e) EE Healing Rates by Baseline Severity

The difference in healing rates for EE by Week 8 in the ITT population for each baseline LA Grade (i.e., the difference in the percentage of patients with healing of EE in the H40 group over that in the O20 group) was 3.0%, 8.1%, 16.8% and 16.2% for LA Grades A, B, C, and D, respectively). These differences were greater at Week 4, when the difference in the percentage of patients with healing of EE in the H40 group over that in the O20 group was 4.5%, 11.8%, 18.7%, and 21.7% for LA Grades A, B, C, and D, respectively.

f) Proportion of Patients Who Exhibited Complete Resolution of Investigator-Recorded Symptoms of GERD After 4 Weeks (Table 22)

- A significantly higher percentage of patients in the H40 group than in the O20 group had complete resolution of heartburn (68.3% vs 58.1%; $p<0.001$) or acid regurgitation (80.1% vs 75.2%; $p=0.003$) by Week 4.

- There were no significant differences between H40 and O20 in the proportions of patients reporting complete resolution of dysphagia or epigastric pain by the end of 4 weeks (Table 22).

TABLE 22
Study No. 222

Number (%) of Patients With Investigator-Recorded Complete Resolution of GERD Symptoms at Week 4
ITT Population

GERD Symptom Treatment Group	N	Week 4	p-value[a]
HEARTBURN			
H 199/18 40 mg qd	1,188	68.3%	<0.001
omeprazole 20 mg qd	1,183	58.1%	
ACID REGURGITATION			
H 199/18 40 mg qd	1,188	80.1%	0.003
omeprazole 20 mg qd	1,182	75.2%	
DYSPHAGIA			
H 199/18 40 mg qd	1,188	92.1%	N.S.
omeprazole 20 mg qd	1,182	91.2%	
EPIGASTRIC PAIN			
H 199/18 40 mg qd	1,188	83.5%	N.S.
omeprazole 20 mg qd	1,182	81.8%	

From sponsor's Table 14.2.13, with major modifications

a) CMH test, comparison of H 199/18 40 mg qd to OME 20 mg qd

g) Assortment of Healing of EE Subgroups

- The subgroups analyzed were gender (M vs F), Age (<65y, ≥65y), race (Caucasian, Black, Asian, Other), *H. pylori* status (positive, negative, missing) and Investigator site.

- No clinically meaningful differences were seen among any of the subgroups examined. As in the study population as a whole, the response rate for each gender subgroup, each age subgroup, each race subgroup (although Asian and "Other" were represented by small numbers of patients) and each *H. pylori* subgroup (most patients were *H. pylori* negative) was higher in the H40 group than in the O20 group.

h) Results of Safety Evaluations

i) Extent of Exposure

- 2,425 patients with EE were randomized to treatment; 2,405 of these received at least one dose of test medication[24] for up to 8 weeks with the following distribution.

	mg qd	n
H 199/18	40	1,205
OME	20	1,200
	Total n =	2,405

ii) Deaths, Other Serious or Potentially Serious AEs

- One death (unrelated to test medication) was reported [Pt. 408/019 in the O20 group died of stab wounds to the heart, aorta and superior vena cava on Day 37 of the trial].

- 16 patients experienced serious AEs in this study. There was no apparent difference between the treatment groups in the proportion of patients (H40 = 9; O20 = 7) with SAEs or discontinuations due to an AE.

- Of the 16 patients with SAEs, 4 were D/C from further treatment (H40 = 3; O20 = 1) due to SAE.

[24] 20 patients (H40=11; O20=9) were excluded from the safety analysis population because they did not take at least one dose of test medication. In these 20 patients, no post-baseline evaluations were completed and there was no documentation of any test medication having been taken. The majority of these patients were lost to follow-up. Others did not meet entry criteria or withdrew consent.

	mg qd	SAEs	Discontinued from Further Treatment
H 199/18	40	9	3[a]
OME	20	7	1
		16[a]	4

a) All of these 16 SAEs were unlikely related to test medication

iii) AEs Leading to Discontinuation (Table 23)

- In Table 34 of their Clinical Report, the sponsor provided a summary of 25 patients who discontinued treatment because of an AE[25] (H40, n=11 (0.9%); O20, n=14 (1.2%).

- From the data summarized in Table 23 of this review, there were no clinically meaningful differences between H40 and O20 groups in the frequency, types or timing of the AEs that led to D/C from the trial and from treatment.

- 7 AE terms were associated with D/C in more than 1 patient: headache (3 O20 patients), diarrhea (1 H40 patient and 2 O20 patients), dizziness (1 H40 patient and 2 O20 patients), urticaria (2 H40 patients), chest pain (2 H40 patients), nausea (2 O20 patients), and rash (1 H40 patient and 1 O20 patient). The investigator considered the adverse events resulting in discontinuation from the study and from study treatment to be of possible or probably relationship to test medication in the majority of patients (H40 = 6/11; O20 = 11/14).

- 3 patients were found to be pregnant during or after treatment with test medication. Patient 069/001 (O20 group) was found to be pregnant shortly after beginning test medication and was discontinued from the study. [Patient 078/016 (O20 group) and Patient 406/016 (H40 group) were both found to be pregnant at completion of the study (Day 39 and Day 66, respectively). As of November 1999, no further follow-up information was available for these pregnancies.]

[25] Action taken with respect to test medication = Test medication stopped on the AE CRF page.

TABLE 23
Study No. 222
Listing of Patients Who Discontinued Treatment or Discontinued the Study Due to an Adverse Event

H 40			O 20		
Patient I.D.	**Preferred Term for AE (Verbatim Term)**		**Patient I.D.**	**Preferred Term for AE (Verbatim Term)**	
001/012 F 52 Caucasian	Urticaria/Dyspnea (Rash with urticaria/Shortness of breath)	**PRO/ POSS**	005/002 M 38 Caucasian	Headache (Headaches)	**PRO**
014/002 F 49 Caucasian	Vision abnormal (Blurred vision)	**UNL**	064/007 M 48 Caucasian	Headache (Headache)	**PRO**
062/009 M 34 Black	Coma (Re-occurrence loss of consciousness)	**UNL**	065/017 M 39 Caucasian	Dizziness (Dizziness)	**POSS**
073/013 F 72 Caucasian	Urticaria (Neck hives)	**POSS**	069/001 F 26 Caucasian	Events of non-medical character[b] (Use during pregnancy)	**UNL**
095/001 M 72 Caucasian	Thrombosis coronary[a] (Coronary Artery occlusion)	**UNL**	102/005 F 52 Caucasian	Vomiting (Vomiting)	**POSS**
131/005 M 50 Caucasian	Insomnia/ Tachycardia (Insomnia/Racing heart)	**PRO/ PRO**	107/011 M 49 Caucasian	Diarrhea/ Headache (Diarrhea/Headache)	
314/011 M 50 Caucasian	Chest pain[a] (Chest pain secondary to GERD)	**UNL**	112/012 F 51 Caucasian	Rash (Generalized body rash)	**PRO**
320/006 F 48 Caucasian	Dizziness (Dizziness)	**PRO**	120/008 F 52 Caucasian	Nausea (Nausea)	**POSS**
321/002 M 50 Caucasian	Rash (Rash)	**PRO**	142/002 F 83 Caucasian	Dizziness (Dizziness)	**POSS**
405/023 F 61 Caucasian	Chest pain[a] (Atypical chest pain)	**UNL**	305/004 M 48 Caucasian	Hepatic neoplasm (Liver lesions)	**UNL**
414/010 F 48 Caucasian	Diarrhea (Diarrhea)	**PRO**	310/014 F 65 Black	Melena/Duodenitis (Fecal occult blood/Duodenal erosion)	**POSS/ POSS**
			408/019 M 45 Caucasian	Accident and/or injury[a] (Stab wounds of heart, aorta & superior vena cava)	**UNL**
			409/018 F 49 Caucasian	Nausea/ Diarrhea (Nausea/Diarrhea)	**PRO/ PRO**
			413/005 M 40 Caucasian	Arthralgia/ Pain/ Edema peripheral (Bilateral knee discomfort/Discomfort in bilateral hands/Edema in bilateral hands)	**PRO/ PRO/ PRO/**

From sponsor's Tables 14.3.1.20 and 16.2.7.1, with major and substantial modifications.
a) There were SAEs (narrative provided in sponsor's Section 12.3.2.)
b) This patient discontinued test medication due to her pregnancy. She was D/C from the trial by sponsor/investigator decision.

iv) Adverse Events

- As summarized in Table 24, there were no clinically meaningful differences between treatment groups in the proportion of patients who reported an AE, treatment related AEs, discontinuation due to an AE, SAEs, nor death (from above-discussed information).

TABLE 24
Study No. 222
Summary of Patients With AEs

AE Category	H 199/18 40 mg qd [n=1,205]	OME 20 mg qd [n=1,200]
I. DURING WEEK 0 TO WEEK 8		
≥ 1 AE	32.2%	34.3%
≥ 1 Treatment-related AE	15.3%	15.1%
Discontinued due to an AE	0.9%	1.2%
≥ 1 Serious AE	0.7%	0.6%
Death	0.0%	0.1%
II. DURING WEEK 0 TO WEEK 4		
≥ 1 AE	28.2%	29.4%
≥ 1 Treatment-related AE	13.2%	14.0%
Discontinued due to an AE	0.8%	0.9%
≥ 1 Serious AE	0.6%	0.4%
Death	0.0%	0.0%
From sponsor's Tables 14.3.1.1 and 14.3.1.2, with major modifications.		

- In Table 25, a summary is given of AEs that occurred in at least 1% of the patients in any treatment group during this study (upper panel=Week 0 to Week 8; lower panel=Week 0 to Week 4). There were no significant differences between the groups.

- The most frequently reported AE was **headache** which occurred in 6.2% of the patients treated with H40 and 5.8% of the patients treated with O20 (Week 0 to Week 8, Table 25). The most frequently reported gastrointestinal side effects were diarrhea, nausea, and abdominal pain. The most frequently occurring AEs during Week 0 to Week 4 were the same as those for Week 0 to Week 8 (table 25).

v) Changes in Laboratory Parameters/Serum Gastrin

- Mean changes from baseline were small and were comparable between the two treatment groups. The laboratory measurement that was most frequently outside predefined limits (identified by the Sponsor as potentially clinically significant) was hemoglobin, for which 13 H40 (1.1%) and 6 O20 (0.5%) patients had values below the predefined lower limit (9.5 g/dL for females and 11.5 g/dL for males).

- Other laboratory values were less frequently observed above or below the predefined limits.

There were no clinically meaningful differences between the treatment groups in the incidence of shifts from WNL to above or below normal limits in individual patients' values.

- Mean increases in serum gastrin were **higher** in the H40 group than in the O20 group, but were an expected outcome of the acid-blocking activity of these PPI agents.

TABLE 25
Study No. 222
Most Frequently Occurring Adverse Events During the Trial:
Patient Incidence at Least 1% in any treatment Group

Body System / Adverse Event	H 199/18 40 mg qd [n=1,205]	OME 20 mg qd [n=1,200]
I. AEs DURING WEEK 0 TO WEEK 8		
Skin and appendages		
Rash	0.9%	1.1%
Central/peripheral nervous system		
Headache	**6.2%**	**5.8%**
Dizziness	1.2%	1.3%
Gastrointestinal system		
Abdominal pain	2.6%	2.7%
Constipation	1.3%	1.0%
Diarrhea	3.9%	4.7%
Eructation	1.5%	1.0%
Flatulence	1.5%	1.9%
Gastritis	1.6%	1.3%
Mouth dry	1.2%	1.1%
Nausea	3.0%	3.0%
Vomiting	0.5%	1.1%
Respiratory system		
Pharyngitis	1.0%	1.2%
Respiratory infection	1.5%	2.0%
Sinusitis	1.9%	1.8%
Body as a Whole		
Accident and/or injury	0.3%	1.0%
Pain	0.6%	1.0%
II. AEs DURING WEEK 0 TO WEEK 4		
Central/peripheral nervous system		
Headache	**5.8%**	**5.4%**
Dizziness	1.0%	1.2%
Gastrointestinal system		
Abdominal pain	2.2%	2.5%
Constipation	1.3%	0.8%
Diarrhea	3.7%	4.3%
Eructation	1.4%	1.0%
Flatulence	1.4%	1.9%
Mouth dry	1.1%	1.1%
Nausea	2.7%	2.9%
Respiratory System		
Pharyngitis	0.9%	1.0%
Respiratory infection	1.4%	1.7%
Sinusitis	1.6%	1.3%

From sponsor's Tables 14.3.1.3 and 14.3.1.4, with major modifications.

vi) Other

POLYPS

- 13 polyps or nodules[26] of the G.I. tract (in 12 patients) identified as AEs by investigators were coded to these preferred terms. The 12 patients included 6 (0.5%) in the H40 group and 6 (0.5%) in the O20 group. All available endoscopy and histology reports were reviewed and relevant information from these patients was summarized in sponsor's Table 36. There was no evidence of adenomatous changes or malignancy. All 12 patients were *H. pylori* negative by serology testing at baseline, and 11 of the 12 patients were *H. pylori* negative by histology baseline (Patient 060/003 was *H. pylori* positive by histology at baseline). Six of the 12 AE reports were from the stomach (3 H40, 3 O20), three were from the duodenum (2 H40, 1 O20), two were from the esophagus (H40=1; O20=1), and 1 patient (Pt. 406/012, O20) had endoscopic findings in both the colon and rectum. Of the 6 patients with gastric polyps and nodules, 4 had polyps or nodules of the antrum and 2 had polyps or nodules of the fundus.

VITAL SIGNS

There were no clinically meaningful changes in any vital sign parameter and no differences between the two treatment groups.

AEs BY SUBGROUPS

- In both the H40 and O20 treatment groups, AE rates were higher for F than for M. However, between the H40 and O20 treatment groups, there were no meaningful effects of gender on the proportion of patients who reported an AE or treatment-related AE, on the proportion of patients who reported a serious AE, nor on the proportion of patients who were discontinued from the study due to an AE. Incidence rates of all AEs by gender and by body system were given in sponsor's Tables 14.3.1.9 (Week 0 to Week 8) and 14.3.1.10 (Week 0 to Week 4).

- There were no meaningful effects of age, either across or within the treatment groups, on the proportion of patients who reported an AE or treatment-related AE, on the proportion of patients who reported a serious AE, nor on the proportion of patients who were discontinued from the study due to an AE. Listings of all AEs by age group and by body system were given in sponsor's Tables 14.3.1.13 (Week 0 to Week 8) and 14.3.1.14 (Week 0 to Week 4).

- Although the sample sizes in the non-Caucasian race subgroups were too small to draw meaningful conclusions, there were no meaningful effects of race apparent, either across or within the treatment groups, on the proportion of patients who reported an AE or treatment-related AE, on the proportion of patients who reported a serious AE, nor on the proportion of

[26] The preferred term from the AED for polyps or nodules of the G.I. tract not believed to be malignant is "G.I. Neoplasm Benign" or "G.I. Neoplasm."

patients who were D/C from the trial due to an AE. Incidence rates of all AEs by race and by body system were given in sponsor's Tables 14.3.1.17 (week 0 to Week 8) and 14.3.1.18 (Week 0 to Week 4).

11. Discussion and Overall Conclusions (Sponsor)

"H 199/18 40 mg qd was a safe and effective treatment for healing of erosive esophagitis, the primary efficacy parameter, within 8 weeks of treatment. The proportion of patients exhibiting healing of EE by Week 8 (ITT population) was significantly higher (p=0.0001) in patients treated with H40 (93.7%) than in patients treated with O20 (84.2%). This difference was also significant at Week 8 in the PP population, as well as in both populations at Week 4 of treatment and when the severity of the patient's EE at baseline was taken into account. Treatment with H40 also produced significant improvements in GERD symptoms, both in time to resolution of heartburn and in proportions of patients with resolution of heartburn and acid regurgitation.

"There were no clinically meaningful differences between the H40 and O20 groups with respect to the proportion of patients experiencing adverse events, not changes in laboratory values or vital signs.

"Overall, H40 showed statistically significant improvements over O20 in healing of EE and resolution of heartburn and acid regurgitation, with a similar safety profile."

12. Reviewer's Additional Comments

Clinical trial under Protocol 222 was one of four critical multicenter studies submitted by the sponsor of this NDA in support of the approval of ESOME Mg for the "short-term treatment of EE associated with GERD". This U.S. trial consisted of two parallel arms: one fixed dose of ESOME (40 mg once-a-day) and OME (20 mg per day), an adequate positive control. As in Study 172, the primary hypothesis was that 4 to 8 weeks of 40 mg ESOME Mg per day will be more effective than OME 20 mg per day in the healing of EE and in the complete resolution of associated GERD symptoms, mainly daytime (and nighttime) heartburn. Although this, as well as Study 172 used a well-designed protocol, it is not a good approach to withdraw from the trial patients whose esophagitis have healed at Week 4 because, in many instances, the esophageal lesions recur (and this could have been detected by Week 8 endoscopy), even when the presumably active treatment is continued.

Study 222 was apparently well-executed. Adherence to the appropriate inclusion-exclusion criteria precluded randomization of experimental subjects with conditions, diseases or concomitant treatments that may confound the results. In study 222, the randomization process was properly executed and accomplished two well-balanced treatment groups with respect to pre-stipulated number of patients per arm, demographic characteristics, severity (LA Classification) of reflux esophagitis, *H. pylori* status and the most commonly used antiulcer/anti-secretory and other medications. As in the other pivotal trials for this indication, analyses of results included evaluations in ITT and PP populations. Of these, the reviewer's comments emphasize results of

analyses in the ITT population. However, results of analyses in the PP population lead to the same conclusions on efficacy as those arrived at using the ITT population.

Examination of the results in the ITT population in Study 222 showed an unequivocal response, as judged by hard endoscopic criteria. This was already shown after 4 weeks of treatment: the healing rates in the ESOME Mg (78.6%) were significantly higher (p=0.001) than the OME group (66.6%). The healing responses were all higher at 8 than at 4 weeks of treatment (ESOME Mg = 89.9%; OME = 80.9%). These results are not surprising because in healing of EE studies, an additional 4 weeks of treatment (regardless of the type of this treatment, including placebo) almost invariably results in a higher benefit than at 4 weeks). The healing rates at 8 weeks resulted in therapeutic gains that were somewhat lower (9%) to those seen at 4 weeks (12%). At 8 weeks, comparing ESOME 40 mg vs omeprazole 20 mg once-a-day yielded highly statistically significant differences (p-values = 0.0001) in both study populations. In the main, analyses in the PP population confirmed those in the ITT analyses for both 4 and 8 weeks data.

With regards to EE symptoms, there was a significant difference for complete resolution of HB and acid regurgitation between H40 and O20 qd but no differences between these treatment groups in the proportion of patients reporting complete resolution of dysphagia or epigastric pain by the end of 4 weeks of treatment.

In study 222, results of safety evaluations demonstrated that the dose of 40 mg of ESOME Mg, given once-a-day was generally safe and well-tolerated. The population for safety analyses included 1,205 patients in the H40 group and 1200 in the O20 group. One patient (O20 group) died during the study, unrelated to test medication. There was no marked differences between H40 and O20 in the incidence of SAEs or discontinuation due to AEs. Most AEs were minor and resolved with discontinuation of treatment. As in Study 172, the AE profile of ESOME Mg appeared to be similar to that of the comparator OME and the other PPIs: the most frequent AE for both treatment groups was headache. The most frequently reported G.I. side effects were diarrhea, nausea and abdominal pain. In this trial, the rate of occurrence of treatment-emergent AEs was similar between the two treatment groups. Mean increases in serum gastrin were higher in the H40 group than in the O20 group, but were an expected outcome of the acid-blocking activity of the PPI agents. There were no significant changes observed in other laboratory evaluations.

FINAL NOTE: Although the comparison H40 > O20 establishes that ESOME is **active** in the healing of EE, this dose of H cannot be said to be "superior" to OME 20 because the dose levels compared do not allow such a conclusion to be made. In other words, none of the pivotal trials in the healing of EE show that ESOME is "clinically superior" to OME.

IV. REVIEW OF CLINICAL TRIALS SUBMITTED IN SUPPORT OF THE INDICATION MAINTENANCE OF HEALING OF EROSIVE ESOPHAGITIS

A. Study 177

"A Multicenter, Randomized, Double-blind, Six-month Maintenance Study to Compare the Efficacy, Safety and Tolerability of H 199/18 40 mg, H 199/18 20 mg, and H 199/18 10 mg with Placebo in Healed Erosive Esophagitis Subjects"

1. Primary Objective

The primary objective of this study, in patients with healed EE, was to assess the maintenance of healing efficacy of H40, H20 and H10 mg qd, each compared to placebo, at month 6.

2. Secondary Objective

This was to assess changes in GERD symptoms by H40, H20 and H10, each compared to placebo.

COMMENTS: The approach/procedure to achieve these primary and secondary objectives were all adequate.

3. Study Population (Table 26)

This was adequate for the proposed study. The study population consisted of 375 patients with healed EE[27] as verified on endoscopy at the completion of study 72 and who were negative for *H. pylori* (by histology) at baseline of Study 72, at ca. 71 investigator sites (only 51 investigator sites enrolled patients).

Listed in Table 26 are: a) criteria for randomization of healed EE patients into the trial; and b) the criteria used to exclude patients from participation in this trial.

[27] Los Angeles Classification Grade = "NOT PRESENT"

TABLE 26
Study No. 177
Characteristics of the Study Population

INCLUSION CRITERIA	REASONS FOR EXCLUSION
• Prior completion of Study 172, with completion defined as healed EE verified by EGD. • Adult between the ages of 18 and 75 y inclusive (and of legal age to consent). • M or non-pregnant, non-lacting F. Fs were to be post-menopausal, surgically sterilized or using a medically acceptable form of birth control as determined by the investigator. Women of child-bearing potential must have agreed to continue using an acceptable form of birth control throughout the conduct of the study. • Negative pregnancy test at baseline for all women of child-bearing potential (ie, those not post-menopausal or surgically sterilized). • Capable of providing written IC, willing and able to comply with all procedures of the study.	• Patients positive for *H. pylori* by histology confirmation as part of the biopsy evaluation during participation in Study 172. • Current or historical evidence (within 3 months) of the following diseases/conditions: Zollinger-Ellison syndrome; the primary esophageal motility disorders achalasia, scleroderma and primary esophageal spasms; esophageal stricture; inflammatory bowel disease; evidence of upper gastrointestinal malignancy at the baseline EGD; pancreatitis; malabsorption; severe cardiovascular or pulmonary disease; severe liver disease. Patients with liver enzymes three times the upper limit of normal were to be excluded from study participation; severe renal disease, including chronic renal disease or impaired renal function as manifested by any of the following: creatinine clearance <50 mL/min, serum creatinine greater than 2.0 mg/dL, or markedly abnormal urine sediment on repeated examinations; active malignant disease except minor superficial skin disease, unstable diabetes mellitus. Stable diabetics controlled on diet, oral agents, or insulin were acceptable; cerebral vascular disease, such as cerebral ischemia, infarction, hemorrhage, or embolus; any condition that may have required surgery during the study. • Endoscopic Barrett's esophagus (>3 cm) or significant dysplastic changes in the esophagus. • Known clinically significant abnormal laboratory values as part of the Pts. medical history. • Use of a PPI (other than test medication in Study 172) within 28 days prior to the baseline visit. • Use of an H_2-receptor antagonist daily during the 2 weeks prior to the baseline EGD (occasional use less than daily was permitted). • Need for continuous concurrent therapy or treatment within 1 week of randomization with: quinidine; diazepam; diphenylhydantoins, mephenytoin; warfarin; anticholinergics; prostaglandin analogs; antineoplastic agents; salicylates (unless ≤165 mg daily for cardiovascular prophylaxis); steroids (oral or intravenous); pro-motility drugs; sucralfate; nonsteroidal anti-inflammatory drugs. • Known hypersensitivity to any component of H 199/18 or GELUSIL. • Use of any other investigational compound (other than test medication in Study 172) within 28 days of starting test medication. • History of drug addiction or alcoholism within the past 12 months.

	• Refusal to sign the consent form or inability to give fully IC due to mental deficiency or language problems. • Prior participation in this study. • Inability to take test med. according to dosing instructions. • Pregnancy or lactation. • Test medication-related SAE in Study 172.

4. Overall Study Design and Schedule of Evaluations

From the review of the evidence, this was a multicenter, double-blind, randomized, placebo-controlled, parallel-group, 4-arm trial.

- Patients who had confirmed healing of EE by the LA Classification Grade of "Not Present" in Study 172 and who met other entry criteria for this trial were randomized to one of the four treatment groups.

- A total of 300 pts. at ca. 75 centers (about half the centers in Study 172) were to be randomized.

- The test medication received in Study 172 was not unblinded as a result of eligibility for the present trial.

- Each pt.'s medical history, P.E., and blood and urine samples from the final visit in Study 172 were used as baseline values for Study 177.

- Gastric biopsy results and histologic *H. pylori* status at baseline of Study 172 were also used as the baseline for Study 177.

- Endoscopy results at the final visit of Study 172 served as the baseline efficacy assessment for Study 177.

- All pts were to be re-evaluated by endoscopy and GERD symptom assessment at Month 1, Month 3 and Month 6 of treatment.

- If erosions (i.e. LA Classification Grade of A, B, C or D) were seen at any visit, the pt. was considered to have **relapsed** and was D/C from the trial.

- At each return visit, the patient had vital signs taken, blood drawn for clinical laboratory evaluations, reported any AEs, provided a history of medications taken since the last visit, returned any unused test medication, and had pill counts performed.

- If the patient was not discontinued from the study, a supply of test medication and GELUSIL sufficient to last until the next scheduled visit was dispensed.

- At the final visit, gastric biopsies were done for histological evaluation.

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

- The dosage strengths, appearance and batch number of test medication were as follows:

Identification of Test Medications

Treatment	Appearance	Batch Number
H 199/18 40 mg	Blue, Size 2 capsule	H1222-04-01-03 H1222-04-01-04
H 199/18 20 mg	Blue, Size 2 capsule	H1189-04-01-02
H 199/18 10 mg	Blue, Size 2 capsule	H1221-02-01-02
Placebo	Blue, Size 2 capsule	H0459-06-03-06
Individual patients receiving the various doses and batches were listed in sponsor's Appendix 16.1.6.		

- Randomization was performed at each center using blinded blocks of four allocation numbers. Patients were randomized to treatments in a 1:1:1:1 ratio (H40: H20: H10: placebo). Eligible patients at each center kept the same enrollment number as they had in Study 172 and were given the next sequential allocation number based on pre-printed numbers on study drug labels. A complete randomization list was provided in sponsor's Appendix 16.1.7.

- All patients were instructed to take the test medication in the morning with a glass of water.

- Procedures to preserve the blinding of the trial, methods to assess compliance and prior and concomitant therapy were all adequate.

6. Criteria for Evaluation of Efficacy

- The primary efficacy variable was the proportion of patients who maintained complete healing of esophageal erosions (i.e., LA Classification "Not Present", no erosions present) on EGD evaluation at Month 6 of treatment.

- Secondary efficacy variables were:

  1) the percentage of patients who maintained complete healing of esophageal erosions on EGD evaluation at Month 1 and Month 3 of treatment; and

2) presence of GERD symptoms of heartburn, acid regurgitation, dysphagia, and epigastric pain, by investigator assessment, at Months 1, 3 and 6 of treatment.

7. Criteria for Evaluation of Safety

All aspects of safety assessment, including the Coding Terminology and Dictionaries used within the Astra Adverse Event Dictionary, were adequate. This included evaluations of reports of AEs, and other safety variables such as routine P.E., endoscopy gastric biopsies,[28] ECL cell classification scale,[29] and other laboratory determinations.

- Biopsies with atrophy and/or intestinal metaplasia that were rated Moderate or Severe at any location were evaluated for atrophic gastritis. **Atrophic gastritis** was defined as the presence of moderate or severe **unequivocal loss of gastric glands** and/or moderate or severe metaplasia (intestinal or pyloric) found in at least 50% of the total gastric mucosa evaluated in all available biopsy specimens. [This definition is in accordance with diagnostic criteria for atrophic gastritis developed at the 1998 Houston Atrophy Meeting.]

- For patients enrolled in the study, biopsy samples from the greater curvature of the fundus were evaluated at baseline (of Study 172) and the final visit in Study 177 for ECL cell hyperplasia using the eight-point classification scale developed by Solcia et al.

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[28] **Chronic Inflammation** - Inflammation in which mononuclear leukocytes, including lymphocytes, plasma cells, and macrophages (monocytes) predominate.
Atrophy - Glands become sparse and small and, in the gastric corpus and fundus, parietal and chief cells disappear from the oxyntic glands.
Intestinal Metaplasia - Replacement of glandular and/or foveolar epithelium by intestinal epithelium.

Each of these gastritis characteristics was rated using the following severity scale: NONE (0)
MILD (1)
MOD (2)
SEV (3)

[29]

Classification	Definition[a]
0	Norman
1	Simple (diffuse) hyperplasia
2	Linear or chain forming hyperplasia
3	Micronodular hyperplasia
4	Adenomatoid hyperplasia
5	Dysplastic (precarcinoid)
6	Intramucosal neoplasm (intramucosal carcinoid)
7	Invasive neoplasm (invasive carcinoid)

[a] Definitions from Solcia E, Bordi C, et al.

8. Statistical Methodology

a) Determination of Sample Size

As noted in the Clinical Report, there were two criteria that were used to determine the sample size for this study. One was the statistical power to detect differences in response rates, specifically a difference between placebo and H 199/18. The other was the probability of seeing a reversal in observed response rates, given assumptions about the expected response rates in the H 199/18 treatment groups.

- To have 95% power to detect a difference in maintenance of healing rates of 70% for H 199/18 and 25% for placebo, it was calculated that a sample size of 44 patients per treatment arm would be necessary. This further assumed an alpha level of 0.0167 (a Bonferroni adjustment for the pairwise comparisons of each of the three Nexium doses versus placebo), and used the arcsine transformation for determining sample size.

- The sponsor further notes that although the purpose of this study was not to compare the H 199/18 doses to each other statistically, it was desirable to have sufficient "power" for the observed responses to identify a true dose response. For this purpose, it was assumed that the true response rates for two hypothetical H 199/18 treatment groups (identified as "H70%" and "H80%") were 70% and 80%. It was calculated that 75 patients would be needed for each of these treatment groups to ensure a less than 10% probability that H70% would result in an observed response rate greater than that for H80%.

- With two different estimates of the sample size, a decision was made to use the larger of the two estimates to ensure that each criterion was adequately powered. Therefore, the sample size used for this study was 75 patients per treatment group.

b) Details of Statistical and Analytical Procedures

- The primary efficacy variable was analyzed for Intent-to-Treat (ITT) and Per-Protocol (PP) populations. Definitions of the ITT and PP populations were set prior to unblinding the data.

- At Month 6, cumulative life-table rates for the maintenance of healing of EE in the H 199/18 treatment groups were compared to placebo in a pairwise fashion using log-rank statistics. For these comparisons, the experiment-wise error rate was preserved at 0.05 using the Hochberg adjustment for multiple comparisons.

- Crude rates for maintenance of healing for each H 199/18 treatment group at each month were compared to placebo in a pairwise fashion using Fisher's exact tests with no adjustment for multiple comparisons.

- The proportions of patients with GERD symptoms present at Month 1 for each H 199/18 treatment group were compared to placebo in a pairwise fashion using Cochran-Mantel-Haenszel statistics adjusting for the presence of the symptom at baseline.

- The presence of GERD symptoms at Month 3 and Month 6 was summarized using descriptive methods. Similar methods were used to compare the proportions of patients with GERD symptoms rated "None" or "Mild".

- Concurrence between maintenance of healing and the absence of GERD symptoms was evaluated by month using descriptive methods.

- Crude maintenance of healing rates were calculated for subgroups of patients based on gender, age group, race, initial EE severity, treatment received during the healing of EE study, duration of treatment in the healing of EE study, and study site. However, no formal statistical comparisons were made.

- All randomized patients who received at least one dose of study drug were included in the assessment of safety. Summaries of AEs, and incidence rates for AEs by body system and preferred term, were tabulated over the entire study period (through Week 26), and for events occurring through Week 13 (Month 3) and through Week 4 (Month 1).

- Laboratory test results were summarized using descriptive statistics for each test by visit, and for the change from baseline in each test by visit, as well as across all visits. Frequencies of patients with values outside the predefined limits of change (identified as potentially clinically significant) were determined.

- Vital signs were summarized by visit and across all visits using descriptive statistics.

- Summaries of gastritis ratings (chronic inflammation, intestinal metaplasia, and atrophy) were tabulated for baseline (baseline of Study 172) and final (end of Study 177) biopsy data for antral sites, fundic sites, and all sites combined. Frequencies of patients with an increase (worsening) from baseline were determined for each rating at each location.

- Biopsy evaluations for atrophic gastritis were also tabulated for baseline and final biopsy data. Frequencies of ECL cell ratings at the baseline and final biopsies were tabulated, as were frequencies of patients who had an increase (worsening) in ECL cell rating.

- Proportions of patients with an increase in ECL cell rating in the H 199/18 treatment groups were compared with the proportion in the placebo group in a pairwise fashion using logistic regression models, with time in the study included as a covariate.

9. Other Aspects of the Study

Other aspects of the trial including data quality assurance and populations to be analyzed were all adequate.

10. Results

a) Disposition of Randomized Patients/Protocol Deviations/ Exclusions from the PP Population and Summary of Patient Disposition and EGD Evaluability (Table 27)

- As summarized in Table 27, a total of 191 patients (50.9%) completed this 6-month study.

- As shown under the heading reasons for not completing the study, lack of therapeutic response was the main reason for not completing the trial and this was related to the H 199/18 dose received: completion rate of 72.8% in the H40 group vs 21.3% in the PL group.

- Ca. 35% of all patients had some protocol deviation. The groups were balanced with respect to PP deviations; the most frequent reason for exclusion from the PP Population was compliance violation (average = 26.7%).

TABLE 27
Study No. 177
Disposition of Randomized Patients[a]

	H40	H20	H10	PL	Total
Number of Patients (Planned and Analyzed)					
Planned	75	75	75	75	300
Enrolled	92	98	91	94	375
Analyzed					
Efficacy: Intent-to-Treat	92	98	91	94	375
Per-Protocol	77	88	79	70	314
Safety	92	98	91	92	373
Reasons for not Completing the Study					
Not Completed[b]	25	36	49	74	184
- Lack of Therapeutic Response	4	11	30	60	105
- AEs	5	5	2	2	14
- Sponsor/Investigator Decision	7	4	6	5	22
- Lost to F/U	5	10	7	2	24
- Consent Withdrawn	4	6	4	5	19
Patients Evaluated for PP Deviations					
Excluded from PP Population	30.8%	35.7%	30.8%	36.2%	35.2%
- Randomized despite entrance criteria violation at baseline	9.8%	9.2%	6.6%	12.8%	9.6%
- H. Pylori (+) at Baseline	3.3%	3.1%	1.1%	3.2%	2.7%
- Compliance Violation	26.1%	26.5%	24.2%	29.8%	26.7%
- Prohibited Concomitant Meds.	7.6%	4.1%	3.3%	9.6%	6.1%
- Other	9.8%	10.2%	8.8%	13.8%	10.7%
Summary of Patient Disposition and EGD Evaluability					
ITT Population	92	98	91	94	375
Patients with Month 1 endoscopy	81	81	74	75	331
Month 3 endoscopy	72	80	61	29	342
Month 6 endoscopy	67	62	49	21	199
PP Population	77	88	79	70	314
Patients with Month 1 endoscopy	71	80	73	66	290
Month 3 endoscopy	69	77	57	27	230
Month 6 endoscopy	65	61	49	21	196

a) The first patient entered the study on 12 November 1997, and the last completed the study on 9 September 1998. Of the 72 investigational sites initiated, 51 enrolled patients in the study. Patient enrollment by site varied from 1 to 31 patients, with most sites (39/51; 76.5%) enrolling at least 4 patients.
b) Includes 2 patients in the placebo group (Patient 039/005 and Patient 039/013) who were withdrawn from the trial prior to receiving their first dose of test medication, and were excluded from all safety evaluations.

- Presented in the lower panel of Table 27 is a summary of the disposition of patients in terms of the presence of an EGD evaluation at each visit. No unexpectedly, ca. 69% of PL patients

had no endoscopic evaluation beyond Month 1 due to the withdrawal of these patients from the trial, most for recurrence of EE.

b) Data Showing Comparability of Treatment Groups at Baseline

- The treatment groups were generally well-balanced with respect to gender, age and race. Small differences in these demographic characteristics are not expected to impact on efficacy results.

- For each symptom, more than 60% of patients in each treatment group had no GERD symptoms at baseline. In symptomatic patients the symptoms were primarily of mild intensity.

c) Compliance[30]

The percentages of patients who were more than 90% compliant with the test medication regimen were similar among all treatment groups (78.3% of H40 patients, 75.5% of H20 patients, 74.7% of H10 patients, and 74.5% of PL patients). More than 78% of patients in each group had test medication compliance rates over 80%. Compliance could not be established for approximately 14, 18, 14, and 12% of the H40, H20, H10, and PL patients, respectively.

d) Evaluation of Maintenance of Healing (Table 28)

- Depicted in this Table is the proportion of patients with **endoscopic remission** (free of endoscopically proven EE; maintenance of EE healing rates) at 1, 3 and 6 months in the four treatment groups. Additional analyses consist of calculation of therapeutic gain (each dose of ESOME vs PL) and comparison of the percent endoscopic remission among the 3 dose levels of the drug (H40 vs H20; H40 vs H10 and H20 vs H10), with the corresponding p-values.

- Both the crude rate [n (%)] and the life-table rate [%] are displayed.

- Cumulative statistics for the primary efficacy variable, maintenance of healing of EE at Month 6 (comparisons of life-table rates) showed that each of the H 199/18 treatment groups (H40=87.9%; H20=78.7%; and H10=54.2%) was significantly greater than the cumulative life-table rate in the placebo group (29.1%). For each pairwise comparison, the p-value associated with the log-rank statistic as well as with the Wilcoxon test was <0.001. This allowed each comparison to be considered statistically significant using the Hochberg adjustment.

- Formal statistical comparisons between each of the H 199/18 doses and PL and among the H 199/18 treatment groups was carried out by Dr. Y. Tsong, FDA statistician, with no

[30] Information from sponsor's Table 14.1.2.6.

Hochberg correction for multiple comparisons. These evaluations provided evidence for a dose-response relationship among the treatment groups. Rates of maintenance of healing of EE at Month 6 increased as the dose of H 199/18 increased.

- Special attention was put on the efficacy of the 40 in comparison to the 20 mg dose. Although, at Month 6, there was a therapeutic gain of 9.2% (life-table rate) this numerical difference was not statistically significant.

- Refer to Table 28. Data at Month 1 and Month 3 showed similar patterns of results in that at each time point, notable differences between the rates of healing in the H 199/18 treatment groups and the placebo group were seen. Through Month 1, life-table methods showed that 54.3% of placebo patients remained healed, while 97.8, 94.9, and 85.7% of the H40, H20, and H10 groups remained healed, respectively. Through Month 3, 41.5% of placebo patients remained healed, compared with 96.5, 87.4 and 67.2% of the H40, H20, and H10 groups, respectively.

- Once again life-table methods showed that H40 was not statistically superior to H20 at 1 (therapeutic gain 3%, p=N.S.) or 3 Months (therapeutic gain 9.1%, p=N.S.).

- Results using the PP Evaluation Population confirmed those in the ITT.

- None of the subgroups examined [GELUSIL Use, gender, age group (<65y, ≥65y), race, LA Classification Grade at entry into healing of EE study, treatment received during healing of EE study, duration of treatment in healing of EE study (4 vs 8 weeks) and investigational site] appeared to be a predictor of endoscopic remission.

TABLE 28
Study No. 177
Analysis of Cumulative Maintenance of Erosive Esophagitis Healing Rates (Endoscopic Remission) by Month
ITT Population

Cumulative Statistic	H 199/18 (mg qd) 40 (n=92)	20 (n=98)	10 (n=91)	PL (n=94)	Therapeutic Gain (%)/Statistical Significance(p-value)[a] H40 vs PL	H20 vs PL	H10 vs PL	H40 vs H20	H40 vs H10	H20 vs H10
Month 1 (through Day 35)										
Crude rate, n (%)	86 (93.5%)	86 (87.8%)	70 (76.9%)	38 (40.4%)	53.1%	47.8%	36.5%	5.7%	16.6%	10.9%
95% Crude CI	(86.3%, 97.6%)	(81.3%, 94.3%)	(68.3%, 85.6%)	(30.5%, 50.4%)	[0.001]	[0.001]	[0.001]	[N.S.]	[0.002]	[0.050]
Life-table rate, %	97.8%	94.9%	85.7%	54.3%	43.5%	40.6%	31.4%	2.9%	12.1%	9.2%
95% Life-table CI	(94.8%, 100%)	(90.5%, 99.3%)	(78.5%, 92.9%)	(44.2%, 64.3%)	[<0.001]	[<0.001]	[<0.001]	[N.S.]	[0.002]	[0.051]
Month 3 (through Day 105)										
Crude rate, n (%)	73 (79.4%)	69 (70.4%)	50 (55.0%)	22 (23.4%)	56.0%	47.0%	31.6%	9.0%	24.4%	15.4%
95% Crude CI	(71.1%, 87.6%)	(61.4%, 79.5%)	(44.7%, 65.2%)	(14.8%, 32.0%)	[0.001]	[0.001]	[0.001]	[N.S.]	[0.001]	[0.028]
Life-table rate, %	96.5%	87.4%	67.2%	41.5%	55.0%	45.9%	25.7%	9.1%	29.3%	20.2%
95% Life-table CI	(92.6%, 100%)	(80.4%, 94.4%)	(56.9%, 77.5%)	(30.2%, 52.8%)	[<0.001]	[<0.001]	[<0.001]	[N.S.]	[<0.001]	[0.022]
Month 6 (through final visit)										
Crude rate, n (%)	61 (66.3%)	54 (55.1%)	37 (40.7%)	14 (14.9%)	51.4%	40.2%	25.8%	11.2%	25.6%	14.4%
95% Crude CI	(56.7%, 76.0%)	(45.3%, 65.0%)	(30.6%, 50.8%)	(7.7%, 22.1%)	[0.001]	[0.001]	[0.001]	[N.S.]	[0.001]	[0.047]
Life-table rate, %	87.9%	78.7%	54.2%	29.1%	58.8%	49.6%	25.1%	9.2%	33.7%	24.5%
95% Life-table CI	(80.4%, 95.4%)	(69.5%, 87.8%)	(42.9%, 65.5%)	(17.6%, 40.6%)	[<0.001]	[<0.001]	[<0.001]	[N.S.]	[<0.001]	[0.026]
Log-rank p-value vs PL	<0.001*	<0.001*	<0.001*	--						
Wilcoxon p-value vs PL	<0.001*	<0.001*	<0.001*	--						

From sponsor's Table 14.2.1, with substantial modifications and major additions. CI=confidence interval
* Statistically significant vs placebo using Hochberg adjustment.
a) These p-values, calculated by Dr. Y. Tsong, were not adjusted for multiple comparisons.

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e) Summary Results of Secondary Evaluation Parameters (Table 29)

- As shown in this Table, the mean time to recurrence of EE was significantly longer in patients receiving H 199/18 (80 to 130 days, depending on the dose) than in those receiving placebo (46 days).

- At Month 1, heartburn (the most prevalent GERD symptom) and other GERD symptoms were absent in the majority of H 199/18 patients but present in most patients receiving placebo. There were statistically significant differences in the proportion of patients who were heartburn-free in the H 199/18 groups (71.3%, 63.7% and 50.6% in the 40, 20 and 10 mg, respectively) when compared to placebo (15.5%).

- For this parameter (heartburn free), the difference between the 40 and the 20 mg dose levels (7.6%) was not statistically significant.

- Also, as per Table 29, at Month 1, there were statistically significant differences between each of the H 199/18 groups and PL in the proportion of patients who were regurgitation free, dysphagia free and epigastric pain free. Once again the differences between the 40 and the 20 mg dose levels (6.9% for regurgitation free, 2% for dysphagia free and actually -7.6% for epigastric pain free) were not statistically significantly different.

f) Results of Safety Evaluations

i) Extent of Exposure

- 375 patients with healed EE were randomized in this study, 99.5% of whom (373)[31] received at least one documented dose of test medication.

- The frequency distributions and descriptive statistics for exposure to test medication in each treatment group is presented in Table 30. At each time point, the percentage of patients remaining in the study increased with the dose of H 199/18.

- Slightly more than one-half of PL patients participated in the study to Week 4, compared with more than 80% of patients in the H 199/18 treatment groups.

- By 18 weeks (4 months), only 21.7% of the PL patients and 48.4% of the H10 patients remained in the study. In contrast, 64.3% of H20 patients and 71.7% of H40 patients remained in the study at this time.

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[31] From sponsor's Appendix 16.2.2.1: There were 2 patients in the PL group who did not receive at least one dose of test medication: Patient 039/005 withdrew consent prior to taking any medication, and Patient 039/013 was *H. pylori* positive by histology and was declared ineligible for the study after being randomized but prior to ingesting any test medication.

TABLE 29
Study No. 177

Summary Results of Secondary Evaluation Parameters

	H 199/18 mg qd				Therapeutic Gain (%)/Statistical Significance (p-value)[a]				
	40 (n=87)	20 (n=91)	10 (n=83)	PL (n=84)	H40 vs PL	H20 vs PL	H10 vs PL	H40 vs H20	H40 Vs H10
Mean Time to Recurrence (days)	130	101	80	46	84	55	34	29	50
Proportion of Patients Who Recurred at Grade C	0%	11.8%	2.8%	16.1%	16% [0.001]	4.1% [N.S.]	13.3% [0.001]	11.8% [0.001]	-2.8% [N.S.]
Proportion of Patients Who Were Heartburn Free	71.3%	63.7%	50.6%	15.5%	55.8% [p=0.001]	48.2% [p=0.001]	35.1% [p=0.001]	7.6% [N.S.]	20.7% [0.005]
Proportion of Patients Who Were Regurgitation Free	80.5%	73.6%	65.1%	27.4%	53.1% [p=0.001]	46.2% [p=0.001]	37.7% [0.001]	6.9% [N.S.]	15.4% [0.018]
Proportion of Patients Who Were Dysphagia Free	94.3%	92.3%	97.6%	81.0%	13.3% [p=0.010]	11.3% [p=0.026]	16.6% [p=0.001]	2.0% [N.S.]	-3.3% [N.S.]
Proportion of Patients Who Were Epigastric Pain Free	77.0%	84.6%	80.7%	45.2%	31.8 [p=0.001]	39.4 [p=0.001]	35.5 [p=0.001]	7.6% [N.S.]	-3.3% [N.S.]

a) These p-values, calculated by Dr. Y. Tsong, were not adjusted for multiple comparisons.

- The mean time on treatment increased as the dose of H 199/18 increased. The mean time on treatment for the PL group was 61.5 days, while the means for all three H 199/18 treatment groups were over 160 days (ca. 5 months).

TABLE 30
Study No. 177

Exposure to Treatment

Time on Treatment (Weeks)	H 199/18 (mg qd)			PL
	40 [n=92]	20 [n=98]	10 [n=91]	[n=92]
Frequencies (%)				
≥2	94.6%	94.9%	91.2%	79.3%
≥4	90.2%	89.8%	82.4%	56.5%
≥8	81.5%	77.6%	64.8%	27.2%
≥12	80.4%	73.5%	60.4%	22.8%
≥18	71.7%	64.3%	48.4%	21.7%
Descriptive statistics, days				
Mean (SD)	146 (58.3)	137 (60.6)	116 (68.0)	61.5 (64.9)
Median	172	170	161	29
Min - Max				
From sponsor's Table 14.3.1.1, with some modifications				

ii) Deaths, Other Serious and Potentially Serious AEs

- There were no deaths in this trial.
- The distribution of SAEs was:

H 199/18 mg qd	SAEs
40	2
20	4
10	1
PL qd	0
Total	7

- None of the SAEs was considered by the investigator to be related to test medication (all were rated unlikely related).

iii) AEs Leading to Discontinuation (Table 31)

This Table presents a listing of all AEs that resulted in the D/C of 18 patients from the trial, with the below summarized distribution:

"Study Drug Stopped" Action
(on the AE CRF)

H 199/18 mg qd	
40	6
20	6 + (1)[a]
10	3 + (1)[b]
PL qd	3 + (1)[c]
	18 + (3)

[redacted]

a,b,c) These 3 patients, 023/016, 023/024 and 046/009, respectively, were coded in the CRF as D/C from the study due to AE but there was no specific indication why the treatment was stopped.

- Pt. 049/004 in the H40 group D/C treatment due to pregnancy. Pt. 077/004 also in the H40 group was found to be pregnant after completing the trial. She was followed without sequelae, to an elective termination.

TABLE 31
Study No. 177
Listing of Patients Who Discontinued Treatment Because of an AE

PATIENT ID	PREFERRED TERM FOR AE (Verbatim term)	
	H 199/18 40 mg qd	
012/030 M 64	Rash maculo-papular/18 (Maculopapular skin rash on torso & extremities)	
014/004 M 40	Flatulence/3 Dizziness/3 Epigastric pain/3 Fatigue/3 Headache/3 Nausea/3 Rigors (chills)/3 Asthenia/3 Chest pain/10 Fever/16 (Abdominal bloating/dizziness/epigastric pain/fatigue/headache/nausea/shivering/weakness/chest pain/fever)	UNL UNL UNL UNL POSS POSS UNL UNL UNL POSS
044/007 F 57	Rash maculo-papular/36 [Erythematous with mild maculo-papular rash on upper chest, back, face (itching)]	POSS
045/009[a] M 65	Headache/29 (Headaches)	UNL

045/017 F 45	Flatulence/57 Abdominal pain/57 Respiratory infection/57 Constipation/60 Gastritis/76 (Abdominal bloating/abdominal pain/upper resp infection/constipation/mild antral gastritis)	POSS POSS UNL POSS POSS
049/004 F 33	Events of non-medical character/86 (Use during pregnancy)	UNL
H 199/18 20 mg qd		
023/016[b] F 50	Respiratory infection/27 (Upper respiratory infection)	UNL
026/003 F 22	Flatulence/34 Hunger pangs/34 (Bloating after meals/severe hunger pains in AM)	POSS POSS
040/004 F 55	Epigastric pain/144 (epigastric pain)	POSS
045/002 M 50	Epigastric pain/118 Gastritis/118 Duodenitis/118 Gastritis (second episode)/118 (Deep epigastric tenderness/mild gastritis/possible duodenitis/slight hyperemia at the GE junction)	POSS POSS POSS POSS
045/018 F 49	Abdominal pain/22 Diarrhea/22 Vomiting/22 Cholecystitis[c]/34 Duodenal ulcer/65 Hernia/65 (Lower abd pain/severe diarrhea/vomiting/cholecystitis/duodenal ulcer/hiatal hernia)	POSS POSS UNL UNL POSS POSS
076/008 F 66	Fibrillation atrial[c]/46 Bundle branch block[c]/46 Cerebrovascular disorder[c]/46 (Reoccurrence of atrial fibrillation/right bundle branch block/transient ischemic attack)	UNL UNL UNL
H 199/18 10 mg qd		
004/008 F 49	Pruritus/2 (Itching)	PRO
023/024[b] M 28	Abdominal pain/37 Chest pain/37 (Abdominal pain/chest pain)	POSS POSS
077/003 M 59	Thrombocytopenia/84 (Thrombocytopenia)	PRO
PLACEBO qd		
004/001 F 68	Mucosal discoloration GI/33 Gastritis/33 Gastric ulcer/33 (Duodenal bulb erythema/stomach erosions/stomach ulcers)	UNL UNL UNL
045/004 F 39	Dyspepsia/2 Increased reflux/2 (Increased heartburn/increased reflux)	PRO PRO

046/009[b] F 26	Acne/28 Mucosal discoloration GI/28 Gastritis/28 (Acne on face/erythema of bulb/gastric erosions)	POSS POSS POSS

Reviewer's Table, based on sponsor's Table 14.3.1.11, with major modifications
a) "Action taken with respect to study drug" coded as "Study drug stopped;" reason for discontinuation on Study Completion page was "Investigator/sponsor decision."
b) Coded as "AE caused subject to discontinue study" = "Yes" but "Action taken with respect to study drug" not coded as "Study drug stopped" (AE CRF).
c) This was a serious AE. More information pertaining to this AE was given in narrative in sponsor's Section 12.3.2.

iv) Adverse Events

- Summarized in Table 32 is the proportion of patients experiencing AEs per length of exposure (0-4, 0-13 and 0-26 weeks in the upper, mid-, and lower panel, respectively).

- There were no meaningful differences among treatment groups in the proportion of patients who reported an AE, a SAE or in the proportion of those who D/C due to an AE during Week 0 to 4 (upper panel of Table 32), but the proportion of these patients was numerically higher in the H20 and especially the H40 group in comparison to the H10 or PL groups (mid- and lower panel of Table 32).

- As shown in Table 32, the proportions of patients experiencing at least one AE were similar among the H 199/18 treatment groups (between 57.1% and 60.9%) (there were no dose responses), but the proportion of patients experiencing at least one AE was lower in the placebo group (45.7%).[32]

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[32] This apparent association of AE occurrence with treatment is confounded by the duration of treatment. These rates should be interpreted in the context of the differential exposure to treatment described above; only 23% of patients remained in the PL group beyond Week 12, compared with 60% to 80% of patients in the H 199/18 treatment groups.

TABLE 32
Study No. 177
Proportion of Patients With AEs per Length of Exposure

AE Category	H 199/18 (mg qd)			PL
	40 [n=92]	20 [n=98]	10 [n=91]	[n=92]
I. During Week 0 to 4				
≥ 1 AE	31.5%	37.8%	34.1%	29.3%
≥ 1 Serious AE	0.0%	0.0%	0.0%	0.0%
Discontinued treatment due to AE	2.2%	1.0%	1.1%	1.1%
II. During Week 0 to 13				
≥ 1 AE	53.3%	52.0%	51.5%	43.5%
≥ 1 Serious AE	1.1%	3.1%	1.1%	0.0%
Discontinued treatment due to AE	6.5%	3.1%	2.2%	2.2%
III. During Week 0 to 26				
≥ 1 AE	60.9%	57.1%	57.1%	45.7%
≥ 1 Serious AE	2.2%	4.1%	1.1%	0.0%
Discontinued treatment due to AE	6.5%	5.1%	2.2%	2.2%
From sponsor's Tables 14.3.1.6, 14.3.1.4 and 14.3.1.2, with major modifications				

- A summary of proportion of patients (incidence ≥3% in any treatment group) with AEs over the entire trial period (0 to 26 weeks) is presented in Table 33. There are some numerical but not striking differences or trends (dose responses) among the four treatment groups.

TABLE 33
Study No. 177
Most Frequently Occurring AEs During Week 0 to Week 26
Patient Incidence ≥ 3% in Any Treatment Group

Body System/AE	H 199/18 (mg qd)			
	40 [n=92]	20 [n=98]	10 [n=91]	PL [n=92]
Central/Peripheral Nervous System				
Dizziness	1.1%	1.0%	3.3%	2.2%
Headache	7.6%	10.2%	6.6%	6.5%
Psychiatric				
Depression	3.3%	1.0%	0.0%	1.1%
Gastrointestinal System				
Abdominal pain	4.3%	7.1%	4.4%	2.2%
Diarrhea	8.7%	5.1%	8.8%	3.3%
Duodenitis[a]	1.1%	2.0%	3.3%	0.0%
Flatulence	7.6%	3.1%	1.1%	1.1%
Nausea	5.4%	4.1%	6.6%	2.2%
Esophageal disorder[a]	1.1%	2.0%	3.3%	0.0%
Tooth disorder	4.3%	3.1%	2.2%	0.0%
Vomiting	1.1%	3.1%	5.5%	1.1%
Cardiovascular System				
Hypertension	2.2%	1.0%	4.4%	0.0%
Respiratory System				
Respiratory infection	8.7%	9.2%	6.6%	2.2%
Body as a Whole				
Accident and/or injury	1.1%	4.1%	8.8%	1.1%
Back pain	1.1%	1.0%	4.4%	2.2%
Chest pain	3.3%	2.0%	2.2%	0.0%
Resistance Mechanisms				
Infection viral	2.2%	4.1%	1.1%	3.3%
From sponsor's Table 14.3.1.3 with major modifications.				
a) Each of these AEs (duodenitis and esophageal disorder) represents an endoscopy finding.				

- Overall the most frequently reported AEs were headache, respiratory infection and diarrhea. There was little difference among the 4 treatment groups in incidence of these AEs as well as SAEs, or discontinuations due to AEs.

v. Changes in Laboratory Parameters/Serum Gastrin

- In general, mean changes in laboratory measurements were small and in general, not clinically meaningful.

- Individual changes from normal at baseline to outside NLs at any time point after baseline were most frequently observed in serum gastrin (see below), Hb, ALAT, ASAT, serum B_{12} and WBC counts. However, individual changes in Hb, ASAT and WBC counts were reported with similar frequencies in the H 199/18 and PL groups. Although the percentage of patients with decreases below the normal limit for serum B_{12} were 7.8, 5.1, 3.9, and 2.5% of patients, respectively, the mean changes were inconsistent across the treatment groups. ALAT increases were more frequently in the H 199/18 treatment groups (11.3, 6.5, and 13.9% of patients in the H40, H20 and H10 groups, respectively) than in the PL group (2.6% of patients); however, the incidence rates at Month 1 were similar across the treatment groups. These findings should, conservatively, be incorporated in the labeling.

- Changes in serum gastrin concentration are summarized below. Given the pharmacological properties of esomeprazole, a proton pump inhibitor, these findings are not unexpected.

	H 199/18 (mg qd)			PL[a] –
	40	20	10	
Mean change (pg/ml)	50.38	21.34	-0.71	-26.21
Increases from normal at baseline to above normal post-baseline	38.1%	29.7%	10.5%	1.6%

a) Among these PL patients, all of whom had received H40, H20 or O20 in EE healing Study No. 172, the mean serum gastrin concentration at Month 1 (35.23 pg/ml) had already returned to the baseline concentrations recorded in Study No. 172.

vi) Other

- In study No. 177, there were no clinically meaningful changes in blood pressure or pulse rate or PE (including weight) over the course of the trial.

- **Gastric biopsy** evaluations revealed very few non-normal ratings for the assessed parameters: chronic inflammation, intestinal metaplasia, or atrophy at either antral or fundic locations.
  - There was no apparent association of these non-normal ratings with H 199/18 treatment.
  - For all three gastritis characteristics, but especially for chronic inflammation, the number of patients with decreased (improved) ratings post-baseline was higher than

the number of patients with increased (worsened) ratings. Increases and decreases were both distributed evenly across the four treatment groups.

- No occurrences of atrophic gastritis were observed at the final biopsy, including evaluation of 1 patient who had atrophic gastritis at baseline.
- ECL cell ratings showed that 1 patient in the H20 group had micronodular hyperplasia at the final biopsy; all other non-normal, post-baseline ECL cell ratings were either linear or simple hyperplasia.
- Increases (worsening) in ECL cell ratings were seen in 13.6% of H40 patients, 14.5% of H20 patients, 4.7% of H10 patients but only in 1.5% of PL patients. There was little numerical difference between H40 and H20 in terms of worsening in ECL cell ratings, but pairwise comparisons of each H 199/18 treatment group with PL showed that the proportion of patients with increased ECL cell ratings was significantly higher in the H20 group than the PL group ($p=0.011$).
- Maximum serum gastrin concentrations for those patients with ECL cell increases tended to be higher than for patients without ECL cell increases. Again, dose-related increases in ECL cell hyperplasia among patients receiving proton pump inhibitors than in those receiving placebo are not unexpected.

- The observed changes in serum gastrin concentration as well as those in ECL cell hyperplasia among patients treated with esomeprazole should be **incorporated in the labeling.**

11. Discussion and Overall Conclusion (Sponsor)

"H 199/18, at doses of 40 mg qd, 20 mg qd, and 10 mg qd, was effective, and was statistically superior to placebo in maintaining healing of EE in previously healed patients at Month 6: 87.9% of H40 patients, 78.7% of H20 patients, 54.2% of H10 patients, and 29.1% of placebo patients ($p<0.001$ for all pairwise comparisons of H 199/18 treatment groups to placebo). Although H10 was statistically superior to placebo, the absolute maintenance of healing rate for this dose suggests that it may not be clinically viable. In patients who had recurrence of EE, the mean time to recurrence was 46 days in the placebo group, 80 days in the H10 group, 101 days in the H20 group, and 130 days in the H40 group. Patients in all three H 199/18 treatment groups had significantly fewer, and less severe, GERD symptoms at Month 1 than did patients in the placebo group. The percentage of patients who were heartburn-free increased as the dose of H 199/18 increased.

"All three H 199/18 doses were well tolerated, with no deaths, no drug-related SAEs, no unexpected clinically meaningful changes in laboratory tests or vital signs, and no treatment-emergent occurrences of atrophic gastritis. Although ECL cell increases were associated with dose-related increases in serum gastrin values, there were no clinically meaningful increases in ECL cells. There were no clinically meaningful differences between the safety results for the H 199/18 treatment groups and the placebo group."

12. Reviewer's Additional Comments

Study No. 177 was one of two controlled clinical trials submitted by the sponsor in support of the efficacy and safety of orally administered NEXIUM (esomeprazole) in the prevention of relapse and maintenance of symptom resolution of erosive esophagitis. According to the sponsor, the recommended adult dosage (capsule to be taken before eating) is 40 mg once daily.

Study No. 177, carried out from 12 November 1997 to 9 September 1998, randomized 375 patients at 51 sites. In addition to being multicenter and randomized, this 4-arm study was double-blind, placebo-controlled, parallel-group, 6-month duration and was designed to evaluate the efficacy and safety of 3 dose levels of H 199/18 vs PL in patients with healed EE. The study was well-designed and, based on the information provided in the sponsor's Clinical Report, apparently well-executed. This (as well as Study 178) was a follow-on trial of patients who had been shown to heal under short-term (4 to 8 weeks) therapy in healing of EE Study No. 172. Because of this approach, the patient population studied was limited to the initial entry criteria of the preceding short-term study No. 172. These were patients in whom healing of EE (Los Angeles Classification Grade "Not Present") had been verified endoscopically and who, in addition, were negative for ***H. pylori*** (by histology) at baseline of Study 172. All patients were to be re-evaluated by upper G.I. endoscopy at Months 1, 3 and 6 of treatment. The primary efficacy variable was the proportion of patients who maintained complete healing of esophageal lesions (i.e. LA Classification "Not Present", no erosions present) on esophago-gastro-duodenoscopy (EGD) assessment at Month 6 of treatment. The secondary efficacy variables included a) the proportion of patients who maintained complete healing of esophageal erosions on EGD assessment on Month 1 and 3 of treatment and b) presence of GERD symptoms of HB, "acid" regurgitation, dysphagia and epigastric pain, as assessed by the investigator, at Months 1, 3 and 6 of treatment. All aspects of safety evaluations were adequate. In addition, biopsy samples taken at baseline of Study 172, and at the final visit in Study 177, were evaluated for: a) chronic inflammation; b) intestinal metaplasia; and c) atrophy by the Sydney System of Classification; as well as for d) enterochromaffin + like (ECL) cell hyperplasia (using Solcia's ECL cell classification system) and e) ***H. pylori*** (evaluated by histologic staining). Also, biopsy samples with intestinal metaplasia or atrophy graded greater than "Mild" were assessed for atrophic gastritis.

At Month 6, the cumulative life-table rate healing of EE was maintained in the following proportion of patients:

	Maintenance of healing of EE Cumulative life-table rate, 95% CI
H40	87.9% [80.4%, 95.4%]
H20	78.7% [69.5%, 87.8%]
H10	54.2% [42.9%, 65.5%]
PL	29.1% [17.6%, 40.6%]

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Rates of maintenance of healing (both life-table and crude estimates) were significantly greater in each H 199/18 group when compared to PL (all p-values <0.001). It was evident that the rates of maintenance of healing (both life-table and crude estimates) increased with the dose of H 199/18 but the H20 dose level gave a response that was **reasonably close** to that seen with the H40 dose level. Several subgroups were examined but none appeared to be a predictor of maintenance of healing.

In this study, the mean time to recurrence was shorter in patients receiving PL (46 days) than in those given the PPI (130, 101 and 80 days for the H40, H20 and H10, respectively).

At Month 1, GERD symptoms were absent in most of H 199/18-treated patients but present in the majority of those given PL, with heartburn (HB) being the most prevalent symptom. Proportion of patients that were HB-free was lowest in the PL group (15.5%) but increased as the dose of the PPI increased (50.6%, 63.7% and 71.3% in the H10, H20 and H40 groups, respectively); each of the PPI dose levels was shown to be superior to PL in pairwise comparisons.

In addition to being efficacious, H 199/18 was also safe and well-tolerated. Study No. 177 showed no deaths, no drug-related SAEs, no unexpected clinically meaningful changes in routine laboratory parameters or vital signs, and no treatment-emergent occurrences of atrophic gastritis. Except as noted below, there were no clinically meaningful differences between the safety data for the H 199/18 treatment groups and the PL groups.

Not surprisingly, this study showed the dose-related increases in ECL cell hyperplasia among patients receiving PPIs. There was little numerical difference between H20 and H40 in terms of worsening in ECL cell rating, but pairwise comparisons of each of the H 199/18 treatment groups with PL showed a statistical difference between the H20 and PL groups (p=0.011). In addition, 1 patient in the H20 group had micronodular hyperplasia (MNH) at the final biopsy while all other non-normal, post-baseline ECL cell ratings were either linear or simple hyperplasia. But none of these changes in ECL cell ratings is considered clinically meaningful.

This study also showed the [by now expected] increases in serum gastrin concentrations induced by PPIs. Again, a dose-response relationship was seen when examining this parameter (pg/ml): 50.4 (H40), 21.3 (H20), -0.71 (H10) and -26.2 (PL).

Although well-known and expected, the observed changes in serum gastrin concentrations and ECL cell ratings should be incorporated in the labeling.

B. Study 178

"A Multicenter, Randomized, Double-blind, Six-month Maintenance Study To Compare The Efficacy, Safety, and Tlerability of H 199/18 40 mg, H 199/18 20 mg, and H 199/18 10 mg with Placebo in Healed Erosive Esophagitis Subjects"

1. through 4. Primary and Secondary Objectives, Study Population, Overall Design and Schedule of Evaluations

All these aspects of this study and other methodological aspects including definitions were as in Study 177.

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

All of these aspects of the study were adequate as in Study 177.

- The dosage strengths, appearance and batch numbers of test medication were as follows:

Identification of Test Medications

Treatment	Appearance	Batch Number
H 199/18 40 mg	Blue, Size 2 capsule	H1222-04-01-04
H 199/18 20 mg	Blue, Size 2 capsule	H1189-04-01-02
H 199/18 10 mg	Blue, Size 2 capsule	H1221-02-01-02
Placebo	Blue, Size 2 capsule	H0459-06-03-06

6. and 7. Criteria for Evaluation of Efficacy and Safety

The criteria for evaluating efficacy (primary and secondary efficacy variables) and safety were the same as in Study 177, all adequate.

8. Statistical Methodology

The determination of sample size and the details of statistical and analytical procedures for efficacy and safety were essentially as those described for Study 177.

9. Other Aspects of the Study

Other aspects of this trial, including data quality assurance and populations to be analyzed, were all adequate.

10. Results

a) Disposition of Randomized Patients/Protocol Deviations/Exclusion from the PP Population and Summary of Patient Disposition and EGD Evaluability (Table 34)

- Of the 65 investigational sites initiated in short-term healing Study 172, 47 sites enrolled patients into Study 178. Patient enrollment by site varied from 1 to 30 patients, with most sites (28/47=59.6%) enrolling at least 4 patients.

- As summarized in Table 34, a total of 187 patients (58.8%) completed this 6-month trial. As in Study 177, completion rates were highest in the H40 and H20 groups, with the highest completion rate in the H20 group (84.1%), and the lowest in the placebo group (16.9%). The most frequent reason for discontinuation in the H40 group was "Lost to follow-up" (11.0%); the most frequent reason for discontinuation in the remaining groups was "Lack of therapeutic response." The rates of discontinuation for this reason increased as the dose of H 199/18 decreased. Three patients each in the H40 and H20 groups discontinued treatment due to an adverse event, compared with 1 patient in the H10 group, and 2 in the placebo group.[33]

- The proportion of patients evaluated for PP deviations was similar among the 4 arms of the trial, with compliance violation the most frequently observed protocol deviation (third panel of Table 34).

- A summary of patient disposition and EGD evaluability for both the ITT and PP populations, is given in the lower panel of Table 34.

b) Data Show Comparability of Treatment Groups at Baseline

- The treatment groups were generally well-balanced with respect to gender, age and race (sponsor's Table 14.1.1.1).

- Similarly, the four treatment arms were generally comparable in the proportion of patients that had GERD symptoms (heartburn, acid regurgitation, dysphagia and epigastric pain) at baseline (the majority of patients were asymptomatic or had symptoms of mild intensity).

c) Compliance

The percentages of patients who were more than 90% compliant with the test medication regimen were similar among all treatment groups (84.1% of H40 patients, 84.1% of H20 patients, 79.2% of H10 patients, and 76.6% of PL patients). More than 80% of the patients in each group had test medication compliance rates greater than 80%. Compliance could not be established in ca. 12, 11, 12, and 9% of the H40, H20, H10 and PL patients.

[33] One of these 9 patients (Patient 160/001 in the H10 group) had an adverse event for which the action taken was noted as "drug stopped" (on the AE CRF page); however, the reason for discontinuation noted on the Study Completion CRF page was "Lost to follow-up." Patients who discontinued test medication due to an AE were discussed in further detail in sponsor's Sections 12.3.1.3 and 12.3.3 of the Clinical Report.

TABLE 34
Study No. 178

Disposition of Randomized Patients[a]					
	H40	H20	H10	PL	TOTAL
Number of Patients (Planned and Analyzed):					
Planned	75	75	75	75	300
Enrolled	82	82	77	77	318
Analyzed					
Efficacy: Intent-to-Treat	82	82	77	77	318
Per Protocol	66	73	65	61	265
Safety	81	81	76	77	315
Reasons for not Completing the Study					
Not Completed[b]	20	13	34	64	131
- Lack of Therapeutic Response	2	5	23	48	78
- AE	3	3	0	2	8
- Sponsor/Investigator Decision	3	0	4	4	11
- Lost to F/U	9	2	4	1	16
- Consent Withdrawn	3	3	3	9	18
Patients Evaluated for PP Deviations					
Protocol Deviations	[n=82]	[n=82]	[n=77]	[n=77]	[n=318]
Excluded from PP Population[c]	36.6%	25.6%	31.2%	35.1%	32.1%
Randomized despite entrance criteria violation at baseline	15.9%	13.4%	15.6%	10.4%	13.8%
H. pylori positive at baseline	2.4%	0.0%	1.3%	3.9%	1.9%
Compliance violation	23.2%	14.6%	19.5%	27.3%	21.1%
Prohibited concomitant medication	2.4%	2.4%	5.2%	6.5%	4.1%
Other	15.9%	3.7%	5.2%	7.8%	8.2%
Summary of Patient Disposition and EGD Evaluability					
ITT Population	82	82	77	77	318
Patients with Month 1 endoscopy	70	72	65	65	272
Patients with Month 3 endoscopy	67	74	51	23	215
Patients with Month 6 endoscopy	64	69	46	13	192
PP Population	66	73	65	61	265
Patients with Month 1 endoscopy	63	67	59	57	246
Patients with Month 3 endoscopy	62	70	47	19	198
Patients with Month 6 endoscopy	60	66	46	12	184

Reviewer's Table, based on sponsor's Tables 14.1.2.3, 14.1.2.4 and 14.1.2.2, with major modifications.

a) The first patient entered the trial on 24 October 1997, and the last patient completed the study on 17 August 1998.

b) Includes 3 patients, 1 in each H 199/18 treatment group (Patient 160/004, Patient 143/009, and Patient 103/008, respectively) who withdrew their consent or were lost to follow-up prior to receiving their first dose of test medication and were excluded from all safety evaluations.

c) Patients may have had more than one type of protocol deviation. Those patients are counted once in the Total Patients Evaluated for Exclusion row and in each protocol deviation for which they qualified.

d) Evaluation of Maintenance of Healing (Table 35)

Depicted in this Table are analyses of cumulative maintenance of EE healing rates (endoscopic remission) by month and dose group. The actual response rate is displayed on the left side of the Table. The therapeutic gains resulting from pairwise comparisons of the different groups and the corresponding p-value for these differences, are shown on the right side of Table 35.

TABLE 35
Study No. 178
Analysis of Cumulative Maintenance of Erosive Esophagitis Healing Rates (Endoscopic Remission) by Month
ITT Population

Cumulative Statistic	H 199/18 (mg qd) 40 [n=82]	20 [n=82]	10 [n=77]	PL [n=77]	Therapeutic Gain (%)/Statistical Significance (p-value)[a] H40 vs PL	H20 vs PL	H10 vs PL	H40 vs H20	H40 vs H10	H20 vs H10
Month 1 (through Day 35)										
Crude rate, n (%)	73 (89.0%)	80 (97.6%)	56 (72.7%)	27 (35.1%)	53.9%	62.5%	37.6%	-8.6%	6.3%	24.9%
95% Crude CI	(80.1%, 94.9%)	(91.4%, 99.8%)	(62.8%, 82.7%)	(24.4%, 45.7%)						
Life-table rate, %	100%	100%	77.9%	42.9%	57.1%	57.1%	35.0%	0.0%	22.1%	22.1%
95% Life-table CI	---	---	(68.7%, 87.2%)	(31.8%, 53.9%)						
Month 3 (through Day 105)										
Crude rate, n (%)	69 (84.1%)	71 (86.6%)	49 (63.6%)	14 (18.2%)	65.9%	68.4%	45.4%	-2.5%	20.5%	23.0%
95% Crude CI	(76.2%, 92.0%)	(77.2%, 93.2%)	(52.9%, 74.4%)	(9.6%, 26.8%)						
Life-table rate, %	98.6%	96.0%	72.0%	29.0%	69.6%	67.0%	43.0%	2.6%	26.6%	24.0%
95% Life-table CI	(95.8%, 100%)	(91.4%, 100%)	(61.8%, 82.2%)	(17.7%, 40.3%)						
Month 6 (through final visit)										
Crude rate, n (%)	56 (68.3%)	67 (81.7%)	34 (44.2%)	12 (15.6%)	52.7%	66.1%	28.6%	-13.4%	24.1%	37.5%
95% Crude CI	(58.2%, 78.4%)	(73.3%, 90.1%)	(33.1%, 55.2%)	(7.4%, 23.7%)						
Life-table rate, %	93.6%	93.2%	57.1%	29.0%	64.6%	64.2%	28.1%	0.4%	36.5%	36.1%
95% Life-table CI	(87.4%, 99.7%)	(87.4%, 99.0%)	(45.2%, 69.0%)	(17.7%, 40.3%)						
Log-rank p-value vs PL	<0.001*	<0.001*	<0.001*	--						
Wilcoxon p-value vs PL	<0.001*	<0.001*	<0.001*	--						

From sponsor's Table 14.2.1, with substantial modifications and major additions. CI=confidence interval * Statistically significant vs placebo using Hochberg adjustment.
a) These p-values, calculated by Dr. Y. Tsong, were not adjusted for multiple comparisons.

- For the primary efficacy variable, maintenance of healing of EE (Endoscopic Remission) at Month 6, the cumulative life-table rate in each of the H 199/18 treatment groups (93.6% in the H40 group, 93.2% in the H20 group, and 57.1% in the H10 group) was significantly greater than the cumulative life-table rate in the placebo group (29.0%). For each pairwise comparison, the p-value associated with the log-rank statistic and the Wilcoxon rank sum test were less than 0.001. This result allowed each comparison to be considered statistically significant using the Hochberg adjustment.

- Formal statistical comparisons among the H 199/18 treatment groups were not conducted by the sponsor. However, as shown in Table 35, the maintenance of healing rates appeared to provide evidence for a dose-response relationship among the treatment groups. The rates of maintenance of healing of EE at Month 6 increased as the dose of H 199/18 increased, although the response in the H40 group was very similar to the H20 group (93.6% and 93.2%, respectively).

- Refer to Table 35. Data at Month 1 and Month 3 showed similar patterns of results as those seen at Month 6. At each time point, notable differences between the rates of healing in the H 199/18 treatment groups and the PL group were seen. Through Month 1, life-table methods showed that 42.9% of PL patients remained healed, compared with 100, 100, and 77.9% of the patients in the H40, H20, and H10 groups, respectively. Through Month 3, 29.0% of PL patients remained healed, compared with 98.6, 96.0 and 72.0% of the patients in the H40, H20 and H10 groups, respectively.

- No formal statistical comparisons were made at these time points, but it was noted that the upper 95% confidence limit for the proportion remaining healed in the PL group was below the lower 95% confidence limit for the proportion remaining healed in each of the H 199/18 treatment groups; i.e., the 95% confidence intervals for the rate estimates, did not overlap. This was true both for cumulative life-table rates and for cumulative maintenance rates (Table 35). Maintenance of healing rates were almost identical in the two higher dose groups (H40 and H20) at each time point, were always higher than in the H10 group and, with the exception of the H40 group and the H10 groups at Month 1, there was no overlap of confidence intervals between the maintenance of healing rates for the H40 and H20 groups with rates for the H10 group.

- The data in Table 35 also show that the proportion of patients that remained healed was consistently higher in the H20 than in the H40 group. According to the sponsor, this may be explained by the higher incidence of patients in the discontinued, presumably healed category in the H40 group.

- Analyses of the PP population showed a similar pattern of results for the primary efficacy variable (endoscopic remission).

i) Mean Time to Recurrence

- For those patients who had recurrence of EE, the mean time to recurrence was sooner for the PL patients (mean time to recurrence = 33 days) than for the H 199/18 patients (mean time to recurrence = 163, 115 and 75 days for the H40, H20 and H10 groups, respectively)

- 3 PL patients, but no H 199/18 patient, had a Grade D classification at recurrence, and few patients recurred at a Grade that was higher (i.e., worse) than their original Grade (sponsor's Table 14.2.12).

- The number (%) of patients who recurred at Grade C or Grade D, as a percentage of those with recurrence in that treatment group, was: 0/4 H40 patients (0%), 1/5 H20 patients (20.0%), 3/30 H10 patients (10.0%) and 9/51 PL patients (17.7%).

ii) Examination of Subgroups

Maintenance of healing of EE status was tabulated for the following patient subgroups: GELUSIL use, gender, age group (<65y, ≥65y), race, LA Classification Grade at entry into healing of EE study, treatment received during healing of EE study, duration of treatment in healing of EE study (4 weeks or 8 weeks), and investigational site. The presentation of results for each of these subgroups in the sponsor's Clinical Report was limited to Month 6 data. These data are summarized as follows.

- There did not appear to be any relationship of GELUSIL use to H 199/18 dose nor, in the H 199/18 treatment groups, to time in the trial.

- Male patients appeared to have a lower rate of maintenance of healing of EE and a higher rate of recurrence than females.

- There were no clinically meaningful differences apparent between the age or race groups.

- With the exception of the PL group, baseline severity did not appear to be a predictor for maintenance of healing. Of the 18 PL patients with a baseline LA Grade C or Grade D, none was maintained to Month 6, while 12/59 PL patients (20.3%) with a baseline LA Grade A or Grade B were maintained at Month 6.

- The pattern of maintenance of healing rates was similar within each previous healing of EE treatment subgroup to that seen for Study 178 as a whole. There was no apparent impact of any of the three healing of EE treatments received in Study 172 on maintenance rates in Study 178 and, therefore, no evidence of a rebound effect specific to H 199/18 (H40 or H20) or omeprazole (20 mg qd).

- Duration of healing of EE treatment in Study 172 or investigational site did not appear to influence maintenance of healing of EE in Study 178.

e) Summary Results of Secondary Efficacy Parameters (Table 36)

In this Table, frequencies of the absence of each of the four GERD symptoms (heartburn, regurgitation, dysphagia, and epigastric pain), evaluated by the investigator at Month 1, are presented.

- At Month 1, 17.8% of PL patients were **heartburn-free** during the week prior to the visit, compared to 78.7% of the H40 patients, 61.3% of the H20 patients, and 51.4% of the H10 patients. Pairwise comparisons of each H 199/18 group with the placebo group were statistically significant (all p-values <0.001), and the percentage of patients without heartburn increased as the dose of H 199/18 increased. For this parameter (heartburn free), the difference between the 40 and 20 mg dose levels was 17.4% [p=0.023] (Table 36).

- A similar pattern among treatment groups was seen in the percentages of patients **without regurgitation** at Month 1. Regurgitation was absent in 34.2% of PL patients during the week preceding the Month 1 visit, compared to 77.3% of H40 patients, 73.8% of H20 patients, and 60.8% of H10 patients. Pairwise comparisons of each H 199/18 group with the PL group were statistically significant (all p-values<0.001), and the percentage of patients without regurgitation increased as the dose of H 199/18 increased. For this parameter (regurgitation free) the difference between the 40 and 20 mg dose levels was 3.5% [p=N.S.] (Table 36).

- In general, few patients reported having **dysphagia** in the week preceding the Month 1 visit. **Dysphagia was absent** in 76.7% of PL patients at this time, compared to 93.3% of H40 patients, 92.5% of H20 patients, and 85.1% of H10 patients. Pairwise comparisons of each H 199/18 group with the PL group were statistically significant (all p-values <0.05) for the H40 and H20 groups, but not for the H10 group (p=0.239) and, the dose response relationship among the treatment groups was less pronounced for this symptom. For this parameter (dysphagia free), the difference between the 40 and 20 mg dose levels was 0.8% [p=N.S.] (Table 36).

- At Month 1, 56.2% of PL patients had **no epigastric pain** in the week preceding the visit, compared with 84.0% of H40 patients, 77.5% of H20 patients, and 68.9% of H10 patients. Pairwise comparisons of the H40 and H20 groups with the PL group were statistically significant (all p-values <0.01); however, the H10 group was not statistically different from placebo (p=0.107). The percentage of patients without epigastric pain increased as H 199/18 dose increased. For this parameter (epigastric pain free), the difference between the 40 and 20 mg dose levels was 6.5% [p=N.S.] (Table 36).

TABLE 36
Study No. 178
Summary Results of Secondary Evaluation Parameters
[Number (%) of Patients Without Investigator-Recorded GERD Symptoms at Month 1]
ITT Population

GERD Symptom	H 199/18 (mg qd)			PL	Therapeutic Gain/[p-value]		
	40 [n=75]	20 [n=80]	10 [n=74]	[n=73]	H40 vs H20	H40 vs H10	H20 Vs H10
Heartburn p-value vs PL[a]	59 (78.7%) <0.001**	49 (61.3%) <0.001**	38 (51.4%) <0.001**	13 (17.8%)	17.4% [0.023]	27.3% [<0.001]	9.9% [N.S.]
Regurgitation p-value vs PL[a]	58 (77.3%) <0.001**	59 (73.8%) <0.001**	45 (60.8%) <0.001**	25 (34.2%)	3.5% [N.S.]	16.5% [0.036]	13.0% [N.S.]
Dysphagia p-value vs PL[a]	70 (93.3%) 0.012*	74 (92.5%) 0.005**	63 (85.1%) N.S.	56 (76.7%)	0.8% [N.S.]	8.2% [N.S.]	7.4% [N.S.]
Epigastric pain p-value vs PL[a]	63 (84.0%) <0.001**	62 (77.5%) 0.004**	51 (68.9% N.S.	41 (56.2%)	6.5% [N.S.]	15.1% [0.022]	8.6% [N.S.]

From sponsor's Table 14.2.13, with major modifications.
a) Cochran-Mantel-Haenszel test stratified by presence or absence of symptom at baseline.
* Statistically significant, $p<0.05$, but $p \geq 0.01$ (comparisons to PL).
** Statistically significant, $p<0.01$ (comparisons to PL).

f) Results of Safety Evaluations

i) Extent of Exposure

- 318 patients with healed EE were randomized in this study, 99.1% of whom (n=315)[34] received at least one documented dose of test medication.
- Only the 315 patients who received at least one dose of study medication were included in the safety summaries and analyses.
- The frequency distributions and descriptive statistics for exposure to test medication in each treatment group are presented in Table 37.
- Slightly more than 70% of PL patients participated in the study to Week 4, compared with more than 88% of patients in the H 199/18 treatment groups.

[34] From sponsor's Appendices 16.2.2.1 and 16.2.1.1. There was 1 patient in each H 199/18 treatment group who did not receive at least one dose of test medication: Patient 160/004 (H40 group) who was lost to follow-up (never returned after randomization and baseline evaluations), Patient 143/009 (H20 group) who withdrew consent prior to taking any study drug, and Patient 103/008 (H10 group) who also withdrew consent prior to taking any test medication.

- By 18 weeks (4 months), only 16.9% of the PL patients remained in the study. In contrast, 76.5% of the H40 patients, 85.2% of the H20 patients, and 57.9% of the H10 patients remained in the study at this time.

- Beginning at week 4, the percentage of patients remaining in the study was highest in the H40 and H20 groups, next highest in the H10, and lowest in the PL group.

- The mean time on treatment for the PL group was 59 days, while the means for the three H 199/18 treatment groups ranged from 124 days to 161 days (ca. 4 to 5 months). the mean time on treatment was longest in the H40 and H20 groups, only slightly shorter in the H10 group, and notably shorter in the PL group.

TABLE 37
Study 178
Exposure to Treatment

Time on Treatment (Weeks)	H 199/18 (mg qd)			PL [n=77]
	40 [n=81]	20 [n=81]	10 [n=76]	
Frequencies (%)				
≥ 2	93.8%	95.1%	96.1%	84.4%
≥ 4	92.6%	92.6%	88.2%	71.4%
≥ 8	87.7%	90.1%	67.1%	26.0%
≥ 12	87.7%	90.1%	64.5%	23.4%
≥ 18	76.5%	85.2%	57.9%	16.9%
≥ 26	25.9%	28.4%	25.0%	3.9%
Descriptive statistics, days				
Mean (SD)	157 (46.7)	161 (48.9)	124 (68.9)	58.7 (58.8)
Median	174	176	167	30.5
Min - Max				

From sponsor's Table 14.3.1.1, with some modifications.

ii) Deaths, Other Serious and Potentially Serious AEs

- There were no deaths in this trial.

- None of the SAEs, distributed as follows, was considered by the investigator to be related to test medication (all were rated unlikely related)

H 199/18 (mg/day)	SAEs
40	2
20	4
10	1
Total	7

iii) AEs Leading to Discontinuation (Table 38)

TABLE 38
Study No. 178
Listing of Patients Who Discontinued Treatment Because of an AE

Patient ID	Preferred Term for AE (verbatim term)	
H 199/18 40 mg qd		
120/014 F 68	Cerebrovascular disorder[a]/154 (Right-sided CVA)	UNL
151/006 M 38 Caucasian	Chest pain/12 (Pressure in chest)	POSS
169/014 F 62	Arteriosclerosis/85 (Carotid artery stenosis)	UNL
H 199/18 20 mg qd		
119/002 M 45 Caucasian	Rash/4 (Rash)	POSS
120/020 F 38	Arterial stenosis NOS[a]/56 Thrombosis arterial leg[a]/56 Postoperative complications[a]/59 (70% Stenosis of left external iliac artery/ Occlusion of left peroneal artery/Postoperative complications)	UNL UNL UNL
151/008 M 48	Purpura[a]/145 (Right temporal intracerebral hematoma secondary to MVA)	UNL
H 199/18 10 mg qd		
160/001 M 43	Diarrhea[b]20 Vomiting[b]/20 (Diarrhea/Vomiting)	POSS UNL
PLACEBO qd		
109/006 M 78	Diarrhea/7 (Diarrhea)	POSS
165/017 M 66	Esophagitis/11 (Grade B erosive esophagitis)	PRO

a) These were serious AEs. More information pertaining to these AEs was provided in sponsor's narratives in Section 12.3.2 of their Clinical Report.
b) "Action taken with respect to study drug" coded as "Study drug stopped", reason for discontinuation on Study Completion page was "Discontinued due to lost to follow-up".

- There were 9 patients who D/C treatment because of an AE, with the following distribution. The number of D/C patients within each treatment group was too small to detect meaningful differences among the treatment arms.