2.0 SYNOPSIS

Name of Company: Astra Pharmaceuticals, L.P.	**Individual Study Table Referring to Item of the Submission:** N/A	**(For National Authority Use only)**
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Title of Study: A Multicenter, Randomized, Double-blind, Six-month Maintenance Study to Compare the Efficacy, Safety, and Tolerability of H 199/18 40 mg, H 199/18 20 mg, and H 199/18 10 mg with Placebo in Healed Erosive Esophagitis Subjects.

Investigator(s): Multicenter

Study Center(s): 65 investigator sites initiated; 47 investigator sites enrolled patients

Publication (reference): N/A

Studied Period (years): <1 year (date of first enrollment) 24 October 1997 (date of last completed) 17 August 1998	**Phase of development:** Phase III

Objectives:

Primary Objective

1. To assess the efficacy of each of H 199/18 40 mg qd (H40), H 199/18 20 mg qd (H20), and H 199/18 10 mg qd (H10) compared to placebo after 6 months of treatment for the maintenance of healing in patients with healed erosive esophagitis (EE).

Secondary Objectives

1. To assess the effects of H40, H20, and H10 compared to placebo on the presence of gastroesophageal reflux disease (GERD) symptoms (any symptoms, and moderate to severe symptoms) after 1, 3, and 6 months of treatment.
2. To assess safety and tolerability of each of H40, H20, and H10 compared to placebo.

Methodology: This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, 6-month study to evaluate the efficacy and safety of H 199/18 in patients with healed erosive esophagitis. Patients with esophagogastroduodenoscopy (EGD)-verified healed EE (Los Angeles Classification Grade "Not Present") who were negative for *H. pylori* (by histology) at baseline of Study 172 were to be included in the study. All patients were to be re-evaluated by EGD at Month 1, Month 3, and Month 6 of treatment. Patients who relapsed (ie, had an LA Classification Grade of esophageal erosions other than "Not Present") were discontinued from the study.

Number of Patients (Planned and Analyzed):

	H40	H20	H10	Placebo
Number of Patients Planned	75	75	75	75
Number of Patients Enrolled	82	82	77	77
Number of Patients Analyzed				
Efficacy: Intent-to-Treat	82	82	77	77
Efficacy: Per-Protocol	66	73	65	61
Safety	81	81	76	77

Diagnosis and Main Criteria for Inclusion: Patients from Study 172 whose EE was reported as healed (Los Angeles Classification Grade = "Not Present") on the final EGD in Study 172 and who were negative for *H. pylori* (by histology) at baseline of Study 172.

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Test Product, Dose and Mode of Administration, Batch or Lot Number:

H 199/18 capsules 10 mg	-	Lot H1221-02-01-02
H 199/18 capsules 20 mg	-	Lot H1189-04-01-02
H 199/18 capsules 40 mg	-	Lot H1222-04-01-04
Placebo capsules	-	Lot H0459-06-03-06

Duration of Treatment: Up to 6 months.

Reference Therapy, Dose and Mode of Administration, Batch or Lot Number:

GELUSIL® Antacid tablets - Lots AM-173 and AM-130

Criteria for Evaluation:

Efficacy: The primary efficacy variable was the percentage of patients who maintained complete healing of esophageal erosions (ie, LA Classification "Not Present," no erosions present) on EGD evaluation at Month 6 of treatment. Secondary efficacy variables were: 1) the percentage of patients who maintained complete healing of esophageal erosions on EGD evaluation at Month 1 and Month 3 of treatment; and 2) presence of GERD symptoms of heartburn, acid regurgitation, dysphagia, and epigastric pain, by investigator assessment, at Months 1, 3, and 6 of treatment.

Safety: Adverse events were recorded at each visit. Fasting clinical laboratory samples were collected at all visits. Clinical laboratory tests included serum chemistry, special chemistry (serum iron, gastrin, and B_{12}), hematology, and urinalysis (dipstick). Vital signs were recorded at each visit and a physical examination done at the baseline and final visits. Biopsy samples taken at baseline of Study 172, and at the final visit in Study 178, were evaluated for chronic inflammation, intestinal metaplasia, and atrophy by the Sydney System of classification, as well as for enterochromaffin-like (ECL) cell hyperplasia (ECL cell classification system), and *H. pylori*. In addition, biopsy samples with intestinal metaplasia or atrophy graded greater than "Mild" were evaluated for atrophic gastritis.

Statistical Methods: The primary efficacy variable was analyzed for Intent-to-Treat (ITT) and Per-Protocol (PP) populations. Definitions of the ITT and PP populations were set prior to unblinding the data. At Month 6, cumulative life-table rates for the maintenance of healing of EE in the H 199/18 treatment groups were compared to placebo in a pairwise fashion using log-rank statistics. For these comparisons, the experiment-wise error rate was preserved at 0.05 using the Hochberg adjustment for multiple comparisons. Crude rates for maintenance of healing for each H 199/18 treatment group at each month were compared to placebo in a pairwise fashion using Fisher's exact tests with no adjustment for multiple comparisons. The proportions of patients with GERD symptoms present at Month 1 for each H 199/18 treatment group were compared to placebo in a pairwise fashion using Cochran-Mantel-Haenszel statistics adjusting for the presence of the symptom at baseline. The presence of GERD symptoms at Month 3 and Month 6 was summarized using descriptive methods. Similar methods were used to compare the proportions of patients with GERD symptoms rated "None" or "Mild." Concurrence between maintenance of healing and the absence of GERD symptoms was evaluated by month using descriptive methods. Crude maintenance of healing rates were calculated for subgroups of patients based on gender, age group, race, initial EE severity, treatment received during the healing of EE study, duration of treatment in the healing of EE study, and study site; however, no formal statistical comparisons were made.

All randomized patients who received at least one dose of study drug were included in the assessment of safety. Summaries of adverse events, and incidence rates for adverse events by body system and preferred term, were tabulated over the entire study period (through Week 26), and for events occurring through Week 13 (Month 3) and through Week 4 (Month 1). Laboratory test results were summarized using descriptive statistics for each test by visit, and for the change from baseline in each test by visit, as well as across all visits. Frequencies of patients with values outside the predefined limits of change (identified as potentially clinically significant) were

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determined. Vital signs were summarized by visit and across all visits using descriptive statistics. Summaries of gastritis ratings (chronic inflammation, intestinal metaplasia, and atrophy) were tabulated for baseline (baseline of Study 172) and final (end of Study 178) biopsy data for antral sites, fundic sites, and all sites combined. Frequencies of patients with an increase (worsening) from baseline were determined for each rating at each location. Biopsy evaluations for atrophic gastritis were also tabulated for baseline and final biopsy data. Frequencies of ECL cell ratings at the baseline and final biopsies were tabulated, as were frequencies of patients who had an increase (worsening) in ECL cell rating. Proportions of patients with an increase in ECL cell rating in the H 199/18 treatment groups were compared with the proportion in the placebo group in a pairwise fashion using Fisher's exact tests.

SUMMARY

Efficacy Results: At Month 6, healing of EE (cumulative life-table rate) was maintained in 93.6% of H40 patients (95%CI = 87.4%, 99.7%), 93.2% of H20 patients (95%CI = 87.4%, 99.0%), and 57.1% of H10 patients (95%CI = 45.2%, 69.0%); compared to 29.0% of placebo patients (95%CI = 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 placebo (all p-values < 0.001). Across the three H 199/18 doses, rates of maintenance of healing (both life-table and crude estimates) were higher in the H40 and H20 groups than in the H10 group, with little difference between the H40 and H20 groups. None of the subgroups examined appeared to be a predictor of maintenance of healing. The mean time to recurrence of EE was shorter in patients receiving placebo (33 days) than in patients receiving H 199/18 (163, 115, and 75 days for the H40, H20, and H10 groups, respectively).

At Month 1, GERD symptoms were absent in the majority of H 199/18 patients, and present in most placebo patients. Heartburn was the most prevalent GERD symptom. Proportions of patients who were heartburn-free increased with H 199/18 dose (78.7, 61.3, 51.4, and 17.8% in the H40, H20, H10, and placebo groups, respectively). Pairwise comparisons of each H 199/18 treatment group with the placebo group were all statistically significant. Concurrence between maintenance of healing of EE and absence of GERD symptoms was high.

Safety Results:

Clinical Adverse Events (AEs): No patient died during the study and there were no drug-related serious AEs. Two H40 patients (2.5%), 4 H20 patients (4.9%), and 1 H10 patient (1.3%) had serious AEs. Three H40 patients (3.7%), 3 H20 patients (3.7%), 1 H10 patient (1.3%), and 2 placebo patients (2.6%) discontinued treatment due to AEs. Proportions of patients reporting at least one AE were similar among the H 199/18 treatment groups (ranging from 49% to 56%), and were higher than the proportion of patients reporting at least one AE in the placebo group (43%). Time on treatment was notably shorter in the placebo group (mean = 59 days) than in the H 199/18 groups (means ranging from 124 to 161 days), thereby confounding the association of AE occurrence with treatment. However, the proportions of patients reporting at least one AE at Month 1 were similar across the treatment groups (37.0, 28.4, 30.3, and 33.8% in the H40, H20, H10, and placebo groups, respectively) and the percentage of occurrences of each AE that the investigator considered of possible or probable relationship to study treatment was similar in the H 199/18 and placebo groups. The most frequently reported AEs were respiratory infection, sinusitis, flatulence, and diarrhoea. For these four adverse events, the incidence rates in all three H 199/18 treatment groups were higher than the incidence rate in the placebo group; however, the incidence rates did not appear to be related to the dose of H 199/18. The most frequently reported gastrointestinal AEs were flatulence, diarrhoea, gastritis (an endoscopy finding), gastrin serum increased, and nausea. Of these events, the incidence of gastritis, gastrin serum increased, and nausea showed a possible relationship to dose of H 199/18, with the highest incidence rates in the H40 and H20 groups (which were similar to each other), and lower rates in the H10 and placebo groups (which were similar to each other). Overall, there was little difference among the treatment groups in incidence of adverse events, serious adverse events, or discontinuations due to adverse events.

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Safety Results:

Laboratory Test Results: Mean changes in laboratory measurements were generally small and were not clinically meaningful. The largest mean changes were expected dose-related mean changes seen in serum gastrin (pg/mL): 51.3 (H40), 22.9 (H20), -5.0 (H10), and –39.5 (placebo). Among the placebo patients, all of whom had received H40, H20, or O20 in Study 172, the mean serum gastrin value at Month 1 (36.5 pg/mL) had already returned to the baseline levels recorded in Study 172. Individual changes from normal at baseline to outside normal limits at any time point after baseline were most frequently observed in serum gastrin, hemoglobin, ALAT, ASAT, serum B_{12}, and platelet counts. However, individual changes in ASAT, serum B_{12}, and platelet counts were reported with similar frequencies in the H 199/18 and placebo groups. Individual changes in serum gastrin, hemoglobin, and ALAT showed apparent dose-related trends across the H40, H20, H10, and placebo groups (44.2, 26.8, 4.3, and 1.9% of patients for serum gastrin; 17.9, 14.7, 10.7, and 1.6% of patients for hemoglobin; and 13.6, 8.7, 6.3, and 1.6% of patients for ALAT, respectively).

Vital Signs and Physical Examinations: There were no clinically meaningful changes in vital signs (blood pressure and pulse rate) or physical examinations (including weight) over the course of the study.

Gastric Biopsy Results: Gastric biopsy evaluations revealed very few non-normal ratings for chronic inflammation, intestinal metaplasia, or atrophy at either antral or fundic locations, with 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 placebo group) had atrophic gastritis at baseline. Both of these patients still had atrophic gastritis at their final visit; however, no patient had treatment-emergent atrophic gastritis. ECL cell ratings showed that 1 patient in the H10 group had micronodular hyperplasia at both the baseline and final biopsies; all other non-normal, post-baseline ECL cell ratings were either linear or simple hyperplasia. Increases (worsening) in ECL cell ratings were seen in 9.8% of H40 patients, 8.3% of H20 patients, 3.4% of H10 patients, and no placebo patients. 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 both the H40 and H20 groups than in the placebo group ($p < 0.05$); the difference between the H10 and placebo groups was not statistically significant. Maximum serum gastrin values for those patients with ECL cell increases tended to be higher than for patients without ECL cell increases.

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