2.0 SYNOPSIS

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

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 with Clarithromycin for the Eradication of *Helicobacter pylori* in Subjects with Active Duodenal Ulcer or History of Duodenal Ulcer Disease

Investigator(s): Multicenter

Study Center(s): 133 investigator sites initiated; 85 investigator sites enrolled patients

Publication (reference): N/A

Studied Period (years): 5 March 1998 (date of first patient enrolled) 11 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 with clarithromycin 500 mg bid 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 with clarithromycin 500 mg bid 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 in combination with clarithromycin 500 mg bid. The primary efficacy endpoint was eradication of *H. pylori* at the Day 38 visit.

The study was designed to enroll approximately 500 patients. 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 (250 planned patients)
2. **H 40 qd + C 500 bid**
   H 199/18 40 mg qd + amoxicillin placebo bid + clarithromycin 500 mg bid (250 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.

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	
Name of Active Ingredient: H 199/18	**Page:** N/A	

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 + C 500 bid**
Number of Patients Planned	250	250
Number of Patients Enrolled	264	251
Number of Patients Analyzed:		
Efficacy Per-Protocol (# evaluable)	211	196
H. pylori eradication at Day 38 visit	196	187
Duodenal ulcer healed by Day 38 visit	156	144
Efficacy Intention-to-Treat (# evaluable)	233	215
H. pylori eradication at Day 38 visit	233	215
Duodenal ulcer healed by Day 38 visit	185	168
Safety Analysis	263[a]	250[a]

[a] 2 patients did not take any study medication and were not included in the safety analysis.

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-0041-01
	Bulk lot # H-1222-04-01-07; Packaging lot # SH-QBE-0041-02
Clarithromycin 250 mg oral tablets	Bulk lot # H-1031-04-01-01; Packaging lot # SH-QBE-0041-01
	Bulk lot # H-1031-04-01-04; Packaging lot # SH-QBE-0041-02
Amoxicillin 500 mg oral tablets	Bulk lot # H-1034-02-01-04; Packaging lot # SH-QBE-0041-01
	Bulk lot # H-1034-02-01-04; Packaging lot # SH-QBE-0041-02
Amoxicillin placebo tablets	Bulk lot # H-1081-02-01-01; Packaging lot # SH-QBE-0041-01
	Bulk lot # H-1081-02-01-02; Packaging lot # SH-QBE-0041-02
GELUSIL oral tablets	Bulk lot # 01497B; Packaging lot # AM-174

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.).

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	
Name of Active Ingredient: H 199/18	**Page:** N/A	

Criteria for Evaluation: (cont.)

Safety: A total of 513 of the 515 enrolled patients were included in the assessment of AEs. Two patients who were documented as taking no study medication were excluded from all safety analyses. 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.

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 (164/196 patients or 84%) than in the H 40 qd + C 500 bid group (103/187 patients or 55%). 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: 117/156 patients or 75%; in the H 40 qd + C 500 bid group: 95/144 patients or 66%). For both treatment groups combined, 76% 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). 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 (179/233 patients or 77%) than in the H 40 qd + C 500 bid group (112/215 patients or 52%). 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: 127/185 patients or 69%; in the H 40 qd + C 500 bid group: 104/168 patients or 62%).

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	
Name of Active Ingredient: H 199/18	**Page:** N/A	

SUMMARY (CONT.)
EFFICACY RESULTS: (CONT.)
Susceptibility results:
All available *H. pylori* isolates were tested for susceptibility to amoxicillin and clarithromycin using agar dilution. There was only 1 patient in this study who had an *H. pylori* isolate which had an amoxicillin MIC value > 0.25 mcg/mL (classified as "not defined"). This *H. pylori* isolate had an amoxicillin MIC value of 0.5 mcg/mL at baseline.

At Baseline for both treatment groups combined, 13% of the patients (42 of 313 patients with baseline susceptibility results) had *H. pylori* isolates resistant to clarithromycin, <1% (2 of 313 patients) had *H. pylori* isolates classified as intermediate for clarithromycin, and 86% of the patients (269 of 313 patients) had *H. pylori* isolates susceptible to clarithromycin. Of these 269 baseline susceptible isolates, 20 isolates were resistant to clarithromycin, 1 isolate was classified as intermediate for clarithromycin, 5 isolates were still susceptible to clarithromycin, and 243 isolates had no susceptibility results for clarithromycin at the Day 38 visit. For the 2 baseline isolates classified as intermediate, 1 isolate was again classified as intermediate and 1 isolate had no result at the Day 38 visit. For the 42 *H. pylori* isolates classified as resistant to clarithromycin at Baseline, 11 isolates were eradicated at the Day 38 visit. For the 269 *H. pylori* isolates classified as susceptible to clarithromycin at Baseline, 190 isolates were eradicated, 62 isolates were not eradicated, and 17 isolates did not have eradication results at the Day 38 visit.

SAFETY RESULTS:
A total of 299 of the 513 patients (58%) who took at least one dose of study medication reported having at least one AE throughout the 38-day study period: 60% of the patients (159 of 263) in the H 40 qd + A 1000 bid + C 500 bid group, 56% of the patients (140 of 250) in the H 40 qd + C 500 bid group. There were 4 patients in this study who had an AE considered to be serious (2 patients in the H 40 qd + A 1000 bid + C 500 bid group, and 2 patients in the H 40 qd + C 500 bid group). All of the serious AEs were considered to be unlikely related to the study drug. Only 19 patients discontinued from the study due to an AE (10 in the H 40 qd + A 1000 bid + C 500 bid group, 9 in the H 40 qd + C 500 bid 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, or who discontinued the study due to an AE. The proportion of patients with an AE classified as drug related by the investigator was significantly higher in the H 40 qd + A 1000 bid + C 500 bid group (91 of 263 patients or 35%) than in the H 40 qd + C 500 bid group (66 of 250 patients or 26%). 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.

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	
Name of Active Ingredient: H 199/18	**Page:** N/A	

Date of the Report: 28 September 1999