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):** N/A
Name of Finished Product:	**Volume:** N/A	
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Title of Study: A Multicenter, Randomized, Double-blind, Safety and Efficacy Study of H 199/18 with Clarithromycin Compared to H 199/18 for the Eradication of *Helicobacter pylori* in Subjects with Active Duodenal Ulcer or History of Duodenal Ulcer Disease.

Investigator(s): Multicenter

Study Center(s): 32 investigator sites initiated; 18 investigator sites enrolled patients

Publication (reference): N/A

Studied Period (years): 7 April 1998 (date of first patient enrolled) 8 January 1999 (date of last patient completed)	**Phase of development:** Phase III

Objectives:

Primary Objectives

1. To assess the efficacy of a 10-day treatment regimen of H 199/18 40 mg qd with clarithromycin 500 mg bid compared to H 199/18 40 mg qd in the eradication of *H. pylori* at 4 weeks post-therapy in *H. pylori* infected patients with active duodenal ulcer or history of duodenal ulcer disease.
2. To assess the safety and tolerability of a 10-day treatment regimen of H 199/18 40 mg qd with clarithromycin 500 mg bid compared to H 199/18 40 mg qd in *H. pylori* infected patients with active duodenal ulcer or history of duodenal ulcer disease.

Secondary Objectives:

1. To assess the susceptibility of *H. pylori* to clarithromycin at Baseline and at 4 weeks post-therapy.

Methodology:

This was a 38-day, multicenter, randomized, double-blind, parallel group study. The trial compared the efficacy and safety of H 199/18 40 mg qd with clarithromycin 500 mg bid to that of H 199/18 40 mg qd in the eradication of *H. pylori* at the Day 38 visit.

The study was designed to enroll approximately 125 patients. The number of planned enrolled patients was reduced to 60, as described in Protocol Amendment 2. Patients were required to have an endoscopically confirmed active DU or a history of endoscopically or radiologically documented DU within 5 years prior to enrollment. In addition, the presence of the bacterium *H. pylori* in gastric biopsies at Baseline was required for enrollment. At Baseline, presence of *H. pylori* was determined by a rapid urease test (CLOtest®) performed on an antral mucosal biopsy. Additional biopsies were collected at Baseline from the antrum and corpus for histological and microbiological confirmation of the presence of *H. pylori.* The *in vitro* culture specimens of *H. pylori* were also tested for susceptibility to clarithromycin based on agar dilution. Eligible patients were stratified according to baseline DU status (active DU or history of DU disease) and randomized to one of the following treatment groups for 10 days:

1. **H 40 qd + C 500 bid**
   H 199/18 40 mg qd + clarithromycin 500 mg bid (45 planned patients)
2. **H 40 qd**
   H 199/18 40 mg qd + clarithromycin placebo bid (15 planned patients)

All patients were given GELUSIL® antacid to take as needed. At each office visit, the investigators assessed the patients' upper gastrointestinal (GI) symptoms.

At the End of Study/Day 38 visit, ulcer status was assessed endoscopically and the status of *H. pylori* infection was assessed by CLOtest®, histology, and culture through biopsy samples. *In vitro* culture testing of *H. pylori* susceptibility to clarithromycin was also performed at the Day 38 visit by agar dilution. Adverse events (AEs) were recorded throughout the study. Routine laboratory safety tests and vital sign assessments were performed at Screening/Baseline, Day 11 and Day 38 visits.

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Number of Patients (Planned and Analyzed):	**H 40 qd + C 500 bid**	**H 40 qd**
Number of Patients Planned (per Protocol Amendment 2)	45	15
Number of Patients Enrolled	51	17
Number of Patients Analyzed:		
Efficacy Per-Protocol (# evaluable)	47	15
H. pylori eradication at Day 38 visit	44	15
DU healed by Day 38 visit	32	11
Efficacy Intention-to-Treat (# evaluable)	50	16
H. pylori eradication at Day 38 visit	50	16
DU healed by Day 38 visit	34	12
Safety Analysis	51	17

Diagnosis and Main Criteria for Inclusion: Males and females (either postmenopausal, surgically sterilized or on contraception), 18 to 75 years of age with *H. pylori* infection at Baseline indicated by a positive rapid urease test (CLOtest®), and one or more DU(s) ≥0.5 cm in diameter confirmed by endoscopy (EGD) or a history of at least one endoscopically or radiologically documented DU within the last 5 years.

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

H 199/18 40 mg oral capsules	Bulk lot # H-1222-04-01-06; Packaging lot # SH-QBE-0042-01
Clarithromycin 250 mg oral tablets	Bulk lot # H-1031-04-01-01; Packaging lot # SH-QBE-0042-01
Clarithromycin placebo tablets	Bulk lot # H-1147-02-01-03; Packaging lot # SH-QBE-0042-01
GELUSIL oral tablets	Bulk lot # 01497B; Packaging lot # AM-175

Duration of Treatment: 10 days

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

Criteria for Evaluation:

Efficacy: The primary analysis of this data was performed using a "per-protocol" patient population. An "intention-to-treat" patient population was also analyzed for some efficacy endpoints. Patients were included in the per-protocol analysis if they had *H. pylori* infection documented at Baseline, had at least one endoscopically verified DU ≥ 0.5 cm in diameter at Baseline or had a documented history of DU disease within the past 5 years, and did not violate the protocol in other ways such as by not taking an appropriate amount of the prescribed study medication. For the intention-to-treat analysis, patients were considered to be evaluable as long as they had *H. pylori* infection documented at Baseline, had at least one documented DU at Baseline or had a documented history of DU disease, and took at least one dose of study medication. (See Section 9.7.1.2.1. in the Clinical Study Report for more details about the evaluability criteria).

Safety: All 68 of the enrolled patients were included in the assessment of AEs. For the analysis of laboratory data or physical exam data, only patients who took at least one dose of study medication and had laboratory tests performed or had physical exam measurements taken were included in the analyses of those safety data.

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Statistical Methods: A logistic regression model was used to analyze the proportion of patients with *H. pylori* eradication at the Day 38 visit. Baseline DU status (active DU or history of DU disease) was included in the model as a covariate, and a test for baseline ulcer status by treatment group interaction was performed. A logistic regression model was also used to analyze the proportion of patients with a healed DU by the Day 38 visit (only for patients with an active DU at Baseline). The proportion of patients experiencing improvement of their upper GI symptoms from the Screening/Baseline visit to the Day 11 and Day 38 visits was analyzed using a Cochran-Mantel-Haenszel test controlling for baseline DU status for each individual symptom assessed. The proportion of patients experiencing no symptoms or mild symptoms at each post-treatment timepoint was also analyzed using a Cochran-Mantel-Haenszel test. A significance level of 0.050 was used for statistical comparisons and 0.100 was used to test for interaction.

For the analysis of safety data, Fisher's Exact test was used to compare the proportions of patients in each treatment group with AEs and the distributions of laboratory data results according to reference ranges. Fisher's Exact test was also used for the analysis of demographic and other baseline patient characteristic data.

SUMMARY

EFFICACY RESULTS:

Per-protocol results:

For the per-protocol analysis, *H. pylori* eradication rates at the Day 38 visit were significantly higher in the H 40 qd + C 500 bid group (22/44 patients or 50%) than in the H 40 qd group (0/15 patients). In addition, the proportion of patients with a healed DU by the Day 38 visit was significantly higher in the H 40 qd + C 500 bid group (26/32 patients or 81%) than in the H 40 qd group (5/11 patients or 45%) (for patients with an active DU at Baseline). For both treatment groups combined, 88% of the patients who had *H. pylori* eradicated at the Day 38 visit also had a healed DU by the Day 38 visit compared to only 57% of the patients who were still *H. pylori* infected at the Day 38 visit (for patients with an active DU at Baseline).

Intention-to-treat results:

For the intention-to-treat analysis, the *H. pylori* eradication rate at the Day 38 visit was significantly higher in the H 40 qd + C 500 bid group (23/50 patients or 46%) than in the H 40 qd group (0/16 patients), which was a consistent result to the per-protocol analysis. However, there was no significant difference between treatment groups for the proportion of patients with a healed DU by the Day 38 visit (26/34 patients or 76% in the H 40 qd + C 500 bid group, 6/12 patients or 50% in the H 40 qd group) (for patients with an active DU at Baseline).

Susceptibility results:

All available *H. pylori* isolates were tested for susceptibility to clarithromycin using agar dilution. At Baseline for both treatment groups combined, 24% of the patients (12 of 50 patients with baseline susceptibility results) had *H. pylori* isolates classified as resistant to clarithromycin, and 76% (38 of 50 patients) had *H. pylori* isolates susceptible to clarithromycin. Of these 38 baseline susceptible isolates, 5 isolates were resistant to clarithromycin, 9 isolates were still susceptible to clarithromycin, and 24 isolates had no susceptibility results for clarithromycin at the Day 38 visit. For the 12 *H. pylori* isolates classified as resistant to clarithromycin at Baseline, none were eradicated at the Day 38 visit. For the 38 *H. pylori* isolates classified as susceptible to clarithromycin at Baseline, 16 isolates were eradicated, 19 isolates were not eradicated, and 3 isolates did not have eradication results at the Day 38 visit.

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SUMMARY (Cont .)

SAFETY RESULTS:

A total of 37 of the 68 patients (54%) who took at least one dose of study medication reported having at least one AE throughout the 38-day study period: 53% of the patients (27 of 51) in the H 40 qd + C 500 bid group, 59% of the patients (10 of 17) in the H 40 qd group. Only one patient in this study had an AE considered to be serious. This patient in the H 40 qd + C 500 bid group was an 80 year old female who died of cardiac arrest during the study period (death unrelated to study medication per investigator). Only 2 patients discontinued from the study due to an AE (both in the H 40 qd + C 500 bid group, this includes the patient who died as described above). There were no significant differences between the treatment groups with respect to the proportion of patients with at least one AE, with at least one drug related AE, or who discontinued the study due to an AE. There were no clinically meaningful mean changes from Baseline at the Day 11 or Day 38 visits for any of the laboratory test results. There were no significant differences between the treatment groups in the distribution of laboratory results classified according to reference ranges (within, above or below reference range) for any laboratory test result.

Date of the Report: 13 July 1999