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 (20 mg), H 199/18 (40 mg) vs Placebo in Study Subjects with Symptomatic GERD

Investigator(s): Multicenter

Study Center(s): 26 investigational sites initiated; 26 investigational sites enrolled patients

Publication (reference): N/A

Studied Period (years): < 1 year (date first drug dispensed) 10 February 1999 (date last patient completed) 02 June 1999	**Phase of development:** Phase III

Objectives:

Primary Objective

To assess the efficacy, defined as complete resolution of heartburn per diary card, of H 199/18 40 mg qd (H40) compared to placebo qd, and H 199/18 20 mg qd (H20) compared to placebo qd, of 4 weeks of treatment in patients with symptomatic gastroesophageal reflux disease (sGERD).

Secondary Objectives

1. To assess the efficacy, defined as complete resolution of heartburn, of both H40 and H20 compared to placebo after 1, 2, and 4 weeks of treatment.
2. To assess the relief of heartburn in patients receiving H40 and H20 compared with patients receiving placebo after 1, 2, and 4 weeks of treatment, and for the last 7 days in the study.
3. To assess the mean severity of heartburn in patients receiving H40 and H20 compared with patients receiving placebo after 1, 2, and 4 weeks of treatment, and for the last 7 days in the study.
4. To assess the percentage of heartburn-free days for patients receiving H40 and H20 compared with patients receiving placebo after 1, 2, and 4 weeks of treatment.
5. To assess the percentage of days without nocturnal heartburn for patients receiving H40 and H20 compared with patients receiving placebo after 1, 2, and 4 weeks of treatment.
6. To assess the time to first resolution of heartburn and time to resolution of nocturnal heartburn for patients receiving H40 and H20 compared with patients receiving placebo.
7. To assess the time to sustained resolution of heartburn and time to sustained resolution of nocturnal heartburn in patients receiving H40 and H20 compared with patients receiving placebo.
8. To assess the resolution of heartburn, acid regurgitation, dysphagia and epigastric pain (per investigator rating) in patients receiving H40 and H20 compared with patients receiving placebo after 2 weeks and 4 weeks of treatment.
9. To assess the overall treatment evaluation (OTE) of patients receiving H40 and H20 compared with patients receiving placebo after 2 and 4 weeks of treatment, and the significance to the patient of any change in the OTE.
10. To assess the safety and tolerability of H40 and H20 as compared to placebo.

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Methodology: This was a placebo-controlled, randomized, double-blind, multicenter, parallel-group, 4-week, efficacy and safety study of H40 and H20 vs placebo in patients with symptomatic GERD. Patients with at least a 6-month history of heartburn episodes who were negative for erosive esophagitis (EE) by esophagogastroduodenoscopy (EGD) and who reported heartburn on at least 4 of the 7 days immediately preceding randomization were included. Patients were treated for 4 weeks with study medication, during which time daily diaries of heartburn occurrence and severity were kept by the patients. Patients returned for clinic visits at Week 2 and Week 4 to return diaries and any unused study medication, to be evaluated by the investigator for GERD symptoms and safety, and to complete the OTE questionnaire. The study was conducted in 26 centers in the continental United States. Eligible patients were randomized to one of three treatment groups—H40, H20, or placebo. GELUSIL® antacid tablets were supplied to be used at the patient's discretion (up to 6 tablets/day) as rescue medication for GERD symptoms.

Number of Patients (Planned and Analyzed):

	H 199/18 40 mg qd	**H 199/18 20 mg qd**	**Placebo qd**
Number of Patients Planned	100	100	100
Number of Patients Enrolled	123	121	124
Number of Patients Analyzed			
Efficacy: Intent-to-Treat	123	121	124
Efficacy: Per Protocol	115	117	114
Safety	122	120	123

Diagnosis and Main Criteria for Inclusion: Six-month history of heartburn episodes as evidence of GERD, no history or evidence of erosive esophagitis (by EGD), and heartburn reported on at least 4 of the 7 days preceding randomization.

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

H 199/18 capsules 40 mg	-	Lot H-1222-04-01-07
H 199/18 capsules 20 mg	-	Lot H-1189-04-01-04

Duration of Treatment: 4 weeks

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

Placebo capsules	-	Lot H-0459-06-03-07
GELUSIL® antacid tablets	-	Lots 02008B and 01908B

Criteria for Evaluation:

Efficacy: The primary efficacy variable was the percentage of patients who exhibited complete resolution of heartburn (defined as no episodes of heartburn during the last 7 days of the study, as recorded on the patient diary card). Secondary efficacy variables were: 1) the percentage of patients at Week 1, Week 2, and Week 4 who exhibited complete resolution of heartburn; 2) the percentage of patients who exhibited relief of heartburn at Week 1, Week 2, Week 4, and for the last 7 days in the study (defined as heartburn = None or Mild, but with no more than 1 episode of Mild heartburn during the last 7 days of the time period being evaluated, as recorded on the patient diary card); 3) the mean severity of heartburn at Week 1, Week 2, Week 4, and for the last 7 days in the study; 4) the percentage of heartburn-free days for patients at Week 1, Week 2, and Week 4; 5) the percentage of days without nocturnal heartburn for patients at Week 1, Week 2, and Week 4; 6) the time (in days) to first resolution of heartburn and first resolution of nocturnal heartburn; 7) the time (in days) to first sustained resolution of heartburn and first sustained resolution of nocturnal heartburn; 8) the percentages of patients with resolution of heartburn, acid regurgitation, dysphagia, and epigastric pain as rated by the investigator at Week 2 and Week 4; and 9) the Overall Treatment Evaluation by the patient, and the importance to the patient of any change in the OTE, at Week 2 and Week 4.

Safety: Adverse events and vital signs were recorded at each visit. Clinical laboratory evaluations and physical examinations were completed at baseline and at the final visit. Clinical laboratory tests included serum chemistry, hematology, and urinalysis (dipstick).

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Statistical Methods: The rate of complete resolution of heartburn for the last 7 days in the study, the primary efficacy variable, was analyzed for Intent-to-Treat (ITT) and Per Protocol (PP) populations, both of which were defined prior to unblinding the data. The ITT population included all randomized patients. The PP population included the subset of patients without certain protocol deviations that were defined prior to unblinding the data. For the primary analysis, data from the last available 7-day period on the diary card were used for all patients. A chi-square statistic was used to compare the rate of resolution of heartburn for each H 199/18 treatment group to the placebo group. Hochberg's method was used to adjust for the two comparisons of interest. Secondary efficacy variables were analyzed using only the ITT population, with no adjustment for multiple comparisons. Chi-square statistics were used for comparisons of all dichotomous response variables. A life-table approach was used to analyze the 'time to' variables; statistical comparisons were made using log-rank tests. The efficacy variables based on the mean severity of heartburn or on the percentages of days/nights without heartburn were compared using a two-way analysis of variance model, with main effects of investigator and treatment. Investigators who contribute fewer than 5 patients to an analysis were combined in a separate 'investigator' for the analysis. Overall treatment evaluation results were compared using a Wilcoxon rank-sum test.

No inferential statistics were used in the analysis of safety data. Incidence rates of adverse event occurrence were calculated by body system and preferred term. All randomized patients who received at least one dose of study medication were included in the assessment of adverse events. Descriptive statistics were calculated for baseline, final, and change from baseline values for clinical laboratory tests and vital signs. 'Shift tables' presenting the frequencies of changes from within to outside of normal limits were produced for each laboratory test. Frequencies of patients having one or more potentially clinically significant results for each laboratory test were calculated using predefined criteria.

SUMMARY

Efficacy Results: For the primary endpoint, each dose of H 199/18 was statistically significant to placebo and clinically relevant in the complete resolution of diary-recorded heartburn after 4 weeks of treatment in patients with symptomatic GERD. At Final Visit, 33.3% of H40 patients and 33.9% of H20 patients reported no heartburn compared to 13.7% of placebo patients. Similarly, each dose of H 199/18 was statistically significant to placebo and clinically relevant in the complete resolution of investigator assessed heartburn after 4 weeks of treatment in patients with symptomatic GERD. At Final Visit, 33.9% of H40 patients and 35.0% of H20 patients reported no heartburn compared to 13.2% of placebo patients. For the majority of secondary endpoints, both H 199/18 doses were statistically significant to placebo.

Safety Results:

Clinical Adverse Events (AEs): Each dose of H 199/18 was well-tolerated, with no deaths and no drug-related serious adverse events.

Clinical Laboratory Tests: There were no unexpected clinically meaningful changes in laboratory tests.

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.

Date of the Report: 24 September 1999