TABLE 55
NDA 21-153
Number of Patients Enrolled in Clinical Trials

	n
Phase I subjects/patients	658
Phase II/III	4277[a]
• Healing of EE (Active-controlled) (includes Phase III [up to 8 weeks] studies 172, 173 and 174)	
• Placebo-controlled maintenance (studies 177 and 178) [6 months]	519[b]
• Uncontrolled, L-T Safety (Study 179)	807
• Placebo-controlled s-GERD (Studies 225 and 226) [4 weeks]	470c
• Active-controlled s-GERD (Studies -0009, -0011 and -0021) [4 weeks]	1530c

		n
a) Distributed as follows:	H40	1229
	H20	1240
	H10	1808
b) Distributed as follows:	H40	173
	H20	179
	H10	167
c) Distributed as follows:	H40	1014
	H20	986

B. Safety Data From Healing of EE Studies

1) Deaths and Other SAEs

Across the 3 healing of EE trials, 1 of the 2,469 patients receiving H and 1 of the 1,808 patients treated with 020 died. These deaths were considered by the investigator as unlikely to be related to test medication; each was the consequence of an underlying disease state.

SAEs were considered by the investigators as unlikely to be related to test medication.

2) Adverse Events

- In the healing of EE studies, the proportion of patients with ≥1 AE, ≥ 1 related AE, D/C due to an AE or ≥ 1 SAE was similar between H 199/18 and omeprazole (20 mg qd). With H, there was no dose response. The body systems with the highest reported incidence of AEs were the G.I. tract (H=22.6%; O=22.1%) and the CNS (H=11.1%; O=8.5%; primarily

headache). For all groups, the most common G.I. AEs were diarrhea, abdominal pain, nausea and flatulence.

The distribution of treatment related AEs was:

	%
H40	22.1%
H20	18.6%
O20	19.0%

Headache was the most common treatment-related AE in the healing of EE studies.

There were no differences in the proportion of patients experiencing AEs as a function of gender (M,F), age (<66y; ≥65y), age of females (<45y; ≥45 y) or race.

3) **Discontinuations Due to AEs**

With H (40 or 20) and O (20), headache, diarrhea, nausea and abdominal pain were the AEs most frequently resulting in early discontinuation.

4) **Changes in Clinical Laboratory Tests, Vital Signs or Body Weight**

With the exception of the expected, dose-related mean increases in serum gastrin (see below), mean changes in laboratory tests, vital signs or body weight were similar among the treatment groups and of no clinical concern.

C. **Safety Data From s-GERD Studies**

Whether the safety data originated from placebo-comparison or omeprazole comparison studies, in s-GERD studies, the safety profile seen with H40 and H20 was consistent with that seen with O20. There were no clinically meaningful differences in AEs, clinical laboratory data (except for the expected increases in serum gastrin, see below), vital signs or body weight.

D. **Safety Data From Maintenance of Healing of EE Studies**

1) **Deaths and Other SAEs**

- None of the 688 patients treated for up to 6 months in the two completed maintenance of healing of EE trials died.

- The distribution of SAEs was:

H40 mg qd [n=4]	H20 mg qd [n=8]	H10 mg qd [n=2]

The relationship of all of these events to test medication was unlikely.

2) **Adverse Events**

- Across both studies, the proportion of patients who reported one or more AEs, including events considered by the investigator to be unrelated to test medication, was comparable among the **H** treatment groups but lower in the placebo group. The proportion of H-treated patients reporting AEs that were considered to be possibly or probably related to test medication was similar to that with placebo.

	H40	H20	H10	PL
One or More AE	(58.4%)	(54.7%)	(53.3%)	(44.4%)
POSS/PROB Related to Test Med.	(23.1%)	(21.8%)	(20.4%)	(20.7%)

- Flatulence and "gastritis" were the only treatment-related AEs reported by 3% or more of the patients exposed to **H** in the two maintenance of healing of EE trials.

The AE profile of H 199/18 was generally similar in the various subgroups distinguished by gender, age or race.

3) **Discontinuation Due to AEs**

The proportion of patients who discontinued study treatment as a result of an AE was comparable in the H40 and the H20 groups, lower in the H10 and PL groups:

H40	H20	H10	PL
(5.2%)	(4.5%)	(1.8%)	(2.4%)

Abdominal pain, epigastric pain, and flatulence were the most frequent treatment-limiting AEs in the H 199/18 dose groups.

4) **Changes in Clinical Laboratory Tests, Vital Signs, or Body Weight**

With the exception of the observed change in serum gastrin (see below) there was no indication that treatment with H 199/18 for up to 6 months had any clinically meaningful effects on laboratory values, systolic or diastolic blood pressure, pulse rate, or body weight.

E. Uncontrolled, Long-Term Safety (Study 179)

1) Highlights of Results of Safety Evaluations

A total of 807 patients with healed EE were enrolled in this L-T (12-month) safety trial, where all patients received H40.

- ca. 38% of the treated patients were female; 94.4% were Caucasian; 11.6% were ≥65 y of age or older and 2.4% were 75 y of age or older.

- 74.7% [n=603] completed this 12-month study.

- The mean (SD) duration of exposure to H40 was 297.4 (113.5) days (median=347 days).

- One patient died 77 days after D/C test medication due to pancreatic cancer.

  Patient 741/005, a 56-y-old F with healed EE after 32 days of treatment with H20 had a history of chronic shortness of breath and fibrous tumors. A biopsy of a scalp lesion revealed adenocarcinoma, that proved to be metastatic. Chemotherapy began on Day 153. Pancreatic cancer was diagnosed on Day 121. The patient was withdrawn from the trial on Day 153 and died on Day 230. This death was unlikely related to test medication.

- 5.4% (n=44) of the patients in this study experienced a SAE, all considered unlikely related to test medication; 11 patients discontinued treatment with H40 due to their SAE. Overdose, reported as a SAE for 9 patients, was not accompanied by adverse effects.

- 78.3% of the patients reported one or more AEs. The most frequently reported AEs over the entire 12-month study period were:

  respiratory infection (13.0%)
  headache (10.3%)
  sinusitis (9.8%)
  diarrhea (9.4%)
  abdominal pain (9.3%)
  accident and/or injury (7.2%)
  nausea (6.1%) and
  back pain (5.9%)

- 23.8% of the AEs were considered by the investigator to be possibly or probably related to test medication.

- 7.6% (n=61) discontinued from the study due to AEs.

- Diarrhea, abdominal pain, flatulence and headache were the only treatment-related AEs reported by 3% or more of the patients.

- Most patients who experienced side effects did so within the first 3 months of therapy. There was no indication of the late emergence of any AE with prolonged H40 exposure.

- The AE profile of H 199/18 with prolonged exposure of up to 12 months did not vary considerably as a function of gender, age or race.

- With the exception of the expected changes in serum gastrin (see below), there were no clinically relevant mean changes from baseline in clinical laboratory parameters, systolic and diastolic blood pressure, pulse rate, or body weight.

	Serum gastrin concentration (pg/ml) [n=723][a]
Baseline	77.78 (65.06)
Change from Baseline[b]	123.08 (124.03)

a) Includes all patients with both a baseline and at least one post-baseline measurement.
b) Averaged are the highest post-baseline measurement.

The reviewer agrees with the sponsor's conclusion. Daily administration of H40 for up to 12 months in patients with healed EE was well-tolerated and safe.

2) Gastritis Ratings and ECL Cell Evaluations

i) ECL Cell Ratings

The frequencies of ECL cell scores at baseline and final biopsies are displayed in Table 56.

- At the baseline biopsy, >98% of the patients had normal ECL ratings.

  11 (1.4%) had a baseline ECL rating other than normal. Of these,
  6 had simple hyperplasia (SH)
  1 had linear hyperplasia (LH)
  4 had micronodular hyperplasia (MNH)

- At the final biopsy (6.5%) had non-normal ECL cell ratings. Of these,

  39 had simple hyperplasia
  2 had linear hyperplaasia
  1 had micronodular hyperplasia

TABLE 56
Uncontrolled L-T Safety Study 179
ECL Cell Ratings and Baseline and Final Biopsies

	H199/18 40 mg qd	
ECL Cell Ratings	**Baseline [n=807]**	**Final Biopsy [n=765]**
Missing	67	153
Normal	98.5%	93.6%
SH	0.8%	6.0%
LH	0.1%	0.3%
MNH	0.5%	0.2%
Reviewer's Table		

These findings are not unexpected. In all instances, these findings were limited to simple, linear, or micronodular hyperplasia. Several patients that had MNH at baseline had a normal ECL cell rating at the final biopsy.

ii) Chronic Inflammation (Table 57)

At baseline, the majority of patients had a maximum chronic inflammation rating of NONE for both the central (90.8%) and fundic biopsy sites (89.3%); these percentages actually increased at the Final Biopsy (94.9% and 94.7%, respectively).

TABLE 57
Uncontrolled L-T Safety Study 179
Change from Baseline in Chronic Inflammation Ratings

	H 199/18 40 mg qd	
	Antral Biopsy Site [n=807]	**Fundic Biopsy Site [n=807]**
Unable to determine	n=150	n=146
Increase (worsening)	3.2%	3.0%
No Change/Decrease	96.8%	97.0%
Reviewer's Table		

iii) Atrophy

At baseline, the majority of patients had a maximum atrophy rating of NONE for both the antral (97.4%) and fundic (98.1%) sites. In addition, 98% of the patients who received L-T treatment

with H40 had a maximum atrophy rating of NONE at the Final Biopsy for antral (98.4%) and fundic (98.5%) biopsy sites. Approximately 98% of the patients receiving L-T therapy with H40 had a maximum intestinal metaplasia rating of NONE at baseline biopsy for both the antral and fundic sites (98.0% and 98.9%, respectively). In addition, 98.8% of the patients had a maximum intestinal metaplasia rating of NONE at the Final Biopsy for both the antral and fundic sites.

vi) Summary of Gastritis Evaluations

The evaluations under ii) through iv) above showed that the number of improvements in gastritis rating from Baseline to Final Biopsy was equal to or greater than the number of ratings that worsened. There were no apparent age, gender or race differences in the occurrence of gastritis.

v) Atrophic Gastritis

All patients with moderate to severe atrophy or intestinal metaplasia had their biopsies evaluated for atrophic gastritis. Patients with no more than MILD atrophy or intestinal metaplasia at any location were assumed to be negative for atrophic gastritis.

- 8 biopsy samples in 5 patients were initially classified as atrophic gastritis; 3 biopsy samples in 2 of the 807 patients treated with H40 met the criteria for atrophic gastritis. Of these 2, one (Pt. 553/001) had atrophic gastritis at both the baseline and final visit. One (Pt. 500/001) had treatment-emergent atrophic gastritis (<0.1%). The reviewer agrees with the sponsor statement that these observations are consistent with the lack of any demonstrated relationship between the clinical use of H 199/18 and gastric carcinogenesis.

F. Summary Finding on Changes of Serum Gastrin Concentration Across Clinical Trials in NDA 21-153

Mean serum gastrin concentrations (pg/ml) at baseline, mean maximum post-baseline values, mean maximum change from baseline, and shift Tables for all patients relative to their baseline values were evaluated for each study submitted by the sponsor for each sought indication. In this section of the ISS, the data are analyzed based on maximum post-baseline results and whether the baseline values were <100 pg/ml or ≥100 pg/ml. The results of these evaluations are summarized as follows.

- Across the H 199/18 trials, gastrin serum concentrations exhibited high interpatient and intrapatient variability.

- There were dose-related mean increases within the first month of treatment. Since the changes of interest are those persisting L-T, serum gastrin concentration in the one year L-T safety trial (No. 179) are summarized in **Table 58**. From these data, the conclusion is reached that at each time point as well as across the entire study period, serum gastrin concentrations were generally increased following treatment with H40. **These increased values could reach ≥300 mg in 13% of the patients whose values were <100 pg/ml at**

baseline and **in 44% of those with serum gastrin values of ≥100 pg/ml at baseline**. Some of these individual serum gastrin changes appear to be clinically meaningful since they seem to be approaching serum gastrin concentrations found in Zollinger-Ellison syndrome patients.

TABLE 58
Number (Proportion=%) of Patients Experiencing Shifting of Serum Gastrin Concentration (pg/ml) in Uncontrolled, L-T Safety Study 179
H 199/18 40 mg [n=807]

Baseline Serum Gastrin Value	Maximum Post-baseline Result for Serum Gastrin (pg/ml)				
	Missing	<100	100-199	200-299	≥300
Missing	5	15	25	12	10
< 100 pg/ml	14	167 (29.9%)	218 (39.1%)	102 (18.3%)	71 (12.7%)
≥100 pg/ml	3	14 (8.5%)	30 (18.2%)	48 (29.1%)	73 (44.2%)
Depicted are shifts in results between baseline and the maximum post-baseline result.					

NOTE: The above displayed data would argue for the use of doses of NEXIUM lower than 40 mg per day because we do not know the long-term consequences of hypergastrinemia in at least some of the patients administered this PPI at this dose.

X. SUMMARY OF BENEFITS VS RISKS

Esomeprazole is a PPI of proven efficacy for the three indications being sought by the sponsor: short-term healing of erosive esophagitis, maintenance of healing of erosive esophagitis and treatment of s-GERD. Esomeprazole is also safe and well tolerated. Both the efficacy as well as the safety profile of esomeprazole are very similar (and in some instances identical) to omeprazole, a PPI of proven efficacy and safety.

It is important to point out that in order to determine whether one compound is superior to another, these drugs need to be tested at comparable amounts: H20 vs O 20; H40 vs O 40. The sponsor's comparisons of H40 vs O 20 do not yield valid conclusions about the superiority of H over O, although these comparisons are adequate to demonstrate that H is active in the assessed indications. Therefore, the sponsor's conclusion that H 199/18 has been shown to provide a significant clinical advance over omeprazole in the first-line treatment of patients with acid-related disorders **is not supported by data**.

Specifically, there are no scientific basis for the sponsor's statement that compared to omeprazole, H 199/18 offers a faster and improved resolution of heartburn symptoms and higher rates of healing in the treatment of erosive esophagitis. The two compounds are comparable in

their efficacy for this indication. Like omeprazole, H 199/18 is highly effective in the maintenance of healing of erosive esophagitis but there are no side-by-side studies to assess comparative efficacy of these two drugs in this indication. Although H 199/18 provides predictably and reproducibly higher rates of symptom resolution than placebo within 4 weeks in patients with s-GERD, these effects are very similar if not identical to those seen with omeprazole.

The reviewer agrees with the sponsor's statement that clinical experience in H 199/18, involving >5000 patients and subjects, indicates that this PPI shares the same benign safety profile of omeprazole. This safety and tolerability profile is not unexpected since H 199/18 is the S-enantiomer of omeprazole. These conclusions are supported by comprehensive quantitative and qualitative evaluations of AEs, clinical laboratory findings, vital sign measurements and results of physical examination. In those trials where omeprazole was used as a comparator, the safety profile of the two drugs was similar. However, for both PPIs, distant safety (>20 y continuous administration) as determined by sustained hypergastrinemia and sustained atrophic gastritis in the presence of *H. pylori* infection, is still unsettled.

XI. FINANCIAL DISCLOSURE (21 CFR Part 54)

Financial information was provided for the adequate and well-controlled studies for the requested indications:

	Study Nos.
Healing of EE	172, 173 and 174 (all 3 U.S. studies)
Maintenance of Healing of EE	177 and 178 (all 2 U.S. studies)
Treatment of s-GERD	225 and 226 (U.S. studies) SH-QBE-009, -0011 and -0021 (non-US studies)

These studies, except 225 and 226, were completed prior to 2 February 1999. According to the sponsor, the certification for these studies is subject to the revisions in the requirements for financial disclosure set forth by FDA in the Federal Register and Regulations, 31 December 1998 (volume 63, Number 251), pages 72171 through 72181. Through due diligence, the sponsor determined that there were no disclosable financial interests. Therefore, FDA Form 3454 was provided along with the list of investigators for these studies (sponsor's Attachment A).

Studies 225 and 226 were completed after 2 February 1999. For these trials financial information was collected regarding the financial interests described in 21 CFR § 54.4(a)(3)(i) compensation affected by the outcome of clinical studies, 54.4(a)(3)(ii) significant payments of other sorts, 54.4(a)(3)(iii) proprietary interest in the tested product, and 54.4(a)(3)(iv) significant equity interest in Merck & Co., Inc. or Astra AB. Through due diligence, it was determined that there were no disclosable financial interests for outcome-based compensation, significant payments, or proprietary interests for studies 225 and 226. Therefore, Form FDA 3454 was provided along with the list of investigators for these studies (sponsor's Attachment B).

According to the sponsor, there were eight investigators (two principal and six subinvestigators at seven centers) for Study 225 and six investigators (two principal and four subinvestigators at five centers) for Study 226 who reported significant equity interests. Per 21 CFR § 54.4(a)(3)(v), the steps taken by the study sponsor to minimize any potential bias for these studies were adequate. These steps included: 1) randomization; 2) a double-blind approach; and 3) the fact that both studies were multicenter. An appropriate randomization process precluded any influence the investigator may have on which treatment would be assigned to a given patient. As all treatment assignments were blinded to both investigators and patients, this approach minimized biasing the results in favor of any given treatment. Study 225 included 26 investigational sites, whereas 226 included 27. In addition, in these studies, no center was permitted to randomize more than 24 patients. Form FDA 3455 was provided along with the list of investigators for studies 225 and 226 in sponsor's Attachment C.

XII. RECOMMENDATIONS FOR REGULATORY ACTION

NDA 21-153 for NEXIUM™ (esomeprazole magnesium; H 199/18), the S-enantiomer of omeprazole, submitted for the following three indications, should be approved.

1. **Healing of erosive esophagitis**. The recommended dose is 20 mg once-a-day. Treatment duration should be up to 8 weeks.

   This recommendation is based on results of studies 172, 173, 174, and 222.

2. **Maintenance of healing of erosive esophagitis**. The recommended dose is 20 mg once-a-day. Treatment duration is ——— the randomized clinical trials assessed efficacy at 6 months ———

   This recommendation is based on results of studies 177, 178, and 179.

3. **Treatment of symptomatic gastroesophageal reflux disease**. The recommended dose is 20 mg once-a-day. Treatment duration should be 4 weeks.

   This recommendation is based on results of studies 225 and 226.

In addition, it is recommended not to allow the sponsor to claim that esomeprazole magnesium has any significant clinical advantage over omeprazole in the first-line treatment of these acid-related disorders because no data in support of such a claim have been submitted.

Labeling will be addressed in a separate document.

September 21, 2000

/S/

Hugo E. Gallo-Torres, M.D., Ph.D.

cc:
NDA 21-153
HFD-180
HFD-180/LTalarico S\9-21-00
HFD-180/SAurecchia
HFD-180/HGallo-Torres
HFD-181/MWalsh
HFD-705/Tpermutt
HFD-705/Ytsong
HFD- 40/PStaub
HFD-180/JChoudary
HFD-180/LZhou
r/d 8/7/00 jgw
f/t 9/21/00 jgw
deg: 9/11/00
REVISED 9/15/00

APPEARS THIS WAY
ON ORIGINAL

The 4-month safety update will be reviewed together with the safety update requested in the AE letter.

Clinical and Statistical Review for New Drug Application # 21-154

Drug: Nexium™ (esomeprazole magnesium, formerly H 199/18)
20 mg and 40 mg Delayed-Release Capsules

Applicant's Proposed Indication: *Triple Therapy (NEXIUM™ plus amoxicillin and clarithromycin):* NEXIUM™, in combination with amoxicillin and clarithromycin, is indicated for the treatment of patients with *H. pylori* infection and active or a history of duodenal ulcer disease to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence.

General Information:

Applicant Name:	AstraZeneca, L.P.
Applicant's Address:	725 Chesterbrook Blvd Wayne, PA 19087
Applicant's Telephone:	(610) 695-1873

Submission/Review Dates:

Date of Submission:	February 28, 2000
Date of Receipt:	February 29, 2000
Date Review Begun:	April 24, 2000
Date Review Completed:	December 15, 2000

Drug Identification:

Generic Name:	Esomeprazole magnesium (formerly H 199/18)
Pharmacologic Category:	substituted benzimidazole (proton pump inhibitor)
Proposed Trade Name:	Nexium™
Chemical Name:	$(C_{17}H_{18}N_3O_3S)_2Mg \times 3\ H_2O$
Molecular Weight:	767.2 daltons
Dosage Form:	20 and 40 mg Delayed-Release Capsules
Route of Administration:	Oral

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EXECUTIVE SUMMARY

I. Summary of Clinical Findings

Overview

Generic Name:	Esomeprazole magnesium (formerly H 199/18)
Pharmacologic Category:	substituted benzimidazole (proton pump inhibitor)
Proposed Trade Name:	Nexium™
Dosage Form:	20 and 40 mg Delayed-Release Capsules
Route of Administration:	Oral

Applicant's Proposed Indication: *Triple Therapy (NEXIUM™ plus amoxicillin and clarithromycin):* NEXIUM™, in combination with amoxicillin and clarithromycin, is indicated for the treatment of patients with *H. pylori* infection and active or a history of duodenal ulcer disease to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence.

The worldwide clinical development program for H 199/18 (esomeprazole) in combination with antimicrobials for the eradication of *H. pylori* includes two Phase I studies (drug-drug interactions) and five Phase III clinical efficacy and safety studies, three of which were conducted in the US.

US Phase III Study 191 is considered primary. Studies 192 and 193 are considered supportive. All three studies used the same design: 38-day, randomized, double blind, parallel group design. Eradication of *H. pylori* was considered the primary endpoint. Duodenal ulcer healing 4 weeks after the end of treatment and upper gastrointestinal symptoms at the end of treatment and 4 weeks after the end of treatment were secondary efficacy parameters. The following treatments were studied for 10 days in a modified factorial design:

US Phase III Studies
Number of Patients Randomized by Study and Treatment Regimen

10-day Treatment	Study Number			Total (%)
	191	**192**	**193**	
H 40 mg qd		17	28	37 (7)
H 40 mg qd + C 500 mg bid	251	51		231 (44)
H 40 mg qd + A 1gm bid + C 500 mg bid	264		85	263 (50)
Total (%)	383 (72)	59 (11)	89 (17)	531 (100)

The two non-US Phase III studies (SH-QBE-0019 and SH-QBE-0020) were also double blind, randomized studies. HAC treatment was compared to an active control, OAC (omeprazole/amoxicillin/clarithromycin), and treatments were administered for 7 days. Patients in SH-QBE-0019 had a history of duodenal ulcer disease and the primary endpoint was to estimate the *H. pylori* eradication rates for the two treatment groups. Study SH-QBE-0020 only enrolled patients with active ulcers. The primary endpoint was to estimate duodenal ulcer healing rates for the two treatment groups and the secondary endpoint was to compare eradication rates for the two treatment groups.

Due to differences in the treatment duration, dosing regimen and patient population studied in the US and non-US studies, the efficacy data from the non-US studies will not be discussed. However, the 446 patients who received HAC (n=224 in SH-QBE-0019 and n=222 in SH-QBE-0020) will be reviewed and discussed in the Integrated Summary of Safety (ISS).

A. Efficacy

1. Phase III US Studies

The *H. pylori* eradication rates at 4 weeks post-treatment in US Studies 191, 192, and 193 individually and combined across studies are displayed for the applicant's per-protocol and intention-to-treat analyses in Tables 1 and 2, respectively. The reviewer is in agreement with the applicant's results.

TABLE 1
***H. pylori* Eradication at Day 38 Visit (4 Weeks Post-Treatment)**
Per-Protocol Analysis
US H 199/18 *H. pylori* Studies 191, 192, 193

H. pylori Eradication at 4 Weeks Post-Treatment	HAC	HC	H	Pairwise Treatment Group Comparisons (Using Logistic Regression)
	n/N (%) [95% CI]	n/N (%) [95% CI]	n/N (%) [95% CI]	P-value
Study 191	164/196 (84%) [78%, 89%]	103/187 (55%) [48%, 62%]		HAC vs. HC: p < 0.001*
Study 192		22/44 (50%) [35%, 65%]	0/15 (0%) [0%, 22%]	HC vs. H: p = 0.022*
Study 193	57/67 (85%) [74%, 93%]		1/22 (5%) [0%, 23%]	HAC vs. H: p < 0.001*
All three studies combined [a]	221/263 (84%) [79%, 88%]	125/231 (54%) [48%, 61%]	1/37 (3%) [0%, 14%]	HAC vs HC: p < 0.001* HAC vs H: p < 0.001* HC vs H: p < 0.001*

* Significant difference observed between the treatment groups, (p < 0.050).
a Test for study by treatment group interaction was not significant, (p = 0.922), using logistic regression.

TABLE 2
***H. pylori* Eradication at Day 38 Visit (4 Weeks Post-Treatment)**
Intention-to-Treat Analysis
US H 199/18 *H. pylori* Studies 191, 192, 193

H. pylori Eradication at 4 Weeks Post-Treatment	HAC	HC	H	Pairwise Treatment Group Comparisons (Using Logistic Regression)	
	n/N (%) [95% CI]	n/N (%) [95% CI]	n/N (%) [95% CI]	P-value	
Study 191	179/233 (77%) [71%, 82%]	112/215 (52%) [45%, 59%]		HAC vs. HC:	p < 0.001*
Study 192		23/50 (46%) [32%, 61%]	0/16 (0%) [0%, 21%]	HC vs. H:	p = 0.028*
Study 193	58/74 (78%) [67%, 87%]		1/24 (4%) [0%, 21%]	HAC vs. H:	p < 0.001*
All three studies combined [a]	237/307 (77%) [72%, 82%]	135/265 (51%) [45%, 57%]	1/40 (3%) [0%, 13%]	HAC vs HC: HAC vs H: HC vs H:	p < 0.001* p < 0.001* p < 0.001*

* Significant difference observed between the treatment groups, (p < 0.050).
[a] Test for study by treatment group interaction was not significant, (p = 0.932), using logistic regression.

The applicant has followed the FDA draft guidance, *Guidance for Industry: Evaluating Clinical Studies of Antimicrobials in the Division of Anti-Infective Drug Products, Draft, February 1997*, in determining efficacy of HAC. According to the document, the following recommendations are made regarding establishment of an efficacy threshold.

- The minimum threshold for efficacy is a lower 95% confidence interval of 60% (using the modified intent-to-treat analysis). However, many factors should be considered in setting this threshold limit. For example; *H. pylori* eradication rates, safety/tolerability levels, rate of emerging resistance, and compliance should all be considered.
- In addition to threshold recommendations, multi-therapy regimens need to include factorial designs, which may demonstrate the contribution of each component to the overall effect.

The *H. pylori* eradication rates for the HAC treatment group satisfy the efficacy threshold recommended in the FDA draft guidance. The 95% confidence intervals for the intention-to-treat eradication rates for the HAC group were (71%, 82%) for Study 191, (67%, 87%) for Study 193, and (72%, 82%) for both studies combined. The lower bounds for all three confidence intervals are above the recommended 60% threshold.

In addition, the *H. pylori* eradication rates for the HAC treatment group were significantly higher than both the HC and H treatment groups, demonstrating the superiority of HAC over the other two regimens and also the positive contribution of amoxicillin to the HAC regimen.

2. Comparison With Other FDA-approved PPI-based Triple Therapy Regimens

Omeprazole and lansoprazole are proton pump inhibitors (PPIs) that are approved in combination with two antibiotics for eradication of *H. pylori*.

- OAC (omeprazole/amoxicillin/clarithromycin)
- LAC (lansoprazole/amoxicillin/clarithromycin)

The clinical development programs for these regimens were similar to that of HAC. All programs enrolled *H. pylori*-positive patients with either an active ulcer or history of ulcer disease. Eradication was the primary endpoint in all studies. The treatment duration of the PPI varied between development programs. In the OAC regimen, the use of omeprazole was continued (at a reduced dose) beyond the duration of eradication therapy for a total duration of 4 weeks. The HAC and LAC regimens did not continue the PPI beyond the initial 10 days of treatment.

As seen in the table below, the eradication rates achieved at 4 weeks post-treatment with HAC therapy appear comparable to those observed with the other approved proton pump inhibitor (PPI)-based triple therapies:

H. pylori Eradication at 4 Weeks Post-Treatment - Comparison of Esomeprazole (H199/18), Omeprazole, and Lansoprazole Triple Therapies

Analysis	N (%) [95% CI]					
	HAC		*OAC**			*LAC*[Ψ]
	Study 191	Study 193	Study 126	Study 127	Study M96-446	M95-399
ITT	233 (77%) [71%, 82%]	74 (78%) [67%, 87%]	80 (69%) [57%, 79%]	73 (77%) [61%, 82%]	84 (83%) [74 %, 91%]	135 (81%) [74%, 88%]
PP	196 (84%) [78%, 89%]	67 (85%) [74%, 93%]	64 (77%) [64%, 86%]	65 (78%) [67%, 88%]	69 (90%) [80 %, 96%]	123 (84%) [76%, 90%]

* Omeprazole 20 mg BID + amoxicillin 1gm BID + Clarithromycin 500 mg BID x 10 days, then omeprazole 20 mg QD for an additional 18 days in patients with an active ulcer present at the Initiation of therapy for ulcer healing and symptom relief. M96-446 was an inactive DU study, therefore omeprazole was used for a duration of 10 days in all patients.

[Ψ] Lansoprazole 30 mg BID + amoxicillin 1 gm BID + clarithromycin 500 mg BID x 10 days

B. Safety - US Phase III studies

In the US Phase III studies, there were no clinically meaningful differences between the HAC and HC groups in the incidence of any AE (54.3% and 55.5%, respectively). These results suggest that the addition of amoxicillin to the HC regimen does not lead to an increased risk of adverse side effects. In contrast, the percentage of patients who reported AEs was generally lower for patients who received H alone (46.7%) compared to those who received HAC or HC. This lower rate was observed specifically for abdominal pain, diarrhea, flatulence, nausea, esophagitis, dizziness, headache, and taste perversion. Dizziness, headache, and abnormal taste have been previously associated with clarithromycin.

The increased incidence of AEs in the HAC and HC groups, as compared to the H group may be due to the increased exposure to H 199/18 that occurs with co-administration of clarithromycin. However, it is more likely to be a direct result of the antibiotic component(s)

of these combination regimens since the AEs are consistent with those commonly reported for clarithromycin and amoxicillin (e.g. GI symptoms and taste perversion).

The overall percentages of patients who discontinued due to an AE or experienced a non-fatal SAE were low. In the HAC, HC, and H groups 3.2%, 3.7%, and 2.2% of patients discontinued due to one or more AEs and 0.6%, 0.7%, and 2.2% of patients experienced a non-fatal SAE, respectively. There were no clinically meaningful differences among treatment groups in the rate of discontinuations due to AEs or non-fatal SAEs. Not unexpectedly, for patients who received HAC or HC, discontinuations due to AEs most frequently involved the GI system.

One death occurred in the US Phase III program for H 199/18. One additional patient died in the non-US Phase III studies. According to the applicant and the reviewer's assessments, both deaths were unlikely to be related to study drug.

There were no clinically meaningful changes from Baseline to the Day 11 visit within or between treatment groups in any of the laboratory parameters analyzed, with the possible exception of ALAT/SGPT and ASAT/SGOT. The clinical relevance of these changes is not known. For ALAT/SGPT, a slightly greater percentage of patients in the HAC group shifted from normal at Baseline to above normal at the Day 11 Visit (16 of 301, 5.3%) compared to that observed in the HC (9 of 265, 3.4%) and H (1 of 42, 2.4%) groups. For ASAT/SGOT, a slightly greater percentage of patients in the HAC group shifted from normal at Baseline to above normal at the Day 11 visit (12 of 314, 3.8%), compared to that in the HC group (3 of 279, 1.1%). In the H group, the percentage of patients who experienced a similar shift (2 of 43, 4.7%) was greater than that observed in the HAC group; however, there were a relatively low number of patients in this group. A moderate increase in ASAT/SGOT has been previously documented with amoxicillin.

There were no clinically meaningful changes within or between treatment groups in any vital sign parameters analyzed.

C. Special Populations

Pediatric patients (< 18 years) and patients with renal or hepatic impairment were specifically excluded from the H 199/18 development program. Therefore it is not possible to comment on the efficacy or adverse event profile in these populations.

3. Efficacy

Covariate analyses using logistic regression were performed by the applicant to determine whether age, gender, or race had a significant effect on the *H. pylori* eradication rates. None of these covariates had a statistically or clinically significant, based on the reviewer's assessment, effect on *H. pylori* eradication status.

4. Safety

Age

In the HAC group, elderly patients (≥ 65 years) tended to report one or more AEs more frequently than those in the younger age groups (≤ 40 years: 51.9%; 41 years - 64 years: 53.2%; ≥ 65 years: 63.2%). Elderly patients who received HAC were more likely to report

GI side effects compared to younger patients (≤ 40 years: 35.3%; 41 years - 64 years: 38.6%; ≥ 65 years: 43.9%).

Gender
In the HAC group, females reported one or more AEs more frequently than males (62.7% vs 49.1%). Female patients were more likely than male patients to report GI side effects (42.5% versus 35.5%) and special senses/other disorders (13.4% versus 2.3%). Males were more likely to have liver and biliary system disorders than females (4.2% versus 0%), although the overall incidence was relatively low.

Race
In the HAC group, a greater percentage of Caucasian patients reported one or more AEs than Black patients (59.0% vs. 41.3%). The only apparent differences between Caucasian and Black patients occurred in the incidence of AEs associated with the GI system (0.8% versus 2.3%).

II. Recommendations

Esomeprazole magnesium (formerly H 199/18) when used in combination with amoxicillin and clarithromycin is safe and effective for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or history of within the past 5 years) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. The recommendation is for approval of esomeprazole 40 mg, amoxicillin 1 gm, plus clarithromycin 500 mg twice daily for 10 days for this indication.

Recommended changes have been incorporated into the applicant's draft labeling and can be found in Appendix 4.

CLINICAL REVIEW

I. Introduction/Background

Generic Name:	Esomeprazole magnesium (formerly H 199/18)
Pharmacologic Category:	substituted benzimidazole (proton pump inhibitor)
Proposed Trade Name:	Nexium™
Dosage Form:	20 and 40 mg Delayed-Release Capsules
Route of Administration:	Oral

A. Applicant's Proposed Indication and Dosage and Administration

H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence
Triple Therapy (NEXIUM™ plus amoxicillin and clarithromycin): NEXIUM™, in combination with amoxicillin and clarithromycin, is indicated for the treatment of patients with *H. pylori* infection and active or a history of duodenal ulcer disease to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. (See CLINICAL STUDIES and DOSAGE AND ADMINISTRATION.)

In patients who fail therapy, susceptibility testing should be done. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, alternative antimicrobial therapy should be instituted. (See Microbiology section, and the clarithromycin package insert, MICROBIOLOGY section.)

H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence
Triple Therapy:

NEXIUM™	40 mg	Once Daily for 10 Days
Amoxicillin	1000 mg	Twice Daily for 10 Days
Clarithromycin	500 mg	Twice Daily for 10 Days

Related Drugs:
Other FDA-approved treatment regimens indicated for *H. pylori* eradication in patients with an active or a history of duodenal ulcer:

Primary Therapy

- Omeprazole 40 mg QD + Clarithromycin 500 mg TID x 2 weeks. In patients with an ulcer present at the time of initiation of therapy, an additional 14 days of Omeprazole 20 mg QD is recommended for ulcer healing and symptom relief.
- Bismuth Subsalicylate 151 mg QID + Metronidazole 500 mg BID + Tetracycline 500 mg QID + an H_2-receptor antagonist (at treatment doses for an active duodenal ulcer) x 4 weeks
- Lansoprazole 30 mg BID + Clarithromycin 500 mg BID + Amoxicillin 1 gram BID x 2 weeks
- Lansoprazole 30 mg BID + Clarithromycin 500 mg BID + Amoxicillin 1 gram BID x 10 days
- Omeprazole 20 mg BID + Clarithromycin 500 mg TID + Amoxicillin 1 gram BID x 10 days. In patients with an ulcer present at the time of initiation of therapy, an additional 18 days of Omeprazole 20 mg QD is recommended for ulcer healing and symptom relief.

Alternative Therapy*

- Lansoprazole 30 mg TID + Amoxicillin 1 gram TID x 2 weeks

*For those patients who are either allergic or intolerant to clarithromycin or in whom resistance to clarithromycin is known or suspected.

B. Overview of Clinical Section

The clinical development program for H 199/18 (esomeprazole) in combination with antimicrobials for the eradication of *H. pylori* includes two Phase I studies (drug-drug interactions) and five Phase III clinical efficacy and safety studies, three of which were conducted in the US. US Study 191 is considered primary, while Studies 192 and 193 are considered supportive. All three will be reviewed in detail.

The US clinical development program for H 199/18 (esomeprazole) was designed to compare the HAC regimen to HC when both are administered for 10 days. A direct comparison of *H. pylori* eradication rates for HAC and HC can be performed in Study 191, while an indirect comparison can be performed across Studies 193 and 192. Comparison of the HAC and HC regimens demonstrates the contribution of amoxicillin to the HAC regimen. In order to demonstrate the contribution of H to the regimen, historical data is used to indirectly compare HAC with AC, which was studied in the omeprazole plus amoxicillin plus clarithromycin (OAC) NDA (#20-916). To show the contribution of clarithromycin to the HAC regimen, historical data from the [redacted] was obtained and used by the reviewer.

The two non-US studies (SH-QBE-0019 and SH-QBE-0020) are supportive and do not use the same dose of H 199/18 or duration of treatment as the US studies. The two Phase I studies (SH-QBE-0040 and SH-QBE-0034) are reviewed and discussed only in the Integrated Safety Summary (ISS).

C. Rationale for Dose Selection in US Clinical Studies

H 199/18 is the S-enantiomer of the racemic drug omeprazole, which has been approved for use in *H. pylori* eradication both in combination with clarithromycin (OC) in 1996 and with clarithromycin plus amoxicillin (OAC) in 1998. Omeprazole has been administered at a total daily dose of 40 mg in all regimens used to eradicate *H. pylori*. Similarly, a dose of H 199/18 40 mg qd has been shown to provide adequate acid inhibition in a pharmacokinetic (PK) and pharmacodynamic (PD) study. In the three pivotal clinical studies, H 199/18 was administered as one 40 mg dose for each day of a 10 day regimen. This once-a-day dosing is analogous to the omeprazole dosing schedule approved for OC dual therapy.

Clarithromycin 500 mg bid and amoxicillin 1000 mg bid were the dosages proven to be effective in the OAC triple combination regimen. Therefore, these antimicrobials were selected at the same dosages for this study.

D. Regulatory Background

[redacted]

The applicant had difficulties with patient enrollment into the three primary US studies. The applicant identified several factors that contributed to enrollment problems: (1) exclusion criteria excluding patients with a history of certain GI conditions. This was modified to exclude only those patients with a history of these GI conditions within 1 year prior to Baseline. (2) In Studies 192 and 193, one of the two treatment arms that patients were randomized to did not contain antimicrobial therapy. This posed an ethical concern since alternative more effective therapies were already approved for eradication. (3) Finally, the population of *H. pylori* infected patients was declining due to successful treatment with other eradication regimens and antibiotics. Due to these difficulties, sample size considerations were re-examined and discussed with the FDA between the October 1997 and 1998 face-to-face meetings. The applicant reached agreement with the Division to reduce the sample sizes for both Studies 192 and 193.

II. Summary of Clinically Relevant Findings from Other Review Disciplines

Esomeprazole (NDA 21-153) was submitted on 12/3/99 to the Division of Gastrointestinal and Coagulation Drug Products (HFD-180) for the following three indications:

- acute healing of erosive esophagitis (EE)
- symptomatic gastroesophageal reflux disease
- maintenance of healing of EE

Clinical Reviewer's Comment: The Division of Special Pathogen and Immunologic Drug Products (DSPIDP, HFD-590) will accept the reviews completed by chemistry, pharmacology/toxicology, and clinical pharmacology/biopharmaceutics prepared by HFD-180.

A. Chemistry

See complete review by Arthur B. Shaw, Ph.D., Chemistry Reviewer in HFD-180 (DGCDP) filed with NDA 21-153.

Multiple minor deficiencies in the application were noted. The applicant was sent a discipline review letter on 9/26/00 outlining deficiencies in the following categories:

- Drug substance: nomenclature, characterization, manufacturing procedure, specifications, and stability
- Drug product: components, manufacturing procedure, in-process controls, specifications, and stability

B. Pharmacology/Toxicology

See complete review by Ke Zhang, Ph.D., Pharmacology/Toxicology Reviewer in HFD-180 (DGCDP) filed with NDA 21-153.

The toxicity profile of H 199/18 was characterized in rats and dogs. The stomach and kidney were the target organs of toxicity as evidenced by histopathological changes in 1-month, 3-month, and 13-week oral toxicity studies in rats and a 3-month oral toxicity study in dogs. In all these studies omeprazole was used as a comparator. Similar histopathological changes to what were observed following treatment with H 199/18 were also observed with omeprazole.

- In the 1-month oral toxicity study the histopathological changes seen in the stomach were minimal foci of chief cell eosinophilia in the gastric mucosa.
- In the 3-month oral toxicity study, the histopathological changes in the stomach were chief cell eosinophilia at vacuolated glandular cells. Basophilic cortical tubules and inflammatory cell infiltration were seen in the kidney.
- In the 13-week oral toxicity study in rats, the histopathological changes seen in the stomach were chief cell eosinophilia, acanthosis, and hyperkeratosis. Basophilic cortical tubules were seen in the kidney.
- In the 3-month oral toxicity study in dogs, histopathological changes were observed in the stomach and included mucosal fibrosis, hyperplasia, chief cell atrophy, and focal necrosis.

In Segment II teratological reproductive toxicity studies in rats and rabbits, H 199/18 was not found to be teratogenic.

No carcinogenicity studies were conducted for H 199/18, instead findings using omeprazole in rats and mice were submitted. Omeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia and carcinoids in both male and female rats in a dose dependent manner in two 2-year rat carcinogenicity studies. The mouse study was considered inconclusive and invalid and was not used for the safety assessment.

H 199/18 was negative when tested in the Ames test in an *in vivo* chromosome aberration test in rat bone marrow cells, and in an *in vivo* mouse micronucleus test. However, it was positive in two in vitro chromosome aberration tests using human peripheral blood lymphocytes.

Due to the genotoxic and tumorigenic potential associated with H 199/18 and/or omeprazole, and lack of a carcinogenicity study in a second species (mouse), long term use of H 199/18 was not recommended from a preclinical standpoint.

C. Clinical Pharmacology/Biopharmaceutics

See complete review by Suliman I. Al-Fayoumi, Ph.D., Clinical Pharmacology /Biopharmaceutics Reviewer in HFD-180 (DGCDP) filed with NDA 21-153.

Because H 199/18 will be used in combination with both clarithromycin and amoxicillin for the treatment of *H. pylori*, it was considered relevant to investigate whether H 199/18 has the potential to interact with the pharmacokinetics of these two drugs. The

pharmacokinetics of H 199/18, clarithromycin and amoxicillin when given in combination was compared to administration of each drug alone at steady state in two separate studies (SH-QBE-0034 and SH-QBE-0040).

One study (SH-QBE-0034) evaluated a dose of 40 mg once daily of H 199/18. In the second study (SH-QBE-0040), H 199/18 was dosed 20 mg twice daily. Clarithromycin and amoxicillin were dosed 500 mg and 1 gm twice daily in both studies. Treatment lasted for 7 days in both studies. The pharmacokinetics of both amoxicillin and clarithromycin after triple combination treatment were very similar to when each drug was given alone. However, the AUC and C_{max} of 14-OH-clarithromycin were about 20% and 53% higher with triple therapy compared to monotherapy in Studies SH-QBE-0034 and –0040, respectively.

When H 199/18 was dosed 40 mg once daily, the AUC of H 199/18 was 70% higher during the triple combination compared to when H 199/18 was given alone (22.7 versus 13.3 μmol*h/L) and the C_{max} was 18% higher. When H 199/18 was dosed 20 mg twice daily, there was greater than a two-fold increase in the AUC of H 199/18 during the triple combination compared to monotherapy (11.3 versus 5.0 μmol*h/L) and the C_{max} was 39% higher. The mechanism for this interaction is thought to be competitive inhibition for metabolism through CYP3A4 and 2C19. Therefore, it appears that co-administration of clarithromycin with H 199/18 inhibits the metabolism of the latter drug.

Clinical Reviewer's Comment: Of note, the AUC of clarithromycin also increases (by 89%) when given in combination with omeprazole. The potential safety implications of the approximate doubling of the AUC of H 199/18 during triple therapy will be addressed in the Integrated Summary of Safety.

D. Microbiology

See complete review by Peter A. Dionne, Microbiologist in HFD-590 (DSPIDP) filed with this NDA (21-154).

About 15% of the *H. pylori* isolates in the clinical trials were resistant (MIC ≥ 1 μg/mL) to clarithromycin pre-treatment. The distribution of pre-treatment MIC values was bimodal. One population had MIC values of ≤ 0.125 μg/mL and the other population had MIC values of ≥ 8 μg/mL. A few isolates had MIC values between these two populations. Patients with isolates that had high clarithromycin MICs did not have their *H. pylori* eradicated as readily as those with isolates with low clarithromycin MIC values. All but one isolate in the clinical trials were susceptible (≤ 0.25 μg/mL) to amoxicillin. Eradication rates did not seem to be related to amoxicillin MIC values.

Treatment with HAC triple therapy eradicated *H. pylori* better than dual therapy with HC for both clarithromycin- (89%, 61%) and amoxicillin-susceptible (83%, 54%) isolates, respectively. Treatment with H 199/18 alone did not eradicate *H. pylori*.

Treatment with HAC triple therapy did not lead to a significant development of isolates with clarithromycin resistance. Of the 197 patients in the HAC group with susceptible baseline isolates only two patients had isolates that developed resistance to clarithromycin (1.0%). Triple therapy treatment did not lead to amoxicillin resistance.

Treatment with HC dual therapy led to a significant number of isolates that developed resistance to clarithromycin. Of the 153 patients in the HC group with susceptible baseline isolates, 23 patients had isolates that developed resistance to clarithromycin (15.0%). Triple therapy treatment did not lead to amoxicillin resistance.

III. Description of Clinical Data and Sources

A. Overall Data

Material Submitted: 93 Volumes
Electronic data, including SAS transport files

Material Reviewed: Volumes 1 and 2, and Volumes 66 through 105
Electronic data, including SAS transport files

B. Phase III Clinical Data

All three US Phase III used the same design: 38-day, randomized, double blind, parallel group design. Treatments were studied for 10 days in a modified factorial design. Eradication of *H. pylori* was considered the primary endpoint. Duodenal ulcer healing 4 weeks after the end of treatment and upper gastrointestinal symptoms at the end of treatment and 4 weeks after the end of treatment were secondary efficacy parameters.

US Phase III Studies
Number of Patients Randomized by Study and Treatment Regimen

Study Number	Treatments (number randomized)
191	HAC (264) HC (251)
192	HC (51) H (17)
193	HAC (85) HC (28)

HAC = H 199/18 40 mg QD + amoxicillin 1000 mg BID + clarithromycin 500 mg BID
HC = H 199/18 40 mg QD + clarithromycin 500 mg BID
H = H 199/18 40 mg QD

The two non-US Phase III studies (SH-QBE-0019 and SH-QBE-0020) were also double blind, randomized studies. HAC treatment was compared to an active control, OAC (omeprazole/amoxicillin/clarithromycin), and treatments were administered for 7 days. Patients in SH-QBE-0019 had a history of duodenal ulcer disease and the primary endpoint was to estimate the *H. pylori* eradication rates for the two treatment groups. Study SH-QBE-0020 only enrolled patients with active ulcers. The primary endpoint was to estimate duodenal ulcer healing rates for the two treatment groups and the secondary endpoint was to compare eradication rates for the two treatment groups.

Due to differences in the treatment duration, dosing regimen, and patient population studied in the US and non-US studies, the efficacy data from the non-US studies will not be discussed. However, the 446 patients who received HAC (n=224 in SH-QBE-0019 and

VI. Clinical and Statistical Review of Study 191

A. Investigators and Study Administrative Structure

Eighty-five (85) primary investigators participated in the trial.

This study was conducted by [redacted] and [redacted] Astra Pharmaceuticals, L.P. [redacted] The study used [redacted] central laboratories. [redacted] performed all laboratory safety tests (blood chemistry, hematology, and urinalysis). Gastric biopsy specimens were sent to [redacted] for histological assessment of *H. pylori*. Gastric biopsy specimens were also sent to [redacted] for microbiological assessment of *H. pylori* and antibiotic susceptibility.

B. Study Objectives

Primary Objectives

- 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 DU or history of DU disease.

- To assess the safety and tolerability 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 *H. pylori* infected patients with active DU or history of DU disease.

Secondary Objectives

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

C. Investigational Plan

This was a 38-day, multicenter, randomized, double blind, parallel group study. *H. pylori* infected patients with one or more endoscopically confirmed DU(s) or a history of duodenal ulcer disease, who met the inclusion criteria, were randomized to one of the following two treatment regimens for 10 days:

- H 199/18 40 mg qd + amoxicillin 1000 mg bid + clarithromycin 500 mg bid (250 patients planned)
- H 199/18 40 mg qd + amoxicillin placebo bid + clarithromycin 500 mg bid (250 patients planned)

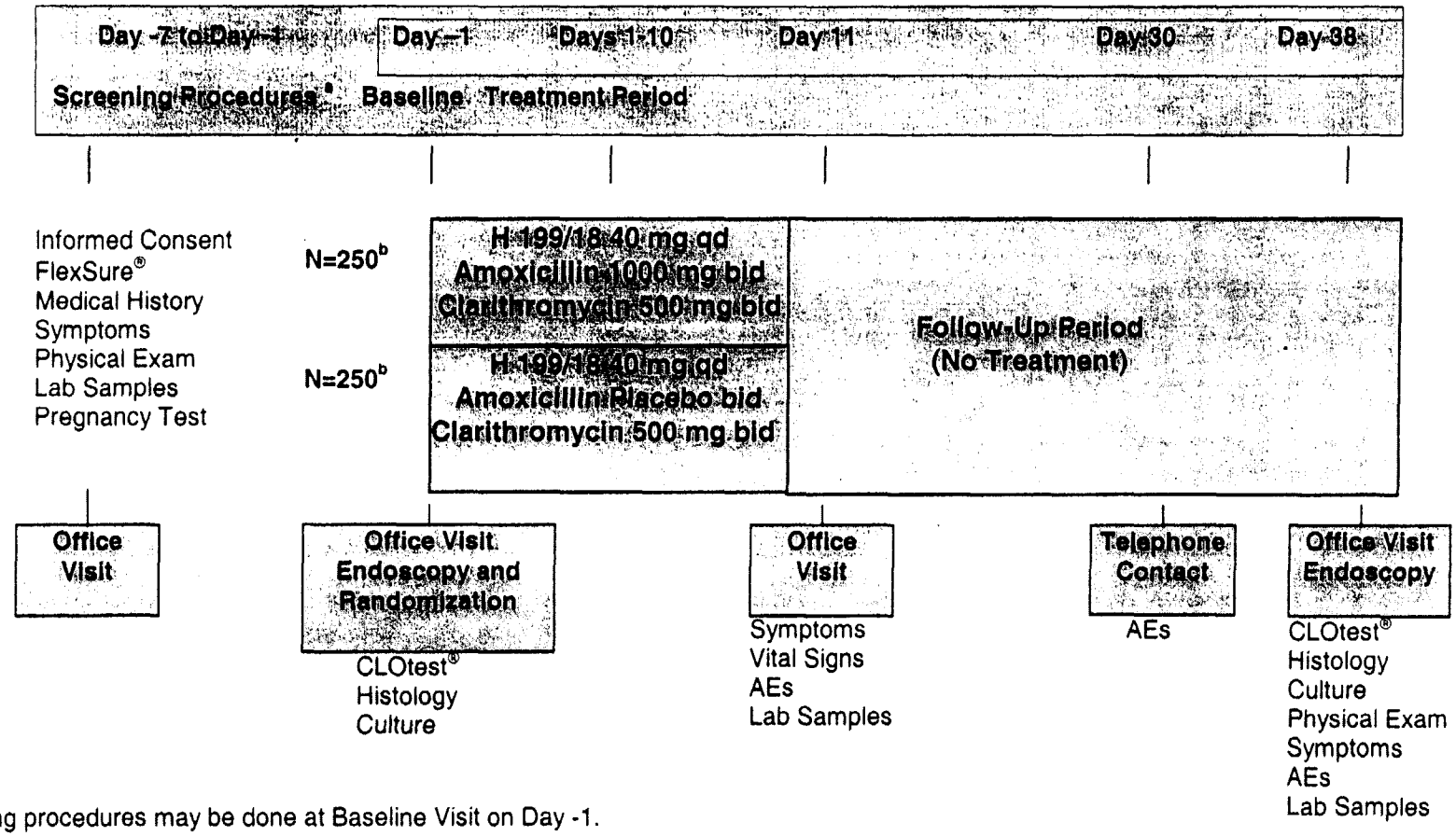
These two treatment groups were selected to examine the benefits of amoxicillin when added to therapy with H 199/18 and clarithromycin.

An esophagogastroduodenoscopy (EGD) was performed at Baseline to document the presence of any current DU(s) at least 0.5 cm in diameter, and the presence of anomalies. Gastric biopsy samples were obtained during baseline EGD to document the presence of *H. pylori* infection via the rapid urease test (CLOtest®), histology, and culture. A final EGD was performed at Day 38 to document ulcer status and the presence of anomalies. Gastric biopsy samples were obtained during the Day 38 EGD to determine the status of *H. pylori* infection via CLOtest®, histology, and culture. The *in vitro* culture samples at Baseline and Day 38 were used to assess the susceptibility of *H. pylori* to amoxicillin and clarithromycin. The investigative sites were instructed to have the same endoscopist perform both endoscopic examinations for a given patient. Documentation for endoscopically or radiologically determined DU(s) within the last five years was collected at the Baseline Visit, if available.

As patients were randomized, they were stratified by their baseline DU status (active DU or history of DU, but no active DU at Baseline). After 10 days of treatment, patients were followed for 4 weeks to assess their *H. pylori* status. DU healing was assessed for patients who entered the study with an active DU at Baseline. All patients were given GELUSIL® antacid to take as needed for symptom relief. During the study, the presence and severity of upper gastrointestinal (GI) symptoms were assessed by the investigator at the Baseline, Day 11, and Day 38 visits.

Adverse events (AEs) were recorded throughout the study. Routine laboratory safety tests were performed at Baseline, Day 11, and Day 38. Study assessments were performed according to the schedule in Figure 1.

FIGURE 1
STUDY OVERVIEW
(All Treatments were Given for 10 Days)



[a] Screening procedures may be done at Baseline Visit on Day -1.
[b] Number of patients planned.

D. Schedule of Visits

The schedule of visits for Study 191 is outlined below in Table 1.

TABLE 1
Flow Chart for Clinical and Laboratory Evaluations (Study #191)

Procedure	Screening[a] Day -7 to Day -1	Baseline Day -1	End of Treatment[b] Day 11 (+ 2 Days)	Telephone Contact Day 30 (± 5 Days)	Final Visit Day 38 (+ 5 Days)
Informed Consent	x				
Medical History	x				
Complete Physical Examination[c]	x				x
Vital Signs			x		
Laboratory Samples (Fasting)[d]	x		x		x
H. pylori Serology Screen[e]	x				
Upper Gastrointestinal Symptom Assessment	x		x		x
EGD (Fasting)		x			x
Biopsy[f] (Rapid Urease Test, Culture, and Histology)		x			x
Pregnancy Test[g]	x				
Telephone Contact				x	
Adverse Event Assessment			x	x	x
Dispense Study Drug		x			
Drug Accountability			x		x
End of Study Status					x

[a] Screening procedures may have been done at Baseline Visit on Day -1.
[b] Patients completed ten days of treatment.
[c] Screening physical examinations were done anytime between Day -7 and Day -1.
[d] Screening laboratory samples were collected anytime between Day -7 and Day -1.
[e] *H. pylori* serology screening for enrollment screening was done prior to EGD.
[f] Biopsy for determination of *H. pylori* status.
[g] Urine dipstick and serum pregnancy tests were required.

E. Inclusion Criteria

- Adults 18 years to 75 years of age inclusive (and of legal age to consent).
- Male or non-pregnant, non-lactating female. Female patients were either postmenopausal, surgically sterilized, or using an acceptable form of birth control as determined by the investigator. Women of childbearing potential had agreed to continue using an acceptable form of birth control throughout the conduct of the study.

- All women of childbearing potential (i.e., those not postmenopausal or surgically sterilized) had a negative pregnancy test result at Baseline.
- Patients who were positive for *H. pylori* at Baseline by rapid urease test (CLOtest®) within 6 hours.
- Patients who had endoscopic documentation of one or more DU(s), greater or equal to 0.5 cm in diameter at Baseline, or a history of at least one endoscopically or radiologically documented DU within the last 5 years.
- Patients who were capable of providing written informed consent, willing and able to comply with all procedures of the study.

F. Exclusion Criteria

- Patients who had a history within 1 year prior to baseline of any of the following: organic pyloric obstruction, prepyloric ulcer, gastric pyloric disease, pyloric channel ulcer, gastric ulcer, or erosive esophagitis.
- Patients who had a history of Barrett's esophagus.
- Patients who had Zollinger Ellison Syndrome.
- Patients who had a history of gastric resection surgery or truncal vagotomy.
- Patients who had a history of refractory DU: patients had a DU that failed to heal after 12 weeks of full dose therapy with H_2-receptor antagonists or 4 weeks of proton pump inhibitors treatment.
- Patients who had active upper GI bleeding at Baseline Visit or a history of upper GI bleeding within 1 year prior to Baseline.
- Patients who had a risk of clinically significant GI bleeding or other bleeding disorders as judged by the investigator.
- Patients who had participated previously in Astra Pharmaceuticals, L.P. Study 191 or patients who were currently or who had previously participated in Astra Pharmaceuticals, L.P. studies involving H 199/18.
- Patients who required the continuous use of bismuth containing compounds or antibiotics with antimicrobial therapy effective against *H. pylori* 4 weeks prior, during, or 4 weeks after the treatment period.
- Patients who had been treated for the eradication of *H. pylori* during the previous year before Baseline.
- Patients who required the use of proton pump inhibitors 2 weeks prior, during, and 4 weeks post treatment.
- Patients who required continuous concurrent therapy during and 4 weeks after treatment with:
    - anticoagulants including warfarin sodium (COUMADIN®) and heparin
    - anticholinergics
    - antineoplastic agents
    - pro-motility drugs
    - nonsteroidal, anti-inflammatory drugs
    - prostaglandin analogs
    - salicylates (unless ≤ 165 mg daily for cardiovascular prophylaxis)
    - steroids (oral or intravenous)
    - sucralfate
    - H_2-receptor antagonists.
- Patients who required the use of terfenadine (SELDANE® and SELDANE-D®), cisapride (PROPULSID®), and/or pimozide (ORAP®) at any time 1 week prior to and during treatment.

- Patients who required the use of astemizole (HISMANAL®) at any time 2 weeks prior to and during treatment.
- Patients who required the use of diazepam, phenytoin, digoxin, disulfiram, propafenone, carbamazepine, or theophylline during the treatment period, unless the patient was adequately monitored.
- Patients who required the use of quinidine, disopyramide phosphate (NORPACE®), and nefazodone hydrochloride (SERZONE®) during the treatment period.
- Patients who required the use of amiodarone (CORDARONE®) 4 months prior to or during treatment.
- Patients who had known hypersensitivity to H 199/18, omeprazole, amoxicillin, clarithromycin, or GELUSIL®.
- Patients who took an investigational drug or those who had taken an investigational drug within 28 days of the Baseline Visit.
- Evidence (within 3 months of randomization) of the following diseases/conditions:
    - Pancreatitis
    - Malabsorption
    - Inflammatory bowel disease
    - Severe pulmonary or liver disease
    - Renal disease or impaired renal function as manifested by any of the following: creatinine clearance less than 50 mL/min, serum creatinine greater than 2.0 mg/dL, or markedly abnormal urine sediment on repeated examinations.
    - Active malignant disease except superficial skin disease
    - Unstable diabetes mellitus. Stable diabetics controlled on diet, oral agents, or insulin were acceptable.
    - Clinically significant untreated or ineffectively treated systolic and/or diastolic (greater than 110 mm Hg) hypertension.
    - Unstable heart disease, e.g., myocardial infarction, congestive heart failure, or serious arrhythmias. Occasional premature ventricular contractions did not exclude a patient from the study. Patients with heart disease were to be currently classified by the New York Heart Association criteria as being in Functional Class I.
    - Cerebral vascular disease, such as cerebral ischemia, infarction, hemorrhage, or embolus.
- Any condition that may have required inpatient surgery during the study.
- History of drug addiction or alcoholism within the past 12 months.
- Clinically significant abnormal laboratory values for any pre-study laboratory test.
- Patients who refused to sign the consent form or were not able to give fully informed consent due to mental deficiency or language problems.
- Patients who were unable to take study medication according to dosing instructions.

G. Patient Removal

Patients were able to discontinue their participation in the study at any time. Investigators were permitted to discontinue a patient from the study because of noncompliance, the development of unacceptable AEs, or the judgment that the patient required additional therapy for his or her DU. Investigators were instructed to consider patients noncompliant due to either lack of attendance at scheduled visits, if they were lost to follow-up or for violations of the protocol.

Clinical Reviewer's Comment: The term "noncompliance" used by the applicant is inclusive of more patients than just those who were documented to not take medication based on pill count. The Reviewer considered the specific reason for "non-compliance" in making patient assessments. See Results section, "Non-Compliance".

H. Other Study Design Features

Patients were instructed to take the morning dose of H 199/18, amoxicillin, and clarithromycin before breakfast between 6:00 am and 8:00 am. Patients were instructed to take the evening dose of amoxicillin and clarithromycin before dinner between 5:00 pm and 8:00 pm.

Open label GELUSIL® tablets were provided to all patients. Each patient was given a box of 100 tablets at randomization. Additional GELUSIL® was provided as necessary. Patients were instructed to take GELUSIL® for relief of ulcer symptoms on an as-needed basis throughout the 38-day study period, but not to take more than six tablets per day.

I. Diagnostic Methods

The presence of *H. pylori* was assessed at Baseline and Day 38 via the CLOtest®, histology, and culture using gastric biopsies. DU status was also assessed during the endoscopic examinations at Baseline and Day 38. During both endoscopic examinations, gastric mucosal biopsies (four antral; three corporeal) were collected using large-cup forceps, or alternatively, using a standard forceps with an elliptical cup. Forceps without a spike were preferred. One antral biopsy was used for the CLOtest®. Two antral and two corporeal biopsies were used for histological assessment of *H. pylori*. One antral and one corporeal biopsy were frozen and used for bacteriological culture of *H. pylori* and subsequent antimicrobial susceptibility testing for amoxicillin and clarithromycin when *H. pylori* was present. Agar dilution was used to assess the susceptibility of *H. pylori* to the antimicrobials.

J. Ulcer Healing Status at Week 8

For those patients with an active DU at Baseline, DU status at the Day 38 EGD was defined as follows:

Healed Duodenal Ulcer: Complete epithelialization of the DU(s) and erosions, which were present at Baseline. New erosions remote from index ulcer site were permitted.

Unhealed Duodenal Ulcer: DU(s) was still present (ulcer sharply circumscribed, three-dimensional lesion with a white base), erosions observed at the baseline EGD were still present, or erosions at the site of the index ulcer were present.

K. GI Symptom Assessment

At each visit, the investigator evaluated the patient's upper GI symptoms including daytime epigastric pain or burning, nighttime epigastric pain or burning, nausea, vomiting, heartburn, and acid regurgitation.

Each of the symptoms was evaluated as follows, and the most severe episode over the 7 days prior to the assessments at Screening and Day 38 visits and over the 3 days prior to the assessment at Day 11 visit was recorded:

None:	No symptoms
Mild:	Bothered a little; symptoms were present but caused little or no discomfort.
Moderate:	Bothered to some degree; symptoms were present most of the time, annoying but did not interfere with daily routine.
Severe:	Bothered intensely; constant symptoms caused marked interference with daily routine.

L. Efficacy Assessments

1. Primary Efficacy Parameter - *H. pylori* Eradication at the Day 38 Visit

A patient was considered to be infected with *H. pylori* at Baseline if 1) a positive CLOtest® was confirmed by the positive results from histology or 2) culture was positive for *H. pylori* (i.e., culture isolated *H. pylori*). *H. pylori* eradication at the Day 38 visit was only determined in patients who had confirmed *H. pylori* infection at Baseline. At the Day 38 visit, a patient was considered to have the *H. pylori* infection eradicated only if no test result was positive and at least two of the test results were negative (CLOtest®, histology, culture). If at least one test demonstrated the presence of *H. pylori* at the Day 38 visit, the patient was considered to still be infected (i.e., *H. pylori* not eradicated), regardless of the number of test results available.

For the determination of the presence of *H. pylori* in biopsies by histology and culture, both antrum and corpus were tested (two biopsies from the antrum and two from the corpus for histology, one biopsy from the antrum and one from the corpus for culture). If at least one of the biopsies (antrum or corpus) was positive, the *H. pylori* status of that particular test was considered to be positive. If only one biopsy (either antrum or corpus) had interpretable results for a given test, the results of that biopsy determined the result of that particular test. For culture, if the biopsy sample was classified as insufficient by the microbiologist, and *H. pylori* isolates were reported as not present, that biopsy sample was considered to be not interpretable. However, if *H. pylori* isolates were reported as present, the biopsy sample was considered to be positive for *H. pylori*, whether or not the biopsy was considered to be sufficient.

Clinical Reviewer's Comment: The definitions of H. pylori infection and eradication are consistent with the Division's draft guidance:

> *DAIDP. Guidance for Industry - Evaluating clinical studies of antimicrobials in the Division of Anti-Infective Drug Products. DRAFT. February 1997.*

In addition, the use of three endoscopic tests post-treatment (rather than two) makes the eradication assessment more conservative than that suggested by the Division.

2. Secondary Efficacy Parameters

Duodenal Ulcer Healed Status by the Day 38 Visit
This determination was made only for the subgroup of patients with an active DU present at the baseline endoscopy.

Not healed = DU present or erosions present at the original site of the ulcer
Healed = no DU present, and no erosions present at original site of the ulcer

Upper GI Symptom Assessment at Day 11 Visit and Day 38 Visit
The number and proportion of patients experiencing improvement of their upper GI symptoms (daytime epigastric pain or burning, nighttime epigastric pain or burning, nausea, vomiting, heartburn, and acid regurgitation) from the Screening/Baseline visit to each post-baseline visit were determined. In addition, the number and proportion of patients experiencing no symptoms or mild upper GI symptoms at each post-baseline visit were determined. This was done at both the End of Treatment/Day 11 visit and the End of Study/Day 38 visit.

Susceptibility of *H. pylori* by Agar Dilution
A central laboratory conducted susceptibility testing of all available *H. pylori* isolates to amoxicillin and clarithromycin using agar dilution. The susceptibility testing was performed at the Screening/Baseline visit and the Day 38 visit for each isolate tested based on minimum inhibitory concentration (MIC) values from agar dilution. Susceptibility of *H. pylori* isolates was classified into three categories for clarithromycin (susceptible, intermediate, and resistant) depending on the MIC breakpoints and two categories for amoxicillin (susceptible, not defined). The National Committee for Clinical Laboratory Standards (NCCLS) has recommended standards for establishing clarithromycin MIC breakpoints for agar dilution testing of *H. pylori* isolates. The FDA has concurred with these susceptibility breakpoints for clarithromycin testing. The FDA has also recommended susceptibility breakpoints for amoxicillin testing. The MIC value agar dilution breakpoints used in this study for susceptibility categories of resistant, intermediate, and susceptible are listed for amoxicillin and clarithromycin in Table 2.

TABLE 2
Minimum Inhibitory Concentration (MIC) Breakpoints from Agar Dilution for Determining *H. pylori* Susceptibility Status

Susceptibility Status	Amoxicillin	Clarithromycin
Resistant	not defined	MIC ≥ 1.0 mcg/mL
Intermediate	not defined	MIC = 0.5 mcg/mL
Susceptible	MIC ≤ 0.25 mcg/mL	MIC ≤ 0.25 mcg/mL

Each patient was to have two biopsies taken at each EGD for culture: one from the antrum and one from the corpus. The higher MIC value from the two biopsies was used to determine the *H. pylori* susceptibility status at a particular timepoint.

M. Statistical Analyses and Evaluability Criteria

For the analysis of primary and secondary efficacy parameters, pairwise treatment group comparisons were performed between the treatment groups of HAC and HC.

The primary statistical analysis of all efficacy data was performed using a "per-protocol" patient population (i.e., an "evaluable" patient population). In addition, analyses for the key efficacy parameters were also performed using a "modified intention-to-treat" patient population. These patient populations are described below.

For the per-protocol (PP) population, patients were analyzed according to the study treatment that was actually given to the patient to take. However, for the modified intent-to-treat population, patients were analyzed according to the study treatment to which they were allocated in the randomization schedule. Each patient in this study took the prescribed study medication as determined by the randomization schedule (with the exception of 2 patients who returned all of their administered study medication after taking none of the medication). Exclusion of patient data from either the PP or ITT patient populations was determined before the treatment group allocation was unblinded.

Clinical Reviewer's Comments: The "modified intention-to-treat" patient population is referred to as the "intent-to-treat" (ITT) patient population throughout this report.

Although the 1997 Guidance document recommends the ITT analysis be considered primary, the Division recently has begun to recommend that both the ITT and PP eradication analyses be considered co-primary. Therefore, for the purpose of this review, both eradication analyses will be considered co-primary. The applicant's definitions for the ITT population are presented first, followed by the PP population.

1. Intention to Treat (ITT) Patient Population

Patients were evaluable in the ITT population for the Eradication and Duodenal Ulcer Healing Analyses, as long as they had not violated any of the following conditions.

Criteria A. *H. pylori* was documented as positive based on:
- the positive results of a baseline CLOtest® (rapid urease test) and confirmed by positive results of histology **or**
- the positive results of culture.

Biopsies for these tests could be taken no more than 10 days prior to the first day of study medication.

Criteria B. Baseline endoscopy documented at least one DU **or** patient had a history of at least one endoscopically or radiologically documented DU.

Criteria C. Patient took at least one dose of study medication.

Clinical Reviewer's Comment: All dropouts should be considered ITT failures for both the Eradication and Healing analyses.

The following day ranges in Table 3 were used for the targeted endoscopies (for both *H. pylori* eradication status and DU healed status for patients with an active DU at Baseline). Study Day 1 was the first day that study medication was taken.

TABLE 3
Day Ranges for Targeted Endoscopies
Intention-to-Treat Analysis

Office Visit	Target Day	Endoscopy Day Range *H. pylori* Status (Day Range Inclusive)	Endoscopy Day Range Duodenal Ulcer Healed Status [a] (Day Range Inclusive)
Screening/ Baseline Visit	Study Day -1	-10 to 1	-10 to 1
Day 38 Visit	Study Day 38	≥ Day 11 if *H. pylori* status is positive ≥ Day 35 if *H. pylori* status is negative	≥ Day 1 if healed ≥ Day 29 if not healed

[a] Only for patients who had an active duodenal ulcer at the baseline endoscopy.

In addition to Criteria A-C, the following additional criteria apply for the Eradication Analysis.

Eradication Analysis
To adequately determine *H. pylori* infection status, testing for *H. pylori* must be performed at least 4 weeks after the end of therapy. Thus, for a patient to be considered eradicated of *H. pylori* infection (ITT success) at the Day 38 visit, the patient must have negative test results and have follow-up testing at ≥ Study Day 35 (allowing for a 3-day time window). A patient was considered to still be infected (ITT failure) with *H. pylori*, if testing was positive and the Day 38 visit occurred on or after Study Day 11. Day 11 was chosen since it was the first day after the end of the study medication period.

If a patient had no available data or did not have the appropriate number of interpretable test results at the Day 38 visit (within day range for that timepoint), the patient was an ITT failure (considered to be *H. pylori* positive at that timepoint).

For this analysis, 95% confidence intervals were calculated using exact binomial calculations for the *H. pylori* eradication rates at the Day 38 visit for both treatment groups.

Clinical Reviewer's Comment: Although never explicitly stated in the protocol, the applicant used the recommendation in the 1997 Draft Guidance document regarding establishment of an efficacy threshold for treatment:

- *A lower 95% confidence interval of 60% (using the modified intent-to-treat population in the eradication analysis) is recommended. However, many factors should be considered in setting this threshold limit. For example; H. pylori eradication rates, safety/tolerability levels, rate of emerging resistance, and compliance should all be considered.*

For the Duodenal Ulcer Healing Analysis, the following criteria apply, in addition to Criteria A-C described above.

Duodenal Ulcer Healing Analysis
If a patient was documented as having a healed DU (only for patients who had an active DU at the baseline endoscopy) at any time during the study period on or after Study Day 1, the patient was considered to have a healed DU by the Day 38 visit. If a patient was not

documented as having a healed DU on or after Study Day 1, but the patient was documented as having an unhealed DU on at least one visit on or after Study Day 29, the patient was considered to have an unhealed DU. However, if a patient was not documented as having a healed DU and had no available data on or after Study Day 29, the patient was an ITT failure (considered to have an unhealed DU by the Day 38 visit).

Clinical Reviewer's Comment: Patients using anti-secretory agents following treatment will be considered ITT failures. However, upon review of the database, it was determined that this situation did not occur.

2. Per-Protocol (PP) Patient Population

Patients were considered to be evaluable in the PP population for the Eradication, Duodenal Ulcer Healing, and Upper GI Symptom Analyses, as long as they did not violate any of the following conditions.

Criteria A. *H. pylori* was documented at baseline as positive based on the following:
- the positive results of a baseline CLOtest® (rapid urease test) and confirmed by positive results of histology, **or**
- the positive results of culture.

Biopsies for these tests could be taken no more than 10 days prior to the first day of study medication.

Criteria B. Baseline endoscopy documented at least one DU greater than or equal to 0.5 cm in diameter at Baseline, no more than 10 days prior to the first day of study medication **or** patient had a history of at least one endoscopically or radiologically documented DU within the last 5 years.

Criteria C. Patient had not received any oral, intravenous, or intramuscular antimicrobial therapy known to be effective *in vivo* against *H. pylori* or bismuth compounds within 4 weeks prior to the first dose of study medication, and patient had not received any proton pump inhibitors within 2 weeks prior to the first dose of study medication.

Criteria D. Patient had taken at least 75% of the prescribed doses of study medication (for each of the three prescribed study drugs). (Study drug compliance was based on tablet/capsule counts by the study coordinators at each investigator site).

Clinical Reviewer's Comment: Although the 1997 Guidance document defines compliance as taking at least 80% of study medication, recently the Division has been accepting a cut off of at least 75% of study medication. Therefore, the applicant's criteria are acceptable.

Criteria E. Patient had not received any non-study oral, intravenous, or intramuscular concomitant antimicrobial therapy known to be effective *in vivo* against *H. pylori* or bismuth containing compounds throughout the entire study period.

Criteria F. Patient had not received more than 5 days of any H_2-receptor antagonists and had not received any non-study proton pump inhibitors or sucralfate throughout the entire study period. (Patients were allowed to take GELUSIL antacid tablets as needed during the study period.)

In addition, a patient was considered PP non-evaluable if the patient had any of the following exclusion criteria as stated in the protocol:

Criteria G. Patient was suspected to have Zollinger-Ellison syndrome.

Patient had current evidence of pancreatitis, malabsorption, inflammatory bowel disease, severe pulmonary, renal or liver disease, or unstable diabetes mellitus.

Patient was considered by the investigator to be an alcoholic not in remission or a known substance abuser.

Criteria H. Patient had not also been enrolled in a previous Astra Pharmaceuticals, L.P. H 199/18 *H. pylori* study (Study 192).

In addition, all patients found to be *H. pylori* infected at Baseline who discontinued from the study due to an AE considered to be related to the study drug by the investigator, were counted as PP failures for the *H. pylori* eradication and DU healing analyses (if they had an active DU at baseline).

The day ranges displayed in Table 4 were used for the targeted endoscopies/office visits (for *H. pylori* eradication status, DU healed status for patients with an active DU at Baseline, and for upper GI symptom assessments). Study Day 1 was the first day study medication was taken.

TABLE 4
Day Ranges for Targeted Endoscopies and Symptom Assessments
Per-Protocol Analysis

Office Visit	Target Day	Endoscopy Day Range *H. pylori* Status (Day Range Inclusive)	Endoscopy Day Range Duodenal Ulcer Healed Status [a] (Day Range Inclusive)	Upper GI Symptom Assessment (Day Range Inclusive)
Screening/ Baseline Visit	Study Day -1	Days -10 to 1	Days -10 to 1	Days -10 to 1
Day 11 Visit	Study Day 11	---	---	Days 10 to 14
Day 38 Visit	Study Day 38	≥ Day 11 if *H. pylori* status is positive ≥ Day 35 if *H. pylori* status is negative	≥ Day 1 if healed ≥ Day 29 if not healed	≥ Day 17

[a] Only for patients who had an active duodenal ulcer at the baseline endoscopy.

In addition to Criteria A-H, the following additional criteria apply for the Eradication Analysis.