2.0 SYNOPSIS

Name of Company: AstraZeneca LP	**Individual Study Table Referring to Item of the Submission:** N/A	**(For National Authority Use only)**
Name of Finished Product:	**Volume:** N/A	
Name of Active Ingredient: H 199/18	**Page:** N/A	

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

Investigator(s): Multicenter

Study Center(s): 178 investigator sites initiated; 163 investigator sites enrolled patients

Publication (reference): N/A

Studied Period (years): < 1 year (date first drug dispensed) 04 February 1999 (date last patient completed) 30 July 1999	**Phase of development:** Phase III

Objectives:

Primary Objective

1. To assess the efficacy, as defined by complete healing of erosive esophagitis, of H 199/18 40 mg qd (H40) compared to omeprazole 20 mg qd (O20) at Week 8 of treatment in subjects with erosive esophagitis.

Secondary Objectives

1. Efficacy, as defined by complete healing of erosive esophagitis, of H40 compared to that of O20 at Week 4 of treatment.
2. Complete resolution and relief of GERD symptoms of heartburn, acid regurgitation, dysphagia, and epigastric pain by H40 compared to O20 at Week 4 of treatment.
3. Time to resolution and relief of heartburn by H40 compared to O20.
4. Safety and tolerability of H40 compared to that of O20.

Methodology: This was a multicenter, randomized, double-blind, parallel-group study to evaluate the healing efficacy and safety of H 199/18 in patients with erosive esophagitis. Patients with EGD-verified erosive esophagitis (graded according to the Los Angeles Classification) were randomized into one of two treatment groups, H40 or O20, for up to 8 weeks of therapy. All patients were to be reevaluated by EGD at Week 4 of treatment and, if unhealed, return at Week 8 of treatment for their final closeout visit and EGD evaluation. Patients healed at Week 4 were considered to have completed the study as treatment successes.

Number of Patients (Planned and Analyzed):

	H40	O20
Number of Subjects Planned	1,040	1,040
Number of Subjects Enrolled	1,216	1,209
Number of Subjects Analyzed		
Efficacy: Intent-to-Treat	1,216	1,209
Efficacy: Per-Protocol	1,066	1,066
Safety	1,205	1,200

Diagnosis and Main Criteria for Inclusion: EGD-verified erosive esophagitis (Los Angeles Classification)

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Test Product, Dose and Mode of Administration, Batch or Lot Number:
H 199/18 capsules 40 mg - Lot H-1222-04-01-07 and Lot H-1222-04-01-08

Duration of Treatment: Up to 8 weeks

Reference Therapy, Dose and Mode of Administration, Batch or Lot Number:
omeprazole capsules 20 mg - Lot H-0431-13-05-06 and Lot H-0431-13-05-08
GELUSIL® Antacid tablets - Lot 02008B/105436 and Lot 01908B/105437

Criteria for Evaluation:

Efficacy: The primary efficacy parameter was the percentage of patients who exhibited healing of esophageal erosions on EGD evaluation (ie, LA Classification Grade = Not Present; no erosions present) by Week 8 of treatment. Secondary efficacy parameters were: 1) the percentage of patients who healed on EGD evaluation at Week 4 of treatment; 2) complete resolution and relief of GERD symptoms, ie, heartburn, acid regurgitation, dysphagia, and epigastric pain assessed by the investigator at Week 4 and Week 8 of treatment (relief defined as a recorded symptom of None or Mild); and 3) time to first resolution and to sustained resolution of heartburn using diary card information (resolution defined as heartburn recorded as None and sustained resolution defined as 7 consecutive days with heartburn recorded as None).

Safety: All randomized patients who received at least one dose of study drug were included in the safety population for analysis. Evaluations for adverse events were made at each post-baseline visit. Clinical laboratory evaluations were completed on fasting patients at baseline and at the final visit. Clinical laboratory tests included serum chemistry (including serum gastrin), hematology, and urinalysis. Vital signs were recorded at each visit.

Statistical Methods: Primary healing efficacy data were analyzed for intent-to-treat (ITT) and per-protocol (PP) populations. Determinations of the PP and ITT populations were set prior to unblinding the data. For the percentage of patients with healed erosive esophagitis (EE) by Week 8 (primary efficacy parameter), a log-rank test was used to assess differences between treatment groups. The primary efficacy parameter was also analyzed using a Wilcoxon test, as well as a Cochran-Mantel-Haenszel (CMH) test with stratification on baseline severity of EE (LA Classification Grade). For investigator-recorded symptoms, CMH tests stratified on baseline severity of each symptom were used to assess differences between treatment groups for resolution and relief. Diary card data were used to compare treatment groups regarding the number of days until the first resolution of heartburn (log-rank test), the number of days until sustained resolution of heartburn (log-rank test), as well as the percentage of heartburn-free days and heartburn-free nights (analysis of variance).
Adverse events, laboratory results, and vital signs data were tabulated to evaluate tolerability profiles between the two treatment groups. Laboratory measurements were also summarized according to predefined limits of change and shifts from baseline.

SUMMARY

Efficacy Results: For both the ITT and PP populations, the proportion of patients with healing of EE by Week 8 was significantly higher in the H40 group than in the O20 group ($p = 0.0001$ for both the log-rank test and Wilcoxon test). Cumulative life-table estimates of healing rates for the ITT population for the H40 and O20 groups were 81.7% and 68.7%, respectively, at Week 4, and 93.7% and 84.2%, respectively, by Week 8 (Table 10). For the PP population (Table 12), cumulative life-table estimates of healing rates for the H40 and O20 groups were 82.2% and 68.0%, respectively, at Week 4, and 93.8% and 84.4%, respectively, by Week 8.
When baseline EE severity grade (LA Classification) was taken into account (CMH test), significant differences between treatments were again seen in the proportion of patients with healing of EE in both the ITT ($p = 0.001$; Table 11) and PP populations ($p = 0.001$; Table 13) by both Week 4 and Week 8. The difference in healing rates for EE by Week 8 in the ITT population for each baseline LA Grade (ie, the difference in the percentage of patients with healing of EE in the H40 group over that in the O20 group) was 3.0%, 8.1%, 16.8%, and 16.2% for LA Grades A, B, C, and D, respectively.

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Efficacy Results: (Continued)

No clinically meaningful differences were seen in summaries of healing of EE in predefined subsets of patients by gender, age, race, *H. pylori* status, nor investigator site, although no statistical analyses were performed on these data. The results of H40 treatment were significantly better than results for O20 treatment for each of the five secondary efficacy parameters: resolution of investigator-recorded symptoms of GERD (significant for heartburn and acid regurgitation), relief of investigator-recorded symptoms of GERD (significant for heartburn and acid regurgitation), number of days to first resolution of heartburn, number of days to sustained resolution of heartburn, mean percent of heartburn-free days (24-hour period), and mean percent of heartburn-free nights.

Safety Results:

Clinical Adverse Events: The incidence of patients reporting any AE was 32.2% with H40 and 34.3% with O20. One patient (O20 group) died during the study, unrelated to study treatment. Nine patients (0.7%) who received H40 and 7 (0.6%) who received O20 had AEs that were considered serious; none of which was related to study treatment. There were 11 patients (0.9%) who received H40 and 14 (1.2%) who received O20 who were discontinued from the study and from treatment due to an AE. The most frequently reported AE was headache, which occurred in 6.2% of the patients treated with H40 and 5.8% of the patients treated with O20. The most frequently reported gastrointestinal AEs were diarrhoea, nausea, and abdominal pain. These side effects were reported at similar rates in both treatment groups.

Laboratory Safety: Mean changes from baseline were small and were comparable between the two treatment groups. The laboratory measurement that was most frequently outside predefined limits (identified by the Sponsor as potentially clinically significant) was hemoglobin, for which 13 H40 (1.1%) and 6 O20 (0.5%) patients had values below the predefined lower limit (9.5 g/dL for females and 11.5 g/dL for males). Other laboratory values were less frequently observed above or below the predefined limits and there were no clinically meaningful differences between the treatment groups in the incidence of shifts from within normal limits to above or below normal limits in individual patients' values.

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

Date of the Report: 13 December 1999