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
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Title of Study: A Multicenter, Randomized, Double-blind, Safety and Efficacy Study of H 199/18 with Amoxicillin plus 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): 35 investigator sites initiated; 22 investigator sites enrolled patients

Publication (reference): N/A

Studied Period (years): 23 March 1998 (date of first patient enrolled) 10 March 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 amoxicillin 1000 mg bid plus 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 amoxicillin 1000 mg bid and 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 amoxicillin and clarithromycin at Baseline and at 4 weeks post-therapy.

Methodology:

This was a 38-day, multicenter, randomized, double-blinded, parallel group study. The study compared the efficacy and safety of H 199/18 40 mg qd in combination with amoxicillin 1000 mg bid and clarithromycin 500 mg bid to that of H 199/18 40 mg qd. The primary efficacy endpoint was eradication of *H. pylori* at the Day 38 visit.

The study was designed to enroll approximately 125 patients. The study was stopped when 113 patients were enrolled. The reduction in the number of patients was necessary because patient enrollment was slower than anticipated. The FDA was consulted and agreed to the proposed reduction of the sample sizes. 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 the susceptibility to amoxicillin and 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 + A 1000 bid + C 500 bid**
   H 199/18 40 mg qd + amoxicillin 1000 mg bid + clarithromycin 500 mg bid
   (90 planned patients)
2. **H 40 qd**
   H 199/18 40 mg qd (35 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.

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Methodology: (cont.)

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 amoxicillin and 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.

Number of Patients (Planned and Analyzed):	**H 40 qd + A 1000 bid + C 500 bid**	**H 40 qd**
Number of Patients Planned	90	35
Number of Patients Enrolled	85	28
Number of Patients Analyzed:	71	
Efficacy Per-Protocol (# evaluable)	67	23
H. pylori eradication at Day 38 visit	60	22
Duodenal ulcer healed by Day 38 visit	74	22
Efficacy Intention-to-Treat (# evaluable)	74	24
H. pylori eradication at Day 38 visit	66	24
Duodenal ulcer healed by Day 38 visit	85	24
Safety Analysis		28

Diagnosis and Main Criteria for Inclusion: Males and females (either postmenopausal, surgically sterilized or on contraception), 18 years 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-0043-01
Clarithromycin 250 mg oral tablets	Bulk lot # H-1031-04-01-03; Packaging lot # SH-QBE-0043-01
Clarithromycin placebo tablets	Bulk lot # H-1147-02-01-03; Packaging lot #

SH-QBE-0043-01	
Amoxicillin 500 mg oral tablets	Bulk lot # H-1034-02-01-04; Packaging lot # SH-QBE-0043-01
Amoxicillin placebo tablets	Bulk lot # H-1081-02-01-01; Packaging lot # SH-QBE-0043-01
GELUSIL oral tablets	Bulk lot # 00897B; Packaging lot # AM-176

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 these 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 of the 113 enrolled patients took at least one dose of study medication and were included in the assessment of AEs. For the analysis of laboratory data or physical examination data, only patients who took at least one dose of study medication and had laboratory tests performed or had physical examination measurements taken were included in the analyses for 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 + A 1000 bid + C 500 bid group (57/67 patients or 85%) than in the H 40 qd group (1/22 patients or 5%). For patients with an active DU at Baseline, there was no significant difference between the treatment groups with respect to the proportion of patients with a healed DU by Day 38 visit (in the H 40 qd + A 1000 bid + C 500 bid group: 34/60 patients or 57%; in the H 40 qd group: 12/22 patients or 55%). For both treatment groups combined, 58% 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 52% of the patients who were still *H. pylori* infected at the Day 38 visit (for patients with an active DU at Baseline). No statistical comparison was performed.

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 + A 1000 bid + C 500 bid group (58/74 patients or 78%) than in the H 40 qd group (1/24 patients or 4%). However, for patients with an active DU at Baseline, there was no significant difference between the treatment groups in the proportion of patients with a healed DU by the Day 38 visit (in the H 40 qd + A 1000 bid + C 500 bid group: 35/66 patients or 53%; in the H 40 qd group: 13/24 patients or 54%).

Susceptibility results:
All available *H. pylori* isolates were tested for susceptibility to amoxicillin and clarithromycin using agar dilution. There were no patients in this study who had an *H. pylori* isolate which had an amoxicillin MIC value > 0.25 mcg/mL. All amoxicillin MIC values, both at Baseline and the Day 38 visit, were classified as susceptible to *H. pylori*.

At Baseline for both treatment groups combined, 15% of the patients (12 of 82 patients with Baseline susceptibility results) had *H. pylori* isolates resistant to clarithromycin, and 85% of the patients (70 of 82 patients) had *H. pylori* isolates susceptible to clarithromycin. Of these 70 Baseline susceptible isolates, 2 isolates were resistant to clarithromycin, 12 isolates were still susceptible to clarithromycin, and 56 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, 6 isolates were eradicated at the Day 38 visit. For the 70 *H. pylori* isolates classified as susceptible to clarithromycin at Baseline, 44 isolates were eradicated, 21 isolates were not eradicated, and 5 isolates did not have eradication results at the Day 38 visit.

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SUMMARY (CONT.)

SAFETY RESULTS:

A total of 41 of the 113 patients (36%) who took at least one dose of study medication reported having at least one AE throughout the 38-day study period: 35% of the patients (30 of 85) in the H 40 qd + A 1000 bid + C 500 bid group, 39% of the patients (11 of 28) in the H 40 qd group. There was 1 patient who had an AE considered to be serious. This patient was in the H 40 qd group, and the serious AE was considered to be unlikely related to the study drug. Only 2 patients discontinued from the study due to an AE (1 patient in each treatment group). There were no significant differences between the treatment groups with respect to the proportion of patients with at least one AE, with a serious 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.

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