TABLE 4
Study No. 172

Study Flowchart Checklist of Clinical and Laboratory Measurements

Procedure	Baseline	Week 4[a]	Week 8 (or Final Visit)
	Day -1	Day 28 (± 4 Days)	Day 56 (± 4 Days)
Informed Consent	x		
Medical History	x		
Physical Examination[b]	x		x
Vital Signs	x	x	x
Laboratory Samples	x[c]		x[c]
H. pylori Serology Screening	x[d]		
EGD	x[c]	x[c]	x[c]
Gastric Biopsy	x[e]		
Pregnancy Test	x[f]		
Dispense Diary Cards	x		
Review Diary Card		x	
GERD Symptom Assessment	x	x	x
Adverse Event Assessment		x	x
Review Concomitant Medications	x	x	x
Dispense Study Drug	x	x[g]	
Drug Accountability		x	x[g]
End of Study Status			x[g]

a) Patients completely healed at the Week 4 visit were also to complete final visit specific procedures
b) Complete physical performed at baseline and final visit
c) Patients required to fast for this visit
d) *H. pylori* serology screening to be done prior to EGD
e) Biopsy at baseline only if EE was present

Gastric biopsy samples were obtained from the antrum and corpus. The antrum biopsy samples were evaluated for verification of *H. pylori* status. The methodology was given in sponsor's Appendix 16.1.1. If patients were to enroll in a L-T maintenance trial as an extension of this study, the antrum and corpus biopsy samples were evaluated for gastritis, atrophy, and intestinal metaplasia. Enterochromaffin-like (ECL) cell hyperplasia was evaluated in corpus samples only. These results are summarized in the L-T study report.[No. 179].

Patients found to be *H. pylori* positive based on the biopsy results were continued in this trial.

f) Females only. Urine dipstick and serum pregnancy tests required
g) Not applicable if patient confirmed healed at Week 4

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

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

Identification of Test Medications

Treatment	Appearance	Batch Number
H 199/18 40 mg	Blue Size 2 Capsule	H-1222-04-01-03 H-1222-04-01-05
H 199/18 20 mg	Blue Size 2 Capsule	H-1189-04-01-02 H-1189-04-01-04
omeprazole 20 mg	Blue Size 2 Capsule	H-0431-13-05-06
Individual patients receiving the various batches were listed in sponsor's appendix 16.1.6.		

- **Randomization** was performed at each center using blinded blocks of six allocation numbers. The proportion of treatments was 1:1:1 (H 199/18 20 mg; H 199/18 40 mg; OME 20 mg). Eligible patients at each center were given the next sequential enrollment number (001, 002, 003, etc.) and were given the next sequential allocation number, based on preprinted numbers on test medication labels. A complete randomization list was provided in sponsor's Appendix 16.1.7.

- To preserve **blinding**, the three test medications had the same appearance. All test medications were packaged in bottles at Astra Hässle AB, Mölndal, 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 and compliance were all adequate. For more details, refer to Table 3. 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 proscribed for the duration of treatment. Patients were excluded from the study if they had taken H_2-receptor antagonists during the 2 weeks prior to baseline esophago-gastro-duodenoscopy (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 6 tablets per day. Other medications which might affect the interpretation of the treatment outcome or are considered drug interactions in the PRILOSEC® (omeprazole) delayed release capsules package insert were proscribed during the study (Protocol; sponsor's Appendix 16.1.1). Other medication considered necessary for the patient's welfare because of intercurrent acute or chronic disease, could be given at the discretion of the investigator.

The administration of any prior or concomitant drugs had to be recorded in the CRF.

- Patients were instructed to return all unused study drugs at the end of each period. Returned capsules were counted and documented to assess compliance. The investigator

was responsible for ensuring that test medications were issued only to participants in the study and for maintaining accurate records of the dispensing of test medications. All drugs issued by Astra Pharmaceuticals had to be accounted for at the end of the study. Unused capsules were sent to [redacted] for destruction.

7. Evaluation Criteria

a) Efficacy

- The **primary endpoint** for demonstrating efficacy was the resolution of all macroscopic esophageal erosions or ulcerations to the grade "NOT PRESENT" by the L.A. classification of esophagitis. This primary parameter is an accepted measure of EE treatment efficacy.

b) Safety, Dictionaries and Coding Terminology

All aspects of safety assessment, including the terminology and Dictionaries used within the Astra companies, were adequate. This included evaluations of reports of AEs, and other safety variables such as routine physical examination (P.E.), endoscopy, gastric biopsies and laboratory determinations.

8. Data Quality Assurance

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

9. Statistical Methodology (as prespecified in the Protocol)

a) Determination of Sample Size

The sample size of 500 patients per treatment arm was calculated based on having 95% power to detect a difference in complete healing rates of 75% for OME 20 mg q.d. and 85% for a given dose of H 199/18. This **10% therapeutic gain** assumed a two-sided test, using the arcsine transformation, and a Bonferroni correction (i.e., an alpha level of 0.025) for the two comparisons (each H 199/18 dose vs OME).

b) Details of Statistical and Analytical Procedures

- The primary question to be addressed by this study was whether H 199/18, at doses of 20 mg q.d. and 40 mg q.d. for up to eight weeks, is more efficacious than OME 20 mg q.d. in healing erosive esophagitis. Secondary questions include whether the same two doses of H 199/18 are more efficacious that OME in healing of esophagitis at Week 4 and in resolution and relief of symptoms.

- The percentage of patients who exhibit complete healing at the Week 8 visit, defined as a reduction in the classification of erosive esophagitis to grade "Not Present" was to be the primary efficacy variable. According to the sponsor, since patients who were healed at the Week 4 visit were not expected to be treated or followed

to Week 8, the data from these patients were carried forward and included at Week 8 also. As such, the primary efficacy variable, "Week 8 Healing Rate" was a cumulative healing rate. This rate was to be calculated based on using a life-table approach (primary) and also as a crude rate (supportive). The primary analysis was based upon an ITT principle, although a per-protocol analysis (PPA) was also performed.

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

- The life-table approach was to be implemented by pre-defining windows corresponding to nominal 'months'. These months were to be used as the discrete timepoints in the life-table analysis. Statistical comparisons between treatment groups were to be performed using a log-rank test for the primary analysis.

- Corrections for the multiple comparisons (each H 199/18 dose vs OME) was to be performed using Hochberg's method. In essence, if both nominal p-values (for each H 199/18 dose vs OME) are less than or equal to 0.05, they were to be deemed statistically significant. If one p-value was greater than 0.05, then the other needed to be less than or equal to 0.025 to be deemed statistically significant.

- For secondary analyses, Mantel-Haenszel statistics were to be used to assess differences in dichotomous response variables between treatments. According to the sponsor, since it was anticipated that there will be relatively few patients per investigator, geographic location was to be used to stratify patients for these analyses. Life-table analyses were to be used to analyze the time-to-event variables from the patient diaries. No corrections for multiple comparisons were to be made for any of the secondary analyses.

- Additional descriptive and graphical displays were to be generated to support and supplement the analyses being performed

Changes in the Conduct of the Study or Planned Analyses

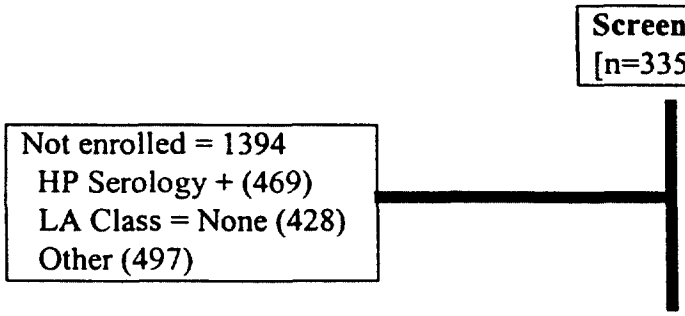
The protocol was amended one time, prior to commencement of the study. No changes were made in the conduct of the study. In the data analysis plan, completed prior to breaking study blind, the intent-to-treat population (ITT) was defined as all patients randomized to treatment who received at least one documented dose of test medication and who were not withdrawn from the study due to baseline characteristics before assessment of efficacy. At the request of the Division, on 24 September 1998, the definition of the ITT population was changed to include all patients who were randomized to treatment, with no exclusions. The analyses in the sponsor's Clinical Report used this revised definition of the ITT population. In addition, the FDA statistician requested that a Wilcoxon rank sum test be conducted on the primary efficacy parameter.

10. Results

a) Disposition of Patients/Per Protocol Deviations (Table 5)

The 150 participating investigators (10 centers did not enroll patients) logged 3,354 patients as screened for inclusion in the study. Of these, 1,960 were enrolled and randomized to treatment. The first patient was treated on 29 September 1997, and the last completed the study on 18 May 1998. As shown in Table 5, the primary reasons for not randomizing screened patients included *H. pylori* serology positive [n=469] and LA Classification=NONE [n=428]. The safety, intent-to-treat (ITT), and per-protocol (PP) populations included 1,957, 1,960, and 1,620 patients, respectively. The upper panel of Table 5 summarizes the disposition of patients in this study by visit as determined by timing and result of EGD evaluations. In the mid-panel, a summary of patients manually evaluated for PP deviations is given. The most frequent deviations were for compliance violation (11.5%), inclusion/exclusion criteria violations (10.4%) and *H. pylori* positive at baseline (9.6%). There were no meaningful differences between treatment groups in the proportion of patients with patient disposition and evaluability is given in the lower panel of Table 5.

TABLE 5
Study No. 172
Distribution of Randomized Patients
Disposition of Patients Entered into Trial



Randomized

	H 199/18 mg q.d. 40	H 199/18 mg q.d. 20	OME mg q.d. 20	Total
Randomized	654	656	650	1960
Week 4				
Completed	465	436	399	1300
Ongoing	146	182[a]	218[a]	526
Discontinued	43	38	33	114
Week 8				
Completed	143	175	208	526
Discontinued	3	8	11	22
Summary of Patients Manually Evaluated for PP Deviations				
Reason[b]				
Inclusion/exclusion criteria	10.4%	10.8%	9.8%	10.4%
Hp positive at baseline	9.9%	8.5%	10.5%	9.6%
Compliance violators	11.2%	11.7%	11.7%	11.5%
Prohibited concomitant medications	1.7%	1.5%	1.5%	1.6%
Other deviations	6.9%	6.1%	5.2%	6.1%
Total patients evaluated for exclusion from PP population	184 (28.1%)	184 (28.0%)	186 (28.6%)	554 (28.3%)
Summary of Patient Disposition and Evaluability				
ITT Population	654	656	650	1960
Patients with Week 4 endoscopy	618	621	622	1861
Patients with Week 8 endoscopy	139	171	204	514
PP Population	536	550	534	1620
Patients with Week 4 endoscopy	535	550	534	1619
Patients with Week 8 endoscopy	128	160	181	469

From sponsor's Tables 14.1.2.2, 14.1.2.3, 14.1.2.4 and 14.1.2.6 with substantial modifications

a) One patient (019/002) treated with H 199/18 20 mg qd and another (006/026) treated with OME 20 mg qd who were completed at Week 4 continued treatment to Week 8. These two patients are counted in this Table as completed at both visits.

b) Patients with multiple reasons to be manually evaluated were counted multiple times.

b) Data Showing Comparability of Treatment Groups at Baseline (Table 6)

The treatment groups were well balanced with respect to all the demographic, disease and other baseline characteristics listed in this Table. Approximately 90% of the patients were <65y of age, mostly Caucasian, with a GERD history of at least 1y, mostly with moderate (45%) to severe (41%) heartburn. Only 7% of the patients had grade D esophagitis, 18% to 21% had grade C, the rest had grade A (31% to 36%) and B (40%) esophagitis.

TABLE 6
Study No. 172
Demographic and Other Baseline Characteristics ITT Population

		H 199/18 mg qd		OME mg qd
		40 [n=654]	20 [n=656]	20 [n=650]
Gender	M	58.7%	59.6%	61.4%
	F	41.3%	40.4%	38.6%
	18-44 y	48.9%	46.0%	42.6%
	≥45 y	51.1%	54.0%	57.4%
Age (years)	Mean	44.8	45.3	46.5
	Minimum/Maximum	18/81	18/77	19/84
	<65 y	91.3%	89.5%	88.3%
	≥65 y	8.7%	10.5%	11.7%
Race	Caucasian	90.4%	90.7%	93.5%
	Black	7.5%	6.6%	5.4%
	Asian	0.5%	0.8%	0.5%
	Other	1.7%	2.0%	0.6%
LA Classification	Grade A	35.9%	33.1%	31.2%
	Grade B	38.7%	41.8%	40.8%
	Grade C	18.2%	18.1%	21.1%
	Grade D	7.2%	7.0%	6.9%
GERD History	Unknown	0.2%	0.0%	0.0%
	<1 y	4.9%	4.6%	6.0%
	1 to 5 y	48.3%	48.3%	46.2%
	>5 y	46.6%	47.1%	47.8%
Heartburn	None	2.1%	3.0%	2.6%
	Mild	10.9%	9.1%	10.6%
	Moderate	43.1%	47.1%	45.5%
	Severe	43.7%	40.7%	41.2%
Acid Regurgitation	None	12.2%	12.8%	12.9%
	Mild	22.6%	22.0%	18.9%
	Moderate	39.6%	38.3%	44.6%
	Severe	25.4%	27.0%	23.5%
Dysphagia	None	62.4%	63.1%	64.3%
	Mild	21.4%	21.3%	18.5%
	Moderate	11.9%	11.3%	13.8%
	Severe	4.1%	4.3%	3.4%
Epigastric Pain	None	32.9%	31.3%	32.2%
	Mild	25.4%	26.8%	29.4%
	Moderate	27.5%	27.1%	27.8%
	Severe	14.1%	14.8%	10.6%
H. pylori Status	Negative biopsy	89.3%	91.2%	89.4%
	positive biopsy	9.9%	8.5%	10.5%
	Missing valve	0.8%	0.3%	0.2%

From sponsor's Tables 14.1.1.1 and 14.1.1.5 with major modifications

c) Compliance[19]

For the ITT population, treatment compliance rates (≥90%) were similar for the three treatments (86.7, 86.6 and 86.5% of patients treated with H 199/18 40 mg qd, H 199/18 20 mg qd, and OME 20 mg qd, respectively). A treatment compliance rate of <80% was also similar (4.3, 4.3, and 4.5%, respectively). Compliance rates (≥90%) for the PP population were higher than for the ITT population (94.2, 93.1 and 93.6%), in part because poor treatment compliance (<80%) was a factor considered for exclusion from this population.

d) Proportion of Patients Healing After 4 and 8 Weeks (Table 7)

In this Table, results for the ITT population are displayed in the upper panel, whereas those for the PP population are shown in the lower panel. Because the results of both study population analyses were similar, only results for the ITT population are commented upon. In Table 7, in addition to the EE healing rates per treatment group, therapeutic gains resulting from comparisons between pertinent treatment groups were mostly modest (at the most 10%) and are shown on the right side of this Table.

- The expected therapeutic gain (10%) with ESOME Mg (over OME 20 mg qd) was achieved but only with 40 mg of test medication (not 20 mg) and only at Week 4 (not at Week 8).

- The difference in the proportion of patients with healing was statistically significant for the H199/18 40 mg vs OME 20 mg comparison at Weeks 4 (Cochran-Mantel-Haenszel=CMH) and 8 (log-rank test and Wilcoxon test).

- The difference in the proportion of patients with healing was statistically significant for the H 199/18 20 mg vs OME 20 mg comparison (log-rank test) at Week 8 in the ITT but not in the PP population.

- When taking baseline severity grade (LA Classification) of EE into account, significant (CMH test) differences between treatments in the proportion of patients with healing of EE were detected in both the ITT and PP populations at Week 4 and by Week 8 for the H 199/18 40 mg comparison to OME 20 mg.

- No significant (CMH test) differences between treatments in the proportion of patients with healing of EE were detected in either the ITT or PP populations at Week 4 or by Week 8 for the H 199/18 20 mg comparison to OME 20 mg.

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[19] From sponsor's Tables 14.1.2.7 and 14.1.2.8 and sponsor's Appendix 16.2.5.1.

- To investigate possible heterogeneity of the healing response by baseline severity strata, Breslow-Day tests were performed using the ITT population at Week 8. No significant Breslow-day test result was seen for the H 199/18 40 mg or 20 mg comparisons to OME 20 mg (Table 7).

TABLE 7
Study No. 172

EE Healing Rates as a Function of Treatment Group and Length of Treatment

Week	H 119/18 mg qd		OME mg qd	Therapeutic Gain (%)/[Statistical Significance=p-value] H 40 vs OME	H 20 vs OME	H 40 vs H 20	Statistical Test
	40	20	20				
I. ITT POPULATION ANALYSIS[a]							
4	[n=654] 465 (71.1%)	[n=656] 436 (66.5%)	[n=650] 399 (61.4%)	**9.7%** [<0.001]	**5.1%** [N.S.]	**4.6%** [N.S.]	CMH
8	573 (87.6%)	550 (83.8%)	529 (81.4%)	**6.2%** [<0.001] [0.0003] [0.003] [N.S.]	**2.4%** [0.042] [N.S.] [N.S.] [N.S.]	**3.8%** [0.035] [0.048] [N.S.] [N.S.]	Log-rank[b] Wilcoxon[c] CMH Breslow-Day
II. PP POPULATION ANALYSIS[d]							
4	[n=536] 401 (74.8%)	[n=550] 381 (69.3%)	[n=534] 346 (64.8%)	**10%** [0.001]	**4.5%** [N.S.]	**5.5%** [N.S.]	CMH
8	498 (92.9%)	486 (88.4%)	461 (86.3%)	**6.6%** [<0.001] [0.0026] [0.001]	**2.1%** [N.S.] [N.S.] [N.S.]	**4.5%** [0.008] [0.023] [0.026]	Log-rank[b] Wilcoxon[c] CMH

Reviewer's Table

Abbreviations: EE=erosive esophagitis; H=H 199/18; OME=omeprazole; CMH=Cochran-Mantel-Haenszel

a) From sponsor's Tables 14.2.1 and 14.2.3.

b, c) Significance levels adjusted for multiple comparisons (Hochberg) for the comparisons H 40 vs OME and H 20 vs OME.

NOTE: The significance levels for the H 40 vs H 20 comparison, calculated by Dr. Y. Tsong, FDA statistician, were not adjusted for multiple comparisons.

d) From sponsor's Tables 14.2.2 and 14.2.4.

e) **Erosive Esophagitis Healing Rates by Baseline Severity (Table 8)**

These analyses showed the expected results among patients treated with H 199/18 40 mg once-a-day. At both, Week 4 and 8, higher healing rates were seen among patients whose EE was grade A or B rather than C. The lowest healing rate was shown in those patients who had grade D esophagitis at baseline (51.1% at Week 4 and 74.5% at Week 8).

TABLE 8
Study No. 172

Analysis of EE Healing Rates by Baseline Severity

	ITT Population			PP Population		
Baseline Severity Grade	H 199/18 mg qd		OME mg qd	H 199/18 mg qd		OME mg qd
	40	20	20	40	20	20
Week 4						
Grade A	79.1%	76.5%	72.4%	85.1%	83.8%	81.0%
B	71.5%	69.7%	63.0%	75.1%	72.2%	65.9%
C	62.2%	47.1%	48.9%	62.2%	47.6%	47.9%
D	51.1%	50.0%	40.0%	56.1%	48.8%	43.9%
Week 8						
Grade A	89.8%	88.9%	84.2%	96.3%	96.4%	91.4%
B	88.9%	84.7%	84.2%	94.7%	89.0%	90.0%
C	85.7%	79.8%	72.3%	87.8%	82.9%	73.9%
D	74.5%	65.2%	80.0%	80.5%	65.9%	82.9%

From sponsor's Tables 14.2.3. and 14.2.5, with major modifications

f) **Proportion of Patients Who Exhibited Complete Resolution of Investigator-Recorded Symptoms of GERD After 4 Weeks (Table 9)**

Results of this secondary efficacy analysis are presented in this Table. There was a significant difference for heartburn between H 199/18 40 mg qd and OME 20 mg qd (p=0.005), but no significant difference between H 199/18 20 mg qd and OME 20 mg qd. There were no significant differences between H 199/18 40 mg qd and OME 20 mg qd or between H 199/18 20 mg qd and OME 20 mg qd in the proportions of patients reporting complete resolution of acid regurgitation, dysphagia or epigastric pain by the end of 4 weeks.

TABLE 9
Study No. 172

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

Treatment Group	n	Week 4	p-Value[a]
Heartburn			
H 199/18 40 mg qd	621	64.7%	0.005*
H 199/18 20 mg qd	626	61.0%	N.S.
OME 20 mg qd	624	57.2%	---
Acid Regurgitation			
H 199/18 40 mg qd	621	77.1%	N.S.
H 199/18 20 mg qd	626	74.9%	N.S.
OME 20 mg qd	624	73.6%	---
Dysphagia			
H 199/18 40 mg qd	621	91.3%	N.S.
H 199/18 20 mg qd	626	89.6%	N.S.
OME 20 mg qd	624	92.1%	---
Epigastric Pain			
H 199/18 40 mg qd	621	76.8%	N.S.
H 199/18 20 mg qd	626	79.1%	N.S.
OME 20 mg qd	624	81.3%	---

From sponsor's Table 14.2.3, with major modifications
a) CMH test, comparison of H 199/18 treatment to OME 20 mg
* Statistically significant $p \leq 0.05$

g) Assessment of Healing of EE by Subgroups (Table 10)

The subgroups examined were gender, age, race and *H. pylori* status (by Histology).

- There was no meaningful effect of gender on the response to treatment.
- There was no meaningful effect of age (<65 vs ≥65y) on the response to treatment in this study.
- There was no meaningful effect of race (Caucasian vs Black vs Asian vs Other) on the response to treatment in this study.
- Efficacy in healing of EE was tabulated separately for patients by histological *H. pylori* status. The proportion of patients healed at Week 4 was greater for *H. pylori* positive patients than for *H. pylori* negative patients, for all treatment groups. The significance of

this finding is unknown. At week 8, there were no meaningful differences between *H. pylori* status (+/-) for each treatment in proportion of patients healed by visit.

TABLE 10
Study No. 172

Cumulative Proportion of Patients Healed by Subgroups

	Treatment Group (mg qd)	n	Week 4	Week 8
I. CUMULATIVE NUMBER OF PATIENTS HEALED BY GENDER[a]				
Male	H 199/18 40	384	70.3%	87.5%
	20	391	65.7%	82.9%
	OME 20	399	59.1%	79.2%
Female	H 199/18 40	270	72.2%	87.8%
	20	265	67.5%	85.3%
	OME 20	251	64.9%	84.9%
II. CUMULATIVE PROPORTION OF PATIENTS HEALED BY AGE[b]				
Age <65 y	H 199/18 40	597	70.9%	87.8%
	20	587	66.8%	83.1%
	OME 20	574	62.0%	81.0%
Age ≥65 y	H 199/18 40	57	73.7%	86.0%
	20	69	63.8%	89.9%
	OME 20	76	56.6%	84.2%
III. CUMULATIVE PROPORTION OF PATIENTS HEALED BY RACE[c]				
Caucasian	H 199/18 40	591	70.9%	88.3%
	20	595	65.5%	83.7%
	OME 20	608	61.8%	82.1%
Black	H 199/18 40	49	77.6%	85.2%
	20	43	83.7%	86.0%
	OME 20	35	54.3%	71.4%
IV. CUMULATIVE PROPORTION OF PATIENTS TREATED BY H. PYLORI STATUS[d]				
H. pylori positive	H 199/18 40	65	81.5%	89.2%
	20	56	73.2%	85.7%
	OME 20	68	66.2%	83.8%
H. pylori negative	H 199/18 40	584	69.9%	87.3%
	20	598	65.7%	83.6%
	OME 20	581	60.9%	81.1%

a) From sponsor's Table 14.2.6, with major modifications.
b) From sponsor's Table 14.2.5, with major modifications.
c) From sponsor's Table 14.2.7, with major modifications. The categories Asian and Other have been excluded because only a few patients fell into these categories.
d) From sponsor's Table 14.2.11, with major modifications. The category missing has been excluded because too few patients fell into this category.

h) Results of Safety Evaluations

i) Extent of Exposure

- 1960 patients with EE were randomized to treatment; 1957 of these received at least one dose of test medication for up to 8 weeks with the following distribution:

		n
H. 199/18	40 mg qd	653
	20 mg qd	655
OME	20 mg qd	649

ii) Deaths, Other Serious and Potentially Serious AEs

DEATH Patient 051/029, 50y-old F (H 199/18 20 mg qd)

This patient was hospitalized on Day 20 for confusion and inability to get out of bed. Admission tests revealed serum potassium of 6.5 mEq/l and resting blood pressure of 110/70 mm Hg and standing blood pressure of 87/41 mm Hg. She was treated with i.v. fluids, Phenergan and Rezulin. The patient's electrolytes normalized within 24 h and she was discharged on Day 24. It was reported that the test medication was interrupted between Day 20 and Day 23. The patient died due to MI on Day 28. The investigator considered the relationship of this event to test medication to be **unlikely**. The reviewer agrees with this assessment.

- The distribution of SAEs was:

		SAEs	Discontinued from Further Treatment
H 199/18	40 mg qd	6	4
	20 mg qd	8[a]	6
OME	20 mg qd	6[b]	1
		20	11

[a] Patient 051/029 had 2 SAEs

[b] Including 4 cases of overdose

Of these 20 patients, 11 were discontinued from further treatment (see above)

iii) AEs Leading to Discontinuation

- In Table 33 of their Clinical Report, the sponsor provided a summary of 47 patients and the AEs that resulted in their discontinuation from treatment/study. This information is summarized in Table 11. Assessment of relationship of the event to test medication is also included in this Table. There were 43 patients who discontinued (D/C) treatment because of an AE ("Action taken with respect to test medication" = "test medication stopped" on AE CRF): 13 who were taking H 199/18 40 mg qd; 17 who were taking H 199/18 20 mg qd; and 13 who were taking omeprazole 20 mg qd. Two of these reports (Patients H40: 080/029 and H20: 176/001) were for patients found to be pregnant during the study and discontinued from further treatment by the investigator. A third patient (020: 014/015) was D/C from the study after prestudy LFTs were found to be abnormal. Because the D/C reason was coded as "AE" in the CRF, these three cases are discussed in this section. Additionally, there were 4 patients who were coded in the CRF as D/C study due to an AE ("AE caused subject to D/C study" = "Yes" on AE CRF) in the absence of coding the specific indication that study drug was stopped (Patients H40: 006/015, H40: 101/014; H 20: 023/013; and 020: 143/036).

TABLE 11
Study No. 172
Listing of Patients Who Discontinued Treatment or Discontinued the Study Due to an AE

Patient ID	Preferred Term for AE (verbatim term)	Patient ID	Preferred Term for AE (verbatim term)	Patient ID	Preferred Term for AE (verbatim term)
002/003 M 53 Caucasian	Abdominal pain/ PRO Diarrhea PRO (Abdominal cramps/Diarrhea)	002/002 F 31 Caucasian	Rash PRO (Rash)	011/005 M 75 Caucasian	Headache PRO (Headache)
004/013 F 58 Caucasian	Urticaria/ PRO Larynx edema PRO (Hives/Laryngeal swelling)	019/007 M 36 Caucasian	Rash PRO (Rash)	014/015[c] M 45 Caucasian	Hepatic function abnormal UNL (Elevated liver enzymes)
005/004 M 37 Caucasian	Asthma aggravated[a] UNL (Exacerbation of known asthma)	023/013[b] F 42 Caucasian	Pharyngitis/ UNL Ear infection NOS/ UNL Bronchitis UNL (Tonsillitis/Left and right ear infection/Bronchitis)	024/008 F 44 Caucasian	Dyspepsia POS (Heartburn)
006/015[b] F 48 Caucasian	Depression aggravated[a] UNL (Worsening of depression)	038/014 M 57 Caucasian	Pruritus Ani/ POS Rash POS (Rectal itching/Rectal rash)	034/001 F 39 Caucasian	Chest pain PRO (Chest pain)
050/017 F 41 Asian	Headache POS (Headache)	045/022 F 49 Caucasian	Headache/ POS Nausea POS (Headaches/Severe nausea)	074/009 M 42 Caucasian	Fatigue POS (Fatigue)
066/004 F 22 Caucasian	Dyspepsia/Headache POS Insomnia/Tachycardia POS (Burning in stomach/Headaches/Insomnia/ Tachycardia)	051/029 F 50 Caucasian	Myocardial infarction[a] UNL (Silent myocardial infarction)	082/004 F 34 Black	Nausea POS (Nausea)
069/005 M 62 Black	Squamous cell carcinoma[a] UNL (Squamous cell carcinoma of the head and neck)	081/005 F 59 Caucasian	Crohn's disease aggravated[a]/ UNL Intestinal obstruction[a] UNL (Exacerbation Crohn's disease/ small bowel obstruction)	102/003 F 67 Other	Overdose[a] UNL (Overdose of study drug)
075/014 M 45 Caucasian	Gastroesophageal reflux UNL (Nocturnal regurgitation)	100/017 M 58 Caucasian	Sweating increased/ PRO Tremor/ PRO Dyspnea PRO (Diaphoresis/shaking/SOB)	102/005 M 71 Caucasian	Dyspepsia POS (Stomach upset)
077/001 M 76 Caucasian	Accident and/or injury[a] UNL (Fall)	103/025 F 51 Caucasian	Paralysis[a] UNL (Paralysis of the left side secondary to motor vehicle accident)	123/004 F 54 Caucasian	Ataxia/ PRO Coordination abnormal/ PRO Nausea/ PRO Somnolence PRO (Ataxia/Discoordination/ Nausea/Sedation)
078/001 F 45 Caucasian	Gastric ulcer POS (Gastric ulcer)	108/005 F 71 Caucasian	Oesophagitis[a] UNL (Distal esophagitis)	124/005 F 37 Caucasian	Abdominal pain/ POS Dizziness/ POS Nausea/ POS Pharyngitis UNL (Abdominal cramps Dizziness/ Nausea/Sore throat)
980/029 F 27 Caucasian	Events of non-medical character UNL (Use during pregnancy)	109/005 M 52 Caucasian	Cramps PRO (Leg cramps)	138/014 F 54 Caucasian	Rash PRO (Rash)
080/031 F 50 Caucasian	Angioedema PRO (Uvulitis)	143/004 F 21 Caucasian	Nausea[a]/ UNL Vomiting[a] UNL (Persistent nausea/Persistent vomiting)	143/033 F 30 Caucasian	Headache PRO (Headache)
101/014[b] M 45 Black	Headache PRO (Headache)	151/016 M 43 Caucasian	Diarrhea/ PRO Headache/ PRO Arthropathy PRO (Diarrhea/Headaches/Stiff neck)	143/036[b] F 72 Caucasian	Tooth disorder UNL (Toothache)

103/014 M 45 Caucasion	Apathy/Headache/ **POS** Nausea/Dyspnea/ **POS** Weight increase **POS** (Decreased energy/Headache (exacerbation of)/Nausea/ Shortness of breath/Weight gain)	151/017 M 50 Caucasian	Anaemia **POS** (Anemia)	178/004 M 66 Caucasian	Barrett's oesophagus **UNL** (Barretts esophagus)
123/002 M 63 Caucasian	Flu-like disorder **UNL** (Flu-like symptoms)	167/008 M 34 Caucasian	Oesophagitis[a]/ **UNL** (Exacerbation of viral esophagitis)		
		168/010 M 52 Caucasian	Abdominal pain/ **POS** Insomnia **POS** Chest pain substernal **POS** (Increased abd pain/Insomnia/ Retrosternal burning)		
		172/029 F 67 Black	Dyspnea **UNL** (Shortness of breath)		
		176/001[c] F 30 Black	Events of non-medical character **UNL** (Use during pregnancy)		

Reviewer's Table, based on sponsor's Tables 14.3.1.20 and 16.2.7.1, with substantial modifications.
a) This was a SAE. More information regarding this AE was provided in sponsor's narrative section 12.3.2.
b) Codes 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) Discontinued by investigator after patient was determined to be pregnant.
d) Patient died.

iv) Adverse Events

- There were no meaningful differences among treatments in the proportion of patients who reported an AE, a SAE or in the proportion of those who D/C treatment due to an AE (Table 12).

TABLE 12
Study No. 172
Summary of Patients with Adverse Events

Number (%) of Patients	H 199/18 mg qd 40 [n=653]	H 199/18 mg qd 20 [n=655]	OME mg qd 20 [n=649]
I. During Week 0 to Week 8			
≥ 1 AE	43.3%	44.7%	41.0%
≥ 1 Serious AE	0.9%	1.2%	0.9%
Discontinued treatment due to AE	2.0%	2.6%	2.0%
II. During Week 9 to Week 4			
≥ 1 AE	34.6%	38.5%	34.2%
≥ 1 Serious AE	0.9%	0.9%	0.3%
Discontinued treatment due to AE	2.0%	2.3%	1.8%

From sponsor's Tables 14.3.1.1 and 14.3.1.2, with major modifications.

- Table 13 presents the AEs (Week 0 to Week 8) according to body system classification. The most frequently reported AE was headache which occurred in similar proportion of patients among the treatment groups. The most frequently G.I. AEs were diarrhea, abdominal pain, nausea, flatulence and gastritis, which also occurred at similar incidences for all three treatment groups.

- Analyses of AEs by subgroups were also presented. Across treatments, AE rates were higher for Fs than for Ms (sponsor's Table 29). There were no meaningful effects of age in the proportion of patients who reported an AE, in the proportion of patients who reported a SAE or in the proportion of patients who D/C treatment because of an AE (Week 0 to Week 8 and also Week 0 to Week 4). There were no meaningful effects of age in the proportion of patients who reported an AE, in the proportion of patients who reported a serious AE or in the proportion of patients who discontinued treatment because of an AE.

TABLE 13
Study No. 172

Number (%) of Most Frequently occurring AEs During Week 0 to Week 8
Patient Incidence ≥ 1% in Any Treatment Group

Body System/ Adverse Event	H 199/18 mg qd 40 [N=653]	20 [N=655]	OME mg qd 20 [n=649]
Musculo-Skeletal System			
Hernia	1.5%	1.4%	1.4%
Central / Peripheral Nervous System			
Dizziness	0.5%	1.1%	1.1%
Headache	8.6%	8.7%	6.9%
GI System Disorder			
Abdominal Pain	3.7%	3.7%	4.2%
Constipation	1.2%	1.2%	1.8%
Diarrhea	4.6%	4.7%	3.9%
Flatulence	1.8%	3.5%	4.0%
Gastrin Serum Increased	1.8%	1.5%	1.5%
Gastritis	2.5%	3.5%	2.5%
Mouth Dry	0.6%	1.8%	0.3%
Mucosal Discolouration GI	1.2%	0.9%	0.9%
Nausea	3.8%	2.9%	3.1%
Oesophageal Disorder	0.8%	0.5%	1.1%
Vomiting	1.7%	1.5%	1.1%
Respiratory System Disorder			
Pharyngitis	1.2%	1.4%	1.1%
Respiratory Infection	4.3%	5.3%	4.6%
Rhinitis	1.1%	1.1%	0.8%
Sinusitis	1.8%	2.4%	1.2%
Neoplasm			
GI Neoplasm Benign	1.4%	0.6%	0.9%
Body As A Whole			
Back Pain	1.1%	0.8%	0.3%
Fatigue	1.2%	0.3%	1.2%
Resistance Mechanism Disorder			
Infection Viral	0.6%	1.7%	1.2%

From sponsor's Table 14.3.1.3, with major modifications.

v) Changes in Laboratory Parameters/Serum Gastrin

- Baseline values of the clinical laboratory tests were generally comparable for the three treatment groups.

- Mean changes from baseline were small and were generally comparable for the three treatment groups.

- The percent increase in the mean gastrin levels for patients treated with H 199/18 40 mg qd (**134%**) was larger than the increase for H 199/18 20 mg qd (**105%**) or for OME 20 mg qd (**83%**).

- Mean post-treatment serum gastrin levels remained within the normal range for all three treatments (0 to 99 pg/mL).

vi) Other

- Mean vital sign values were similar for the 3 treatment groups. There were no clinically meaningful changes in body weight, blood pressure, and heart rate over the course of the trial and in comparison to baseline observations.

11. Discussion and Overall Conclusions (Sponsor)

"H 199/18 40 mg qd and H 199/18 20 mg qd are safe and effective treatments for healing of erosive esophagitis (EE). H 199/18 40 mg qd and H 199/18 20 mg qd are significantly superior to omeprazole 20 mg qd in the primary efficacy analysis, healing of EE following 4 weeks to 8 weeks of treatment. There are no clinically meaningful differences between treatment groups with respect to the patients experiencing AEs, changes in laboratory values or vital signs."

12. Reviewer's Additional Comments

Clinical trial under Protocol No. 172 is one of two critical multicenter studies submitted by the sponsor of this NDA in support of the approval of ESOME Mg for the "short term treatment of erosive esophagitis associated with GERD". This U.S. trial consisted of three parallel arms: two fixed doses of ESOME Mg (20 or 40 mg once-a-day) and OME (20 mg per day), an adequate positive control. The primary hypothesis was that 4 to 8 weeks of ESOME Mg per day is 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. A well designed protocol was used, but it is not a good idea 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 No. 172 was apparently well-executed. Adherence to the appropriate inclusion/exclusion criteria precluded randomization of patients with conditions, diseases or concomitant treatments that may confound the results. The randomization process was properly executed and accomplished three well-balanced treatment groups with respect to the pre-stipulated number of patients per arm, demographic characteristics, severity (L.A. classification) of reflux esophagitis, *H. pylori* status (nearly 90% of the patients were *H. pylori* negative, on histology) and the most commonly used antiulcer/anti-secretory and other medications. Analyses of results included evaluations in ITT and PP population. Of these, the reviewer's comments emphasized results of

analysis 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 172 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 (71.1%) were significantly higher than the OME group (61.4%). A dose-response relationship was not seen as the therapeutic gains with 40 over 20 mg per day ESOME Mg were rather modest and not statistically significant. As expected, regardless of the study population analyzed or the treatment arm, the healing responses were all higher at 8 than 4 weeks of treatment (an additional 4 weeks of treatment almost invariably results in a higher benefit than at 4 weeks). The healing rates at 8 weeks resulted in therapeutic gains that were very similar to those seen at 4 weeks; again, the main comparison ESOME 40 mg once-a-day, yielded highly statistically significant differences (p-values 0.003 or less) in both study populations. In the main, analyses in the PP population confirmed those in the ITT analysis for both 4 and 8 weeks data.

The results of erosive esophagitis rates by initial severity of the esophageal lesion were predictable. The concept that regardless of the esophagitis classification used, more severe lesions are more difficult and take longer to heal applies here. For example, in the ITT population, with ESOME Mg 40 mg per day, the healing rates in those patients whose esophagitis at baseline was grade A, B, C or D progressively decreased from 79.1% to 71.5%, 62.2% and 51.1%, respectively, at 4 weeks and from 89.8% to 88.9%, 85.7% and 74.5%, respectively, at 8 weeks. Since there were not too many patients with grade D (severe) esophagitis, the reviewer concludes that ESOME Mg 40 mg per day provided the greatest healing rates for both mild and moderate (there is little experience with severe) esophagitis.

With respect to EE symptoms, there was a significant difference for complete resolution of heartburn between H 199/18 40 mg qd and OME 20 mg qd but no differences between these treatment groups in the proportion of patients reporting complete resolution of acid regurgitation, dysphagia or epigastric pain by the end of 4 weeks of treatment.

In Study 172, results of safety evaluations demonstrated that doses of 20 and 40 mg of ESOME Mg, given once-a-day, were generally safe and well-tolerated. One death occurred in a 20 mg H 199/18 group patient; the cause of death was MI and this event was considered unlikely related to treatment with H199/18. There were no marked differences between the H199/18 groups and OME in the incidence of SAEs or discontinuations because of AEs. Most AEs were minor and resolved with discontinuation of treatment. The adverse event profile of ESOME Mg appears to be as that of the comparator OME and the other PPIs: the most frequent AE for all three treatment groups was headache. In Study 172, the rate of occurrence of treatment-emergent AEs was similar among the 3 treatment groups. Other than the expected significant increases in serum gastrin (and this is because H199/18 is a PPI and all PPIs induce hypergastrinemia), there were no significant changes observed in laboratory evaluations.

B. Study 173

NOTE: As this trial used a protocol similar in most respects to that in study 172, only certain aspects of study 173 will be highlighted.

"A Multicenter, Randomized, Double-blind, Eight Week Comparative Efficacy and Safety Study of H 199/18 40 mg and Omeprazole 20 mg in Study Subjects with Erosive Esophagitis"

1. Primary Objective

To assess the efficacy, as defined by complete healing of erosive esophagitis, of H199/18 40 mg, q.d. compared to omeprazole 20 mg, q.d. at Week 8 of treatment in subjects with erosive esophagitis.

2. Secondary Objectives

- Efficacy, as defined by complete healing of erosive esophagitis, of H199/18 40 mg q.d. to that of OME 20 mg q.d. at Week 4 of treatment.
- Safety and tolerability of H199/18 40 mg q.d. compared to that of OME 20 mg q.d.
- Complete resolution and relief of GERD symptoms of heartburn, acid regurgitation, dysphagia, and epigastric pain by H199/18 40 mg q.d. compared to OME 20 mg q.d. at Week 4 and Week 8 of treatment.
- Time to resolution and relief of heartburn by H199/18 40 mg q.d. compared to OME 20 mg q.d.

3. Study Population

This was adequate for this type of study. The study population consisted of ca. 1000 patients with symptomatic EE, recruited at ca. 75 centers. The criteria for randomization of EE patients into the trial and the reasons to exclude patients from participation into the study were the same as those described in Study 172 (Table 3).

4. Overall Study Design and Schedule of Evaluation

These were as per Study 172 (refer to Table 4). From the review of the evidence, this was a multicenter, randomized, double-blind, 2-arm, parallel-trial that investigated the efficacy of ESOME Mg 40 mg once daily in comparison to OME 20 mg once daily in patients with symptomatic GERD. All in all, there were 3 visits (at Weeks 0, 4 and 8 or final) and 3 endoscopies [at initial visit (Day -1), visit 2 (Day 28 $\pm$ 4 days) and visit 3 (Day 56 $\pm$ 4 days). Final efficacy and safety determinations were to be made for all patients with endoscopic evidence of healing to the "NOT PRESENT' grade of the Los Angeles classification of

esophagitis [No breaks (erosions) in the esophageal mucosa] at study Week 4 or 8 or in the last day they took a full dose of test medication. Assessment of symptomatic response was as in Study 172.

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

- The dosage strengths, appearance and batch number of test medications were as follows.

Identification of Test Medications

Treatment	Appearance	Batch Number
H 199/18 40 mg	**Blue Size 2 Capsule**	**H1222-04-01-03** **H1222-04-01-05**
omeprazole 20 mg	**Blue Size 2 Capsule**	**H0431-13-05-06**
Individual patients receiving the various batches were listed in sponsor's Appendix 16.1.6.		

- Randomization was performed at each center using blinded blocks of four allocation numbers. The proportion of treatments was 1:1 (H199/18 40 mg: OME 20 mg). Eligible patients at each center were given the next sequential enrollment number (001, 002, 003, etc.) 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.

- The procedures to preserve blinding were all adequate.

6. Prior and Concomitant Therapy: Compliance

The procedures to assess prior and concomitant therapy and compliance were all adequate (refer to Table 3).

7. Evaluation Criteria

- The primary and secondary endpoints for demonstrating efficacy and safety were all adequate, as per Study 172.

8. Data Quality Assurance

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

9. Statistical Methodology

a) Determination of Sample Size

The sample size of 500 patients per treatment group was calculated based on having 95% power to detect a difference in healing rates of 75% for OME 20 mg qd and 85% for H199/18 40 mg qd. This **10% therapeutic gain** assumed a two-sided test, using the arcsine transformation, and an alpha level of 0.05.

b) Details of Statistical and Analytical Procedures

The approach was similar to that used in Study 172.

10. Results

a) Disposition of Patients/Per protocol Deviations (Table 14)

The 79 participating investigators (7 centers did not enrolled patients) logged 1946 patients as screened for inclusion in the study. Of these 1148 were enrolled and randomized to treatment. The first patient was treated on 14 October 1997, and the last patient completed the study on 11 May 1998. As shown in Table 14, the primary reasons for not randomizing screened patients included *H. pylori*, serology positive [n=273] and LA Classification=none [n=238]. The safety, intent-to-treat (ITT) and per-protocol (PP) populations included 1147, 1148 and 973 patients, respectively. The upper panel of Table 14 summarizes the disposition of patients in this study by visit as determined by timing and result of EGD evaluations. The most frequent protocol deviations (mid-panel of Table 14) were *H. pylori* positive (ca. 10%) and randomization despite baseline criteria violation (10%), compliance violation (6%). There were no meaningful differences between treatment groups in the proportion of patients with protocol deviations. The overall summary of patient disposition and evaluability is given in the lower panel of Table 14.

TABLE 14
Study No. 173
Distribution of Randomized Patients
Disposition of Patients Entered into Trials

Screened
[n=1946]

Not enrolled = 798
HP Serology + 273)
LA Class = None (238)
Other (287)

Randomized

	H 199/18 (mg qd) 40	Omeprazole (mg qd) 20	Total
Randomized	**576**	**572**	**1148**
Week 4			
Completed	393	379	772
Ongoing	152[a]	174	326
Discontinued	31	19	50
Week 8			
Completed	150	166	316
Discontinued	3	8	11
Summary of Subjects Manually Evaluated for PP Deviations			
Reason[b]			
Randomized despite baseline criteria violation	7.8%	11.0%	9.4%
H. pylori positive at baseline	9.0%	10.5%	9.8%
Compliance violation	6.9%	5.8%	6.4%
Prohibited concomitant medication	1.6%	1.6%	1.6%
Other deviations	5.2%	4.5%	4.9%
Total patients evaluated for exclusion from PP population	129 (22.4%)	152 (26.6%)	281 (24.5%)
Summary of Patient Disposition and Evaluability			
ITT Population	576	572	1148
Patients with Week 4 endoscopy	552	556	1108
Patients with Week 8 endoscopy	145	163	308
PP Population	487	486	973
Patients with Week 4 endoscopy	487	486	973
Patients with Week 8 endoscopy	131	146	277

From sponsor's Tables 14.1.2.2, 14.1.2.4 and 14.1.2.6, with substantial modifications
a) One patient (527/006) treated with H199/18 40 mg qd who was healed (completed) at Week 4 continued treatment to Week 8. This patient is counted in this table as completed at both visits.
b) Patients with multiple reasons to be manually evaluated were counted multiple times.

b) Data Showing Comparability of Treatment Groups at Baseline (Table 15)

The treatment groups were well balanced with respect to all the demographic, disease and other baseline characteristics listed in this Table. Ca. 88% of the patients were <65y of age, mostly Caucasian, with a GERD history of at least 1y, mostly with moderate (43%) to severe (43.5%)

heartburn. Just as in Study No. 172, only 8% of the patients had grade D esophagitis, 23.5% had grade C and the rest had grade A (33%) and grade B (36%) esophagitis.

TABLE 15
Study No. 173

Demographic and Other Baseline Characteristics
ITT Population

		H199/18 mg qd 40 [n=576]	OME mg qd 20 [n=572]
Gender	M	60.1%	58.6%
	F	39.9%	41.4%
	18-44 y	39.6%	45.6%
	≥ 45 y	60.4%	54.4%
Age (years)	Mean	47.1	46.2
	Minimum/Maximum	18/83	18/81
	< 65 y	88.0%	87.9%
	≥ 65 y	12.0%	12.1%
Race	Caucasian	93.6%	94.8%
	Black	4.3%	4.0%
	Asian	0.5%	0.3%
	Other	1.6%	0.9%
LA Classification	Grade A	32.5%	33.0%
	Grade B	34.7%	37.4%
	Grade C	25.0%	22.0%
	Grade D	7.8%	7.5%
GERD History	< 1 y	6.1%	5.8%
	1 to 5 y	44.3%	44.8%
	> 5 y	49.7%	49.5%
Heartburn	None	2.3%	1.0%
	Mild	11.6%	13.1%
	Moderate	42.4%	42.8%
	Severe	43.8%	43.0%
Acid Regurgitation	None	9.0%	8.7%
	Mild	24.5%	25.0%
	Moderate	41.5%	39.7%
	Severe	25.0%	26.6%
Dysphagia	None	60.4%	61.7%
	Mild	22.2%	20.1%
	Moderate	13.2%	14.5%
	Severe	4.2%	3.7%
Epigastric Pain	None	32.1%	30.9%
	Mild	25.2%	29.0%
	Moderate	30.4%	26.7%
	Severe	12.3%	13.3%
***H. pylori* Status**	Negative biopsy	89.9%	88.8%
	Positive biopsy	9.0%	10.5%
	Missing value	1.0%	0.7%

From sponsor's Tables 14.1.1.1 and 14.1.1.5, with major modifications

c) Compliance[20]

For the ITT population, treatment compliance rates (≥90%) were similar for the two treatment groups (88.0% and 89.0% for H199/18 40 mg qd and OME 20 mg qd, respectively). Treatment compliance <80% was 4.7% and 1.9% of patients, respectively. Compliance rates (≥90%) for the PP population were higher (94.7% and 93.2%, respectively), in part because poor treatment compliance (<80%) was a factor considered for exclusion from this population.

d) Proportion of Patients Healing After 4 and 8 Weeks (Table 16)

This Table displays results for both the ITT (upper panel) and the PP population (lower panel). In Table 16, in addition to the EE healing rates per treatment group, therapeutic gains resulting from the comparison between the H199/18 vs the OME group were very modest (at the most 4%) and are displayed on the right side of the Table.

- The expected therapeutic gain (10%) with ESOME Mg 40 mg qd (over OME 20 mg qd) was achieved neither at 4 nor at 8 weeks of treatment.

- In neither the ITT nor in the PP population was the difference in the proportion of patients with healing significant for the comparison at Weeks 4 and 8.

- When taking baseline severity grade (LA Classification) of EE into account, no significant (CMH test) differences between treatments in the proportion of patients with healing of EE were detected in either the ITT (Table 16, upper panel) or PP (Table 16, lower panel) population by Week 4 or by Week 8.

- A significant Breslow-Day test result was seen at Week 8 (p=0.032) for the ITT population. Breslow-Day test results of <0.10 indicate heterogenicity in the treatment effect across baseline severity grades. That is to say, according to this interpretation, that treatment effect within each severity grade was different. Because a significant Breslow-Day result was seen in the primary analysis, the ITT population at Week 8, the test was repeated for this population at Week 4 as well. A significant Breslow-Day result was also seen at Week 4 (p=0.089).

[20] From sponsor's Table 14.1.2.7 and 14.1.2.8, and sponsor's Appendix 16.2.5.1.

TABLE 16
Study No. 173

EE Healing Rates as a Function of Treatment Group and Length of Treatment

Week	H199/18 mg qd 40	OME mg qd 20	Therapeutic Gain (%)/ [Statistical Significance = p-value] H 40 vs OME 20	Statistical Test
I. ITT POPULATION ANALYSIS[a]				
4	[n=576] 393 (68.2%)	[n=572] 379 (66.3%)	**1.9%** [N.S.] [0.089]	 CMH Breslow-Day
8	501 (87.0%)	491 (85.8%)	**1.2%** [[N.S.] [N.S.] [N.S.] [0.032]	 Log-rank Wilcoxon CMH Breslow-Day
II. PP POPULATION ANALYSIS[b]				
4	[n=487] 348 (71.5%)	[n=486] 330 (67.9%)	**3.6%** [N.S.]	 CMH
8	446 (91.6%)	430 (88.5%)	**3.1%** [N.S.] [N.S.] [N.S.]	 Log-rank Wilcoxon CMH

Reviewer's Table
Abbreviations as in Table 7.
a) From sponsor's Tables 14.2.1 and 12.2.3.
b) From sponsor's Tables 14.2.2 and 14.2.4.

e) EE Healing Rates by Baseline Severity (Table 17)

The rates of healing at Week 4 and Week 8 for each baseline severity grade for both the ITT and PP populations are presented in this Table. The sponsor proposes that the lack of superiority of H199/18 40 mg qd over OME 20 mg qd is due to a different treatment effect within each severity grade. The reviewer does not agree with this explanation of different healing rates for grades A + B (higher) than C + D (lower). The reviewer believes that this is an arbitrary and not validated separation. It is to be noted that, for the PP population, within grade B is identical to that within grade C at 4 weeks (67.0% vs 67.4%); at Week 8, the healing rate within grade C was actually higher than within grade B (91.0% vs 85.0%, respectively). Although the lowest healing rates are seen within grade D, regardless of the treatment group or study population analyzed, the number of patients with grade D esophagitis was considerably smaller than any of the other three severity grades.

NOTE Results of efficacy evaluations from Study No. 173 are not further reviewed because there were no statistically significant differences between H199/18 40 mg qd and OME 20 mg qd in the analysis of the **primary efficacy parameter**, healing of EE by Week 8.

TABLE 17
Study No. 173

Analyses of EE Healing Rates by Baseline Severity

Baseline Severity Grade	ITT Population		PP Population	
	H199/18 mg qd 40	OME mg qd 20	H199/18 mg qd 40	OME mg qd 20
Week 4				
Grade A	77.0%	80.4%	82.1%	83.8%
B	67.0%	68.2%	71.6%	69.4%
C	67.4%	52.4%	68.5%	54.5%
D	40.0%	34.9%	38.5%	35.1%
Week 8				
A	87.7%	90.5%	93.6%	93.5%
B	85.0%	88.3%	92.0%	91.3%
C	91.0%	81.7%	92.3%	83.0%
D	80.0%	65.1%	79.5%	70.3%

From sponsor's Tables 14.2.3 and 14.2.5, with major modifications

f) Results of Safety Evaluations

From his assessment of the evidence presented in NDA 21-153, the reviewer agrees with the sponsor's conclusion that, in Study No. 173, there were no clinically meaningful differences between H199/18 40 mg qd and OME 20 mg qd with respect to the patients experiencing AEs, SAEs, changes in laboratory values or vital signs.

11. Discussion and Overall Conclusions (Sponsor)

"H 199/18 40 mg qd is a safe and effective treatment for healing of erosive esophagitis (EE). No significant difference between treatments was found in the planned analysis of the primary efficacy parameter, healing of EE. H 199/18 40 mg qd is significantly superior to omeprazole 20 mg qd in providing healing of EE following 4 weeks to 8 weeks of treatment in patients with baseline LA Grade C and D. No significant difference between treatments was found in patients with baseline LA Grade A and B. There are no clinically meaningful differences between treatment groups with respect to the patients experiencing AEs, changes in laboratory values or vital signs."

12. Reviewer's Additional Comments

Clinical trial under Protocol 173 is the second critical multicenter study submitted by the sponsor of this NDA in support of the approval of orally administered ESOME Mg for the "short-term treatment of erosive esophagitis associated with GERD". This U.S. trial consisted of two parallel arms: one fixed dose of ESOME Mg (40 mg once daily) and OME (20 mg once daily).

The study was well-designed. OME (20 mg qd) is an adequate positive control because this drug, consisting of two enantiomers, S and R, is approved for the same indication the sponsor is pursuing with the S-enantiomer and is being tested at the recommended oral dose of 20 mg once daily. The hypothesis tested in Study 173 was that 4 and 8 weeks of H 199/18 40 mg once daily is more effective than the approved OME dose (20 mg qd) in the healing of EE and the complete relief of associated heartburn and other symptoms associated with GERD. In a fashion identical to that for Study 172, pre-study estimates of healing rates were 85% for H 199/18 40 mg per day and 75% for OME 20 mg qd. Based on a number of considerations, the estimated healing rates of H 199/18 and OME are not unreasonable. Similarly, based on results of Study 172, the expected therapeutic gains of H 199/18 over OME (10%) did not seem unrealistic. Study 173 made use of a protocol that was, in most respects, similar to the protocol used in Study 172. Primary objective of Study 173 was to compare healing rates of the two drugs at 4 and 8 weeks.

The study was apparently well executed. The inclusion/exclusion criteria were adequate to minimize the effects of potential confounders. Study 173 offered the same opportunities as Study 172 to demonstrate the proposed superiority of the **H** drug over **OME**. Instead, therapeutic gains of ESOME Mg 40 mg qd over OME 20 mg qd were **very modest** and statistically insignificant at both 4 and 8 weeks and in both the ITT as well as the PP population. Because the primary efficacy parameter, healing of EE by Week 8, was not different between treatment groups, and therefore results in Study 173 did not replicate those in Study 172, the reviewer decided not to carry out further efficacy evaluations. This lack of replication of the primary efficacy endpoint is a very significant impediment against the recommendation to approve ESOME Mg for the short-term treatment of erosive esophagitis associated with GERD.

Regarding safety evaluations, there were no clinically meaningful differences between H 199/18 40 mg qd and OME 20 mg qd with respect to the results of safety evaluations. This included comparisons of proportion of patients experiencing AEs, SAEs, changes in laboratory values or vital signs.

C. Study 222

NOTE: Because this study used a very similar protocol to that in Study 172 (actually the main reason to do the study was to replicate the findings with the 40 mg dose of **H** in Study 172) only certain aspects of Study 222 will be highlighted.

"A Comparative Efficacy and Safety Study of H 199/18 (40 mg) and Omeprazole (20 mg) in Study Subjects with Erosive Esophagitis"

1. Primary Objective

The primary study objective was to assess the efficacy, as defined by **complete healing of erosive esophagitis** of H 199/18 40 mg compared to OME 20 mg at Week 8 of treatment in subjects with EE.

2. Secondary Objectives

- One secondary objective was to assess the healing efficacy of H 199/18 40 mg compared to OME 20 mg at Week 4 of treatment.

- Other secondary objectives were to assess complete resolution and relief of GERD symptoms by H 199/18 40 mg compared to OME 20 mg at Week 4 and Week 8 of treatment, and to assess time to resolution and sustained resolution of heartburn by 40 mg of one compared to 20 mg of the other.

- Another objective of this study was to compare the safety and tolerability of H 199/18 40 mg to that of OME 20 mg.

3. Study Population

This was adequate for this type of study. The study population consisted of ca. 1200 patients with symptomatic EE. These patients were recruited at 163 investigator sites (out of 178 that were initiated but 15 of them did not enroll any patients).

The criteria for randomization of EE patients into this trial and the reasons to exclude patients from participation into the study were the same as those described in Study 172 (Table 3).

4. Overall Study Design and Schedule of Evaluations

- Refer to Table 4. From the reviewer's appraisal of the provided evidence, this was a multicenter, randomized, double-blind, 2-arm, parallel-group that investigated the healing efficacy of ESOME Mg (40 mg once daily) in comparison to OME 20 mg once daily in patients with symptomatic GERD.

- All in all, there were 3 visits (at Weeks 0, 4 and 8) and 3 endoscopies [at initial visit (Day -1), visit 2 (Day 28 $\pm$ 4 days) and visit 3 (Day 56 $\pm$ 4 days)].

- As in the previous pivotal trials, final efficacy and safety determinations were to be made for all patients with endoscopic evidence of healing to the "NOT PRESENT" grade of the Los Angeles classification of esophagitis [No breaks (erosions) into the esophageal mucosa] at Study Week 8 or in the last day the patients took a full dose of test medication.

- Assessment of symptomatic response was as in Study No. 172.

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	H-1222-04-01-07 H-1222-04-01-08
Omeprazole 20 mg	Blue, Size 2 Capsule	H-0431-13-05-06 H-0431-13-05-08
Allocation records (individual patients) generated for each batch were listed in sponsor's appendix 16.1.6.		

- **Randomization** was performed at each center using blinded blocks of four allocation numbers. The proportion of treatments was 1:1 (H 199/18 40 mg: OME 20 mg). Eligible patients at each center were given the next sequential enrollment number (001, 002, 003, etc.) 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.

- The procedures to prescribe blinding were all adequate.

6. Prior and Concomitant Therapy: Compliance

As in the other pivotal trials, the procedures to assess prior and concomitant therapy and compliance were all adequate (refer to Table 3).

7. Evaluation Criteria

- The primary and secondary endpoints for demonstrating efficacy and safety were all adequate.

8. Data Quality Assurance

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

9. Statistical Methodology (as prespecified in the protocol)

a) Determination of Sample Size

The sample size of 1040 patients per treatment group was calculated based on having 95% power to detect a difference in healing rates of 88% for omeprazole 20 mg qd and 93% for H 199/18 40 mg qd. This assumed a therapeutic gain of 5%, a two-sided test, using the arcsine transformation, and an alpha level of 0.05.

b) Statistical and Analytical Plans

The following summary outlines the statistical analyses that were performed for this study.

- For the primary efficacy analysis (percentage of patients whose erosive esophagitis was healed by Week 8), a log-rank test was used to assess differences between treatment groups. While this test is sensitive to differences between treatment groups in the magnitude of the observed healing rates, it is also sensitive to the timing of healing. For example, a patient who was healed at Week 4 was given greater weight than a patient healed at Week 8. Since the dates on which endoscopies were performed did not necessarily reflect the actual date of healing (for healed patients), the dates were grouped into 2-week intervals relative to the first day of test medication treatment, as follows: Days 1 to 14, Days 15 to 28, Days 29 to 42, and Days greater than 42. This very wide endoscopic window approach is different from that used in Study 172.

- Due to the design of the study, in which healed patients at Week 4 were discontinued from treatment as a treatment success, the Week 8 analysis was a cumulative analysis, in which patients who discontinued prior to Week 8 had their response at the time of discontinuation used in the analysis. A basic assumption of such an approach (for a crude rate) was that the response at the earlier time point would have continued to Week 8. But, as already mentioned, this is not always so. For healed patients, this assumption was the rationale for discontinuing a Week 4 healed patient; for the non-healed patients, this was a conservative approach, in that it assumed the worst response for the patient.

- The percentage of patients healed was also analyzed by a Cochran-Mantel-Haenszel (CMH) test, stratified on baseline severity (LA Classification) of erosive esophagitis, a more conservative approach than the log-rank test. In the CMH test, all patients who did not contribute 'appropriate' data were considered to be failures. As examples, a patient who had no post-baseline endoscopies performed was treated as a failure in the CMH test but as a censored patient in the log-rank test; a patient with a Week 4 endoscopy with evidence of erosions, but no Week 8 endoscopy, was also considered a failure by the CMH test, but was censored at Week 4 for the log-rank test; and a patient who had a Week 4 endoscopy that exhibited healing of the erosions was considered a success in both analyses, including the Week 8 CMH analysis (a Week 4 endoscopy with healing was appropriate for a Week 8 analysis). The CMH test was performed separately at Week 4 and Week 8. Because there was variation in the scheduling of the endoscopies, which was mainly unrelated to response, time windows were used to identify the data to be used for each analysis. For the Week 4 analysis, the first post-baseline endoscopy performed prior to Day 43 was used for each patient; patients with no endoscopy in this window were considered failures (in the Week 4 analysis). For the Week 8 analysis, the final post-baseline endoscopy was used for each patient (week 4 healed patients were included as Week 8 healed patients), and patients with no post-baseline endoscopy were considered failures.

  NOTE: Although valid, the above-described approach precluded the gathering of important information. It would have been of interest to determine if patients that healed at Week 4 remained healed at Week 8. EE that has "healed" at Week 4 may recur at Week 8. This may have been due to: a) poor quality of healing, or b) the definition of healed esophagitis was not standardized. Different results may be obtained

if the endoscopy is carried out by the Principal Investigator instead of an inexperienced gastroenterologist since endoscopic visualization of the upper G.I. mucosa is a **subjective approach that requires training**. In addition, there are convincing data available in the literature that once a PPI (i.e. omeprazole) is discontinued, the GERD-related symptoms and endoscopic lesions of GERD return within 48h; during this interval, normalization of serum gastrin levels is concomitantly observed.

- The percentage of patients who exhibited resolution of investigator-recorded symptoms of GERD and relief of investigator-recorded symptoms of GERD, were analyzed with a CMH test stratified on baseline severity of the particular symptom. These secondary analyses were done at Week 4 only. The sponsor explained that a cumulative analysis by Week 8 was not done because patients could complete the study at Week 4 with healed erosive esophagitis even if symptoms were present.

- The number of days until the first resolution of the diary recorded symptom of heartburn and the number of days until sustained resolution of the diary-recorded symptom of heartburn were analyzed with a log-rank test. Differences between treatments in the mean percentage of heartburn-free days and the mean percentage of patients with heartburn-free nights were compared using analysis-of-variance.

- No inferential statistics were used in comparing any safety variables, since there were no *a priori* hypotheses concerning safety. Incidence rates for AEs were calculated using the number of patients having one or more occurrences of an AE and the number of patients who received that treatment. Since it was anticipated that a substantial number of the patients would complete (be healed) at Week 4, incidence rates for AEs were summarized for Week 0 to Week 4 as well as for the entire treatment period of the study (week 0 to Week 8). Incidence rates of AEs, by preferred term, were summarized by severity and by the investigators' assessment of relationship to treatment. Adverse event incidence rates for summary of AE occurrence and for AEs by body system and preferred term were also created for three specific demographic subgroups: gender, age (<65 years, ≥65 years), and race (Caucasian, Black, Asian, or Other). Listings of all serious AEs and all AEs resulting in discontinuation from the study were also generated.

- Clinical laboratory data were presented by the sponsor in various ways to investigate group trends as well as to identify any outlying values that were potentially clinically significant. Cumulative distribution plots for each laboratory test were generated for each patient's baseline and maximum (or minimum) post-baseline value for each treatment group. These plots allowed identification of any aggregate shifts in the laboratory test results, provided a basis for comparison of any such shifts between treatment groups, and also displayed outlying values that might have been of concern. Tables of summary statistics (mean, standard deviation) and "shift" tables for each laboratory test were also generated. Each laboratory test result was classified as within, above, or below the reference range for that laboratory test. Each patient's baseline and post-baseline classifications were cross-tabulated by treatment group. Numbers and percentages of patients were calculated from each cell of the cross-tabulation.

- Laboratory values outside of the prespecified limits (identified by the sponsor as potentially clinically significant values) were tabulated and frequencies of patients with at least one post-baseline result that was potentially clinically significant were produced.

- Summary statistics for vital signs (PR and BP) and body weight were generated by treatment group.

- All summaries and analyses were performed with the statistical software package SAS®, Version 6.12.

c) Populations Analyzed

Two populations were defined for purposes of the analysis of efficacy data: the intent-to-treat (ITT) population, and the per-protocol (PP) population (Data Analysis Plan, Appendix 16.1.9). The ITT population was defined as all patients who were randomized to treatment. The PP population consisted of a subset of the ITT patients who met certain predefined inclusion/exclusion criteria and measures of compliance with the conduct of the study. A listing of patients excluded from the PP population was included in sponsor Appendix 16.1.3.2.

The primary efficacy variable, the percentage of patients whose EE was healed by Week 8, was analyzed for both the ITT and the PP populations. All secondary efficacy variables were analyzed for the ITT population only.

The population for the analysis of safety consisted of all patients who received at least one dose of test medication. The sponsor took the conservative approach of excluding from the safety population all patients who did not receive at least one dose of study drug.

d) Variables Analyzed

Baseline measurements were taken within 7 days prior to the first day of medication. Post-treatment measurements were taken at the Week 4 (Day 28 $\pm$ 4 days) and Week 8 visits (Day 56 $\pm$ 4 days). Patients were to fill out diary cards detailing the presence and severity of heartburn during the previous 24-hour period, for the first 4 weeks of the study. Also recorded on the diary was whether the patient experienced any nighttime heartburn.

Baseline demographic variables were summarized by treatment group.

The parameters summarized or analyzed were:

- The percentage of patients whose EE is healed by Week 8. A healed patient is defined as a patient whose LA Classification of EE is "Not Present".

- The percentage of patients whose EE is healed at Week 4. A healed patient is defined as a patient whose LA Classification of EE is "Not Present".

- The percentage of patients who exhibit resolution of investigator-recorded GERD symptoms (i.e., heartburn, acid regurgitation, dysphagia, and epigastric pain) at each of Week 4 and Week 8. Resolution is defined as a recorded symptom severity of "None".

- The percentage of patients who exhibit relief of investigator-recorded GERD symptoms (i.e., heartburn, acid regurgitation, dysphagia, and epigastric pain) at each of Week 4 and Week 8. Relief is defined as a recorded symptom severity of "None" or "Mild".

- Summaries of the Week 8 crude healing rates were presented by baseline esophagitis classification, *H. pylori* status (by histology), age (<65 years, ≥65 years), gender, race, and investigator.

- Summaries of the healing status (healed, not healed) are presented by the resolution of the investigator-recorded GERD symptoms (i.e., heartburn, acid regurgitation, dysphagia, and epigastric pain) at each of Week 4 and Week 8.

- The number of days until the first resolution of the diary-recorded symptom of heartburn. Resolution is defined as heartburn recorded as "None".

- The number of days until sustained resolution of the diary-recorded symptom of heartburn. Sustained resolution is defined as seven consecutive days with heartburn recorded as "None". The first day of the seven is used for analysis (i.e., if a patient were to have "None" recorded on each of Day 5 through Day 11, the patient would be said to have a sustained resolution on Day 5).

- The number of days until the first resolution and the number of days until the first sustained resolution of the diary-recorded symptom of nighttime heartburn.

- The percentage of heartburn-free days for each patient.

- The percentage of heartburn-free nights for each patient.

- The percentage of patients who reported: 1) any AE; 2) an AE in each coded body system; 3) each unique coded AE; 4) any serious AE; 5) any treatment related AE; and 6) discontinuation of treatment due to an AE (defined as 'study drug stopped' on the AE CRF page).

- Clinical laboratory tests using descriptive statistics, graphs, and shift tables.

- Summaries of vital signs (pulse rate and blood pressure) and body weight were presented descriptively by treatment group.

e) Changes in the Conduct of the Study or Planned Analyses

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

10. Results

a) Disposition of Patients/Per Protocol Deviations (Table 18)

- The investigators (n=163)[21] screened a total of 4,798 patients for inclusion into the trial and half of these (2,425 or 50.5%)[22] were randomized to test medication.

- Patient enrollment by site varied from 1 to 32 patients. Most sites (102/163 or 62.6%) enrolled at least 12 patients.

- A primary reason for not randomizing screened patients were LA Classification=NOT PRESENT (1,032 patients) and *H. pylori* serology positive (691 patients).

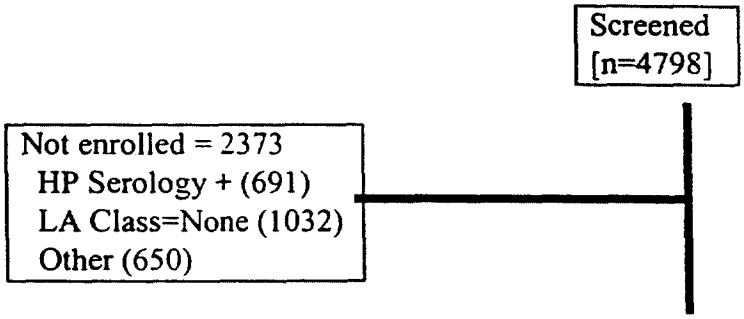
- The number of patients randomized per arm is given in the upper panel of Table 18. The summary of patients manually evaluated for PP Deviation can be found in the mid-panel of this Table and the Summary of Patient Disposition and Evaluability in the lower panel of Table 18. The most frequent deviations were for inclusion/exclusion criteria violations (9.5%), *H. pylori* positive at baseline (7.7%), and compliance violations (7.0%).

- There were no meaningful differences between treatment groups in the proportion of patients with protocol deviations. The number of patients included in the ITT and PP populations, by investigator, are shown in the lower panel of Table 18. There were no meaningful differences between treatment groups in the proportion of patients excluded by the various reasons. A full listing of potential protocol violations was given in sponsor's Appendix 16.2.2.2.

[21] The planned number of centers was — test medication was delivered to 178 centers and of these, 163 enrolled patients.

[22] The first patient was dispensed test medication on 04 February 1999. The last patient completed the trial (last patient contact) on 30 July 1999.

TABLE 18
Study No. 222
Distribution of Randomized Patients
Disposition of Patients Entered into Trial



Randomized

	H 199/18 mg q.d. 40	OME mg q.d. 20	Total
Randomized	1,217	1,209	2.425
Week 4			
Completed (healed)	956	805	1.761
Ongoing	217	364	581
Discontinued (not healed)	43	40	83
Week 8	n=217	n=364	
Completed (healed)	137	173	310
Unhealed	72	177	249
Discontinued (not healed)	8	14	22
Summary of Patients Manually Evaluated for PP Deviations			
Total patients evaluated for exclusion from per protocol (PP) population	277 (22.8%)	261 (21.6%)	538 (22.2%)
Possible per-protocol deviation[a]			
Inclusion/exclusion criteria violation	123 (10.1%)	107 (8.9%)	230 (9.5%)
H. pylori positive at baseline	90 (7.4%)	96 (7.9%)	186 (7.7%)
Compliance violation	94 (7.7%)	75 (6.2%)	169 (7.0%)
Prohibited concomitant medication	21 (1.7%)	14 (0.2%)	35 (1.4%)
Other deviations	55 (4.5%)	41 (3.4%)	96 (4.0%)
Summary of Patient Disposition and Evaluability			
Intent-to-treat (ITT) population	1,216	1,209	2,425
Patients with evaluable Week 4 endoscopy	1.177	1.180	2,357
Patients with evaluable Week 8 endoscopy	207	351	558
Per-protocol (PP) population	1,066	1,066	2,132
Patients with evaluable Week 4 endoscopy	1,066	1,066	2,132
Patients with evaluable Week 8 endoscopy	185	325	510

From sponsor's Tables 14.1.2.2, 14.1.2.3, 14.1.2.4 and 14.1.2.6, with substantial modifications

a) These deviation categories were derived from a series of programming evaluability criteria, which intentionally identified all patients with possible deviations. As such, not all deviations listed in sponsor's Table 5 reflected true protocol deviations . Patients with multiple deviations are counted multiple times (once for each deviation).

b) Data Showing Comparability of Treatment Groups at Baseline (Tables 19 and 20)

- The data in these two tables show that the treatment groups were well balanced with respect to all the demographic, disease and other baseline characteristics. The two groups were also comparable to each other with respect to GERD symptoms recorded by the investigator at baseline.

- Most patients (73% to 74%) had grade A or B LA classification esophagitis, while 20% had grade C and **only 5% to 7% had grade D esophagitis** by this classification.

- Ca. 92% of the patients in each treatment group were not infected with *H. pylori* (negative biopsy).

- Approximately 10% of the patients had mild heartburn, and 48% had moderate heartburn and 39% had severe heartburn, with no significant difference between the groups.

c) Compliance[23]

For the ITT population, the proportion of patients with a treatment compliance rate ≥90% was similar for the two treatment groups (90.5% and 93.0% for H40 and O20, respectively). The proportion of patients with a treatment compliance rate <80% or an unknown treatment compliance rate was 6.8% and 5.1% of the patients in the H40 and O20 groups, respectively. The proportion of patients with a compliance rate ≥90% was higher for the PP population (94.8% and 96.7%, in the H40 and O20 groups, respectively), in part because poor treatment compliance (<80%) was a factor considered for exclusion from this population.

[23] Summaries of patient compliance with regard to taking test medication were found in sponsor's Tables 14.1.2.7 and 14.1.2.8 for ITT and PP populations, respectively. Drug accountability data for each patient was provided in sponsor's Appendix 16.2.5.1.

TABLE 19
Study No. 222

Demographic and Baseline Characteristics
ITT Population

Demographic or Baseline Characteristic		H 199/18 40 mg qd [n=1,216]	omeprazole 20 mg qd [n=1,209]
Gender, (%)	Male	59.4%	62.9%
	Female	40.6%	37.1%
	18 - 44 y	37.9%	36.7%
	≥45 y	62.1%	63.3%
Age, y	Mean	46.5	46.8
	Min – Max	19 to 81	18 to 83
Age category (%)	<65 y	91.1%	90.0%
	≥65 y	8.9%	10.0%
	≥75 y	1.1%	0.5%
Race (%)	Caucasian	93.3%	93.7%
	Black	4.9%	4.5%
	Asian	0.3%	0.4%
	Other	1.6%	1.3%
LA Classification (%)	Not present	0.2%	0.1%
	Grade A	35.1%	31.9%
	Grade B	38.7%	41.5%
	Grade C	21.1%	19.9%
	Grade D	4.9%	6.6%
GERD History (%)	< 1 y	6.1%	6.8%
	1 to 5 y	44.2%	39.9%
	> 5 y	49.8%	53.3%
***H. pylori* status (%)**	Missing	0.3%	0.4%
	Negative biopsy	92.3%	91.6%
	Positive biopsy	7.4%	7.9%

From sponsor's Tables 14.1.1.1 and 14.1.1.5 with major modifications

TABLE 20
Study No. 222

Investigator-Recorded GERD Symptoms at Baseline
ITT Population

Investigator-Recorded GERD Symptom / Severity		H 199/18 40 mg qd [n=1,216]	omeprazole 20 mg qd [n=1,209]
Heartburn (%)	None	1.5%	1.9%
	Mild	10.0%	10.4%
	Moderate	48.3%	49.4%
	Severe	40.3%	38.0%
	Missing	0.0%	0.2%
Acid regurgitation (%)	None	11.1%	10.8%
	Mild	20.8%	22.5%
	Moderate	42.4%	42.9%
	Severe	25.7%	23.5%
	Missing	0.0%	0.2%
Dysphagia (%)	None	64.2%	60.0%
	Mild	19.7%	22.2%
	Moderate	12.0%	12.8%
	Severe	4.0%	4.6%
	Missing	0.0%	0.2%
Epigastric pain (%)	None	35.5%	37.6%
	Mild	23.9%	24.2%
	Moderate	26.8%	26.1%
	Severe	13.7%	11.9%
	Missing	0.0%	0.2%

From sponsor's Table 14.1.1.1 with major modifications.

d) Proportion of Patients Healing After 4 and 8 Weeks (Table 21)

In this Table, results for the ITT population are displayed in the upper panel, whereas those for the PP population are shown in the lower panel. Because the results of both study population analyses were similar, only results for the ITT population are commented upon. In Table 21, in addition to the EE healing rates per treatment groups, therapeutic gains resulting from comparisons of both treatment groups varied from 9% to 14.4% and are shown on the right side of this Table.

- A therapeutic gain of 12% with ESOME Mg (over OME 20 mg qd) was obtained at Week 4 and this difference was statistically significant.

- The difference in the proportion of patients with healing (9%) was statistically significant for the comparison H 199/18 40 mg vs OME 20 mg at Week 8 (Log-rank, Wilcoxon and CMH tests, p-values of 0.0001, 0.0001 and 0.001, respectively).

- Significant (CMH test) differences between treatments in the proportion of patients with healing of EE were also detected in both the ITT (p=0.001; data not shown) and PP populations (p=0.001; data not shown) by Week 4 and Week 8, when baseline EE severity grade (LA Classification) was taken into account.

- To investigate possible heterogeneity of the healing response by baseline severity strata, Breslow-day tests were performed on the ITT population at Week 8. No significant Breslow-Day test result was seen for the H40 comparison to O20 (Table 21).

TABLE 21
Study No. 222

EE Healing Rates as a Function of Treatment Group and Length of Treatment

Week[a]	H 199/18 mg qd 40	OME mg qd 20	Therapeutic Gain (%)/[Statistical Significance = p-value] H 40 vs OME	Statistical Test
I. ITT POPULATION ANALYSIS				
4	[n=1,216] 956 (78.6%)	[n=1,209] 805 (66.6%)	**12%** [0.001]	CMH[b]
8	1,093 (89.9%)	978 (80.9%)	**9%** [0.0001] [0.0001] [0.001] [N.S.][c]	Log-rank Wilcoxon CMH[b] Breslow-Day
II. PP POPULATION ANALYSIS				
4	[n=1,066] 874 (82.0%)	[n=1,066] 721 (67.6%)	**14.4%** [0.001]	CMH[b]
8	994 (93.3%)	887 (83.2%)	**10.1%** [0.0001] [0.0001] [0.001]	Log-rank Wilcoxon CMH[b]

Reviewer's Table
Abbreviations: As in Table 7

a) Week 4 included all EGD evaluations through Day 42. Week 8 included all EGD evaluations through the final visit.
b) Stratified on the baseline severity (LA Classification Grade) of EE.
c) Breslow-Day test at Week 8 was not significant, indicating homogeneity of healing rate differences between H40 and O20 across the baseline LA Grades.