection site pain	0	0	7.9
Cardiovascular system			
Tachycardia	0	0	2.0
Digestive system			
Diarrhea	0	5.5	3.0
Dry mouth	1.1	0.6	1.0
Dyspepsia	0.6	2.2	2.0
Flatulence	0	2.2	1.0
Liver function tests abnormal	0	1.1	0
Nausea	1.1	1.7	3.0
Vomiting	0.6	1.1	0

Musculoskeletal system Myalgia	0	1.1	1.0
Nervous system, Dizziness Thinking abnormal	2.2 0	3.3 1.1	6.9 0
Skin and appendages Acne	0	1.7	0
Special senses Visual field defect	0	1.1	0
Urogenital system Gynecomastia	0	1.1	0
Studies	<u>Single Dose</u> F88-144, F89-167, F90-178, F90-198, F90-199, F93-238, M88-243, M90-412	<u>Multiple-Dose^a</u> M87-049, M88-289, M89-353, M90-412 ^b , M90-450, M90-466, M90-485, M90-504, M91-642, M91-643	<u>Drug-Interaction</u> M90-419, M90-444, M90-445, M90-469, M91-698, M92-843

a) Does not include interaction studies that were multiple-dose.

b) Study M90-412 had some subjects receiving multiple doses and some subjects receiving single doses.

- The incidence of possibly/probably Tx-related AEs and Tx-emergent AEs for the clinical pharmacology studies was summarized by COSTART body system and term and by type of clinical pharmacology study in sponsor's End-of-Text Tables 62 and 63, respectively.

b. AEs by Indication: S-T Controlled Trials

AEs were analyzed by study category and indication (DU, and RE) in the S-T controlled studies. In these analyses, the most commonly reported possibly/probably Tx-related and Tx-emergent AEs reflected those seen in the analyses of the PL- and positive-controlled studies. In these analyses, there were no significant differences between the LANSO and PL Tx groups in the incidence of all Tx-emergent AEs and possibly/probably Tx-related AEs. All active Tx groups had similar percentages of pts. reporting AEs.

c. AEs by Dose and Indication: Maintenance Tx Studies

i) RE Maintenance Tx Studies (Table 12)

- The incidence of events was 2 times higher in the LANSO groups than in the PL group.
- The incidence of possibly/probably Tx-related AEs was also higher in the LANSO groups than in the PL group.
- The incidence of events was 5% higher in the LANSO 30 mg Tx group than in the LANSO 15 mg Tx group. The incidence, possibly/probably Tx related AEs was 7.5% in the 30 mg Tx group than in the LANSO 15 mg Tx group.

TABLE 12
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AEs by Dose and Relationship to Tx for PL and LANSO Pts. to First Recurrence^a of Dz in RE Maintenance Tx Studies in the TAP Safety Database^b

Tx Group	No. of Pts.	Mean Days of Exposure	All Tx-Emergent AEs N (%)	Possibly/Probably Tx-Related AEs N (%)
PL	113	83.6	39 (34.5)	7 (6.2)
LANSO 15 mg	113	267.0	80 (70.8)	9 (8.0)
LANSO 30 mg	110	271.7	83 (75.5)	17 (15.5)

a) Until time of first recurrence, withdrawal, or end of maintenance Tx.

b) Studies: M88-271, M89-350

- The most commonly (≥2% incidence in any dose group) reported Tx-emergent AEs by dose from the start of maintenance Tx to the time of first recurrence of RE are presented in Table 13. Overall, the number of patients reporting events was similar in the two LANSO dosing groups.
- This Table show some numerical differences between the 30 and 15 mg LANSO doses for total events, abdominal pain, headache, gastroenteritis, rash and especially, diarrhea.
- The most commonly (≥2% incidence) reported possibly/probably Tx-related AEs during this Tx period were headache and diarrhea. Headache was reported in 2.7% and 1.8% of the LANSO 15-mg and 30-mg Tx groups, respectively. Patients in the PL treatment group did not report headaches during this period. Diarrhea was reported in 1.8% of the PL Tx group and in 0.9% and 5.5% of the patients in the LANSO 15-mg and 30-mg Tx groups, respectively.

TABLE 13
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Most Frequently (≥2%) Reported Tx-Emergent AEs by Dose to First Recurrence^a of Dz in the RE Maintenance Tx Studies in the TAP Safety Database^{b,c}

Dose	PL N=113	LANSO	
		15 mg N=113	30 mg N=110
Mean Exposure (Days)	83.6	267.0	271.7
Body system/COSTART term	%	%	%
Total patients Any event	34.5	70.8	75.5
Body as a whole			
Abdominal pain	2.7	4.4	6.4
Accidental injury	1.8	2.7	6.4
Back pain	4.4	1.8	5.5
Chest pain	1.8	3.5	4.5
Flu syndrome	2.7	6.2	5.5
Headache	3.5	10.6	13.6
Infection	1.8	3.5	0.9
Pain	1.8	0.9	3.6
Digestive system			
Diarrhea	5.3	3.5	12.7
Gastroenteritis	0	1.8	3.6
Gastrointestinal anomaly	0	4.4	2.7
Nausea	0.9	2.7	1.8
Rectal disorder	0.9	2.7	1.8
Tooth disorder	0	3.5	0
Vomiting	0.9	0.9	3.6
Musculoskeletal system			
Arthralgia	0.9	5.3	4.5
Joint disorder	0	2.7	2.7
Myalgia	0.9	2.7	2.7
Nervous system			
Anxiety	0	1.8	2.7
Depression	0.9	4.4	0.9
Dizziness	0	3.5	1.8
Respiratory system			
Asthma	0	0	2.7
Bronchitis	0.9	3.5	2.7
Cough increased	0	4.4	0.9
Pharyngitis	8.0	18.6	13.6
Rhinitis	0.9	4.4	7.3
Sinusitis	1.8	7.1	6.4
Skin and appendages			
Rash	0	3.5	5.5
Urogenital system			
Urinary tract infection	2.7	6.2	6.4

- a) Until time of first recurrence, withdrawal, or end of maintenance Tx.
b) Studies: M86-271, M89-350
c) All possibly/probably Tx-related and Tx-emergent AEs were summarized by body system and COSTART term for the RE maintenance Tx studies in sponsor's End-of-Text Tables 78 and 79, respectively.

ii) DU Maintenance Tx Studies (Table 14)

- The following AEs were higher (but not significantly so) in the LANSO 15 mg Tx group than in the PL group:

	PL %	LANSO 15 mg %
Abdominal pain	3.4	7.6
Diarrhea	8.0	12.0
Abnormal LFTs	0	2.2
Nausea	1.1	4.3
Vomiting	0	4.3

TABLE 14
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AEs by Relationship to Tx for PL or LANSO Pts. to First Recurrence^a of Dx in the DU Maintenance Tx Study in the TAP Safety Database^{b,c}

Tx Group	No. of Pts.	Mean Day of Exposure	All Tx-Emergent AEs N (%)	Possibly/Probably Tx-related AEs N (%)
PL	88	153.0	42 (47.7)	3 (3.4)
LANSO 15 mg	92	200.4	59 (64.1)	6 (6.5)

- a) Until time of first recurrence, withdrawal or end of maintenance Tx.
- b) Study: N88-270
- c) All possibly/probably Tx-related and Tx-emergent AEs were summarized by body system and COSTART term for the DU maintenance Tx study in sponsor's End-of-Text Tables 80 and 81, respectively.

- The most commonly ($\geq 2\%$ incidence) reported possibly/probably Tx-related AE occurring up to the time of first recurrence of DU was diarrhea [2.3% of the pts. in the PL Tx group and in 3.3% of the pts. in the LANSO 15-mg Tx group].

d. AEs by Age, Gender or Race (Table 15)

- The mean exposure from start of maintenance Tx to time of first recurrence was similar for older and younger LANSO pts. The mean exposure to LANSO for older LANSO pts. was 279 days and for the younger LANSO patients was 271 days. The mean exposure to PL was significantly less (77 and 120 days for older and younger patients, respectively).
- The incidence of possibly/probably Tx-related AEs reported by older patients was low and similar to that reported by younger patients in both Tx groups. There were no possibly/probably Tx-related AEs with higher incidence in older than younger LANSO patients by the time of first recurrence, withdrawal or end of Tx reported by at least 2% of the older LANSO pts. in the maintenance Tx studies.

TABLE 15
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AEs by Relationship to Tx for All Pts. by Age (Upper Panel), Gender (Middle Panel) or Race (Lower Panel) Group to First Recurrence^a of Disease in all Maintenance Tx Studies in the TAP Safety Database^{b,c}

Tx Group	All Tx-emergent AEs n/N (%)		Possibly/Probably Tx-related AEs n/N (%)	
	<65 Y Old	≥65 Y Old	<65 Y Old	≥65 Y Old
PL	70/173 (40.5)	11/28 (39.3)	9/173 (5.2)	1/28 (3.6)
LANSO	185/260 (71.2)	37/55 (67.3)	25/260 (9.6)	7/55 (12.7)
	F	M	F	M
PL	39/75 (52.0)	42/126 (33.3)	5/75 (6.7)	5/126 (4.0)
LANSO	83/113 (73.5)	139/202 (68.8)	11/113 (9.7)	21/202 (10.4)
	Caucasian	Black	Caucasian	Black
PL	67/172 (39.0)	8/14 (57.1)	7/172 (4.1)	1/14 (7.1)
LANSO	204/285 (71.6)	16/25 (64.0)	29/285 (10.2)	3/25 (12.0)

- a) Until time of first recurrence, withdrawal, or end of maintenance Tx.
b) Studies: M88-270, M88-271, M89-350
c) The possibly/probably Tx-related AEs were displayed by age and Tx group and by COSTART body system and term in sponsor's End-of-Text Table 86.
- Tx-emergent AEs (regardless of adjudication) were presented in sponsor's End-of-Text Tables 87.
 - The AEs were displayed by gender and Tx group and by COSTART body system and term in sponsor's End-of-Text Table 92.
 - Tx-emergent AEs reported by LANSO patients by the time of first recurrence, withdrawal or end of Tx in the maintenance Tx studies were presented by gender in sponsor's End-of-Text Table 93.
 - Possibly/probably Tx-related AEs were displayed by race and Tx group and COSTART body system and term in sponsor's End-of-Text Table 98.
 - Tx-emergent AEs reported by LANSO pts. by the time of first recurrence, withdrawal or end of Tx in the maintenance treatment studies were presented by race in sponsor's End-of-Text Table 99.

- Women reported somewhat higher overall Tx-emergent AE rates in both Tx groups in the PL-controlled trials, but the rates of possibly/probably Tx-related AEs were similar between M and F pts.
- The mean exposure from start of maintenance Tx to time of first recurrence was similar for M and F LANSO pts. The mean exposure to LANSO for F LANSO pts. was 277 days and for M LANSO patients was 270 days. The mean exposure to PL was significantly less (75 and 126 days for F and M patients, respectively).
- The incidence of possibly/probably Tx-related AEs reported by F and M pts. was similar in both Tx groups. The only possibly/probably Tx-related AE reported by LANSO patients by the time of first recurrence, withdrawal or end of Tx with an incidence of at least 2% in either

gender group in the maintenance Tx studies was diarrhea (3.5% and 3.0% for F and M pts., respectively).

- The mean LANSO exposure from start of maintenance Tx to time of first recurrence was similar for Caucasian and Black patients. The mean exposure to LANSO for Caucasian patients was 276 days and for Black patients was 255 days. The mean exposure to PL was less (107 and 180 days for Caucasian and Black patients, respectively).
- The incidence of possibly/probably Tx-related AEs reported by Caucasian and Black pts. was similar in both Tx groups. No possibly/probably Tx-related AE was reported by more than one Black patient in the LANSO group. The only possibly/probably Tx-related AE reported by LANSO pts. by the time of first recurrence, withdrawal or end of Tx with an incidence of at least 2% in the Caucasian group in the maintenance Tx studies was diarrhea. The observed rates were 3.2% (9/285) and 4.05 (1/25) for Caucasian and Black patients, respectively.
 - When Tx-emergent AEs were evaluated, the reporting rate for Caucasian and Black patients was similar in the LANSO group.

e. Diarrhea and Histologic Findings (Table 16)

- The most commonly reported Tx-emergent AEs were headache, diarrhea, abdominal pain, nausea and dizziness. While the proportion of patients reporting headache, nausea, dizziness, and abdominal pain was similar between LANSO and the comparative groups, the relative incidence of diarrhea suggested a possible drug-related effect of LANSO. This was primarily due to a higher incidence in the 60-mg group.
- In an analysis of S-T dose-response, PL-controlled studies across indications, the incidence of Tx-emergent diarrhea was 6.2% among PL-treated patients, compared to 3.2%, 6.5% and 11.1% among LANSO 15 mg, 30 mg and 60 mg treated patients, respectively.
 - These numbers indicate that the incidence of diarrhea on LANSO is dose-related, but the incidence of diarrhea was higher than PL only for the 60-mg dose.
 - In the S-T positive-controlled studies, the incidence of Tx-emergent diarrhea was significantly higher for LANSO (6.1%) than for RAN (3.0%).
 - The diarrhea usually resolved while still taking LANSO (resolved in 34 to 45 cases).
- In the maintenance Tx studies, in the analysis of AEs occurring during the period until first recurrence of D₂, the incidence of diarrhea was numerically higher but not significantly different between the LANSO and PL groups (9.2% and 6.5%, respectively). It is however important to consider that the duration of exposure to LANSO was twice as long as exposure to PL (the mean exposure to LANSO was 273 days compared to the mean exposure to PL of 114 days).
- 18 pts. underwent sigmoidoscopy or colonoscopy with Bx during the S-T controlled and maintenance-Tx studies because of an episode of diarrhea or in one case (Sabesin) because of severe abdominal pain (Table 16).
- A prestudy Hx of bowel disease, suggesting a predisposition to diarrhea, was present in 10 of the 18 cases. The preexisting diagnoses in these

patients included colitis, IBS, possible helicobacter (campylobacter) infection and diverticulitis.

- Of the 18 patients, 15 received LANSO, 1 received PL only, and 2 received RAN and/or PL only.
- Diarrhea occurred at all three LANSO doses (15 mg=2; 30 mg=11, 60 mg=2) and at the 300 mg dose of RAN.
- The severity of the diarrhea reported among these patients was rated from mild to severe. The duration of Tx at the time the diarrhea began ranged from 4 to 186 days.
- The following three pts. were terminated earlier because of the diarrhea:

	<u>Tx</u>
(Movva)	LANSO 30 mg
(Fisher)	RAN 150 mg BID
(Brunner)	LANSO 60 mg

- Histologic findings from colon Bxs indicated 7 cases of acute superficial colitis or nonspecific reactive changes, 1 case of UC, and one case of Crohn's disease.
 - The possible etiologies for the cases with a pathological Dx of acute superficial colitis or nonspecific reactive changes include bacterial overgrowth, concomitant medications, a direct effect of LANSO, or an effect of the diarrhea itself. The cases could also have occurred coincidentally, independent of drug Tx.
- Pt. (Brunner; LANSO 60 mg), with a Bx consistent with UC developed a recurrence of diarrhea upon rechallenge with LANSO, suggesting a drug-induced AE, possibly an idiosyncratic Rx, as diagnosed by the investigator.
- Pt. (Sabesin; LANSO 30 mg) had a Hx of intermittent diarrhea and abdominal pain. Because these symptoms antedated the adm. of LANSO, the sponsor speculates that exacerbation of diarrhea could have been induced by LANSO by unknown mechanisms or could simply represent a spontaneous relapse that is typical of this IBD.
- In reality, the pathogenesis of LANSO-induced diarrhea remains unknown.

TABLE 16
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Summary of Data Including Histological Diagnosis in Patients Undergoing a Workup to Determine the Cause of Diarrhea in all Short- and L-T, Phase II/III Studies and Maintenance Tx Studies in the TAP Safety Database*

Pt. No. (Investigator) [Study No.]	Relevant Hx	Tx*	Length of Tx at Onset* (Days)	Severity/Premature Termination	Histologic Dx
PLACEBO					
(Aronson) [N87-092]	Diverticulosis, rectal bleeding, nonspecific colitis, UC, rectal inflammation	PL Post-Tx	55 72	MOD NO	Glandular hyperplasia
RANITIDINE					
(Novva) [N88-268]	Diverticulosis and colonic polyps	RAN 300 mg HS	6	MOD NO	No pathology
(Aronson) [N88-270]	IBS, bowel obstruction	RAN 300 mg HS PL	28 141	MOD NO	Polypoid hyperplasia of colonic mucosa
LANSOPRAZOLE					
(Aronson) [N87-090]	IBS	LANSO 30 mg Post-Tx	27 28*	MOD NO	IBS, no intrinsic lesions seen
(Novva) [N87-090]	None	LANSO 60 mg Post-Tx	26 102	MOD NO	Diverticulitis
(Novva) [N87-091]	Colon polyps	LANSO 15 mg	44	MOD NO	Small polyp and non-specific colitis
(Thume) [N87-092]	None	LANSO 15 mg	42	SEV NO	Acute superficial colitis, mild
(Sebes (n) [N88-251])	Intermittent diarrhea and abdominal pain	LANSO 30 mg	4	SEV* NO	Crohn's Dz
(Kogut) [N89-349]	IBS, hemorrhoids, campylobacter spp. infection	LANSO 30 mg	26	MOD NO	No pathology

(Arner) [M88-270]	IBS	LANSO 15 mg GAP PL LANSO 30 mg	32 3 28 11	MOD NO	Acute superficial colitis, minimal
(Howa) [M88-270]	Diverticulitis and colonic polyps	LANSO 30 mg	35	SEV YES	Acute superficial colitis, mild to mod.
(Fisher) [M88-271]	Colitis, diarrhea reported on RAN	RAN 150 mg BID GAP LANSO 30 mg	60 84 85	MOD YES	No pathology
(Feldman) [M89-393]	Hemorrhoids, colon polyps	LANSO 30 mg	32	MOD NO	Mild cryptitis with acute and chronic inflammation and hemorrhage of lamina propria
(Fisher) [M89-393]	Family history of colon Ca.	LANSO 30 mg	17	MILD NO	2 small anal fissures
(Kogut) [M89-350]	Hemorrhoids, polyp removal, constipation, diarrhea	RAN 150 mg BID LANSO 30 mg	58 67	MOD NO	Nonspecific changes and minimal colitis
(Kogut) [M89-350]	None	RAN 150 mg BID PL LANSO 30 mg PL LANSO 30 mg	63 30 66 9 18	SEV NO	Mild nonspecific reactive changes
(Kogut) [M89-350]	None	RAN 150 mg BID GAP LANSO 30 mg PL LANSO 30 mg	62 1 55 32 55	MILD NO	Acute colitis, focal, minimal
(Brunner) [KF4801/08]	Hx not available to medical monitor	LANSO 60 mg	44	SEV YES	UC ^a

^a from Study KF 4801/08 not included in the IAP Safety Database

- a) Includes one patient (Brunner)
- b) Includes dosing regimens received in both the acute and maintenance studies.
- c) Total treatment in both the acute and maintenance studies.
- d) Reported alternating diarrhea and constipation 28 days Post-Tx.
- e) Reported severe abdominal pain rather than diarrhea.
- f) Reported loose stool with small amount of blood.
- g) Positive rechallenge

GAP=Period between acute and maintenance studies in which no Tx was received.

5. Deaths

- A total of 44 deaths occurred worldwide by May 23, 1994. Of these,
 - 40 deaths were reported from worldwide controlled and uncontrolled clinical studies [sponsor's Table 74 also listed deaths in studies that were included in the TAP Safety Database or the European or Asian AE Database separately from those that were from studies not included in those databases].
 - 4 were from LANSO post-marketing reports by a health professional.
- Details of deaths for subcategories are given in Table 17.

TABLE 17
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Number of Deaths by Tx at Time of Death

I. Studies Included in the TAP Safety Database or the European or Asian AE Database

		N or n/N	Rate
A. <u>Controlled Studies</u> ^a	LANSO	0/4592	0%
	RAN	1	
	PL	0 (Comparator: 1/2727)	0.04%
B. <u>Uncontrolled Studies</u> ^b	LANSO	5/2160	0.2%

II. Studies Not Included in the TAP Safety Database or the European or Asian AE Database

A. <u>Controlled Studies</u>	LANSO	8
	RAN	2
	BLINDED ^c	9
B. <u>Uncontrolled Studies</u>	LANSO	15
	LANSO + BLINDED	32 ^d

Total deaths while receiving Tx in clinical studies worldwide	LANSO	28
	RAN	3
	PL	0
	BLINDED	9
	Total	40

a) Number of deaths/number of patients in Tx arm in controlled studies

b) Number of deaths/total number of patients in uncontrolled studies including Phase I trials.

c) Study Drug Blinded

-LANSO or RAN	-LANSO or PL	-LANSO or OME
-LANSO 15 or 30	-LANSO 30 ± tranexamic acid	-LANSO 30 or PL
-LANSO 15 or 30	-Ibid	-LANSO 30 or PL
-LANSO or RAN	-Ibid	-LANSO 30 ± tranexamic acid
-LANSO or RAN	-Ibid	-LANSO 30 or PL
-LANSO 30 ± tranexamic acid	-LANSO or PL	
*Ibid	-LANSO 30 or tranexamic acid	

d) 14 of these 32 deaths were reported from the following three trials in critically-ill pts.

Study D75p523 (active GI hemorrhage, = 8 deaths
Study FH/92/749/44 (esophageal varices = 5 deaths
Study JPN/CCT-003/12/2 (surgical stress = 1 death

- 12 deaths were related to a cardiovascular event.

All of these deaths occurred in patients who were >60y old; 7 of the 12 pts. were >70y old; 5 of the 12 pts. had a Hx of CVD. Death was attributed to atherosclerotic Dz in one patient at a post-mortem examination. The reviewer agrees with the sponsor that there were no apparent drug-related trends upon review of these causes of death.

- The remaining 6 deaths were related to:

pre-existing liver Dz	(N=1)
Carcinoma of the lung	(N=2)
Pulmonary aspiration	(N=1)
Suicide	(N=1)
Unknown etiology	(N=1)

NOTE: The sponsor presented narrative summaries of all pts. who died receiving LANSO or study drug in their End-of-Text Table No. 165. CRFs for these cases were also made available (Vol. 2.588 to 2.592 of original NDA 20-406 and Vol. 20.36 to 20.37 of ISS Update).

- 4 deaths [2=hemorrhage (Japan); 1=unknown cause (Japan); 1=90y old woman with atrial fibrillation (France)] were reported by health professionals in pts. that were not enrolled in a clinical study.
- A total of 36 deaths occurred worldwide within 90 days following LANSO or blinded study Tx and were reported by May 23, 1994. Six (6) deaths occurred in patients not in a clinical study and were reported by a health professional. Thirty deaths were reported from clinical studies worldwide.² There was no apparent drug-related trend upon review of these cases.
- Cases, briefly summarized below, were reported as remotely, possibly or probably related to test med. by the investigator.

- Pt. _____ Study D75p506; UK)

This 79y old pt. with a Hx of hypertension and RE suffered an M.I. and died after 7 weeks of continuously taking LANSO 30 mg.

In the original NDA, this death was assessed as possibly related to LANSO. In the ISS Update this assessment has been changed to remotely related but the sponsor offers no explanation for this modification.

- Pt. _____ (Study D75p506); UK)

This 72y old woman with RE suffered a sudden CVA and died almost immediately after 58 weeks of LANSO 30 mg Tx.

Death assessed as remotely related to LANSO.

- Pt. _____ /90/749/37 (France)

This pt., who was being treated because of peptic esophagitis, died of unknown reasons (suspected arrhythmia), while taking LANSO 30 mg for less than one month.

This death was assessed as possibly related to LANSO.

²Details of these deaths were listed in End-of-Text Table 166 and End-of-Text Table 166A.

• Pt. _____ Study D75p507; UK)

This 71y old M with esophageal stricture died of an M.I. while taking LANSO 30 mg for 61 days.

This death was assessed as remotely related to LANSO.

• Pt. _____ Study D75p523; UK)

This 76y old M [date of birth=2/3/17; date of admission=8/27/93; date of death=9/09/93] had Hx of previous M.I. and was being treated because of G.I. bleed. Pt. died of an M.I. 14 days after entry into trial. Code is not yet broken. Tx consisted of LANSO 30 mg in the presence or absence of tranexamic acid.

Relationship of this death to test med. was assessed as unknown.

• Pt. _____ (EC083; UK)

This RE pt. died of left ventricular failure and myocardial ischemia 121 days after having started and continuing taking test med. Code is not yet broken. Tx consisted of LANSO or OME.

This death was assessed as remotely related to LANSO.

- Pt. _____ Study D75p512; UK)

This 50y old M with G.I. bleed (and nonlegible information in CRF) died of cardiac arrest 1 day after starting test med. The Code has not been opened. He took LANSO 30 mg in the presence or absence of tranexamic acid.

- The reviewer agrees with the sponsor that the number of deaths in NDA 20-406 is not unexpected if one considers that >9000 patients have been enrolled in LANSO clinical trials worldwide.

6. Serious AEs

- 17 pts. worldwide had serious AEs that have been reported to the FDA as 10-day safety reports.
- Summary information on those pts. in whom the experience was considered possibly (POSS) or probably (PROB) related to LANSO is given in Table 18. If approved, information that, in rare instances, Prevacid may be associated with development of exacerbation of UC should be included in the labeling.

7. Premature Terminations Due to AEs (L-T Studies)

- Of the 66 pts. who enrolled in the 2-ES/hypersecretor studies in the TAP Safety Database, 6 pts. W/D prematurely due to an AE. Two of these premature terminations were deaths (both in Study M88-139) and have been discussed.

³ 6 pts. were reported to have prematurely terminated from the 2-ES/hypersecretor studies in the ISS (MOR of September 19, 1994, p. 314). This was an error. Five (5) patients had prematurely terminated; however, one patient was inadvertently counted twice. Since the ISS was submitted, an additional patient (Feldman) (Study M90-436) has prematurely terminated from a 2-ES/hypersecretory study. Therefore, a total of 6 patients are reported in this update as prematurely terminating from a 2-ES/hypersecretory study in the TAP Safety Database.

- 8 (PL=2; LANSO=6) of the 36 pts. enrolled in the PL-controlled, L-T study of Barrett's epithelium (Study M88-249) W/D from the study during the D-B Tx period, at least in part due to AEs. None of the patients had AEs causing premature termination which were judged by the investigator to be possibly/probably Tx-related.
- 4 of the 27 Barrett's epithelium-pts. who entered the open-label, LANSO L-T extension (Study M89-375) W/D prematurely due to AEs. One of these premature terminations (Sampliver) was due to death (discussed above).

8. Premature Terminations Due to AEs in Maintenance Tx Studies
(Table 19)

- A greater proportion of PL (possibly intermittent LANSO) patients prematurely terminated due to AEs than did LANSO patients in the maintenance Tx studies.
 - During maintenance Tx, 16 (8%) of the patients in the PL group (possibly Tx with LANSO intermittently) prematurely terminated due to AEs, compared to 19 (6.0%) of the LANSO patients receiving continuous LANSO therapy.
 - The AEs experienced by more than one PL patient which resulted in premature termination included
 - abdominal pain,
 - diarrhea,
 - abnormal LFTs,
 - depression,
 - nervousness and
 - rash.
 - No AE resulting in premature termination was experienced by more than one LANSO patient.

TABLE 1B
Updated ISS of NDA 20-406
Ten-day Safety Reports Submitted to the FDA for All Studies in the TAP or European and Asian AE Databases in Which Relationship to Drug Was Considered Possible (POSS) or Probable (PROB)

Safety Report #	Study Pt. # (Inv.)	Date (Amend #)	LANSO Dose (mg)	No. of Days of Tx when AE Started	AE	Due to Drug
6	M87-090 Phase II DU (Dorsch)	06/23/88 (#11) 04/17/91 (#99)	15	LANSO, 20 days	Chest and abdominal pain possibly esophageal spasm	POSS
10	M88-268 Acute DU (Novva)		30	LANSO, 27 days		
12	M88-270 MIT-DU (Novva)	09/20/90 (#74)	30	LANSO, 7 days	Severe diarrhea - colitis with ulcerations	POSS
13	KF 4801/08 Resistant PUD (Brunner)	01/08/90 (#45) 07/17/90 (#66)	60	LANSO, 45 days	Diarrhea and abdominal pain - UC	PROB
15	KF 4801/07 GU (Gloker and Rogge)	06/15/90 (#63) 06/18/90 (#64) 09/21/90 (#75)	30	Two days after 6 weeks of LANSO therapy	GI bleed	POSS
	M89-349 Acute RE (Fleischmann)	04/04/91 (#95)	30	LANSO, 26 days	Insulin dependent D.M.	POSS
	M89-350 MIT Resistant RE (Fleischmann)	03/18/92 (#126)	60 30	LANSO, 28 days LANSO, 57 days		

TABLE 19
Updated ISS of NDA 20-406

**AEs Resulting in Premature Termination Occurring in
More Than One PL or LANSO Pt. in the
Maintenance Tx Studies in the TAP Safety Database^{a,b}**

Treatment Groups	PL N = 201 260	LANSO N = 315 317
Mean Exposure (Days)		
Body system/COSTART term	%	%
Total patients Any event	8.0	6.0
Body as a whole Abdominal Pain	1.0	0
Digestive system Diarrhea Liver Function tests abnormal	1.0 1.0	0.3 0.3
Nervous system Depression Nervousness	1.0 1.0	0 0.3
Skin and appendages Rash	1.0	0

- a) Studies: M88-270, M88-271, M89-350.
b) A summary of all AEs indicated as the reason for premature termination during maintenance Tx in the maintenance Tx studies was presented in sponsor's End-of-Text Table 170. Narrative descriptions for all patients prematurely terminating from maintenance Tx studies in the TAP Safety Database were found in sponsor's End-of-Text Table 174.

9. Premature Terminations Due to AEs in the TAP Safety Database:
Phase I, Clinical Pharmacology Studies

- Of the 460 subjects who received LANSO in the Phase I, clinical pharmacology studies in the TAP Safety Database, 12 withdrew prematurely from LANSO therapy due to AEs.

- The reasons for discontinuation were

back injury (1),
syncope (1),
asthma (1),
pharyngitis (1),
increased gamma glutamyl transpeptidase (GGT) (1),
flu syndrome (1),
pyuria (1),
urticaria (1) and
liver function tests abnormal (4).

- A listing of all subjects in Phase I, clinical pharmacology studies who prematurely terminated from study was given in sponsor's End-of-Text Table 171.

10. Worldwide: Serious AEs (Ten-day Safety Reports)

- A total of 17 pts. worldwide had serious AEs that have been reported to the FDA as ten-day safety reports.
 - 10 of these patients were enrolled in a Phase II/III study included in the TAP Safety Database.
 - 6 patients with serious AEs were reported from non-U.S. studies or post-marketing experience.
 - The remaining patient report was from an ongoing TAP Pharmaceutical Inc. study not included in this NDA⁴.
- Summary information on those pts. in whom the experience was considered possibly (POSS) or probably (PROB) related to LANSO was given in Table 18 of this review. The reviewer agrees with the sponsor that there was no apparent relationship between LANSO and the occurrence of any specific type of serious AEs.

⁴sponsor's Table 79 summarized the AEs for all 17 patients. Narrative summaries of these patients were found in sponsor's End-of-Text Table 175.

TABLE 20
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Patients With Gastric Nodules/Polyps Identified During the Tx
Period in all Maintenance Tx Studies in the TAP Safety
Database (Studies M88-270, -271, and M89-350)

Pt. # (Investigator)/ Study No.	Tx (Daily)	Total Length of Tx (Days)	Macroscopic / Lesion (Bx location)	Diagnosis
I. Pts. With Neither Nodules Nor Polyps Present at Screen				
(Schwartz) [M88-271]	LANSO 30 PL	475	Nodule (Antrum)	Chronic, active gastritis, associated with <i>H. pylori</i>
(Lanza) [M88-271]	LANSO 30	85	Modules (Antrum)	Consistent with reflux (chemical) gastritis
	LANSO 15	85	Modules (Fundus)	Consistent with reflux (chemical) gastritis
(Avner) [M88-271]	LANSO 30	332	Nodule (Antrum)	Mild, chronic active gastritis, <i>H. pylori</i>
(Fisher) [M88-271]	LANSO 30	290	Nodule (Antrum)	Changes consistent with reflux (chemical) gastritis
	LANSO 15	290	Nodule (Antrum)	Hyperplastic polyp
(Fisher) [M88-271]	RAN 300 LANSO 30 PL	348	Polyps (Fundus)	Fundic gland polyp
(Kogut) [M88-271]	RAN 300 LANSO 30 LANSO 15	245	Polyp (Fundus)	Fundic gland polyp
(Campbell) [M89-350]	RAN 300 LANSO 15 LANSO 30	464	Nodule (Fundus)	No pathology
(Campbell) [M89-350]	LANSO 30 PL	137	Nodule (Fundus)	Signet-ring cells, highly suspicious for malignancy ^b
(Fleischmann) [M89-350]	LANSO 60 LANSO 30	426	Nodule (Antrum)	Chronic active gastritis, <i>H. pylori</i>
(Fisher) [M89-350]	LANSO 30 PL	448	Polyp (Fundus)	Fundic gland polyp
(Fisher) [M89-350] (see below)	LANSO 30	172	Nodules (Antrum)	Mild, chronic inflammation. Surface with ulceration and acute inflammation

(Pleischmann) [M89-350]	LANSO 30 PL	250	Nodule (Antrum)	Foveolar hyperplasia, focal mild
(Richter) [M89-350]	LANSO 30	56	Polyp (Fundus)	Benign, fundic gland polyp
	LANSO 30	142	Polyp (Fundus)	Hyperplastic polyp
(Richter) [M89-350]	LANSO 30 LANSO 60 LANSO 15	431	Nodule (Antrum)	Consistent with reflux (chemical) gastritis
(Fisher) [M89-350]	LANSO 30	338	Nodule (Body)	Chronic, active gastritis, <i>H. pylori</i>
		429	Nodule (Fundus)	Erosive acute and chronic gastritis, <i>H. pylori</i>
(Kovac) [M89-350]	RAN 300 LANSO 15	229	Nodule (Fundus)	Hyperplastic polyps with chronic inflammation
		395	Nodule (Antrum)	Nonspecific acute and chronic gastritis, <i>H. pylori</i>
II. Pts. With Nodules or Polyps Present at Screen				
(Kogut) [M88-271]	RAN 300 LANSO 15	119	Polyp (Antrofundal)	Mild chronic nonspecific reactive changes
(Fisher) [M89-350]	LANSO 60	118	Polyp (Fundus)	Mild, chronic inflammation surface with ulceration and acute inflammation
(Richter) [M89-350]	LANSO 30 PL	154	Nodule (Antrum)	Chronic, active gastritis, mild focal intestinal metaplasia. Devoid of atypia.
(Robinson) [M89-350]	RAN 300 PL LANSO 30	87	Polyp (Fundus)	Fundic type gastric mucosa with mild acute and moderate diffuse chronic nonspecific gastritis. There is focal follicular hyperplasia and mucosal hyperplasia; negative for neoplastic process. <i>H. pylori</i>

a) Total length of Tx includes acute and maintenance study Tx.

b) Pathology consultant J. Lechago states "signet-ring cells in biopsy specimen are highly suggestive for malignancy. However, lack of inflammatory reaction and of staining with CEA antibodies raises questions as to their true nature."

IV. CHANGES IN LABORATORY PARAMETERS (LFTs NOT INCLUDED)

- As pointed out during the review of ISS of NDA 20-406, there were no trends of concern for changes in hematological, biochemical or urinalysis. Some small but statistically significant differences were reported for some parameters at some points of L-T observations [ex. a mean decrease in hematocrit, Hb and basophils, as pointed out in

Statistical Review of October 27, 1994 (Dr. F. Harrison)]. However, these changes were minimal, did not worsen with dose duration and were not always consistent between study types. These changes are not considered to be clinically relevant.

V. ADDITIONAL SAFETY MATTERS OF POTENTIAL RELEVANCE TO THE L-T SAFETY OF LANSO

In this section, issues regarding the safety of LANSO for L-T human use are addressed.

A. Reports of Upper Gastrointestinal, Colonic and Other Tumors

1. Gastric Nodules in S-T Studies

From gastric Bx, the histological diagnoses of nodules/polyps in patients in S-T studies revealed the following

- gastritis in 2 pts. Tx with RAN
- No Dx features in a nodule in another RAN-Tx patient
- 1 fundic gland polyp in 1 pt. Tx with FL
- changes consistent with reflux gastritis in 1 pt. treated with LANSO

2. Gastric Nodules/Polyps⁵ in Maintenance Tx Studies (Table 20)

Findings in those pts. in whom neither nodules nor polyps were present at screen are depicted in the upper panel of this Table. Data from those pts. in whom nodules and/or polyp were present at screen are shown in the lower panel of Table 20.

- Of the 19 pts. (NOTE: (Fisher) is listed twice), in Table 20,
 - 10 (12 Bxs) had acute chronic gastritis. This was usually (but not always) associated with *H. Pylori* and in most cases had not been present at screen.
 - 4 had findings consistent with reflux ("chemical") gastritis
 - 4 had fundic gland polyps
 - 3 had hyperplastic polyps
 - 1 had foveolar hyperplasia
 - 1 was diagnosed as having "no pathology"
 - 1 [Pt. (Campbell)] had a signet-ring tumor highly suspicious for malignancy. This had not been present at screen.
 - In another [Pt. (Richter)] the chronic active gastritis, which was present at screen, was accompanied by mild focal metaplasia but devoid of atipia.
- These nodules/polyps occurred in pts. treated with LANSO, RAN and PL. Most of the pts. had been treated with two or more of these agents during the acute and maintenance Tx studies combined.

3. Pts. With Granulomas in the S-T Controlled and Maintenance Tx Studies

- During review of routine H&E evaluation of random Bxs in the body of the stomach of pts. in these studies (TAP Safety Database), the sponsor identified six (6) pts. with gastric granuloma.

⁵Some pts. had more than one nodule and multiple histopathological findings.

- The investigators were asked to reassess their pts. for signs and symptoms of known causes of granulomatous gastritis. This included Hx and tests for Infectious processes or vasculitis, sarcoid, Crohn's Dz, cancer/lymphoma, and tuberculosis, fungal and parasitic infections. Results of these reevaluations are summarized in Table 21.
- These gastric granulomas appear to be incidental findings, unrelated to antisecretory therapy. Three pts. had no manifestations of Dz known to produce gastric granulomas. The remaining three had no manifestation of the existence of systemic Dz. Two of the 6 pts. reside in the same area in the southern U.S. where mycosis is endemic.
- In 5 of the 6 pts. the gastric granuloma was accompanied by *H. Pylori*.

TABLE 21
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Pts. With Gastric Granulomas Identified During the Tx Period
in the S-T Controlled and Maintenance (MAINT) Tx Studies

Pt. # (Investigator) [Study No.] Gender•Age	Tx ^a	Length of Tx (Days)	Isolated Granulom- atous gastritis	<i>H.</i> <i>Pylori</i> on Bx	Comments
(Mertesdorf) [M87-091] M52 (GU)	LANSO 30	58	YES	YES	• Pt. had noncaseinated granulomas in hemigastrectomy specimen. • No evidence of systemic Dz. • Neither Hx of infectious process or vasculitis, Crohn's Dz, Ca. nor lymphoma. • Culture and stain were negative for sarcoid.
(Nelson) [M88-270] F33 (MAINT)	RAN 300 LANSO 30 PL LANSO 30 PL LANSO 30	26 28 169 26 165 28	YES	YES	• Pt. had no manifestations of Dz known to produce gastric granuloma but resided in an area of the southern U.S. where blastomycosis and histoplasmosis are endemic.
(Novva) [M88-270] M41 (MAINT)	LANSO 30 PL	22 360	YES	YES	• Pt. had restrictive lung lesion suggestive of tuberculosis or histoplasmosis but otherwise had insufficient clinical findings to support the existence of underlying systemic Dz.
(Jones) [M88-270] F42 (MAINT)	LANSO 30 LANSO 15	58 358	YES	YES	• Pt. had noncaseinated granulomas in hemigastrectomy specimen. • No evidence of systemic Dz. • Also negative was culture and stain for sarcoid.
(Jones) [M88-271] F27 (MAINT)	LANSO 30 PL	28 355	YES	NO	• Pt. had no manifestations of Dz known to produce gastric granulomas but resided in an area of the southern U.S. where blastomycosis and histoplasmosis are endemic.
(Kogut) [M89-350] F48 (MAINT)	LANSO 30 LANSO 15	61 368	YES	YES	• Pt. had no manifestations of Dz known to produce gastric granulomas.

a) Total Daily Dose

4. Additional Tumors

The following findings, unrelated to antisecretory Tx, are included here for completeness on the subject of upper g.i. tumors.

a. Pt. _____ (Campbell) (Gastric Xanthoma) (Study M89-350)

After ca. 7 months of intermittent Tx with open-label LANSO 30 mg, elevated white plaques were noted on routine endoscopy, biopsied and diagnosed as gastric xanthoma. Therefore, there was no change noted in the appearance of the xanthoma. The pt. went on to complete his maintenance trial.

b. Pt. _____ (Silvers) (Leiomyoma) (Study M88-270)

After 28 days of LANSO 15 mg Tx, antral tissue suggestive of a leiomyoma was noted on routine endoscopy and biopsied. The histological Dx did not confirm the leiomyoma. Instead, it described gastric mucosa showing moderate chronic inflammation. No tumor or proliferation of smooth muscle was demonstrated. The patient went on to complete the DU Maintenance trial with no further complications.

c. Pts. _____ (Brand) and _____ (Campbell) (Duodenal Nodules) (Study M89-350)

In one of several Bxs in Pt. _____ the presence of Brunner's glands was noted.

The other pt. prematurely terminated from the maintenance of healing of RE study due to therapeutic failure after receiving 9 mo. of LANSO 30 mg therapy. At the final study visit a Bx was taken which noted mild chronic inflammation in the lamina propria which could represent heterotropic gastric tissue.

In both cases, abnormalities were noted in the duodenal bulb before the pt. entered the acute studies.

5. Gastrointestinal Nodules and Polyps in Z-ES/Hypersecretors

In spite of an FDA request, the sponsor did not submit an update of this important section. This information is important because at the time of the NDA review the three trials in Z-ES/Hypersecretor patients were still ongoing.

Pertinent information is summarized in Table 22.

- No nodules/polyps/masses during Tx or even at BL were shown in the upper g.i. tract among the 30 pts. that entered trial M89-405.
- At BL, 2 of the 6 pts. enrolled by Feldman _____ had nodules or nodular folds in the fundus of the stomach. No Bx was done in Pt. _____ but endoscopies at Month 3 and 6 in this pt. revealed the continued presence of the nodular folds. In the other (Pt. _____) a lesion of concern was found. This was a pre-malignant lesion consisting of chronic active atrophic gastritis + intestinal metaplasia + *H. Pylori*. This pre-malignant condition may be a manifestation of the natural evolution of the disease. Nonetheless, the reviewer has requested of the sponsor a thorough investigation of the antisecretory medication(s) and length of administration of drugs in these patients. This is specially important in view of the many instances of nodules/polyps observed in trial M88-139.

- In NIH trial M88-139 upper g.i. tract lesions were the norm (Table 22).
 - These lesions were variously identified as nodules, polyps, masses or anomalies.
 - In five (5) pts. =nodules/masses in the duodenum and in #18=nodules in the esophagus] anomalies were already reported at the BL (screening) endoscopy. Other lesions in 3 of these 5 pts. or in the other pts. were observed at least 89 days after the start of Tx.
 - In all, 15/21 patients enrolled in this trial has g.i. anomalies (variously identified as duodenal, gastric or antral nodules/polyps) detected by upper g.i. endoscopy or colonoscopy.
 - The information on these patients is certainly incomplete especially because histological examinations were not done in at least 12 of these patients.

TABLE 22
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Pts. With Gastrointestinal Nodules or Polyps in the Z-ES/Hypersecretory Trials

Pt. #	Location and Description	Study Day(s) Observed
I. Study M88-139 (NIH)		
A. Pts. With No Nodules/Masses at BL Screening Endoscopy (N=13)		
	Duodenal submucosal mass [see below] Ampulla (no location provided) Gastric nodules	517 934 [Bx=No ↑ in endocrine cells]
	Duodenal nodule Antral nodule	838 1188 [Bx=No ↑ in endocrine cells]
	Pyloric nodules Duodenal nodules Gastric nodule	105, 196 581 1134 [Bx=No ↑ in endocrine cells]
	Antral polyp Duodenal nodules	965 [Bx=No ↑ in endocrine cells] 965
	Duodenal nodule	954 Histological Evaluation Not Done
	Duodenal nodules	728, 1064 Bx Not Done
	Duodenal nodule	646 Bx Not Done
	Duodenal nodules Laryngeal nodule Gastroesophageal junction nodule	414, 778, 974 414 974 Bx Not Done
	Colon polyp Antral nodule Duodenal nodule	212 425 (Bx=Inflammation with no increase in neuroendocrine cells and no evidence of carcinoid tumors) 845
	Duodenal nodules [see below] Duodenal submucosal mass	645 Bx Not Done

	Esophageal nodules [see below] Esophageal polyp	943 Bx Not Done
	Duodenal nodules	405, 611 Bx Not Done
	Duodenal polyp Duodenal nodule	89 439 Bx Not Done
B. Pts. Who Already Had Nodules/Mass at BL (Screening) Endoscopy (N=5)		
	Duodenal nodules	-8, -1, 85, 358, 581, 749, 945, 1267 Bx Not Done
	Duodenal submucosal mass	-1 (Bx=No ? in endocrine cells)
	Duodenal nodules	1, 141, 234, 414, 596, 764 Bx Not Done
	Duodenal nodules	1, 113, 211, 289, 477, 813 Bx Not Done
	Esophageal nodules	1 Bx Not Done
II. Study M90-436 (M. Feldman)		
A. Pts. With No Nodules/Polyps at BL (Screening) Endoscopy (N=0)		
5. Pts. Who Already Had Nodules at the BL (Screening) Endoscopy (N=2)		
	Nodule in gastric fundus	BL endoscopy
	NOTE: Bx of the nodule revealed a pre-malignant lesion consisting of chronic active atrophic gastritis with intestinal metaplasia and the presence of <i>H. pylori</i>. Subsequent endoscopies noted the continued presence of the nodule; the patient did not develop any other nodules or polyps. A more complete clinical Hx, especially dose and length of exposure to antisecretory medication <u>before</u> enrollment into the trial and F/U on this pt's nodule has been requested of the sponsor.	
	Nodular folds in the fundus	Endoscopies at Months 3 and 6 revealed the continued presence of the nodular folds. (No Bx Data).
C. Study M89-405 (N=0) ^a		

a) No nodules, polyps or masses during Tx or even at BL were reported in this trial.

B. Gastric Atrophy

In response to an FDA request, the sponsor performed an analysis of the effect of L-T LANSO Tx on gastric Bx in mucosa from pts. in either maintenance Tx or Barrett's epithelium studies. The sponsor elected not to include data from L-T evaluations in Z-ES and hypersecretor pts. "because of the well documented changes in gastric mucosa from the respective Dz process".

The sponsor claims that their analysis were similar to those of L-T OME Tx published by Solcia et al., [Digestion 51(Suppl.1):82-92 (1992)] with emphasis on gastric endocrine cells and gastritis.

1. Effects on Endocrine Cells (Fig. 1)

Following L-T LANSO Tx:

- Data from 186 patients were included in this analysis. Qualitative analyses of Grimelius-positive cell distribution in Bxs obtained at BL were compared to final Bxs obtained following at least 270 days up to a maximum of 52 months of LANSO Tx.
- 185 of the 186 or 99.5% of the pts. exhibited a normal distribution pattern of Grimelius-positive cells at BL.
- This changed little at the time of the final Bx (183 of 186 or 98.4% of the pts.).
- 3 of the 186 pts. exhibited SH (1.6%).
- 1 patient exhibited LH at the time of the BL Bx (0.5%).
- None of the 186 patients exhibited LH or MNH at the time of the final biopsy.
- These changes were not statistically significant ($p=0.446$).

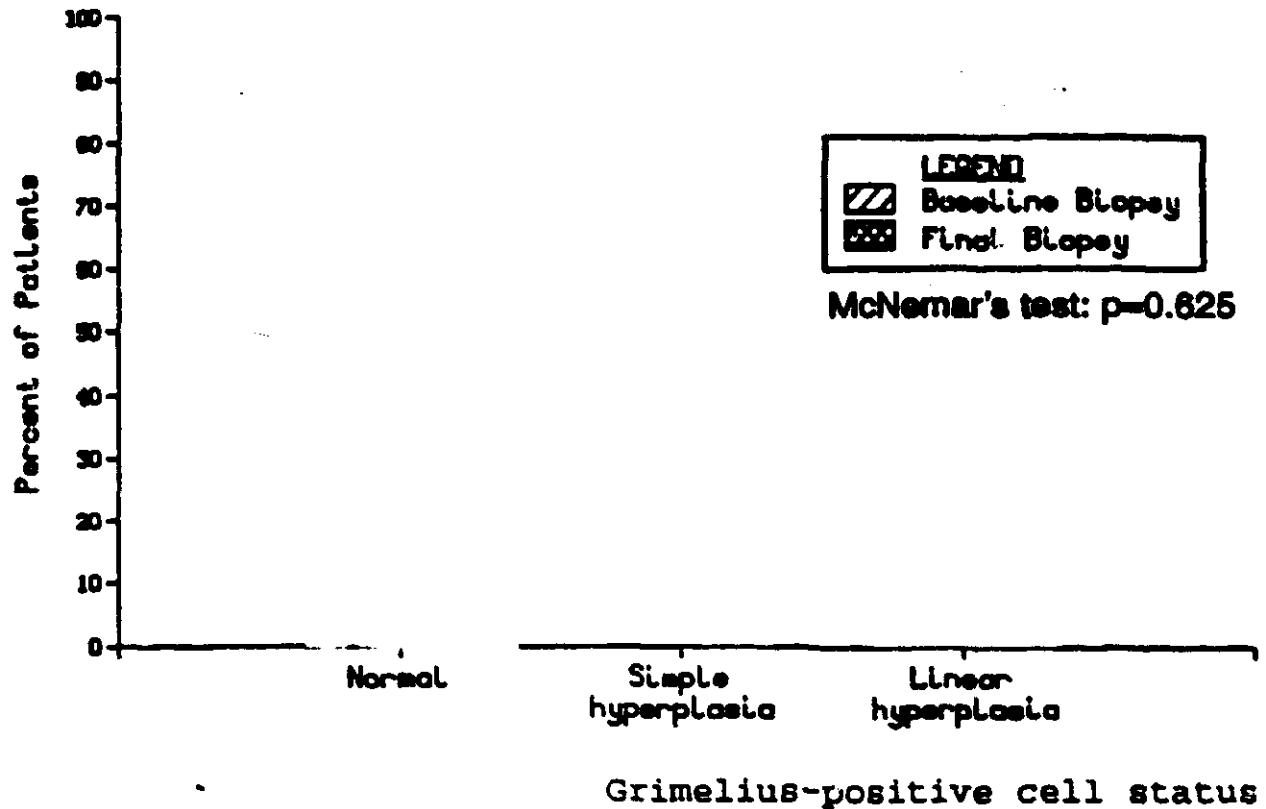


Fig. 1. - The Distribution of Grimelius-Positive Cells Seen at the BL and Final Bxs From Patients Who Were Tx With LANSO for at Least 270 Days (n=186)

2. Effects on Gastric Inflammation and Atrophy (Fig. 2)

For evaluations of Bx data from L-T studies with LANSO the sponsor used a chronic inflammation scale that incorporates, but is not limited to, an evaluation of gastric atrophy. The assessment of gastric atrophy with LANSO is of importance because Solcia et al. [Digestion (locus cited) (1992)] reported a significant ($p < 0.001$) increase in the incidence of chronic atrophic gastritis following L-T (233 days) OME Tx.

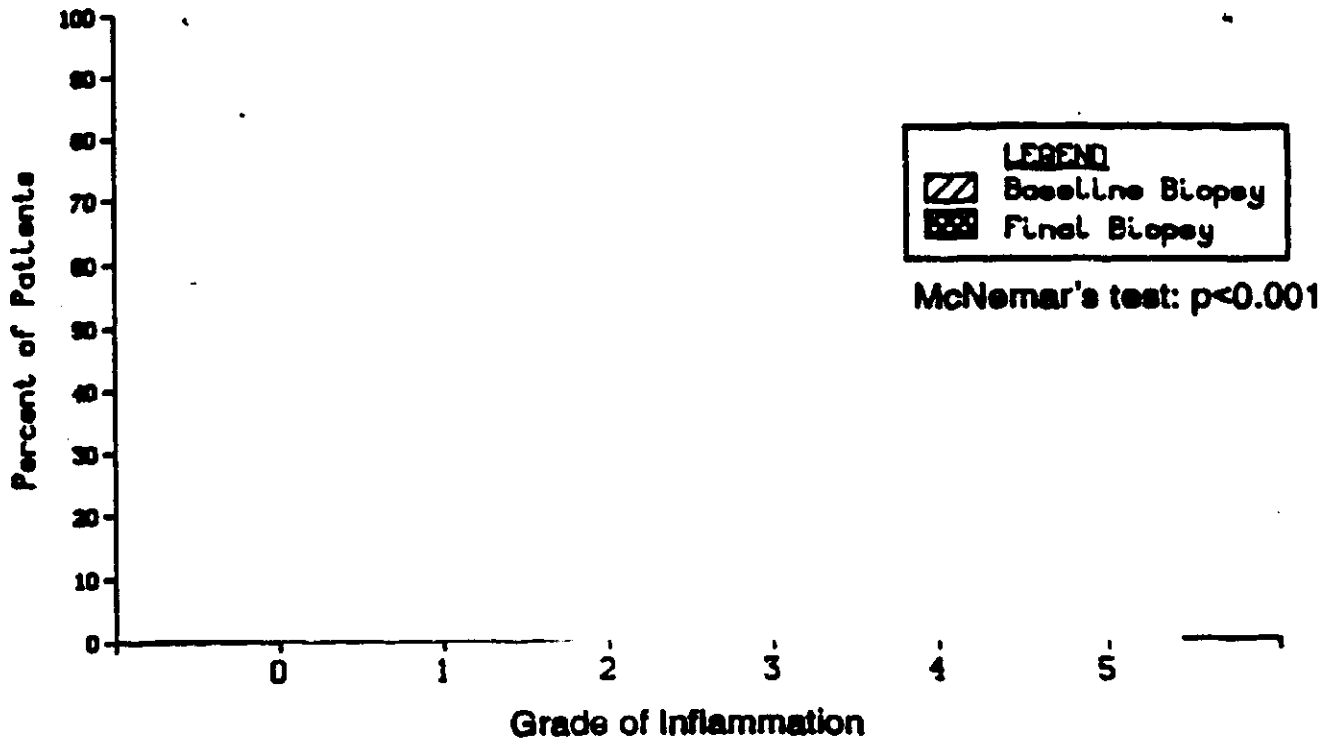


Fig. 2. - The Severity of Chronic Inflammation Seen at the BL and Final Bxs from 198 Patients who were Tx with LANSO for at least 270 Days up to a Maximum of 52 No.

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Chronic Inflammation

0	Normal including some lymphocytes and plasma cells, and up to one lymph follicle per Bx fragment.
1	Mildly increased lymphocytes and/or plasma cells in the lamina propria or several lymph follicles ("almost normal").
2	Same as above but more prominent; patchy, not diffuse, often the lymphocytes are confined to the peri-foveolar lamina propria and there are two to three lymph follicles.
3	Very prominent and diffuse lymphocytes, plasma cells and lymph follicles usually involving the full thickness of the mucosa.
4	Mild or equivocal gland/pit atrophy (often glands are separated by the inflammatory infiltrate into clusters) and/or metaplasia (goblet cell, Paneth cell, intestinal, or other to be specified).
5	Definite or marked atrophy and/or fibrosis (scarring).

- At BL, 134 of the 198 pts. (67.7%) were classified as normal (chronic inflammation Grade 0).
- At the time of the final Bx, 105 of the 198 pts. (53%) were classified as normal.
- Numerical increases were seen in the number of pts. exhibiting chronic inflammation Grade 1 (BL Bx=11.1%; Final Bx=15.7%) and Grade 2 (BL Bx=17.7%; Final Bx=26.3%).
- There was a statistically significant (McNemar's test, $p < 0.001$) difference in chronic inflammation grade between BL and final visits.
- There was a very slight numerical increase (1%) in the number of pts. with Bx Grade 3 at the Final Bx (3.5%) in relation to the findings at the BL Bx (2.5%, the pts.).
- 3 of the 189 pts. (1.5%) exhibited chronic inflammation Grade 4 at Final Bx. One case of interest is very briefly described below.

Pt. (Sontag)/(Study 89-350)

In this pt. chronic inflammation Grade 4 but without gastric atrophy was observed at BL Bx.

- There were no patients exhibiting definite or marked atrophy and/or fibrosis (Grade 5) at BL or at F/U Bx after L-T LANSO Tx.
- 6 of 409 pts. (1.5%) were identified as having an observation of gastric atrophy at some timepoint during L-T maintenance study or Barrett's epithelium. Events in each of these 6 pts. are summarized below.

- [Jones] Study M88-271 [LANSO 30 mg]

At BL, this patient's gastric Bx had a chronic inflammation grade of 2. Following 61 days of Tx with RAN 150 mg BID in acute DU Study M88-268 the patient's Bx had a chronic inflammation grade of 2. The patient subsequently entered the RE maintenance Tx study and was Tx with LANSO 30 mg QD for 338 days, interrupted by no Tx on one occasion. Following 60 days of Tx with LANSO 30 mg QD, a Bx was classified as chronic inflammation Grade 4 with an observation of atrophy. All subsequent Bxs were classified at chronic inflammation Grade 2 or 3.

- [Sontag] Study M89-350 [LANSO 30 mg]

At BL, this patient's gastric Bx had a chronic inflammation grade of 0. Following 58 days of Tx with LANSO 30 mg QD in acute study M89-349 ("Poorly Responsive RE"), the patient's Bx had a chronic inflammation grade of 0. The pt. subsequently entered the maintenance Tx study and was Tx with PL interrupted by LANSO 30 mg QD Tx each time the RE recurred. Immediately following 60 days of PL Tx the patient had a Bx with chronic inflammation Grade 5 (with fibrosis but without atrophy). The pt. was next treated with LANSO 30 mg QD, healed, and returned to placebo Tx. The patient's next Bx, obtained after another 64 days of PL Tx was classified as chronic inflammation Grade 4 with possible atrophy. All subsequent Bxs were classified at chronic inflammation Grade 0. This patient received LANSO Tx for a combined total of 177 days.

- [Redinger] Study M89-350 [LANSO 30 mg]

At BL, this pt's gastric Bx had a chronic inflammation grade of 3. Following 69 days of Tx with LANSO 30 mg QD in acute Study M89-349 ("Poorly Responsive RE"), the patient's Bx had a chronic inflammation grade of 3. The patient's RE remained unhealed; another 50 days of LANSO 30 mg QD was administered. At this timepoint, after a combined total of 119 days of LANSO Tx, a gastric Bx showed a chronic inflammation grade of 2. The patient's RE was healed and PL Tx continued for 357 days, interrupted only by 8 days without any Tx. A single Bx with a chronic inflammation grade of 4 with focal atrophy was observed after 6 mo. of PL Tx; 2 subsequent Bxs had a chronic inflammation grade of 2. This pt. received LANSO Tx for a combined total of 119 days.

- [Fumo] Study M88-271 [LANSO 15 mg and LANSO 30 mg]

At BL, this patient's gastric Bx had a chronic inflammation grade of 2. Following 56 days of Tx with RAN 150 mg BID in acute DU study M88-268, the patient's Bx had a chronic inflammation grade of 2. The patient remained unhealed and was treated with open-label LANSO 30 mg for 62 days. Following this Tx, the patient had a biopsy with chronic inflammation Grade 4 with atrophy. The patient subsequently was treated with LANSO 15 mg QD for 361 days, uninterrupted by any other Tx. All subsequent Bxs were classified at chronic inflammation Grade 2 or 3.

- [Sontag] Study M89-350 [LANSO 15 mg]

At BL, this patient's gastric Bx had a chronic inflammation grade of 4 without an observation of gastric atrophy. Following 60 days of Tx with LANSO 30 mg QD in acute study M89-349 ("Poorly Responsive RE"), the patient's Bx had a chronic inflammation grade of 2. Four subsequent Bxs obtained during the RE maintenance Tx period had a chronic inflammation grade of 0, 2 or 3. Following 265 days of Tx with LANSO 15 mg QD a Bx with chronic inflammation Grade 4 with atrophy was observed. Another biopsy with the same finding was obtained following 364 days of LANSO 15 mg Tx. The last Bx obtained from this patient after 30 days post-Tx was inadequate for any analysis.

- [De Micco] Study M88-270 [PL]

At BL, this patient's gastric Bx had a chronic inflammation grade of 2. Following 28 days of Tx with LANSO 15 mg QD in acute DU study M88-268, the patient's Bx had a chronic inflammation grade of 4 with an observation of atrophy. The patient subsequently entered the DU maintenance Tx study and was treated with PL for 365 days, uninterrupted by any other Tx. Five subsequent biopsies during and following PL Tx had chronic inflammation grades of 1 or 2.

C. Intestinal Metaplasia

- 1,007 pts. enrolled in 14 Phase II/III clinical studies in the TAP Safety database, underwent a total of 7,348 gastric Bxs. These Bx specimens were evaluated for changes in EC-L cell density and reviewed for the presence of inflammation in the gastric mucosa. When signs of intestinalization, such as goblet cells or Paneth cells within the gastric mucosa, were detected by the reviewing pathologist at the Med. College of Pennsylvania, all histological slides available for that pt. were sent to Dr. Juan Lechago at Baylor Univ. in Houston, TX for further review. What follows is a summary of Dr. Lechago's findings.
- Intestinal metaplasia was observed and confirmed by Dr. Lechago in gastric Bxs from 44 pts⁷. This represents 4.4% (44 of 1007 pts.) of patients exhibiting intestinal metaplasia in the TAP Safety database.
- 11 of the 44 pts. exhibited intestinal metaplasia at the time of the screening Bx, at a biopsy prior to administration of LANSO, or represented pts. who never received LANSO.
- 31 of the remaining 33 pts. exhibited the complete (Type I or small intestine) type of intestinal metaplasia.
- 3 Bxs from 2 pts. exhibited incomplete (colonic) metaplasia. These 2 pts. are detailed below.

⁷Material for 43 of these patients was obtained from routine gastric Bxs and sent to Dr. Lechago from the Medical College of Pennsylvania. Material from one additional patient was from an extra-protocol Bx (a gastric nodule observed at the time of endoscopy) which was sent to Dr. Lechago for review and found to exhibit intestinal metaplasia.

- Pt. _____ (Avner), 36y-old M

This pt. was treated with RAN 300 mg in acute DU study M88-268. When he entered the study the pt. had previously experienced two episodes of DU. Following 4 weeks of Tx with RAN 300 mg HS, the patient entered maintenance of DU study M88-270. He received LANSO 15 mg QD for ca. one year. A total of 20 (10 antral, 10 fundic) gastric Bxs were obtained from this pt. over his 14-month course of Tx with RAN followed by LANSO 15 mg. Helicobacter pylori was observed as "numerous diffuse organisms" or "numerous focal organisms" in gastric Bxs obtained at screen, at the end of the acute study, and at 1 month and 3 months post-Tx. In one antral Bx obtained after five months of LANSO therapy, a finding of "some colonic metaplasia with dysplasia" was noted. Subsequent gastric Bxs obtained from this patient exhibited no intestinal metaplasia.

- Pt. _____ (Kogut) 67y-old F

This pt. entered RE study M88-269 and was treated with LANSO 30 mg for eight weeks. She subsequently entered the maintenance of RE study, M88-271, and received LANSO 30 mg QD for one year. Intestinal metaplasia with "abundant reactive atypia" was observed in two Bxs, one obtained following three and another following four months of LANSO Tx in the maintenance Tx study. Subsequent gastric Bxs obtained from this same patient following nine months and one year of LANSO Tx failed to exhibit intestinal metaplasia of any type. Gastric biopsies obtained one month post-LANSO Tx were also devoid of intestinal metaplasia. Helicobacter pylori was observed as "numerous focal organisms" in Bx sections stained with Warthin-Starry stain.

Reviewer's Comments on Intestinal Metaplasia

It is important to put intestinal metaplasia in the proper context. By itself, the information that 4.4% of the pts. in the TAP Safety Database had intestinal metaplasia is not very useful. Important information to be included is whether this is an isolated finding or whether it is accompanied by other findings such as chronic gastric atrophy, ECL-cell hyperplasia, dysplasia, atypia and even *H. pylori*. The best example the reviewer can give to document such a situation - not properly addressed by the sponsor in this subsection - is that of Pt. _____ in the Z-E study by Feldman. At the screening (BL) endoscopy, this pt. had a nodule in the gastric fundus. Bx of this nodule revealed a lesion that appeared to be pre-malignant. This consisted of chronic active atrophic gastritis plus intestinal metaplasia plus the presence of *H. pylori*. Subsequent endoscopies noted the continuous presence of the gastric nodule in this pt. The reviewer has requested of the sponsor a more complete clinical Hx, including dose and dose response to antisecretory medication(s) before enrollment into the trial. Obviously, F/U of this pt.'s nodule is important. This finding also stresses the need to biopsy upper g.i. mucosal lesions and assess for the presence or absence of *H. pylori*.

D. Effects on the Eyes1. Tx-Emergent Vision-Related AEs in the TAP Safety Database (Table 23)

- This Table lists summary information on all 31 pts. reporting vision-related AEs⁸ in all LANSO studies included in the NDA.
- Of the 31 pts. listed in this Table, 5 were treated with other drugs (PL=2; RAN 150mg BID=2; RAN 300 mg=1).

⁸These were described by one of the following COSTART terms: abnormal vision, amblyopia, cataract, chromatopsia, corneal ulcer, eye disorder, eye or retinal hemorrhage, eye pain, glaucoma, photophobia, or visual field defect.

- In a few pts. the vision related events occurred soon after starting Tx. Many resolved spontaneously during the study.
- Concurrent conditions such as conjunctivitis, D.M. or hemorrhage may explain the vision-related AEs in some pts.
- Except for the cases stated below, most of the AEs were of mild severity. Only LANSO-Tx pts. are listed.

MODERATE

- 1 pt. with pain around eyes and blurred vision
- 1 pt. with cataract surgery
- 1 case of eye disorder (cornea transplant; Hx of interstitial keratitis)
- An additional case of eye disorder
- 2 cases of eye pain, both of which resolved while on study
- 1 case of glaucoma with onset at ca. 4 mo. following cessation of test med.
- 1 case of visual field defect also occurring during the post-Tx phase. The pt. had L hemianopsia accompanied by R CVA and L hemiplegia.

SEVERE

- Pt. (Robinson) [Study M88-193]
1 case of eye pain occurring in a pt. treated by optometrist because of corneal tear.

- Except as noted below, most AEs were considered not related to test medication.

	Test Med. (mg)	Relationship to Test Med.
<u>Pt. (Kovacs) [Study M89-393]</u>		
1 case of blurred vision with dizziness that resolved while on study. The pt. had a Hx of left CVA.	LANSO 30	POSS
<u>Pt. (Buchi) [Study M88-243]</u>		
1 case of shooting white stars in vision for 15 min. upon awakening. The pt. also had concurrent conjunctivitis and Hx of extra-ocular muscle surgery.	LANSO 30	POSS
<u>Pts. (Buchi); Pt. (Long)</u>		
3 cases of visual field defect, 2 of which resolved during the study.	LANSO 60	POSS

- In the TAP Safety Database, the incidence of eye AEs is as follows:

	LANSO	RAN	PL
Total length of exposure (patient-years)	779	55.8	140.2
Any Ocular AE	26/1778 (1.5%)	3/429 (0.7%)	2/454 (0.4%)
Events/pt.-year	0.033	0.054	0.014

2. Ophthalmologic Examinations in L-T LANSO Studies

- These are being conducted in the following four L-T trials: M88-139 (Z-E=NIH), M89-375 (Barrett's), M89-405 (Z-E=Hirschowitz) and M90-436 (Z-E=Feldman).
- The ophthalmology examination includes routine⁹ as well as specialized¹⁰ eye tests.
- LANSO pts. undergo this examination at BL, months 3, 6, 12 and every 6 mo. thereafter.

NOTE: This BL visit is defined as the visit where the routine and specialized eye tests are first conducted on patients. All subsequent ophthalmology examination visits must be scheduled based upon the date of this initial evaluation. As shown below, as a result of this approach, very few pts. have normal ophthalmological tests at "BL". So what is really being evaluated is effects of drug on pre-existing visual abnormalities.

- 2 control subjects are to be assigned to each LANSO patient and these subjects will participate in the ophthalmology examination portion of the study only.
 - Ophthalmologic results from the control subjects will be used as a comparison for results obtained for LANSO patients to control for changes occurring over time, across race, gender, age, and, if applicable, with diabetes.

⁹Routine Ophthalmology Examination

- Targeted personal Hx
- Visual acuity
- Lens, cornea and anterior chamber assessment
- Vitreous evaluation
- Funduscopy exam of the retina
- Measurement of intraocular pressure
- Evaluation of ocular motility
- Evaluation of afferent pupil reaction
- Evaluation of peripheral visual fields

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Specialized Retinal Studies

- Psychophysical threshold-dark adapted
- Fluorescein angiography (to be performed only if medically indicated)
- Photographs of the retina
- Full-field ERG

TABLE 23
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Tx-Emergent Vision-Related AEs in the TAP Safety Database

Pt. # (Investig.) [Study No.]	Tx	Length of Tx at AE Start (Days)	Severity/ Relationship	Duration (Days)	Additional Information
<u>Amblyopia and Abnormal Vision</u>					
(Gardner) [M88-139]	LANSO [®]	1142	MILD (NO)	Cont.	Blurred vision. Screen Hx of D.M.
(Campbell) [M88-193]	LANSO 30	69	MOD (NO)	Cont.	Pain around eyes and blurred vision, normal ophthalmologic exam.
(Brand) [M89-350]	LANSO 15	93	MILD (NO)	Cont.	Blurred vision in a.m.
(Saplimer) [M89-375]	LANSO 60	631	MILD (NO)	62	Blurred vision, resolved while on study, no Hx or alternative etiology
(Saplimer) [M89-375]	LANSO 60	632	MILD (NO)	73	Dry eyes and blurred vision. Resolved while on study. Hx of scleroderma. Elevated blood glucose.
(Kovacs) [M89-393]	LANSO 30	4	MILD (POSS)	7	Blurred vision with dizziness resolved while on study Tx. Hx of left CVA.
(Sontag) [M90-422]	RAH 150 BID	17	MILD (NO)	7	Blurred vision, resolved while on study.
(Buchi) [M88-243]	LANSO 30	3	MILD (POSS)	15 min.	"Shooting white stars in vision" for 15 min. upon awakening. Patient also had concurrent conjunctivitis. Hx of extra-ocular muscle surgery.
(Bruna) [M88-269]	RAH 150 BID	9	MILD (NO)	18	Difficulty focusing at close range. Resolved while on study. Hx of foreign body in L and R eye.

<u>Cataract</u>						
(Aronson) [M88-270]	LANSO 15	362 (84) ^a [ISS: 446(84)]	MILD (NO)	Cont.	Found on routine exam ca. 3 mo. after last dose of test med. No Tx required.	
(Campbell) [M89-350]	LANSO 15	351 (1) ^b [ISS: 352(1)]	MILD (NO)	Cont.	No relevant Mx	
(Fleishmann) [M89-350]	LANSO 15	223	MOD (NO)	1	Cataract surgery.	
<u>Chromopsia</u>						
(Campbell) [M89-349]	LANSO 30/60	51	MILD (NO)	6	Pre-existing condition treated with laser therapy, resolved while on study. Mx of retinal vitreous hemorrhage.	
<u>Corneal Ulcer</u>						
(Robinson) [M88-271]	PL	41	MOD (NO)	7	Resolved while on study	
<u>Eye Disorder</u>						
(Aronson) [M87-091]	LANSO 15	38	MOD (NO)	1	Cornea transplant. Mx of interstitial keratitis.	
(Sontag) [M89-350]	LANSO 15	253	MILD (NO)	28	"Eyes ache, painful to touch eye area", resolved while on study.	
(Campbell) [M89-349]	LANSO 30	9	MOD (NO)	18	Cellulitis in R eye. Total blindness in R eye since 1935. Early cataract in L eye. Fixed upward, outward gaze since 1985.	
<u>Eye or Retinal Hemorrhage</u>						
(Sampfliner) [M88-249]	LANSO 60	143	MILD (NO)	Cont.	Mx of bilateral diabetic retinopathy. Alternative etiology: HTN diabetes.	
(Kogut) ^c [M88-268]	RAN 300	4	MILD (NO)	Cont.	Scleral hemorrhage. Questionable eye infection.	

(Kogut) ^a [M88-270]	LANSO 15	-85	MILD (NO)	45	Continued from previous study, resolved while on study.
(Sinha) [M88-271]	PL	-7	MOD (NO)	32	Conjunctival hemorrhage occurred 5 mos. after acute study and one week prior to entering the maintenance study. Capillary fragility resolved while on study.
<u>Eye Pain</u>					
(Oliver) [M87-090]	LANSO 15	20	MOD (NO)	10	Resolved while on study. Alternative etiology: worsening of cataracts. Eye drops prescribed for tired eyes.
(Robinson) [M88-193]	LANSO 30	11	SEV (NO)	7	Alternative etiology: corneal tear. Patient treated by optometrist.
(Sontag) [M89-350]	LANSO 30	121	MOD (NO)	3	Resolved while on study. Alternative etiology: Mild contact overwear.
(Brand) [M89-350]	LANSO 15	60	MILD (NO)	36	L eye pain, resolved on study.
<u>Glaucoma or Increased Intraocular Pressure</u>					
(Whitaker) [M87-090]	LANSO 15	30 (116) ^b [ISS: 146(116) ^b]	MOD (NO)	Cont.	Onset ca. 4 mo. following cessation of test med.
(Sontag) [M89-350]	LANSO 15	210	MILD (NO)	Cont.	Hx of glaucoma.
(Aaronsen) [M87-091]	LANSO 15	57 (67) ^b [ISS: 134(67) ^b]	MILD (NO)	11	Eye examination normal two months following cessation of Tx.
<u>Photophobia</u>					
(Sampfliner) [M88-249]	LANSO 60	211	MILD (NO)	153	Accompanied by dry eyes and resolved while on study. Hx of septal nasal deformity.

Visual Field Defect					
(Buch1) [190-466]	LANSO 60	13	MILD (POSS)	43	↑ peripheral vision resolved while on study.
(Buch1) [190-466]	LANSO 60	13	MILD (POSS)	6	Clouded peripheral vision resolved while on study.
(Long) [191-066]	LANSO 60	56 (24) ^a [ISS: 80(26) ^b]	MCD (POSS)	Cont.	L hemianopia accompanied by R CVA & left hemiplegia. Occurred during post-tx phase.

a) LANSO titrated

b) [Days]=No. of Days Post-Tx at AE start

c,d) Pt. (Kogut) and (Kogut)

are the same pt. in acute and maintenance studies, respectively.

- The first control group consists of subjects who are currently being Tx with OME.
- The second control group consists of subjects with g.i. pathology not currently being treated with a PPI.
- A control subject from each group will be matched to each LANSO patient.
- OME-treated and non-proton pump inhibitor-treated (non-PPI) controls undergo the ophthalmology examination at BL, Months 6 and 12 and every 12 months thereafter.
- Of the total of 58 pts. that are currently on the four above-mentioned L-T LANSO studies and who will be participating in the ophthalmology examinations, 56 had undergone the BL ophthalmology exam.
- But for only those 12 pts., listed in Table 24, evaluations at the Month 3 visit were available.
 - In only 3 of these pts., psychophysical threshold, visual fields and ERG were all normal at BL. In the other 9 pts., one, two or all three of these tests were abnormal at BL.
- The dose duration (ca. 90 days) is too short so that conclusions cannot be drawn from these very incomplete data.

3. Reviewer's Conclusions on LANSO and Visual Disturbances

The available data is too incipient and needs to be expanded considerably, especially if one is going to consider approval of indications where this drug needs to be given/taken long term. This is important because the i.v. formulation of another PPI appeared to induce irreversible eye damage in some pts. and has been withdrawn from the market in Germany. A review of the available U.S. and worldwide data on visual disturbances with the oral formulation of this other PPI also revealed some instances (although the problem is of far less concern) of irreversible eye injury that may be drug-related.

Aside of the L-T observations in Z-E and Barrett's patients, patients in RE and DU maintenance studies should be monitored for visual disturbance at BL (pre-drug) and as a function of time. Patients with normal pre-drug examinations should be clearly differentiated from those who already have visual disturbances at BL.

E. Abnormalities in LFTs

1. Trend Analyses

- Depicted in Table 25 are hepatic analytes with statistically significant findings in the analyses of mean change, % change and/or % of pts. with lab. values reaching levels requiring further clinical review.

TABLE 24
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Pts. With Follow-up Ophthalmological Tests After Having Had Normal (I) or Abnormal (II) BL Evaluations

Pt. # (Investigator) Age-Sex	Opth Exam	LANSO Dose (mg) at Exam	LANSO Tx (Days)	Psychophysical Threshold	Visual Fields	ERG	Alternate Etiology
I. Pts. With Normal (N) BL Evaluations and Follow-up Data							
Study M89-405 (Z-E)							
(Hirschowitz) (47M)	BL	75 BID	592	N	N	N	UNK
	M3	75 BID	690	N	Nasal field misses	N	
Study M90-436 (Z-E)							
(Feldman) (66M)	BL	15 QD	393	N	N	N	UNK
	M3	15 QD	496	Slight ↑	N	N	slightly ↓ amplitude
(Feldman) (49M)	BL	75 QD	155	N	N	N	UNK
	M3	75 QD	251	N	Scattered defects	N	Smaller than BL
II. Pts. With Abnormal BL Evaluation(s) and Follow-up Data							
Study M89-405 (Z-E)							
(Hirschowitz) (59F)	BL	45 QD	1167	N	inferior defects OS	N	UNK
	M3	45 QD	1281	N	N	N	

Study M90-636 (Z-E)									
(Feldman) (61M)	BL	75 BID	923	M	M	Field change superiorly OS	↓ rod amplitude ↓ field sensitivity OS	ERG: age-related Visual Field: unknown	
Study M89-375 (BE)									
(Simpliner) (65M)	BL	60 OD	1390	M	M	Constricted fields OU	Delayed implicit times OU	CVA, diabetes	
(Simpliner) (72M)	M3	60 OD	1481	M	M	No change	No change		
(Simpliner) (53M)	BL	60 OD	1259	M	M	Nasal field defects	N	Glaucoma	
(Simpliner) (63M)	M3	60 OD	1357	M	M	No change	N		
(Simpliner) (63M)	BL	60 OD	1543	M	M	Nasal field loss	N	Possible glaucoma	
(Simpliner) (63M)	M3	60 OD	1661	M	M	No changes	N		
(Simpliner) (81M)	BL	60 OD	1514	↑	M	Nasal field defects OS	↓ rod, cone amplitudes	Plaquenil use	
(Simpliner) (73M)	M3	60 OD	1612	M	M	No change	No change		
(Simpliner) (48F)	BL	60 OD	1518	M	M	Inferonasal loss OD, peripheral loss OS	Interocular differences	Vein occlusion OD, unknown OS	
(Simpliner) (48F)	M3	60 OD	1611	M	M	No change	No change		
(Simpliner) (48F)	BL	60 OD	1477	slight ↑	M	No change	N	Age-related	
(Simpliner) (48F)	M3	60 OD	1568	No change	M	No change	N		
(Simpliner) (48F)	BL	60 OD	1412	M	M	Nasal field loss OD Improved	N	UNK	
(Simpliner) (48F)	M3	60 OD	1511	M	M	No change	N		

Abbreviations Used: Z-E=Zollinger Ellison Syndrome; BE=Barrett's Epithelium; M=Male; F=Female; OD=right eye; OS=left eye; OU=both eyes;
M=Normal; CVA=Cerebrovascular Accident; ERG=Electroretinogram; BL=Baseline Exam; M3=Month 3 exam.

TABLE 25
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Summary of Statistically Significant Findings in Trend Analysis for Hepatic Chemistry Variables in the Phase II/III Studies in the TAP Safety Database

	S-T		L-T		Maintenance Tx	
	PL-Controlled Studies ^a (Final Visit)	Positive-Controlled Studies ^a (Final Visit)	Barrett's Studies ^b (Final Visit)	ZES Studies ^b (Final Visit)	First Recurrence ^a	After 12 Months of Continuous Therapy ^a
AST (OT)		†				
ALT (PT)		†				
γ-GT		†				†
Total BIL				†		
AP		†				†

- a) Significance (p≤0.05) based on 1x difference from reference group for mean or %change from BL or percentage of pts. with laboratory value reaching clinical review level. If reference group change from BL was larger than that of LANSO group for a given analyte, that analyte is not shown even if there was a significant difference between Txs.
- b) Significance (p≤0.05) based on change from BL to indicated visit.

- There were no statistically significant findings in any of the three trend analyses for the S-T PL-controlled studies. Significant findings in mean change, percent change, and percentage of patients with hepatic values reaching levels requiring clinical review analyses were noted in the positive controlled studies. Data on ALT/SGPT are summarized in Table 26.

- No significant differences between Tx groups in percentage of patients reaching levels of clinical review were noted for any other study type.

TABLE 26
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Statistically Significant Tx Group Differences in % of Pts. with Laboratory Values Reaching Levels Requiring Further Clinical Review at Any Timepoint in S-T, Phase II/III, Positive-Controlled Studies^a Stratified by BL Laboratory Values in the TAP Safety Database

	RAM (Total n=402)			LANSO (Total n=667)					
	Patients With Clinical Review Values n (%)	BL Laboratory Value			Patients With Clinical Review Values n (%)	BL Laboratory Value			p-Value ^b
IN n		H n	TN n	IN n		N n	TN n		
ALT (PT)	2 (0.5)	0	1	1	16 (2.4)	0	10	6	0.024

- a) Studies: M88-268, -269, M89-349, -393, M90-422, P91-066
- b) Based on Fisher's Exact test.,.

- For the L-T studies, statistically significant findings in mean change from BL are shown in Table 27. In the maintenance Tx studies, no significant findings were noted in trend analyses at the time of first recurrence but statistically significant findings in the mean change after 12 mo. of continuous LANSO Tx were noted (sponsor's Table 96). Complete details for these trend analyses were found in sponsor's Tables 82, 83, 84, 85, 86, 87 and End-of-Text Tables 176-187. These were individually described in sponsor's Section 8.12.6.2.
- No clinically relevant results were noted in the trend analyses. The reviewer agrees with the sponsor that the changes seen were generally small and not consistent among study types.

TABLE 27
Updated ISS of NDA 20-406

Statistically Significant Mean Changes from BL in Hepatic Chemistry Variables During L-T or Maintenance Tx Studies in the TAP Safety Database

	N	Mean BL	Mean Change	p-Value ^b
<u>AP (U/L)</u> Maintenance Studies ^a - Change after 12 mo.	242	71.2	3.4	<0.001
<u>γ-GT (U/L)</u> Maintenance Studies ^a - Change after 12 mo.	243	31.0	3.1	0.046
<u>Total BIL (mg/dL)</u> L-T Studies in ZES/hypersecretors ^d - Change after final visit	59	0.5	0.17	0.038

- a) Studies reviewed: M88-139, M89-405, M90-436, M88-269, M89-375, M88-270, -271, M89-350
 b) Based on paired t-test for change from baseline equal to zero
 c) Studies M88-270, -271, M89-350
 d) Studies M88-139, M89-405, M90-436

2. Findings by Variable

a. Total BIL

- For this parameter, significant ts were noted in the L-T ZES/hypersecretor studies only, at the Months 12, 30 and final visit timepoints.
 - The changes seen were small and, although they represented a statistically significant change from BL, were not considered clinically relevant (mean increases of 0.07, 0.11 and 0.17 mg/dL from a BL value of 0.5 mg/dL at each of the Months 12, 30 and final visits, respectively). The final values were still WNL.

b. AST (OT) and ALT (PT)

- For these parameters, no significant findings were noted in the S-T PL-controlled studies or any L-T or maintenance Tx studies.

- However, in the S-T positive-controlled studies, significant ts from BL in the LANSO group were detected in the mean and % change analyses for both analytes.
- For ALT (PT) a significantly larger percentage of LANSO pts. from S-T positive-controlled studies reached levels requiring clinical review as compared to RAN pts.
- The % change analysis in S-T positive-controlled studies showed more patients treated with LANSO had increases in AST(OT) and ALT (PT) values than pts. treated with RAN.
- In the mean change analysis for the same studies, the significant findings were mean ts in the LANSO group of 2.1 and 1.7 U/L from BLs of 21 and 24 U/L in AST (OT) and ALT (PT), respectively (compared to a mean increase of 0.2 U/L and a decrease of 0.3 U/L in the RAN group from BLs of 21 and 22 U/L for AST (OT) and ALT (PT), respectively).
- On the other hand, in the maintenance Tx studies, all changes from BL for AST (OT) and ALT (PT) at all timepoints [except Month 1 for AST (OT)] evaluated in the continuous LANSO Tx analysis were not significant and were numerically smaller than those observed in the S-T positive-controlled studies.
- For levels requiring further clinical review, in the S-T positive-controlled studies, significantly more LANSO pts. had ALT (PT) values reaching these levels (2.4%) than the RAN patients (0.5%). However in the maintenance Tx studies after continuous LANSO Tx, up to 12 mo., the percentage of LANSO patients with AST (OT) and ALT (PT) values requiring clinical review at first recurrence (0.3% and 0.6%, respectively) or at final visit of continuous LANSO Tx (1.0% and 1.0%, respectively) were similar to that of the PL group at first recurrence (1.1% and 1.6%, respectively).
- Thus, the reviewer agrees with the sponsor that effects seen in the positive-controlled studies were minimal and clearly not increasing with extended Tx. These small changes are assessed as not being clinically important.

c. AP

- For this parameter, significant findings were seen for mean change and percent change analyses in the S-T positive-controlled studies and in the maintenance Tx studies after 12 mo. of continuous LANSO Tx.
 - These findings resulted from mean increases of 3.3 U/L and 3.4 U/L from BLs of 83 and 71 in the LANSO group in the S-T positive-controlled studies and after 12 mo. of continuous LANSO Tx in the maintenance Tx studies, respectively.
 - However, the percentage of LANSO patients with AP values reaching levels requiring further clinical review in the S-T positive-controlled studies (0.2%, 1/665) was similar to that of the RAN group (0.5%, 2/404).

- Also, no LANSO patients reached these levels at their final Tx visit in the S-T PL-controlled Tx studies or at first recurrence or end of continuous LANSO therapy in the maintenance studies. Thus, the reviewer agrees with the sponsor that the effects seen in the studies were minimal and assessed as not clinically relevant.

d. γ -GT

- For this parameter, the only significant findings were for the analyses of S-T, positive-controlled and maintenance Tx studies.
 - For the S-T studies, a significant difference between the LANSO and RAN group in the % change analysis was seen.
 - For the maintenance Tx studies, a significant mean change from BL was seen after 12 mo. of continuous LANSO Tx.
 - The % change analysis showed more pts. treated with LANSO had $\uparrow$ s in γ -GT values than patients treated with RAN in the S-T, positive-controlled studies only.
 - A mean $\uparrow$ from BL of 3.1 U/L from BL of 31.0 U/L was found after 12 mo. of continuous LANSO Tx in the maintenance Tx studies. However, the percentage of LANSO patients with γ -GT values requiring clinical review at first recurrence (2.6%, 8/310) or at final visit of continuous LANSO Tx (2.1%, 11/524) were similar to that of the PL group at first recurrence (2.1%, 4/188).

In conclusion, the effects seen in the studies were minimal and assessed as not clinically relevant.

3. Mean Change for Older Patients

- To evaluate the effects of LANSO on hepatic variables in older patients (65y or older), a separate mean change analysis was completed for S-T PL- and positive-controlled and maintenance continuous therapy studies (sponsor's End-of-Text Tables 161, 162 and 163).
 - The only significant differences seen were in the S-T positive-controlled studies.

4. Additional Analyses

- The trend analyses showed sporadic, sometimes statistically significant but minor changes in hepatic parameters in S-T, L-T and maintenance Tx studies. In order to develop a clearer patient profile and to further evaluate patients with hepatic changes, individual patient data were reviewed to identify patients with hepatic parameters reaching levels requiring further clinical review.
- Summaries of individual patient hepatic values reaching levels requiring further clinical review were included in sponsor's End-of-Text Tables 189, 193, 194, 195, 196 and 197 with narrative descriptions of patient case Hxs in sponsor's Appendices I, J and K for the S-T, L-T and maintenance studies, respectively.¹¹ In addition, patients were also

¹¹This is a correction to the ISS, where sponsor's End-of-Text Tables 165, 169, 170, 171 and 173 were incorrectly identified for the S-T, L-T and maintenance Tx studies, respectively.

two or more hepatic variables shifting from normal range to abnormal range at the final visit. In the maintenance studies, patients with two or more hepatic variables above normal range at baseline, regardless of BL values, were evaluated.¹²

Table 28 summarizes the percentage of pts. in each L-T or maintenance study who had shifting in two or more hepatic parameters.

- In Barrett's studies, the # of PL-Tx pts. is small (N=8). There were no RAN or other positive comparators in either Barrett's or Z-ES/Hypersecretor trials. In all, the proportion of pts. that had a shift in two or more hepatic chemistry values ranged from 7.4 to 15%.
- In maintenance studies, the average proportion of PL-Tx pts. that had a shift in two or more hepatic chemistry values was similar to that in LANSO-Tx pts. This was shown in comparisons of data to first recurrence (PL=9.6%; LANSO=7.7%) or from continuous LANSO therapy (LANSO=8%).

TABLE 28
Updated ISS of NDA 20-406

Patients With Two or More Hepatic Chemistry Values Shifting From Below the ULM at BL to Above the Normal Range at the Final Tx Visit in All Phase II/III Studies in the TAP Safety Database

Treatment Groups	PL n/N (%)	LANSO n/N (%)
I. L-T STUDIES		
Barrett's Epithelium		
M88-249 M89-375	0/8 N/A	0/7 ^a 2/27 (7.4)
Z-ES/hypersecretor		
M88-139 M89-405 M90-436	N/A N/A N/A	3/20 (15.0) 3/33 (9.1) 0/8
Total (%) L-T studies	0/8	8/95 (8.4)
II. MAINTENANCE TX STUDIES		
First Recurrence		
M88-270 M88-271 M89-350	9/85 (10.6) 4/56 (7.1) 5/47 (10.6)	5/90 (5.6) 7/116 (6.0) 12/104 (11.5)
Total (%)	18/188 (9.6)	24/310 (7.7)

¹²A summary of individual patient values for these patients, as well as those with similar shifts any time during the study, were presented in sponsor's End-of-Trial Tables 201, 202, 203 and 204 with narrative descriptions of patient case files in their Appendix L.

Continuous LANSO Therapy		
M88-270	---	12/170 (7.1)
M88-271	---	13/175 (7.4)
M89-350	---	17/179 (9.5)
Total (%) maintenance Tx studies	---	42/524 (8.0)

- a) Includes only patients who did not continue into Study M89-375.
b) For maintenance treatment studies, all patients with two or more hepatic chemistry values above the normal range are tabulated regardless of BL levels.

5. Clinical Summaries¹³ of Early Terminations From the Trial due to Elevated LFTs

- 2 pts. (Robinson) and #6345 (Fisher) were withdrawn prematurely from the S-T RE study M88-269 as a result of elevated hepatic chemistry values.
- 3 pts. were W/D prematurely from the maintenance Tx studies. Short clinical summaries on these three pts. are given below.

- Pt. (Nelson) [Study M88-270]

This pt., with an elevated γ -GT at BL, experienced elevated γ -GT, ALT (PT) and AP (120, 63 and 136 I/L, respectively) after 183 days of LANSO 15-mg Tx during the maintenance phase. Hepatic viral studies and CT of abdomen were normal. Throughout the study the pt. was taking Tylenol® Extra-Strength. Elevations in the LFTs persisted. The patient was prematurely terminated.

The patient was followed and continued to demonstrate fluctuations outside of normal range in liver enzymes.

NOTE: This pt. appears to have a chronic, insidious liver condition, already present before drug. Information on gallstone Dz or alcohol consumption is not available.

- Pt. (Sahba) [Study M88-270]

This pt. demonstrated elevated AST (OT) and ALT (PT) [128 and 209 U/L, respectively] levels after receiving one month open-label LANSO 30-mg Tx for recurrent DU. The patient returned to his D-B medication, which was PL, and these analytes returned to WNLs. A hepatitis panel was performed; this indicated that the patient had exposure to both Hepatitis B and Hepatitis C. Because of his hepatitis exposure, the patient was prematurely terminated.

NOTE: The reviewer agrees with the investigator that the hepatic chemistry elevations in this pt. does not appear to be related to test med.

- Pt. (Campbell) [Study M89-350]

This pt. presented with elevated AST (PT), ALT (OT) and γ -GT values prior to beginning Tx with LANSO. LFTs continued to be elevated throughout study and the pt. was prematurely D/C from study on Study Day 33 due to these elevations. During further evaluations, it was determined that the patient was positive for hepatitis C antibodies. In addition, the investigator suspected alcohol abuse as contributing to his hepatic chemistry value elevations.

¹³Complete narratives for these pts. were given in sponsor's Appendix K.

NOTE: Elevations of LFTs in this pt. do not appear to be related to test med.

6. Reviewer's Summary and Comments of Changes in LFTs

The small although statistically significant differences between LANSO and RAN in the trial analyses for AP, AST (OT), ALT (PT) and γ -GT shown in the S-T positive-controlled trials apparently occurred by chance and are not seen as clinically significant. There were no comparable differences between LANSO and PL in the S-T PL-controlled studies. In the L-T studies, total BIL demonstrated a significant mean change from BL but again, these changes were small and values were still WNLs. Small but significant changes from BL were seen in γ -GT and AP in analyses at 12 mo. of continuous LANSO therapy but not on analyses of time to the first recurrence. Changes occurring in patients ≥ 65 y of age were similar to those for the total population studied.

Among those patients with single values reaching the level requiring further clinical review, the LANSO group had significantly higher percentages for ALT (PT) than the RAN group in the S-T positive-controlled studies. But neither the PL-controlled S-T nor the maintenance Tx studies showed differences between LANSO and PL in this regard. Analyses by the number of patients with two or more hepatic chemistry values shifting from normal at BL to above normal at the final Tx visit showed that the proportion of patients demonstrating these changes was comparable among the Tx groups (LANSO=2.8%; PL=2.8%; and RAN=2.6%) in the S-T studies. There was no evidence of a dose-related effect for LANSO. The greater number of patients demonstrating these shifts [6/61] seen in the L-T studies in Z-ES/Hypersecretors, are not unexpected. These types of pts. are chronically ill, have pre-existing liver Dz and often have clinical abnormalities that may include gastrinoma-induced metastatic liver Dz.

Increases in hepatic chemistry values during LANSO Tx were seen on occasional pts. Statistically significant changes from BL or differences between Tx groups were noted upon analysis. The reviewer agrees with the sponsor that, the analyses, taken together, do not give consistent evidence to suggest a clinically significant Tx-related effect of LANSO on hepatic chemistry values. In addition, withdrawals from the maintenance trial of LANSO-Tx pts. due to hepatic chemistry elevations did not appear to be related to test medication.

F. Results of Gastric Bxs to Monitor EC-L Cell Hyperplasia and Carcinoid Tumors

1. Gastric Bxs in L-T Studies

Results from studies in patients with Barrett's epithelium, pts. with Z-ES and in gastric acid hypersecretors, were assessed in considerable detail in MOR of NDA 20-406 (September 19, 1994). The ISS update does not contain information that would alter conclusions from those evaluations.

2. Gastric Bxs in Maintenance Tx Studies

a. Bxs from the Body of the Stomach

- As summarized in Table 29, the mean Grimelius-positive cell density was statistically significantly higher in the LANSO as compared to the PL group at first recurrence of Dz.

TABLE 29
Updated ISS of NDA 20-406

Grimelius-Positive Cell Density of the Body of the Stomach
at First Recurrence of Dz in the Maintenance Tx
Studies^a in the TAP Safety Database

	PL (N=108)	LANSO (N=217)
Grimelius-Positive Cell Density (cells/mm ²)	126.78	161.30 ^b

a) M88-270, -271, M89-350

b) Statistically significant different from PL at p<0.001 level
of significance.

- Overall, Grimelius-positive cell density seemed to increase during continuous LANSO therapy. Statistically significant increases from LANSO therapy BL were seen at Months 2, 3 and 15 (Table 30). At the Month 15 visit, a mean increase of 20.21 cells/mm² was observed with 64 patients comprising the analysis. At Post-Tx Visit Months 1 and 3, Grimelius-positive cell densities were statistically significantly lower than LANSO therapy BL¹⁴.

TABLE 30
Updated ISS of NDA 20-460

Grimelius-Positive Cell Density of the Body of the Stomach
During Continuous LANSO Therapy in the Maintenance
Tx Studies^a in the TAP Safety Database

Visit (Month)	N	BL Mean Grimelius-Positive Cell Density (cells/mm ²)	Mean Change (cells/mm ²)
1	93	159.15	7.16
2	230	152.75	9.29 ^b
3	170	154.97	11.21 ^c
6	133	155.51	4.24
9	115	153.66	-7.13
12	115	154.86	-0.77
15	64	150.04	20.21 ^d
1 Post	179	157.34	-15.72 ^e
3 Post	73	156.03	-17.81 ^f

a) M88-270, -271, M89-350

b through f) Statistically significant at p<0.05

¹⁴These results were presented in sponsor's End-of-Text Table 252.

- There was no correlation between changes in Grimelius-positive cell density and fasting serum gastrin concentrations (sponsor's Fig. 9).
- Changes in the Modified Solcia classification
 - In the analysis from maintenance BL to the time of first recurrence of Dz, 206/210 (98%) of the LANSO-treated patients exhibited normal gastric endocrine cell growth (Modified Solcia Classification 1 or 2). Of the remaining 4 (2%) pts., histopathologic changes classified as hyperplasia were seen. Three (3) of these patients were classified as normal at maintenance BL and as simple hyperplasia at the end of the Tx period. The fourth patient was classified as MNH at the maintenance BL and did not change at the end of the Tx period.
 - No dysplasia or carcinoids were seen in any patient at any timepoint in the maintenance studies.
 - Only one patient had biopsy classified as linear or MNH at any time during maintenance study. This LANSO pt. had a Bx classified as MNH one month post-Tx; a Bx obtained 3 months post-Tx was classified as normal.¹⁵
 - Similar results were shown during continuous LANSO therapy. 320/325 (98%) of the patients exhibited normal gastric endocrine cell growth at the end of continuous therapy. Of the remaining 5 pts. (2%), histopathologic changes classified as simple hyperplasia were seen as a change from normal at the end of continuous LANSO therapy. No dysplasia was seen in any patient.¹⁶

Table 31 summarizes the percentage of patients with changes from maintenance BL to first recurrence of Dz and from LANSO therapy BL to final visit during continuous LANSO therapy for the Modified Solcia Classification in Bxs from the body of the stomach. For the analysis to first recurrence, 91% and 90% of the PL- and LANSO-treated patients, respectively, remained unchanged from their BL classification. Eight percent (8%, 16/210) of LANSO-treated patients experienced an increase from their BL classification, while only 4% (4/108) of PL-treated patients did so. [No statistically significant differences.]

For the analysis to the end of continuous LANSO therapy, 289-325 (89%) of the pts. remained unchanged from their BL classification at the final Tx visit. Seven percent (7%, 22/325) of these patients experienced an ↑ from their BL classification, while 4% (14/325) experienced a ↓. These changes were similar to those seen from maintenance BL to the time of first recurrence of Dz.

¹⁵These results were presented in sponsor's End-of-Text Table 253.

¹⁶These results were presented in sponsor's End-of-Text Table 254.

TABLE 31
Updated ISS of NDA 20-406

Changes in the Modified Solcia Classification in Bxs From
the Body of the Stomach for Maintenance Tx
Studies in the TAP Safety Database

Modified Solcia Classification

Tx Interval	↓ From BL	Unchanged from BL	↑ From BL	Between Groups p-value ^a
n (%)				
<u>To First Recurrence</u>				
PL (N=108)	6 (6)	98 (91)	4 (4)	0.055
LANSO (N=210)	5 (2)	189 (90)	16 (8)	
<u>To Final Visit of Continuous LANSO Therapy</u>				
LANSO (N=325)	14 (4)	289 (89)	22 (7)	

a) Based on Cochran-Mantel-Haenszel methodology for ordered categories.

- Bxs were also taken from the body of the stomach during the maintenance Tx studies and assessed for acute and chronic inflammation. For the period from maintenance BL to the time of first recurrence of Dz, similar percentages of patients exhibited ↑s and ↓s in levels of acute and chronic inflammation in the PL and LANSO groups.

For the assessment of acute inflammation, 23% and 18% of PL and LANSO patients, respectively, demonstrated a ↓. Thirteen percent (13%) and 9% of PL and LANSO patients, respectively, demonstrated an ↑. For the assessment of chronic inflammation, 17% and 10% of PL and LANSO patients, respectively, experienced a ↓. The same percentage (25%) of patients for each of the Tx groups demonstrated an ↑ in chronic inflammation.

- The above summarized differences between the PL and LANSO dosing groups were not statistically significant (Table 31).¹⁷
- For those patients receiving continuous LANSO therapy, 7% experienced a ↓ in their acute inflammation, 20% experienced an ↑, and 73% remained unchanged in their assessments of acute inflammation.
- For chronic inflammation, 6% experienced a ↓, 32% experienced an ↑ and 61% remained unchanged. These results are summarized in Table 32.¹⁸

¹⁷ These results were presented in sponsor's End-of-Text Table 255.

¹⁸ These results were presented in sponsor's End-of-Text Table 256.

TABLE 32
Updated ISS of NDA 20-406

Summary of Changes in Inflammation Grade for Bx's from the Body
of the Stomach in Maintenance Tx Studies in the
TAP Safety Database^a

	<u>Inflammation</u>			Between Groups p-value
	↓	Unchanged	↑	
----- n (%) -----				
Acute Inflammation				
<u>To First Recurrence of Dz</u>				
PL (N=118)	27 (23)	76 (64)	15 (13)	N.S.
LANSO (N=221)	39 (18)	163 (74)	19 (9)	
<u>To Final Visit of Continuous LANSO Therapy</u>				
LANSO (N=362)	25 (7)	265 (73)	72 (20)	
Chronic Inflammation				
<u>To First Recurrence of Dz</u>				
PL (N=118)	20 (17)	69 (58)	29 (25)	N.S.
LANSO (N=221)	23 (10)	143 (65)	55 (25)	
<u>To Final Visit of Continuous LANSO Therapy</u>				
LANSO (N=361)	22 (6)	222 (61)	117 (32)	

a) Studies M88-270, -271 and M89-350

b) Based on Cochran-Mantel methodology for ordered categories.

b. Bxs from the Antrum of the Stomach

- Summarized in Table 33 are the changes in G, EC, and D cell density for the antral Bxs available from studies M88-270 and -271. This comparison showed a statistically significant difference in G-cell density in the LANSO group when compared to PL at the time of first recurrence of Dz. There were no statistically significant differences between the LANSO and PL groups in EC- and D-cell densities at this time point.¹⁹

TABLE 33
Updated ISS of NDA 20-406

Mean G, EC and D Cell Densities in Antral Bxs at First Recurrence of Disease for Maintenance Tx Studies in the TAP Safety Database^a

	G-Cells (gastrin-positive cells)	EC Cells (serotonin-positive cells)	D-Cells (somatostatin-positive cells)
PL	616.08	44.97	114.25
LANSO	786.73 ^b	42.95	127.76

a) Studies M88-270 and -271.

b) Statistically significant difference from the PL group (p≤0.05).

- During continuous LANSO therapy, statistically significant mean ↓s from LANSO therapy BL were observed in EC- and D-cell densities at various timepoints. There was no significant change from BL for G-cell density at any timepoint during continuous LANSO therapy, but significant ↓s were seen at both post-Tx Months 1 and 3. The G-, EC- and D-cell densities of the antral mucosa biopsies during continuous LANSO therapy are summarized in Table 34.²⁰
- There was no correlation between changes in G-cell density and percent change in fasting serum gastrin concentrations (sponsor's Fig. 10).

¹⁹Data presented in sponsor's End-of-Text Table 257.

²⁰Data presented in sponsor's End-of-Text Table 258.

TABLE 34
Updated ISS of NDA 20-406
**Mean G, EC and D Cell Densities in Antral Bx for Maintenance
Tx Studies in the TAP Safety Database^a**

Visit (Month)	G-Cells (gastrin-positive cells)			EC-Cells (serotonin-positive cells)			D-Cells (somatostatin-positive cells)		
	N	BL Mean	Mean Change From BL	N	BL Mean	Mean Change From BL	N	BL Mean	Mean Change From BL
1	94	743.97	18.41	94	73.64	-18.98	93	140.61	-16.21
2	117	762.16	-3.51	117	60.08	-19.44 ^b	117	159.65	-27.67 ^b
3	98	772.04	4.46	98	64.72	-18.57 ^b	98	155.01	-23.85 ^b
6	79	771.52	38.95	79	69.67	-17.95	79	157.85	-7.57
9	80	800.68	-16.50	79	72.26	-35.79 ^b	80	166.25	-29.77 ^b
12	68	804.11	23.35	67	64.17	-12.65	68	159.51	-15.61
15	34	755.05	101.79	34	51.42	-3.41	34	162.66	-31.48
1 Post	117	753.09	-61.75 ^b	116	72.67	-22.38 ^b	115	154.04	-26.45 ^b
3 Post	54	735.24	-80.78 ^b	54	66.57	-27.09 ^b	54	151.64	-29.57

^a Studies M03-270, -271, M09-350
^b through 1) Statistically significant at p<0.05.

- In Studies M88-270 and -271, LANSO was statistically significantly more effective than PL in reducing acute inflammation in antral Bxs from maintenance BL to the time of first recurrence of disease.
 - 17% of LANSO patients experienced a ↓ in acute inflammation compared to 6% of the PL patients.
 - Reviewing ↑s in acute inflammation, 14% of LANSO patients experienced an ↑; 29% of PL patients did so.
 - 69% and 64% of LANSO and PL patients, respectively, remained unchanged throughout this Tx period.
- During continuous LANSO therapy, 25% of patients experienced a ↓ in acute inflammation while 6% of patients experienced an ↑.
 - 68% of the patients remained unchanged.
- Results were similar for the analysis of chronic inflammation in antral Bx specimens.
 - LANSO was statistically more effective than PL in reducing chronic inflammation from maintenance BL to the time of first occurrence of Dz.
 - 18% of LANSO and 15% of PL patients experienced a ↓ in chronic inflammation from maintenance BL at the time of first recurrence of Dz.
 - Reviewing the ↑s in chronic inflammation, 16% of LANSO patients experienced an ↑ in chronic inflammation compared to 36% of PL patients.
 - Also, 66% of LANSO patients remained unchanged while 49% of PL patients did so. These results are summarized in Table 35.²¹
 - During continuous LANSO therapy, 21% of patients experienced a ↓ in chronic inflammation, 15% of patients experienced an ↑, and 64% remained unchanged. The results are summarized in Table 35.²²

²¹These data were presented in sponsor's End-of-Text Table 259.

²²These data were presented in sponsor's End-of-Text Table 260.

TABLE 35
Updated ISS of NDA 20-406

Summary of Changes in Inflammation Grade in Antral Bxs
from Maintenance Tx Studies in the
TAP Safety Database^a

	Inflammation			Between Groups p-value ^b
	↓	Unchanged n (%)	↑	
Acute Inflammation				
<u>To First Recurrence of Disease</u> PL (N=78) LANSO (N=127)	5 (6) 21 (17)	50 (64) 88 (69)	23 (29) 18 (14)	0.002 ^c
<u>To Final Visit of Continuous LANSO Therapy</u> LANSO (N=190)	48 (25)	130 (68)	12 (6)	
Chronic Inflammation				
<u>To First Recurrence of Disease</u> PL (N=78) LANSO (N=127)	12 (15) 23 (18)	38 (49) 84 (66)	28 (36) 20 (16)	0.012 ^d
<u>To Final Visit of Continuous LANSO Therapy</u> LANSO (N=190)	40 (21)	122 (64)	28 (15)	

- a) Studies M88-270 and -271.
b) Based on Cochran-Mantel methodology for ordered categories.
c, d) Statistically significant at p≤0.05.

3. Electron Microscopic Analysis of Gastric Bxs

- Selected Bxs from the greater curvature of the body of the stomach (oxyntic mucosa) were evaluated using EM by Walter Rubin, M.D. and colleagues at the Medical College of Pennsylvania. Three subsets of patients were evaluated including RE and GU patients receiving S-T LANSO 60 mg therapy, ZES patients receiving titrated doses of L-T LANSO therapy (up to 180 mg per day) and patients receiving L-T LANSO 60 mg treatment for regression of Barrett's epithelium. For all subsets, endocrine cells were counted and evaluated morphologically. The complete report was included as sponsor's Appendix K. What follows is a summary and conclusions from that report.
- S-T therapy of RE or GU patients with LANSO 60 mg did not significantly change the density of the oxyntic endocrine cells.
 - After 8 weeks of Tx, however, the EM morphology of many ECL cells suggested that they had been stimulated to synthesize and secrete at an increased rate.
 - By 3 mo. post-Tx the ECL cells no longer appeared stimulated.

- Preliminary study of the oxyntic endocrine cells in patients with Barrett's epithelium suggested that ECL cells remained stimulated after 18 mo. of continuous LANSO therapy.
 - The EM appearance of the granules in stimulated ECL cells was also altered, indicating that granule morphology of oxyntic endocrine cells is also dependent on the metabolic or physiologic state of the cells.
- ECL cells in patients with ZES appeared more "stimulated" than for patients in S-T or Barrett's epithelium L-T studies.
- The stimulated ECL cells from the S-T and L-T LANSO-Tx patients resembled the ECL cells observed in ZES patients.

G. Changes in Fasting Serum Gastrin Concentrations (FSGCs)

1. L-T Studies (Table 36)

- For all timepoints in the L-T Barrett's epithelium studies, the changes in FSGC were statistically significant and ranged from a median † of 33% to 125%. No suggestion of continued increase over time was noted.
- Changes in the L-T ZES patients or hypersecretors were more erratic, due to greater variability given the very high values arising from the Dz.
- As seen in FSGC in patients in the L-T Barrett's epithelium studies treated with LANSO for up to 48 mo. were similar to the †s seen in patients who received S-T Tx. Median percent change from BL in these LANSO-Tx patients varied from 33% to 125% at timepoints up to 48 mo. and these †s plateaued after one month of therapy.

2. Maintenance Tx Studies

- LANSO Tx was associated with significantly higher FSGC than PL at the time of first recurrence of Dz (or withdrawal or completion of Tx if no recurrence).
 - The median FSGCs in patients Tx with LANSO remained within normal range (0 to 100 pg/mL) but were statistically significantly greater than those of PL patients (median values: 83.0 pg/mL and 50.0 pg/mL, respectively).²³
- 88 patients in the PL group had at least two, 4 or 8-week, open-label LANSO Tx periods (interrupted with further PL Tx) and had FSGC obtained at the end of the First and Second Open-Label Tx Periods.
 - No significant difference for FSGC (medians of 91 pg/mL and 88 pg/mL at the End of the First and Second Open-Label Tx Periods, respectively) was observed between the two evaluation time points. Thus, repeated 4 to 8-week Tx periods separated by PL Tx did not appear to result in † gastrin levels.²⁴
- Percent changes in FSGC from LANSO therapy BL to visits during continuous LANSO therapy were analyzed (Table 37).

²³These results were presented in sponsor's End-of-Text Table 224.

²⁴These results were presented in sponsor's End-of-Text Table 225.

- The median percent $\uparrow$ s in FSGC from LANSO therapy BL ranged from 49% to 65% during the 15 mos. of LANSO Tx and were significantly increased at all time points.

TABLE 36
Updated ISS of NDA 20-406

Median Percent Change from Baseline in FSGC from L-T
Studies in the TAP Safety Database

Visit (Month)	Patients with Barrett's Epithelium ^a	ZES Patients ^b	Hypersecretors ^c
----- n (%)-----			
1	<u>ISS Update</u> 26 (+102)*	<u>ISS Update</u> N/A	<u>ISS Update</u> N/A
3	N/A	39 (+3)*	9 (60)*
6	27 (+33)*	40 (+5)	8 (+71)*
12	26 (+125)*	38 (+21)*	4 (+33)
18	19 (+79)*	29 (+9)	5 (-13)
24	21 (+44)*	29 (+19)*	3 (+103)
30	21 (+92)*	23 (+23)*	3 (+23)
36	16 (+71)*	11 (-4)	2 (+30)
42	14 (+109)*	6 (+360)	N/A
48	6 (+5)	6 (+92)	N/A

NOTE: Gastrin normal range 0 to 100 pg/L
a) Studies M88-249, M89-375
b) Studies M88-139, M89-405 and M90-436
c) Study M89-405

* Statistically significant ($p < 0.05$) $\uparrow$ from BL, based on Wilcoxon signed rank test for no percent change from BL.

- However, median FSGC remained WNR (0-100 pg/mL) at all time points.
- The median percent change in FSGC did not continue to increase throughout LANSO therapy, but instead reached a plateau after 2 mo. of LANSO therapy.
- By one month post-Tx, median FSGC returned to LANSO therapy BL concentrations.²⁵

²⁵ These results were presented in sponsor's End-of-Text Table 226.

TABLE 37
Updated ISS of NDA 20-406

Median and Percentile Values for FSGC During Continuous
LANSO Therapy in the Maintenance Tx Studies
in the TAP Safety Database^a

Visit ^b (Month)	n	BL	Visit	Percent Change from BL
-----Median (25%, 75% Percentiles)-----				
1	337	51 (41, 67)	79 (56, 123)	53 (14, 112)*
2	421	49 (41, 67)	83 (58, 123)	62 (15, 121)*
3	303	49 (40, 65)	81 (56, 124)	49 (12, 125)*
6	276	50 (40, 65)	86 (55, 134)	63 (20, 146)*
9	243	49 (39, 65)	83 (55, 141)	59 (16, 141)*
12	230	50 (40, 65)	86 (55, 123)	62 (15, 124)*
15	128	49 (39, 61)	81 (59, 114)	65 (24, 148)*
1 Post-Tx	375	49 (40, 65)	51 (41, 67)	0 (-19, 27)
3 Post-Tx	172	50 (40, 67)	50 (40, 70)	0 (-19, 30)

NOTE: Gastrin normal range 0 to 100 pg/mL.

a) Studies: M88-270, -271, M89-350.

b) Months of continuous LANSO therapy.

* Statistically significant ($p \leq 0.05$) from BL, based upon Wilcoxon signed rank sum test for no percent change from BL.

- The distribution of pts in FSGC during the maintenance Tx studies was similar to those observed during the S-T PL-controlled studies. At the time of first recurrence, withdrawal or completion of maintenance Tx if no recurrence, 95% of PL patients had FSGC <100 pg/mL and the remaining 5% had levels between 101-200, inclusive. The % distribution of pts. as a function of FSGC is given in Table 38.

TABLE 38
Updated ISS of NDA 20-406

FSGC for PL and LANSO Pts. at First Recurrence of Dz
in the Maintenance Tx Studies in the
TAP Safety Database

Visit	Number of Patients n (%)			
	-----Gastrin-----			
	≤100	101-200	201-400	>400
At First Recurrence				
PL	174 (95)	9 (5)	0	0
LANSO	191 (62)	82 (27)	31 (10)	5 (2)

NOTE: Gastrin normal range 0 to 100 pg/mL.

- Median gastrin levels obtained during continuous LANSO therapy (up to 15 months) were presented in sponsor's Table 124 and Fig. 5.
 - At BL, 92% of the LANSO-Tx patients had FSGC $\leq$ 100 pg/mL, 8% had levels between 101-200 pg/mL, inclusive, 1% had levels between 201-400 pg/mL, inclusive, and, none of the patients had levels greater than 400 pg/mL.
 - After one month of therapy the percentage of patients with FSGC $\leq$ 100 pg/mL $\downarrow$ to 64%; those with gastrin levels between 101-200 pg/mL, inclusive, $\uparrow$ to 26%; those with gastrin levels between 201-400 pg/mL, inclusive, $\uparrow$ to 9%; and those with gastrin levels $\geq$ 400 $\uparrow$ to 1%.
 - The percentages of patients with FSGC $>$ 200 pg/mL reached a plateau after one month of therapy.
 - After 12 months of continuous LANSO therapy, 1% of the patients experienced FSGC $>$ 400 pg/mL.
 - After one and three months post-Tx, the percentages reflected those observed at BL.²⁶

VI. REVIEWER'S OVERALL SUMMARY AND CONCLUSIONS ON L-T SAFETY OF LANSO

This Review deals with information provided by the sponsor as part of an Update of Integrated Summary of Safety for LANSO. One of the indications sought by the sponsor is Because this would require L-T administration (years) of this drug, during the review of the evidence, emphasis is put on safety matters of potential relevance to the long-term safety of this compound. Included are assessments on gastrointestinal tumors, especially nodules and polyps, gastric atrophy, intestinal metaplasia and hyperplasia of the gastric mucosa, visual disturbances, effects on laboratory parameters with emphasis on LFTs.

Because animal toxicology studies with LANSO demonstrate tumors (in multiple organs) one of the reviewer's concerns is the reporting of gastrointestinal nodules and polyps (and other tumors) in patients given LANSO. These lesions have been described in Z-ES/hypersecretor as well as RE patients that were maintained after having healed with a S-T course of antisecretory agents (RAN, LANSO). A complete characterization of these lesions (nodules/polyps) is not possible at the present time due to the incomplete information provided. The reviewer comments are in many cases descriptive and in the form of questions that need to be asked of the sponsor in order to fill the many gaps of information needed about the incidence, anatomical location, size, shape, histological nature, evolution, related morbidity and general evolution of these lesions.

The nodules and polyps (N/P) described here are definite morphological lesions that should be clearly differentiated from incidental findings such as granulomas or other tumors. The latter, examples of which were also found in these patients, are sought to be unrelated to antisecretory therapy. One initial point to be made is that the N/P were seen not only in Z-ES/H patients but also in RE HTN patients. In the latter patients, the N/P were located in

²⁶Gastrin values for all patients who experienced 1s of FSGC above 400 pg/mL at any timepoint during the maintenance Tx studies were presented in sponsor's End-of-Text Table 231.

the antrum, fundus or both, they occurred in patients in whom the gastric mucosa was normal at screen endoscopy and persisted in those patients with lesions already demonstrable before the start of the therapy. In some (but not all) patients these N/Ps were accompanied by acute chronic gastritis in association with *H. pylori*. An initial difficulty in the characterization of these N/Ps is that many were not biopsied so that it is not possible to establish their true histopathological nature (for example, non-adenomatous versus adenomatous lesions). Nonetheless, 4 pts. were described as having fundic gland polyps, 3 had hyperplastic polyps, 1 had foveolar hyperplasia, 4 had findings consistent with reflux ("chemical") gastritis. It is not known what is meant by the latter, but whatever the description, the N/Ps described in these RE MTN patients appear very high in incidence. The question is in comparison to what.

It is admittedly difficult to choose an adequate comparator group. In the literature, fundic gastric polyps were diagnosed in 44 of 5554 patients (prevalence of 0.8%), followed up for 24 months, in whom the most frequent complaints were symptoms of gastroesophageal reflux disease and abdominal pain [M.A. Marcial et al., *Amer. J. Gastroenterol.* 88:1711-1713 (1993)]. Previous to this publication, documented prevalence of fundic gland polyps among endoscoped patients had been even lower: 9/15,000 [P. Sipponen et al., *Histopathology* 7:729-737 (1983)] and 23/27,000 gastroscopies [M. Iida, *Gastroenterology*, 86:1437-1442 (1984)] for prevalence rates of 0.06% and 0.085%, respectively. The higher incidence is explained, in part, as due to familiarity with the endoscopic appearance of fundic gland polyps because one of the last group of authors cited noted that in latter years, they were able to identify these lesions in 43 out of ca. 3,000 gastroscoped patients, a prevalence rate of 1.40% [K. Haruma et al., *J. Clin. Gastroenterol.* 13:565-569 (1991)]. The possibility exists that the very high incidence of N/Ps reported in the present MTN of RE trials is somehow associated to the use of antisecretory therapy (OME>RAN). This issue should remain open until more information is available.

Another issue that should remain open is the potential for these N/Ps to become malignant. Several lines of evidence indicate that there is potential for some of these lesions to become pre- or even malignant. But the magnitude of this problem cannot be assessed because of the lack of biopsy data and sufficient follow-up of these LANSO-treated patients. In one pt. (Richter) (LANSO 30 mg x 154 days) the chronic active gastritis, which was present at screen, was accompanied by mild focal metaplasia but devoid of atypia. Another (Campbell) (LANSO 30 mg x 137 days) had a signet-ring tumor. One of the z-es patients being treated by Feldman in Study M90-436 had a nodule in the gastric fundus revealing a pre-malignant lesion. This consisted of chronic active atrophic gastritis with intestinal metaplasia and the presence of *H.pylori* (more on this below).

In reality, whether these lesions (N/Ps) have the potential to become malignant is debatable. In a 1990 publication, Orłowska and Pietrow state that gastric polyps are uncommon [*Amer. J. Gastroenterol.* 85:1629-1634]. They mention that, according to the WHO classification [K. Oota et al., In: *International Classification of Tumors*, No. 18, Geneva WHO (1977)], benign gastric epithelial polyps come under two major categories: adenomas and hyperplastic. Adenomas are composed of dysplastic epithelium not normally present in the stomach. It is believed that gastric adenomas, like their counterparts in the colon, are pre-malignant lesions [Orłowska and Pietrow (1990) (locus cited)]. The percentage of focal carcinoma in gastric adenomas has been reported to range between 1.4% and 75%, with an average of 41% [Orłowska and Pietrow (1990) (locus cited)]. Hyperplastic polyps (like the three plus the one case of foveolar hyperplasia reported in the MTN RE trials) are formed from overgrown normal gastric foveolar and glandular elements. Unlike adenomas, gastric hyperplastic polyps are considered to be fairly

harmless [Orlowska and Pietrow (1990) (locus cited)] but, in large series of observations, the rate of their liability to malignant changes has varied from 0.3% to 0.5% with an average of 2.1% [Orlowska and Pietrow (1990) (locus cited)]. In summary then, the possibility exists for at least some of these N/Ps to become malignant and this dictates that all lesions of this type found on endoscopy should be biopsed.

Incidentally, the many times quoted article here by Orlowska and Pietrow describes a case of a 61-y-old woman with multiple gastric cancers. Two of the cancers were found in the hyperplastic polyps (and one in the adenoma). This case also had three other hyperplastic polyps with no signs of malignancy (and four separate polypoid or flat gastric carcinomas).

Whether the polyp should be removed through endoscopic polypectomy or the patient should undergo a surgical intervention depends upon the individual clinical situation. What should be reiterated is that follow-up endoscopy (yearly) with Bx is needed to r/o malignancy. But the sponsor has presented insufficient Bx data. Even if these lesions are proven to be of non-malignant nature, they are adding significant morbidity to the patient. Several investigators have suggested that a stomach with polyp might be more vulnerable to carcinogenic stimulation than a polyp-free one [K. Elster, In: Morson B.C., ed. Pathology of the Gastrointestinal Tract: Curr. Top. Pathol. 63:77-93 (1976); F. Laxen et al., Acta Pathol. Microbiol. Immunol. Scand. [A]:90:221-228 (1982); F. Laxen, Scand. J. Gastroenterol. 19:535-540 (1984); R. Botticher et al., Dtsch. Med. Wochenschr. 100:167-170 (1975); and E. Seifert and K. Elster, 1977, cited by Orlowska and Pietrow, Ref. 26]. The percentage of co-existence of benign polyps with carcinoma elsewhere in the stomach is between 4% and 60%, with an average of 18.4% [Ref. 5, 7, 13, 16, 26-30 in the Orlowska and Pietrow article]. Laxen et al. [(1984) (locus cited)] strongly emphasized that, despite a rather low proportion, the risk of cancer in patients with benign polyps was seven times greater than expected in the population at large.²⁷

Another important differentiation is that the N/Ps described here are different from other lesions described in Z-ES/hypersecretory patients. Maton et al. [Gastroenterology 97:827-836 (1989)] noted that before starting therapy with OME, the majority of Z-ES/hypersecretors in their studies - who were already taking histamine H₂-receptor antagonists had evidence of gastric rugal hyperplasia and Brunner's gland hyperplasia of the duodenum. In this series, 17 patients did have endoscopic evidence of mucosal abnormalities ["7 had esophagitis (3 with stricture formation), 3 had mild gastritis, 5 had mild duodenitis, and 3 who had undergone Billroth II gastrectomies had inflammation or ulceration at the jejunostomy site"]. But in no patient did gastric polyps develop during OME therapy, although particular care was taken to examine the body and fundus of the stomach for such findings.

The above information on OME, brings up one of the very important observations in need of an explanation in the Z-ES/Hypersecretor trials with LANSO. The NIH trial (same institution that carried out the OME study) reported an extremely high number of patients (most without lesions at BL) with duodenal nodules, gastric nodules, pyloric nodules, antral nodules, even esophageal and laryngeal nodules. Most of these patients were being treated with LANSO L-T

²⁷ Recent data should be compared to data published in the 1950s showing that the development of cancer in the stomach with benign polyps was not the rule, even after very long follow-up period (up to 23 years) [A. Plachta and F.D. Speer, Amer. J. Gastroenterol. 28:160-175 (1957); J.B. Carey and L.J. Hay, Gastroenterology, 14:280-291 (1950)].

(years). But again, because Bx was not done in many cases, the histologic nature (benign/malignant adenomatous, hyperplastic, etc.) of these lesions was not fully characterized.

During the above assessment, the reviewer has been careful not to ascribe these N/P and other anomalies (lesions) to LANSO. This is because some of these lesions were already present at screen, and they may represent a manifestation of the underlying hypersecretory condition. Besides, in the MTN studies, these lesions were seen in pts. being treated with RAN or even PL. But it is important to define "BL" or "screen". Although this refers to the beginning of Tx with a test medication (i.e. LANSO) the pt. may have been treated already with the same compound, H₂ or even another PPI (OME). This is why the historical treatment for these Z-ES/Hypersecretory and RE MTN pts. becomes very important. The gastric mucosa may already be altered (predisposed to develop N/Ps, etc.) before the initiation of L-T or MTN therapy with LANSO.

The sponsor has presented little information on atrophic gastritis and intestinal metaplasia. These areas need to be further expanded if one is to consider the MTN RE indication. The story that seems to be evolving is that atrophic gastritis and intestinal metaplasia (and EC-L cell hyperplasia for that matter) should be evaluated in conjunction with *H. Pylori* [T.J. Borody et al., Amer. J. Gastroenterol. 88:1266-1268 (1993)]. Indeed, this may also be true for N/Ps and other anomalies (see Table 20). The introduction of *H. Pylori* as a factor in these evaluations offers both opportunities and constraints. It is relatively easy to eradicate this bacteria (ex: triple therapy for 3 to 4 weeks). However, in the present series, not all patients developing N/Ps, etc. were shown to be infected with *H. Pylori*. An important constraint is that *H. Pylori* may be difficult to detect in individuals with atrophic gastritis [W.E. Karens, Jr. Gastroenterology 101:167-174 (1991)] even though such patients may continue to have high *H. Pylori* antibody levels. Bacteria may still be present, but perhaps due to low colonization rates or localization in "sanctuary" sites, the organisms may not be detectable by routine endoscopic detection tests. However, this is important because in view of the known progression of mucosal changes, such patients could be considered to be at risk of developing gastric carcinoma. An important opportunity is that, if *H. pylori* is - indeed - a slow, antecedent "carcinogenic infection," then, potentially, a proportion of gastric cancers could be prevented by early detection and eradication of the *H. pylori* infection.

An example of this potentially important opportunity has been given in the literature. In the above mentioned publication, Borody et al. [(1993)] presented the case of a patient with marked visible gastric mucosal changes, early histological mucosal atrophy, and gastric mucosa already negative by the urease test, histology, and culture for *H. pylori*, but whose serum antibodies remained positive, suggesting the ongoing presence of *H. pylori*. After eradication treatment for *H. pylori*, antibody levels decreased significantly, and the appearance and morphology of gastric mucosa returned to normal.

It is important to acknowledge that, even though EC-L cell hyperplasia may develop upon S-T and L-T administration of LANSO, no cases of adenomatoid hyperplasia, dysplasia, atypia or carcinoids, that could be attributed to this compound, have been reported.

The concern of permanent visual disturbances among some patients treated with oral PPIs long-term is real. Further assessment is needed. There are presently no data to determine if patients being treated with LANSO for prolonged periods of time (years) in MTN or Z-ES/Hypersecretor studies develop visual disturbances. These studies should include not only patients with pre-

existing visual abnormalities but also patients with normal eye function before LANSO treatment.

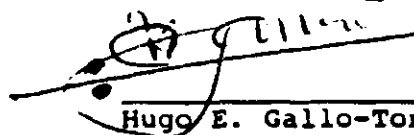
Statistically significant differences (from BL) has been reported for some hematological parameters (Hb, Hct, basophils) and LFTs in MTN RE studies with LANSO. But these changes were minor, did not worsen with time (or higher dose) and cannot be considered clinically relevant. Nonetheless, if LANSO is approved, these findings should be included in the labeling.

Some predictable changes in fasting serum gastrin concentrations were reported in patients treated with LANSO in both MTN RE and Z-ES/Hypersecretor trials. But, in this reviewer's opinion, these data are not very useful. More informative is the AUC of post prandial gastrin during 24-hour observations. This is why the reviewer described these gastrin data but had no special consideration in regards to their significance.

In conclusion, the available data suggests that LANSO is safe and well tolerated if one considers routine safety parameters. There are, however, insufficient data to assess the effect of this compound on special safety parameters related to the L-T administration of this PPI. There are no data to evaluate long-term effects on visual function and too little information on chronic atrophic gastritis and/or intestinal metaplasia. The presence of nodules, polyps and other anomalies in the absence of Bx data is of concern. The reviewer reiterates his recommendation of not to approve LANSO for the

In addition to the safety concerns discussed in this review there is the important question of what is being maintained. From the review of the evidence, the answer to this question appears to be: mild to moderate lesions of RE. This type of lesions do not appear to justify the use of potent antisecretory drugs such as LANSO.

December 29, 1994


Hugo E. Gallo-Torres, M.D., Ph.D.

cc:
NDA 20-406
HFD-180
HFD-180/SFredd
HFD-180/HGallo-Torres
HFD-181/CSO
HFD-180/JChoudary
HFD-180/JGibbs
r/d 11/18/94 jgw
f/t 12/1/94 jgw
MED\N\20406410.1HG

Memos

Corres

NDA 20-406

Wargel
APR 19 1995

TAP Holdings Inc.
Attention: Judy Decker Wargel
Bannockburn Lake Office Plaza
2355 Waukegan Road
Deerfield, IL 60015

Dear Ms. Wargel:

We acknowledge receipt of your correspondence notifying the Food and Drug Administration that TAP Pharmaceuticals Inc. is changing its corporate name. This change affects the following new drug application:

Name of Drug: Prevacid (lansoprazole) Delayed-Release Capsules

NDA Number: 20-406

Date of Submission: April 13, 1995

Date of Receipt: April 14, 1995

New Corporate Name: TAP Holdings Inc.

Previous Corporate Name: TAP Pharmaceuticals Inc.

We note that TAP Pharmaceuticals Inc. will be the distributor of the drug.

Sincerely yours,

Maria R. Walsh
Consumer Safety Officer
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

NDA 20-406
Page 2

CC:

Orig NDA

HFD-180

~~HFD-80~~

HFD-180/CSO/M. Walsh

HFD-180/H. Gallo-Torres

J. Gibbs

J. Choudary

MRW/4/18/95

MRW 4/18/95

CHANGE OF OWNER

NDA 20-406

MAR 31 1994

TAP Pharmaceutical Inc.
Attention: Ms. Judy Decker Wargel
Bannockburn Lake Office Plaza
2355 Waukegan Road
Deerfield, Illinois 60015

Dear Ms. Wargel:

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Prevacid (lansoprazole) Capsules.

We also refer to the following: 1) our letter of January 7, 1994 informing you of our filing concerns regarding the gastric ulcer (GU) indication at the proposed dose of 15 mg; 2) the informal conference held on March 10, 1994 between representatives of your firm and this Agency to discuss our refusal to file the GU indication; and 3) your submission of March 25, 1994, in which you identified two pivotal studies in the NDA to support the safety and efficacy of Prevacid for the treatment of GU at the newly proposed dose of 30 mg together with your request that we review the GU indication as amended therein.

We have reviewed your March 25, 1994 submission and conclude that we will review the GU indication as amended with draft labeling.

In addition, you requested a copy of our summary of the informal conference which follows.

MEMORANDUM OF MEETING

March 10, 1994

Application Number: NDA 20-406

Drug: Prevacid (lansoprazole) Capsules

Attendees:

TAP Pharmaceuticals Inc.

Dr. James Freston, University of Connecticut
Ms. Jennifer Ackerman, Operations Manager
Dr. Pamela Rose, Assistant Director of Clinical Research
Dr. John Seely, Vice President
Dr. Dennis Jennings, Statistician, Abbott Lab

FDA

Dr. Steven Fredd, Director, HFD-180

Dr. Hugo Gallo-Torres, Medical Officer, HFD-180
Ms. Maria Walsh, CSO, HFD-180
Dr. Mohammed Huque, Supervisory Statistician, HFD-713
Dr. Ferrin Harrison, Statistician, HFD-713

Background

TAP Pharmaceuticals submitted NDA 20-406 for Prevacid (lansoprazole) Capsules, a proton-pump inhibitor, on November 12, 1993 for the following indications: 1) Reflux esophagitis, 2) 3) Duodenal ulcer, 4) and 5) Pathological hypersecretory conditions including Zollinger-Ellison syndrome.

The indication was not filed under 21 CFR 314.101 (d) on January 7, 1994 because the application did not contain the necessary adequate and well-controlled studies to support the safety and efficacy of Prevacid for the at the proposed 15 mg dose. Specifically, the second pivotal study (P91-066) for this indication did not include a treatment arm using the recommended dose of 15 mg.

The sponsor requested an informal conference to discuss the refusal to file the indication.

Purged Pages

3-4

NDA 20-406
Page 6

If you have any questions concerning this NDA, please contact:

Maria R. Walsh
Consumer Safety Officer
(301) 443-0487

Sincerely yours,

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Orig NDA
HFD-180
HFD-180/H.Gallo-Torres
 J.Gibbs
 J.Choudary
HFD-181/M.Walsh
R/D init: S.Fredd 3/29/94
MRW/3/31/94/C:\wp51\cso\n\20406403.3MW

ACKNOWLEDGEMENT/ADVICE

END

MD

J.H.M. RESEARCH & DEVELOPMENT, INC. 5776 SECOND STREET, N.E. WASH. DC 20011

Fon si

ENVIRONMENTAL ASSESSMENT
AND
FINDING OF NO SIGNIFICANT IMPACT
FOR

Prevacid
(lansoprazole)
15/30 mg capsule

NDA 20-406

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-406

**Prevacid
(lansoprazole)**

15/30 mg capsule

The Food and Drug Administration (FDA) recognizes the National Environmental Policy Act of 1969 (NEPA) as the national charter for protection, restoration, and enhancement of the environment. NEPA establishes policy, sets goals (section 101), and provides procedures (section 102) for carrying out the policy.

Environmental information is to be available to the public and the decisionmaker before decisions are made about actions that may significantly affect the quality of the human environment; FDA actions are to be supported by accurate scientific analyses; and environmental documents are to concentrate on timely and significant issues, not to amass needless detail.

The Food and Drug Administration Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Prevacid, Tap Pharmaceuticals has conducted a number of environmental studies and prepared an environmental assessment (21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Prevacid (lansoprazole) is indicated for reflux esophagitis--maintenance-healing/duodenal-

ulcer/gastric ulcer, pathological hypersecretory conditions including Zollinger-Ellison syndrome. The drug acts by selective and irreversible inhibition of parietal cell membrane enzyme (H^+ , K^+ -ATPase).

The drug is manufactured in Japan. Letters from the appropriate officials were obtained to supplement environmental concerns at point source of manufacture (attached). Certification of compliance of Abbott Laboratories was provided (attached). The substance that is the subject of this environmental assessment is lansoprazole. Lansoprazole is listed as RTECS number DD9487500. Proprietary manufacturing/synthesis information was also provided.

The physicochemical data for lansoprazole are presented in appendix A. The data show the drug substance is highly water soluble, will be released as a neutral compound, is photolabile, is highly adsorbed, and undergoes rearrangement in solution.

The environmental effects data presented in appendix A show the drug substance showed no observed inhibition to environmental microorganisms, no apparent effects to Daphnia, and no apparent effect to fresh water fish.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

February 3, 1995 Phillip G. Vincent
DATE Approved
Phillip G. Vincent, Ph. D.
Environmental Assessment Officer
Center for Drug Evaluation and Research

2/6/95 Robert A. Jerussi and 2/8/95
DATE Concurred
Robert Jerussi, Ph.D.
Associate Director for Chemistry
CDER

Attachment: ENVIRONMENTAL ASSESSMENT

Bio

20-406

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH



DATE: April 5, 1995
FROM: Hae-Ryun Choi, Ph.D., Reviewer
Division of Biopharmaceutics, HFD-427
TO: Stephen B. Fredd, M.D., Director
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
THROUGH: Mei-Ling Chen, Ph.D., Branch Chief *[Signature]* 4/5/95
Division of Biopharmaceutics, HFD-427
SUBJECT: Labeling for patients with hepatic dysfunction for lansoprazole and omeprazole

This memorandum is in response to the request of HFD-180 on the labeling issue for patients with hepatic dysfunction for lansoprazole and omeprazole. TAP Pharmaceuticals, Inc., the sponsor of NDA 20-406 for lansoprazole, has requested that the labeling regarding dosage recommendation in patients with hepatic impairment be the same for lansoprazole as it is for omeprazole.

In the Pharmacokinetics and Metabolism Section for omeprazole, the label states that "In patients with chronic hepatic disease.....the plasma half-life of the drug increased to nearly 3 hours compared to the half-life in normals of 0.5-1 hour. Plasma clearance averaged 70 mL/min, compared to a value of 500-600 mL/min in normal subjects". However, the approved label for omeprazole in the Dosage and Administration Section reads "No dosage adjustment is necessary for patients with renal impairment, hepatic dysfunction or for the elderly".

As for lansoprazole, the half-life of the drug was prolonged from 1.5 to 3.2-7.2 hours and the AUC increased up to 500% at steady-state in patients with various degrees of chronic hepatic disease as compared to normal subjects. Because of these findings, the Agency has requested that the statement of "Dose reduction in patients with severe hepatic disease should be considered" be added to the proposed label for lansoprazole.

The pharmacokinetics of lansoprazole and omeprazole in patients with hepatic impairment are summarized in Tables 1 through 6 (Attached). These data indicated that the increase in omeprazole AUC values due to hepatic impairment is greater than that for lansoprazole. In addition, in the Medical Officer Review (MOR) of NDA 19-810 for omeprazole (March 10, 1989; Page 52), Dr. Gallo-Torres had suggested that an adjustment of the omeprazole dose in patients with liver dysfunction should be considered.

On the basis of all of the above, we recommend that the omeprazole labeling be revised to reflect the necessity of dosage reduction in patients with severe hepatic disease.

Hae-Ryun Choi 04/05/95

Hae-Ryun Choi, Ph.D.
Division of Biopharmaceutics

cc: NDA 20-406, HFD-180, HFD-180 (H.Gallo-Torres), HFD-427 (M.Chen, Choi), HFD-426 (Fleischer), HFD-420 (Chron, Drug, Reviewer), HFD-340 (Viswanathan)

Table 1. AUC Ratios of Healthy Subjects versus Subjects with Hepatic Impairment for Lansoprazole and Omeprazole.

Drug Study	Child-Pugh Class A	Child-Pugh Class B	Subacute Hepatitis	Compensated Cirrhosis	Decompensated Cirrhosis	Cirrhotic
Lansoprazole						
Study M90-450 ¹	2.55	3.41				
Study 7000 ²			2.57	5.65	4.58	
Study 26000 ³						5.27
Omeprazole						
M. Rinetti ⁴						8.39
T. Andersson ⁵	7.06	7.77				

Table 2. Lansoprazole Pharmacokinetic Parameters on Days 1 and 7 in subjects with Impaired Hepatic Function (Study M90-450)¹

Parameter	Day	Healthy Subjects		Child-Pugh Class A		Child-Pugh Class B	
		Mean	(SD)	Mean	(SD)	Mean	(SD)
C _{max} (ng/mL)	1	848	(224)	1178	(450)	907	(338)
	7	933	(424)	1272	(162)	1075	(371)
T _{max} (h)	1	1.6	(0.7)	1.8	(1.5)	2.5	(1.2)
	7	1.6	(0.6)	1.5	(0.6)	2.1	(1.3)
t _{1/2} (h)	1	1.4	(0.4)	3.8	(3.4)	4.7	(2.4)*
	7	1.5	(0.4)	3.9	(3.6)	5.2	(2.9)*
AUC (ng·h/mL)	1	2645	(1007)	5457	(3005)	7096	(3955)*
	7	2931	(1548)	7462	(6287)	9983	(7225)

Mean (SD)

*Statistically Significant difference as compared to Healthy Subjects

Table 3. Lansoprazole Pharmacokinetic Parameters in subjects with Impaired Hepatic Function (Study 7000) ²

Parameter	Healthy Subjects		Subacute Hepatitis		Compensated Cirrhosis		Decompensated Cirrhosis	
	Mean	(SD)	Mean	(SD)	Mean	(SD)*	Mean	(SD)*
C _{max} (ng/mL)	796	(412)	1080	(658)	1438	(280)*	1140	(385)
T _{max} (h)	1.5	(0.4)	1.4	(0.6)	2.1	(0.5)	2.1	(0.6)
t _{1/2} (h)	1.19	(0.29)	3.2	(2.07)	6.1	(1.51)*	7.2	(2.50)*
AUC (ng•h/mL)	2020	(1436)	5191	(5134)	11404	(3061)*	9251	(4375)*

Mean (SD)

*Statistically Significant difference as compared to Healthy Subjects

Table 4. Pharmacokinetics of Lansoprazole in Cirrhotic Patients (Study 26000) ³

Parameter	Healthy Subjects		Cirrhotic			
	Mean	(SD)	Day 1		Day 9	
C _{max} (µg/mL)	1033	(408)	1115	(334)	1377	(128)*
T _{max} (h)	1.5	(0.5)	2.3	(1.1)	1.6	(0.6)
t _{1/2} (h)	1.4	(0.8)	6.4	(1.4)	6.3	(1.6)
AUC (µg•h/mL)	2668	(1734)	9207	(3303)	14077	(5095)*

Mean (SD)

*Statistically Significant difference as compared to Healthy Subjects

Table 5. Pharmacokinetics of Omeprazole in Cirrhotic Patients (Publication by M.R. Inetti) ⁴

Parameter	Healthy Subjects		Cirrhotic	
	Mean	(SD)	Mean	(SD)
C _{max} (µg/mL)	0.29	(0.09)	0.74	(0.14)*
T _{max} (h)	1.10	(0.58)	2.12	(0.83)
t _{1/2} (h)	0.73	(0.04)	2.85	(1.68)*
AUC (µg•h/mL)	0.49	(0.22)	4.11	(1.86)†

Mean (SD)

*Statistically Significant difference as compared to Healthy Subjects

† Authors did not provide results of statistical analysis.

Table 6. Pharmacokinetics of Omeprazole in Cirrhotic Patients (Publication by T. Anderson) ⁵

Parameter	Healthy Subjects		Child-Pugh Class A [†]		Child-Pugh Class B [†]	
	C_{max} ($\mu\text{mol/L}$)	3.28	(0.51)	9.43	(2.58)	8.14
T_{max} (h)	0.25	(0.02)	0.24	(0.10)	0.28	(0.10)
$t_{1/2}$ (h)	0.72	(0.17)	2.91	(0.66)	2.99	(0.66)
AUC ($\mu\text{mol/L}$)	4.0	(1.7)	28.23	(6.85)	31.08	(6.96)

Mean (SD)

[†] Authors did not provide results of statistical analysis.

Chem. Rvs

APR 25 1995

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA: # 20-406 CHEM REVIEW # 3 REVIEW DATE: April 10, 1995

SUBMISSION TYPE	DOCUMENT			DATES		NUM	LETTER	ST
	DOCUMENT	CDER	ASSIGNED	REVIEW	REVIEW			
ORIGINAL	12-Nov-93	15-Nov-93	26-Nov-93					
AZ	18-Feb-94	22-Feb-94	01-Mar-94					
BC	14-Mar-94	15-Mar-94	22-Mar-94					
AZ	29-Mar-94	30-Mar-94	04-Apr-94					
BC	13-May-94	16-May-94	18-May-94					
BC	14-Jun-94	20-Jun-94	21-Jun-94	13-Oct-94	1	13-Oct-94		AE
AC	18-Jan-95	18-Jan-95	23-Jan-95	27-Mar-95	2	29-Mar-95		AE
BC	06-Apr-95	07-Apr-95	10-Apr-95	Current				

NAME & ADDRESS OF APPLICANT :

TAP Pharmaceuticals Inc.
T85 J15
2355 Waukegan Road
Deerfield, IL 60015

DRUG PRODUCT NAME:

Proprietary: Prevacid
Nonproprietary/USAN: lansoprazole
Code Name/#: AG-1749, A-65006
Chem. Type/Ther. Class: 1S

PHARMACOLOGICAL CATEGORY: H2-inhibitor

INDICATIONS: Reflux esophagitis/Reflux esophagitis
Duodenal ulcer Pathological conditions
including Zollinger-Ellison syndrome

DOSAGE FORM: Capsules, enteric coated

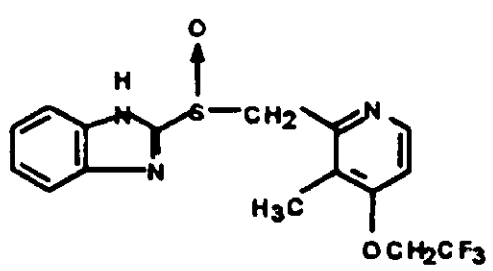
STRENGTHS: 15 mg and 30 mg

ROUTE OF ADMINISTRATION: Oral

HOW DISPENSED: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT.:

2-[[[3-methyl-4-(2,2,-tri
fluoroethoxy)-2-pyridyl]
methyl]-
sulfinyl]benzimidazole
C₁₇H₁₄F₃N₃O₂S
MW =369.37



SUPPORTING DOCUMENTS: See Chem Review #1

RELATED DOCUMENT IND

CONSULTS: EA:
Stability:
EER:

REMARKS/COMMENTS: All questions concerning approvability issues have been answered satisfactorily. There are five post-approval commitments requested in the Draft Letter, two of which concern the Compliance should be notified that the new The Office of may require inspection after the applicant confirms that the equipment has been validated.

CONCLUSIONS & RECOMMENDATIONS: The application may be approved, pending the commitments from the applicant as specified and pending a satisfactory FUR. The applicant should be asked to fulfill the requested post-approval commitments in the first Annual Report.

 4/25/95

Arthur B. Shaw, Ph.D.
Review Chemist, HFD-180

 4/25/95

John J. Gibbs, Ph.D.
Supervisory Chemist, HFD-180

CC:
NDA 20-406
HFD-180/SFredd
HFD-180/Division File/NDA 20-406
HFD-181/CSO
HFD-180/AShaw
R/D Init by:JGibbs/4-21-95
ABS/dob F/T 4-24-95\Wp:c:\wpfiles\chem\N\20406504.3AS

DOB- wyl
MAR 27 1995

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA: # 20-406 CHEM REVIEW # 2 REVIEW DATE: March 1, 1995

SUBMISSION TYPE	DATES			NUM	LETTER	ST
	DOCUMENT	CDER	ASSIGNED REVIEW			
ORIGINAL	12-Nov-93	15-Nov-93	26-Nov-93			
AZ	18-Feb-94	22-Feb-94	01-Mar-94			
BC	14-Mar-94	15-Mar-94	22-Mar-94			
AZ	29-Mar-94	30-Mar-94	04-Apr-94			
BC	13-May-94	16-May-94	18-May-94			
BC	14-Jun-94	20-Jun-94	21-Jun-94	13-Oct-94	1	13-Oct-94 AE
AC	18-Jan-95	18-Jan-95	23-Jan-95	Current		

NAME & ADDRESS OF APPLICANT :

TAP Pharmaceuticals Inc.
T85 J15
2355 Waukegan Road
Deerfield, IL 60015

DRUG PRODUCT NAME:

Proprietary: Prevacid
Nonproprietary/USAN: lansoprazole
Code Name/#: AG-1749, A-65006
Chem. Type/Ther. Class: 1S

PHARMACOLOGICAL CATEGORY: H2-inhibitor

INDICATIONS: Reflux esophagitis/Reflux esophagitis: maintenance of healing/Duodenal ulcer/Gastric ulcer/Pathological conditions including Zollinger-Ellison syndrome

DOSAGE FORM: Capsules, enteric coated

STRENGTHS: 15 mg and 30 mg

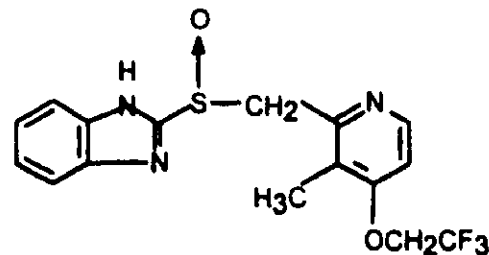
ROUTE OF ADMINISTRATION: Oral

HOW DISPENSED: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WT.:

2-[[[3-methyl-4-(2,2,-tri
fluoroethoxy)-2-pyridyl]methyl]-sulfinyl]benzimidazole

C₁₆H₁₄F₃N₃O₂S
MW =369.37



SUPPORTING DOCUMENTS: See Chem Review #1

RELATED DOCUMENT IND

CONSULTS: EA:

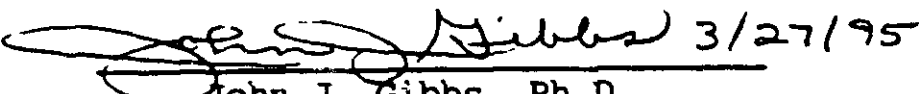
Stability: Report from Biometrics received June 20, 1994. Data support expiration date of 30 months for the manufacturing site and packaging submitted in the original NDA

EER:

REMARKS/COMMENTS: Most questions have been answered.

CONCLUSIONS & RECOMMENDATIONS: The application is approvable for drug product marketed in bottles only pending a satisfactory response to some of the questions in the Draft Letter. Other questions may be answered post-approval.


Arthur B. Shaw, Ph.D.
Review Chemist, HFD-180


John J. Gibbs, Ph.D.
Supervisory Chemist, HFD-180

CC:
NDA 20-406
HFD-180/SFredd
HFD-180/
HFD-180/Division File/NDA 20-406
HFD-181/CSO
R/D Init by:JGibbs/3-23-95
ABS/dob F/T 3-24-95\Wp #c:\wpfiles\ng\20406501.2AS

Wadh

OCT 13 1994

**DIVISION OF GASTROINTESTINAL AND COAGULATION
DRUG PRODUCTS**
Review of Chemistry, Manufacturing, and Controls

NDA: # 20-406 **CHEM REVIEW # 1** **REVIEW DATE:** September 16, 1994

SUBMISSION TYPE	DATES			NUM LETTER	ST
	DOCUMENT	CDER	ASSIGNED REVIEW		
ORIGINAL	12-Nov-93	15-Nov-93	26-Nov-93		
AZ	18-Feb-94	22-Feb-94	01-Mar-94		
BC	14-Mar-94	15-Mar-94	22-Mar-94		
AZ	29-Mar-94	30-Mar-94	04-Apr-94		
BC	13-May-94	16-May-94	18-May-94		
BC	14-Jun-94	20-Jun-94	21-Jun-94		

NAME & ADDRESS OF APPLICANT :

TAP Pharmaceuticals Inc.
T85 J15
2355 Waukegan Road
Deerfield, IL 60015

DRUG PRODUCT NAME:

Proprietary: Prevacid
Nonproprietary/USAN: lansoprazole
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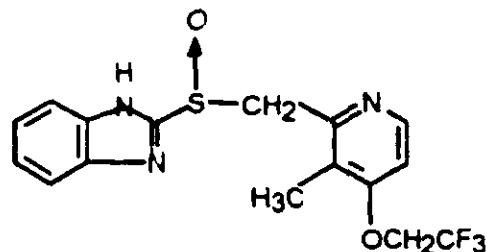
ROUTE OF ADMINISTRATION: Oral

HOW DISPENSED: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT.:

2-[[[3-methyl-4-(2,2,-trifluoroethoxy)-2-pyridyl]methyl]-sulfinyl]benzimidazole

C₁₆H₁₄F₃N₃O₂S
MW =369.37



SUPPORTING DOCUMENTS: See list

RELATED DOCUMENT IND

CONSULTS: EA: This was consulted out to the
for review.

Stability: Report from Biometrics received June 20,
1994. Data support expiration date of 30 months for
the manufacturing site and packaging submitted in the
original NDA

EER: Requested March 7, 1994

REMARKS/COMMENTS: This application is, in general, complete.
The applicant has made matters confusing with inconsistent
nomenclature and with no specific ID numbers for the assays.

CONCLUSIONS & RECOMMENDATIONS: There are a number of questions
which the applicant should be asked in a Not Approvable letter.
The applicant should be notified that DMF for the
coating is deficient and the holder has been notified.

 9/28/94

Arthur B. Shaw, Ph. D.
Review Chemist, HFD-180

 10/13/94

John J. Gibbs, Ph.D.
Supervisory Chemist, HFD-180

CC:

NDA 20-406

HFD-180/SFredd

HFD-180/AShaw

HFD-180/JGibbs

HFD-180/Division File/NDA 20-406

HFD-181/CSO

R/D Init by: JGibbs 9/23/94

F/T abs/9/28/94 Wp #c:\wpfiles\ang\20406402.1AS

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION -
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 2, 1995

FROM: Arthur B. Shaw, Ph.D., Review Chemist, Division of
Gastrointestinal and Coagulation Drug Products, HFD-180

THROUGH: John Gibbs, Ph.D., Supervisory Chemist, Division of
Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Draft Labeling: Solubility and Stability of Lansoprazole

TO: NDA 20-406

The applicant has responded to the suggestions in my memo dated January 9, 1995 with an amendment (AL) dated February 24, 1995.

Solubility:

The draft labeling for Prevacid has been changed from

*Lansoprazole is freely soluble in dimethylformamide;
slightly soluble in methanol; sparingly soluble in ethanol;
slightly soluble in ethyl acetate, dichloromethane and
acetonitrile; very slightly soluble in ether; and practically
insoluble in hexane and water.*

to the following (remove the word "slightly" before "soluble in methanol")

*Lansoprazole is freely soluble in dimethylformamide;
soluble in methanol; sparingly soluble in ethanol;
slightly soluble in ethyl acetate, dichloromethane and
acetonitrile; very slightly soluble in ether; and
practically insoluble in hexane and water.*

ACCEPTABLE

Stability:

The label has been changed to give the half-life of lansoprazole at pH 5.0 from "approximately one hour" to "approximately 1/2". In addition the applicant has added the phrase "At 25°C" before the description of the $t_{1/2}$. The addition of the temperature is acceptable. However the applicant should correct the $t_{1/2}$ at pH 5.0 to read "approximately one-half hour."

NDA 20-406

Page 2

CC:

NDA 20-406

HFD-180/SFredd

HFD-181/MWalsh

R/D init: Jgibbs/3-3-95

ABS/dob F/T 3-6-95/WP: c:\wpfiles\chem\N\20406501.AS5

Walsh

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 9, 1995

FROM: Arthur B. Shaw, Ph.D., Review Chemist, Division of
Gastrointestinal and Coagulation Drug Products, HFD-180

Arthur B. Shaw 1/9/95

THROUGH: John Gibbs, Ph.D., Supervisory Chemist, Division of
Gastrointestinal and Coagulation Drug Products, HFD-180

1/27/95

SUBJECT: Draft Labeling: Solubility and Stability of Lansoprazole

TO: NDA 20-406

Solubility:

The labeling for Prevacid contains the following description for the solubility of lansoprazole:

Lansoprazole is freely soluble in dimethylformamide; slightly soluble in methanol; sparingly soluble in ethanol; slightly soluble in ethyl acetate, dichloromethane and acetonitrile; very slightly soluble in ether; and practically insoluble in hexane and water.

However the solubility in the NDA is somewhat different. The USP defines different solubilities as follows (USP 23, Page 10):

Descriptive Term	Parts of Solvent Required for 1 Part of Solute
Very Soluble	< 1
Freely soluble	1 to 10
Soluble	10 to 30
Sparingly soluble	30 to 100
Slightly soluble	100 to 1,000
Very slightly soluble	1,000 to 10,000
Practically insoluble or Insoluble	> 10,000

The solubilities are given in the NDA in terms of mg/mL which are parts of solute per 1000 parts of solvent. Therefore the parts of solvent necessary to dissolve 1 part of solute = $1000 / (\text{mg/mL})$. The following table uses information taken from Chem Review #1

The only real difference is in the solubility for methanol. With a solubility of 48 mg/mL, this should be "Soluble".

Solvent	Solubility		Solubility		Draft Labeling
	mg/mL	USP Definition	mg/mL	USP Definition	
Acetonitrile	6.6	Slightly Soluble	n.d.		Slightly soluble
Dichloro methane	9.9	Slightly Soluble	15	Sparingly Soluble	Slightly soluble
Dimethyl formamide	290	Freely Soluble	290	Freely Soluble	Freely soluble
Ethanol	19	Sparingly Soluble	18	Sparingly Soluble	Sparingly soluble
Ether	0.54	Very Slightly Soluble	0.57	Very Slightly Soluble	Very Slightly soluble
Ethyl acetate	10	Sparingly Soluble	8.8	Slightly Soluble	Slightly soluble
Hexane	<0.001	Practically Insoluble	0	Practically Insoluble	Practically Insoluble
Methanol	48	Soluble	45	Soluble	Slightly soluble
Water	0.033	Practically Insoluble	0.03	Practically Insoluble	Practically insoluble

Stability:

The label lists the half-lives of lansoprazole at pH 5.0 as "approximately one hour" and at pH 7.0 as "approximately ten hours." The data on Page 288 of Volume 1.4 show the respective half-lives are 0.5 hours (pH 5.0) and eighteen hours (pH 7.0). The label should be amended to conform with the data.

cc:

NDA 20-406

HFD-180/SFredd

HFD-181/MWalsh

R/D init: JGibbs/1-23-95

ABS/dob DRAFT 1-26-95/F/T 1-26-95\WP: c:\wp51\chem\N\20406501.AS4

Stat Rvs

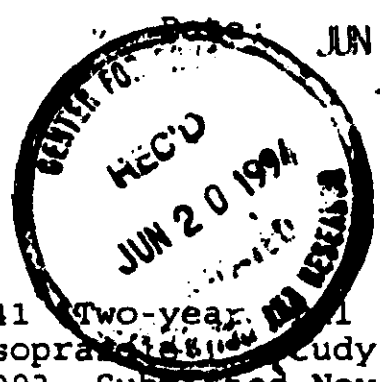
Ms. Walsk

Statistical Review and Evaluation

NDA #: 20-406

Applicant: TAP Pharmaceuticals

Name of Drug: Prevacid (Lansoprazole)



JUN 17 1994

Documents Reviewed:

1. NDA submission volumes 2.31 and 2.41 "Two-year Oral Oncogenicity Study in Mice of Lansoprazole.", Study TD91-025, Report No. R&D/93/547, Oct. 28, 1993, Submitted Nov. 12, 1993.
2. NDA submission volumes 4.2 and 4.5 "Two-year Oral Oncogenicity Study in Mice of Lansoprazole.", Study TD91-276, Report No. R&D/93/731, Dec. 17, 1993. Submitted Dec. 22, 1993.
3. NDA submission volumes 2.59 and 2.71 "Two-year Oral Oncogenicity Study in Rats of Lansoprazole.", Study TA91-024, Report No. R&D/93/546, Nov. 2, 1993. Submitted Nov. 12, 1993.
4. NDA submission volume 2.54 "A Twenty-Four-Month Oral Oncogenicity Study of AG-1749 in Rats.", Study 1148/CA, Report No. A-29-1863, Aug. 2, 1993. Submitted Nov. 12, 1993.
5. NDA submission volume 2.22 "A Eighteen Month Oral Gavage Oncogenicity Study of AG-1749 in Mice.", Study 87-3158, Report No. A-29-680, Jan. 25, 1990. Submitted Nov. 12, 1993.
6. NDA submission volume 2.43 "A Two Year Oral Gavage Oncogenicity Study of AG-1749 in Rats.", Study 86-3028, Report No. A-29-681, Jan. 25, 1990. Submitted Nov. 12, 1993.
7. NDA submission volume 5.3 to 5.5, Special NDA submission, Date of Document, Feb. 18, 1994, Data Diskettes for six animal tumorigenicity studies.

I. Background

Six animal carcinogenicity studies (three in rats and three in mice) were included in this NDA submission. The purpose of these studies was to assess the potential tumorigenicity of the test material, Prevacid (Lansoprazole), when given orally or gavage to rats and mice for 18 to 24 months. Dr. Chopra, HFD-180, who is the reviewing pharmacologist of this NDA has requested the Division of Biometrics to perform the statistical review and evaluation of these six studies. The data submitted on computer floppy diskettes were used in the reviewer's independent analyses. Since the data sets of study numbers 87-3158 and 86-3028 do not have all the information we need to do the statistical review, the following statistical reviews perform data analyses only on four of the six studies (studies no.

TA91-024, 1148/CA, TD91-025, and TD91-276).

II. The First Rat Study - TA91-024 (Report R&D/93/546)

II. a. Design

In this study, five groups of main study (oncogenicity) rats received lansoprazole (prevacid, AG-1749) at dosages of 0, 5, 25, 75, or 150 mg/kg/day each day, seven days a week, for two years. Doses were administered by gavage in a vehicle of 5% gum arabic in deionized water (final vehicle pH adjusted to 7). Each of the main study groups contained 70 male and 70 female Charles River CD rats, and complete histopathological evaluations were conducted for these rats. Additional 70 animals/sex were included as second control group, and only the livers of the females from this group were examined histopathologically. Another group (recovery group) of 70 males received lansoprazole at a dosage of 150 mg/kg/day for 18 months and vehicle alone for the remaining six months. The treatment regimen for this group was designated "150/0 mg/kg/day." Hormone assays were conducted on blood and urine samples collected from these rats. Also the 150/0 mg/kg/day rats were subjected to complete necropsies, but histopathologic examination were limited to the testes, stomach, eyes and lesions observed grossly at necropsy. Additional satellite rats (70/sex/group) were treated with dosages of 0, 5, 25, 75 or 150 mg/kg/day and were used solely for hormone and drug level assays. Each rat was observed twice daily for mortality, moribundity and overt signs of toxicity. Detailed observations on main study groups and other 150/0 mg/kg/day animals were performed at least once weekly. Individual body weights for all groups were recorded weekly for the first 14 weeks and once every 2 weeks thereafter. Food consumption values of the main study and other 150/0 mg/kg/day animals were recorded weekly for the first 14 weeks of study and once every 4 weeks thereafter. This study was conducted at International Research and Development Corporation, Mattawan, MI. Treatment began on April 1, 1991, and terminal necropsies ended on April 9, 1993.

II. b. Sponsor's Analyses

Although there are two control groups in this study, the sponsor included only the first control group in his statistical analysis. The mortality and tumor incidence data in main study (groups 1 to 5) were analyzed separately by sex. In addition, a separate analysis was conducted to compare the mortality and tumor incidences in recovery males with those in first control and in high dose males.

The Cox test ("Regression models and life tables (with discussion)", J. Royal Stat. Soc., Series B, 34: 187-220, 1972) was used to compare the mortality data of the control group and the respective treated groups. The Tarone test ("Tests for trends in life tables analysis, Biometrika, 62: 679-682, 1975) was used to test for dose-response trends. In addition, the Kaplan-Meier estimate of survival curve ("Nonparametric estimation from incomplete observations", Journal of

the American Statistical Association, 53, 457-481, 1958) was calculated for each sex/treatment group and displayed graphically over time. The above analyses showed that there was no statistically significant differences in the mortality rates for the males in the main study (groups 1 to 5), nor was the mortality rate of the recovery males significantly different from that of the control males or the high dose males. However, there were statistically significant decreased mortality rates in both the low and the high dose females compared to that of the controls. The trend test also showed a significant decreasing dose-response mortality rate in female rats. Noted that for pairwise comparison, the Bonferroni inequality was used to obtain an overall 0.05 level of significance. Figures 1.1 and 1.2 graphed the Kaplan-Meier survival curves over the weeks of the main study for males and females, respectively. Figure 1.3 shows similar curves for the males in the recovery, first control, and high dose groups.

The tumor incidence data were analyzed using the methods given in the paper of Peto et al. ("Guidelines for Simple, Sensitive Significance Tests for Carcinogenic Effects in Long-Term Animal Experiments", In Long-Term and Short-Term Screening Assays for Carcinogens: A Critical Appraisal, International Agency for Research on Cancer Monographs, Annex to Supplement 2, World Health Organization, 311-426, 1980). Two analyses were performed for each individual tumor site: the comparison of tumor incidence rate of the high dose group with that of the control group and the test of a positive dose-response trend. The high dose vs. control group comparison was done with continuity correction. The trend test was computed using the ordinal scale coding (0, 1, 2, 3, and 4) of the dose levels for the control, low, mid-low, mid-high, and high dose groups, respectively. If the tumor incidence across treatment groups was fewer than 10, and if the context of these tumors was all incidental, then the exact permutation test of trend was performed to obtain the p-value, otherwise the analysis based on normal approximation was used.

In addition to the Peto analysis of tumor incidences for each individual site, simultaneous analyses using the method of Westfall and Young ("p-value adjustments for multiple tests in multivariate binomial models", J. Amer. Stat. Assoc., 84: 780-786, 1989) were performed to compute adjusted p-values. The adjusted p-values were obtained using the bootstrap procedure of Westfall and Young in conjunction with the Cochran-Armitage test stratified over five time intervals: weeks 0-52, 53-78, 79-92, 93-106, and terminal necropsy. The multiplicity adjustment was made separately within each sex for the high vs. control group comparisons and for the trend tests.

In order to limit the number of tests and comparisons in multiplicity adjustment to only those that have a chance to exhibit statistical significance, the following site selection criterion was used: for a site to be selected it must have at least two tumor occurrences in any one treatment group. Applying this criterion to the tumor data resulted in 28 out of 43 tissue/tumor types in male rats and 24 out

of 35 tissue/tumor types in female rats being included for multiplicity adjustment. Each adjusted p-value was based on 10000 bootstrap samples.

The results of the above analyses showed that there was a significant (at 0.05 level) positive linear trend in the following neoplastic lesions:

(1) Testes interstitial cell benign tumor (unadjusted p = 0.0001, adjusted p = 0.0001) in males.

(2) Liver hepatocellular adenoma (unadjusted p = 0.0225, adjusted p = 0.2846), stomach (fundus) carcinoid intramucosal (unadjusted p = 0.0001, adjusted p = 0.0001), stomach (fundus) carcinoid invasive (unadjusted p = 0.0001, adjusted p = 0.0001), stomach (fundus) carcinoid intramucosal/invasive (unadjusted p = 0.0001, adjusted p = 0.0001), and uterus squamous cell carcinoma (unadjusted p = 0.0218, adjusted p = 0.3631) in females.

The pairwise comparison between control and high dose groups showed that there are significant increases in the incidences of stomach (fundus) carcinoid intramucosal/invasive (unadjusted p = 0.0492, adjusted p = 0.1875), and testes interstitial cell tumor (unadjusted p = 0.0001, adjusted p = 0.0001) in males; and in stomach (fundus) carcinoid intramucosal (unadjusted p = 0.0016, adjusted p = 0.0031), stomach (fundus) carcinoid invasive (unadjusted p = 0.0006, adjusted p = 0.0010), stomach (fundus) carcinoid intramucosal/invasive (unadjusted p = 0.0001, adjusted p = 0.0001) in females.

For the pairwise comparisons between the recovery males with those in control and in high dose males, the results showed that the incidence of testes interstitial cell tumor in the recovery males was significantly higher (unadjusted p < 0.0001) than that of the control group, but was significantly lower (unadjusted p = 0.0189) than that in the high dose males.

Based on the above analyses, the sponsor concluded that "on the bases of reduced weight gains, clinical signs and hematologic changes, the MTD for lansoprazole in rats was exceeded at dosages of 75 and 150 mg/kg/day. Changes in the stomach and pancreas were results of the pharmacologic activity of lansoprazole, i.e., inhibition of gastric acid secretion, and induction of gastric mucosal carcinoids was thought to stem from a species - and sex-related sensitivity to the resultant hypergastrinemia. Degenerative changes in the male reproductive tract, exhibiting some reversibility in the recovery males, with the induction of leydig cell tumors were thought to be species-selective, hormonally-mediated effects. Therefore, apart from tumors caused by exaggerated pharmacologic activity or perturbations of the endocrine system, lansoprazole was not oncogenic at dosages up to and exceeding the MTD in rats."

II.c. Reviewer's analyses and Comments

There are two control groups in this study, however, the sponsor did not submit the data of second control group. In the following analyses, two approaches were used to analyze the survival and tumor data. The first approach included the data of control, low, medium, and high dose groups in the analyses. The second approach included data of high dose and recovery groups.

The Cox test and the generalized Wilcoxon test described in the paper of Thomas, Breslow, and Gart ("Trend and Homogeneity Analyses of Proportions and Life Table Data", Computers and Biomedical Research, 10, 373-381, 1977) were used to test for heterogeneity in survival distributions. The p-values of the Cox test were 0.9326 and 0.0011 for males and females, respectively. Hence, there was a statistically significant difference (at 0.05 level) in the survival distribution in female rats. A similar conclusion was obtained in the generalized Wilcoxon test. The p-values were 0.9574 and 0.0015 for males and females, respectively. Also for male rats, the high dose group survival was compared with the recovery group survival. The test results did not reveal any significant difference in survival between high dose and recovery group male rats ($p = 0.3932$).

The intercurrent mortality rates for both male and female rats (see Table 1.1) were tested for linear trend according to the death rate method described in the paper of Peto et al. (1980) using the time intervals 0-50, 51-80, 81-104 weeks. The actual dose levels 0, 5, 25, 75, and 150 mg/kg/day were the scores assigned to the control, low, medium-1, medium-2, and high dose groups, respectively. The results of the analyses showed that there was no significant (at 0.05 level) linear trend in the intercurrent mortality rate in male rats ($p = 0.4737$). However, there was a significant linear trend in the intercurrent mortality rate in female rats ($p = 0.0193$).

The methods described in Peto et al. (1980) and the methods of age-adjusted exact permutation trend test were used to test the linear trend in the tumor data. The results of the above analyses showed that there was a significant (at 0.05 level) positive linear trend in the following neoplastic lesions:

- (1) Testes interstitial cell benign tumor ($p < 0.0001$) in males.
- (2) Liver hepatocellular adenoma ($p = 0.0041$), stomach (fundus) carcinoid intramucosal ($p = 0.0002$), stomach (fundus) carcinoid invasive ($p < 0.0001$), stomach (fundus) carcinoid intramucosal/invasive ($p < 0.0001$), and uterus squamous cell carcinoma ($p = 0.0382$) in females.

The incidence rates of the tumor types with significant linear trends are given in Tables 1.2 to 1.7.

The pairwise comparisons between control and high dose groups showed that there are significant increases in the incidences of stomach (fundus) carcinoid intramucosal ($p = 0.0005$), stomach (fundus)

carcinoid invasive ($p = 0.0001$), and stomach (fundus) carcinoid intramucosal/invasive ($p < 0.0001$) in females, and testes interstitial cell tumor ($p < 0.0001$) in males.

For the pairwise comparisons between the recovery males with those in control and in high dose males, the results showed that the incidence of testes interstitial cell tumor in the recovery males was significantly higher ($p < 0.0001$) than that of the control group, but was significantly lower ($p = 0.04$) than that in the high dose males. The incidence rates of testes interstitial cell tumor of recovery, high and control groups in males is given in Table 1.8.

Comparing the incidence rates of testes interstitial cell benign tumor of high dose group (67.14%) and recovery group (51.42%) in this study with those of 10 historical control data in Table 1.9, we found that the incidences of testes interstitial cell benign tumor of this study are outside the historical control ranges (1.33% to 22.22%).

III. The Second Rat Study - 1148/CA (Report A-29-1863)

III. a. Design

In this study, 420 male and 340 female Charles River Sprague-Dawley derived Crl:CD(SD)BR rats (SPF animals) were allocated randomly to six male groups and five female groups each comprised of 60 animals. The test compound, lansoprazole (prevacid, AG-1749) was administered daily via oral gavage to rats at dose levels of 5, 15, and 50 mg/kg/day for 97 to 104 weeks. The control animals received 5% gum arabic solution by the same dosage volume as that administered to the treated animals. The experimental groups are listed as follows:

Group	Test substance	Dose level (mg/kg/day)	No. of Animals	
			Male	female
1	Control	0	60+15	60+10
2	Control	0	60	60
3	AG-1749	5	60+15	60+10
4	AG-1749	15	60+15	60+10
5	AG-1749	50	60+15	60+10
6	AG-1749	50	60**	-

** Recovery group

The scheduled dosing period was 104 weeks (February 11, 1991 to February 17, 1993) except the recovery group, which was treated for 18 months followed by a six-month drug-free period. However, owing to reduced survival in control males, the necropsy of the males, except for the recovery group animals, was performed after 97 weeks of dosing, and the recovery group was killed after 104 weeks. The female rats were killed at the 104th week as scheduled.

All animals were observed twice daily for survival and for overt pharmacological signs. In addition to the cage-side observations, further detailed observations and palpation for masses were carried out once each week. Body weights were recorded weekly for the first 14 weeks, once every four weeks from weeks 15 to 71 and once a week thereafter. Food consumptions were recorded weekly for the first 14 weeks, once every four weeks from weeks 15 to 51 and once a week thereafter. After proper fixing, selected tissues and organs from all animals in the control and high dose groups and from rats which died spontaneously or were killed in extremis in the course of the study were routinely processed, embedded in paraffin, sectioned, stained with hematoxylin and eosin, and then examined by light microscopy. The stomachs, testes, livers and eyes and all gross neoplastic lesions from the middle and low dose groups and the recovery group were also processed routinely and were examined microscopically.

III. b. Sponsor's Analyses

There are two control groups in this study, however, the sponsor combined both control groups in his analyses for comparison, unless otherwise specified.

The Kaplan-Meier product-limit method was used to estimate the probability of survival. The heterogeneity and the dose-related trend on survival were analyzed using Tarone's test. The sponsor indicated that increased mortality was recorded in the control, low, and medium dose groups. This necessitated terminating some groups before the scheduled kill of 104 weeks. A statistically significant decrease in mortality rate was noted in the high dose groups of both sexes in comparison with the control groups ($p < 0.05$). A statistically significant negative trend in mortality was also found for the female groups ($p < 0.05$). Survival rates at termination are 32.5%, 38.3%, 31.7%, and 45% for control, low, medium, and high dose groups, respectively, for males, and 29.2%, 30.0%, 36.7%, and 46.7%, respectively, for females. The Kaplan-Meier survival curves for both sexes are plotted in Figures 2.1 and 2.2 for males and females, respectively. Table 2.1 listed the results of survival analysis.

The sponsor did not perform any statistical analysis on all of tumor/organ data. The method of Peto et al. (1980) and the Fisher's exact test were applied to tumors found in more than 3 animals/group between the control and high dose groups. In the case of tumors found in the stomach, testes, and liver, which were examined histologically in all animals, they were tested among all the experimental groups according to the methods of Peto et al (1980). Hyperplasia of testicular interstitial cells and gastric argyrophil cells, and altered foci of the hepatocytes were also tested in the same manner as tumors.

Among the tumors analyzed, the sponsor found that there were statistically significant positive linear trends in stomach carcinoid

tumor ($p < 0.01$) in both sexes, and in interstitial cell tumor in male rats. There was a marginally significant positive linear trend ($p = 0.051$) in hepatocellular adenoma in males between the combined control groups and the high dose group. However, the sponsor indicated that the incidences of hepatocellular adenoma were 5/60 in one control group and 0/60 in the other control group. Thus, the incidence of benign hepatocellular neoplasms was considered to be within natural variation. The incidence of the proliferative lesions of neuroendocrine cells (stomach) and testis tumors are summarized in the following table:

Sex	Male						Female					
	Dose (mg/kg/day)	0	0	5	15	50	50*	0	0	5	15	50
# of animals exam.	59	60	60	60	60	60	60	60	60	60	60	60
Hyperplasia, Argyrophil cell,												
Diffuse	12	14	22	13	9	15	12	15	17	11	2	
Aggregate	1	1	5	13	10	13	0	0	0	5	15	
Linear	0	0	8	3	3	3	0	0	10	5	8	
Nodular	0	0	0	0	0	0	0	0	1	3	6	
Carcinoid	0	1	1	4	9	3	0	1	6	15	24	

* : Recovery group

Dose (mg/kg/day)	0	0	5	15	50	50*
# of animals exam.	60	60	60	60	60	60
Hyperplasia,						
Interstitial cell	3	2	5	4	11	14
Interstitial cell tumor (unilateral)	0	1	2	7	12	14
	(0	1	2	5	4	7)

* : Recovery group

Based on the above test results, the sponsor concluded that "dosing with AG-1749 for up to 24-month oral administration induced hyperplasia of gastric ECL-cells and testicular interstitial cells and tumors of these cell types under the present conditions of the study."

III.c. Reviewer's analyses and Comments

As mentioned in the previous paragraph, there are two control and two

high dose groups in males, the necropsy of the males, except for the recovery group animals, was performed after 97 weeks of dosing, and the recovery group was killed after 104 weeks. The dosing period was 104 weeks for females, 97 weeks for males, except the recovery group, which was treated for 18 months followed by a 6-month of drug-free period. Hence, the reviewer performed two sets of analyses on the survival and tumor data. The first set used the data of both controls, low, medium, and high dose groups. The second set, which applied only to the tumor data, used data of both high dose groups.

The Cox test and the generalized Wilcoxon test described in the paper of Thomas, Breslow, and Gart (1977) were used to test for heterogeneity in survival distributions. The p-values of the Cox test were 0.3415 and 0.0473 for males and females, respectively. Hence, no statistically significant difference (at 0.05 level) in survival distribution in male rats was detected. However, there was a statistically significant difference (at 0.05 level) in the survival distribution in female rats. A similar conclusion was obtained in the generalized Wilcoxon test. The p-values were 0.2789 and 0.0461 for males and females, respectively. Also for both sexes, the first control group survival was compared with that of the second control group. The test results did not reveal any significant difference in survival between two control groups for both sexes.

The intercurrent mortality rates for both male and female rats (see Table 2.2) were tested for linear trend according to the death rate method described in the paper of Peto et al. (1980) using the time intervals 0-50, 51-80, 81-104 weeks for females, and 0-50, 51-80, 81-97 weeks for male rats. Since there were two control groups in this study, three separate sets of analyses were performed on these data sets. In the first set of analyses (called C1), the data of first control, low, medium, and high dose groups were used. In the second set of analyses (called C2), the data of second control, low, medium, and high dose groups were used. In the third set of analyses (called C1+C2), the data of both controls, low, medium, and high dose groups were used. The actual dose levels 0, 0, 5, 15, and 50 mg/kg/day were the scores assigned to the controls, low, medium, and high dose groups, respectively. The results of the analyses showed that there was no significant (at 0.05 level) linear trend in the intercurrent mortality rate in males (C1: $p = 0.0849$, C2: $p = 0.081$, C1+C2: $p = 0.0556$). However, there was a significant (at 0.05 level) linear trend in the intercurrent mortality rate in females (C1: $p = 0.0094$, C2: $p = 0.051$, C1+C2: $p = 0.0096$).

The methods described in Peto et al. (1980) and the methods of age-adjusted exact permutation trend test were used to test the linear trend in the tumor data. Similar to the analyses of mortality data, three sets (C1, C2, and C1+C2) of analyses were performed on the tumor data. The results of the above analyses showed that there was a significant (at 0.05 level) positive linear trend in the following neoplastic lesions:

(a) Stomach carcinoid tumor (C1: $P < 0.0001$, C2: $P < 0.0001$, C1+C2: $P < 0.0001$) and uterus squamous cell carcinoma (C1: $P = 0.0556$, C2: $P = 0.0596$, C1+C2: $P = 0.0297$) in female rats.

(b) Liver hepatocellular adenoma (C1: $P = 0.1381$, C2: $P = 0.0071$, C1+C2: $P = 0.0351$), stomach carcinoid tumor (C1: $P = 0.0004$, C2: $P = 0.0014$, C1+C2: $P = 0.0002$), and testes interstitial cell tumor (C1: $P = 0.0002$, C2: $P = 0.0005$, C1+C2: $P < 0.0001$) in male rats.

The incidence rates of the tumor types with significant linear trends are given in Tables 2.3 to 2.7.

The pairwise comparison between both controls and high dose groups showed that there are significant increases in the incidences of stomach carcinoid tumor in both sexes (female: $P < 0.0001$; male: $P = 0.0005$) and in the incidences of testes interstitial cell tumor ($P < 0.0001$) in males. The pairwise comparison between high dose and recovery groups showed that there is a significant decrease in the incidence of adrenal gland pheochromocytoma in males ($P = 0.0365$). The incidence rates of adrenal gland pheochromocytoma of high and recovery groups in males is given in Table 2.8.

IV. The First Mouse Study - TD91-025 (Report # R&D/93/547)

IV. a. Design

In this study, Lansoprazole was administered by gavage once daily to 70 Crl:CD-1 BR mice/sex/group at dosage levels of 15, 75, 150, and 300 mg/kg/day for two years. Two control groups received the vehicle, 5% gum arabic in deionized water, on a comparable regimen. Satellite groups of 30 mice/sex/group were placed on study at each dosage level and in a vehicle control group for blood drug level assays. Each mouse was observed twice daily for mortality, moribundity and overt signs of toxicity. Detailed observations on main group animals were performed at least once weekly. Individual body weights for all groups were recorded weekly for the first 14 weeks and once every 2 weeks thereafter. Food consumption values of the main study animals were recorded weekly for the first 14 weeks of study and once every 4 weeks thereafter. At the termination of the study period, all remaining mice were euthanized and a thorough postmortem examination was conducted. Representative photographs of gross stomach lesions were taken. Protocol-specified tissues were processed histologically and microscopic examinations were conducted. The study initiated on February 20, 1991, dosing initiated on March 12, 1991, and terminal necropsy started from March 9, 1993 to March 19, 1993.

IV. b. Sponsor's Analyses

Although there are six groups of animals per sex in the study, group 6 (vehicle control B) was not included in the sponsor's statistical

analysis. The sponsor indicated that group 6 was only to be used to provide further perspective if deemed necessary.

Similar to the rats studies, the Kaplan-Meier estimate of the survival curve, Cox's test and Tarone's test were used to analyze the survival data for control and treated groups for both sexes. The analysis of survival data revealed that the test for increased mortality with increasing dose was statistically significant ($p = 0.0004$) as was the comparison of the mortality rates between the 150 mg/kg/day and the control group of male mice. For female mice, no statistical significance was detected in the test of trend nor in pairwise comparisons. The Kaplan-Meier survival curves for the treatment groups for both sexes are plotted in Figures 3.1 and 3.2 for males and females, respectively. The sponsor indicated that Kaplan-Meier survival curves showed a dose-related increase in mortality which indicated that the maximum-tolerated dosage was exceeded in this carcinogenicity study.

In addition to the Peto analysis of tumor incidences for each individual site, simultaneous analyses using the method of Westfall and Young, which adjusts for the effect of multiplicity of tests, were performed to compute adjusted p-values. If the tumor incidence across treatment groups was fewer than 10, and if the context of these tumors was all incidental, then the exact permutation test of trend was performed to obtain the p-value, otherwise the normal approximation was used. The trend test was computed using the ordinal scale coding (0, 1, 2, 3, and 4) of the dose levels for the control, low, medium-1, medium-2, and high dose groups, respectively.

The above test results showed that there is a statistically significant positive linear trend in stomach (fundus) carcinoid intramucosal/invasive in males (unadjusted $p = 0.0455$, adjusted $p = 0.3813$), liver hepatocellular adenoma (unadjusted $p = 0.0007$, adjusted $p = 0.0053$), and liver hepatocellular combined adenoma and carcinoma (unadjusted $p = 0.0002$, adjusted $p = 0.0015$) in females. The sponsor indicated that the increase in liver tumor was not considered treatment-related since the incidence was similar to the upper limits of the historical control data of this and other laboratories and that no increase in altered foci in the liver was seen in the current carcinogenicity study. Table 3.1 listed the historical control data of liver tumors.

Based on the above test results, the sponsor concluded that "there is no evidence that lansoprazole has a direct carcinogenic effect even when examined at dosages predicted by the 13-week range finding study and confirmed by this carcinogenicity study to substantially exceed the true maximum tolerated dosage."

IV.c. Reviewer's analyses and Comments

The Cox test and the generalized Wilcoxon test described in the paper of Thomas et al. (1977) were used to test for heterogeneity in

survival distributions. The p-values of the Cox test were 0.0005 and 0.0820 for males and females, respectively. Hence, there was no statistically significant difference (at 0.05 level) in survival distribution in female mice. However, there was a statistically significant difference in the survival distribution in males. The p-values of the generalized Wilcoxon test were 0.0001 and 0.0125 for males and females, respectively. Hence, there were statistically significant differences (at 0.05 level) in the survival distribution in both sexes. The different results from the above two tests are due to that the generalized Wilcoxon test places greater weights on early deaths in a study and that the Cox test places equal weights on all deaths.

The intercurrent mortality rates for both male and female mice (see Table 3.2) were tested for linear trend according to the death rate method described in the paper of Peto et al. (1980) using the time intervals 0-50, 51-80, and 81-104 weeks. The actual dose levels 0, 0, 15, 75, 150, and 300 mg/kg/day were the scores assigned to the control, low, medium-1, medium-2, and high dose groups, respectively. The results of the analyses showed that there were significant (at 0.05 level) linear trends in the intercurrent mortality rate in female ($p = 0.016$) and male ($P = 0.0011$) mice.

The methods described in Peto et al. (1980) and the methods of age-adjusted exact permutation trend test were used to test the linear trend in the tumor data. The results of the above analyses showed that there were significant (at 0.05 level) positive linear trends in the liver hepatocellular adenoma ($P = 0.0004$) and hepatocellular adenoma/carcinoma ($P = 0.0001$) in females and in stomach fundus, carcinoid intramucosal/invasive ($p = 0.0401$) in male mice. The pairwise comparisons between the high dose and control groups also showed that there are significantly higher incidence rates in the liver hepatocellular adenoma ($P = 0.0188$) and hepatocellular adenoma/carcinoma ($P = 0.008$) in females but not in stomach fundus, carcinoid intramucosal/invasive ($p = 0.5375$) in male mice. The incidence rates of the above tumors are given in Table 3.3 to 3.5.

Noted that the sponsor listed 69 animals examined microscopically for control males in stomach fundus, carcinoid intramucosal/invasive. However, the above analyses are assumed that 70 animals/sex/group were examined microscopically.

Comparing the incidence rates of liver hepatocellular adenoma (8.57%) and combined adenoma/carcinoma (10%) in the high dose female group in this study with those of historical control data of 13 studies in Table 3.1, we found that the incidences of above tumors exceeded the historical control ranges based on those 12 historical studies.

V. The Second Mouse Study - TD91-276 (Report # R&D/93/731)

V. a. Design

In this study, Lansoprazole was administered by gavage once daily to 70 Crl:CD-1 BR mice/sex at dosage level of 600 mg/kg/day for two years. One control group received the vehicle, 5% gum arabic in deionized water, on a comparable regimen. Satellite groups of 30 mice/sex/group were placed on study at a dosage level of 600 mg/kg/day and in a vehicle control group for blood drug level assays. The 600 mg/kg/day dosage was higher than dosages used on an ongoing study and was selected following discussions with the agency. The sponsor mentioned that animals that died during the first month of the study were replaced one-on-one by healthy animals not selected in the randomization process. During the second and third month of the study, ten female mice from the 600 mg/kg/day main group died or were euthanized in extremis due to gavage injury. Beginning week 21, 10 high dose satellite females were selected and reassigned to the main high dose group to compensate for the early loss of animals in the group. Each mouse was observed twice daily for mortality, moribundity and overt signs of toxicity. Detailed observations on main group animals were performed at least once weekly. Individual body weights for all groups were recorded weekly for the first 14 weeks and once every 2 weeks thereafter. Food consumption values of the main study animals were recorded weekly for the first 14 weeks of study and once every 4 weeks thereafter. At the termination of the study period, all remaining mice were euthanized and a thorough postmortem examination was conducted. Representative photographs of gross stomach lesions were taken. Protocol-specified tissues were processed histologically and microscopic examinations were conducted. The study initiated on September 9, 1991, dosing initiated on September 12, 1991, and terminal necropsy started on August 18, 1993 for females and September 9, 1993 for males.

V. b. Sponsor's Analyses

The sponsor's statistical report included 10 females transferred from high dose satellite animals, the data of 10 high dose females that died early are excluded from the statistical analyses and table summaries. This resulted in differences in denominators between the tables presented in the statistical report and the comparable tables given by IRDC.

Similar to the rats studies, the Kaplan-Meier estimate of the survival curve, Cox's test and Tarone's test were used to analyze the survival data for control and high dose groups for both sexes. The analysis of survival data revealed that the mortality of male and female mice receiving 600 mg/kg/day was significantly increased when compared to the corresponding controls (females: $p = 0.0001$; males: $p = 0.0001$). Due to an excessive mortality in the female drug-treated group, all surviving females were euthanized early at week 101 (instead of week 105). The Kaplan-Meier survival curves for the treatment groups for both sexes are plotted in Figures 4.1 and 4.2 for males and females, respectively.

In addition to the Peto and the exact permutation trend test to

analyze the tumor incidences for each individual type, simultaneous analyses using the method of Westfall and Young, which adjusts for the effect of multiplicity of tests, were performed to compute adjusted p-values. The above test results showed that there are statistically significant increases in the incidences of liver hepatocellular adenoma (unadjusted $p = 0.0001$, adjusted $p = 0.0004$), liver hepatocellular carcinoma (unadjusted $p = 0.0013$, adjusted $p = 0.0217$), combined hepatocellular adenoma and carcinoma (unadjusted $p = 0.0001$, adjusted $p = 0.0006$), and testes adenoma, rete testis (unadjusted $p = 0.0474$, adjusted $p = 0.1512$) in males and in the incidence of liver hepatocellular adenoma (unadjusted $p = 0.0256$, adjusted $p = 0.0448$) in females.

Based on the above test results, the sponsor concluded that "the dosage level of 600 mg/kg/day exceeded the maximum tolerated dose (MTD) based on increased mortality and hematologic effects in both sexes. The microscopic findings in the glandular stomach, including ECL cell hyperplasia and mucosal hypertrophy and/or hyperplasia, and other stomach changes, were expected as a result of the pharmacological action of lansoprazole. An increased incidence of hepatocellular adenomas (both sexes) and carcinomas (males only) was noted when compared to concurrent controls; however, these incidences were still within the historical control ranges of this laboratory."

V.c. Reviewer's analyses and Comments

The Cox test and the generalized Wilcoxon test described in the paper of Thomas et al. (1977) were used to test for heterogeneity in survival distributions. The p-values of the Cox test were < 0.0001 for both sexes. Hence, there were statistically significant differences in the survival distribution between control and high dose groups for both sexes. A similar conclusion was obtained in the generalized Wilcoxon test. The p-values of the generalized Wilcoxon test were < 0.0001 for both sexes.

The intercurrent mortality rates for both male and female mice (see Table 4.1) were tested for linear trend according to the death rate method described in the paper of Peto et al. (1980) using the time intervals 0-50, 51-80, and 81-100 weeks for females, and 0-50, 51-80, and 81-104 weeks for males. The actual dose levels 0, 600 mg/kg/day were the scores assigned to the control and high dose groups, respectively. The results of the analyses showed that there were significant (at 0.05 level) differences in the intercurrent mortality rate in female ($p < 0.0001$) and male ($p < 0.0001$) mice.

Since there are only control and high dose groups/sex in the study, the age-adjusted pairwise comparison was used to test the difference in the tumor data. The results of the above analyses showed that there were significantly (at 0.05 level) higher incidence rates in the liver hepatocellular adenoma ($p = 0.0184$) in females, and in the liver hepatocellular adenoma ($p = 0.0002$), hepatocellular carcinoma ($p = 0.0087$), hepatocellular adenoma/carcinoma ($p = 0.0003$), and

testes adenoma, rete testis ($p = 0.0451$) in male mice. The incidence rates of the above tumors are given in Table 4.2 to 4.6.

Comparing the incidence rates of liver hepatocellular adenoma (21.42%), hepatocellular carcinoma (12.85%), and combined adenoma/carcinoma (27.14%) of high dose male group and liver hepatocellular adenoma (5.71%) of high dose female group in this study with those of historical control data in Table 3.1, we found that the incidences of the above tumors were within the historical control ranges.

VI. Summary

VI.a. The First Rat Study - TA91-024 (Report R&D/93/546)

The Cox and the generalized Wilcoxon methods were used to test the heterogeneity in survival distribution. The test results revealed that there was no statistically significant difference (at 0.05 level) in the survival distribution in male rats from both tests. However, there was a statistically significant difference in the survival distribution in female rats (Cox: $p = 0.0011$; Wilcoxon: $p = 0.0015$). In addition, the test results did not reveal any significant difference in survival between high dose and recovery group male rats ($p = 0.3932$).

The statistical methods given in the paper of Peto et al. (1980) and an exact permutation trend test were used to test the positive linear trend in intercurrent mortality and incidental tumor rates. Applying the above methods to the data on sponsor's computer diskettes, the results of the analyses showed that there was no significant (at 0.05 level) linear trend in the intercurrent mortality rate in male rats. However, there was a significant linear trend in the intercurrent mortality rate in female rats ($p = 0.0193$).

Results of tumor data analyses showed a significant dose-related trend (at 0.05 level) in the following neoplastic lesions:

- (1) Testes interstitial cell benign tumor ($p < 0.0001$) in males.
- (2) Liver hepatocellular adenoma ($p = 0.0041$), stomach (fundus) carcinoid intramucosal ($p = 0.0002$), stomach (fundus) carcinoid invasive ($p < 0.0001$), stomach (fundus) carcinoid intramucosal/invasive ($p < 0.0001$), and uterus squamous cell carcinoma ($p = 0.0382$) in females.

Pairwise comparisons between control and high dose groups showed that there are significant increases in the incidences of stomach (fundus) carcinoid intramucosal ($p = 0.0005$), stomach (fundus) carcinoid invasive ($p = 0.0001$), and stomach (fundus) carcinoid intramucosal/invasive ($p < 0.0001$) in females, and testes interstitial cell tumor ($p < 0.0001$) in males.

For the pairwise comparisons between the recovery males with those in control and in high dose males, the results showed that the incidence of testes interstitial cell tumor in the recovery males was significantly higher ($p < 0.0001$) than that of the control group, but was significantly lower ($p = 0.04$) than that in the high dose males.

Comparing the incidence rates of testes interstitial cell benign tumor of the high dose group (67.14%) and the recovery group (51.42%) in this study with those of historical control data of 10 studies in Table 1.8, we found that the incidences of testes interstitial cell benign tumor exceeded the historical control ranges (1.33% to 22.22%).

VI.b. The Second Rat Study - 1148/CA (Report A-29-1863)

The Cox and the generalized Wilcoxon methods were used to test the heterogeneity in survival distribution. The test results revealed that there was no statistically significant difference (at 0.05 level) in the survival distribution in male rats. However, there was a statistically significant difference (at 0.05 level) in the survival distribution in female rats. In addition, no significant difference in survival between two control groups was detected in both sexes.

Applying Peto's method and an exact permutation trend test to test the positive linear trend in intercurrent mortality and incidental tumor rates, the results of the analyses showed that there was no significant linear trend in the intercurrent mortality rate in males (C1: $p = 0.0849$, C2: $p = 0.081$, C1+C2: $p = 0.0556$). However, there was a significant linear trend in the intercurrent mortality rate in females (C1: $p = 0.0094$, C2: $p = 0.051$, C1+C2: $p = 0.0096$).

Results of tumor data analyses showed that there was a significant (at 0.05 level) positive linear trend in the following neoplastic lesions:

(a) Stomach carcinoid tumor (C1: $P < 0.0001$, C2: $P < 0.0001$, C1+C2: $P < 0.0001$) and uterus squamous cell carcinoma (C1: $P = 0.0556$, C2: $P = 0.0596$, C1+C2: $P = 0.0297$) in female rats.

(b) Liver hepatocellular adenoma (C1: $P = 0.1381$, C2: $P = 0.0071$, C1+C2: $P = 0.0351$), stomach carcinoid tumor (C1: $P = 0.0004$, C2: $P = 0.0014$, C1+C2: $P = 0.0002$), and testes interstitial cell tumor (C1: $P = 0.0002$, C2: $P = 0.0005$, C1+C2: $P < 0.0001$) in male rats.

Pairwise comparisons between both controls and high dose groups showed that there are significant increases in the incidences of stomach carcinoid tumor in both sexes (female: $P < 0.0001$; male: $P = 0.0005$) and in the incidences of testes interstitial cell tumor ($P < 0.0001$) in males. The pairwise comparison between high dose and recovery groups showed that there is a significant decrease in the incidence of adrenal gland pheochromocytoma in males ($P = 0.0365$).

VI.c. The First Mouse Study - TD91-025 (Report # R&D/93/547)

The Cox and the generalized Wilcoxon methods were used to test the heterogeneity in survival distribution. The test results revealed that there was a statistically significant difference (at 0.05 level) in the survival distribution in male mice in both tests. There was no statistically significant difference (at 0.05 level) in the survival distribution in female mice from the Cox test. However, there was a statistically significant difference in the survival distribution in females in the generalized Wilcoxon test. The different results from the above two tests are due to the fact that the generalized Wilcoxon test places greater weights on early deaths in a study and that the Cox test places equal weights on all deaths.

Applying Peto's method and an exact permutation trend test to test the positive linear trend in intercurrent mortality and incidental tumor rates, the results of the analyses showed that there were significant (at 0.05 level) linear trends in the intercurrent mortality rate in female ($p = 0.016$) and male ($P = 0.0011$) mice.

Results of tumor data analyses showed that there were significant positive linear trends in the liver hepatocellular adenoma ($P = 0.0004$) and hepatocellular adenoma/carcinoma ($P = 0.0001$) in females and in stomach fundus, carcinoid intramucosal/invasive ($p = 0.0401$) in male mice. The pairwise comparisons between the high dose and control groups also showed that there are significantly higher incidence rates in the liver hepatocellular adenoma ($P = 0.0188$) and hepatocellular adenoma/carcinoma ($P = 0.008$) in females but not in stomach fundus, carcinoid intramucosal/invasive ($p = 0.5375$) in male mice.

Comparing the incidence rates of liver hepatocellular adenoma (8.57%) and combined adenoma/carcinoma (10%) of high dose female group in this study with those of historical control data of the 13 studies in Table 3.1, we found that the incidences of above tumors exceeded the historical control range based on those 12 historical studies.

VI.d. The Second Mouse Study - TD91-276 (Report # R&D/93/731)

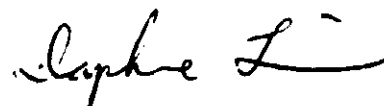
The Cox and the generalized Wilcoxon methods were used to test the heterogeneity in survival distribution. The test results revealed that there were statistically significant differences in the survival distribution in both sexes.

Applying Peto's method to test the positive linear trend in intercurrent mortality rates, the results of the analyses showed that there were significant (at 0.05 level) differences in the intercurrent mortality rate in female ($p < 0.0001$) and male ($p < 0.0001$) mice.

Since there were only control and high dose groups/sex in the study, the age-adjusted pairwise comparison was used to test the difference

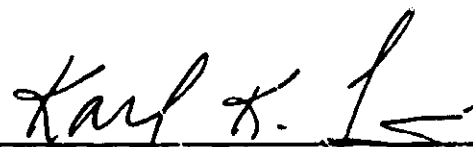
in the tumor data. The results of the above analyses showed that there were significant (at 0.05 level) higher incidences rates in the liver hepatocellular adenoma ($p = 0.0184$) in females, and in the liver hepatocellular adenoma ($p = 0.0002$), hepatocellular carcinoma ($p = 0.0087$), hepatocellular adenoma/carcinoma ($p = 0.0003$), and testes adenoma, rete testis ($p = 0.0451$) in male mice.

Comparing the incidence rates of liver hepatocellular adenoma (21.42%), hepatocellular carcinoma (12.85%), and combined adenoma/carcinoma (27.14%) of high dose male group and liver hepatocellular adenoma (5.71%) of high dose female group in this study with those of historical control data in Table 3.1, we found that the incidences of the above tumors were within the historical control ranges.



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Concur:

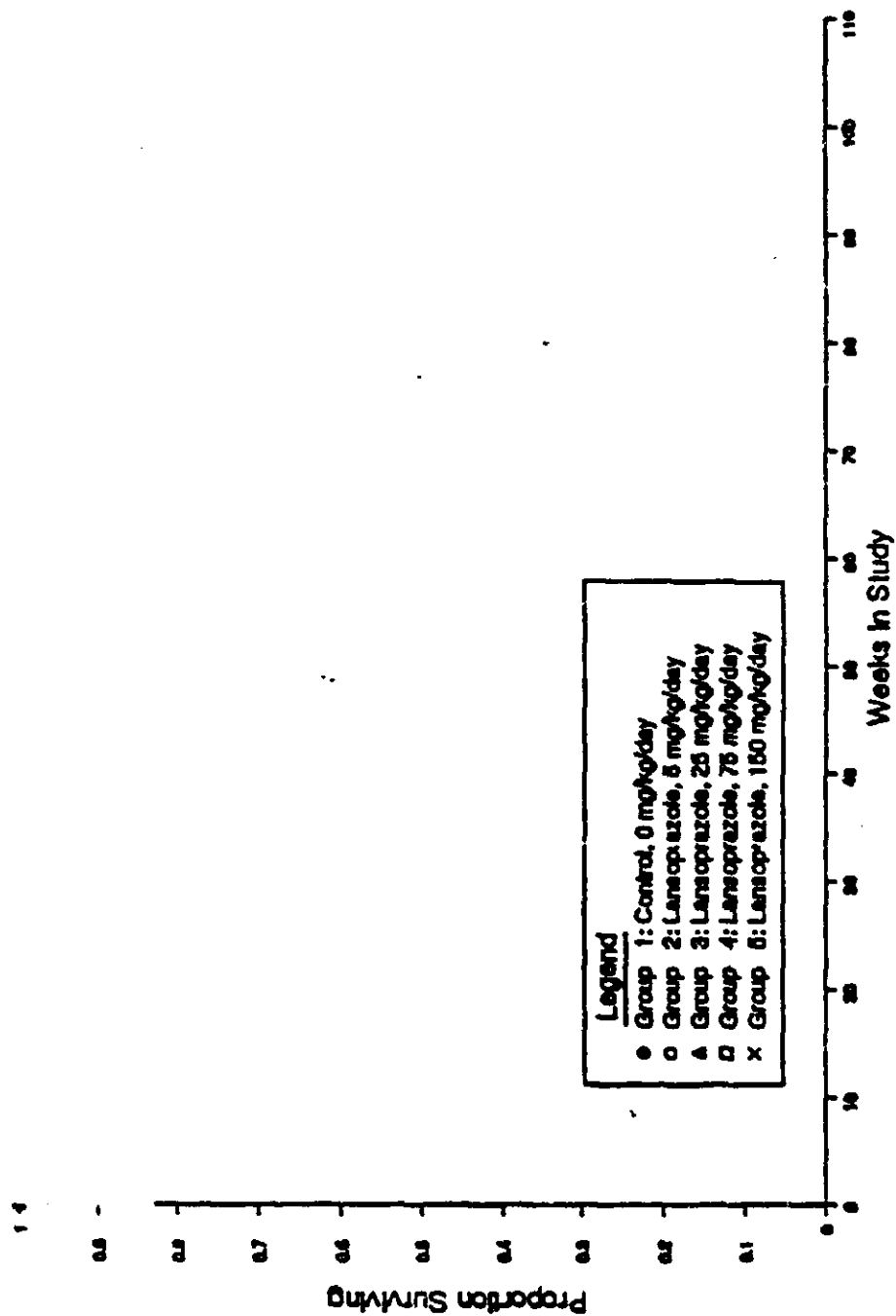

6/15/94
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Figure 1. Kaplan-Meier Survival Curves (Groups 1 to 5) - Males



RAD/93/515 - Statistical Report
Study No. TA91-024

Figure 2. Kaplan-Meier Survival Curves (Groups 1 to 5) - Females

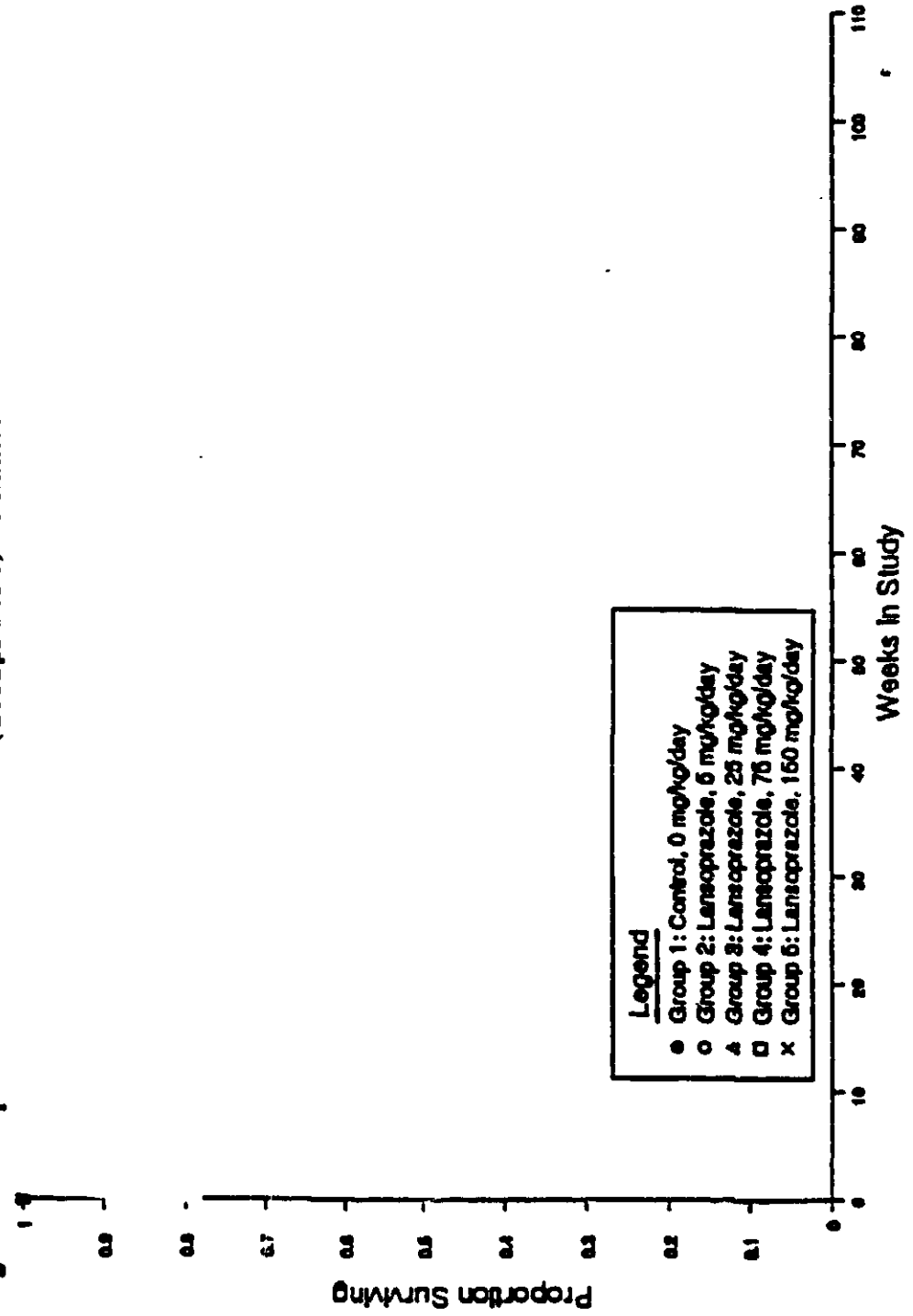


Figure 1.3

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R&D/93/515 - Statistical Report
Study No. TA91-024

Figure 3. Kaplan-Meier Survival Curves (Groups 1, 5 and 12) - Males

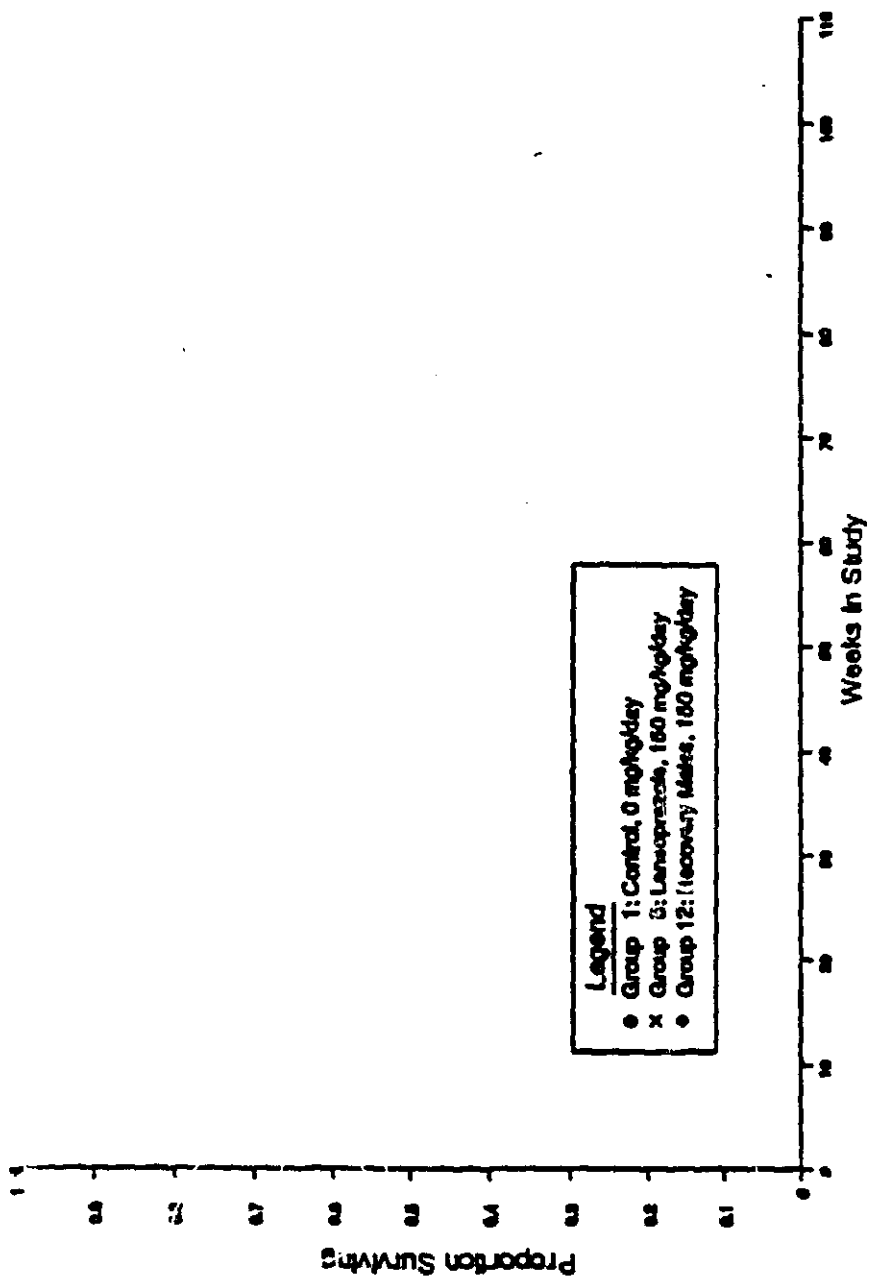


Figure 2.1

1148/CA

FIG. 2 KAPLAN-MEIER SURVIVAL CURVES FOR RAT

SEX=M

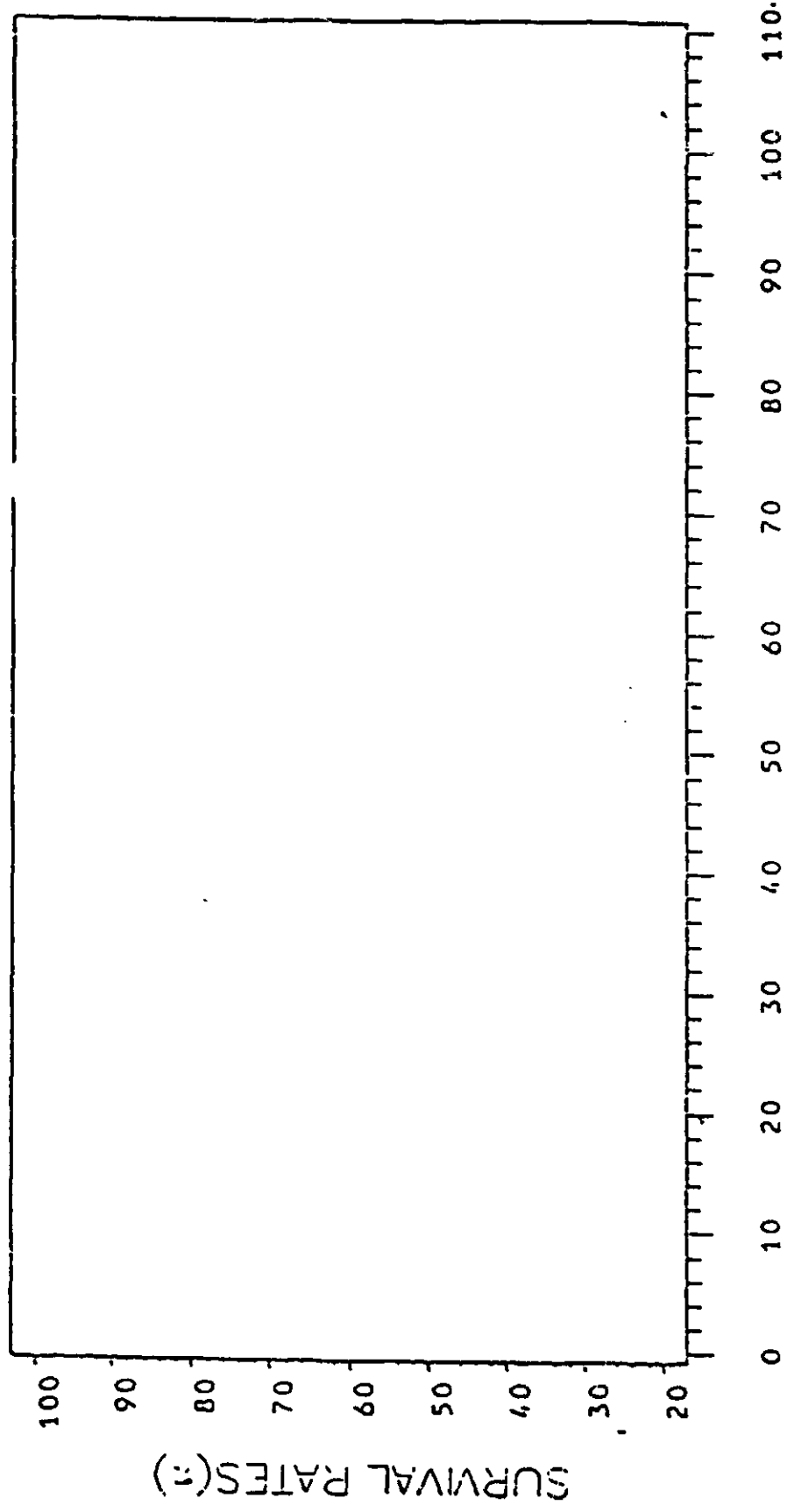


Fig. - 2.2

11148/CA

FIG. 2 KAPLAN-MEIER SURVIVAL CURVES FOR RAT
SEX=F

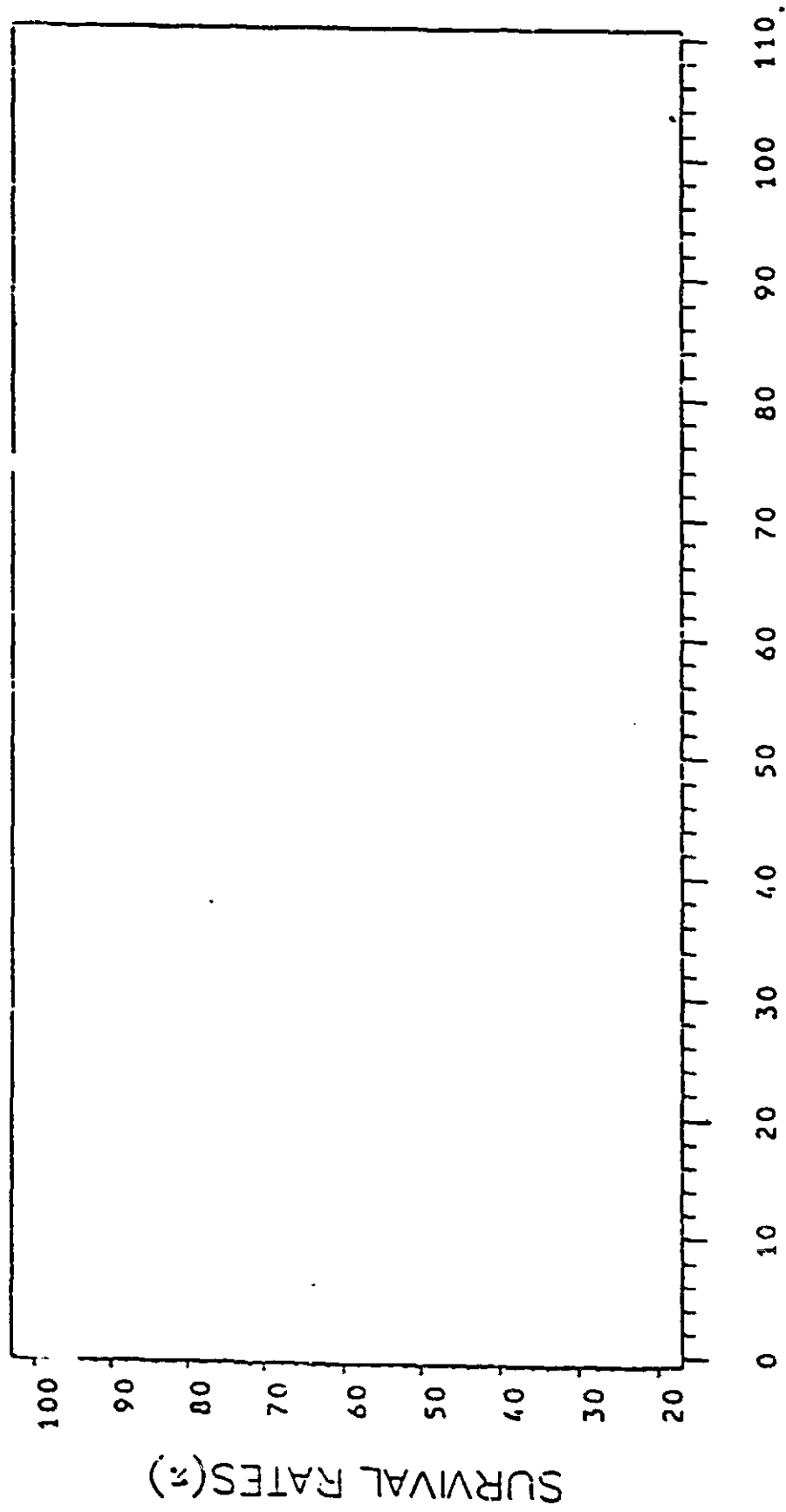


Figure 5.-

Figure 1. Kaplan-Meier Survival Curves - Males

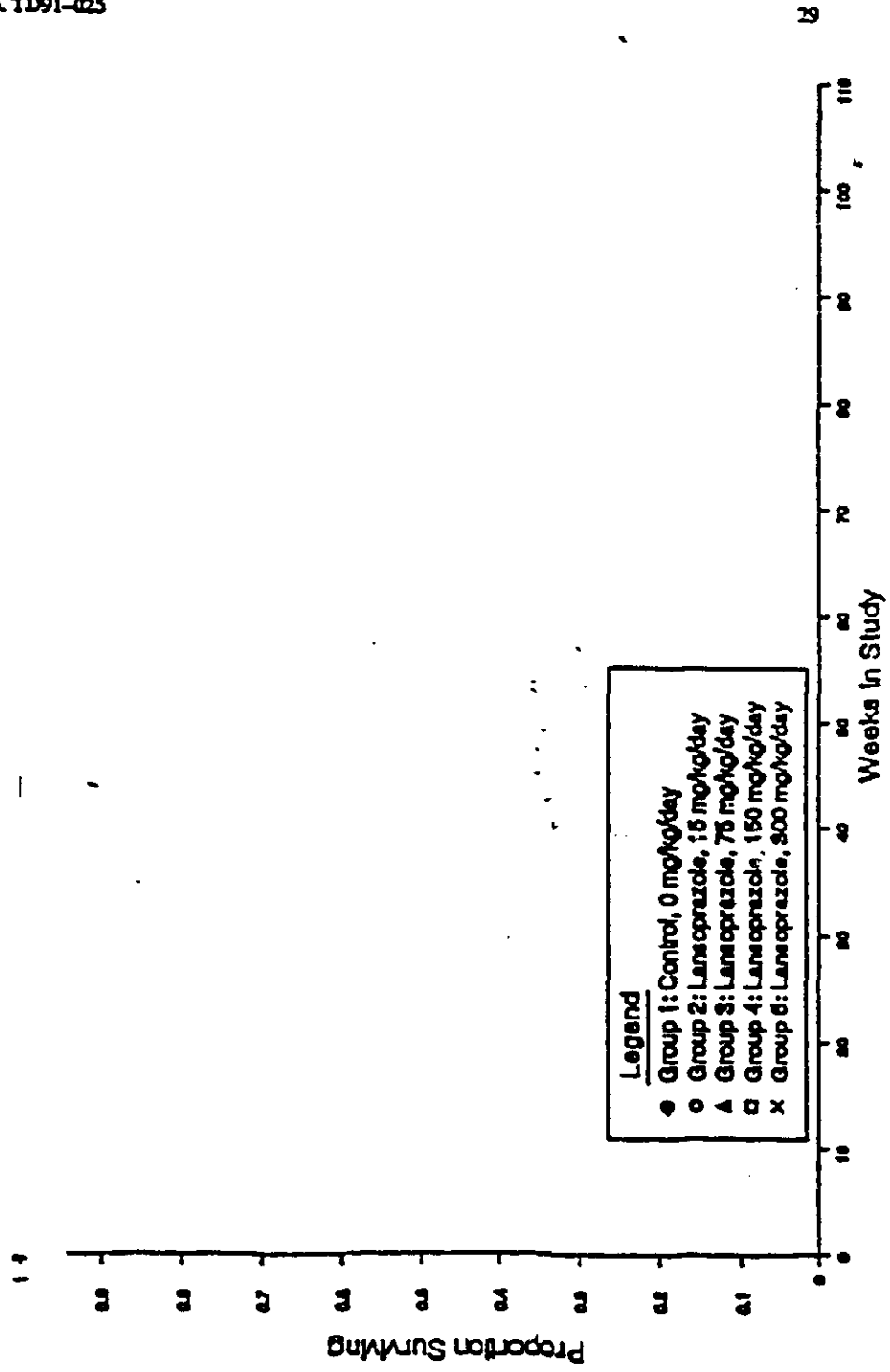


Fig. 3.2

Figure 2. Kaplan-Meier Survival Curves - Females

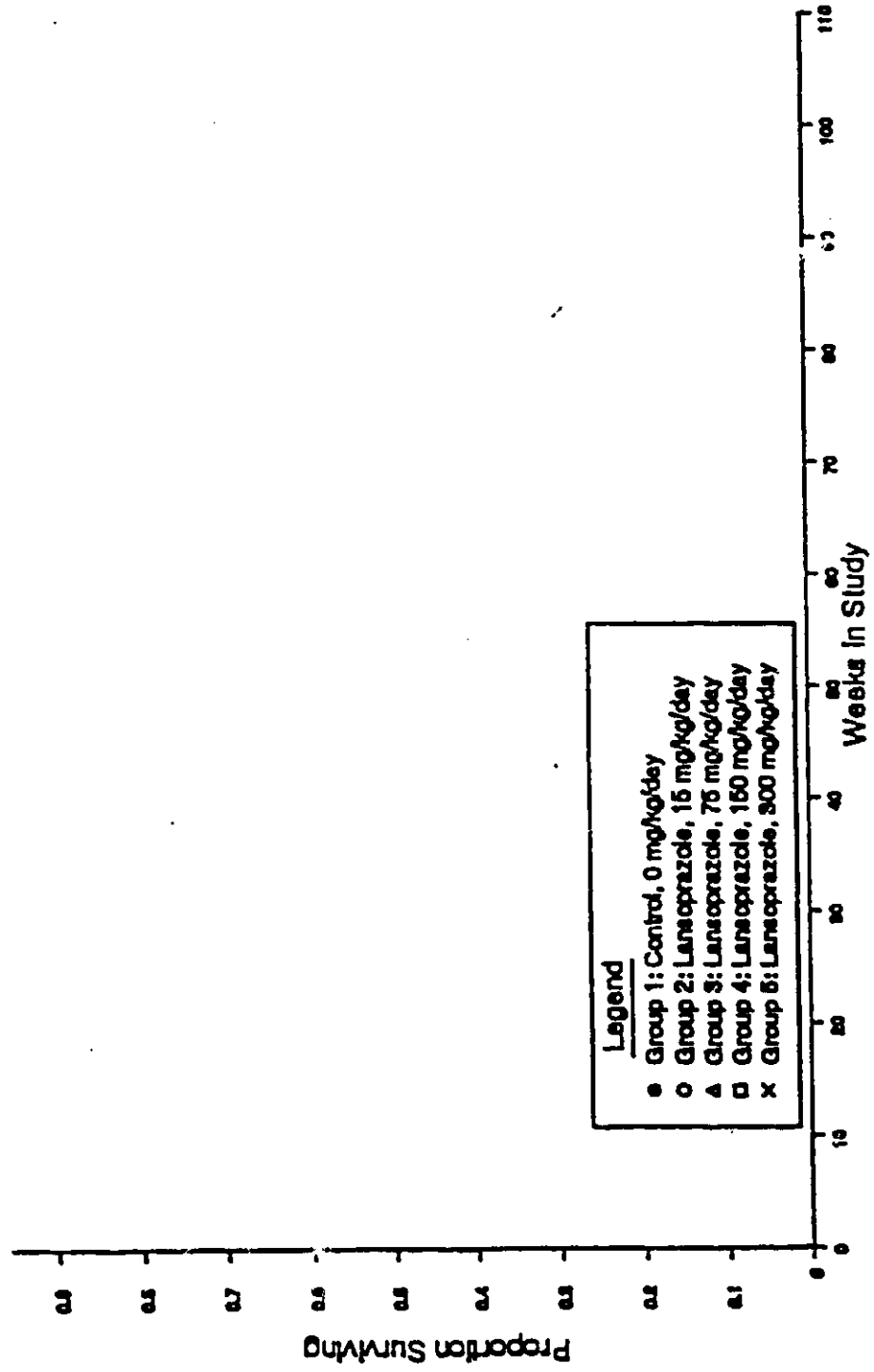


Figure 4.1

Figure 1. Kaplan-Meier Survival Curves - Males

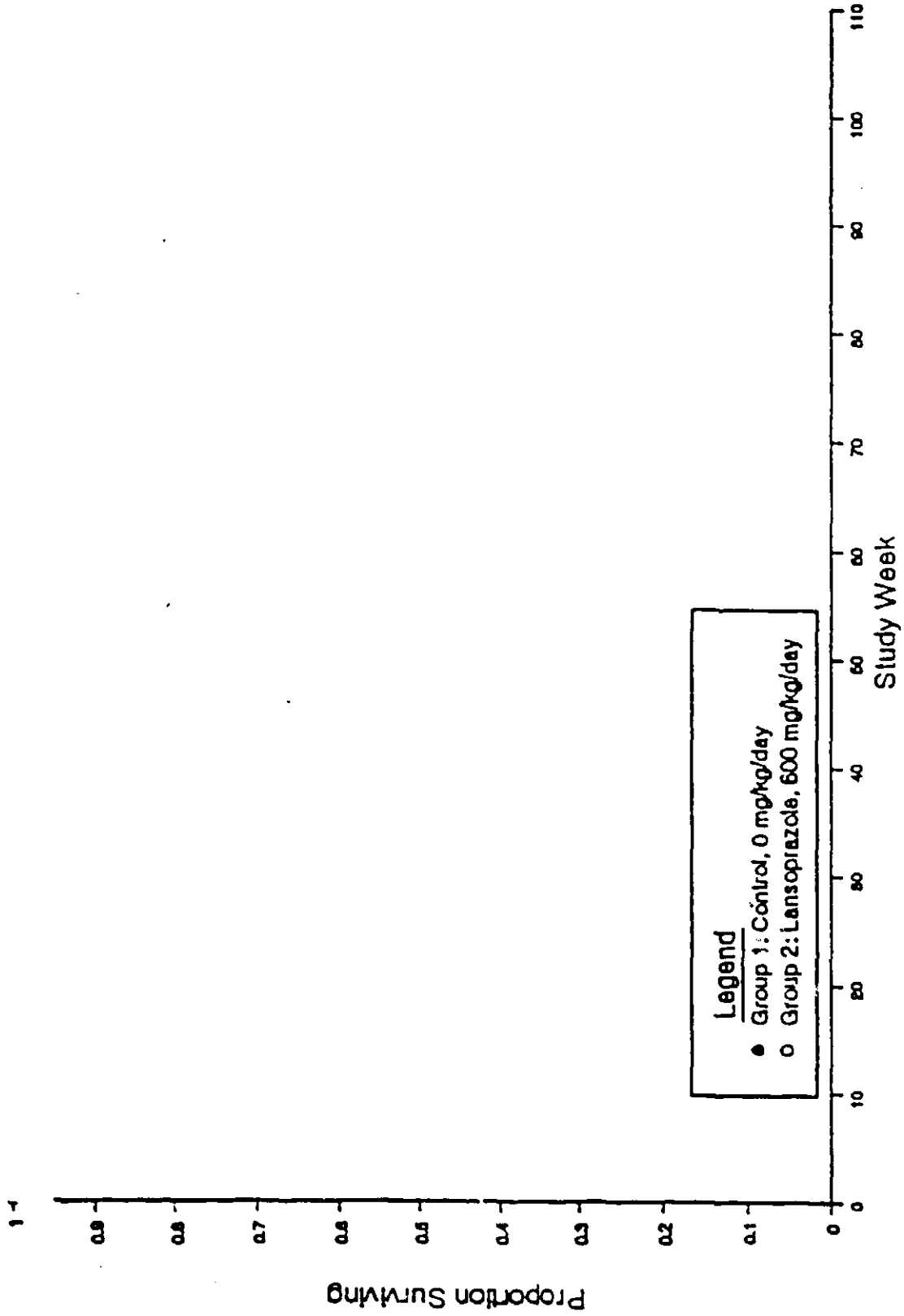


Figure 2.2

Figure 2. Kaplan-Meier Survival Curves - Females

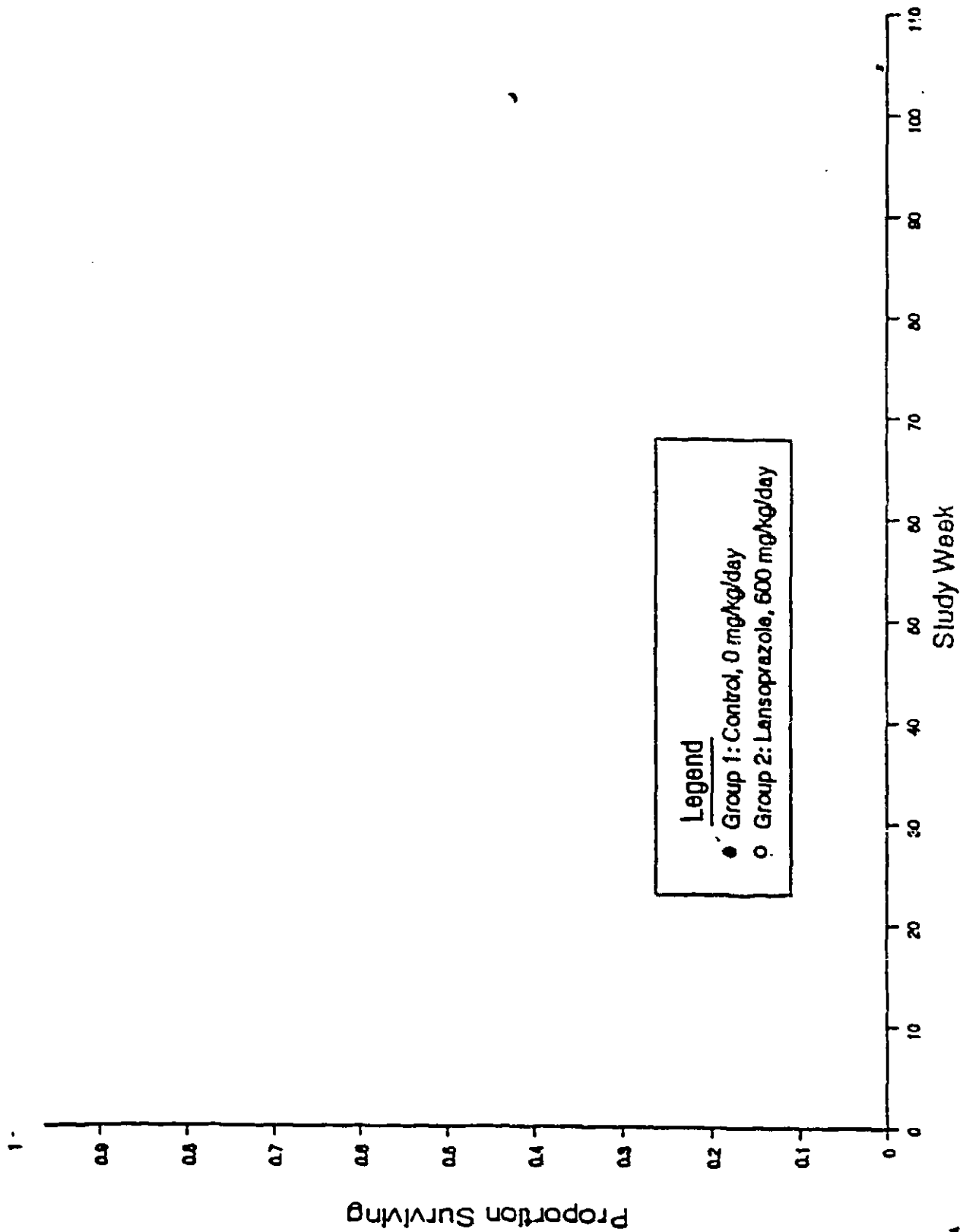


Table 1.1
Intercurrent Mortality Rates
Male Rats

<u>Weeks</u>	<u>Control</u>			<u>Low</u>			<u>Medium-1</u>			<u>Medium-2</u>			<u>High</u>		
	S	D	%	S	D	%	S	D	%	S	D	%	S	D	%
0-50	70	2	2.8	70	7	10	70	8	11.4	70	6	8.6	70	8	11.4
51-80	68	15	22.1	63	11	17.5	62	10	16.1	64	12	18.7	62	10	16.1
81-104	53	23	43.4	52	27	51.9	52	25	48.1	52	21	40.4	52	25	48.1
Term.	30			25			27			31			27		

Peto Test: p-value = 0.4737

Female Rats

<u>Weeks</u>	<u>Control</u>			<u>Low</u>			<u>Medium-1</u>			<u>Medium-2</u>			<u>High</u>		
	S	D	%	S	D	%	S	D	%	S	D	%	S	D	%
0-50	70	3	4.3	70	1	1.4	70	5	7.1	70	5	7.1	70	3	4.3
51-80	67	18	26.9	69	8	11.6	65	14	21.5	65	8	12.3	67	9	13.4
81-104	49	25	51	61	18	29.5	51	23	45.1	57	18	31.6	58	16	27.6
Term.	24			43			28			39			42		

Peto Test: p-value = 0.0193

Notes: S: Number of animals starting during the period
D: Deaths
%: Percent of death during the period

Table 1.2
Tumor Incidence Rates
Female Rats, Stomach (Fundus) Carcinoid, Intramucosal

<u>Weeks</u>	<u>Control</u>		<u>Low</u>		<u>Medium-1</u>		<u>Medium-2</u>		<u>High</u>	
	T	N	T	N	T	N	T	N	T	N
0-50	0	3	0	1	0	5	0	5	0	3
51-80	0	18	0	8	0	14	0	8	0	9
81-104	0	25	0	18	0	23	2	18	1	16
Terminal	0	24	3	43	8	28	13	39	13	42
<u>Total</u>	0	70	3	70	8	70	15	70	14	70

Peto Test: p-value = 0.0002
Pairwise Comparison: High vs. Control: P-value = 0.0005 (one-sided)

Table 1.3
Tumor Incidence Rates
Female Rats, Stomach (Fundus) Carcinoid, Invasive

<u>Weeks</u>	<u>Control</u>		<u>Low</u>		<u>Medium-1</u>		<u>Medium-2</u>		<u>High</u>	
	T	N	T	N	T	N	T	N	T	N
0-50	0	3	0	1	0	5	0	5	0	3
51-80	0	18	0	8	0	14	0	8	0	9
81-104	0	25	0	18	2	23	2	18	2	16
Terminal	0	24	3	43	5	28	14	39	14	42
<u>Total</u>	0	70	3	70	7	70	16	70	16	70

Peto Test: p-value < 0.0001
Pairwise Comparison: High vs. Control: P-value = 0.0001 (one-sided)

Notes: T: Number of necropsies with the above tumor.
N: Number of necropsies.

Table 1.4
Tumor Incidence Rates
Female Rats, Stomach (Fundus) Carcinoid, Intramucosal/Invasive

Weeks	Control		Low		Medium-1		Medium-2		High	
	T	N	T	N	T	N	T	N	T	N
0-50	0	3	0	1	0	5	0	5	0	3
51-80	0	18	0	8	0	14	0	8	0	9
81-104	0	25	0	18	2	23	4	18	2	16
Terminal	0	24	5	43	10	28	19	39	19	42
Total	0	70	5	70	12	70	23	70	21	70

Peto Test: p-value < 0.0001
Pairwise Comparison: High vs. Control: P-value < 0.0001 (one-sided)

Table 1.5
Tumor Incidence Rates
Female Rats, Liver Hepatocellular Adenoma

Weeks	Control		Low		Medium-1		Medium-2		High	
	T	N	T	N	T	N	T	N	T	N
0-50	0	3	0	1	0	5	0	5	0	3
51-80	0	18	0	8	0	14	0	8	0	9
81-104	0	25	0	18	0	23	0	18	1	16
Terminal	1	24	0	43	0	28	0	39	4	42
Total	1	70	0	70	0	70	0	70	5	70

Peto Test: p-value = 0.0041
Pairwise Comparison: High vs. Control: P-value = 0.2125 (one-sided)

Notes: T: Number of necropsies with the above tumor.
N: Number of necropsies.

Table 1.6
Tumor Incidence Rates
Female Rats, Uterus Squamous cell carcinoma

Weeks	Control		Low		Medium-1		Medium-2		High	
	T	N	T	N	T	N	T	N	T	N
0-50	0	3	0	1	0	5	0	5	0	3
51-80	0	18	0	8	0	14	0	8	0	9
81-104	0	25	0	18	0	23	0	18	1	16
Terminal	0	24	0	43	0	28	0	39	1	42
Total	0	70	0	70	0	70	0	70	2	70

Peto Test: p-value = 0.0382
 Pairwise Comparison: High vs. Control: P-value = 0.2483 (one-sided)

Table 1.7
Tumor Incidence Rates
Male Rats, Testes Interstitial Cell Benign Tumor

Weeks	Control		Low		Medium-1		Medium-2		High	
	T	N	T	N	T	N	T	N	T	N
0-50	0	2	0	7	0	8	0	6	0	8
51-80	0	15	0	11	0	10	4	12	7	10
81-104	1	23	1	27	4	25	14	21	18	25
Terminal	1	30	3	25	5	27	21	31	22	27
Total	2	70	4	70	9	70	39	70	47	70

Peto Test: p-value < 0.0001
 Pairwise Comparison: High vs. Control: P-value < 0.0001 (one-sided)

Notes: T: Number of necropsies with the above tumor.
 N: Number of necropsies.

Table 1.8
 Tumor Incidence Rates
 Male Rats, Testes Interstitial Cell Benign Tumor

<u>Weeks</u>	<u>Control</u>		<u>High</u>		<u>Recovery</u>	
	T	N	T	N	T	N
0-50	0	2	0	8	1	9
51-80	0	15	7	10	7	13
81-104	1	23	18	25	9	15
Terminal	1	30	22	27	19	33
<u>Total</u>	<u>2</u>	<u>70</u>	<u>47</u>	<u>70</u>	<u>36</u>	<u>70</u>

Pairwise Comparison: Recovery vs. Control: p-value < 0.0001 (one-sided)

Recovery vs. High: p-value = 0.04 (one-sided)

Notes: T: Number of necropsies with the above tumor.
 N: Number of necropsies.

Table 4

International Research and Development Corporation
 Historical Control Data 2-Year CD Rat
 Neoplastic Lesions - MALE

STUDY INITIATION/ TERMINATION DATES ROUTE OF ADMINISTRATION NUMBER OF ANIMALS INITIATED ON STUDY	A		B		C		D		E		F		G		H		I	
	70	130	70	70	70	70	70	70	50	50	60	60	70	60	60	60	60	75
EXAMINATION GROUPS	C-1	C-2	C-1	C-2	C-1	C-2	C-1	C-2	C-1	C-2	C-1	C-2	C-1	C-2	C-1	C-2	C-1	C-2
Interstitial cell tumor, benign inc.	(69)	(129)	(70)	(18)	(69)	(17)	(50)	(50)	(50)	(60)	(60)	(70)	(60)	(60)	(60)	(60)	(75)	(75)
% inc.																		
Interstitial cell tumor, malignant inc.																		
% inc.																		
Interstitial cell tumor, benign inc.																		
% inc.																		
Mesothelioma, benign inc.																		
% inc.																		
Mesothelioma, malignant inc.																		
% inc.																		

C-1 = Control group
 C-2 = Vehicle or comparative control group
 () = Number of animals examined microscopically
 inc. = Incidence
 % inc. = Percent of incidence

Table 1.4 (continued)

International Research and Development Corporation
 Historical Control Data 2-Year CD Rat
 Neoplastic Lesions - MALE

STUDY	J	K	L
INITIATION/	9 08 88/	2 10 89/	4-13-89/
TERMINATION DATES	9 08 90	2 19 91	4-26-91
HOUSE IN ADMINISTRATION	Dietary	Dietary	Gavage
NUMBER OF ANIMALS INITIATED ON STUDY	60	50	75
CONTROL GROUPS	C-1	C-1	C-2
Interstitial cell tumor, benign	(60)	(50)	(0)
% Inc.			(75)
Interstitial cell tumor, malignant			
% Inc.			
Leydig Cell tumor, benign			
% Inc.			
Mesothelioma, benign			
% Inc.			
Mesothelioma, malignant			
% Inc.			

C-1 = Control group
 C-2 = Vehicle or comparative control group
 () = Number of animals examined microscopically
 Inc. = Incidence
 % Inc. = Percent of incidence

Table 2.2
Intercurrent Mortality Rates
Male Rats

<u>Weeks</u>	<u>Control-1</u>			<u>Control-1</u>			<u>Low</u>			<u>Medium</u>			<u>High</u>		
	S	D	%	S	D	%	S	D	%	S	D	%	S	D	%
0-50	60	2	3.3	60	4	6.6	60	3	5	60	2	3.3	60	3	5
51-80	58	19	32.7	56	19	33.9	57	13	22.8	58	16	27.6	57	12	21.1
81-97	39	20	51.3	37	17	45.9	44	21	47.7	42	23	54.7	45	18	40
Term.	19			20			23			19			27		

Peto Test: C1: p-value = 0.0849
C2: p-value = 0.081
C1+C2: p-value = 0.0556

Female Rats

<u>Weeks</u>	<u>Control-1</u>			<u>Control-1</u>			<u>Low</u>			<u>Medium</u>			<u>High</u>		
	S	D	%	S	D	%	S	D	%	S	D	%	S	D	%
0-50	60	0	0	60	2	3.3	60	1	1.6	60	0	0	60	3	5
51-80	60	20	33.3	58	17	29.3	59	12	20.3	60	6	10	57	10	17.5
81-104	40	26	65	41	20	48.8	47	29	61.7	54	32	59.2	47	19	40.4
Term.	14			21			18			22			28		

Peto Test: C1: p-value = 0.0094
C2: p-value = 0.0508
C1+C2: p-value = 0.0096

Notes: S: Number of animals starting during the period
D: Deaths
%: Percent of death during the period

Table 2.3
Tumor Incidence Rates
Female Rats, Stomach carcinoid Tumor

<u>Weeks</u>	<u>Control-1</u>		<u>Control-2</u>		<u>Low</u>		<u>Medium</u>		<u>High</u>	
	T	N	T	N	T	N	T	N	T	N
0-50	0	0	0	2	0	1	0	0	0	3
51-80	0	20	0	17	1	12	0	6	0	10
81-104	0	26	0	20	1	29	7	32	5	19
Terminal	0	14	1	21	4	18	8	22	19	28
<u>Total</u>	0	60	1	60	6	60	15	60	24	60

Peto Test: C1: p-value < 0.0001

C2: p-value < 0.0001

C1+C2: p-value < 0.0001

Pairwise Comparison: High vs. Controls: P-value < 0.0001 (one-sided)

Table 2.4
Tumor Incidence Rates
Female Rats, Uterus Squamous cell carcinoma

<u>Weeks</u>	<u>Control-1</u>		<u>Control-2</u>		<u>Low</u>		<u>Medium</u>		<u>High</u>	
	T	N	T	N	T	N	T	N	T	N
0-50	0	0	0	2	0	1	0	0	0	3
51-80	0	20	0	17	0	12	0	6	0	10
81-104	0	26	0	20	0	29	2	32	1	19
Terminal	0	14	0	21	0	18	0	22	1	28
<u>Total</u>	0	60	0	60	0	60	2	60	2	60

Peto Test: C1: p-value = 0.0556

C2: p-value = 0.0596

C1+C2: p-value = 0.0297

Pairwise Comparison: High vs. Controls: P-value = 0.1299 (one-sided)

Notes: T: Number of necropsies with the above tumor.

N: Number of necropsies.

Table 2.5
Tumor Incidence Rates
Male Rats, Liver Hepatocellular Adenoma

Weeks	Control-1		Control-2		Low		Medium		High	
	T	N	T	N	T	N	T	N	T	N
0-50	0	2	0	4	0	3	0	2	0	3
51-80	1	19	0	19	0	13	0	16	0	12
81-97	1	20	0	17	2	21	1	23	3	18
Terminal	3	19	0	20	0	23	3	19	4	27
Total	5	60	0	60	2	60	4	60	7	60

Peto Test: C1: p-value = 0.1381

C2: p-value = 0.0071

C1+C2: p-value = 0.0351

Pairwise Comparison: High vs. Controls: P-value = 0.0965 (one-sided)

Table 2.6
Tumor Incidence Rates
Male Rats, Stomach Carcinoid Tumor

Weeks	Control-1		Control-2		Low		Medium		High	
	T	N	T	N	T	N	T	N	T	N
0-50	0	2	0	4	0	3	0	2	0	3
51-80	0	19	0	19	0	13	0	16	1	12
81-97	0	20	0	17	0	21	1	23	3	18
Terminal	0	19	1	20	1	23	3	19	5	27
Total	0	60	1	60	1	60	4	60	9	60

Peto Test: C1: p-value = 0.0004

C2: p-value = 0.0014

C1+C2: p-value = 0.0002

Fairwise Comparison: High vs. Controls: P-value = 0.0005 (one-sided)

Notes: T: Number of necropsies with the above tumor.

N: Number of necropsies.

Table 2.7
Tumor Incidence Rates
Male Rats, Testes Interstitial Cell Tumor

<u>Weeks</u>	<u>Control-1</u>		<u>Control-2</u>		<u>Low</u>		<u>Medium</u>		<u>High</u>	
	T	N	T	N	T	N	T	N	T	N
0-50	0	2	0	4	0	3	0	2	0	3
51-80	0	19	0	19	0	13	1	16	2	12
81-97	0	20	1	17	0	21	1	23	2	18
Terminal	0	19	0	20	2	23	5	19	8	27
<u>Total</u>	<u>0</u>	<u>60</u>	<u>1</u>	<u>60</u>	<u>2</u>	<u>60</u>	<u>7</u>	<u>60</u>	<u>12</u>	<u>60</u>

Pe+o Test: C1: p-value = 0.0002

C2: p-value = 0.0005

C1+C2: p-value < 0.0001

Pairwise Comparison: High vs. Controls: P-value < 0.0001 (one-sided)

Table 2.8
Tumor Incidence Rates
Male Rats, Adrenal Gland Pheochromocytoma

<u>Weeks</u>	<u>High</u>		<u>Recovery</u>	
	T	N	T	N
0-50	0	3	0	2
51-78	0	12	0	8
78-97	2	18	2	28
Terminal (98/98-106)	6	27	0	22
<u>Total</u>	<u>8</u>	<u>60</u>	<u>2</u>	<u>60</u>

Pairwise Comparison: p-value = 0.0365 (one-sided)

Notes: T: Number of necropsies with the above tumor.
N: Number of necropsies.

INTERNATIONAL RESEARCH AND DEVELOPMENT CORPORATION
 HISTORICAL CONTROL DATA - NEOPLASTIC LESIONS
 TWO-YEAR CD-1 MOUSE - MALE

STUDY	A	B	C	D	E	F	G	H	I
INITIATION DATE	6-25-85/ 6-26-87	8-22-85/ 8-25-87	6-20-86/ 6-21-88	6-24-86/ 6-27-88	11-03-86/ 11-04-88	2-10-87/ 1-05-89	1-15-87/ 1-16-89	1-30-87/ 2-09-89	1-29-87/ 2-14-89
TERMINATION DATE									
ROUTE OF ADMIN.	Dietary	Gavage	Dietary	Dietary	Dietary	Gavage	Drinking Water	Dietary	Gavage
NUMBER OF ANIMALS INITIATED ON STUDY	50	50	50	50	60	60	90	50	55
CONTROL GROUPS	C-1	C-1	C-1	C-1	C-1	C-1	C-1	C-1	C-1
	(50)	(50)	(50)	(50)	(60)	(60)	(90)	(50)	(55)
Liver Hemangioma				(16)	(24)	(60)	(90)	(50)	(55)
inc.									
x inc.									
Hemangiosarcoma									
inc.									
x inc.									
Hepatocellular adenoma									
inc.									
x inc.									
Hepatocellular carcinoma									
inc.									
x inc.									
Hepatocellular adenoma/carcinoma									
inc.									
x inc.									

C-1 = Control group
 C-2 = Vehicle or comparative control group
 () = Number of animals examined at necropsy
 () = Number of animals examined microscopically
 inc. = Incidence
 x inc. = Percent of incidence

Table (continued)

INTERNATIONAL RESEARCH AND DEVELOPMENT CORPORATION
 HISTORICAL CONTROL DATA - NEOPLASTIC LESIONS
 TWO-YEAR CD-1 MOUSE - MALE

STUDY	J	K	L	M
INITIATION DATE	8-13-87/	9-08-88/	12-06-88/	3-11-91/
TERMINATION DATE	8-12-89	9-24-90	12-07-90	3-19-93
ROUTE OF ADMIN.	Drinking water	Dietary	Dietary	Gavage
NUMBER OF ANIMALS INITIATED ON STUDY	90	50	50	70
	C-1	C-1	C-1	C-1
	(90)	(50)	(50)	(70)
CONTROL GROUPS				
Liver Hemangioma				
inc.				
x inc.				
Hemangiosarcoma				
inc.				
x inc.				
Hepatocellular adenoma				
inc.				
x inc.				
Hepatocellular carcinoma				
inc.				
x inc.				
Hepatocellular adenoma/carcinoma				
inc.				
x inc.				

C-1 = Control group
 C-2 = Vehicle or comparative control group
 () = Number of animals examined microscopically
 inc. = incidence
 x inc. = Percent of incidence

Tabl (continued)

INTERNATIONAL RESEARCH AND DEVELOPMENT CORPORATION
 HISTORICAL CONTROL DATA - NEOPLASTIC LESIONS
 TWO-YEAR CD-1 MOUSE - FEMALE

STUDY	J	K	L	M
INITIATION DATE	5-12-87/	9-08-88/	12-06-88/	3-05-91/
TERMINATION DATE	5-12-89	9-24-90	12-07-90	3-12-93
ROUTE OF ADMIN.	Drinking Water	Dietary	Dietary	Gavage
NUMBER OF ANIMALS INITIATED ON STUDY	90	50	50	70
CONTROL GROUPS	C-1	C-1	C-1	C-1 C-2
Liver Hemangioma	(89)	(50)	(50)	(70) (70)
inc.				
% inc.				
Hemangiosarcoma				
inc.				
% inc.				
Hepatocellular adenoma				
inc.				
% inc.				
Intratubular carcinoma				
inc.				
% inc.				
Hepatocellular adenoma/ carcinoma				
inc.				
% inc.				

C-1 = Control group
 C-2 = Vehicle or comparative control group
 [] = Number of animals examined at necropsy
 () = Number of animals examined microscopically
 inc. = incidence
 % inc. = Percent of incidence

Table 3.2
Intercurrent Mortality Rates
Male Mice

<u>Weeks</u>	<u>Control</u>			<u>Low</u>			<u>Medium-1</u>			<u>Medium-2</u>			<u>High</u>		
	S	D	%	S	D	%	S	D	%	S	D	%	S	D	%
0-50	70	1	1.4	70	0	0	70	7	10	70	6	8.6	70	6	8.6
51-80	69	6	8.7	70	10	14.3	63	20	31.7	64	23	35.9	64	17	26.6
81-104	63	25	39.7	60	19	31.7	43	13	30.2	41	19	46.3	47	18	38.3
Term.	38			41			30			22			29		

Peto Test: P-value = 0.0011

Female Mice

<u>Weeks</u>	<u>Control</u>			<u>Low</u>			<u>Medium-1</u>			<u>Medium-2</u>			<u>High</u>		
	S	D	%	S	D	%	S	D	%	S	D	%	S	D	%
0-50	70	1	1.4	70	0	0	70	1	1.4	70	1	1.4	70	7	10
51-80	69	11	15.9	70	19	27.1	69	22	31.8	69	19	27.5	63	25	39.7
81-104	58	26	44.8	51	21	41.2	47	22	46.8	50	16	32	38	14	36.8
Term.	32			30			25			34			24		

Peto Test: P-value = 0.016

Notes: S: Number of animals starting during the period
D: Deaths
%: Percent of death during the period

Table 3.3
Tumor Incidence Rates
Female Mice, Hepatocellular adenoma

<u>Weeks</u>	<u>Control</u>		<u>Low</u>		<u>Medium-1</u>		<u>Medium-2</u>		<u>High</u>	
	T	N	T	N	T	N	T	N	T	N
0-50	0	1	0	0	0	1	0	1	0	7
51-80	0	11	0	19	0	22	0	19	0	25
81-104	1	26	0	21	0	22	0	16	0	14
Terminal	0	32	0	30	1	25	4	34	6	24
<u>Total</u>	<u>1</u>	<u>70</u>	<u>0</u>	<u>70</u>	<u>1</u>	<u>70</u>	<u>4</u>	<u>70</u>	<u>6</u>	<u>70</u>

Peto Test: P-value = 0.0004

Pairwise Comparison: High vs. Control: P-value = 0.0188 (one-sided)

Table 3.4
Tumor Incidence Rates
Female Mice, Hepatocellular adenoma/carcinoma

<u>Weeks</u>	<u>Control</u>		<u>Low</u>		<u>Medium-1</u>		<u>Medium-2</u>		<u>High</u>	
	T	N	T	N	T	N	T	N	T	N
0-50	0	1	0	0	0	1	0	1	0	7
51-80	0	11	0	19	0	22	0	19	0	25
81-104	1	26	0	21	0	22	0	16	0	14
Terminal	0	32	0	30	1	25	4	34	7	24
<u>Total</u>	<u>1</u>	<u>70</u>	<u>0</u>	<u>70</u>	<u>1</u>	<u>70</u>	<u>4</u>	<u>70</u>	<u>7</u>	<u>70</u>

Peto Test: P-value = 0.0001

Pairwise Comparison: High vs. Control: P-value = 0.008 (one-sided)

Notes: T: Number of necropsies with the above tumor.
N: Number of necropsies.

Table 3.5
Tumor Incidence Rates
Male Mice, stomach fundus, carcinoid intramucosal/invasive

<u>Weeks</u>	<u>Control</u>		<u>Low</u>		<u>Medium-1</u>		<u>Medium-2</u>		<u>High</u>	
	T	N	T	N	T	N	T	N	T	N
0-50	0	1	0	0	0	7	0	6	0	6
51-80	0	6	0	10	0	20	0	23	2	17
81-104	0	25	0	19	0	13	0	19	0	18
Terminal	0	38	0	41	0	30	1	22	0	29
<u>Total</u>	0	70	0	70	0	70	1	70	2	70

Peto Test: P-value = 0.0401

Pairwise Comparison: High vs. Control: P-value = 0.5375 (one-sided)

Notes: T: Number of necropsies with the above tumor.
N: Number of necropsies.

Table 4.1
Intercurrent Mortality Rates
Male Mice

<u>Weeks</u>	<u>Control</u>			<u>High</u>		
	S	D	%	S	D	%
0-50	70	2	2.85	70	6	8.57
51-80	68	10	14.7	64	24	37.5
81-104	58	19	32.75	40	24	60.0
Term.	39			16		

Peto Test: P-value < 0.0001

Female Mice

<u>Weeks</u>	<u>Control</u>			<u>High</u>		
	S	D	%	S	D	%
0-50	70	4	5.71	70	13	18.57
51-80	66	11	16.6	57	30	52.6
81-100	55	25	45.45	27	15	55.5
Term.	30			12		

Peto Test: P-value < 0.0001

Notes: S: Number of animals starting during the period
D: Deaths
%: Percent of death during the period

Table 4.2
Tumor Incidence Rates
Female Mice, Hepatocellular adenoma

<u>Weeks</u>	<u>Control</u>		<u>High</u>	
	T	N	T	N
0-50	0	4	0	13
51-80	0	11	0	30
81-100	0	25	0	15
Terminal	1	30	4	12
<u>Total</u>	<u>1</u>	<u>70</u>	<u>4</u>	<u>70</u>

Pairwise Comparison: p-value = 0.0184 (one-sided)

Table 4.3
Tumor Incidence Rates
Male Mice, Hepatocellular adenoma

<u>Weeks</u>	<u>Control</u>		<u>High</u>	
	T	N	T	N
0-50	0	2	0	6
51-80	1	10	0	24
81-104	2	19	4	24
Terminal	2	39	11	16
<u>Total</u>	<u>5</u>	<u>70</u>	<u>15</u>	<u>70</u>

Pairwise Comparison: p-value = 0.0002 (one-sided)

Notes: T: Number of necropsies with the above tumor.
N: Number of necropsies.

Table 4.4
Tumor Incidence Rates
Male Mice, Hepatocellular Carcinoma

<u>Weeks</u>	<u>Control</u>		<u>High</u>	
	T	N	T	N
0-50	0	2	0	6
51-80	0	10	0	24
81-104	2	19	3	24
Terminal	1	39	6	16
<u>Total</u>	<u>3</u>	<u>70</u>	<u>9</u>	<u>70</u>

Pairwise Comparison: p-value = 0.0087 (one-sided)

Table 4.5
Tumor Incidence Rates
Male Mice, Hepatocellular Adenoma/Carcinoma

<u>Weeks</u>	<u>Control</u>		<u>High</u>	
	T	N	T	N
0-50	0	2	0	6
51-80	1	10	0	24
81-104	4	19	7	24
Terminal	3	39	12	16
<u>Total</u>	<u>8</u>	<u>70</u>	<u>19</u>	<u>70</u>

Pairwise Comparison: p-value = 0.0003 (one-sided)

Notes: T: Number of necropsies with the above tumor.
N: Number of necropsies.

Table 4.6
 Tumor Incidence Rates
 Male Mice, Testis, Adenoma, Rete Testis.

<u>Weeks</u>	<u>Control</u>		<u>High</u>	
	<u>T</u>	<u>N</u>	<u>T</u>	<u>N</u>
0-50	0	2	0	6
51-80	0	10	0	24
81-104	0	19	1	24
Terminal	0	39	2	16
<u>Total</u>	<u>0</u>	<u>70</u>	<u>3</u>	<u>70</u>

Pairwise Comparison: p-value = 0.0451 (one-sided)

Notes: T: Number of necropsies with the above tumor.
 N: Number of necropsies.