Eradication Analysis
See description under ITT population.

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 PP non-evaluable in the analysis of *H. pylori* eradication.

Clinical Reviewer's Comment: All other dropouts (without a follow-up endoscopy) unrelated to study drug will be considered PP non-evaluable.

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

Duodenal Ulcer Healing Analysis
For the analysis of DU healed status (only for patients who had an active DU at the baseline endoscopy), if a patient was documented as having a healed DU 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 PP non-evaluable in the analysis of DU healed status by the Day 38 visit.

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

Upper GI Symptom Analysis
In addition to the criteria described above, for the per-protocol analysis of upper GI symptoms, only patients with at least mild symptoms at the baseline visit were PP evaluable in the analysis for a particular symptom.

For the analysis of upper GI symptoms, if a patient had no available data at the Day 11 visit or Day 38 visit (within day range for those timepoints), the patient was PP non-evaluable in the analysis of upper GI symptoms at those timepoints.

Clinical Reviewer's Data Validation Methods
Validation of the efficacy data was performed by reviewing the electronic and line listing raw data for patients considered not evaluable by the applicant for either the per-protocol or intent-to-treat population. Evaluability for both populations was made according to the DAIDP (Draft) Evaluability Criteria Document. An independent assessment was made for both H. pylori eradication and duodenal ulcer healing efficacy analyses.

In addition, 10% of the evaluable population (N=50) was randomly selected (blinded to treatment) and independently reviewed. The reviewer's assessment of evaluability was the same as the applicant's for all patients in this sample.

N. Results

1. Investigators

There were 133 investigator sites initiated for this study. Of these 133 investigator sites, 85 sites randomized and enrolled a total of 515 patients. The other 48 initiated investigator sites (36%) never enrolled any patients.

Of the 85 investigator sites that enrolled patients, 52 sites enrolled 5 or fewer patients and 66 sites enrolled 8 or fewer patients. The site with the highest enrollment (Site 080) enrolled 5% (25 of 515 patients) of the total number of patients enrolled in the study.

Clinical Reviewer's Comment: The number of sites that were initiated for this study, but did not enroll any patients, is large.

Table 1 in Appendix 1 presents the distribution of patient enrollment by treatment group for each investigator site.

2. Patient Accountability

The number of patients in each treatment group who completed the study as stated in the protocol, and the number of patients who discontinued from the study are listed in Table 5.

The applicant indicated that there were no significant differences observed between the treatment groups for the proportion of patients who completed the study or for any reason discontinued from the study, ($p > 0.050$), using Fisher's Exact Test.

TABLE 5
Patient Accounting - All Randomized Patients
Study #191

	H 40 qd + A 1000 bid + C 500 bid		H 40 qd + C 500 bid	
Study Status	n	(%)	n	(%)
Patients Enrolled	264		251	
Completed the Study Period	235	(89%)	233	(93%)
Discontinued from Study	29	(11%)	18	(7%)
Adverse Event	10	(4%)	9	(4%)
Consent Withdrawn	6	(2%)	3	(1%)
Investigator/Sponsor Decision	2	(<1%)	1	(<1%)
Lack of Therapeutic Response	2	(<1%)	0	(0%)
Lost to Follow Up	9	(3%)	5	(2%)

The number of patients who were included (considered evaluable) or excluded (considered non-evaluable) from the ITT and PP analyses is summarized by treatment group in Table 6 according to the reason considered non-evaluable.

For the PP analysis, if an evaluable patient had a missing value (within day ranges) for a particular efficacy parameter, the patient was not included in the analysis of that parameter. Thus, the total number of patients included in the PP analysis for a particular efficacy parameter may be less than 407 patients (n=211 for HAC and n=196 for HC).

Also, a patient may have been counted under more than one violation. *H. pylori* infected patients who discontinued from the study due to an adverse event related to the study drug were determined to be evaluable failures in the PP analysis.

TABLE 6
Number of Patients Included and Excluded in the Statistical Analyses (Study #191)

	H 40 qd + A 1000 bid + C 500 bid		H 40 qd + C 500 bid	
	n	(%)	n	(%)
Total enrolled	264		251	
Included in Efficacy Analysis				
Intention-To-Treat	233	(88%)	215	(86%)
Per-Protocol	211	(80%)	196	(78%)
Excluded from Efficacy Analysis				
Intention-To-Treat	31	(12%)	36	(14%)
A. *H. pylori* not positive at Baseline	30		35	
B. No baseline DU and no history of DU	0		2	
C. No study medication taken	1		1	
Per-Protocol	53	(20%)	55	(22%)
A. *H. pylori* not positive at Baseline	30		35	
B. Baseline DU not at least 0.5 cm and no history of DU within last 5 years	3		5	
C. Took antimicrobials, bismuth, or PPI prior to enrollment	8		6	
D. Noncompliance of study medication	8		4	
E. Concomitant antimicrobials or bismuth compounds	7		7	
F. Concomitant H2-RA, PPI or sucralfate	4		4	
G. Other conditions/diseases	0		2	
H. Enrolled in previous H 199/18 *H. pylori* study (Study 192)	0		0	
Included in Safety Analysis [a]	263	(99.6%)	250	(99.6%)

[a] Two patients (AN 1566 in the H 40 qd + A 1000 bid + C 500 bid group and AN 1642 in the H 40 qd + C 500 bid group) did not take any study medication and were not included in the analysis of safety data.

Clinical Reviewer's Comments: Within Criteria C for the PP analysis, 4 of the 14 patients were excluded for previous and/or concomitant use of cephalosporins (HAC AN: 1766, 1009, 1855 and HC AN: 1633). Two of these patients were eradicated (1766 and 1009). Although cephalosporins have in vitro activity against H. pylori, the reviewer feels it is unlikely that these agents will eradicate H. pylori in vivo. Therefore, the applicant has taken a conservative approach and excluded these patients from the PP analysis. The reviewer agrees with this action.

Three patients taking concomitant antimicrobials and one patient who took previous antimicrobials were not excluded from the applicant's PP population. Two patients were taking griseofulvin (HAC AN 1458; eradicated and HC AN 1750; not eradicated). One patient was taking oral vancomycin (HAC AN 1658; eradicated). One patient took one day's worth of norfloxacin ten days prior to enrollment (HC 1465; not eradicated). The reviewer agrees with the applicant's decision not to exclude these patients from the PP analysis, since it is unlikely that these antimicrobials will eradicate H. pylori in vivo.

One patient was excluded based on criteria G alone (HC: 1834). This patient was reported to have focal inflammation of the descending colon, noninfectious gastroenteritis. It appears this patient was excluded based on current evidence of inflammatory bowel disease. This patient was eradicated of H. pylori.

Table 2 in Appendix 1 lists each patient who was considered non-evaluable for either the ITT or PP analysis and the reason(s) that each patient was considered non-evaluable.

Patients may have been excluded from either analysis for more than one reason. Two of the 67 patients (3%) who were excluded from the ITT analysis were considered non-evaluable for more than one reason, and 13 of the 108 patients (12%) who were excluded from the PP analysis were considered to be non-evaluable for more than one reason.

Clinical Reviewer's Comment: Table 2 in Appendix 1 has been modified from the applicant's original table for simplicity.

The individual results for the *H. pylori* Eradication Analysis at the Day 38 visit and DU Healing Analysis by the Day 38 visit, as well as the day the patient discontinued from the study and reason for discontinuing from the study, are summarized in Table 3 in Appendix 1 for those patients considered non-evaluable for the ITT analysis. Table 4 in Appendix 1 presents the same results for those patients considered non-evaluable for the PP analysis.

Clinical Reviewer's Comments: Tables 3 and 4 in Appendix 1 have been modified from the applicant's original tables for simplicity.

3. Demographic Characteristics

A total of 515 patients were randomized and given study medication to take for one of the two treatment groups in this study. A summary of the baseline patient demographic data is displayed in Table 7 for all 515 randomized patients. There were no significant differences observed between the two treatment groups, HAC and HC, for any baseline demographic characteristic for the all randomized patients, ITT, or PP patient populations.

The applicant indicated there were no significant differences observed between the treatment groups for any baseline demographic or characteristic ($p > 0.050$), using Fisher's Exact Test or Analysis of Variance (ANOVA).

TABLE 7
Baseline Patient Demographics and Characteristics
All Randomized Patients
Study #191

Baseline Patient Demographic/Characteristic	H 40 qd + A 1000 bid + C 500 bid (N=264)		H 40 qd + C 500 bid (N=251)	
	n	(%)	n	(%)
Gender				
Male	163	(62%)	152	(61%)
Female	101	(38%)	99	(39%)
Age (years)				
Mean (SD)	48.6 (14.0)		48.4 (14.1)	
Median	48		48	
Range	20 to 79		19 to 78	
≤ 65 years	224	(85%)	216	(86%)
> 65 years	40	(15%)	35	(14%)
Race				
Caucasian	196	(74%)	173	(69%)
Black	57	(22%)	61	(24%)
Other	11	(4%)	17	(7%)
Smoking Status				
Smoker	79	(30%)	86	(34%)
Nonsmoker	185	(70%)	165	(66%)
Baseline DU Status				
Active DU	205	(78%)	192	(76%)
No active DU	59	(22%)	59	(24%)
Any Upper GI Symptoms				
Yes	243	(92%)	232	(92%)
No	21	(8%)	19	(8%)
Duration of DU Disease				
< 1 year	196	(74%)	190	(76%)
1 to 5 years	35	(13%)	37	(15%)
> 5 years	33	(13%)	24	(10%)
Number of previous episodes of documented active DU [a]				
0	133	(50%)	143	(57%)
1	100	(38%)	84	(34%)
2	20	(8%)	15	(6%)
≥ 3	11	(4%)	8	(3%)
Number of previous attempts to eradicate *H. pylori*				
0	224	(85%)	221	(88%)
1	34	(13%)	23	(9%)
≥ 2	6	(2%)	7	(3%)

[a] One patient in the H 40 qd + C 500 bid treatment group did not have data recorded for the number of previous episodes of documented active duodenal ulcer.

4. Compliance Results

Patients in both treatment groups were able to complete most of their study medication. The amounts of study medications taken were similar between the treatment groups. No significant differences were observed by the applicant between the treatment groups ($p > 0.050$ by Fisher's Exact Test) in the distributions of patients according to the number of capsules or tablets taken for any of the study drugs (H 199/18, clarithromycin, or amoxicillin/amoxicillin placebo).

Table 5 in Appendix 1 shows the distribution of the number of individual study medications (tablets and capsules) taken in each treatment group.

A patient was considered to be compliant if he/she took at least 75% of the prescribed doses of study medication (for each of the three study drugs). As shown in Table 8, compliance in this study was very high: 95% of the patients (251 of 264 patients) in the HAC group and 96% of the patients (241 of 251 patients) in the HC group were compliant. There was no significant difference observed by the applicant in the proportion of non-compliant patients between the treatment groups ($p > 0.050$) using Fisher's Exact Test.

TABLE 8
Patient Compliance with Study Medication
Number (%) of Patients
All Randomized Patients
Study #191

	H 40 qd +A 1000 bid + C 500 bid (N=264)		H 40 qd + C 500 bid (N=251)	
Patient Compliance Status	n	(%)	n	(%)
Compliant [a]	251	(95%)	241	(96%)
Noncompliant	13	(5%)	10	(4%)

[a] Patients were considered to be compliant if they took at least 75% of the prescribed doses of each study medication.

Clinical Reviewer's Comment: Only 6 patients total (5 patients in the HAC group and 1 patient in the HC group) were truly non-compliant. The other patients had other reasons for discontinuing study medication, primarily treatment-related adverse events.

5. Eradication

ITT and PP Analyses

For both the ITT and PP analyses, the applicant noted there was no significant interaction between baseline ulcer status and treatment group in the logistic regression model (i.e., treatment group differences were similar between patients with an active DU at Baseline and patients with a history of DU disease but without an active DU at Baseline). In addition,

there was no significant effect of baseline ulcer status on *H. pylori* eradication at the Day 38 visit.

As shown in Table 9, for the PP analysis, the HAC group had a significantly higher proportion of patients considered to have *H. pylori* eradication at the Day 38 visit (84%) than the HC group (55%). Similarly, in the ITT analysis, the HAC group had a significantly higher proportion of patients considered to have *H. pylori* eradication at the Day 38 visit (77%) than the HC group (52%).

TABLE 9
***H. pylori* Eradication at Day 38 Visit**
Per-Protocol and Intention-to-Treat Analyses
Study #191

	H 40 qd + A 1000 bid + C 500 bid	H 40 qd + C 500 bid	p-value
H. pylori Eradicated Day 38 Visit	n/N (%) [95% CI]	n/N (%) [95% CI]	
Per-Protocol	164/196 (84%) [78%, 89%]	103/187 (55%) [48%, 62%]	$p < 0.0001$*
Intention-to-Treat	179/233 (77%) [71%, 82%]	112/215 (52%) [45%, 59%]	$p < 0.0001$*

* Significant difference between the treatment groups, ($p \leq 0.050$), using a logistic regression model with treatment group and baseline duodenal ulcer status as terms in the model.

Clinical Reviewer's Comment: Table 6, as well as Table 4, in Appendix 1 contains Criteria A-H as reasons for a patient to be considered non-evaluable for the PP analysis. In addition, a patient was excluded from the PP analysis for the assessment of Eradication if he/she did not have available data from the follow-up endoscopy or returned before Day 35 and had negative test results. As seen below in the table, the following additional patients were excluded from the PP Eradication Analysis due to no follow-up data or a negative H. pylori status before Day 35. Therefore, the denominators used in Table 9 are correct for the PP Analysis.

	HAC	***HC***
Included in PP Eradication Analyses (from Table 6)	*211*	*196*
*Additional Patients Excluded from PP Eradication Analysis**		
No follow-up data or negative for Hp before Day 35	*15*	*9*
Total Included in PP Eradication Analysis	*196*	*187*

**not listed in Table 6, or Table 4 in Appendix 1*

Subgroup Analysis

Table 10 presents the *H. pylori* eradication rates at the Day 38 visit based on gender, race (Caucasian, Black or other), age (≤ 65 years or > 65 years), baseline smoking status (smoker or non-smoker), baseline DU status (active DU or no DU), baseline clarithromycin susceptibility status (resistant/intermediate, susceptible, or no result), and compliance to study medication (compliant or not compliant). No formal statistical analyses were performed by the applicant to compare treatment groups within each of these subgroups since the sample sizes for some of the subgroups were relatively small.

In addition to summarizing *H. pylori* eradication rates within the subgroups, covariate analyses using logistic regression were performed by the applicant to determine whether gender, race, age, baseline smoking status, baseline clarithromycin susceptibility status or compliance to study medication had a significant effect on the *H. pylori* eradication rates at the Day 38 visit. Gender, race, age, and baseline smoking status did not have any significant effects on *H. pylori* eradication status. The effect of compliance to study medication was not assessed because of zero cells in the logistic regression model. All 11 patients who were not compliant were also not *H. pylori* eradicated.

Clinical Reviewer's Comment: These 11 patients discontinued from the study due to a drug-related AE. Therefore, they are included in the PP population and are considered failures for H. pylori eradication.

Only baseline clarithromycin susceptibility status had a significant effect on *H. pylori* eradication rates at the Day 38 visit. For both treatment groups combined, there were 38 patients with *H. pylori* resistant to clarithromycin at Baseline. Of those, 12 patients (32%) achieved *H. pylori* eradication at Day 38. In contrast, there were 233 patients with *H. pylori* susceptible to clarithromycin at Baseline, and 176 of those patients (76%) achieved eradication at Day 38. The treatment group effect remained significant when each of these covariates was added to the logistic regression model.

TABLE 10
***H. pylori* Eradication at Day 38 Visit - Subgroup Analysis**
Number (%) of Patients, Per-Protocol Analysis
Study #191

	H 40 qd A 1000 bid + C 500 bid		H 40 qd + C 500 bid	
	n/N	(%)	n/N	(%)
Overall Eradication Rates	164/196	(84%)	103/187	(55%)
Gender				
Males	107/122	(88%)	63/118	(53%)
Females	57/74	(77%)	40/69	(58%)
Race				
Caucasian	119/142	(84%)	68/126	(54%)
Black	38/45	(84%)	27/47	(57%)
Other	7/9	(78%)	8/14	(57%)
Age				
≤ 65 years	140/168	(83%)	90/161	(56%)
> 65 years	24/28	(86%)	13/26	(50%)
Baseline Smoking Status				
Smokers	54/60	(90%)	36/60	(60%)
Non-Smokers	110/136	(81%)	67/127	(53%)
Baseline Duodenal Ulcer Status				
Active duodenal ulcer	132/154	(86%)	82/144	(57%)
No active duodenal ulcer	32/42	(76%)	21/43	(49%)
Baseline Clarithromycin Susceptibility Status				
Resistant/Intermediate	8/19	(42%)	4/19	(21%)
Susceptible	111/124	(90%)	65/109	(60%)
No Result	45/53	(85%)	34/59	(58%)
Compliance to Study Medication				
Patient compliant	164/191	(86%)	103/181	(57%)
Patient not compliant[a]	0/5	(0%)	0/6	(0%)

[a] Compliance to study medication was a criteria for inclusion in the PP population. These 11 patients discontinued from the study due to a drug-related AE and satisfied PP criteria A and B. Therefore, they are included in the PP population and are considered failures for *H. pylori* eradication - regardless of compliance status.

Clinical and Statistical Reviewers' Comment: The applicant did not do a formal statistical analysis of baseline DU status and so we performed our own calculation. It has previously been suggested, although not proven, that patients with active ulcers may more easily eradicate H. pylori than those with a history of ulcer disease due to the active inflammation and potentially better penetration of antimicrobials into the site of infection.

There was no significant difference in the eradication rates obtained in patients with an active ulcer versus a history of ulcer disease for either treatment group. This finding is consistent with what has been observed with other approved treatment regimens.

Eradication Rates by Ulcer Status

Treatment	*Active Ulcer*	*History of Ulcer*	*P-value**
HAC	*132/154 (86%)*	*32/42 (76%)*	*0.159*
HC	*82/144 (57%)*	*21/43 (49%)*	*0.385*

** Two-sided Fisher's Exact test.*

Sensitivity Analysis

In the PP population, 24 patients had missing *H. pylori* status at Day 38 (15 patients in the HAC group and 9 patients in the HC group). These patients were not included in the analysis of *H. pylori* eradication. However, to examine the potential effects that these patients may have had on the *H. pylori* eradication rates if data to determine *H. pylori* status had been available at Day 38, the applicant conducted a sensitivity analysis.

The missing values were imputed in two ways: a worst-case analysis and a best-case analysis. The worst-case analysis assumed patients with missing values were not eradicated at Day 38. The best-case analysis assumed patients with missing values were eradicated at Day 38. As shown in Table 11, for the HAC group, the eradication rates ranged between 78% for the worst-case analysis to 85% for the best-case analysis. For the HC group, the eradication rates ranged between 53% for the worst-case analysis to 57% for the best-case analysis. The applicant performed no statistical comparisons between the treatment groups. The results of the applicant's PP sensitivity analysis demonstrated that the effect of any missing values was slight.

TABLE 11
Per-Protocol Sensitivity Analysis for Missing Data
***H. pylori* Eradication at Day 38 Visit**
[95% Confidence Intervals]
Study #191

	H 40 qd + A 1000 bid + C 500 bid	H 40 qd + C 500 bid
H. pylori Eradication at Day 38	n/N (%) [95% CI]	n/N (%) [95% CI]
Worst-case estimation	164/211 (78%) [72%, 83%]	103/196 (53%) [45%, 60%]
Best-case estimation	179/211 (85%) [79%, 89%]	112/196 (57%) [50%, 64%]

A summary of the proportion of patients experiencing AEs at any time throughout the 38-day study period is presented in Table 17.

TABLE 17
Adverse Event Summary Throughout Entire Study Period
Number (%) of Patients
All Randomized Patients Who Took At Least One Dose of Study Medication
Study #191

	H 40 qd + A 1000 bid + C 500 bid (N=263)		H 40 qd + C 500 bid (N=250)	
Number (%) of Patients:	n	(%)	n	(%)
With ≥1 AE	159	(60%)	140	(56%)
With a possibly or probably drug related AE	91	(35%)*	66	(26%)
With a serious AE	2	(< 1%)	2	(< 1%)
Discontinued due to an AE	10	(4%)	9	(4%)

* Significantly different from the H 40 qd + C 500 bid treatment group, ($p \leq 0.050$), using a Fisher's Exact Test.

There were no significant differences between the treatment groups with respect to the proportion of patients experiencing at least one AE, the proportion of patients experiencing serious AEs, or the proportion of patients who discontinued from the study early due to an AE. However, the proportion of patients experiencing at least one AE classified as possibly or probably related to the study drugs by the investigator was significantly higher in the HAC group (91 of 263 patients or 35%) than in the HC group (66 of 250 patients or 26%).

Four patients in this study experienced an AE considered to be serious (2 patients in the HAC group and 2 patients in the HC group). Also, 19 patients in this study discontinued from the study due to an AE (10 patients in the HAC group, 9 patients in the HC group).

Based on all randomized patients, of the 118 patients enrolled in this study who did not have an active DU at the baseline endoscopy, there were 4 patients (3%) who developed an ulcer (3 duodenal ulcers and one gastric ulcer) at some time during the study period. Three of these patients were enrolled in the HAC group and one was in the HC group.

Table 18 presents individual AEs under each body system category if at least 1% of the patients in either of the two treatment groups had experienced that particular AE.
The most common AEs occurring in this study (with an incidence of ≥ 5% in both treatment groups combined) were gastritis (62/513 or 12%), diarrhea (54/513 or 11%), taste perversion (43/513 patients or 8%), headache (42/513 or 8%), esophagitis (37/513 or 7%), abdominal pain (30/513 or 6%), and nausea (26/513 or 5%).

TABLE 18
Adverse Events (AEs) Throughout Entire Study Period By Body System
Number (%) of Patients
(Patient Incidence ≥ 1% in Either Treatment Group for Individual AEs)
All Randomized Patients Who Took At Least One Dose of Study Medication
Study #191

Body System AE	H 40 qd + A 1000 bid + C 500 bid (N=263)			H 40 qd + C 500 bid (N=250)		
	n	(%)		n	(%)	
Body as a Whole						
asthenia	0	---	[0]	4	(2%)	[2]
back pain	3	(1%)	[0]	5	(2%)	[0]
Central and Periph Nervous System	11	(4%)	[8]	10	(4%)	[6]
dizziness	21	(8%)	[10]	21	(8%)	[13]
headache						
Gastrointestinal System Disorders						
abdominal pain	15	(6%)	[11]	15	(6%)	[6]
constipation	4	(2%)	[1]	10	(4%)	[7]
diarrhoea	29	(11%)	[27]	25	(10%)	[19]
duodenitis	15	(6%)	[1]	8	(3%)	[2]
dyspepsia	7	(3%)	[2]	6	(2%)	[1]
epigastric pain	3	(1%)	[2]	4	(2%)	[0]
flatulence	8	(3%)	[7]	5	(2%)	[3]
gastritis	35	(13%)	[4]	27	(11%)	[5]
gastro-intestinal system dis nos	4	(2%)	[0]	5	(2%)	[0]
gastroesophageal reflux	0	---	[0]	3	(1%)	[0]
mouth dry	2	(<1%)	[2]	5	(2%)	[4]
nausea	12	(5%)	[12]	14	(6%)	[12]
oesophagitis	21	(8%)	[3]	16	(6%)	[3]
vomiting	6	(2%)	[5]	2	(<1%)	[2]
Liver Bil System Disorders						
SGOT increased	3	(1%)	[3]	0	---	[0]
SGPT increased	6	(2%)	[5]	0	---	[0]
Musculoskeletal System Disorders						
hernia	7	(3%)	[1]	4	(2%)	[0]
Platelet, Bleeding and Clotting						
purpura	0	---	[0]	3	(1%)	[0]

[ ] The numbers in brackets are counts of patients who had AEs that were rated possibly or probably drug-related by the investigator.

* Significantly different from the H 40 qd + C 500 bid treatment group, ($p \leq 0.050$), using a Fisher's Exact Test.

TABLE 18 (continued)
Adverse Events (AEs) Throughout Entire Study Period By Body System
Number (%) of Patients
(Patient Incidence ≥ 1% in Either Treatment Group for Individual AEs)
All Randomized Patients Who Took At Least One Dose of Study Medication
Study #191

Body System AE	H 40 qd + A 1000 bid + C 500 bid (N=263)			H 40 qd + C 500 bid (N=250)		
	n	(%)		n	(%)	
Psychiatric Disorders						
anxiety	3	(1%)	[0]	2	(< 1%)	[1]
insomnia	4	(2%)	[2]	4	(2%)	[0]
somnolence	4	(2%)	[3]	0	---	[0]
Resistance Mechanism Disorders moniliasis	4	(2%)	[4]	0	---	[0]
Respiratory System Disorders						
respiratory infection	7	(3%)	[0]	6	(2%)	[1]
rhinitis	4	(2%)	[1]	1	(< 1%)	[0]
sinusitis	0*	---	[0]	5	(2%)	[0]
Skin and Appendages Disorders						
rash	3	(1%)	[2]	3	(1%)	[2]
Special Senses Other Disorders						
taste perversion	20	(8%)	[20]	23	(9%)	[21]
Urinary System Disorders						
urinary tract infection	4	(2%)	[0]	2	(< 1%)	[1]

[ ] The numbers in brackets are counts of patients who had AEs that were rated possibly or probably drug-related by the investigator.

* Significantly different from the H 40 qd + C 500 bid treatment group, ($p \leq 0.050$), using a Fisher's Exact Test.

APPEARS THIS WAY
ON ORIGINAL

Serious Adverse Events

Of the 513 patients enrolled into this study who took at least one dose of study medication, 4 patients experienced an AE considered to be serious (2 patients in the HAC group, 2 patients in the HC group). All of these serious AEs were considered to be unlikely related to the study drug by the investigator and the reviewer. These serious AEs are presented in Table 19.

TABLE 19
Listing of Serious Adverse Events Occurring Throughout the Entire Study Period
Study #191

Site/ Enroll-ment #	AN	Gender/ Age (yrs)	Relative day of Onset	AE	Dur. (Days)	Intensity	Drug Rel.	Action Taken With Drug	Serious Outcome
H 40 qd + A 1000 bid + C 500 bid group									
040/003	1607	F/43	13	Renal dysfunction aggravated	Cont.	Severe	Unlikely	None	Intervention required
053/006	1858	M/67	9	Anxiety	Cont.	Moderate	Unlikely	Stopped	Hospitalization
			9	Dementia	Cont.	Moderate	Unlikely	Stopped	Hospitalization
H 40 qd + C 500 bid group									
025/001	1253	F/71	119	Gastric carcinoma	Cont.	Severe	Unlikely	None	Cancer
075/006	1518	M/55	25	Cellulitis skin	16	Moderate	Unlikely	None	Hospitalization

APPEARS THIS WAY
ON ORIGINAL

A total of 19 of the 513 patients (4%) enrolled into this study who took at least one dose of study medication experienced an AE which caused the patient to discontinue from the study. Table 20 lists the patients who discontinued from the study due to an AE.

TABLE 20
Patients Discontinued from Study Due to Adverse Events
Occurring Throughout Entire Study Period
Study #191

Site/ Enroll-ment #	AN	Gender/ Age (yrs)	Rel. Day of Onset	AE	Dur. (Days)	Inten-sity	Drug Rel.	Serious	Last Day of Study Med.	Study Day Discon-tinued	Action Taken w/ Drug
H 40 qd + A 1000 bid + C 500 bid group											
008/004	1336	F/62	3 3 3	Hallucination Dizziness Nausea	1 1 1	Mod. Mild Mild	Poss. Poss. Poss.	No No No	3	24	Drug stopped
013/001	1020	F/59	1	Abdominal pain	2	Sev.	Poss.	No	1	2	Drug stopped
014/009	1773	M/31	28	Oesophagitis	Cont.	Mild	Unlik.	No	10	28	Drug stopped
014/011	1775	F/72	1	Nausea	15	Mod.	Prob.	No	3	21	Drug stopped
017/016	1640	M/30	1 3 3	Diarrhoea Dizziness Hypoaesthesia	2 1 3	Mild Mild Mod.	Poss. Unlik. Unlik.	No No No	5	8	Drug stopped
038/002	1237	M/34	27	Abdominal pain	Cont.	Mod.	Unlik.	No	13	49	Drug stopped
063/002	1058	F/30	13 13	Diarrhoea Epigastric pain	9 9	Mild Mod.	Poss. Poss.	No No	10	19	Drug stopped
074/002	1258	F/28	5	Pharynx disorder	6	Mild	Poss.	No	8	21	Drug stopped
080/006	1359	F/34	1	Abdominal pain	4	Mod.	Prob.	No	3	23	Drug stopped
084/019	1790	F/77	1 1 1 1	Abdominal pain Taste perversion Headache Nausea	6 6 6 6	Mod. Sev. Sev. Mod.	Poss. Poss. Poss. Poss.	No No No No	6	45	Drug stopped

APPEARS THIS WAY
ON ORIGINAL

TABLE 20 (Cont.)
Patients Discontinued from Study Due to Adverse Events
Occurring Throughout Entire Study Period
Study #191

Site/ Enroll-ment #	AN	Gender/ Age (yrs)	Rel. Day of Onset	AE	Dur. (Days)	Inten-sity	Drug Rel.	Serious	Last Day of Study Med.	Study Day Discon -tinued	Action Taken w/ Drug
H 40 qd + C 500 bid group											
003/012	1767	F/49	2	Headache	1	Mod.	Poss.	No	1	11	Drug stopped
014/010	1774	F/45	20	Gastritis	Cont.	Mild	Unlik.	No	10	20	Drug stopped
015/006	1510	M/46	2 2 2	Dizziness Nausea Vomiting	<1 <1 <1	Mod. Mod. Mod.	Poss. Poss. Poss.	No No No	2	6	Drug stopped
018/010	1562	M/20	25 25 25	Gastroesoph-ageal reflux Oesophagitis Dyspepsia	4 4 4	Sev. Mod. Sev.	Unlik. Unlik. Unlik.	No No No	10	29	None
038/005	1853	M/72	1	Abdominal pain	3	Mod.	Poss.	No	3	12	Drug stopped
040/002	1608	M/44	3 3 3 3 5 5 5	Allergic reaction Pruritus Pruritus Rash Anxiety Dyspnoea Chest pain	5 6 6 4 5 2 4	Mod. Mild Mild Mod. Mild Mild Mild	Prob. Prob. Prob. Prob. Prob. Prob. Prob.	No No No No No No No	6	10	Drug stopped
042/008	1611	F/43	1 6 6	Headache Dyspepsia Epigastric pain (aggravated)	6 8 1	Sev. Sev. Sev.	Prob. Poss. Poss.	No No No	6	14	Drug stopped
057/007	1623	M/28	1	Diarrhoea	1	Sev.	Prob.	No	1	24	Drug stopped
078/006	1486	M/34	22	Epigastric pain	Cont.	Mod.	Unlik.	No	10	24	Drug stopped

Clinical Laboratory Evaluation

Laboratory measurements were collected from each patient at the Screening/Baseline visit as well as at the Day 11 and Day 38 Visits. For each quantitative laboratory test in the chemistry and hematology groups, the mean change from the baseline measurement was analyzed. There were no clinically meaningful mean changes from Baseline to the Day 11 Visit, Baseline to the Day 38 Visit, or from Baseline to the Day 11 Visit or the Day 38 Visit for any of the laboratory tests for either treatment group. No statistical comparisons were performed between the treatment groups.

Laboratory test data were also analyzed in relation to the laboratory test reference ranges specified by [redacted] Statistical comparisons were made between the treatment groups for the distribution of patients across the classifications according to the reference range at the Day 11 Visit and the Day 38 Visit for each of the

hematology and blood chemistry tests. There was one laboratory test with a significant difference observed between the treatment groups. This significant difference was observed in ASAT (SGOT) levels at the Day 38 Visit ($p \leq 0.050$). At the Day 38 Visit, 13 out of 233 patients in the HAC group had ASAT (SGOT) values above the normal reference range (9 of these patients had values within the normal range at baseline); whereas, 3 out of 229 patients in the HC group had ASAT (SGOT) values above the normal reference range (1 of these patients had values within the normal range at baseline).

Clinical Reviewer's Comment: A further discussion of this increase in ASAT levels can be found in the Integrated Summary of Safety (ISS).

11. Vital Signs, Physical Findings and Other Observations Related to Safety

Measurements for weight, pulse, and blood pressure were to be collected for each patient at the Screening/Baseline Visit, as well as other visits throughout the study (Day 11 and Day 38 Visits for pulse and blood pressure, Day 38 Visit for weight). There were no clinically meaningful mean changes from Baseline for any of the vital sign measurements at any timepoint for any treatment group.

O. Reviewers' Conclusions of Study 191

This was a well conducted, randomized, clinical trial which demonstrated the superiority of triple therapy (HAC) over dual therapy (HC) when given for 10 days with twice daily dosing. The lower bound of the 95% confidence interval of the point estimate for triple therapy using the ITT analysis was 71%, which is above the 60 percent threshold as suggested by the Division.

In addition, several interesting observations were made:

- *The overall eradication rate for the combined treatment groups was not significantly higher for patients with an active DU (214/298; 71.8%) versus those with a history of DU (53/85; 62.4%). P=0.095.*
- *Clarithromycin resistance developed in only one patient who received HAC versus 19 who received HC.*

VII. Clinical and Statistical Review of Study 192

A. Investigators and Study Administrative Structure

Thirty-two (32) primary investigators participated in the trial.

This study used identical contract organizations and central laboratories to those used in Study 191.

B. Study Objectives

Primary Objectives

- To assess the efficacy of a 10-day treatment regimen of H 199/18 40 mg QD with clarithromycin 500 mg BID compared to H 199/18 40 mg QD in the eradication of *H. pylori* at 4 weeks post-therapy in *H. pylori*-infected patients with active 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 clarithromycin 500 mg BID compared to H 199/18 40 mg QD in *H. pylori* infected patients with active DU or history of DU disease.

Secondary Objectives

- To assess the susceptibility of *H. pylori* to 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 + clarithromycin 500 mg bid (45 patients planned, revised from 90 patients)
- H 199/18 40 mg qd (15 patients planned, revised from 35 patients)

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

The overall study design was identical to Study 191.

The study was designed to enroll approximately 125 patients. Amendment 2 of the protocol documented a reduction in the total number of patients from 125 to 60. Randomization of the two treatment groups was defined as follows: 45 patients for Group 1, (H 199/18 40 mg qd and clarithromycin 500 mg bid) and 15 patients for Group 2, (H 199/18 40 mg qd). The reduction in the number of patients was necessary because patient enrollment was slower than anticipated. The Division was consulted regarding the proposed reduction in sample size. According to the applicant, the study would remain adequately powered with the reduction in sample size to 60 patients.

D. Results

1. Investigators

There were 32 investigator sites initiated for this study. Of these sites, eighteen randomized and enrolled a total of 68 patients. The other 14 (44%) sites never enrolled any patients. Of the 18 sites that enrolled patients, 14 sites enrolled 5 or fewer patients and 17 sites enrolled 8 or fewer patients. The site with the highest enrollment (Site 218) enrolled 21% (14 of 68 patients) of the total number of patients enrolled in the study.

Clinical Reviewer's Comment: The number of sites that were initiated for this study, but did not enroll any patients, is large.

Table 1 in Appendix 2 presents the distribution of patient enrollment by treatment group for each investigator site.

2. Patient Accountability

The number of patients in each treatment group who completed the study as stated in the protocol, and the number of patients who discontinued from the study are listed in Table 1. The applicant indicated that there were no significant differences observed between the treatment groups for the proportion of patients who completed the study or for any reason discontinued from the study, ($p > 0.050$), using Fisher's Exact Test.

TABLE 1
Patient Accounting - All Randomized Patients
Study #192

	H 40 qd + C 500 bid		H 40 qd	
Study Status	n	(%)	n	(%)
Patients Enrolled	51		17	
Completed the Study Period	48	(94%)	17	(100%)
Discontinued from Study	3	(6%)	0	(0%)
Lack of Therapeutic Response	0	---	0	---
AE	2	(4%)	0	---
Consent Withdrawn	0	---	0	---
Lost to Follow Up	1	(2%)	0	---
Sponsor/Investigator Decision	0	---	0	---

The number of patients who were included (considered evaluable) or excluded (considered non-evaluable) from each analysis is summarized by treatment group in Table 2 according to the reason considered non-evaluable. No patient was counted under more than one violation for either the ITT or PP analysis.

For the PP analysis, if an evaluable patient had a missing value (within day ranges) for a particular efficacy parameter, the patient was not included in the analysis of that parameter.

H. pylori infected patients who discontinued from the study due to an AE related to the study drug were determined to be evaluable failures for the PP analysis.

TABLE 2
Number of Patients Included and Excluded in the Statistical Analyses (Study #192)

	H 40 qd + C 500 bid		H 40 qd	
	n	(%)	n	(%)
Total enrolled	51		17	
Included in Efficacy Analysis				
Intention-To-Treat	50	(98%)	16	(94%)
Per-Protocol	47	(92%)	15	(88%)
Excluded from Efficacy Analysis				
Intention-To-Treat	1	(2%)	1	(6%)
A. *H. pylori* not positive at Baseline	1		1	
B. No baseline DU and no history of DU	0		0	
C. No study medication taken	0		0	
Per-Protocol	4	(8%)	2	(12%)
A. *H. pylori* not positive at Baseline	1		1	
B. Baseline DU not at least 0.5 cm and no history of DU within last 5 years	1		0	
C. Took antimicrobials, bismuth, or PPI prior to enrollment	0		0	
D. Noncompliance of study medication	2		0	
E. Concomitant antimicrobials or bismuth compounds	0		1	
F. Concomitant H2-RA, PPI or sucralfate	0		0	
G. Other conditions/diseases	0		0	
Included in Safety Analysis	51	(100%)	17	(100%)

Clinical Reviewer's Comments: Two patients taking concomitant antimicrobials were not excluded from the applicant's analysis. Both patients were in the HC group and took TMP/SMX (218/012 AN 2140 eradicated H. pylori and 231/001 AN 2172 did not eradicate H. pylori). The reviewer agrees with the applicant's decision not to exclude these patients from the PP analysis, since it is unlikely that TMP/SMX will eradicate H. pylori in vivo.

Table 3 lists each patient who was considered non-evaluable for either the ITT or PP analysis and the reason(s) that each patient was considered non-evaluable.

TABLE 3
Patients Excluded from Efficacy Analysis
All Randomized Patients
Study #192

Treatment Group	Site No/ Enrollment No	AN	Excluded from ITT Analysis	Reason(s) for Exclusion	Excluded from PP Analysis	Reason(s) for Exclusion
H 40 qd + C 500 bid	200/001	2045	No		Yes	D
H 40 qd + C 500 bid	209/008	2112	No		Yes	D
H 40 qd + C 500 bid	218/007	2091	Yes	A	Yes	A
H 40 qd + C 500 bid	221/001	2088	No		Yes	B
H 40 qd	209/006	2110	Yes	A	Yes	A
H 40 qd	229/003	2161	No		Yes	E

Clinical Reviewer's Comment: One of the two patients excluded from the PP analysis for noncompliance (2001/001; 2045) in the HC group, discontinued the study due to an adverse event (death) not felt to be related to study drug. This patient should still be considered non-evaluable for the PP analysis.

The individual results for the *H. pylori* eradication analysis at the Day 38 visit and DU healing analysis by the Day 38 visit, as well as the day the patient discontinued from the study and reason for discontinuing from the study, are summarized in Table 2 in Appendix 2 for those patients considered non-evaluable for the ITT analysis. Table 3 in Appendix 2 presents the same results for those patients considered non-evaluable for the PP analysis.

Clinical Reviewer's Comment: Tables 2 and 3 in Appendix 2 have been modified from the applicant's original tables for simplicity.

3. Demographic Characteristics

A total of 68 patients were randomized and given study medication to take for one of the two treatment groups in this study. A summary of the baseline patient demographic data is displayed in Table 4 for all 68 randomized patients. There were no significant differences observed between the two treatment groups, HC and H, for any baseline demographic characteristic for the all randomized patients, ITT, or PP patient populations.

The applicant indicated there were no significant differences observed between the treatment groups for any baseline demographic or characteristic ($p > 0.050$), using Fisher's Exact Test or Analysis of Variance (ANOVA).

TABLE 4
Baseline Patient Demographics and Characteristics
All Randomized Patients
Study #192

	H 40 qd + C 500 bid (N=51)		H 40 qd (N=17)	
	n	(%)	n	(%)
Gender				
Male	34	(67%)	10	(59%)
Female	17	(33%)	7	(41%)
Age (years)				
Mean (SD)	48.4 (12.9)		52.2 (11.3)	
Median	46		49	
Range	26 to 80		37 to 77	
≤ 65 years	45	(88%)	15	(88%)
> 65 years	6	(12%)	2	(12%)
Race				
Caucasian	29	(57%)	9	(53%)
Black	21	(41%)	6	(35%)
Other	1	(2%)	2	(12%)
Smoking Status				
Smoker	22	(43%)	8	(47%)
Nonsmoker	29	(57%)	9	(53%)
Baseline DU Status				
Active DU	34	(67%)	13	(76%)
No active DU	17	(33%)	4	(24%)
Any Upper GI Symptoms				
Yes	47	(92%)	15	(88%)
No	4	(8%)	2	(12%)
Duration of DU Disease				
< 1 year	20	(39%)	7	(41%)
1 to 5 years	21	(41%)	7	(41%)
> 5 years	10	(20%)	3	(18%)
Number of previous episodes of documented active DU				
0	17	(33%)	5	(29%)
1	23	(45%)	7	(41%)
2	4	(8%)	4	(24%)
≥ 3	7	(14%)	1	(6%)
Number of previous attempts to eradicate *H. pylori*				
0	35	(69%)	13	(76%)
1	14	(27%)	3	(18%)
2	2	(4%)	1	(6%)
≥ 3	0	(0%)	0	(0%)

4. Compliance Results

Patients in both treatment groups were able to complete most of their study medication. The amounts of study medications taken were similar between the treatment groups. No significant differences were observed by the applicant between the treatment groups ($p > 0.050$ by Fisher's Exact Test) in the distributions of patients according to the number of capsules or tablets taken for any of the study drugs (H 199/18 or clarithromycin/ clarithromycin placebo).

Table 4 in Appendix 2 shows the distribution of the number of individual study medications (tablets and capsules) taken in each treatment group.

A patient was considered to be compliant if he/she took at least 75% of the prescribed doses of study medication (for each of the two study drugs). As shown in Table 5, compliance in this study was very high: 94% of the patients (48 of 51 patients) in the HC group and 100% of the patients (17 of 17 patients) in the H group were compliant. There was no significant difference observed by the applicant in the proportion of non-compliant patients between the treatment groups ($p > 0.050$) using Fisher's Exact Test.

TABLE 5
Patient Compliance with Study Medication
Number (%) of Patients
All Randomized Patients
Study #192

	H 40 qd + C 500 bid (N=51)		H 40 qd (N=17)	
Number (%) of Patients	n	(%)	n	(%)
Compliant [a]	48	(94%)	17	(100%)
Noncompliant	3	(6%)	0	(0%)

[a] Patients were considered to be compliant if they took at least 75% of the prescribed doses of each study medication.

Clinical Reviewer's Comment: The following three patients in the HC group were noncompliant for the following reasons: (200/001 AN 2045) experienced a serious adverse event (death) not felt to be related to study drug, (223/001 AN 2053) experienced adverse events felt to be probably related to study drug; and (209/008 AN 2112) did not return study medications.

5. Eradication

ITT and PP Analyses

For both the ITT and the PP analyses, the applicant noted there was no significant interaction between baseline ulcer status and treatment group in the logistic regression model (i.e., treatment group differences were similar between patients with an active DU at Baseline and patients with a history of DU disease but without an active DU at Baseline). In

addition, there was no significant effect of baseline ulcer status on *H. pylori* eradication at the Day 38 visit.

As seen in Table 6, for the PP analysis, the HC group had a significantly higher proportion of patients considered to have *H. pylori* eradication at the Day 38 visit (50%) than the H group (0%). Similarly, in the ITT analysis, the HC group had a significantly higher proportion of patients considered to have *H. pylori* eradication at the Day 38 visit (46%) than the H group (0%).

TABLE 6
***H. pylori* Eradication at Day 38 Visit**
Per-Protocol and Intention-to-Treat Analyses
Study #192

	H 40 qd + C 500 bid	H 40 qd	p-value
H. pylori Eradicated Day 38 Visit	n/N (%) [95% CI]	n/N (%) [95% CI]	
Per protocol	22/44 (50%) * [35%, 65%]	0/15 (0%) [0%, 22%]	p = 0.022
Intention-to-Treat	23/50 (46%) * [32%, 61%]	0/16 (0%) [0%, 21%]	p = 0.028

* Significantly different from H 40 qd , ($p < 0.050$), using a logistic regression model.

Clinical Reviewer's Comment: Table 2, as well as Table 3, in Appendix 2 contains Criteria A-H as reasons for a patient to be considered non-evaluable for the PP analysis. In addition, a patient was excluded from the PP analysis for the assessment of Eradication if he/she did not have available data from the follow-up endoscopy or returned before Day 35 and had negative test results. As seen below in the table, the following additional patients were excluded from the PP Eradication Analysis due to no follow-up data or a negative H. pylori status before Day 35. Therefore, the denominators used in Table 6 are correct for the PP Analysis.

	HC	***H***
Included in PP Eradication Analyses (from Table 2)	*47*	*15*
*Additional Patients Excluded from PP Eradication Analysis**		
No follow-up data or negative for Hp before Day 35	*3*	*0*
Total Included in PP Eradication Analysis	*44*	*15*

**not listed in Table 2, or Table 3 in Appendix 2*

Subgroup Analysis

Table 7 presents the *H. pylori* eradication rates at the Day 38 visit based on gender, race (Caucasian, Black or other), age (≤ 65 years or > 65 years), baseline smoking status (smoker or non-smoker), baseline DU status (active DU or no DU), baseline clarithromycin susceptibility status (resistant/intermediate, susceptible, or no result), and compliance to

study medication (compliant or not compliant). No formal statistical analyses were performed by the applicant to compare treatment groups within each of these subgroups since the sample sizes for some of the subgroups were relatively small.

In addition to descriptive statistics for the subgroups, statistical analyses using logistic regression were performed by the applicant to determine whether gender, race, age, baseline smoking status, baseline clarithromycin susceptibility status or compliance to study medication had a significant effect on the *H. pylori* eradication rates at the Day 38 visit. Only baseline clarithromycin susceptibility status had a significant effect on *H. pylori* eradication rates at the Day 38 visit. The treatment group effect remained significant when each of these covariates was added to the logistic regression model.

TABLE 7
***H. pylori* Eradication at Day 38 Visit - Subgroup Analysis**
Number (%) of Patients
Per-Protocol Analysis
Study #192

	H 40 qd + C 500 bid		H 40 qd	
	n/N	(%)	n/N	(%)
Overall Eradication Rates	22/44	(50%)	0/15	(0%)
Gender				
Males	16/31	(52%)	0/8	(0%)
Females	6/13	(46%)	0/7	(0%)
Race				
Caucasian	14/25	(56%)	0/8	(0%)
Black	8/18	(44%)	0/6	(0%)
Other	0/1	(0%)	0/1	(0%)
Age				
≤ 65 years	18/39	(46%)	0/13	(0%)
> 65 years	4/5	(80%)	0/2	(0%)
Baseline Smoking Status				
Smokers	10/19	(53%)	0/7	(0%)
Non-Smokers	12/25	(48%)	0/8	(0%)
Baseline DU Status				
Active DU	17/29	(59%)	0/11	(0%)
No active DU	5/15	(33%)	0/4	(0%)
Baseline Clarithromycin Susceptibility Status				
Resistant/Intermediate	0/9	(0%)	0/3	(0%)
Susceptible	16/24	(67%)	0/10	(0%)
No Result	6/11	(55%)	0/2	(0%)
Compliance to Study Medication				
Patient compliant	22/43	(51%)	0/15	(0%)
Patient not compliant	0/1	(0%)	0/0	---

Sensitivity Analysis

In the PP population, 3 patients in HC group were missing *H. pylori* status at Day 38. These patients were not included in the analysis of *H. pylori* eradication. However, to examine the potential effects that these patients may have had on the *H. pylori* eradication rates if data

to determine *H. pylori* status had been available at Day 38, a sensitivity analysis was conducted by the applicant (see Table 8). The missing values were imputed in two ways: a worst-case analysis and a best-case analysis. The worst-case analysis assumes patients with missing values were not eradicated at Day 38. The best-case analysis assumes patients with missing values were eradicated at Day 38. The applicant performed no statistical comparisons between the treatment groups. The results demonstrated that the effect of any missing values was slight.

TABLE 8
Per-Protocol Sensitivity Analysis for Missing Data
***H. pylori* Eradication at Day 38 Visit**
[95% Confidence Intervals]
Study #192

	H 40 qd + C 500 bid	H 40 qd
H. pylori Eradication at Day 38	n/N (%) [95% CI]	n/N (%) [95% CI]
Worst-case estimation	22/47 (47%) [32%, 62%]	0/15 (0%) [0%, 22%]
Best-case estimation	25/47 (53%) [38%, 68%]	0/15 (0%) [0%, 22%]

Evaluability Status

A total of 2 patients were considered not infected at Baseline (1 patient in the HC group and 1 patient in the H group). The Day 38 visit results show that 4 of the 68 patients (6%) enrolled in this study did not have any final *H. pylori* test results for any of the three diagnostic tests.

The classification of various combinations of outcomes for the three *H. pylori* diagnostic tests along with the number of patients for each combination are presented in Tables 5 and 6 in Appendix 2 for the baseline visit and the Day 38 visit, respectively.

Clinical Reviewer's Comment: The evaluability status of all patients was considered appropriately classified for the baseline and Day 38 visits.

6. Duodenal Ulcer Healing

The proportion of patients considered to have a healed DU by the Day 38 visit (for patients with an active DU at Baseline) is presented in Table 9 for each of the two treatment groups.

For the PP analysis, the HC group had a significantly higher proportion of patients considered to have a healed DU by the Day 38 visit (81%) than the H group (45%). While the same trend was evident for the ITT analysis, the difference between the DU healing rates in the two treatment groups was not significantly different.

TABLE 9
DU Healed Status by Day 38 Visit
For Patients with an Active DU at Baseline
Per-Protocol and Intention-to-Treat Analyses
Study #192

	H 40 qd + C 500 bid	H 40 qd	p-value
DU Healed by Day 38 visit	n/N (%)	n/N (%)	
Per-Protocol	26/32 (81%)*	5/11 (45%)	p = 0.029
Intention-To-Treat	26/34 (76%)	6/12 (50%)	p = 0.095

* Significantly different from H 40 qd , ($p < 0.050$), using a logistic regression model.

Clinical Reviewer's Comment: There were 34 patients randomized to the HC group and 13 patients randomized to the H group with an active DU at baseline. In the HC group, 2 were excluded from the PP analysis (see Table 3 in Appendix 2). In the H group, 1 was excluded from the ITT analysis (see Table 2 in Appendix 2) and 2 were excluded from the PP analysis (see Table 3 in Appendix 2). See table below for final numbers of patients included in each analysis. The denominators used in Table 9 are correct for the ITT and PP analyses.

Intent-to-Treat (ITT)

	HC	***H***
All Randomized Patients with an Active DU at Baseline	*34*	*13*
Patients Excluded from DU Healing ITT Analysis (Table 2 in Appendix 2)	*0*	*1*
Patients Included in DU Healing ITT Analysis	*34*	*12*

Per-Protocol (PP)

	HC	***H***
All Randomized Patients with an Active DU at Baseline	*34*	*13*
Patients Excluded from DU Healing PP Analysis (Table 3 in Appendix 2)	*2*	*2*
Patients Included in DU Healing PP Analysis	*32*	*11*

7. Comparison of Duodenal Ulcer (DU) Healed Status vs. *H. pylori* Eradication Status

A comparison of the *H. pylori* eradication results at the Day 38 visit and the DU healed results by the Day 38 visit (only for patients with an active DU at Baseline) is displayed in Table 10 for each of the treatment groups, as well as for both treatment groups combined. This table presents the number of patients with various combinations of results for the two assessments. Only patients with interpretable results for both of the assessments are included in the table. If a patient was missing a result for either *H. pylori* eradication at the Day 38 visit or DU healed by the Day 38 visit, the patient was not included in the table. The applicant performed no statistical comparisons.

TABLE 10
DU Healed Status by Day 38 Visit vs. *H. pylori* Eradication Status at Day 38 Visit
Number of Patients
For Patients With An Active DU at Baseline
Per-Protocol Analysis
Study #192

	H 40 qd + C 500 bid			H 40 qd			Both Treatment Groups Combined		
	DU Healed by Day 38 Visit								
H. pylori Eradicated at Day 38 Visit	Yes	No	Total	Yes	No	Total	Yes	No	Total
Yes	15	2	17	0	0	0	15	2	17
No	8	4	12	5	6	11	13	10	23
Total	23	6	29	5	6	11	28	12	40

Clinical Reviewer's Comment: The incidence of ulcers (unhealed/recurrent/new) at 4-6 weeks post-treatment in relation to H. pylori eradication was determined. Although not tested statistically, it appears that ulcer prevalence is lower in patients eradicated of H. pylori in both the H and HC groups.

Incidence of Ulcers in Relation to H. pylori Status

Treatment Group	*H. pylori Eradicated*	*H. pylori Not Eradicated*
H	*0/0*	*6/11 (55%)*
HC	*2/17 (12%)*	*4/12 (33%)*
Combined	*2/17 (11.8%)*	*10/23 (43.5%)*

Based on all randomized patients, of the 21 patients enrolled in this study who did not have an active DU at the baseline endoscopy, there was only 1 patient (5%) who developed an ulcer (either duodenal or gastric) at some time during the study period. This patient (AN 2091) enrolled in the HC group did not have an active DU at Baseline, but developed a 0.3 cm DU at some time during the study period. The patient was not considered *H. pylori* infected at Baseline or at the Day 38 visit.

8. Upper GI Ulcer Symptom Assessment

The investigator assessed upper GI ulcer symptoms experienced by the patient at each office visit (Screening/Baseline Visit, Day 11 Visit, and Day 38 Visit). The symptoms assessed included daytime epigastric pain or burning, nighttime epigastric pain or burning, nausea, vomiting, heartburn and acid regurgitation. The severity of symptoms was assessed on a 4-point scale: none, mild, moderate, or severe.

The number and proportion of patients with baseline upper GI symptoms were evaluated by treatment group for each individual symptom assessed according to severity. The

distribution across severity appeared similar between the two treatment groups for each of the upper GI symptoms. The applicant made no statistical comparisons between treatment groups.

At both the Day 11 Visit and the Day 38 Visit, the proportion of patients with at least mild upper GI symptoms at baseline who had improvement in symptoms from baseline was high (ranging from 81% to 100% of the patients for the various symptoms and treatment groups). Each of the symptoms assessed showed improvement from baseline at both the Day 11 visit and the Day 38 visit.

The applicant stated the proportion of patients with improvement in vomiting from Baseline to the Day 11 visit was significantly higher in the HC group (7 of 7 patients; 100%) than in the H group (no patients; 0%). However, these sample sizes are too small to make any meaningful comparisons. There were no other significant differences between the treatment groups for any symptom at any of the two timepoints.

9. Susceptibility

The susceptibility of all available *H. pylori* isolates to clarithromycin, both pre-treatment and post-treatment, was tested using agar dilution. If MIC results of *H. pylori* isolates from two different biopsies were available at a particular timepoint for a given patient (i.e., one antrum and one corpus result), the higher MIC value was used for the analysis. Only data from patients considered *H. pylori* infected at Baseline are included in the following table.

A total of 24% of the patients (12 of 50 patients with known susceptibility results) had *H. pylori* isolates which were considered to be resistant to clarithromycin at Baseline, no patient had isolates classified as intermediate, and 76% of the patients (38 of 50 patients with known susceptibility results) had isolates considered to be susceptible to clarithromycin at Baseline. The distributions of susceptibility status were similar for each treatment group.

Table 11 displays the clarithromycin susceptibility results of patients with *H. pylori* isolates according to whether or not the patients had previously taken *H. pylori* eradication regimens containing clarithromycin prior to entering the study. For the 12 patients with *H. pylori* isolates resistant to clarithromycin at the baseline visit, 33% of the patients (4 of 12 patients) had previously taken *H. pylori* eradication regimens containing clarithromycin while 67% of the patients (8 of 12 patients) had not taken such previous regimens.

TABLE 11
Baseline *H. pylori* Susceptibility Results to Clarithromycin
By Previous *H. pylori* Eradication Regimens Containing Clarithromycin
Based on Agar Dilution
Number (%) of Patients
All Available Data
Study #192

Baseline *H. pylori* Susceptibility to Clarithromycin	Previous *H. pylori* Eradication Regimens Taken Which Contained Clarithromycin				
	Yes		No		Total
Both Treatment Groups Combined	n	%	n	%	N
Resistant	4	(33%)	8	(67%)	12
Intermediate	0	(0%)	0	(0%)	0
Susceptible	0	(0%)	38	(100%)	38
No Result [a]	4	(25%)	12	(75%)	16
TOTAL	8	(12%)	58	(88%)	66

[a] "No result" includes patients considered to be *H. pylori* infected at Baseline, but who had no susceptibility results for culture.

Clinical Reviewer's Comment: It is unusual that more isolates with baseline resistance to clarithromycin were obtained from patients who had not taken previous eradication regimens containing clarithromycin as compared to those patients who had taken clarithromycin-containing regimens. Although the numbers in this study are small, they are consistent with the results in Study #191. The explanation for this finding is unknown, but may have to do with other undetermined risk factors for resistance.

A comparison of the baseline *H. pylori* clarithromycin susceptibility status results and the *H. pylori* eradication status at the Day 38 Visit is presented in Table 12. Results are presented for each treatment group, as well as for both treatment groups combined.

A total of 38 patients had *H. pylori* isolates considered to be susceptible to clarithromycin at Baseline (27 patients in the HC group, 11 patients in the H group). Of these 38 patients, 5 patients had isolates that developed resistance to clarithromycin by the Day 38 visit (4 patients in the HC group and 1 patient in the H group).

APPEARS THIS WAY
ON ORIGINAL

TABLE 12
Baseline *H. pylori* Susceptibility Results vs. *H. pylori* Eradication Status at Day 38
Susceptibility to Clarithromycin Based on Agar Dilution
Number of Patients
All Available Data
Study #192

	Day 38 Visit *H. pylori* Eradication Status							
Baseline *H. pylori* Susceptibility to Clarithromycin	*H. pylori* Eradicated	*H. pylori* Not Eradicated					No *H. pylori* Eradication Result	Total
		Day 38 Visit Susceptibility to Clarithromycin						
		Res.	*Int.*	*Susc.*	*No Result*	*Total*		
H 40 qd + C 500 bid								
Resistant	0	9	0	0	0	9	0	9
Intermediate	0	0	0	0	0	0	0	0
Susceptible	16	4	0	0	4	8	3	27
No Result [a]	7	1	0	0	4	5	2	14
Total	23	14	0	0	8	22	5	50
H 40 qd								
Resistant	0	1	0	1	1	3	0	3
Intermediate	0	0	0	0	0	0	0	0
Susceptible	0	1	0	9	1	11	0	11
No Result [a]	0	0	0	0	2	2	0	2
Total	0	2	0	10	4	16	0	16
Both Treatment Groups Combined								
Resistant	0	10	0	1	1	12	0	12
Intermediate	0	0	0	0	0	0	0	0
Susceptible	16	5	0	9	5	19	3	38
No Result [a]	7	1	0	0	6	7	2	16
Total	23	16	0	10	12	38	5	66

[a] "No result" includes patients considered to be *H. pylori* infected at Baseline, but who had no susceptibility results for culture.

10. Safety Analyses

A total of 68 patients were randomized to one of the two treatment groups in this study. All 68 took at least one dose of medication and were included in the analysis of AE's. For the analysis of laboratory data and physical examination data, all patients who took at least one dose of study medication and who had laboratory tests performed or who had physical examination measurements taken at various post-baseline timepoints were included in the analysis of those data.

A summary of the proportion of patients experiencing AEs at any time throughout the 38-day study period is presented in Table 13.

TABLE 13
Adverse Event Summary Throughout Entire Study Period
Number (%) of Patients
All Randomized Patients Who Took At Least One Dose of Study Medication
Study #192

	H 40 qd + C 500 bid (N=51)		H 40 qd (N=17)	
Number (%) of Patients	n	(%)	n	(%)
With ≥1 AE	27	(53%)	10	(59%)
With a possibly or probably drug related AE	14	(27%)	5	(29%)
With a serious AE	1	(2%)	0	(0%)
Discontinued due to an AE	2	(4%)	0	(0%)

There were no significant differences between the treatment groups ($p > 0.050$ using Fisher's Exact Test) with respect to the proportion of patients experiencing at least one AE, the proportion of patients experiencing at least one AE classified as possibly or probably drug-related by the investigator, the proportion of patients experiencing serious AEs, or the proportion of patients who discontinued from the study early due to an AE.

Two patients in this study discontinued from the study early due to experiencing an AE (both in the HC group). One of these patients had an AE considered to be serious.

Table 14 presents individual AEs under each body system category if at least 1% of the patients in either of the two treatment groups had experienced that particular AE.

The most common AEs occurring in this study were gastritis (7 of 68 patients or 10%), headache (6 of 68 patients or 9%), esophagitis (3 of 68 patients or 4%), and dyspepsia (3 of 68 patients or 4%). There were no significant differences between the treatment groups with respect to the proportion of patients who had any particular AE. While not significantly different, the incidence of taste perversion was numerically higher in the HC group (8 of 51 patients or 16%) than in the H group (0 of 17 patients). Taste perversion is a known adverse event associated with clarithromycin. Also, there were no significant differences

between the treatment groups in the proportion of patients who had experienced AEs according to any of the body system classifications ($p > 0.050$ using Fisher's Exact Test).

TABLE 14
Adverse Events (AEs) Throughout Entire Study Period By Body System
Number (%) of Patients
(Patient Incidence ≥ 1% in Either Treatment Group for Individual AEs)
All Randomized Patients Who Took At Least One Dose of Study Medication
Study #192

Body System AE	H 40 qd + C 500 bid (N=51)			H 40 qd (N=17)		
	n	(%)		n	(%)	
Body as a Whole						
accident/injury	1	(2%)	[0]	0	(0%)	---
back pain	0	(0%)	---	1	(6%)	[0]
fatigue	1	(2%)	[1]	0	(0%)	---
fever	0	(0%)	---	1	(6%)	[0]
pain	1	(2%)	[0]	0	(0%)	---
Central and Periph Nervous System						
headache	5	(10%)	[1]	1	(6%)	[0]
paraesthesia	1	(2%)	[1]	0	(0%)	---
Gastrointestinal System						
abdominal pain	0	(0%)	---	1	(6%)	[0]
constipation	0	(0%)	---	1	(6%)	[1]
diarrhoea	2	(4%)	[2]	0	(0%)	---
duodenitis	1	(2%)	[0]	0	(0%)	---
dyspepsia	2	(4%)	[2]	1	(6%)	[1]
flatulence	1	(2%)	[1]	0	(0%)	---
gastritis	4	(8%)	[1]	3	(18%)	[2]
hunger pangs	1	(2%)	[1]	0	(0%)	---
irritable bowel	0	(0%)	---	1	(6%)	[0]
mouth dry	2	(4%)	[2]	0	(0%)	---
nausea	2	(4%)	[1]	0	(0%)	---
oesophagitis	3	(6%)	[2]	0	(0%)	---
Heart Rhythm Disorders						
cardiac arrest	1	(2%)	[0]	0	(0%)	---
Metabolic Nutritional Disorders						
hyperglycaemia	1	(2%)	[0]	0	(0%)	---
Musculoskeletal System						
arthralgia	1	(2%)	[0]	0	(0%)	---
Psychiatric Disorders						
anorexia	1	(2%)	[1]	0	(0%)	---
concentration impaired	1	(2%)	[1]	0	(0%)	---

[ ] The numbers in brackets are counts of patients who had AEs that were rated possibly or probably drug-related by the investigator.

TABLE 14 (Cont.)
Adverse Events (AEs) Throughout Entire Study Period By Body System
Number (%) of Patients
(Patient Incidence ≥ 1% in Either Treatment Group for Individual AEs)
All Randomized Patients Who Took At Least One Dose of Study Medication
Study #192

Body System AE	H 40 qd + C 500 bid (N=51)			H 40 qd (N=17)		
	n	(%)		n	(%)	
Respiratory System						
bronchitis	1	(2%)	[0]	1	(6%)	[0]
coughing	1	(2%)	[0]	0	(0%)	---
pharyngitis	1	(2%)	[0]	0	(0%)	---
respiratory infection	2	(4%)	[0]	0	(0%)	---
sinusitis	0	(0%)	---	1	(6%)	[0]
Skin Append Disorders						
pruritus	1	(2%)	[1]	0	(0%)	---
pruritus genital	1	(2%)	[0]	0	(0%)	---
Special Senses						
taste perversion	8	(16%)	[7]	0	(0%)	---
Urinary System						
cystitis	1	(2%)	[0]	0	(0%)	---
micturition frequency	1	(2%)	[0]	0	(0%)	---
nocturia	1	(2%)	[0]	0	(0%)	---
WBC & Resistance Disorders						
leukopenia	0	(0%)	---	1	(6%)	[1]

[ ] The numbers in brackets are counts of patients who had AEs that were rated possibly or probably drug-related by the investigator.

APPEARS THIS WAY
ON ORIGINAL

Serious Adverse Events

Of the 68 patients enrolled into this study who took at least one dose of study medication, 1 patient experienced an AE considered to be serious (HC group). This serious AE (death) was considered to be unlikely related to the study drug by the investigator and the reviewer. This serious AE is presented in Table 15.

TABLE 15
Listing of Serious Adverse Event Occurring Throughout the Entire Study Period
Study #192

Site/ Enroll-ment #	AN	Gender /Age	Relative Day of Onset	AE	Dur. (Days)	Intensity	Drug Rel.	Action Taken	Outcome
H 40 qd + C 500 bid group									
200/ 001	2045	F/80	8	Cardiac arrest	1	Severe	Unlikely	Drug stopped	Death
H 40 qd group									
No patients experienced a serious AE in this treatment group.									

Clinical Reviewer's Comment: A narrative on Patient 200/001 (AN 2045) can be found in the Integrated Summary of Safety (ISS).

Of the 68 patients enrolled in this study, only 1 other patient besides Patient 200/001 (AN 2045) experienced an AE which caused the patient to discontinue from the study. Table 16 lists these two patients who discontinued from the study due to an AE.

TABLE 16
Patients Discontinued from Study Due to Adverse Events
Occurring Throughout Entire Study Period
Study #192

Site/ Enroll-ment #	AN	Gender/ Age	Relative Day of Onset	AE	Dur. (Days)	Intensity	Drug Rel.	Serious	Last Day of Study Med.	Study Day Discon-tinued	Action Taken
H 40 qd + C 500 bid group											
200/ 001	2045	F/80	8	Cardiac arrest	<1	Severe	Unlikely	Yes	7	8	Drug stopped
223/ 001	2053	F/48	2 2 2	Concentration Impaired Dyspepsia Paraesthesia	1 1 1	Mod. Mod. Mod.	Prob. Prob. Prob.	No No No	4	10	Drug stopped
H 40 qd group											
No patients discontinued from the study due to an AE in this treatment group.											

Clinical Laboratory Evaluation

Laboratory measurements were collected from each patient at the Screening/Baseline visit as well as at the Day 11 and Day 38 Visits. For each quantitative laboratory test in the

chemistry and hematology groups, the mean change from the baseline measurement was analyzed. There were no clinically meaningful mean changes from Baseline to the Day 11 Visit, Baseline to the Day 38 Visit, or from Baseline to the Day 11 Visit or the Day 38 Visit for any of the laboratory tests for either treatment group. The applicant performed no statistical comparisons between the treatment groups.

Laboratory test data were also analyzed in relation to the laboratory test reference ranges specified by [redacted] Statistical comparisons were made by the applicant between the treatment groups for the distribution of patients across the classifications according to the reference range at the Day 11 Visit and the Day 38 Visit for each of the hematology and blood chemistry tests. There were no significant differences between treatment groups for any of the laboratory parameters at either of the timepoints. In addition, there were no clinically meaningful changes from Baseline to either timepoint in the distribution of laboratory values from the normal range for either treatment group.

11. Vital Signs, Physical Findings and Other Observations Related to Safety

Measurements for weight, pulse, and blood pressure were to be collected for each patient at the Screening/Baseline Visit, as well as other visits throughout the study (Day 11 and Day 38 Visits for pulse and blood pressure, Day 38 Visit for weight). There were no clinically meaningful mean changes from Baseline for any of the vital sign measurements at any timepoint for any treatment group.

E. Reviewers' Conclusions of Study 192

This was a well conducted, randomized, clinical trial which demonstrated the superiority of dual therapy (HC) over monotherapy (H) when given for 10 days with twice daily dosing. However, the lower bound of the 95% confidence interval of the point estimate for dual therapy using the ITT analysis was 32%, which is considerably below the 60% threshold as suggested by the Division.

APPEARS THIS WAY
ON ORIGINAL

VIII. Clinical and Statistical Review of Study 193

A. Investigators and Study Administrative Structure

Thirty-five (35) primary investigators participated in the trial.

This study used identical contract organizations and central laboratories to those used in study 191.

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 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 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 (90 patients planned)
- H 199/18 40 mg qd (35 patients planned)

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

The overall study design was identical to Study 191.

The study was designed to enroll approximately 125 patients. The study was stopped when 113 patients were enrolled. The reduction in the number of patients was necessary because patient enrollment was slower than anticipated. The FDA was consulted and agreed to the proposed reduction of the sample sizes.

D. Results

1. Investigators

There were 35 investigator sites initiated for this study. Of these 35 sites, 22 randomized and enrolled a total of 113 patients. The other 13 initiated sites (37%) never enrolled any patients. Of the 22 investigator sites that enrolled patients, 16 sites enrolled 5 or fewer patients and 18 sites enrolled 8 or fewer patients. The site with the highest enrollment (Site 324) enrolled 15% (17 of 113 patients) of the total number of patients enrolled in the study.

Clinical Reviewer's Comment: The number of sites that were initiated for this study, but did not enroll any patients, is large.

Table 1 in Appendix 3 presents the distribution of patient enrollment by treatment group for each investigator site.

2. Patient Accountability

The number of patients in each treatment group who completed the study as stated in the protocol, and the number of patients who discontinued from the study are listed in Table 1. The applicant noted there were no significant differences observed between the treatment groups for the proportion of patients who completed the study or for any reason discontinued from the study, ($p > 0.050$), using Fisher's Exact Test.

TABLE 1
Patient Accounting - All Randomized Patients
Study #193

	H 40 qd + A 1000 bid + C 500 bid		H 40 qd	
Study Status	n	(%)	n	(%)
Patients Enrolled	85		28	
Completed the Study Period	79	(93%)	27	(96%)
Discontinued from Study				
Adverse Event	1	(1%)	1	(4%)
Consent Withdrawn	1	(1%)	0	(0%)
Investigator/Sponsor Decision	2	(2%)	0	(0%)
Lack of Therapeutic Response	1	(1%)	0	(0%)
Lost to Follow Up	1	(1%)	0	(0%)

Clinical Reviewer's Comment: Two patients were withdrawn by the Investigator. One patient was in the H group (334/007 AN 3231) and was withdrawn for persistently abnormal liver function tests (SGPT, SGOT, Alk Phos) on Day 9. The other patient (310/001 AN 3048) was in the HAC group and was inappropriately enrolled due to a negative rapid urease test.

The number of patients who were included (considered evaluable) or excluded (considered non-evaluable) from each analysis is summarized by treatment group in Table 2 according to the reason considered non-evaluable. No patient was counted under more than one violation for either the ITT or PP analysis.

For the PP analysis, if an evaluable patient had a missing value (within day ranges) for a particular efficacy parameter, the patient was not included in the analysis of that parameter. Thus, the total number of patients included in the PP analysis for a particular efficacy parameter may be less than 94 patients (n=71 for HAC and n=23 for H).

Clinical Reviewer's Comment: The protocol states that H. pylori infected patients who discontinue from the study due to an AE related to the study drug are considered evaluable failures for the PP analysis. No patient in this study discontinued due to a drug-related AE.