H 199/18 mg qd	"Study Drug Stopped" Action (on the AE Section of CRF)
40	3
20	3
10	1
PL qd	2
Total	9

iv) Adverse Events

- Summarized in Table 39 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 39).

- The proportion of patients experiencing at least one AE during Weeks 0 to 13 or 0 to 26 was numerically higher in the H40 than in the other H groups or PL, with an insinuation of dose response (Table 39).

TABLE 39
Study No. 178

Proportion of Patients With AEs With Length of Exposure

AE Category	H 199/18 (mg qd)			PL
	40 [n=81]	20 [n=81]	10 [n=76]	[n=77]
I. During Week 0 to Week 4				
≥ 1 AE	37.0%	28.4%	30.3%	33.8%
≥ 1 Serious AE	0.0%	0.0%	0.0%	0.0%
Discontinued treatment due to AE	1.2%	1.2%	1.3%	2.6%
II. During Week 0 to Week 13				
≥ 1 AE	50.6%	45.7%	44.7%	41.5%
≥ 1 Serious AE	0.0%	3.7%	0.0%	0.0%
Discontinued treatment due to AE	2,5%	2.5%	1.3%	2.6%
III. During Week 0 to Week 26				
≥ 1 AE	55.6%	51.9%	48.7%	42.9%
≥ 1 Serious AE	2.5%	4.9%	1.3%	0.0%
Discontinued treatment due to AE	3.7%	3.7%	1.3%	2.6%
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 40. There were no striking differences or trends (dose responses) among the four treatment groups. It is to be noted that

AEs related to the respiratory system (coughing, respiratory infection and sinusitis) and headache occurred more frequently among those patients treated with H 199/18 (any dose) than placebo (Table 40).

TABLE 40
Study No. 178

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			PL
	40 [n=81]	20 [n=81]	10 [n=76]	[n=77]
Musculoskeletal System				
Fracture	0.0%	3.7%	1.3%	0.0%
Hernia	4.9%	0.0%	0.0%	2.6%
Central/Peripheral Nervous System				
Headache	4.9%	4.9%	3.9%	1.3%
Gastrointestinal System				
Diarrhea	6.2%	4.9%	6.6%	2.6%
Dyspepsia	2.5%	3.7%	2.6%	2.6%
Epigastric pain	1.2%	0.0%	3.9%	2.6%
Flatulence	7.4%	4.9%	6.6%	2.6%
Gastrin serum increased	6.2%	6.2%	1.3%	0.0%
Gastritis[a]	6.2%	6.2%	2.6%	2.6%
Nausea	7.4%	3.7%	0.0%	2.6%
Tooth disorder	0.0%	3.7%	1.3%	1.3%
Vomiting	6.2%	0.0%	3.9%	1.3%
Cardiovascular System				
Hypertension	0.0%	3.7%	1.3%	0.0%
Respiratory System				
Coughing	3.7%	2.5%	1.3%	0.0%
Respiratory infection	9.9%	9.9%	6.6%	3.9%
Sinusitis	7.4%	11.1%	3.9%	2.6%
Red Blood Cell				
Anemia	1.2%	3.7%	0.0%	1.3%
Resistance Mechanisms				
Infection viral	6.2%	3.7%	5.3%	0.0%

From sponsor's Table 14.3.1.3, with major modifications.
a) Each of these AEs (gastritis) represents an endoscopy finding.

v) Changes in Laboratory Parameters/Serum Gastrin

- There were some differences among the treatment groups in incidence of these AEs, either as AEs or discontinuations due to AEs. However, the interpretation of results is limited by the smaller number of PL patients available for laboratory test sample collection at Month 3 and Month 6 compared to the PPI treatment groups. These small changes were not seen at Month 1.

- Over the entire period, ALAT and ASAT had changes from normal (at baseline) to outside normal limits (post-baseline) in more than 3% of the patients in the study (≥ 10 patients).

However, at Month 1, the incidence of shifts from normal to above normal were generally similar across the treatment groups.

- For ALAT, the percentages of patients with results that changed from normal to above the normal limit (>48 U/L) over the entire study period in the H40, H20, H10, and PL groups were 13.6, 8.7, 6.3, and 1.6%, respectively; compared to 3.0, 4.3, 1.6, and 1.6%, respectively, at Month 1.
- For ASAT, the percentages of patients with results that changed from normal to above the normal range (>42 U/L for patients <65 years, and >55 U/L for patients ≥65 years) over the entire study period in the H40, H20, H10 and PL groups were 8.6, 2.7, 4.5, and 3.1%, respectively; compared to 1.4, 1.4, 3.1 and 1.6%, respectively, at Month 1. **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[b]
	40	20	10	
Mean Change (pg/ml)	51.3	22.9	-5.0	-39.5
Increase[a] from normal at baseline to above normal post-baseline	44.2%	26.8%	4.3%	1.9%

a) Increase=shift from WNLs at baseline to above NLs at any post-baseline measurement. As expected, most of the shift in serum gastrin concentrations occurred by Month 1.
b) Among the placebo patients, all of whom had received H40, H20 or 020 in Study 172, the mean serum gastrin concentrations at Month 1 (34.7 pg/ml) had already returned to the baseline concentrations recorded in Study 172.

vi) Other

- In Study No. 178, there were no clinically meaningful changes in blood pressure, or pulse rate, or P.E. (including weight) over the course of the trial.

- Biopsy evaluations revealed very few non-normal ratings for the parameters evaluated, including 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 atrophy, 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.

- Of the 11 patients evaluated for atrophic gastritis, 2 patients (both in the PL group) were determined to have atrophic gastritis at baseline; both patients still had atrophic gastritis at their final visit, but no patient had treatment-emergent atrophic gastritis.

- ECL cell ratings showed that 1 patient in the H10 group had micronodular hyperplasia (**MNH**) at the baseline and final biopsy; all other non-normal, post-baseline ECL cell ratings were either linear (**L**) or simple hyperplasia (**SH**).

- Increases (worsening) in ECL cell ratings were seen in the following proportion of patients:

	H199/18 (mg qd)			PL
	40	20	10	
Proportion of Pts. with increases (worsening) in ECL cell ratings	9.8%	8.3%	3.4%	0%

NOTE i: Pairwise comparisons of each H 199/18 treatment group with placebo showed that the proportion of patients with increased ECL cell ratings was significantly higher in the H40 and H20 groups than in the placebo group ($p<0.05$); the H10 group was not statistically different than the placebo group.

NOTE ii: Maximum serum gastrin concentrations for patients with ECL cell increases tended to be higher than for the patients without ECL cell increases.

- As per Study No. 177, the observed changes in serum gastrin concentration as well as those in ECL cell hyperplasia among patients treated with esomeprazole should be - conservatively - incorporated in the **labeling**.

11. Sponsor's Discussion and Overall Conclusion

"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: 93.6% of H40 patients, 93.2% of H20 patients, 57.1% of H10 patients, and 29.0% 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 33 days in the placebo group, 75 days in the H10 group, 115 days in the H20 group, and 163 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 178 was the other controlled clinical trial submitted by the sponsor in support of efficacy and safety of orally administered NEXIUM (esomeprazole) in the maintenance of healing of EE.

Study 178, carried out from 24 October 1997 to 17 August 1998, randomized a total of 318 patients at 47 investigator sites; 187 of these patients completed the 6-month trial. In addition to being multicenter and randomized, this 4-arm study was double-blind, PL-controlled, parallel-group of 6-month duration and was set to evaluate the efficacy and safety of 3 dose levels of the PPI in patients with healed EE and compare these effects to PL. This study was well-designed and, based on the information provided in the sponsor's Clinical Report, apparently well-executed. As in Study 177, this was a follow-on trial of patients that had been shown to heal under short-term (4 to 8 weeks) therapy in healing of EE Study 172. The study population consisted of 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 aspects of the design, execution, primary and secondary efficacy parameters and all aspects of safety evaluations, including evaluation of biopsies, were as in Study 177.

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	93.6% [87.4%, 99.7%]
H20	93.2% [87.4%, 99.0%]
H10	57.1% [45.2%, 69.0%]
PL	29.0% [17.7%, 40.3%]

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]. In this study, the H20 dose level gave a **nearly identical response** to that seen with H40, which confirms the reviewer's observation for the results in Study No. 177. Although H20 was superior to H10 (and to PL) the efficacy of this dose could not be differentiated from H40. Again, as in Study 177, several subgroups were examined but none appeared to be a predictor of maintenance of healing.

In Study 178, the mean time to recurrence of EE was shorter in patients receiving PL (33 days) than in those receiving the PPI (163, 115, and 75 days for the H40, H20 and H10 groups, 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 HB being the most prevalent symptom. Proportion of

patients that were HB-free was lowest in the PL group (17.8%) but increased as the dose of the PPI increased (51.4%, 61.3%, and 78.7% 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. 178 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.

Not surprisingly, this study showed the dose-related increases in cell hyperplasia among patients receiving PPIs. Gastric biopsy evaluations revealed very few non-normal changes for chronic inflammation, intestinal metaplasia or atrophy at either antral or fundic locations. ECL cell ratings showed that 1 patient in the H10 group had **MNH** at both the baseline and final biopsies; all other non-normal, post-baseline ECL cell ratings were either linear or simple hyperplasia. 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 both the H40 and H20 groups than in the PL group ($p<0.05$). But none of these changes in ECL cell rating is considered clinically meaningful. No progression to dysplasia or neoplasia has been reported.

Study 178 (as 177) 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): 51.3 (H40); 22.9 (H20); -5.0 (H10) and -39.5 (PL).

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

In conclusion, the sponsor has submitted results of two studies (178 and 177) demonstrating that NEXIUM (esomeprazole) is effective and safe in the maintenance of healing of EE. However, from the review of the evidence, the reviewer concludes that H20 is as effective and similarly safe and well-tolerated as H40, the dose recommended by the sponsor.

VII. REVIEW OF CLINICAL TRIALS FOR THE INDICATION TREATMENT OF SYMPTOMATIC GASTROESOPHAGEAL REFLUX DISEASE (s-GERD)

A. Study 225

"A Comparative Efficacy and Safety Study of H 199/18 (20 mg), H 199/18 (40 mg) vs Placebo in Study Subjects With Symptomatic GERD"

1. Primary Objective

To assess the efficacy, as defined by complete resolution of heartburn (HB) per diary card, of 4 weeks of treatment of H 199/18 40 mg qd compared to PL qd and H 199/18 20 mg qd compared to PL qd in subjects with symptomatic gastro-esophageal reflux disease (s-GERD).

2. Secondary Objectives

To assess the following:

- Efficacy, as defined by complete resolution of HB per diary card, of H 199/18 40 mg qd compared to PL qd and H 199/18 20 mg qd compared to PL qd at each of Weeks 1, 2 and 4.

  NOTE: The '4 week' secondary objective will differ from the primary objective, in that it will only consider data from the subset of subjects with data at Week 4.

- Efficacy, as defined by **relief of HB per diary card**, of H 199/18 40 mg qd compared to PL qd and H 199/18 20 mg qd compared to PL qd at each of Weeks 1, 2 and 4.

- Efficacy as defined by the **percentage of days without HB** per diary card, of H 199/18 40 mg qd to PL qd and H 199/18 20 mg qd to PL qd, at each of Weeks 1, 2, and 4.

- Efficacy, as defined by the **percentage of days without nocturnal HB**, per diary card, of H 199/18 40 mg qd to PL qd and H 199/18 20 mg qd to PL qd, at each of Weeks 1, 2, and 4.

- Efficacy, as defined by **time to first resolution of HB** and **time to first resolution of nocturnal HB** per diary card, of H 199/18 40 mg qd compared to PL qd and H 199/18 20 mg qd compared to PL qd.

- Efficacy, as defined by **time to sustained resolution of HB** and **time to sustained resolution of nocturnal HB** per diary card, of H 199/18 40 mg qd compared to PL qd and H 199/18 20 mg qd compared to PL qd.

- Efficacy, as defined by resolution of HB, acid regurgitation, dysphagia, and epigastric pain symptoms per **investigator assessment** of H 199/18 40 mg qd compared to PL qd and H 199/18 20 mg qd compared to PL qd at each of Weeks 2 and 4.

- Efficacy, as defined as a measure by the Overall Treatment Evaluation (OTE), of H 199/18 40 mg qd compared to PL qd and H 199/18 20 mg qd compared to PL qd at each of Weeks 2 and 4.

- To evaluate the safety and tolerability of H 199/18 40 mg qd compared to PL qd and H 199/18 20 mg qd compared to PL qd.

3. Study Population (Table 44)

This was adequate for this type of study. The study population consisted of 368 patients (from a total of 1,021 screened) with s-GERD at 26 participating investigational centers in the U.S. Listed in Table 41 are: a) criteria for randomization of s-GERD patients into this trial; and b) the criteria used to exclude patients from participating in the study.

TABLE 41
Study 225
Characteristics of the Study Population

INCLUSION CRITERIA	REASONS FOR EXCLUSION
• Adults between the ages of 18 and 75 inclusive (and of legal age to consent). • M or non-pregnant, non-lactating F. Fs must be post-menopausal, surgically sterilized or using a medically acceptable form of birth control, as determined by the investigator[a,b]. • Those identifying their main symptom as a burning feeling, rising from the stomach or lower part of the chest up towards the neck, ie, heartburn. • History of episodes of HB for 6 months or longer. • Those with episodes of HB for 4 days or more during the last 7 days prior to baseline. • Patients negative for erosive esophagitis confirmed by esophagogastroduodenoscopy (EGD) performed within 10 days of study randomization. • Capable of providing written informed consent, willing and able to comply with all procedures of the study.	• Bleeding disorder or signs of G.I. bleeding at the time of the screening EGD or within 3 days prior to randomization. • History of or current endoscopic EE at screening EGD. • History of gastric or esophageal surgery, except for simple closure of perforated ulcer. • Current or historical evidence (within 3 months) of the following diseases/conditions: Zollinger-Ellison syndrome, the primary esophageal motility disorders achalasia, scleroderma and/or primary esophageal spasm, esophageal stricture, DU or GU, IBD, evidence of upper G.I. malignancy at the screening, pancreatitis, malabsorption, severe cardiovascular or pulmonary disease, severe liver disease [subjects with liver enzymes three times the upper limit of normal will 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 DM [stable diabetics controlled on diet, oral agents or insulin are acceptable], cerebral vascular disease, such as cerebral ischemia, infarction, hemorrhage, or embolus. Any condition that may require surgery during the study. • Endoscopic Barrett's esophagus or significant dysplastic changes in the esophagus. • Known clinically significant abnormal laboratory values as part of their medical history [should be reviewed and discussed with the Medical Monitor]. • PPI within 28 days prior to the baseline visit. • H_2-receptor antagonist daily during the 2 weeks prior to the screening EGD or between the screening EGD and study enrollment study [occasional use less than daily will be permitted].

APPEARS THIS WAY ON ORIGINAL	• 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], H_2-receptor antagonists, proton pump inhibitors (other than test medication), 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 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 not able to give fully informed consent due to mental deficiency or language problems. • Prior or concurrent participation in this study or any other study associated with the H 199/18 program. • Unable to take test medication according to dosing instructions. • Pregnancy or lactation (F only).

Reviewer's Table.
Abbreviations used: **M=male; F=female; HB=heartburn; EGD=esophagogastroduodenoscopy; G.I.=gastrointestinal; EE=Erosive esophagitis; DU=duodenal ulcer; GU=gastric ulcer; IBD=inflammatory bowel disease; DM=diabetes mellitus; PPI=proton pump inhibitor**

a) Women of child-bearing potential must agree to continue using an acceptable form of birth control throughout the conduct of the trial.
b) All women of child-bearing potential (ie, those not post-menopausal or surgically sterilized), must have a negative pregnancy test at baseline.

4. Overall Study Design and Schedule of Evaluations

From the review of the evidence presented by the sponsor this was a multi-center, randomized, double-blind, 3-arm, parallel-trial that investigated the efficacy of H 199/18 (20, 40 mg once-a-day) in comparison to placebo (PL) once daily in patients with symptomatic (endoscopy-proven absence of EE) GERD. The allocation of treatment was 1:1:1. Patients had return visits at Week 2 and Week 4. At each return visit, the patient submitted the daily HB diary cards (which the study coordinator reviewed with the patient at each visit for completeness and accuracy), reported all AEs, provided a history of medications taken during the previous interval, returned unused test medication, and had tablet counts performed. Patients also had GERD symptoms assessed by the investigator and completed the overall treatment evaluations (OTE) questionnaire at each of these visits. At the final visit, in addition to the assessments completed at each return visit, each patient underwent a P.E. and had fasting laboratory samples taken. The definitions of HB and its severity (none, mild, moderate and severe), were adequate.

5. Clinical Supplies/Randomization/Selection of Doses and Timing of Dosing/ Blinding

All of these aspects of the study were adequate.

- The dosage strengths, appearances and batch number of test medications used in this trial were as follows:

Identification of Test Medications

Treatment	Appearance	Batch Number
H 199/18 40 mg	Blue, Size 2 capsule	H-1222-04-01-07
H 199/18 20 mg	Blue, Size 2 capsule	H-1189-04-01-04
Placebo	Blue, Size 2 capsule	H-0459-06-03-07
Individual patients receiving the various batches were listed in sponsor's Appendix 16.1.6.		

- Randomization[35] was performed at each center using blinding blocks of 6 allocation numbers. A complete randomization list was provided in sponsor's Appendix 16.1.7.

- The **selection of dose** was based on PK and PD studies, which indicated that both H40 and H20 may demonstrate efficacy. Since H5 and H10 daily doses were less effective than omeprazole 20 mg qd at inhibition of pentagastrin-stimulated acid secretion, these doses were not investigated further. All patients were instructed to take the test medications in the morning with a glass of water.

- To preserve blinding[36] all 3 test medications had the same appearance.

[35] The randomization scheme was generated by Astra Hässle, Molndal, Sweden, now AstraZeneca LP. Patients were randomized to treatment in a 1:1:1 ratio (H40:H20:PL). Eligible patients at each center were given the next sequential enrollment number (001, 002, 003, etc.) and the next sequential allocation number based on pre-printed numbers on the study drug labels.

[36] All test medications were packaged in bottles at Astra Hässle AB, Molndal, Sweden. Investigators were provided with individually sealed and blinded randomization envelopes indicating the treatment allocation for each patient. These envelopes were stored in a secure location at the investigational site. All envelopes were collected and checked by the monitor at the end of the study to ensure the integrity of the blind.

6. Prior and Concomitant Therapy/Compliance

- The procedures to assess prior and concomitant therapy[37] (Table 41) and compliance with test medication were all adequate.

Also adequate were the procedures to assess compliance.

7. Evaluation Criteria

a) Efficacy

- The primary efficacy variable was complete resolution of HB symptoms (defined as no episodes of HB during the last 7 days of treatment, as documented on the patient's diary card). This is an accepted measure of the efficacy of s-GERD treatments.

- The secondary efficacy variables were based on the percentage of patients with either complete resolution or relief of diary-recorded HB and other symptoms (HB, regurgitation, dysphagia and epigastric pain) assessed by the investigator.

- HB was assessed by the patient each morning during the 4-week, double-blind treatment period. All patients were instructed to record the severity of their most severe HB episode as documented by adequate definitions. Diary card entries made by the patient were to be for the 24-h period prior to that morning's test medication dose. Patients also indicated whether nocturnal HB (during normal sleeping hours) was present. Patients were to turn in their diary cards at the Week 2 and Week 4 visits, at which time the study coordinator reviewed the diary cards with the patient for accuracy and completeness.

b) Safety, Dictionaries and Coding Safety Terminology

All aspects of safety assessments including dictionaries and coding terminology were adequate. These included evaluation of reports of AEs, and other safety variables such as routine P.E., endoscopy, gastric biopsies and laboratory determinations.

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[37] Patients were excluded from the trial if they had taken PPIs within 28 days prior to the baseline visit. Use of PPIs (other than test medication) was prohibited for the duration of treatment. Patients were excluded from the trial if they had taken H_2-receptor antagonists during the 2 weeks prior to baseline EGD (occasional use less than daily was permitted). Use of H_2-receptor antagonists was prohibited for the duration of treatment. Concomitant use of GELUSIL tablets as a rescue medication for acute GERD symptoms was permitted, up to a maximum of six GELUSIL tablets per day. Other medications that might have affected the interpretation of the treatment outcome or were considered drug interactions in the PRILOSEC® (omeprazole) delayed-release capsules package insert [sponsor's Ref(s). 5] were not permitted during the study (Protocol, sponsor's Appendix 16.1.1). Other medication considered necessary for the patient's welfare could have been given at the discretion of the investigator.

8. Data Quality Assurance

The procedures, reviews and verification processes instituted by the sponsor to ensure that the data collected were accurate, consistent, complete and reliable were all adequate.

9. Statistical Methodology (as specified in the Protocol)

a) Determination of Sample Size

The sample size of 100 patients per treatment arm was calculated based on having 95% power to detect a difference in resolution rates of 60% for an H 199/18 treatment group and 30% for the PL treatment group (**30% therapeutic gain**). This assumed a two-sided test, using the arcsine transformation, and a Bonferroni correction (ie, an alpha level of 0.025) for the two comparisons (each H 199/18 treatment group to PL).

b) Details of Statistical and Analytical Procedure

- Two populations were defined for purposes of the analysis of efficacy data: ITT and PP.

- For the **primary efficacy analysis** (the percentage of patients who exhibit complete resolution of HB at the end of the study), a Chi-square test was used to assess differences between "H40 vs PL" and "H20 vs PL". The statistical significance level of these nominal p-values was determined based on Hochberg's procedure. that is, adjusting for multiple comparisons.

- For the **secondary efficacy variables** that were based on the percentage of patients with either complete resolution or relief of diary-recorded heartburn, similar Chi-square tests were performed for each of the "H40 vs PL" and "H20 vs PL" comparisons. No corrections for multiple comparisons were made for any secondary variables; nominal p-values were used for determination of statistical significance. For the other symptoms of GERD that were assessed by the investigator, the percentage of patients with resolution (defined as a rating of NONE) were analyzed using a Cochran-Mantel-Haenszel Chi-square test, stratified by the baseline rating of the symptom being analyzed.

- The efficacy variables that were based on the mean severity of HB or on the percentage of days or nights without heartburn were analyzed using a two-way analysis of variance (ANOVA) model, with main effects of investigator and treatment. Investigators who contributed fewer than 5 patients to an analysis were combined into a separate 'investigator' for the analysis. The efficacy variables that were based on the time to an event were analyzed using a log-rank test.

- Analysis of the OTE results was performed using a Wilcoxon rank-sum test.

- Comparison of H20 and H40 were presented descriptively.

- Subgroup analysis of the primary endpoint in the ITT population was presented descriptively for gender, age group (<65 y, ≥65 y), race, investigator, and *H. pylori* status (by histology).

- No protocol amendments were issued for this trial and there were no changes made to the analyses specified in the Data Analysis Plan (sponsor's Appendix 16.1.9) completed prior to the data being unblinded. Two

additional summaries/analyses of the existing efficacy data that were not specified in the protocol were included in the Data Analysis Plan and in the sponsor's study report:

i) The mean severity of HB for each patient at Week 1, Week 2, Week 4, and at the end of the study was summarized and the H40 and H20 groups compared to the PL group using a two-way ANOVA.

ii) The percentage of patients with relief of HB at the end of the study (PL included only summaries at Week 1, Week 2, and Week 4).

10. Results

a) Disposition of Patients (Table 42)/Protocol Deviations

- The 20 participating investigators screened a total of 1,021 patients, of whom 368 (H40, n=123; H20, n=121; PL, n=124) were randomized. The primary reason for not randomizing screened patients was EE positive status [n=503; other, n=150] for a total of 653 (Table 42).

- Of the 368 patients enrolled in the trial 344 (93.5%) completed the study and 24 (H40, n=9; H20, n=8; PL, n=7) or 6.5% discontinued from the trial before completion (Table 42).

- Among discontinued patients, the most frequent reason for D/C was the withdrawal of consent (3 patients in each treatment arm = 2.4%).

- 3 patients (H40, n=2; H20, n=1; PL, n=0) or 0.8% D/C due to AEs and these are discussed under Results of Safety Evaluations.

- The rates of protocol deviations among the three treatment groups were generally similar.

b) Data Showing Comparability of Treatment Groups at Baseline (Table 43)

The treatment groups were well-balanced with respect to all the demographic, disease, and other baseline characteristics enumerated in this Table. Approximately 2/3 of the patients were female, 90% were <65y of age, mostly Caucasian, with a GERD history of at least 1y, mostly with moderate (58 to 66%), less with severe HB (23 to 26%).

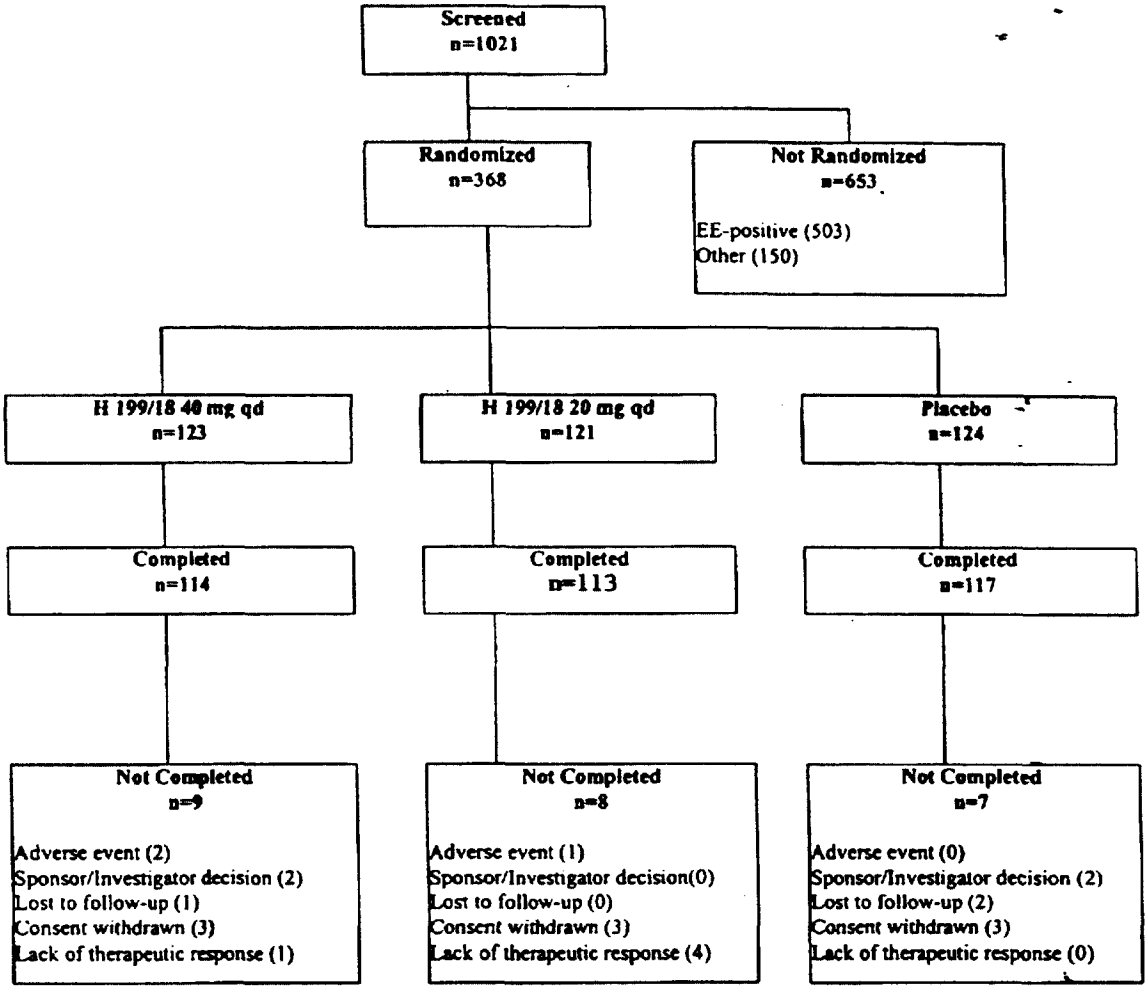
c) Compliance[38]

More than 91% of the patients in each group had test medication compliance rates greater than 80%. For the ITT population, the percentage of patients who were more than 90% compliant with the test medication regimen were similar among the treatment groups (89.4% for the H40 group, 90.9% for the H20 group, and 92.7% for the PL group). Compliance could not be established in ca. 4.9%, 1.7%, and 3.2% of the H40, H20, and PL patients, respectively.

[38] A summary of study medication compliance for the ITT population was given in sponsor;s Table 14.1.2.6.

TABLE 42
Study No. 225

Disposition of Screened and Randomized Patients



From sponsor's Table 14.1.2.3.

NOTE: The first patient entered the study on 10 February 1999 (date that first drug was dispensed), and the last patient completed the study on 02 June 1999. Of the 1,021 patients screened, 368 (36%) were randomized. These 368 patients comprised the ITT population.

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TABLE 43
Study No. 225
Demographic and Other Baseline Characteristics
ITT Population

		H 199/18 (mg qd)		PL
		40 [n=123]	20 [n=121]	[n=124]
Gender	M	39.0%	40.5%	37.1%
	F	61.0%	59.5%	62.9%
	18-44 y	37.3%	38.9%	42.3%
	≥ 45 y	62.7%	61.1%	57.7%
Age, y	Mean (SD)	47.2 (13.5)	47.0 (13.4)	46.0 (12.6)
	Min – Max	20 - 78	21 - 75	19 - 82
Age category	<65 y	90.2%	86.0%	93.5%
	≥65 y	9.8%	14.0%	6.5%
Race	Caucasian	81.3%	93.4%	83.9%
	Black	13.8%	5.0%	8.9%
	Asian	3.3%	0.0%	3.2%
	Other	1.6%	1.7%	4.0%
Body weight, lb	Mean (SD)	181.3 (46.8)	178.3 (38.3)	177.7 (41.0)
	Min - Max	108 - 350	105 - 299	100 - 295
Height, in	Mean (SD)	66.5 (4.4)	66.4 (3.8)	66.1 (3.7)
GERD history	< 1 y	8.9%	9.9%	11.3%
	1 to 5 y	47.2%	51.2%	50.0%
	> 5 y	43.9%	38.8%	38.7%
Heartburn	None	0.0%	0.8%	0.0%
	Mild	11.4%	15.7%	15.3%
	Moderate	65.9%	57.9%	59.7%
	Severe	22.8%	25.6%	25.0%
Acid regurgitation	None	8.9%	13.2%	10.5%
	Mild	32.5%	26.4%	27.4%
	Moderate	38.2%	40.5%	46.0%
	Severe	20.3%	19.8%	16.1%
Dysphagia	None	60.2%	61.2%	62.9%
	Mild	22.0%	19.0%	20.2%
	Moderate	11.4%	14.9%	12.9%
	Severe	6.5%	5.0%	4.0%
Epigastric pain	None	26.8%	33.9%	32.3%
	Mild	30.1%	28.1%	35.5%
	Moderate	26.8%	29.8%	22.6%
	Severe	16.3%	8.3%	9.7%
***H. pylori* status**	Negative	68.3%	67.8%	75.8%
	Positive	31.7%	30.6%	23.4%
	Missing	0.0%	1.7%	0.8%

From sponsor's Table 14.1.1.1, with major modifications.

d) Proportion of Patients With Complete Resolution of HB at Final Visit (Table 44)

As shown in this Table, the proportion of patients with complete resolution reporting NO HB by the end of the trial was 33.3%, 33.9% and 13.7% for treatment with H40, H20 and PL, respectively. There was a significant difference between the H40 and PL groups ($p<0.001$), as well as between the H20 and PL groups ($p<0.001$). The therapeutic gain (ca. 20%) was less than

the expected according to the Protocol (30%). Results for the PP population (Table 44) were similar to those for the ITT population, with both H40 and H20 showing significantly higher proportions of patients with complete resolution of HB at the end of the study ($p<0.001$ for each of the two comparisons to PL). In neither the ITT nor the PP population analysis further benefit was obtained when the dose of H 199/18 was increased from 20 to 40 mg once a day.

TABLE 44
Study No. 225

Proportion of Patients With Complete HB Resolution at Final Visit

I. ITT POPULATION ANALYSIS						
	H 199/18 mg qd		PL	Therapeutic Gain (%)/Statistical Significance [p-value][a]		
	40 [n=123]	20 [n=121]	[n=124]	40 vs PL	20 vs PL	40 vs 20
Responders	41 (33.3%)	41 (33.9%)	17 (13.7%)	**19.6%** [<0.001][b]	**20.2%** [<0.001]	**-0.6%** [N.S.]
II. PER-PROTOCOL POPULATION ANALYSIS						
	[n=115]	[n=117]	[n=114]			
Responders	39 (33.9%)	41 (35.0%)	15 (13.2%)	**20.7%** [<0.001]	**21.8%** [<0.001]	**-1.1%** [N.S.]

Reviewer's Table.
a) Chi-square test; comparison of each H 199/18 treatment to PL and each H 199/18 group to each other.
b) Statistical significance vs PL ($p<0.05$) using Hochberg adjustment.

e) Proportion of Patients With Complete Resolution of HB at 1, 2 and 4 Weeks (Table 45)

Regardless of the assigned test medication, the proportion of patients that reported NO HB increased with time (Week 4 > Week 2 > Week 1). However, at each time point, the therapeutic gain (H vs PL) was not very dissimilar to that seen at final visit (Table 44). There was a significant difference between the H40 and the PL groups ($p\leq0.001$), as well as between the H20 and PL groups ($p\leq0.014$) at each of the time points.

There was no further benefit when increasing the H dose from 20 to 40 mg qd at Week 2 or 4. However, at Week 1, the frequencies of patients responding to treatment was noted to occur at a 2-fold increase in the H40 group as compared to the H20 group (therapeutic gain=10.2%, $p=0.028$). This observation (superiority of the 40 mg qd dose over the 20 mg qd dose) needs to be replicated as it seems to be **the exception, not the rule**. In addition, the 95% CI of the H40 mg qd dose (13.0%, 27.4%) overlaps with those of the H20 mg qd dose (4.6%, 15.4%).

TABLE 45
Study No. 225

Proportion of Patients With Complete Resolution of HB as Recorded in the Diary Card (ITT Population)

	H 199/18 mg qd		PL	Therapeutic Gain (%)/Statistical Significance [p-value][a]		
	40 [n=119]	20 [n=120]	[n=123]	40 vs PL	20 vs PL	40 vs 20
I. WEEK 1						
Responders	24 (20.2%)	12 (10.0%)	3 (2.4%)	17.8% [<0.001][b]	7.6% [0.014][b]	10.2% [0.028][c]
II. WEEK 2						
	[n=119]	[n=119]	[n=122]			
Responders	31 (26.1%)	30 (25.2%)	11 (9.0%)	17.1% [<0.001]	16.2% [0.001]	0.9% [N.S.]
III. WEEK 4						
	[n=115]	[n=110]	[n=117]			
Responders	39 (33.9%)	36 (32.7%)	17 (14.5%)	19.4% [0.001]	18.2% [0.001]	1.2% [N.S.]

Reviewer's Table.
a) Chi-square test; comparison of each H 199/18 treatment to PL and each H 199/18 group to each other.
b) Statistical significance vs PL ($p<0.05$) using Hochberg adjustment.
c) This comparison did not use Hochberg adjustment.

f) Other Secondary Efficacy Parameters

Additional results of secondary efficacy parameters are noted:

- For **relief of HB** at 1, 2 and 4 Weeks and at the end of the study, there was a significant difference between the H40 and PL groups ($p\leq 0.001$), as well as between the H20 and PL groups ($p\leq 0.022$) at each of the 4 time points [sponsor's Table 14.2.4].

- For **mean severity of HB** at 1, 2 and 4 Weeks, and at the end of the study, there was a significant difference between the H40 and PL groups ($p\leq 0.005$), as well as between the H20 and PL groups ($p\leq 0.007$) at each of the 4 time points [sponsor's Table 14.2.5].

- For **percentage of days without HB at 1, 2 and 4 Weeks,** there was a significant difference between the H40 (mean=63% at 4 weeks) and PL (mean=46.4%) [$p\leq 0.001$], as well as between the H20 (mean=63% at 4 weeks) and PL (mean=46.4% at 4 weeks) [$p\leq 0.001$] at each of the 3 time points. At no time point, there was an increase in benefit when increasing the PPI dose from 20 to 40 mg once-a-day.

- For **percentage of days without nocturnal HB at 1, 2 and 4 Weeks** there was a significant difference between the H40 (mean at Week 4=88%) and PL groups (mean at Week 4=79%) [p≤0.006], as well as between the H20 (mean at Week 4=88%) and PL groups (mean at Week 4=79%) [p≤0.006] at each of the 3 time points. Once again, at no time point, was there further benefit when increasing the PPI dose from 20 to 40 mg once-a-day.

- Assessment of two additional secondary efficacy analyses, the time to first resolution of HB and nocturnal HB and time to sustained resolution of HB and nocturnal HB yielded results as those summarized above for the secondary endpoints of evaluation.

- Results for investigator-assessed resolution of **acid regurgitation** at Week 2 were significantly improved for H40 and H20 over PL (p≤0.004), with no differences between the 40 and 20 mg qd of the PPI. Results for investigator-assessed resolution of **acid regurgitation** at Week 4 were also significantly improved for H40 and H20 over PL (p≤0.001), again with no discernible differences between the dose levels of esomeprazole.

- Finally, results for investigator-assessed resolution of **dysphagia** and **epigastric pain** at Week 2 and Week 4 were not significant for either H40 or H20 over PL.

- In their Table 16, the sponsor summarized the OTE results at Week 2 and Week 4 from the initial 3-point scale (ie, Worse, About the Same, and Better), as well as the analysis of the distribution of patients across the 15-point scale. The distribution of patients across the 15-point scale was significantly different in the H40 and H20 groups vs PL (p<0.001 and <0.001, respectively) at Week 2 as well as at Week 4 (p<0.001 and <0.001, respectively).

- No formal assessment of GELUSIL use by treatment group was planned or done; however, review of the data showed that patients in the PL group took more GELUSIL than patients in each of the H 199/18 groups (sponsor's Table 14.2.23). There did not appear to be any relationship of GELUSIL use to H 199/18 dose nor to time in the trial.

g) Analysis of the Primary Efficacy Endpoint by Subgroups

The complete resolution of HB at the end of the study (final visit) was presented descriptively for the ITT population for the following subgroups: gender, age group (<65 y, ≥65 y), race, and *H. pylori* status (by histology).

- Relative treatment effects were similar for each gender, although male patients appeared to respond more favorable for the H40 and PL treatment arms, but the difference was not clinically meaningful.

- Although there was a lower response rate observed in patients ≥65 y of age vs those <65 y of age, the small number of patients in the former age group (H40, n=12; H20, n=17; PL, n=8) make these rates difficult to interpret.

- The bulk of the patients enrolled in this trial were Caucasian. Only 9% were Black, 2% Asian, and 2% Other. This makes any interpretation of rates of HB resolution across races difficult.

- The rates of complete resolution of HB at the final visit by *H. pylori* status are summarized in Table 46. The presence of *H. pylori* at baseline as assessed by histology, appeared to improve the chance of complete resolution of HB at final visit in all 3 treatment groups:

  i) In the PL group, there were a larger percentage of patients who experienced complete resolution of HB at the final visit for patients who were *H. pylori*-positive at baseline as compared to those who were *H. pylori*-negative at baseline (27.6% vs 8.5%, respectively).

  ii) In the H 199/18 treatment groups, the rates for complete resolution of HB in *H. pylori*-positive patients were higher (H40=46.2%; H20=40.5%) than those for *H. pylori*-negative patients (H40=27.4%; H20=31.7%).

TABLE 46
Study No. 225

Number (%) of Patients with Complete Resolution of Heartburn at Final Visit, by *H. pylori* Status at Baseline

Resolution of HB at Final Visit	H 199/18 mg qd		PL
	40 [n=123]	20 [n=121][a]	[n=124][a]
***H. pylori* negative at baseline (by histology)**			
	[84]	[82]	[94]
Resolved	23 (27.4%)	26 (31.7%)	8 (8.5%)
Not resolved	61 (72.6%)	56 (68.3%)	86 (91.5%)
***H. pylori* positive at baseline (by histology)**			
	[39]	[37]	[29]
Resolved	18 (46.2%)	15 (40.5%)	8 (27.6%
Not resolved	21 (53.8%)	22 (59.5%)	21 (72.4%)

From sponsor's Table 14.2.21, with minor modifications.
a) Missing *H. pylori* histology results included 2 patients from the H20 group with HB Not Resolved and 1 patient from the PL group with HB Resolved.

h) Results of Safety Evaluations

i) Extent of Exposure

- 365 patients were included in the safety population, with the distribution that follows. Treatment lasted for up to 4 weeks.

	mg qd	n
H 199/18	40	122
	20	120
Placebo		123
	Total n =	365[a]

a) Of the 368 randomized patients, 3 did not have a documented dose of test medication and were therefore excluded from the Safety Population (sponsor's Appendix 16.2.2.1).

ii) Deaths and Other SAEs

- There were no deaths in this trial.

- One patient in the PL arm of the study experienced a SAE: pharynx disorder (throat swelling), unlikely related to test medication.

iii) AEs Leading to Discontinuation

- As summarized below, 3 patients D/C treatment because of an AE.

Study No. 255: Listing of Patients Who D/C Treatment Because of an AE

Treatment	Site	Enrollment Number	Gender Age Race	Day of AE Onset	Preferred Term for Adverse Event (verbatim term)	
H40	301	012	F 60 Caucasian	23	Arthralgia (Left Knee Pain)	UNL
	303	010	F 55 Caucasian	1 1 2	Flatulence (Bloating) Nausea (Nausea) Vomiting (Intermittent Vomiting)	POSS POSS POSS
H20	313	006	M 63 Caucasian	10 10 12 12	Flatulence (Bloating) Diarrhea (Diarrhea) Abdominal Pain (Abdominal Pain) Constipation (Constipation)	POSS POSS POSS POSS

From sponsor's Table 14.3.1.12, with some modifications.

iv) Adverse Events

- There were no apparent differences between the H 199/18 treatment groups and the PL group in the proportion of patients reporting at least one AE (between 35% to 41%). The most frequently reported AEs were headache and G.I. events, which occurred at the following [similar] rates.

Study No. 225: Rates of AEs by Treatment Group (Patient Incidence ≥3% in Any Treatment Group

	H40 [n=122]	H20 [n=120]	PL [n=123]
Headache	5.7%	7.5%	8.9%
G.I. System Disorder			
-Abdominal pain	2.5%	6.7%	2.4%
-Diarrhea	1.6%	5.0%	4.1%
-Nausea	4.9%	7.5%	6.5%
-Increased Serum gastrin	4.1%	1.7%	1.6%
From sponsor's Table 14.3.1.2, with major modifications			

v) Changes in Laboratory Parameters/Serum Gastrin

- Baseline values for all laboratory parameters were generally similar. Mean changes from baseline were generally small and were similar across the three treatment arms of the trial. There were no clinically meaningful mean changes from baseline in any laboratory test parameter. As summarized below, the largest mean changes were expected dose-related mean changes seen in serum gastrin concentration.

Study No. 225: Serum Gastrin Concentration (mean pg/ml)

	H40 [n=118]	H20 [n=116]	PL [n=118]
Baseline	46.7	45.4	48.4
Post-Baseline	135.0	107.3	58.8
INCREASE	88.3	61.9	10.4

vi) Other

Mean changes from baseline in vital signs and weight at each time point were small, and generally similar across the three treatment groups. There were no meaningful shifts from baseline to post-baseline in weight, nor in any of the vital signs measures in any of the treatment groups.

11. Sponsor's Discussion and Overall Conclusions

"H 199/18, at doses of 40 mg qd and 20 mg qd, was statistically significant and clinically relevant to placebo in the complete resolution of diary-recorded heartburn after 4 weeks of treatment in patients with s-GERD.

"Each H 199/18 dose was statistically significant and clinically relevant to placebo for the majority of secondary endpoints.

"Each H 199/18 dose was well-tolerated, with no deaths, no drug-related serious AEs, no unexpected clinically meaningful changes in laboratory tests or vital signs.

"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

In support of the approval of NEXIUM (esomeprazole) for the indication treatment of symptomatic gastroesophageal reflux disease (s-GERD) the sponsor submitted the results of two critical clinical studies, Nos. 225 and 226. According to the sponsor, the recommended dose is 20 mg once daily for 4 weeks. Both trials were well designed and apparently well executed.

Study 225 randomized 368 patients at 26 sites. In addition to being multicenter and randomized, this 3-arm study was double-blind, placebo-controlled, parallel-group, of 1-month duration and was designed to evaluate the efficacy and safety of 2 dose levels of H 199/18 (H40 and H20 mg qd) vs PL in the complete resolution of heartburn (HB) in patients with s-GERD. As noted above, based on the review of the evidence presented by the sponsor in the Clinical Report, all aspects of the design and execution of this trial were adequate.

Each of the two dose levels of H 199/18 was statistically significant superior to PL in the complete resolution of diary-recorded HB after 4 weeks of treatment in these patients with s-GERD. Although in this study, the 30% protocol expected therapeutic gain (H > PL) in complete resolution of HB at 4 weeks was not realized, the observed therapeutic gain (ca. 20%) is clinically relevant. The results of secondary parameters of evaluation supported the efficacy of this PPI for this indication. There was a significant difference between the H40 and the PL groups as well as between the H20 and PL groups at 1, 2 and 4 weeks time points. There was a statistically significant difference between each of the H groups and PL in: relief of HB at 1, 2, and 4 weeks and at end of study, mean severity of HB at 1, 2, and 4 weeks and end of study, percentage of days without nocturnal HB at 1, 2 and 4 weeks, time to first resolution of HB and nocturnal HB and time to sustained resolution of HB and nocturnal HB.

Similarly, results for investigator-assessed resolution of "acid" regurgitation were significantly improved for H40 and H20 over PL at both Week 2 and 4, while results for investigator-assessed resolution of dysphagia or epigastric pain at Week 2 and 4 were not significant for any of the 2 dose levels of H over PL. In this study, there was no convincing evidence due primarily to the

small number of observations in some cells, that efficacy was different in the following subgroups: gender, age group (<65 y, ≥65 y), and race. In this study, the presence of *H. pylori* at baseline, as assessed by histology, appeared to improve the chances of complete resolution of HB at final visit in all treatment groups. This might be an interesting finding, but **it needs to be replicated** (see Additional Reviewer's Comments for Study 226).

The reviewer agrees with the sponsor's conclusion that, in this 4 week study, there were no clinically meaningful differences between the H 199/18 treatment groups and the PL groups in the occurrence of AEs, changes in laboratory values or changes in vital signs. As expected, there were changes (baseline to Week 4) in mean serum gastrin concentration that were higher among patients receiving the PPI than in those receiving PL (mean increase of 88.3, 61.9 and 10.4 pg/ml for the H40, H20 and PL groups, respectively).

B. Study No. 226

"A Comparative Efficacy and Safety Study of H 199/18 (20 mg), H 199/18 (40 mg) vs Placebo in Study Subjects with Symptomatic GERD"

NOTE: This study used an identical protocol to Study 225, only certain items will be highlighted.

1. Primary Objective

To assess the efficacy, as defined by complete resolution of heartburn (HB) per diary card, of 4 weeks of treatment of H 199/18 40 mg qd compared to PL qd and H 199/18 20 mg qd compared to PL qd in subjects with symptomatic gastroesophageal reflux disease (s-GERD).

2. Secondary Objectives

These were the same, as described in detail above, for Study 225.

3. Study Population

This was the same as in Study 225 (see details in Table 41).

4. Overall Study Design and Schedule of Evaluations

This was as per Study 225. From the review of the evidence presented by the sponsor, Study 226 was a multi-center, randomized, double-blind, 3-arm, parallel-trial that investigated the efficacy of H 199/18 (20 or 40 mg once-a-day) in comparison to placebo (PL) once daily in patients with symptomatic (endoscopy-proven absence of EE) GERD. The allocation of treatment was 1:1:1. Patients had return visits at Week 2 and Week 4, at which time they submitted the daily HB daily cards, reported all AEs, provided a history of medications taken during the previous interval, returned unused test medication, and had tablet counts performed.

5 Clinical Supplies/Randomization/Selection of Doses and Timing of Dosing/Blinding

All these aspects of the trial were adequate and carried out as in Study 225. The dosage strengths, appearances and batch number of test medications used in this trial were as follows.

Identification of Test Medications

Treatment	Appearance	Batch Number
H 199/18 40 mg	Blue, Size 2 capsule	H-1222-04-01-07
H 199/18 20 mg	Blue, Size 2 capsule	H-1189-04-01-04
Placebo	Blue, Size 2 capsule	H-0459-06-03-07
[Identical to Study No. 225] Individual patients receiving the various batches were listed in sponsor's Appendix 16.1.6.		

6. Prior and Concomitant Therapy/Compliance

The procedures to assess prior and concomitant therapy or compliance were all adequate.

7. Evaluation Criteria

a) Efficacy

As in Study 225, the primary efficacy variable was complete resolution of HB symptoms (defined as no episodes of HB during the last 7 days of treatment, as documented on the patient's diary card). This is an accepted measure of the efficacy of s-GERD treatments. The secondary variables evaluated were also the same as those described for Study 225.

b) Safety, Dictionaries and Coding Safety Terminology

These aspects of safety assessments were adequate.

8. Data Quality Assurance

The procedures, reviews and verification processes instituted by the sponsor to ensure that the data collected were accurate, consistent, complete and reliable were all adequate.

9. Statistical Methodology (as specified in the Protocol)

This was as in Study 225.

It is worth to reiterate that the sample size of 100 patients per treatment arm was calculated based on having 95% power to detect a difference in resolution rates of 60% for an H 199/18 treatment group and 30% for the PL treatment group (30% therapeutic gain). This assumed a two-sided test, using the arcsine transformation, and a Bonferroni correction (ie, an alpha level of 0.025) for

the two comparisons (each H 199/18 treatment group to PL). As in Study 225, the study population analyzed were ITT and PP.

10. Results

a) Disposition of Patients (Table 47)/Protocol Deviations

- The 28 participating investigator sites screened a total of 913 patients, of whom 349 (H40, n=118; H20, n=113; PL, n=118) were randomized. The primary reason for not randomizing screened patients was EE-positive status [n=426; other, n=138] for a total of 564 (Table 47).

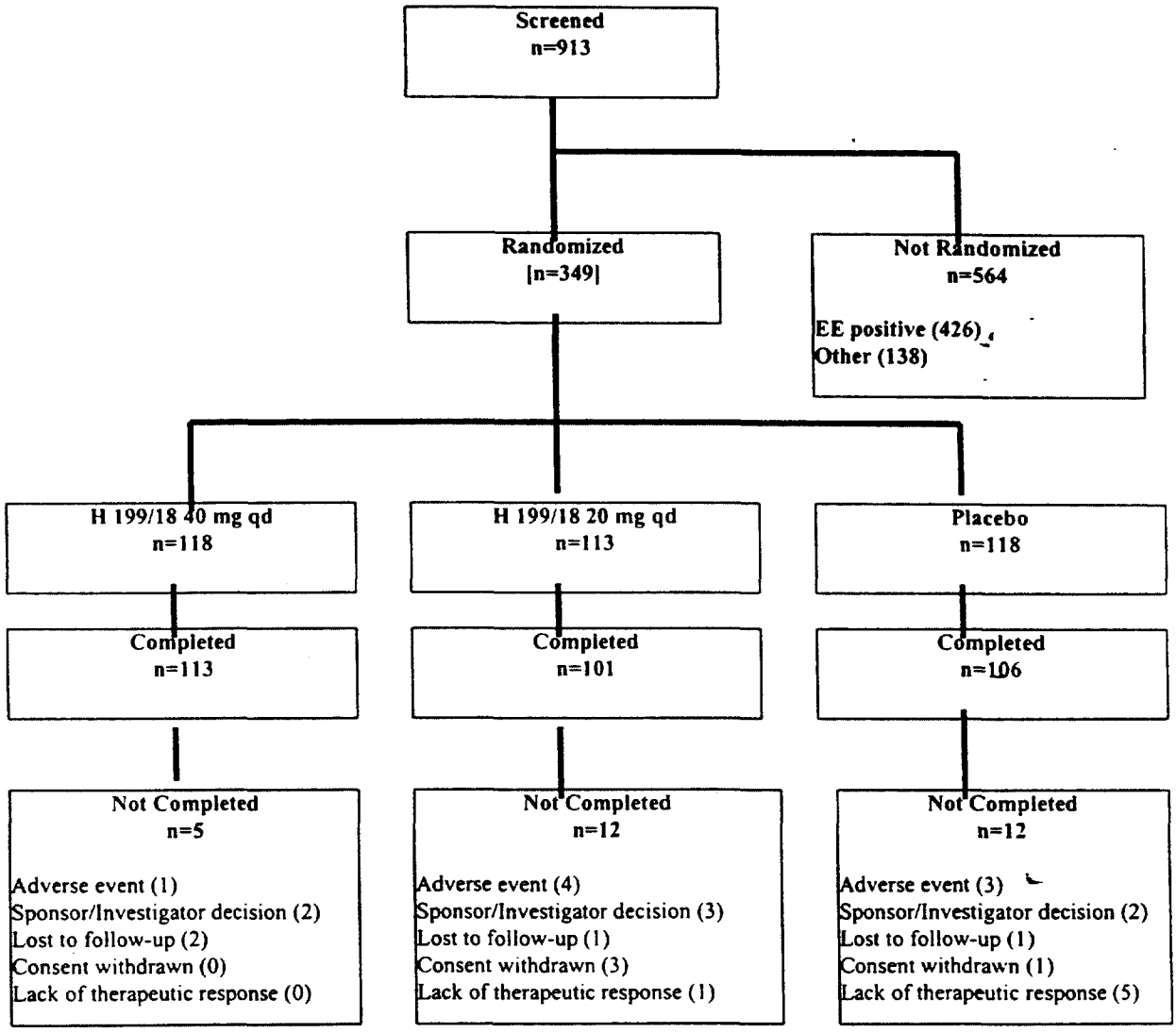
- Of the 349 patients enrolled in the trial, 320 (91.7%) completed the study and 29 (H40, n=5; H20, n=12; PL, n=12) or 8.3% discontinued from the trial before completion (Table 47).

- Among patients discontinued from the trial the most frequent reason for D/C was the occurrence of an AE [H40, n=1; H20, n=4; PL, n=3].

- The rates of protocol deviations among the 3 treatment arms were, roughly, similar.

TABLE 47
Study No. 226

Disposition of Screened and Randomized Patients



From sponsor's Table 14.1.2.3.

NOTE: The first patient entered the study on 3 February 1999 (date that first drug was dispensed), and the last patient completed the study on 3 June 1999. Of the 913 patients screened, 349 (38.2%) were randomized. These 349 patients comprise the ITT population.

b) Data Showing Comparability of Treatment Groups at Baseline (Table 48)

The treatment groups were well-balanced with respect to all the demographic disease, and other baseline characteristics enumerated in this Table. Approximately ⅔ of the patients were female, 90% were <65 y of age, mostly Caucasian, with a GERD history of at least 1 y, mostly with moderate (54% to 61%), less with severe (26% to 37%) HB.

TABLE 48
Study No. 226

Demographic and Other Baseline Characteristics
ITT Population

		H 199/18 (mg qd)		PL
		40 [n=118]	20 [n=113]	[n=118]
Gender	M	35.6%	30.1%	42.4%
	F	64.4%	69.9%	57.6%
	18-44 y	47.4%	44.3%	38.2%
	≥45 y	52.6%	55.7%	61.8%
Age, y	Mean (SD)	45.0 (13.1)	46.0 (14.0)	47.0 (13.2)
	Min – Max	19 - 77	19 - 75	21 - 77
Age category	<65 y	90.7%	86.7%	89.9%
	≥65 y	9.3%	13.3%	10.2%
Race	Caucasian	88.1%	79.6%	83.9%
	Black	11.0%	16.8%	14.4%
	Asian	0.0%	2.7%	0.8%
	Other	0.8%	0.9%	0.8%
Body weight, lb	Mean (SD)	178.3 (43.1)	176 (40.6)	179.3 (39.3)
	Min – Max	100 - 294	105 - 350	109 - 300
Height, in	Mean (SD)	66.6 (3.9)	65.7 (3.4)	66.4 (4.1)
GERD history	< 1 y	8.5%	13.3%	4.2%
	1 to 5 y	49.2%	38.9%	41.5%
	> 5 y	42.4%	47.8%	54.2%
Heartburn	None	0.8%	0.0%	0.0%
	Mild	18.6%	8.0%	9.3%
	Moderate	54.2%	54.9%	61.0%
	Severe	26.3%	37.2%	29.7%
Acid regurgitation	None	7.6%	13.3%	6.8%
	Mild	29.7%	23.9%	26.3%
	Moderate	45.8%	41.6%	40.7%
	Severe	16.9%	21.2%	26.3%
Dysphagia	None	66.1%	73.5%	70.3%
	Mild	22.0%	15.9%	17.8%
	Moderate	6.8%	8.0%	5.1%
	Severe	5.1%	2.7%	6.8%
Epigastric pain	None	28.0%	32.7%	31.4%
	Mild	31.4%	29.2%	19.5%
	Moderate	28.0%	27.4%	30.5%
	Severe	12.7%	10.6%	18.6%
***H. pylori* status**	Positive	25.4%	38.1%	32.2%
	Negative	73.7%	61.1%	67.8%
	Missing	0.8%	0.9%	0.0%

From sponsor's Table 14.1.1.1, with major modifications.

c) Compliance[39]

More than 92% of the patients in each group had test medication compliance rates greater than 80%. For the ITT population, the percentage of patients who were more than 90% compliant with the test medication regimen were similar among the treatment groups (94.1% for the H40 group, 87.6% for the H20 group, and 87.3% for the PL group). Compliance could not be established in ca. 1.7%, 2.7% and 2.5% of the H40, H20 and PL patients, respectively.

d) Proportion of Patients With Complete Resolution of HB at Final Visit (Table 49)

As shown in this Table, the proportion of patients with complete resolution reporting NO HB by the end of the trial was 36.4%, 41.6%, 11.9% for treatment with H40, H20 and PL, respectively. There was a significant difference between the H40 and PL groups ($p<0.001$), as well as between the H20 and PL groups ($p<0.001$). The therapeutic gain either approached (25% with the H40 mg dose level) or actually achieved (30% with the H20 mg dose level) the therapeutic gain of 30 % prospectively stipulated in the protocol. Results for the PP population were similar to those for the ITT population, with both H40 and H20 showing significantly higher proportions of patients with complete resolution of HB at the end of the study ($p<0.001$ for both comparisons to PL). In neither the ITT nor the PP population analysis further benefit was obtained when the dose of H 199/18 was increased from 20 to 40 mg once-a-day.

TABLE 49
Study 226

Proportion of Patients With Complete HB Resolution at Final Visit

I. ITT POPULATION ANALYSIS						
	H 199/18 mg qd		PL	Therapeutic Gain (%)/Statistical Significance [p-value][a]		
	40 [n=118]	20 [n=113]	[n=118]	40 vs PL	20 vs PL	40 vs 20
Responders	43 (36.4%)	47 (41.6%)	14 (11.9%)	24.5% [<0.001][b]	29.7% [<0.001]	-5.2% [N.S.][c]
II. PER-PROTOCOL POPULATION ANALYSIS						
	[n=106]	[n=103]	[n=109]			
Responders	41 (38.7%)	45 (43.7%)	14 (12.8%)	25.9% [<0.001]	30.9% [<0.001]	-5.0% [N.S.]

Reviewer's Table
a) Chi-square test; comparison of each H 199/18 treatment to PL and each H 199/18 group to each other.
b) Statistical significance vs PL ($p<0.05$) using Hochberg adjustment.
c) This comparison (H40 vs H20) did not use Hochberg adjustment.

[39] A summary of test medication compliance for the ITT population was given in sponsor's Table 14.1.2.6.

e) Proportion of Patients With Complete Resolution of HB at 1, 2, and 4 Weeks (Table 50)

As in Study 225, regardless of the assigned test medication, the proportion of patients that reported NO HB increased with time (Week 4 > Week 2 > Week 1). Both H groups were more efficacious than PL at all three time points. The therapeutic gain (H > PL) at Weeks 2 and 4 was similar to that seen for Complete HB Resolution at Final Visit (Table 49). The therapeutic gain (H > PL) at Week 1 was lower, but still clinically meaningful (H40=18.1%; H20=14.3%). At this time (Week 1) the H40 dose level was slightly more effective than H20 (therapeutic gain=3.8%) but this was not a clinically meaningful difference. Therefore, the Week 1 **"superiority"** of H40 over H20 seen in Study 225 (therapeutic gain=10.2%) was not replicated in Study 226. On the other hand, as it has been repeatedly shown in so many comparisons, neither at Week 2 nor at Week 4 was there further benefit when increasing the PPI dose from 20 to 40 mg once-a-day. Indeed, at all 3 times of evaluation (Weeks 1, 2 and 4), although well differentiated from PL, the 95% CI for the H40 overlapped and/or was very similar to that of H20:

Complete Resolution of HB As Recorded on the Diary Card
ITT Population
[95% CI]

Week	H40	H20	PL
1	19% [11.8%, 26.1%]	15.2% [8.5%, 21.8%]	0.9% [0.0%, 2.5%]
2	35% [26.6%, 44.0%]	35.7% [26.8%, 44.6%]	3.4% [0.1%, 6.8%]
4	40.0% [31.0%, 49.0%]	41.4% [32.3%, 50.6%]	11.2% [5.5%, 16.9%]
From sponsor's Table 8 in the Clinical Report, Study 226.			

TABLE 50
Study 226
Proportion of Patients with Complete Resolution of HB as Recorded on the Diary Card
ITT Population

	H 199/18 mg qd		PL	Therapeutic Gain (%)/Statistical Significance [p-value][a]		
	40 [n=116]	20 [n=112]	[n=116]	40 vs PL	20 vs PL	40 vs 20
I. WEEK 1						
Responders	22 (19.0%)	17 (15.2%)	1 (0.9%)	18.1% [<0.001]	14.3% [<0.001]	3.8% [N.S.][b]
II. WEEK 2						
	[n=116]	[n=112]	[n=116]			
Responders	41 (35.3%)	40 (35.7%)	4 (3.4%)	31.9% [<0.001]	**32.3%** [<0.001]	-0.4% [N.S.]
III. WEEK 4						
	[n=115]	[n=111]	[n=116]			
Responders	46 (40.0%)	46 (41.4%)	13 (11.2%)	28.8% [<0.001]	**30.2%** [<0.001]	-1.4% [N.S.]

Reviewer's Table.
a) Chi-square test; comparison of each H 199/18 treatment to PL and each H 199/18 group to each other.
b) This comparison (H40 vs H20) did not use Hochberg adjustment.

f) Other Secondary Efficacy Parameters

- For **relief of HB** at 1, 2, and 4 weeks and at the end of the study, there was a significant difference between the H40 and PL groups ($p<0.001$), as well as between the H20 and PL groups ($p<0.001$) at each of the 4 time points [sponsor's Table 14.2.4].

- For **mean severity of HB** at 1, 2, and 4 weeks, and at the end of the study, there was a significant difference between the H40 and PL groups ($p<0.001$), as well as between the H20 and PL group ($p<0.001$) at each of the 4 time points [sponsor's Table 14.2.5].

- For **percentage of days without HB 1, 2, and 4 weeks,** there was a significant difference between the H40 (mean=66.4% at 4 weeks) and PL (mean=36.2% at 4 weeks), [$p<0.001$], as well as between the H20 (mean=68.0% at 4 weeks) and PL (mean=36.2% at 4 weeks), [$p<0.001$], at each of the 3 timepoints. At no time point there was further benefit when increasing the PPI dose from 20 to 40 mg once-a-day [sponsor's Table 14.2.6].

- For **percentage of days without nocturnal HB at 1, 2, and 4 weeks,** there was a significant difference between the H40 (mean at Week 4=88.5%) and PL group (mean at Week 4=79.5%), [$p=0.005$], as well as between the H20 (mean at Week 4=89.9%) and PL group (mean at Week 4=79.5%), [$p=0.002$] at each of the 3 time points. Once again. at no time point, was there an increase in benefit when increasing the PPI dose from 20 to 40 mg once-a-day.

- Assessment of two additional secondary efficacy analyses, the time to first resolution of HB and nocturnal HB and the time to sustained resolution of HB and nocturnal HB yielded results as those summarized above for the secondary endpoints of evaluation.

- Results for **investigator-assessed resolution of HB**[40] at Week 2 and Week 4 (sponsor's Table 15) were similar to those for the diary card assessments and were significantly improved for H40 and H20 over PL ($p<0.001$ and <0.001, respectively), with no differences between the H40 vs the H20 mg qd of the PPI.

- Results for **investigator-assessed resolution of acid regurgitation** at Week 2 and Week 4 were significantly improved for H40 and H20 over PL ($p<0.001$ and <0.001, respectively), with no difference between the H40 vs the H20 mg qd of the PPI.

- Results for **investigator-assessed resolution of dysphagia** for H40 and H20 over PL were not significantly improved at Week 2 nor at Week 4 [both p-values=N.S.].

- Results for **investigator-assessed resolution of epigastric pain** for H40 and H20 over PL were not significantly improved at Week 2, but were significantly improved at Week 4 for

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[40] Investigator-assessed GERD symptoms by baseline severity at Week 2 and Week 4, respectively, were summarized in sponsor's Tables 14.2.12 and 14.2.13.

H40 and H20 over PL (p=0.023 and 0.024, respectively); once again with no difference between the H40 vs the H20 mg qd of the PPI.

- In their Table 16, the sponsor summarized the OTE results at Week 2 and Week 4 from the initial 3-point scale (ie, Worse, About the Same, and Better), as well as the analysis of the distribution of patients across the 15-point scale. The distribution of patients across the 15-point scale was significantly different in the H40 and H20 groups vs PL (p<0.001 and <0.001, respectively) at Week 2 and at Week 4 (p <0.001 and <0.001, respectively).

- In a fashion similar to that used in Study 225, no formal assessment of GELUSIL use by treatment group was planned or done; however, review of the data showed that patients in the PL group took more GELUSIL than patients in each of the H 199/18 groups (sponsor's Table 14.2.23). There did not appear to be any relationship of GELUSIL use to H 199/18 dose nor to time in the study.

g) Analysis of the Primary Efficacy Endpoint by Subgroups

The complete resolution of HB at the end of the study (final visit) was presented descriptively for the ITT population for the following subgroups: gender, age group (<65 y, ≥65 y), race, and *H. pylori* status (by histology).

- Relative treatment effects were similar for each gender, although male patients responded more favorably across treatment groups. This difference in response was not clinically meaningful.

- Patients ≥65 y of age responded more favorably to treatment with a larger number of patients achieving complete resolution of HB than those <65 y of age. However, the small number of patients 65 y of age or older in the study make these rates difficult to interpret.

- Because only 56 (16%) of the patients enrolled in this study were non-Caucasian (14% Black; 1% Asian; 1% Other), interpretation of rates of HB resolution across races is difficult.

- The rates of complete resolution of HB at the final visit by *H. pylori* status are summarized in Table 51.

  - In the PL group, there was a larger percentage of patients who experienced complete resolution of HB at the final visit for patients who were *H. pylori*-positive at baseline as compared to those who were *H. pylori*-negative at baseline (18.4% vs 8.8%, respectively). This results for PL is similar to that found in Study 225.
  - However, in the H 199/18 treatment groups, the rates for complete resolution of HB in *H. pylori*-positive patients were lower than those for *H. pylori*-negative patients. These results are opposite to those found in Study 225.

- From the above, the reviewer concludes that the assessment of the primary endpoint PPI-induced complete resolution of HB at the end of the study by *H. pylori* status gave inconsistent results (Study 225 vs 226). No valid conclusions can be drawn from these comparisons.

TABLE 51
Study No. 226

Number (%) of Patients With Complete Resolution of Heartburn at Final Visit, by *H. pylori* Status at Baseline

Resolution of HB at Final Visit	H 199/18 mg qd		PL
	40 [n=118][a]	20 [n=113][a]	[n=118]
***H. pylori*-negative at baseline (by histology)**			
	[87]	[69]	[80]
Resolved	34 (39.1%)	31 (44.9%)	7 (8.8%)
Not resolved	53 (60.9%)	38 (55.1%)	73 (91.3%)
***H. pylori*-positive at baseline (by histology)**			
	[30]	[43]	[38]
Resolved	9 (30.0%)	15 (34.9%)	7 (18.4%)
Not resolved	21 (70.0%)	28 (65.1%)	31 (81.6%)

From sponsor's Table 14.2.21, with minor modifications.
a) Missing *H. pylori* histology results included 1 patient from the H40 group with HB Not Resolved and 1 patient from the H20 group with HB Resolved.

h) Results of Safety Evaluations

i) Extent of Exposure

- 345 patients were included in the safety population, with the distribution that follows. Treatment lasted for up to 4 weeks.

mg qd		n
H 199/18	40	116
	20	112
Placebo		117
		345[a]

a) 4 of the 349 patients randomized did not have a documented dose of test medication and were therefore excluded from the safety population analyses. [sponsor's Appendiz 16.2.2.1).

ii) Deaths and Other SAEs

There were no deaths in this trial.

- There were 4 SAEs reported in this study: 3 (MI, pneumonia and intestinal obstruction) in the H40 group and 1 (abdominal pain) in the PL group. The narratives of these SAEs were provided in sponsor's Section 12.3.2 of the Clinical Report. All 4 were considered to be unlikely related to test medication.

iii) AEs Leading to Discontinuation

- As summarized in Table 52, six patients (H40, n=1; H20, n=5) D/C treatment because of an AE. A patient receiving H 199/18 at the daily dose of 20 mg experienced headaches that needed D/C to drug and were considered to be probably related to test medication. **This information should be included in the labeling.**

TABLE 52
Study 226

Listing of Patients Who D/C Treatment Because of an AE

Treatment	Site	Enrollment Number	Gender Age Race	Day of AE Onset	Preferred Term For Adverse Event (verbatim term)	
H40	416	003	F 19 Black	21 21	Abdominal Pain (Abdominal Cramps) Abdominal Pain (Abdominal Pain)	POSS POSS
H20	402	007	F 74 Caucasian	14 16 16 16	Fever (Fever) Clammy (Skin Cold Clammy) Urinary Tract Infections (Urinary Tract Infection) Asthenia (Weak)	UNL UNL; UNL UNL
	413	007	F 49 Caucasian	11	Aspiration Pneumonia (Aspiration Pneumonia)	UNL
	416	014	F 26 Black	29	Events of Non-medical Character[a] (Use During Pregnancy)	UNL
	416	015	M 43 Black	3	Headache (Headache)	PRO
	418	016	F 28 Caucasian	4	Gastroentertis (Stomach Flu)	UNL

From sponsor's Table 14.3.1.12, with some modifications.
a) "Action taken with respect to study drug" coded as "Drug Stopped"; reason for discontinuation on Study Completion page was "Sponsor/Investigator decision".

iv) Adverse Events

- There were no apparent differences between the H 199/18 treatment groups and the PL group in the proportion of patients reporting at least one AE (between 40.2% and 43.1%). The most frequently reported AEs were headache and G.I. events (Table 53). Except for nausea, the G.I. events occurred at a higher rate among patients being treated with the PPI than in those receiving PL.

TABLE 53
Study 226

Rates of AEs by Treatment Group
(Patient Incidence >3% in any Treatment Group)

	H40 [n=116]	H20 [n=112]	PL [n=117]
Central/Peripheral Nervous System			
Headache	5.2%	8.0%	6.0%
Gastrointestinal System Disorder			
Abdominal Pain	6.0%	8.0%	2.6%
Diarrhea	8.6%	8.0%	4.3%
Flatulence	3.4%	5.4%	0.0%
Gastrin Serum Increased	3.4%	3.6%	0.9%
Nausea	2.6%	5.4%	4.3%
From sponsor's Table 14.3.1.2, with major modifications.			

v) Changes in Laboratory Parameters/Serum Gastrin

- Baseline values for all laboratory parameters were generally similar. Mean changes from baseline were generally small and similar across the three treatment groups. There were no clinically meaningful mean changes from baseline in any laboratory test parameter. The largest mean changes were the expected dose-related mean changes in serum gastrin.

Study 226
Serum gastrin concentration (mean pg/ml).

	H40 [n=115]	H20 [n=111]	PL [n=111]
Baseline	51.5	49.7	44.5
Post-Baseline	151.7	127.1	60.3
Increase	100.2	77.4	15.8

vi) Other

Mean changes from baseline in pulse, blood pressure and weight at each time point were minimal, and similar across the three treatment groups. There were no meaningful shifts from baseline to post-baseline in weight, nor in any of the vital signs measures in any of the treatment groups.

11. Sponsor's Discussion and Overall Conclusions

"H 199/18 at doses of 40 mg qd and 20 mg qd, was statistically significant.and clinically relevant to placebo in the complete resolution of diary-recorded heartburn after 4 weeks of treatment in patients with s-GERD.

"Each H 199/18 dose was statistically significant and clinically relevant to placebo for the majority of secondary endpoints.

"Each H 199/18 dose was well-tolerated, with no deaths, no drug-related serious AEs, no unexpected clinically meaningful changes in laboratory tests or vital signs.

"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 226 was the other controlled clinical trial submitted by the sponsor in support of efficacy and safety of orally administered NEXIUM (esomeprazole) in the treatment of s-GERD.

Study 226 randomized 349 patients at 28 sites. In addition to being multicenter and randomized, this 3-arm trial (an exact replica of Study 225) was double-blind, placebo-controlled, parallel-group, of 1-month duration and was set to evaluate the efficacy and safety of 2 dose levels of H 199/18 (H40 and H20 mg qd) vs PL in the complete resolution of HB in patients with s-GERD.

In a fashion similar to that seen in Study 225, each of the two dose levels of H 199/18 was statistically significant superior to PL in the complete resolution of diary-recorded HB after 4 weeks of treatment in these patients with s-GERD. This observed therapeutic gain was not only statistically significant, but also clinically relevant. For the H20 mg qd group, it was as the protocol expected **therapeutic gain of 30%**. The results of secondary parameters of evaluation supported the efficacy of this PPI for this indication. There was a significant difference between the H40 and the PL group as well as the H20 and the PL group at 1, 2, and 4 week time points. There was a statistically significant difference between each of the H groups and PL in: relief of HB at 1, 2, and 4 weeks and at the end of study, mean severity of HB at 1, 2, and 4 weeks and end of study, percentage of days without HB at 1, 2, and 4 weeks, percentage of days without nocturnal HB at 1, 2, and 4 weeks, time to first resolution of HB and nocturnal HB and time to sustained resolution of HB and nocturnal HB.

Similarly, results for investigator-assessed resolution of HB and investigator-assessed resolution of "acid" regurgitation at Week 2 and Week 4 were significantly improved for both the H40 and H20 groups over PL. Results for investigator-assessed resolution of dysphagia for H40 and H20 over PL were not significantly improved at Week 2 nor at Week 4. Although results for investigator-assessed resolution of epigastric pain for H40 and H20 over PL were not significantly improved at Week 2, results for this parameter were significantly improved for H40 and H20 over PL. In Study 226, just as in Study 225, there was no convincing evidence, due primarily to the small number of observations in some cells, that efficacy was different in the following subgroups: gender, age group (<65 y, ≥65 y) and race. Regarding the presence of *H. pylori* at baseline, Study 226 replicated only the findings in the PL group in Study 225: the presence of *H. pylori* appeared to improve the chances of complete resolution of HB at final visit. Results with either H40 or H20 were not replicated. It is therefore concluded that the presence of *H. pylori* at baseline has no consistent predictable effect on the complete resolution of HB at the end of 4 weeks treatment with H 199/18.

The reviewer agrees with the sponsor's conclusion that, in this 4-week study, there were no clinically meaningful differences between the H 199/18 treatment groups and the PL groups in the occurrence of AEs, changes in laboratory values or changes in vital signs. As expected. there were changes (baseline to Week 4) in mean serum gastrin concentration that were higher among patients receiving the PPI than in those receiving PL (mean increase of 100.2, 77.4 and 15.8 pg/ml for the H40, H20 and PL groups, respectively).

In conclusion, the sponsor has submitted results of two studies (225 and 226) demonstrating that NEXIUM (esomeprazole) is effective and safe in the treatment of s-GERD. For both primary and secondary parameters of efficacy H20 is as effective as H40. No increased benefit is achieved by increasing the dose of this PPI from 20 to 40 mg once-a-day.

VIII. INTEGRATED SUMMARY OF EFFICACY

A. Generalities/Questions to be Addressed

Esomeprazole (H199/18 NEXIUM™), the **s-enantiomer** of omeprazole, is a substituted benzimidazole that suppresses gastric acid secretion by specific inhibition of the action of the enzyme H^+/K^+-ATPase. Like omeprazole and **all PPIs**, esomeprazole is a prodrug that needs to be activated to exert its antisecretory effects. Omeprazole, approved for a number of indications related to inhibition of gastric acid secretion, is administered at its S and R racemates. The sponsor's approach to assess the efficacy and safety of one of the two isomers in the omeprazole moiety may be clinically important. This is because the use of only one enantiomer of omeprazole may allow separation of efficacy and toxicity. This approach may theoretically lead to a significant increase in therapeutic ratio and a more rational approach in therapeutics. In this instance, the demonstration of a better therapeutic ratio must be eminently clinic because a review of the pharmacologic data demonstrate that optical isomer S does not have a greater affinity than isomer R at the receptor site, is not metabolized at significantly different rates and does not seem to have significantly different affinity for tissue and protein binding sites. It is

worth mentioning that some differences in pharmacodynamic effects may exist between the parent moiety omeprazole and its S-isomer, especially on the first day of administration. But - even if real - it needs to be proven that these differences in PD matter in the healing of EE (evaluated at 8 weeks), the maintenance of healing of EE (assessed at 6 months), and the response to heartburn-associated symptoms in symptomatic GERD (evaluated at 4 weeks). Consequently, any meaningful differences between esomeprazole and omeprazole must be proven in the **clinical arena**. Moreover, any superiority of one compound over the other must be demonstrated at equimolar antisecretory concentrations namely in a weight by weight comparison. This point may be relevant because the S and R isomers possess roughly, the same antisecretory activity. In order to declare the S-form **superior** to omeprazole, these drugs must be tested. at the same amount per day (i.e. 40 H vs 40 O; 20 H vs 20 O). Note that in the comparison H40 vs O20, because of difference in tissue uptake and in particular residence time, the amount of s-isomer in H40 is ca. three times higher than in O20.

In the discussion that follows, the demonstration that 40 H is statistically different from 20 O might demonstrate that the 40 H **is effective** but **not necessarily superior** to omeprazole.

As pointed out in section II of this review, the sponsor's recommended dosage schedules of NEXIUM for the three indications sought are: healing of EE: 40 mg (once daily for 4 to 8 weeks); maintenance of healing of EE: ——— once daily; "clinical trials extended to —— months"); and treatment of s-GERD: 20 mg [once daily for 4 weeks, "if symptoms do not resolve completely after 4 weeks, an additional 4 weeks of treatment should be considered"].

The results of primary efficacy parameter evaluations from the three groups of trials that assessed the efficacy of esomeprazole in the three proposed indications are summarized in Table 54. From each group of trials, those submitted as critical to the specific indication were reviewed in detail. At the end of the review of each trial, the reviewer provided "Additional Comments" with a critique to the adequacy of the design and execution of the trial. In short, all trials depicted in Table 54 were adequately designed (to show what the sponsor set to demonstrate) and apparently well-executed. All in all, the trials had adequate negative (placebo) or positive controls (omeprazole, 20 mg once-a-day), appropriate study populations, consistent inclusion/criteria, sufficient sample sizes for appropriate statistical power and adequate and consistent timing for endoscopic or clinical evaluations. The groups being compared were very similar in demographic and disease baseline characteristics and patients were compliant. It is concluded that the efficacy comparison between the arms of the various trials is valid.

Using the rules of the game specified above and the data displayed in Table 54, the reviewer now attempts to answer the following questions regarding NEXIUM'S efficacy **per each indication**:

1. What studies demonstrate efficacy?
2. Is the reviewer's recommended dose and regimen the same as that recommended by the sponsor?
3. What studies demonstrate that esomeprazole is more efficacious **(clinically superior)** than omeprazole?

TABLE 54

Overall Summary of Efficacy in NDA 21-153

Protocol (Study) No.	Time of Eval.	Treatments Being Compared					Therapeutic Gain/[p-value]						
		PL	Esomeprazole (mg qd)			OME	40 vs PL	20 vs PL	10 vs PL	40H vs 20H	20H vs 10H	40H vs 20 OME	20H vs 20 OME
			40	20	10	20							
I. HEALING OF EROSIVE ESOPHAGITIS													
172	W 4	N/A	71.1%	66.5%	N/A	61.4%	N/A	N/A	N/A	4.6% [N.S.]	N/A	9.7% [<0.001]	5.1% [N.S.]
	W 8	N/A	87.6%	83.8%	N/A	81.4%	N/A	N/A	N/A	3.8% [N.S.]	N/A	6.2% [<0.001]	2.4% [N.S.]
173	W 4	N/A	68.2	N/A	N/A	66.3%	N/A	N/A	N/A	N/A	N/A	1.9% [N.S.]	N/A
	W 8	N/A	87.0%	N/A	N/A	85.8%	N/A	N/A	N/A	N/A	N/A	1.2% [N.S.]	N/A
174	W 4	N/A	N/A	68.7%	N/A	69.5%	N/A	N/A	N/A	N/A	N/A	N/A	-0.8% [N.S.]
	W 8	N/A	N/A	90.6%	N/A	88.3%	N/A	N/A	N/A	N/A	N/A	N/A	2.3% [N.S.]
222	W 4	N/A	78.6%	N/A	N/A	66.6%	N/A	N/A	N/A	N/A	N/A	12% [0.001]	N/A
	W 8	N/A	89.9%	N/A	N/A	80.9%	N/A	N/A	N/A	N/A	N/A	9% [0.001]	N/A
II. MAINTENANCE OF HEALING OF EE													
177	6 mo.	29.1%	87.9%	78.7%	54.2%	N/A	58.8% [<0.001]	49.6% [<0.001]	25.1% [<0.001]	9.2% [N.S.]	24.5% [0.026]	N/A	N/A
178	6 mo.	29.0%	93.6%	93.2%	57.1%	N/A	64.6% [<0.001]	64.2% [<0.001]	28.1% [<0.001]	0.4% [N.S.]	36.1% [0.001]	N/A	N/A
III. SYMPTOMATIC GASTROESOPHAGEAL REFLUX DISEASE (s-GERD)													
225	W 4	13.7%	33.3%	33.9%	N/A	N/A	19.6% [<0.001]	20.2% [<0.001]	N/A	-0.6% [N.S.]	N/A	N/A	N/A
226	W 4	11.9%	36.4%	41.6%	N/A	N/A	24.5% [<0.001]	29.7% [<0.001]	N/A	-5.2% [N.S.]	N/A	M/A	N/A
-0009	W 4	N/A	56.7%	60.5%	N/A	58.1%	N/A	N/A	N/A	-3.8% [N.S.]	N/A	-1.4% [N.S.]	2.5% [N.S.]
-0011	W 4	N/A	70.3%	N/A	N/A	67.9%	N/A	N/A	N/A	N/A	N/A	2.4% [N.S.]	N/A
-021	W 4	N/A	N/A	61.9%	N/A	59.6%	N/A	N/A	N/A	N/A	N/A	N/A	2.3% [N.S.]

Reviewer's Table

B. HEALING OF EROSIVE ESOPHAGITIS

1. For this indication, the question of greater efficacy is not entirely settled. Although study 172 shows statistical difference between H40 and O20 in the proportion of patients healed at 4 and 8 weeks, the therapeutic gain at 8 weeks (6.2%) is of borderline clinical significance. These results (statistical superiority of H40 over O20) are confirmed by those of Study 222. However, in Study 173, H40 could not be differentiated from O20. The conclusion is that, since O20 is known to be active and H40 is not very different from O20, H40 **is also active**. Activity is also shown for H20 because in two trials (172 and 174) the efficacy of this dose of esomeprazole is similar to O20. In conclusion for this indication: a) both H40 and H20 **are active; b) H20 is as active as H40**.

2. The reviewer dose not agree with the sponsor's dose recommendation of H40. If a dose of H is to be recommended it would be 20. This is because the only study assessing side by side effects, **172**, shows that at Week 8, H20 is as efficacious as H40 (Table 54).

3. There are no studies which demonstrate that H is superior to O, clinically or even statistically. As shown in Table 54, in Study 172, the effects of H20 are not differentiated from those of O20. This conclusion is supported by results in Study 174.

C. MAINTENANCE OF HEALING OF EROSIVE ESOPHAGITIS

1. For this indication both studies submitted by the sponsor in support of this indication, 177 and 178, provide excellent evidence that esomeprazole is very effective in maintaining reflux esophagitis healed for up to 6 months. Each of the three dose levels of the drug tested (H40, H20, and H10) is shown to be superior to placebo in one trial and these results are replicated in the other.

   In assessing risk to benefit matters related to this indication it is very important to consider **what** is being maintained healed. The answer is in Table 6 (Study 172). The bulk of these patients had LA classification A or B, equivalent to mild to moderate esophagitis. Roughly, 1/5 of the patients had LA classification C (18%) and few (7%) had LA classification D. In this reviewer's opinion, this information argues in favor of maintaining these lesions healed with a lower but definitely efficacious dose of the drug (20 mg once-a-day) rather than 40 mg qd.

[redacted]

2. The reviewer does not agree with the sponsor's dose recommendation of H40. Although study 177 shows some difference between H40 and H20, this difference (9.2%) is: a) not statistically significant and b) of borderline clinical relevance. Furthermore, study 178 shows neither statistical nor clinical difference between these two dose levels of

drug. In addition to being very well differentiated from placebo, both dose levels of H are superior to the lowest dose tested (H10). In summary, it is the reviewer's conclusion that H20 is as efficacious as H40 in maintaining erosive esophagitis healed.

3. The sponsor has presented no results of studies assessing the efficacy of H in comparison to O in the maintenance of healing of EE.

D. TREATMENT OF s-GERD

1. For this indication, the question of efficacy is settled by results of the two pivotal trials, submitted by the sponsor in support of this indication, 225 and 226. These provide unquestionable evidence that esomeprazole is more effective than placebo in the treatment of s-GERD. Each of the two dose levels of drug tested (H40 and H20) is shown to be superior to placebo in one trial and these results are replicated in the other.

Although the therapeutic gains (H > PL) are clinically meaningful (20% in one trial, 30% in the other), the proportion of patients experiencing complete relief of heartburn after 4 weeks of treatment with the drug is low: 34% in trial 225 and 42% in study 226. These proportion of patients experiencing complete relief of HB is considerably lower than the proportion of patients with investigator-recorded complete resolution of heartburn at Week 4 in healing of erosive esophagitis trials: Study 172 (H40=65%; H20=61%): Studies 173 and 222 (H40=68%). The same pattern of response (less symptomatic efficacy for s-GERD than for EE) has been observed with omeprazole and is included in the labeling for this PPI.

2. The reviewer agrees with the sponsor's recommended dose and regimen for this indication since both critical trials demonstrate that there is no added benefit by increasing the dose from 20 to 40 mg once-a-day (Table 54).

3. Results from three clinical trials, -0009, -0011 and -021 (Table 54) clearly show that whether one compares H40 or H20, the effects of esomeprazole in the treatment of s-GERD are **nearly identical** to those seen with O20. **There is clearly no indication that esomeprazole is superior to omeprazole for the treatment of s-GERD.**

E. OVERALL CONCLUSIONS ON EFFICACY

In summary, the overall assessment in NDA 21-153, demonstrate that adequate and well-controlled studies support the efficacy of orally administered esomeprazole in three indications: healing of erosive esophagitis (20 mg once daily for 4 to 8 weeks), maintenance of healing of

erosive esophagitis (20 mg once daily for at least 6 months)[41] and treatment of symptomatic GERD (20 mg once-a-day for 4 weeks).

IX. INTEGRATED SUMMARY OF SAFETY (ISS)

A. Generalities

The ISS includes information from 44 completed clinical trials that provide data to support the claims made for H 199/18 in NDA 21-153. These 44 completed studies consisted of

33 Phase I studies: 4 *in vitro* investigations
28 in subjects with acid-related disorders
1 in patients with s-GERD

44 Phase II/III studies: 3 controlled E+S studies in healing of EE
2 in maintenance of healing of EE
5 controlled E+S studies in s-GERD
1 uncontrolled, L-T, safety study

There are also [redacted] studies.

1. The total number of H 199/18 subjects/patients enrolled, per study Phase is summarized in Table 55.

APPEARS THIS WAY
ON ORIGINAL

[41] The sponsor proposes to add the sentence [redacted] apparently based on results of mintenance trial 179. This open-label, 12 month trial was not reviewed as a critical source of evidence but it will be briefly commented upon in the integrated Summary of Safety and the duration of maintenance treatment will be reconsidered at that time.